

Article

One-Pot Access to Functionalised Malamides via Organocatalytic Enantioselective Formation of Spirocyclic β -Lactone-Oxindoles and Double Ring-Opening [†]

Alastair J. Nimmo, Kevin Kasten , George White, Julia Roeterdink, Aidan P. McKay , David B. Cordes  and Andrew David Smith * 

EaStCHEM, School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, UK; an52@st-andrews.ac.uk (A.J.N.); kk47@st-andrews.ac.uk (K.K.); george.white@chem.ox.ac.uk (G.W.); jr275@st-andrews.ac.uk (J.R.); apm31@st-andrews.ac.uk (A.P.M.)

* Correspondence: ads10@st-andrews.ac.uk; Tel.: +44-(0)-1334-463896

[†] Dedication: This manuscript is dedicated to the long-standing achievements of Prof. John Walton (University of St Andrews) and his dedication to understanding synthetic chemistry.

Abstract: Malamides (diamide derivatives of malic acid) are prevalent in nature and of significant biological interest, yet only limited synthetic methods to access functionalised enantiopure derivatives have been established to date. Herein, an effective synthetic method to generate this molecular class is developed through in situ formation of spirocyclic β -lactone-oxindoles (employing a known enantioselective isothiurea-catalysed formal [2+2] cycloaddition of C(1)-ammonium enolates and isatin derivatives) followed by a subsequent dual ring-opening protocol (of the β -lactone and oxindole) with amine nucleophiles. The application of this protocol is demonstrated across twelve examples to give densely functionalised malamide derivatives with high enantio- and diastereo-selectivity (up to >95:5 dr and >99:1 er).

Keywords: malamides; organocatalysis; isothiurea; β -lactone ring-opening; oxindole ring-opening; asymmetric synthesis; [2+2] cycloaddition



Citation: Nimmo, A.J.; Kasten, K.; White, G.; Roeterdink, J.; McKay, A.P.; Cordes, D.B.; Smith, A.D. One-Pot Access to Functionalised Malamides via Organocatalytic Enantioselective Formation of Spirocyclic β -Lactone-Oxindoles and Double Ring-Opening. *Molecules* **2024**, *29*, 3635. <https://doi.org/10.3390/molecules29153635>

Academic Editor: Vito Capriati

Received: 28 June 2024

Revised: 29 July 2024

Accepted: 29 July 2024

Published: 31 July 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Malic acid (2-hydroxybutanedioic acid) is a readily available platform chemical that is widely used in the food and cosmetic industries [1–4]. It is readily available in an enantiomerically pure form and has been utilised as a versatile C(4)-synthetic building block for a range of natural product syntheses [5]. Amide derivatives of malic acid (generally known as malamides) are prevalent in nature [6–10] and are of significant biological interest, as they are isosteric to asparagine and aspartic acid and have been used against HCV infections [11] and as a constituent of agents that provide DNA binding to p53 [12]. They can also be used as metalating reagents [13,14] and serve as metalloprotease inhibitors [15–20] or as peptidomimetics (Figure 1A) [13,17,21–23]. As a representative example, DuPont Merck developed a chiral auxiliary-based route to a range of matrix metalloproteinase (MMP) inhibitors based upon the malamide motif, with the absolute configuration at C(2) essential for bioactivity [17]. Despite this interest, catalytic enantioselective protocols to access bespoke highly functionalised malamide derivatives with high stereocontrol are generally lacking but could be of widespread interest to the synthetic community.

Our proposed strategy to access a series of malamides was built upon the established precedent for β -lactones and oxindoles to undergo nucleophilic ring-opening under defined reaction conditions. β -Lactones are prevalent in medicinally active compounds and natural products [24–29] but are susceptible to ring-opening [30–54], decarboxylation [55–57], β -elimination [37,58], or acid-catalysed ring expansions [48,59–66]. Ring-opening of β -lactones to generate isolable compounds is a common strategy, typically employing alcohols, alkoxides or primary/secondary amines as nucleophiles. Ring-opening can occur

either through the scission of the O-alkyl bond (via an S_N2 pathway) or the scission of the O-acyl bond (via an addition elimination process). The preference for the major reaction pathway is dependent upon the nucleophile and the reaction conditions, with O-alkyl cleavage typically being favoured with hard nucleophiles under neutral or acidic conditions and O-acyl cleavage favoured under basic conditions with softer nucleophiles [37,66]. However, the inherent preference for O-alkyl or O-acyl bond scission can be altered by the strategic placement of substituents that introduce a steric bias to favour one reaction mode over the other (Figure 1B, left). In a similar fashion, isatins and oxindoles are common motifs within bioactive compounds [67–81] and are known to be susceptible to ring-opening. For example, the incorporation of electron-deficient N-substituents within isatins and oxindoles is known to promote facile ring-opening, with the literature conditions indicating they can be readily opened by alcohols, alkoxides, hydroxides and amines [82–97] to give the corresponding esters and amides (Figure 1B, right). Using this approach, substituents that contain pendant or masked amines and alcohol functionality have also been employed to generate pyrrolidones [98–107] and butyrolactones [108–110], respectively, via intramolecular ring-opening.

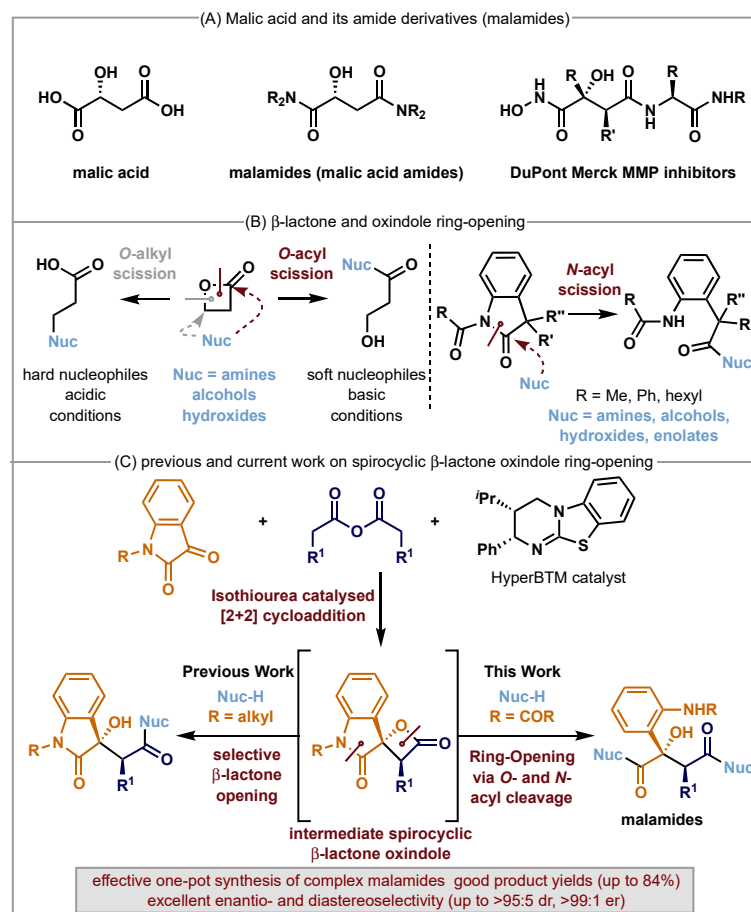


Figure 1. (A) Malic acid and malamide derivatives; (B) β -lactone and oxindole ring-opening; (C) previous and current work on spiro-oxindole- β -lactone ring-opening to generate malamide derivatives.

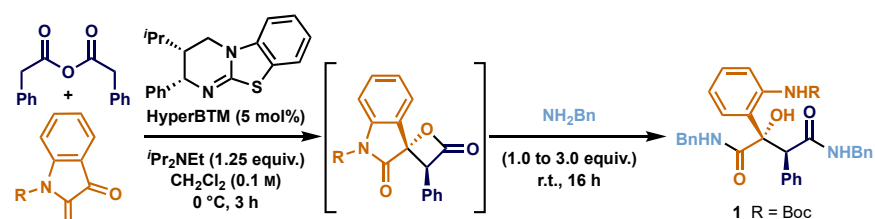
Building upon these precedents, this work develops a strategy to access stereodefined and densely functionalised malamides in enantiopure form. Over the last decade, the use of isothioureas as enantiopure Lewis base catalysts have expanded widely. In recent work, the isothiourea HyperBTM promoted the in situ formation of β -lactone spirocyclic oxindoles via a [2+2] cycloaddition of C(1)-ammonium enolates to N-alkyl isatin derivatives, with selective β -lactone ring-opening facilitating product isolation [30]. In this work, the use of N-acyl isatins facilitates an enantioselective route to spirocyclic isatin-derived β -lactones,

with double ring-opening (of the β -lactone and oxindole motifs) revealing the linear and densely functionalised malamide structure, including two contiguous stereogenic centres (Figure 1C). To the best of our knowledge, while reports of selectively opening either β -lactones or (spiro)oxindoles [111–114] have been disclosed previously, this double ring-opening strategy has hitherto been unknown.

2. Results

Building upon the literature precedent, initial studies probed the hypothesis that changing from an N-alkyl-protected isatin to incorporating a conjugating electron-withdrawing N-substituent would facilitate double ring-opening after enantioselective [2+2] cycloaddition. Initially, an N-phenyl substituent was considered, with N-phenyl isatin treated under the previously optimised reaction conditions for the [2+2] addition of C(1)-ammonium enolates to N-alkyl isatins [11a], followed by the addition of benzylamine (Table 1, entry 1). Unfortunately, no malamide is observed, and only the ring-opening of the isatin starting material is observed ($\approx 30\%$ yield by ^1H NMR spectroscopic analysis). Unfortunately, the installation of an N-C(O)NHP substituent led to the resulting isatin starting material being insoluble under the reaction conditions, returning only the starting material (entry 2). While the use of N-Ts protected isatin led to a complex product mixture (entry 3), N-Boc-substituted isatin gave the desired malamide product 1 resulting from double ring-opening in a good 67% yield and with excellent stereocontrol (entry 4, >95:5 dr, 99:1 er) when 3.0 equivalents of benzylamine were applied. Interestingly, when the 1.0 equivalent of benzylamine was used to investigate the potential of sequential ring-opening, only the double ring-opened product 1 was obtained in 32% yield with high stereoselectivity maintained (entry 5, >95:5 dr, 98:2 er).

Table 1. Reaction optimisation.



Entry	R	NH ₂ Bn (equiv.)	Product Yield [%] ^b	dr/er ^c
1 ^a	Ph	1.5	0	-
2	C(O)NHPH	3.0	0	-
3	Ts	3.0	Complex mixture	-
4	Boc	3.0	67	>95:5/99:1
5	Boc	1.0	32	>95:5/98:2

^a A total of 30% product derived from direct ring-opening of the isatin starting material was observed by analysis of the ^1H NMR spectra of the crude reaction mixture. ^b Yield refers to isolated product yield after chromatographic purification. ^c Enantiomeric ratios (er) were determined by HPLC analysis on a chiral stationary phase. Diastereomeric ratios (dr) were obtained by ^1H NMR analysis of the isolated product mixture.

Subsequent work focused on probing the generality of this process to make a range of substituted malamide derivatives (Figure 2). The capability of alternative primary and secondary amines towards the double ring-opening process was investigated, with good product yields and excellent levels of enantio- and diastereoselectivity (>95:5 dr, >98:2 er) observed with benzylamine, (2-pyridylmethyl)amine and morpholine (to give 1, 2 and 3, respectively). The relative configuration within 2 was assigned unambiguously by single crystal X-ray analysis. The absolute configuration was assigned based on the established reactivity of **HyperBTM** in C(1)-ammonium enolate transformations, with all other products assigned by analogy. Inspired by the DuPont Merck MMP inhibitor structure (see Figure 1A), methyl glycinate was employed as a nucleophile, giving the tripeptide mimic malamide 4 in 28% yield with high stereoselectivity (>95:5 dr, 99:1 er). Subsequently,

different alkenyl- and aryl-acetic acid-derived homoanhydrides were employed in this protocol using either morpholine or benzylamine as the nucleophilic ring-opening reagent. Electron-rich 4-methoxyphenylacetic anhydride gave the desired product **5** in 63% yield and excellent stereoselectivity (>95:5 dr, 99:1 er). The use of 4-bromophenylacetic anhydride, 3-thienylacetic anhydride and 5-methylhex-3-enoic anhydride were also successfully employed, giving **6–8**, respectively, albeit with reduced product yields. While high stereoselectivity was observed for **7** and **8** (>95:5 dr, 97:3 er), for 4-bromophenyl derivative **6**, reduced diastereoselectivity was detected (80:20 dr, 97:3 er), potentially consistent with previous observations of β -lactone epimerisation [115]. Substitution within the isatin scaffold was altered next. The incorporation of an electron-donating 5-MeO-, as well as halogen substituents (5-Br and 6-Cl), were all tolerated, giving **9–11** in 79–84% yield and excellent selectivity (\geq 94:6 dr, 99:1 er). Variation of the N-substituent showed that an N-alloc-substituted product was also tolerated, giving **12** in 77% yield, 92:8 dr and >99:1 er.

