Benzyltetrahydroisoquinoline and Bis-benzyltetrahydroisoquinoline Alkaloids as Anti-parasitic Agents



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A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of

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This thesis is dedicated to my parents,

Alida E. & Răzvan L. Sozanschi

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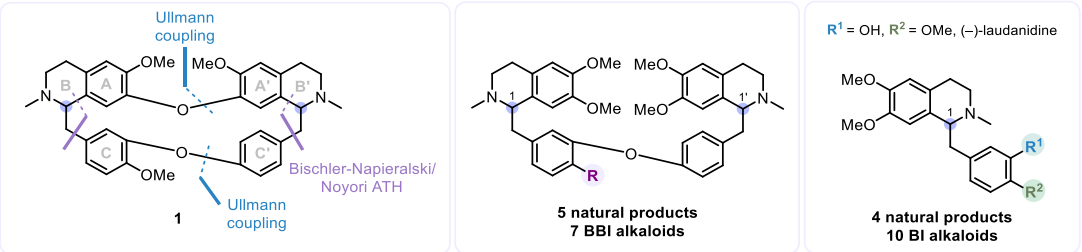
Visceral leishmaniasis and Chagas disease are protozoan neglected tropical diseases that have a significant impact in developing countries. Current therapies are limited and suffer from poor safety profiles, creating a dire need for novel drug leads. Bis-benzyltetrahydroisoquinoline (BBI) alkaloids have shown promising anti-parasitic activity, but have yet to be evaluated as potential leads. Questioning whether the structural complexity of BBIs is vital to the bioactivity, this thesis describes the studies towards simplified analogue **1**. Key strategic steps include an Ullmann coupling to form the diaryl ether linkages and a Bischler-Napieralski cyclisation/Noyori asymmetric transfer hydrogenation to build the tetrahydroisoquinoline units (**Chapter 2**). To further simply the scaffold, the diaryl ether linkages are removed sequentially leading to the synthesis of linear BBI and benzyltetrahydroisoquinoline (BI) alkaloids. The acyclic BBIs were made from the individual BIs using a seven- or nine-step modular, convergent, and enantioselective strategy using the same key reactions. This enabled access to four natural and ten non-natural BI alkaloids and five BBI natural products and seven analogues. All diastereomers were synthesised to assess the effect of stereochemistry on bioactivity (**Chapter 3**). These compounds were tested against *Leishmania infantum* and *Trypanosoma cruzi*, and mammalian cytotoxicity was evaluated (**Chapter 4**). While acyclic BBI alkaloids were found to be cytotoxic and unfit as drug scaffolds, the lead BI (–)-laudanidine showed an IC_{50} of 2.60 ± 0.31 μM against *T. cruzi* amastigotes and SI >77 compared to current gold standard benznidazole (IC_{50} of 5.00 ± 1.53 μM, SI >40), thus promisingly meeting the DND*i*'s criteria for a hit against Chagas Disease.



Declaration

The work presented in this thesis was conducted at the Department of Chemistry and Nuffield Department of Medicine, University of Oxford. This thesis is a product of my own work and includes no results obtained through collaboration, except for the biological assays performed for *L. infantum*, *T. cruzi* and fibroblasts NCTC cells (clone 929). The IC_{50} and CC_{50} values were obtained by Prof. André Tempone's research group at the Instituto Adolfo Lutz in São Paulo, Brazil. The work presented has not been submitted, either partially or in full, for any qualification at this or at any other institution.

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Mulțumesc.

Abbreviations

$[\alpha]_D$	Specific optical rotation
D	Heat (reflux)
°C	Degrees Celsius
δ	Chemical shift
µ	Micro-
Ab	Amphotericin B
Ac	Acyl
ADME	Absorption, distribution, metabolism, excretion
AIDS	Acquired immune deficiency syndrome
APCI	Atmospheric-pressure chemical ionisation
aq	Aqueous
Ar	Aryl
ATH	Asymmetric transfer hydrogenation
ATP	Adenosine triphosphate
BI	Benzyltetrahydroisoquinoline
BBB	Blood brain barrier
BBI	Bis-benzyltetrahydroisoquinoline
Bn	Benzyl
BN	Bischler-Napierlaski
Boc	*tert*-Butyloxycarbonyl
BOP	Benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate
BSA	Bovine serum albumin
B–THF	Borane-tetrahydrofuran complex
c	Concentration (specific optical rotation)
CC_{50}	Half-maximal cytotoxic ceoncentration
CAM	Hanessian's stain
Cas9	CRISPR-associated protein 9
cat	Catalytic
Cbz	Benzyloxycarbonyl
CCE	Constant current electrolysis
CD	Chagas disease
CDC	Centre for disease control and prevention
CL	Cutaneous leishmaniasis
cm	Centimetre(s)
COSY	Correlation spectroscopy
CPSF3	Cleavage and polyadenylation specificity factor
CRISPR	clustered regularly interspaced short palindromic repeats
CYP	Cytochrome P450
d	Doublet
DALY	Death and disability adjusted life years
DCC	*N,N*-Dicyclohexylcarbodiimide
DHIQ	Dihydroisoquinoline
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	2-Deoxyribonucleic acid
DND*i*	Drugs for neglected diseases initiative
dppf	1,1′-Bis(diphenylphosphino) ferrocene

dr	Diastereomeric ratio
EDA	Ethylenediamine
EDC	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	Enantiomeric excess
EI	Electron ionisation
equiv	Equivalent(s)
er	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
Fig	Figure
g	Gram(s)
GI	Gastrointestinal
GTP	Guanosine triphosphate
h	Hour(s)
HAT	Human African trypanosomiasis
HBA	H-bond acceptor
HBD	H-bond donor
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond correlation
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
IC_{50}	Half-maximal inhibitory concentration
IDPi	Imidodiphosphorimidate
i.e.	*id est* (that is)
IFN-γ	Interferon-gamma
IPA	2-Propanol
IR	Infra-red
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
L. braziliensis	*Leishmania braziliensis*
L. donovani	*Leishmania donovani*
L. infantum	*Leishmania infantum*
L. major	*Leishmania major*
L. mexicana	*Leishmania mexicana*
LLS	Longest linear sequence
Lit	Literature
LRMS	Low resolution mass spectrometry
m	Multiplet
(m)	Minor rotamer
(M)	Major rotamer
M	Molar concentration
MCL	Mucocutaneous leishmaniasis
Me	Methyl
min	Minute(s)
mmol	Millimole(s)
mol	Mole(s)
MOM	Methoxymethyl
m.p.	Melting point
MS	Molecular sieves

MW	Molecular weight
NA	Not active
^{n}BuLi	*n*-Buthyllithium
NBS	*N*-Bromosuccinimide
NCS	Norcoclaurine synthase
ND	Not determined
NIH	National institute of health
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect correlation spectroscopy
NTD	Neglected tropical disease(s)
o	*Ortho*
PAINS	Pan-assay intereference compounds
PBS	Phosphate Buffer Saline
PFB	Pomeranz-Fritsch-Bobbit
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PKDL	Post-kala-azar dermal leishmaniasis
PMA	Phosphomolybdic acid stain
PMB	*para*-Methoxybenzene
ppm	Parts per million
PPSE	Trimethylsilyl polyphosphate
PS	Pictet-Spengler
p	*Para*
pTLC	Preparative thin layer chromatography
*p*TSA	*para*-Toluensulfonic acid
q	Quartet
rac	Racemic
R&D	Research and development
R_f	Retention factor
ROS	Reactive oxygen species
rt	Room temperature
s	Singlet
SAR	Structure-activity-relationship
sat	Saturated
SD	Standard deviation
SFC	Chiral supercritical fluid chromatography
SI	Selectivity index
Su	Succinimide
t	Triplet
T. brucei	*Trypanosoma brucei*
T. cruzi	*Trypanosoma cruzi*
T3P	Propylphosphonic anhydride
TB	Tuberculosis
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
Temp.	Temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl
tert-	Tertiary
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
THIQ	Tetrahydroisoquinoline
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TPSA	Topological polar surface area
t_R	Retention time
Ts	*para*-Toluenesulfonyl
TsDPEN	*N*-(*para*-toluenesulfonyl)-1,2-diphenylethylenediamine
νmax	Wavelength of maximum absorbance
vs	Versus
v/v	Volume by volume
VL	Visceral leishmaniasis
WHO	World Health Organization
wt	Weight percent

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1

Introduction

1.1 Neglected Tropical Diseases

Neglected tropical diseases (NTDs) are bacterial, viral or parasitic infectious diseases which predominantly affect populations in tropical and subtropical regions of the world.[1] These diseases are often distinguished from the "big-three" infectious diseases – tuberculosis (TB), malaria and HIV/AIDS – towards which many R&D efforts have been made over the years.[2] While the list of NTDs[3,4] differs to some extent between major global health organisations, what all NTDs have in common is that they affect the world's most poor and vulnerable communities, making NTDs the diseases of "neglected people" while also being neglected from efforts and resources going into drug research and development.[2] For example, a recent breakdown of funding provided by the U.S. Government for global health initiatives (excluding funding to the Centre for Disease Control and Prevention (CDC) and the National Institute of Health (NIH)) shows that NTDs continue to receive the least attention in comparison to other areas (1% of the allocated $12.2 billion).[5] A 2013 study showed that only 1% of the clinical trials registered in 2011 were targeting NTDs, TB or malaria.[6] More recently, a 2018 review on the

shortcomings of drug innovation for NTDs showed that between 2000 and 2014 only around 2% of phase I clinical trials involved drugs targeting NTDs.[1]

The World Health Organisation (WHO) states that NTDs affect over a billion people worldwide, with some of these cases resulting in death, but more often leading to long-term disability and disfigurement, giving rise to further social and economic hardship.[1,2] With current available treatments suffering from severe drawbacks such as high cost, patient-compliance issues, high toxicity and emerging resistance, there is a clear need for novel therapeutic agents.[7] For this reason and the significant lack of research on NTDs, the formation of non-profit organisations such as the Drugs for Neglected Diseases initiative (DND*i*) was initiated in the early 2000s. This type of organisation works towards bringing repurposed and/or novel therapeutic agents against NTDs to the patient.[4,7]

1.1.1 Protozoan Parasitic NTDs

Parasites are eukaryotic organisms that live on or in another organism (the host), from which they obtain the required nutrients for survival. In the majority of cases, the host does not benefit from this relationship but rather suffers from it. The three main classes of parasites which can elicit diseases in human are: protozoa, helminths and ectoparasites.[7] This work focuses on protozoan parasites. Protozoa are microscopic single-cell eukaryotes that possess a relatively complex intracellular structure with organelles that carry out functions similar to those in animals. Kinetoplastids are a subgroup of protozoans characterised by the presence of a circular DNA network called a kinetoplast in their mitochondrion. Representative genres of this subgroup include *Leishmania* spp. and *Trypanosoma cruzi*, the causative organisms of leishmaniasis and Chagas disease respectively.[8]

Our group's interest in these two diseases arose for several reasons. Visceral leishmaniasis, the most severe form of the disease, has been ranked the deadliest parasitic disease amongst NTDs.[9] Moreover, both leishmaniasis and Chagas disease have high death and disability-adjusted life years (DALYs) which pose significant social and economic hardship in the affected regions.[10] With limited resources of the pharmaceutical industry being invested into R&D, the burden of bringing effective therapeutics to these neglected patients often falls on non-profit organisations and academic research.

1.1.1.1 Leishmaniasis

Leishmaniasis is an NTD caused by at least 20 species of the *Leishmania* genus, and is transmitted between mammalian hosts through infected female sandflies.[11] The disease can be both anthroponotic and zoonotic, meaning both humans and animals can serve as a reservoir.[12] It has been estimated that roughly 12 million people suffer from leishmaniasis with over 350 million people at risk of infection and nearly one million new cases every year.[13] Four main forms are known: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL) and post-kala-azar dermal leishmaniasis (PKDL). Infection with different *Leishmania* species is accompanied by a range of clinical manifestations ranging from minor skin lesions to lethal organ damage.[11,12]

Visceral Leishmaniasis

Visceral leishmaniasis (VL), also known by the Hindi name kala-azar (i.e., 'black fever') is the most severe form of the disease and is typically lethal unless treated. The characteristic clinical manifestations include sporadic fever, splenomegaly and pancytopenia, which arise as a consequence of the parasite multiplying and migrating

from the site of infection to the targeted organs.[11,14] A particular complication is posed by the co-infection with HIV/AIDS as both diseases affect the immune system, thus acting synergistically.[15] VL allows for HIV/AIDS progression to occur at a faster rate while the latter increases the chances of asymptomatic leishmaniasis becoming symptomatic, thus increasing the risk of developing VL and other secondary infections. Curing VL in these patients is essentially impossible as standard drugs become ineffective, resistance emerges and relapse rates increase.[15] As of 2020, the WHO estimated that there are between 50,000 and 90,000 new cases each year with over 90% occurring in the following countries: Brazil, China, Ethiopia, India, Kenya, Somalia, South Sudan, Sudan and Yemen.[16] VL is caused exclusively by two species: *L. donovani*, which is endemic in Eastern Africa and Asia, and *L. infantum*, which predominantly affects regions in Central Asia, the Mediterranean Basin, the Middle East and Latin America.[11,17] In the case of *L. infantum*, dogs play a crucial role in the spread of the disease as they act as a reservoir.[18]

Post-kala-azar Dermal Leishmaniasis

Post-Kala-Azar dermal leishmaniasis (PKDL) is a complication that arises in 2.5 to 20% of patients post recovery from VL and is mainly observed in regions where *L. donovani* is endemic, namely Sudan and India. These complications tend to arise in the first six months after patients recover from VL, however longer intervals of up to several years have been reported.[19] In a small percentage of cases, these complications appear without any history of VL.[20] Typically, PKDL manifests in the form of a papular or nodular rash that can be misdiagnosed for leprosy. Mild cases of PKDL have been known to spontaneously heal and in cases where treatment is required, cure rates of up to 92% have been reported. While PKDL may not be lethal, it has significant epidemiological

implications as the lesions contain parasites that can act as a reservoir in interepidemic times.[19,20]

Cutaneous and Mucocutaneous Leishmaniasis

Cutaneous leishmaniasis (CL) is the most common form of the disease with 95% of cases occurring in the Middle East, Central Asia, the Mediterranean basin and the Americas.[16] A variety of *Leishmania* and vector species combine with a dispersed geographical distribution, resulting in a wide range of clinical manifestation making the diseases difficult to diagnose, treat and even more difficult to eradicate. The rate of incidence has been estimated to be around one million new cases per year, however poor diagnosis and asymptomatic cases make it likely that these numbers are underestimated.[21] The main clinical manifestation is a small papule at the biting site which develops slowly over the course of weeks or months into a nodule which can ultimately start to ulcerate.[11] While the disease is not life-threatening, these lesions tend to be itchy and painful and can lead to scarring, disfigurement and social stigmatistion.[11,22] Although CL poses a major global health issue affecting millions of people worldwide, the low mortality risk sparks little financial incentive for curing and/or controlling the dispersion of the disease, hence its belonging to the list of neglected tropical diseases.[23]

Mucocutaneous leishmaniasis (MCL) is a potentially life-threatening complication of CL characterised by the spread of the parasite to the mucous tissues where it leads to partial or complete destruction of the lips, palate and nasal septum.[23] This loss of tissue can result in permanent disfiguration and disability and, in certain cases where the larynx is affected, aspiration pneumonia.[11,22] MCL is observed mainly in Bolivia, Brazil, Ethiopia and Peru and is commonly linked to *L. braziliensis*, although other Leishmania species can also elicit it.[22]

Parasite Life Cycle

The *Leishmania* parasite has two major cell morphologies that it assumes during its life cycle (**Figure 1.1**), namely the promastigote and the amastigote form. While the shape of the cells differs significantly in these two forms, the internal architecture is highly conserved. In both forms the cell contains a nucleus, a large mitochondrion, a Golgi apparatus, an endoplasmic reticulum, a network of mitochondrial DNA called a kinetoplast, and a flagellum extending from the cell body. The promastigote form is the extracellular form that the parasite assumes within the sandfly. Its morphology is characterised by an elongated cell body with a long motile flagellum whose role is to facilitate movement through the sandfly's digestive tract and into the host. Once the parasite enters the host's cells, the cell body becomes smaller and more spherical, the flagellum shortens and loses its motility. This form is known as the amastigote form and is the clinically more relevant form of the parasite, as it assumes this morphology during human infection. [24]

When an infected sandfly takes a blood meal, metacyclic promastigotes are transferred to the human host. The immune system of the host recruits macrophages at the bite site, where they become infected by phagocytosing the parasites.[24] Once engulfed, the promastigotes resist degradation within the macrophage *via* the formation of a parasitophorous vacuole, and start the transition into the amastigote form.[24, 25] The newly adopted morphology means a smaller surface area to volume ratio, which minimises the exposed surface to the harsh environment within the macrophage (e.g. low pH) and aids successful infection. The smaller size also means a smaller metabolic load and, combined with a slower growth rate, prevents the macrophages from being overwhelmed, thus permitting the infected host cells to survive for longer. This allows the parasites to proliferate, propagate infection and increase the chances of transmission to an uninfected

sandfly.[24] The parasite can infect other phagocytic cells either at the bite site where lesions develop in the case of CL, or accumulate in secondary lymphoid organs leading to parasitaemia, which is seen in the case of VL.[26] More sandflies can become infected by taking a blood meal from an infected host. Once in the sandfly's digestive system, the amastigotes are released from the macrophages and transition into the motile promastigote form.[24] The life cycle comes full circle by promastigotes travelling to the salivary glands of the sandfly and converting into the infectious metacyclic promastigotes ready to infect the next host.[26]

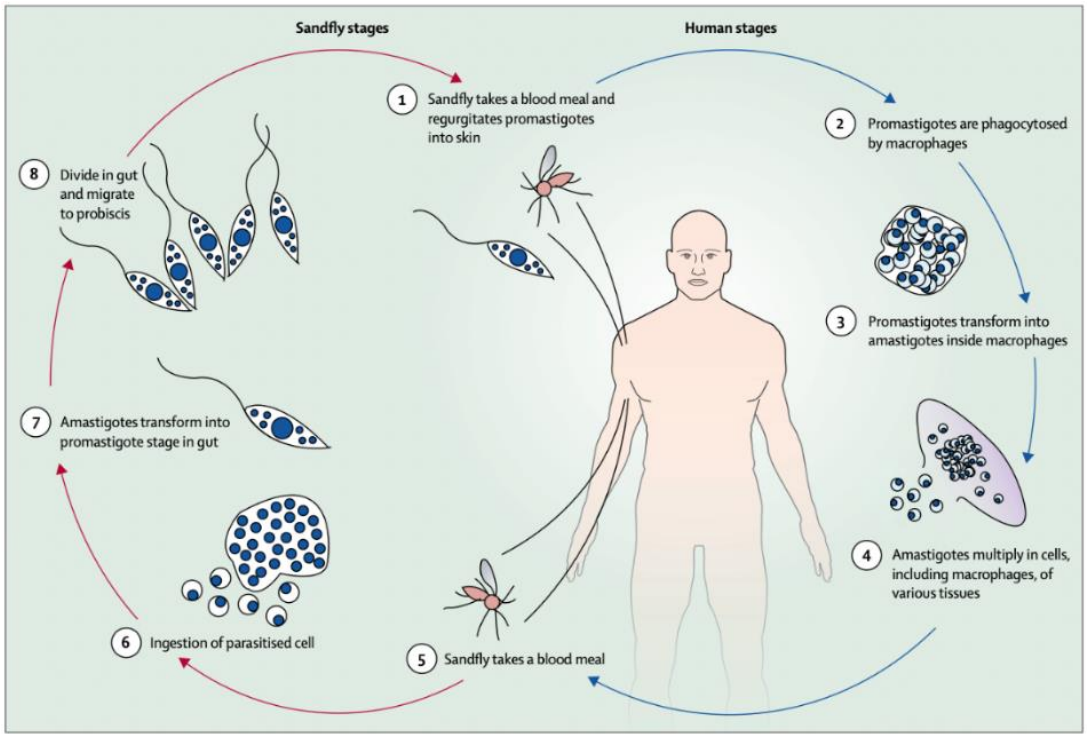
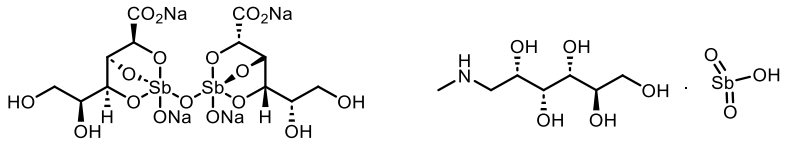


Figure 1.1. Scheme of the *Leishmania* parasite's life cycle. Figure taken from Reference 11.[11]

Current Treatments for Leishmaniasis

Current treatments against leishmaniasis are based solely on chemotherapy, with the few options suffering from severe drawbacks such as high toxicity, high cost of production and emerging resistance.[27]

At the beginning of the 20th century, tartar emetic, a trivalent antimony-based (Sb(III)) compound was used for the first time as an effective treatment against leishmaniasis. By the 1940s, pentavalent antimonials (Sb(V)) such as Pentostam® (**2**) or Glucantime® (**3**, **Figure 1.2**) were developed in an attempt to overcome the extreme cardiac toxicity associated with Sb(III) based compounds. In many areas, these remain the first-line treatment for leishmaniasis.[28]



2 **3**

Figure 1.2. Structures of antimonial drugs Pentostam® (*left*) and Glucantime® (*right*).

Despite their extensive use in the last six decades, the precise structures of these antimony compounds were only elucidated recently, while their mechanism of action remains uncertain. Sb(V) complexes have been suggested to act by one or a combination of the following mechanisms:[28] The first model suggests a prodrug behaviour whereby Sb(V) is reduced *in vivo* by both mammalian and parasitic thiols into the more toxic Sb(III) complex which may interfere with thiol redox metabolism. The second mechanism proposes an intrinsic anti-parasitic effect of Sb(V) complexes by inhibiting DNA topoisomerase I and by forming a complex with ribonucleosides, thus depleting adenosine triphosphate (ATP) and guanosine triphosphate (GTP).[28] Finally, it has been suggested that these complexes could also play a role in modulating the human immune response, thus helping the host to fight off the infection.

Pentavalent antimonials have limitations including painful and long treatment courses (daily injections for up to 30 days) that need medical supervision, and side effects such as gastrointestinal issues, skin rashes, nephro-, hepato- and cardiotoxicity.[27, 28] Finally, the

major issues with these chemotherapeutics are emerging resistance and decreased efficacy. For example, in Bihar, a region in northern India, unrestricted access, disregard of treatment guidelines and continuous misuse have been the main reasons why antimony-based treatments have started to fail.[28, 29]

Nearly all alternative clinical treatments against leishmaniasis have been in the form of repurposed drugs. This is a rather straightforward and common process in drug development especially when little information is known about the target.[30] Having known safety and pharmacokinetic profiles makes the drug development process cheaper and more rapid by bypassing several preclinical and clinical stages.[31] However, this process does not come without its challenges such as limitations imposed by intellectual property protection or reaching a therapeutic effect within the pre-approved safety margins and dosage regimen.[32]

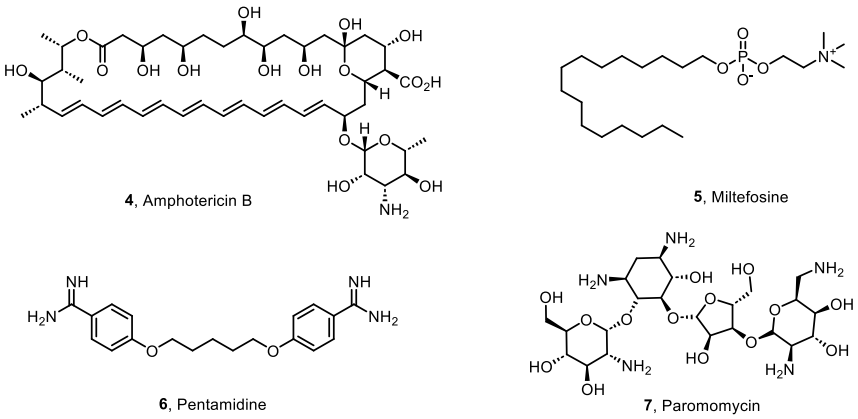


Figure 1.3. Structure of anti-leishmanial drugs currently in clinical use.

Amphotericin B (Ab) (**4**, **Figure 1.3**), an anti-fungal agent isolated from *Streptomyces nodosus*, was repurposed as an anti-leishmanial drug in the 1960s and has become the drug of choice for VL in regions where antimonial resistance is prevalent.[9, 31] Various formulations have been developed such as Ab deoxycholate and liposomal Ab to improve the pharmacokinetic profile and bioavailability, while diminishing side effects such as gastrointestinal issues, anorexia, hypotension and nephrotoxicity.[9, 27] Liposomal

formulations have been reported to achieve this by accumulating in the liver and spleen, and having preferential uptake by phagocytic cells like macrophages where it has a therapeutic effect.[33] The drug has a high affinity for ergosterol, a steroid abundant in the cell membrane of the *Leishmania* parasite. By forming a complex with it, the drug disrupts the ergosterol pathway giving rise to transmembrane pores causing an influx of ions and small metabolites and ultimately cell death.[9, 33, 34]

Miltefosine (**5**, **Figure 1.3**), originally an anti-cancer agent, was introduced as a drug against leishmaniasis in the 1980s and became the first drug that could be administered orally, effective even against antimonial-resistant strains.[9] Results from clinical trials showed a 95% cure rate (*i.e.* the proportion of infected patients completely cured after the treatment[35]) in VL patients and 91% in CL patients, with a treatment course of 2.5 mg/kg for 28 consecutive days.[27, 36] However, the drug is considerably inferior to pentavalent antimonials against strains such as *L. braziliensis* and *L. mexicana* where only 53% cure rates have been observed. Miltefosine also has associated side effects such as gastrointestinal problems, reversible hepato- and nephrotoxicity as well as teratogenic effects which make it unsuitable for use during pregnancy.[9] While the mechanism of action still requires a more in-depth analysis, it has been suggested that the drug acts by interfering with the biosynthesis of phospholipids and sterols, disrupting calcium homeostasis and hindering proliferation. Miltefosine has also been shown to induce nitric oxide production within the macrophage, thus aiding the host's system in killing the parasite.[9, 27] While no clinical resistance has been reported to date, some laboratory strains have been shown to develop resistance.[9] Moreover, surveilling drug resistance to clinically used anti-leishmanial agents remains a major challenge due to the lack of validated molecular resistance markers. Current protocols rely on phenotypic testing

lacking standardised assays and endpoints and while a streamlined process to monitor drug resistance has been recommended it has yet to be implemented on a global scale.[37]

Pentamidine (**6**, **Figure 1.3**) is another repurposed drug that was initially discovered in the search for hypoglycaemic drugs and was used extensively against leishmaniasis in antimonial-resistance cases.[31] The drug has been used against both CL and VL, however severe side effects such as myalgia, cardiotoxicity, and irreversible diabetes together with decreased efficacy and emerging resistance rendered it a poor alternative treatment.[9, 31] While the mechanism of action has yet to be elucidated, the drug is thought to interfere with parasite DNA synthesis.[27]

Paromomycin (**7**, **Figure 1.3**) is a relatively new broad-spectrum aminoglycoside antibiotic that has been in clinical use against leishmaniasis.[27] Various formulations are available to treat different forms of the diseases, for example, ointments for CL and intramuscular injections for VL. Even though the treatment has the added benefit of being comparatively inexpensive, it still causes side effects such as gastrointestinal problems, oto- and hepatotoxicity.[9] The mechanism by which paromomycin acts against the parasite is still unknown, although it has been suggested that it inhibits *Leishmania* protein synthesis by interfering with the ribosomal subunits.[9]

Recent Advances and Potential Treatments

While there are a handful of available treatments for leishmaniasis, all of them are marred by at least one intolerable drawback such as high toxicity, long and expensive treatment courses and emerging clinical resistance. As such there is a clear need for novel therapies that are both safe and effective.[11]

Local thermotherapy is a potential cost-effective treatment for CL based on the observation that various *Leishmania* species stop growing at a temperature above 39 °C *in vitro*. A 2013 study reports the treatment of CL patients by applying a temperature of 52 °C for three minutes for seven consecutive days with a cure rate of 60%. In comparison to other CL treatments, local thermotherapy is inexpensive and safe with the only drawbacks being the need for local sterilisation, pain at the site of application and potential burns.[38] Alternatively, cryotherapy has also been studied as a method of treating CL and reported to be almost as effective as pentavalent antimonials with fewer and less severe side effects (local pigmentation, oedema or pain). This type of therapy involves applying a temperature of −195 °C for up to 30 seconds to the lesion, up to twice a week for several weeks.[39]

Combinatorial therapy is an attractive strategy which involves prescribing a course of two or more drugs concomitantly with the aim of decreasing treatment time, toxicity, and emerging drug resistance.[27] A recent clinical trial has shown that a combination of liposomal amphotericin B infusions together with oral miltefosine achieves a cure rate of 81% after 28 days in HIV-VL coinfected patients.[40] Another clinical trial demonstrated that a combination of paromomycin/miltefosine given for 14 days is just as effective as the sodium stibogluconate/paromomycin combination (given for 17 days) achieving comparable cure rates of 91% with a reduced treatment time and no antimonial-associated risk of cardiotoxicity.[41]

Immunotherapy is a different potential strategy investigated in the fight against leishmaniasis and involves using agents which stimulate and/or modulate the immune system individually or concomitantly with chemotherapeutics for a synergistic effect. The advantages of immunotherapy include drug sparing, fewer side effects and decreased resistance. For example, the use of interferon-gamma (IFN-γ) in combination with

pentavalent antimonials results in higher cure rates than individual chemotherapy. Vaccines have also been gaining significant attention as an alternative treatment. Currently, more than a dozen vaccines are in clinical trials for both human and canine immunisation. While there is no effective vaccine currently on the market for use in humans, there are three anti-leishmanial vaccines that have been approved for use against canine-VL, although their efficacy has been questioned.[27]

Drug repurposing continues to aid the discovery and development of novel chemotherapeutics. For example, anti-fungals such as fluconazole (**8**, **Figure 1.4**) have been demonstrated to be both safe and effective in treating CL caused by *L. major* or *L. (vianna) braziliensis*.[30] The drug has been suggested to interfere with ergosterol biosynthesis, mechanism similar to that of Amphotericin B.[42]

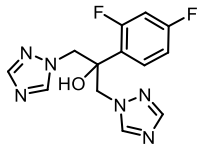


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Figure 1.4. Structure of Fluconazole.

Andrade-Neto *et al.* investigated various types of drugs ranging from anti-parasitic to anti-cancer agents that could be repurposed as anti-leishmanial agents.[31] However, of particular interest are a handful of new chemical agents that are undergoing clinical trial evaluation for VL. These compounds typically contain nitrogen-rich heterocycles and have the advantage of exploring novel targets and modes of action.[43]

1.1.1.2 Chagas Disease

Chagas disease (CD), also known as American trypanosomiasis, is a parasitic infection caused by *Trypanosoma cruzi* and is endemic to Latin America. However, in recent years the disease has spread to non-endemic regions through migration of the endemic population, thus becoming a world health problem.[44] As of 2005, CD has been recognised as an NTD by the WHO and it has been estimated that up to eight million people suffer from it throughout the world, with the majority of patients unknowingly carrying this potentially life-threatening disease.[45, 46] Further estimates suggest that there are up to 56,000 new cases per year and 12,000 associated deaths.[47] CD is anthropozoonotic and is spread by triatomine bugs.[44] The infection can also be spread by congenital transmission, blood transfusions, organ donation and ingestion of contaminated food and liquids. The clinical manifestation involves an acute phase and a chronic phase.[44]

The Acute Phase

The acute phase is predominantly seen in young children, however there is no age limit. Typically, this phase is asymptomatic and lasts up to two months after which it spontaneously resolves, and patients become chronically infected if left untreated.[44] In symptomatic cases, fever and inflammation at the biting site is observed and in cases where inoculation occurs *via* the ocular conjunctiva, the so called Romaña sign (unilateral oedema) can be observed.[48] Severe acute disease occurs in less than 5% of cases and can be accompanied by inflammation of the myocardium, hepatosplenomegaly, pericardial effusion and meningoencephalitis.[44] Nervous disorders, myalgia and chills followed by death caused by heart failure within three to four weeks from the infection time have also been reported.[48]

The Chronic Phase

The majority of Chagas disease patients remain asymptomatic and never develop visceral disease, or alternatively any clinical manifestations resolve themselves after the initial eight-week acute phase. While these patients are physically well, they still test positive for *T. cruzi* either by parasitological tests or conventional detection of IgG antibodies against the parasite. Where no treatment was given, the levels of parasitaemia drop, possibly owing to an equilibrium between the parasite and the host's immune response being established.[44, 49] A good prognosis is seen for patients where signs of cardiac and gastrointestinal abnormalities are absent, however with increasing sensitivity of diagnostic methods, subtle changes in the myocardium and digestive tract have been noticed. It is yet to be determined whether these indicate a worse prognosis.[44] These characteristics have been referred to as an indeterminate or latent phase of CD that will last for the rest of the patient's life whereby the patient can act as a reservoir and aid propagation of the disease in endemic regions.[49] Up to 40% of patients suffering from the chronic form develop visceral involvement even up to thirty years after the initial infection. Cardiomyopathy and other cardiac abnormalities are the most common and severe symptoms and constitute the main cause of sudden death in CD patients. Inflammation and scarring of the myocardium can lead to thromboembolisms, arrhythmias, and heart failure. While less common, the digestive system is also affected with severe cases suffering from megacolon and mega-oesophagus. Finally, the disease can also affect the peripheral nervous system with 10% of patients reporting sensory impairment.[44, 49]

Parasitic Life Cycle

Belonging to the Kinetoplastida family, *T. cruzi* possesses a classical intracellular architecture. During its life cycle, the parasite will assume cell morphologies that differ significantly in terms of shape and size, the length of the flagellum, and protein and RNA profiles.[50] The parasitic cycle (**Figure 1.5**) has three major morphological forms: (metacyclic and bloodstream) trypomastigotes, amastigotes and epimastigotes.[48]

When an infected triatomine bug takes a blood meal, it will excrete faeces containing the metacyclic trypomastigotes near the bite site. This form is characterised by a slender cell body, a long flagellum and the inability to replicate.[51] The parasite will then enter the host *via* the bite site, any other open wound, or alternatively *via* mucous membranes and infect a range of different cells. This process is proposed to proceed through the recruitment of the host's lysosomes which aid in the insertion of the parasite into the cell *via* formation of a parasitophorous vacuole.[48] Once inside the cell, the metacyclic trypomastigotes differentiate into amastigotes which are more spherical-shaped, have shorter flagella and are able to replicate.[50] The parasites proliferate until a sufficiently high parasitic density is reached, at which stage they convert into bloodstream trypomastigotes, reacquiring their slender cell body shape and flagella. This differentiation phase is followed by the release into the mammalian system where the parasites can either infect more proximate cells or enter and circulate the bloodstream and lymphatic system. When an uninfected triatomine bug takes a blood meal it will ingest bloodstream trypomastigotes and become infected. Once in the mid-gut of the bug, the trypomastigotes differentiate into elongated epimastigotes characterised by a long flagellum and an elongated cell shape. The epimastigotes travel towards the hind-gut of the bug where the transition into infectious metacyclic trypomastigotes is initiated, thus completing the cell cycle.[50]

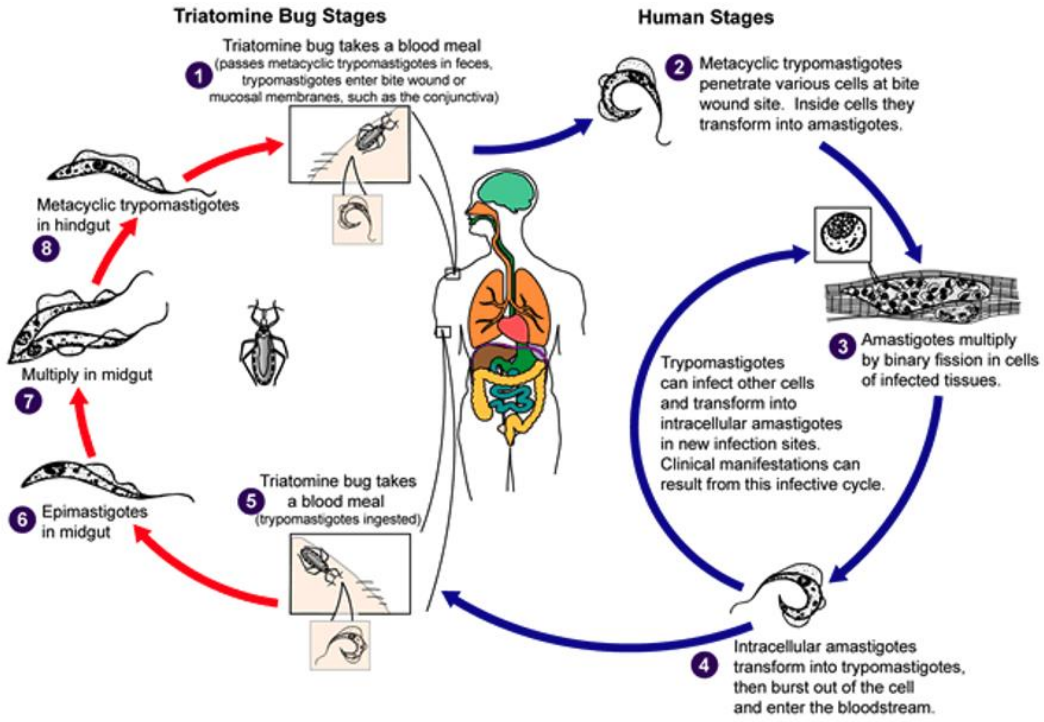


Figure 1.5. Life cycle of *T. cruzi.* Figure taken from Reference 46.[46]

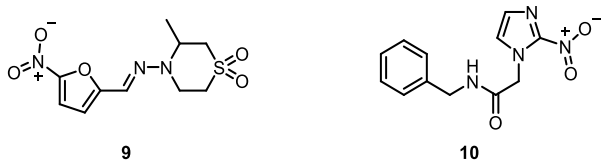
Current Treatments

There are two types of treatments available for patients suffering from CD. The etiologic treatment refers to agents which target the parasitic infection such as nifurtimox and benznidazole; on the other hand, non-etiologic treatments target the symptoms, in particular those concerning the heart and digestive system.[47] To date, there are only two parasiticidal treatments licenced for CD and despite their extensive use over the past 50 years, these drugs suffer from drawbacks such as poor efficacy and safety profiles as well as emerging resistance.[44, 52]

Nifurtimox (**9**, **Figure 1.6**) was developed in the 1970s and was the first drug used against *T. cruzi*. Its efficacy varies considerably depending on the phase of the infection, individual strain of the parasite, age of the patient and treatment duration. Cure rates of up to 100% have been observed for patients in the acute phase that take a full treatment

course (oral tablets, 10 mg/kg/day for up to 90 days), thus demonstrating that timely diagnosis and access to treatment are paramount. However, the efficacy drops significantly in chronically infected patients with reported cure rates as low as 8%.[52] The drug is associated with side effects such as anorexia, weight loss, fever, rashes, gastrointestinal and neurological disturbances, with some cases severe enough that interruption of treatment is required.[44, 52] Resistance as a consequence of incomplete treatment courses, as well as naturally resistant *T. cruzi* strains, has also been reported.[52]

Benznidazole (**10**, **Figure 1.6**) was introduced as an anti-trypanosomal agent soon after nifurtimox and has a similar efficacy profile: high cure rates of up to 80% in acute CD patients and low cure rates (8%) in chronically infected patients. Typically, the treatment is given orally for up to 60 days although shorter courses have been prescribed. While the drug is regarded as safer than its forerunner, it exhibits similar side effects such as skin problems, weight loss, anorexia, and peripheral neuropathy. More severe side effects such as decreased bone marrow and agranulocytosis have resulted in interrupted treatment courses, although seemingly to a lesser extent than nifurtimox. *T. cruzi* strains that are insensitive to benznidazole have also been reported.[52]



9 **10**

Figure 1.6. Structures of anti-trypanosomal drugs nifurtimox (*left*) and benznidazole (*right*).

While their mechanism of action is not completely understood, both drugs are thought to be reduced by nitroreductases to the radical anion form which gives rise to reactive oxygen species (ROS). The parasite is more vulnerable to oxidative stress than mammalian cells as it lacks an efficient detoxification mechanism. This is in part

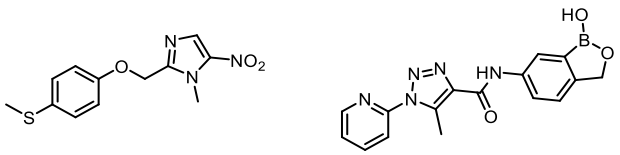
supported by studies that claim nifurtimox and benznidazole act as prodrugs that require *in vivo* reduction of the nitro moiety by an enzyme. Consequently, low levels of these nitroreductases have been associated with resistance and high levels with hypersensitivity towards the drugs *in vitro*.[52]

Both nifurtimox and benznidazole are on the WHO list of essential medicines for CD. Efforts have been made to enable free access to the people most in need; for example, in 2020 a three-year partnership between the WHO, Mundo Sano Foundation and INSud Pharma allowed benznidazole to be made available for free to patients under the age of 19 in endemic countries.[53, 54]

Recent Advances and Potential Treatments

As with leishmaniasis, new treatments for CD mostly come from repurposed drugs or combinatorial therapies, and the number of novel drugs that undergo clinical trial evaluation is even more limited. Modifications to the current benznidazole treatment regimen are being investigated with clinical trials indicating that shorter treatment courses could be beneficial.[43]

Flexinidazole (**11**, **Figure 1.7**), a drug developed by the DND*i* against Human African Trypanosomiasis (HAT) has recently been shown to be superior to benznidazole in terms of cure rates and prevention of cardiac issues. Moreover, the drug has been shown to be effective against both the acute and chronic phase and, more importantly, against benznidazole-resistant strains.[55] The drug is currently in clinical trials for use against *T. cruzi* with phase II findings showing promising results.[43] Oxaborole DNDI-6148 (**12**, **Figure 1.7**) is the only other molecule currently undergoing clinical trial evaluation (phase I) for CD.[43]



11 12

Figure 1.7. Drugs in clinical trials for CD – Flexinidazole (*left*) and DNDI-6148 (*right*).

As it stands, the clinical picture for Chagas Disease is marked by limited treatment options with less-than-ideal safety and efficacy profiles, emerging resistance, and lack of novel therapeutics in the pipeline. Therefore, there is an urgent need not only for better treatments and cures, as well as new validated targets, better animal models and earlier diagnosis as to avoid chronic heart disease, visceral complications, and death.[43, 44]

1.2 Anti-kinetoplastid Drug Discovery

The DND*i* is a non-profit organisation that facilitates partnerships between the pharmaceutical and non-pharmaceutical sectors. Their mission is to deliver treatments to the poor and vulnerable communities that are affected by diseases that are otherwise ignored by most drug R&D efforts. A big portion of their portfolio involves kinetoplastid infections such as leishmaniasis, Chagas diseases and HAT (also known as African sleeping sickness).[56]

Many modern drug screening programmes rely on having a validated target (in infections for example, a vital protein of the pathogen) based on which an assay is developed, thus enabling high-throughput screening of chemical libraries.[57] In the case of NTDs however, despite the extensive knowledge brought by the 'Tritryp' program in 2005, where the full genomes of *L. mexicana*, *T. cruzi* and *T. brucei* were sequenced, there remains a scarcity of validated targets that can facilitate high-throughput screening. Moreover, known validated targets have failed to deliver candidates that have reached clinical development

and drugs that are currently in use have either an unknown, or partially understood, mechanism.[56]

To overcome this, the DND*i* (in collaboration with the University of Dundee and Institut Pasteur Korea) have developed high-content assays for intracellular *L. donovani* and *T. cruzi* amastigotes. While these assays only have a medium throughput, they allow for discrimination between infected and non-infected cells as well as whether the observed parasiticidal activity arises due to specific pathogen killing or as a consequence of damaging the host cell.[56] Through partnerships with the pharmaceutical industry, the DND*i* has accessed a large diversity of compounds, however the limitations imposed by the throughput and relative complexity of these assays guide which libraries are selected. Typically, the following classes of libraries have been of most interest: repositioning libraries (i.e., small libraries that are already in preclinical or clinical development or currently in use for other diseases), specific pharmacokinetic libraries (i.e., compounds that meet specific absorption, distribution, metabolism and/or excretion (ADME) characteristics), known anti-infective libraries and diversity libraries (i.e., specific compounds that are representative of a larger class).[56]

The number of hits discovered *via* these screenings has been low, roughly 0.1% for *L. donovani* and 0.3% for *T. cruzi* respectively. However, these low hit-rates against intracellular parasites are not surprising as drugs would have to cross two cell membranes to reach their target(s) in addition to having to survive the harsh environment (acidic pH) of the parasitophorous vacuole. Additionally, the progression from hit to lead and subsequent lead optimisation are more challenging given the unknown mechanisms of action and lack of understanding of structure-activity relationships. As such, the risk-averse strategy relies on an initial drug demonstrating a significant potency in phenotypic screening assays followed by refinement of the pharmacokinetic/ADME properties to

improve the efficacy of the drug *in vivo*. The following parameters (**Table 1.1**) have been suggested by the DND*i* for what constitutes a hit and what it requires to be progressed to a lead.[56]

	Leishmania spp.		***T. cruzi***	
	Hit	Lead	Hit	Lead
Activity	IC_{50} ≤ 10 µM[a]	IC_{50} ≤ 1 µM[b]	IC_{50} ≤ 10 µM[c]	IC_{50} increased; 10-20-fold over initial Hit
Selectivity[d]	10-fold	Increased; Ideally, 50-fold	10-fold	Increased; Ideally, 50-fold
Chemical profile	Acceptable synthesis < 8 steps	Scalable synthesis Preliminary SAR Ideally no stereogenic centre	Acceptable synthesis < 8 steps	Scalable synthesis Preliminary SAR Ideally no stereogenic centre

a) *L. donovani*, *L. infantum* intracellular amastigote assay b) active against various clinical isolates and antimonial-resistant strains c) *T. cruzi* intracellular amastigote assay (TcVI or TcII/Y strains) d) more active than mammalian cell line

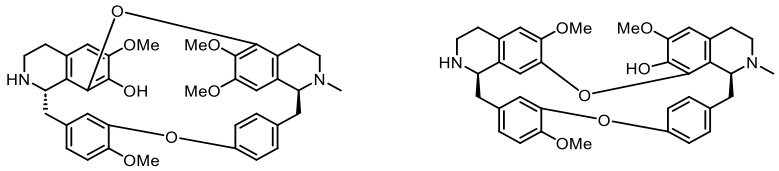
Table 1.1. Criteria for hit and lead compounds as per the guidelines of the DND*i*.[56]

1.3 Anti-parasitic Natural Products

Nature has provided a diverse array of compounds that have been historically used as treatments for various diseases, from indigenous medicines to more contemporary herbal remedies. In modern times natural products have also been a source of inspiration for the pharmaceutical industry when developing novel drugs, as shown by the fact that more than half of all FDA-approved drugs contain scaffolds that originate in natural products. This is also illustrated by anti-leishmanial drugs such as amphotericin B and paromomycin, compounds which were isolated from *Streptomyces nodosus* and *Streptomyces rimosus* bacteria respectively.[58]

1.3.1 Bis-benzyltetrahydroisoquinoline Alkaloids

A vast number of natural products present anti-leishmanial and anti-trypanosomal activity, suggesting they could serve as hits for drug discovery.[9, 59] Of particular interest to our group are the bis-benzyltetrahydroisoquinoline (BBI) alkaloids that have been sporadically investigated in this context for over 50 years. Examples include daphnandrine (**14**) which was shown to be active against *T. cruzi* epimastigotes, and northalrugosidine (**13**, **Figure 1.8**) which is a potent agent against *L. donovani* promastigotes and has a high selectivity index (i.e. the ratio between CC_{50} (half maximal cytotoxic concentration in mammalian cells) and IC_{50} (half maximal effective concentration in parasites)).[60 58 61]



13, northalrugosidine

IC_{50} = 0.28 μM (*L. donovani* promastigotes)
SI = 29.3

14, daphnandrine

IC_{50} = 43 μM (*T. cruzi* epimastigotes)

Figure 1.8. Structure of northalrugosidine (**13**), and daphnadrine (**14**).

The biological evaluation of these natural products has predominantly been carried out on the extracellular forms of the parasites, most likely due to the lower associated complexity of the required assays. However, these assays are rarely successful in yielding viable drug candidates, thus leaving BBIs yet to be investigated in more detail as anti-parasitic agents. Intrigued by the synthetic challenge these molecules pose, and in line with the group's interest in anti-parasitic agents, these alkaloids became attractive targets.

1.3.2 Bis-benzyltetrahydroisoquinoline Alkaloid Classification

BBI alkaloids are an alkaloid family typically encountered in plants from tropical and subtropical regions. They consist of two benzyltetrahydroisoquinoline (BI) units joined together *via* one or more linkages. The classification is generally based on the oxygenation pattern, number (≤ 3), type (biphenyl, benzyl phenyl ether or diphenyl ether) and orientation (head-to-head or head-to-tail) of the connecting bonds between the individual units. The conventional numbering is shown in **Figure 1.9** where rings A and B forming the tetrahydroisoquinoline (THIQ) unit are referred to as the 'head' and the benzyl group (ring C) is referred to as the 'tail'.[62]

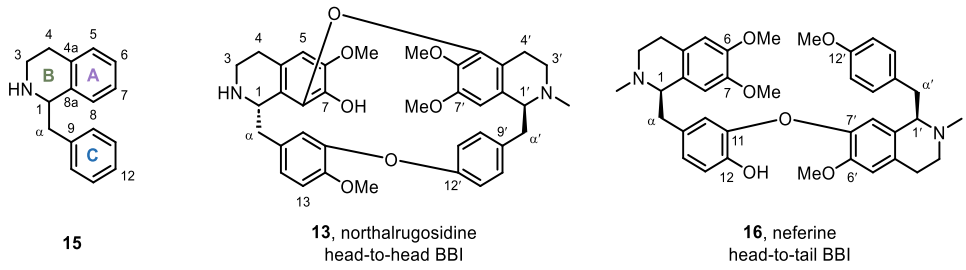
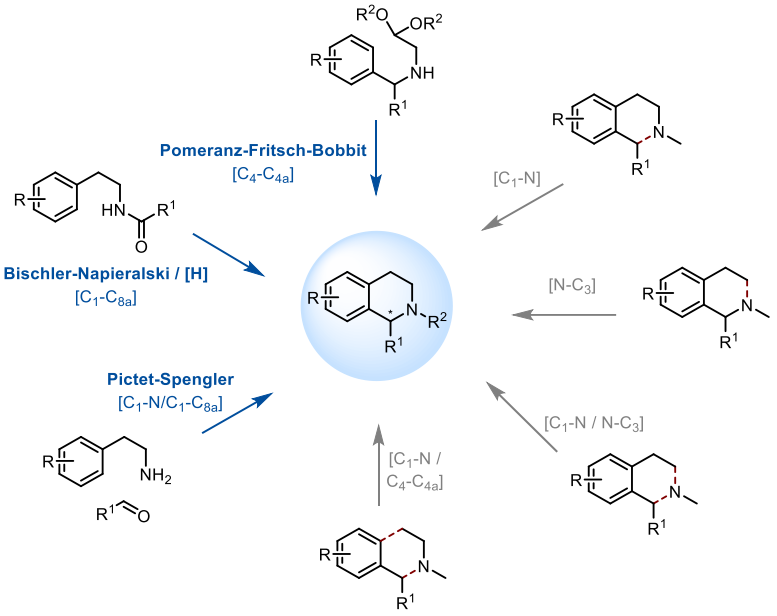


Figure 1.9. Conventional numbering (*left*) head-to-head BBI (*middle*) head-to-tail BBI (*right*).

1.4 Synthesis of the Tetrahydroisoquinoline Unit

Historically, significant effort has been put into developing various methodologies that access the THIQ core due to its prevalence in many natural products that present interesting biological properties. The presence of a stereogenic centre at the C-1 carbon has led to many methods for diastereoselective and enantioselective syntheses.[63]

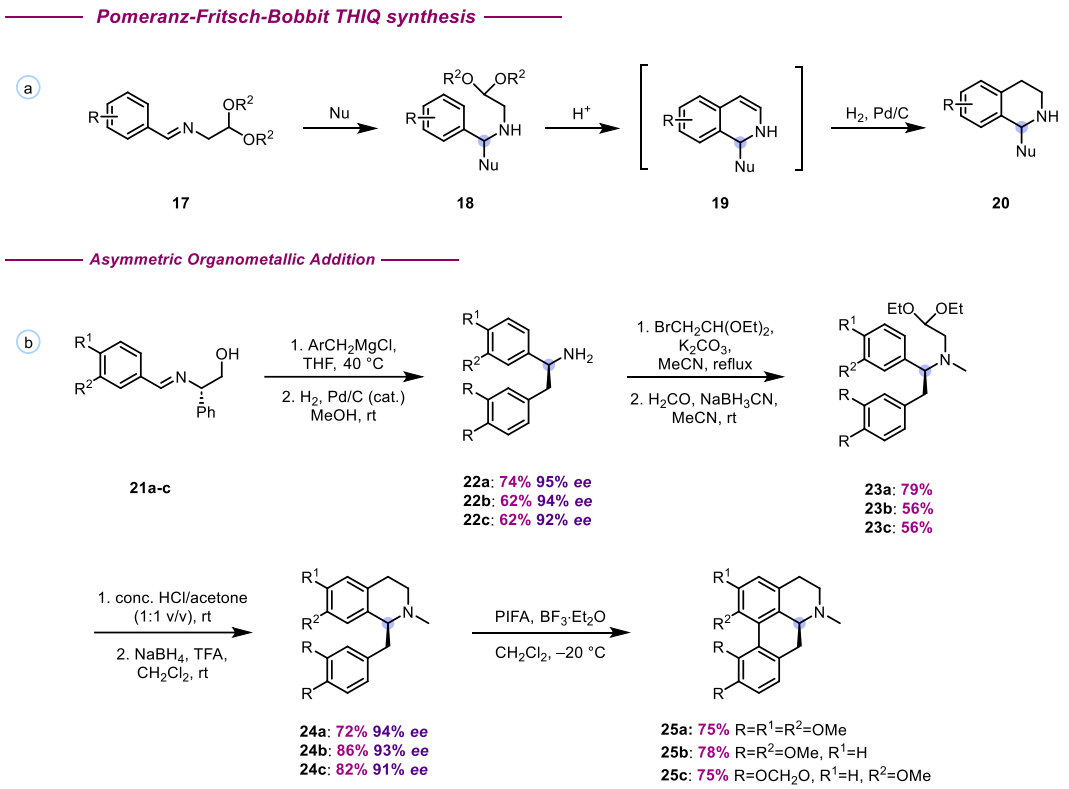


Scheme 1.1. Strategies used to access THIQs *via* B ring formation.

No one traditional method (blue arrows in **Scheme 1.1**) allows access to all THIQs, and as such alternative methods (grey arrows in **Scheme 1.1**) have been developed to access the B ring *via* the formation of a single bond (C_1–N or N–C_3) or two bonds (C_1–N/N–C_3 and C_1–N/C_4–C_{4a}). However, the classical transformations such as the Pictet-Spengler reaction (PSR), the Bischler-Napieralski (BN) cyclisation/reduction and the Pomeranz-Fritsch-Bobbit (PFB) cyclisation remain the most commonly employed approaches.[63]

1.4.1 The Pomeranz-Fritsch-Bobbit Approach

The Pomeranz-Fritsch-Bobbit (PFB) synthesis typically involves treating benzylidenoacetals **17** with a nucleophile (hydrides or organometallics) followed by Brønsted acid-catalysed cyclisation and hydrogenation to afford the desired THIQs (**Scheme 1.2a**).



Scheme 1.2. The Pomeranz-Fritsch-Bobbit (PFB) approach for THIQ synthesis.

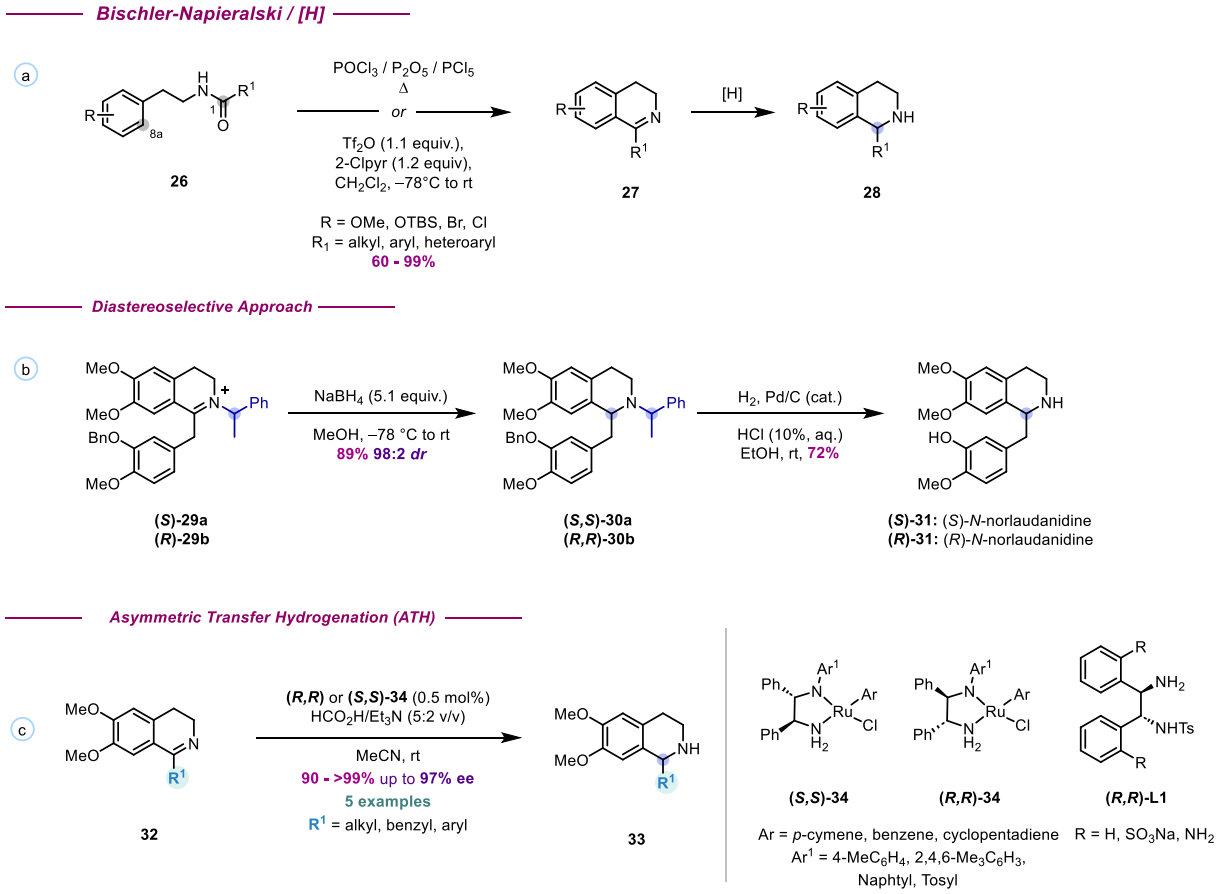
The most popular approach is the preparation of chiral benzylamines of type **22** (**Scheme 1.2b**) by asymmetric organometallic addition to the corresponding imine, followed by *N*-alkylation with bromoacetaldehyde acetals and the PFB reaction. One way of making these chiral benzylamines is by using *N*-linked chiral auxiliaries. An example of the utility of this sequence in the formation of BI alkaloids is illustrated by Badia and co-workers'[64] aporphine synthesis. Grignard addition to imines **21a-c** bearing an *N*-linked β-amino alcohol chiral auxiliary followed by hydrogenolysis afforded primary amines **22a-c** in good yields and excellent enantiomeric excess (92 – 95% *ee*). Subsequent *N*-alkylations and PFB reaction afforded key BIs **24a-c** which were converted into the desired aporphines **25** with minimal erosion of enantiopurity (**Scheme 1.2b**).

In comparison to the BN cyclisation or PS condensation, the PFB sequence has not been explored as extensively for the synthesis of BIs as demonstrated by the scarcity of enantioselective approaches available. Chiral auxiliaries afford good enantioselectivity but introduce additional steps in the synthesis. Finally, the relatively harsh conditions limit the scope of the suitable substrates making the other two traditional approaches more appealing.

1.4.2 The Bischler-Napieralski / Reduction Approach

An alternative approach to synthesising THIQs is the closure of the B ring *via* formation of the C1–C8a bond. This has commonly been achieved by the Bischler-Napieralski (BN) cyclisation followed by a stereoselective reduction (**Scheme 1.3a**). In the first step, β-phenylethylamides **26** cyclise to the corresponding imine **27** or isoquinolinium salt.[63] The most employed condensing agents are phosphorus oxychloride, phosphorus pentoxide or phosphorus pentachloride which have been used successfully in the synthesis of an array of isoquinoline alkaloids. However these conditions are harsh, often requiring temperatures >100 °C, which limit functional group tolerance.[65] Milder conditions have been reported recently by Movassaghi *et al.*[66] using trifluoromethanesulfonic anhydride and 2-chloropyridine as cyclodehydration agents that allow a broader scope of THIQs to be synthesised in good to excellent yields (**Scheme 1.3a**). The second step involves reduction of the prochiral imine to the corresponding THIQ, process which can be done in a diastereoselective or enantioselective way.

Chiral auxiliaries have often been used in the diastereoselective reduction of imines formed *via* the BN cyclisation. An example illustrating the utility of this method in the context of BI synthesis is the work of Georghiou and co-workers (**Scheme 1.3b)**.[67]



Scheme 1.3. The Bischler-Napieralski cyclisation/asymmetric reduction.

The use of (*S*)- and (*R*)-α-methyl benzylamine as an *N*-linked chiral auxiliary enabled the enantioselective synthesis of (*S*)-*N*-norlaudanidine and (*R*)-*N*-norlaudanidine. Sodium borohydride reduction of **(*S*)-29** and **(*R*)-29** gave diastereomers **(*S,S*)-30** and **(*R,R*)-30** in 89% yield and 98:2 diastereomeric ratio (*dr*). Acidic hydrogenolysis of the chiral auxiliary and benzyl group afforded enantiomeric natural products **(*S*)-31** and **(*R*)-31** in 72% yield (**Scheme 1.3b**). While α-methyl benzylamine is the most widely used auxiliary, others are known.[68, 69]

Most efforts have been directed towards developing transition-metal catalysed enantioselective reductions either using hydrogenation or asymmetric transfer hydrogenation (ATH) conditions. In the case of catalytic asymmetric hydrogenation of 3,4-dihydroisoquinolines (3,4-DHIQs), many catalysts use chiral phosphate-containing

ligands that yield THIQs with less-than-ideal enantioselectivity (<90% *ee*).[70] However, recent efforts have been directed towards employing chiral metal catalysts such as Rh, Ru or Ir with chiral diamine ligands and various additives for the enantioselective hydrogenation of isoquinolines to the corresponding THIQs.[63] These methods will not be covered here.

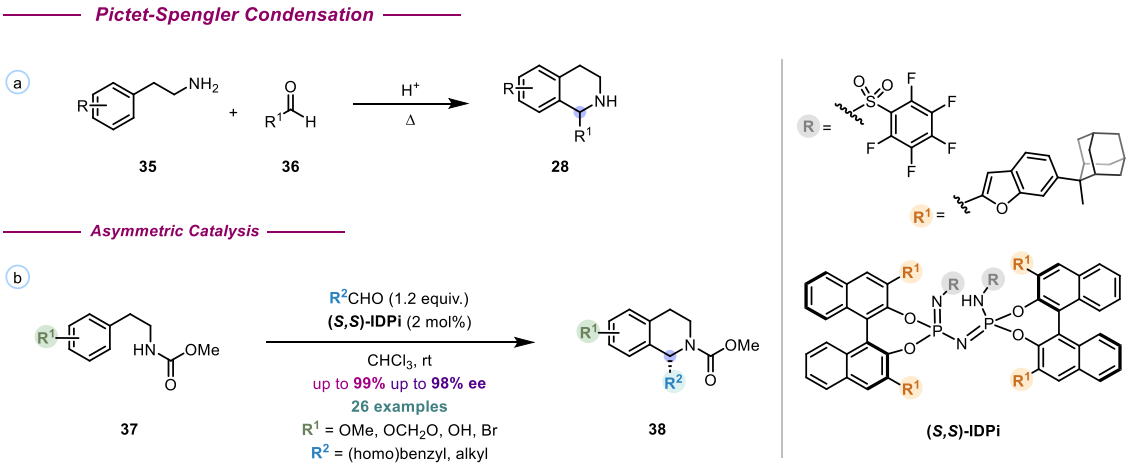
ATH methods typically employ Ru(II) and Rh(III) complexes with chiral diamine ligands such as **L1** and an azeotropic mixture of formic acid and triethylamine (or formate salts) as the hydrogen source. Noyori's[71] initial report of catalyst **34** secured access to both enantiomers of several THIQs of type **33** with excellent conversion and enantioselectivity making this protocol the go-to method for the asymmetric reduction of cyclic imines (**Scheme 1.3c**). Over the past three decades, many other research groups have successfully used Noyori's catalyst **34** to synthesise a range of isoquinoline alkaloids and many modifications have been reported including choice of metal and ligands, hydrogen source, and aqueous conditions.[63]

Finally, the use of enzymes for the asymmetric reduction of 3,4-DHIQs has been reported, however the method is sensitive to steric hindrance, only tolerating small alkyl groups (Me, Et) at the C-1 position. Larger groups resulted in loss of enantioselectivity, thus limiting the usefulness of the protocol.[72]

In comparison to the Pictet-Spengler condensation, the BN cyclisation followed by an asymmetric reduction is less atom- and step-economical. Nonetheless, the remarkable advances in catalytic asymmetric hydrogenation methods make this approach a more appealing and frequently employed strategy in the synthesis of THIQs.

1.4.3 The Pictet-Spengler Approach

The Pictet-Spengler (PS) condensation is a convenient one-pot method used in the synthesis of tetrahydroisoquinoline alkaloids. Traditionally, the reaction involves an acid-catalysed condensation between an aldehyde and a β-arylethylamine followed by an intramolecular cyclisation that proceeds *via* an iminium ion undergoing a nucleophilic attack by the aryl group (**Scheme 1.4a**).[63] However, reactions often require harsh conditions such as strong Brønsted acids and high temperatures.[73] The substitution pattern of the aromatic ring is important for regioselectivity with the least sterically hindered *ortho* position being favoured.[74] Moreover, electron-donating groups on the aryl ring *para* to the nucleophilic attack site are also required for good yields.[73] Similar to the methods described earlier, the PS condensation can be performed in a diastereoselective or enantioselective manner.



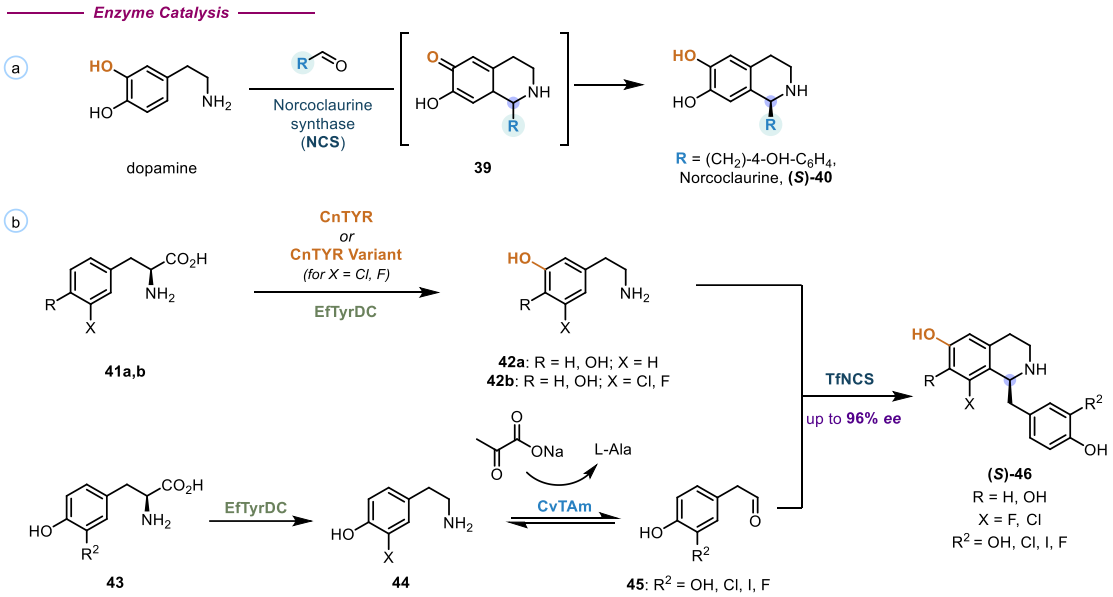
Scheme 1.4. TH IQ synthesis *via* an enantioselective PS condensation.

Although the PS condensation has been known and extensively used in alkaloid synthesis for over a century, it remains underdeveloped when 1,2,3,4-THIQs are concerned with only a few methods for non-enzymatic catalytic asymmetric methodologies being

reported. A powerful catalytic system was recently developed by Scharf and List[75] which, in comparison to earlier work (enzymatic and non-enzymatic catalysis) is not limited to phenolic substrates that direct stereocontrol *via* hydrogen bonding. Catalyst **(*S,S*)-IDPi** was shown to afford a broad range of 1-substituted THIQs of type **38** in good to excellent yields and enantioselectivity of up to 98% *ee* (**Scheme 1.4b**). While the method requires an *N*-protecting group, a simple carbamate is used which can be removed subsequently or reduced to a methyl group. The reaction tolerates a broad scope of aliphatic and aryl aldehydes as well as various substituted β-phenylethylamines. Although the catalyst is not commercially available, low loadings are needed and the authors demonstrate that **(*S,S*)-IDPi** can be recovered in near-quantitative amounts (98%).

From a biosynthetic perspective, all natural BIs are derived from a common intermediate; namely, norcoclaurine **(*S*)-40** which is formed *via* a PS type reaction from L-dopamine and 4-hydroxy-phenylacetaldehyde catalysed by norcoclaurine synthase (NCS) (**Scheme 1.5a**).[62] This type of enzyme has been exploited in catalytic PS condensations of phenolic □-arylethylamines with a variety of aldehydes and ketones.[76-83] However, the reaction is highly substrate-specific as far as the amine component is concerned and solely delivers the (*S*)-enantiomeric products, thus making it less useful as a general method for accessing non-natural BI alkaloids. The specificity of the enzyme arises due to the amine component requiring a *meta*-hydroxyl group which binds to the active site and is ultimately deprotonated allowing the formation of the ring *via* intermediate **39**. A remarkable development was reported by Hailes[84] and co-workers where non-natural BI alkaloids of type **(*S*)-46**, bearing halogen substituents, were synthesised with high enantioselectivity using enzymatic catalysis (**Scheme 1.5b**). The □-arylethylamines are derived from L-tyrosine-like amino acids **41a,b** in a one-pot two-step cascade.

