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Supporting Information

Stereocontrolled Total Synthesis of (−)-Stemaphylline

Ana Varela, Lennart K. B. Garve, Daniele Leonori,* and Varinder K. Aggarwal*

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Supporting Information
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1. General Experimental Details

All required fine chemicals were used directly without purification unless mentioned. All air- and water-sensitive reactions were carried out in flame-dried glassware under nitrogen atmosphere using standard Schlenk manifold technique. $^1$H and $^{13}$C Nuclear Magnetic Resonance (NMR) spectra were acquired at various field strengths as indicated, and were referenced to CHCl$_3$ (7.27 and 77.0 ppm for $^1$H and $^{13}$C respectively) or DMSO (2.50 and 39.5 ppm for $^1$H and $^{13}$C respectively). Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (J) are in Hertz (Hz). Letters are assigned to protons in chemical structures for $^1$H NMR assignment purposes only (assigning in alphabetical order from downfield to upfield). Carbons attached to boron atoms are often not observed due to quadrupolar relaxation. $^{11}$B NMR spectra were measured using boron-free quartz NMR tubes, and recorded with complete proton decoupling using BF$_3$·Et$_2$O (0.0 ppm) as an external standard. High-resolution mass spectra (HRMS) were recorded using Electron Spray Ionization (ESI). All IR data was obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer 241MC polarimeter. Analytical TLC: Aluminium-backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F254. Compounds were visualized by exposure to UV-light or and/or developed with potassium permanganate or anisaldehyde. Flash column chromatography was performed using Aldrich Silica Gel 60 (40-63 µm). Chiral HPLC was performed using a Diacel Chiralpak IA or IB column (4.6 × 250 mm × 5 µm) fitted with the respective guard (4 × 10 mm) and monitored by DAD (Diode Array Detector). Chiral SFC was performed using a Chiralpak IA, IB, IC or Whelk-01 column (4.6 × 250 mm × 5 µm) on a Waters TharSFC system and monitored by DAD (Diode Array Detector). Chiral GC was performed using a Chiraldex β-DM column and monitored by FID (Flame Ionisation Detector). Solvents were purified by standard methods. TMEDA was distilled over CaH$_2$. (–)-Sparteine was obtained from the commercially available sulfate pentahydrate salt (99%, Acros) and isolated according to literature procedure$^{[1]}$. (+)-Sparteine was purchased from BOC sciences and was distilled over CaH$_2$ prior to use. The sparteine free base readily absorbs atmospheric carbon dioxide (CO$_2$) and should be stored under argon/nitrogen at -20 °C in a Schlenk tube. (+)-Sparteine surrogate was synthesised from (–)-cytisine (purchased from Carbosynth) according to literature procedure$^{[2]}$ and was purified by kugelrohr distillation no more than 24 h prior to its use. s-BuLi was purchased from
Acros. n-BuLi and t-BuLi were purchased from Sigma-Aldrich. The molarity of organolithium solutions was determined by titration using benzylbenzamide\textsuperscript{[3]}. Anhydrous DMF was purchased from Acros and stored over activated 4Å molecular sieves. 2-Isopropanoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (\(i\)-PrOB(pin)) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Sigma-Aldrich and distilled under reduced pressure prior to their use. \((R)\)-2-methylbutane-1,4-diol (14) was purchased from TCI. *In situ* IR monitoring was performed on a ReactIR15 instrument, equipped with a DST 9.5mm x 1.5m x 305mm probe with a DiComp (Diamond) sensor and a gold seal. For reverse phase purification of 37, flash chromatography was performed on a Grace Discovery Sciences Reveleris Prep System with a Phenomenex Luna 12 g C\textsubscript{18}(2) 100 Å AXIA packed column. The instrument was set to monitor the ELSD signal. Flow rates were 14 mL / min. The mobile phases used were 0.05 % formic acid in water for the aqueous phase and 0.05 % formic acid in MeCN for the organic phase. The gradient was from 5 % organic phase for 5 minutes at the start to 40 % organic phase over 10 minutes, then holding at 40 % organic phase for 10 minutes before rising to 80 % organic phase over 10 minutes, with 10 minutes at 100 % organic phase followed by 5 minutes at 5 % organic phase.
2. Model Studies for the Lithiation-Borylation with Boronic Ester 7

2.1. Starting Material Synthesis

3-Phenylpropyl 2,4,6-triisopropylbenzoate (8)

![Chemical structure of 3-Phenylpropyl 2,4,6-triisopropylbenzoate (8)]

To a solution of 3-phenyl-1-propanol (0.90 g, 6.64 mmol, 1.10 equiv.) in THF (25 mL, 0.25 M) were added Ph$_3$P (1.74 g, 6.64 mmol, 1.10 equiv.) and 2,4,6-triisopropylbenzoic acid (1.50 g, 6.04 mmol, 1.00 equiv.). The mixture was cooled to 0 °C, then diisopropylazodicarboxylate (1.31 mL, 6.64 mmol, 1.10 equiv.) was added dropwise. The solution was stirred for 30 min at 0 °C, then it was warmed to room temperature and stirred for 4 h. Saturated NH$_4$Cl (10 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with Et$_2$O (3 x 10 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was triturated with petrol to remove Ph$_3$P=O, then it was purified by column chromatography on silica gel, eluting with petrol:EtOAc 95:5 to 90:10, to give 8 as a colourless oil (2.10 g, 95%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.34-7.18 (5H, m), 7.00 (2H, s), 4.34 (2H, t, $J$ 6.5 Hz), 2.88 (3H, sept, $J$ 6.9 Hz), 2.75 (2H, t, $J$ 7.8 Hz), 2.06 (2H, dt, $J$ 7.8, 6.5 Hz), 1.27 (12H, d, $J$ 6.9 Hz), 1.24 (6H, d, $J$ 6.9 Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 170.9 (C=O), 150.1 (C), 144.7 (2 x C), 141.1 (C), 130.6 (C), 128.5 (2 x CH), 128.4 (2 x CH), 126.1 (CH), 120.9 (2 x CH), 64.2 (CH$_2$), 34.4 (CH$_2$), 32.3 (CH), 31.5 (2 x CH), 30.4 (CH$_2$), 24.2 (4 x CH$_3$), 23.9 (2 x CH$_3$). Data in accordance with the literature.$^{[4]}$
** tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate (7)**

\[
\begin{align*}
\text{N-Boc-pyrrolidine (1.00 g, 5.84 mmol, 1.00 equiv.) and TMEDA (1.1 mL, 7.00 mmol, 1.20 equiv.) were dissolved in Et}_2\text{O (50 mL). The solution was cooled to } -78 \, ^\circ\text{C and s-BuLi (1.3 M in hexanes, 6.00 mL, 7.00 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h at } -78 \, ^\circ\text{C, then } i-\text{PrO}B(\text{pin}) (1.63 g, 8.80 mmol, 1.30 equiv.) was added dropwise. The solution was stirred for 1 h at } -78 \, ^\circ\text{C, then allowed to warm up to room temperature slowly. Aqueous 1 M HCl (50 mL) was added and the layers were separated. The organic layers were washed with Brine (3 x 20 mL) and the combined aqueous layers were extracted with Et}_2\text{O (3 x 50 mL). The organic layers were combined, dried over MgSO}_4\text{ and concentrated under vacuum. The crude product was purified by fast column chromatography on silica gel, eluting with petrol:EtOAc 85:15, to give 7 as a white solid (1.20 g, 69%).} \\
\text{1H NMR (500 MHz, DMSO-}d_6, 90^\circ\text{C): } \delta = 3.23 (1H, m), 3.14 (1H, m), 2.80 (1H, m), 1.87 (2H, m), 1.74 (2H, m), 1.37 (9H, s), 1.19 (12H, m). \text{13C NMR (125 MHz, DMSO-}d_6, 90^\circ\text{C): } \delta = 83.48 (2 \times \text{C}), 78.54 (\text{C}), 46.42 (\text{CH}_2), 28.72 (3 \times \text{CH}_3), 25.37 (\text{CH}_2), 25.18 (4 \times \text{CH}_3), 24.83 (\text{CH}_2). \text{C=O peak not observed.} \\
\text{11B NMR (96 MHz, CDCl}_3\text{): } \delta = 33. \text{ Data in accordance with the literature.}^{[5]} \\
\text{Resolution between the enantiomers of 7 was achieved using chiral SFC analysis (Whelk 01 column, 10% IPA/hexane – iso 20%, 4 mL/min, 125 bar). } t_R = 3.53 (R), 4.47 (S).\end{align*}
\]
2.2. Optimisation of the Reaction Conditions

General Procedure for the Lithiation-Borylation Between TIB ester 8 and boronic ester 7 – GP1

8 (130 mg, 0.36 mmol, 1.10 equiv.) and TMEDA (0.05 mL, 0.32 mmol, 1.00 equiv.) were dissolved in Et₂O (3.5 mL). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.28 mL, 0.32 mmol, 1.00 equiv.) was added dropwise. The solution was stirred for 3 h at −78 °C, then 7 (100 mg, 0.33 mmol, 1.05 equiv.) was added, dissolved in Et₂O (0.5 mL). The solution was stirred for 45 min at −78 °C, after which ¹¹B NMR analysis of the crude mixture showed complete formation of boronate complex 9 [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. For conditions for the 1,2-metallate rearrangement from 9 to 10, see Table 1 below.
Table 1. Optimisation of migration conditions from ate complex 9 to boronic ester 10

| Entry | Conditions | Yield (%) |
|-------|------------|-----------|
| 1     | Et₂O, rt, 12 h | –         |
| 2     | Et₂O, reflux, 12 h | traces    |
| 3     | MgBr₂·Et₂O (2.0 equiv.), Et₂O, rt, 12 h | traces    |
| 4     | MgBr₂·Et₂O (2.0 equiv.), Et₂O, reflux, 12 h | 19%       |
| 5     | µW, Et₂O, 50 °C, 1 h | traces    |
| 6     | µW, Et₂O, 100 °C, 1 h | 56%       |
| 7     | 12-crown-4 (1.2 equiv.), Et₂O, rt, 1 h then TMSCl (1.2 equiv.), Et₂O, rt, 12 h | –         |
| 8     | H₂O (0.1 equiv.), Et₂O, rt, 1h then TMSCl (1.2 equiv.), Et₂O, rt, 12 h | –         |
| 9     | 12-crown-4 (1.2 equiv.), H₂O (0.1 equiv.), Et₂O, rt, 1 h then TMSCl (1.2 equiv.), Et₂O, rt, 12 h | –         |
| 10    | Solvent exchange to CHCl₃, rt, 12 h | traces    |
| 11    | Solvent exchange to CHCl₃, reflux, 12 h | 85%       |
| 12    | Solvent exchange to CHCl₃, MgBr₂·Et₂O (2.0 equiv.), reflux, 12 h | 73%       |
| 13    | Solvent exchange to toluene, rt, 12 h | traces    |
| 14    | Solvent exchange to toluene, reflux, 12 h | 67%       |