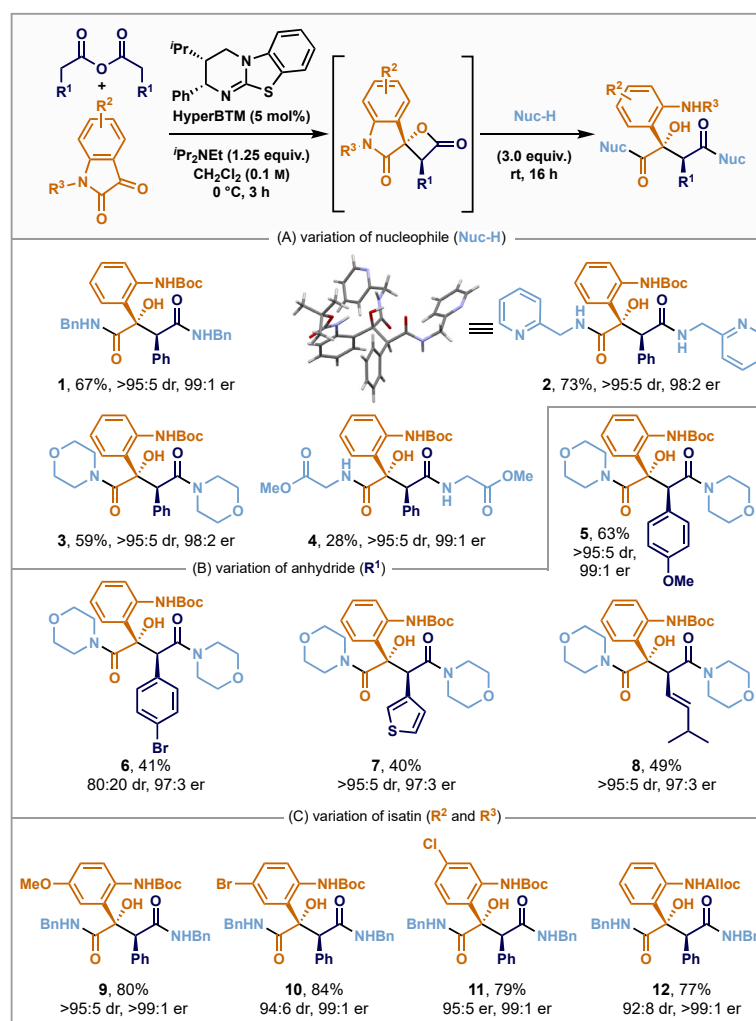


Figure 2. Reaction scope. **(A)** Variation of nucleophile, **(B)** variation of anhydride, **(C)** variation of isatin; typical reaction conditions: The respective isatin (0.50 mmol), homoanhydride (0.33 mmol) and HyperBTM (0.02 mmol) were dissolved in CH_2Cl_2 (8.5 mL), $i\text{Pr}_2\text{NEt}$ (0.42 mmol) was added, and the reaction was stirred for 3 h at 0 °C. The respective nucleophile (1.00 mmol) was added, and the reaction was stirred overnight at room temperature. Enantiomeric ratios (er) were determined by HPLC analysis on a chiral stationary phase. Diastereomeric ratios (dr) were obtained by ^1H NMR analysis of the purified reaction product as it could not be determined unambiguously from the crude reaction mixture. Yields are isolated yields.

3. Discussion

The proposed mechanism for the formation of malamide derivatives involves the previously reported enantioselective [2+2] cycloaddition strategy that is initiated through attack of the isothiurea Lewis base organocatalyst **HyperBTM** to phenylacetic anhydride, giving acyl ammonium species **13** (Figure 3). Deprotonation by the carboxylate counterion generates the C(1)-ammonium enolate intermediate **14** [36], which, based on previous computational studies with CF₃-ketones, undergoes a concerted asynchronous [2+2] cycloaddition with *N*-Boc isatin via pre-transition state intermediate **14**. Stereoselectivity is induced by the stereodirecting Ph group derived from the catalyst blocking the approach of the electrophile from the *Re*-face, with the enolate geometry rigidified by a $n_O \rightarrow \sigma^*_{S-C}$ chalcogen bond [116–123]. The β -lactol intermediate **15** then collapses to regenerate the isothiurea catalyst **HyperBTM** and the corresponding spirocyclic β -lactone-oxindole **16**. Upon addition of the nucleophilic amine (illustrated using benzylamine), it is assumed that ring-opening of the β -lactone is favoured to initially give **17**. From **17**, two potential pathways to product **1** can be envisaged. Simplistically, ring-opening of **17** may lead directly to **1**. However, a potential explanation for the observation that only double ring-opened malamide products are obtained when using one equivalent of benzylamine, even though an excess of β -lactone is present, could involve in situ intramolecular ring-opening of the oxindole motif from **17**, leading to a reactive pyrrolidindione intermediate **18**, that in turn is ring-opened to generate the observed malamide product **1**. We are currently unable to discriminate between these potential reaction pathways, but both lead to the observed product.

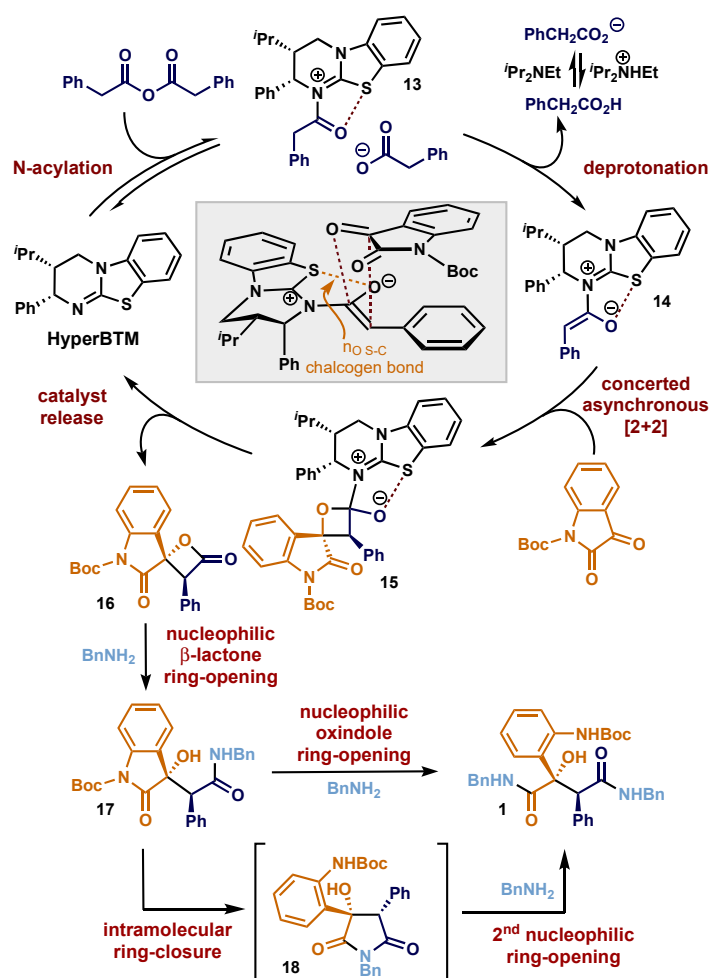


Figure 3. Illustrative proposed reaction mechanism for the generation of stereodefined malamide derivatives.

4. Materials and Methods

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Anhydrides and *N*-Boc isatin were prepared in accordance with the literature [30,124]. Reactions involving moisture-sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N₂ or Ar) using standard vacuum line techniques. Anhydrous and ethanol-free CH₂Cl₂ was obtained after passing through an alumina column (MBraun SPS-800). Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica), and visualisation was achieved using ultraviolet light (254 nm) and/or staining with aqueous KMnO₄ solution by heating. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated.

General procedure: The appropriate anhydride (1.5 equiv.), protected isatin (1.0 equiv.) and (2*S*,3*R*)-HyperBTM (5 mol%) were dissolved in anhydrous CH₂Cl₂ (0.04 M) and cooled to 0 °C. The reaction was started by the addition of *i*-Pr₂NEt (1.25 equiv.) and was stirred at 0 °C for 3 h. Then, the appropriate amine (3.0 equiv.) was added, and the mixture was allowed to warm to room temperature to stir overnight. Once complete, the solvent was removed and reduced pressure and the crude reaction mixture was directly subjected to flash silica column chromatography.

Preparation of *tert*-butyl (2-((2*S*,3*S*)-1,4-bis(benzylamino)-2-hydroxy-1,4-dioxo-3-phenylbutan-2-yl)phenyl)carbamate (1): Following the general procedure, phenylacetic anhydride (95.3 mg, 0.38 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (61.8 mg, 0.25 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (3.9 mg, 0.012 mmol, 5 mol%) and *i*-Pr₂NEt (54 µL, 0.31 mmol, 1.3 equiv.) in CH₂Cl₂ (0.04 M), followed by benzylamine (82 µL, 0.75 mmol, 3.0 equiv.) gave crude product that was purified by flash silica column chromatography (hexane:EtOAc 90:10 to 40:60) to give **1** as a pale yellow glass (91 mg, 77%). $[\alpha]_D^{20}$ –127.0 (*c* 2.3 in CHCl₃); **Chiral HPLC analysis** (Supplementary Materials), Chiralpak IA (95:5 *n*-hexane: *i*-PrOH, flow rate 2.0 mL·min^{–1}, 211 nm and 40 °C) *t*_R (2*S*,3*S*)-**1** 23.8 min, *t*_R (2*R*,3*R*)-**1** 28.1 min and >99:1 er; **IR** ν_{\max} (film) 3397, 3316, 3088, 3065, 3030, 2978, 2928, 2249, 1717, 1651, 1639, 1587, 1522, 1497, 1452, 1441, 1391, 1366, 1308, 1231, 1157, 1121, 1045, 1026, 961, 908, 831 and 754; **¹H NMR** (400 MHz, CDCl₃) δ_H : 1.46 (9H, s, OC(CH₃)₃), 4.25 (1H, dd, *J* 15.1, 5.4, NCH₂), 4.35 (1H, dd, *J* 15.2, 5.5, NCH₂), 4.47 (1H, dd, *J* 15.1, 6.2, NCH₂), 4.50 (1H, dd, *J* 15.2, 6.1, NCH₂), 4.73 (1H, br s, C(3)*H*), 6.86 (1H, dd, *J* 8.0, 7.2, Ar*H*), 7.05 (2H, d, *J* 7.4, Ar*H*), 7.11–7.39 (16H, m, Ar*H* and OH), 7.54 (1H, d, *J* 8.0, Ar*H*), 7.99 (1H, s, NH), 8.01 (1H, s, NH) and 9.15 (1H, br s, NH); **¹³C{¹H} NMR** (101 MHz, CDCl₃) δ_C : 28.5 (OC(CH₃)₃), 43.5 (NCH₂), 43.6 (NCH₂), 55.8 (C(2)), 79.4 (OC(CH₃)₃), 85.0 (C(3)*H*), 122.0 (ArCH), 126.3 (ArCH), 127.3 (ArCH), 127.4 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 128.0 (ArCH), 128.4 (ArCH), 128.7 (ArCH), 128.9 (ArCH), 129.3 (ArCH), 133.5 (ArC), 137.5 (ArC), 137.6 (ArC), 138.8 (ArC), 152.5 (C=O), 174.4 (C=O) and 175.2 (C=O); **HRMS** (ESI⁺) C₂₅H₃₇N₃O₅Na [M + Na]⁺ found 602.2622, requires 602.2625 (–0.5 ppm).