A tyrosinase (CnTYR) was used to install the required *meta*-hydroxyl group followed by the decarboxylation. For halogen-bearing amines, a tyrosinase mutant (CnTYR variant) was developed to allow halogenated substrates that are not well tolerated by the wildtype enzyme. In parallel, the aldehyde component is also synthesised from L-tyrosine type amino acids **43** *via* a decarboxylative step followed by a transamination. Amines **42a,b** and arylaldehydes **45** are then subjected to a TfNCS mediated PS condensation to deliver 13 non-natural BIs **(*S*)-46** with high enantioselectivity (85 – 96% *ee*).

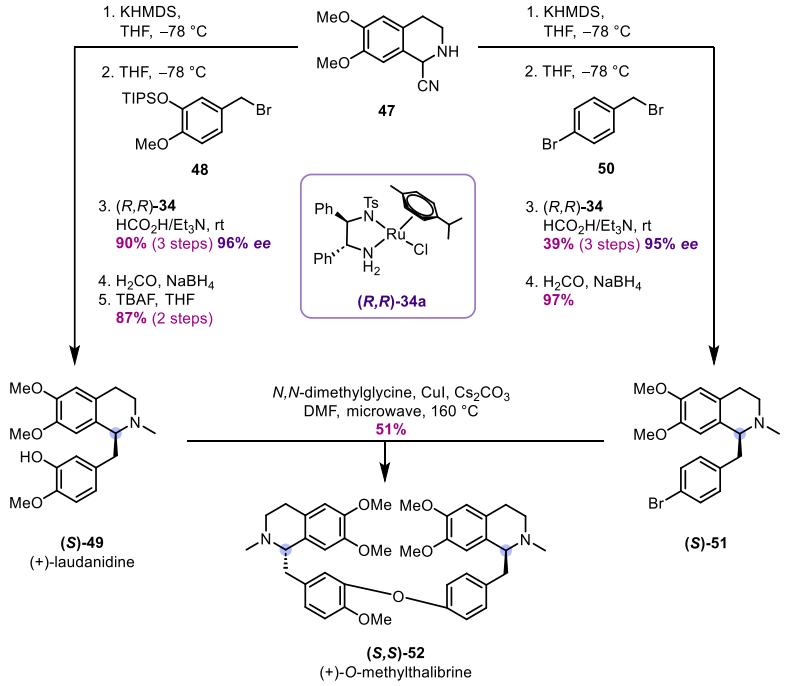


Scheme 1.5. THIQ synthesis *via* enzyme-catalysed PS condensations.

One of the key benefits of this approach is the fact that arylacetaldehydes of type **45** are typically challenging to access using traditional chemical syntheses since they are prone to oxidation and aldol-type self-condensation. Additionally, the method uses mild, non-toxic, and environmentally friendly conditions. While there are some limitations in terms of substrate scope and yields of isolated compounds, enzymatic catalysis can represent a powerful complementary tool in the synthesis of isoquinoline alkaloids.

1.5 Previous Syntheses of Bis-benzyltetrahydroisoquinoline Alkaloids

Despite their interesting and diverse biological activity, there is a surprisingly small number of total syntheses of BBI alkaloids in comparison to other alkaloid families. This scarcity has been largely attributed to the lack of suitable methods to form the diaryl ether linkage. In the last two decades, most syntheses have relied on late-stage Ullmann couplings for the formation of these ether bridges, however this reaction often requires harsh conditions such as high temperatures, stoichiometric amounts of copper catalysts and long reaction times, while suffering from suboptimal reaction yields.

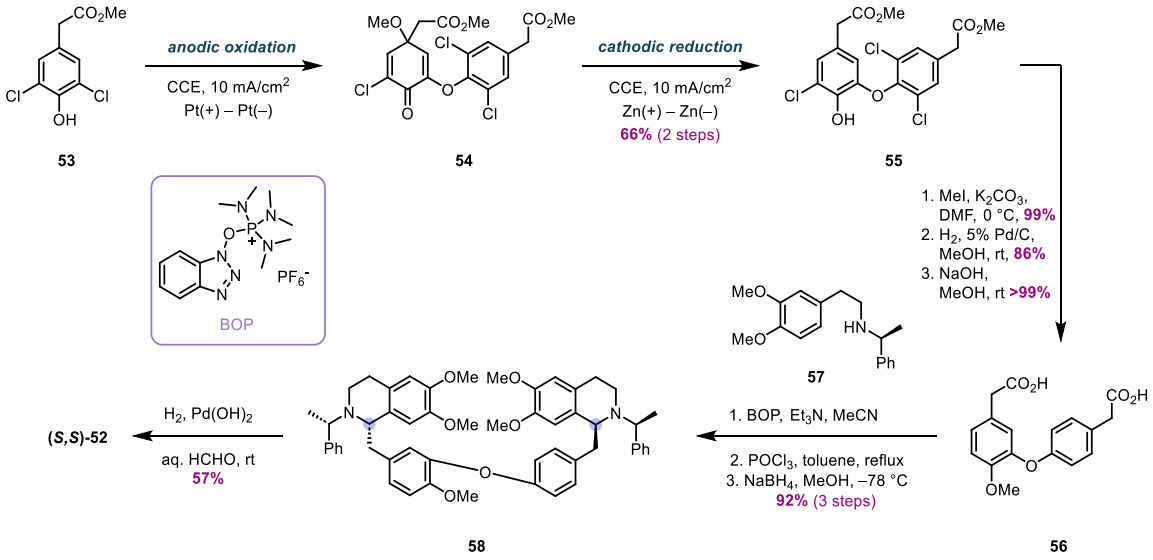


Scheme 1.6. Total synthesis of (+)-*O*-methylthalibrine *via* a late-stage Ullmann coupling.

Blank and Opatz's[85] total synthesis of (+)-*O*-methylthalibrine **(*S*,*S*)-52** (**Scheme 1.6**) relies on building the BI units first and then forming the diaryl ether linkage *via* a late-stage Ullmann coupling. BIs **(*S*)-49** and **(*S*)-51** were synthesised from carbonitrile **47** by a deprotonation with KHMDS followed by α-alkylation with benzylic bromides **48** and **50**. The second equivalent of base allows a spontaneous dehydrocyanation affording the corresponding 3,4-DHIQs, which are subsequently reduced using Noyori's ATH

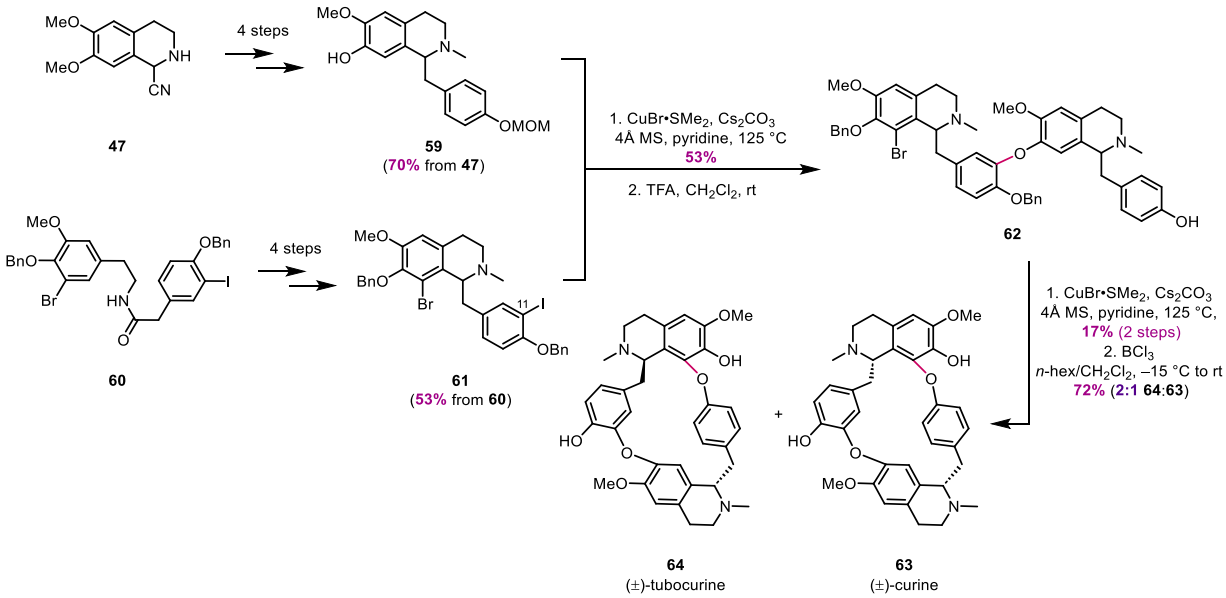
conditions in modest to excellent yields and high enantioselectivity. Reductive *N*-alkylation and TIPS deprotection afford (+)-laudanidine (**(*S*)-49**) and non-natural brominated BI **(*S*)-51,** which are then subjected to an Ullmann coupling. The use of *N,N*-dimethylglycine as a ligand and microwave irradiation were found to be the best conditions to deliver linear BBI **(*S,S*)-52** in a good yield of 51%.

An alternative route to linear BBI (+)-*O*-methylthalibrine was reported by Nishiyama and co-workers[86] whereby an early-stage electrochemical phenol dimerisation is offered as a fruitful alternative to the Ullmann coupling (**Scheme 1.7**, CCE = constant current electrolysis). Using a protocol developed within the same group, phenol **53** is dimerised using anodic oxidation conditions followed by cathodic reduction to yield biaryl ether **55** in 66% yield over two steps. *O*-Alkylation followed by catalytic hydrogenation and alkaline hydrolysis afforded diacid **56** which is subjected to double BOP-mediated amide coupling with amine **57** bearing a chiral auxiliary. The resulting amide undergoes a double diastereoselective Bischler-Napieralski cyclisation followed by sodium borohydride reduction to yield intermediate **58**. Finally, one-pot conversion of the chiral auxiliaries into methyl groups afforded the desired BBI **(*S,S*)-52** in 29% overall yield and >86% *ee*.



Scheme 1.7. Total synthesis of **(*S,S*)-52** *via* an electrochemical approach.

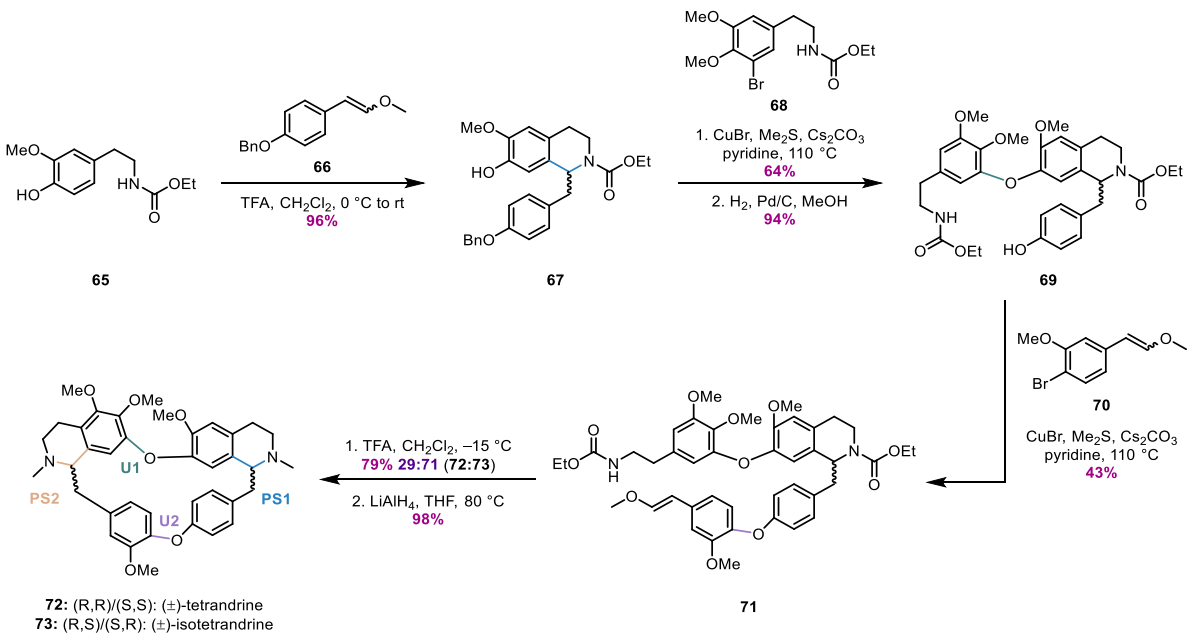
A racemic total synthesis of (±)-tubocurine **64** and (±)-curine **63** was reported by Otto and Opatz (**Scheme 1.8**).[87] Similar to their earlier work, the strategy relied on synthesising the BI units first followed by late-stage Ullmann couplings to generate the diphenyl ether linkages. To generate the ether linkages at the correct positions, the coupling partners must demonstrate different regioselectivity and reactivity. This is achieved by subjecting BI **60** having a bromo-substituent at C-8 and an iodo-substituent at C-11 to an Ullmann coupling with phenol **59**, thus directing the formation of the first diaryl ether linkage at C-11. MOM-deprotection forming **62** reveals the second phenol group required for the coupling and subsequent macrocyclisation results in a 17% yield over two steps. Finally, cleavage of the benzyl group delivers a diastereomeric mixture of **64** and **63** in a 2:1 ratio.



Scheme 1.8. Synthesis of BBIs *via* two consecutive late-stage Ullmann couplings.

A different approach towards macrocyclic BBIs (±)-tetrandrine **72** and (±)-isotetrandrine **73** was reported by Bracher *et al.*[88] (**Scheme 1.9**). Their racemic synthesis relies on *N*-acyl Pictet-Spengler cyclisations for the formation of the THIQ units (orange and blue bonds) and on Ullmann couplings to generate the diaryl ether linkages (green and purple bonds). Furthermore, the group examined four routes where the order

of the key steps (PS1, PS2, U1, U2) was varied, in order to evaluate which reaction is better suited for the final macrocyclisation. The route shown in **Scheme 1.9** proved to be the highest yielding with an overall yield of 19% (over 12 steps) and a diastereomeric ratio of 29:71 **72:73** was observed when macrocyclisation occurs *via* PS2. When the macrocyclisation step occurs *via* PS1, the opposite selectivity was observed (87:13, **72:73**), albeit in a poor overall yield of 3%. A computational approach was undertaken to explain the conformations of the cationic intermediates that lead to the observed reaction diastereoselectivity. In comparison to other total syntheses, the route is more divergent, allowing more flexibility in the synthesis of analogues and the building blocks are derived from readily available substituted benzaldehydes. However, the main disadvantage remains the limited stereoselectivity, as this approach is unfit for the synthesis of enantioenriched BBIs.



Scheme 1.9. Racemic synthesis of (±)-tetrandrine **72** and (±)-isotetrandrine **73**.

1.6 Project Overview

Inspired by the potent anti-leishmanial activity and good selectivity index demonstrated by northalrugosidine, and building on previous work in the group on the aporphine family of natural products as well as studies towards northalrugosidine,[89, 90] this project focuses on a deconstructive approach towards BBIs to investigate the vital features of these molecules required for anti-parasitic activity. The first target is non-natural BBI **1** which is more synthetically accessible than **13**; key strategic steps include a BN cyclisation/Noyori ATH (purple disconnection) for the asymmetric synthesis of the THIQ units and an Ullmann coupling (blue disconnections, **Figure 1.10**) to establish the diaryl ether linkages. The importance of the macrocycle will be assessed by comparison to the biological activity of linear BBIs. Further deconstructing the molecule into the individual BIs will provide insight whether these smaller, more accessible targets are suitable as anti-parasitic agents. Finally, the importance of the compound's stereochemistry will be assessed by preparing and evaluating all diastereomers of linear BBIs and enantiomers of BIs. Preliminary evaluation of one BI and one linear BBI will be carried out on *L. mexicana* to verify whether these compounds demonstrate any anti-parasitic activity. Should these assays present promising results, a small library of BI and acyclic BBI alkaloids will be prepared and sent for testing against *L. infantum* and *T. cruzi* with our collaborator in São Paulo, Prof. André Tempone, as well as evaluation of mammalian cytotoxicity.

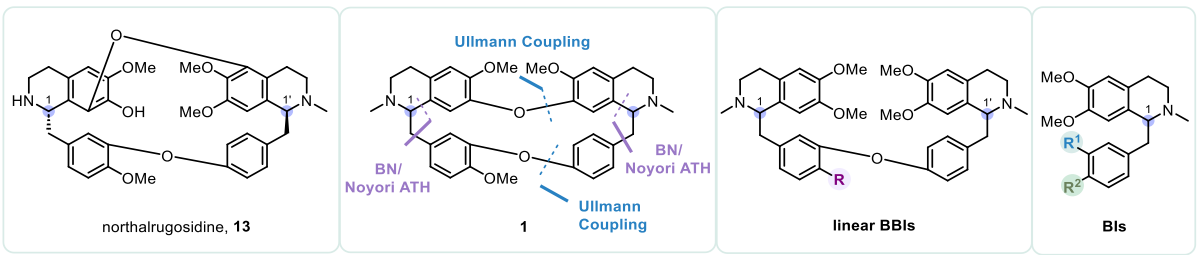
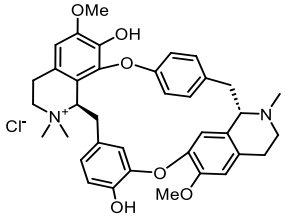


Figure 1.10. Target BBIs and BIs inspired by northalrugosidine.

2

Studies Towards the Synthesis of a Non-natural Macrocyclic BBI

BBIs have sparked the interest of many researchers throughout the years due to their intriguing structures and diverse biological properties. For example, tubocurarine (**74**, **Figure 2.1**) has been known as the active ingredient in the poisonous arrows used by certain indigenous people in South America. The purified alkaloid found later use as a muscle relaxant.[91] Other examples in this class of alkaloids have been studied as anti-cancer, anti-HIV, and anti-microbial agents to name a few, and reports of anti-leishmanial activity date back to as early as the 1980s.[61, 92]



74

Figure 2.1. Structure of tubocurarine, the active ingredient in poisonous arrows.

It was decided that a review of BBIs previously tested against *Leishmania spp*. would help the design of our targets. However, several challenges were encountered as different studies would employ different assays, different strains of the parasites and/or different forms of the parasite (promastigotes *vs* amastigotes). Much of the biological evaluation of these compounds has been done on the promastigote form, possibly due to the lower complexity of these assays. Testing the compounds against the amastigote form requires infected macrophages, whereas the promastigote can be grown as a liquid culture. A structure-activity-relationship (SAR) study (full details, **Appendix 6.1**) was carried out based on four reports[60, 61, 93, 94] which provide IC_{50} values (half maximal inhibitory concentration) for a range of macrocyclic BBIs against *L. donovani* promastigotes (some data is also provided against amastigotes). From our observations, activity against the promastigote form does not appear to translate well into activity against the amastigote form. This is most likely explained by the drug having to cross two cell membranes to reach its target, as well as survive the acidic pH within the parasitophorous vacuole, rather than loss of activity. Several key aspects found to be important for anti-leishmanial activity are highlighted in **Figure 2.2**. Compounds having saturated B rings showed better activity than aromatic analogues. The configuration of the two stereocentres (C-1, C-1′) also affects activity, however no particular configuration showed improving potency consistently. The 'tail-to-tail' ether bridge and the oxygenation pattern at C-6, C-6′, C-7, C-7′ and C-12 are conserved structural motifs amongst most BBIs.

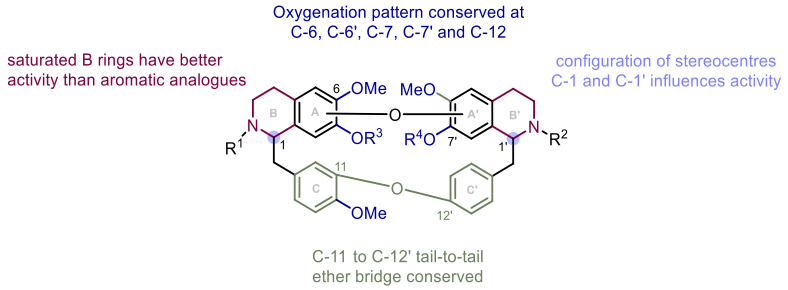
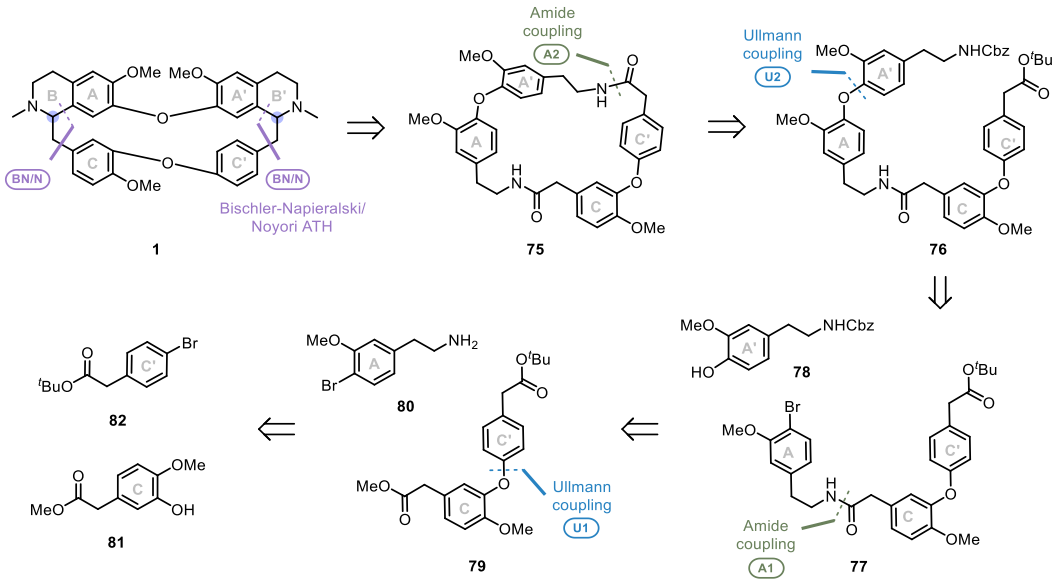


Figure 2.2. General structure of BBIs with conserved structural motifs highlighted in green.

2.1 Double Bischler-Napieralski/Noyori ATH strategy

While these alkaloids are suggested to have evolved as a plant defence mechanism against herbivores and other pathogens, the extent to which they have developed as anti-parasitic agents specifically is poorly understood.[95] As such we questioned whether their structural complexity is required for the biological activity. This work seeks to explore whether a simplified and more synthetically accessible non-natural BBI such as **1** would exhibit similar anti-parasitic activity. The conserved structural aspects mentioned earlier (position of the 'tail-to-tail' linkage, oxygenation pattern, degree of saturation of B rings) were conserved in the design of the target non-natural analogue. Building on established work in the Anderson group, the proposed strategy is convergent, efficiency-oriented and uses cheap, readily available starting materials.



Scheme 2.1. Retrosynthetic strategy of non-natural BBI **1**.

With the aim of accessing enantiomerically pure BBIs, the Bischler-Napieralski/Noyori ATH sequence was chosen as the optimal strategy since the precursor amides are easily accessible and the conditions are known to afford the desired THIQs in high yields and enantioselectivity.[63] Alternative methods are limited in terms of substrate tolerability,

require uncommon activating groups or provide only modest enantioselectivity. Moreover, Noyori's conditions enable access to both enantiomers, depending on which chiral diamine ligand is employed. We envisaged both THIQ units being formed in the same step from the corresponding macrocyclic lactam **75** followed by *N*-methylation (**Scheme 2.1**). The amide coupling is a well-explored reaction,[96] and a large variety of conditions are available that deliver the desired products in high yields. As such, the second key step of this strategy relied on forming **75** *via* a macrolactamisation (**Scheme 2.1**). This key intermediate can in turn be disconnected into linear precursor **76** which is afforded by Ullmann coupling U2 between phenol **78** and amide **77**. The latter is further disconnected into amine **80** and diester **79** *via* amide bond A1. Finally, biaryl ether **79** is constructed from esters **81** and **82** through Ullmann coupling U1.

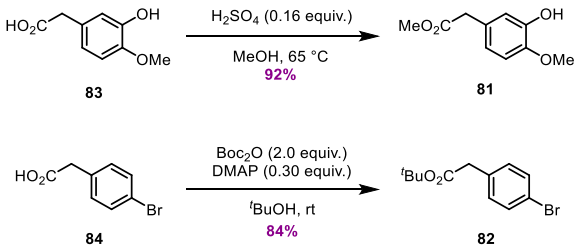
2.1.1 Synthesis of the 'tail-to-tail' fragment

The key step in the synthesis of this fragment is the biaryl ether bond formation. While this linkage is commonly formed by a nucleophilic aromatic substitution reaction (S_NAr), these reactions require a phenol as a nucleophile and arenes that bear fluoride or chloride substituents acting as a leaving group, together with an appropriate electron-withdrawing group on the ring. As such, this strategy is unfit for the current system as the haloarenes are not electronically deficient. A more suitable alternative is transition metal-catalysed C–O couplings. While powerful methods have been developed using Pd and Ni complexes, these methods have their own limitations in terms of substrate tolerability. Additionally, there is a concerted effort to move away from precious metals and alternatively employ more abundant metals such as copper.

In the last two decades, Ullmann couplings have been a largely ubiquitous approach to generating the biaryl ether linkages in the context of BBIs, with just one other method

reported.[62] A major benefit of employing this reaction is the plethora of catalytic systems that have been developed, thus allowing access to a broad range of substrates having various functional groups, electronic and steric properties.[97, 98] On the other hand, several challenges are associated with this strategy. It is a well-established trend that electron-rich phenols and electron-deficient haloarenes are required for the coupling to proceed smoothly. Additionally, *ortho*-substituents are known to impede the reaction through steric hindrance, particularly methoxy and acetoxy substituents are problematic as they can also chelate the copper catalyst. In the context of BBI synthesis, both coupling partners are typically electron rich, often bearing one or more *ortho*-methoxy substituents, thus making the system even more demanding. Finally, these reactions are inherently fickle, requiring stoichiometric or excess amounts of copper, high temperatures, basic conditions, and long reaction times. To overcome these challenges, much effort within our group has focused on the optimisation of these couplings.

Building on established work in the group, the tail-to-tail fragment of the molecule was built from esters **81** and **82** *via* an Ullmann coupling. Attempting the coupling on the readily available phenylacetic acids resulted in returned starting materials and as such their esterification was necessary. Esterification of **83** proceeded to afford **81** in excellent yields (92%) and following a short investigation into optimal conditions (**Table 2.1**), ester **82** was obtained in 84% yield (**Scheme 2.2**).



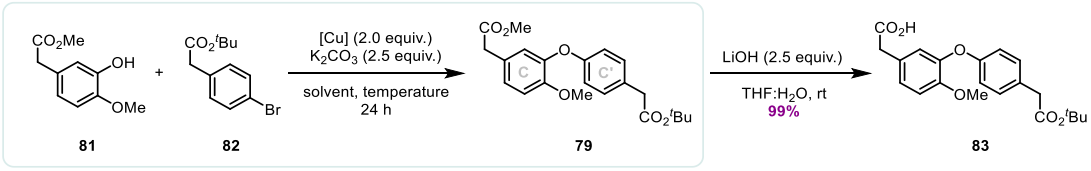
Scheme 2.2. Synthesis of ester **81** and **82** from the corresponding phenylacetic acids.

Entry	Conditions	Solvent	Temperature	Time	Yield[a]
1	DCC (1.2 equiv.), DMAP (0.01 equiv.), ^{t}BuOH (2.0 equiv.)	CH_2Cl_2	rt	3.5 h	35%
2	i) $SOCl_2$ (1.5 equiv.), DMF (0.1 equiv.) ii) ^{t}BuOH (4.0 equiv.), Et_3N (1.1 equiv.)	CH_2Cl_2	rt	i) 3 h ii) 18 h	37%
3	^{t}BuOH (5.0 equiv.), H_2SO_4 (1.0 equiv.), $MgSO_4$ (4.0 equiv.)	-	rt	18 h	58%[b]
4	Boc_2O (2.0 equiv), DMAP (0.3 equiv.)	^{t}BuOH	rt	12 h	84%

[a] Yields of isolated product **82**. [b] Conversion determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

Table 2.1. Optimisation of conditions for the formation of *tert*-butyl ester **82**.

With esters **81** and **82** in hand, a brief optimisation of the Ullmann coupling conditions was carried out (**Table 2.2**). Based on the extensive screen performed within the group[90] on a model coupling of ester **81** with *para*-bromotoluene, cupric oxide (CuO, 2.0 equiv.), K_2CO_3 (2.5 equiv.) heated in pyridine to 110 °C for 24 hours gave the best results. However, these conditions gave poor yields when the *para*-bromotoluene was replaced with ester **82**. Increasing the amount of the phenol (1.1 equiv.), the temperature and the concentration significantly improved the yields along with the observation that the reaction is sensitive to moisture, and as such anhydrous conditions were paramount (**Table 2.2**, Entry 5). Biaryl ether **79** was obtained in 63% yield.



81 82 79 83

Entry	CuO source	Solvent	Concentration	Temperature	Yield
1	CuO	pyridine[d]	0.3 M	140 °C	20%[a]
2	CuO	pyridine[d]	0.8 M	140 °C	32%[a]
3	CuO	4-Me-pyridine	0.3 M	165 °C	10%[a]
4	CuO	4-Et-pyridine	0.7 M	150 °C	57%[b]
5[c]	CuO	pyridine[d]	1.4 M	140 °C	63%[b]
6	CuO (<50 nm)[e]	4-Et-pyridine	0.7 M	150 °C	18%[b]

[a] Yield was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using mesitylene as an internal standard. [b] Yield of isolated product **79**. [c] 1.1 equiv. of phenol **81** was used. [d] Distilled [e] CuO (<50 nm) refers to cupric oxide nanopowder.

Table 2.2. Optimisation of Ullmann coupling U1.

It is worth mentioning that the coupling was performed on a 4.6 mmol scale, but attempts to scale up further (e.g. 9 mmol scale) resulted in numerous issues including the formation of tar-like reaction mixtures with difficult work-up procedures and lower, irreproducible yields. Finally, chemoselective hydrolysis of ester **79** was achieved using commonly employed conditions of lithium hydroxide in aqueous THF affording **83** in quantitative yields (**Table 2.2**).

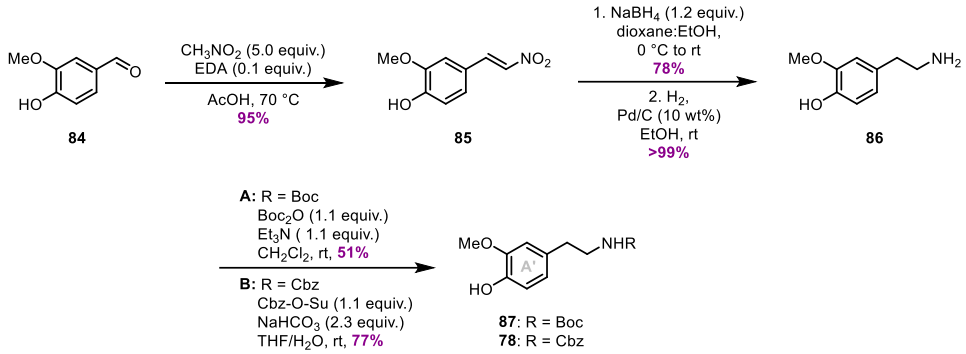
2.1.2 Synthesis of the β-phenylethylamine units

With the tail-to-tail fragment in hand, focus turned towards the synthesis of the β-phenylethylamine units. We envisaged these building blocks being formed from the corresponding aldehydes *via* a Henry reaction/reduction sequence.

2.1.2.1 Synthesis of the phenolic β-phenylethylamine

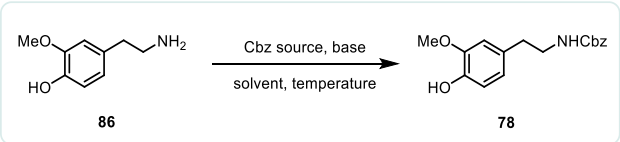
The sequence towards amine **86** commenced by subjecting vanillin (**84**) to a Henry reaction affording **85** in 95% yield (**Scheme 2.3**). The subsequent reduction of β-nitrostyrene **85** to the corresponding amine has been studied previously and while a one-step reduction using either catalytic hydrogenation conditions or lithium aluminium hydride would be ideal, scaling up these reactions had proved to be capricious.[99] The latter is impractical for large-scale synthesis due to the associated hazards and challenging work-up procedures. On the other hand, hydrogenolytic conditions gave unsatisfactory and irreproducible yields in addition to high exothermic reaction profiles, and as such a two-step procedure was preferred. Reduction of β-nitrostyrene **85** using sodium borohydride followed by hydrogenolysis afforded amine **86** in 74% yield over three steps from vanillin (**84**) **(Scheme 2.3**), which is comparable to previously reported yields (30 – 68%).[99, 100]

To avoid any chemoselectivity issues in the subsequent Ullmann reaction, protection of the amine group was necessary. Therefore, Boc- and Cbz protected amines **87** and **78** were prepared (**Scheme 2.3**) to test which group would survive the harsh conditions of the coupling.



Scheme 2.3. Synthesis of protected β-phenylethylamines **87** and **78**.

The Cbz group was concluded to be more suitable, and conditions which would afford good yields whilst avoiding the simultaneous protection of the phenol were investigated (**Table 2.3**). Best results were obtained when equimolar amounts of amine **86** and *N*-(benzyloxycarbonyloxy)succinimide were used in combination with excess sodium bicarbonate as a base (Entry 5).



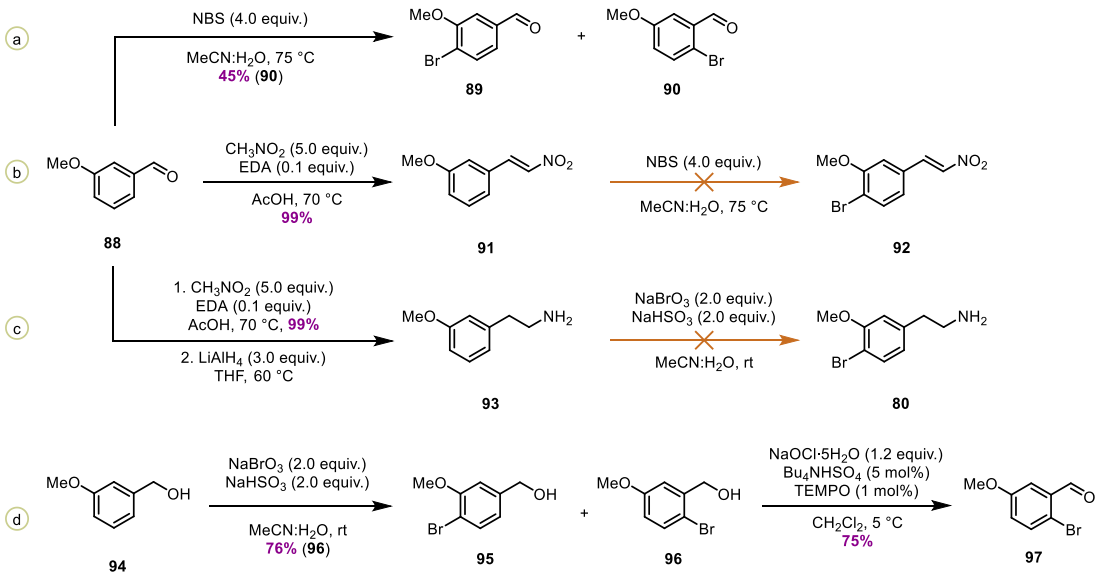
Entry	Cbz source	Base	Solvent	Temperature	Time	Yield[a]
1	CbzCl (1.0 equiv.)	K_2CO_3 (1.85 equiv.)	DMF	0 °C	1 h	37%
2	i) CbzCl (1.5 equiv.) ii) -	i) Et_3N (2.0 equiv.) ii) KOH (1 equiv.)	i) CH_2Cl_2 ii) MeOH/THF [b]	i) 0 °C to rt ii) rt	i) 18 h ii) 3 h	16%
3	CbzCl (0.95 equiv.)	DIPEA (1.1 equiv.)	CH_2Cl_2	–20 °C	3 h	55%
4	Cbz-OSu (1.1 equiv.)	$NaHCO_3$ (2.3 equiv.)	THF/H_2O[b]	rt	18 h	50%
5	Cbz-OSu (1.0 equiv.)	$NaHCO_3$ (2.3 equiv.)	THF/H_2O[b]	rt	6 h	77%

Su = succinimide; [a] Yields of isolated product **78**. [b] Solvents are in a 1:1 v/v ratio.

Table 2.3. Optimisation conditions for the Cbz protection of amine **86**.

2.1.2.2 Synthesis of the bromo-substituted β-phenylethylamine

Following a literature precedent,[101] bromination of **88** was attempted using *N*-bromosuccinimide (NBS) (**Scheme 2.4a**). The report claims formation of **89**, thus implying the reaction is *ortho*-selective relative to the methoxy group without supplying any spectroscopic data for benzaldehyde **89**. However, HMBC analysis of the experimentally obtained product instead indicated formation of **90**, the identity of which was further supported by ^{1}H and ^{13}C spectroscopic NMR data matching those previously reported for **90**. The formation of **90** can be explained by the methoxy group being a strong *para* directing group by facilitating the delocalisation of the positive charge of the arenium ion onto the oxygen atom through resonance effects.[102] Subjecting **91** to the same bromination conditions also failed to deliver the desired product **92** (**Scheme 2.4b**).

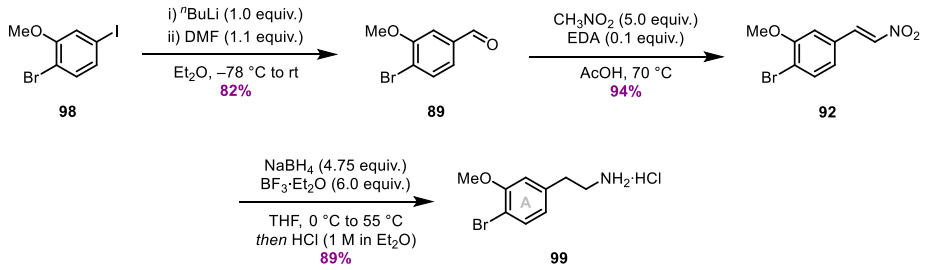


Scheme 2.4. Attempted routes towards the synthesis of amine **80**.

The third method[103] attempted for the formation of desired benzaldehyde **89** commenced with the bromination of benzyl alcohol **94** using $NaBrO_3/NaHSO_3$ (**Scheme 2.4d**). As before, the bromination occurred at the *para* position with respect to the methoxy

substituent despite the reported *ortho*-selectivity. HMBC analysis confirmed the structure of the experimentally obtained product to be **96**. This was further supported by spectroscopic analysis of oxidised product **97**. Attempting the same bromination conditions on amine **93** (**Scheme 2.4c**) failed to deliver the desired halogenated β-phenylethylamine **80**.

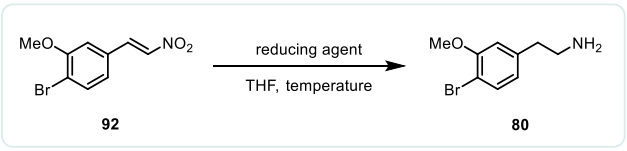
A different strategy was therefore adopted, which completely bypasses the regioselectivity issue imposed by the bromination step, in which the desired brominated benzaldehyde would be obtained *via* a lithium-halogen exchange/formylation sequence from the corresponding haloarene. The aldehyde would then be subjected to a nitro-aldol condensation followed by a reduction to form the required amine (**Scheme 2.5**).



Scheme 2.5. Synthesis of bromo-substituted β-phenylethylamine hydrochloride **99**.

The lithium-halogen exchange/formylation sequence proved to be more troublesome than expected, initially yielding complex mixtures of various aldehydes and modest, irreproducible yields of the anticipated product. At this point, it was discovered that the commercially available haloarene **98** was ~50% contaminated with an unknown impurity as a result of a faulty batch. Once this issue was solved and after a short optimisation of the conditions (order of addition, solvent, time), bromo-benzaldehyde **89** was obtained in 82% yield. This was then subjected to Henry reaction conditions affording β-nitrostyrene **92** in excellent yields (94%, **Scheme 2.5**). The subsequent reduction also proved challenging and required optimisation (**Table 2.4**).

Treatment of β-nitrostyrene **92** with $LiAlH_4$ resulted in dehalogenation (Entry 1) and milder conditions were sought. The Borane–THF complex (Entries 2, 3) gave trace amount of product at room temperature and complex mixtures upon heating to reflux, potentially due to the fact that the complex is known to decompose at temperatures >50 °C.[104] The best conditions were found to be a mixture of $NaBH_4$ and $BF_3{\cdot}Et_2O$ at 55 °C (Entry 10). Lower temperatures gave trace amount of product or complex mixtures and lower loadings of the reactants resulted in unsatisfactory yields. As might be expected, the reaction was sensitive to moisture and best yields were obtained when anhydrous $NaBH_4$ and THF were used. Careful optimisation of these parameters allowed desired amine **99** to be synthesised in 69% yield over 3 steps on multigram scale. The amine was then converted into the HCl salt for improved stability during storage.



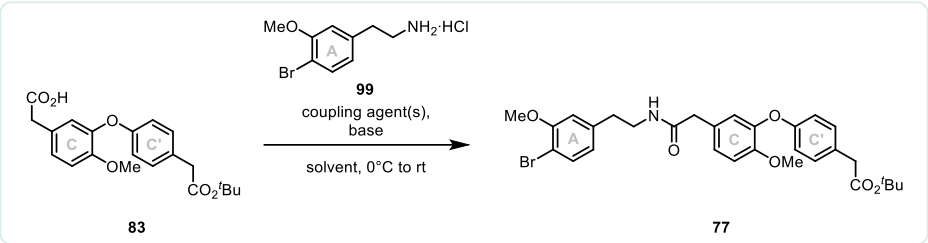
Entry	Conditions	Temperature	Time	Yield[b]
1	$LiAlH_4$ (3.0 equiv.)	0 °C to 60 °C	4 h	debromination
2	$NaBH_4$ (0.5 equiv.) BH_3-THF (4.5 equiv.)	0°C to rt	20 h	trace
3	$NaBH_4$ (0.5 equiv.) BH_3-THF (4.5 equiv.)	0 °C to 60 °C	20 h	Complex mixture
4	$BH_3{\cdot}SMe_2$ (4.0 equiv.)	0 °C to 50 °C	4 h	Complex mixture
5	DIBAL-H (7.0 equiv)	0 °C to 65 °C	2 h	84%
6	$NaBH_4$ (4.75 equiv.) $BF_3{\cdot}Et_2O$ (6.00 equiv.)	0 °C to 65 °C	2 h	Complex mixture
7	$NaBH_4$ (4.75 equiv.) $BF_3{\cdot}Et_2O$ (6.00 equiv.)	0 °C to rt	5 h	trace
8	$NaBH_4$ (4.75 equiv.) $BF_3{\cdot}Et_2O$ (6.00 equiv.)	0 °C to 40 °C	5 h	Complex mixture
9	$NaBH_4$ (4.75 equiv.) $BF_3{\cdot}Et_2O$ (6.00 equiv.)	0 °C to 55 °C	5 h	35%
10	$NaBH_4$ (4.75 equiv.)[a] $BF_3{\cdot}Et_2O$ (6.00 equiv.)	0 °C to 55 °C	5 h	94%

[a] Fresh reagent bottle. [b] Yields of isolated product **80**.

Table 2.4. Optimisation of conditions for the reduction of β-nitrostyrene **92**.

2.1.3 Coupling of the fragments and subsequent macrocyclisation

With all fragments in hand, their coupling was commenced with formation of **77** *via* amide coupling A1. This was obtained in 73% yield following a brief evaluation of optimal conditions (**Table 2.5**).

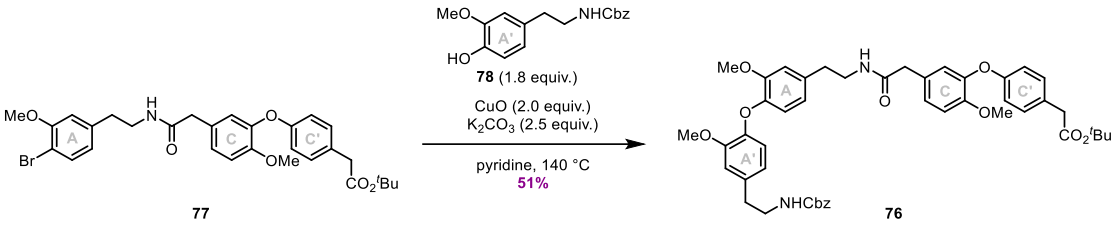


Entry	Amine 99[a] (equiv.)	Coupling Agent(s)	Base	Solvent	Time	Yield[b]
1	1.0	$COCl_2$ (1.2 equiv.), DMF (1 drop)	Et_3N (1.3 equiv.)	CH_2Cl_2	18 h	Complex mixture
2	1.0	EDC·HCl (1.0 equiv.), HOBt (1.2 equiv.)	NMM (2.8 equiv.)	DMF	18 h	56%
3	1.1	EDC·HCl (1.0 equiv.), HOBt (1.2 equiv.)	DIPEA (3.5 equiv.)	CH_2Cl_2	18 h	57%
4	1.1	T3P (1.7 equiv.)	DIPEA (3.5 equiv.)	CH_2Cl_2	18 h	64%
5	1.1	T3P (1.7 equiv.)	DIPEA (4.4 equiv.)	CH_2Cl_2	5 h	73%

[a] All reactions were carried out using 1.0 equiv. of acid **83**. [b] Yields of isolated product **77**.

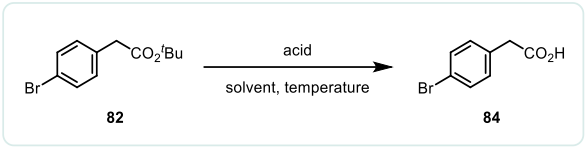
Table 2.5. Reaction optimisation of amide coupling A1.

To our delight, subjection of amide **77** to an Ullmann coupling with phenol **78** (optimisation in **Appendix 6.2**) afforded biaryl ether **76** in 51% yield despite the system being quite sterically demanding with both coupling partners having an *ortho*-methoxy substituent (**Scheme 2.6**). Biaryl **76** would first require deprotection of both the *tert*-butyl ester and Cbz group before subjecting it to the macrolactamisation. Cbz groups are known to be cleaved under hydrogenolytic conditions using catalytic Pd/C, reactions which tend to be clean with carbon dioxide and toluene as the sole by-products. Therefore, the ester hydrolysis was performed first to avoid having to purify amino acid **100**.



Scheme 2.6. Synthesis of biaryl **76**.

The ester hydrolysis was modelled on ester **82** with all conditions giving similar yields (**Table 2.6**). However, the use of sulfuric acid resulted in a mixture that required further purification, thus making TFA and HCO_2H more convenient to use on the actual substrate.

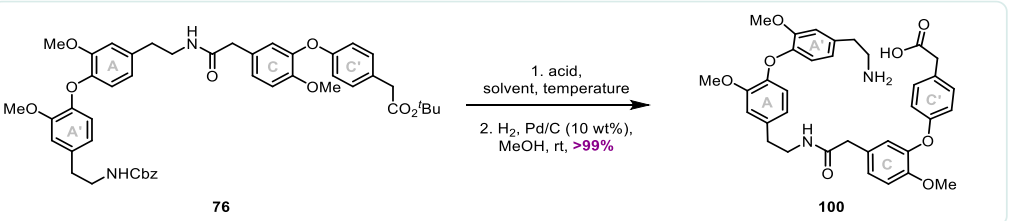


Entry	Acid	Solvent	Temperature	Yield[a]
1	TFA (0.21 mL)	CH_2Cl_2	30 °C	87%
2	HCO_2H (0.9 mL)	-	rt	91%
3	H_2SO_4 (1.0 equiv.)	CH_2Cl_2	0 °C to rt	87%

All reactions were performed on a 0.18 mmol scale. [a] Yield was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using mesitylene as an internal standard.

Table 2.6. Exploration of conditions for *tert*-butyl ester deprotection on a model system.

When employed on ester **76**, formic acid gave modest yields (**Table 2.7**, Entry 1) while TFA (Entry 4) afforded the corresponding carboxylic acid in quantitative yields. The subsequent hydrogenolysis proceeded smoothly to give amino acid **100** in >99% yield.

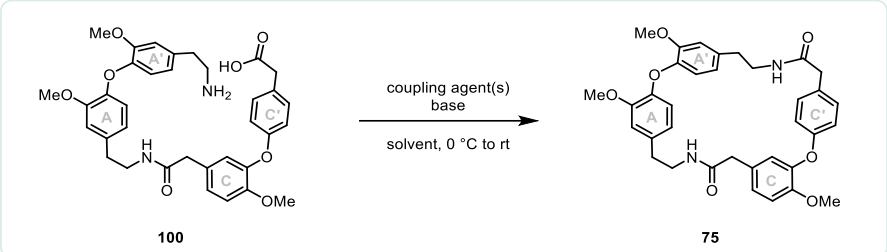


Entry	Acid	Solvent	Temperature	Time	Yield[a]
1	HCO_2H (excess)	-	rt	2 h	52%
2	TFA (7.5 equiv.)	CH_2Cl_2	0 °C to rt	18 h	68%
3	TFA (15 equiv.)	CH_2Cl_2	rt[b]	5 h	93%
4	TFA (18 equiv.)	CH_2Cl_2	30 °C	3 h	>99%

[a] Yields of isolated product **100**. [b] rt was 28 °C.

Table 2.7. Optimisation of *tert*-butyl hydrolysis on **76** and subsequent hydrogenolysis.

Subjecting **100** to macrocyclisation conditions using EDC·HCl/HOBt and NMM resulted in a complex mixture and very poor yields of the desired product (**Table 2.8**, Entry 1). T3P/DIPEA proved to be a much better system, however, the reaction concentration played a major role in terms of the time required and yield afforded. To our delight, macrolactam **75** was afforded in 63% yield using optimised conditions with a reaction concentration of 0.02 M (Entry 3). Higher dilution only afforded trace amounts of the product (Entry 2) despite longer reaction times, whereas doubling the concentration resulted in a poor yield.



Entry	Coupling Agent(s)	Base	Solvent	Concentration	Time	Yield[a]
1	EDC·HCl (1.2 equiv.), HOBt (1.2 equiv.)	NMM (2.8 equiv.)	DMF	0.02 M	7 days	6%
2	T3P (1.7 equiv.)	DIPEA (3.4 equiv.)	CH_2Cl_2	0.003 M	3 days	trace
3	T3P (1.7 equiv.)	DIPEA (3.4 equiv.)	CH_2Cl_2	0.02 M	24 h	63%
4	T3P (1.7 equiv.)	DIPEA (3.4 equiv.)	CH_2Cl_2	0.04 M	24 h	28%

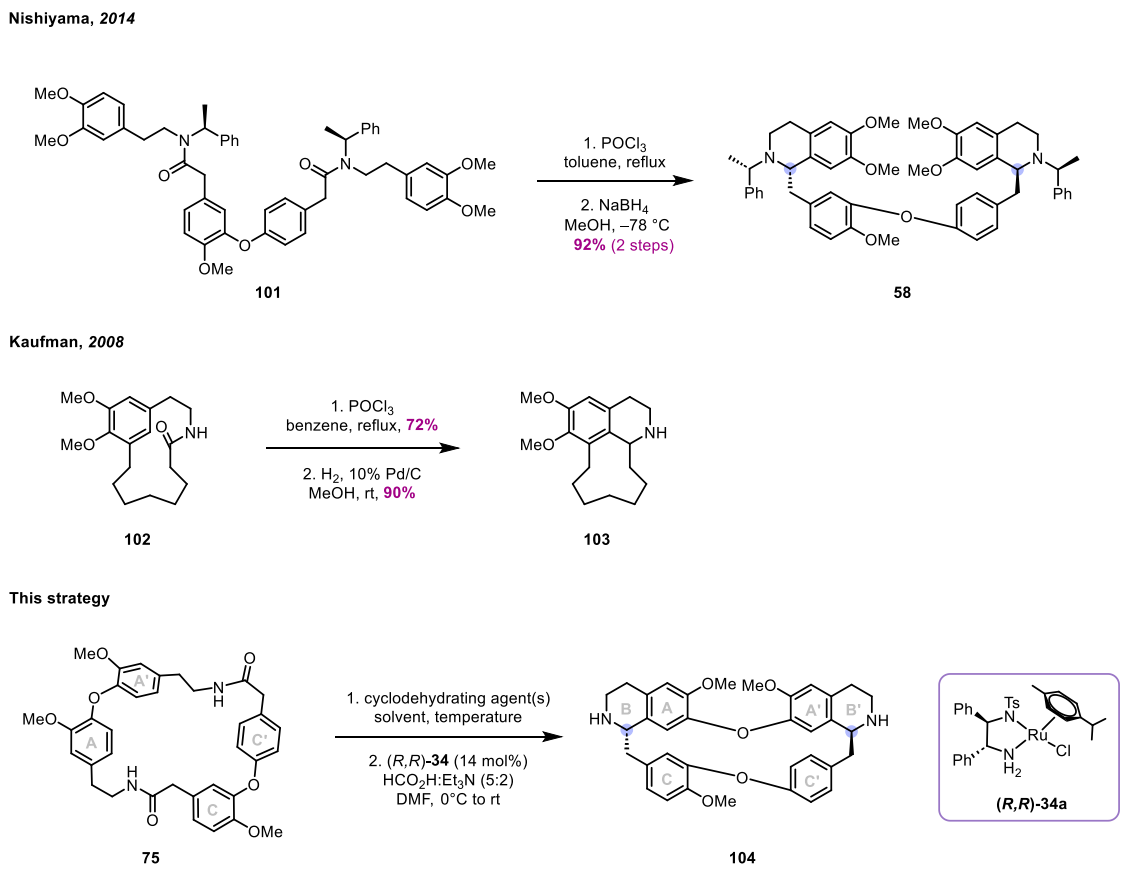
[a] Yields of isolated product **75**.

Table 2.8. Optimisation of the macrocyclisation reaction *via* A2.

2.1.4 Studies of the double BN/ATH

The strategy of a double Bischler-Napieralski cyclisation/asymmetric reduction has been previously demonstrated in the synthesis of linear BBI (+)-*O*-methylthalibrine by Nishiyama *et al.* as previously mentioned (**Chapter 1.5**).[86] Their method employs chiral auxiliaries on both amides that undergo cyclodehydration and subsequent sodium borohydride reduction to afford the corresponding BBI **58** (**Scheme 2.7**). Additionally,

the cyclodehydration reaction has been shown to work on 14-membered macrolactams and was followed up by a reduction under hydrogenolytic conditions to afford **103** (**Scheme 2.7**).[105] To the best of our knowledge, a double BN cyclisation/reduction of a macrolactam has not been reported. While our proposed strategy of performing a double cyclodehydration of a 27-member macrolactam followed by an enantioselective reduction is ambitious, these precedents supported its feasibility.

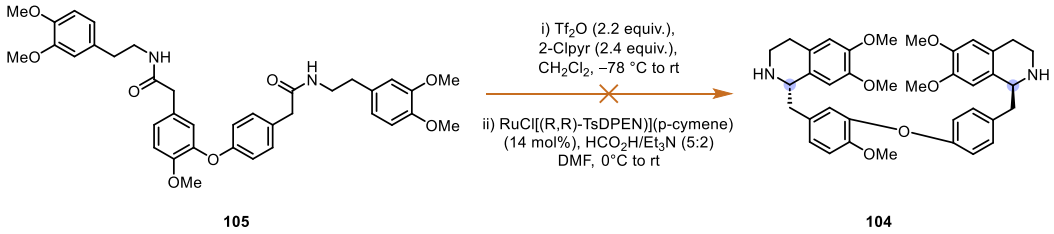


Scheme 2.7. Precedents supporting the feasibility of the proposed strategy.

Entry	1. BN conditions	2. Reduction conditions	Yield (104)
1	Tf_2O (2.2 equiv.), 2-Clpyr. (2.4 equiv.), CH_2Cl_2, –78 °C to rt, 1h	**(*R,R*)-34a** (14 mol%), HCO_2H/Et_3N (5:2 v/v), DMF, 24 h	decomposition
2	Tf_2O (2.2 equiv.), 2-Clpyr. (2.4 equiv.), CH_2Cl_2, –78 °C to rt, 1h	$NaBH_4$ (3.0 equiv.), EtOH, 18 h	trace
3	$POCl_3$ (75 equiv.), toluene, reflux, 16 h	**(*R,R*)-34a** (14 mol%), HCO_2H/Et_3N (5:2 v/v), DMF, 24 h	decomposition

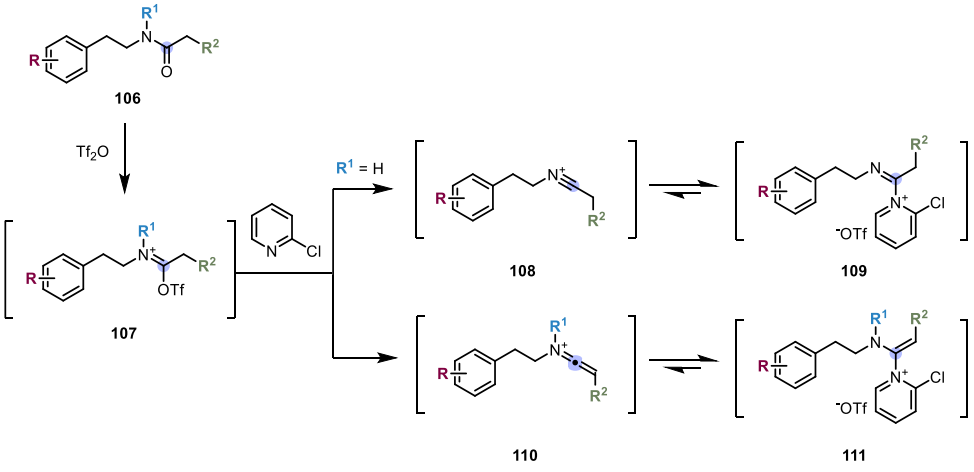
Table 2.9. Conditions attempted for the formation of BBI **104**.

Our studies began by subjecting macrolactam **75** to trifluoromethanesulfonic anhydride and 2-chloropyridine followed by ATH using Noyori's catalyst **(*R,R*)-34a** (**Table 2.9**, Entry 1; These conditions had been previously optimised; full details in **Chapter 3**). However, these conditions resulted in decomposition of the starting material. To gain insight into where the challenge lies, and encouraged by the precedent reported by Nishiyama, macrolactam **75** was subjected to BN cyclisation conditions followed by a sodium borohydride reduction (**Table 2.9**, Entry 2). This gave a complex ^{1}H NMR spectrum of the crude reaction mixture and an inseparable mixture of products, however low-resolution mass spectrometry (LRMS) analysis indicated the potential formation of two compounds: the desired BBI, and a mono-cyclisation product (i.e. single THIQ unit formed). It was hypothesised that using harsher conditions, namely phosphorus(V) oxychloride in refluxing toluene (**Table 2.9**, Entry 3), would drive the reactions to form the desired product despite the possible higher strain imposed by the macrocyclic conformation. Unfortunately, these conditions also led to decomposition of the starting material. Proposing that the conformational rigidity of the macrocycle may have prevented the desired outcome or enabled side reactions, a double cyclodehydration/ATH was attempted on a linear analogue to further verify this. Bis-amide **105** was subjected to identical reaction conditions (**Scheme 2.8**), but regrettably resulted in decomposed starting material. Since the linear analogue also failed to deliver the expected outcome, it was suggested that the reaction was most likely unsuccessful due to substrate incompatibility rather than solely macrocyclic constraint.



Scheme 2.8. Attempted double BN cyclisation/ ATH of linear bis-amide **105**.

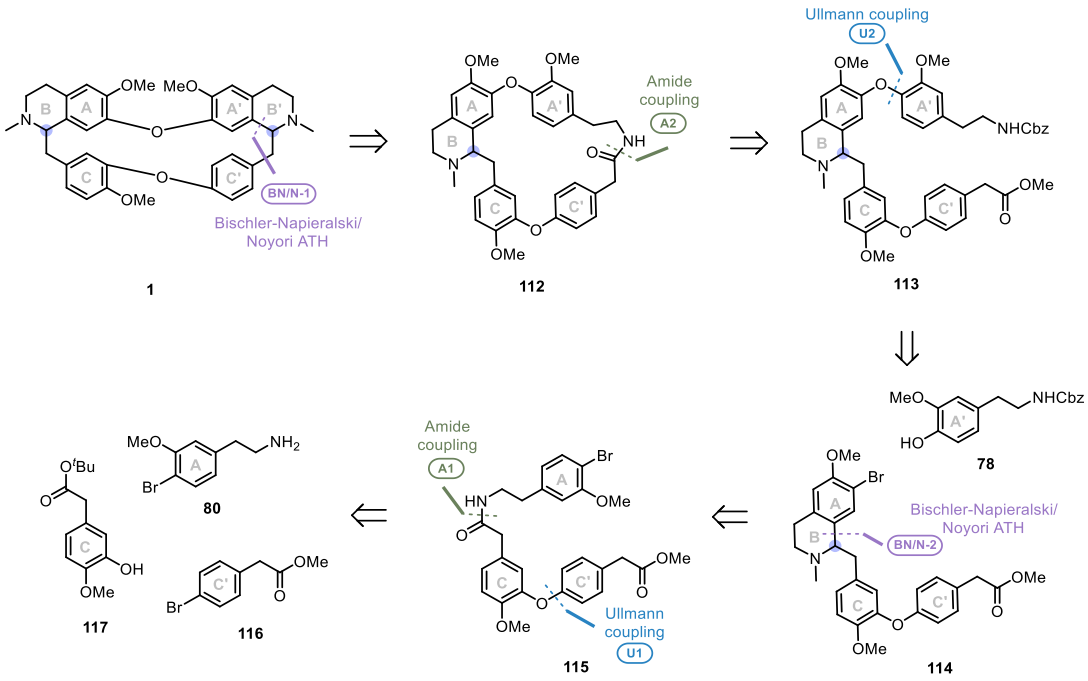
In the case of the Bischler-Napieralski cyclisation, following amide activation, the mechanism can proceed *via* a nitrilium or keteniminium intermediate depending on the reaction conditions and substitution of the amide (**Scheme 2.9**). In the case of Nishiyama's example, the presence of chiral auxiliaries on the amide's nitrogen atoms likely favours the formation of a keteniminium **110** intermediate, which in this case underwent subsequent electrophilic aromatic substitution. In our case, the secondary amides most likely undergo amide activation *via* formation of a nitrilium **108** intermediate. From the experimental observations, it seems that despite the nitrilium ion being typically a good electrophile , this mechanism leads to decomposition. As such, we proposed that beyond the strain imposed by the macrocycle, the electrophilicity of the intermediate undergoing the electrophilic aromatic substitution also plays a key role in allowing the double cyclodehydration reaction to occur. A change in strategy was proposed whereby the THIQ units would be installed sequentially; in future work, the use of a strategy that proceeds *via* keteniminium ions could be considered, although the strain of this ion may be significant if formed.



Scheme 2.9. Electrophilic activation of amide **106**.

2.2 Sequential Bischler-Napieralski/Noyori ATH sequence

The second strategy is based on the premise that a single cyclodehydration/reduction sequence would be more facile to achieve on intermediate **112** where one THIQ unit has been preinstalled (**Scheme 2.10**). Provided that **112** is flexible enough, such that the substrate does not develop a strong substrate bias with respect to the preference of the catalyst, the key benefit of this strategy is that all four diastereomers of **1** could be synthesised. Despite the extra steps imposed by the new route, the improved control of the formation of each stereocentre outweighed this drawback.

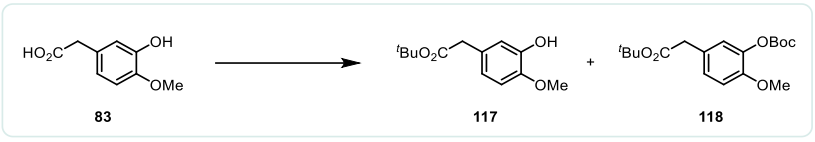


Scheme 2.10. Revised retrosynthetic strategy of **1**.

Similar to the first strategy, macrocycle **112** would be formed by a macrolactamisation from **113** following deprotection. This in turn is disconnected into BI **114** and phenol **78** *via* Ullmann coupling U2. Early attempts at the BN cyclisation/Noyori ATH on amide **77** revealed the lability of the *tert*-butyl ester under these conditions and as such, the new strategy requires amide **115** to have a methyl ester instead. This is further disconnected into amine **80** and a biaryl formed by an Ullmann coupling U1 between **116** and **117**.

2.2.1 Forward Synthesis

Although starting from the same commercially available phenylacetic acid **83** and **84**, the ester groups installed on each of these building blocks were exchanged. Formation of *tert*-butyl ester **117** was challenging, since previously established optimal conditions yielded **118** as the major compound and only trace amounts of the desired product (**Table 2.10**, Entry 1). Subjecting acid **83** to *N,N*-dimethylformamaide di-*tert*-butyl acetal gave modest yields (Entry 2). As such, a two-step procedure was preferred, whereby the *tert*-butyl carbonate of **118** is selectively cleaved over the ester yielding phenol **117** in 51% yield over two steps (Entry 3).

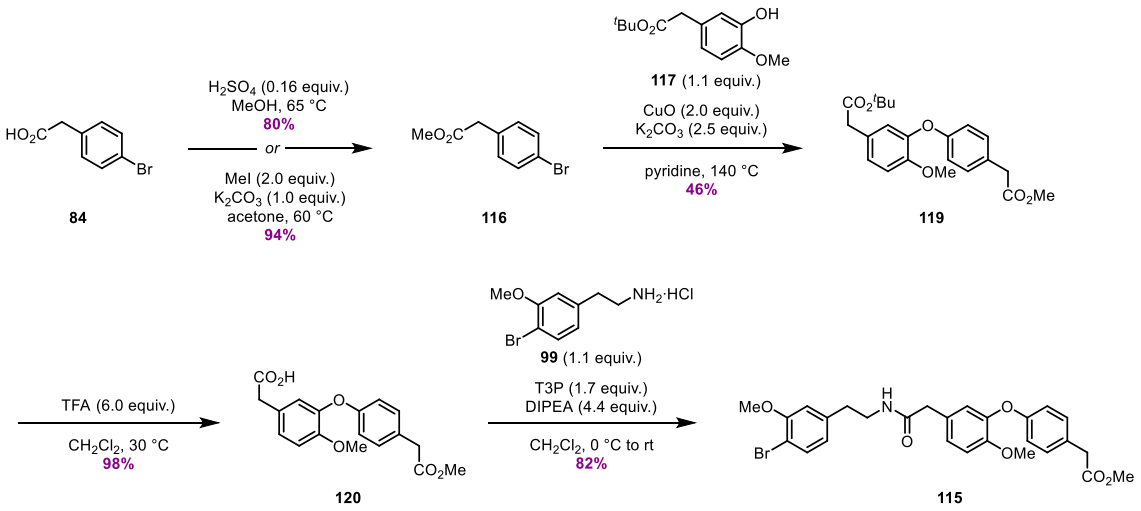


Entry	Reagent(s)	Solvent	Temp.	Time	Yield[a]
1	Boc_2O (2.0 equiv.), DMAP (0.30 equiv.)	^{t}BuOH	rt	18 h	66% (**118**)
2	$CH(O^tBu)_2NMe_2$ (4.0 equiv.)	PhMe	80 °C	30 min	38% (**117**)
3	i) Boc_2O (2.0 equiv.), DMAP (0.30 equiv.) ii) K_2CO_3 (1.0 equiv.)	i) ^{t}BuOH ii) MeOH	rt	i) 18 h ii) 6 h	51% (**117**, over 2 steps)
4	i) Boc_2O (2.0 equiv.), DMAP (0.30 equiv.) ii) aq. NaOH (10 equiv.)	i) ^{t}BuOH ii) MeOH	rt	i) 18 h ii) 6 h	16% (**117**, over two steps)

[a] Yields of isolated products.

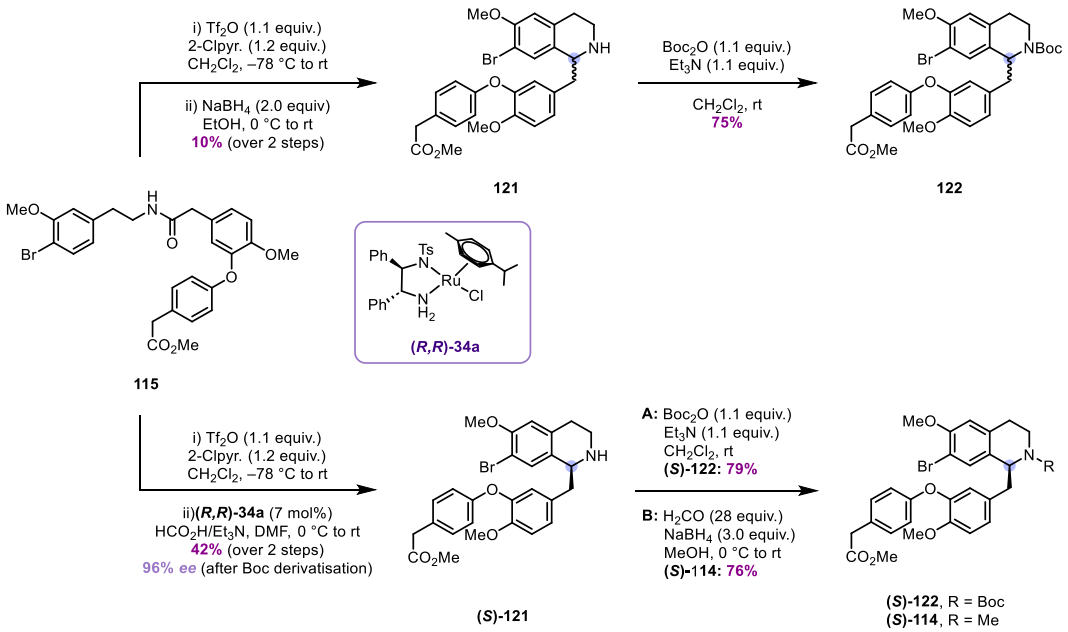
Table 2.10. Conditions for the formation of ester **117**.

Esterification of **84** using iodomethane and potassium carbonate gave better results than catalytic sulfuric acid (**Scheme 2.11**), affording methyl ester **116** in 94% yield. Ullmann coupling of **116** with **117** afforded biaryl ether **119** in 46% yield, which was then chemoselectively hydrolysed to acid **120** in excellent yield (98%). Finally, amide coupling of acid **120** with amine **99** afforded key intermediate **115** in 82% yield.



Scheme 2.11. Synthetic route towards amide **115**.

