Enantioselective Construction of the ABCDE Pentacyclic Core of the *Strychnos* Alkaloids

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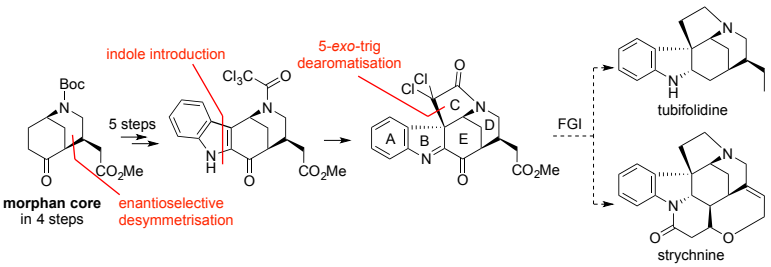
Supporting Information Placeholder



ABSTRACT: An efficient enantioselective 12 step synthesis to the ABCDE pentacyclic core of the *Strychnos* alkaloids is described. A key feature of this approach is an organocatalysed enantioselective desymmetrisation to generate the morphan core in high ee and dr. After palladium-catalysed installation of the indole moiety, a subsequent 5-*exo*-trig dearomatising atom transfer radical cyclisation was developed to construct the C-ring. Following a series of functional group interconversions, the pentacyclic amine core was obtained with all the relevant architecture including five stereocentres pertaining to the *Strychnos* alkaloids.

The *Strychnos* alkaloids encompass a large group of architecturally complex indole alkaloids of which strychnine is its most prominent member (Figure 1). Strychnine is a structurally dense alkaloid with many challenging features and, as such, has attracted significant interest from the synthetic community ever since it was first synthesised by Woodward in 1954.[1] Many different strategies for the synthesis of strychnine, other *Strychos* alkaloids and their cores exist.[2] All the *Strychnos* alkaloids posses the same common 6,5,5,6,6-pentacyclic ring system but differ about the N-1, C-16, and C-18 nodes.

Our strategy targeted a core structure with functional groups at carbons C-16 and C-18 that would allow access to a variety of these alkaloids after further synthetic manipulation.

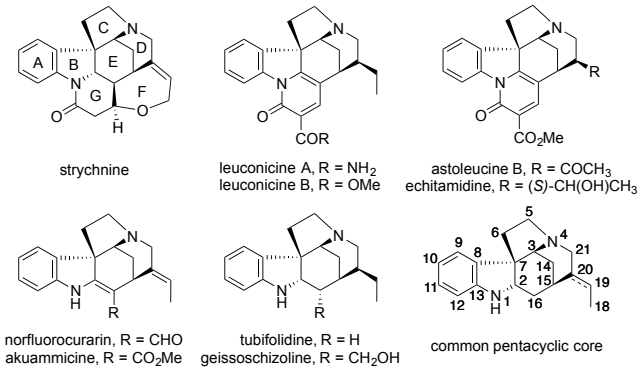
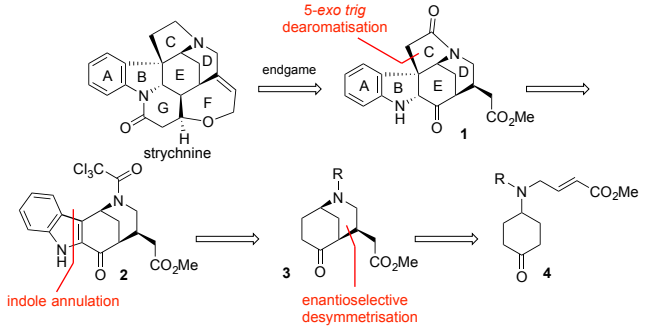


Figure 1. A selection of the *Strychnos* alkaloids (Strychnan skeletal type with biogenetic numbering)

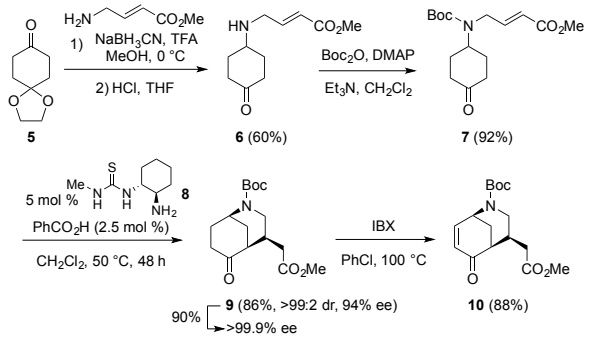
Scheme 1. Synthetic plan towards the *Strychnos* alkaloid core