Preparation of *tert*-butyl (2-((2*S*,3*S*)-2-hydroxy-1,4-dioxo-3-phenyl-1,4-bis((pyridin-2-ylmethyl)amino)butan-2-yl)phenyl)carbamate (2): Following the general procedure, phenylacetic anhydride (127 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (81.6 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and *i*-Pr₂NEt (75 µL, 0.43 mmol, 1.3 equiv.) in CH₂Cl₂ (0.04 M), followed by 2-picolyamine (104 µL, 1.00 mmol, 3.0 equiv.), gave crude product that was purified by flash silica column chromatography (CH₂Cl₂:10% NH₄OH in MeOH 99:1 to 93:7) to give **2** as a clear glass (142 mg, 73%). $[\alpha]_D^{20}$ –138.5 (*c* 1.4 in CHCl₃); **Chiral HPLC analysis**, Chiralpak IA (80:20 *n*-hexane: *i*-PrOH, flow rate 1.0 mL·min^{–1}, 270 nm, 30 °C) *t*_R (2*R*,3*R*)-**2** 15.9 min, *t*_R (2*S*,3*S*)-**2** 18.5 min and 98:2 er; **IR** ν_{\max} (film) 3345, 2972, 1722, 1651, 1589, 1518, 1476, 1437, 1366, 1306, 1233, 1157, 1045, 1024 and 951; **¹H NMR** (500 MHz, CDCl₃) δ_H : 1.50 (9H, s, OC(CH₃)₃), 4.48 (1H, dd, *J* 16.3, 4.9, NCH₂), 4.52 (1H, dd, *J* 16.3, 5.1, NCH₂), 4.60 (1H, dd, *J* 16.5, 5.3, NCH₂), 4.67 (1H, dd, *J* 16.5, 5.9, NCH₂), 4.76 (1H, s, C(3)*H*), 6.90 (1H, ddd, *J* 8.3, 7.2, 1.4, Ar*H*), 7.01

(2H, m, ArH), 7.11–7.20 (9H, m, ArH), 7.23 (1H, d, J 7.8, ArH), 7.35 (1H, t, J 4.2, NH), 7.53 (1H, dd, J 8.1, 1.6, ArH), 7.59 (1H, ddd, J 7.9, 7.7, 1.9, ArH), 7.62 (1H, ddd, J 7.9, 7.8, 1.9, ArH), 7.92 (1H, br s, NH), 8.47 (1H, ddd, J 4.9, 1.8, 0.9, ArH), 8.52 (1H, ddd, J 4.9, 1.8, 1.0, ArH) and 9.22 (1H, br s, NH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 28.5 ($\text{C}(\text{CH}_3)_3$), 44.4 (NCH_2), 44.8 (NCH_2), 79.4 ($\text{OC}(\text{CH}_3)_3$), 121.2 (ArCH), 121.6 (ArCH), 122.2 (ArCH), 122.4 (ArCH), 122.6 (ArC), 126.3 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 128.7 (ArCH), 129.3 (ArCH), 133.5 (ArC), 136.7 (ArCH), 136.8 (ArCH), 138.9 (ArC), 148.9 (ArCH), 149.1 (ArCH), 155.4 (ArC), 156.5 (ArC), 174.8 (C=O) and 175.0 (C=O); HRMS (ESI^+) $\text{C}_{33}\text{H}_{35}\text{N}_5\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$ found 604.2522, requires 604.2530 (−1.4 ppm).

Preparation of *tert*-butyl 2-((2*S*,3*S*)-2-hydroxy-1,4-dimorpholino-1,4-dioxo-3-phenylbutan-2-yl)phenyl carbamate (3): Following the general procedure, phenylacetic anhydride (127 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (81.6 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and $i\text{Pr}_2\text{NEt}$ (75 μL , 0.43 mmol, 1.3 equiv.) in CH_2Cl_2 (0.04 M), followed by morpholine (87 μL , 1.0 mmol, 3.0 equiv.), gave a crude product that was purified by flash silica column chromatography (CH_2Cl_2 :10% NH_4OH in MeOH 99:1 to 95:5) to give **3** as a clear glass (106 mg, 59%). $[\alpha]_{\text{D}}^{20}$ −176.3 (c 0.4 in CHCl_3); **Chiral HPLC analysis**, Chiralpak IA (98:2 *n*-hexane: $i\text{PrOH}$, flow rate 1.5 $\text{mL}\cdot\text{min}^{-1}$, 254 nm, 40 °C) t_{R} (2*S*,3*S*)-**3** 10.9 min, t_{R} (2*R*,3*R*)-**3** 21.3 min and 98:2 er; **IR** ν_{max} (film) 3339, 2855, 1722, 1632, 1614, 1587, 1529, 1439, 1366, 1304, 1242, 1227, 1157, 1111 and 1045; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.98–3.06 (2H, m, OCH_2), 3.26–3.33 (2H, m, NCH_2), 3.44 (1H, ddd, J 11.4, 5.8, 2.9, OCH_2), 3.49–3.67 (7H, m, NCH_2 and OCH_2), 3.71–3.86 (4H, m, NCH_2 and OCH_2), 4.41 (1H, s, $\text{C}(3)\text{H}$), 6.82 (2H, d, J 7.1, ArH), 6.95 (1H, ddd, J 8.1, 7.2, 1.3, ArH), 7.08 (1H, dd, J 7.9, 1.6, ArH), 7.13–7.22 (4H, m, ArH), 8.03 (1H, d, J 8.4, ArH), 8.63 (1H, s, OH) and 8.91 (1H, s, NH); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 28.4 ($\text{C}(\text{CH}_3)_3$), 42.3 (NCH_2), 43.5 (NCH_2), 46.2 (NCH_2), 47.2 (NCH_2), 55.1 ($\text{C}(3)\text{H}$), 66.0 (OCH_2), 66.5 (OCH_2), 66.6 (OCH_2), 79.2 ($\text{OC}(\text{CH}_3)_3$), 86.6 ($\text{C}(2)$), 119.2 (ArCH), 121.4 (ArCH), 123.0 (ArC), 125.7 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.9 (ArCH), 129.6 (ArCH), 132.6 (ArC), 139.3 (ArC), 151.9 (C=O), 171.8 (C=O) and 174.5 (C=O); HRMS (ESI^+) $\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$ found 562.2515, requires 562.2524 (−1.6 ppm).

Preparation of dimethyl 2,2'-(((2*S*,3*S*)-2-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-hydroxy-3-phenylsuccinyl)bis(azanediyl))diacetate (4): Following the general procedure, phenylacetic anhydride (127 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (81.6 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and $i\text{Pr}_2\text{NEt}$ (75 μL , 0.43 mmol, 1.3 equiv.) in CH_2Cl_2 (0.04 M), followed by glycine methyl ester hydrochloride (126 mg, 1.00 mmol, 3.0 equiv.) and $i\text{Pr}_2\text{NEt}$ (170 μL , 1.00 mmol, 3.0 equiv.), gave a crude product that was purified by flash silica column chromatography (hexane:EtOAc 100:0 to 0:100) to give **4** as a colourless glass (50 mg, 28%). $[\alpha]_{\text{D}}^{20}$ −106.9 (c 1.5 in CHCl_3); **Chiral HPLC analysis**, Chiralpak IA (70:30 *n*-hexane: $i\text{PrOH}$, flow rate 1.0 $\text{mL}\cdot\text{min}^{-1}$, 254 nm, 30 °C) t_{R} (2*S*,3*S*)-**4** 6.7 min, t_{R} (2*R*,3*R*)-**4** 12.7 min and 99:1 er; **IR** ν_{max} (film) 3335, 2978, 1749, 1728, 1655, 1589, 1526, 1443, 1368, 1308, 1234, 1209, 1163, 1047, 1026 and 756; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.46 (9H, s, $\text{OC}(\text{CH}_3)_3$), 3.69 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.92–4.08 (4H, m, NCH_2), 4.64 (1H, br s, OH), 6.72 (1H, br s, NH), 6.84 (1H, ddd, J 8.2, 7.2, 1.3, ArH), 6.94–7.00 (2H, m, ArH), 7.09–7.19 (4H, m, ArH), 7.37 (1H, br s, ArH), 7.42 (1H, dd, J 8.1, 1.5, ArH), 7.89 (1H, br s, NH) and 9.01 (1H, br s, NH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 28.6 ($\text{C}(\text{CH}_3)_3$), 41.5 (NCH_2), 41.7 (NCH_2), 52.4 (OCH_3), 52.5 (OCH_3), 79.5 ($\text{OC}(\text{CH}_3)_3$), 120.9 (ArC), 122.2 (ArCH), 126.4 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.9 (ArCH), 129.4 (ArCH), 133.0 (ArCH), 138.5 (ArC), 152.6 (ArC), 169.5 (C=O), 169.6 (C=O), 174.7 (C=O) and 175.2 (C=O); HRMS (ESI^+) $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_9\text{Na}$ $[\text{M} + \text{Na}]^+$ found 566.2108, requires 566.2109 (−0.2 ppm).

Preparation of *tert*-butyl 2-((2*S*,3*S*)-2-hydroxy-3-(*p*-anisyl)-1,4-dimorpholino-1,4-dioxobutan-2-yl)phenyl carbamate (5): Following the general procedure, *p*-anisylacetic anhydride (157 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (81.6 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and $i\text{Pr}_2\text{NEt}$ (75 μL , 0.43 mmol,

1.3 equiv.) in CH_2Cl_2 (0.04 M), followed by morpholine (87 μL , 1.0 mmol, 3.0 equiv.), gave a crude product that was purified by flash silica column chromatography (hexane:EtOAc 70:30 to 20:80) to give **5** as clear glass (120 mg, 63%). $[\alpha]_{\text{D}}^{20} -108.0$ (c 1.4 in CHCl_3); **Chiral HPLC analysis**, Chiralpak IA (98:2 *n*-hexane: i PrOH, flow rate $1.5 \text{ mL} \cdot \text{min}^{-1}$, 254 nm, 40°C) t_{R} (2*S*,3*S*)-**5** 12.3 min, t_{R} (2*R*,3*R*)-**5** 28.1 min and 99:1 er; **IR** ν_{max} (film) 3337, 2972, 2856, 1722, 1632, 1611, 1589, 1512, 1439, 1366, 1302, 1242, 1159, 1113, 1034 and 910; **^1H NMR** (400 MHz, CDCl_3) δ_{H} : 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.99 (1H, ddd, J 10.9, 7.5, 2.8, OCH_2), 3.05 (1H, ddd, J 11.1, 7.81, 2.9, OCH_2), 3.24–3.34 (2H, m, NCH_2), 3.40–3.64 (10H, m, NCH_2 and OCH_2), 3.72 (3H, s, OCH_3), 3.74–3.86 (2H, m, NCH_2), 4.35 (1H, s, $\text{C}(3)\text{H}$), 6.64–6.74 (4H, m, *ArH*), 6.94 (1H, ddd, J 8.1, 7.2, 1.3, *ArH*), 7.07 (1H, dd, J 7.9, 1.5, *ArH*), 7.14–7.22 (1H, m, *ArH*), 8.07 (1H, d, J 8.5, *ArH*), 8.52 (1H, s, *OH*) and 8.91 (1H, s, *NH*); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (101 MHz, CDCl_3) δ_{C} : 28.3 ($\text{C}(\text{CH}_3)_3$), 42.3 (NCH_2), 43.5 (NCH_2), 46.2 (NCH_2), 47.2 (NCH_2), 54.3 ($\text{C}(3)\text{H}$), 55.0 (OCH_3), 66.0 (OCH_2), 66.1 (OCH_2), 66.5 (OCH_2), 66.6 (OCH_2), 79.2 ($\text{OC}(\text{CH}_3)_3$), 86.6 ($\text{C}(2)$), 113.8 (*ArCH*), 119.2 (*ArCH*), 121.4 (*ArCH*), 123.2 (*ArC*), 124.3 (*ArC*), 125.8 (*ArCH*), 128.9 (*ArCH*), 130.7 (*ArCH*), 139.4 (*ArC*), 152.1 ($\text{C}=\text{O}$), 159.1 (*ArC*), 171.9 ($\text{C}=\text{O}$) and 174.8 ($\text{C}=\text{O}$); **HRMS** (ESI^+) $\text{C}_{30}\text{H}_{39}\text{N}_3\text{O}_8\text{Na}$ $[\text{M} + \text{Na}]^+$ found 592.2624, requires 592.2629 (-0.9 ppm).