With amide **115** in hand, the first cyclodehydration/reduction sequence was performed. The intermediate 3,4-dihydroisoquinolines are known to be quite sensitive towards oxidation at the α-position and their purification *via* column chromatography is best avoided.[85] As such, following the cyclisation, the crude products were immediately subjected to reduction. Noyori ATH yielded BI **(*S*)-121** in 42% yield and 96% *ee* (over two steps) which was subsequently *N*-methylated (conditions B, **Scheme 2.12**) to BI **(*S*)-114** in 76% yield using reductive amination conditions.

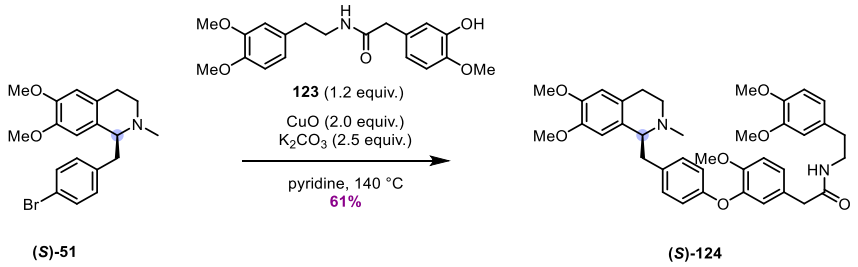


Scheme 2.12. Synthesis of BI **(*S*)-114**.

The secondary amine would not be tolerated by the conditions required in the ensuing Ullman coupling. It was therefore decided to install the *N*-methyl group which is present in the final product at this point, as it is present in the target BBI and may serve as a protecting group in the following step.

The racemic synthesis was carried out in parallel to measure the enantioselectivity afforded by the ATH. Cyclisation of **115** followed by sodium borohydride reduction afforded amine **121** (**Scheme 2.12**). Separation of the racemate by chiral HPLC or chiral SFC using secondary amines such as **121** or the *N*-methyl analogues was unsuccessful. Therefore, Boc-protected amines **122** and **(*S*)-122** were prepared (**Scheme 2.12**) which allowed successful separation of enantiomers, and determination of *ee*, by chiral supercritical fluid chromatography (SFC).

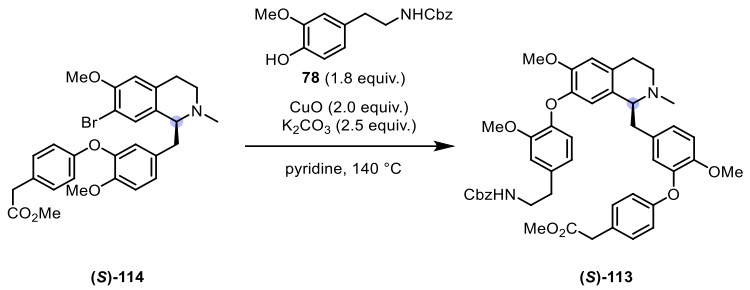
The coupling of a BI alkaloid to a phenol was modelled (**Scheme 2.13**) on a system developed in the synthesis of linear BBIs (**Chapter 3**). Subjecting **(*S*)-51** and phenol **123** to optimised Ullmann conditions afforded the desired product **(*S*)-124** in 61% yield.



Scheme 2.13. Model Ullmann coupling of BI (*S*)-**51** and phenol **123**.

Encouraged by these results and with **(*S*)-114** in hand, the coupling to phenol **78** was attempted (**Scheme 2.14**). While the presence of the desired product **(*S*)-113** was confirmed by analysis of the ^{1}H NMR spectrum of the crude reaction mixture and LRMS, attempting to purify the compound by column chromatography resulted in

decomposition, and a change in the strategy was proposed to circumvent this issue. The proposed route involved interchanging the order of the steps and performing the Ullmann coupling prior to installing the THIQ unit. The resulting amide could then be subjected to the BN cyclisation/Noyori ATH step prior to macrolactamisation. Unfortunately, due to the time constraints of the project, the change in strategy was not investigated and the completion of this synthesis remains part of future work.



Scheme 2.14. Attempted Ullmann coupling of BI **(*S*)-114** and phenol **78**.

3

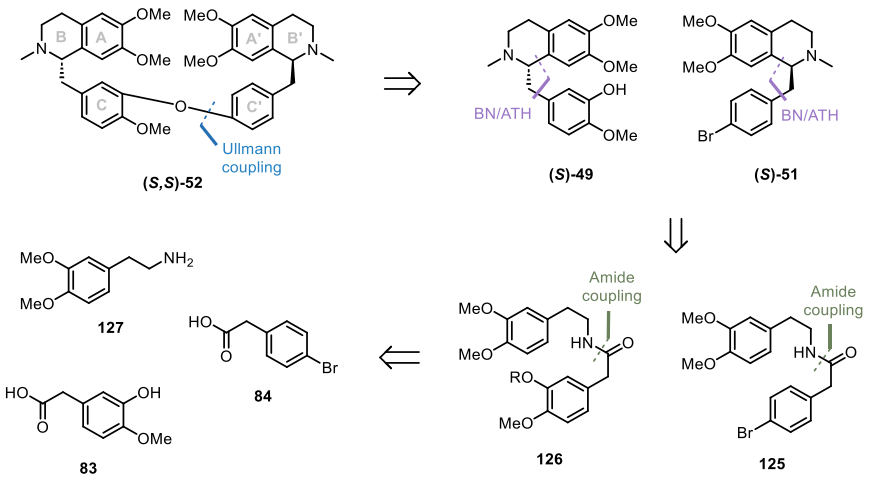
Synthesis of Linear Bis-benzyltetrahydroisoquinoline Alkaloids

Continuing with our investigation into alkaloids in the context of anti-parasitic agents, we set out to explore which structural motifs are vital for biological activity. The 'deconstructive' approach sequentially removes one key structural aspect of BBIs – namely their macrocyclic form – to probe whether similar bioactivity is observed in acyclic dimers. While the benzylisoquinoline units and the tail-to-tail linkage are conserved, the head-to-head ether linkage is removed. Moreover, the proposed strategy to access the desired targets involves the formation of the individual BIs prior to their coupling. This strategy was chosen to enable access to a range of BIs, compounds which constitute the targets of the next deconstructive step, *i.e.* the cleavage of the tail-to-tail linkage. As previously mentioned, the benzylic stereochemistry is thought to be important for the anti-parasitic effect; therefore, the route was designed to allow access to both enantiomers of the BI targets as well as all four diastereomers of the linear BBI targets.

3.1 Synthesis of (+)-*O*-methylthalibrine and its diastereomers

Naturally occurring BBI **(*S,S*)-52** (known as (+)-*O*-methylthalibrine) was chosen as the first target as it conserves the benzylisoquinoline units and the tail-to-tail linkage identical to that of macrocyclic BBIs northalrugosidine (**13**) and analogue **1**. The oxygenation pattern is maintained with methoxy substituents at C-12, C-6, C-6′ C-7 and C-7′.

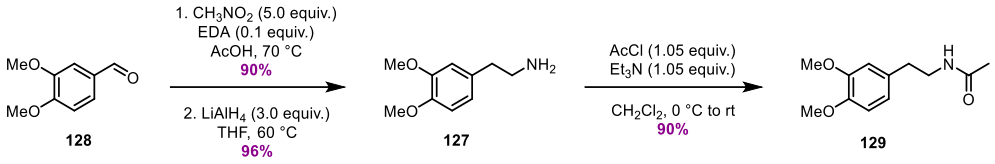
The first strategy to synthesise acyclic BBIs such as **(*S,S*)-52** relied on a late-stage Ullmann coupling of BIs **(*S*)-49** and **(*S*)-51**, which in turn can be formed *via* a BN cyclisation/Noyori ATH sequence from the corresponding amides **126** and **125**, respectively. The amides are easily accessed through an amide coupling of commercially available acids **83** and **84** with amine **127** (**Scheme 3.1**).



Scheme 3.1. Retrosynthetic strategy of **(*S,S*)-52**.

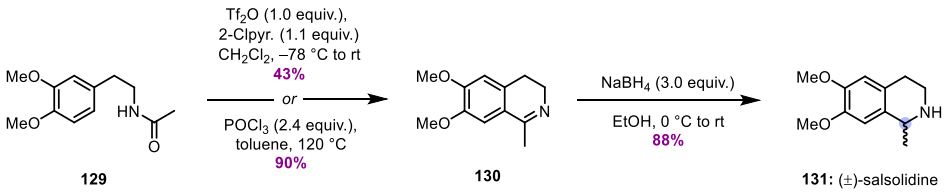
The investigation began with testing the reproducibility of the reaction as well as the exploration of optimal practical aspects for the ATH. Salsolidine **131** was chosen as the best target for the optimisation as it is easily made from amine **127** through acetylation. Moreover, this natural product is often used as a reference when comparing the effectiveness of various ATH catalytic systems.[63]

Subjection of benzaldehyde **128** to a nitro aldol reaction followed by a lithium aluminium hydride reduction afforded amine **127** in 86% yield over two steps (**Scheme 3.2**). The subsequent acetylation yielded **129** in 90% yield to be used as the substrate for the ATH optimisation.



Scheme 3.2. Synthesis of acetamide **129**.

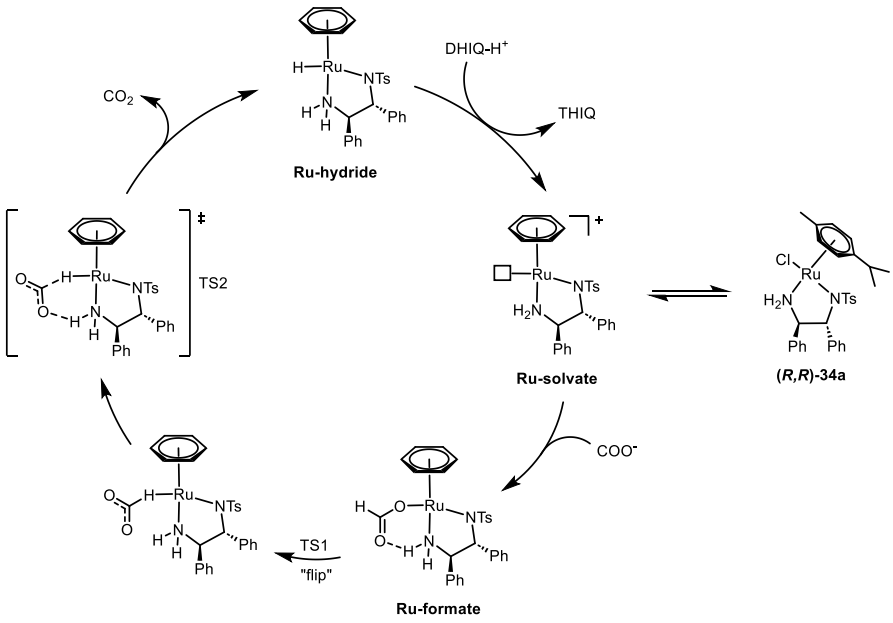
Acetamide **129** was subjected to BN cyclisation using Movassaghi's[66] conditions, yielding the corresponding 3,4-DHIQ **130** in 40% yield (**Scheme 3.3**). These compounds are known to be sensitive towards aerobic oxidation and as such their purification *via* column chromatography is not recommended; however, it was found that these conditions required subsequent product purification leading to an unsatisfactory yield. Pleasingly, **130** can also be obtained using phosphorus oxychloride which only required an aqueous work-up procedure, thus leading to a much-improved yield (90%). With desired **130** in hand, the racemic synthesis of **131** was carried out in order to measure the enantioselectivity of the ATH. Reduction of imine using sodium borohydride delivered (±)-salsolidine in 88% yield (**Scheme 3.3**).



Scheme 3.3. Racemic synthesis of (±)-salsolidine (**131**).

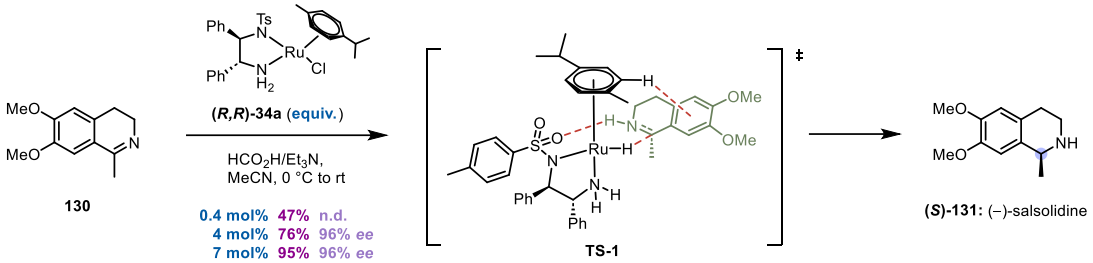
The asymmetric reduction of **130** was performed using Noyori's catalyst **(*R*,*R*)-34a** and ATH conditions.[71] The reaction is catalysed by a Ru(II) species coordinating to a chiral

diamine ligand, and an azeotrope mixture of formic acid and triethylamine acting as a hydrogen source. Excess formic acid is required as imines are known to be reduced only under acidic conditions. Although not entirely confirmed, this supports the proposed protonation of the imine and an ionic reaction mechanism. It has been proposed that the RuCl species slowly dissociates and forms an equilibrium with the cationic Ru-solvate species (**Scheme 3.4**). The suggestion that triethylamine abstracts HCl, thus giving rise to a 16 e^- Ru-complex, has been challenged by the fact that in the presence of excess formic acid, a large amount of the amine base would be protonated. However, in the presence of formate, a Ru-formate complex is formed with further stabilisation offered by a H-bond between the carbonyl oxygen and the TsDPEN ligand. The formate anion reorients such that the hydrogen points towards the metal centre, and a Ru hydride species can thus be generated. Since the coordination sphere is saturated, brief de-coordination of a ligand has been suggested to allow for this "flip" to occur. The active Ru hydride species is then formed through loss of CO_2, and reduces the protonated 3,4-DHIQ to the corresponding THIQ.[106-108]



Scheme 3.4. Catalytic cycle of Noyori's catalyst **(*R,R*)-34a** in ATH of DHIQs.

A proposed transition state for the ATH of imine **130** is shown in **Scheme 3.5**, which is supported by mechanistic studies, and highlights the key interactions that stabilise the complex: a) the protonated nitrogen atom of the DHIQ, which forms a H-bond with the sulfonyl moiety of the diamine ligand, and b) the C(sp^2)H–π interaction between the *p*-cymene ligand and the substrate. These interactions also account for the observed stereochemistry.

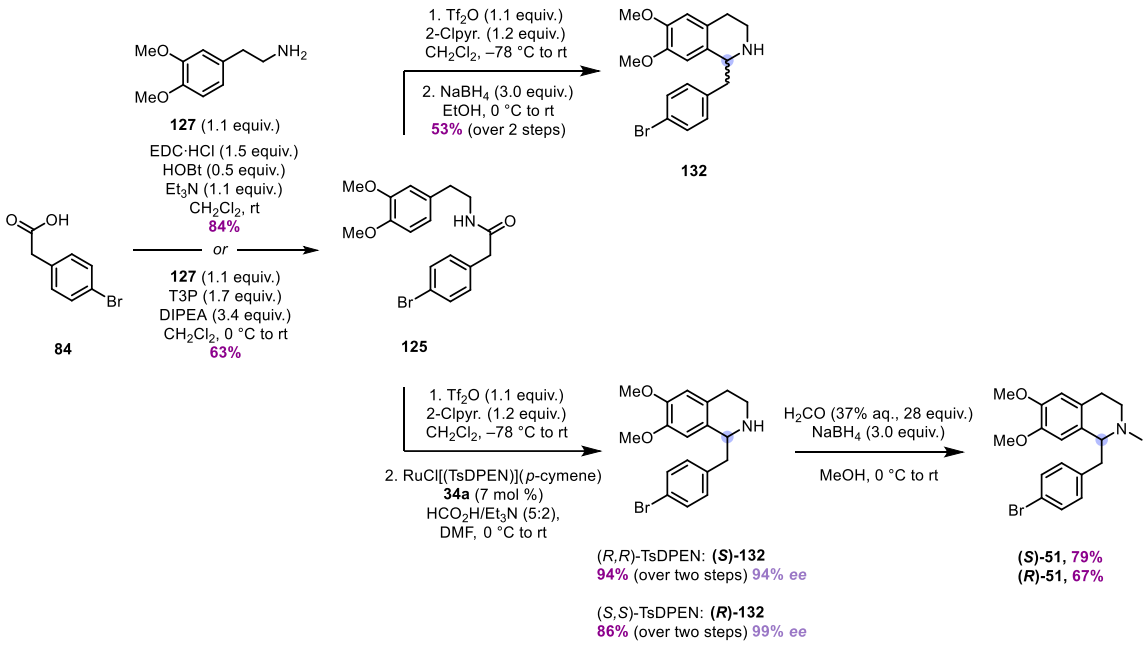


Scheme 3.5. ATH of **130** using Noyori's catalyst with the proposed transition state.

Initial low catalyst loadings of 0.4–4 mol% afforded the desired THIQ in modest yields (47 – 76%). Increasing the loading to 7 mol% maintained the excellent enantioselectivity observed earlier, but offered an improved, near-quantitative yield (95%, 96% *ee*) (**Scheme 3.5**). With optimal conditions in hand, our attention turned towards the synthesis of the individual BI units.

3.1.1 Synthesis of bromo-BIs

The synthesis commenced with the formation of amide **125** from acid **84** and amine **127**. In this case, a mixture of EDC·HCl/HOBt proved to be a superior coupling agent to T3P, affording the desired amide in 84% yield (**Scheme 3.6**). Subjecting the amide to BN cyclisation followed by sodium borohydride reduction yielded racemic BI **132** in 53% yield (over two steps) to be used as a standard for enantioselectivity analysis (**Scheme 3.6**). The Boc-protected BIs were prepared to measure the enantioselectivity of the ATH (See **Appendix 6.3**).



Scheme 3.6. Synthesis of non-natural BIs **(*S*)-51** and **(*R*)-51**.

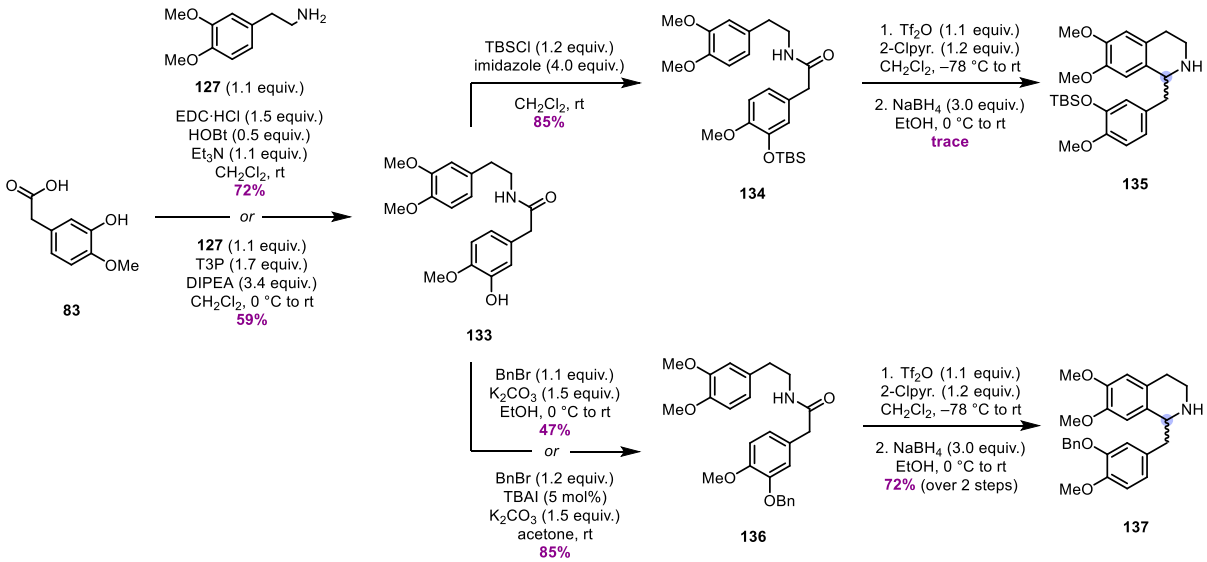
It is worth mentioning that secondary amines such as **132** were observed to undergo decomposition (at room temperature, within hours), thus explaining the modest yield observed. Best results were obtained when, following their purification, the secondary amines were immediately subjected to the next step.

Initial studies of the BN cyclisation showed that Movassaghi's conditions afforded better yields than 'classic' conditions using phosphorus oxychloride and heat. This is in part due to the development of a two-step procedure that avoids the isolation of the intermediate imine. Moreover, it was found that simply quenching the triflate salts using one equivalent of triethylamine upon completion of the BN cyclisation, and changing the solvent to DMF without performing an aqueous work-up, resulted in improved yields. BI **(*S*)-132** was obtained using **(*R*,*R*)-34a** in 94% yield over two steps and in 94% *ee*. Its enantiomer **(*R*)-132** was obtained in 86% yield over two steps and excellent enantioselectivity (99% *ee*) from the same precursor amide using **(*S*,*S*)-34a**. Subsequent reductive *N*-alkylation gave non-natural BIs **(*S*)-51** and **(*R*)-51** in 79% and 67% yield, respectively (**Scheme 3.6**).

3.1.2 Synthesis of the phenolic BIs

The synthesis of the phenolic BIs was next addressed. Unfortunately, free phenols are not tolerated under the cyclodehydration conditions, and a protecting group was required. To avoid any chemoselectivity issues imposed by the carboxylic acid moiety, **83** was first subjected to an amide coupling.

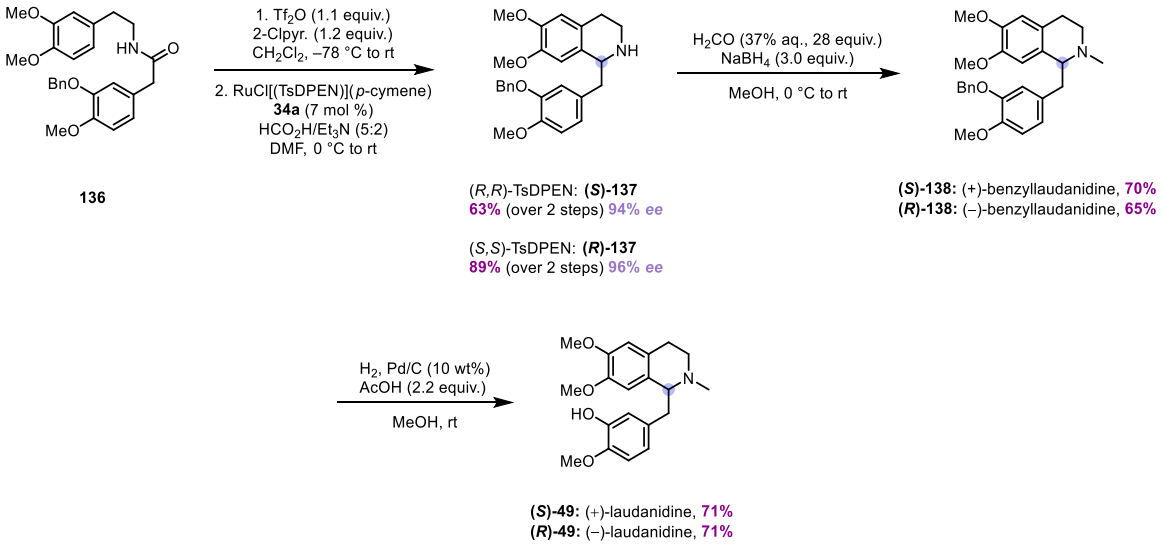
Similar to the synthesis of amide **125**, EDC·HCl/HOBt afforded amide **133** in higher yields than T3P. Subsequent TBS protection to **134** was achieved in 85% yield using standard conditions of TBSCl and imidazole (**Scheme 3.7**). Despite silyl protecting groups being generally tolerated under these mild conditions used for the BN cyclisation, subjection of **134** to the reaction conditions only afforded trace amounts of the desired BI **135**. Since silyl groups are known to be acid-labile, their undesired cleavage could potentially arise as a consequence of water reacting with the trifluoromethanesulfonic anhydride to give the corresponding acid. It was decided that replacing the TBS with a benzyl protecting group would be a more fruitful strategy since the benzyl group is more stable under the reaction conditions. Additionally, the benzyl-BIs would be tested for biological activity as silyl groups are a rather uncommon moiety in drug scaffolds.



Scheme 3.7. Synthesis of amides **134** and **136** and their subsequent BN cyclisation/reduction.

Performing the benzylation under standard conditions using benzyl bromide and potassium carbonate yielded amide **136** in a modest yield. However, it was found that addition of 5 mol% tetra-*n*-butylammonium iodide (TBAI) and changing the solvent to acetone significantly improved the yield to 88% (**Scheme 3.7**).

BN cyclisation followed by ATH using **(*R*,*R*)-34a** or **(*S*,*S*)-34a** of amide **136** afforded BIs **(*S*)-137** and **(*R*)-137** in good yields (63% and 89%) and excellent enantioselectivity (94% and 96% *ee*). *N*-Methylation using reductive alkylation conditions with formaldehyde yielded (+)-*O*-benzyllaudanidine and (–)-*O*-benzyllaudanidine in 70% and 65% yield respectively. The removal of the benzyl group was achieved using acidic hydrogenolysis, delivering the desired naturally occurring phenolic BIs (+)-laudanidine (**(*S*)-49**) and (–)-laudanidine (**(*R*)-49**) in 71% yield (**Scheme 3.8**). Racemisation did not occurr during the deprotection step, as indicated by the optical rotation values obtained (**(*R*)-49**: $[\alpha]_D^{25}$ –93.5 (c. 1.18, $CHCl_3$). Ref. [109] $[\alpha]_D^{25}$ –94.7 (c. 0.4, $CHCl_3$)).



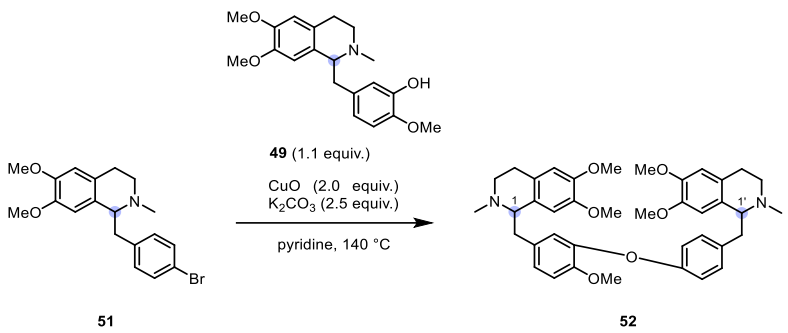
Scheme 3.8. Synthesis of phenolic BIs (+)-laudanidine and (–)-laudanidine.

3.1.3 Coupling of the BIs

With enantiomeric bromo-BIs **(*S*)-51** and **(*R*)-51** and phenolic BIs **(*S*)-49** and **(*R*)-49** in hand, all four diastereomers of BBI **52** were synthesised. Subjecting **(*S*)-51** and **(*S*)-49** to Ullmann coupling conditions afforded (+)-*O*-methylthalibrine in 37% yield (**Table 3.1**, Entry 1). Despite the harsh conditions of the Ullmann reaction, racemisation was not observed as indicated by the optical rotation ($[\alpha]_D^{25}$ +72.8 (c. 1.21, $CHCl_3$). Ref.[85] $[\alpha]_D^{25}$ +79.2 (c. 0.45, $CHCl_3$)). Using this strategy, the natural product was synthesised in 7% overall yield (from phenol **83**) and excellent enantioselectivity (>94% *ee*). While Nishiyama's[86] strategy to access the same natural product is more efficient (29% overall yield), their use of chiral auxiliaries delivers only moderate enantioselectivity (>86% *ee*). Moreover, the strategy only allows access to two diastereomers since both stereocentres are set in the same step. Opatz's[85] strategy of α-alkylation of carbonitriles with benzylic bromides yields **(*S,S*)-52** with similar enantioselectivity (>95% *ee*), and improved overall yield (21%). However, our BN/ATH approach is more efficient in the synthesis of BIs bearing halogen atoms (62% *vs* 20% yield). Additionally, the yield reported by Opatz for the final Ullmann coupling (51%) is questionable; the ^{1}H NMR spectrum of the natural product formed contains impurities which would suggest an inaccurate yield, and perhaps to erroneous integration of signals in the upfield region of the spectrum.[85]

(–)-*O*-Methyldauricine (**(*R,R*)-52**) was obtained in a similar fashion in 17% yield from **(*R*)-51** and **(*R*)-49** (**Table 3.1**, Entry 4). The third natural product (***S,R*)-52** (known as (–)-*O*,*O*′-dimethylgrisabine) was synthesised in 23% yield (Entry 3), while the final diastereomer **(*R,S*)-52** was isolated in 22% yield (Entry 2). While these yields are poor to modest at best, they are not representative of the coupling itself but rather of the challenging purification procedure required. Preparative TLC was found to be the most suitable purification method whereby some material was sacrificed due to coelution.

However, since the main objective of this project was the biological evaluation of these compounds as potential anti-parasitic agents, prioritising the purity of the compounds over the yield was deemed a necessary compromise. Due to the complexity of the ^{1}H NMR spectra of the crude reaction mixtures, a *dr* could not be established. In the absence of HPLC or SFC traces, the enantiomeric ratio (*er*) of BBIs **52** were estimated statistically to be >99.9:0.1.



51 52

Entry	Bromide 51	Phenol 49	BBI 52	Yield[a,b]
1	(*S*)-**51**	(*S*)-**49**	(*1S,1'S*)-**52**	37%
2	(*S*)-**51**	(*R*)-**49**	(*1R,1'S*)-**52**	22%
3	(*R*)-**51**	(*S*)-**49**	(*1S,1'R*)-**52**	23%
4	(*R*)-**51**	(*R*)-**49**	(*1R,1'R*)-**52**	17%

[a] Reactions were carried out on a 0.16 mmol scale [b] Yields of isolated products.

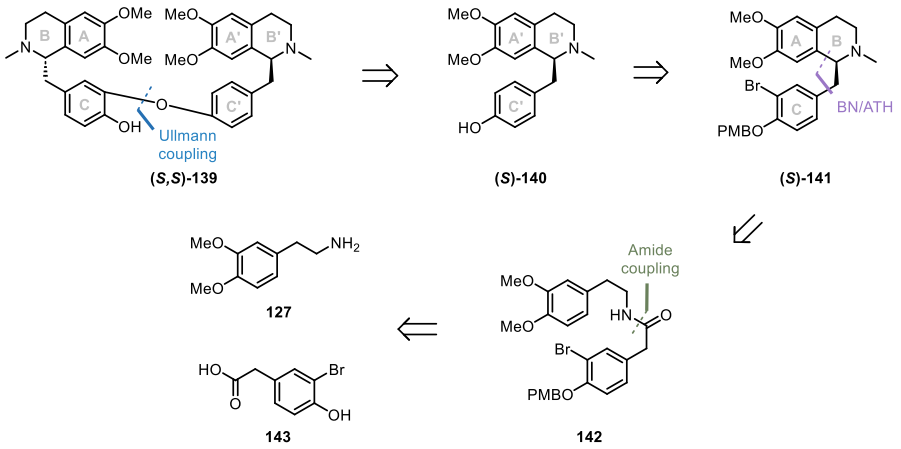
Table 3.1. Synthesis of BBIs **52** *via* an Ullmann coupling.

3.2 Synthesis of (+)-dauricine and its Diastereomers

The next target chosen was (+)-dauricine **(*S,S*)-139**. The same criteria were used in choosing this target as the earlier one: a similar oxygenation pattern having methoxy substituents at C-6, C-6′, C-7 and C-7′ and a conserved C11–C12′ tail-to-tail ether linkage. Besides exploring the importance of the macrocycle, these molecules would provide insight into the importance of the substituent at C-11 (methoxy *vs para*-methoxybenzene (PMB) *vs* phenol) as well as whether any differences in bioactivity of diastereomers can be observed as a general trend. Moreover, a free phenol allows for late-stage

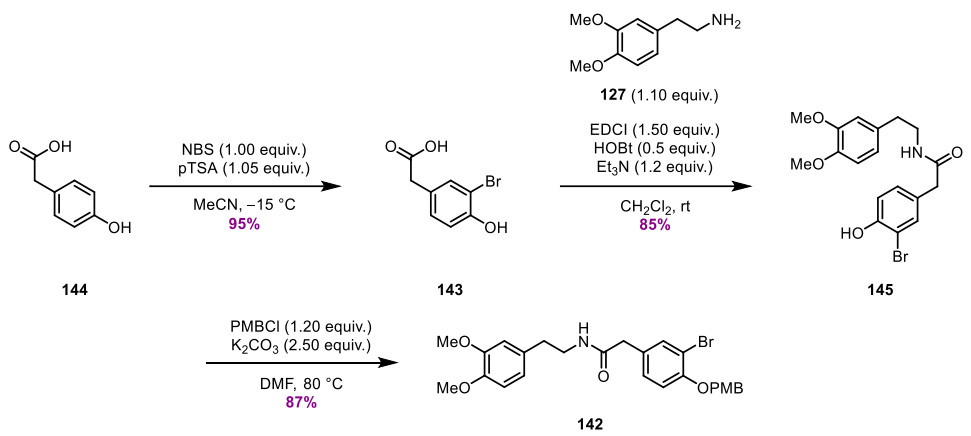
modifications which would be useful in a structure-activity-relationship (SAR) study. Alternatively, a fluorescent probe could be attached to visualise where the drug accumulates within the parasite and establish a mode of action.

Having a free phenol at C-12 requires a change in the strategy used to access these molecules. Attempting to use the same strategy as before would require a catechol-like BI which would introduce several regioselectivity issues. To avoid this issue, BIs **(*S*)-140** and **(*S*)-141** were proposed as the precursors for **(*S*,*S*)-139**. The protected phenol would be revealed after the final coupling to afford the desired BBI. While these BIs could be formed from the corresponding amides, we envisaged subjecting **(*S*)-141** to hydrogenolysis conditions to afford **(*S*)-140**, as this would reduce the number of total steps required in the synthesis. BI **(*S*)-141** would be formed *via* a BN cyclisation/Noyori ATH/*N*-alkylation sequence from amide **142**. This in turn is disconnected into amine **127** and carboxylic acid **143** (**Scheme 3.9**).



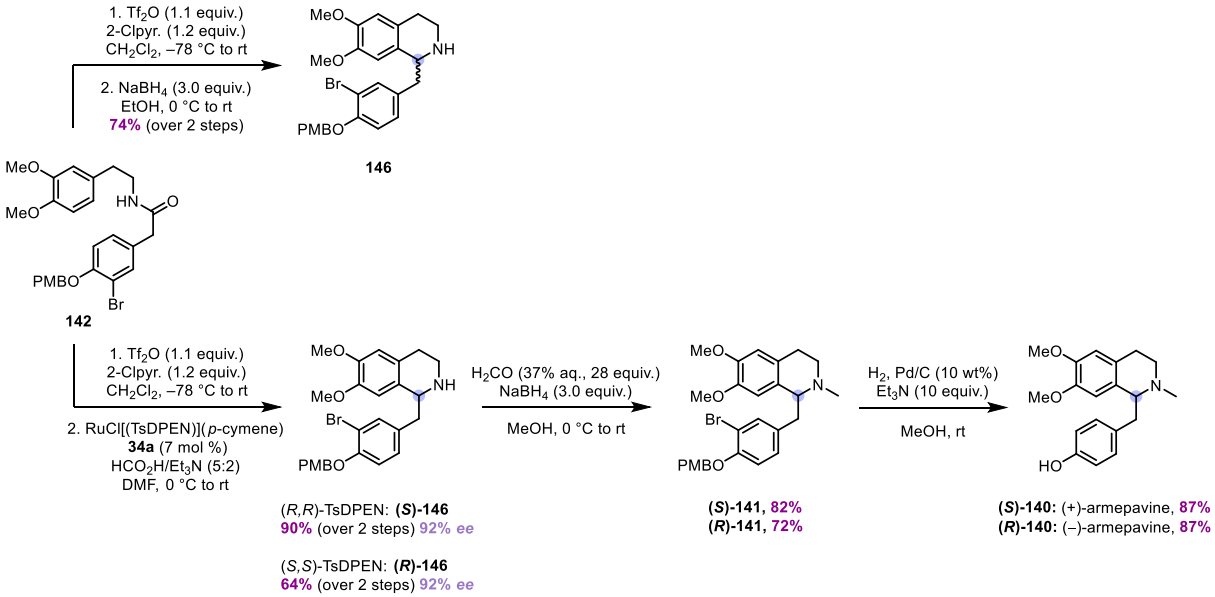
Scheme 3.9. Retrosynthetic strategy towards (+)-dauricine **(*S*,*S*)-139**.

The forward synthesis started with the bromination of phenol **144** using NBS and *para*-toluensulfonic acid (*p*-TSA) to form **143** in near-quantitative yields. This was then coupled to amine **127** yielding amide **145** in 85% yield. Subsequent PMB-protection using typical conditions for this transformation afforded amide **142** in 70% overall yield (**Scheme 3.10**).



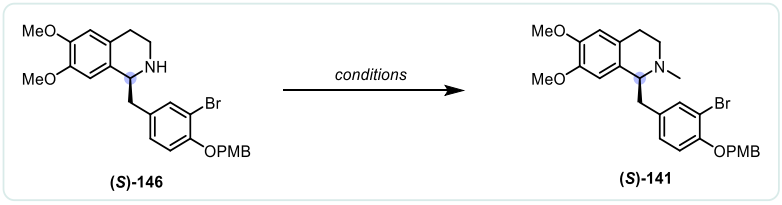
Scheme 3.10. Synthesis of PMB-protected amide **142**.

As before, the racemic synthesis was carried out in parallel to the enantioselective one and Boc derivatisation of BIs **146** was performed in order to measure the enantioselectivity of the ATH (See **Appendix 6.3**). BN cyclisation followed by sodium borohydride reduction yielded **146** in 74% yield (**Scheme 3.11**). BI **(*S*)-146** was obtained with high enantiopurity (96% *ee*) and 90% yield over two steps from the corresponding amide using **(*R*,*R*)-34a**. The enantiomer **(*R*)-146** was made in a similar fashion and isolated in 66% yield (over two steps) and 92% *ee*. Subjecting the secondary amines to reductive alkylating conditions and subsequent hydrogenolysis afforded **(*S*)-140** in 64% and **(*R*)-140** in 40% overall yield (**Scheme 3.11**).



Scheme 3.11. Synthesis of (+)-armepavine and (–)-armepavine from amide **142**.

Alternative conditions for the *N*-alkylation reaction of secondary amines **146** were explored in an attempt to improve the yield and remove the need for a purification procedure (**Table 3.2**). Alkylating conditions using methyl iodide and potassium carbonate resulted in returned starting material (Entry 2). Eschweiler-Clarke reaction of **(*S*)-146** (Entry 1) gave similar results to the reductive alkylation conditions used by Opatz *et al.*[85] (Entry 3). However, the initial conditions used (Entry 4) were found to be the most successful ones.



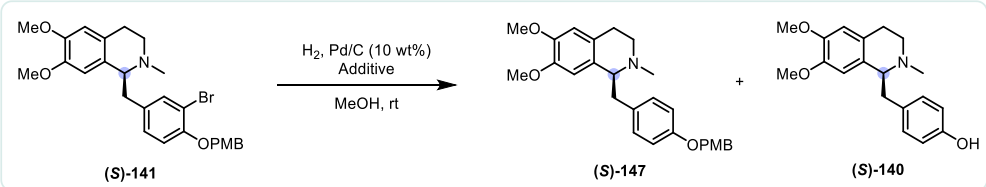
Entry	Reagents	Solvent	Temperature	Time	Yield
1[a]	HCO_2H (2.0 equiv.), H_2CO (1.1 equiv.)	-	0 °C to 80 °C	24 h	41%
2[a]	MeI (1.2 equiv.), K_2CO_3 (1.2 equiv.)	DMF	0 °C to rt	24 h	0%[b]
3[a]	H_2CO (37% aq., 28 equiv.) $NaBH_4$ (30 equiv.)	MeOH	0 °C to rt	1 h	54%
4[c]	H_2CO (37% aq., 28 equiv.) $NaBH_4$ (3.0 equiv.)	MeOH	0 °C to rt	1.5 h	82%

[a] Reactions were performed on a 0.16 mmol scale; Yield was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using nitromethane as an internal standard. [b] Returned starting material. [c] Reaction was performed on 1.65 mmol scale and yield is given for the isolated product.

Table 3.2. Optimisation of the *N*-alkylation conditions of BI **(*S*)-146**.

The subsequent hydrogenolysis proved to be more challenging than anticipated. Subjection of BI **(*S*)-141** to standard conditions using 10 mol% Pd/C resulted in incomplete conversion even after 48 hours (**Table 3.3**, Entry 1). Increasing the temperature to 40 °C resulted in dehalogenation to form **(*S*)-147** with no trace of the desired product. From our earlier studies on deprotecting benzyl groups, the use of acetic acid was beneficial. However, in this case the reaction delivered the dehalogenated product **(*S*)-147** in quantitative yield whilst leaving the PMB group unaffected. The use

of triethylamine has also been reported to be beneficial for these transformations,[110] and in the event this turned out to be the case: the addition of triethylamine (and increasing the Pd/C loading to 14 mol%) gave a mixture of the dehalogenation product **(*S*)-147** and desired product **(*S*)-140**, even with extended reaction times (Entries 4, 5). It was proposed that an increased pressure of hydrogen gas might drive the reaction to completion, and after the optimisation of the reaction set up, it was found that the use of a 1-gallon gas bag to continuously bubble hydrogen gas through the reaction mixture for 30 hours in the presence of triethylamine yielded phenol **(*S*)-140** in excellent yield (Entry 6).

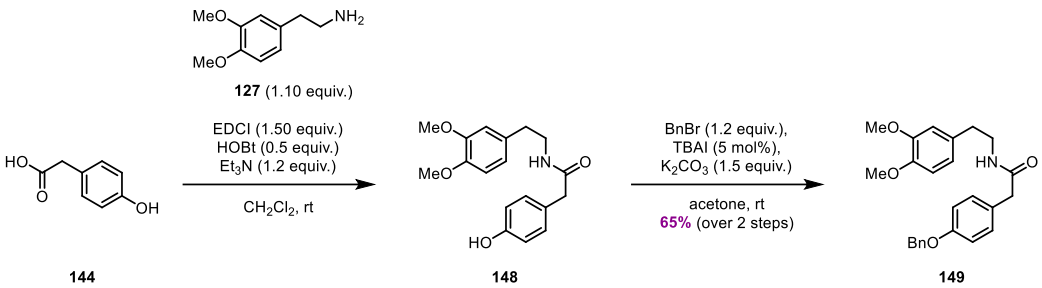


Entry	H_2 balloon [a]	Pd/C loading	Additive	Time	Temp.	Yield[a]
1	Triple balloon	10 mol%	-	48 h	rt	Incomplete conversion
2	Triple balloon	10 mol%	-	24 h	40 °C	73% **(*S*)-147**
3	Triple balloon	14 mol%	Et_3N (1.5 equiv.)	48 h	rt	Mixture
4	Triple balloon	14 mol%	Et_3N (24 equiv.)	48 h	rt	Mixture
5	Triple balloon	10 mol%	AcOH (2.2 equiv.)	24 h	rt	>99% **(*S*)-147**
6	Gas bag [b]	14 mol%	Et_3N (10 equiv.)	30	rt	90% **(*S*)-140**

[a] Yields of isolated products. [b] H_2 gas was bubbled through the reaction mixture for the stated time. [c] The gas bag was purchased from Sigma Aldrich with a capacity of 1 gallon.

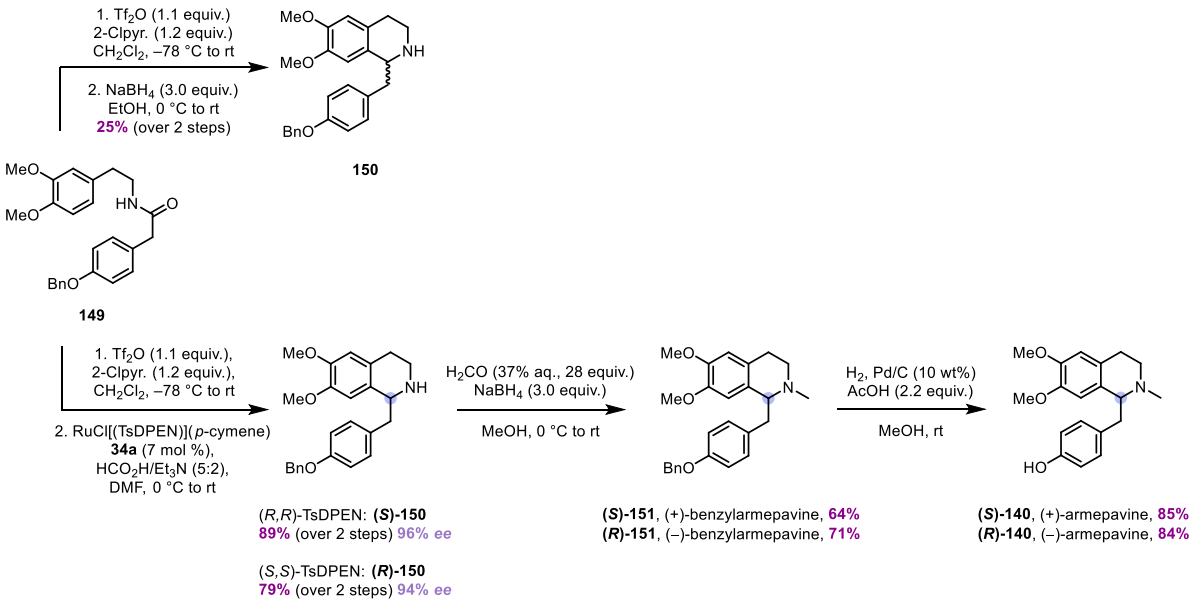
Table 3.3. Optimisation of the dehalogenation/PMB deprotection reaction.

For comparison of the overall efficiency of the route, it was decided that phenols **(*S*)-140** and **(*R*)-140** should also be synthesised from the precursor amide. This was formed from carboxylic acid **144** *via* an amide bond formation and subsequent benzylation of the phenol in 65% yield over two steps (**Scheme 3.12**).



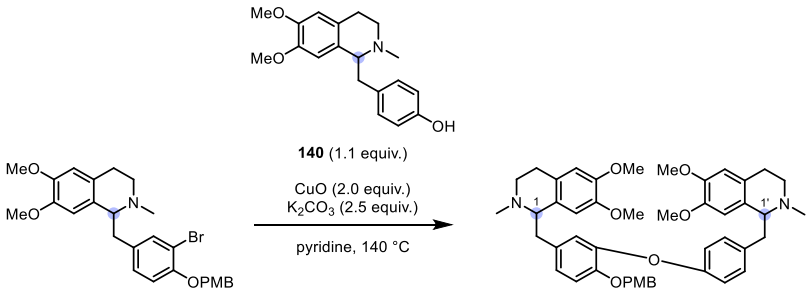
Scheme 3.12. Synthesis of the precursor amide **149**.

With key amide **149** in hand, the BN cyclisation/Noyori's ATH sequence was performed to obtain **(*S*)-150** and **(*R*)-150** in good yields (89% and 79% respectively) and high enantiopurity (96% *ee* and 94% *ee* respectively). *N*-Methylation of the secondary amines using reductive alkylation conditions proceeded smoothly to afford **(*S*)-151** and **(*R*)-151** in 64% and 71% yield respectively. Finally, benzyl-deprotection using acidic hydrogenolysis conditions afforded the desired phenolic BIs (+)-armepavine (**(*S*)-140**) in 93% yield and (–)-armepavine (**(*R*)-140**) in 90% yield (**Scheme 3.13**).



Scheme 3.13. Synthesis of BIs **(*S*)-140** and **(*R*)-140** from amide **149**.

With the coupling partners in hand, the synthesis of all diastereomers of BBI **152** was performed as illustrated in **Table 3.4**. The phenolic BIs **(*S*)-140** and **(*R*)-140** obtained *via* the second route from amide **149** were used in the Ullmann couplings due to their superior enantiopurity (96% and 94% *ee vs* 92% *ee*). Acyclic BBIs **152** were obtained in 25 – 37% yield, results similar to those obtained earlier for the same reason: the purity of these products was prioritised over the quantity isolated during the challenging purification process. Due to the complexity of the ^{1}H NMR spectra of the crude reaction mixtures, a *dr* could not be established. In the absence of HPLC or SFC traces, the enantiomeric ratio (*er*) of BBIs **152** were estimated statistically to be >99.9:0.1.



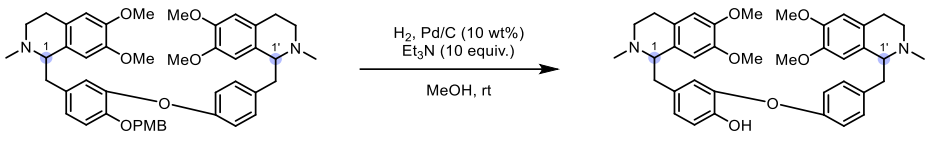
141 **152**

Entry	Bromide 141	Phenol 140[b]	BBI 152	Yield[a]
1	(*S*)-**141**	(*S*)-**140**	(*1S,1'S*)-**152**	37%
2	(*S*)-**141**	(*R*)-**140**	(*1R,1'S*)-**152**	29%
3	(*R*)-**141**	(*S*)-**140**	(*1S,1'R*)-**152**	25%
4	(*R*)-**141**	(*R*)-**140**	(*1R,1'R*)-**152**	25%

[a] Yields of isolated products. [b] BIs obtained from amide **149**.

Table 3.4. Ullmann coupling of phenolic BIs **140** to bromo-BIs **141**.

Deprotection of acyclic BBI **(*R,R*)-152** using the conditions optimised earlier for the cleavage of the PMB group afforded (–)-dauricine in 56% yield (**Table 3.5**, Entry 4). (+)-Dauricine was afforded in 65% yield by subjecting **(*S,S*)-152** to identical reaction conditions (Entry 1). Diastereomers **(*R,S*)-139** and **(*S,R*)-139** were isolated in 60% (Entry 2) and 54% yield respectively (Entry 3).



152 139

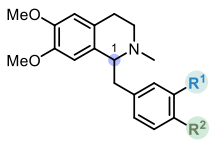
Entry	BBI 152	BBI 139	Yield[a]
1	(*1S,1'S*)-**152**	(*1S,1'S*)-**139**	65%
2	(*1R,1'S*)-**152**	(*1R,1'S*)-**139**	60%
3	(*1S,1'R*)-**152**	(*1S,1'R*)-**139**	54%
4	(*1R,1'R*)-**152**	(*1R,1'R*)-**139**	56%

[a] Yields of isolated products.

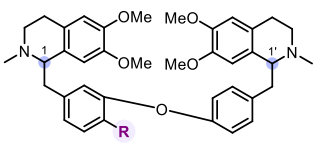
Table 3.5. Final PMB-deprotection affording BBIs **139**.

In terms of the overall yield, the two strategies present similar results. The first route whereby the phenolic BI **(*S*)-140** is synthesised from the bromo-BI **(*S*)-141** *via* hydrogenolysis afforded (+)-dauricine in 11% overall yield. In this case, the longest linear sequence and total number of steps are equal (9 steps). On the other hand, the second strategy where the BIs are made individually from the corresponding amides afforded (+)-dauricine in 12% overall yield. While the LLS is one step shorter, the total number of steps increases to 14. The only minimal advantage offered by the second route is the slightly higher enantiomeric purity obtained (96% and 94% *vs* 92% *ee*). However, this could be improved by further optimising the ATH step.

In summary, four natural and ten non-natural BIs were synthesised together with five natural and seven non-natural BBI alkaloids for anti-parasitic evaluation (**Scheme 3.14**).



R^1 = H, R^2 = Br: (*S*)-**51**, (*R*)-**51**
R^1 = OBn, R^2 = OMe: (*S*)-**138**, (*R*)-**138**
R^1 = OH, R^2 = OMe: (+)-laudanidine, (*S*)-**49**
R^1 = OH, R^2 = OMe: (–)-laudanidine, (*R*)-**49**
R^1 = Br, R^2 = OPMB: (*S*)-**141**, (*R*)-**141**
R^1 = H, R^2 = OPMB: (*S*)-**147**, (*R*)-**147**
R^1 = H, R^2 = OBn: (*S*)-**151**, (*R*)-**151**
R^1 = H, R^2 = OH: (+)-armepavine, (*S*)-**140**
R^1 = H, R^2 = OH: (–)-armepavine, (*R*)-**140**



R = OMe, (+)-*O*-methylthalibrine, (*1S,1'S*)-**52**
(–)-*O*-methyldauricine, (*1R,1'R*)-**52**
(–)-*O,O'*-dimethylgrisabine, (*1S,1'R*)-**52**
(*1R,1'S*)-**52**
R = OPMB, (*1S,1'S*)-**152**
(*1R,1'S*)-**152**
(*1S,1'R*)-**152**
(*1R,1'R*)-**152**
R = OH, (+)-dauricine, (*1S,1'S*)-**139**
(*1R,1'S*)-**139**
(*1S,1'R*)-**139**
(–)-dauricine, (*1R,1'R*)-**139**

Scheme 3.14. BI and BBI alkaloids prepared for anti-parasitic evaluation.

4

Evaluation of Anti-parasitic Activity

Preliminary studies of two BIs and one acyclic BBI were performed against *L. mexicana* promastigotes in Dr R. Wheeler's laboratory in the Nuffield Department of Medicine, University of Oxford in order to evaluate whether these classes of alkaloids demonstrate appreciable anti-leishmanial activity. *L. mexicana* is known to give rise to CL, a milder form of the disease, but debilitating nonetheless.[12] Following positive results, the BIs and acyclic BBIs presented in Chapter 3 were sent to our collaborator Prof. A. Tempone at the Instituto Adolfo Lutz, São Paolo, Brazil, for a more extensive biological evaluation. This was done against *L. infantum* as it is one of the three strains that gives rise to VL.[11] The IC_{50} values against both *L. infantum* promastigotes and amastigotes as well as against *T. cruzi* trypomastigotes and amastigotes were determined. Cytotoxicity against mammalian NCTC fibroblasts (L929 cells) was also evaluated enabling access to CC_{50} values and determination of the selectivity indices (SIs). This chapter will describe the assays and imaging performed by this author, whereas the data obtained from the

collaborators (IC_{50}, CC_{50} and SI values) will be used for discussing the structure-activity-relationship. Finally, an *in silico* analysis of selected compounds was performed to assess their physicochemical properties and their suitability as potential drugs. The effects on the anti-parasitic activity arising from variation of the C-ring substituents and stereochemistry at C-1 and C-1′ respectively are discussed.

4.1 Preliminary Studies of Anti-leishmanial Activity

Since the testing of the compounds against *Leishmania* amastigotes is both time-consuming and requires animal sacrifice, it was decided that a preliminary evaluation should be done to assess whether any activity is observed for representative examples of the BIs and linear BBIs. Three compounds were chosen: a BI featuring one C-ring substituent, a BI with two C-ring substituents and one linear BBI.

The simplest assay that verifies whether these compounds present any parasiticidal activity is a growth study experiment. This validates whether treatment with a compound of interest affects the growth of the cells. The assay is set up by treating a Cas9T7 *L. mexicana* promastigote culture (1×10^6 cells mL^{-1}) in 5 mL of M199 medium with 5 µL of compound in DMSO (final carryover DMSO 0.1%). The cells are then incubated at 28 °C for 24 h, and the culture density measured using a haemocytometer. The growth study experiments were performed at three different concentrations for each compound, in triplicate, with the results plotted in graphs B, D and F (**Figure 4.1**).

A control experiment (no solvent) was performed to ensure that the culture grows as expected and any changes in proliferation pattern arise from the treatments with the compound. A second control was performed by treating the cells with DMSO (0.1%) alone to validate that the observed activity is not affected by the solvent.

Cultures of *L. mexicana* promastigotes grow logarithmically for densities under 1×10^7 cells mL^{-1}, doubling their numbers in 7.1 h, so that a growth factor ~8-9 is expected for untreated controls.[111]

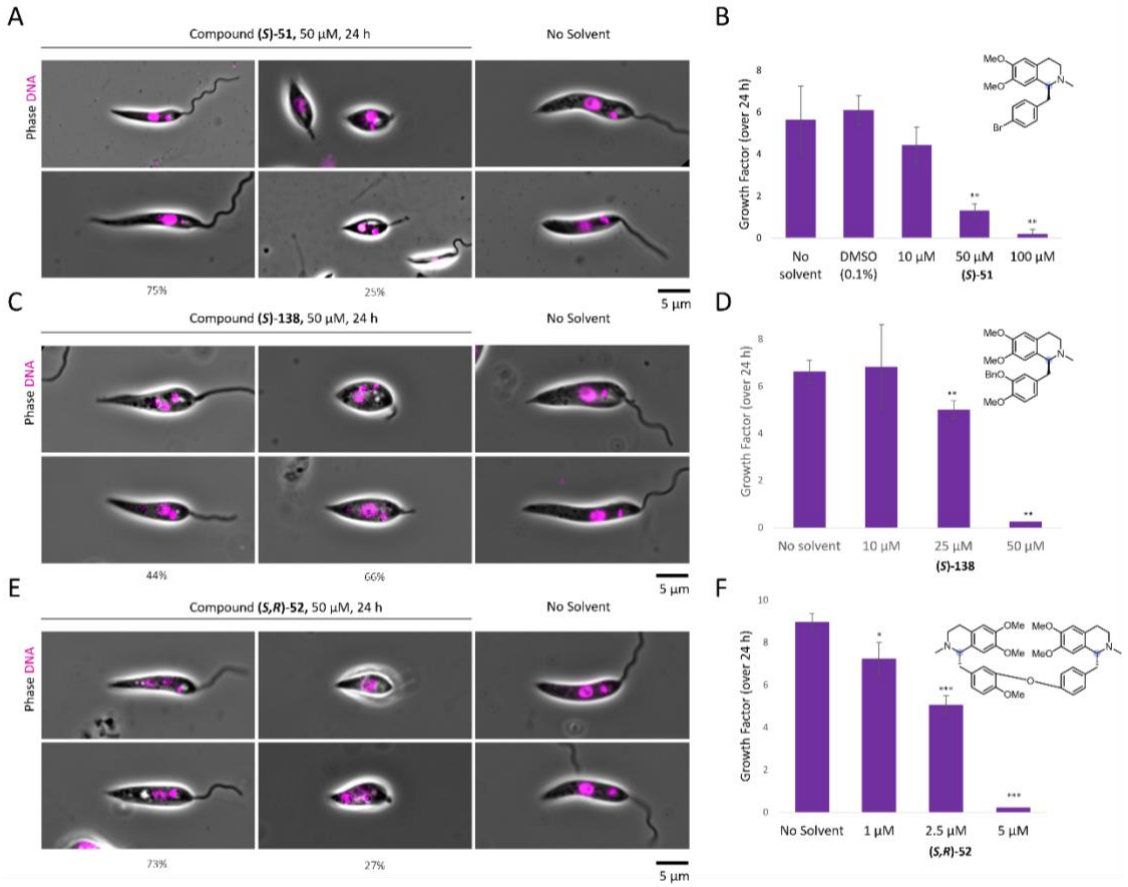


Figure 4.1. A, C, E Representative light microscopy images from >100 cells (**C**: >80 cells) showing morphological changes (short flagellum, more spherical cell body), **A**: n = 2 repeats; **B, C**: n = 1. **B, D, F** Compound structure and 24 h growth factor, mean ± SD from n = 3. Statistical significance derived from a two-tailed T-test: * for $p \leq 0.05$, ** for $p \leq 0.01$ and *** for $p \leq 0.001$.

Compound **(*S*)-51** (**Figure 4.1B**) was tested at concentrations of 10, 50 and 100 µM. The control showed normal growth of the culture, and the minor difference observed for the DMSO control was statistically insignificant. Treatment at 10 µM resulted in a slower growth rate, although the difference was too small to be considered meaningful. The IC_{50} value can thus be estimated to be between 10 and 50 µM, with higher concentrations

having a significant impact on the growth of the cells. At 100 μM almost no growth was observed over 24 h. Comparable values were obtained for compound **(*S*)-138** (**Figure 4.1D**) with lower concentrations (10 μM) having little effect and 50 μM sufficient to almost impede cell growth completely. The BIs thus present modest activity against *L. mexicana* promastigotes, and while they are not estimated to be sufficiently potent to serve as hit compounds, the results were encouraging. The third compound evaluated was BBI **(*S,R*)-52** which showed the ability to reduce the proliferation rate at concentrations as low as 1 μM, with 5 μM being sufficient to achieve almost no growth over the span of 24 h (**Figure 4.1F**). The preliminary results obtained for **(*S,R*)-52** indicated that the activity of linear BBIs could be comparable to that of macrocyclic BBIs.

During cell counting, it was observed that upon treatment with higher concentrations (50 – 100 μM) of **(*S*)-51**, the few cells that remained alive were less motile and possessed an abnormal cell morphology. This was further investigated by imaging using light microscopy. The treated cultures were pelleted by centrifugation and washed with phosphate buffered saline (PBS ×3) to improve glass slide adhesion and increase cell density. In order to visualise the DNA within the cells, a nucleic acid stain (Hoescht 33342) was used in the first wash. The resuspended pellet (in PBS) was then placed on a microscope slide and imaging was performed immediately.

Typically, promastigotes will have an elongated shape with a long flagellum and their DNA (stained in magenta, **Figure 4.1A, C, E**) will be observed in both the nucleus (positioned in the centre of the cell) and the kinetoplast (posterior position relative to the nucleus). When exposed to BI **(*S*)-51**, the cells became more spherical in shape and their flagella shortened significantly (**Figure 4.1A**, middle). At 50 μM, this effect was observed in almost 30% of the population with the rest of the cells having a normal cell morphology. The same effect was observed for BI **(*S*)-138** and a larger share of the

population (66%) was observed to suffer from these effects (**Figure 4.1C**). In the case of BBI **(*S,R*)-52**, the cells suffered from the same shortening of the flagellum. For these cells, the DNA stain looks highly irregular with no clear definition of the DNA-containing organelles (**Figure 4.1E**). These effects could indicate that the compounds may elicit their activity by interfering with the cell cycle, and while various BI and BBI alkaloids have been shown to be able to bind DNA,[112, 113] a more thorough investigation would be required to assess whether this is their mechanism of action.

4.2 Anti-leishmanial Activity and SAR

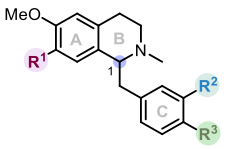
Since the anti-leishmanial activity of northalrugosidine (**13**), the initial inspiration of this project, was reported only from *in vitro* studies, all compounds were tested against *L. infantum* promastigotes to allow for comparison of the obtained IC_{50} values. However, a phenotypic assay is better suited for meaningful results. The assay involves infecting mammalian macrophages with the parasite followed by treatment with the compound of choice, thus allowing the determination of IC_{50} values for intracellular *L. infantum* amastigotes.

Mammalian cytotoxicity was evaluated using NCTC fibroblasts, allowing determination of CC_{50} and selectivity index (SI) values which gives a measure of compound specificity for the parasite over the host. This assay is important to assess both the intrinsic toxicity of the compounds as well as to ensure that the observed parasiticidal effect is afforded by the compound and not by the host cell becoming compromised. Low mammalian cytotoxicity is also desirable to avoid undesired side effects to the host.

4.2.1 BI-type Compounds

Table 4.1 shows the activity against *L. infantum* promastigotes of all BI alkaloids tested. Out of the fifteen compounds tested, ten (Entries 4–10 and 13–15) showed good activity (<10 μM). The different configuration at C-1 influences the activity, with a general trend observed for (*R*)-enantiomers to be two to three times more active than the corresponding (*S*)-enantiomer. The exception is the anomalous result obtained for (–)-armepavine (**(*R*)-140**) (Entry 4), which is nearly 10 times more active than its enantiomer (Entry 3). With respect to the substitution pattern on the C-ring, larger hydrophobic groups such as aromatic rings are preferred either at R^2 or R^3 such as in entries 5–10 and 13–15. Small hydrophilic moieties such as hydroxyl groups lead to modest or poor activity (Entries 3, 11 and 12), with the exception of unusual compound **(*R*)-140** (Entry 4). Similar IC_{50} values are observed when R^3 is either a benzyl or PMB group suggesting that further derivatisation of that aromatic ring could be tolerated. The best activity was observed for (–)-benzylarmepavine (Entry 6) with an IC_{50} of 1.10 ± 0.49 μM.

Most compounds are significantly cytotoxic, apart from the phenolic compounds (Entries 3,4,11 and 12, CC_{50} >200 μM). The stereochemistry also impacts the toxicity of the compounds with (*S*)-enantiomers being more toxic than (*R*)-enantiomers. When taking this parameter into account, compound **(*R*)-140** becomes the best hit of this series as it has potent activity, low associated cytotoxicity, and an SI of >42. These results are comparable to those reported for northalrugosidine (IC_{50} of 0.28 μM against *L. donovani* promastigotes, SI of 29). However, since the amastigote is the clinically relevant form that causes disease in humans, SIs are typically calculated using the IC_{50} values for the compounds obtained against the amastigote form rather than the promastigote.



Entry	Compound	(C-1)	R^1	R^2	R^3	*L. infantum* promastigotes IC_{50} (µM ± SD)	CC_{50} (µM ± SD)	SI
1	**(*S*)-51**	(*1S*)	OMe	H	Br	18.40 ± 2.06	42.49 ± 1.48	2.3
2	**(*R*)-51**	(*1R*)	OMe	H	Br	15.53 ± 5.75	86.75 ± 2.91	5.6
3	**(*S*)-140** (+)-armepavine	(*1S*)	OMe	H	OH	36.19 ± 5.15	>200	>5.5
4	**(*R*)-140** (–)-armepavine	(*1R*)	OMe	H	OH	4.76 ± 0.78	>200	>42
5	**(*S*)-151** (+)-benzylarmepavine	(*1S*)	OMe	H	OBn	3.72 ± 0.15	6.64 ± 1.45	1.8
6	**(*R*)-151** (–)-benzylarmepavine	(*1R*)	OMe	H	OBn	1.10 ± 0.49	28.10 ± 0.52	26
7	**(*S*)-147**	(*1S*)	OMe	H	OPMB	4.79 ± 0.24	5.80 ± 0.51	1.2
8	**(*R*)-147**	(*1R*)	OMe	H	OPMB	2.35 ± 0.85	28.14 ± 5.47	12
9	**(*S*)-141**	(*1S*)	OMe	Br	OPMB	5.22 ± 1.34	6.29 ± 2.30	1.2
10	**(*R*)-141**	(*1R*)	OMe	Br	OPMB	3.53 ± 1.20	13.38 ± 1.28	3.8
11	**(*S*)-49** (+)-laudanidine	(*1S*)	OMe	OH	OMe	95.40 ± 2.00	>200	>2.1
12	**(*R*)-49** (–)-laudanidine	(*1R*)	OMe	OH	OMe	30.20 ± 4.80	>200	>6.6
13	**(*S*)-138** (+)-benzyllaudanidine	(*1S*)	OMe	OBn	OMe	8.60 ± 0.80	47.1 ± 11.20	5.5
14	**(*R*)-138** (–)-benzyllaudanidine	(*1R*)	OMe	OBn	OMe	3.30 ± 1.60	57.3 ± 3.30	17
15	**(*S*)-114**	(*1S*)	Br	X	OMe	3.15 ± 1.17	45.4 ± 4.60	14

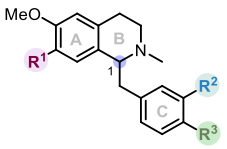
SD = standard deviation. ND = not determined. X = O-4-CO_2Me-(C_6H_4). SI = CC_{50} / IC_{50} (promastigotes).

Table 4.1. Activity of BI alkaloids against *L. infantum* promastigotes and their associated toxicity against mammalian cells. Data supplied by collaborators at Instituto Adolfo Lutz.

The SAR resulting from the assay against *L. infantum* promastigotes bears some significant differences to the data obtained for the phenotypic assay against intracellular amastigotes (**Table 4.2**). In this latter assay, seven compounds are not active and only four (Entries 5,6, 8 and 15) present good anti-parasitic activity (<10 μM). All phenolic compounds tested are not active against the amastigote form including (–)-armepavine (**(*R*)-140**), the previous best hit of the series against promastigotes. The configuration at C-1 continues to influence the activity, however no obvious trend for one enantiomer being more active than the other is observed where both are active. Moreover, an unusual result is obtained for highly active compound **(*R*)-147** (Entry 8) as its enantiomer **(*S*)-147** is not active. In the case of compounds **(*S*)-51**, **(*R*)-51**, **(*S*)-151** and **(*R*)-151** the (*S*) enantiomer is more toxic to mammalian cells. An interesting result was obtained for compound **(*S*)-151** (Entry 5) that shows an SI <1. This arose as the macrophages presented a different susceptibility to the compound in comparison to the NCTC cells. While the compound is toxic to both types of cells, it is seemingly less so to the macrophages.

Taking into account both the anti-parasitic ability as well as the associated mammalian toxicity, compound **(*S*)-114** (Entry 15) is the lead compound of this series. However, in comparison to the current clinically used drug miltefosine, it is a poor drug candidate. The activity is suboptimal, and the compound is significantly toxic (SI of 4.7 compared to 18 for miltefosine).

While some compounds possess the required activity (< 10 μM in a phenotypic assay) to be considered a hit by the DND*i* guidelines (as discussed in **Section 1.2**), the high cytotoxicity (SI < 10) unfortunately renders them unsuitable to be progressed to the next stage of drug discovery.



Entry	Compound	(C-1)	R^1	R^2	R^3	*L. infantum* amastigotes IC_{50} (µM ± SD)	SI	CC_{50} (µM ± SD)
1	**(*S*)-51**	(*1S*)	OMe	H	Br	13.27 ± 0.86	3.2	42.49 ± 1.48
2	**(*R*)-51**	(*1R*)	OMe	H	Br	23.41 ± 3.41	3.7	86.75 ± 2.91
3	**(*S*)-140** (+)-armepavine	(*1S*)	OMe	H	OH	NA	ND	>200
4	**(*R*)-140** (–)-armepavine	(*1R*)	OMe	H	OH	NA	ND	>200
5	**(*S*)-151** (+)-benzylarmepavine	(*1S*)	OMe	H	OBn	7.46 ± 2.17	<1	6.64 ± 1.45
6	**(*R*)-151** (–)-benzylarmepavine	(*1R*)	OMe	H	OBn	9.35 ± 0.50	3.0	28.10 ± 0.52
7	**(*S*)-147**	(*1S*)	OMe	H	OPMB	NA	ND	5.80 ± 0.51
8	**(*R*)-147**	(*1R*)	OMe	H	OPMB	9.33 ± 0.39	3.0	28.14 ± 5.47
9	**(*S*)-141**	(*1S*)	OMe	Br	OPMB	NA	ND	6.29 ± 2.30
10	**(*R*)-141**	(*1R*)	OMe	Br	OPMB	NA	ND	13.38 ± 1.28
11	**(*S*)-49** (+)-laudanidine	(*1S*)	OMe	OH	OMe	NA	ND	>200
12	**(*R*)-49** (–)-laudanidine	(*1R*)	OMe	OH	OMe	NA	ND	>200
13	**(*S*)-138** (+)-benzyllaudanidine	(*1S*)	OMe	OBn	OMe	26.7 ± 2.0	1.8	47.1 ± 11.2
14	**(*R*)-138** (–)-benzyllaudanidine	(*1R*)	OMe	OBn	OMe	13.1 ± 0.8	4.4	57.3 ± 3.3
15	**(*S*)-114**	(*1S*)	Br	X	OMe	9.70 ± 0.57	4.7	45.4 ± 4.6
16	**Miltefosine**	-	-	-	-	6.5 ± 3.0	18	119.7 ± 4.2

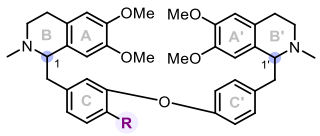
SD = standard deviation. SI = selectivity index; NA = not active; ND = not determined;
X = O-4-CO_2Me-(C_6H_4). SI = CC_{50} / IC_{50} (amastigotes).