**tert-Butyl 2-(3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl) pyrrolidine-1-carboxylate (10)**

8 (200 mg, 0.55 mmol, 1.30 equiv.) and TMEDA (59 mg, 0.076 mL, 0.51 mmol, 1.20 equiv.) were dissolved in Et₂O (5.5 mL). The solution was cooled to –78 °C and s-BuLi (1.3 M in hexanes, 0.39 mL, 0.51 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h at –78 °C, then 7 (125 mg, 0.42 mmol, 1.00 equiv.) was
added, dissolved in Et₂O (1 mL). The solution was stirred for 45 min at −78 °C, after which ¹¹B NMR analysis of the crude mixture showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to room temperature, Et₂O was removed under high vacuum and CHCl₃ was added. The solution was heated under reflux (70 °C) for 12 h. ¹¹B NMR analysis of the crude mixture showed full product formation [¹¹B NMR (92.6 MHz, no solvent) δ = 33]. Water (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 2 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 95:5 to 90:10, to give 10 as a colourless oil (153 mg, 85%). FT-IR ν_max (film)/cm⁻¹: 2974, 1688, 1388, 1141, 698. ¹H NMR (500 MHz, DMSO-d₆, 90°C): δ = 7.28-7.12 (5H, m, Hᴬ), 3.84 (1H, m, Hᴮ), 3.40 (1H, m, Hᶜ), 3.09 (1H, m, Hᶜ), 2.62 (1H, m, Hᴰ), 2.50 (1H, m, Hᴰ), 1.94-1.47 (7H, m, Hᴱ & Hᴱ & Hᴳ & Hᴴ), 1.36 (9H, s, Hᴵ), 1.22 (12H, s, Hᴴ). ¹³C NMR (125 MHz, DMSO-d₆, 90°C): δ = 154.4 (C=O), 143.0 (C), 128.6 (2 x CH), 128.5 (2 x CH), 125.9 (CH), 83.2 (2 x C), 78.4 (C), 58.9 & 58.6 (CH), 47.6 & 46.7 (CH₂), 35.8 & 35.4 (CH₂), 30.7 & 30.1 (CH₂), 27.7 (CH₂), 24.0 & 23.6 (CH₂). ¹¹B NMR (96 MHz, CDCl₃): δ = 33. HRMS (ESI) Found: [M+Na]⁺, 438.2791. C₂₄H₃₈BNaO₄ requires [M+Na]⁺, 438.2790.
2.3. Kinetic studies for 1,2-metallate rearrangement

Preparation of 9: 8 (75 mg, 0.20 mmol, 1.20 equiv.) and TMEDA (0.03 mL, 0.19 mmol, 1.15 equiv.) were dissolved in Et₂O (3 mL). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.15 mL, 0.19 mmol, 1.15 equiv.) was added dropwise. The solution was stirred for 3 h at −78 °C, then 7 (50 mg, 0.17 mmol, 1.00 equiv.) was added, dissolved in Et₂O (0.5 mL). The solution was stirred for 45 min at −78 °C, after which ¹¹B NMR analysis of the crude mixture showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. All the volatiles were removed under high vacuum to give crude 9 that was used without further purification.

General Procedure for the ¹¹B NMR Kinetic studies – GP 2.
9 (0.17 mmol) was dissolved in the appropriate solvent (TBME or CDCl₃, 0.5 mL) and the resulting mixture was stirred for 5 min. The reaction mixture was transferred into a quartz NMR tube, immediately placed in a 300 MHz spectrometer pre-equilibrated at the desired temperature (24, 29, 35 or 45 °C) and the ¹¹B NMR acquisitions were started. The reaction progression was monitored every 30 min following the disappearance of 9 [¹¹B NMR (92.6 MHz, no solvent) δ = 7] and the appearance of 10 [¹¹B NMR (92.6 MHz, no solvent) δ = 33].
The observed rate constants at each temperature were introduced in the Eyring equation to obtain the $\Delta H^\ddagger$ and $\Delta S^\ddagger$ and entropy of the migration in each solvent:

$$\ln \frac{k_{obs}}{T} = -\frac{\Delta H^\ddagger}{R} \cdot \frac{1}{T} + \ln \frac{k_B}{h} \cdot \frac{\Delta S^\ddagger}{R}$$
Hence, plotting the logarithm of the quotient between the observed rate constant and the corresponding temperature versus the inverse of that temperature, the activation enthalpy can be obtained from the slope and the activation entropy from the intercept. The following Eyring plots were obtained:

- **TBME**: $\Delta H^* = 34 \pm 17 \text{ kcal}, \Delta S^* = 0.04 \pm 0.08 \text{ kcal/K}$
- **CHCl$_3$**: $\Delta H^* = 27 \pm 3 \text{ kcal}, \Delta S^* = 0.02 \pm 0.01 \text{ kcal/K}$

Showing a negligible variation in activation entropy between the two solvents, but a change of approximately 7 kcal between the activation entropy in TBME and CHCl$_3$, indicating a significant solvent effect for the 1,2-metallate rearrangement.
2.4. Stereocontrolled Functionalizations of 7

(R)-tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate [(R)-7]

N-Boc-pyrrolidine (3.00 g, 17.5 mmol, 1.00 equiv.) and (+)-sparteine (4.93 g, 4.80 mL, 21.0 mmol, 1.20 equiv.) were dissolved in Et₂O (180 mL). The solution was cooled to –78 °C and s-BuLi (1.3 M in hexanes, 16.2 mL, 21.0 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h at –78 °C, then i-PrOBO(pin) (4.24 g, 22.8 mmol, 1.30 equiv.) was added dropwise. The solution was stirred for 1 h at –78 °C, then allowed to warm up to room temperature slowly. Aqueous 1 M HCl (150 mL) was added and the layers were separated. The organic layers were washed with Brine (3 x 50 mL) and the combined aqueous layers were extracted with Et₂O (3 x 100 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by fast column chromatography on silica gel, eluting with petrol:EtOAc 85:15, to give (R)-7 as a white solid (4.22 g, 81%, 98:2 e.r.). [α]_D (20 °C, CHCl₃, c 1.0) = −60 [lit.⁵] for (S)-7, er 95:5, [α]_D (20 °C, CHCl₃, c 1.0) = +50.6]. Other data as above (section 2.1).

Chiral SFC analysis (Whelk 01 column, 10% IPA/hexane – iso 20%, 4 mL/min, 125 bar): t_R = 3.53 [major, (R)], 4.47 [minor, (S)].
**tert-Butyl 2-(1-hydroxy-3-phenylpropyl)pyrrolidine-1-carboxylate (11)**

10 (75 mg, 0.18 mmol, 1.0 equiv.) was dissolved in THF (2 mL). The solution was cooled to 0 °C and an aqueous solution of 2 M NaOH and 30% H₂O₂ (2:1 v/v, 6 mL) was added dropwise. The solution was stirred vigorously for 2 h at 0 °C, then it was warmed to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The layers were separated, the organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 80:20, to give 11 as an oil (53 mg, 96%). See below for spectroscopic data of the pure diastereomers.

Resolution between the enantiomers and diastereomers of 11 was achieved using chiral SFC analysis (IC column, 50% IPA/hexane – iso 10%, 3 mL/min, 125 bar). tᵣ = 10.39, 12.03 ((S,S)-11), 14.47, 17.09 ((S,R)-11).

(S)-**tert-Butyl 2-((R)-1-hydroxy-3-phenylpropyl)pyrrolidine-1-carboxylate** [(S, R)-11]

8 (200 mg, 0.55 mmol, 1.30 equiv.) and (–)-sparteine (119 mg, 0.12 mL, 0.51 mmol, 1.20 equiv.) we dissolved in Et₂O (5.5 mL). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.39 mL, 0.51 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h at −78 °C, then 7 (125 mg, 0.42 mmol, 1.00 equiv.) was
added, dissolved in Et$_2$O (1 mL). The solution was stirred for 45 min at −78 °C, after which $^{11}$B NMR analysis of the crude mixture showed complete boronate complex formation [$^{11}$B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to room temperature, Et$_2$O was removed under high vacuum and CHCl$_3$ was added. The solution was heated under reflux (70 °C) for 12 h. $^{11}$B NMR analysis of the crude mixture showed full product formation [$^{11}$B NMR (92.6 MHz, no solvent) δ = 33]. The solution was cooled to room temperature, CHCl$_3$ was removed under high vacuum and THF (6 mL) was added. The solution was cooled to 0 °C and an aqueous solution of 2 M NaOH and 30% H$_2$O$_2$ (2:1 v/v, 6 mL) was added dropwise. The solution was stirred vigorously for 2 h at 0 °C, then it was warmed to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The layers were separated, the organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 80:20, to give (S,R)-11 as an oil (99 mg, 77%, 99:1 d.r., 99:1 e.r.). [α]$_D$ (20 °C, CHCl$_3$, c 1.0) = −36. FT-IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3417 (broad), 2971, 1666, 1396, 1162, 698. $^1$H NMR (500 MHz, DMSO-$d_6$, 90°C): δ = 7.25 (2H, t, J 7.4 Hz, H$^A_1$), 7.19 (2H, d, J 7.4 Hz, H$^A_2$), 7.14 (1H, t, J 7.4 Hz, H$^A_3$), 4.38 (1H, d, J 5.5 Hz, H$^B$), 3.74 (1H, m, H$^C$), 3.62 (1H, m, H$^D$), 3.36 (1H, dt, J 10.5, 7.4 Hz, H$^E$), 3.17 (1H, ddd, J 10.5, 7.4, 6.2 Hz, H$^F$), 2.76 (1H, ddd, J 14.0, 8.2, 5.8 Hz, H$^G$), 2.58 (1H, dt, J 14.0, 8.2 Hz, H$^F$), 1.95 (1H, m, H$^G$), 1.86 (1H, dqnt, J 11.2, 7.8 Hz, H$^H_1$), 1.73 (1H, dq, J 11.8, 7.8 Hz, H$^H_2$), 1.67 (1H, m, H$^H_3$), 1.60 (2H, m, H$^I$), 1.35 (9H, s, H$^J$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, 90 °C): δ = 142.8 (C), 128.7 (2 x CH), 128.5 (2 x CH), 125.9 (CH), 78.5 (C), 70.6 (CH), 62.1 (CH), 47.1 (CH$_2$), 36.4 (CH$_2$), 32.3 (CH$_2$), 28.7 (3 x CH$_3$), 25.5 (CH$_2$), 23.4 (CH$_2$), C=O peak not observed. HRMS (ESI) Found: [M+Na]$^+$, 328.1885. C$_{18}$H$_{27}$NNaO$_3$ requires [M+Na]$^+$, 328.1883.
(S)-**tert-Butyl 2-((S)-1-hydroxy-3-phenylpropyl)pyrrolidine-1-carboxylate**

\[
(S,S)-11
\]

Following the same experimental procedure described for \((S,R)-11\) using (+)-sparteine as the chiral diamine, \((S,S)-11\) was obtained as an oil (105 mg, 82%, 99:1 d.r., 99:1 e.r.).

\[\alpha\] \(D\) (20 °C, CHCl\(_3\), c 1.0) = \(-71\)°. FT-IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3377 (broad), 2973, 1663, 1394, 1161, 699.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\), 90°C): \(\delta = 7.24\) (2H, t, \(J 7.5\) Hz, \(H^A_1\)), 7.18 (2H, d, \(J 7.5\) Hz, \(H^A_2\)), 7.44 (1H, t, \(J 7.5\) Hz, \(H^A_3\)), 4.43 (1H, br d, \(J 4.4\) Hz, \(H^B\)), 3.81 (1H, q, \(J 5.7\) Hz, \(H^C\)), 3.71 (1H, td, \(J 8.8, 5.7\) Hz, \(H^D\)), 3.39 (1H, dt, \(J 10.7, 7.6\) Hz, \(H^E\)), 3.17 (1H, dt, \(J 10.7, 6.6\) Hz, \(H^F\)), 2.78 (1H, ddd, \(J 13.8, 9.4, 5.2\) Hz, \(H^G\)), 2.58 (1H, dt, \(J 13.8, 8.0\) Hz, \(H^H\)), 1.83 (2H, m, \(H^I\)), 1.78 (1H, m, \(H^J\)), 1.69 (1H, m, \(H^K\)), 1.61 (1H, m, \(H^L\)), 1.55 (1H, m, \(H^M\)), 1.36 (9H, s, \(H^N\)).

\(^13\)C NMR (125 MHz, DMSO-\(d_6\), 90°C): \(\delta = 143.0\) (C), 128.7 (2 x CH), 128.5 (2 x CH), 125.9 (CH), 78.8 (C), 71.5 (CH), 61.6 (CH), 47.5 (CH\(_2\)), 34.4 (CH\(_2\)), 32.3 (CH\(_2\)), 28.7 (3 x CH\(_3\)), 27.0 (CH\(_2\)), 24.0 (CH\(_2\)), C=O peak not observed. HRMS (ESI) Found: [M+Na]\(^+\), 328.1887. \(C_{18}H_{27}N\)NaO\(_3\) requires [M+Na]\(^+\), 328.1883.