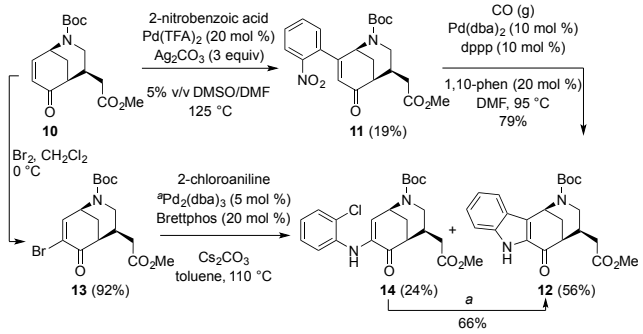
The synthesis of pentacyclic core **1** would rely on a key 5-*exo*-trig dearomatising cyclisation of tetracyclic indole **2**.[3] In turn, tetracycle **2** would be synthesised by introduction of an indole moiety into enantioenriched morphan **3**. Morphan **3** could be accessed in high ee and dr from prochiral cyclohexanone **4** using the organocatalysed enantioselective desymmetrisation reaction that we previously reported.[4] We envisioned this synthetic route would quickly build the desired pentacyclic core **1** with the appropriate architecture relevant, not only to strychnine but other *Strychnos* alkaloids such as tubifolidine with an additional stereocenter at C-20.

Synthesis of prochiral substrate **7** was achieved in three steps starting from ketone **5** (Scheme 2). First, a reductive amination with methyl (*E*)-4-aminobut-2-enoate using $NaBH_3CN$ and TFA and subsequent acetal deprotection of the crude product using aqueous HCl in THF gave **6**, which was

Scheme 2. Synthesis of the enantioenriched morphan core



Scheme 3. Introduction of the indole moiety



purified and *N*-Boc protected to afford desymmetrisation precursor **7** in good overall yield.

In our previously reported enantioselective desymmetrisation of prochiral cyclohexanones by organocatalytic intramolecular Michael additions to α,β-unsaturated esters, a new and effective low-molecular-weight cyclohexanediamine–derived primary amine thiourea organocatalyst (**8**) was identified by computational studies and subsequently validated.[4] Treatment of substrate **7** with organocatalyst **8** (5 mol %) and benzoic acid as co-catalyst in CH_2Cl_2 at 50 °C in a sealed vessel afforded morphan **9** with three stereogenic centers in 86% yield, 94% ee, and as a single diastereomer. Subsequent recrystallisation from refluxing methanol enhanced the ee to >99.9% in an overall yield of 77% for both the cyclisation and recrystallisation steps. Oxidation to enone **10** was necessary for further functionalisation towards an indole moiety and proceeded in excellent yield using IBX in PhCl at 100 °C.

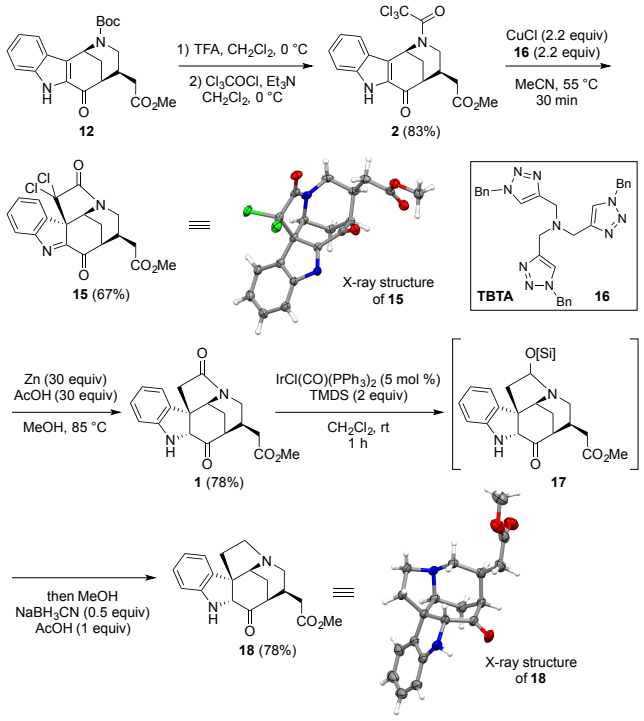
Two methods were explored for installing the indole moiety into enone **10** (Scheme 3). The first consisted of coupling a 2-nitroaryl group to the β-carbon of the enone and a subsequent reductive *N*-heteroannulation to complete the construction of the indole. To this end, the decarboxylative Heck reaction has been demonstrated to be a useful method for coupling 2-nitro aryl groups to olefins.[5] However, bicyclic enone **10** was a challenging substrate for this reaction and after much optimisation, its reaction with 2-nitrobenzoic acid, $Pd(TFA)_2$ as catalyst and Ag_2CO_3 as stoichiometric oxidant gave **11** in only 19% yield. Nonetheless, the reductive *N*-heteroannulation of **11** to give indole **12** proceeded in excellent yield using CO as the external reductant and with catalytic amounts of $Pd(dba)_2$, 1,10-phen (1,10-phenantroline),[6] and dppp (1,3-bis(diphenylphosphino)propane). Overall, the combined yield of these two steps was 15%, which was unacceptable and insufficient for generating large quantities of indole **12**. As an alternative, the Barluenga indolisation of vinyl halides was explored.[7] Bromination of enone **10** using bromine in CH_2Cl_2 at 0 °C and *in situ* E1cB elimination using Et_3N afforded bromoenone **13** in excellent yield (Scheme 3). A subsequent screen of ligands in the *N*-vinylation reaction reaction of bromide **13** with 2-chloroaniline in the presence of $Pd_2(dba)_3$ and Cs_2CO_3 in toluene at 110 °C identified Brettphos as a good Pd-ligand for this transformation (see Supporting Information (SI) for the full screen of biaryl phosphane ligands). Indole **12** was obtained in 56% yield along with intermediate product **14** in 24% yield. It was possible to resubject isolated intermediate **14** to the cross-coupling conditions to afford more indole product **12** in 66% yield. Following this approach, the combined yield for the generation of indole **12** from enone **10** was dramatically improved to 66%. With indole intermediate **12** in hand, a method of C-ring closure was sought.