Preparation of *tert*-butyl (2-((2*S*,3*S*)-1,4-bis(benzylamino)-3-(4-bromophenyl)-2-hydroxy-1,4-dioxobutan-2-yl)phenyl)carbamate (6): Following the general procedure, 2-(4-bromophenyl) acetic anhydride (206 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (81.6 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and i Pr₂NEt (75 μL , 0.43 mmol, 1.3 equiv.) in CH_2Cl_2 (0.04 M) followed by benzylamine (109 μL , 1.00 mmol, 3.0 equiv.) gave a crude product that was purified by flash silica column chromatography (hexane:EtOAc 100:0 to 70:30) to give **6** as an inseparable mixture of *anti* and *syn* diastereoisomers (80:20 dr) (88 mg, 41%) as a pale yellow glass. $[\alpha]_{\text{D}}^{20} -56.2$ (c 1.3 in CHCl_3); **Chiral HPLC analysis**, Chiralpak AD-H (70:30 *n*-hexane: i PrOH, flow rate $1.0 \text{ mL} \cdot \text{min}^{-1}$, 211 nm, 30°C) t_{R} (2*R*,3*R*)-**6** 9.7 min, t_{R} (2*S*,3*S*)-**6** 19.7 min and 97:3 er; t_{R} (2*S*,3*R*)-**6** 11.4 min, t_{R} (2*R*,3*S*)-**6** 15.0 min and 77:23 er; **IR** ν_{max} (film) 3312, 3030, 2976, 2930, 2357, 2320, 1717, 1647, 1587, 1522, 1489, 1443, 1366, 1308, 1234, 1161, 1047, 1026 and 1013; **HRMS** (ESI^+) $\text{C}_{35}\text{H}_{36}\text{O}_5\text{N}_3\text{BrNa}$ $[\text{M} + \text{Na}]^+$ found 680.1712, requires 680.1731 (-2.8 ppm); **NMR data for major diastereoisomer**: **^1H NMR** (500 MHz, CDCl_3) δ_{H} : 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 4.16–4.53 (4H, m, CH_2N), 4.66 (1H, br s, *OH*), 6.77–6.90 (4H, m, *ArH*), 7.06–7.29 (14H, m, *ArH*), 7.99 (2H, br s, $2 \times \text{NH}$) and 9.12 (1H, br s, *NH*); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (126 MHz, CDCl_3) δ_{C} : 28.6 ($\text{C}(\text{CH}_3)_3$), 43.6 (CH_2N), 43.6 (CH_2N), 55.4 ($\text{C}(3)\text{H}$), 79.7 ($\text{C}(\text{CH}_3)_3$), 86.6 ($\text{C}(2)$), 122.3 (*ArCH*), 126.2 (*ArCH*), 127.1 (*ArCH*), 127.3 (*ArCH*), 127.3 (*ArCH*), 127.4 (*ArCH*), 127.6 (*ArCH*), 127.7 (*ArCH*), 128.7 (*ArCH*), 128.8 (*ArCH*), 129.3 (*ArC*), 131.0 (*ArCH*), 131.3 (*ArCH*), 131.7 (*ArC*), 132.0 (*ArC*), 132.7 (*ArC*), 136.9 (*ArC*), 137.3 (*ArC*), 137.5 (*ArC*), 152.5 ($\text{C}=\text{O}$), 174.4 ($\text{C}=\text{O}$) and 174.8 ($\text{C}=\text{O}$); **NMR data for minor diastereoisomer**: **^1H NMR** (500 MHz, CDCl_3) (*selected*) δ_{H} : 1.52 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.81–3.88 (1H, m, NCH_2), 4.00–4.07 (1H, m, NCH_2), 4.97–4.97 (1H, m, NCH_2), 6.57–6.62 (2H, m, *ArH*), 7.34–7.39 (1H, m, *ArH*), 7.65–7.70 (1H, m, *ArH*), 7.74–7.78 (1H, m, *ArH*) and 10.03 (1H, br s, *NH*); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (126 MHz, CDCl_3) (*selected*) δ_{C} : 28.7 ($\text{C}(\text{CH}_3)_3$), 43.1 (CH_2N), 43.7 (CH_2N), 80.4 ($\text{C}(\text{CH}_3)_3$), 86.6 ($\text{C}(2)$), 122.7 (*ArCH*), 125.1 (*ArCH*), 128.7 (*ArCH*), 133.1 (*ArC*), 136.2 (*ArC*), 155.0 ($\text{C}=\text{O}$), 171.8 ($\text{C}=\text{O}$) and 172.4 ($\text{C}=\text{O}$).

Preparation of *tert*-butyl (2-((2*S*,3*S*)-2-hydroxy-1,4-dimorpholino-1,4-dioxo-3-(thiophen-3-yl)butan-2-yl)phenyl) carbamate (7): Following the general procedure, (thiophen-3-yl)acetic anhydride (133 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (81.6 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and i Pr₂NEt (75 μL , 0.43 mmol, 1.3 equiv.) in CH_2Cl_2 (0.04 M), followed by morpholine (87 μL , 1.0 mmol, 3.0 equiv.), gave a crude product that was purified by flash silica column chromatography (hexane:EtOAc 50:50 to 10:90) to give **7** as clear glass (73 mg, 40%). $[\alpha]_{\text{D}}^{20} -151.8$ (c 0.9 in CHCl_3); **Chiral HPLC analysis**, Chiralpak IA (98:2 *n*-hexane: i PrOH, flow rate $1.5 \text{ mL} \cdot \text{min}^{-1}$, 211 nm, 40°C) t_{R} (2*S*,3*S*)-**7** 13.1 min, t_{R} (2*R*,3*R*)-**7** 26.5 min and 98:2 er; **IR** ν_{max} (film) 3335, 2857, 1721, 1632, 1614, 1587, 1530, 1439, 1365, 1233, 1157, 1111, 1045 and 995; **^1H NMR** (400 MHz,

CDCl₃) δ_H : 1.45 (9H, s, OC(CH₃)₃), 3.00 (1H, ddd, *J* 10.8, 7.4, 2.8, OCH₂), 3.12 (1H, ddd, *J* 11.1, 7.8, 2.9, OCH₂), 3.26–3.36 (2H, m, NCH₂), 3.41–3.46 (1H, m, OCH₂), 3.50–3.63 (6H, m, NCH₂ and OCH₂), 3.67–3.87 (5H, m, NCH₂ and OCH₂), 4.55 (1H, s, C(3)H), 6.43 (1H, dd, *J* 5.0, 1.3, ArH), 6.82 (1H, dd, *J* 3.1, 1.3, ArH), 6.95 (1H, ddd, *J* 8.1, 7.2, 1.3, ArH), 7.05 (1H, dd, *J* 7.9, 1.5, ArH), 7.12 (1H, dd, *J* 4.9, 3.0, ArH), 7.21 (1H, ddd, *J* 8.5, 7.1, 1.5, ArH), 8.12 (1H, d, *J* 8.4, ArH), 8.66 (1H, s, OH) and 9.06 (1H, s, NH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C : 28.4 (C(CH₃)₃), 42.3 (NCH₂), 43.5 (NCH₂), 46.3 (NCH₂), 47.1 (NCH₂), 50.5 (C(3)H), 66.0 (OCH₂), 66.1 (OCH₂), 66.5 (OCH₂), 66.6 (OCH₂), 79.4 (OC(CH₃)₃), 86.3 (C(2)), 119.3 (ArCH), 121.5 (ArCH), 123.3 (ArC), 124.5 (ArCH), 125.4 (ArCH), 125.6 (ArCH), 128.3 (ArCH), 129.0 (ArCH), 132.7 (ArC), 139.4 (ArC), 152.3 (C=O), 171.6 (C=O) and 174.6 (C=O); HRMS (ESI⁺) C₂₇H₃₅N₃O₇SNa [M + Na]⁺ found 568.2083, requires 568.2088 (−0.9 ppm).

Preparation of *tert*-butyl (2-((2*S*,3*S*,*E*)-1-(benzylamino)-3-(benzylcarbamoyl)-2-hydroxy-6-methyl-1-oxohept-4-en-2-yl)phenyl)carbamate (8): Following the general procedure, (*E*)-5-methylhex-3-enoic anhydride (119 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 2,3-dioxindoline-1-carboxylate (81.6 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and ⁱPr₂NEt (75 μ L, 0.43 mmol, 1.3 equiv.) in CH₂Cl₂ (0.04 M) followed by benzylamine (109 μ L, 1.00 mmol, 3.0 equiv.) gave crude product that was purified by flash silica column chromatography (hexane:EtOAc 100:0 to 70:30) to give **8** (93 mg, 49%) as a colourless solid. **mp** 80–82 °C; [α]_D²⁰ −89.7 (*c* 0.7 in CHCl₃); **Chiral HPLC analysis**, Chiralpak IA (97:3 *n*-hexane: ⁱPrOH, flow rate 1.0 mL·min^{−1}, 211 nm, 40 °C) *t*_R (2*S*,3*S*)-**8** 30.6 min, *t*_R (2*R*,3*R*)-**8** 34.4 min and 97:3 er; **IR** ν_{\max} (film) 3312, 2961, 2928, 2359, 2344, 1732, 1717, 1636, 1589, 1558, 1522, 1437, 1364, 1306, 1234, 1161, 1045, 1026 and 972; **¹H NMR** (400 MHz, CDCl₃) δ_H : 0.75 (3H, d, *J* 6.7, CHCH₃), 0.80 (3H, d, *J* 6.8, CHCH₃), 1.53 (9H, s, C(CH₃)₃), 2.06–2.16 (1H, m, CH(CH₃)₂), 4.08–4.17 (1H, m, C(3)H), 4.25–4.38 (2H, m, CH^AH^BN and CH^AH^BN), 4.46 (1H, dd, *J* 15.1, 6.3, CH^AH^BN), 4.56 (1H, dd, *J* 15.1, 6.3, CH^AH^BN), 5.34 (1H, dd, *J* 15.5, 6.5, C(5)H), 5.45 (1H, dd, *J* 15.5, 8.7, C(4)H), 6.68 (1H, br s, NH), 6.93 (1H, t, *J* 7.4, ArH), 7.11–7.16 (2H, m, ArH), 7.21–7.36 (9H, m, ArH), 7.40 (1H, br s, NH), 7.57 (2H, d, *J* 8.1, ArH), 8.07 (1H, br s, OH) and 9.76 (1H, br s, NH); **¹³C{¹H} NMR** (126 MHz, CDCl₃) δ_C : 21.8 (CHCH₃), 22.1 (CHCH₃), 28.6 (C(CH₃)₃), 31.2 (CH(CH₃)₂), 43.4 (CH₂N), 43.5 (CH₂N), 53.6 (C(3)H), 79.9 (C(CH₃)₃), 83.1 (C(2)OH), 119.4 (C(4)H), 121.7 (ArC), 122.6 (2 × ArCH), 126.4 (ArCH), 127.3 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 127.7 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 137.5 (ArC), 137.6 (ArC), 137.9 (ArC), 144.5 (C(5)H), 153.2 (C=O), 174.6 (C=O) and 175.5 (C=O); **HRMS** (ESI⁺) C₃₄H₄₁O₅N₃Na [M + Na]⁺ found 594.2928, requires 594.2938 (−1.7 ppm).

Preparation of *tert*-butyl (2-((2*S*,3*S*)-1,4-bis(benzylamino)-2-hydroxy-1,4-dioxo-3-phenylbutan-2-yl)-4-methoxyphenyl)carbamate (9): Following the general procedure, phenylacetic anhydride (127 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 5-methoxy-2,3-dioxindoline-1-carboxylate (91.5 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and ⁱPr₂NEt (75 μ L, 0.43 mmol, 1.3 equiv.) in CH₂Cl₂ (0.04 M) followed by benzylamine (109 μ L, 1.00 mmol, 3.0 equiv.) gave crude product that was purified by flash silica column chromatography (hexane:EtOAc 95:5 to 50:50) to give **9** (160 mg, 80%) as a colourless solid. **mp** 78–80 °C; [α]_D²⁰ −116.8 (*c* 1.0 in CHCl₃); **Chiral HPLC analysis**, Chiralpak IA (90:10 *n*-hexane: ⁱPrOH, flow rate 1.0 mL·min^{−1}, 211 nm, 30 °C) *t*_R (2*S*,3*S*)-**9** 29.0 min, *t*_R (2*R*,3*R*)-**9** 46.5 min, >99:1 er; **IR** ν_{\max} (film) 3318, 3063, 3030, 2976, 2932, 1719, 1653, 1522, 1454, 1412, 1366, 1288, 1227, 1163, 1042, 1026 and 810; **¹H NMR** (400 MHz, CDCl₃) δ_H : 1.45 (9H, s, C(CH₃)₃), 3.63 (3H, s, OCH₃), 4.25 (1H, dd, *J* 15.1, 5.4, CH^AH^BN), 4.34 (1H, dd, *J* 15.1, 5.5, CH^AH^BN), 4.40–4.53 (2H, m, CH₂N), 4.76 (1H, br s, OH), 6.72 (1H, dd, *J* 9.1, 3.0, ArH), 7.05–7.19 (10H, m, ArH), 7.19–7.29 (7H, m, ArH), 7.29–7.38 (1H, m, NH), 7.81 (1H, br s, NH) and 8.95 (1H, br s, NH); **¹³C{¹H} NMR** (126 MHz, CDCl₃) δ_C : 28.6 (C(CH₃)₃), 43.5 (CH₂N), 43.5 (CH₂N), 55.4 (OCH₃), 77.4 (CH), 79.3 (C(CH₃)₃), 83.6 (COH), 112.0 (ArCH), 113.7 (ArCH), 122.4 (ArC), 127.3 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 127.5 (ArCH), 128.0 (ArCH), 128.2 (ArCH), 128.7 (ArCH), 128.7 (ArCH), 129.4 (ArCH), 131.4 (ArC), 133.5 (ArC), 137.4 (ArC), 137.6 (ArC), 152.9 (C=O), 154.8 (ArC), 174.6 (C=O) and

175.1 (C=O); **HRMS** (ESI⁺) C₃₆H₃₉O₆N₃Na [M + Na]⁺ found 632.2721, requires 632.2731 (−1.6 ppm).