Chiral SFC analysis (IC column, 50% IPA/hexane – iso 10%, 3 mL/min, 125 bar): \(t_R = 10.39, 12.03\) ((S,S)-11), 14.47, 17.09 ((S,R)-11).
tert-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (12)

7 (200 mg, 0.67 mmol, 1.00 equiv.) and BrCH₂Cl (261 mg, 0.14 mL, 2.00 mmol, 3.00 equiv.) were dissolved in Et₂O (6 mL). The solution was cooled to −78 °C and n-BuLi (1.6 M in hexanes, 1.0 mL, 1.68 mmol, 2.5 equiv.) was added dropwise (very slowly). The solution was stirred for 30 min at −78 °C, then it was warmed to room temperature. ¹¹B NMR analysis of the crude mixture showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. Et₂O was removed under high vacuum and CHCl₃ was added. The solution was heated under reflux (70 °C) for 20 h. ¹¹B NMR analysis of the crude mixture showed full product formation [¹¹B NMR (92.6 MHz, no solvent) δ = 33]. The solution was cooled to room temperature, CHCl₃ was removed under high vacuum and THF (6 mL) was added. The solution was cooled to 0 °C and an
aqueous solution of 2 M NaOH and 30% H₂O₂ (2:1 v/v, 6 mL) was added dropwise. The solution was stirred vigorously for 2 h at 0 °C, then it was warmed to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The layers were separated, the organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 80:20 to 70:30, to give 12 as an oil (70 mg, 52%). ¹H NMR (500 MHz, DMSO-d₆, 90 °C): δ = 4.79 (1H, br s), 3.96 (1H, m), 3.60 (2H, m), 3.44 (1H, m), 3.32 (1H, m), 2.00 (1H, m), 1.88-1.71 (3H, m), 1.46 (9H, s). ¹³C NMR (125 MHz, DMSO-d₆, 90 °C): δ = 80.2 (C), 67.8 (CH₂), 60.2 (CH), 47.5 (CH₂), 28.7 (CH₂), 28.4 (3 x CH₃), 24.0 (CH₂), C=O peak not observed. Data in accordance with the literature.[6] Resolution of the enantiomers of 12 was achieved using chiral SFC analysis after derivatisation to 12a (vide infra).

**tert-Butyl 2-((benzoyloxy)methyl)pyrrolidine-1-carboxylate (12a)**

12 (30 mg, 0.15 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂:pyridine (2:1 v/v, 1.5 mL). The solution was cooled to 0 °C and benzoyle chloride (31 mg, 0.026 mL, 0.22 mmol, 1.5 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred for 6 h. Aqueous NH₄Cl (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 3 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 95:5, to give 12a as an oil (42 mg, 95%). ¹H NMR (500 MHz, DMSO-d₆, 90 °C): δ = 7.96 (2H, d, J 7.5 Hz), 7.64 (1H, t, J 7.5 Hz), 7.52 (2H, t, J 7.5 Hz), 4.33 (2H, m), 4.07 (1H, m), 3.36 (1H, m), 3.27 (1H, m), 2.02 (1H, m), 1.95-1.77 (3H, m), 1.39 (9H, s). ¹³C NMR (125 MHz, DMSO-d₆, 90 °C): δ = 166.1 (C=O), 154.1 (C=O), 133.6 (CH), 130.4 (C), 129.6 (2 x CH), 129.1 (2 x CH), 79.1 (C), 65.5 (CH₂), 55.9 (CH), 46.8 (CH₂), 28.6 (3 x CH₃), 23.5 (CH₂), 19.3 (CH₃). Data in accordance with the literature.[7] Resolution of the enantiomers of 12a was achieved using chiral SFC analysis (Whelk-01 column, 10% IPA/hexane – iso 20%, 4 mL/min, 125 bar). tᵣ = 11.9 min, 15.6 min.
(S)-*tert*-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate [(S)-12]

(R)-7 (200 mg, 0.67 mmol, 1.00 equiv.) and BrCH₂Cl (261 mg, 0.14 mL, 2.00 mmol, 3.00 equiv.) were dissolved in Et₂O (6 mL). The solution was cooled to −78 °C and n-BuLi (1.6 M in hexanes, 1.0 mL, 1.68 mmol, 2.5 equiv.) was added dropwise (very slowly). The solution was stirred for 30 min at −78 °C, then it was warmed to room temperature. ¹¹B NMR analysis of the crude mixture showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. Et₂O was removed under high vacuum and CHCl₃ was added. The solution was heated under reflux (70 °C) for 20 h. ¹¹B NMR analysis of the crude mixture showed full product formation [¹¹B NMR (92.6 MHz, no solvent) δ = 33]. The solution was cooled to room temperature, CHCl₃ was removed under high vacuum and THF (6 mL) was added. The solution was cooled to 0 °C and an aqueous solution of 2 M NaOH and 30% H₂O₂ (2:1 v/v, 6 mL) was added dropwise. The solution was stirred vigorously for 2 h at 0 °C, then it was warmed to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The layers were separated, the organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 80:20 to 70:30, to give (S)-12 as an oil (105 mg, 79%, 97:3 e.r., 98% e.s. - determined after derivatisation to 12a, *vide infra*). [α]D (20 °C, CHCl₃, c 1.0) = −35. Other data as above. Data in accordance with the literature[6].

When the reaction was carried out without solvent exchange (heating to reflux in Et₂O for 20 h), 12 was obtained in 40% yield (54 mg).
(S)-*tert*-Butyl 2-((benzoyloxy)methyl)pyrrolidine-1-carboxylate [(S)-12a]

(S)-12 (30 mg, 0.15 mmol, 1.0 equiv.) was dissolved in CH$_2$Cl$_2$:pyridine (2:1 v/v, 1.5 mL). The solution was cooled to 0 °C and benzoyl chloride (31 mg, 0.026 mL, 0.22 mmol, 1.5 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred for 6 h. Aqueous NH$_4$Cl (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 3 mL) and the combined aqueous layers were extracted with CH$_2$Cl$_2$ (3 x 5 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 95:5, to give 12a as an oil (44 mg, 96%, 97:3 e.r., 98% e.s.). Other data as above. Data in accordance with the literature.$^{[7]}$

Chiral SFC analysis (Whelk-01 column, 10% IPA/hexane – iso 20%, 4 mL/min, 125 bar). $t_R = 11.9$ min [(R), minor], 15.6 min [(S), major].

tert-Butyl 2-vinylpyrrolidine-1-carboxylate (13)

$n$-BuLi (1.6 M in hexanes, 1.26 mL, 2.01 mmol, 3.00 equiv.) was added dropwise to neat tetravinyltin (228 mg, 0.18 mL, 1.01 mmol, 1.50 equiv.) at room temperature under a N$_2$ atmosphere. The solution was stirred for 30 min, after which the stirring was
stopped, the white solid deposited and the colourless solution was decanted. The solid was washed with pentane (3 x 1 mL), stirring for 5 minutes and decanting the solution after each wash, then it was dissolved in THF (1.5 mL). 7 (200 mg, 0.67 mmol, 1.00 equiv.) was dissolved in Et₂O (5 mL) and cooled to −78 °C. The vinyl lithium solution was added dropwise. The solution was stirred for 30 min at −78 °C, then it was warmed to −42 °C and stirred for 20 min. ¹¹B crude NMR showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. The solution was cooled to −78 °C and a solution of iodine (533 mg, 2.01 mmol, 3.00 equiv.) in THF (2 mL) was added dropwise. The solution was stirred for 15 min at −78 °C, then a suspension of MeONa (216 mg, 4.02 mmol, 6.0 equiv.) in MeOH (2 mL) was added. The solution was warmed to room temperature and stirred for 1 h. Aqueous Na₂S₂O₃ (10 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with Et₂O (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 93:7, to give 13 as a colourless oil (100 mg, 76%). ¹H NMR (500 MHz, DMSO-d₆, 90 °C): δ = 5.76 (1H, m), 4.99 (2H, m), 4.19 (1H, m), 3.27 (2H, m), 1.97 (1H, m), 1.76 (2H, m), 1.65 (1H, m), 1.38 (9H, s). ¹³C NMR (125 MHz, DMSO-d₆, 90 °C): δ = 154.0 (C=O), 139.8 (CH), 113.7 (CH₂), 78.6 (C), 59.0 (CH), 46.5 (CH₂), 31.7 (CH₂), 28.7 (3 x CH₃), 23.1 (CH₂). Data in accordance with the literature.[⁶]

Resolution of the enantiomers of 13 was achieved using chiral GC analysis (Chiraldex β-DM column, injector T = 250 °C, detector T = 300 °C, oven conditions: T = 70 °C for 3 min then ramp (0.5 °C/min) until 110 °C, hold for 5 min then ramp (15 °C/min) until 180 °C, He carrier gas at 1.0 mL/min, tR (major) = 46.2 min, tR (minor) = 47.9 min, total analysis time 93 min).
(S)-tert-Butyl 2-vinylpyrrolidine-1-carboxylate [(S)-13]

\[ \text{N-Boc} \rightarrow \text{Li} \xrightarrow{(i)} \text{thf} \rightarrow \text{MeONa, MeOH} \rightarrow \text{N-Boc} \]

\( n\)-BuLi (1.6 M in hexanes, 1.26 mL, 2.01 mmol, 3.00 equiv.) was added dropwise to neat tetravinyltin (228 mg, 0.18 mL, 1.01 mmol, 1.50 equiv.) at room temperature under a \( \text{N}_2 \) atmosphere. The solution was stirred for 30 min, after which the stirring was stopped, the white solid deposited and the colourless solution was decanted. The solid was washed with pentane (3 x 1 mL), stirring for 5 minutes and decanting the solution after each wash, then it was dissolved in THF (1.5 mL). \( (R)\)-7 (200 mg, 0.67 mmol, 1.00 equiv.) was dissolved in Et\(_2\)O (5 mL) and cooled to \(-78^\circ\text{C}\). The vinyl lithium solution was added dropwise. The solution was stirred for 30 min at \(-78^\circ\text{C}\), then it was warmed to \(-42^\circ\text{C}\) and stirred for 20 min. \(^{11}\)B crude NMR showed complete boronate complex formation [\(^{11}\)B NMR (92.6 MHz, no solvent) \( \delta = 7 \)]. The solution was cooled to \(-78^\circ\text{C}\) and a solution of iodine (533 mg, 2.01 mmol, 3.00 equiv.) in THF (2 mL) was added dropwise. The solution was stirred for 15 min at \(-78^\circ\text{C}\), then a suspension of MeONa (216 mg, 4.02 mmol, 6.0 equiv.) in MeOH (2 mL) was added. The solution was warmed to room temperature and stirred for 1 h. Aqueous \( \text{Na}_2\text{S}_2\text{O}_3 \) (10 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with Et\(_2\)O (3 x 5 mL). The organic layers were combined, dried over MgSO\(_4\) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 93:7, to give (S)-13 as a colourless oil (107 mg, 81\%, 98:2 e.r., 100\% e.s.). \([\alpha]_D \) (20 °C, CHCl\(_3\), c 1.0) = \(-6\). Other data as above. Data in accordance with the literature.\(^{[6]}\)

Chiral GC analysis (Chiraldex \( \beta\)-DM column, injector \( T = 250^\circ\text{C} \), detector \( T = 300^\circ\text{C} \), oven conditions: \( T = 70^\circ\text{C} \) for 3 min then ramp (0.5 °C/min) until 110 °C, hold for 5 min then ramp (15 °C/min) until 180 °C, He carrier gas at 1.0 mL/min, \( t_R \) (major) = 46.2 min, \( t_R \) (minor) = 47.9 min, total analysis time 93 min):
2.5. Natural charge (NBO) calculations

Matteson homologation boron-ate complex

- Comparison between migrating groups – N-Boc pyrrolidine (I) vs. isopropyl (II)