The synthesis of this ring in the *Strychnos* alkaloids from the ABDE-tetracycle has been previously reported using a cationic Pummerer ring closure of the electron rich indole onto a thionium ion derived from a dithiane.[8] Initial attempts to use the same method for the synthesis of the C-ring were unsuccessful on our system and an alternative atom transfer radical cyclisation (ATRC) was developed (Scheme 4).[9] The *N*-Boc group of **12** was exchanged for a reactive trichloroacetamide *via* treatment with TFA and *N*-acylation using trichloroacetyl chloride to give **2** ready for attempted C-ring formation. Attempted cyclisation of **2** with CuCl and typical ligands[10] for Cu(I) in ATRC reactions was unsuccessful and it was evident from color changes that Cu(I) was undergoing disproportionation/degradation. Whilst TBTA (**16**, tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine) has not been used as a ligand in ATRC reactions, it has been reported as an excellent ligand for Cu(I) stabilisation in CuAAC reactions.[11] Treating indole **12** with 2.2 equivalents of both CuCl and TBTA, afforded pentacycle **15** in 67% yield, after spontaneous elimination of HCl. Attempts to reduce the amount of CuCl/TBTA to 10 mol % afforded only trace amounts of product presumably because of interference from the *in situ* generated HCl (see SI for full optimisation table).

With a successful route to the pentacyclic structure established, removal of the *gem*-dichloride group, that had been necessary for the ATRC, was now required (Scheme 4). Protodechlorination of both chlorine atoms and reduction of the imine in **15** was achieved in one step using activated zinc dust in superheated methanol with acetic acid as additive, giving pentacycle **1** in excellent yield. Chemoselective reduction of the amide in **1** was achieved using a one-pot, two-step reductive procedure. First Vaska's complex ($IrCl(CO)(PPh_3)_2$, 5 mol %) and stoichiometric amounts of the silane reductant TMDS (1,1,3,3-tetramethyldisiloxane) efficiently gave hemiaminal **17** after 1 h.[12] Subsequent addition of MeOH, $NaBH_3CN$ and AcOH afforded the desired pentacyclic amine **18**, which was confirmed by single crystal X-ray diffraction.[13]

In summary, we have developed a concise enantioselective synthesis of the pentacyclic (ABCDE) core of the *Strychnos* alkaloids. Our strategy was based upon using a key enantioselective organocatalysed enantioselective desymmetrisation to generate the morphan core containing three stereogenic centers in high enantio- and diastereoselectivity. Subsequent introduction of the indole motif was achieved using the Barluenga indolisation protocol. We identified TBTA as a new ligand for Cu(I) in ATRC and successfully used this system for a dearomatising cyclisation to give the C-ring, furnishing

Scheme 4. Formation of the C-ring using an ATRC and subsequent chemoselective reduction of the amide moiety



the pentacyclic core of the *Strychnos* alkaloids. Further studies towards the synthesis of strychnine and other *Strychnos* alkaloids are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectroscopic and analytical data, NMR spectra (PDF) and X-ray data (CIF).

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Notes

The authors declare no competing financial interest.

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