Preparation of *tert*-butyl (2-((2*S*,3*S*)-1,4-bis(benzylamino)-2-hydroxy-1,4-dioxo-3-phenylbutan-2-yl)-4-bromophenyl)carbamate (10): Following the general procedure, phenylacetic anhydride (127 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 5-bromo-2,3-dioxindoline-1-carboxylate (108 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and ⁱPr₂NEt (75 µL, 0.43 mmol, 1.3 equiv.) in CH₂Cl₂ (0.04 M), followed by benzylamine (109 µL, 1.00 mmol, 3.0 equiv.), gave a crude product that was purified by flash silica column chromatography (hexane:EtOAc 100:0 to 70:30) to give **10** as an inseparable mixture of *anti* and *syn* diastereoisomers (94:6 dr) (182 mg, 84%) and as a colourless solid. **mp** 77–79 °C; [α]_D²⁰ −88.4 (c 0.9 in CHCl₃); **Chiral HPLC analysis**, Chiralpak IA (90:10 *n*-hexane: ⁱPrOH, flow rate 1.0 mL·min^{−1}, 211 nm, 30 °C) t_R (2*S*,3*S*)-**10** 12.2 min, t_R (2*R*,3*R*)-**10** 30.7 min and 99:1 er; **IR** ν_{max} (film) 3316, 3030, 2978, 2928, 2357, 2320, 1717, 1647, 1454, 1393, 1366, 1300, 1233, 1161, 1049, 1026 and 824; **¹H NMR** (500 MHz, CDCl₃) δ_H: 1.44 (9H, s, C(CH₃)₃), 4.21–4.44 (3H, m, CH₂N), 4.51 (1H, dd, *J* 15.1, 6.2, CH^AH^BN), 4.67 (1H, br s, C(3)H), 7.04–7.33 (17H, m, ArH), 7.68 (1H, d, *J* 2.4, ArH), 7.90 (1H, br s, NH), 8.07 (1H, br s, NH) and 9.03 (1H, br s, NH); **¹³C{¹H} NMR** (126 MHz, CDCl₃) δ_C: 28.5 (C(CH₃)₃), 43.5 (CH₂N), 43.6 (CH₂N), 56.5 (C(3)H), 79.7 (C(CH₃)₃), 84.9 (COH), 114.8 (ArC), 121.3 (ArCH), 127.4 (2 × ArCH), 127.6 (ArCH), 127.6 (ArCH), 128.2 (ArCH), 128.4 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 129.4 (ArCH), 131.8 (ArC), 133.2 (ArC), 137.3 (ArC), 137.5 (ArC), 152.2 (C=O), 174.0 (C=O) and 175.0 (C=O); **HRMS** (ESI⁺) C₃₅H₃₆O₅N₃BrNa [M + Na]⁺ found 680.1723, requires 680.1731 (−1.2 ppm).

Preparation of *tert*-butyl (2-((2*S*,3*S*)-1,4-bis(benzylamino)-2-hydroxy-1,4-dioxo-3-phenylbutan-2-yl)-5-chlorophenyl)carbamate (11): Following the general procedure, phenylacetic anhydride (127 mg, 0.50 mmol, 1.5 equiv.), *tert*-butyl 6-chloro-2,3-dioxindoline-1-carboxylate (93.0 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and ⁱPr₂NEt (75 µL, 0.43 mmol, 1.3 equiv.) in CH₂Cl₂ (0.04 M), followed by benzylamine (109 µL, 1.00 mmol, 3.0 equiv.), gave a crude product that was purified by flash silica column chromatography (hexane:EtOAc 100:0 to 70:30) to give **11** as an inseparable mixture of *anti* and *syn* diastereoisomers (95:5 dr) (160 mg, 79%) and as a colourless solid. **mp** 83–85 °C; [α]_D²⁰ −109.0 (c 0.7 in CHCl₃); **Chiral HPLC analysis**, Chiralpak ID (90:10 *n*-hexane: ⁱPrOH, flow rate 1.0 mL·min^{−1}, 254 nm, 30 °C) t_R (2*S*,3*S*)-**11** 10.1 min, t_R (2*R*,3*R*)-**11** 28.6 min and 99:1 er; **IR** ν_{max} (film) 3319, 3063, 3030, 2978, 2930, 1730, 1717, 1653, 1578, 1522, 1454, 1414, 1366, 1281, 1233, 1161, 1051, 1028, 860; **¹H NMR** (500 MHz, CDCl₃) δ_H: 1.46 (9H, s, C(CH₃)₃), 4.27 (1H, dd, *J* 15.0, 5.5, CH^AH^BN), 4.36 (1H, dd, *J* 15.1, 5.7, CH^AH^BN), 4.41–4.52 (2H, m, CH₂N), 4.61 (1H, br s, CH), 6.83 (1H, dd, *J* 8.6, 2.2, ArH), 6.99–7.07 (2H, m, ArH), 7.11–7.18 (4H, m, ArH), 7.18–7.36 (10H, m, ArH), 7.44–7.50 (1H, m, ArH), 8.12 (2H, br s, NH) and 9.14 (1H, br s, NH); **¹³C{¹H} NMR** (126 MHz, CDCl₃) δ_C: 28.5 (C(CH₃)₃), 43.5 (CH₂N), 43.6 (CH₂N), 56.4 (CH), 79.8 (C(CH₃)₃), 84.8 (COH), 121.8 (ArCH), 127.3 (ArCH), 127.4 (ArCH), 127.6 (ArCH), 127.6 (ArCH), 128.2 (ArCH), 128.4 (ArCH), 128.7 (2 × ArCH), 129.3 (ArCH), 133.2 (ArC), 134.8 (ArC), 137.3 (ArC), 137.5 (ArC), 140.2 (ArC), 152.1 (C=O), 174.0 (C=O) and 175.0 (C=O); **HRMS** (ESI⁺) C₃₅H₃₆O₅N₃ClNa [M + Na]⁺ found 636.2232, requires 636.2236 (−0.6 ppm).

Preparation of allyl (2-((2*S*,3*S*)-1,4-bis(benzylamino)-2-hydroxy-1,4-dioxo-3-phenylbutan-2-yl)phenyl)carbamate (12): Following the general procedure, phenylacetic anhydride (127 mg, 0.50 mmol, 1.5 equiv.), allyl 2,3-dioxindoline-1-carboxylate (76.3 mg, 0.33 mmol, 1.0 equiv.), (2*S*,3*R*)-HyperBTM (5.1 mg, 0.017 mmol, 5 mol%) and ⁱPr₂NEt (75 µL, 0.43 mmol, 1.3 equiv.) in CH₂Cl₂ (0.04 M) followed by benzylamine (109 µL, 1.00 mmol, 3.0 equiv.), gave a crude product that was purified by flash silica column chromatography (hexane:EtOAc 90:10 to 70:30) to give **12** as an inseparable mixture of *anti* and *syn* diastereoisomers (92:8 dr) (143 mg, 77%) and as a colourless solid. **mp** 73–75 °C; [α]_D²⁰ −115.6 (c 1.0 in CHCl₃); **Chiral HPLC analysis**, Chiralpak ID (60:40 *n*-hexane: ⁱPrOH, flow rate 1.0 mL·min^{−1}, 254 nm, 40 °C) t_R (2*S*,3*S*)-**12** 6.4 min, t_R (2*R*,3*R*)-**12** 12.3 min, and >99:1 er; **IR** ν_{max} (film) 3316, 3063,

3030, 1732, 1717, 1647, 1589, 1526, 1447, 1308, 1219 and 1045; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 4.26 (1H, dd, J 15.2, 5.5, $\text{CH}^{\text{A}}\text{H}^{\text{B}}\text{N}$), 4.33 (1H, dd, J 15.2, 5.9, $\text{CH}^{\text{A}}\text{H}^{\text{B}}\text{N}$), 4.40–4.58 (4H, m, CH_2O and CH_2N), 4.72 (1H, br s, CH), 5.22–5.28 (1H, m, $\text{CH}=\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 5.31–5.38 (1H, m, $\text{CH}=\text{CH}^{\text{A}}\text{H}^{\text{B}}$), 5.88–6.02 (1H, m, $\text{CH}=\text{CH}_2$), 6.87–6.93 (1H, m, ArH), 7.00–7.06 (2H, m, ArH), 7.11–7.31 (14H, m, ArH), 7.33–7.46 (1H, m, NH), 7.52–7.59 (1H, m, ArH), 7.89–7.96 (1H, m, ArH), 8.09 (1H, br s, NH) and 9.38 (1H, br s, NH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 43.4 (CH_2N), 43.5 (CH_2N), 56.2 (CH), 65.3 (CH_2O), 85.0 (COH), 117.6 ($\text{CH}=\text{CH}_2$), 120.6 (ArCH), 122.6 (ArCH), 126.3 (ArC), 127.3 (ArCH), 127.4 (ArCH), 127.5 (ArCH), 127.5 (ArCH), 127.8 (ArCH), 128.3 (ArCH), 128.7 ($2 \times \text{ArCH}$), 129.0 (ArCH), 129.3 (ArCH), 133.0 ($\text{CH}=\text{CH}_2$), 133.5 (ArC), 137.4 (ArC), 137.6 (ArC), 152.9 (C=O), 174.3 (C=O) and 175.1 (C=O); HRMS (ESI^+) $\text{C}_{34}\text{H}_{33}\text{O}_5\text{N}_3\text{Na}$ $[\text{M} + \text{Na}]^+$ found 586.2306, requires 586.2312 (−1.1 ppm).

5. Conclusions

In conclusion, this manuscript demonstrates an effective one-pot process for the synthesis of stereodefined functionalised malamides through employing an enantioselective organocatalytic [2+2]-cycloaddition of C(1)-ammonium enolates with isatin derivatives and consecutive double ring-opening of the corresponding β -lactone-spirooxindole. The malamide products can be isolated in moderate to good yields (28% to 84% yield) and excellent enantio- and diastereo-selectivity (up to >95:5 dr, >99:1 er). This route exemplifies a simple and efficient one-pot synthetic protocol to access enantiomerically pure malamide materials using isothiureas as Lewis base catalysts.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/molecules29153635/s1>, Full experimental procedures, characterisation data, NMR spectra and HPLC chromatograms for all new compounds. Table S1: X-ray data for 2; Figure S1: ORTEP and Sketch of X-ray of 2. References [30,124–128] are cited in the Supplementary Materials.

Author Contributions: Conceptualisation, A.D.S. and K.K.; methodology A.D.S., K.K. and A.J.N.; investigation, A.J.N., G.W. and J.R.; formal analysis (X-ray), A.P.M. and D.B.C.; writing—original draft preparation, K.K.; writing—review and editing, A.D.S. and K.K.; supervision, A.J.N.; project administration, A.D.S.; funding acquisition, A.D.S. All authors have read and agreed to the published version of the manuscript.

Funding: The research leading to these results has received funding from the EPSRC (K.K., EP/T023643/1) and the EaSI-CAT Centre for Doctoral Training (A.J.N.). A.D.S. and K.K. Thank the EPSRC Programme Grant “Boron: Beyond the Reagent” (EP/W007517) for support.