To further probe the substituent effect on the reactivity, theoretical calculations were performed. Molecular mechanics (MM) conformational searches were completed on I and II using the default MMFF force field in Spartan ‘14.\[^8\] A number of conformers were selected for further geometry optimisation using the GAUSSIAN (version GAUSSIAN09)\[^9\] software package and were carried out at the density functional level of theory, using the hybrid functional B3LYP.\[^10\] For all elements, the split-valence double-zeta polarized basis set 6-31G* was employed. Calculations were performed on isolated molecules and NPA charge analysis was carried out by using NBO 3.1.\[^11\] Vibrational frequencies were not computed. Results from NPA analysis are shown below. Note that only results from the lowest energy conformer are displayed, with conformers of higher energy showing negligible deviation in charges.

|          | C\textsubscript{10}  | B\textsubscript{29} | C\textsubscript{50} | Cl\textsubscript{53} | OBO fragm. | CH\textsubscript{2}Cl fragm. |
|----------|----------------------|---------------------|---------------------|---------------------|-------------|-----------------------------|
| Pyrrolidine | −0.363               | 0.949               | −0.680              | −0.196              | −0.154      | −0.421                      |
| C\textsubscript{4} | B\textsubscript{5}    | C\textsubscript{26} | Cl\textsubscript{29} | OBO fragm.         | CH\textsubscript{2}Cl fragm. |
| Isopropyl   | −0.594               | 0.967               | −0.680              | −0.206              | −0.162      | −0.429                      |
XYZ coordinates for calculated structures discussed

**Pyrrolidine (I)**

E = -1468.68539886 H

| Atom | X          | Y          | Z         |
|------|------------|------------|-----------|
| C    | 0.49287700 | 2.60220600 | 1.49087000|
| H    | -0.26171400| 3.09578200 | 2.12417700|
| H    | 1.42153900 | 2.54519400 | 2.06755400|
| C    | 0.67501700 | 3.39024000 | 0.18199600|
| H    | 1.61929100 | 3.09314200 | -0.28345700|
| C    | 0.67501700 | 3.39024000 | 0.18199600|
| H    | -0.26171400| 2.60220600 | 1.49087000|
| C    | 0.00103900 | 1.21185200 | 1.02176500|
| H    | -0.68014100| 0.78417600 | 1.76300100|
| N    | -0.83113100| 1.59860300 | -0.16681100|
| C    | -1.97080700| 1.01148300 | -0.58098900|
| O    | 0.75699100 | 2.30182500 | 0.02593600|
| O    | 1.74546700 | 2.10555000 | -0.96370100|
| H    | 1.83529700 | -2.37179400| -1.76883800|
| H    | 2.09891700 | -2.01852700| -1.59069600|
| C    | -3.18016400| -0.81674900| -2.34259000|
| C    | -3.25017100| -2.06950200| 0.89916600|
| C    | -3.41025000| -1.64258600| 1.89559800|
| C    | -2.25126400| -2.51622700| 0.88133900|
| C    | -4.00015900| -2.85223900| 0.72745700|
| C    | -4.73011700| -0.28615700| -1.00428000|
| C    | -4.87192200| 0.15875800 | 0.89221300|
| C    | -5.53090600| -1.02022200| -0.26410600|
| C    | -4.80617400| 0.50222100 | -0.85243300|
| B    | 1.22012700 | 0.11762700 | 0.75364300|
| O    | 2.37920800 | 0.64516600 | 0.00507400|
| O    | 0.75699100 | 1.05619600 | -0.02539600|
| C    | 2.50491400 | -0.08401900| -1.26658700|
| C    | 1.74546700 | -1.44092000| 0.96370100|
| C    | 1.83855600 | 0.71534000 | -2.40772600|
| C    | 2.27927100 | 1.71957600 | -2.43536900|
| C    | 0.76420000 | 0.81903400 | -2.23635300|
| H    | 1.99354300 | 0.24820300 | -3.39000200|
| C    | 3.99807200 | -0.24326300| -1.59730500|
| H    | 4.54622800 | -0.69206300| -0.76393100|
| C    | 4.43561300 | 0.74471900 | -1.78985700|
| H    | 4.15083100 | -0.86201000| -2.49296500|
| C    | 1.04677900 | -2.06476700| -2.18344200|
| H    | 0.55654400 | -2.99945200| -1.88276700|
| H    | 1.76356300 | -2.30065900| -2.98265800|
| H    | 0.27900000 | -1.39933500| -2.58574700|
| C    | 2.66922800 | -2.52269500| -0.35346600|
| H    | 3.27065200 | -2.13128200| 0.47044200|
| H    | 3.35130500 | -2.95059800| -1.10148900|
| H    | 2.04117900 | -3.32917700| 0.04304800|
| C    | 1.91343600 | -0.26924800| 2.21925400|
| H    | 2.39699200 | 0.58850700 | 2.69863300|
| H    | 2.66136300 | -1.06017600| 2.13224100|
| Cl   | 0.75811500 | -0.91678200| 3.54030900|

SI-26
Isopropyl (II)

E = -1029.37521109 H

|  | x       | y       | z        |
|---|---------|---------|----------|
| C | 2.251286 | 2.122001 | -0.796452 |
| H | 2.696844 | 3.089313 | -0.504020 |
| H | 3.084424 | 1.445473 | -1.036517 |
| C | 1.361500 | 1.532903 | 0.313943  |
| B | 0.523923 | 0.190341 | -0.159956 |
| O | -0.563624 | 0.526886 | -1.165189 |
| O | -0.245712 | -0.371328 | 0.993631  |
| C | -1.835043 | 0.403973 | -0.559099 |
| C | -1.584164 | -0.623518 | 0.622028  |
| C | -2.292052 | 1.789866 | -0.043445 |
| H | -2.242670 | 2.502111 | -0.876281 |
| H | -1.631827 | 2.153739 | 0.748655  |
| H | -3.322761 | 1.774376 | 0.339020  |
| C | -2.847854 | -0.069371 | -1.615358 |
| H | -2.308027 | -0.985259 | -2.107398 |
| H | -2.957298 | 0.702671 | -2.388053 |
| H | -3.838523 | -0.252641 | -1.174878 |
| C | -2.480599 | -0.413957 | 1.855095  |
| H | -2.233875 | -1.167194 | 2.614247  |
| H | -3.546878 | -0.516707 | 1.607142  |
| H | -2.315946 | 0.571455 | 2.299988  |
| C | -1.740459 | -2.096379 | 0.171160  |
| H | -1.186959 | -2.297030 | -0.749907 |
| H | -2.792313 | -2.371477 | 0.008474  |
| H | -1.330340 | -2.742190 | 0.956754  |
| C | 1.412845 | -0.938840 | -0.994329 |
| H | 1.828093 | -0.526709 | -1.920016 |
| H | 0.820405 | -1.817695 | -1.259921 |
| Cl | 2.906965 | -1.687827 | -0.143573 |
| H | 1.678633 | 2.285087 | -1.720082 |
| H | 0.584271 | 2.287929 | 0.526443 |
| C | 2.172141 | 1.362310 | 1.612907 |
| H | 1.542130 | 0.957796 | 2.414950 |
| H | 2.594020 | 2.322537 | 1.961695 |
| H | 3.009665 | 0.667375 | 1.473982 |
3. Lithiation-Borylation with Boronic Ester 15

** tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (15)**

N-Boc-piperidine (14) (2.00 g, 10.8 mmol, 1.00 equiv.) and TMEDA (1.95 mL, 13.0 mmol, 1.20 equiv.) were dissolved in Et₂O (100 mL). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 10.0 mL, 13.0 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h at −78 °C, then i-PrOB(pin) (2.61 g, 2.86 mL, 14.0 mmol, 1.30 equiv.) was added dropwise. The solution was stirred for 1 h at −78 °C, then allowed to warm up to room temperature slowly. Aqueous 1 M HCl (150 mL) was added and the layers were separated. The organic layers were washed with Brine (3 x 50 mL) and the combined aqueous layers were extracted with Et₂O (3 x 100 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by fast column chromatography on silica gel, eluting with petrol:EtOAc 85:15, to give 15 as an oil (1.89 g, 56%).

** FT-IR νmax (film)/cm⁻¹:** 2933, 1609, 1370, 1157.

** ¹H NMR (400 MHz, CDCl₃):** δ = 3.72 (1H, br d, J 12.7, H⁴), 2.74 (1H, td, J 12.4, 2.93, H⁵), 2.30 (1H, dd, J 12.6, 3.2, H⁶), 1.81 (1H, m, H⁷), 1.65-1.54 (2H, m, H⁸ & H⁹), 1.49 (9H, s, H¹⁰), 1.44 (1H, m, H¹¹), 1.40-1.29 (2H, m, H¹² & H¹³), 1.19 (12H, s, H¹⁴). ¹³C NMR (100 MHz, CHCl₃): δ = 139.8 (C=O), 85.6 (2 x C), 79.9 (C), 42.4 (CH₂), 28.4 (3 x CH₃), 26.5 (CH₂), 25.1 (4 x CH₃), 24.9 (CH₂), 24.4 (CH₂). ¹¹B NMR (96 MHz, CDCl₃): δ = 16. HRMS (ESI) Found: [M+Na]⁺, 334.2170. C₂₀H₃₁NNaO₃ requires [M+Na]⁺, 334.2160.

** tert-Butyl 2-(3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)piperidine-1-carboxylate (16)**

8 (200 mg, 0.55 mmol, 1.30 equiv.) and TMEDA (59 mg, 0.076 mL, 0.51 mmol, 1.20 equiv.) we dissolved in Et₂O (5.5 mL). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.39 mL, 0.51 mmol, 1.20 equiv.) was added dropwise. The
solution was stirred for 3 h at −78 °C, then 15 (131 mg, 0.42 mmol, 1.00 equiv.) was added, dissolved in Et₂O (1 mL). The solution was stirred for 45 min at −78 °C, after which ¹¹B NMR analysis of the crude mixture showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to room temperature, Et₂O was removed under high vacuum and CHCl₃ was added. The solution was heated under reflux (70 °C) for 12 h. ¹¹B NMR analysis of the crude mixture showed full product formation [¹¹B NMR (92.6 MHz, no solvent) δ = 33]. Water (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 2 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 95:5 to 90:10, to give 16 as a colourless oil (150 mg, 83%). FT-IR ν max (film)/cm⁻¹: 2930, 1685, 1414, 1253, 1160, 1029, 698. ¹H NMR (500 MHz, DMSO-d₆, 90°C): δ = 7.27-7.09 (5H, m, H₅), 4.22 (1H, app. d, J 11.6 Hz, H¹), 3.78 (1H, app. d, J 13.1 Hz, H₃), 2.64 (1H, m, H²), 2.55 (1H, app. t, J 13.1 Hz, H₄), 2.44 (1H, m, H³), 1.65-1.41 (8H, m, H⁵ & H⁶ & H⁷ & H⁸), 1.35 (9H, s, H¹), 1.24 (12H, s, H¹), 1.18 (1H, m, H¹). ¹³C NMR (125 MHz, DMSO-d₆, 90°C): δ = 154.8 (C=O), 142.9 (C), 128.6 (2 x CH), 128.4 (2 x CH), 125.9 (CH), 83.5 (2 x C), 78.6 (C), 51.7 (CH), 38.5 (CH₂), 34.9 (CH₂), 30.2 (CH₂), 29.6 (CH₂), 28.7 (3 x CH₃), 25.6 (CH₂), 25.1 (4 x CH₃), 19.2 (CH₂). ¹¹B NMR (96 MHz, CDCl₃): δ = 33. HRMS (ESI) Found: [M+Na]⁺, 452.2941. C₂₅H₄₀BNNaO₄ requires [M+Na]⁺, 452.2947.
4. Synthesis of Building Block 6

\[
\begin{array}{c}
\text{HO} \quad \text{DBU} \quad \text{DMF, } -42 \degree C \\
\text{14} \quad \text{86%} \quad \text{OTBDPS} \\
\text{28} \\
\text{OTBDPS} \\
\text{6}
\end{array}
\]

\((R)-4-((\text{tert-Butyldiphenylsilyl})\text{oxy})-2\text{-methylbutan-1-ol (28)}\)