Table 4.2. Activity of BI-type compounds against *L. infantum* amastigotes, Miltefosine used as a positive control. Data supplied by collaborators at Instituto Adolfo Lutz.

4.2.3 Linear BBIs

In terms of the BBIs tested, the direct activity on the cells is better when the R substituent is a methoxy group, which results in sub-micromolar activity (**Table 4.3**, Entries 1–4). A similar behaviour against promastigotes is observed when the methoxy substituent is replaced by a PMB group (Entries 9–12). Unfortunately, neither the methoxy nor the PMB substituted BBIs were active against intracellular amastigotes. This was most likely a result of the high associated toxicity of the compounds exerted on the macrophages at the tested concentration, effectively killing the host cell before the compound reaches the parasite. Lower concentrations that did not result in the macrophages becoming compromised were unsuccessful at inhibiting the parasite. While minor differences can be seen for the different diastereomers, the discrepancy is negligible and no obvious trend for one configuration consistently being more successful was observed.

The only compounds active against the amastigote form were (–)-dauricine **(*R,R*)-139** and its diastereomer **(*S,R*)-139**, possibly indicating that an (*R*) configuration is required at C-1′. Both compounds are however highly toxic, as demonstrated by the obtained CC_{50} values, with (–)-dauricine being twice as toxic as diastereomer **(*S,R*)-139**. This results in **(*S,R*)-139** being the lead BBI compound against *L. infantum* amastigotes. Unfortunately, as it was the case with the BI-type compounds, the high toxicity (SI <10) renders these compounds unsuitable as hits for drug discovery despite their potent anti-leishmanial activity.



Entry	Compound	(C-1,C-1')	R	*L. infantum* IC_{50} (µM ± SD)		SI	CC_{50} (µM ± SD)
				Promastigotes	Amastigotes		
1	**(*R*,*S*)-52**	(*1R,1'S*)	OMe	0.56 ± 0.07	NA	ND	7.29 ± 0.68
2	**(*S*,*R*)-52** (–)-*O,O'*-dimethylgrisabine	(*1S,1'R*)	OMe	0.76 ± 0.01	NA	ND	10.18 ± 1.44
3	**(*R*,*R*)-52** (–)-*O*-methyldauricine	(*1R,1'R*)	OMe	0.69 ± 0.08	NA	ND	11.35 ± 4.81
4	**(*S*,*S*)-52** (+)-*O*-methylthalibrine	(*1S,1'S*)	OMe	0.74 ± 0.01	NA	ND	11.42 ± 0.18
5	**(*R*,*S*)-139**	(*1R,1'S*)	OH	3.24 ± 1.74	NA	ND	13.31 ± 1.64
6	**(*S*,*R*)-139**	(*1S,1'R*)	OH	5.67 ± 1.31	3.57 ± 0.25	4.4	15.59 ± 1.55
7	**(*R*,*R*)-139** (–)-dauricine	(*1R,1'R*)	OH	3.15 ± 1.11	3.74 ± 0.62	1.9	6.97 ± 0.96
8	**(*S*,*S*)-139** (+)-dauricine	(*1S,1'S*)	OH	5.45 ± 0.56	NA	ND	15.87 ± 0.77
9	**(*R*,*S*)-152**	(*1R,1'S*)	OPMB	0.40 ± 0.21	NA	ND	2.70 ± 1.64
10	**(*S*,*R*)-152**	(*1S,1'R*)	OPMB	0.67 ± 0.09	NA	ND	4.68 ± 1.69
11	**(*R*,*R*)-152**	(*1R,1'R*)	OPMB	1.12 ± 0.51	NA	ND	13.90 ± 1.60
12	**(*S*,*S*)-152**	(*1S,1'S*)	OPMB	1.10 ± 0.49	NA	ND	20.81 ± 5.43
13	**Miltefosine**	-	-	ND	6.5 ± 3.0	18	119.7 ± 4.2

SD = standard deviation. SI = selectivity index. NA = not active. ND = not determined. SI = CC_{50} / IC_{50} (amastigotes).

Table 4.3. Anti-leishmanial activity of linear BBIs. Data supplied by collaborators at Instituto Adolfo Lutz.

4.3 Anti-trypanosomal Activity and SAR

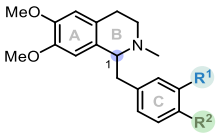
In the case of *T. cruzi*, both the bloodstream trypomastigotes and intracellular amastigotes are clinically relevant, particularly in the acute phase of the disease when the levels of extracellular trypomastigotes in the blood are high. For this reason, the BI and BBI libraries were tested against both forms of the parasite. The observed structure-cytotoxicity relationship was already discussed for the BI alkaloids (**Section 4.2.1**) and BBIs (**Section 4.2.2**) and as such the values will only be referred to when describing the potential of a certain molecule to become a hit compound.

4.3.1 BI-type Compounds

In terms of activity against extracellular trypomastigotes, no enantiomer showed consistently superior activity than the other. Phenolic compounds showed very poor or no activity at all (**Table 4.4**, Entries 3, 4, 11 and 12). Sterically demanding substituents such as benzyl ethers at R^1 are the least well tolerated (Entries 13 and 14), displaying the worst activity (except for the phenolic compounds). Only two compounds present IC_{50} values below 10 μM (Entries 5, 10) with no major difference in their activity and both are significantly toxic to mammalian cells.

Analysis of the results obtained for the *T. cruzi* amastigote assay revealed seven compounds with good activity (**Table 4.4**, Entries 5, 6, 9, 11, 12, 14 and 15), however more than half are marred by high cytotoxicity. An anomalous result was obtained for compound **(*R*)-141** (Entry 10) showing no activity while its enantiomer **(*S*)-141** is a potent agent. Nonetheless, (+)-laudanidine, (–)-laudanidine and (–)-benzyllaudanidine show promising results that fit the DND*i* criteria for what constitutes a hit against Chagas Disease. All three compounds exhibit inhibitory activity below 10 μM, more than a ten-fold SI, and can be synthesised in fewer than eight steps.[56] (–)-Laudanidine **(*R*)-49** displays twice the selectivity of currently used drug benznidazole. Unfortunately, these compounds exhibit poor activity against the extracellular trypomastigotes rendering them less-than-ideal drug candidates. Since the direct activity on the cells is poor, it is possible that active metabolites are formed intracellularly, explaining the potency observed in the amastigote assay. Alternatively, this behaviour could also be explained by the compound inducing an immune response in the macrophages, thus indirectly aiding the host to fight off the infection. However, no evidence can be presented in support of either of these statements and more studies are required to justify this behaviour. It would be worth investigating whether maintaining the hydroxyl group at R^1, but exchanging the R^2

methoxy group for a bulkier aromatic ring improves the anti-trypomastigote activity whilst maintaining the potent anti-amastigote activity and the low cytotoxicity.



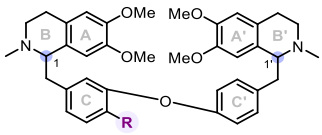
Entry	Compound	(C-1)	R^1	R^2	*T. cruzi* IC_{50} (µM ± SD)		SI
					Trypomastigotes	Amastigotes	
1	**(*S*)-51**	(*1S*)	H	Br	14.40 ± 5.47	25.06 ± 3.14	1.7
2	**(*R*)-51**	(*1R*)	H	Br	28.27 ± 11.7	31.77 ± 4.32	2.7
3	**(*S*)-140** (+)-armepavine	(*1S*)	H	OH	123.60 ± 2.26	NA	ND
4	**(*R*)-140** (–)-armepavine	(*1R*)	H	OH	106.75 ± 1.77	NA	ND
5	**(*S*)-151** (+)-benzylarmepavine	(*1S*)	H	OBn	7.57 ± 0.37	3.24 ± 0.47	2.0
6	**(*R*)-151** (–)-benzylarmepavine	(*1R*)	H	OBn	16.52 ± 6.08	6.21 ± 5.89	4.5
7	**(*S*)-147**	(*1S*)	H	OPMB	20.40 ± 11.43	NA	ND
8	**(*R*)-147**	(*1R*)	H	OPMB	25.30 ± 2.12	NA	ND
9	**(*S*)-141**	(*1S*)	Br	OPMB	11.07 ± 1.73	3.27 ± 0.01	1.9
10	**(*R*)-141**	(*1R*)	Br	OPMB	8.54 ± 3.05	NA	ND
11	**(*S*)-49** (+)-laudanidine	(*1S*)	OH	OMe	>150	5.90 ± 0.94	>34
12	**(*R*)-49** (–)-laudanidine	(*1R*)	OH	OMe	>150	2.60 ± 0.31	>77
13	**(*S*)-138** (+)-benzyllaudanidine	(*1S*)	OBn	OMe	57.68 2.32	12.15 ± 0.54	3.9
14	**(*R*)-138** (–)-benzyllaudanidine	(*1R*)	OBn	OMe	72.31 ± 2.99	4.27 ± 0.41	13
15	Benznidazole	-	-	-	12.81 ± 0.74	5.00 ± 1.53	>40

SD = standard deviation. SI = selectivity index. NA = not active. ND = not determined. SI = CC_{50} / IC_{50} (amastigotes).

Table 4.4. Anti-trypanosomal activity of BI-type compounds. Data supplied by collaborators at Instituto Adolfo Lutz.

4.3.2 Linear BBIs

Similar to the anti-leishmanial profile, the acyclic BBIs show promising inhibition against extracellular trypomastigotes (**Table 4.5**). However, nearly 60% of the compounds tested are not active against the intracellular amastigotes. The BBIs that display an anti-trypanosomal effect are more potent than the clinically used drug benznidazole, however significantly more toxic to the mammalian cells. (–)-*O*-Methyldauricine (Entry 3) was the best compound of this series, yet the low selectivity index renders it unfit to be used as a hit compound in drug discovery.



Entry	Compound	(C-1, C-1′)	R^1	*T. cruzi* IC_{50} (µM ± SD)		SI
				Trypomastigotes	Amastigotes	
1	**(*R,S*)-52**	(*1R, 1′S*)	OMe	6.51 ± 2.09	NA	ND
2	**(*S,R*)-52** (–)-*O,O′*-dimethylgrisabine	(*1S, 1′R*)	OMe	2.57 ± 2.91	2.15 ± 0.68	4.7
3	**(*R,R*)-52** (–)-*O*-methyldauricine	(*1R, 1′R*)	OMe	7.22 ± 0.60	1.45 ± 0.15	7.8
4	**(*S,S*)-52** (+)-*O*-methylthalibrine	(*1S, 1′S*)	OMe	3.68 ± 3.61	NA	ND
5	**(*R,S*)-139**	(*1R, 1′S*)	OH	10.10 ± 3.92	2.77 ± 0.62	4.8
6	**(*S,R*)-139**	(*1S, 1′R*)	OH	4.16 ± 4.76	4.35 ± 0.39	3.6
7	**(*R,R*)-139** (–)-dauricine	(*1R, 1′R*)	OH	3.73 ± 2.91	NA	ND
8	**(*S,S*)-139** (+)-dauricine	(*1S, 1′S*)	OH	5.13 ± 4.82	2.27 ± 1.06	7.0
9	**(*R,S*)-152**	(*1R, 1′S*)	OPMB	1.28 ± 0.73	NA	ND
10	**(*S,R*)-152**	(*1S, 1′R*)	OPMB	1.68 ± 0.33	NA	ND
11	**(*R,R*)-152**	(*1R, 1′R*)	OPMB	7.31 ± 1.52	NA	ND
12	**(*S,S*)-152**	(*1S, 1′S*)	OPMB	5.58 ± 2.08	NA	ND
13	Benznidazole	-	-	12.81 ± 0.74	5.00 ± 1.53	>40

SD = standard deviation. SI = selectivity index. NA = not active. ND = not determined. SI = CC_{50} / IC_{50} (amastigotes).

Table 4.5. Anti-trypanosomal activity of linear BBIs. Data supplied by collaborators at Instituto Adolfo Lutz.

4.4 *In silico* Prediction of Pharmacokinetic Properties

High potency and low toxicity are not the only required characteristics for a drug to progress in the drug discovery and development process. The pharmacokinetic properties, often referred to as Absorption, Distribution, Metabolism and Excretion (ADME), refer to a group of parameters that evaluate what happens to the molecule within the organism. While they can be experimentally evaluated individually, computer models have been created to allow early-on prediction of these parameters. These models are particularly useful for SAR studies where the libraries are vast but the access to compounds is limited. Moreover, they have been shown to significantly reduce the number of compounds that fail in the clinical trial stages of drug development due to suboptimal pharmacokinetic profiles.[114]

According to the DNDi's criteria for a hit or lead compounds, the *in silico* DMPK profile should follow Lipinski's rules and is useful in prioritising compounds with drug-like profiles, however it is not used as a definitive selection criterion.[56]

Investigating these parameters for the lead BI and BBI compounds tested against each parasite could be used in the design of future analogues or explain certain shortcomings. As such, the most potent and least cytotoxic BI and BBI compounds were chosen for each disease and submitted to *in silico* analysis using the SwissADME® web tool;[114] selected results are presented in **Table 4.6**. For a rapid evaluation, the web tool generates a 'Bioavailability Radar'. Providing the radar plot of a molecule falls completely within the pink area, the compound is considered drug-like. For a visual comparison of where the candidates fall short in terms of oral bioavailability, a radar plot is provided for each compound (**Figure 4.2**).

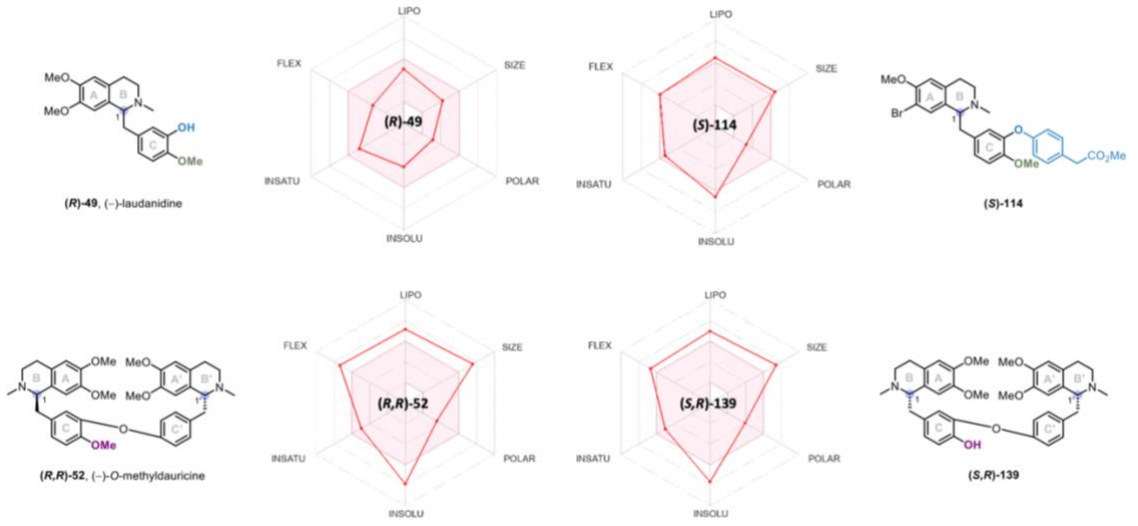


Figure 4.2. Bioavailability radars for compounds **(*R*)-49, (*S*)-114, (*R,R*)-52 and (*S,R*)-139** as generated by SwissADME®.[114]

The first challenge that may be encountered with all four compounds is their high basicity. Under physiological conditions (acidic pH of stomach and GI tract[115]), these compounds would get protonated and become charged molecules leading to reduced cell permeability and metabolic instability.

BI **(*S*)-114** and BBIs **(*S,R*)-139** and **(*R,R*)-52** were shown to be poor drug candidates both due to their high toxicity as well as their pharmacokinetic profile. Characteristics such as a molecular weight greater than 500 g/mol that violates the Lipinski rules,[116] high lipophilicity and poor solubility decrease the oral bioavailability. Additionally, BI **(*S*)-114** was predicted to inhibit several cytochrome P450 enzymes (CYPs). This can be concerning as there are various possible implications resulting from CYP-inhibition.[117] These include for example altered pharmacokinetic properties as a consequence of decreased metabolism, adverse side effects due to the fact that CYPs are responsible for the metabolism of endogenous biomolecules such as hormones or fatty acids and drug-drug interactions.

On the other hand, (–)-laudanidine (**(*R*)-49**), besides the high potency against *T. cruzi* amastigotes and high SI, also shows a promising pharmacokinetic profile. The molecule is predicted to have good oral bioavailability based on the parameters evaluated. The saturation degree, polar surface area and lipophilicity fall within desired ranges and no similarities to pan-assay interference compounds were found. Minor concerns are posed by the basicity, moderate solubility and predicted inhibition of two CYP 450 enzymes. Nonetheless, the *in silico* analysis performed does not predict any major concerns or risks, thus making **(*R*)-49** the most promising candidate in our library.

	BI (*S*)-114	**BBI (*S,R*)-139**	**(–)-laudanidine (*R*)-49**	**(–)-*O*-methyldauricine (*R,R*)-52**
IC_{50} *L. infantum* (μM) [a]	9.70 ± 0.57	3.57 ± 0.25		
IC_{50} *T. cruzi* (μM) [a]			2.60 ± 0.31	1.45 ± 0.15
SI	4.7	4.4	>77	7.8
MW (g mol^{-1})	540.45	624.77	343.42	638.79
Fractions Csp^3	0.32	0.37	0.40	0.38
TPSA ($Å^2$)	57.23	72.86	51.16	61.86
LogP	5.20	5.56	2.95	5.84
Solubility Class	Poor	Poor	Moderate	Poor
GI Absorption	High	High	High	High
BBB permeant	Yes	No	Yes	No
CYP1A2 inhibitor	No	No	No	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	Yes	No	No	No
CYP2D6 inhibitor	Yes	No	Yes	No
CYP3A4 inhibitor	Yes	No	Yes	No
Lipinski violations	1	1	0	1
PAINS	0	0	0	0

IC_{50} and SI values refer to those obtained from the intracellular amastigote assays. SI = selectivity index (CC_{50} / IC_{50} amastigotes). MW = molecular weight. TPSA = topological polar surface area. GI = gastrointestinal. BBB = blood brain barrier. CYP = cytochrome P450. PAINS = pan assay interference compounds.

Table 4.6. Selected pharmacokinetic parameters predicted for lead compounds.

In conclusion, upon treatment of *L. mexicana* promastigotes with BIs **(*S*)-51** and **(S)-138** as well as BBI **(*S,R*)-52**, morphology changes become apparent, possibly indicating that these compounds interfere with the cell cycle of the parasite. In the case of BIs some SAR trends could be observed including the (*R*)-enantiomers being more active and having better CC_{50} profiles than the (*S*)-enantiomers. Nonetheless, despite the promising and potent activity of both BI and BBI alkaloids, most compounds were found to be significantly toxic to mammalian cells and non-selective against the parasites, thus rendering them unfit as drug leads according to the DND*i* criteria. The exception laid with the phenolic BIs which did not show any toxicity below 200 μM; unfortunately, these compounds were also not active against the clinically relevant amastigote form of *L. infantum*.

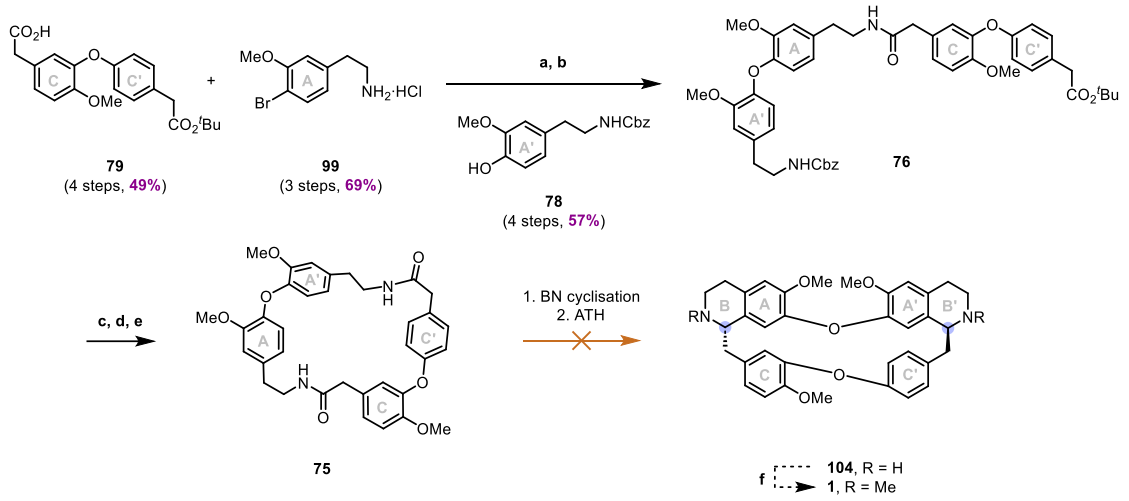
The picture is more promising for Chagas Disease, with several BIs meeting the DND*i* criteria for a hit compound against *T. cruzi*. Lead compound (–)-laudanidine **(*R*)-49** shows a better efficacy and safety profile than clinically used benznidazole with an IC_{50} against intracellular amastigotes of 2.60 ± 0.31 μM and an SI >77. Additionally, the compound shows a very promising pharmacokinetic profile as predicted by the *in silico* ADME analysis. However, the direct action on the cells is suboptimal (>150 μM), possibly indicating the formation of a more active metabolite.

5

Conclusions and Future Work

Leishmaniasis and Chagas disease affect over 20 million people worldwide and are lethal unless treated, but more often give rise to disability and disfigurement, thus leading to substantial social and economic hardships. Unfortunately, NTDs remain a low-priority venture within the pharmaceutical sector; the current clinical picture is marked by limited therapeutic agents that suffer from poor efficacy and safety profiles and emerging resistance. While there is a promising pipeline for VL with several candidates currently undergoing clinical trials, this is not mirrored for the other forms of leishmaniasis nor Chagas disease. There is an urgent need for improved diagnostic methods, new validated targets and better animal models, but ultimately, better treatments and novel cures are vital for the eradication of these diseases.[43] Prior to the efforts described in this thesis, a limited number of BBI alkaloids had been evaluated for anti-parasitic activity against intracellular amastigotes, most likely owing it to the time-consuming nature of the assays and the animal sacrifice required. Additionally, very little structure-activity relationship data is available and there is no information on the mechanism of action.

Known total syntheses of macrocyclic BBIs rely on lengthy, low-yielding synthetic routes which are unfit for the synthesis of enantiopure libraries for medicinal chemistry purposes. This work sought to address the lack of a general, concise and efficient method to access these molecules in an enantioselective fashion. Additionally, since the extent to which these alkaloids have evolved as anti-parasitic agents is poorly understood,[95] we questioned whether the structural complexity found in the natural products is actually required to maintain potent activity. The proposed deconstructive approach simplifies the parent BBI northalrugosidine (**13**) giving rise to analogue **1** which is more synthetically accessible.

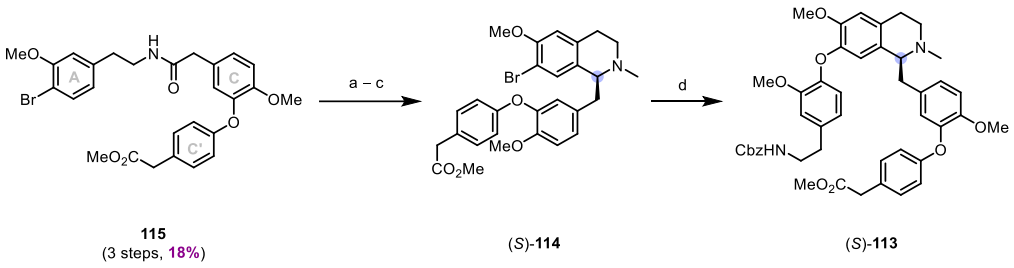


a) T3P, DIPEA, CH_2Cl_2, 0 °C to rt, 73% **b) 78**, CuO, K_2CO_3, pyridine, 140 °C, 51% **c)** TFA, CH_2Cl_2, 30 °C, >99%
d) H_2, Pd/C (10 wt%), MeOH, rt, >99% **e)** T3P, DIPEA, CH_2Cl_2, 0 °C to rt, 63% **f)** H_2CO, $NaBH_4$, MeOH, 0 °C to rt

Scheme 5.1. Synthesis of key macrocycle **75** and attempted double BN/ATH sequence.

The studies towards non-natural macrocyclic BBI **1** (**Chapter 2**) commenced with a strategy that relied on a double BN cyclisation followed by an ATH of key macrocycle **75** (**Scheme 5.1**). A highly optimised route to macrolactam **75** (11% over 9 steps) was developed, however, initial attempts to achieve a double BN/ATH sequence failed, raising the question of whether the macrocycle is too strained to allow for the simultaneous formation of both THIQ units, or in other ways cannot tolerate the reactive intermediates generated in the cyclisation.

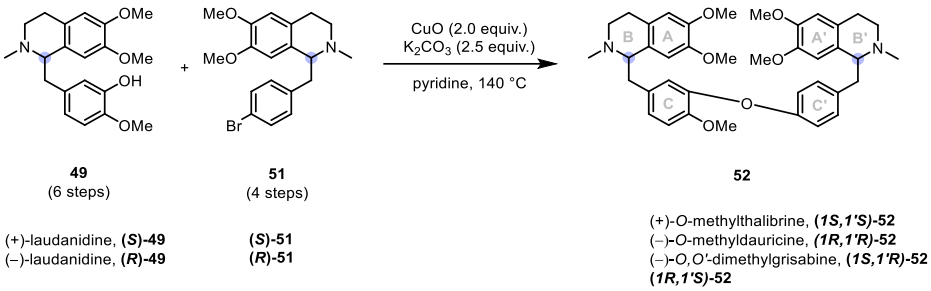
In line with our interest of evaluating how the stereochemistry affects the bioactivity, a second strategy was devised whereby the THIQ units would be installed sequentially (**Scheme 5.2**), thus enabling access to all diastereomers. Disappointingly, key intermediate **(*S*)-113** decomposed during the chromatographic purification process and the route had to be amended. Unfortunately, due to the time constraints of the project the completion of this synthesis remains as part of future work.



a) Tf_2O, 2-Clpyr., CH_2Cl_2, –78 °C to rt **b)** RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (7 mol%), HCO_2H/Et_3N, DMF, 0 °C to rt, **41%**, 94% *ee* **c)** H_2CO, $NaBH_4$, MeOH, 0 °C to rt, **76%** **d)** **78**, CuO, K_2CO_3, pyridine, 140 °C

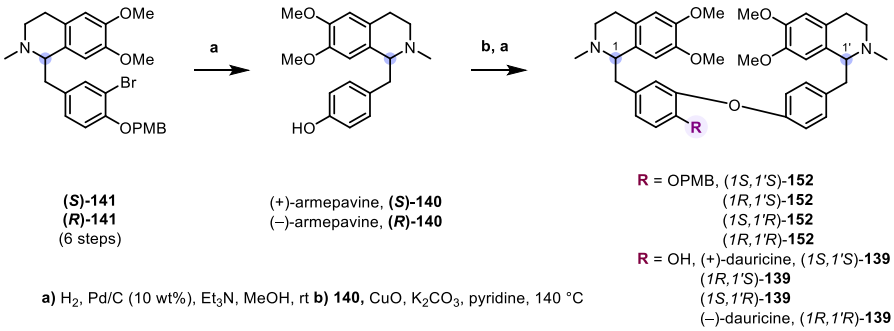
Scheme 5.2. Synthesis of key BI intermediate **(*S*)-113**.

The next stage of the deconstructive approach relied on removing the head-to-head diaryl ether bridge leading to acyclic BBIs (**Chapter 3**). In order to investigate whether a particular configuration is superior to the rest with respect to the bioactivity, all four possible diastereomers were synthesised. A robust route for the synthesis of linear BBIs was developed, *via* a seven- or nine-step convergent sequence that enabled access to five natural and seven non-natural BBI alkaloids. The route relied on formation of the individual BIs followed by a late-stage Ullmann coupling to install the diaryl ether linkage.



Scheme 5.3. Synthesis of linear BBIs **52**.

For the first series of BBIs (**Scheme 5.3**), the individual BI units were synthesised from the precursor amides *via* a BN/ATH sequence. Subjecting the crude imines directly to Noyori's ATH conditions yielded the desired BIs in good to excellent yields (63 – 94%) and excellent enantioselectivity (>94% *ee*).



Scheme 5.4. Alternative strategy towards BBIs **139**.

An alternative strategy was also employed for the formation of the phenolic BIs **(*S*)-140** and **(*R*)-140** (**Scheme 5.4**). Subjecting BIs **(*Sdndi*)-141** and **(*R*)-141** to hydrogenolytic conditions afforded the desired phenols, thus shortening the total number of steps towards the phenolic BBIs **139** from fourteen to nine. For comparison, both strategies were carried out in parallel. The route accessing the BIs from the corresponding amide afforded **(*S*)-140** in 31% yield (over six steps) whereas the second strategy proceeded in 45% yield (over seven steps). Finally, two BBI natural products (+)-dauricine and (–)-dauricine and six other non-natural BBI alkaloids were prepared (**Scheme 5.4**). The synthesis of the individual BIs facilitated the final deconstructive step, namely the removal of the tail-to-tail linkage.

In summary, five natural and seven non-natural BBIs were prepared alongside four natural and ten non-natural BI alkaloids. The robustness and highly divergent nature of the second strategy (**Scheme 5.4**) make this route suitable for the synthesis of a library of analogues. Employing hydrogenolysis conditions to form the phenol coupling partner from the bromide removes five steps typically required to form the phenolic BI from the corresponding amide. Additionally, the free hydroxyl group of the final BBIs offers a handle for late-stage functionalisation. Besides the preparation of various ether analogues, in the future a fluorescent and/or cross-linking probe could be attached in order to visualise where the compound accumulates within the parasite and thus elucidate the mechanism of action. The high basicity of the molecules leading to reduced cell permeability and metabolic instability could be addressed by synthesising analogues containing electron-withdrawing substituents (such as F, CF_3) that decrease the ability of the molecule of become protonated under physiological conditions.

Kindly hosted in the laboratory of Dr R. Wheeler, at the Nuffield Department of Medicine, University of Oxford, preliminary biological evaluation of BIs **(*S*)-51**, **(*S*)-138** and BBI **(*S*,*R*)-52** was performed on *L. mexicana* (**Chapter 4**) which confirmed the anti-parasitic effect of these alkaloids. Post-treatment morphological changes such as the cells becoming more spherical and possessing shorter flagella were observed, potentially indicating that these compounds interfere with the cell cycle.

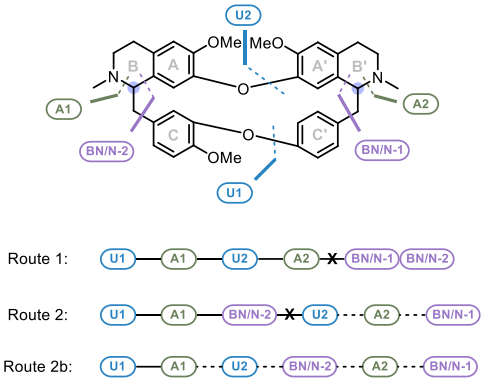
In total, fifteen BI and twelve BBI alkaloids were sent to our collaborator Prof. A. Tempone at the Instituto Adolfo Lutz in São Paulo, Brazil for a more in-depth biological analysis (**Chapter 4**). The compounds were tested against *L. infantum* promastigotes and amastigotes as well as against *T. cruzi* trypomastigotes and amastigotes. Mammalian cytotoxicity was evaluated against fibroblasts NCTC cells. The results confirmed that the

configuration at C-1 and C-1′ influences the observed bioactivity. In the case of the BI alkaloids, the (*R*)-enantiomers were found to be more active against *L. infantum* promastigotes and less toxic. The same trend was not consistently observed against the intracellular amastigote form. When the BBIs were tested, only minor differences were found for the activity and toxicity of different diastereomers, however no configuration was consistently superior. All compounds tested were active against *L. infantum* promastigotes. Disappointingly, the majority of compounds also presented high mammalian cytotoxicity and low selectivity indices making them unsuitable as potential drug scaffolds. The phenolic BIs were the only compounds that were found to be non-toxic with CC_{50} values >200 μM, however, they were also inactive against the amastigote form. While discouraging, the latter aspect may relate to cellular uptake into the macrophage host cell, which could perhaps be overcome by using a pro-drug form of the natural product (e.g. phenols protected as acetate groups). In line with this hypothesis, several other compounds that exhibited potent activity directly against the parasite cells were observed to be inactive when tested intracellularly – possibly indicating an issue in reaching the target.

More promising results were found against Chagas disease; (+)-laudanidine **(*S*)-49** and (–)-laudanidine **(*R*)-49** demonstrated an improved activity against *T. cruzi* intracellular amastigotes and SI to that of clinically used benznidazole. Additionally, they meet all the DND*i*'s criteria for a hit compound. Alas, the direct action of the compounds on the trypomastigotes is suboptimal, possibly suggesting that a more potent metabolite is formed within the cell, or an immune response is induced in the macrophage.

As far as the macrocyclic BBI analogue **1** is concerned, due to the instability of the key intermediate to chromatographic purification, the sequence of the steps should be revised such that the Ullmann coupling takes place prior to the BN/ATH sequence (**Scheme 5.5**,

Route 2b). While the formation of a THIQ unit within a macrolactam is precedented, its asymmetric reduction is not. Should the Noyori ATH fail to deliver the desired outcome, other imine hydrogenation or transfer hydrogenation conditions can be explored. While there are many avenues that could be explored, the strategy where the THIQ moieties are sequentially installed offers more stereocontrol and is more likely to provide a robust route to all diastereomers for further biological evaluation.



Scheme 5.5. Strategies towards **1** highlighting key reactions a) Bischler-Napieralski/Noyori ATH (BN/N), b) Ullmann coupling (U) and amide coupling (A).

Both BBI and BI alkaloids have been shown to be unsuitable as drug scaffolds against leishmaniasis due to high mammalian cytotoxicity and poor selectivity against the parasite. However, these compounds may be exploited in a different setting. BI alkaloids in particular have been researched as anti-cancer agents due to their ability to intercalate DNA and induce cell apoptosis.[118] It would therefore be of high interest to evaluate such activities of the compounds prepared in this project.

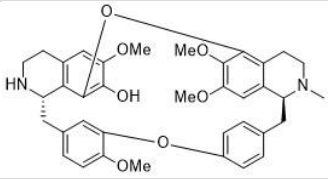
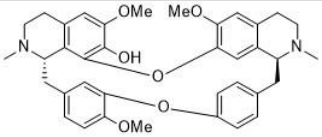
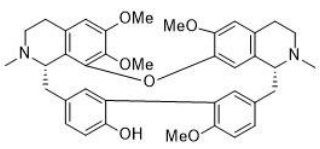
The results obtained for Chagas disease were more encouraging. The focus of future work should be directed towards using metabolomic studies to investigate whether the intracellular activity arises from an active metabolite and elucidate its structure. This should improve the community's understanding of these compounds, and could – potentially – lead to a cure against Chagas disease.

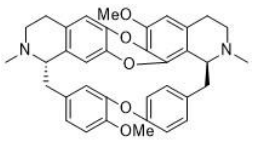
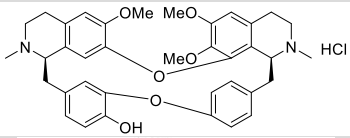
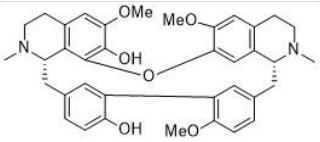
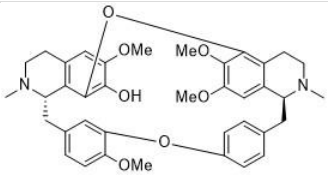
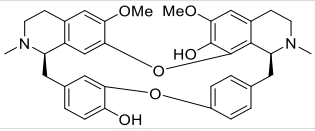
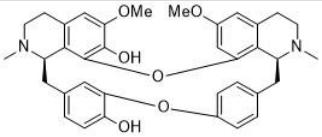
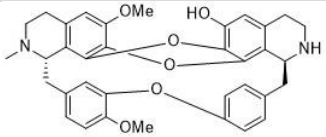
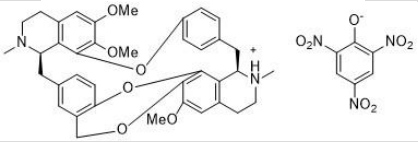
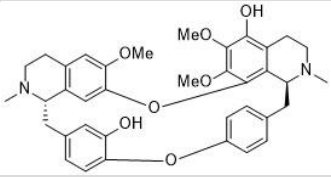
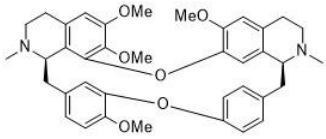
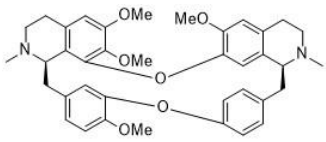
6

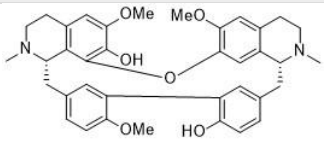
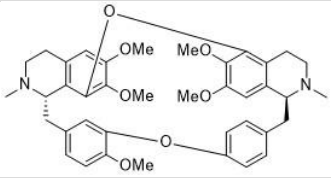
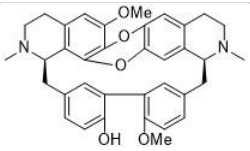
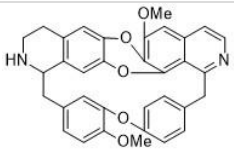
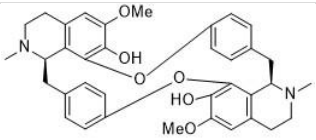
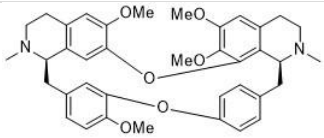
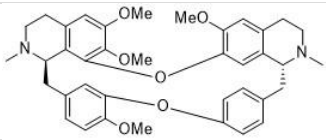
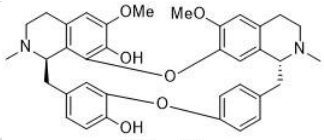
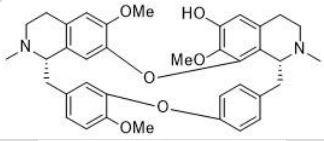
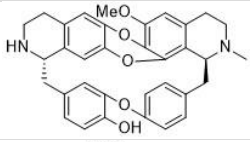
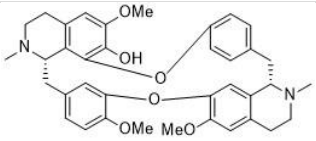
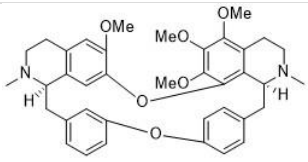
Appendix

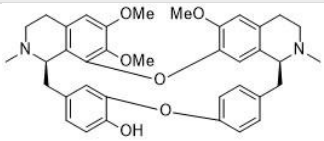
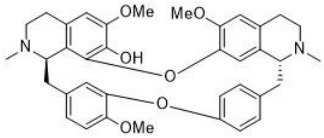
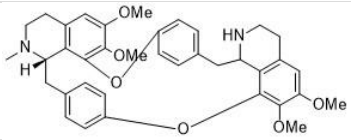
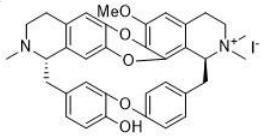
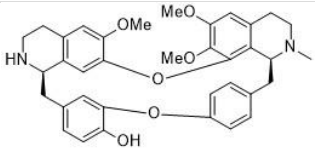
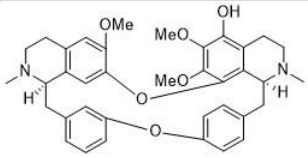
6.1 SAR Study on BBIs Previously Tested Against *L. donovani*

Data was obtained from four studies. [60, 93, 94, 119]

Entry	BBI Structure	BBI Name	IC_{50} (µM) (*L. donovani*)	
			Promastigotes	Amastigotes
1		northalrugosidine	0.28	ND
2		fangchinoline	0.39	ND
3		funiferine	0.53	Toxic

Entry	BBI Structure	BBI Name	IC_{50} (µM) (*L. donovani*)	
			Promastigotes	Amastigotes
4		isotrilobine	0.57	ND
5		oxyacanthine·HCl	0.68	ND
6		tiliageine	0.79	Toxic
7		thalrugosidine	1.00	ND
8		aromoline	1.04	ND
9		bbamegine	1.26	Toxic
10		gilletine	1.28	Toxic
11		insularine picrate	1.35	Toxic
12		thalisopidine	1.36	Toxic
13		isotetrandrine	2.22	Toxic
14		trilobine	2.47	ND

Entry	BBI Structure	BBI Name	IC_{50} (µM) (*L. donovani*)	
			Promastigotes	Amastigotes
15		antioquine	2.55	ND
16		thalidasine	3.70	ND
17		dinklacorine	4.15	Toxic
18		trigilletimine	8.60	>90
19		iso-chondrodendrine	11.80	>90
20		obaberine	11.80	ND
21		phaeanthine	15.70	2.41
22		krukovine	15.80	ND
23		gyrocarpine	15.95	ND
24		cocsoline	16.60	12.30
25		chondodendrine	16.65	ND
26		BBI **153**	6.80	ND [a]

Entry	BBI Structure	BBI Name	IC_{50} (µM) (*L. donovani*)	
			Promastigotes	Amastigotes
27		berbamine	24.70	Toxic
28		limacine	26.40	ND
29		cycleanine	32.15	ND
30		cocsuline methiodide	138.50	>90
31		daphnoline	>86	Toxic
32		BBI **154**	NA	ND

ND = not determined; Toxic = toxic to the macrophages at the tested concentration; NA = not active [a] Compound was found to kill 20 – 22% of macrophages at 100 µM when tested for mammalian cytotoxicity.

Table 6.1. BBI alkaloids tested against *L. donovani* promastigotes and amastigotes.

Northalrugosidine is the most active BBI in this library with an IC_{50} of 0.28 µM. Fangchinoline is the second best hit and is as potent as the standard antimonial drug pentamidine with an IC_{50} value of 0.4 µM. From the ones tested against the amastigote form, cocsoline was the only active alkaloid with an IC_{50} of 12.30 µM.

The activity observed against the promastigote form does not translate well to activity against the amastigote form. For example, trigilletimine is active against the promastigote form, but inactive against amastigotes at the tested concentrations. This is most likely a

consequence of the drug having to pass two membranes to reach its target, as well as survive the harsh environment of the parasitophorous vacuole.

Several structural characteristics appear to be conserved amongst the majority of BBIs. While the position of the head-to-head linkage varies, the C-11 to C-12′ (tail-to-tail) ether linkage remains consistent. The benzyl groups remain unsubstituted except for a conserved methoxy group at C-12 (occasionally replaced for a hydroxyl group). The oxygenation pattern on the THIQ units is predominantly observed at C-6, C-6′, C-7 and C-7′.

The SAR study was done by comparison of the activity against promastigotes demonstrated by BBIs in **Table 6.1** and revealed that both head-to-head and head-to-tail linked BBIs are active (**Figure 6.1**).

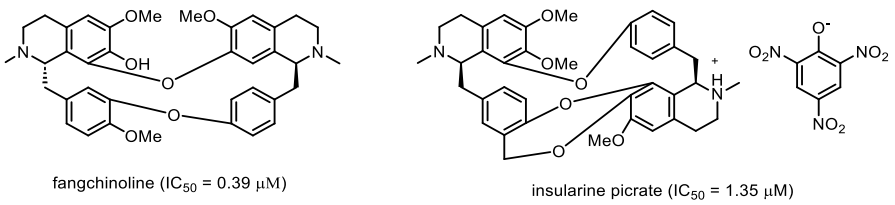


Figure 6.1. Structures of fangchinoline (head-to-head) and insularine picrate (head-to-tail).

The degree of saturation of the B rings is important for activity; a fully saturated B ring increases the activity 15 times in comparison to the aromatic analogue (**Figure 6.2**).

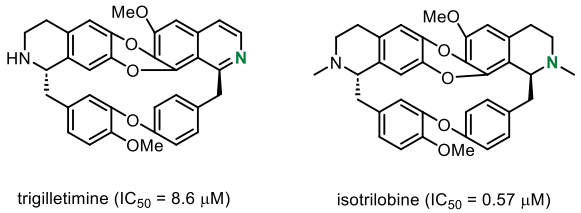


Figure 6.2. Structures of trigilletimine and isotrilobine.

Similarly, tertiary amine aromoline is significantly more active than secondary amine daphnoline (**Figure 6.3**).

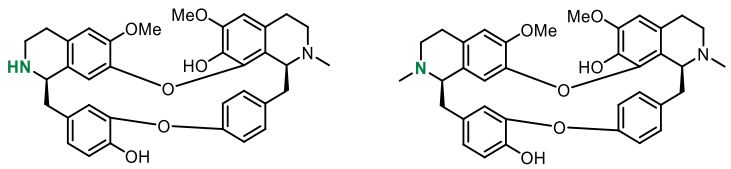


Figure 6.3. Structures of daphnoline and aromoline.

Having a phenol at C-5′ resulted in complete loss of activity, however a methoxy substituent at the same position is well tolerated (**Figure 6.4**).

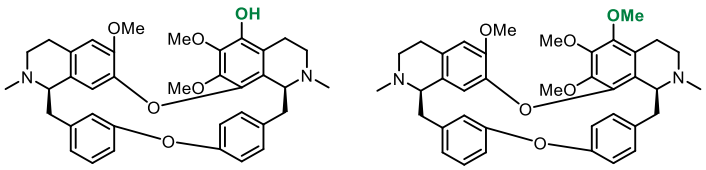


Figure 6.4. Structures of BBI 1 and BBI 2.

The configuration of the two stereocentres affects the anti-leishmanial activity. Isotetrandrine is nearly eight times more active than its diastereomer phaeanthine. No trend was observed that would indicate one configuration is preferred.

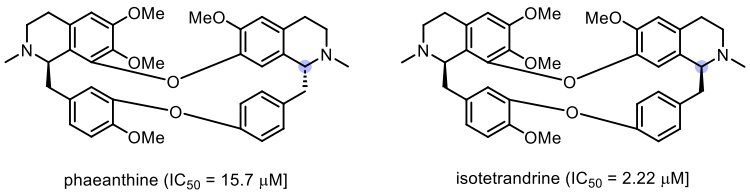
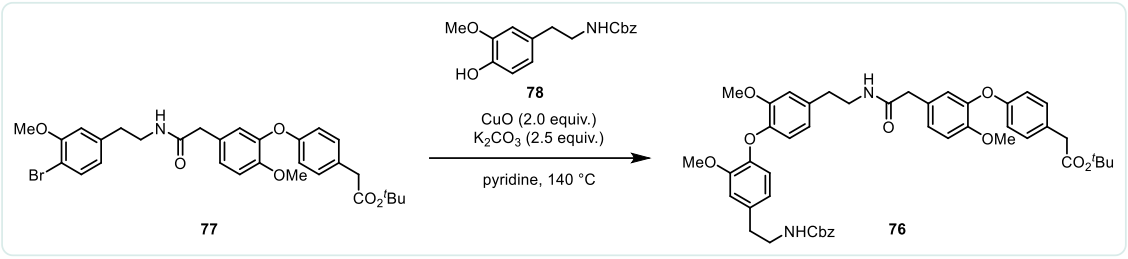


Figure 6.5. Structures of phaeanthanine and isotetrandrine.

While these observations were useful when designing analogue **1** and having a starting point for the project, in the absence of a clear drug target and extensive molecular modelling, predicting which compounds will be active on the amastigote form and thus be useful in a clinical setting is incredibly challenging. For this reason and as previously explained in **Section 1.2**, phenotypic assays are required for meaningful results.

6.2 Optimisation of the Ullmann Coupling U2

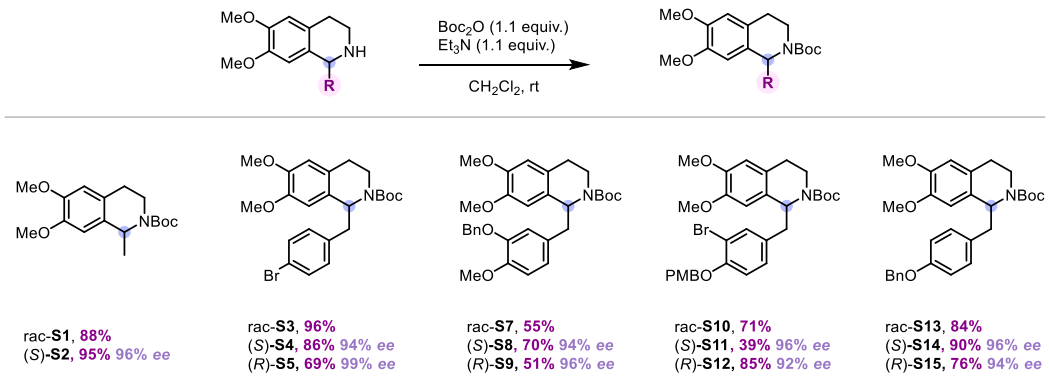


Entry	Phenol	Time	Yield[a]
1	1.0 equiv.	24 h	13%
2	1.8 equiv.	24 h	51%
3	1.8 equiv.	48 h	36%

[a] Yields of isolated product **76**.

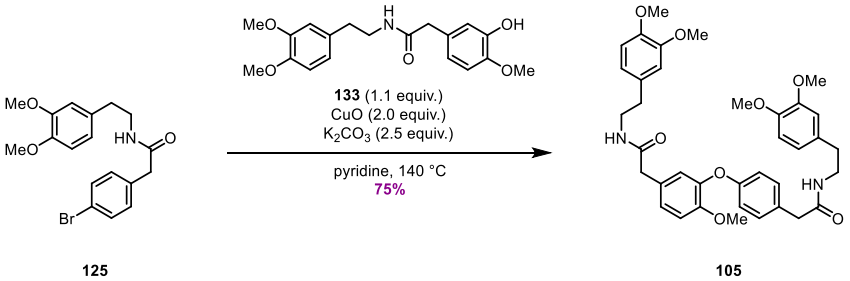
Table 6.2. Optimisation of Ullmann coupling U2.

6.3 Synthesis of the Boc-derivatised BIs



Scheme 6.1. Synthesis of Boc-protected BIs for *ee* measurement by chiral SFC.

6.4 Synthesis of bis-amide 105



Scheme 6.2. Synthesis of amide **105**.

6.5 ADME Properties of Selected Compounds

	BI (*S*)-114	**BBI (*S,R*)-139**	**(–)-laudanidine (*R*)-49**	**(–)-*O*-methyldauricine (*R,R*)-52**
IC_{50} *L. infantum* [a]	9.70 ± 0.57	3.57 ± 0.25		
IC_{50} *T. cruzi* [a]			2.60 ± 0.31	1.45 ± 0.15
SI	4.7	4.4	>77	7.8
Formula	$C_{28}H_{30}BrNO_5$	$C_{38}H_{44}N_2O_6$	$C_{20}H_{25}NO_4$	$C_{39}H_{46}N_2O_6$
Molecular Weight (g mol^{-1})	540.45	624.77	343.42	638.79
Heavy Atoms	35	46	25	47
Aromatic Heavy Atoms	18	24	12	24
Fractions Csp^3	0.32	0.37	0.40	0.38
Rotatable Bonds	9	10	5	11
H-bond Acceptors (HBA)	6	8	5	8
H-bond donors (HBD)	0	1	1	0
Molar Refractivity	143.04	188.02	101.48	192.49
TPSA ($Å^2$)	57.23	72.86	51.16	61.86
Consensus LogP	5.20	5.56	2.95	5.84
LogS (ESOL)	–6.59	–7.66	–4.10	–7.88
Solubility (mg ml^{-1})	1.40e-04	1.36e-05	2.74e-02	8.40e-06
Solubility Class	Poor	Poor	Moderate	Poor
GI Absorption	High	High	High	High
BBB permeant	Yes	No	Yes	No
P-gp substrate	Yes	No	No	No
CYP1A2 inhibitor	No	No	No	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	Yes	No	No	No
CYP2D6 inhibitor	Yes	No	Yes	No
CYP3A4 inhibitor	Yes	No	Yes	No
$LogK_p$ (cm s^{-1}) (skin permeation)	–5.53	–5.35	–6.02	–5.21
Lipinski violations	1	1	0	1
Ghose	No, 2 violations	No, 3 violations	Yes	No, 4 violations
Veber	Yes	Yes	Yes	No, 1 violation
Egan	Yes	Yes	Yes	Yes
Muegge	No, 1 violation	No, 2 violations	Yes	No, 2 violations
PAINS	0 alerts	0 alerts	0 alerts	0 alerts
Brenk	0 alerts	0 alerts	0 alerts	0 alerts
Leadlikeness	No	No	Yes	No

IC_{50} and SI values refer to those obtained from the intracellular amastigote assays. SI = selectivity index. MW = molecular weight. TPSA = topological polar surface area. GI = gastrointestinal. BBB = blood brain barrier. P-gp = permeability glycoprotein; CYP = cytochrome P450. PAINS = pan assay interference compounds.

Table 6.3. Pharmacokinetic parameters predicted by the SwissADME®[114] webtool.

LogS (ESOL)[120]: insoluble: –10 to –6; moderate: –6 to –4; soluble: –4 to –2; very: –2 to 0; highly >0.

Lipinski[116]: MW ≤ 500; HBD ≤ 5; HBA ≤ 10; LogP ≤ 4.15.

Ghose[121]: MW: 160 – 480; LogP: –0.4 – 5.6; Molar Refractivity 40 – 130; Atoms: 20 – 70.

Veber[122]: Rotatable bonds ≤ 10; TPSA ≤ 140.

Egan[123]: LogP ≤ 5.88; TPSA ≤ 131.6.

Muegge[124]: MW: 200 – 600; LogP: –2 – 5; TPSA ≤ 150; Rings ≤ 7; Carbon atoms > 4; Heteroatoms >1; Rotatable bonds ≤ 15; HBA ≤ 10; HBD ≤ 5.

Leadlikeness[125]: MW: 250 – 350; LogP ≤ 3.5; Rotatable bonds ≤ 7.

PAINS[126]: Compounds which give rise to a potent response in biological assays irrespective of the protein target.

Brenk[127]: Alerts to fragments identified as toxic, unstable or correlated to a poor pharmacokinetic profile.

7

Supplementary Information

7.1 Biological Evaluation – Methods

Cell culture

Leishmania mexicana promastigotes (expressing Cas9 and T7 RNA polymerase, derived from the WHO strain MNYC/BZ/62/M379) were grown in M199 medium (containing Earle's salts and L-glutamine (Gibco, 31100019); medium was supplemented with 10% v/v heat inactivated Foetal Calf Serum (Gibco, 10500064), 5 mM HEPES·NaOH (pH 7.4), 26 mM $NaHCO_3$ and 5 μg mL^{-1} hemin (Sigma-Aldrich H9039)) at 28 °C.

A continuous log-phase culture with a density between 1×10^5 and 1×10^7 cells mL^{-1} was maintained by sub-culturing.

Growth studies

L. mexicana promastigotes (1×10^6 cells mL^{-1}) in M199 medium (5 mL) were treated with 5 µL of compound in DMSO (0.1% final DMSO carryover) and incubated for 24 h at 28 °C. The culture density was measured using an Improved Neubauer haemocytometer and all growth study experiments were executed at least three times.

Light microscopy

Microscopy was performed with a Zeiss Axio Observer A1 widefield fluorescence microscope using a 63 × NA 1.4 Plan-Apochromat oil immersion objective lens and a Zeiss, HXP 120 V metal halide fluorescence light source and a Hamamatsu ORCA-Flash 4.0 camera. Standard fluorescence microscopy was performed with a Zeiss 49 filter cube.

Log-phase promastigotes (1×10^8 cells) were pelleted by centrifugation for three minutes at 2500 min^{-1}. Phosphate Buffered Saline (PBS) solution increases cell density and improves adhesion to the glass slide, therefore the pellet was washed three times with PBS. A nucleic acid stain (Hoescht 33342, 1 µg mL^{-1}) was used in the first wash.
The pellet was then resuspended in up to 30 µL PBS. A sample of 1 µL was placed on a microscope slide and covered with a coverslip. Imaging was performed immediately.

7.2 General Experimental Consideration

Materials/procedures: All air- or moisture-sensitive reactions were performed under a nitrogen atmosphere, with anhydrous solvents and in oven-dried glassware or glassware dried under vacuum and heated using a heat gun. Commercial reagents were obtained from Acros Organics, Alfa Aesar, Fluorochem, Fisher Scientific, Merck, Sigma Aldrich or TCI and were used without any further purification unless otherwise stated. Anhydrous solvents were collected fresh from an MBraun SPS-800 solvent purification system. Additionally, for Ullmann cross-couplings, pyridine was distilled from CaH_2 and stored over NaOH pellets for no longer than 7 days. Brine refers to an aqueous solution saturated with sodium chloride. RuCl[TsDPEN(*p*-cymene)] was stored and weighed out in the glove box under a nitrogen atmosphere. Heating was performed using an oil bath. The gas bag with a capacity of 1 gallon was purchased from Sigma Aldrich. 4 Å molecular sieves were activated by heating using a heat gun under vacuum for 3-5 minutes.

Infrared Spectroscopy: Infrared spectra were obtained in $CHCl_3$ as the solvent using a Bruker Tensor 27 Fourier FT-IR spectrometer. Samples were prepared as a thin film on a diamond PIKE Miracle ATR module and the absorbance maxima (ν_{max}) are reported in cm^{-1}.

Mass Spectrometry: Electrospray ionisation (ESI) low-resolution mass spectra (LRMS) were recorded on a Waters LCT Premier XE system. High-resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Thermo Exactive or Bruker MicroTOF Mass Spectrometer. Values are calculated to 4 decimal places from the molecular formula, and all values reported are within a tolerance of 5 ppm.

NMR Spectroscopy: (^{1}H) Proton and carbon (^{13}C) NMR spectra were recorded on a Bruker AVIII HD 400, AVIII HD 500, AVII 500 or AVIII HD 600 spectrometer. Chemical shifts (δ_H, δ_C) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR spectra, and 0.1 ppm for ^{13}C NMR spectra. NMR spectra were referenced to the residual solvent peak stated: $CDCl_3$ (δ = 7.26 / δ = 77.16) or methanol-*d*$_4$ (δ = 3.31 / δ = 49.00). Assignments were determined based on unambiguous chemical shifts, coupling patterns and 2D NMR experiments. Peak multiplicities are defined as s (singlet), d (doublet), dd (doublet of doublets), dt (double triplet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (*J*) are reported to the nearest 0.1 Hz. We would like to thank the University of Oxford Departmental NMR Service, in particular Dr Nader Amin and Caitlin Salter for assistance in acquiring NMR spectra.

Chromatography: Column chromatography refers to normal phase column chromatography and was performed on silica gel (Merck, Si 60, 0.040 – 0.063 mm) using the solvent system stated and under a positive pressure. Preparative thin-layer chromatography (pTLC) was performed on silica gel GF uniplates with fluorescent indicator, (500 µm, 20 × 20 cm) from Miles Scientific (Analtech). Analytical thin-layer chromatography (TLC) was used to monitor reaction progress and performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254} plates). Visualisation was performed using ultraviolet light (254 nm) and/or by staining with potassium permanganate, vanillin, ninhydrin, phosphomolybdic acid (PMA) or Hanessian′s stain (CAM). Retention factors (R_f) are reported with the solvent system in parentheses.

Polarimetry: Optical rotations were recorded using a Perkin Elmer 241 Polarimeter (using the sodium D line, 589 nm) with a path length of 1 dm at 25 °C. $[\alpha]_D^{25}$ are reported in units of 10^{-1} deg cm^2 g^{-1} and the concentrations (c) are reported in g/100 mL.

Chiral supercritical fluid chromatography (SFC): Separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150 × 3 mm, 3 μm particle size) were used as specified in the text. The solvents used were of HPLC grade (obtained from Fisher Scientific, Sigma Aldrich or Rathburn).

7.3 General Experimental Procedures

General Procedure A: Henry reaction

Following the procedure of Pieper, P. et al.[89] To a flask containing activated 4 Å molecular sieves and acetic acid (14 equiv.) under an inert atmosphere at room temperature, was added aldehyde (1.0 equiv.). Nitromethane (5.0 equiv.) and ethylenediamine (0.1 equiv.) were added sequentially to the flask and the reaction mixture was heated to 70 °C for 18 h. Upon completion, the reaction mixture was cooled to room temperature, poured into ice-cold H_2O (0 °C), filtered under vacuum and washed with more ice-cold H_2O to yield the desired β-nitrostyrene. No further purification was necessary.

General Procedure B: Ullmann cross-coupling

Following the procedure of Pieper P.[90] To a flask containing bromide (1.0 equiv.) and phenol (1.1 – 1.8 equiv.) was added potassium carbonate (2.5 equiv.) and the flask was evacuated and backfilled with nitrogen (× 3). After addition of anhydrous pyridine (0.65 – 1.6 mL/mmol bromide), the mixture was heated to 120 °C. Cupric oxide (2.0 equiv.) was added under a flow of nitrogen and the mixture was heated to 140 °C for 24 h (unless otherwise stated). Unless otherwise specified, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a pad of Celite®. The filter cake was washed with CH_2Cl_2 (3 ×) and the filtrate was washed with HCl (aq., 1 M, 2 ×). The combined organic extracts were washed with brine, dried (Mg_2SO_4), filtered and concentrated *in vacuo.* Purification by flash column chromatography afforded the desired biarylethers.

General Procedure C: Bischler-Napieralski reaction

Adapted from the procedure of Movassaghi et al.[66] Trifluoromethanesulfonic anhydride (1.1 equiv.) was added *via* syringe over 1 min to a stirred solution of amide (1.0 equiv.) and 2-chloropyridine (1.2 equiv.) in anhydrous CH_2Cl_2 (5 mL/mmol of amide) at −78 ºC under an inert atmosphere. After 20 min the reaction mixture was warmed to room temperature and stirred for 1 h. Triethylamine (1.0 equiv.) was then added to neutralise the triflate salts. The mixture was concentrated *in vacuo* and immediately submitted to the next step without further purification.

General Procedure D: $NaBH_4$ reduction of imines

To a solution of crude imine in EtOH (5 mL/mmol of imine) at 0 ºC under an inert atmosphere was added sodium borohydride (3.0 equiv.). The mixture was warmed to room temperature and stirred for 18 h. The mixture was then cooled to 0 ºC and H_2O was added until gas evolution ceased. The mixture was extracted with CH_2Cl_2 (× 3), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the desired amines.

General Procedure E: Asymmetric transfer hydrogenation of imines

Adapted from the procedure of Uematsu et al.[71] To a flask containing the crude imine (1.0 equiv.) under an inert atmosphere was added RuCl[(*R,R*)-TsDPEN](*p*-cymene) or RuCl[(*S,S*)-TsDPEN](*p*-cymene) (0.07 equiv.) as a solution in anhydrous DMF (5 mL/mmol of amide) and the mixture was cooled to 0 ºC. An azeotrope mixture of HCO_2H:Et_3N (5:2 v/v, 0.5 mL/mmol imine) was added slowly, then the mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched by addition

of $NaHCO_3$ (aq., sat.,) and the aqueous phase was extracted with EtOAc (× 3). The combined organic extracts were washed with H_2O (× 3) and brine (× 2), dried ($MgSO_4$), filtered and concentrate *in vacuo*. Flash column chromatography afforded the desired tetrahydroisoquinolines.

General Procedure F: *N*-Methylation

Adapted from the procedure of Blank et al.[85] To a solution of tetrahydroisoquinoline (1.0 equiv.) in MeOH (20 mL/mmol of tetrahydrosioquinoline) was added formalin (37% aq., 28 equiv.) and the resulting mixture was stirred for 20 min. The reaction mixture was then cooled to 0 ºC for 10 min and sodium borohydride (3.0 equiv.) was added portion-wise over two min. The mixture was warmed to room temperature and stirred for 1 h. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, washed with NaOH (aq., 1 M), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography afforded the desired *N*-methyl tetrahydroisoquinolines.

General Procedure G: *N*-Boc protection

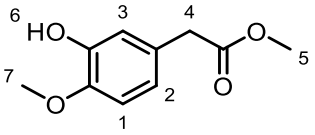
To a solution of tetrahydroisoquinoline (1.0 equiv.) in anhydrous CH_2Cl_2 (6 mL/mmol of tetrahydroisoquinoline) at room temperature under an inert atmosphere was added di-*tert*-butyl dicarbonate (1.2 equiv.) and triethylamine (1.2 equiv.), and the reaction mixture was stirred for 4 h. Upon completion, the mixture was concentrated *in vacuo*. Flash column chromatography afforded the desired *N*-Boc protected tetrahydroisoquinolines.

General Procedure H: Amide coupling (EDC·HCl/HOBt)

Adapted from the procedure of Mäder et al.[128] To a solution of carboxylic acid (1.0 equiv.) in anhydrous CH_2Cl_2 (3.3 mL/mmol of carboxylic acid) at 0 ºC under an inert atmosphere was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.5 equiv.) and hydroxybenzotriazole hydrate (0.5 equiv.) and the mixture was stirred for 10 min. Amine (1.1 equiv.) and triethylamine (1.1 equiv.) were added to the mixture at 0 ºC, then the mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was washed sequentially with H_2O, HCl (aq., 1 M) and $NaHCO_3$ (aq. sat.). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography afforded the desired amides.

7.4 Experimental Procedures

Methyl 2-(3-hydroxy-4-methoxyphenyl)acetate, 81



Following the procedure of Epple et al.[129] To a solution of 3-hydroxy-4-methoxy-phenylacetic acid (5.0 g, 27 mmol, 1.0 equiv.) in MeOH (45 mL), was added concentrated sulphuric acid (0.24 mL, 4.4 mmol, 0.16 equiv.) dropwise over three minutes. The reaction mixture was then heated to 70 °C and stirred for 18 h then cooled to room temperature and concentrated *in vacuo*. The residue was poured into $NaHCO_3$ (aq., sat., 50 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a colourless liquid (4.92 g, 25.1 mmol, 92%).

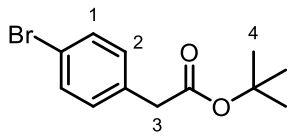
R_f 0.34 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 2.1 Hz, 1H, H3), 6.80 (d, *J* = 8.1 Hz, 1H, H1), 6.75 (dd, *J* = 8.1, 2.1 Hz, 1H, H2), 5.60 (s, br, 1H, H6), 3.87 (s, 3H, H7), 3.68 (s, 3H, H5), 3.53 (s, 2H, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 145.9, 145.8, 127.3, 120.9, 115.7, 110.9, 56.1, 52.1, 40.7.

Spectroscopic data is in agreement with that reported previously.[130]

***tert*-Butyl 2-(4-bromophenyl)acetate**, **82**



Following the procedure of Li et al.[131] To a solution of 4-bromophenylacetic acid (5.00 g, 23.3 mmol, 1.0 equiv.) in *tert*-butanol (25 mL) at room temperature under an inert atmosphere was added 4-dimethylaminopyridine (0.852 g, 6.98 mmol, 0.3 equiv.) and di-*tert*-butyl dicarbonate (10.2 g, 46.5 mmol, 2.0 equiv.). The reaction mixture was stirred for 24 h. The solvent was then removed azeotropically with EtOAc. Purification by flash column chromatography (pentane/CH_2Cl_2, 5:1) afforded the title compound as a colourless oil (5.33 g, 19.7 mmol, 84%).

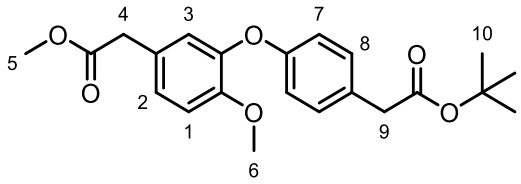
R_f 0.19 (pentane/CH_2Cl_2, 5:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H, H1), 7.14 (d, *J* = 8.5 Hz, H2), 3.47 (s, 2H, H3), 1.43 (s, 9H, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 133.8, 131.7(2C), 131.1(2C), 121.0, 81.3, 42.2, 28.2(3C).

Spectroscopic data is in agreement with that reported previously.[131]

***tert*-Butyl 2-(4-(2-methoxy-5-(2-methoxy-2-oxoethyl)phenoxy)phenyl)acetate, 79**



tert-Butyl 2-(4-bromophenyl)acetate **82** (1.26 g, 4.64 mmol), methyl 2-(3-hydroxy-4-methoxyphenyl)acetate **81** (1.00 g, 5.10 mmol), potassium carbonate (1.60 g, 11.6 mmol) and cupric oxide (0.738 g, 9.28 mmol) in anhydrous pyridine (3 mL) were submitted to **General Procedure B** for 18 h. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as an off-white solid (1.12 g, 2.91 mmol, 63%).

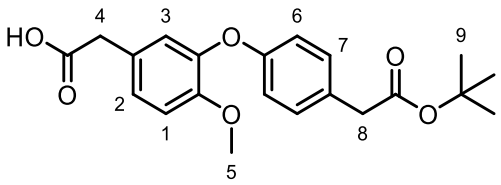
R*f* 0.42 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 2H, H8), 7.03 (dd, *J* = 8.4, 2.2 Hz, 1H, H2), 6.94 (d, *J* = 8.4 Hz, 1H, H1), 6.91 – 6.87 (m, 3H, H3, H7), 3.82 (s, 3H, H6), 3.67 (s, 3H, H5), 3.52 (s, 2H, H4), 3.48 (s, 2H, H9), 1.44 (s, 9H, H10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 171.2, 156.9, 150.7, 145.2, 130.5(2C), 129.0, 127.0, 125.5, 122.1, 117.4(2C), 113.0, 80.9, 56.2, 52.2, 42.0, 40.4, 28.2(3C).

Spectroscopic data is in agreement with that reported previously.[90]

2-(3-(4-(2-(*tert*-Butoxy)-2-oxoethyl)phenoxy)-4-methoxyphenyl)acetic acid, 83



To a solution of *tert*-butyl 2-(4-(2-methoxy-5-(2-methoxy-2-oxoethyl)phenoxy) phenyl)acetate **79** (0.30 g, 0.76 mmol, 1.0 equiv.) in THF (1.5 mL) was added lithium hydroxide (aq., 1 M, 2.0 mL, 2.5 equiv.). The mixture was stirred at room temperature for 4 h and then acidified with HCl (aq., 1 M) to pH 5. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 7 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound as an off-white solid (0.28 g, 0.75 mmol, 99%). No further purification was necessary.