Data Availability Statement: All data (experimental procedures and characterisation data) that support the findings of this study are available within the article and its Supplementary Information. Crystallographic data for compound 2 have been deposited with the Cambridge Crystallographic Data Centre under deposition number 2364405. The research data supporting this publication can be accessed from the St Andrews Research Portal PURE ID 303816895; “One-pot Access to Functionalised Malamides via Organocatalytic Enantioselective Formation and Double Ring-opening of Spirocyclic β -Lactone-Oxindoles” <https://doi.org/10.17630/c2137162-53d3-4722-bc51-ae2ee579ce61>.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Klimek-Szzykutowicz, M.; Szopa, A.; Ekiert, H. Citrus limon (Lemon) Phenomenon—A Review of the Chemistry, Pharmacological Properties, Applications in the Modern Pharmaceutical, Food, and Cosmetics Industries, and Biotechnological Studies. *Plants* **2020**, *9*, 119. [CrossRef] [PubMed]
2. Ghai, M.; Agnihotri, N.; Kumar, V.; Agnihotri, R.; Kumar, A.; Sahu, K. Global organic acids production and their industrial applications. *Phys. Sci. Rev.* **2023**. [CrossRef]
3. Zou, X.; Cheng, C.; Feng, J.; Song, X.; Lin, M.; Yang, S.-T. Biosynthesis of polymalic acid in fermentation: Advances and prospects for industrial application. *Crit. Rev. Biotechnol.* **2019**, *39*, 408–421. [CrossRef] [PubMed]
4. Bharathiraja, B.; Selvakumari, I.A.E.; Jayamuthunagai, J.; Kumar, R.P.; Varjani, S.; Pandey, A.; Gnansounou, E. Biochemical conversion of biodiesel by-product into malic acid: A way towards sustainability. *Sci. Total Environ.* **2020**, *709*, 136206. [CrossRef]
5. Luo Shipeng, H.P. Malic acid—A Versatile Chiral Building Block in the Enantioselective Total Synthesis of Natural Products and in Synthetic Methodologies. *Prog. Chem.* **2020**, *32*, 1846–1868.

6. Wu, D.; Chang, H.; Wang, Y.; Xin, M. Isolation, structure determination and antibacterial activities of succinamide conjugate diacid from *Acinetobacter* sp. BJ-L. *Microbiol. Res.* **2011**, *166*, 155–160. [[CrossRef](#)] [[PubMed](#)]
7. Bernardini, J.-J.; Linget-Morice, C.; Hoh, F.; Collinson, S.K.; Kyslik, P.; Page, W.J.; Dell, A.; Abdallah, M.A. Bacterial siderophores: Structure elucidation, and ¹H, ¹³C and ¹⁵N two-dimensional NMR assignments of azoverdin and related siderophores synthesized by *Azomonas macrocytogenes* ATCC 12334. *Biomolecules* **1996**, *9*, 107–120. [[CrossRef](#)]
8. Michalke, R.; Taraz, K.; Budzikiewicz, H. Azoverdin -an Isopyoverdin. *Z. Naturforsch. C* **1996**, *51*, 772–780. [[CrossRef](#)]
9. Demange, P.; Bateman, A.; Mertz, C.; Dell, A.; Piemont, Y.; Abdallah, M.A. Bacterial siderophores: Structures of pyoverdins Pt, siderophores of *Pseudomonas tolaasii* NCPPB 2192, and pyoverdins Pf, siderophores of *Pseudomonas fluorescens* CCM 2798. Identification of an unusual natural amino acid. *Biochemistry* **1990**, *29*, 11041–11051. [[CrossRef](#)]
10. Buyer, J.S.; Wright, J.M.; Leong, J. Structure of pseudobactin A214, a siderophore from a bean-deleterious *Pseudomonas*. *Biochemistry* **1986**, *25*, 5492–5499. [[CrossRef](#)]
11. Sudo, M.; Sakamoto, H. Pharmaceutical Agents for Treating HCV Infections. US008183005B1, 22 May 2012.
12. Sato, M.; Wada, H.; Amada, H. Tetraamine Derivative. JP2006008533A, 2006.
13. Moreno, M.; Sani, M.; Raos, G.; Meille, S.V.; Belotti, D.; Giavazzi, R.; Bellosa, S.; Volonterio, A.; Zanda, M. Stereochemically pure α -trifluoromethyl-malic hydroxamates: Synthesis and evaluation as inhibitors of matrix metalloproteinases. *Tetrahedron* **2006**, *62*, 10171–10181. [[CrossRef](#)]
14. Nonoyama, K.; Mori, W.; Nakajima, K.; Nonoyama, M. Copper(II) complexes of optically active binucleating ligands, N,N'-bis [2-pyridylmethyl and 2-(2-pyridyl)ethyl]-(S)-malamide and related amides. *Polyhedron* **1997**, *16*, 3815–3826. [[CrossRef](#)]
15. Cohen, S.M.; Jacobson, F.E.; Lewis, J.A. Metalloprotein Inhibitors Containing Nitrogen Based Ligands. US20120135959A1, 31 May 2012.
16. Alpegiani, M.; Palladino, M.; Corigli, R.; Jabes, D.; Perrone, E.; Abrate, F.; Bissolino, P.; Lombroso, M. Matrix Metalloproteinase Inhibitors. WO 98/33788, 6 August 1998.
17. Jacobson, I.C.; Reddy, P.G.; Wasserman, Z.R.; Hardman, K.D.; Covington, M.B.; Arner, E.C.; Copeland, R.A.; Decicco, C.P.; Magolda, R.L. Structure-based design and synthesis of a series of hydroxamic acids with a quaternary-hydroxy group in P1 as inhibitors of matrix metalloproteinases. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 837–842. [[CrossRef](#)]
18. Jeanpetit, C.; Pringent, D.; Settembre, P.-A.; Trancart, M.-M. Derives D'Amino-Acides Inhibiteurs des Metalloproteases de la Matrice Extracellulaire et de la Liberation du TNF. WO 98/47863, 29 October 1998.
19. Jacobson, I.C.; Decicco, C.P.; Cherney, R.J. Hydroxamic and Carbocyclic Acids as Metalloprotease Inhibitors. US005691381A, 25 November 1997.
20. Jacobson, I.C.; Decicco, C.P.; Cherney, R.J. Hydroxamic and Carboxylic Acids as Metalloprotease Inhibitors. WO 96/33166, 24 October 1996.
21. Wiles, J.A.; Karra, S.; Grau, D.; Ray, S. Mannose 6-Phosphate or ASGPR Receptor Binding Compounds for the Degradation of Extracellular Proteins. WO2023028338, 2 March 2023.
22. Molteni, M.; Pesenti, C.; Sani, M.; Volonterio, A.; Zanda, M. Fluorinated peptidomimetics: Synthesis, conformational and biological features. *J. Fluorine Chem.* **2004**, *125*, 1735–1743. [[CrossRef](#)]
23. Sani, M.; Belotti, D.; Giavazzi, R.; Panzeri, W.; Volonterio, A.; Zanda, M. Synthesis and evaluation of stereopure α -trifluoromethyl-malic hydroxamates as inhibitors of matrix metalloproteinases. *Tetrahedron Lett.* **2004**, *45*, 1611–1615. [[CrossRef](#)]
24. Böttcher, T.; Sieber, S.A. β -Lactams and β -lactones as activity-based probes in chemical biology. *MedChemComm* **2012**, *3*, 408–417. [[CrossRef](#)]
25. Atta, H.; Alzahaby, N.; Hamdy, N.M.; Emam, S.H.; Sonousi, A.; Ziko, L. New trends in synthetic drugs and natural products targeting 20S proteasomes in cancers. *Bioorg. Chem.* **2023**, *133*, 106427. [[CrossRef](#)]
26. Groll, M.; Potts, B.C. Proteasome Structure, Function, and Lessons Learned from Beta-Lactone Inhibitors. *Curr. Top. Med. Chem.* **2011**, *11*, 2850–2878. [[CrossRef](#)]
27. Fenical, W.; Jensen, P.R.; Palladino, M.A.; Lam, K.S.; Lloyd, G.K.; Potts, B.C. Discovery and development of the anticancer agent salinosporamide A (NPI-0052). *Bioorg. Med. Chem.* **2009**, *17*, 2175–2180. [[CrossRef](#)]
28. Tomoda, H.; Omura, S. Lactacystin, a Proteasome Inhibitor: Discovery and its Application in Cell Biology. *Yakugaku Zasshi* **2000**, *120*, 935–949. [[CrossRef](#)]
29. Fenteany, G.; Standaert, R.F.; Lane, W.S.; Choi, S.; Corey, E.J.; Schreiber, S.L. Inhibition of Proteasome Activities and Subunit-Specific Amino-Terminal Threonine Modification by Lactacystin. *Science* **1995**, *268*, 726–731. [[CrossRef](#)] [[PubMed](#)]
30. Abdelhamid, Y.; Kasten, K.; Dunne, J.; Hartley, W.C.; Young, C.M.; Cordes, D.B.; Slawin, A.M.Z.; Ng, S.; Smith, A.D. Isothiourea-Catalyzed [2 + 2] Cycloaddition of C(1)-Ammonium Enolates and N-Alkyl Isatins. *Org. Lett.* **2022**, *24*, 5444–5449. [[CrossRef](#)] [[PubMed](#)]
31. Kawasaki, M.; Shirai, T.; Yatsuzuka, K.; Shirai, R. Hydrolytic dynamic kinetic resolution of racemic 3-phenyl-2-oxetanone to chiral tropic acid. *RSC Adv.* **2024**, *14*, 6121–6126. [[CrossRef](#)] [[PubMed](#)]
32. Qiu, Y.; Liang, Z.-Q.; Chen, K.-Q.; Dai, L.; Ye, S. Enantioselective N-heterocyclic carbene-catalyzed rearrangement of enol ϵ -lactones. *Org. Chem. Front.* **2023**, *10*, 799–805. [[CrossRef](#)]
33. Wang, X.; Yang, K.; Wang, Y.-N.; Li, S.-J.; Wei, D.; Lan, Y. Origins of Catalyst-Controlled Chemoselectivity in Transition-Metal-Catalyzed Divergent Epoxide Conversion. *ACS Catal.* **2023**, *13*, 7616–7626. [[CrossRef](#)]