Following a literature procedure\[12\], a solution of \((R)-2\text{-methylbutane-1,4-diol (14)}\) (500 mg, 0.51 mL, 4.80 mmol, 1.00 equiv.) in dry DMF (20 mL) was cooled to \(-42 \degree C\). DBU (1.10 g, 1.08 mL, 7.20 mmol, 1.50 equiv.) was added, followed by a slow dropwise addition of tert-butyldiphenylsilyl chloride (1.39 g, 1.29 mL, 5.04 mmol, 1.05 equiv.). The solution was stirred for 8 h at \(-42 \degree C\), then aqueous \(\text{NaHCO}_3\) (20 mL) was added. The solution was diluted with \(\text{Et}_2\text{O}\) and the layers were separated. The organic layer was washed with \(\text{Brine (10 mL)}\) and the combined aqueous layers were extracted with \(\text{Et}_2\text{O (3 x 10 mL)}\). The organic layers were combined, dried over \(\text{MgSO}_4\) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 90:10 to 80:20, to give 28 as a colourless oil (1.42 g, 86%). \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 7.70-7.65 (4\text{H, m}), 7.47-7.36 (6\text{H, m}), 3.80-3.65 (2\text{H, m}), 3.54-3.44 (2\text{H, m}), 1.90-1.79 (1\text{H, m}), 1.69-1.58 (1\text{H, m}), 1.54-1.44 (1\text{H, m}), 1.05 (9\text{H, s}), 0.90 (3\text{H, d, } J = 6.5 \text{ Hz})\). \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta = 135.6 (4 \text{ x CH}), 133.4 (2 \text{ x C}), 129.6 (2 \text{ x CH}), 127.7 (4 \text{ x CH}), 68.3 (\text{CH}_2), 63.8 (\text{CH}_2), 36.7 (\text{CH}_2), 33.9 (\text{CH}), 26.8 (3 \text{ x CH}_3), 19.1 (\text{C}), 17.2 (\text{CH}_3)\). Data in accordance with the literature\[12\].

\((R)-4-((\text{Ter}-\text{butyldiphenylsilyl})\text{oxy})-2\text{-methylbutyl 2,4,6-triisopropylbenzoate (6)}\)

To a solution of 28 (1.24 g, 3.6 mmol, 1.1 equiv.) in THF (15 mL, 0.25 M) were added \(\text{Ph}_3\text{P (944 mg, 3.6 mmol, 1.1 equiv.)}\) and 2,4,6-triisopropylbenzoic acid (813 mg, 3.3 mmol, 1.0 equiv.). The mixture was cooled to 0 \degree C, then diisopropylaceticarboxylate (729 mg, 0.71 mL, 3.6 mmol, 1.1 equiv.) was added dropwise. The solution was stirred
for 30 min at 0 °C, then it was warmed to room temperature and stirred for 4 h. Saturated NH₄Cl (10 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with Et₂O (3 x 10 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was triturated with petrol, then it was purified by column chromatography on silica gel, eluting with petrol:EtOAc 99:1 to 97:3, to give 6 as a colourless oil (1.70 g, 90%). [α]D (20 °C, CHCl₃, c 1.0) = −3. FT-IR νmax (film)/cm⁻¹: 2960, 1724, 1461, 1249, 1074, 700. ¹H NMR (400 MHz, CDCl₃): δ = 7.69-7.63 (4H, m, H₁), 7.45-7.33 (6H, m, H₆ & H₇), 7.00 (2H, s, H₁), 4.22 (1H, dd, J = 10.9, 5.5 Hz, H₁), 4.11 (1H, dd, J = 10.9, 6.7 Hz, H₁), 3.73 (2H, m, H₁), 2.90 (1H, sept, J = 6.8 Hz, H₁), 2.85 (2H, sept, J = 6.8 Hz, H₁), 2.14 (1H, m, H₁), 1.76 (1H, m, H₁), 1.44 (1H, m, H₁), 1.26 (6H, d, J = 6.8 Hz, H₁), 1.24 (12H, d, J = 6.8 Hz, H₁), 1.05 (9H, s, H₁), 0.97 (3H, d, J = 6.4 Hz, H₁). ¹³C NMR (100 MHz, CDCl₃): δ = 171.2 (C=O), 150.0 (C), 144.7 (2 x C), 135.5 (4 x CH), 133.8 (2 x C), 130.7 (C), 129.6 (2 x CH), 127.6 (4 x CH), 120.8 (2 x CH), 70.0 (CH₂), 61.5 (CH₂), 36.0 (CH₂), 34.4 (CH), 31.5 (2 x CH), 29.3 (CH), 26.8 (3 x CH₃), 24.2 (2 x CH₃), 23.9 (4 x CH₃), 19.2 (C), 16.9 (CH₃). HRMS (ESI) Found: [M+Na]⁺, 595.3596. C₃₇H₅₂NaO₃Si requires [M+Na]⁺, 595.3578.
4. Synthesis of 5 via Lithiation-Borylation-Zweifel Olefination

**tert-Butyl** (S)-2-((1R,2R)-4-((tert-butylidiphenylsilyloxy)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pyrrolidine-1-carboxylate (18)

6 (100 mg, 0.17 mmol, 1.30 equiv.) and (−)-sparteine (37.5 mg, 0.037 mL, 0.16 mmol, 1.20 equiv.) were dissolved in Et₂O (2 mL, 0.1 M). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.12 mL, 0.16 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h 30 min at −78 °C, then (R)-7 (40 mg, 0.13 mmol, 1.00 equiv.) was added, dissolved in Et₂O (0.5 mL). The solution was stirred for 45 min at −78 °C, after which ¹¹B NMR analysis of the crude mixture showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to room temperature, Et₂O was removed under high vacuum and CHCl₃ was added. The solution was heated under reflux (70 °C) for 36 h. ¹¹B NMR analysis of the crude mixture showed full product formation [¹¹B NMR (92.6 MHz, no solvent) δ = 33]. Water (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 2 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 90:10, to give 18 as a colourless oil (47 mg, 58%, 96:4 d.r.). [α]₀ (20 °C, CHCl₃, c 1.0) = −27. FT-IR ν_max (film)/cm⁻¹: 2930, 1690, 1388, 1106, 701. ¹H NMR (500 MHz, DMSO-d₆, 90°C): δ = 7.62 (4H, m, H⁴), 7.42 (6H, m, H₆ & H₆'), 3.85 (1H, m, H³), 3.71 (2H, m, H⁵), 3.44 (1H, m, H⁶), 3.08 (1H, m, H⁶'), 1.93-1.56 (7H, m, H⁴ & H⁴' & H⁵ & H⁵' & H⁷), 1.39 (9H, s, H₇), 1.32 (1H, m, H₈), 1.19 (6H, s, H₉), 1.17 (6H, s, H₉'), 1.02 (9H, s, H₉''), 0.84 (3H, d, J 6.5 Hz, H₈). ¹³C NMR (125 MHz, DMSO-d₆, 90 °C): δ = 155.4 (C=O), 135.4 (4 x CH), 134.3 (2 x
C), 130.2 (2 x CH), 128.1 (4 x CH), 83.0 (2 x C), 78.4 (CH2), 57.5 (CH), 46.8 (CH2), 39.4 (CH), 29.6 (CH2), 29.3 (CH), 27.3 (3 x CH3), 25.2 (2 x CH3), 25.1 (2 x CH3), 19.7 (CH3), 19.2 (C).

$^{11}$B NMR (96 MHz, CDCl3): δ = 33. HRMS (ESI) Found: [M+Na]$^+$, 644.3893, [M+H]$^+$, 622.4076. C$_{36}$H$_{56}$NaBNO$_5$Si requires [M+Na]$^+$, 644.3893, C$_{36}$H$_{56}$BNO$_5$Si requires [M+H]$^+$, 622.4100.

(2S)-tert-Butyl 2-((2R)-4-((tert-butyldiphenylsilyl)oxy)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pyrrolidine-1-carboxylate (18b)

6 (150 mg, 0.26 mmol, 1.30 equiv.) and TMEDA (0.035 mL, 0.24 mmol, 1.20 equiv.) were dissolved in Et$_2$O (2 mL, 0.1 M). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.18 mL, 0.24 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h 30 min at −78 °C, then (R)-7 (60 mg, 0.20 mmol, 1.00 equiv.) was added, dissolved in Et$_2$O (0.5 mL). The solution was stirred for 45 min at −78 °C, after which $^{11}$B NMR analysis of the crude mixture showed complete boronate complex formation [$^{11}$B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to room temperature, Et$_2$O was removed under high vacuum and CHCl$_3$ was added. The solution was heated under reflux (70 °C) for 36 h. $^{11}$B NMR analysis of the crude mixture showed full product formation [$^{11}$B NMR (92.6 MHz, no solvent) δ = 33]. Water (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 2 mL) and the combined aqueous layers were extracted with CH$_2$Cl$_2$ (3 x 5 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 90:10, to give 18b as a colourless oil (78 mg, 63%). Characterisation data as above.
**tert-Butyl 2-((2R)-4-((tert-butyldiphenylsilyl)oxy)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)pyrrolidine-1-carboxylate (18a)**

6 (100 mg, 0.26 mmol, 1.30 equiv.) and TMEDA (0.037 mL, 0.24 mmol, 1.20 equiv.) were dissolved in Et₂O (2 mL, 0.1 M). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.18 mL, 0.24 mmol, 1.20 equiv.) was added dropwise. The solution was stirred for 3 h 30 min at −78 °C, then 7 (60 mg, 0.20 mmol, 1.00 equiv.) was added, dissolved in Et₂O (0.5 mL). The solution was stirred for 45 min at −78 °C, after which ¹¹B NMR analysis of the crude mixture showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to room temperature, Et₂O was removed under high vacuum and CHCl₃ was added. The solution was heated under reflux (70 °C) for 36 h. ¹¹B NMR analysis of the crude mixture showed full product formation [¹¹B NMR (92.6 MHz, no solvent) δ = 33]. Water (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 2 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 90:10, to give 18 as a colourless oil (72 mg, 58%). Characterisation data as above.

Resolution between the diastereomers in 18a and 18b was achieved using chiral SFC analysis (Whelk-01 column, 10% IPA/Hexane – iso 20%, 4 mL/min, 125 bar). tᵣ 7.29, 8.28, 8.77, 10.96 (major, 18).
18a
4 diastereomers