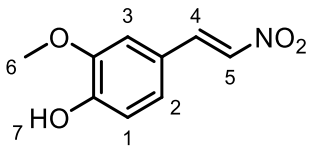
R_f 0.73 (EtOAc), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 2H, H7), 7.03 (dd, *J* = 8.4, 2.2 Hz, 1H, H2), 6.95 (d, *J* = 8.4 Hz, 1H, H1), 6.93 – 6.85 (m, 3H, H3, H6), 3.81 (s, 3H, H5), 3.53 (s, 2H, H4), 3.49 (s, 2H, H8), 1.44 (s, 9H, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 171.3, 156.7, 150.7, 145.1, 130.4(2C), 128.9, 126.2, 125.6, 122.1, 117.3(2C), 112.9, 80.1, 56.1, 41.9, 40.1, 28.1(3C).

Spectroscopic data is in agreement with that reported previously.[90]

***(E)*-2-Methoxy-4-(2-nitrovinyl)phenol, 85**



Vanillin (3.00 g, 19.7 mmol), nitromethane (4.92 mL, 98.6 mmol) and ethylenediamine (0.130 mL, 1.98 mmol) in acetic acid (16 mL) were submitted to **General Procedure A**. The title compound was obtained as a yellow powder (3.64 g, 18.6 mmol, 95%).

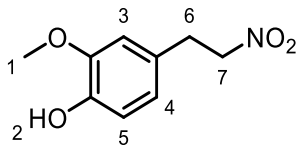
R*f* 0.27 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 13.6 Hz, 1H, H4), 7.52 (d, *J* = 13.6 Hz, 1H, H5), 7.14 (dd, *J* = 8.2, 2.0 Hz, 1H, H2), 7.00 (d, *J* = 2.0 Hz, 1H, H3), 6.98 (d, *J* = 8.2 Hz, 1H, H1), 6.04 (s, 1H, H7), 3.96 (s, 3H, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 147.2, 139.6, 135.2, 125.1, 122.6, 115.5, 110.3, 56.3.

Spectroscopic data is in agreement with that reported previously.[132]

2-Methoxy-4-(2-nitroethyl)phenol, 85b



Adapted from the procedure of Wang et al.[100] To a suspension of sodium borohydride (0.35 g, 9.2 mmol, 1.2 equiv.) in a mixture of dioxane:EtOH (5:2 v/v, 14 mL) at 0 °C under an inert atmosphere, was added (*E*)-2-methoxy-4-(2-nitrovinyl)phenol **85** (1.5 g, 7.7 mmol, 1.0 equiv.) as a solution in dioxane:EtOH (5:2 v/v, 14 mL) in a dropwise fashion over ten minutes. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then cooled to 0 °C, quenched with NH_4Cl (aq., sat., 20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a pale-yellow oil (1.18 g, 5.98 mmol, 78%).

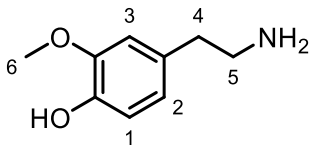
R_f 0.56 (pentane/EtOAc, 7:4), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 8.6 Hz, 1H, H1), H3, 6.73 – 6.66 (m, 2H, H2, H3), 5.57 (s, 1H, H7), 4.58 (t, *J* = 7.4 Hz, 2H, H5), 3.88 (s, 3H, H6), 3.25 (t, *J* = 7.4 Hz, 2H, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 145.1, 127.6, 121.5, 114.9, 111.2, 76.8, 56.1, 33.4.

Spectroscopic data is in agreement with that reported previously.[100]

4-(2-Aminoethyl)-2-methoxyphenol, 86



Adapted from the procedure of Wang et al.[100] To a flask containing Pd/C (10% wt., 1.25 g, 1.17 mmol, 0.04 equiv.) under an inert atmosphere, was added EtOH (160 mL) and the flask was evacuated and backfilled with hydrogen (× 3). 2-Methoxy-4-(2-nitroethyl)phenol **85b** (5.50 g, 27.8 mmol, 1.0 equiv.) was then added as a solution in EtOH (50 mL) and the resulting mixture was stirred under a hydrogen atmosphere for 24 h. The reaction mixture was filtered through a pad of Celite®, and the filter cake was washed with CH_2Cl_2/MeOH (9:1). The filtrate was concentrated in vacuo to afford the title compound as a light brown solid (4.64 g, 27.8 mmol, >99%). No further purification was necessary.

R*f* 0.01 (EtOAc), [UV, ninhydrin]

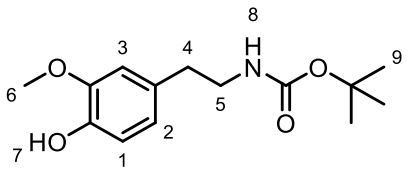
^{1}H NMR (400 MHz, methanol-*d*4) δ 6.74 (d, *J* = 2.0 Hz, 1H, H3), 6.68 (d, *J* = 8.0 Hz, 1H, H1), 6.60 (dd, *J* = 8.0, 2.0 Hz, 1H, H2), 3.80 (s, 3H, H6), 2.80 (t, *J* = 7.2 Hz, 2H, H5), 2.63 (t, *J* = 7.2 Hz, 2H, H4).

Note: O*H* resonance was not observed.

^{13}C NMR (101 MHz, methanol-*d*4) δ 147.7, 144.7, 130.8, 120.8, 114.9, 112.0, 54.9, 42.8, 38.0.

Spectroscopic data is in agreement with that reported previously.[133]

***tert*-Butyl (4-hydroxy-3-methoxyphenethyl)carbamate, 87**



To a solution of 4-(2-aminoethyl)-2-methoxyphenol **86** (0.34 g, 2.6 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) at room temperature under an inert atmosphere was added di-*tert*-butyl dicarbonate (0.45 g, 2.9 mmol, 1.1 equiv.) and triethylamine (0.30 mL, 2.9 mmol, 1.1 equiv.) and the reaction mixture was stirred for 6 h. The reaction mixture was then washed with HCl (aq., 1 M, 5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a white solid (0.36 g, 1.3 mmol, 51%).

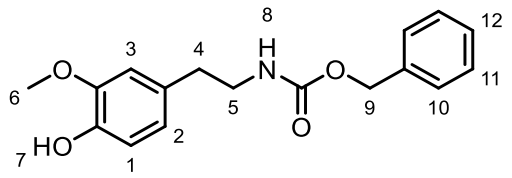
R_f 0.15 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, J = 8.3 Hz, 1H, H1), 6.71 – 6.65 (m, 2H, H2, H3), 5.52 (s, 1H, H7), 4.54 (s, 1H, H8), 3.88 (s, 3H, H6), 3.34 (q, J = 7.0 Hz, 2H, H5), 2.72 (t, J = 7.0 Hz, 2H, H4), 1.44 (s, 9H, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 146.7, 144.3, 130.9, 121.5, 114.5, 111.4, 79.4, 56.0, 42.1, 36.0, 28.5(3C).

Spectroscopic data is in agreement with that reported previously.[134]

Benzyl (4-hydroxy-3-methoxyphenethyl)carbamate, 78



Following the procedure of Stanek et al.[135] To a solution of 4-(2-aminoethyl)-2-methoxyphenol **86** (200 mg, 1.20 mmol, 1.0 equiv.), $NaHCO_3$ (232 mg, 2.76 mmol, 2.3 equiv.) in THF/H_2O (1:1 v/v, 28 mL) was added *N*-(benzyloxycarbonyloxy) succinimide (300 mg, 1.20 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 6 h. Upon completion, the organic solvent was removed *in vacuo* and the remaining aqueous phase was extracted with EtOAc (3 × 8 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 3:1) afforded the title compound as an off-white amorphous solid (0.28 g, 0.92 mmol, 77%).

m.p. 72 – 74 ºC

R$_f$ 0.26 (pentane/EtOAc, 3:1), [UV, ninhydrin / PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H, H10, H11, H12), 6.84 (d, *J* = 8.0 Hz, 1H, H1), 6.68 – 6.64 (m, 2H, H2, H3), 5.66 (s, 1H, H7), 5.10 (s, 2H, H9), 4.83 (s, br, 1H, H8), 3.83 (s, 3H, H6), 3.43 (app. q, *J* = 6.9 Hz, 2H, H5), 2.74 (t, *J* = 6.9 Hz, 2H, H4).

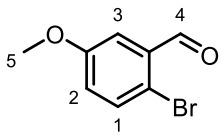
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 146.7, 144.4, 136.7, 130.6, 128.6(2C), 128.2(3C), 121.5, 114.6, 111.4, 66.7, 56.0, 42.5, 35.2.

IR (film) ν_{max}/cm^{-1} 3395, 3348, 3239, 2918, 2849, 1699, 1602, 1515, 1455.

HRMS (ESI$^+$) $C_{17}H_{19}NO_4$ found $[M+Na]^+$ at 324.1205, expected at 324.1206.

Some spectroscopic data has been reported previously.[136]

2-Bromo-5-methoxybenzaldehyde, 90



Procedure 1: *Following the procedure of Natarajan et al.*[101] To a solution of *m*-anisaldehyde (0.45 mL, 3.7 mmol, 1.0 equiv.) in a mixture of DMF:H_2O (95:5 v/v, 37 mL) was added *N*-bromosuccinimide (2.6 g, 15 mmol, 4.0 equiv.). The mixture was stirred at room temperature for ten min then heated to 75 °C for 24 h. Upon completion, the mixture was cooled to room temperature and quenched with $NaHCO_3$ (aq., sat., 20 mL). Upon further cooling to 0 °C, an insoluble precipitate formed which was filtered under vacuum to afford the title compound as off-white solid (0.36 g, 1.7 mmol, 45%). No further purification was necessary.

R*f* 0.47 (pentane/Et_2O, 95:5), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H, H4), 7.53 (d, *J* = 8.8 Hz, 1H, H1), 7.42 (d, *J* = 3.2 Hz, 1H, H3), 7.04 (dd, *J* = 8.8, 3.2 Hz, 1H, H2), 3.84 (s, 3H, H5).

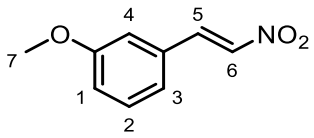
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.8, 159.3, 134.6, 134.0, 123.2, 118.0, 112.7, 55.8.

The literature procedure reports the product having the Br atom *ortho* relative to the methoxy substituent without providing any NMR data. HMBC NMR spectroscopic analysis of **90** indicates that the product has the Br atom at *para* to the methoxy group instead. This is further supported by ^{1}H NMR signals of **90** corresponding with values found in literature.[137]

Procedure 2: *Following the procedure of Okada et al.*[138] To a solution of (2-bromo-5-methoxyphenyl)methanol **96** (0.61 g, 2.8 mmol, 1.0 equiv.) in CH_2Cl_2 (9 mL), was added Bu_4NHSO_4 (48 mg, 0.14 mmol, 0.05 equiv.) and TEMPO (4.0 mg, 30 µmol, 0.01 equiv.) and the reaction mixture was cooled to 5 °C. $NaOCl \cdot 5H_2O$ (0.56 g, 3.4 mmol, 1.2 equiv.) was added in two portions and the mixture was stirred at 5 °C for 2 h. The reaction was quenched with Na_2SO_4 (aq., sat., 10 mL) and the phases were separated. The resulting aqueous phase was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/Et_2O, 95:5) afforded the title compound as a white solid (0.45 g, 2.1 mmol, 75%).

Spectroscopic data as reported above.

(*E*)-1-Methoxy-3-(2-nitrovinyl)benzene, 91



m-Anisaldehyde (0.45 mL, 3.7 mmol), nitromethane (1.0 mL, 18 mmol) and ethylenediamine (11 μL, 0.17 mmol) in acetic acid (3 mL) were submitted to **General Procedure A**. The title compound was collected as a pale-yellow solid (0.65 g, 3.7 mmol, 99%).

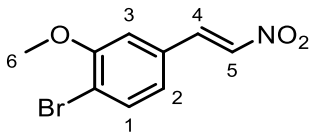
R*f* 0.91 (EtOAc), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 13.7 Hz, 1H, H5), 7.56 (d, *J* = 13.7 Hz, 1H, H6), 7.39 – 7.32 (m, 1H, 45), 7.13 (dt, *J* = 7.7, 1.1 Hz, 1H, H2), 7.05 – 7.02 (m, 2H, H1, H3), 3.85 (s, 3H, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 139.2, 137.4, 131.4, 130.5, 121.9, 118.1, 114.1, 55.5.

Spectroscopic data is in agreement with that reported previously.[139]

(*E*)-1-Bromo-2-methoxy-4-(2-nitrovinyl)benzene, 92



4-Bromo-3-methoxybenzaldehyde **89** (2.38 g, 11.1 mmol), nitromethane (3.00 mL, 55.4 mmol) and ethylenediamine (75.0 µL, 1.11 mmol) in acetic acid (9.0 mL) were submitted to **General Procedure A**. The title compound was collected as a yellow powder (2.69 g, 10.4 mmol, 94%).

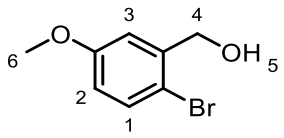
R$_f$ 0.58 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 13.7 Hz, 1H, H4), 7.65 – 7.57 (m, 2H, H5, H1), 7.04 (dd, *J* = 8.1, 2.0 Hz, 1H, H2), 6.99 (d, *J* = 2.0 Hz, 1H, H3), 3.95 (s, 3H, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 138.3, 137.7, 134.4, 130.7, 122.7, 116.7, 111.5, 56.5.

Spectroscopic data is in agreement with that reported previously.[140]

(4-Bromo-3-methoxyphenyl)methanol, 96



Following the procedure from Zhang et al.[103] To a solution of 3-methoxybenzyl alcohol **94** (1.00 mL, 8.04 mmol, 1.0 equiv.) in MeCN:H_2O (1:1 v/v, 48 mL) was added $NaBrO_3$ (2.42 g, 16.1 mmol, 2.0 equiv.) and $NaHSO_3$ (1.68 g, 16.1 mmol, 2.0 equiv.) sequentially. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was then quenched with $Na_2S_2O_3$ (aq., sat., 50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with Na_2CO_3 (aq., sat., 50 mL), H_2O (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 10:1) afforded the title compound as a white solid (1.33 g, 6.12 mmol, 76%).

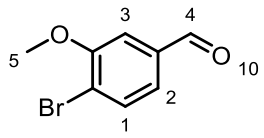
R$_f$ 0.17 (pentane/EtOAc, 10:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 1H, H1), 7.05 (d, *J* = 3.1 Hz, 1H, H3), 6.71 (dd, *J* = 8.7, 3.1 Hz, 1H, H2), 4.70 (s, 2H, H4), 3.80 (s, 3H, H6) 2.13 (s, br, 1H, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 140.9, 133.3, 114.9, 114.4, 112.6, 65.2, 55.6.

The literature procedure used for this experiment reports the product having the Br atom *ortho* relative to the methoxy group. HMBC NMR spectroscopic analysis indicates the product having the Br atom *para* relative to the methoxy group instead. This is further supported by ^{1}H NMR spectroscopic analysis of the products obtained in subsequent reactions of alcohol **96**.

4-Bromo-3-methoxybenzaldehyde, 89



Adapted from the procedure of Dobrowski et al.[141] To a solution of *n*-butyllithium (2.2 M in hexanes, 2.62 mL, 5.76 mmol, 1.0 equiv.) in diethyl ether (5.76 mL) at –78 °C under an inert atmosphere, was added 2-Bromo-5-iodoanisole **98** (1.80 g, 5.76 mmol, 1.0 equiv.) as a solution in diethyl ether (5.76 mL) in a dropwise manner over two min. The reaction mixture was stirred for 20 min at –78 °C. DMF (0.490 mL, 6.34 mmol, 1.1 equiv.) was then added dropwise and the resulting mixture was stirred for a further 20 min at –78 °C. Sulphuric acid (aq., 1 M, 5.76 mL) was added, the cooling bath was removed, and the solution was stirred until it reached room temperature. The reaction mixture was washed with brine (2 × 20 mL) and the resulting aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by recrystallisation from hot hexane afforded the title compound as colourless needle-like crystals (1.02 g, 4.75 mmol, 82%).

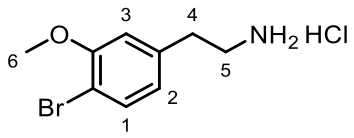
R$_f$ 0.32 (pentane/EtOAc, 8:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H, H4), 7.74 (d, *J* = 7.9 Hz, 1H, H1), 7.39 (d, *J* = 1.8 Hz, 1H, H3), 7.33 (dd, *J* = 7.9, 1.8 Hz, 1H, H2), 3.97 (s, 3H, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 156.8, 136.9, 134.2, 124.7, 119.7, 110.0, 56.6.

Spectroscopic data is in agreement with that reported previously.[141]

2-(4-Bromo-3-methoxyphenyl)ethan-1-amine hydrochloride, 99



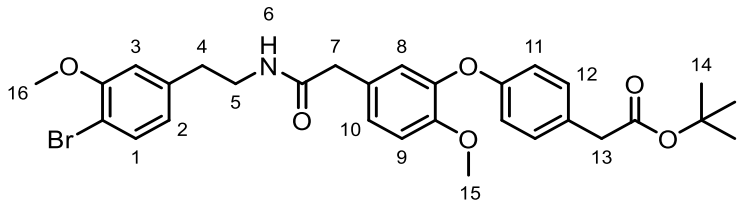
Adapted from the procedure of Pieper[90] To a suspension of sodium borohydride (1.25 g, 33.1 mmol, 4.75 equiv.) in THF (10 mL) at 0 °C under an inert atmosphere, was added boron trifluoride–diethyl etherate (5.17 mL, 41.9 mmol, 6.00 equiv.) dropwise. The mixture was stirred at room temperature for 15 min and then a solution of (*E*)-1-bromo-2-methoxy-4-(2-nitrovinyl)benzene **92** (1.80 g, 7.00 mmol, 1.00 equiv.) in THF (50 mL) was added dropwise at 0 °C. The mixture was then heated to 50 °C for 12 h. The reaction mixture was then cooled to 0 °C and H_2O was added dropwise until gas evolution had ceased. The mixture was then acidified with HCl (aq., 1 M) to pH 2, and the solution was stirred at room temperature for 2 h. The reaction mixture was then washed with Et_2O (10 mL). The resulting aqueous phase was basified with NaOH (aq., 1 M) to pH 12 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The free base was then treated with HCl (1.0 M in diethyl ether) and the volatiles were evaporated to afford the title compound as a white amorphous solid (1.66 g, 6.23 mmol, 89%). The compound was stored as the hydrochloride salt for stability reasons.

R_f 0.01 (EtOAc), [UV, ninhydrin]

^{1}H NMR (400 MHz, methanol-d_4) δ 7.48 (d, J = 8.0 Hz, 1H, H1), 6.98 (d, J = 2.0 Hz, 1H, H3), 6.78 (dd, J = 8.0, 2.0 Hz, 1H, H2), 3.89 (s, 3H, H6), 3.18 (t, J = 7.6 Hz, 2H, H4), 2.94 (t, J = 7.6 Hz, 2H, H5). Note: NH_2 resonance was not observed.

^{13}C NMR (101 MHz, methanol-d_4) δ 156.3, 137.7, 133.2, 121.7, 112.6, 109.8, 55.3, 40.4, 33.2. Spectroscopic data is in agreement with that reported previously.[140]

***tert*-Butyl 2-(4-(5-(2-((4-bromo-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy)phenyl)acetate, 77**



Adapted from the Procedure of McHugh[142] To a solution of 2-(3-(4-(2-(*tert*-butoxy)-2-oxoethyl)phenoxy)-4-methoxyphenyl)acetic acid **83** (0.28 g, 0.75 mmol, 1.0 equiv.), 2-(4-bromo-3-methoxyphenyl)ethan-1-amine hydrochloride **99** (0.22 g, 0.81 mmol, 1.1 equiv.) and *N,N*-diisopropylethylamine (0.58 mL, 3.3 mmol, 4.4 equiv.) in anhydrous CH_2Cl_2 (2.5 mL) at 0 ºC under an inert atmosphere was added propylphosphonic anhydride solution (50% in DMF, 0.76 mL, 1.3 mmol, 1.7 equiv.) dropwise over 2 min. The reaction mixture was warmed to room temperature and stirred for 6 h. Upon completion, the mixture was diluted with CH_2Cl_2 (5 mL) and washed sequentially with H_2O (10 mL), HCl (aq., 1 M, 10 mL) and $NaHCO_3$ (aq., sat., 10 mL). The organic phase was then washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography (pentane/EtOAc, 1:3) afforded the title compound as an off-white solid (0.32 mg, 0.55 mmol, 73%).

m.p. 83 – 85 ºC

R_f 0.21 (pentane/EtOAc, 1:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 1H, H1), 7.18 (d, *J* = 8.6 Hz, 2H, H12), 6.94 – 6.82 (m, 4H, H10, H9, H11), 6.78 (d, *J* = 1.9 Hz, 1H, H8), 6.64 (d, *J* = 1.8 Hz, 1H, H3), 6.51 (dd, *J* = 8.0, 1.8 Hz, 1H, H2), 5.45 (s, br, 1H, H6), 3.83 (2s, 6H, H15,

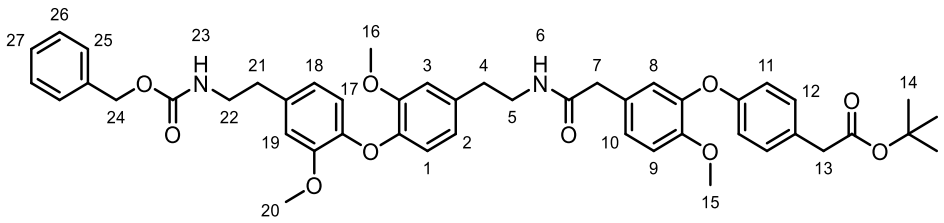
H16), 3.48 (s, 2H, H7), 3.47 – 3.43 (m, 2H, H5), 3.39 (s, 2H, H13), 2.69 (t, J = 6.8 Hz, 2H, H4), 1.43 (s, 9H, H14).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 171.1, 156.6, 156.0, 150.7, 145.4, 139.7, 133.3, 130.5(2C), 129.2, 127.5, 125.6, 122.1, 121.9, 117.4(2C), 113.2, 112.5, 109.7, 80.9, 56.3, 56.2, 42.9, 41.9, 40.5, 35.5, 28.2(3C).

IR (film) ν_{max}/cm^{-1} 3735, 2971, 2919, 1732, 1716, 1699, 1669, 1647, 1558, 1541.

HRMS (APCI) $C_{30}H_{34}Br^{79}NO_6$ found $[M+Na]^+$ at 608.1432, expected at 608.1444.

***tert*-Butyl 2-(4-(5-(2-((4-(4-(2-(((benzyloxy)carbonyl)amino)ethyl)-2-methoxy phenoxy)-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy)phenyl) acetate, 76**



Benzyl (4-hydroxy-3-methoxyphenethyl)carbamate **78** (0.21 g, 0.70 mmol, 1.8 equiv.), *tert*-butyl 2-(4-(5-(2-((4-bromo-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxy phenoxy)phenyl)acetate **77** (225 mg, 0.385 mmol, 1.0 equiv.), potassium carbonate (133 mg, 0.963 mmol) and cupric oxide (61 mg, 0.77 mmol) in anhydrous pyridine (1 mL) were submitted to **General Procedure B**. Purification by flash column chromatography (pentane/EtOAc, 1:1) afforded the title compound as a bright yellow oil (158 mg, 0.196 mmol, 51%).

R$_f$ 0.11 (pentane/EtOAc, 1:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H, H25, H26, H27), 7.17 (d, *J* = 8.6 Hz, 2H, H12), 6.92 – 6.89 (m, 2H, H8, H9 or H10), 6.85 (d, *J* = 8.6 Hz, 2H, H11), 6.82 – 6.76 (m, 2H, H19, H9 or H10), 6.75 – 6.61 (m, 4H, H1, H3, H18, H17), 6.52 (dd, *J* = 7.5, 1.9 Hz, 1H, H2), 5.44 (s, br, 1H, H6), 5.10 (s, 2H, H24), 4.83 (s, br, 1H, H23), 3.83 – 3.75 (m, 9H, H15, H16, H20), 3.50 – 3.38 (m, 8H, H22, H13, H7, H5), 2.78 (t, *J* = 7.0 Hz, 2H, H21), 2.69 (t, *J* = 7.0 Hz, 2H, H4), 1.43 (s, 9H, H14).

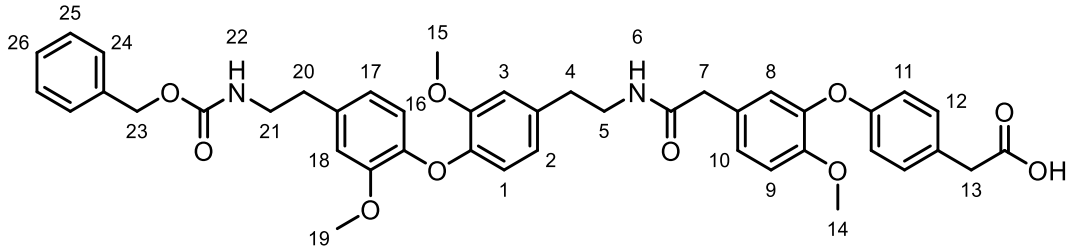
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 171.0, 156.6, 156.4, 150.7, 150.6, 150.5, 145.4, 144.8, 144.6, 136.6, 134.4(2C), 130.5(2C), 129.1, 128.6(2C), 128.2(3C), 127.6, 125.6,

121.9, 120.9, 120.8, 118.9, 118.7, 117.4(2C), 113.3, 113.1, 113.0, 80.9, 66.7, 56.10, 56.06, 56.0, 42.9, 42.3, 41.8, 40.8, 35.9, 35.4, 28.1(3C).

IR (film) ν_{max}/cm^{-1} 2928, 1729, 1720, 1702, 1649, 1595, 1506, 1466, 1453, 1418, 1367.

HRMS (ESI$^+$) $C_{47}H_{52}N_2O_{10}$ found $[M+H]^+$ at 805.3688, expected at 805.3695.

2-(4-(5-(2-((4-(4-(2-(((Benzyloxy)carbonyl)amino)ethyl)-2-methoxyphenoxy)-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy)phenyl)acetic acid, 76b



To a solution of *tert*-butyl 2-(4-(5-(2-((4-(4-(2-(((benzyloxy)carbonyl)amino)ethyl)-2-methoxyphenoxy)-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy) phenyl) acetate **76** (510 mg, 0.630 mmol, 1.0 equiv.) in CH_2Cl_2 (2.1 mL) was added trifluoroacetic acid (870 μL, 11.4 mmol, 18 equiv.) and the mixture was stirred at 30 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (aq., sat., 8 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 1:9 → EtOAc/MeOH, 9:1) afforded the title compound as a pale-yellow foam (475 mg, 0.630 mmol, >99%).

R_f 0.28 (EtOAc/AcOH, 99:1), [UV, bromocresol green]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 5H, H24, H25, H26), 7.13 (d, *J* = 8.2 Hz, 2H, H12), 6.91 – 6.85 (m, 2H, ArH), 6.81 – 6.73 (m, 4H, H11, ArH), 6.71 – 6.58 (m, 4H, ArH), 6.49 (dd, *J* = 8.2, 1.9 Hz, 1H, H2), 5.84 (s, br, 1H, H6), 5.11 – 5.00 (m, 3H, H22, H23), 3.79 – 3.68 (m, 9H, H14, H15, H19), 3.50 (s, 2H, H13), 3.46 – 3.33 (m, 6H, H5, H7, H21), 2.74 (t, *J* = 7.1 Hz, 2H, H20), 2.66 (t, *J* = 7.1 Hz, 2H, H4).

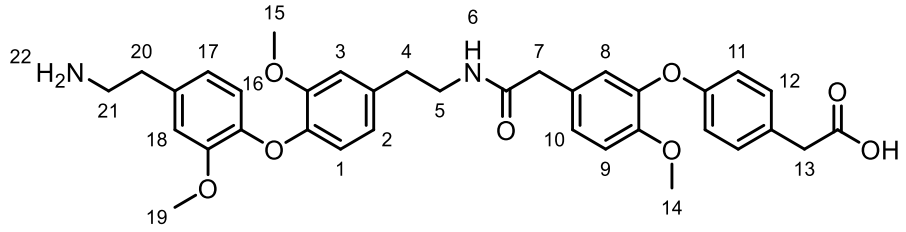
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 171.5, 156.6, 156.5, 150.6, 150.5, 150.4, 148.3, 145.1, 144.6, 136.5, 134.43, 134.38, 130.6(2C), 128.7, 128.5(3C), 128.2(2C), 128.1(2C),

127.6, 125.5, 121.9, 120.9, 120.8, 118.73, 118.65, 117.3, 113.2, 113.1, 113.0, 66.7, 55.99, 55.95(2C), 42.6, 42.3, 40.80, 40.75, 35.8, 35.1.

IR (film) ν_{max}/cm^{-1} 3360, 2937, 2839, 2360, 1697, 1649, 1596, 1539, 1506, 1453, 1268, 1220.

HRMS (ESI^+) $C_{43}H_{44}N_2O_{10}$ found $[M+2Na-H]^+$ at 749.3064, expected at 749.3069.

2-(4-(5-(2-((4-(4-(2-Aminoethyl)-2-methoxyphenoxy)-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy)phenyl)acetic acid, 100



To a flask containing Pd/C (10% wt., 8.2 mg, 7.7 μmol, 0.07 equiv.) under an inert atmosphere, was added MeOH (0.1 mL) and the flask was evacuated and backfilled with hydrogen (×3). 2-(4-(5-(2-((4-(4-(2-(((Benzyloxy)carbonyl)amino)ethyl)-2-methoxy phenoxy)-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy)phenyl) acetic acid **76b** (82 mg, 0.11 mmol, 1.0 equiv.) was then added as a solution in MeOH (0.5 mL) and the resulting mixture was stirred under a hydrogen atmosphere for 3 h. The reaction mixture was filtered through a pad of Celite®, the filter cake was washed (CH_2Cl_2/MeOH, 9:1) and the filtrate was concentrated *in vacuo.* The title compound was collected as a white foam (67 mg, 0.11 mmol, >99%). No further purification was necessary.

R_f 0.10 (CH_2Cl_2/MeOH, 9:1), [UV, ninhydrin]

^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 7.19 (d, *J* = 8.6 Hz, 2H, H12), 6.98 – 6.96 (m, 2H, H9, H10), 6.93 (d, *J* = 1.9 Hz, 1H, H18), 6.89 (d, *J* = 1.9 Hz, 1H, H3), 6.88 – 6.82 (m, 1H, H8), 6.71 (d, *J* = 8.6 Hz, 2H, H11), 6.67 (dd, *J* = 8.2, 1.9 Hz, 1H, H17), 6.65 – 6.61 (m, 2H, H1, H16), 6.57 (dd, *J* = 8.2, 1.9 Hz, 1H, H2), 3.82 (s, 3H, H19), 3.77 (s, 3H, H15), 3.70 (s, 3H, H14), 3.43 (t, *J* = 6.7 Hz, 2H, H5), 3.40 (s, 2H, H13), 3.34 (s, 2H, H7), 2.98 (t, *J* = 7.3 Hz, 2H, H21), 2.80 (t, *J* = 7.3 Hz, 2H, H20), 2.73 (t, *J* = 6.7 Hz, 2H, H4).

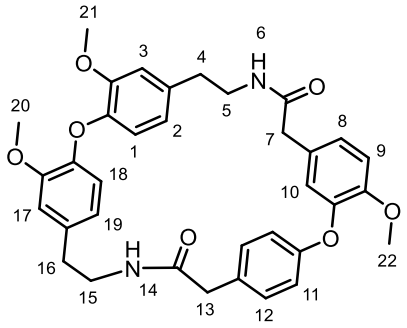
Note: CO_2H and NH_2 resonance were not observed.

^{13}C NMR (126 MHz, methanol-d_4) δ 180.5, 173.9, 157.7, 151.8, 151.75(2C), 146.4, 146.1, 145.6, 136.6, 134.8, 133.4, 131.2(2C), 129.9, 126.5, 123.0, 122.4, 122.2, 119.9, 119.6, 117.6(2C), 114.6(2C), 114.3, 56.6, 56.5, 56.4, 45.5, 43.0, 42.7, 41.8, 36.2, 36.0.

IR (film) ν_{max}/cm^{-1} 3399, 1679, 1641, 1508, 1467, 1426, 1274, 1205, 1132.

HRMS (ESI$^+$) $C_{35}H_{38}N_2O_8$ found $[M+H]^+$ at 614.2701, expected at 614.2695.

1^6,9^3,11^2-Trimethoxy-2,10-dioxa-6,14-diaza-1(1,3),3,9,11(1,4)-tetrabenzenacyclohexa decaphane-5,15-dione, 75



Adapted from the Procedure of McHugh[142] To a solution of 2-(4-(5-(2-((4-(4-(2-aminoethyl)-2-methoxyphenoxy)-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxy phenoxy)phenyl)acetic acid **100** (35 mg, 57 µmol, 1.0 equiv.) and *N,N*-diisopropylethylamine (34 µL, 0.19 mmol, 3.4 equiv.) in anhydrous CH_2Cl_2 (2.9 mL) at 0 ºC under an inert atmosphere was added propylphosphonic anhydride solution (50% in DMF, 60 µL, 97 µmol, 1.7 equiv.) dropwise over 5 min. The reaction mixture was warmed to room temperature and stirred for 20 h. Upon completion, the mixture was diluted with CH_2Cl_2 (3 mL) and washed sequentially with H_2O (4 mL), HCl (aq., 1 M, 4 mL) and $NaHCO_3$ (aq., sat., 4 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography (CH_2Cl_2/MeOH, 93:7) afforded the title compound as an off-white foam (22 mg, 36 µmol, 63%).

R_f 0.36 (CH_2Cl_2/MeOH, 93:7), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dd, *J* = 8.3, 2.1 Hz, 1H, H8), 6.93 (d, *J* = 8.3 Hz, 1H, H9), 6.90 (d, *J* = 8.5 Hz, 2H, H12), 6.69 – 6.65 (m, 2H, H3, H17), 6.63 – 6.59 (m, 3H, H11, H10), 6.56 (d, *J* = 8.1 Hz, 1H, H18), 6.54 (d, *J* = 8.2 Hz, 1H, H1), 6.49 (dd, *J* = 8.2, 1.9 Hz, 1H, H2), 5.99 (dd, *J* = 8.1, 1.9 Hz, 1H, H19), 5.19 – 5.11 (m, 2H, H6, H14),

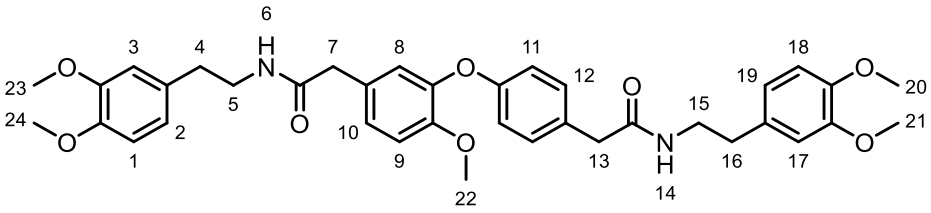
3.90 (s, 3H, H21), 3.83 (s, 3H, H22), 3.79 (s, 3H, H20), 3.58 – 3.52 (m, 2H, H5), 3.47 – 3.40 (m, 6H, H7, H13, H15), 2.73 (t, J = 6.0 Hz, 2H, H4), 2.68 – 2.62 (m, 2H, H16).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 170.9, 157.7, 151.5, 151.2, 150.1, 145.1, 144.0, 143.7, 134.7, 133.5, 130.8(2C), 128.4, 127.3, 126.8, 123.4, 121.1, 120.0, 119.7, 117.8, 116.4(2C), 113.30, 113.25, 112.1, 56.03, 55.97, 55.9, 43.2, 43.1, 40.1, 39.5, 34.5, 34.3.

IR (film) ν_{max}/cm^{-1} 3272.39, 2936, 1647, 1506, 1463, 1419, 1362, 1268, 1222.

HRMS (ESI+) $C_{35}H_{36}N_2O_7$ found $[M+H]^+$ at 597.2593, expected at 597.2595.

_N_-(3,4-Dimethoxyphenethyl)-2-(4-(5-(2-((3,4-dimethoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy)phenyl)acetamide, 105



_N_-(3,4-Dimethoxyphenethyl)-2-(3-hydroxy-4-methoxyphenyl)acetamide **133** (0.10 g, 0.29 mmol) and 2-(4-bromophenyl)-_N_-(3,4-dimethoxyphenethyl)acetamide **125** (0.10 g, 0.26 mmol), potassium carbonate (0.10 g, 0.73 mmol) and cupric oxide (46 mg, 0.58 mmol) in anhydrous pyridine (0.4 mL) were submitted to **General Procedure B**. Purification by flash column chromatography (EtOAc/MeOH 1:0 → 9:1) afforded the title compound as a brown amorphous solid (125 mg, 0.19 mmol, 75%).

R_f 0.10 (EtOAc), [UV, PMA]

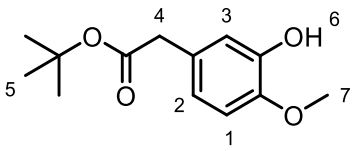
^{1}H NMR (500 MHz, CDCl3) δ 7.08 (d, *J* = 8.5 Hz, 2H, H12), 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H, H10), 6.93 (d, *J* = 8.4 Hz, 1H, H9), 6.83 (d, *J* = 8.5 Hz, 2H, H11), 6.80 (d, *J* = 2.0 Hz, 1H, H8), 6.74 (d, *J* = 8.2 Hz, 1H, H1 or H18), 6.72 (d, *J* = 8.1 Hz, 1H, H1 or H18), 6.63 (dd, *J* = 5.0, 2.0 Hz, 2H, H3, H17), 6.58 – 6.54 (m, 2H, H2, H19), 5.51 (t, *J* = 5.7 Hz, 1H, NH), 5.46 (t, *J* = 6.0 Hz, 1H, NH), 3.87 – 3.75 (m, 15H, H20, H21, H22, H23, H24), 3.49 – 3.39 (m, 8H, H5, H7, H13, H15), 2.70 – 2.65 (m, 4H, H4, H16).

^{13}C NMR (126 MHz, CDCl3) δ 171.1, 170.9, 157.1, 150.8, 149.2, 149.1, 147.8, 147.7, 144.9, 131.3, 131.2, 130.8(2C), 129.0, 127.9, 125.9, 122.2, 120.8, 120.7, 117.6(2C), 113.2, 111.9(2C), 111.4, 111.3, 56.12, 55.99, 55.97, 55.93(2C), 43.1, 42.9, 40.9, 40.9, 35.2, 35.2.

IR (film) ν_{max}/cm^{-1} 3265, 2358, 2341, 1647, 1557, 1540, 1515.

HRMS (ESI$^+$) $C_{37}H_{42}N_2O_8$ found $[M+H]^+$ at 643.3014, expected at 643.3014.

***tert*-Butyl 2-(3-hydroxy-4-methoxyphenyl)acetate, 117**



Procedure 1: To a solution of 3-hydroxy-4-methoxyphenylacetic acid **83** (2.00 g, 11.0 mmol, 1.0 equiv.) in anhydrous toluene (14 mL) at room temperature under an inert atmosphere was added *N,N*-dimethylformamide di-*tert*-butyl acetal (10.5 mL, 43.9 mmol, 4.0 equiv.). The mixture was heated to 80 ºC and stirred for 30 min then concentrated *in vacuo*. The residue was diluted with EtOAc and washed sequentially with $NaHCO_3$ (aq., sat., 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 9:1) afforded the title compound as a pale-yellow liquid (992 mg, 4.16 mmol, 38%).

Procedure 2: *Following the procedure of Li et al.*[131] To a solution of 3-hydroxy-4-methoxyphenylacetic acid **83** (100 mg, 0.549 mmol, 1.0 equiv.) in *tert*-butanol (0.6 mL) at room temperature under and inert atmosphere was added 4-dimethylaminopyridine (20.2 mg, 0.165 mmol, 0.3 equiv.) and di-*tert*-butyl dicarbonate (240 mg, 1.10 mmol, 2.0 equiv.). The reaction mixture was stirred for 24 h then the solvent was removed azeotropically with EtOAc. The residue was then dissolved in MeOH (2.7 mL) and potassium carbonate (76.0 mg, 0.549 mmol, 1.0 equiv.) was added. The mixture was stirred for 18 h then filtered and concentrated *in vacuo*. Purification by flash column chromatography (pentane/EtOAc, 9:1) afforded the title compound as a colourless oil (66.7 mg, 0.280 mmol, 51% over two steps).

R_f 0.19 (pentane/EtOAc, 9:1), [UV, PMA]

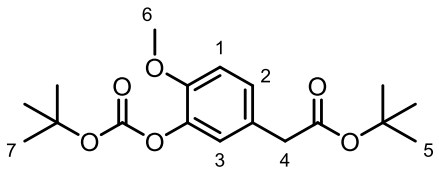
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 2.1 Hz, 1H, H3), 6.79 (d, *J* = 8.3 Hz, 1H, H1), 6.74 (dd, *J* = 8.3, 2.1 Hz, 1H, H2), 5.70 (s, 1H, H6), 3.85 (s, 3H, H7), 3.42 (s, 2H, H4), 1.44 (s, 9H, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 145.7, 145.6, 128.0, 120.8, 115.6, 110.7, 80.8, 56.0, 42.1, 28.1(3C).

IR (film) ν_{max}/cm^{-1} 3434, 2978, 1726, 1592, 1138, 761.

HRMS (ESI$^+$) $C_{13}H_{18}O_4$ found $[M+Na]^+$ at 261.1098, expected at 261.1097.

tert-Butyl 2-(3-((_tert_-butoxycarbonyl)oxy)-4-methoxyphenyl)acetate, 118



Following the procedure of Li et al.[131] To a solution of 3-hydroxy-4-methoxyphenylacetic acid **83** (200 mg, 1.10 mmol, 1.0 equiv.) in *tert*-butanol (1.25 mL) at room temperature under an inert atmosphere was added 4-dimethylaminopyridine (40 mg, 0.33 mmol, 0.3 equiv.) and di-*tert*-butyl dicarbonate (0.48 g, 2.2 mmol, 2.0 equiv.). The reaction mixture was stirred for 24 h. The solvent was then removed azeotropically with EtOAc. Purification by flash column chromatography (pentane/EtOAc, 9:1) afforded the title compound as a colourless oil (0.17 g, 0.73 mmol, 66%).

R$_f$ 0.31 (pentane/EtOAc, 9:1), [UV, PMA]

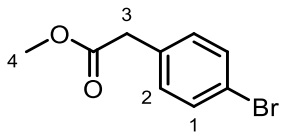
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.4, 2.2 Hz, 1H, H2), 7.05 (d, *J* = 2.2 Hz, 1H, H3), 6.90 (d, *J* = 8.4 Hz, 1H, H1), 3.83 (s, 3H, H6), 3.45 (s, 2H, H4), 1.55 (s, 9H, H7), 1.42 (s, 9H, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 151.7, 150.3, 140.1, 127.5, 127.3, 123.5, 112.5, 83.5, 81.0, 56.1, 41.8, 28.2, 27.8.

IR (film) ν_{max}/cm^{-1} 2979, 1761, 1731, 1514, 1129, 781.

HRMS (ESI$^+$) $C_{18}H_{26}O_6$ found $[M+Na]^+$ at 361.1620, expected at 361.1622.

Methyl 2-(4-bromophenyl)acetate, 116



Following the procedure of Okada et al.[143] To a solution of 4-bromophenylacetic acid **84** (5.0 g, 23 mmol, 1.0 equiv.) in acetone (200 mL) was added potassium carbonate (3.2 g, 23 mmol, 1.0 equiv.) and iodomethane (2.9 mL, 47 mmol, 2.0 equiv.). The reaction mixture was heated to 60 ºC for 18 h. The mixture was then filtered and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (100 mL), washed with H_2O (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as a colourless liquid (4.9 g, 22 mmol, 94%). No further purification was necessary.

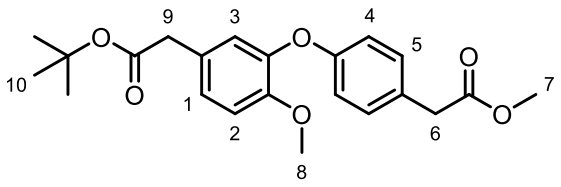
R_f 0.63 (pentane/EtOAc, 6:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 1H, H1), 7.16 (d, *J* = 8.4 Hz, 2H, H2), 3.69 (s, 3H, H4), 3.58 (s, 2H, H3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 133.0, 131.8(2C), 131.2(2C), 121.3, 52.3, 40.7.

Spectroscopic data is in agreement with that reported previously.[143]

***tert*-Butyl 2-(4-methoxy-3-(4-(2-methoxy-2-oxoethyl)phenoxy)phenyl)acetate, 119**



Methyl 2-(4-bromophenyl)acetate **116** (1.00 g, 4.37 mmol), *tert*-butyl 2-(3-hydroxy-4-methoxyphenyl)acetate **117** (1.14 g, 4.80 mmol), potassium carbonate (1.51 g, 10.9 mmol) and cupric oxide (694 mg, 8.73 mmol) in anhydrous pyridine (2.9 mL) were submitted to **General Procedure B**. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a white solid. (773 mg, 2.00 mmol, 46%).

R$_f$ 0.35 (pentane/EtOAc, 4:1), [UV, PMA]

m.p. 78 – 79 ºC.

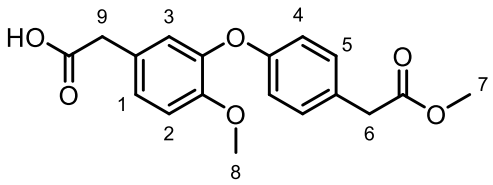
^{1}H NMR (400 MHz, $CDCl_3$) 7.19 (d, *J* = 8.6 Hz, 2H, H5) 7.02 (dd, *J* = 8.4, 2.2 Hz, 1H, H1), 6.94 (d, *J* = 8.4 Hz, 1H, H2), 6.92 – 6.87 (m, 3H, H3, H4), 3.82 (s, 3H, H8), 3.69 (s, 3H, H7), 3.58 (s, 2H, H6), 3.41 (s, 2H, H9), 1.40 (s, 9H, H10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 171.0, 157.2, 150.5, 144.9, 130.5(2C), 128.1, 127.8, 125.6, 122.1, 117.5(2C), 112.9, 81.0, 56.2, 52.2, 41.9, 40.5, 28.2(3C).

IR (film) ν_{max}/cm^{-1} 2948, 2838, 1734, 1609, 1508, 769.

HRMS (ESI$^+$) $C_{22}H_{26}O_6$ found $[M+NH_4]^+$ at 404.2062, expected at 404.2067.

2-(4-Methoxy-3-(4-(2-methoxy-2-oxoethyl)phenoxy)phenyl)acetic acid, 120



To a solution of *tert*-butyl 2-(4-methoxy-3-(4-(2-methoxy-2-oxoethyl)phenoxy) phenyl)acetate **119** (1.22 g, 3.17 mmol, 1.0 equiv.) in CH_2Cl_2 (11 mL) was added TFA (1.46 mL, 19.0 mmol, 6.0 equiv.) and mixture stirred at 30 ºC for 3 h. The reaction mixture was neutralised with $NaHCO_3$ (aq., sat.) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as a white solid (1.03 g, 3.11 mmol, 98%). No further purification was necessary.

R$_f$ 0.57 (EtOAc), [UV, PMA]

m.p. 95 – 97 ºC.

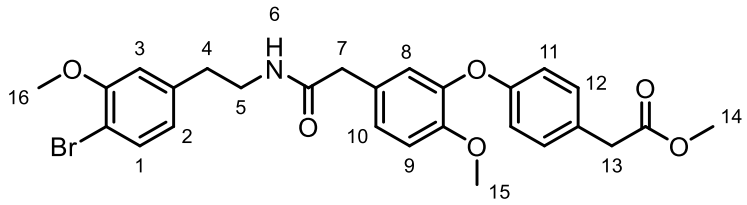
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 2H, H5), 7.03 (dd, *J* = 8.4, 2.2 Hz, 1H, H1), 6.95 (d, *J* = 8.4 Hz, 1H, H2), 6.92 – 6.85 (m, 3H, H3, H4), 3.82 (s, 3H, H8), 3.69 (s, 3H, H7), 3.58 (s, 2H, H6), 3.54 (s, 2H, H9).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 172.4, 157.0, 150.8, 145.0, 130.6(2C), 128.2, 126.4, 125.7, 122.2, 117.5(2C), 113.0, 56.2, 52.2, 40.5, 40.1.

IR (film) ν_{max}/cm^{-1} 3039, 2953, 2842, 1735, 1712, 1507, 1270, 1026, 773.

HRMS (ESI$^+$) $C_{18}H_{18}O_6$ found $[M+Na]^+$ at 353.0993, expected at 353.0996.

Methyl 2-(4-(5-(2-((4-bromo-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxyphenoxy)phenyl)acetate, 115



Adapted from the Procedure of McHugh[142] To a solution of 2-(4-methoxy-3-(4-(2-methoxy-2-oxoethyl)phenoxy)phenyl)acetic acid **120** (365 mg, 1.10 mmol, 1.00 equiv.) and 2-(4-Bromo-3-methoxyphenyl)ethan-1-amine hydrochloride **99** (323 mg, 1.21 mmol, 1.10 equiv.) in anhydrous CH_2Cl_2 (4.4 mL) under an inert atmosphere was added *N,N*-diisopropylethylamine (0.840 mL, 4.84 mmol, 4.40 equiv.) and the mixture was cooled to 0 ºC. Propylphosphonic anhydride solution (50% in DMF, 1.11 mL, 1.87 mmol, 1.70 equiv.) was then added dropwise over 5 min. The reaction mixture was brought to room temperature and stirred for 6 h. Upon completion, the mixture was diluted with CH_2Cl_2 (10 mL) and washed sequentially with H_2O (6 mL), HCl (aq., 1 M, 6 mL) and $NaHCO_3$ (aq., sat., 6 mL). The organic phase was then washed with brine (4 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) afforded the title compound as a pale-yellow oil (491 mg, 0.906 mmol, 82%).

R_f 0.43 (EtOAc), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.0 Hz, 1H, H1), 7.18 (d, *J* = 8.6 Hz, 2H, H12), 6.90 (d, *J* = 8.4 Hz, 1H, H9), 6.88 (dd, *J* = 8.4, 1.9 Hz, 1H, H10), 6.85 (d, *J* = 8.6 Hz, 2H, H11), 6.78 (d, *J* = 2.0 Hz, 1H, H3), 6.63 (d, *J* = 1.9 Hz, 1H, H8), 6.49 (dd, *J* = 8.0, 2.0 Hz, 1H, H2), 5.53 (s, br, 1H, H6), 3.82 (s, 3H, H16) 3.81(s, 3H, H15), 3.67 (s,

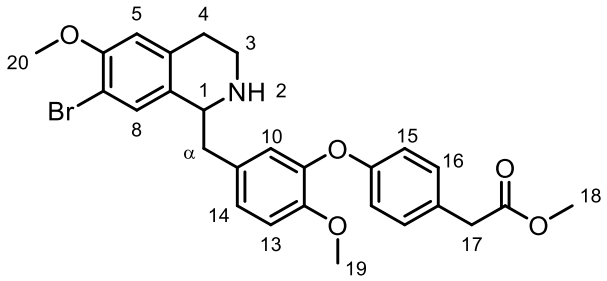
3H, H14), 3.57 (s, 2H, H13), 3.42 (q, J = 6.8 Hz, 2H, H5), 3.37 (s, 2H, H7), 2.68 (t, J = 6.8 Hz, 2H, H4).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 170.9, 156.8, 156.0, 150.7, 145.2, 139.7, 133.2, 130.5(2C), 128.3, 127.6, 125.6, 122.1, 121.9, 117.3(2C), 113.2, 112.5, 109.6, 56.2, 56.1, 52.1, 42.9, 40.4, 40.4, 35.4.

IR (film) ν_{max}/cm^{-1} 3300, 2949, 1735, 1647, 1506.

HRMS (ESI$^+$) $C_{27}H_{28}Br^{79}NO_6$ found $[M+H]^+$ at 542.1172, expected at 542.1173.

Methyl 2-(4-(5-((7-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxy phenoxy)phenyl)acetate, 121



Methyl 2-(4-(5-(2-((4-bromo-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxy phenoxy)phenyl)acetate **115** (43 mg, 80 µmol), 2-chloropyridine (9.0 µL, 95 µmol) and trifluoromethanesulfonic anhydride (15 µL, 87 µmol) in anhydrous CH_2Cl_2 (0.40 mL) were submitted to **General Procedure C**. The crude imine and sodium borohydride (6.0 mg, 0.16 mmol) in EtOH (0.55 mL) were submitted to **General Procedure D**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (4 mg, 7.6 µmol, 10% over 2 steps).

R_f 0.31 (EtOAc), [UV, PMA]

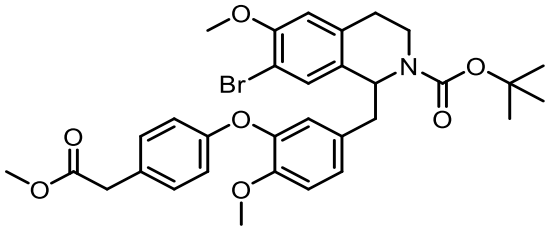
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H, H5), 7.20 (d, *J* = 8.6 Hz, 2H, H16), 6.99 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.95 (d, *J* = 8.3 Hz, 1H, H13), 6.89 (d, *J* = 8.6 Hz, 1H, H15) 6.86 (d, *J* = 2.1 Hz, 1H, H10), 6.60 (s, 1H, H8), 4.04 (dd, *J* = 9.7, 4.0 Hz, 1H, H1), 3.86 (s, 3H, H20), 3.83 (s, 3H, H19), 3.70 (s, 3H, H18), 3.59 (s, 2H, H17), 3.20 – 3.13 (m, 1H, $H3_A$), 3.09 (dd, *J* = 13.8, 4.0 Hz, 1H, $H\alpha_A$), 2.92 – 2.85 (m, 1H, $H3_B$), 2.81 – 2.65 (m, 3H, $H\alpha_B$, H4), 1.79 (s, br, 1H, H2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 157.1, 154.1, 150.3, 145.1, 136.0, 132.3, 131.8, 131.0, 130.6(2C), 128.1, 125.7, 121.9, 117.4(2C), 113.1, 112.5, 108.9, 56.5, 56.34, 56.26, 52.2, 41.7, 40.6, 40.5, 30.2.

IR (film) ν_{max}/cm^{-1} 2951, 2838, 1772, 1734, 1653, 1599, 1507.

HRMS (ESI$^+$) $C_{27}H_{28}Br^{79}NO_5$ $[M+H]^+$ at 526.1220, expected at 526.1224.

***tert*-Butyl 7-bromo-6-methoxy-1-(4-methoxy-3-(4-(2-methoxy-2-oxoethyl)phenoxy) benzyl)-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, 122**



Methyl 2-(4-(5-((7-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)phenyl)acetate **121** (4.0 mg, 7.6 µmol), di-*tert*-butyl dicarbonate (2.0 mg, 9.2 µmol) and triethylamine (1.0 µL, 9.2 µmol) in anhydrous CH_2Cl_2 (0.10 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 2:1) afforded the title compound as a pale-yellow oil (3.6 mg, 5.7 µmol, 75%).

R*f* 0.32 (pentane/EtOAc, 2:1), [UV, PMA]

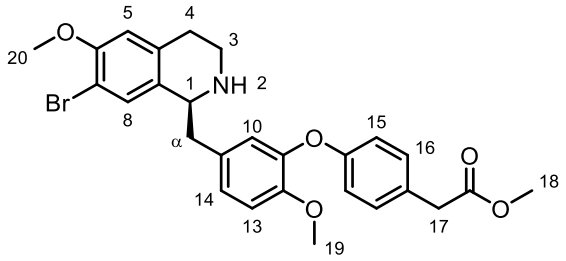
^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.20 – 7.14 (m, 2H, both rotamers), 7.09 (s, 0.64H, (M)), 7.01 (s, 0.36H, (m)), 6.94 – 6.80 (m, 4H, both rotamers), 6.70 – 6.55 (m, 2H, both rotamers), 5.21 (t, *J* = 6.9 Hz, 0.36H, (m)), 5.05 (t, *J* = 6.9 Hz, 0.64H, (M)), 4.12 – 4.05 (m, 0.64H, (M)), 3.86 – 3.83 (m, 3H, both rotamers), 3.81 (s, 2H, (M)), 3.79 (s, 1H, 0.36H, (m)), 3.70 (s, 3H, both rotamers), 3.60 – 3.55 (m, 2H, both rotamers), 3.27 – 3.11 (m, 1H, both rotamers), 2.95 – 2.50 (m, 4H, both rotamers), 1.41 (s, 3.3H, (m)), 1.31 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 172.4, 157.0, 154.5, 154.4, 150.2, 145.0, 135.4, 131.9, 131.3, 130.6(2C), 130.5, 128.2, 125.8, 122.1, 117.6(2C), 113.1, 112.2, 109.1, 80.0, 56.4(2C), 55.9, 52.2, 42.1, 40.5, 37.1, 29.0, 28.4(3C).

IR (film) ν_{max}/cm^{-1} 2933, 2839, 1767, 1687, 1602, 1559, 1507, 1165.

HRMS (ESI$^+$) $C_{32}H_{36}Br^{79}NO_7$ found $[M+Na]^+$ at 648.1567, expected at 648.1564.

Methyl (*S*)-2-(4-(5-((7-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)phenyl)acetate, (*S*)-121



Methyl 2-(4-(5-(2-((4-bromo-3-methoxyphenethyl)amino)-2-oxoethyl)-2-methoxy phenoxy)phenyl)acetate **115** (1.79 g, 3.31 mmol)**,** 2-chloropyridine (380 µL, 3.97 mmol) and trifluoromethanesulfonic anhydride (610 µL, 3.64 mmol) in anhydrous CH_2Cl_2 (16 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*R,R*)-TsDPEN](*p*-cymene) (147 mg, 230 µmol) and HCO_2H:Et_3N (5:2 v/v, 1.65 mL) in anhydrous DMF (16 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as an amber oil (733 mg, 1.39 mmol, 42% over 2 steps, 96% *ee* after Boc derivatisation).

R_f 0.31 (7:1:0.1, EtOAc/pentane/7N ammonia solution in MeOH), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H, H5), 7.20 (d, *J* = 8.2 Hz, 2H, H16), 6.99 (dd, *J* = 8.3, 2.0 Hz, 1H, H14), 6.95 (d, *J* = 8.3 Hz, 1H, H13), 6.88 (d, *J* = 8.2 Hz, 2H, H15), 6.85 (d, *J* = 2.0 Hz, 1H, H10), 6.60 (s, 1H, H8), 4.05 (dd, *J* = 9.8, 3.9 Hz, 1H, H1), 3.85 (s, 3H, H20), 3.83 (s, 3H, H19), 3.69 (s, 3H, H18), 3.59 (s, 2H, H17), 3.20 – 3.13 (m, 1H, $H3_A$), 3.09 (dd, *J* = 13.8, 3.9 Hz, 1H, $H\alpha_A$), 2.89 (dt, *J* = 12.3, 6.0 Hz, 1H, $H3_B$), 2.80 – 2.65 (m, 3H, $H\alpha_B$, H4), 2.13 (s, br, 1H, H2).

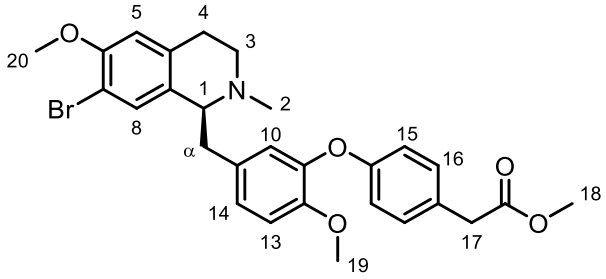
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 157.1, 154.1, 150.3, 145.1, 135.9, 132.1, 131.7, 131.0, 130.5(2C), 128.1, 125.7, 121.9, 117.4(2C), 113.1, 112.5, 108.9, 56.4, 56.3, 56.2, 52.2, 41.7, 40.7, 40.5, 30.1.

IR (film) ν_{max}/cm^{-1} 2837, 1735, 1653, 1599, 1507.

HRMS (ESI$^+$) $C_{27}H_{28}Br^{79}NO_5$ found $[M+H]^+$ at 526.1219, expected at 526.1224.

$[\alpha]_D^{25}$ –25.2 (c. 0.78, $CHCl_3$).

Methyl (*S*)-2-(4-(5-((7-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl) methyl)-2-methoxyphenoxy)phenyl)acetate, (*S*)-114



(S)-2-(4-(5-((7-Bromo-6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)phenyl)acetate **(*S*)-121** (0.12 g, 0.23 mmol), formalin (37% aq., 0.47 mL, 6.31 mmol), and sodium borohydride (26 mg, 0.69 mmol) in MeOH (4.6 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc → EtOAc:MeOH, 94:6) afforded the title compound as a green oil (94 mg, 0.17 mmol, 76%).

R_f 0.31 (EtOAc/MeOH, 94:6), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 2H, H16), 6.89 – 6.83 (m, 4H, H5, H10, H15), 6.81 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.55 (s, 1H, H8), 3.83 (s, 3H, H20), 3.80 (s, 3H, H19), 3.69 (s, 3H, H18), 3.66 – 3.52 (m, 1H, H1), 3.58 (s, 2H, H17), 3.15 – 3.06 (m, 1H, $H3_A$), 2.99 (dd, *J* = 13.9, 5.8 Hz, 1H, $H\alpha_A$), 2.81 – 2.73 (m, 2H, $H\alpha_B$, $H4_A$), 2.69 (dt, *J* = 12.4, 5.0 Hz, 1H, $H3_B$), 2.54 (dt, *J* = 16.1, 5.0 Hz, 1H, $H4_B$), 2.45 (s, 3H, H2).

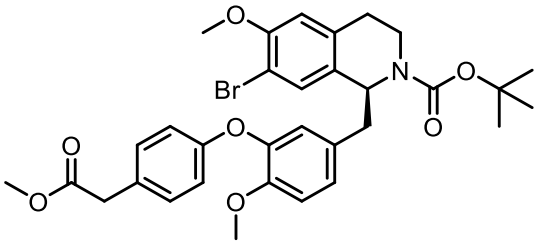
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 157.4, 153.9, 150.0, 144.3, 135.2, 132.6, 132.5, 131.2, 130.4(2C), 127.8, 126.2, 122.7, 117.1(2C), 112.7, 111.9, 108.4, 64.2, 56.3(2C), 52.1, 47.0, 42.8, 40.5, 40.2, 26.3.

IR (film) ν_{max}/cm^{-1} 2947, 2909, 2837, 1736, 1599, 1506, 1222, 731.

HRMS (ESI$^+$) $C_{28}H_{30}Br^{79}NO_5$ found $[M+H]^+$ at 540.1373, expected at 540.1380.

$[\alpha]_D^{25}$ +9.82 (c. 1.71, $CHCl_3$).

***tert*-Butyl (*S*)-7-bromo-6-methoxy-1-(4-methoxy-3-(4-(2-methoxy-2-oxoethyl)phenoxy) benzyl)-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, (*S*)-122**



(S)-2-(4-(5-((7-Bromo-6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)phenyl)acetate **(*S*)-121** (26 mg, 50 µmol), di-*tert*-butyl dicarbonate (13 mg, 58 µmol) and triethylamine (8.0 µL, 58 µmol) in anhydrous CH_2Cl_2 (0.26 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 2:1) afforded the title compound as a pale-yellow oil (25 mg, 39 µmol, 79%, 96% *ee*).

R*f* 0.32 (pentane/EtOAc, 2:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.22 – 7.14 (m, 2H, both rotamers), 7.08 (s, 0.64H, (M)), 7.01 (m, 0.36H, (m)), 6.95 – 6.78 (m, 4H, both rotamers), 6.70 – 6.56 (m, 2H, both rotamers), 5.21 (t, *J* = 6.9 Hz, 0.36H, (m)), 5.05 (t, *J* = 6.9 Hz, 0.64H, (M)), 4.14 – 4.05 (m, 0.64H, (M)), 3.86 (s, 3H, both rotamers), 3.82 – 3.78 (m, 3H, both rotamers), 3.77 – 3.73 (m, 0.36H, (m)), 3.69 (s, 3H, both rotamers), 3.61 – 3.65 (m, 2H, both rotamers), 3.28 – 3.10 (m, 1H, both rotamers), 3.00 – 2.66 (m, 3H, both rotamers), 2.64 – 2.47 (m, 1H, both rotamers), 1.41 (s, 3.3H, (m)), 1.31 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 172.3, 157.0, 154.5, 154.4, 150.2, 145.0, 135.4, 131.9, 131.2, 130.5(2C), 130.4, 128.1, 125.8, 122.1, 117.6(2C), 113.0, 112.1, 109.0, 80.0, 56.4(2C), 55.9, 52.1, 42.1, 40.5, 37.0, 28.7, 28.4(3C).

IR (film) ν_{max}/cm^{-1} 2933, 2839, 1767, 1687, 1602, 1559, 1507, 1165.

HRMS (ESI$^+$) $C_{32}H_{36}Br^{79}NO_7$ found $[M+H]^+$ at 626.1750, expected at 626.1748.

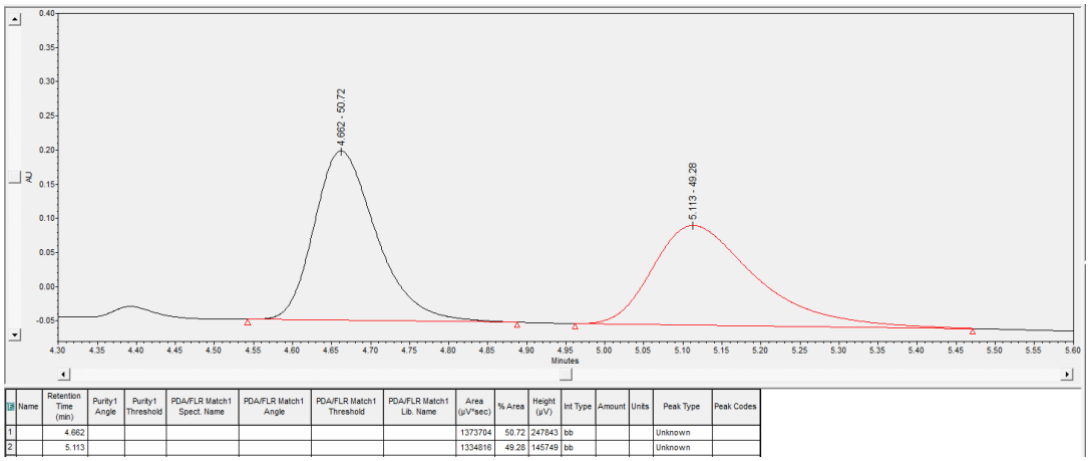
$[\alpha]_D^{25}$ +29.1 (c. 1.23, $CHCl_3$).

SFC trace of racemic (±)-**122** and enantioenriched (+)-**122**

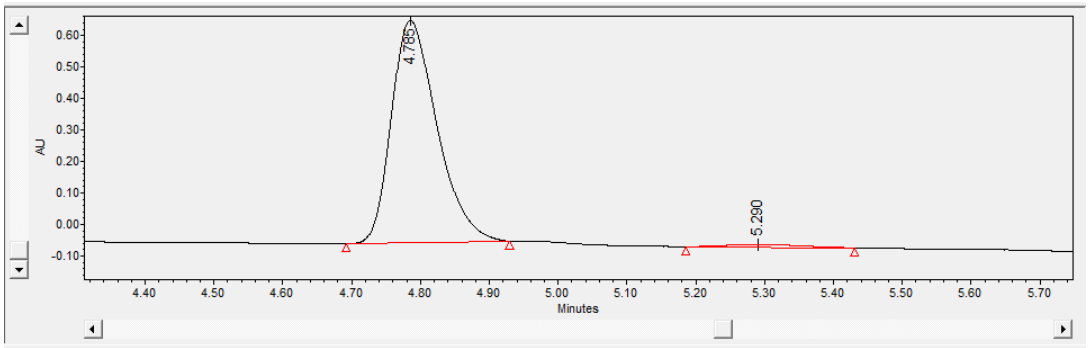
SFC Chiralpak® IA 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min.

(+)-**122**: 98.1:1.9 *e.r.* (major enantiomer t_R = 4.78 min; minor enantiomer t_R = 5.29 min).

λ = 215.0 nm.

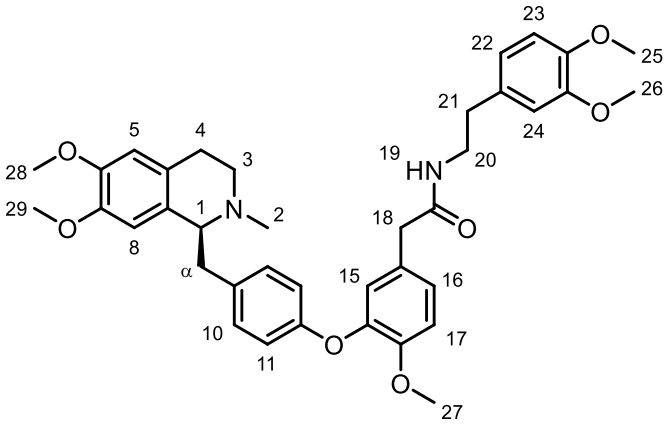


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		4.662							1373704	50.72	247843	bb			Unknown	
2		5.113							1334816	49.28	145749	bb			Unknown	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Pe
1		4.785							3250726	98.12	705593	bb			Unknown	
2		5.290							62405	1.88	8851	bb			Unknown	

(*S*)-2-(3-(4-((6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenoxy)-4-methoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide, (*S*)-124



(*S*)-1-(4-bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-51** (50 mg, 0.14 mmol), *N*-(3,4-dimethoxyphenethyl)-2-(3-hydroxy-4-methoxyphenyl) acetamide **123** (56 mg, 0.16 mmol), potassium carbonate (47 mg, 0.27 mmol) and cupric oxide (22 mg, 0.34 mmol) in anhydrous pyridine (0.25 mL) were submitted to **General Procedure B**. Purification by flash column chromatography (EtOAC/7N ammonia solution in MeOH, 7:0.1) afforded the title compound as a pale-yellow foam (54 mg, 83 μmol, 61%).