34. Atkin, L.; Robertson, A.; White, J.M.; Rizzacasa, M.A. Total Synthesis of Viridifungins A and B. *Org. Lett.* **2021**, *23*, 3557–3560. [\[CrossRef\]](#)
35. Fung, J.; Duong, T.-V.; Bracerros, K.C.A.; Brooks, M.L.; Schloesser-Lingscheit, K.; Tagawa, T.K.S.; Wilson, J.M.; Jones, K.K.; Valente, E.J. Arylpyran Pseudoacid Racemization: Rate Estimation and Structural Influences. *J. Chem. Crystallogr.* **2021**, *51*, 14–41. [\[CrossRef\]](#)
36. Barrios Antúnez, D.-J.; Greenhalgh, M.D.; Brueckner, A.C.; Walden, D.M.; Elías-Rodríguez, P.; Roberts, P.; Young, B.G.; West, T.H.; Slawin, A.M.Z.; Ha-Yeon Cheong, P.; et al. Catalytic enantioselective synthesis of perfluoroalkyl-substituted β -lactones via a concerted asynchronous [2 + 2] cycloaddition: A synthetic and computational study. *Chem. Sci.* **2019**, *10*, 6162–6173. [\[CrossRef\]](#)
37. Khalil, A.; Cammas-Marion, S.; Coulembier, O. Organocatalysis applied to the ring-opening polymerization of β -lactones: A brief overview. *J. Polym. Sci. A Polym. Chem.* **2019**, *57*, 657–672. [\[CrossRef\]](#)
38. Xu, L.; Zhou, F.; Liao, M.; Hu, R.; Tang, B.Z. Room temperature multicomponent polymerizations of alkynes, sulfonyl azides, and N-protected isatins toward oxindole-containing poly(N-acylsulfonamide)s. *Polym. Chem.* **2018**, *9*, 1674–1683. [\[CrossRef\]](#)
39. Malapit, C.A.; Caldwell, D.R.; Sassu, N.; Milbin, S.; Howell, A.R. Pd-Catalyzed Acyl C–O Bond Activation for Selective Ring-Opening of α -Methylene- β -lactones with Amines. *Org. Lett.* **2017**, *19*, 1966–1969. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Mondal, S.; Mukherjee, S.; Das, T.K.; Gonnade, R.; Biju, A.T. N-Heterocyclic Carbene-Catalyzed Aldol-Lactonization of Ketoacids via Dynamic Kinetic Resolution. *ACS Catal.* **2017**, *7*, 3995–3999. [\[CrossRef\]](#)
41. Yang, S.; Sankar, K.; Skepper, C.K.; Barker, T.J.; Lukesh Iii, J.C.; Brody, D.M.; Brütsch, M.M.; Boger, D.L. Total synthesis of a key series of vinblastines modified at C4 that define the importance and surprising trends in activity. *Chem. Sci.* **2017**, *8*, 1560–1569. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Chen, S.; Mondal, M.; Ibrahim, A.A.; Wheeler, K.A.; Kerrigan, N.J. Asymmetric Synthesis of Dipropionate Derivatives through Catalytic Hydrogenation of Enantioenriched E-Ketene Heterodimers. *Synthesis* **2016**, *48*, 2619–2626. [\[CrossRef\]](#)
43. Cheng, D.; Ling, F.; Zheng, C.; Ma, C. Tuning of Copper-Catalyzed Multicomponent Reactions toward 3-Functionalized Oxindoles. *Org. Lett.* **2016**, *18*, 2435–2438. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Wiedemann, E.N.; Mandl, F.A.; Blank, I.D.; Ochsenfeld, C.; Ofial, A.R.; Sieber, S.A. Kinetic and Theoretical Studies of Beta-Lactone Reactivity—A Quantitative Scale for Biological Application. *ChemPlusChem* **2015**, *80*, 1673–1679. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Hao, X.; Liu, X.; Li, W.; Tan, F.; Chu, Y.; Zhao, X.; Lin, L.; Feng, X. Chiral Lewis Acid Catalyzed Asymmetric Cycloadditions of Disubstituted Ketenes for the Synthesis of β -Lactones and δ -Lactones. *Org. Lett.* **2014**, *16*, 134–137. [\[CrossRef\]](#)
46. Douglas, J.; Taylor, J.E.; Churchill, G.; Slawin, A.M.Z.; Smith, A.D. NHC-Promoted Asymmetric β -Lactone Formation from Arylalkylketenes and Electron-Deficient Benzaldehydes or Pyridinecarboxaldehydes. *J. Org. Chem.* **2013**, *78*, 3925–3938. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Lim, J.Y.; Jeon, N.Y.; Park, A.-R.; Min, B.; Kim, B.T.; Park, S.; Lee, H. Experimental and Computation Studies on Candida antarctica Lipase B-Catalyzed Enantioselective Alcoholysis of 4-Bromomethyl- β -lactone Leading to Enantiopure 4-Bromo-3-hydroxybutanoate. *Adv. Synth. Catal.* **2013**, *355*, 1808–1816. [\[CrossRef\]](#)
48. Rousseau, G.; Robin, S. Four-Membered Heterocycles: Structure and Reactivity. In *Modern Heterocyclic Chemistry*; Wiley-VCH: Weinheim, Germany, 2011; pp. 163–268.
49. Frébault, F.; Luparia, M.; Oliveira, M.T.; Goddard, R.; Maulide, N. A Versatile and Stereoselective Synthesis of Functionalized Cyclobutenes. *Angew. Chem. Int. Ed.* **2010**, *49*, 5672–5676. [\[CrossRef\]](#)
50. Kull, T.; Cabrera, J.; Peters, R. Catalytic Asymmetric Synthesis of trans-Configured β -Lactones: Cooperation of Lewis Acid and Ion Pair Catalysis. *Chem. Eur. J.* **2010**, *16*, 9132–9139. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Coulembier, O.; Degée, P.; Hedrick, J.L.; Dubois, P. From controlled ring-opening polymerization to biodegradable aliphatic polyester: Especially poly(β -malic acid) derivatives. *Prog. Polym. Sci.* **2006**, *31*, 723–747. [\[CrossRef\]](#)
52. Groll, M.; Huber, R.; Potts, B.C.M. Crystal Structures of Salinosporamide A (NPI-0052) and B (NPI-0047) in Complex with the 20S Proteasome Reveal Important Consequences of β -Lactone Ring Opening and a Mechanism for Irreversible Binding. *J. Am. Chem. Soc.* **2006**, *128*, 5136–5141. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G.-I. Lactols in stereoselection 3: Highly anti-cram selective 1,2-asymmetric induction. *Tetrahedron Lett.* **1989**, *30*, 1563–1566. [\[CrossRef\]](#)
54. Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G.-I. Lactols in stereoselection 1. Highly selective 1,4- and 1,5-asymmetric induction. *Tetrahedron Lett.* **1987**, *28*, 6335–6338. [\[CrossRef\]](#)
55. Christenson, J.K.; Robinson, S.L.; Engel, T.A.; Richman, J.E.; Kim, A.N.; Wackett, L.P. OleB from Bacterial Hydrocarbon Biosynthesis Is a β -Lactone Decarboxylase That Shares Key Features with Haloalkane Dehalogenases. *Biochemistry* **2017**, *56*, 5278–5287. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Morao, I.; Lecea, B.; Arrieta, A.; Cossío, F.P. Structural and Solvent Effects on the Mechanism of the Thermal Decarboxylation of 2-Oxetanones. A Limiting Case between Concerted and Stepwise Pathways in Pericyclic Reactions. *J. Am. Chem. Soc.* **1997**, *119*, 816–825. [\[CrossRef\]](#)
57. Moyano, A.; Pericas, M.A.; Valenti, E. A theoretical study on the mechanism of the thermal and the acid-catalyzed decarboxylation of 2-oxetanones (β -lactones). *J. Org. Chem.* **1989**, *54*, 573–582. [\[CrossRef\]](#)
58. Mulzer, J.; Kerkmann, T. α Deprotonation of β -lactones—An example of a forbidden β -elimination. *J. Am. Chem. Soc.* **1980**, *102*, 3620–3622. [\[CrossRef\]](#)

59. Mead, K.T.; Yang, H.-L. A new approach to the preparation of 2-substituted tetrahydrofurans with alpha-syn selectivity. *Tetrahedron Lett.* **1989**, *30*, 6829–6832. [[CrossRef](#)]
60. Alcaide, B.; Almendros, P.; Aragoncillo, C. Ring Expansions of β -Lactams and β -(thio)lactones. In *Synthesis of 4- to 7-Membered Heterocycles by Ring Expansion: Aza-, Oxa- and Thiaheterocyclic Small-Ring Systems*; D'hooghe, M., Ha, H.-J., Eds.; Springer International Publishing: Cham, Switzerland, 2016; pp. 233–280.
61. Romo, D.; Tennyson, R.L.; Wang, Y. β -Lactones as intermediates for natural product total synthesis and new transformations. *Heterocycles* **2004**, *64*, 605–658. [[CrossRef](#)] [[PubMed](#)]
62. Black, T.H.; Hall, J.A.; Sheu, R.G. Improved, stereospecific synthesis of highly substituted butyrolactones via dyotropic rearrangement. *J. Org. Chem.* **1988**, *53*, 2371–2374. [[CrossRef](#)]
63. Black, T.H.; Jianhua, H. A new synthesis of substituted butenolides via cation-initiated ring expansion/elimination of β -lactones. *Tetrahedron Lett.* **1993**, *34*, 1411–1412. [[CrossRef](#)]
64. Black, T.H.; Smith, D.C.; Eisenbeis, S.A.; Peterson, K.A.; Harmon, M.S. cis-Fused γ -lactones from simple precursors via β -lactone rearrangements. *Chem. Commun.* **2001**, *8*, 753–754. [[CrossRef](#)]
65. Park, H.D.; Dină, M.; Román-Leshkov, Y. Continuous-Flow Production of Succinic Anhydrides via Catalytic β -Lactone Carbonylation by $\text{Co}(\text{CO})_4\text{Cr-MIL-101}$. *J. Am. Chem. Soc.* **2018**, *140*, 10669–10672. [[CrossRef](#)]
66. Pommier, A.; Pons, J.-M. Recent Advances in β -Lactone Chemistry. *Synthesis* **1993**, *1993*, 441–459. [[CrossRef](#)]
67. Cheke, R.S.; Patil, V.M.; Firke, S.D.; Ambhore, J.P.; Ansari, I.A.; Patel, H.M.; Shinde, S.D.; Pasupuleti, V.R.; Hassan, M.I.; Adnan, M.; et al. Therapeutic Outcomes of Isatin and Its Derivatives against Multiple Diseases: Recent Developments in Drug Discovery. *Pharmaceuticals* **2022**, *15*, 272. [[CrossRef](#)] [[PubMed](#)]
68. Elsaman, T.; Mohamed, M.S.; Eltayib, E.M.; Abdel-aziz, H.A.; Abdalla, A.E.; Munir, M.U.; Mohamed, M.A. Isatin derivatives as broad-spectrum antiviral agents: The current landscape. *Med. Chem. Res.* **2022**, *31*, 244–273. [[CrossRef](#)]
69. Nath, R.; Pathania, S.; Grover, G.; Akhtar, M.J. Isatin containing heterocycles for different biological activities: Analysis of structure activity relationship. *J. Mol. Struct.* **2020**, *1222*, 128900. [[CrossRef](#)]
70. Chahal, V.; Sonam; Kakkar, R. Isatin and its derivatives: A survey of recent syntheses, reactions, and applications. *MedChemComm* **2019**, *10*, 351–368.
71. Guo, H. Isatin derivatives and their anti-bacterial activities. *Eur. J. Med. Chem.* **2019**, *164*, 678–688. [[CrossRef](#)] [[PubMed](#)]
72. Jiang, D.; Wang, G.-Q.; Liu, X.; Zhang, Z.; Feng, L.-S.; Liu, M.-L. Isatin Derivatives with Potential Antitubercular Activities. *J. Heterocycl. Chem.* **2018**, *55*, 1263–1279. [[CrossRef](#)]
73. Vandana, K.; Akash, M.; Thushara, B.S.; Rajitha, K. A Review on Isatin Derivatives with Diverse Biological Activities. *World J. Pharm. Res.* **2017**, *6*, 318–332.
74. Grewal, A.S. Isatin Derivatives with Several Biological Activities. *Int. J. Pharm. Res.* **2014**, *6*, 1–7.
75. Pakravan, P.; Kashanian, S.; Khodaei, M.M.; Harding, F.J. Biochemical and pharmacological characterization of isatin and its derivatives: From structure to activity. *Pharmacol. Rep.* **2013**, *65*, 313–335. [[CrossRef](#)] [[PubMed](#)]
76. Vine, K.L.; Matesic, L.; Locke, J.M.; Ranson, M.; Skropeta, D. Cytotoxic and Anticancer Activities of Isatin and Its Derivatives: A Comprehensive Review from 2000–2008. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 397–414. [[CrossRef](#)]
77. Medvedev, A.; Buneeva, O.; Glover, V. Biological targets for isatin and its analogues: Implications for therapy. *Biol. Targets Ther.* **2007**, *1*, 151–162.
78. Pandeya, S.N.; Smitha, S.; Jyoti, M.; Sridhar, S.K. Biological Activities of Isatin and its Derivatives. *Acta Pharm.* **2005**, *55*, 27–46.
79. Khetmalis, Y.M.; Shivani, M.; Murugesan, S.; Chandra Sekhar, K.V.G. Oxindole and its derivatives: A review on recent progress in biological activities. *Biomed. Pharmacother.* **2021**, *141*, 111842. [[CrossRef](#)]
80. Kaur, M.; Singh, M.; Chadha, N.; Silakari, O. Oxindole: A chemical prism carrying plethora of therapeutic benefits. *Eur. J. Med. Chem.* **2016**, *123*, 858–894. [[CrossRef](#)]
81. Badillo, J.J.; Hanhan, N.V.; Franz, A.K. Enantioselective synthesis of substituted oxindoles and spirooxindoles with applications in drug discovery. *Curr. Opin. Drug Discov. Dev.* **2010**, *13*, 758–776.
82. Zhang, S.; Huang, D.; Wu, J.; Wang, Z. Decade Advance of Isatin in Three-component Reactions. *Asian J. Org. Chem.* **2023**, *12*, e202200591. [[CrossRef](#)]
83. Sadeghian, Z.; Bayat, M. Synthesis of Heterocyclic Compounds Based on Isatins. *Curr. Org. Chem.* **2022**, *26*, 756–770. [[CrossRef](#)]
84. Salvio, R.; Placidi, S.; Sinibaldi, A.; Di Sabato, A.; Buscemi, D.C.; Rossi, A.; Antenucci, A.; Malkov, A.; Bella, M. Organocatalytic Synthesis of Benzazetidines by Trapping Hemiaminals with Protecting Groups. *J. Org. Chem.* **2019**, *84*, 7395–7404. [[CrossRef](#)] [[PubMed](#)]
85. Nizalapur, S.; Kimyon, Ö.; Biswas, N.N.; Gardner, C.R.; Griffith, R.; Rice, S.A.; Manefield, M.; Willcox, M.; Black, D.S.; Kumar, N. Design, synthesis and evaluation of N-aryl-glyoxamide derivatives as structurally novel bacterial quorum sensing inhibitors. *Org. Biomol. Chem.* **2016**, *14*, 680–693. [[CrossRef](#)] [[PubMed](#)]
86. Nizalapur, S.; Ho, K.K.K.; Kimyon, Ö.; Yee, E.; Berry, T.; Manefield, M.; Cranfield, C.G.; Willcox, M.; Black, D.S.; Kumar, N. Synthesis and biological evaluation of N-naphthoyl-phenylglyoxamide-based small molecular antimicrobial peptide mimics as novel antimicrobial agents and biofilm inhibitors. *Org. Biomol. Chem.* **2016**, *14*, 3623–3637. [[CrossRef](#)] [[PubMed](#)]
87. Nardi, D.; Tajana, A.; Portioli, F.; Bonola, G. Nucleophilic opening of the hetero-ring of N-acylisatins by acylhydrazines. *Il Farm. Ed. Sci.* **1982**, *37*, 815–823.