18b
2 diastereomers

18
single diastereomer
**tert-Butyl (S)-2-(((3R,4R)-6-((tert-butyldiphenylsilyl)oxy)-4-methylhex-1-en-3-yl)pyrrolidine-1-carboxylate (5)**

\[ \text{5} \] 0.50 mmol, 1.00 equiv.) was dissolved in Et\(_2\)O (5 mL) and cooled to –78 °C. The vinyl lithium solution was added dropwise. The solution was stirred for 30 min at –78 °C, then it was warmed to –42 °C and stirred for 20 min. \(^{11}\)B crude NMR showed complete boronate complex formation \([^{11}\text{B NMR (92.6 MHz, no solvent) } \delta = 7]\). The solution was cooled to –78 °C and a solution of iodine (630 mg, 2.48 mmol, 5.00 equiv.) in THF (4 mL) was added dropwise. The solution was stirred for 15 min at –78 °C, then a suspension of MeONa (268 mg, 4.96 mmol, 10.0 equiv.) in MeOH (2 mL) was added. The solution was warmed to room temperature and stirred for 1 h. Aqueous Na\(_2\)S\(_2\)O\(_3\) (10 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with Et\(_2\)O (3 x 5 mL). The organic layers were combined, dried over MgSO\(_4\) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 95:5, to give 5 as a colourless oil (185 mg, 71%). \([\alpha]_D(20 ^\circ \text{C}, \text{CHCl}_3, c 1.0) = -47\). **FT-IR** \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2930, 1690, 1456, 1389, 1105, 700. **\(^1\)H NMR** (500 MHz, DMSO-\(d_6\), 90°C): \(\delta = 7.62\) (4H, m, H\(^A\)), 7.42 (6H, m, H\(^B\) & H\(^B1\)), 5.60 (1H, dt, \(J \text{ 10.5, 1.2 Hz}\), H\(^C\)), 5.05 (1H, dd, \(J 10.5, 2.5 \text{ Hz}\), H\(^D\)), 4.90 (1H, dd, \(J 17.2, 2.5 \text{ Hz}\), H\(^E\)), 3.92 (1H, m, H\(^F\)), 3.71 (2H, m, H\(^G\)), 3.36 (1H, m, H\(^H\)), 3.04 (1H, m, H\(^I\)), 2.38 (1H, m, H\(^J\)), 1.87-1.56 (6H, m, H\(^K\) & H\(^L\) & H\(^M\) & H\(^N\)), 1.39 (9H, s, H\(^O\)), 1.23 (1H, m, H\(^P\)), 1.02 (9H, s, H\(^Q\)), 0.86 (3H d, \(J 6.4 \text{ Hz}\), H\(^R\)). **\(^{13}\)C NMR** (125 MHz, DMSO-\(d_6\), 90°C): \(\delta = 153.9\) (C=O), 138.1 (CH), 135.5 (4 x CH), 134.1 (2 x C), 130.1 (2 x CH), 128.1 (4 x CH), 118.0 (CH\(_2\)), 78.5 (C), 62.4 (CH\(_2\)), 58.7 (CH), 51.8 (CH), 46.9 (CH\(_2\)), 37.4 (CH\(_2\)), 30.8 (CH), 28.7 (3 x CH\(_3\)), 27.3 (3 x CH\(_3\)), 26.4 (CH\(_2\)), 23.8 (CH\(_2\)), 19.2 (C),
17.9 (CH₃). **HRMS** (ESI) Found: [M+Na]+, 544.3209, [M+H]+, 522.3391. C₃₂H₄₇NaNO₃Si requires [M+Na]+, 544.3217, C₃₂H₄₇NO₃Si requires [M+H]+, 522.3398.

**One-pot lithiation-borylation-Zweifel olefination procedure from 6 and 7 to 5:**

6 (2.52 g, 4.40 mmol, 1.00 equiv.) and (−)-sparteine (1.24 g, 1.20 mL, 5.30 mmol, 1.20 equiv.) were dissolved in Et₂O (45 mL). The mixture was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 4.08 mL, 5.30 mmol, 1.20 equiv.) was added. The mixture was stirred for 4 h at −78 °C, then 7 (1.58 g, 5.30 mmol, 1.20 equiv.) in Et₂O (5 mL) was added. The solution was stirred for 45 min at −78 °C, after which crude ¹¹B NMR showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to room temperature, Et₂O was removed under high vacuum and CHCl₃ (45 mL) was added. The solution was heated under reflux (70 °C) for 36 h. Crude ¹¹B NMR showed full product formation [¹¹B NMR (92.6 MHz, no solvent) δ = 33]. CHCl₃ was removed under vacuum and Et₂O (45 mL) was added. The mixture was cooled to −78 °C and a freshly prepared solution of vinyl lithium (from tetravinyl tin 2.5 g, 2.0 mL, 11 mmol, 2.5 equiv, and n-BuLi, 1.6 M in hexanes, 13.75 mL, 22 mmol, 5.0 equiv.) in THF (20 mL) was added. The solution was stirred for 30 min at −78 °C, then it was warmed to −42 °C and stirred for 20 min. ¹¹B crude NMR showed complete boronate complex formation [¹¹B NMR (92.6 MHz, no solvent) δ = 7]. The solution was cooled to −78 °C and a solution of iodine (5.60 g, 22.0 mmol, 5.00 equiv.) in THF (15 mL) was added dropwise. The solution was stirred for 15 min at −78 °C, then a suspension of MeONa (2.38 mg, 44.0 mmol, 10.0 equiv.) in MeOH (10 mL) was added. The solution was warmed to room temperature and stirred for 1 h. Aqueous Na₂S₂O₃ (70 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 30 mL) and the combined aqueous layers were extracted with Et₂O (3 x 30 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 95:5, to give 5 as a colourless oil (1.6 g, 70%). Data as above.
5. Synthesis of 20

[Diagram of synthetic pathway]

**tert-Butyl** (S)-2-((3R,4R)-6-hydroxy-4-methylhex-1-en-3-yl)pyrrolidine-1-carboxylate (29)

To a solution of 5 (970 mg, 1.86 mmol, 1.0 equiv.) in THF (20 mL) was added tetrabutylammonium fluoride (1.00 M in THF, 3.70 mL, 3.71 mmol, 2.00 equiv.) dropwise at 0 °C. The solution was stirred for 16 h warming to room temperature. Aqueous NH₄Cl (20 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with Et₂O (3 x 10 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol: EtOAc 80:20 to 75:25, to give 29 as a colourless oil (525 mg, 98%). [α]D (20 °C, CHCl₃, c 1.0) = –2.

**FT-IR** ν<sub>max</sub> (film)/cm⁻¹: 3410 (broad), 2925, 1693, 1392, 1168.

**1H NMR** (500 MHz, DMSO-d₆, 90 °C): δ = 5.64 (1H, dt, J 17.0, 9.7 Hz, H<sup>A</sup>), 5.07 (1H, dd, J 9.7, 2.0 Hz, H<sup>B</sup>), 4.92 (1H, dd, J 17.0, 2.0 Hz, H<sup>C</sup>), 3.95 (1H, m, H<sup>D</sup>), 3.51-3.34 (3H, m, H<sup>E</sup> & H<sup>F</sup>), 3.05 (1H, m, H<sup>G</sup>), 2.39 (1H, m, H<sup>H</sup>), 1.90-1.62 (5H, m, H<sup>I</sup> & H<sup>J</sup> & H<sup>K</sup>), 1.57 (1H, m, H<sup>L</sup>), 1.42 (9H, s, H<sup>M</sup>), 1.11 (1H, m, H<sup>N</sup>), 0.91 (3H, d, J 7.7 Hz, H<sup>0</sup>). **13C NMR** (125 MHz, DMSO-d₆, 90 °C): δ = 154.0 (C=O), 138.4 (CH), 117.8 (CH₂), 78.5 (C), 59.5 (CH₂), 58.7 (CH), 52.1 (CH), 46.9 (CH₂), 37.8 (CH₂), 30.9 (CH), 28.8 (3 x CH₃), 26.5 (CH₂), 23.9 (CH₂), 18.0 (CH₃).

**HRMS** (ESI) Found: [M+Na]<sup>+</sup>, 306.2028, [M+H]<sup>+</sup>, 284.2211. C<sub>16</sub>H<sub>29</sub>NaNO₃ requires [M+Na]<sup>+</sup>, 306.2040, C<sub>16</sub>H<sub>29</sub>NO₃ requires [M+H]<sup>+</sup>, 284.2220.
**tert-Butyl (S)-2-((3R,4R)-4-methyl-6-((2,4,6-trisopropylbenzoyl)oxy)hex-1-en-3-yl)pyrrolidine-1-carboxylate (19)**

To a solution of 29 (431 mg, 1.52 mmol, 1.10 equiv.) in THF (0.25 M, 6 mL) were added triphenylphosphine (400 mg, 1.52 mmol, 1.10 equiv.) and triisopropylbenzoic acid (343 mg, 1.38 mmol, 1.00 equiv.). The solution was cooled to 0 °C and diisopropylazadicarbozylate (307 mg, 0.30 mL, 1.52 mmol, 1.10 equiv.) was added dropwise. The solution was stirred for 30 min at 0 °C, then it was warmed to room temperature and stirred for another 4 h. Aqueous NH₄Cl (10 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with Et₂O (3 x 10 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 95:5 to 90:10, to give 19 as an oil (685 mg, 96%). |α|<sub>d</sub> (20 °C, CHCl₃, c 1.0) = −50. **FT-IR** ν<sub>max</sub> (film)/cm<sup>−1</sup>: 2962, 1722, 1681, 1460, 1391, 1250, 753. **¹H NMR** (500 MHz, DMSO-<sup>d₆</sup>, 90 °C): δ = 7.05 (2H, s, H<sub>A</sub>), 5.65 (1H, dt, J<sub>16.8, 9.9 Hz</sub>, H<sub>B</sub>), 5.09 (1H, dd, J<sub>9.9, 1.8 Hz</sub>, H<sub>C</sub>), 4.96 (1H, dd, J<sub>16.8, 1.8 Hz</sub>, H<sub>D</sub>), 4.30 (2H, m, H<sub>E</sub>), 3.96 (1H, m, H<sub>F</sub>), 3.38 (1H, m, H<sub>G</sub>), 3.06 (1H, m, H<sub>G</sub>), 2.90 (1H, sept, J<sub>6.7 Hz</sub>, H<sub>I</sub>), 2.80 (2H, sept, J<sub>6.7 Hz</sub>, H<sub>J</sub>), 2.43 (1H, m, H<sub>J</sub>), 1.97 (1H, m, H<sub>K</sub>), 1.85 (1H, m, H<sub>L</sub>), 1.80-1.57 (4H, m, H<sub>L</sub> & H<sub>M</sub> & H<sub>N</sub>), 1.41 (9H, s, H<sub>O</sub>), 1.36 (1H, m, H<sub>K</sub>), 1.22 (6H, d, J<sub>6.7 Hz</sub>, H<sub>P</sub>), 1.19 (12 H, d, J<sub>6.7 Hz</sub>, H<sub>Q</sub>), 0.98 (3H, d, J<sub>7.0 Hz</sub>, H<sub>R</sub>). **¹³C NMR** (125 MHz, DMSO-<sup>d₆</sup>, 90 °C): δ = 170.3 (C=O), 154.0 (C=O), 150.2 (C), 144.8 (2 x C), 137.8 (CH), 121.0 (2 x CH), 118.2 (CH<sub>2</sub>), 78.6 (C), 63.5 (CH<sub>2</sub>), 58.5 (CH), 51.6 (CH), 46.9 (CH<sub>2</sub>), 34.0 (CH), 33.4 (CH<sub>2</sub>), 31.3 (2 x CH), 31.1 (CH), 28.7 (3 x CH<sub>3</sub>), 26.6 (CH<sub>2</sub>), 24.2 (4 x CH<sub>3</sub>), 24.1 (2 x CH<sub>3</sub>), 23.8 (CH<sub>2</sub>), 17.6 (CH<sub>3</sub>). **HRMS** (ESI) Found: [M+Na]<sup>+</sup>, 536.3710, [M+H]<sup>+</sup>, 514.3892. C<sub>32</sub>H<sub>51</sub>NaNO₄ requires [M+Na]<sup>+</sup>, 536.3710, C<sub>32</sub>H<sub>52</sub>NO₄ requires [M+H]<sup>+</sup>, 514.3891.
(3R,4R)-3-Methyl-4-((S)-pyrrolidin-2-yl)hex-5-en-1-yl 2,4,6-triisopropylbenzoate (30)