R*f* 0.07 (EtOAc/7N ammonia solution in MeOH, 7:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.6 Hz, 2H, H10), 6.91 – 6.89 (m, 2H, ArH), 6.80 (d, *J* = 8.6 Hz, 2H, H11), 6.75 – 6.70 (m, 2H, ArH), 6.62 (d, *J* = 2.0 Hz, 1H, ArH), 6.56 – 6.53 (m, 2H, H5, ArH), 6.07 (s, 1H, H8), 5.40 (t, *J* = 5.7 Hz, 1H, H19), 3.88 – 3.78 (m, 12H, H25, H26, H27, H29), 3.69 (dd, *J* = 7.3, 5.1 Hz, 1H, H1), 3.60 (s, 3H, H28), 3.45 – 3.40 (m, 2H, H20), 3.39 (s, 2H, H18), 3.22 – 3.10 (m, 2H, $H3_A$, $H\alpha_A$), 2.86 – 2.71 (m, 3H, $H4_A$, $H\alpha_B$, $H3_B$), 2.66 (t, *J* = 6.9 Hz, 2H, H21), 2.56 (dt, *J* = 15.5, 4.7 Hz, 1H, $H4_B$), 2.52 (s, 3H, H2).

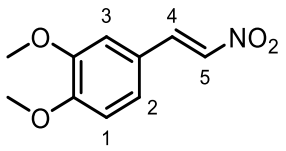
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 155.8, 150.6, 149.2, 147.8, 147.4, 146.4, 145.8, 134.6, 131.2, 131.0(2C), 129.3, 127.7, 126.2, 125.4, 121.5, 120.7, 117.3(2C), 113.2, 111.8, 111.3, 111.3, 111.2, 64.9, 56.2, 56.0, 55.9, 55.8, 55.7, 47.0, 43.1, 42.8, 40.8, 40.6, 35.2, 25.6.

IR (film) ν_{max}/cm^{-1} 3013, 2936, 2835, 1653, 1609, 1506, 1465, 1262, 1226.

HRMS (ESI^+) $C_{38}H_{44}N_2O_7$ found $[M+H]^+$ at 641.3217, expected at 641.3212.

$[\alpha]_D^{25}$ +38.0 (c. 1.13, $CHCl_3$).

***(E)*-1,2-Dimethoxy-4-(2-nitrovinyl)benzene, 128b**



3,4-Dimethoxybenzaldehyde **128** (5.00 g, 30.1 mmol), nitromethane (8.15 mL, 150 mmol) and ethylenediamine (200 μL, 3.01 mmol) in acetic acid (24.0 mL) were submitted to **General Procedure A**. The title compound was obtained as a yellow powder (5.71 g, 27.3 mmol, 91%).

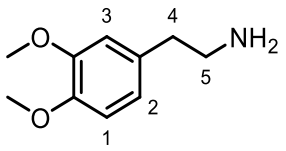
R*f* 0.89 (EtOAc), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 13.5 Hz, 1H, H4), 7.53 (d, *J* = 13.5 Hz, 1H, H5), 7.18 (dd, *J* = 8.3, 2.1 Hz, 1H, H2), 7.01 (d, *J* = 2.1 Hz, 1H, H3), 6.91 (d, *J* = 8.3 Hz, 1H, H1), 3.94 (s, 3H, ArOC*H*$_3$), 3.93 (s, 3H, ArOC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 149.7, 139.5, 135.3, 124.8, 123.0, 111.5, 110.4, 56.24, 56.17.

Spectroscopic data is in agreement with that reported previously.[89]

2-(3,4-Dimethoxyphenyl)ethan-1-amine, 127



To a suspension of $LiAlH_4$ (54.4 mg, 1.43 mmol, 3.0 equiv.) in anhydrous THF (1.9 mL) at 0 ºC under an inert atmosphere was added *(E)*-1,2-dimethoxy-4-(2-nitrovinyl)benzene **128b** (100 g, 0.478 mmol, 1.0 equiv.) slowly as a solution in THF (1.5 mL). The reaction mixture was then heated to 55 ºC for 18 h. The mixture was cooled to 0 ºC and diluted with diethyl ether (5 mL). H_2O (0.5 mL) was added slowly, and mixture stirred for 15 min then NaOH (aq., 1 M, 0.5 mL) was added slowly, and mixture stirred for a further 15 min. Finally, H_2O (1.5 mL) was added, and mixture stirred at room temperature for 30 min. The mixture was then dried over $MgSO_4$, filtered through Celite® and concentrated *in vacuo* to afford the title compound as a yellow liquid (83.2 mg, 0.459 mmol, 96%).

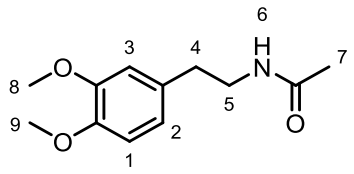
R_f 0.01 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.0 Hz, 1H, H1), 6.78 – 6.69 (m, 2H, H2, H3), 3.87 (s, 3H, ArOC*H*$_3$), 3.85 (s, 3H, ArOC*H*$_3$), 2.94 (t, *J* = 6.9 Hz, 2H, H5), 2.69 (t, *J* = 6.9 Hz, 2H, H4), 1.04 (s, br, 2H, NH_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 147.6, 132.6, 120.9, 112.2, 111.4, 56.1, 56.0, 43.8, 39.8.

Spectroscopic data is in agreement with that reported previously.[89]

***N*-(3,4-Dimethoxyphenethyl)acetamide, 129**



To a solution of 2-(3,4-dimethoxyphenyl)ethan-1-amine **127** (280 µL, 1.66 mmol, 1.0 equiv.) and triethylamine (0.240 mL, 1.74 mmol, 1.05 equiv.) in anhydrous CH_2Cl_2 (3.0 mL) at 0 ºC under an inert atmosphere was added acetyl chloride (0.120 mL, 1.74 mmol, 1.05 equiv.) dropwise. The reaction mixture was warmed to room temperature and stirred for 3 h. Upon completion, the reaction was quenched by addition of H_2O (3 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were sequentially washed with HCl (aq., 1 M, 5 mL), NaOH (aq., 1 M, 5 mL), $NaHCO_3$ (aq., sat., 5 mL) and brine (10 mL). The organic phase was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography (EtOAc) afforded the title compound as a white powder (323 mg, 1.49 mmol, 90%).

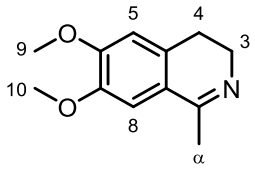
R$_f$ 0.16 (EtOAc), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.0 Hz, 1H, H1), 6.75 – 6.69 (m, 2H, H2, H3), 5.47 (s, 1H, H6), 3.87 (s, 3H, H9), 3.86 (s, 3H, H8), 3.52 – 3.47 (m, 2H, H5), 2.76 (t, *J* = 7.0 Hz, 2H, H4), 1.94 (s, 3H, H7).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 149.2, 147.9, 131.5, 120.7, 112.0, 111.5, 56.1, 56.0, 40.9, 35.3, 23.5.

Spectroscopic data is in agreement with that reported previously.[144]

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline, 25



Procedure 1: *N*-(3,4-Dimethoxyphenethyl)acetamide **129** (0.20 g, 0.90 mmol), 2-chloropyridine (0.10 mL, 1.1 mmol) and trifluoromethanesulfonic anhydride (0.17 mL, 0.99 mmol) in CH_2Cl_2 (1.6 mL) were submitted to **General Procedure C**. Purification by flash column chromatography (EtOAc/MeOH, 9:1) afforded the title compound as a brown solid (80 mg, 0.39 mmol, 43%).

Procedure 2: *Following the procedure from Zhu et al.*[144] To a solution of *N*-(3,4-dimethoxyphenethyl)acetamide **129** (0.20 g, 90 μmol, 1.0 equiv.) in anhydrous toluene (1.0 mL) at 40 ºC under an inert atmosphere was added phosphoryl chloride (0.20 mL, 2.2 mmol, 2.4 equiv.) dropwise over 1 min. The mixture was then heated to 110 ºC and stirred for 2 h. Upon completion, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. NaOH (aq., 1 M, 5 mL) was poured over the residue and the mixture was stirred for 10 min. The mixture was then extracted with CH_2Cl_2 (3 × 8 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* affording the title compound as a brownish solid (164 mg, 0.80 mmol, 89%).

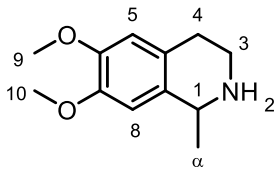
$\mathbf{R}_f$ 0.08 (CH_2Cl_2/MeOH, 9:1), [UV, CAM]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H, H5), 6.69 (s, 1H, H8), 3.92 (s, 3H, H10), 3.91 (s, 3H, H9), 3.66 – 3.62 (m, 2H, H3), 2.72 – 2.56 (m, 2H, H4), 2.37 (t, J = 1.5 Hz, 3H, Hα).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 151.1, 147.6, 131.3, 122.6, 110.4, 109.2, 56.4, 56.1, 47.1, 25.9, 23.5.

Spectroscopic data is in agreement with that reported previously.[144]

6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, 131, (±)-salsolidine



6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline **130** (50 mg, 0.24 mmol), sodium borohydride (28 mg, 0.72 mmol) in EtOH (1.6 mL) were submitted to **General Procedure D**. Purification by silica plug filtration (eluting with CH_2Cl_2/MeOH, 9:1) afforded the title compound as a yellow oil (43 mg, 0.21 mmol, 88%).

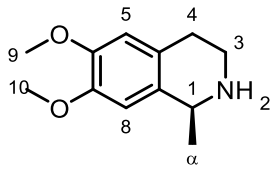
R_f 0.24 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H, H5), 6.54 (s, 1H, H8), 4.02 (q, *J* = 6.8 Hz, 1H, H1), 3.82 (s, 6H, H9, H10), 3.26 – 3.18 (m, 1H, $H3_A$), 3.03 – 2.91 (m, 1H, $H4_A$), 2.83 – 2.70 (m, 1H, $H3_B$), 2.68 – 2.56 (m, 1H, $H4_B$), 2.13 (s, br, 1H, H2), 1.42 (d, *J* = 6.8, 3H, Hα)

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 147.3, 132.4, 126.8, 111.8, 109.1, 56.0, 55.9, 51.3, 41.8, 29.5, 22.8.

Spectroscopic data is in agreement with that reported previously.[144]

***(S)*-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-131, (–)-salsolidine**



6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline **130** (35 mg, 0.17 mmol, 1.0 equiv.), RuCl[(*R,R*)-TsDPEN](*p*-cymene) (4.3 mg, 6.8 μmol, 0.040 equiv.), HCO_2H/Et_3N (5:2 v/v, 85 μL) in acetonitrile (0.27 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/MeOH, 7:3) afforded the title compound as a yellow oil (26 mg, 0.13 mmol, 76%, 96% *ee* after Boc derivatisation).

R_f 0.24 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

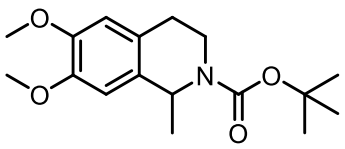
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H, H5), 6.54 (s, 1H, H8), 4.02 (q, *J* = 6.7 Hz, 1H, H1), 3.82 (s, 6H, H9, H10), 3.33 – 3.12 (m, 1H, $H3_A$), 3.08 – 2.50 (m, 3H, $H3_B$, H4), 2.08 (s, br, H2), 1.41 (d, *J* = 6.7 Hz, 3H, $H_α$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 147.3, 132.4, 126.8, 111.8, 109.1, 56.0, 55.9, 51.3, 41.8, 29.5, 22.8.

$[α]_D^{25}$ –39.3 (c. 1.3, $CHCl_3$). Ref [145] $[α]_D^{30}$ –40.1 (c. 0.06, $CHCl_3$), 96% *ee*.

Spectroscopic data is in agreement with that reported previously.[144]

***tert*-Butyl 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S1**



6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **131** (36 mg, 0.17 mmol), di-*tert*-butyl dicarbonate (45 mg, 0.20 mmol) and triethylamine (28 µL, 0.20 mmol) in anhydrous CH_2Cl_2 (1.0 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a colourless oil (47 mg, 0.15 mmol, 88%).

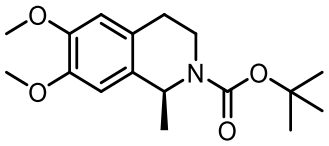
R*f* 0.45 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.6:0.4 ratio, Major(M) and minor(m)) δ 6.59 (s, 2H), 5.17 (s, br, 0.4H, (m)), 5.02 (s, br, 0.6H, (M)), 4.20 (s, br, 0.6H, (M)), 4.00 (m, 0.4H, (m)), 3.86 (s, 3H), 3.85 (s, 3H), 3.21 (s, 0.4H, (m)), 3.12 (s, 0.6H, (M)), 2.84 (s, 1H, both rotamers), 2.64 – 2.60 (m, 1H, both rotamers), 1.49 (s, 9H), 1.42 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 154.6, 147.6(2C), 130.4, 126.3, 111.4, 109.8, 79.6, 56.1, 56.0, 50.3, 36.6, 28.7, 28.6(3C), 21.9.

Spectroscopic data is in agreement with that reported previously.[146]

***tert*-Butyl (*S*)-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S2**



(S)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-131** (45 mg, 0.22 mmol), di-*tert*-butyl dicarbonate (58 mg, 0.26 mmol) and triethylamine (37 µL, 0.26 mmol) in anhydrous CH_2Cl_2 (1.3 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a colourless oil (66 mg, 0.21 mmol, 95%, 96% *ee*).

R_f 0.45 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.6:0.4 ratio, Major(M) and minor(m)) δ 6.59 (s, 2H), 5.16 (s, br, 0.4H, (m)), 5.03 (s, br, 0.6H, (M)), 4.20 (s, br, 0.6H, (M)), 4.00 (m, 0.4H, (m)), 3.86 (s, 3H), 3.85 (s, 3H,), 3.21 (s, 0.4H, (m)), 3.13 (s, 0.6H, (M)), 2.85 (s, 1H, both rotamers), 2.64 – 2.60 (m, 1H, both rotamers), 1.49 (s, 9H), 1.42 (d, J = 6.7 Hz, 3H).

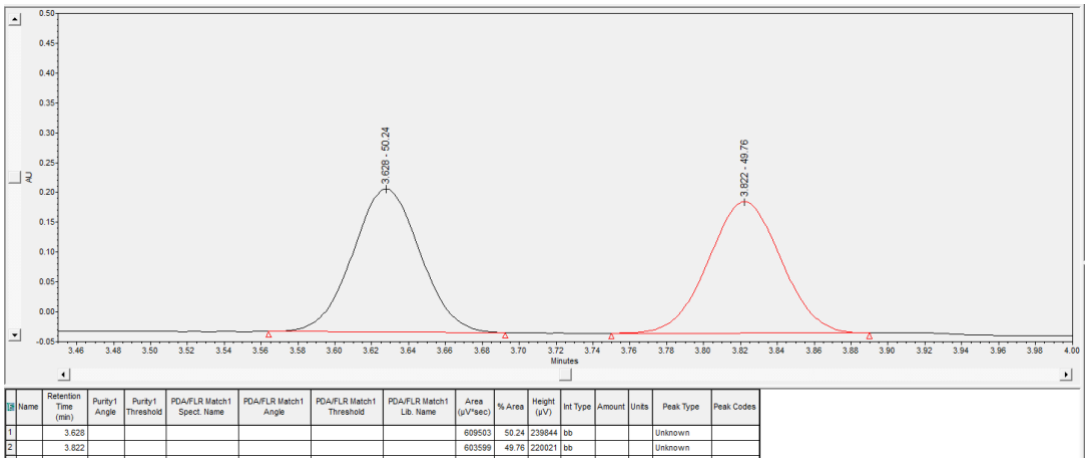
^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 154.6, 147.6(2C), 130.4, 126.3, 111.4, 109.8, 79.6, 56.1, 56.0, 50.3, 36.6, 28.7, 28.6(3C), 21.9.

$[\alpha]_D^{25}$ +52.3 (c. 1.3, $CHCl_3$). Ref [147] $[\alpha]_D^{25}$ +49.5 (c. 0.40, CH_2Cl_2).

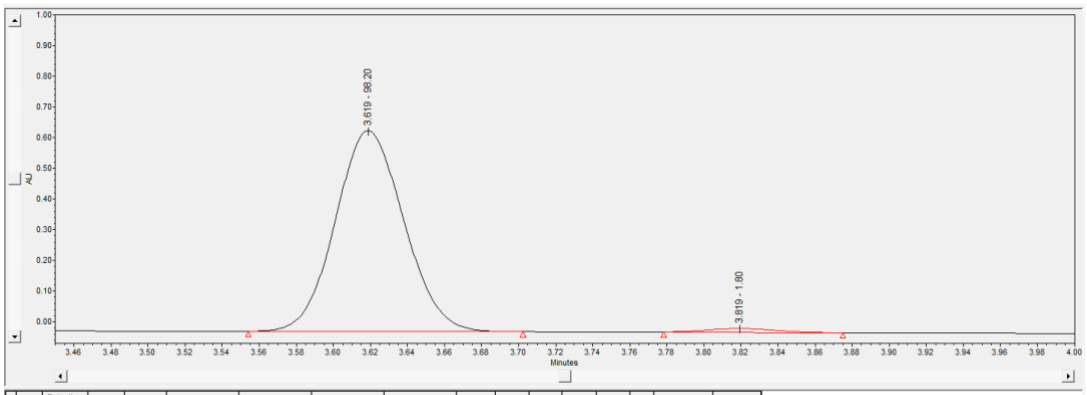
Spectroscopic data is in agreement with that reported previously.[146]

SFC trace of racemic (±)-**S1** and enantioenriched (+)-**S2**

SFC Chiralpak® IC 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; (+)-**S2**: 98.2:1.8 *e.r.* (major enantiomer t_R = 3.62 min; minor enantiomer t_R = 3.82 min), λ = 215.0 nm.

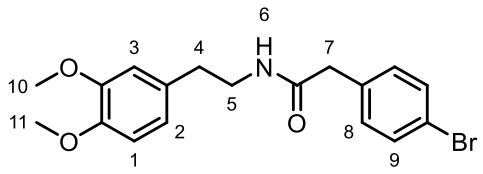


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		3.628							609503	50.24	239844	bb			Unknown	
2		3.822							603599	49.76	220021	bb			Unknown	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		3.619							1678300	98.20	652991	bb			Unknown	
2		3.819							30775	1.80	11945	bb			Unknown	

2-(4-Bromophenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide, 125



Procedure 1: *Adapted from the Procedure of McHugh et al.*[142] To a solution of 2-(3,4-dimethoxyphenyl)ethan-1-amine **127** (500 µL, 2.96 mmol, 1.1 equiv.) and 4-bromophenylactic acid **84** (578 mg, 2.69 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (11 mL) under an inert atmosphere was added *N,N*-diisopropylethylamine (1.60 mL, 9.16 mmol, 3.4 equiv.) and the mixture was cooled to 0 ºC. Propylphosphonic anhydride solution (50% in DMF, 2.73 mL, 4.58 mmol, 1.7 equiv.) was then added dropwise over 2 min. The reaction mixture was brought to room temperature and stirred for 6 h. The mixture was diluted with CH_2Cl_2 (10 mL) and sequentially washed with H_2O (10 mL), HCl (aq., 1 M, 10 mL), $NaHCO_3$ (aq., sat., 10 mL), brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) afforded the title compound as an off-white amorphous solid (530 mg, 1.40 mmol, 63%).
Procedure 2: 2-(3,4-Dimethoxyphenyl)ethan-1-amine **127** (860 µL, 5.12 mmol), 4-bromophenylactic acid **84** (1.00 g, 4.65 mmol), triethylamine (710 µL, 5.12 mmol), hydroxybenzotriazole hydrate (315 mg, 2.33 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.34 g, 6.98 mmol) in anhydrous CH_2Cl_2 (16 mL) were submitted to **General Procedure H**. Purification by flash column chromatography (dry loading, EtOAc) afforded the title compound as an off-white amorphous solid (1.52 g, 4.40 mmol, 95%).

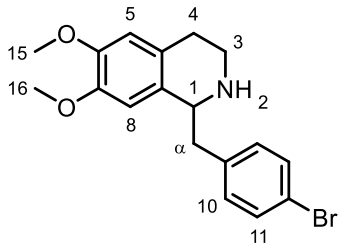
R_f 0.49 (EtOAc), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 1H, H9), 7.05 (d, *J* = 8.4 Hz, 1H, H8), 6.73 (d, *J* = 8.1 Hz, 1H, H1), 6.61 (d, *J* = 2.1 Hz, 1H, H3), 6.51 (dd, *J* = 8.1, 2.1 Hz, 1H, H2), 5.30 (s, br, 1H, H6), 3.87 (s, 3H, H11), 3.83 (s, 3H, H10), 3.50 – 3.40 (m, 4H, H5, H7), 2.68 (t, *J* = 6.8 Hz, 2H, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 149.3, 147.9, 133.9, 132.2(2C), 131.2(2C), 131.1, 121.5, 120.7, 111.9, 111.4, 56.1, 56.0, 43.4, 40.8, 35.1.

Spectroscopic data is in agreement with that reported previously.[128]

1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 132



2-(4-Bromophenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **125** (60 mg, 0.16 mmol), 2-chloropyridine (18 µL, 0.19 mmol), and trifluoromethanesulfonic anhydride (30 µL, 0.17 mmol) in CH_2Cl_2 (0.8 mL) were submitted to **General Procedure C**. The crude imine and sodium borohydride (18 mg, 0.48 mmol) in EtOH (0.8 mL) were submitted to **General Procedure D**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (31 mg, 86 µmol, 53% over 2 steps).

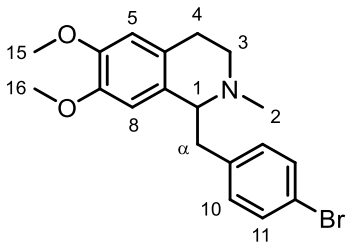
R_f 0.10 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 1H, H11), 7.13 (d, *J* = 8.3 Hz, 1H, H10), 6.54 (s, 1H, H5), 6.06 (s, 1H, H8), 4.13 (dd, *J* = 9.4, 4.5 Hz, 1H, H1), 3.86 (s, 3H, H16), 3.81 (s, 3H, H15), 3.23 – 3.11 (m, 2H, $H3_A$, $H\alpha_A$), 2.97 – 2.85 (m, 2H, $H3_B$, $H\alpha_B$), 2.80 – 2.62 (m, 2H, H4), 2.00 (s, br, 1H, H2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 147.2, 138.2, 131.8(2C), 131.3(2C), 130.1, 127.4, 120.5, 112.0, 109.5, 56.8, 56.1, 56.0, 42.3, 40.8, 29.5.

Spectroscopic data is in agreement with that reported previously.[148]

1-(4-Bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 51



1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **132** (21 mg, 58 μmol), formalin (37% aq., 0.12 mL, 1.6 mmol) and sodium borohydride (6.6 mg, 0.17 mmol) in MeOH (0.4 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/MeOH, 98:2) afforded the title compound as a yellow oil (18 mg, 0.48 mmol, 82%).

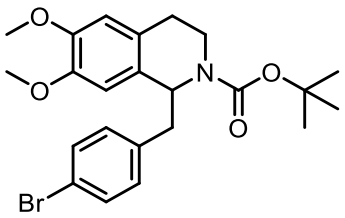
R*f* 0.12 (EtOAc/MeOH, 98:2), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 1H, H11), 6.96 (d, *J* = 8.4 Hz, 2H, H10), 6.54 (s, 1H, H5), 6.06 (s, 1H, H8), 3.84 (s, 3H, H16), 3.68 (dd, *J* = 7.3, 5.4 Hz, 1H, H1), 3.61 (s, 3H, H15), 3.22 – 3.05 (m, 2H, $H3_A$, $H\alpha_A$), 2.86 – 2.69 (m, 3H, $H\alpha_B$, $H4_A$, $H3_B$,), 2.58 – 2.53 (m, 1H, $H4_B$), 2.51 (s, 3H, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 146.5, 139.0, 131.7(2C), 131.1(2C), 128.9, 126.3, 119.8, 111.3, 110.9, 64.7, 55.8, 55.6, 47.0, 42.8, 40.6, 25.6.

Spectroscopic data is in agreement with that reported previously.[149]

***tert*-Butyl 1-(4-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S3**



1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **132** (30 mg, 80 µmol), di-*tert*-butyl dicarbonate (21 mg, 96 µmol) and triethylamine (14 µL, 96 µmol) in anhydrous CH_2Cl_2 (0.4 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a colourless oil (35 mg, 77 µmol, 96%).

R_f 0.31 (pentane/EtOAc, 4:1), [UV, PMA]

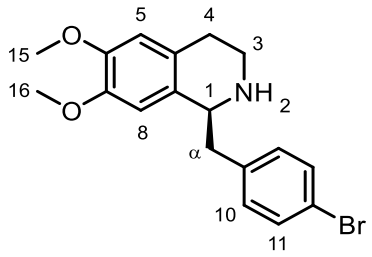
^{1}H NMR (400 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.63:37 ratio, Major(M) and minor(m)) δ 7.48 – 7.29 (m, 2H, both rotamers), 7.01 – 6.93 (m, 2H, both rotamers), 6.63 – 6.56 (m, 1H, both rotamers), 6.34 (s, 0.63H, (M)), 6.18 (s, 0.37H, (m)), 5.21 (t, *J* = 7.0 Hz, 0.37H, (m)), 5.06 (t, *J* = 7.0 Hz, 0.63H, (M)), 4.20 – 4.10 (m, 0.63H, (M)), 3.87 – 3.82 (m, 3H, both rotamers) 3.83 – 3.77 (m, 0.37H, (m)), 3.75 (s, 2H, (M)), 3.65 (s, 1H, (m)), 3.36 – 3.17 (m, 1H, both rotamers), 3.08 – 2.69 (m, 3H, both rotamers), 2.65 – 2.51 (m, 1H, both rotamers), 1.42 (s, 3.3H, (m)), 1.30 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 154.5, 148.0, 147.2, 137.7, 131.6(2C), 131.5(2C), 128.3, 126.8, 120.4, 111.6, 110.3, 80.0, 56.4, 56.0(2C), 42.4, 37.6, 28.3(3C), 28.2.

IR (film) ν_{max}/cm^{-1} 2973, 2933, 2835, 1686, 1612, 1517, 1486.

HRMS (ESI$^+$) $C_{23}H_{28}Br^{79}NO_4$ found $[M+Na]^+$ at 484.1098, expected at 484.1094.

(*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*S*)-132



2-(4-Bromophenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **125** (0.25 g, 0.66 mmol), 2-chloropyridine (70 µL, 0.79 mmol) and trifluoromethanesulfonic anhydride (0.12 mL, 0.73 mmol) in anhydrous CH_2Cl_2 (3.3 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*R,R*)-TsDPEN](*p*-cymene) (29 mg, 0.046 mmol) and HCO_2H/Et_3N (5:2 v/v, 0.33 mL) in anhydrous DMF (3.3 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (0.22 g, 0.62 mmol, 94% over 2 steps, 94% *ee*, after Boc derivatisation).

R*f* 0.10 (7:1:0.1, EtOAc/pentane/7N ammonia solution in MeOH), [UV, PMA]

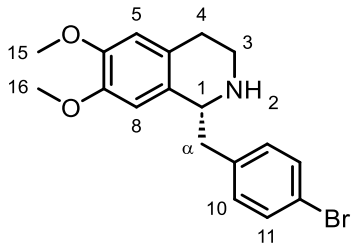
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 1H, H11), 7.13 (d, *J* = 8.3 Hz, 2H, H10), 6.59 (2s, 2H, H5, H8), 4.12 (dd, *J* = 9.5, 4.4 Hz, 1H, H1), 3.86 (s, 3H, H15), 3.82 (s, 3H, H16), 3.24 – 3.10 (m, 2H, $H3_A$, $H\alpha_A$), 2.98 – 2.82 (m, 2H, $H3_B$, $H\alpha_B$), 2.80 – 2.63 (m, 2H, H4), 1.64 (s, br, 1H, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 147.2, 138.3, 131.8(2C), 131.3(2C), 130.3, 127.6, 120.4, 112.0, 109.5, 56.9, 56.1, 56.0, 42.4, 40.8, 29.6.

$[\alpha]_D^{25}$ –12.8 (c. 1.2, $CHCl_3$). Ref [85] $[\alpha]_D^{25}$ –8.5 (c. 1.0, $CHCl_3$), 95% *ee*.

Spectroscopic data is in agreement with that reported previously.[148]

(*R*)-1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*R*)-132



2-(4-Bromophenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **125** (600 mg, 1.59 mmol), 2-chloropyridine (180 µL, 1.91 mmol) and trifluoromethanesulfonic anhydride (290 µL, 1.74 mmol) in anhydrous CH_2Cl_2 (8.0 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*S,S*)-TsDPEN](*p*-cymene) (71.0 mg, 0.11 mmol) and HCO_2H/Et_3N (5:2 v/v, 0.81 mL) in anhydrous DMF (8.0 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (494 mg, 1.36 mmol, 86% over 2 steps, 99% *ee* after Boc derivatisation).

R_f 0.10 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 1H, H11), 7.13 (d, *J* = 8.3 Hz, 2H, H10), 6.59 (s, 2H, H5, H8), 4.13 (dd, *J* = 9.5, 4.4 Hz, 1H, H1), 3.86 (s, 3H, H16), 3.82 (s, 3H, H15), 3.24 – 3.11 (m, 2H, $H3_A$, $H\alpha_A$), 2.98 – 2.83 (m, 2H, $H3_B$, $H\alpha_B$), 2.79 – 2.64 (m, 2H, H4) 1.68 (s, br, 1H, H2).

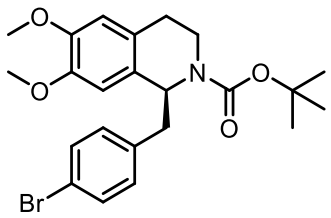
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 147.2, 138.3, 131.8(2C), 131.3(2C), 130.3, 127.6, 120.5, 112.0, 109.5, 56.9, 56.1, 56.0, 42.4, 40.9, 29.6.

IR (film) ν_{max}/cm^{-1} 2997, 2931, 1610, 1514, 1487, 1464, 1448.

HRMS (ESI$^+$) $C_{18}H_{20}Br^{79}NO_2$ found $[M+H]^+$ at 362.0748, expected at 362.0750.

$[\alpha]_D^{25}$ +13.5 (c. 1.11, $CHCl_3$). Ref [85] **(*S*)-132**: $[\alpha]_D^{25}$ –8.5 (c. 1.0, $CHCl_3$), 95% *ee*.

***tert*-Butyl (*S*)-1-(4-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S4**



(*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-132** (52 mg, 0.14 mmol), di-*tert*-butyl dicarbonate (38 mg, 0.17 mmol) and triethylamine (24 μL, 0.17 mmol) in anhydrous CH_2Cl_2 (0.7 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a colourless oil (57 mg, 0.12 mmol, 86%, 94% *ee*).

R*f* 0.31 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.45 – 7.30 (m, 2H, both rotamers), 7.01 – 6.93 (m, both rotamers), 6.64 – 6.56 (m, 1H, both rotamers), 6.34 (s, 0.64H, (M)), 6.18 (s, 0.36H, (m)), 5.21 (t, *J* = 7.0 Hz, 0.36H, (m)), 5.05 (t, *J* = 7.0 Hz, 0.64H, (M)), 4.19 – 4.10 (m, 0.64H, (M)), 3.89 – 3.77 (m, 3H, both rotamers), 3.83 – 3.77 (m, 0.36H, (m)), 3.75 (s, 2H, (M)), 3.65 (s, 1H, (m)), 3.37 – 3.15 (m, 1H, both rotamers), 3.10 – 2.68 (m, 3H, both rotamers), 2.65 – 2.50 (m, 1H, both rotamers), 1.42 (s, 3.3H, (m)), 1.30 (m, 5.7H, (M)).

^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 154.5, 148.0, 147.2, 137.7, 131.6(2C), 131.5(2C), 128.3, 126.8, 120.4, 111.6, 110.6, 79.9, 56.4, 56.0(2C), 42.4, 37.3, 28.3(3C), 28.2.

IR (film) ν_{max}/cm^{-1} 2973, 2933, 1686, 1612, 1517, 1488.

HRMS (ESI$^+$) $C_{23}H_{28}Br^{79}NO_4$ found $[M+Na]^+$ at 484.1113, expected at 484.1118.

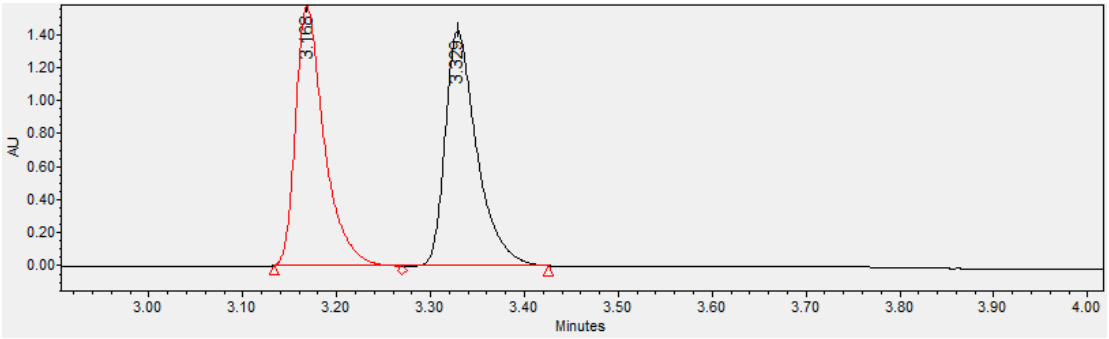
$[\alpha]_D^{25}$ +71.7 (c. 1.23, $CHCl_3$).

SFC trace of racemic (±)-**S3** and enantioenriched (+)-**S4**

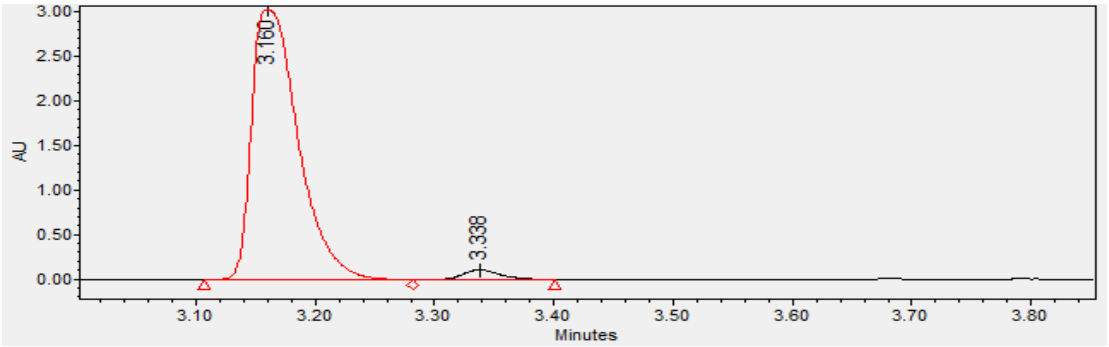
SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min;

(+)-**S4**: 97.2:2.8 *e.r.* (major enantiomer t_R = 3.16 min; minor enantiomer t_R = 3.34 min).

λ = 215.0 nm.

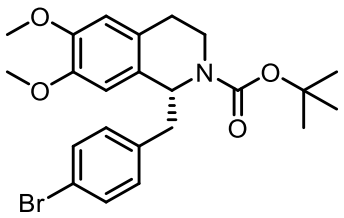


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount
1		3.168							3310035	49.79	1570562	bv	
2		3.329							3338141	50.21	1423018	vb	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount
1		3.160							8225941	97.19	3030269	bv	
2		3.338							237629	2.81	110221	vb	

***tert*-Butyl (*R*)-1-(4-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S5**



(*R*)-1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-132** (14 mg, 39 μmol), di-*tert*-butyl dicarbonate (10 mg, 46 μmol) and triethylamine (6.0 μL, 46 μmol) in anhydrous CH_2Cl_2 (0.2 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 4:1) afforded the title compound as a colourless oil (13 mg, 27 μmol, 69%, 99% *ee*).

R*f* 0.31 (pentane/EtOAc, 4:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.43 – 7.33 (m, 2H, both rotamers), 7.01 – 6.94 (m, 2H, both rotamers), 6.63 – 6.65 (m, 1H, both rotamers), 6.34 (s, 0.64H, (M)), 6.18 (s, 0.36H, (m)), 5.21 (t, *J* = 7.0 Hz, 0.36H, (m)), 5.06 (t, *J* = 7.0 Hz, 0.64H, (M)), 4.19 – 4.12 (m, 0.64H, (M)), 3.88 – 3.83 (m, 3H, both rotamers), 3.83 – 3.77 (m, 0.36H, (m)), 3.75 (s, 2H, (M)), 3.65 (s, 1H, (m)), 3.36 – 3.16 (m, 1H, both rotamers), 3.08 – 2.69 (m, 3H, both rotamers), 2.65 – 2.52 (m, 1H, both rotamers), 1.42 (s, 3.3H, (m)), 1.30 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 154.5, 148.0, 147.2, 137.7, 131.6(2C), 131.5(2C), 128.3, 126.9, 120.5, 111.6, 110.3, 80.0, 56.3, 56.0(2C), 42.5, 37.4, 28.4(3C), 28.2.

IR (film) ν_{max}/cm^{-1} 2973, 2933, 1687, 1612, 1518, 1488.

HRMS (ESI$^+$) $C_{23}H_{28}Br^{79}NO_4$ found $[M+Na]^+$ at 484.1095, expected at 484.1118.

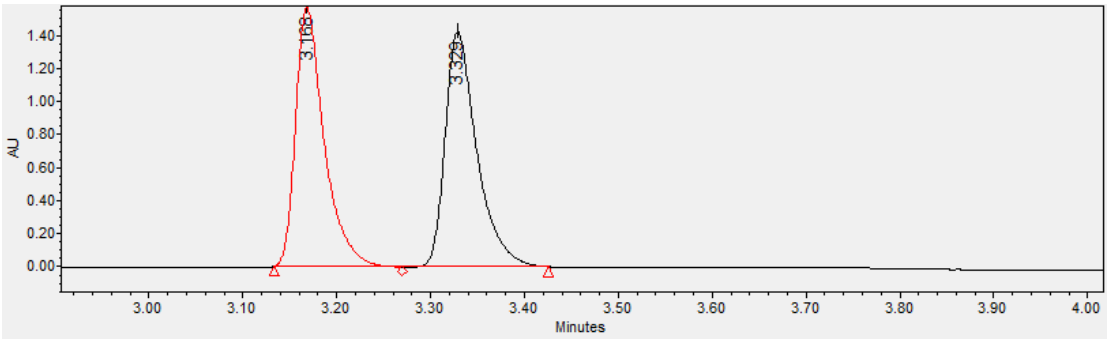
$[\alpha]_D^{25}$ –73.8 (c. 0.89, $CHCl_3$).

SFC trace of racemic (±)-**S3** and enantioenriched (–)-**S5**

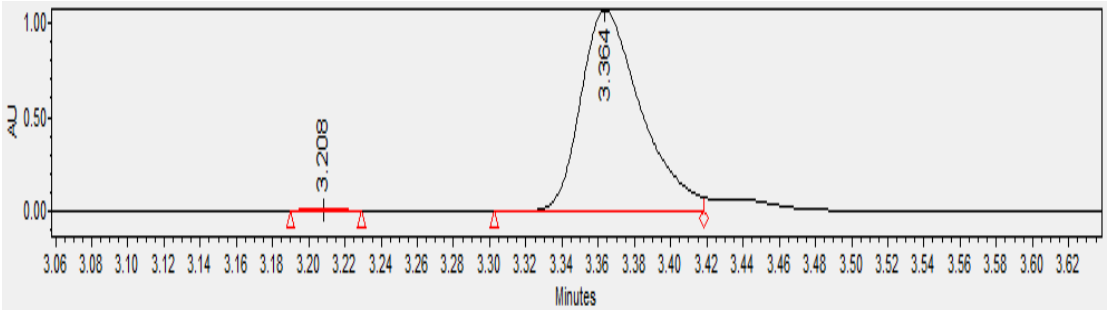
SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min;

(–)-**S5**: 99.6:0.4 *e.r.* (major enantiomer t_R = 3.36 min; minor enantiomer t_R = 3.20 min).

λ = 215.0 nm.

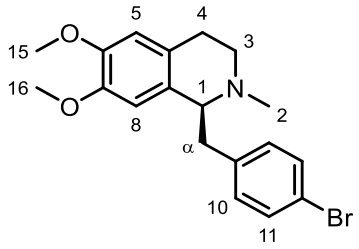


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount
1		3.168							3310035	49.79	1570562	bv	
2		3.329							3338141	50.21	1423018	vb	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		3.208							10288	0.41	7929	bb			Unknown	
2		3.364							2492900	99.59	1078836	bv			Unknown	

(*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-51



(*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-132** (0.10 g, 0.29 mmol), formalin (37% aq., 0.60 mL, 8.1 mmol) and sodium borohydride (33 mg, 0.87 mmol) in MeOH (1.9 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/MeOH, 98:2) afforded the title compound as a pale-yellow oil (84 mg, 0.23 mmol, 79%).

R*f* 0.12 (EtOAc/MeOH, 98:2), [UV, PMA]

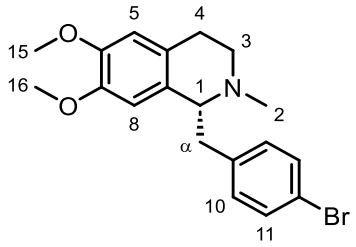
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 2H, H11), 6.95 (d, *J* = 8.3 Hz, 2H, H10), 6.54 (s, 1H, H5), 6.06 (s, 1H, H8), 3.83 (s, 3H, H16), 3.68 (dd, *J* = 7.2, 5.4 Hz, 1H, H1), 3.61 (s, 3H, H15), 3.21 – 3.04 (m, 2H, $H3_A$, $H\alpha_A$), 2.85 – 2.68 (m, 3H, $H\alpha_B$, $H4_A$, $H3_B$), 2.57 – 2.51 (m, 1H, $H4_B$), 2.50 (s, 3H, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 146.5, 139.0, 131.7(2C), 131.1(2C), 128.9, 126.3, 119.8, 111.3, 110.9, 64.7, 55.8, 55.6, 47.0, 42.8, 40.6, 25.6.

$[\alpha]_D^{25}$ +49.5 (c. 1.06, $CHCl_3$). Ref [85] $[\alpha]_D^{25}$ +35.3 (c. 0.8, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[85]

(*R*)-1-(4-Bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*)-51



(*R*)-1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-132** (494 mg, 1.36 mmol), formalin (37% aq., 2.80 mL, 37.6 mmol) and sodium borohydride (155 mg, 4.08 mmol) in MeOH (13.6 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/MeOH, 98:2) afforded the title compound as a pale-yellow oil (325 mg, 0.884 mmol, 65%).

R_f 0.12 (EtOAc/MeOH, 98:2), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 2H, H11), 6.96 (d, *J* = 8.3 Hz, 2H, H10), 6.54 (s, 1H, H5), 6.06 (s, 1H, H8), 3.83 (s, 3H, H16), 3.68 (dd, *J* = 7.3, 5.4 Hz, 1H, H1), 3.61 (s, 3H, H15), 3.20 – 3.05 (m, 2H, $H3_A$, $H\alpha_A$), 2.85 – 2.69 (m, 3H, $H\alpha_B$, $H4_A$, $H3_B$), 2.57 – 2.51 (m, 1H, $H4_B$), 2.50 (s, 3H, H2).

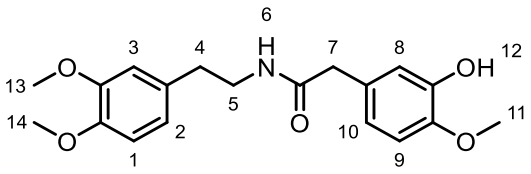
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 146.5, 139.0, 131.7(2C), 131.1(2C), 128.9, 126.4, 119.8, 111.3, 110.9, 64.7, 55.8, 55.7, 47.0, 42.8, 40.6, 25.6.

IR (film) ν_{max}/cm^{-1} 2933, 2832, 2794, 1610, 1514, 1487.

HRMS (ESI$^+$) $C_{19}H_{22}Br^{79}NO_2$ found $[M+H]^+$ at 376.0903, expected at 376.0907.

$[\alpha]_D^{25}$ –50.6 (c. 1.01, $CHCl_3$). Ref [85] **(*S*)-51** $[\alpha]_D^{25}$ +35.3 (c. 0.8, $CHCl_3$).

_N_-(3,4-Dimethoxyphenethyl)-2-(3-hydroxy-4-methoxyphenyl)acetamide, 133



3-Hydroxy-4-methoxyphenylacetic acid **83** (1.00 g, 4.65 mmol), 2-(3,4-dimethoxyphenyl)ethan-1-amine **127** (860 µL, 5.58 mmol), triethylamine (713 µL, 5.12 mmol), hydroxybenzotriazole hydrate (315 mg, 2.33 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.34 g, 6.98 mmol) in anhydrous CH_2Cl_2 (16 mL) were submitted to **General Procedure H**. Purification by trituration (cold EtOAc) afforded the title compound as an off-white amorphous solid (1.36 g, 3.95 mmol, 85%).

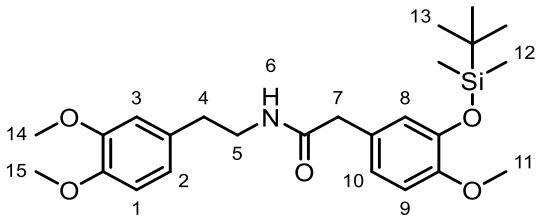
R_f 0.44 (EtOAc), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.70 (m, 3H, ArH), 6.65 – 6.53 (m, 3H, ArH), 5.97 (s, br, 1H, H12), 5.49 (s, br, 1H, H6), 3.87 (s, 3H, H14), 3.84 (s, 3H, H13), 3.81 (s, 3H, H11), 3.47 – 3.37 (m, 4H, H5, H7), 2.66 (t, *J* = 6.9 Hz, 2H, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 149.0, 147.7, 146.1(2C), 131.2, 127.8, 121.0, 120.8, 115.9, 111.9, 111.4, 111.2, 56.0, 55.9, 55.9, 43.2, 40.8, 35.1.

Spectroscopic data is in agreement with that reported previously.[150]

2-(3-((*tert*-Butyldimethylsilyl)oxy)-4-methoxyphenyl)-N-(3,4-dimethoxyphenethyl) acetamide, 134



To a solution of *N*-(3,4-dimethoxyphenethyl)-2-(3-hydroxy-4-methoxyphenyl)acetamide **133** (0.10 g, 0.29 mmol, 1.0 equiv.) and imidazole (79 mg, 1.2 mmol, 4.0 equiv.) in anhydrous CH_2Cl_2 (1.5 mL), under an inert atmosphere was added TBDMSCl (53 mg, 0.35 mmol, 1.2 equiv.) and the mixture was stirred for 4 h. Upon completion, H_2O (0.5 mL) was added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrate *in vacuo*. Purification by flash column chromatography (EtOAc/pentane, 5:1) afforded the title compound as a colourless oil (0.12 g, 0.26 mmol, 91%).

R_f 0.43 (EtOAc/pentane, 5:1), [UV, PMA]

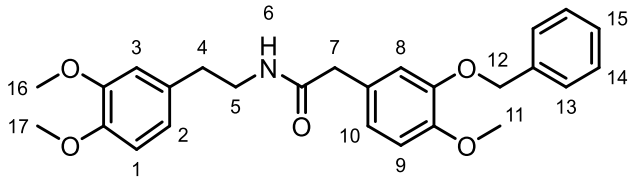
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.4 Hz, 1H, H9), 6.72 (d, *J* = 8.1 Hz, 1H, H1), 6.71 – 6.66 (m, 2H, H8, H10), 6.61 (d, *J* = 2.0 Hz, 1H, H3), 6.55 (dd, *J* = 8.1, 2.0 Hz, 1H, H2), 5.39 (t, *J* = 5.9 Hz, 1H, H6), 3.84 (s, 3H, H15), 3.83 (s, 3H, H14), 3.79 (s, 3H, H11), 3.45 – 3.38 (m, 4H, H5, H7), 2.65 (t, *J* = 7.0 Hz, 2H, H4), 0.99 (s, 9H, H13), 0.14 (s, 6H, H12).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 150.5, 149.1, 147.7, 145.4, 131.3, 127.3, 122.8, 122.4, 120.8, 112.5, 111.8, 111.3, 56.0, 55.9, 55.6, 43.3, 40.9, 35.3, 25.8(3C), 18.6, –4.5(2C).

IR (film) ν_{max}/cm^{-1} 3291, 2931, 2906, 2857, 2835, 2360, 2340, 1645, 1584, 1511, 1464.

HRMS (ESI$^+$) $C_{25}H_{37}NO_5Si$ found $[M+H]^+$ at 460.2508, expected at 460.2514.

2-(3-(Benzyloxy)-4-methoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide, 136



To a solution of *N*-(3,4-dimethoxyphenethyl)-2-(3-hydroxy-4-methoxyphenyl)acetamide **133** (500 mg, 1.45 mmol, 1.0 equiv.) in acetone (7.5 mL) were added potassium carbonate (301 mg, 2.18 mmol, 1.5 equiv.), tetrabutylammonium iodide (27.0 mg, 73.1 µmol, 0.05 equiv.) and benzyl bromide (210 µL, 1.74 mmol, 1.2 equiv.) and the mixture was stirred for 30 h. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The organic phase was washed sequentially with HCl (aq., 1M, 10 mL), NaOH (aq., 1M, 10 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (dry loading, CH_2Cl_2/acetone, 9:1) afforded the title compound as a white solid (621 mg, 1.43 mmol, 85%).

m.p. 85 – 87 ºC. **R*f*** 0.19 (EtOAc/pentane, 2:1), [UV, PMA]

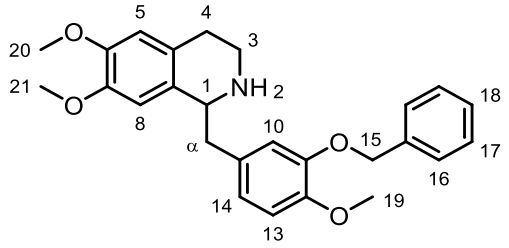
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H, H13), 7.38 – 7.33 (m, 2H, H14), 7.31 – 7.27 (m, 1H, H15), 6.82 (d, *J* = 8.1 Hz, 1H, H9), 6.73 – 6.68 (m, 3H, H1, H10, H8), 6.60 (d, *J* = 2.0 Hz, 1H, H3), 6.51 (dd, *J* = 8.1, 2.0 Hz, 1H, H2), 5.30 (s, br, 1H, H6), 5.10 (s, 2H, H12), 3.89 (s, 3H, H17), 3.82 (s, 6H, H16, H11), 3.42 (s, 2H, H7), 3.39 (q, *J* = 6.9 Hz, 2H, H5), 2.62 (t, *J* = 6.9 Hz, 2H, H4).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 149.17, 149.15, 148.5, 147.8, 137.0, 131.2, 128.7(2C), 128.1, 127.5(2C), 127.2, 122.4, 120.7, 115.4, 112.3, 111.9, 111.3, 71.1, 56.2, 56.0, 55.9, 43.5, 40.8, 35.2.

IR (film) ν_{max}/cm^{-1} 3295, 2933, 2835, 2360, 1646, 1589, 1513, 1454.

HRMS (ESI$^+$) $C_{26}H_{29}NO_5$ found $[M+H]^+$ at 436.2118, expected at 436.2117.

1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 137



2-(3-(Benzyloxy)-4-methoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **136** (87 mg, 0.20 mmol), 2-chloropyridine (20 μL, 0.24 mmol) and trifluoromethanesulfonic anhydride (40 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (1.0 mL) were submitted to **General Procedure C**. The crude imine and sodium borohydride (23 mg, 0.60 mmol) in EtOH (1.0 mL) were submitted to **General Procedure D**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (60 mg, 0.14 mmol, 72% over 2 steps).

R_f 0.15 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H, H16), 7.38 – 7.33 (m, 2H, H17), 7.31 – 7.25 (m, 1H, H18), 6.85 (d, J = 8.1 Hz, 1H, H13), 6.80 – 6.75 (m, 2H, H10, H14), 6.61 (s, 1H, H5), 6.58 (s, 1H, H8), 5.13 (d, J = 2.8 Hz, 2H, H15), 4.04 (dd, J = 9.2, 4.2 Hz, 1H, H1), 3.88 (s, 3H, H19), 3.85 (s, 3H, H21), 3.82 (s, 3H, H20), 3.21 – 3.05 (m, 2H, $H3_A$, $H\alpha_A$), 2.88 – 2.59 (m, 4H, $H3_B$, $H\alpha_B$, H4), 1.72 (s, br, 1H, H2).

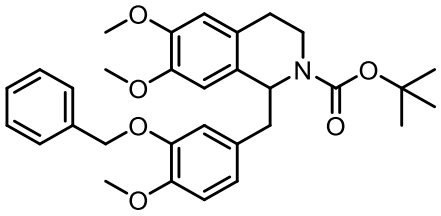
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 148.1, 147.5, 147.1, 137.2, 131.5, 130.6, 128.6(2C), 127.9, 127.6, 127.4(2C), 122.2, 115.4, 112.1, 111.9, 109.4, 71.1, 56.9, 56.2, 56.1, 56.0, 42.2, 41.0, 29.7.

IR (film) ν_{max}/cm^{-1} 2951, 2833, 2360, 2341, 1609, 1588, 1514, 1261.

HRMS (ESI$^+$) $C_{26}H_{29}NO_4$ found $[M+H]^+$ at 420.2165, expected at 410.2169.

Some spectroscopic data has been reported previously.[151]

***tert*-Butyl 1-(3-(benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S7**



1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **137** (60 mg, 0.14 mmol), di-*tert*-butyl dicarbonate (37 mg, 0.17 mmol) and triethylamine (24 µL, 0.17 mmol) in anhydrous CH_2Cl_2 (0.7 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 1:1) afforded the title compound as a colourless oil (40 mg, 76 µmol, 55%).

R*f* 0.41 (pentane/EtOAc, 1:1), [UV, PMA]

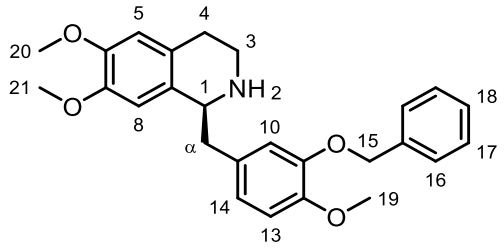
^{1}H NMR (400 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.44 – 7.39 (m, 2H, both rotamers), 7.39 – 7.32 (m, 2H, both rotamers), 7.31 – 7.26 (m, 1H, both rotamers), 6.84 – 6.72 (m, 1H, both rotamers), 6.68 – 6.54 (m, 3H, both rotamers), 6.27 (s, 0.64H, (M)), 6.19 (s, 0.36H, (m)), 5.22 (t, *J* = 6.7 Hz, 0.36H, (m)), 5.24 – 4.97 (m, 2H, both rotamers + 0.64H, (M)), 4.13 – 4.05 (m, 0.64H, (M)), 3.88 – 3.85 (m, 6H, both rotamers), 3.79 – 3.72 (m, 0.36H, (m)), 3.70 (s, 2H, (M)), 3.62 (s, 1H, (m)), 3.27 – 3.12 (m, 1H, both rotamers), 3.05 – 2.66 (m, 3H, both rotamers), 2.61 – 2.42 (m, 1H, both rotamers), 1.46 (s, 3.3H, (m)), 1.37 (s, 5.7H, (M)).

^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 154.6, 148.6, 148.2, 147.8, 147.0, 137.3, 131.2, 128.6(3C), 127.9, 127.4(2C), 126.8, 122.7, 115.9, 112.0, 111.4, 110.5, 79.7, 71.2, 56.6, 56.3, 56.0(2C), 42.5, 37.5, 28.4(3C), 28.3.

IR (film) ν_{max}/cm^{-1} 2972, 2934, 2836, 1684, 1611, 1590, 1515.

HRMS (ESI$^+$) $C_{31}H_{37}NO_6$ found $[M+Na]^+$ at 542.2508, expected at 542.2513.

(*S*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*S*)-137



2-(3-(Benzyloxy)-4-methoxyphenyl)-N-(3,4-dimethoxyphenethyl)acetamide **136** (0.40 g, 0.92 mmol), 2-chloropyridine (0.10 mL, 1.1 mmol) and trifluoromethanesulfonic anhydride (0.17 mL, 1.0 mmol) in anhydrous CH_2Cl_2 (4.6 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*R,R*)-TsDPEN](*p*-cymene) (41 mg, 64 μmol), HCO_2H/Et_3N (5:2 v/v, 0.46 mL) in anhydrous DMF (4.6 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (0.24 g, 0.58 mmol, 63% over 2 steps, 94% *ee* after Boc derivatisation).

R_f 0.15 (7:1:0.1, EtOAc/pentane/7N ammonia solution in MeOH), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H, H16), 7.38 – 7.32 (m, 2H, H17), 7.31 – 7.27 (m, 1H, H18), 6.85 (d, *J* = 8.1 Hz, 1H, H13), 6.81 – 6.75 (m, 2H, H10, H14), 6.61 (s, 1H, H5), 6.58 (s, 1H, H8), 5.14 – 5.11 (m, 2H, H15), 4.04 (dd, *J* = 9.2, 4.4 Hz, 1H, H1), 3.88 (s, 3H, H19), 3.85 (s, 3H, H21), 3.82 (s, 3H, H20), 3.21 – 3.05 (m, 2H, $H3_A$, $H\alpha_A$), 2.88 – 2.61 (m, 4H, $H3_B$, $H\alpha_B$, H4), 1.62 (s, br, 1H, H2).

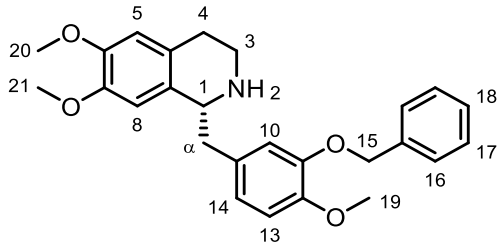
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 148.1, 147.6, 147.1, 137.3, 131.5, 130.7, 128.6(2C), 127.9, 127.6, 127.4(2C), 122.3, 115.6, 112.2, 112.0, 109.5, 71.1, 57.0, 56.2, 56.1, 56.0, 42.2, 41.0, 29.7.

IR (film) ν_{max}/cm^{-1} 2950, 2833, 1609, 1589, 1513, 1260.

HRMS (ESI$^+$) $C_{26}H_{29}NO_4$ found $[M+H]^+$ at 420.2164, expected at 420.2169.

$[\alpha]_D^{25}$ –21.8 (c. 0.99, $CHCl_3$).

(*R*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*R*)-137



2-(3-(Benzyloxy)-4-methoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **136** (1.0 g, 2.3 mmol), 2-chloropyridine (0.26 mL, 2.8 mmol) and trifluoromethanesulfonic anhydride (0.43 mL, 2.5 mmol) in anhydrous CH_2Cl_2 (12 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*S,S*)-TsDPEN](*p*-cymene) (0.10 g, 0.16 mmol), HCO_2H/Et_3N (5:2 v/v, 1.2 mL) in anhydrous DMF (12 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (0.86 g, 2.1 mmol, 89% over 2 steps, 96% *ee* after Boc derivatisation).

R_f 0.15 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H, H16), 7.38 – 7.32 (m, 2H, H17), 7.31 – 7.27 (m, 1H, H18), 6.85 (d, *J* = 8.1 Hz, 1H, H13), 6.83 – 6.74 (m, 2H, H10, H14), 6.61 (s, 1H, H5), 6.58 (s, 1H, H8), 5.13 (d, *J* = 3.9 Hz, 2H, H15), 4.04 (dt, *J* = 13.0, 6.6 Hz, 1H, H1), 3.88 (s, 3H, H19), 3.85 (s, 3H, H21), 3.81 (s, 3H, H20), 3.16 – 3.06 (m, 2H, $H3_A$, $H\alpha_A$), 2.87 – 2.69 (m, 4H, $H3_B$, $H\alpha_B$, H4), 1.93 (s, br, 1H, H2).

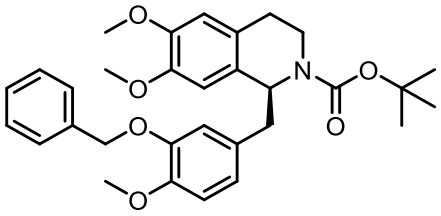
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 148.1, 147.5, 147.1, 137.2, 131.4, 130.5, 128.6(2C), 127.9, 127.5, 127.4(2C), 122.3, 115.5, 112.1, 111.9, 109.5, 71.1, 56.9, 56.2, 56.1, 55.9, 42.1, 41.0, 29.6.

IR (film) ν_{max}/cm^{-1} 2933, 2834, 1609, 1589, 1513, 1262.

HRMS (ESI^+) $C_{26}H_{29}NO_4$ found $[M+H]^+$ at 420.2162, expected at 420.2169.

$[\alpha]_D^{25}$ +23.6 (c. 1.29, $CHCl_3$).

***tert*-Butyl (*S*)-1-(3-(benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S8**



(*S*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-137** (0.12 g, 0.29 mmol), di-*tert*-butyl dicarbonate (76 mg, 0.35 mmol) and triethylamine (49 µL, 0.35 mmol) in anhydrous CH_2Cl_2 (1.5 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 1:1) afforded the title compound as a colourless oil (0.11 g, 0.20 mmol, 70%, 94% *ee*).

R$_f$ 0.41 (pentane/EtOAc, 1:1), [UV, PMA]

^{1}H NMR (600 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.45 – 7.39 (m, 2H, both rotamers), 7.38 – 7.33 (m, 2H, both rotamers), 7.31 – 7.26 (m, 1H, both rotamers), 6.80 (d, *J* = 8.1 Hz, 0.64H, (M)), 6.76 (d, *J* = 8.1 Hz, 0.36H, (m)), 6.67 – 6.55 (m, 3H, both rotamers), 6.26 (s, 0.64H, (M)), 6.23 (s, 0.36H, (m)), 5.21 (t, *J* = 6.8 Hz, 0.36H, (m)), 5.10 – 4.98 (m, 2H, both rotamers + 0.64H, (M)), 4.12 – 4.04 (m, 0.64H, (M)), 3.88 – 3.81 (m, 6H, both rotamers), 3.77 – 3.74 (m, 0.36H, (m)), 3.70 (s, 2H, (M)), 3.62 (s, 1H, (m)), 3.25 – 3.14 (m, 1H, both rotamers), 3.05 – 2.67 (m, 3H, both rotamers), 2.59 – 2.45 (m, 1H, both rotamers), 1.46 (s, 3.3H, (m)), 1.36 (s, 5.7H, (M)).

^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 154.6, 148.6, 148.2, 147.8, 147.1, 137.3, 131.3, 128.6(3C), 127.9, 127.4(2C), 126.8, 122.7, 115.9, 112.1, 111.5, 110.5, 79.7, 71.3, 56.6, 56.3, 56.1(2C), 42.5, 37.6, 28.5(3C), 28.3.

IR (film) ν_{max}/cm^{-1} 2971, 2933, 2835, 1686, 1610, 1590, 1515.

HRMS (ESI$^+$) $C_{31}H_{37}NO_6$ found $[M+Na]^+$ at 542.2514, expected at 542.2513.

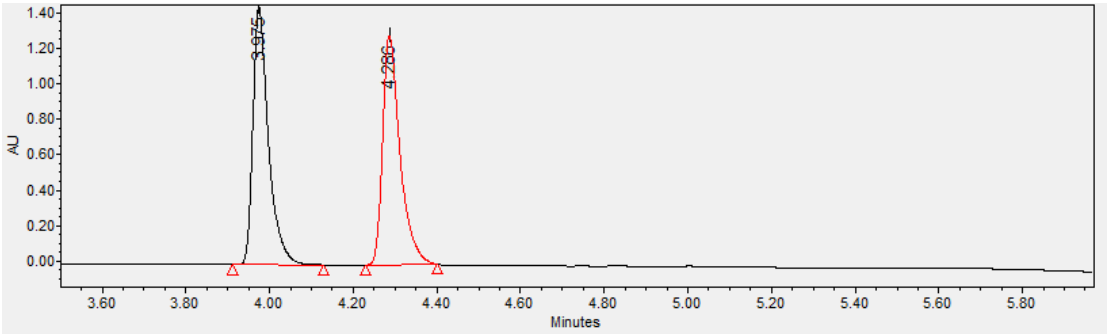
$[\alpha]_D^{25}$ +45.7 (c. 1.17, $CHCl_3$).

SFC trace of racemic (±)-**S7** and enantioenriched (+)-**S8**.

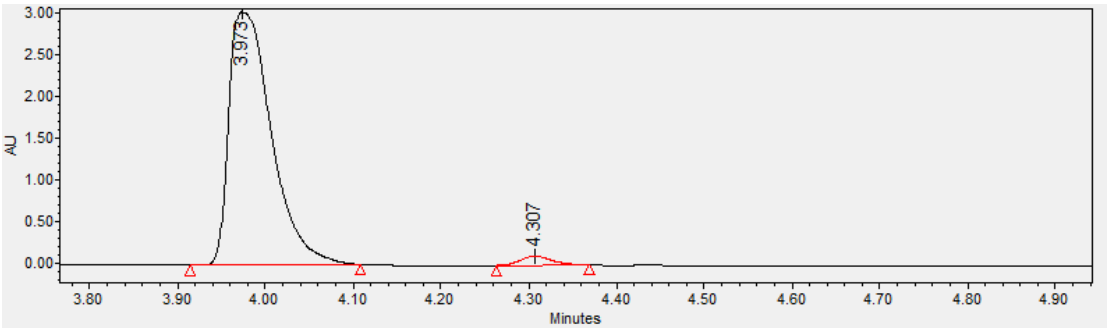
SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min;

(+)-**S8:** 97.4:2.6 *e.r.* (major enantiomer t_R = 3.97 min; minor enantiomer t_R = 4.31 min).

λ = 215.0 nm.

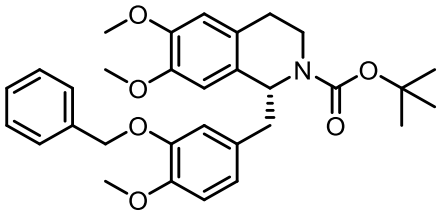


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount
1		3.975							3734697	50.00	1452542	bb	
2		4.286							3734271	50.00	1291503	bb	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Am
1		3.973							10222212	97.39	3027015	bb	
2		4.307							274377	2.61	109575	bb	

***tert*-Butyl (*S*)-1-(3-(benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S9**



(*R*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-137** (12 mg, 28 µmol), di-*tert*-butyl dicarbonate (7.3 mg, 34 µmol) and triethylamine (5.0 µL, 34 µmol) in anhydrous CH_2Cl_2 (0.14 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/EtOAc, 1:1) afforded the title compound as a colourless oil (7.4 mg, 14 µmol, 51%, 96% *ee*).

R*f* 0.41 (1:1, pentane/EtOAc), [UV, PMA]

^{1}H NMR (600 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.43 – 7.49 (m, 2H, both rotamers), 7.38 – 7.31 (m, 2H, both rotamers), 7.31 – 7.27 (m, 1H, both rotamers), 6.80 (d, *J* = 8.2 Hz, 0.64H, (M)), 6.76 (d, J = 8.2 Hz, 0.36H, (m)), 6.68 – 6.49 (m, 3H, both rotamers), 6.26 (s, 0.64H, (M)), 6.19 (s, 0.36H, (m)), 5.21 (t, *J* = 6.7 Hz, 0.36H, (m)), 5.10 – 4.98 (m, 2H, both rotamers + 0.64H, (M)), 4.13 – 4.06 (m, 0.64H, (M)), 3.86 – 3.81 (m, 6H, both rotamers), 3.79 – 3.71 (m, 0.36H, (m)), 3.70 (s, 2H, (M)), 3.62 (s, 1H, (m)), 3.26 – 3.13 (m, 1H, both rotamers), 3.05 – 2.67 (m, 3H, both rotamers), 2.61 – 2.44 (m, 1H, both rotamers), 1.46 (s, 3.3H, (m)), 1.37 (s, 5.7H, (M)).

^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 154.7, 148.7, 148.2, 147.9, 147.1, 137.3, 131.3, 128.7(3C), 128.0, 127.4(2C), 126.9, 122.8, 116.0, 112.1, 111.5, 110.5, 79.8, 71.3, 56.6, 56.4, 56.0(2C), 42.6, 37.6, 28.4(3C), 28.3.

IR (film) ν_{max}/cm^{-1} 2979, 2903, 2834, 1684, 1647, 1590, 1516.

HRMS (ESI$^+$) $C_{31}H_{37}NO_6$ found $[M+Na]^+$ at 542.2510, expected at 542.2513.

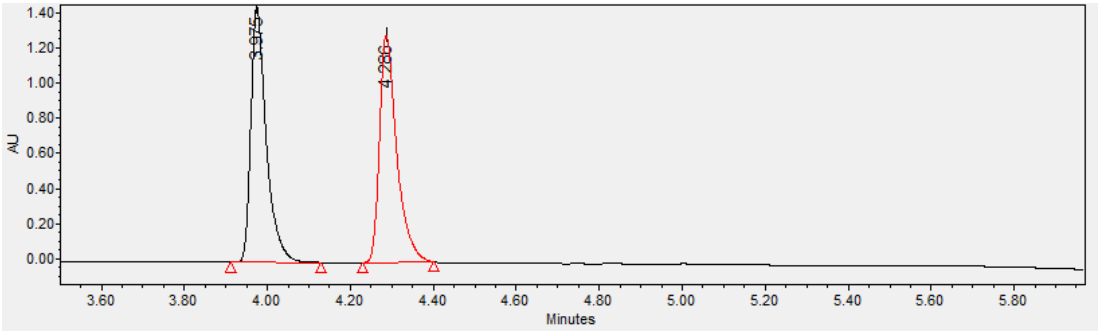
$[\alpha]_D^{25}$ –47.4 (c. 0.76, $CHCl_3$).

SFC trace of racemic (±)-**S7** and enantioenriched (–)-**S9**.

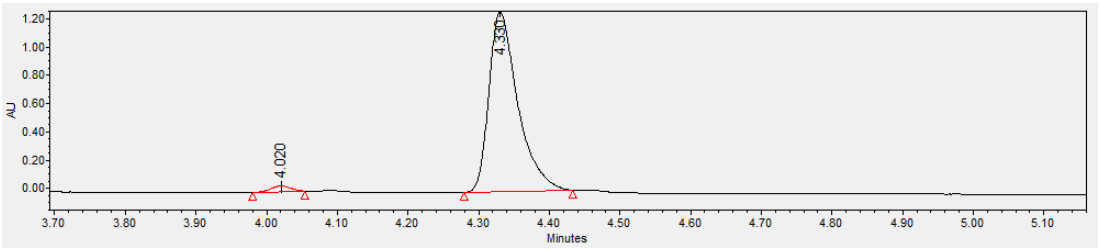
SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min;

(–)-**S9:** 97.9:2.1 *e.r.* (major enantiomer t_R = 4.33 min; minor enantiomer t_R = 4.02 min).

λ = 215.0 nm.