88. Black, D.S.C.; Ian Moss, G.; Wong, L.C.H. A versatile new synthesis of macrocyclic amide complexes. *Tetrahedron Lett.* **1978**, *19*, 2837–2838. [\[CrossRef\]](#)
89. Suarez-Castillo, O.R.; Bautista-Hernandez, C.I.; Sanchez-Zavala, M.; Melenez-Rodriguez, M.; Sierra-Zenteno, A.; Morales-Rios, M.S.; Joseph-Nathan, P. Microwave-assisted synthesis of 3,1-benzoxazin-2-ones from 3-hydroxyoxindoles. *Heterocycles* **2012**, *85*, 2147–2171. [\[CrossRef\]](#)
90. Mandai, H.; Shiimoto, R.; Fujii, K.; Mitsudo, K.; Suga, S. Kinetic Resolution of Tertiary Alcohols by Chiral DMAP Derivatives: Enantioselective Access to 3-Hydroxy-3-substituted 2-Oxindoles. *Org. Lett.* **2021**, *23*, 1169–1174. [\[CrossRef\]](#)
91. Papaioannou, N.; Blank, J.T.; Miller, S.J. Enantioselective Synthesis of an Aziridinomitosane and Selective Functionalizations of a Key Intermediate. *J. Org. Chem.* **2003**, *68*, 2728–2734. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. Efficient Entry to Diversely Functionalized Spirocyclic Oxindoles from Isatins through Carbonyl-Addition/Cyclization Reaction Sequences. *J. Org. Chem.* **2006**, *71*, 2346–2351. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Bergman, J.; Stensland, B. Cyclization of Cyanoethylated Ketones as a Route to 6-Substituted Indole Derivatives. *J. Heterocycl. Chem.* **2014**, *51*, 1–10. [\[CrossRef\]](#)
94. Tan, Z.; Zhu, S.; Liu, Y.; Feng, X. Photoinduced Chemo-, Site- and Stereoselective α -C(sp³)-H Functionalization of Sulfides. *Angew. Chem. Int. Ed.* **2022**, *61*, e202203374. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. Synthesis of 3-hydroxyindolin-2-one alkaloids, (\pm)-donaxaridine and (\pm)-convolutamydines A and E, through enolization–Claisen rearrangement of 2-allyloxyindolin-3-ones. *Tetrahedron* **2004**, *60*, 3493–3503. [\[CrossRef\]](#)
96. Gao, M.; Luo, Y.; Xu, Q.; Zhao, Y.; Gong, X.; Xia, Y.; Hu, L. A Unified Catalytic Asymmetric (4+1) and (5+1) Annulation Strategy to Access Chiral Spirooxindole-Fused Oxacycles. *Angew. Chem. Int. Ed.* **2021**, *60*, 19813–19820. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Pinto, Á.C.; Da Silva, R.S.; Hollins, R.A. A simple synthesis of 1-phenothiazineethanolamines: Potential antimalarials. *J. Heterocycl. Chem.* **1979**, *16*, 1085–1086. [\[CrossRef\]](#)
98. Inoue, M.; Sakazaki, H.; Furuyama, H.; Hiram, M. Total Synthesis of TMC-95A. *Angew. Chem. Int. Ed.* **2003**, *42*, 2654–2657. [\[CrossRef\]](#) [\[PubMed\]](#)
99. Kawasaki, T.; Takamiya, W.; Okamoto, N.; Nagaoka, M.; Hirayama, T. Silyl-enolization-asymmetric Claisen rearrangement of 2-allyloxyindolin-3-one: Enantioselective total synthesis of 3a-hydroxypyrrolo [2,3-b]indoline alkaloid alline. *Tetrahedron Lett.* **2006**, *47*, 5379–5382. [\[CrossRef\]](#)
100. Kim, S.C.; Gowrisankar, S.; Kim, J.N. Synthesis of 3-aryl-3-hydroxypyrrolidin-2-ones and 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2H-pyrrolo[3,4-c]quinoline-1,4-dione derivatives from the Baylis–Hillman adducts of isatins. *Tetrahedron Lett.* **2006**, *47*, 3463–3466. [\[CrossRef\]](#)
101. Kim, S.C.; Lee, K.Y.; Gowrisankar, S.; Kim, J.N. Synthesis of 3-Aryl-3-Hydroxypyrrolidin-2-Ones and 2-Benzyl-9b-Hydroxy-3,3a,5,9b-Tetrahydro-2H-Pyrrolo[3,4-c]Quinoline-1,4-Dione Derivatives from the Baylis–Hillman Adducts of Isatins. *Bull. Korean Chem. Soc.* **2006**, *27*, 1133–1139.
102. Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. Highly enantioselective aldol reaction of acetaldehyde and isatins only with 4-hydroxydiarylprolinol as catalyst: Concise stereoselective synthesis of (R)-convolutamydines B and E, (–)-donaxaridine and (R)-chimonamidine. *Tetrahedron* **2010**, *66*, 1441–1446. [\[CrossRef\]](#)
103. Wu, H.; Xue, F.; Xiao, X.; Qin, Y. Total Synthesis of (+)-Perophoramidine and Determination of the Absolute Configuration. *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Sarraf, D.; Richy, N.; Vidal, J. Synthesis of Lactams by Isomerization of Oxindoles Substituted at C-3 by an ω -Amino Chain. *J. Org. Chem.* **2014**, *79*, 10945–10955. [\[CrossRef\]](#)
105. Subba Reddy, U.V.; Chennapuram, M.; Seki, K.; Seki, C.; Anusha, B.; Kwon, E.; Okuyama, Y.; Uwai, K.; Tokiwa, M.; Takeshita, M.; et al. A Diamino Alcohol Catalyzed Enantioselective Crossed Aldol Reaction of Acetaldehyde with Isatins—A Concise Total Synthesis of Antitumor Agents. *Eur. J. Org. Chem.* **2017**, *2017*, 3874–3885. [\[CrossRef\]](#)
106. Richy, N.; Sarraf, D.; Maréchal, X.; Janmamode, N.; Le Guével, R.; Genin, E.; Reboud-Ravaux, M.; Vidal, J. Structure-based design of human immuno- and constitutive proteasomes inhibitors. *Eur. J. Med. Chem.* **2018**, *145*, 570–587. [\[CrossRef\]](#) [\[PubMed\]](#)
107. Moskowitz, M.; Wolf, C. Catalytic Enantioselective Ynamide Additions to Isatins: Concise Access to Oxindole Alkaloids. *Angew. Chem. Int. Ed.* **2019**, *58*, 3402–3406. [\[CrossRef\]](#) [\[PubMed\]](#)
108. Shanmugam, P.; Vaithyanathan, V.; Viswambharan, B. A Facile and Efficient Synthesis of Functionalized -Butyrolactones from BaylisHillman Adducts of Isatin. *Aust. J. Chem.* **2007**, *60*, 296–301. [\[CrossRef\]](#)
109. Liu, Y.-L.; Wang, B.-L.; Cao, J.-J.; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. Organocatalytic Asymmetric Synthesis of Substituted 3-Hydroxy-2-oxindoles via Morita–Baylis–Hillman Reaction. *J. Am. Chem. Soc.* **2010**, *132*, 15176–15178. [\[CrossRef\]](#)
110. Dong, Z.; Yan, C.; Gao, Y.; Dong, C.; Qiu, G.; Zhou, H.-B. Tunable Bifunctional Phosphine–Squaramide Promoted Morita–Baylis–Hillman Reaction of N-Alkyl Isatins with Acrylates. *Adv. Synth. Catal.* **2015**, *357*, 2132–2142. [\[CrossRef\]](#)
111. Sakla, A.P.; Kansal, P.; Shankaraiah, N. Syntheses and reactivity of spiro-epoxy/aziridine oxindole cores: Developments in the past decade. *Org. Biomol. Chem.* **2020**, *18*, 8572–8596. [\[CrossRef\]](#) [\[PubMed\]](#)
112. Hajra, S.; Singha Roy, S.; Biswas, A.; Saleh, S.A. Catalyst-Free Ring Opening of Spiroaziridine Oxindoles by Heteronucleophiles: An Approach to the Synthesis of Enantiopure 3-Substituted Oxindoles. *J. Org. Chem.* **2018**, *83*, 3633–3644. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Hajra, S.; Hazra, A.; Mandal, P. Stereocontrolled Nucleophilic Fluorination at the Tertiary sp³-Carbon Center for Enantiopure Synthesis of 3-Fluorooxindoles. *Org. Lett.* **2018**, *20*, 6471–6475. [\[CrossRef\]](#) [\[PubMed\]](#)

114. Sakla, A.P.; Kansal, P.; Shankaraiah, N. Syntheses and Applications of Spirocyclopropyl Oxindoles: A Decade Review. *Eur. J. Org. Chem.* **2021**, *2021*, 757–772. [[CrossRef](#)]
115. Conboy, A.; Goodfellow, A.S.; Kasten, K.; Dunne, J.; Cordes, D.B.; Bühl, M.; Smith, A.D. De-epimerizing DyKAT of β -lactones generated by isothiourea-catalysed enantioselective [2 + 2] cycloaddition. *Chem. Sci.* **2024**, *15*, 8896–8904. [[CrossRef](#)] [[PubMed](#)]
116. Bleiholder, C.; Gleiter, R.; Werz, D.B.; Köppel, H. Theoretical Investigations on Heteronuclear Chalcogen–Chalcogen Interactions: On the Nature of Weak Bonds between Chalcogen Centers. *Inorg. Chem.* **2007**, *46*, 2249–2260. [[CrossRef](#)] [[PubMed](#)]
117. Liu, P.; Yang, X.; Birman, V.B.; Houk, K.N. Origin of Enantioselectivity in Benzotetramisole-Catalyzed Dynamic Kinetic Resolution of Azlactones. *Org. Lett.* **2012**, *14*, 3288–3291. [[CrossRef](#)] [[PubMed](#)]
118. Robinson, E.R.T.; Walden, D.M.; Fallan, C.; Greenhalgh, M.D.; Cheong, P.H.-Y.; Smith, A.D. Non-bonding 1,5-S \cdots O interactions govern chemo- and enantioselectivity in isothiourea-catalyzed annulations of benzazoles. *Chem. Sci.* **2016**, *7*, 6919–6927. [[CrossRef](#)] [[PubMed](#)]
119. Pascoe, D.J.; Ling, K.B.; Cockroft, S.L. The Origin of Chalcogen-Bonding Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 15160–15167. [[CrossRef](#)]
120. Greenhalgh, M.D.; Smith, S.M.; Walden, D.M.; Taylor, J.E.; Brice, Z.; Robinson, E.R.T.; Fallan, C.; Cordes, D.B.; Slawin, A.M.Z.; Richardson, H.C.; et al. A C=O \cdots Isothiuronium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolutions of Tertiary Heterocyclic Alcohols. *Angew. Chem. Int. Ed.* **2018**, *57*, 3200–3206. [[CrossRef](#)]
121. Breugst, M.; Koenig, J.J. σ -Hole Interactions in Catalysis. *Eur. J. Org. Chem.* **2020**, *2020*, 5473–5487. [[CrossRef](#)]
122. Kolb, S.; Oliver, G.A.; Werz, D.B. Chemistry Evolves, Terms Evolve, but Phenomena Do Not Evolve: From Chalcogen–Chalcogen Interactions to Chalcogen Bonding. *Angew. Chem. Int. Ed.* **2020**, *59*, 22306–22310. [[CrossRef](#)] [[PubMed](#)]
123. Young, C.M.; Elmi, A.; Pascoe, D.J.; Morris, R.K.; McLaughlin, C.; Woods, A.M.; Frost, A.B.; de la Houpliere, A.; Ling, K.B.; Smith, T.K.; et al. The Importance of 1,5-Oxygen \cdots Chalcogen Interactions in Enantioselective Isochalcogenourea Catalysis. *Angew. Chem. Int. Ed.* **2020**, *59*, 3705–3710. [[CrossRef](#)] [[PubMed](#)]
124. Wille, G.; Steglich, W. A Short Synthesis of the Bacterial Pigments Violacein and Deoxyviolacein. *Synthesis* **2001**, *2001*, 759–762. [[CrossRef](#)]
125. Rigaku, O.D. *CrysAlisPro*, v1.171.42.94a; Rigaku Oxford Diffraction; Rigaku Corporation: Tokyo, Japan, 2023.
126. Sheldrick, G.M. SHELXT-Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr. A* **2015**, *71*, 3–8. [[CrossRef](#)] [[PubMed](#)]
127. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Crystallogr. C* **2015**, *71*, 3–8. [[CrossRef](#)]
128. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.