\[
\begin{align*}
\text{To a solution of 19 (835 mg, 1.62 mmol, 1.00 equiv.) in CH}_2\text{Cl}_2 (15 mL) was added dropwise TFA (1.24 mL, 16.2 mmol, 10.0 equiv.) at room temperature. The solution was stirred for 90 min, then water (15 mL) was added. The biphasic solution was cooled to 0 °C and NH}_4\text{OH was added until the pH of the aqueous layer was basic. The layers were separated and the aqueous layer was extracted with CH}_2\text{Cl}_2:\text{MeOH:NH}_4\text{OH 89.9:10:0.1 (4 x 10 mL). The organic layers were combined, dried over MgSO}_4 \text{ and concentrated under vacuum, to give 30 as an oil, which was used in the following step without further purification (670 mg, quantitative crude yield).} \\
[\alpha]_D^{(20 °C, \text{CHCl}_3, c 1.0)} = -13. \text{ FT-IR } \nu_{\text{max}} (\text{film})/\text{cm}^{-1}: 2960, 1721, 1606, 1460, 1250, 1076, 737. \text{ }^1\text{H NMR (400 MHz, CDCl}_3): \delta = 6.98 (2H, s, H^A), 5.53 (1H, dt, J 17.0, 10.1 Hz, H^B), 5.15 (1H, dd, J 10.1, 2.1 Hz, H^C), 5.09 (1H, dd, J 17.0, 2.1 Hz, H^D), 4.38 (1H, ddd, J 11.0, 8.0, 5.0 Hz, H^E), 4.27 (1H, dt, J 11.0, 7.7 Hz, H^F), 3.16 (1H, m, H^G), 3.01 (1H, dt, J 11.1, 6.5 Hz, H^H), 2.93-2.76 (4H, m, H^G & H^I), 2.03 (1H, m, H^J), 1.97 (1H, m, H^K), 1.81 (1H, m, H^K), 1.76-1.65 (3H, m, H^L & H^M), 1.36 (2H, m, H^N), 1.22 (18H, d, J 6.9 Hz, H^O), 0.98 (3H, d, J 6.6 Hz, H^P). \text{ }^{13}\text{C NMR (100 MHz, CDCl}_3): \delta = 171.1 \text{ (C=O), 150.2 (C), 144.8 (2 x C), 136.1 (CH), 130.7 (C), 120.9 (2 x CH), 119.2 (CH}_2, 63.7 \text{ (CH}_2, 59.5 \text{ (CH), 54.6 (CH), 46.4 (CH}_2, 34.5 \text{ (CH}_2, 31.6 \text{ (CH), 31.5 (2 x CH), 31.4 \text{ (CH}_2, 28.6 \text{ (CH), 25.3 (CH}_2, 24.2 (4 x CH}_3, 24.0 (2 x CH}_3, 17.9 \text{ (CH}_3). \text{ HRMS (ESI) Found: [M+H]^+, 414.3385. C}_{27}\text{H}_{44}\text{NO}_2 requires [M+H]^+, 414.3367.} \end{align*}
\]
(3R,4R)-4-((S)-1-(but-3-en-1-yl)pyrrolidin-2-yl)-3-methylhex-5-en-1-yl 2,4,6-triisopropylbenzoate (20)

To a solution of 30 (670 mg, 1.62 mmol, 1.00 equiv.) in toluene (0.3 M, 5.5 mL) was added K₂CO₃ (448 mg, 3.24 mmol, 2.00 equiv.). The solution was cooled to 0 °C and 4-bromo-1-butene (0.25 mL, 2.43 mmol, 1.50 equiv.) was added dropwise, followed by addition of KI (54 mg, 0.32 mmol, 0.20 equiv.) and DMF (0.2 mL). The solution was heated to reflux and stirred for 72 h. Water (5 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with CH₂Cl₂:MeOH:NH₄OH 99.5:0:0.5 to 96.5:3:0.5, to give 20 as an oil (663 mg, 87%). [α]
D (20 °C, CHCl₃, c 1.0) = −47. FT-IR νmax (film)/cm⁻¹: 2960, 1723, 1460, 1250, 1074, 909, 756. ¹H NMR (500 MHz, CDCl₃): δ = 7.02 (2H, s, Hₐ), 5.80 (1H, m, H₈), 5.68 (1H, dt, J 17.0, 9.9 Hz, H₅), 5.18-4.97 (4H, m, H₁⁻H₄), 4.41 (1H, ddd, J 11.0, 7.9, 5.0 Hz, H₆), 4.31 (1H, dt, J 11.0, 7.6 Hz, H₅), 3.19 (1H, m, H₇), 2.95-2.79 (4H, m, H₈⁻H₂), 2.47 (1H, m, H₃), 2.24 (2H, m, H₉), 2.14-2.00 (4H, m, H₁⁻H₂), 1.77-1.64 (5H, m, H₀⁻H¹ & H⁹), 1.40 (1H, m, H⁸), 1.26 (6H, d, J 6.7 Hz, H₉), 1.25 (12H, d, J 6.7 Hz, H¹₀), 1.02 (3H, d, J 6.8 Hz, H₅). ¹³C NMR (125 MHz, CDCl₃): δ = 171.0 (C=O), 150.1 (C), 144.7 (2 x C), 137.1 (CH), 136.8 (CH), 130.7 (C), 120.8 (2 x CH), 117.2 (CH₂), 115.3 (CH₂), 65.2 (CH), 63.3 (CH₂), 53.8 (CH₂), 53.7 (CH₂), 51.3 (CH), 34.4 (CH), 33.3 (CH₂), 32.9 (CH₂), 31.5 (2 x CH), 30.9 (CH), 25.5 (CH₂), 24.2 (4 x CH₃), 24.1 (2 x CH₃), 22.2 (CH₂), 17.6 (CH₃). HRMS (ESI) Found: [M+H]⁺, 468.3829. C₃₃H₅₅NO₂ requires [M+H]⁺, 468.3836.
6. Synthesis of 3

(R)-3-((9S,9aS)-2,3,5,6,9,9a-Hexahydro-1H-pyrrolo[1,2-a]azepin-9-yl)butyl 2,4,6-triisopropylbenzoate (31)

20 (350 mg, 0.75 mmol, 1.00 equiv.) was dissolved in toluene (0.01 M, 75 mL). The solution was degassed, then camphorsulfonic acid (184 mg, 0.79 mmol, 1.05 equiv.) was added. The solution was stirred for 20 min, then Hoveyda-Grubbs 2nd Generation catalyst (94 mg, 0.15 mmol, 0.20 equiv.) was added. The solution was heated to 80 °C and stirred at that temperature for 5 h. Ethyl vinyl ether (0.2 mL) was added, followed by water (50 mL) and NH₄OH, until the aqueous layer reached basic pH. The layers were separated, the organic layer was washed with Brine (2 x 20 mL) and the combined aqueous layers were extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with CH₂Cl₂:MeOH:NH₄OH 99.5:0.5 to 94.5:5:0.5, to give 31 as an oil (275 mg, 84%). 

[α]D (20 °C, CHCl₃, c 1.0) = +42. FT-IR νmax (film)/cm⁻¹: 2960, 1721, 1460, 1250, 1075, 908, 731. ¹H NMR (500 MHz, CDCl₃): δ = 7.03 (2H, s, Hₐ), 5.72 (1H, ddd, J 11.3, 5.8, 4.3 Hz, Hₐ), 5.64 (1H, dd, J 11.3, 6.4, H₉), 4.41 (1H, ddd, J 11.1, 7.9, 5.1 Hz, H₈), 4.31 (1H, dt, J 11.1, 7.6 Hz, H₈), 3.10-2.97 (3H, m, H₇ & H₈ & H₉), 2.91 (1H, sept, J 7.0 Hz, H₇), 2.87 (2H, sept, J 7.0 Hz, H₇), 2.74-2.59 (2H, m, H₇ & H₈ & H₉), 2.46 (1H, m, H₇), 2.43-2.34 (2H, m, H₉ & H₈), 2.29 (1H, m, H₇), 1.96-1.88 (2H, m, H₉ & H₈), 1.83-1.71 (3H, m, H₉ & H₈), 1.45 (1H, m, H₉), 1.26 (12H, d, J 7.0 Hz, H₈), 1.25 (6H, d, J 7.0 Hz, H₉), 1.05 (3H, d, J 6.7 Hz, H₉). ¹³C NMR (125 MHz, CDCl₃): δ = 171.0 (C=O), 150.0 (C), 144.7 (2 x C), 132.2 (CH), 130.7 (C), 129.4 (CH), 120.8 (2 x CH), 66.9 (CH), 63.8 (CH₂), 55.2 (CH₂), 51.0 (CH₂), 46.3 (CH), 34.4 (CH), 33.2 (CH₂), 31.7 (CH), 31.5 (2 x CH), 28.5 (CH₂), 28.1 (CH₂), 24.2 (4 x CH₃), 24.0 (2 x CH₃), 23.3 (CH₂), 18.6 (CH₃). HRMS (ESI)
Found: [M+H]⁺, 440.3524. C₃₀H₄₆NO₂ requires [M+H]⁺, 440.3523.

(R)-3-((9R,9αS)-Octahydro-1H-pyrrolo[1,2-a]azepin-9-yl)butyl 2,4,6-triisopropylbenzoate (3)

To a solution of 31 (373 mg, 0.85 mmol, 1.00 equiv.) in EtOAc (0.1 M, 8.5 mL) was added PtO₂ (19.3 mg, 0.085 mmol, 0.10 equiv.) under a N₂ atmosphere. The solution was purged with H₂ (g) for 30 min, after which it was stirred under a H₂ atmosphere for 24 h. The solution was filtered through celite, washing copiously with EtOAc, then the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, eluting with CH₂Cl₂:MeOH:NH₄OH 96.9:3:0.1, to give 3 as an oil (334 mg, 90%). [α]D (20 °C, CHCl₃, c 1.0) = −10. FT-IR νmax (film)/cm⁻¹: 2962, 1718, 1264, 1076, 733. ¹H NMR (500 MHz, CDCl₃): δ = 7.02 (2H, s, HₓA), 4.40 (1H, ddd, J 10.8, 7.8, 5.3 Hz, HₓB), 4.32 (1H, dt, J 10.8, 7.8 Hz, HₓB), 3.18 (1H, br m, HₓC), 3.06-2.99 (2H, m, HₓD & HₓE), 2.90 (1H, sept, J 7.0 Hz, HₓF), 2.86 (2H, sept, J 7.0 Hz, HₓG), 2.78-2.64 (2H, m, HₓD & HₓE), 2.16 (1H, m, HₓH), 1.86-1.72 (4H, m, HₓI & HₓJ), 1.70-1.60 (3H, m, HₓK & HₓL & HₓM), 1.55 (1H, m, HₓN), 1.52-1.41 (2H, m, HₓH & HₓN), 1.32-1.19 (21H, m, HₓK & HₓO & HₓP & HₓP'), 0.97 (3H, d, J 6.5 Hz, HₓO). ¹³C NMR (125 MHz, CDCl₃): δ = 171.0 (C=O), 150.1 (C), 144.7 (2 x C), 130.7 (C), 120.9 (2 x CH), 65.3 (CH), 63.7 (CH₂), 53.9 (CH₂), 51.8 (CH₂), 46.0 (CH), 34.4 (CH), 32.6 (CH₂), 32.5 (CH), 31.5 (2 x CH), 29.7 (CH₂), 28.0 (CH₂), 27.7 (CH₂), 25.8 (CH₂), 24.2 (4 x CH₃), 23.9 (2 x CH₃), 23.7 (CH₂), 18.3 (CH₃). HRMS (ESI) Found: [M+H]⁺, 442.3678. C₃₀H₄₆NO₂ requires [M+H]⁺, 442.3680.