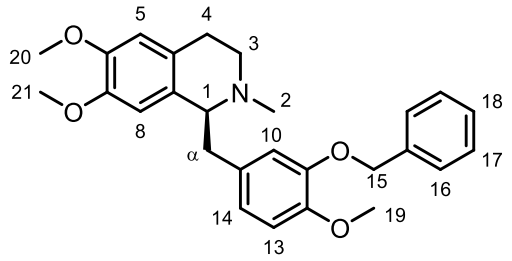


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount
1		3.975							3734697	50.00	1452542	bb	
2		4.286							3734271	50.00	1291503	bb	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		4.020							76744	2.08	39614	bb			Unknown	
2		4.330							3606961	97.92	1271252	bb			Unknown	

(*S*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-138, (+)-*O*-benzyllaudanidine



(*S*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-137** (0.20 g, 0.48 mmol), formalin (37% aq., 1.0 mL, 13 mmol) and sodium borohydride (55 mg, 1.4 mmol) in MeOH (9.6 mL) were submitted to **General Procedure F.** Purification by flash column chromatography (EtOAc/MeOH, 98:2) afforded the title compound as a yellow oil (0.18 g, 0.40 mmol, 84%).

R_f 0.41 (1:1, pentane/EtOAc), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H, H16), 7.34 (dd, *J* = 8.5, 6.8 Hz, 2H, H17), 7.31 – 7.24 (m, 1H, H18), 6.77 (d, *J* = 8.1 Hz, 1H, H13), 6.67 (d, *J* = 2.1 Hz, 1H, H10), 6.61 (dd, *J* = 8.1, 2.1 Hz, 1H, H14), 6.54 (s, 1H, H5), 6.01 (s, 1H, H8), 5.07 (d, *J* = 1.6 Hz, 2H, H15), 3.85 (s, 3H, H19), 3.83 (s, 3H, H21), 3.63 – 3.58 (m, 1H, H1), 3.57 (s, 3H, H20), 3.16 – 3.03 (m, 2H, $H3_A$, $H\alpha_A$), 2.85 – 2.67 (m, 3H, $H4_A$, $H\alpha_B$, $H3_B$), 2.59 – 2.50 (m, 1H, $H4_B$), 2.48 (s, 3H, H2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 147.9, 147.3, 146.4, 137.4, 132.6, 129.4, 128.6(2C), 127.9, 127.4(2C), 126.2, 122.7, 116.0, 111.7, 111.2, 111.1, 71.1, 64.9, 56.2, 55.9, 55.7, 47.1, 42.8, 40.8, 25.7.

IR (film) ν_{max}/cm^{-1} 2934, 2833, 1608, 1588, 1514.

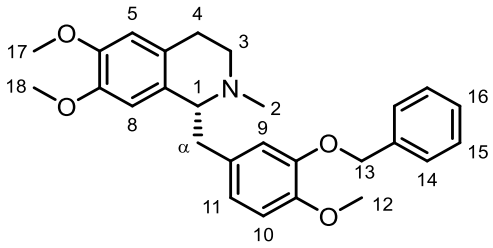
HRMS (ESI^+) $C_{27}H_{31}NO_4$ found $[M+H]^+$ at 434.2331, expected at 434.2326.

$[\alpha]_D^{25}$ +71.1 (c. 1.19, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[152]

Note: Spectroscopic data is reported for rac-**138**.

(*R*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*)-138, (−)-O-benzyllaudanidine



(*R*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-137** (647 mg, 1.54 mmol), formalin (37% aq., 2.30 mL, 30.1 mmol) and sodium borohydride (175 mg, 4.62 mmol) in MeOH (16 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/MeOH, 98:2) afforded the title compound as a yellow oil (0.430 g, 0.990 mmol, 65%).

R*f* 0.41 (1:1, pentane/EtOAc), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H, H16), 7.38 – 7.31 (m, 2H, H17), 7.30 – 7.23 (m, 1H, H18), 6.77 (d, *J* = 8.2 Hz, 1H, H13), 6.67 (d, *J* = 2.0 Hz, 1H, H10) 6.61 (dd, *J* = 8.1, 2.0 Hz, 1H, H14), 6.54 (s, 1H, H5), 6.01 (s, 1H, H8), 5.07 (s, 2H, H15), 3.85 (s, 3H, H19), 3.83 (s, 3H, H21), 3.64 – 3.56 (m, 1H, H1), 3.57 (s, 3H, H20), 3.17 – 3.02 (m, 2H, $H3_A$, $H\alpha_A$), 2.86 – 2.66 (m, 3H, $H4_A$, $H\alpha_B$, $H3_B$), 2.54 (dt, *J* = 15.5, 4.7 Hz, 1H, $H4_B$), 2.49 (s, 3H, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 147.8, 147.3, 146.4, 137.4, 132.5, 129.4, 128.6(2C), 127.8, 127.4(2C), 126.1, 122.7, 116.0, 111.7, 111.2, 111.0, 71.1, 64.9, 56.2, 55.8, 55.6, 47.1, 42.8, 40.8, 25.7.

IR (film) ν_{max}/cm^{-1} 2937, 2833, 1610, 1589, 1513.

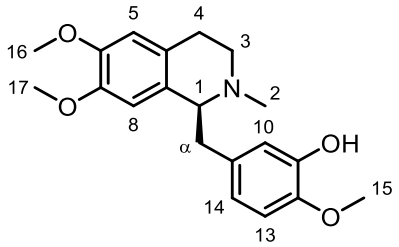
HRMS (ESI$^+$) $C_{27}H_{31}NO_4$ found $[M+H]^+$ at 434.2325, expected at 434.2326.

[α]$_D^{25}$ –74.6 (c. 1.33, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[152]

Note: Spectroscopic data is reported for rac-**138**.

(*S*)-5-((6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenol, (*S*)-49, (+)-laudanidine



To an oven-dried flask containing Pd/C (10% wt., 21 mg, 20 µmol, 0.04 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.2 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*S*)-1-(3-(Benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-138** (210 mg, 0.484 mmol, 1.0 equiv.) was then added as a solution in anhydrous MeOH (4.60 mL) and AcOH (60.0 µL, 0.107 mmol, 2.20 equiv.). The resulting mixture was stirred under a hydrogen atmosphere for 24 h. The reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (9:1, 20 mL) and the filtrate was concentrated *in vacuo*. The residue was then diluted with CH_2Cl_2 (5 mL) and washed with $NaHCO_3$ (aq., sat., to pH 7) and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed with brine (7 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as a white solid (116 mg, 0.34 mmol, 71%).

R$_f$ 0.29 (EtOAc), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 2.1 Hz, 1H, H10), 6.71 (d, *J* = 8.1 Hz, 1H, H13), 6.55 (s, 1H, H5), 6.51 (dd, *J* = 8.1, 2.1 Hz, 1H, H14), 6.04 (s, 1H, H8), 3.84 (s, 3H, H17), 3.83 (s, 3H, H15), 3.71 (dd, *J* = 8.1, 5.1 Hz, 1H, H1), 3.55 (s, 3H, H16), 3.23 – 3.19

(m, 1H, H3$_A$), 3.13 (dd, *J* = 13.7, 7.0 Hz, 1H, Hα_A), 2.91 – 2.75 (m, 2H, H4$_A$, H3$_B$), 2.70 (dd, *J* = 13.7, 7.0 Hz, 1H, Hα_B), 2.61 (dt, *J* = 15.6, 4.7 Hz, 1H, H4$_B$), 2.52 (s, 3H, H2).

Note: O*H* resonance was not observed.

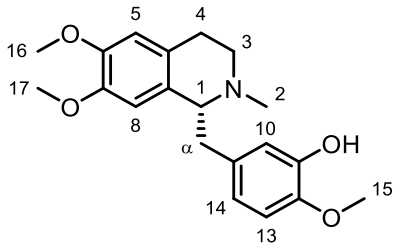
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 146.4, 145.7, 145.3, 133.2, 129.2, 125.6, 121.3, 116.0, 111.2, 111.1, 110.6, 64.9, 56.1, 55.8, 55.6, 46.6, 42.5, 40.9, 25.1.

HRMS (ESI^+) $C_{20}H_{25}NO_4$ found $[M+H]^+$ at 344.1850, expected at 344.1856.

$[\alpha]_D^{25}$ +94.4 (c. 1.18, $CHCl_3$). Ref [85] $[\alpha]_D^{25}$ +83.7 (c. 1.0, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[85]

(*R*)-5-((6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenol, (*R*)-49, (−)-laudanidine



To an oven-dried flask containing Pd/C (10% wt., 36 mg, 34 μmol, 0.04 equiv.) under an inert atmosphere, was added anhydrous MeOH (1.0 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*S*)-1-(3-(benzyloxy)-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-138** (0.36 g, 0.83 mmol, 1.0 equiv.) was then added as a solution in anhydrous MeOH (5.5 mL) and AcOH (0.11 mL, 1.8 mmol, 2.2 equiv.). The resulting mixture was stirred under a hydrogen atmosphere for 24 h. The reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (9:1, 20 mL) and the filtrate was concentrated *in vacuo*. The residue was then diluted with CH_2Cl_2 (5 mL) and washed with $NaHCO_3$ (aq., sat., to pH 7) and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed with brine (7 mL), dried (MgSO4), filtered and concentrated *in vacuo*. The title compound was collected as a white solid (0.20 g, 0.59 mmol, 71%).

R*f* 0.29 (EtOAc), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 2.1 Hz, 1H, H10), 6.71 (d, *J* = 8.2 Hz, 1H, H13), 6.53 (s, 1H, H5), 6.50 (dd, *J* = 8.2, 2.1 Hz, 1H, H14), 6.03 (s, 1H, H8), 3.84 (s, 3H, H17), 3.83 (s, 3H, H15), 3.72 – 3.68 (m, 1H, H1), 3.54 (s, 3H, H16), 3.25 – 3.10 (m, 2H,

$H3_A$, $H\alpha_A$), 2.90 – 2.75 (m, 2H, $H4_A$, $H3_B$), 2.70 (dd, J = 13.6, 8.1 Hz, 1H, $H\alpha_B$), 2.65 – 2.57 (m, 1H, $H4_B$), 2.51 (s, 3H, H2).

Note: O*H* resonance was not observed.

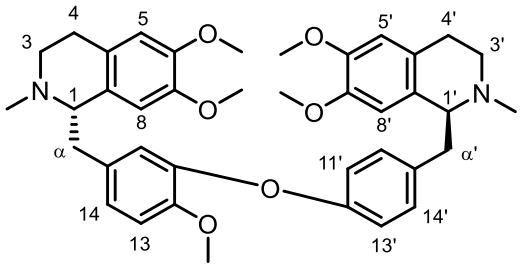
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 146.4, 145.7, 145.3, 133.1, 129.1, 125.5, 121.3, 116.0, 111.2, 111.1, 110.6, 64.9, 56.0, 55.8, 55.5, 46.5, 42.4, 40.9, 25.0.

HRMS (ESI^+) $C_{20}H_{25}NO_4$ found $[M+H]^+$ at 344.1854, expected at 344.1856.

$[\alpha]_D^{25}$ –93.5 (c. 1.18, $CHCl_3$). Ref [109] $[\alpha]_D^{25}$ –94.7 (c. 0.4, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously for (+)-laudanidine **(*S*)-49**.[85]

(*S*)-1-(4-(5-(((*S*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S,S*)-52, (+)-*O*-methylthalibrine



(*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-51** (60 mg, 0.16 mmol), (*S*)-5-((6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenol **(*S*)-49** (61 mg, 0.18 mmol), potassium carbonate (55 mg, 0.40 mmol) and cupric oxide (25 mg, 0.32 mmol) in anhydrous pyridine (0.25 mL) were submitted to **General Procedure B**. The organic phase was washed with ammonia (aq., 35%, 4 × 6 mL) instead of filtering it through Celite® and no acidic wash was performed. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as a pale-yellow foam (38 mg, 59 µmol, 37%).

R_f 0.35 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (500 MHz, CDCl3) δ 6.99 (d, *J* = 8.5 Hz, 2H, H10′, H14′), 6.87 (d, *J* = 8.3 Hz, 1H, H13), 6.82 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.77 (d, *J* = 8.5 Hz, 2H, H11′, H13′), 6.73 (d, *J* = 2.1 Hz, 1H, H10), 6.54 (s, 1H, H5 or H5′), 6.51 (s, 1H, H5 or H5′), 6.09 (s, 1H, H8 or H8′), 6.03 (s, 1H, H8 or H8′), 3.82 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.80 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.79 (s, 3H, C12-OCH_3), 3.68 (dd, *J* = 7.9, 5.0 Hz, 1H, H1′), 3.64 (dd, *J* = 7.3, 5.4 Hz, 1H, H1), 3.61 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.57 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.21 – 3.02 (m, 4H, Hα$_A$, Hα′$_A$, H3$_A$, H3′$_A$), 2.87 – 2.67 (m,

6H, Hα$_B$, Hα′$_B$, H3$_B$, H3′$_B$, H4$_A$, H4′$_A$), 2.59 – 2.55 (m, 2H, H4$_B$, H4′$_B$), 2.52 (s, 3H, N–CH_3 or N′–CH_3), 2.48 (s, 3H, N–CH_3 or N′–CH_3).

^{13}C NMR (126 MHz, CDCl3) δ 156.4(C12′), 149.8(C12), 147.38(C6 or C6′), 147.36(C6 or C6′), 146.5(C7 or C7′), 146.4(C7 or C7′), 144.7(C11), 134.0(C9′), 133.1(C9), 130.9(2C, C10′, C14′), 129.4(C8a or C8a′), 129.2(C8a or C8a′), 126.3(C4a or C4a′), 126.0(C4a or C4a′), 126.1(C14), 122.6(C10), 116.8(2C, C11′, C13′), 112.6(C13), 111.31(C5 or C5′), 111.28(C5 or C5′), 111.2(C8 or C8′), 111.0(C8 or C8′), 65.0(C1′), 64.8(C1), 56.2(C12–OCH$_3$), 55.9(C7–OCH$_3$ or C7′–OCH$_3$), 55.8(C7–OCH$_3$ or C7′–OCH$_3$), 55.71(C6–OCH$_3$ or C6′–OCH$_3$), 55.65(C7–OCH$_3$ or C7′–OCH$_3$), 47.1(C3 or C3′), 47.0(C3 or C3′), 42.83(N–CH$_3$ or N′–CH$_3$), 42.79(N–CH$_3$ or N′–CH$_3$), 40.7(Cα or Cα′), 40.4(Cα or Cα′), 25.7(C4 or C4′) , 25.6(C4 or C4′).

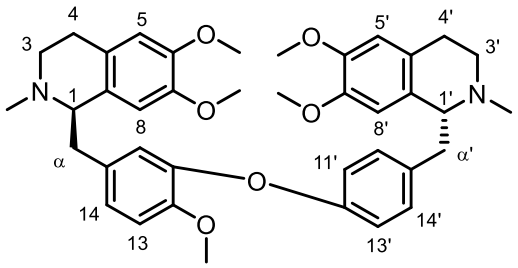
IR (film) ν_{max}/cm^{-1} 2998, 2935, 2907, 2834, 2795, 1609, 1507, 1463, 1444, 1259, 1225, 1168, 1138, 757.

HRMS (ESI$^+$) $C_{39}H_{46}N_2O_6$ found $[M+H]^+$ at 639.3427, expected at 639.3429.

$[\alpha]_D^{25}$ +72.8 (c. 1.21, $CHCl_3$). Ref [85] $[\alpha]_D^{25}$ +79.2 (c. 0.45, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[85]

(*R*)-1-(4-(5-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*,*R*)-52, (−)-*O*-methyldauricine



(*R*)-1-(4-Bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-51** (60 mg, 0.16 mmol), (*R*)-5-((6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenol **(R)-49** (60 mg, 0.18 mmol), potassium carbonate (55 mg, 0.40 mmol) and cupric oxide (25 mg, 0.32 mmol) in anhydrous pyridine (0.25 mL) were subjected to **General Procedure B.** The organic phase was washed with ammonia (aq., 35%, 4 × 6 mL) instead of filtering it through Celite® and no acidic wash was performed. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as a pale-yellow foam (17 mg, 27 μmol, 17%)

R_f 0.35 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.6 Hz, 2H, H10′, H14′), 6.87 (d, *J* = 8.3 Hz, 1H, H13), 6.82 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.78 (d, *J* = 8.6 Hz, 2H, H11′, H13′), 6.73 (d, *J* = 2.1 Hz, 1H, H10), 6.54 (s, 1H, H5 or H5′), 6.51 (s, 1H, H5 or H5′), 6.08 (s, 1H, H8 or H8′), 6.03 (s, 1H, H8 or H8′), 3.83 (s, 3H, C7–O*C*H$_3$ or C7′–O*C*H$_3$), 3.81 (s, 3H, C7–O*C*H$_3$ or C7′–O*C*H$_3$), 3.79 (s, 3H, C12 – O*C*H$_3$), 3.68 (dd, *J* = 7.7, 5.1 Hz, 1H, H1′), 3.64 (dd, *J* = 7.3, 5.4 Hz, 1H, H1), 3.61 (s, 3H, C6–O*C*H$_3$ or C6′–O*C*H$_3$), 3.57 (s, 3H, C6–O*C*H$_3$ or C6′–O*C*H$_3$), 3.23 – 3.01 (m, 4H, Hα$_A$, Hα′$_A$, H3$_A$, H3′$_A$), 2.87 – 2.68 (m,

6H, Hα$_B$, Hα′$_B$, H3$_B$, H3′$_B$, H4$_A$, H4′$_A$), 2.60 – 2.66 (m, 2H, H4$_B$, H4′$_B$), 2.52 (s, 3H, N–*C*H$_3$ or N′–*C*H$_3$), 2.48 (s, 3H, N–*C*H$_3$ or N′–*C*H$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4(C12′), 149.8(C12), 147.37(C6 or C6′), 147.34(C6 or C6′), 146.5(C7 or C7′), 146.4(C7 or C7′), 144.7(C11), 134.0(C9′), 133.1(C9), 130.9(2C, C10′, C14′), 129.4(C8a or C8a′), 129.2(C8a or C8a′), 126.3(C4a or C4a′), 126.0(C4a or C4a′), 126.1(C14), 122.6(C10), 116.8(2C, C11′, C13′), 112.6(C13), 111.29(C5 or C5′), 111.26(C5 or C5′), 111.2(C8 or C8′), 111.0(C8 or C8′), 65.0(C1′), 64.8(C1), 56.2(C12–O*C*H$_3$), 55.9(C7–O*C*H$_3$ or C7′–O*C*H$_3$), 55.8(C7–O*C*H$_3$ or C7′–O*C*H$_3$), 55.72(C6–O*C*H$_3$ or C6′–O*C*H$_3$), 55.65(C6–O*C*H$_3$ or C6′–O*C*H$_3$), 47.1(C3 or C3′), 47.0(C3 or C3′), 42.84(N–*C*H$_3$ or N′–*C*H$_3$), 42.81(N–*C*H$_3$ or N′–*C*H$_3$), 40.7(Cα or Cα′), 40.4(Cα or Cα′), 25.7(C4 or C4′), 25.6(C4 or C4′).

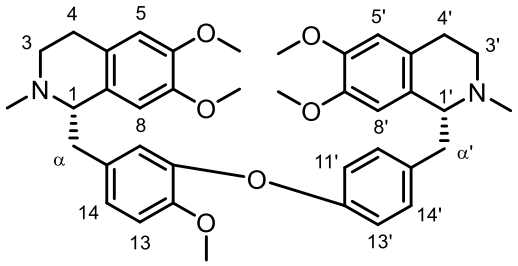
IR (film) ν_{max}/cm^{-1} 3017, 2937, 2907, 2834, 2795, 1609, 1507, 1464, 1450, 1257, 1225, 1169, 1126, 756.

HRMS (ESI$^+$) $C_{39}H_{46}N_2O_6$ found $[M+H]^+$ at 639.3424, expected at 639.3429.

$[\alpha]_D^{25}$ –81.7 (c. 1.15, $CHCl_3$). Ref [153] $[\alpha]_D^9$ –64.2 (c. 1.32, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[153]

(R)-1-(4-(5-(((S)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S,R*)-52, (−)-*O,O′*-dimethylgrisabine



(*R*)-1-(4-bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-51** (66 mg, 0.18 mmol), (*S*)-5-((6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenol **(*S*)-49** (66 mg, 0.19 mmol), potassium carbonate (61 mg, 0.44 mmol) and cupric oxide (28 mg, 0.35 mmol) in anhydrous pyridine (0.28 mL) were submitted to **General Procedure B**. The organic phase was washed with ammonia (aq., 35%, 4 × 8 mL) instead of filtering it through Celite® and no acidic wash was performed. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as a pale-yellow foam (25 mg, 40 µmol, 23%)

R_f 0.28 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.6 Hz, 2H, H10′, H14′), 6.87 (d, *J* = 8.3 Hz, 1H, H13), 6.82 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.78 (d, *J* = 8.6 Hz, 2H, H11′, H13′), 6.74 (d, *J* = 2.1 Hz, 1H, H10), 6.54 (s, 1H, H5 or H5′), 6.52 (s, 1H, H5 or H5′), 6.08 (s, 1H, H8 or H8′), 6.02 (s, 1H, H8 or H8′), 3.83 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.82 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.79 (s, 3H, C12–OCH_3), 3.69 (dd, *J* = 7.8, 5.1 Hz, 1H, H1′), 3.64 (dd, *J* = 7.4, 5.3 Hz, 1H, H1), 3.61 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.57 (s, 3H, C6–O*C*H$_3$ or C6′–O*C*H$_3$), 3.23 – 3.01 (m, 4H, H3$_A$, H3′$_A$, Hα$_A$, Hα′$_A$), 2.88 – 2.68 (m,

6H, H3$_B$, H3′$_B$, Hα$_B$, Hα′$_B$, H4$_A$, H4′$_A$), 2.62 – 2.54 (m, 2H, H4$_B$, H4′$_B$), 2.53 (s, 3H, N–CH_3 or N′–CH_3), 2.48 (s, 3H, N–CH_3 or N′–CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4(C12′), 149.8(C12), 147.38(C6 or C6′), 147.34(C6 or C6′), 146.5(C7 or C7′), 146.4(C7 or C7′), 144.7(C11), 134.0(C9′), 133.1(C9), 130.9(2C, C10′, C14′), 129.3(C8a or C8a′), 129.2(C8a or C8a′), 126.2(C4a or C4a′), 126.01(C4a or C4a′), 126.02(C14), 122.6(C10), 116.8(2C, C11′, C13′), 112.6(C13), 111.30(C5 or C5′), 111.26(C5 or C5′), 111.14(C8 or C8′), 110.98(C8 or C8′), 65.0(C1′), 64.8(C1), 56.2(C12-OCH$_3$), 55.87(C7–OCH$_3$ or C7′–OCH$_3$), 55.85(C7–OCH$_3$ or C7′–OCH$_3$), 55.71(C6–OCH$_3$ or C6′–OCH$_3$), 55.66(C6–OCH$_3$ or C6′–OCH$_3$), 47.02(C3 or C3′), 46.98(C3 or C3′), 42.81(N–CH$_3$ or N′–CH$_3$), 42.80(N–CH$_3$ or N′–CH$_3$), 40.6(Cα or Cα′), 40.4(Cα or Cα′), 25.6(2C, C4, C4′).

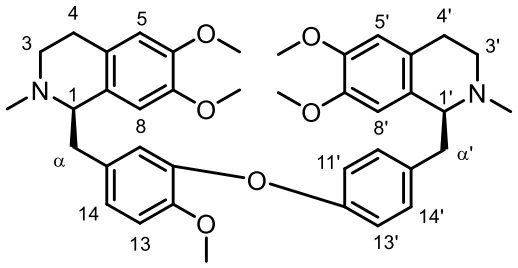
IR (film) ν_{max}/cm^{-1} 3000, 2935, 2909, 2835, 2795, 1610, 1507, 1464, 1450, 1258, 1226, 1169, 1138, 760.

HRMS (ESI$^+$) $C_{39}H_{46}N_2O_6$ found $[M+H]^+$ at 639.3432, expected at 639.3429.

$[\alpha]_D^{25}$ –25.0 (c. 1.12, $CHCl_3$). Ref [154] $[\alpha]_D$ –10 (c. 1.0, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[154]

(*S*)-1-(4-(5-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*,*S*)-53



(*S*)-1-(4-bromobenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-51** (60 mg, 0.16 mmol), (*R*)-5-((6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-methoxyphenol **(*R*)-49** (60 mg, 0.18 mmol), potassium carbonate (55 mg, 0.40 mmol) and cupric oxide (25 mg, 0.32 mmol) in anhydrous pyridine (0.25 mL) were submitted to **General Procedure B**. The organic phase was washed with ammonia (aq., 35%, 4 × 8 mL) instead of filtering it through Celite® and no acidic wash was performed. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as a pale-yellow foam (22 mg, 0.035 mmol, 22%).

R_f 0.28 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.5 Hz, 2H, H10′, H14′), 6.87 (d, *J* = 8.3 Hz, 1H, H13), 6.82 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.78 (d, *J* = 8.5 Hz, 2H, H11′, H13′), 6.73 (d, *J* = 2.1 Hz, 1H, H10), 6.55 (s, 1H, H5 or H5′), 6.52 (s, 1H, H5 or H5′), 6.06 (s, 1H, H8 or H8′), 6.00 (s, 1H, H8 or H8′), 3.83 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.82 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.79 (s, 3H, C12–OCH_3), 3.72 (dd, *J* = 8.0, 4.9 Hz, 1H, H1′), 3.66 (dd, *J* = 7.4, 5.3 Hz, 1H, H1), 3.60 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.56 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.24 – 3.05 (m, 4H, H3$_A$, H3′$_A$, Hα$_A$, Hα′$_A$), 2.89 – 2.70 (m,

6H, $H3_B$, $H3'_B$, $H\alpha_B$, $H\alpha'_B$, $H4_A$, $H4'_A$), 2.63 – 2.56 (m, 2H, $H4_B$, $H4'_B$), 2.55 (s, 3H, N–CH_3 or N′–CH_3), 2.49 (s, 3H, N–CH_3 or N′–CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5(C12′), 149.9(C12), 147.40(C6 or C6′), 147.37(C6 or C6′), 146.5(C7 or C7′), 146.4(C7 or C7′), 144.7(C11), 134.0(C9′), 133.1(C9), 130.9(2C, C10′, C14′), 129.3(C8a or C8a′), 129.2(C8a or C8a′), 126.2(C4a or C4a′), 126.0(C4a or C4a′), 126.1(C14), 122.6(C10), 116.8(2C, C11′, C13′), 112.6(C13), 111.31(C5 or C5′), 111.28(C5 or C5′), 111.2(C8 or C8′), 111.0(C8 or C8′), 65.0(C1′), 64.8(C1), 56.2(C12–OCH_3), 55.89(C7–OCH_3 or C7′–OCH_3), 55.87(C7–OCH_3 or C7′–OCH_3), 55.72(C6–OCH_3 or C6′–OCH_3), 55.68(C6–OCH_3 or C6′–OCH_3), 47.03(C3 or C3′), 46.98(C3 or C3′), 42.81(N–CH_3 or N′–CH_3), 42.80(N–CH_3 or N′–CH_3), 40.7(Cα or Cα′), 40.5(Cα or Cα′), 25.6(2C, C4, C4′).

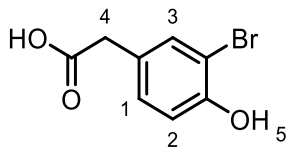
IR (film) ν_{max}/cm^{-1} 3020, 2935, 2907, 2835, 2794, 1610, 1509, 1464, 1443, 1259, 1226, 1169, 1126, 762.

HRMS (ESI$^+$) $C_{39}H_{46}N_2O_6$ found $[M+H]^+$ at 639.3425, expected at 639.3429.

$[\alpha]_D^{25}$ +23.7 (c. 0.88, $CHCl_3$). Ref [155] $[\alpha]_D$ +14 (c. unknown, $CHCl_3$).

Some spectroscopic data has been reported previously.[155]

2-(3-Bromo-4-hydroxyphenyl)acetic acid, 143



Adapted from the procedure of Weicheng et al.[156] To a solution of 4-hydroxyphenylacetic acid **144** (5.00 g, 32.9 mmol, 1.0 equiv.) and *p*-toluensulfonic acid (6.56 g, 34.5 mmol, 1.05 equiv.) in acetonitrile (66 mL) at −15 ºC (1:2 w/w NaCl/ice cooling bath) was added *N*-bromosuccinimide (5.85 g, 32.9 mmol, 1.0 equiv.) and the mixture was stirred at −15 ºC for 2.5 h. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was diluted with EtOAc (100 mL), washed sequentially with $Na_2S_2O_4$ (aq., sat., 2 × 100 mL) and H_2O (2 × 70 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a white solid (7.27 g, 31.5 mmol, 96%). No further purification was necessary.

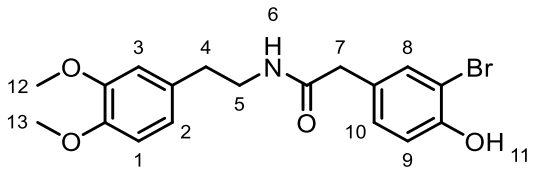
R_f 0.23 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (400 MHz, methanol-d_4) δ 7.38 (d, J = 2.2 Hz, 1H, H3), 7.06 (dd, J = 8.3, 2.2 Hz, 1H, H1), 6.83 (d, J = 8.3 Hz, 1H, H2), 4.97 (s, br, 1H, H5), 3.49 (s, 2H, H4).

^{13}C NMR (101 MHz, methanol-d_4) δ 174.2, 152.9, 133.4, 129.2, 127.2, 115.7, 109.2, 39.1.

Spectroscopic data is in agreement with that reported previously.[85]

2-(3-Bromo-4-hydroxyphenyl)-N-(3,4-dimethoxyphenethyl)acetamide, 145



2-(3,4-Dimethoxyphenyl)ethan-1-amine **127** (375 mg, 2.07 mmol), 2-(3-bromo-4-hydroxy phenyl)acetic acid **143** (435 mg, 1.88 mmol), triethylamine (289 µL, 2.07 mmol), hydroxybenzotriazole hydrate (127 mg, 0.940 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (540 mg, 2.82 mmol) in anhydrous CH_2Cl_2 (6.3 mL) were submitted to **General Procedure H**. Purification by flash column chromatography (EtOAc) afforded the title compound as an off-white amorphous solid (630 mg, 1.60 mmol, 85%).

R_f 0.49 (EtOAc), [UV, PMA]

m.p. 146 – 147 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 2.1 Hz, 1H, H8), 7.00 (dd, *J* = 8.3, 2.1 Hz, 1H, H10), 6.94 (d, *J* = 8.3 Hz, 1H, H9), 6.74 (d, *J* = 8.2 Hz, 1H, H1), 6.62 (d, *J* = 2.0 Hz, 1H, H3), 6.55 (dd, *J* = 8.2, 2.0 Hz, 1H, H2), 5.76 (s, br, 1H, H11), 5.36 (s, br, 1H, H6), 3.86 (s, 3H, H13), 3.83 (s, 3H, H12), 3.46 (q, *J* = 6.7 Hz, 2H, H5), 3.42 (s, 2H, H7), 2.69 (t, *J* = 6.7 Hz, 2H, H4).

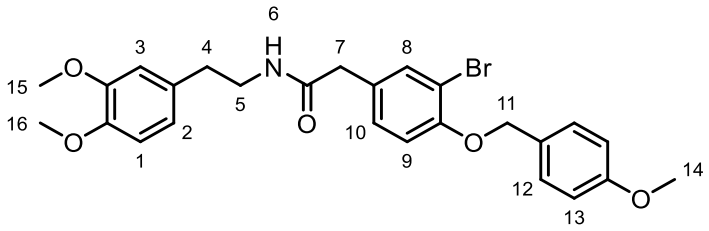
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 151.8, 149.2, 147.9, 132.9, 131.1, 130.3, 128.4, 120.8, 116.7, 111.8, 111.4, 110.6, 56.1, 56.0, 42.6, 40.9, 35.1.

IR (film) ν_{max}/cm^{-1} 2957, 2837, 1646, 1515, 1464, 1261, 1236, 1157, 1141, 1028, 912.

HRMS (ESI$^+$) $C_{18}H_{20}Br^{79}NO_4$ found $[M+H]^+$ at 394.0649, expected at 394.0648.

Some spectroscopic data has been reported previously.[157]

2-(3-Bromo-4-((4-methoxybenzyl)oxy)phenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide, 142



To a solution of 2-(3-bromo-4-hydroxyphenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **145** (3.30 g, 8.37 mmol, 1.0 equiv.) and potassium carbonate (2.89 g, 20.9 mmol, 2.5 equiv.) in DMF (12 mL) was added 4-methoxybenzyl chloride (1.36 mL, 10.0 mmol, 1.2 equiv.). The reaction mixture was heated to 80 ºC for 18 h. Upon completion, the mixture was diluted with EtOAc (40 mL) and washed sequentially with $NaHCO_3$ (aq., sat., 10 mL), HCl (aq., 1 M, 15 mL) and H_2O (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (dry-loading, EtOAc/pentane, 2:1 → 1:0) afforded the title compound as an off-white solid (3.75 g, 7.29 mmol, 87%).

R*f* 0.36 (EtOAc/pentane, 4:1), [UV, PMA]

m.p. 113 – 114 ºC

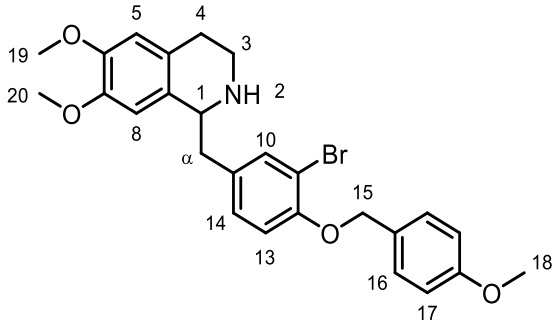
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 3H, H8, H12), 7.03 (dd, *J* = 8.4, 2.2 Hz, 1H, H10), 6.92 (d, *J* = 8.7 Hz, 2H, H13), 6.86 (d, *J* = 8.4 Hz, 1H, H9), 6.74 (d, *J* = 8.1 Hz, 1H, H1), 6.62 (d, *J* = 2.1 Hz, 1H, H3), 6.54 (dd, *J* = 8.1, 2.1 Hz, 1H, H2), 5.37 (s, br, 1H, H6), 5.07 (s, 2H, H11), 3.84 (s, 3H, H16), 3.83 (s, 3H, H15), 3.81 (s, 3H, H14), 3.45 (q, *J* = 6.7 Hz, 2H, H5), 3.42 (s, 2H, H7), 2.68 (t, *J* = 6.7 Hz, 2H, H4).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 159.6, 154.5, 149.2, 147.8, 134.3, 131.1, 129.5, 128.9(2C), 128.7, 128.5, 120.8, 114.3, 114.2(2C), 113.0, 111.8, 111.4, 70.9, 56.05, 55.98, 55.4, 42.7, 40.8, 35.2.

IR (film) ν_{max}/cm^{-1} 2937, 2835, 1648, 1312, 1515, 1494, 1246, 1029, 735.

HRMS (ESI$^+$) $C_{26}H_{28}Br^{79}NO_5$ found $[M+H]^+$ at 514.1244, expected at 514.1224.

1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 146



2-(3-Bromo-4-((4-methoxybenzyl)oxy)phenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **142** (0.10 g, 0.19 mmol), 2-chloropyridine (22 µL, 0.23 mmol) and trifluoromethanesulfonic anhydride (35 µL, 0.21 mmol) in anhydrous CH_2Cl_2 (1 mL) were submitted to **General Procedure C**. The crude imine and sodium borohydride (14 mg, 0.38 mmol) in EtOH (1 mL) were submitted to **General Procedure D**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (70 mg, 0.14 mmol, 74%).

R_f 0.19 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

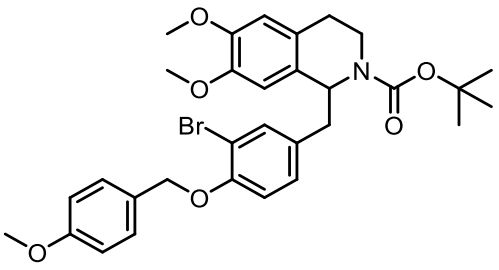
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.2 Hz, 1H, H10), 7.39 (d, *J* = 8.6 Hz, 2H, H16), 7.10 (dd, *J* = 8.3, 2.2 Hz, 1H, H14), 6.91 (d, *J* = 8.6 Hz, 2H, H17), 6.89 (d, *J* = 8.3 Hz, 1H, H13), 6.59 (2s, 2H, H5, H8), 5.06 (s, 2H, H15), 4.09 (dd, *J* = 9.5, 4.3 Hz, 1H, H1), 3.85 (s, 3H, H20), 3.81 (2s, 6H, H18, H19), 3.19 (dt, *J* = 11.7, 5.6 Hz, 1H, $H3_A$), 3.11 (dd, *J* = 13.8, 4.3 Hz, 1H, $H\alpha_A$), 2.95 – 2.88 (m, 1H, $H3_B$), 2.85 – 2.64 (m, 3H, $H\alpha_B$, H4), 2.03 (s, br, 1H, H2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 153.8, 147.6, 147.1, 134.1, 133.2, 130.2, 129.3, 128.8(2C), 128.7, 127.4, 114.2, 114.0(2C), 112.7, 111.9, 109.4, 70.9, 56.9, 56.0, 55.9, 55.3, 41.7, 40.7, 29.5.

IR (film) ν_{max}/cm^{-1} 2952, 2935, 2835, 1612, 1587, 1515, 1494, 1464, 1247, 1175, 730.

HRMS (ESI$^+$) $C_{26}H_{28}Br^{79}NO_4$ found $[M+H]^+$ at 498.1262, expected at 498.1275.

***tert*-Butyl 1-(3-bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S10**



1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **146** (70 mg, 0.14 mmol), di-*tert*-butyl dicarbonate (37 mg, 0.17 µmol) and triethylamine (24 µL, 0.17 µmol) in anhydrous CH_2Cl_2 (0.7 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/Et_2O, 1:1) afforded the title compound as a colourless oil (60 mg, 99 µmol, 71%).

R*f* 0.15 (pentane/Et_2O, 1:1), [UV, PMA]

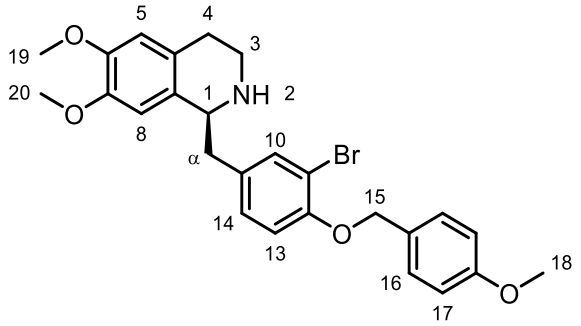
^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.66:034 ratio, Major(M) and minor(m)) δ 7.42 – 7.27 (m, 3H, both rotamers), 7.00 – 6.87 (m, 3H, both rotamers), 6.86 – 6.79 (m, 1H, both rotamers), 6.64 – 4.57 (m, 1H, both rotamers), 6.38 (s, 0.66H, (M)) 6.22 (s, 0.34H, (m)), 5.18 (t, *J* = 7.0 Hz, (m)), 5.08 – 5.02 (m, 2H, both rotamers + 0.66H, (M)), 4.21 – 4.16 (m, 0.66H, (M)), 3.87 – 3.83 (m, 3H, both rotamers + 0.34H, (m)), 3.81 (s, 3H, both rotamers), 3.78 – 3.60 (m, 3H, both rotamers), 3.35 – 3.18 (m, 1H, both rotamers), 3.04 – 2.70 (m, 3H, both rotamers), 2.65 – 2.51 (m, 1H, both rotamers), 1.43 (s, 3.3H, (m)), 1.30 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 159.5, 154.5, 153.9, 147.9, 147.2, 134.4, 132.8, 129.7, 128.8, 128.7(2C), 128.5, 126.7, 114.1(2C), 114.0, 112.5, 111.6, 110.2, 79.9, 70.9, 56.4, 55.9(2C), 55.4, 41.9, 37.1, 28.3(3C), 28.2.

IR (film) ν_{max}/cm^{-1} 3005, 2934, 2836, 1684, 1613, 1516, 1494, 1246, 1172, 910, 731.

HRMS (ESI$^+$) $C_{31}H_{36}Br^{79}NO_6$ found $[M+H]^+$ at 598.1782, expected at 598.1799.

(*S*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*S*)-146



2-(3-Bromo-4-((4-methoxybenzyl)oxy)phenyl)-N-(3,4-dimethoxyphenethyl)acetamide **142** (1.00 g, 1.94 mmol), 2-chloropyridine (220 µL, 2.33 mmol) and trifluoromethanesulfonic anhydride (360 µL, 2.14 mmol) in anhydrous CH_2Cl_2 (10 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*R,R*)-TsDPEN] (*p*-cymene) (87 mg, 0.14 mmol) and HCO_2H/Et_3N (5:2 v/v, 1.00 mL) in anhydrous DMF (10 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as an amber oil (0.868 g, 1.74 mmol, 90% over 2 steps, 96% *ee* after Boc derivatisation).

R_f 0.19 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.1 Hz, 1H, H10), 7.40 (d, *J* = 8.5 Hz, 2H, H16), 7.11 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.92 (d, *J* = 8.5 Hz, 2H, H17), 6.90 (d, *J* = 8.3 Hz, 1H, H13), 6.60 (2s, 2H, H5, H8), 5.08 (s, 2H, H15), 4.09 (dd, *J* = 9.7, 4.3 Hz, 1H, H1), 3.86 (s, 3H, H20), 3.82 (2s, 6H, H18, H19), 3.19 (dt, *J* = 12.0, 5.4 Hz, 1H, $H3_A$), 3.12 (dd, *J* = 13.8, 4.3 Hz, 1H, $H\alpha_A$), 2.93 (ddd, *J* = 12.0, 7.0, 5.4 Hz, 1H, $H3_B$), 2.85 – 2.64 (m, 3H, $H\alpha_B$, H4), 1.72 (s, br, 1H, H2).

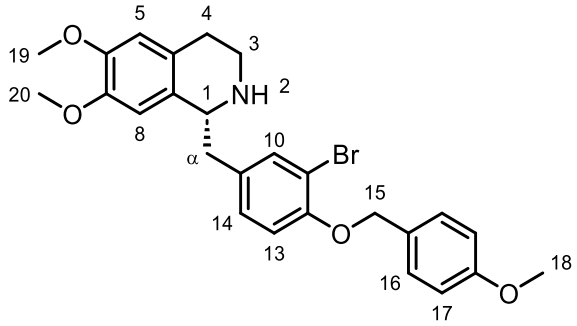
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 153.9, 147.7, 147.2, 134.2, 133.3, 130.4, 129.4, 128.9, 128.8(2C), 127.5, 114.3, 114.1(2C), 112.8, 112.0, 109.5, 71.0, 57.0, 56.1, 56.0, 55.4, 41.8, 40.9, 29.6.

IR (film) ν_{max}/cm^{-1} 2934, 2834, 1612, 1587, 1515, 1494, 1464, 1247, 1175.

HRMS (ESI$^+$) $C_{26}H_{28}Br^{79}NO_4$ found $[M+H]^+$ at 498.1266, expected at 498.1275.

$[\alpha]_D^{25}$ –3.8 (c. 0.86, $CHCl_3$).

(*R*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*R*)-146



2-(3-Bromo-4-((4-methoxybenzyl)oxy)phenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **142** (1.00 g, 1.94 mmol), 2-chloropyridine (220 µL, 2.33 mmol) and trifluoromethanesulfonic anhydride (360 µL, 2.14 mmol) in anhydrous CH_2Cl_2 (10 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*S,S*)-TsDPEN] (*p*-cymene) (87 mg, 0.14 mmol) and HCO_2H/Et_3N (5:2 v/v, 1.00 mL) in anhydrous DMF (10 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as an amber oil (638 mg, 1.28 mmol, 66% over 2 steps, 92% *ee* after Boc derivatisation).

R_f 0.19 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.1 Hz, 1H, H10), 7.40 (d, *J* = 8.7 Hz, 2H, H16), 7.11 (dd, *J* = 8.3, 2.1 Hz, 1H, H14), 6.97 – 6.86 (m, 3H, H13, H17), 6.60 (2s, 2H, H5, H8), 5.08 (s, 2H, H15), 4.09 (dd, *J* = 9.6, 4.3 Hz, 1H, H1), 3.86 (s, 3H, H20), 3.82 (2s, 6H, H18, H19), δ 3.19 (dt, *J* = 11.7, 5.6 Hz, 1H, $H3_A$), 3.11 (dd, *J* = 14.0, 4.3 Hz, 1H, $H\alpha_A$), 2.98 – 2.86 (m, 1H, $H3_B$), 2.86 – 2.63 (m, 3H, $H\alpha_B$, H4), 1.70 (s, br, 1H, H2).

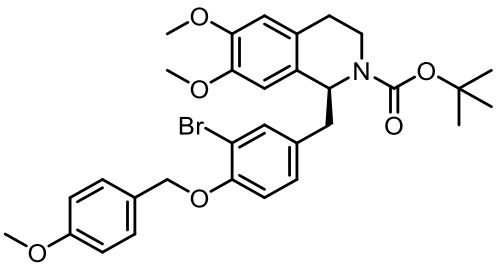
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 153.9, 147.7, 147.2, 134.2, 133.3, 130.4, 129.4, 128.9(2C), 128.8, 127.5, 114.3, 114.1(2C), 112.8, 112.0, 109.5, 71.0, 57.0, 56.1, 56.0, 55.4, 41.8, 40.8, 29.6.

IR (film) ν_{max}/cm^{-1} 2934, 2834, 1612, 1587, 1515, 1494, 1464, 1248, 1175.

HRMS (ESI^+) $C_{26}H_{28}Br^{79}NO_4$ found $[M+H]^+$ at 512.1426, expected at 512.1431.

$[\alpha]_D^{25}$ +3.6 (c. 1.28, $CHCl_3$).

***tert*-Butyl (*S*)-1-(3-bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S11**



(*S*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-146** (17 mg, 35 µmol), di-*tert*-butyl dicarbonate (9.0 mg, 41 µmol) and triethylamine (5.8 µL, 41 µmol) in anhydrous CH_2Cl_2 (0.2 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/Et_2O, 1:1) afforded the title compound as a colourless oil (8.1 mg, 14 µmol, 39%, 96% *ee*).

R*f* 0.15 (pentane/Et_2O, 1:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.66:034 ratio, Major(M) and minor(m)) δ 7.42 – 7.27 (m, 3H, both rotamers), 7.00 – 6.88 (m, 3H, both rotamers), 6.86 – 6.80 (m, 1H, both rotamers), 6.62 – 6.54 (m, 1H, both rotamers), 6.38 (s, 0.66H, (M)), 6.22 (s, 0.34H, (m)), 5.18 (t, *J* = 7.0 Hz, 0.34H, (m)), 5.08 – 5.01 (m, 2H, both rotamers + 0.66H, (M)), 4.21 – 4.14 (m, 0.66H, (M)), 3.87 – 3.83 (m, 3H, both rotamers), 3.83 – 3.78 (m, 3H, both rotamers + 0.34H, (m)), 3.75 – 3.61 (m, 3H, both rotamers), 3.34 – 3.19 (m, 1H, both rotamers), 3.04 – 2.70 (m, 3H, both rotamers), 2.65 – 2.51 (m, 1H, both rotamers), 1.43 (s, 3.3H, (m)), 1.30 (m, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 159.5, 154.5, 153.9, 148.0, 147.3, 134.4, 132.9, 129.7, 128.9, 128.8(2C), 128.6, 126.7, 114.13(2C), 114.08, 112.6, 111.6, 110.3, 79.9, 71.0, 56.5, 56.1(2C), 55.4, 42.0, 37.2, 28.4(3C), 28.2.

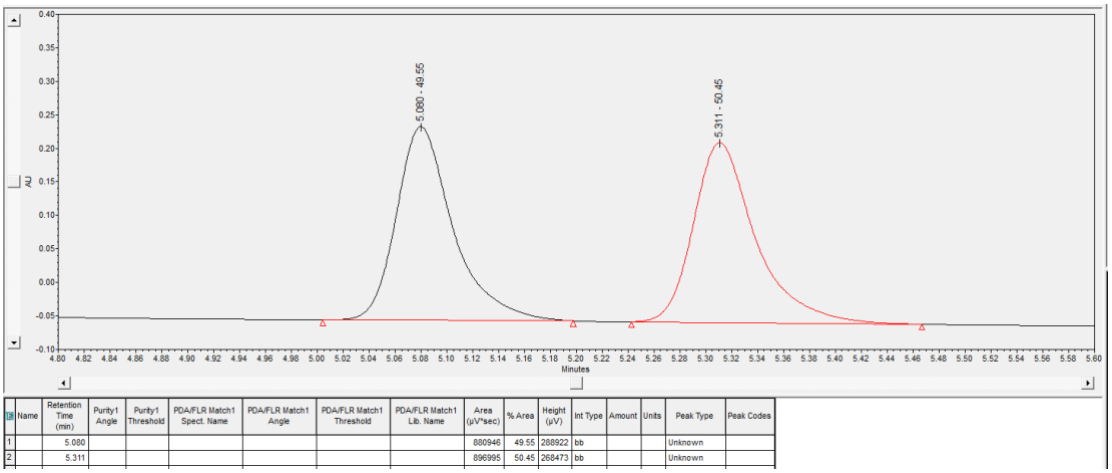
IR (film) ν_{max}/cm^{-1} 3001, 2932, 2837, 1686, 1613, 1516, 1494, 1246, 1172.

HRMS (ESI$^+$) $C_{31}H_{36}Br^{79}NO_6$ found $[M+H]^+$ at 598.1798, expected at 598.1799.

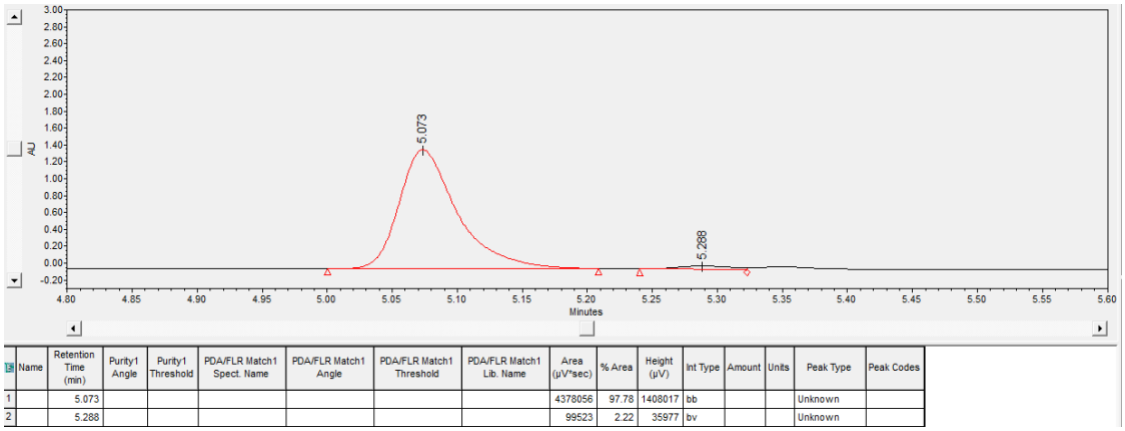
$[\alpha]_D^{25}$ +69.4 (c. 1.16, $CHCl_3$).

SFC trace of racemic (±)-**S10** and enantioenriched (+)-**S11**.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; (+)-**S11**: 97.8:2.2 *e.r.* (major enantiomer t_R = 5.07 min; minor enantiomer t_R = 5.29 min). λ = 215.0 nm.

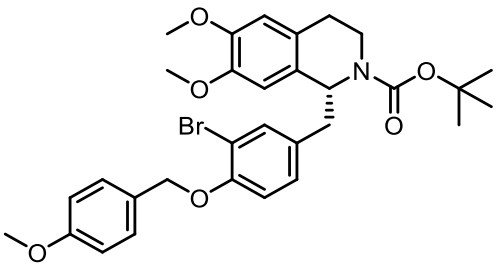


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		5.080							880946	49.55	288922	bb			Unknown	
2		5.311							896995	50.45	268473	bb			Unknown	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		5.073							4378056	97.78	1408017	bb			Unknown	
2		5.288							99523	2.22	35977	bv			Unknown	

***tert*-Butyl (*R*)-1-(3-bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S12**



(*R*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-146** (13 mg, 26 µmol), di-*tert*-butyl dicarbonate (6.7 mg, 31 µmol) and triethylamine (4.3 µL, 31 µmol) in anhydrous CH_2Cl_2 (0.13 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/Et_2O, 1:1) afforded the title compound as a colourless oil (13 mg, 22 µmol, 85%, 92% *ee*).

R*f* 0.15 (pentane/Et_2O, 1:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:036 ratio, Major(M) and minor(m)) δ 7.44 – 7.27 (m, 3H, both rotamers), 6.99 – 6.88 (m, 3H, both rotamers), 6.86 – 6.78 (m, 1H, both rotamers) 6.63 – 6.57 (m, 1H, both rotamers), 6.37 (s, 0.64H, (M)), 6.22 (s, 0.34H, (m)), 5.18 (t, *J* = 7.0 Hz, 0.36H, (m)), 5.08 – 4.99 (m, 2H, both rotamers + 0.64H, (M)), 4.21 – 4.14 (m, 0.64H, (M)), 3.88 – 3.83 (m, 3H, both rotamers), 3.83 – 3.77 (m, 3H, both rotamers + 0.36H, (m)), 3.75 (s, 2H, (M)), 3.64 (s, 1H, (m)), 3.37 – 3.16 (m, 1H, both rotamers), 3.04 – 2.70 (m, 3H, both rotamers), 2.64 – 2.51 (m, 1H, both rotamers), 1.43 (s, 3.3H, (m)), 1.30 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 159.6, 154.5, 153.9, 148.0, 147.3, 134.4, 132.9, 129.7, 128.9, 128.8(2C), 128.6, 126.7, 114.14(2C), 114.10, 112.6, 111.7, 110.3, 79.9, 71.0, 56.5, 56.1(2C), 55.5, 42.0, 37.2, 28.4(3C), 28.3.

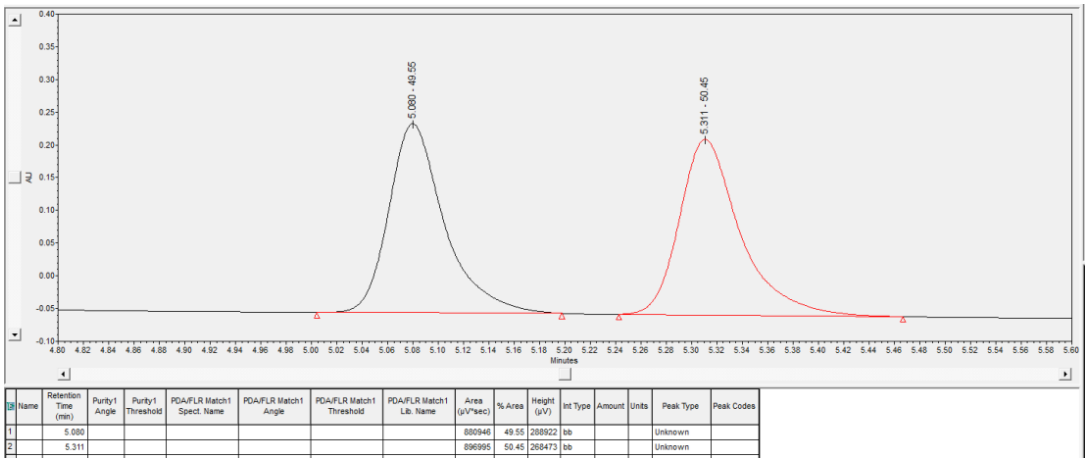
IR (film) ν_{max}/cm^{-1} 3005, 2930, 2837, 1687, 1613, 1516, 1494, 1246, 1172.

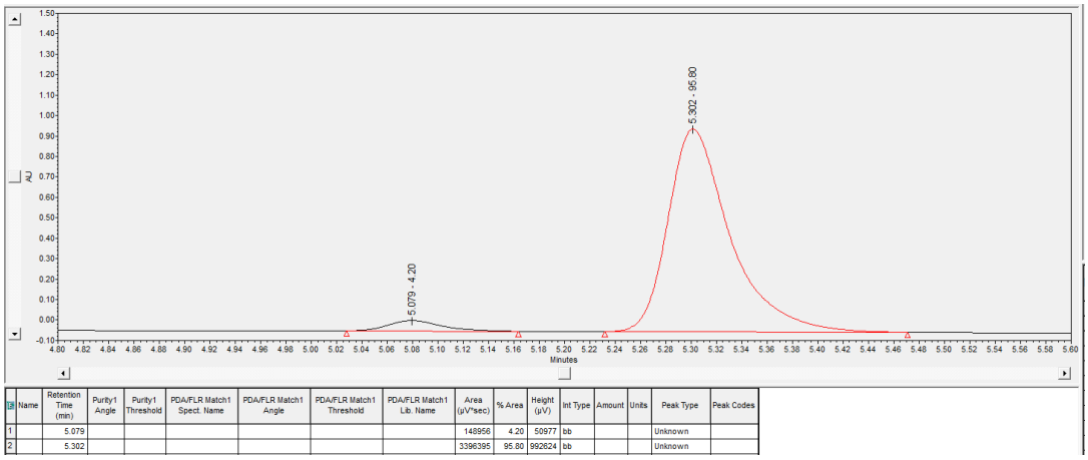
HRMS (ESI$^+$) $C_{31}H_{36}Br^{79}NO_6$ found $[M+H]^+$ at 598.1797, expected at 598.1799.

[α]$_D^{25}$ –66.4 (c. 0.96, $CHCl_3$).

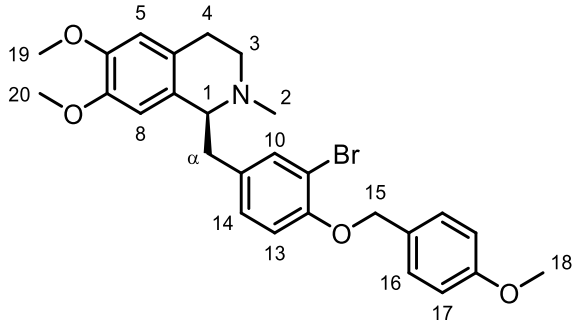
SFC trace of racemic (±)-**S10** and enantioenriched (–)-**S12**.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; (–)-**S12**: 95.8:4.2 *e.r.* (major enantiomer t_R = 5.30 min; minor enantiomer t_R = 5.08 min). λ = 215.0 nm.





(*S*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-141



(*S*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-146** (824 mg, 1.65 mmol), formalin (37% aq., 3.40 mL, 45.7 mmol) and sodium borohydride (187 mg, 4.95 mmol) in MeOH (33 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/7N ammonia solution in MeOH, 99:1) afforded the title compounds as an amber foam (692 mg, 1.35 mmol, 82%).

R*f* 0.35 (EtOAc/7N ammonia solution in MeOH, 99:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.7 Hz, 2H, H16), 7.34 (d, *J* = 2.1 Hz, 1H, H10), 6.93 – 6.89 (m, 3H, H14, H17), 6.81 (d, *J* = 8.4 Hz, 1H, H13), 6.55 (s, 1H, H5), 6.08 (s, 1H, H8), 5.05 (s, 2H, H15), 3.84 (s, 3H, H20), 3.81 (s, 3H, H18), 3.64 (dd, *J* = 7.3, 5.3 Hz, 1H, H1), 3.58 (s, 3H, H19), 3.19 – 3.12 (m, 1H, $H3_A$), 3.07 (dd, *J* = 13.8, 5.3 Hz, 1H, $H\alpha_A$), 2.84 – 2.70 (m, 3H, $H4_A$, $H3_B$, $H\alpha_B$), 2.56 (dt, *J* = 15.6, 4.6 Hz, 1H, $H4_B$), 2.52 (s, 3H, H2).

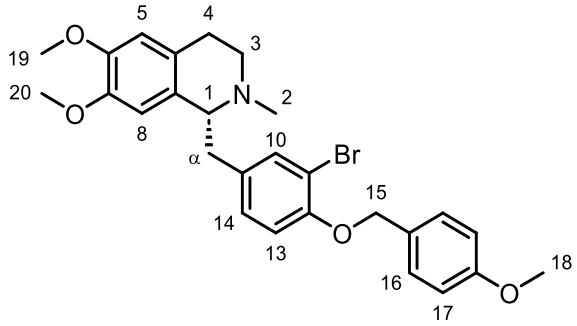
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 153.5, 147.7, 146.6, 134.5, 134.3, 129.8, 129.2, 128.8(3C), 126.2, 114.1(2C), 114.0, 112.3, 111.4, 111.0, 70.9, 64.9, 55.9, 55.7, 55.4, 47.0, 42.8, 40.3, 25.6.

IR (film) ν_{max}/cm^{-1} 3002, 2936, 2834, 1612, 1515, 1494, 1464, 1228, 761.

HRMS (ESI$^+$) $C_{27}H_{30}Br^{79}NO_4$ found $[M+H]^+$ at 512.1420, expected at 512.1431.

$[\alpha]_D^{25}$ +44.1 (c. 1.39, $CHCl_3$).

(*R*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*)-141



(*R*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-146** (544 mg, 1.09 mmol), formalin (37% aq., 2.25 mL, 30.2 mmol) and sodium borohydride (124 mg, 3.27 mmol) in MeOH (22 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/7N ammonia solution in MeOH, 99:1) afforded the title compounds as an amber foam (444 mg, 0.866 mmol, 79%).

R*f* 0.35 (EtOAc/7N ammonia solution in MeOH, 99:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$ δ 7.38 (d, *J* = 8.7 Hz, 2H, H16), 7.34 (d, *J* = 2.1 Hz, 1H, H10), 6.99 – 6.89 (m, 3H, H14, H17), 6.81 (d, *J* = 8.4 Hz, 1H, H13), 6.55 (s, 1H, H5), 6.08 (s, 1H, H8), 5.05 (s, 2H, H15), 3.84 (s, 3H, H20), 3.81 (s, 3H, H19), 3.64 (dd, *J* = 7.2, 5.4 Hz, 1H, H1), 3.58 (s, 3H, H18), 3.20 – 3.11 (m, 1H, $H3_A$), 3.06 (dd, *J* = 13.8, 5.4 Hz, 1H, $H\alpha_A$), 2.86 – 2.70 (m, 3H, $H4_A$, $H3_B$, $H\alpha_B$), 2.56 (dt, *J* = 15.7, 4.7 Hz, 1H, $H4_B$), 2.51 (s, 3H, H2).

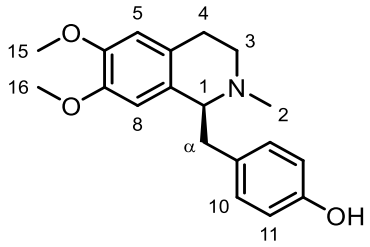
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 153.5, 147.5, 146.6, 134.6, 134.3, 129.8, 129.2, 128.9(3C), 126.3, 114.1(2C), 114.0, 112.3, 111.4, 111.0, 71.0, 64.9, 55.9, 55.8, 55.4, 47.1, 42.8, 40.3, 25.6.

IR (film) ν_{max}/cm^{-1} 3002, 2936, 2834, 1612, 1515, 1494, 1464, 1228, 761.

HRMS (ESI$^+$) $C_{27}H_{30}Br^{79}NO_4$ found $[M+H]^+$ at 512.1421, expected at 512.1431.

$[\alpha]_D^{25}$ –43.6 (c. 0.80, $CHCl_3$).

(*S*)-4-((6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenol, (*S*)-140, (+)-armepavine



Procedure 1: To an oven-dried flask containing Pd/C (10% wt., 87.0 mg, 81.8 µmol, 0.14 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.7 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*S*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-141** (290 mg, 0.566 mmol, 1.0 equiv.) was then added as a solution in MeOH (5.0 mL) and triethylamine (790 µL, 5.66 mmol, 10 equiv.). Using a gas bag, hydrogen was continuously bubbled through the reaction mixture by having the needle submerged in the reaction mixture and a second exit needle for 30 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 100 mL) and the filtrate was concentrated *in vacuo*. The residue was then diluted with $CHCl_3$, washed sequentially with HCl (aq., 1 M, 3 mL) and $NaHCO_3$ (aq., sat., to pH 7). The aqueous phase was extracted with $CHCl_3$:IPA (9:1, 3 × 15 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as an off-white foam (160 mg, 0.511 mmol, 90%). No further purification was necessary.

Procedure 2: To an oven-dried flask containing Pd/C (10% wt., 33 mg, 31 µmol, 0.04 equiv.) under an inert atmosphere, was added anhydrous MeOH (1.0 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*S*)-1-(4-(Benzyloxy)benzyl)-

6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-151** (0.33 g, 0.82 mmol, 1.0 equiv.) was then added as a solution in MeOH (7.0 mL) and AcOH (0.10 mL, 1.8 mmol, 2.2 equiv.). Using a gas bag, hydrogen was continuously bubbled through the reaction mixture by having the needle submerged in the reaction mixture and a second exit needle for 18 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 60 mL) and the filtrate was concentrated *in vacuo*. The residue was then diluted with $CHCl_3$ and washed with $NaHCO_3$ (aq., sat., to pH 7). The aqueous phase was then extracted with $CHCl_3$:IPA (9:1, 3 × 10 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as an off-white foam (0.24 g, 0.77 mmol, 94%). No further purification was necessary.

R_f 0.31 (CH_2Cl_2/MeOH/7N ammonia solution in MeOH, 9:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.4 Hz, 2H, H10), 6.63 (d, *J* = 8.4 Hz, 2H, H11), 6.56 (s, 1H, H5), 6.01 (s, 1H, H8), 3.83 (s, 3H, H16), 3.73 (dd, *J* = 8.1, 5.3 Hz, 1H, H1), 3.56 (s, 3H, H15), 3.32 – 3.21 (m, 1H, $H3_A$), 3.14 (dd, *J* = 13.7, 5.3 Hz, 1H, $H\alpha_A$), 2.93 – 2.79 (m, 2H, $H4_A$, $H3_B$), 2.75 (dd, *J* = 13.7, 8.1 Hz, 1H, $H\alpha_B$), 2.67 – 2.58 (m, 1H, $H4_B$), 2.53 (s, 3H, H2).

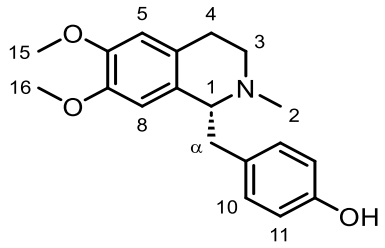
Note: O*H* resonance was not observed.

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 147.5, 146.4, 131.1, 130.9(2C), 128.8, 125.4, 115.5(2C), 111.32, 111.30, 65.1, 55.9, 55.6, 46.2, 42.3, 40.6, 24.7.

$[\alpha]_D^{25}$ +95.3 (c. 0.93, $CHCl_3$). Ref.[85] $[\alpha]_D^{25}$ +94.2 (c. 1.0, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[85]

(*R*)-4-((6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenol, (*R*)-140, (−)-armepavine



Procedure 1: To an oven-dried flask containing Pd/C (10% wt., 66.0 mg, 62.0 µmol, 0.14 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.3 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*R*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-141** (220 mg, 0.429 mmol, 1.0 equiv.) was then added as a solution in MeOH (4.0 mL) and triethylamine (600 µL, 4.29 mmol, 10 equiv.). Using a gas bag, hydrogen was continuously bubbled through the reaction mixture by having the needle submerged in the reaction mixture and a second exit needle for 30 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 100 mL) and the filtrate was concentrated *in vacuo*. The residue was then diluted with $CHCl_3$, washed with HCl (aq., 1 M, 3 mL) and $NaHCO_3$ (aq., sat., to pH 7). The aqueous phase was extracted with $CHCl_3$:IPA (9:1, 3 × 15 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as an off-white foam (116 mg, 0.370 mmol, 86%). No further purification was necessary.

$[\alpha]_D^{25}$ –92.8 (c. 0.90, $CHCl_3$).

Procedure 2: To an oven-dried flask containing Pd/C (10% wt., 34 mg, 32 µmol, 0.04 equiv.) under an inert atmosphere, was added anhydrous MeOH (1.0 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*R*)-1-(4-(Benzyloxy)benzyl)-

6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-151** (0.34 g, 0.84 mmol, 1.0 equiv.) was then added as a solution in MeOH (7.0 mL) and AcOH (0.11 mL, 1.8 mmol, 2.2 equiv.). Using a gas bag, hydrogen was continuously bubbled through the reaction mixture by having the needle submerged in the reaction mixture and a second exit needle for 18 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 60 mL) and the filtrate was concentrated *in vacuo*. The residue was then diluted with $CHCl_3$ and washed with $NaHCO_3$ (aq., sat., to pH 7). The aqueous phase was then extracted with $CHCl_3$:IPA (9:1, 3 × 15 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as an off-white foam (0.24 g, 0.75 mmol, 90%). No further purification was necessary.

R_f 0.31 (CH_2Cl_2/MeOH/7N ammonia solution in MeOH, 9:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.5 Hz, 2H, H10), 6.62 (d, *J* = 8.5 Hz, 2H, H11), 6.56 (s, 1H, H5), 5.96 (s, 1H, H8), 3.82 (s, 3H, H16), 3.74 (dd, *J* = 8.5, 5.0 Hz, 1H, H1), 3.52 (s, 3H, H16), 3.27 (ddd, *J* = 12.7, 9.2, 5.4 Hz, 1H, $H3_A$), 3.16 (dd, *J* = 13.6, 5.0 Hz, 1H, $H\alpha_A$), 2.95 – 2.80 (m, 2H, $H4_A$, $H3_B$), 2.73 (dd, *J* = 13.6, 8.5 Hz, 1H, $H\alpha_B$), 2.63 (ddd, *J* = 15.3, 5.4, 2.5 Hz, 1H, $H4_B$), 2.53 (s, 3H, H2).

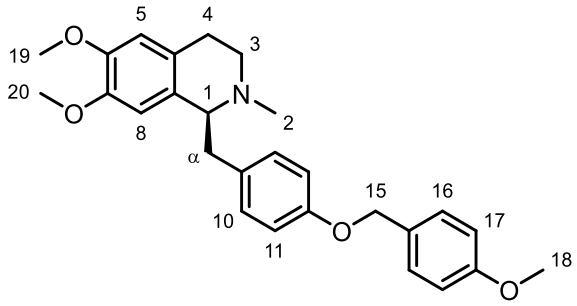
Note: O*H* resonance was not observed.

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 147.5, 146.0, 130.9(2C), 130.5, 128.5, 125.1, 115.6(2C), 111.34, 111.26, 65.0, 55.8, 55.5, 45.9, 42.0, 40.5, 24.5.

$[\alpha]_D^{25}$ –94.9 (c. 0.84, $CHCl_3$). Ref.[85] (+)-armepavine $[\alpha]_D^{25}$ +94.2 (c. 1.0, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[158]

***(S)*-6,7-Dimethoxy-1-(4-((4-methoxybenzyl)oxy)benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-147**



To an oven-dried vial containing Pd/C (10% wt., 6.5 mg, 6.1 µmol, 0.10 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.1 mL) and the vial was evacuated and backfilled with hydrogen (× 3). (*S*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-141** (31 mg, 61 µmol, 1.0 equiv.) was then added as a solution in MeOH (0.5 mL) followed by the addition of AcOH (7.0 µL, 13 µmol, 2.2 equiv.). The mixture was stirred under a hydrogen atmosphere (three-layered balloon) for 18 h. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (9:1) and the filtrate was concentrated *in vacuo*. The residue was then diluted with CH_2Cl_2, neutralised with $NaHCO_3$ (aq., sat.) and the aqueous phase was extracted with $CHCl_3$/IPA (9:1, 2 × 7 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as an off-white foam (26 mg, 60 µmol, 98%). No further purification was necessary.

R_f 0.31 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.7 Hz, 2H, H16), 7.00 (d, *J* = 8.6 Hz, 2H, H10), 6.91 (d, *J* = 8.7 Hz, 2H, H17), 6.87 (d, *J* = 8.6 Hz, 2H, H11), 6.55 (s, 1H, H5), 6.00 (s, 1H, H8), 4.96 (s, 2H, H15), 3.83 (s, 3H, H20), 3.81 (s, 3H, H18), 3.68 (dd, *J* = 7.9, 5.0

Hz, 1H, H1), 3.52 (s, 3H, H19), 3.22 – 3.17 (m, 1H, $H3_A$), 3.15 (dd, J = 13.7, 5.0 Hz, 1H, $H\alpha_A$), 2.89 – 2.70 (m, 3H, $H4_A$, $H3_B$, $H\alpha_B$), 2.60 (dt, J = 15.8, 4.6 Hz, 1H, $H4_B$), 2.53 (s, 3H, H2).

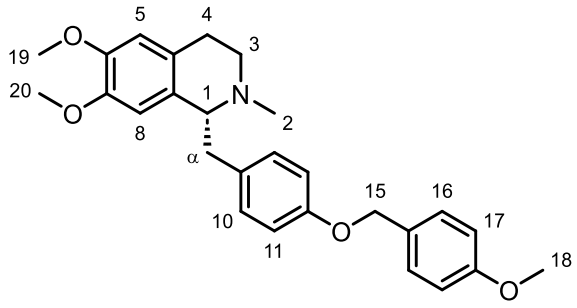
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 157.3, 147.3, 146.4, 132.3, 130.9(2C), 129.3(2C), 129.2(2C), 125.9, 114.7(2C), 114.1(2C), 111.3, 111.2, 69.9, 65.1, 55.9, 55.6, 55.4, 46.9, 42.7, 40.5, 25.5.

IR (film) ν_{max}/cm^{-1} 3001, 2836, 1612, 1514, 1465, 1252, 1175, 1139, 1102.

HRMS (ESI^+) $C_{27}H_{31}NO_4$ found $[M+H]^+$ at 434.2315, expected at 434.2326.

$[\alpha]_D^{25}$ +58.1 (c. 1.31, $CHCl_3$).

***(R)*-6,7-Dimethoxy-1-(4-((4-methoxybenzyl)oxy)benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*)-147**



To an oven-dried vial containing Pd/C (10% wt., 9 mg, 0.84 mmol, 0.10 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.05 mL) and the vial was evacuated and backfilled with hydrogen (× 3). (*R*)-1-(3-Bromo-4-((4-methoxybenzyl)oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-141** (42 mg, 8.2 mmol, 1.0 equiv.) was then added as a solution in MeOH (0.5 mL) followed by the addition of AcOH (9.5 μL, 18 mmol, 2.2 equiv.). The mixture was stirred under a hydrogen atmosphere (three-layered balloon) for 18 h. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (9:1) and the filtrate was concentrated *in vacuo*. The residue was then diluted with CH_2Cl_2, neutralised with $NaHCO_3$ (aq., sat.) and the aqueous phase was extracted with $CHCl_3$/IPA (9:1, 2 × 5 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound was collected as an off-white foam (35 mg, 8.1 mmol, 99%). No further purification was necessary.

R_f 0.31 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.7 Hz, 2H, H16), 7.00 (d, *J* = 8.5 Hz, 2H, H10), 6.91 (d, *J* = 8.7 Hz, 2H, H17), 6.87 (d, *J* = 8.5 Hz, 2H, H11), 6.55 (s, 1H, H5), 5.98 (s, 1H, H8), 4.96 (s, 2H, H15), 3.83 (s, 3H, H20), 3.81 (s, 3H, H18), 3.69 (dd, *J* = 8.0, 5.0

Hz, 1H, H1), 3.52 (s, 3H, H19), 3.24 – 3.19 (m, 1H, $H3_A$), 3.16 (dd, J = 13.4, 5.0 Hz, 1H, $H\alpha_A$), 2.89 – 2.70 (m, 3H, $H4_A$, $H3_B$, $H\alpha_B$), 2.60 (dt, J = 15.6, 4.5 Hz, 1H, $H4_B$), 2.54 (s, 3H, H2).

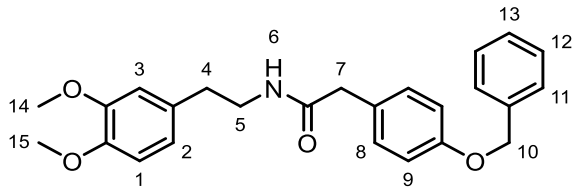
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 157.3, 147.4, 146.4, 132.3, 130.9(2C), 129.3, 129.24(2C), 129.19, 125.8, 114.8(2C), 114.1(2C), 111.3, 111.2, 69.9, 65.0, 55.9, 55.6, 55.4, 46.8, 42.7, 40.5, 25.5.

IR (film) ν_{max}/cm^{-1} 3997, 2837, 1613, 1515, 1466, 1253, 1176, 1139, 1103.

HRMS (ESI$^+$) $C_{27}H_{31}NO_4$ found $[M+H]^+$ at 434.2316, expected at 434.2326.

$[\alpha]_D^{25}$ –57.4 (c. 0.35, $CHCl_3$).

2-(4-(Benzyloxy)phenyl)-N-(3,4-dimethoxyphenethyl)acetamide, 149



2-(3,4-Dimethoxyphenyl)ethan-1-amine **127** (2.44 mL, 14.5 mmol), 4-hydroxyphenylacetic acid **144** (2.00 g, 13.1 mmol), triethylamine (2.20 mL, 15.7 mmol), hydroxybenzotriazole hydrate (885 mg, 6.55 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (3.77 g, 19.7 mmol) in anhydrous CH_2Cl_2 (66 mL) were submitted to **General Procedure H**. To a solution of the crude amide in acetone (66 mL) was added potassium carbonate (2.72 g, 19.7 mmol, 1.5 equiv.), tetrabutylammonium iodide (242 mg, 0.655 mmol, 0.05 equiv.) and benzyl bromide (1.87 mL, 15.7 mmol, 1.2 equiv.), and the mixture stirred for 24 h. The reaction mixture was concentrated *in vacuo.* The residue was diluted with CH_2Cl_2 (30 mL) and washed sequentially with HCl (aq., 1 M, 10 mL) and $NaHCO_3$ (aq., sat., 10 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (dry loading, CH_2Cl_2/acetone, 9:1) afforded the title compound as a white solid (3.47 g, 1.43 mmol, 65% over two steps).

R_f 0.38 (CH_2Cl_2/acetone, 9:1), [UV, PMA]

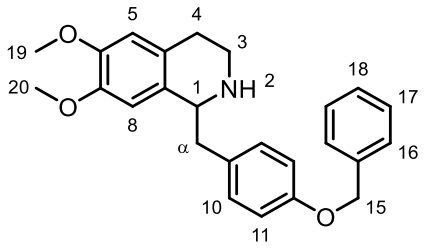
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 2H, H11), 7.41 – 7.37 (m, 2H, H12), 7.36 – 7.31 (m, 1H, H13), 7.07 (d, *J* = 8.6 Hz, 2H, H8), 6.91 (d, *J* = 8.6 Hz, 2H, H9), 6.72 (d, *J* = 8.1 Hz, 1H, H1), 6.61 (d, *J* = 2.0 Hz, 1H, H3), 6.55 (dd, *J* = 8.1, 2.0 Hz, 1H, H2),

5.35 (s, br, 1H, H6), 5.06 (s, 2H, H10), 3.84 (s, 3H, H15) 3.83 (s, 3H, H14), 3.47 (s, 2H, H7), 3.44 (q, J = 6.8 Hz, 2H, H5), 2.67 (t, J = 6.8 Hz, 2H, H4).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 158.2, 149.2, 147.8, 137.0, 131.3, 130.7(2C), 128.8(2C), 128.2, 127.6(2C), 127.2, 120.7, 115.5(2C), 111.9, 111.4, 70.2, 56.1, 56.0, 43.1, 40.9, 35.2.

Spectroscopic data is in agreement with that reported previously.[159]

1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 150



2-(4-(Benzyloxy)phenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **149** (0.10 g, 0.25 mmol), 2-chloropyridine (28 μL, 0.30 mmol) and trifluoromethanesulfonic anhydride (46 μL, 0.27 mmol) in anhydrous CH_2Cl_2 (1.2 mL) were submitted to **General Procedure C**. The crude imine and sodium borohydride (18.6 mg, 0.493 mmol) in EtOH (1.2 mL) were submitted to **General Procedure D**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as a yellow oil (24 mg, 61 μmol, 25%).

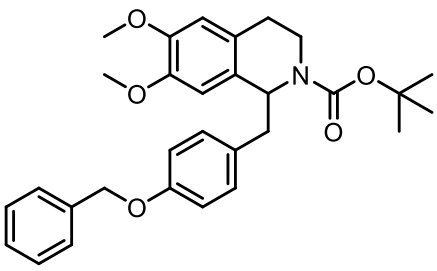
R_f 0.31 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 2H, H16), 7.42 – 7.36 (m, 2H, H17), 7.36 – 7.30 (m, 1H, H18), 7.16 (d, *J* = 8.6 Hz, 2H, H10), 6.94 (d, *J* = 8.6 Hz, 2H, H11), 6.60 (s, 1H, H5), 6.59 (s, 1H, H8), 5.06 (s, 2H, H15), 4.10 (dd, *J* = 9.5, 4.5 Hz, 1H, H1), 3.86 (s, 3H, H20), 3.80 (s, 3H, H19), 3.24 – 3.17 (m, 1H, $H3_A$), 3.14 (dd, *J* = 13.8, 4.5 Hz, 1H, $H\alpha_A$), 2.97 – 2.83 (m, 2H, $H\alpha_B$, $H3_B$), 2.80 – 2.65 (m, 2H, H4), 2.17 (s, br, 1H, H2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 147.6, 147.1, 137.2, 131.4, 130.5(2), 130.4, 128.7(2C), 128.1, 127.6(2C), 127.3, 115.1(2C), 111.9, 109.6, 70.2, 57.1, 56.1, 56.0, 41.9, 40.8, 29.5.

Spectroscopic data is in agreement with that reported previously.[159]

Methyl-1-(4-(benzyloxy)benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S13



1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **150** (24 mg, 61 µmol), di-*tert*-butyl dicarbonate (16 mg, 73 µmol) and triethylamine (10 µL, 73 µmol) in anhydrous CH_2Cl_2 (0.30 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/Et_2O, 1:1) afforded the title compound as a colourless oil (25 mg, 51 µmol, 84%).

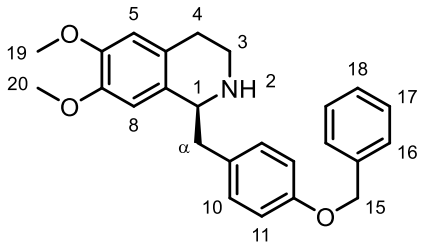
R_f 0.36 (pentane/Et_2O, 1:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.43 – 7.39 (m, 2H, both rotamers), 7.39 – 7.35 (m, 2H, both rotamers), 7.34 – 7.29 (m, 1H, both rotamers), 7.05 – 6.96 (m, 2H, both rotamers), 6.92 – 6.83 (m, 2H, both rotamers), 6.62 – 6.59 (m, 1H, both rotamers), 6.32 (s, 0.64H, (M)), 6.17 (s, 0.34H, (m)), 5.20 (t, J = 6.9 Hz, 0.34H, (m)), 5.08 – 4.99 (m, 2H, both rotamers + 0.64H, (M)), 4.19 – 4.12 (m, 0.64H, (M)), 3.88 – 3.77 (m, 3H, both rotamers + 0.34H, (m)), 3.70 (s, 2H, (M)), 3.60 (s, 1H, (m)), 3.36 – 3.20 (m, 1H, both rotamers), 3.10 – 2.98 (m, 1H, both rotamers), 2.94 – 2.70 (m, 2H, both rotamers), 2.66 – 2.52 (m, 1H, both rotamers), 1.43 (s, 3.3H, (m)), 1.30 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 157.6, 154.6, 147.8, 147.1, 137.3, 131.1, 131.0, 130.8(2C), 128.7(2C), 128.1, 127.5(2C), 126.7, 114.9(2C), 111.5, 110.4, 79.7, 70.2, 56.6, 56.00, 55.95, 42.2, 37.4, 28.4(3C), 28.3.

Spectroscopic data is in agreement with that reported previously.[159]

(*S*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*S*)-150



2-(4-(Benzyloxy)phenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **149** (500 mg, 1.23 mmol), 2-chloropyridine (140 μL, 1.48 mmol) and trifluoromethanesulfonic anhydride (230 μL, 1.36 mmol) in anhydrous CH_2Cl_2 (6.0 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*R,R*)-TsDPEN](*p*-cymene) (55 mg, 86 μmol) and HCO_2H/Et_3N (5:2 v/v, 0.60 mL) in anhydrous DMF (6.0 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as an amber oil (444 mg, 1.14 mmol, 93% over 2 steps, 96% *ee* after Boc derivatisation).

R_f 0.31 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 2H, H16), 7.42 – 7.36 (m, 2H, H17), 7.36 – 7.30 (m, 1H, H18), 7.17 (d, *J* = 8.6 Hz, 2H, H10), 6.95 (d, *J* = 8.6 Hz, 2H, H11), 6.63 (s, 1H, H5), 6.59 (s, 1H, H8), 5.06 (s, 2H, H15), 4.10 (dd, *J* = 9.5, 4.4 Hz, 1H, H1), 3.86 (s, 3H, H20), 3.81 (s, 3H, H19), 3.23 – 3.17 (m, 1H, $H3_A$), 3.15 (dd, *J* = 13.7, 4.4 Hz, 1H, $H\alpha_A$), 2.97 – 2.82 (m, 2H, $H\alpha_B$, $H3_B$), 2.80 – 2.65 (m, 2H, H4), 1.69 (s, br, 1H, H2).

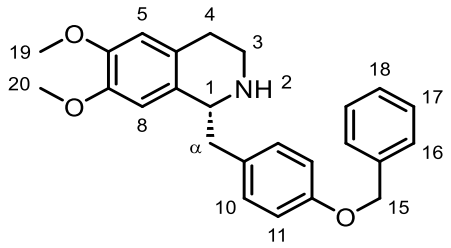
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 147.5, 147.1, 137.2, 131.5, 130.8, 130.5(2C), 128.7(2C), 128.1, 127.6(2C), 127.5, 115.1(2C), 112.0, 109.6, 70.2, 57.1, 56.1, 56.0, 42.0, 40.9, 29.7.

$[\alpha]_D^{25}$ +6.3 (c. 0.63, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[159]

Note: Spectroscopic data is reported for **150**.

(*R*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (*R*)-150



2-(4-(Benzyloxy)phenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide **149** (500 mg, 1.23 mmol), 2-chloropyridine (140 µL, 1.48 mmol) and trifluoromethanesulfonic anhydride (230 µL, 1.36 mmol) in anhydrous CH_2Cl_2 (6.0 mL) were submitted to **General Procedure C**. The crude imine, RuCl[(*S,S*)-TsDPEN](*p*-cymene) (55 mg, 86 µmol) and HCO_2H/Et_3N (5:2 v/v, 0.60 mL) in anhydrous DMF (6.0 mL) were submitted to **General Procedure E**. Purification by flash column chromatography (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1 → 1:0:0.1) afforded the title compound as an amber oil (454 mg, 1.16 mmol, 94% over 2 steps, 94% *ee* after Boc derivatisation).

R_f 0.31 (EtOAc/pentane/7N ammonia solution in MeOH, 7:1:0.1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H, H16), 7.41 – 7.35 (m, 2H, H17), 7.35 – 7.30 (m, 1H, H18), 7.17 (d, *J* = 8.6 Hz, 2H, H10), 6.95 (d, *J* = 8.6 Hz, 2H, H11), 6.63 (s, 1H, H5), 6.59 (s, 1H, H8), 5.06 (s, 2H, H15), 4.10 (dd, *J* = 9.4, 4.4 Hz, 1H, H1), 3.86 (s, 3H, H20), 3.81 (s, 3H, H19), 3.25 – 3.18 (m, 1H, $H3_A$), 3.15 (dd, *J* = 13.8, 4.4 Hz, 1H, $H\alpha_A$), 2.97 – 2.81 (m, 2H, $H3_B$, $H\alpha_B$), 2.80 – 2.65 (m, 2H, H4), 1.66 (s, br, 1H, H2).

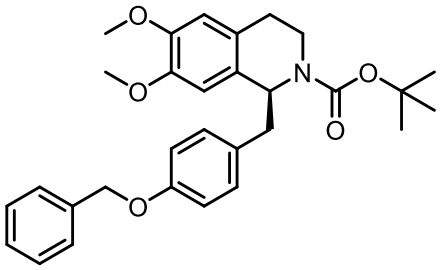
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 147.6, 147.1, 137.3, 131.6, 130.8, 130.5(2C), 128.7(2C), 128.1, 127.6(2C), 127.5, 115.1(2C), 112.0, 109.6, 70.2, 57.1, 56.1, 56.0, 42.0, 40.9, 29.7.

[α]$_D^{25}$ –6.9 (c. 0.49, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[159]

Note: Spectroscopic data is reported for **150**.

Methyl (*S*)-1-(4-(benzyloxy)benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S14



(*S*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-150** (16 mg, 41 µmol), di-*tert*-butyl dicarbonate (11 mg, 49 µmol) and triethylamine (6.8 µL, 49 µmol) in anhydrous CH_2Cl_2 (0.2 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/Et_2O, 1:1) afforded the title compound as a colourless oil (18 mg, 37 µmol, 90%, 96% *ee*).

R*f* 0.36 (pentane/Et_2O, 1:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.44 – 7.28 (m, 5H, both rotamers), 7.05 – 6.96 (m, 2H, both rotamers), 6.92 – 6.83 (m, 2H, both rotamers), 6.62 – 6.59 (m, 1H, both rotamers), 6.32 (s, 0.64H, (M)), 6.17 (s, 0.34H, (m)), 5.20 (t, *J* = 6.9 Hz, 0.34H, (m)), 5.08 – 5.01 (m, 2H, both rotamers + 0.64H, (M)), 4.20 – 4.13 (m, 0.64H, (M)), 3.89 – 3.86 (m, 3H, both rotamers + 0.34H, (m)), 3.71 (s, 2H, (M)), 3.60 (s, 1H, (m)), 3.36 – 3.20 (m, 1H, both rotamers), 3.10 – 2.98 (m, 1H, both rotamers), 2.94 – 2.70 (m, 2H, both rotamers), 2.66 – 2.52 (m, 1H, both rotamers), 1.44 (s, 3.3H, (m)), 1.31 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 157.7, 154.7, 147.8, 147.1, 137.3, 131.2, 131.0, 130.8(2C), 128.7(2C), 128.1, 127.5(2C), 126.8, 114.9(2C), 111.5, 110.5, 79.8, 70.2, 56.7, 56.02, 55.97, 42.2, 37.4, 28.4(3C), 28.3.

[α]$_D^{25}$ +59.5 (c. 1.16, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[159]

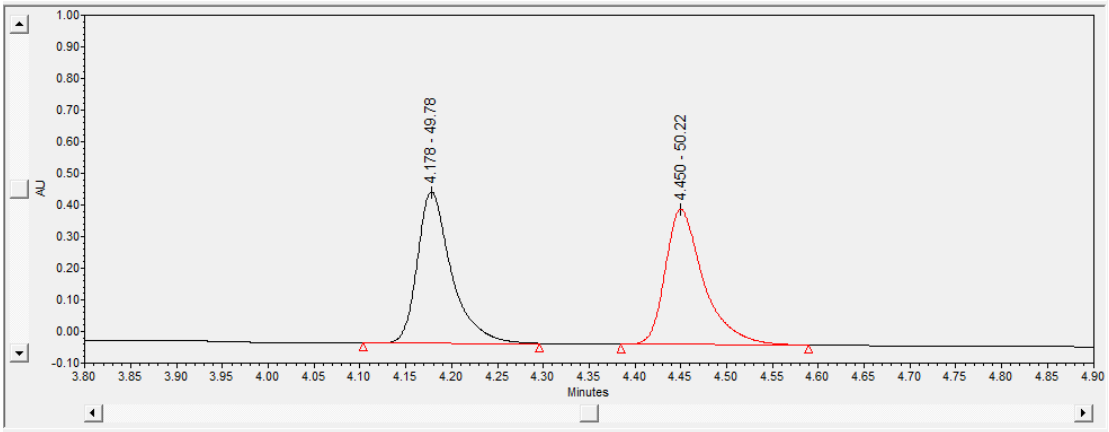
Note: Spectroscopic data is reported for **S13**.

SFC trace of racemic (±)-**S13** and enantioenriched (+)-**S14**.

SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min;

(+)-**S14**: 97.8:2.2 *e.r.* (major enantiomer t_R = 4.19 min; minor enantiomer t_R = 4.47 min).

λ = 215.0 nm.



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak
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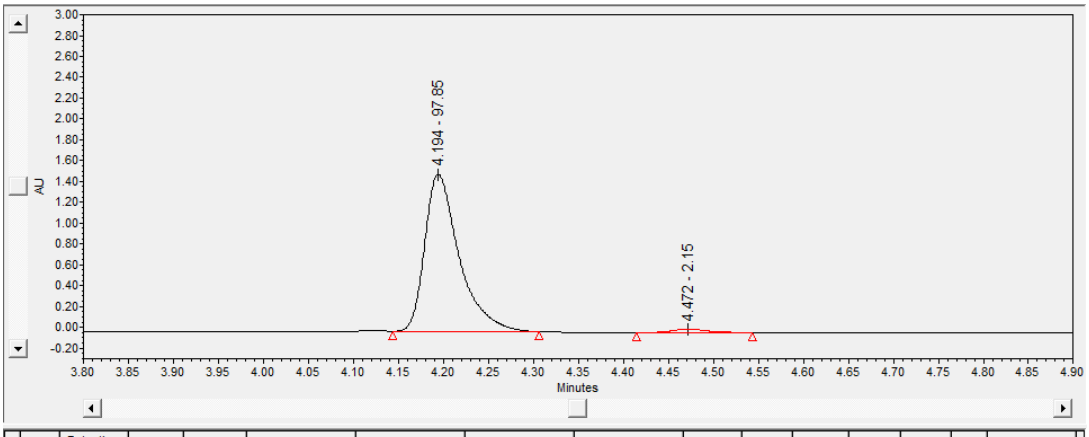
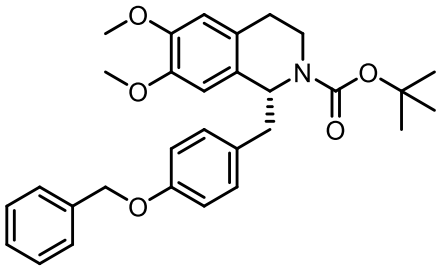
2		4.450							1245064	50.22	428800	bb			Unknown	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type
1		4.194							4011250	97.85	1510175	bb			Unknown
2		4.472							88338	2.15	33229	bb			Unknown

Methyl (*R*)-1-(4-(benzyloxy)benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(*1H*)-carboxylate, S15



(*R*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-150** (9.8 mg, 25 µmol), di-*tert*-butyl dicarbonate (6.5 mg, 30 µmol) and triethylamine (4.2 µL, 30 µmol) in anhydrous CH_2Cl_2 (0.2 mL) were submitted to **General Procedure G**. Purification by flash column chromatography (pentane/Et_2O, 1:1) afforded the title compound as a colourless oil (9.3 mg, 19 µmol, 76%, 94% *ee*).

R*f* 0.36 (pentane/Et_2O, 1:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$, analysis revealed the presence of two rotamers present in a 0.64:0.36 ratio, Major(M) and minor(m)) δ 7.44 – 7.29 (m, 5H, both rotamers), 7.05 – 6.96 (m, 2H, both rotamers), 6.92 – 6.83 (m, 2H, both rotamers), 6.62 – 6.54 (m, 1H, both rotamers), 6.32 (s, 0.64H, (M)), 6.17 (s, 0.34H, (m)), 5.20 (t, *J* = 6.9 Hz, 0.34H, (m)), 5.07 – 5.00 (m, *2H,* both rotamers + 0.64H, (M)), 4.20 – 4.11 (m, 0.64H, (M)), 3.89 – 3.77 (m, 3H, both rotamers + 0.34H, (m)), 3.70 (s, 2H, (M)), 3.59 (s, 1H, (m)), 3.36 – 3.20 (m, 1H, both rotamers), 3.10 – 2.98 (m, 1H, both rotamers), 2.94 – 2.70 (m, 2H, both rotamers), 2.66 – 2.52 (m, 1H, both rotamers), 1.43 (s, 3.3H, (m)), 1.30 (s, 5.7H, (M)).

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer) δ 157.7, 154.7, 147.8, 147.1, 137.3, 131.2, 131.0, 130.8(2C), 128.7(2C), 128.1, 127.5(2C), 126.8, 114.9(2C), 111.5, 110.5, 79.8, 70.2, 56.7, 56.02, 56.97, 42.2, 37.4, 28.4(3C), 28.3.

[α]D^{25} –58.9 (c. 0.36, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[159]

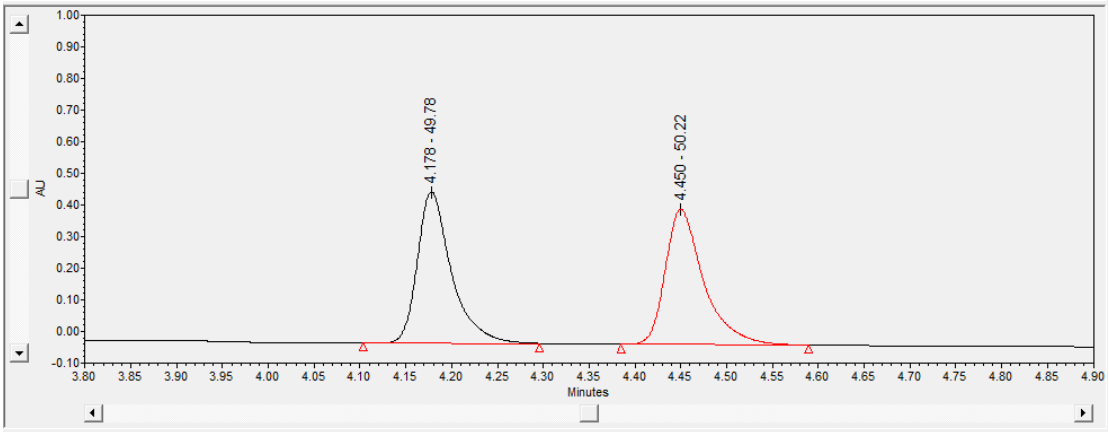
Note: Spectroscopic data is reported for rac-**S13**.

SFC trace of racemic (±)-**S13** and enantioenriched (–)-**S15**.

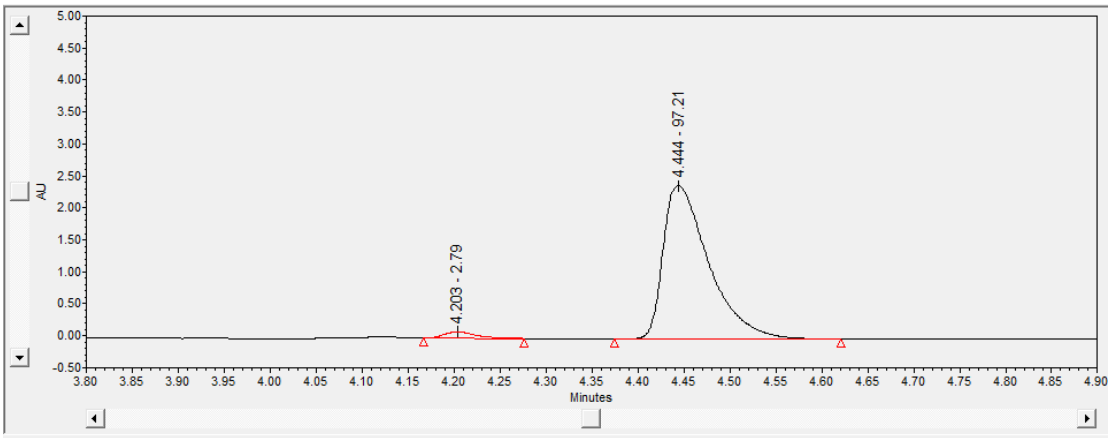
SFC Chiralpak® IB 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min;

(–)-**S15**: 97.2:2.8 *e.r.* (major enantiomer t_R = 4.44 min; minor enantiomer t_R = 4.20 min).

λ = 215.0 nm.

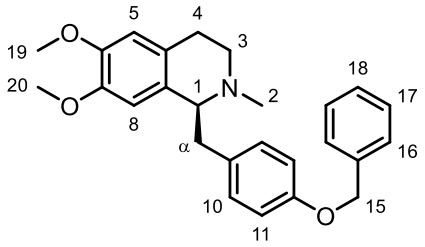


	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak
1		4.178							1234387	49.78	479097	bb			Unknown	
2		4.450							1245064	50.22	428800	bb			Unknown	



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type
1		4.203							237441	2.79	100363	bb			Unknown
2		4.444							8281538	97.21	2396901	bb			Unknown

(*S*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-151, (+)-*O*-benzylarmepavine



(*S*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*S*)-150** (443 mg, 1.14 mmol), formalin (37% aq., 2.3 mL, 30.9 mmol) and sodium borohydride (130 mg, 3.42 mmol) in MeOH (23 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/MeOH, 94:6) afforded the title compounds as an orange oil (358 mg, 0.887 mmol, 78%).

R*f* 0.23 (EtOAc/MeOH, 94:6), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H, H16), 7.41 – 7.35 (m, 2H, H17), 7.35 – 7.29 (m, 1H, H18), 7.01 (d, *J* = 8.7 Hz, 2H, H10), 6.88 (d, *J* = 8.7 Hz, 2H, H11), 6.56 (s, 1H, H5), 6.01 (s, 1H, H8), 5.04 (s, 2H, H15), 3.84 (s, 3H, H20), 3.67 (dd, *J* = 8.0, 5.0 Hz, 1H, H1), 3.53 (s, 3H, H19), 3.24 – 3.11 (m, 2H, $H3_A$, $H\alpha_A$), 2.90 – 2.72 (m, 3H, $H4_A$, $H3_B$, $H\alpha_B$), 2.59 (dt, *J* = 15.9, 4.6 Hz, 1H, $H4_B$), 2.54 (s, 3H, H2).

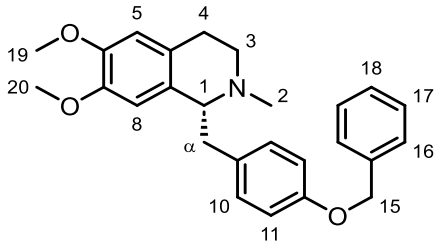
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 147.3, 146.3, 137.3, 132.5, 130.9(2C), 129.4, 128.7(2C), 128.0, 127.5(2C), 126.0, 114.7(2C), 111.2, 111.1, 70.1, 65.0, 55.8, 55.6, 47.0, 42.8, 40.5, 25.6.

$[\alpha]_D^{25}$ +69.4 (c. 1.74, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[152]

Note: Spectroscopic data is reported for rac-**151**.

(*R*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*)-151, (–)-*O*-benzylarmepavine



(*R*)-1-(4-(Benzyloxy)benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(*R*)-150** (410 mg, 1.05 mmol), formalin (37% aq., 2.16 mL, 29.0 mmol) and sodium borohydride (120 mg, 3.15 mmol) in MeOH (20 mL) were submitted to **General Procedure F**. Purification by flash column chromatography (EtOAc/MeOH, 94:6) afforded the title compounds as an orange oil (337 mg, 0.835 mmol, 80%).

R*f* 0.23 (EtOAc/MeOH, 94:6), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H, H16), 7.40 – 7.34 (m, 2H, H17), 7.34 – 7.29 (m, 1H, H18), 7.03 (d, *J* = 8.7 Hz, 2H, H10), 6.89 (d, *J* = 8.7 Hz, 2H, H11), 6.57 (s, 1H, H5), 6.03 (s, 1H, H8), 5.04 (s, 2H, H15), 3.84 (s, 3H, H20), 3.69 (dd, *J* = 7.9, 5.0 Hz, 1H, H1), 3.54 (s, 3H, H19), 3.24 – 3.13 (m, 1H, $H3_A$, $H\alpha_A$), 2.90 – 2.72 (m, 3H, $H4_A$, $H3_B$, $H\alpha_B$), 2.60 (dt, *J* = 15.9, 4.6 Hz, 1H, $H4_B$), 2.55 (s, 3H, H2).

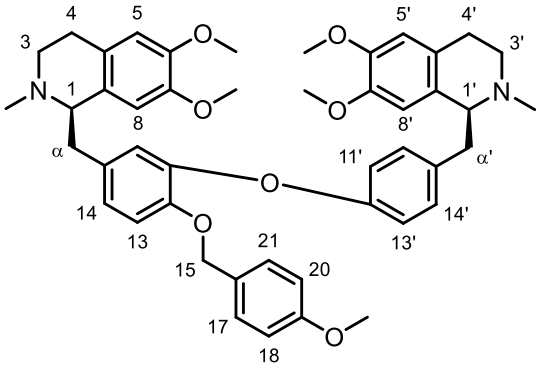
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1, 147.2, 146.2, 137.2, 132.3, 130.7(2C), 129.3, 128.5(2C), 127.9, 127.4(2C), 125.9, 114.5(2C), 111.1, 111.0, 69.9, 64.9, 55.7, 55.4, 46.8, 42.7, 40.4, 25.5.

$[\alpha]_D^{25}$ –68.5 (c. 1.06, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[152]

Note: Spectroscopic data is reported for rac-**151**.

(*S*)-1-(4-(5-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S,R*)-152



(+)-Armepavine **(*S*)-140** (80.0 mg, 0.255 mmol), (*R*)-1-(3-bromo-4-((4-methoxybenzyl) oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-141** (119 mg, 0.232 mmol), potassium carbonate (80.2 mg, 0.580 mmol) and cupric oxide (36.8 mg, 0.463 mmol) in anhydrous pyridine (0.40 mL) were submitted to **General Procedure B**. The organic phase was washed with ammonia (aq., 35%, 4 × 7 mL) instead of filtering it through Celite® and no acidic wash was performed. Pyridine was removed azeotropically with toluene. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as an off-white foam (50.6 mg, 67.9 µmol, 29%).

R*f* 0.24 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2H, H17, H21), 7.01 (d, J = 8.6 Hz, 2H, H10′, H14′), 6.90 (d, J = 8.8 Hz, 1H, H13), 6.83 – 6.75 (m, 6H, H10, H14, H18, H20, H11′, H13′), 6.55 (s, 1H, H5 or H5′), 6.52 (s, 1H, H5 or H5′), 6.05 (s, 1H, H8 or H8′), 6.04 (s, 1H, H8 or H8′), 4.98 (s, 2H, H15), 3.82 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.81 (s, 3H, C7–OCH_3 or C7′–OCH_3), 3.76 (s, 3H, C19–OCH_3), 3.69 (dd, J = 7.7, 5.1 Hz, 1H, H1 or H1′), 3.65 (dd, J = 7.6, 5.2 Hz, 1H, H1 or H1′), 3.55 (s, 3H, C6–OCH_3 or C6′–OCH_3),

3.52 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.23 – 3.04 (m, 4H, H3$_A$, H3′$_A$, Hα$_A$, Hα′$_A$), 2.88 – 2.68 (m, 6H, H4$_A$, H4′$_A$, H3$_B$, H3′$_B$, Hα$_B$, Hα′$_B$), 2.64 – 2.60 (m, 1H, H4$_B$ or H4′$_B$), 2.59 – 2.55 (m, 1H, H4$_B$ or H4′$_B$), 2.53 (s, 3H, N–CH_3 or N′–CH_3), 2.48 (s, 3H, N–CH_3 or N′–CH_3).

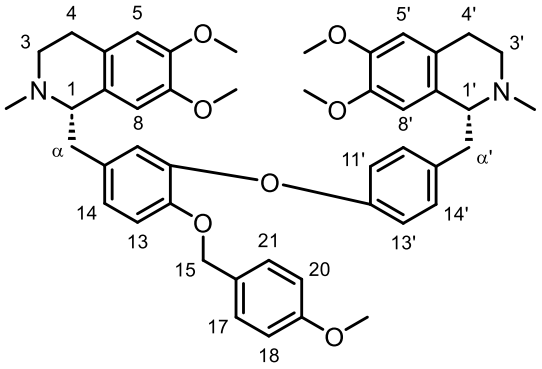
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4(C19), 156.8(C12′), 148.9(C12), 147.41(2C, C7, C7′), 146.5(C6 or C6′), 146.4(C6 or C6′), 145.4(C11), 133.71(C9′), 133.67(C9), 130.8(2C, C10′, C14′), 129.2(C16), 129.1(C4a or C4a′), 129.0(C4a or C4a′), 128.9(2C, C17, C21), 126.1(C14), 125.9(C8a or C8a′), 125.8(C8a or C8a′), 123.2(C10), 116.7(2C, C11′, C13′), 115.6(C13), 113.9(2C, C18, C20), 111.28(C5 or C5′), 111.26(C5 or C5′), 111.1(C8 or C8′), 111.0(C8 or C8′), 71.0(C15), 65.0(C1 or C1′), 64.8(C1 or C1′), 55.86(2C, C7–O*C*H$_3$, C7′–O*C*H$_3$), 55.6(2C, C6–O*C*H$_3$, C6′–O*C*H$_3$), 55.4(C19–O*C*H$_3$), 46.9(C3 or C3′), 46.8(C3 or C3′), 42.7(2C, N–*C*H$_3$, N′–*C*H$_3$), 40.7(Cα or Cα′), 40.5(Cα or Cα′), 25.5(C4 or C4′), 25.4(C4 or C4′).

IR (film) ν_{max}/cm^{-1} 3019, 2934, 2835, 2796, 1612, 1577, 1513, 1464, 1253, 1219, 1173, 1138, 1122, 1102, 1068, 753.

HRMS (ESI$^+$) $C_{46}H_{52}N_2O_7$ found $[M+H]^+$ at 745.3830, expected at 745.3847.

$[\alpha]_D^{25}$ +5.47 (c. 1.51, $CHCl_3$).

(*R*)-1-(4-(5-(((*S*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*,*S*)-152



(–)-Armepavine **(*R*)-140** (100 mg, 0.319 mmol), (*S*)-1-(3-bromo-4-((4-methoxybenzyl) oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-141** (149 mg, 0.290 mmol), potassium carbonate (100 mg, 0.725 mmol) and cupric oxide (46.1 mg, 0.580 mmol) in anhydrous pyridine (0.50 mL) were submitted to **General Procedure B**. The organic phase was washed with ammonia (aq., 35%, 4 × 7 mL) instead of filtering it through Celite® and no acidic wash was performed. Pyridine was removed azeotropically with toluene. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as an off-white foam (54.9 mg, 73.6 μmol, 25%).

R*f* 0.24 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.6 Hz, 2H, H17, H21), 7.01 (d, *J* = 8.5 Hz, 2H, H10′, H14′), 6.90 (d, *J* = 8.9 Hz, 1H, H13), 6.83 – 6.75 (m, 6H, H10, H14, H18, H20, H11′, H13′), 6.55 (s, 1H, H5 or H5′), 6.52 (s, 1H, H5 or H5′), 6.05 (s, 1H, H8 or H8′), 6.04 (1s, 1H, H8 or H8′), 4.98 (s, 2H, H15), 3.82 (s, 3H, C7–OC*H*$_3$ or C7′–OC*H*$_3$), 3.81 (s, 3H, C7–OC*H*$_3$ or C7′–OC*H*$_3$), 3.77 (s, 3H, C19–OC*H*$_3$), 3.69 (dd, *J* = 7.7, 5.1 Hz, 1H,

H1 or H1′), 3.65 (dd, J = 7.6, 5.2 Hz, 1H, H1 or H1′), 3.55 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.53 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.24 – 3.03 (m, 4H, $H3_A$, $H3'_A$, $H\alpha_A$, $H\alpha'_A$), 2.88 – 2.68 (m, 6H, $H4_A$, $H4'_A$, $H3_B$, $H3'_B$, $H\alpha_B$, $H\alpha'_B$), 2.60 (t, J = 4.7 Hz, 1H, $H4_B$ or $H4'_B$), 2.57 (q, J = 4.3 Hz, 1H, $H4_B$ or $H4'_B$), 2.53 (s, 3H, N–CH_3 or N′–CH_3), 2.49 (s, 3H, N–CH_3 or N′–CH_3).

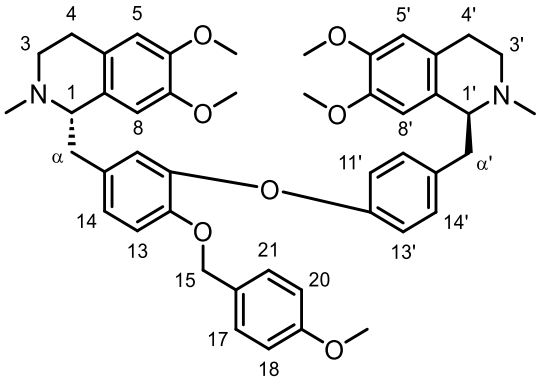
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3(C19), 156.8(C12′), 148.9(C12), 147.4(2C, C7, C7′), 146.5(C6 or C6′), 146.4(C6 or C6′), 145.4(C11), 133.83(C9′), 133.77(C9), 130.8(2C, C10′, C14′), 129.3(C4a or C4a′), 129.20(C16), 129.17(C4a or C4a′), 128.9(2C, C17, C21), 126.1(2C, C14, C8a or C8a′), 125.9(C8a or C8a′), 123.2(C10), 116.7(2C, C11′, C13′), 115.6(C13), 113.9(2C, C18, C20), 111.28(C5 or C5′), 111.26(C5 or C5′), 111.1(C8 or C8′), 111.0(C8 or C8′), 71.0(C15), 65.0(C1 or C1′), 64.8(C1 or C1′), 55.85(C7–O*C*H$_3$ or C7′–O*C*H$_3$), 55.84(C7–O*C*H$_3$ or C7′–O*C*H$_3$), 55.6(2C, C6–O*C*H$_3$, C6′–O*C*H$_3$), 55.3(C19–O*C*H$_3$), 47.0(C3 or C3′), 46.9(C3 or C3′), 42.8(2C, N–*C*H$_3$, N′–*C*H$_3$), 40.7(Cα or Cα′), 40.5(Cα or Cα′), 25.6(C4 or C4′), 25.5(C4 or C4′).

IR (film) ν_{max}/cm^{-1} 3016, 2935, 2835, 2795, 1611, 1585, 1513, 1464, 1253, 1219, 1173, 1138, 1123, 1102, 1067, 757.

HRMS (ESI$^+$) $C_{46}H_{52}N_2O_7$ found $[M+H]^+$ at 745.3833, expected at 745.3847.

$[\alpha]_D^{25}$ −5.81 (c. 2.39, $CHCl_3$).

(*S*)-1-(4-(5-(((*S*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*S,S*)-152



(+)-Armepavine **(*S*)-140** (135 mg, 0.431 mmol), (*S*)-1-(3-bromo-4-((4-methoxybenzyl) oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S*)-141** (200 mg, 0.390 mmol), potassium carbonate (135 mg, 0.976 mmol) and cupric oxide (62.0 mg, 0.779 mmol) in anhydrous pyridine (0.70 mL) were submitted to **General Procedure B**. The organic phase was washed with ammonia (aq., 35%, 4 × 8 mL) instead of filtering it through Celite® and no acidic wash was performed. Pyridine was removed azeotropically with toluene. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as an off-white foam (108 mg, 0.146 mmol, 37%).

R*f* 0.25 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.7 Hz, 2H, H17, H21), 7.00 (d, *J* = 8.6 Hz, 2H, H10′, H14′), 6.89 (d, *J* = 8.8 Hz, 1H, H13), 6.83 – 6.75 (m, 6H, H11′, H13′, H10, H14, H18, H20), 6.55 (s, 1H, H5 or H5′), 6.52 (s, 1H, H5 or H5′), 6.05 (s, 2H, H8, H8′), 4.98 (s, 2H, H15), 3.82 (s, 3H, C7–OC*H*$_3$ or C7′–OC*H*$_3$), 3.80 (s, 3H, C7–OC*H*$_3$ or C7′–OC*H*$_3$), 3.76 (s, 3H, C19–OC*H*$_3$), 3.69 (dd, *J* = 7.6, 5.2 Hz, 1H, H1′),

3.65 (dd, J = 7.5, 5.1 Hz, 1H, H1), 3.55 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.53 (s, 3H, C6–OCH_3 or C6′–OCH_3), 3.24 – 3.03 (m, 4H, $H3_A$, $H3'_A$, $H\alpha_A$, $H\alpha'_A$), 2.88 – 2.68 (m, 6H, $H4_A$, $H4'_A$, $H3_B$, $H3'_B$, $H\alpha_B$, $H\alpha'_B$), 2.60 (t, J = 4.7 Hz, 1H, $H4_B$ or $H4'_B$), 2.57 (t, J = 4.5 Hz, 1H, $H4_B$ or $H4'_B$), 2.53 (s, 3H, N–CH_3 or N′–CH_3), 2.49 (s, 3H, N–CH_3 or N′–CH_3).

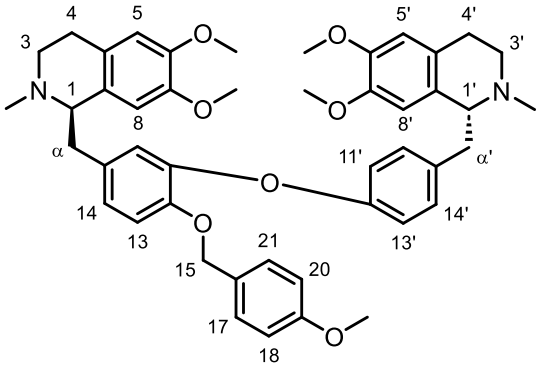
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3(C19), 156.7(C12′), 148.9(C12), 147.35(C7 or C7′), 147.34(C7 or C7′), 146.44(C6 or C6′), 146.42(C6 or C6′), 145.41(C11), 133.8(C9′), 133.7(C9), 130.8(2C, C10′, C14′), 129.3(C4a or C4a′), 129.2(C16), 129.1(C4a or C4a′), 128.9(2C, C17, C21), 126.10(2C, C14, C8a or C8a′), 125.9(C8a or C8a′), 123.1(C10), 116.7(2C, C11′, C13′), 115.6(C13), 113.9(2C, C18, C20), 111.25(2C, C5, C5′), 111.1(C8 or C8′), 110.9(C8 or C8′), 71.0(C15), 65.0(C1 or C1′), 64.8(C1 or C1′), 55.84(C7–OCH$_3$ or C7′–OCH$_3$), 55.80(C7–OCH$_3$ or C7′–OCH$_3$), 55.64(C6–OCH$_3$ or C6′–OCH$_3$), 55.63(C6–OCH$_3$ or C6′–OCH$_3$), 55.33(C19-OCH$_3$), 47.0(C3 or C3′), 46.9(C3 or C3′), 42.78(N–CH$_3$ or N′–CH$_3$), 42.75(N–CH$_3$ or N′–CH$_3$), 40.7(Cα or Cα′), 40.5(Cα or Cα′), 25.6(C4 or C4′), 25.5(C4 or C4′).

IR (film) ν_{max}/cm^{-1} 3021, 2935, 2835, 2794, 1612, 1586, 1514, 1464, 1253, 1220, 1173, 1138, 1122, 1103, 1033, 759.

HRMS (ESI$^+$) $C_{46}H_{52}N_2O_7$ found $[M+H]^+$ at 745.3833, expected at 745.3847.

$[\alpha]_D^{25}$ +76.9 (c. 1.81, $CHCl_3$).

(*R*)-1-(4-(5-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, (*R*,*R*)-152



(–)-Armepavine **(*R*)-140** (80.0 mg, 0.255 mmol), (*R*)-1-(3-bromo-4-((4-methoxybenzyl) oxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R*)-141** (119 mg, 0.232 mmol), potassium carbonate (80.2 mg, 0.580 mmol) and cupric oxide (36.8 mg, 0.463 mmol) in anhydrous pyridine (0.40 mL) were submitted to **General Procedure B**. The organic phase was washed with ammonia (aq., 35%, 4 × 7 mL) instead of filtering it through Celite® and no acidic wash was performed. Pyridine was removed azeotropically with toluene. Purification by preparative TLC (CH_2Cl_2/7N ammonia solution in MeOH, 90:5) afforded the title compound as an off-white foam (42.4 mg, 56.9 µmol, 25%).

R*f* 0.25 (CH_2Cl_2/7N ammonia solution in MeOH, 90:5), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.7 Hz, 2H, H17, H21), 7.00 (d, *J* = 8.5 Hz, 2H, H10′, H14′), 6.89 (d, *J* = 8.8 Hz, 1H, H13), 6.83 – 6.75 (m, 6H, H11′, H13′, H10, H14, H18, H20), 6.55 (s, 1H, H5 or H5′), 6.52 (s, 1H, H5 or H5′), 6.05 (s, 2H, H8, H8′), 4.98 (s, 2H, H15), 3.82 (s, 3H, C7–OC*H*$_3$ or C7′–OC*H*$_3$), 3.81 (s, 3H, C7–OC*H*$_3$ or C7′–OC*H*$_3$), 3.77 (s, 3H, C19-OC*H*$_3$), 3.69 (dd, *J* = 7.7, 5.1 Hz, 1H, H1′), 3.65 (dd, *J* = 7.5, 5.2 Hz, 1H, H1), 3.55 (s, 3H, C6–OC*H*$_3$ or C6′–OC*H*$_3$),

3.53 (s, 3H, C6–OC*H*$_3$ or C6′–OC*H*$_3$), 3.24 – 3.03 (m, 4H, H3$_A$, H3′$_A$, Hα$_A$, Hα′$_A$), 2.88 – 2.69 (m, 6H, H4$_A$, H4′$_A$, H3$_B$, H3′$_B$, Hα$_B$, Hα′$_B$), 2.60 (t, *J* = 4.7 Hz, 1H, H4$_B$ or H4′$_B$), 2.57 (t, *J* = 4.6 Hz, 1H, H4$_B$ or H4′$_B$), 2.53 (s, 3H, N–C*H*$_3$ or N′–C*H*$_3$), 2.49 (s, 3H, N–C*H*$_3$ or N′–C*H*$_3$).

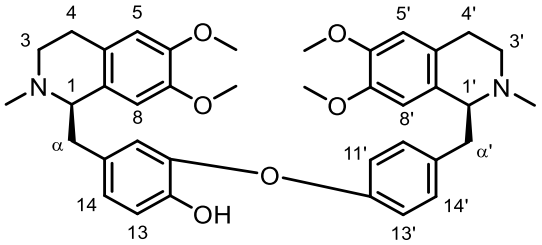
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4(C19), 156.7(C12′), 148.9(C12), 147.37(C7 or C7′), 147.38(C7 or C7′), 146.46(C6 or C6′), 146.44(C6 or C6′), 145.42(C11), 133.8(C9′), 133.7(C9), 130.8(2C, C10′, C14′), 129.3 (C4a or C4a′), 129.2 (C16), 129.1(C4a or C4a′), 128.9(2C, C17, C21), 126.1(2C, C14, C8 or C8a), 125.9(C8a or C8a′), 123.1(C10), 116.7(2C, C11′, C13′), 115.6(C13), 113.9(2C, C18, C20), 111.26(2C, C5, C5′), 111.1(C8 or C8′), 110.9(C8 or C8′), 71.1(C15), 65.1(C1 or C1′), 64.8(C1 or C1′), 55.85(C7–O*C*H$_3$ or C7′–O*C*H$_3$), 55.82(C7–O*C*H$_3$ or C7′–O*C*H$_3$), 55.65(C6–O*C*H$_3$ or C6′–O*C*H$_3$), 55.64(C6–O*C*H$_3$ or C6′–O*C*H$_3$), 55.4(C19-O*C*H$_3$), 47.0(C3 or C3′), 46.9(C3 or C3′), 42.79(N–*C*H$_3$ or N′–*C*H$_3$), 42.75(N–*C*H$_3$ or N′–*C*H$_3$), 40.8(Cα or Cα′), 40.5(Cα or Cα′), 25.6(C4 or C4′), 25.5(C4 or C4′).

IR (film) ν_{max}/cm^{-} 3014, 2934, 2835, 2794, 1611, 1585, 1513, 1464, 1253, 1223, 1173, 1138, 1123, 1103, 1016, 759.

HRMS (ESI$^+$) $C_{46}H_{52}N_2O_7$ found $[M+H]^+$ at 745.3829, expected at 745.3847.

[α]$_D^{25}$ −75.9 (c. 1.40, $CHCl_3$).

4-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-(4-(((*S*)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenoxy)phenol, (*S,R*)-139



To an oven-dried flask containing Pd/C (10% wt., 5.4 mg, 5.1 µmol, 0.20 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.1 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*S*)-1-(4-(5-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*S,R*)-152** (18 mg, 25 µmol, 1.0 equiv.) was then added as a solution in MeOH (0.15 mL) and triethylamine (30 µL, 25 mmol, 10 equiv.). Using a gas bag, hydrogen was continuously bubbled through the reaction mixture by having the needle submerged in the reaction mixture and a second exit-needle for 20 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 50 mL) and the filtrate was concentrated *in vacuo*. The title compound was collected as an off-white foam (9.1 mg, 15 µmol, 60%). No further purification was necessary.

R*f* 0.21 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.5 Hz, 2H, H10′, H14′), 6.95 (d, *J* = 8.2 Hz, 1H, H13), 6.85 – 6.81 (m, 3H, H14, H11′, H13′), 6.59 (s, 2H, H10, H5 or 5′), 6.55 (s, 1H,

H5 or 5′), 6.05 (s, 1H, H8a or H8a′), 6.01 (s, 1H, H8a or H8a′), 3.86 (s, 3H, C7–OCH_3 or C7'–OCH_3), 3.84 (s, 3H, C7–OCH_3 or C7'–OCH_3), 3.84 – 3.80 (m, 1H H1 or H1′), 3.77 – 3.72 (m, 1H, H1 or H1′), 3.61 (s, 3H, C6–OCH_3 or C6'–OCH_3), 3.59 (s, 3H, C6–OCH_3 or C6'–OCH_3), 3.34 – 3.16 (m, 4H, $H3_A$, $H3'_A$, $H\alpha_A$, $H\alpha'_A$), 2.94 – 2.81 (m, 5H, $H4_A$, $H4'_A$, $H\alpha_B$, $H\alpha'_B$, $H3_B$ or $H3'_B$,), 2.72 (dd, J = 13.6, 8.2 Hz, 1H, $H3_B$ or $H3'_B$), 2.69 – 2.61 (m, 2H, $H4_B$, $H4'_B$), 2.60 (s, 3H, N–CH_3 or N'–CH_3), 2.56 (s, 3H, N–CH_3 or N'–CH_3).

Note: O*H* resonance was not observed.

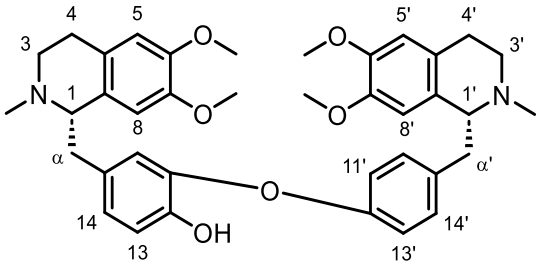
^{13}C NMR (151 MHz, $CDCl_3$) δ 155.5(C12′), 147.83(C7 or C7′), 147.78(C7 or C7′), 146.77(C6 or C6′), 146.67(C6 or C6′), 146.14(C12), 143.10(C11′), 134.4(C9′), 131.7(C9), 131.2(2C, C10′, C14′), 127.7(2C, C4a, C4a′), 126.2(C14), 125.3(2C, C8a, C8a′), 120.8(C10), 117.5(2C, C11′, C13′), 116.1(C13), 111.40(C5 or C5′), 111.35(C5 or C5′), 111.2(2C, C8, C8′), 64.89(C1 or C1′), 64.85(C1 or C1′), 55.9(2C, C7–OCH_3, C7′–OCH_3), 55.8(C6–OCH_3 or C6′–OCH_3), 55.7(C6–OCH_3 or C6′–OCH_3), 46.5(2C, C3, C3′), 42.2(2C, N–CH_3, N′–CH_3), 40.6(Cα or Cα′), 40.5(Cα or Cα′), 24.8(2C, C4, C4′).

IR (film) ν_{max}/cm^{-1} 3022, 2933, 2850, 2836, 1611, 1593, 1512, 1465, 1451, 1289, 1256, 1226, 1137, 1116, 1015.

HRMS (ESI$^+$) $C_{38}H_{44}N_2O_6$ found $[M+H]^+$ at 625.3264, expected at 625.3272.

$[\alpha]_D^{25}$ +15.8 (c. 1.03, $CHCl_3$).

4-(((*S*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-(4-(((*R*)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenoxy)phenol, (*R,S*)-139



To an oven-dried flask containing Pd/C (10% wt., 9.3 mg, 8.7 µmol, 0.20 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.1 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*R*)-1-(4-(5-(((*S*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroiso quinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R,S*)-152** (32 mg, 43 µmol, 1.0 equiv.) was then added as a solution in MeOH (0.33 mL) and triethylamine (60 µL, 43 mmol, 10 equiv.). Using a gas bag, hydrogen was continuously bubbled through the reaction mixture by having the needle submerged in the reaction mixture and a second exit-needle for 20 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 50 mL) and the filtrate was concentrated *in vacuo*. The title compound was collected as an off-white foam (15 mg, 23 µmol, 54%). No further purification was necessary.

R*f* 0.21 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4 Hz, 2H, H10′, H14′), 6.96 (d, *J* = 8.2 Hz, 1H, H13), 6.85 – 6.83 (m, 3H, H14, H11′, H13′), 6.59 (s, 2H, H10, H5 or 5′), 6.55 (s, 1H,

H5 or 5′), 6.04 (s, 1H, H8a or H8a′), 6.01 (s, 1H, H8a or H8a′), 3.86 (s, 3H, C7–OCH_3 or C7'–OCH_3), 3.85 – 3.82 (m, 4H, C7–OCH_3 or C7'–OCH_3, H1 or H1′), 3.81 – 3.74 (m, 1H, H1 or H1′), 3.60(s, 3H, C6–OCH_3 or C6'–OCH_3), 3.59 (s, 3H, C6–OCH_3 or C6'–OCH_3), 3.34 – 3.20 (m, 4H, $H3_A$, $H3'_A$, $H\alpha_A$, $H\alpha'_A$), 2.95 – 2.81 (m, 5H, $H4_A$, $H4'_A$, $H\alpha_B$, $H\alpha'_B$, $H3_B$ or $H3'_B$), 2.73 (dd, J = 13.6, 8.4 Hz, 1H, $H3_B$ or $H3'_B$), 2.70 – 2.63 (m, 2H, $H4_B$, $H4'_B$), 2.61 (s, 3H, N–CH_3 or N'–CH_3), 2.58 (s, 3H, N–CH_3 or N'–CH_3).

Note: O*H* resonance was not observed.

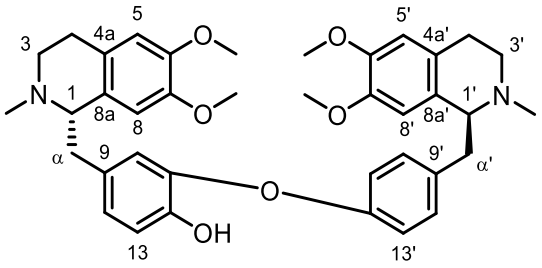
^{13}C NMR (151 MHz, $CDCl_3$) δ 155.5(C12′), 147.90(C7 or C7′), 147.85(C7 or C7′), 146.8(C6 or C6′), 146.7(C6 or C6′), 146.3(C12), 143.1(C11′), 134.2(C9′), 131.4(C9), 131.2(2C, C10′, C14′), 127.7(2C, C4a, C4a′), 126.2(C14), 125.2(2C, C8a, C8a′), 120.9(C10), 117.5(2C, C11′, C13′), 116.2(C13), 111.39(C5 or C5′), 111.34(C5 or C5′), 111.2(2C, C8, C8′), 64.91(C1 or C1′), 64.87(C1 or C1′), 55.93(2C, C7–OCH_3, C7′–OCH_3), 55.79(C6–OCH_3 or C6′–OCH_3), 55.71(C6–OCH_3 or C6′–OCH_3), 46.5(C3 or C3′), 46.4(C3 or C3′), 42.1(2C, N–CH_3, N′–CH_3), 40.6(Cα or Cα′), 40.5(Cα or Cα′), 24.7(2C, C4, C4′).

IR (film) ν_{max}/cm^{-1} 3021, 2935, 2850, 2836, 1611, 1592, 1512, 1465, 1450, 1289, 1256, 1225, 1137, 1116, 1015.

HRMS (ESI$^+$) $C_{38}H_{44}N_2O_6$ found $[M+H]^+$ at 625.3266, expected at 625.3272.

$[\alpha]_D^{25}$ –14.4 (c. 1.32, $CHCl_3$).

4-(((*(S)*-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-(4-(((*(S)*-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenoxy)phenol, (*S,S*)-139, (+)-dauricine



To an oven-dried flask containing Pd/C (10% wt., 5.3 mg, 5.0 µmol, 0.21 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.1 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*S*)-1-(4-(5-(((*S*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, **(*S,S*)-152** (17 mg, 23 µmol, 1.0 equiv.) was then added as a solution in MeOH (0.15 mL) and triethylamine (30 µL, 23 mmol, 10 equiv.). Using a gas bag, hydrogen was continuously bubbled through the reaction mixture by having the needle submerged in the reaction mixture and a second exit-needle for 20 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 50 mL) and the filtrate was concentrated *in vacuo*. The title compound was collected as an off-white foam (9.1 mg, 15 µmol, 65%). No further purification was necessary.

R$_f$ 0.21 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.1 Hz, 2H, H10′, H14′), 6.92 (d, *J* = 8.2 Hz, 1H, H13), 6.85 – 6.77 (m, 3H, H14, H11′, H13′), 6.57 (d, *J* = 2.0 Hz, 1H, H10),

6.55 (s, 1H, H5 or H5′), 6.51 (s, 1H, H5 or H5′), 6.09 (s, 1H, H8 or H8′), 6.03 (s, 1H, H8 or H8′), 3.83 (s, 3H, C7–OCH_3 or C7'–OCH_3), 3.80 (s, 3H, C7–OCH_3 or C7'–OCH_3), 3.75 – 3.69 (m, 1H, H1′), 3.64 (dd, J = 8.0, 4.8 Hz, 1H, H1), 3.60 (s, 6H, C6–OCH_3, C6'–OCH_3), 3.24 – 3.09 (m, 3H, $H3_A$, $H3'_A$, $H\alpha_A$ or $H\alpha'_A$), 3.06 (dd, J = 13.7, 5.1 Hz, 1H, $H\alpha_A$ or $H\alpha'_A$), 2.88 – 2.65 (m, 6H, $H4_A$, $H4'_A$, $H3_B$, $H3'_B$, $H\alpha_B$, $H\alpha'_B$), 2.62 – 2.53 (m, 2H, $H4_B$, $H4'_B$), 2.52 (s, 3H, N–CH_3 or N′–CH_3), 2.49 (s, 3H, N–CH_3 or N′–CH_3).

Note: OH resonance was not observed.

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3(C12′), 147.54(C7 or C7′), 147.46(C7 or C7′), 146.6(C6 or C6′), 146.5(C6 or C6′), 145.9(C12), 143.0(C11), 135.0(C9′), 132.3(C9), 131.2(2C, C10′,C14′), 129.0(C4a or C4a′), 128.9(C4a or C4a′), 126.1(3C, C14, C8a, C8a′), 120.6(C10), 117.5(2C, C11′, C13′), 115.9(C13), 111.4(C5 or C5′), 111.3(C5 or C5′), 111.10(C8 or C8′), 111.08(C8 or C8′), 64.87(C1 or C1′), 64.86(C1 or C1′), 55.9(C7–OCH$_3$ or C7′–OCH$_3$), 55.8(C7–OCH$_3$ or C7′–OCH$_3$), 55.74(C6–OCH$_3$ or C6′–OCH$_3$), 55.71(C6–OCH$_3$ or C6′–OCH$_3$), 46.93(C3 or C3′), 46.85(C3 or C3′), 42.69(N–CH$_3$ or N′–CH$_3$), 42.66(N–CH$_3$ or N′–CH$_3$), 40.7(Cα or Cα′), 40.5(Cα or Cα′), 25.5(C4 or C4′), 25.3(C4 or C4′).

IR (film) ν_{max}/cm^{-1} 3021, 2936, 2834, 1611, 1593, 1509, 1465, 1450, 1288, 1256, 1226, 1137, 1116, 1016, 758.

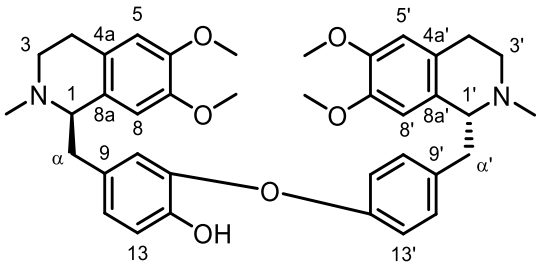
HRMS (ESI$^+$) $C_{38}H_{44}N_2O_6$ found $[M+H]^+$ at 625.3262, expected at 625.3272.

$[\alpha]_D^{25}$ +68.2 (c. 0.83, $CHCl_3$).

Spectroscopic data is in agreement with that reported previously.[112, 160]

Note: data is reported for (–)-dauricine ***(R,R)*-139**.

4-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-(4-(((*R*)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenoxy)phenol, (*R,R*)-139, (−)-dauricine



To an oven-dried vial containing Pd/C (10% wt., 12 mg, 11.3 μmol, 0.20 equiv.) under an inert atmosphere, was added anhydrous MeOH (0.1 mL) and the flask was evacuated and backfilled with hydrogen (× 3). (*R*)-1-(4-(5-(((*R*)-6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-2-((4-methoxybenzyl)oxy)phenoxy)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **(*R,R*)-152** (40 mg, 54 μmol, 1.0 equiv.) was then added as a solution in MeOH (0.44 mL) and triethylamine (70 μL, 0.54 mmol, 10 equiv.). Hydrogen was continuously bubbled through the reaction mixture using a gas bag and having the needle submerged in the reaction mixture and a second exit-needle for 20 h. The gas bag was refilled as needed. Upon completion, the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2/MeOH (8:2, 50 mL) and the filtrate was concentrated *in vacuo*. The title compound was collected as an off-white foam (19 mg, 30 μmol, 56%). No further purification was necessary.

R_f 0.21 (CH_2Cl_2/MeOH, 9:1), [UV, PMA]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.4 Hz, 1H, H10′, H14′), 6.91 (d, *J* = 8.2 Hz, 1H, H13), 6.85 – 6.77 (m, 3H, H14, H11′, H13′), 6.57 (d, *J* = 2.0 Hz, 1H, H10),

6.55 (s, 1H, H5 or H5′), 6.51 (s, 1H, H5 or H5′), 6.08 (s, 1H, H8 or H8′), 6.03 (s, 1H, H8 or H8′), 3.83 (s, 3H, C7–OCH_3 or C7'–OCH_3), 3.80 (s, 3H, C7–OCH_3 or C7'–OCH_3), 3.74 – 3.68 (m, 1H, H1′), 3.64 (dd, J = 7.6, 5.3 Hz, 1H, H1), 3.59 (s, 6H, C6–OCH_3, C6'–OCH_3), 3.23 – 3.10 (m, 3H, $H3_A$, $H3'_A$, $H\alpha_A$ or $H\alpha'_A$), 3.05 (dd, J = 13.7, 5.1 Hz, 1H, $H\alpha_A$ or $H\alpha'_A$), 2.88 – 2.65 (m, 6H, $H4_A$, $H4'_A$, $H3_B$, $H3'_B$, $H\alpha_B$, $H\alpha'_B$), 2.61 – 2.53 (m, 2H, $H4_B$, $H4'_B$), 2.52 (s, 3H, N–CH_3 or N′–CH_3), 2.49 (s, 3H, N–CH_3 or N′–CH_3).

Note: OH resonance was not observed.

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3(C12′), 147.53(C7 or C7′), 147.45(C7 or C7′), 146.6(C6 or C6′), 146.5(C6 or C6′), 145.9(C12), 143.0(C11), 135.0(C9′), 132.3(C9), 131.1(2C, C10′, C14′), 129.0(C4a or C4a′), 128.9(C4a or C4a′), 126.0(3C, C14, C8a, C8a′), 120.6(C10), 117.4(2C, C11′, C13′), 115.9(C13), 111.4(C5 or C5′), 111.3(C5 or C5′), 111.10(C8 or C8′), 111.08(C8 or C8′), 64.87(C1 or C1′), 64.85(C1 or C1′), 55.9(C7–OCH$_3$ or C7′–OCH$_3$), 55.8(C7–OCH$_3$ or C7′–OCH$_3$), 55.73(C6–OCH$_3$ or C6′–OCH$_3$), 55.70(C6–OCH$_3$ or C6′–OCH$_3$), 46.9(C3 or C3′), 46.8(C3 or C3′), 42.69(N–CH$_3$ or N′–CH$_3$), 42.65(N–CH$_3$ or N′–CH$_3$), 40.7(Cα or Cα′), 40.5(Cα or Cα′), 25.5(C4 or C4′), 25.3(C4 or C4′).

IR (film) ν_{max}/cm^{-1} 3018, 2938, 2835, 2799, 1611, 1593, 1509, 1465, 1451, 1288, 1255, 1226, 1137, 1116, 1016, 757.

HRMS (ESI$^+$) $C_{38}H_{44}N_2O_6$ found $[M+H]^+$ at 625.3262, expected at 625.3272.

$[\alpha]_D^{25}$ –69.5 (c. 1.2, $CHCl_3$). Ref [160] $[\alpha]_D^{19}$ –115.1 (c. 0.73, MeOH).

Spectroscopic data is in agreement with that reported previously.[112, 160]

8

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