One-pot RCM-hydrogenation procedure from 17 to 3:
17 (200 mg, 0.43 mmol, 1.00 equiv.) was dissolved in toluene (0.01 M, 45 mL). The solution was degassed, then camphorsulfonic acid (105 mg, 0.45 mmol, 1.05 equiv.) was added. The solution was stirred for 30 min, then Hoveyda-Grubbs 2nd Generation catalyst (53 mg, 0.085 mmol, 0.20 equiv.) was added. The solution was stirred at 80 °C for 5 h, then it was cooled to room temperature. PtO₂ (10 mg, 0.043 mmol, 0.1 equiv.) was added under a N₂ atmosphere. The solution was purged with H₂ (g) for 30 min, after which it was stirred under a H₂ atmosphere for 24 h. The solution was filtered
through celite, washing copiously with EtOAc, then the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, eluting with CH$_2$Cl$_2$:MeOH:NH$_4$OH 96.9:3:0.1, to give 3 as an oil (155 mg, 82%).
7. Optimisation of the Asymmetric Lithiation of 3

7.1. Initial *in situ* React-IR Monitoring

To a three-necked round-bottomed flask equipped with a ReactIR probe was added a solution of TIB ester 3 (140 mg, 0.32 mmol, 1.00 equiv.) and (+)-sparteine (73 mg, 0.07 mL, 0.32 mmol, 1.00 equiv.) in Et₂O (1.5 mL). A peak at 1727 cm⁻¹ was observed, which was assigned to the C=O bond stretch in 3. The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 0.24 mL, 0.32 mmol, 1.00 equiv.) was added dropwise. After 1 h no change in the IR signals was observed, which indicated that the lithiation to give 3a was not taking place. Upon addition of a second equivalent of s-BuLi, the peak at 1727 cm⁻¹ started to decrease slowly, accompanied by the appearance of a peak at 1633 cm⁻¹, characteristic of the C=O bond stretch of lithiated TIB ester 3a. The reaction mixture was stirred for another 3 h, observing a very slow conversion, and after another 2 h of no evolution the reaction was quenched with MeOD (0.1 mL). The reaction mixture was diluted with EtOAc (5 mL), water was added (5 mL) and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. After purification by column chromatography on silica gel, eluting with CH₂Cl₂:MeOH:NH₄OH 99.9:0:0.1 to 96.9:3:0.1, TIB ester 3 was recovered (110 mg, 79%) with <5% D incorporation observed by ¹H NMR.
1727 cm$^{-1}$

1633 cm$^{-1}$
7.2. Optimization of the Asymmetric Lithiation of 3 Using (+)-Sparteine Surrogate

General Procedure for the Asymmetric Lithiation of 3 – GP3

3 (20 mg, 0.045 mmol, 1.0 equiv.) and (+)-sparteine surrogate (see Table 2 for equiv.) were dissolved in the appropriate solvent (1 mL). The solution was cooled to the appropriate temperature and s-BuLi (1.3 M in hexanes, see Table 2 for equiv.) was added dropwise. The mixture was stirred for 5 h at the appropriate temperature, then Me₃SnCl (1.0 M in hexane, 1.1 equiv. with respect to s-BuLi/(+)/sps) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h then slowly warmed to room temperature. Aqueous KF (5 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The ratio between 3 and stannane 27 was determined by ¹H NMR analysis of the crude mixture.

| Entry | Solvent | s-BuLi(+)-sps (equiv.) | T (°C) | 3:27 | Yield (%) |
|-------|---------|-----------------------|--------|------|-----------|
| 1     | Et₂O   | 2.0                   | −78    | 100:0 | -         |
| 2     | Toluene | 2.0                   | −78    | 100:0 | -         |
| 3     | TBME   | 2.0                   | −78    | 49:51 | -         |
| 4     | CPME   | 2.0                   | −78    | 35:65 | -         |
| 5     | CPME   | 2.0                   | −63    | 0:100 | 55        |
| 6     | CPME   | 2.5                   | −78    | 0:100 | 67        |
| 7     | CPME   | 3.0⁺                   | −78    | 65:35 | -         |
| 8     | CPME   | 3.0                   | −78    | 0:100 | 84        |
| 9     | CPME   | 3.0                   | −78    | 0:100 | 92ᵇ       |

⁺ Reaction carried out with (+)-sparteine instead of (+)-sparteine surrogate
ᵇ Reaction carried out in a 230 mg (0.50 mmol) scale under optimised conditions (1 h lithiation - vide infra for ReactIR analysis)
7.3. *in situ* React-IR monitoring

To a three-necked round-bottomed flask equipped with a ReactIR probe was added a solution of TIB ester 3 (100 mg, 0.23 mmol, 1.00 equiv.) and (+)-sparteine surrogate (132 mg, 0.13 mL, 0.68 mmol, 3.00 equiv.) in CPME (3.0 mL). A peak at 1727 cm\(^{-1}\) was observed, which was assigned to the C=O bond stretch in 3. The solution was cooled to \(-78^\circ\)C and s-BuLi (1.3 M in hexanes, 0.52 mL, 0.68 mmol, 3.00 equiv.) was added dropwise. This led to the gradual disappearance of the signal at 1727 cm\(^{-1}\) and the appearance of a new signal at 1633 cm\(^{-1}\), characteristic of the C=O bond stretch of lithiated TIB ester 3a. This signal rose to a plateau over a period of 20 min following completion of s-BuLi addition. After another 20 min, Me$_3$SnCl (1.0 M in hexanes, 0.76 mL, 0.76 mmol, 3.00 equiv.) was added dropwise. This led to the almost immediate disappearance of the signal at 1633 cm\(^{-1}\) and the simultaneous appearance of a third signal at 1703 cm\(^{-1}\), characteristic of the C=O bond stretch of stannane 27. The reaction mixture was stirred at \(-78^\circ\)C for 1 h then slowly warmed to room temperature. Aqueous KF (3 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. $^1$H NMR analysis of the crude product showed no presence of TIB ester 7, indicating that its lithiation was complete. The crude product was purified by column chromatography on silica gel, eluting with CH$_2$Cl$_2$:MeOH:NH$_4$OH 99.9:0:0.1 to 96.9:3:0.1, to give 27 as an oil (105 mg, 76%).
(1R,3R)-3-((9R,9aS)-octahydro-1H-pyrrolo[1,2-a]azepin-9-yl)-1-(trimethylstanny)butyl 2,4,6-triisopropylbenzoate (27)

A solution of 3 (230 mg, 0.52 mmol, 1.00 equiv.) and (+)-sparteine surrogate (303 mg, 0.30 mL, 1.56 mmol, 3.00 equiv.) in CPME (0.1 M, 5.0 mL) was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 1.20 mL, 1.56 mmol, 3.00 equiv.) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, then Me₃SnCl (1.0 M in hexanes, 1.72 mL, 1.72 mmol, 3.30 equiv.) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h then slowly warmed to room temperature. Aqueous KF (5 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with CH₂Cl₂:MeOH:NH₄OH 99.9:0:0.1 to 96.9:3:0.1, to give 27 as an oil (288 mg, 92%, 94:6 d.r. as seen by ¹H NMR). [α]D (20 °C, CHCl₃, c 1.0) = −29. FT-IR νmax (film)/cm⁻¹: 2960, 1703, 1460, 1250, 876, 767. ¹H NMR (500 MHz, CDCl₃): δ = 7.01 (2H, s, 2 x CH₃), 5.20 (1H, dd, J 9.5, 6.2 Hz, CH₃), 3.89 (1H, m, CH), 3.47 (1H, m, CH₂), 3.24

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(2H, m, CH$_2^E$), 3.02 (1H, m, CH$_2^D$), 2.89 (1H, sept, J 6.9 Hz, CH$_2^F$), 2.82 (2H, sept, J 6.9 Hz, 2 x CH$_2^G$), 2.15-1.34 (14H, m, CH$_2^H$ & CH$_2^I$ & CH$_2^J$ & CH$_2^K$ & CH$_2^L$ & CH$_2^M$ & CH$_2^N$ & CH$_2^K$), 1.25 (12H, d, J 6.9 Hz, 4 x CH$_3^P$), 1.24 (6H, d, J 6.9 Hz, 2 x CH$_3^P'$), 0.99 (3H, d, J 7.0 Hz, CH$_3^Q$), 0.24 (9H, s and d, J 53.0 Hz, 3 x CH$_3^R$). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 171.3 (C=O), 150.0 (C), 144.8 (2 x C), 130.7 (C), 120.8 (2 x CH), 71.3 (CH), 64.6 (CH), 53.4 (CH$_2$), 50.7 (CH$_2$), 44.9 (CH), 38.2 (CH$_2$), 35.3 (CH), 34.4 (CH), 31.5 (2 x CH), 28.5 (CH$_2$), 27.7 (CH$_2$), 26.5 (CH$_2$), 24.4 (2 x CH$_3$), 24.3 (4 x CH$_3$), 23.9 (CH$_2$), 23.4 (CH$_2$), 18.8 (CH$_3$), –9.0 (CH$_3$, s and d, J 330.6 Hz, and d, J 316.2 Hz) HRMS (ESI) Found: [M+H]$^+$, 442.3678. C$_{29}$H$_{48}$NO$_2$ requires [M+H]$^+$, 442.3680.
8. Synthesis of Building Block 4

**tert-Butyl 2-(hydroxymethyl)acrylate (32)**

Following a literature procedure,[13] *tert*-butyl acrylate (22) (1.00 g, 1.14 mL, 7.80 mmol, 1.00 equiv.) was dissolved in H₂O:dioxane (50 mL, 0.15 M). DABCO (2.62 g, 23.4 mmol, 3.00 equiv.) and formaldehyde (37% w/w solution in H₂O, 1.90 mL, 23.4 mmol, 3.00 equiv.) were added and the solution was stirred at room temperature for 48 h. Et₂O (30 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 20 mL) and the combined aqueous layers were extracted with Et₂O (3 x 20 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 3:1, to give 32 as a colourless oil (1.04 g, 85%).

**FT-IR** ν_{max} (film)/cm⁻¹: 3418 (broad), 2978, 1705, 1368, 1147, 1051, 847. **¹H NMR** (400 MHz, CDCl₃): δ = 6.14 (1H, m), 5.73 (1H, dt, J 2.8, 1.3 Hz), 4.27 (2H, br m), 2.34 (1H, br s), 1.49 (9H, s). **¹³C NMR** (100 MHz, CDCl₃): δ = 165.7 (C=O), 140.8 (C), 124.8 (CH₂), 81.4 (C), 62.8 (CH₂), 28.1 (3 x CH₃). LRMS (ESI) Found [M+Na]⁺, 181.0840. Data in accordance with the literature.[13]

**tert-butyl 3-hydroxy-2-methylpropanoate (23)**

32 (100 mg, 0.63 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (3 mL). 5% Palladium on charcoal (116 mg, 0.10 equiv. Pd) was added. The solution was placed under H₂ atmosphere (20 bar) for 2 h. The Pd salts were filtered through celite, washing with
CH₂Cl₂, to give crude rac-23 as an oil (50 mg, 50%), which was used in the next step without further purification. FT-IR \( \nu_{\text{max}} \) (film)/cm\(^{-1} \): 3442 (broad), 2977, 1724, 1367, 1152, 1030, 846. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 3.67 \) (1H, dd, \( J = 11.2, 7.0 \) Hz), 3.63 (1H, dd, \( J = 11.2, 5.0 \) Hz), 2.54 (1H, ap. pd, \( J = 7.1, 5.0 \) Hz), 1.45 (9H, s), 1.12 (3H, d, \( J = 7 \) Hz). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 175.3 \) (C=O), 81.0 (C), 64.8 (CH\(_2\)), 42.5 (CH), 28.2 (3 x CH\(_3\)), 13.6 (CH\(_3\)). LRMS (ESI) Found [M+Na\(^+\)], 183.0992. Data in accordance with the literature.\(^{[13]}\)

**tert-Butyl (R)-3-hydroxy-2-methylproanoate [(R)-23]**

Following a literature procedure,\(^{[13]}\) Ru(COD)(methylallyl)_2 \( \text{S-Synphos} \) HBF\(_4\)·Et\(_2\)O \( \text{H}_2 \) (5 bar), MeOH 89%, 95:5 e.r. was added dropwise. The solution was stirred for 30 min at room temperature, at which time an orange suspension appeared. The solvent was removed under vacuum, and a solution of 32 (475 mg, 3.00 mmol, 1.00 equiv.) in degassed MeOH (9 mL) was added. The solution was placed under H\(_2\) atmosphere (5 bar) and stirred at room temperature for 24 h. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 3:1, to give 23 as a colourless oil (427 mg, 89%, 95: e.r. – determined after derivatisation to 23a, vide infra). \([\alpha]_D \) (20 °C, CHCl\(_3\), c 1.0) = −12. Other data as above. Data in accordance with the literature.\(^{[13]}\)

**3-(tert-butoxy)-2-methyl-3-oxopropyl benzoate (23a)**

Following a modified literature procedure\(^{[14]}\), a solution of 23 (72 mg, 0.45 mmol, 1.00 equiv.) in CH\(_2\)Cl\(_2\):pyridine 2:1 (0.5 M, 0.3 mL) was cooled to 0 °C and benzoyl chloride (100 mg, 0.84 mL, 0.72 mmol, 1.50 equiv.) was added dropwise. The solution was warmed to room temperature and stirred for 6 h. Aqueous NH\(_4\)Cl (0.5 mL) was
added and the layers were separated. The organic layer was washed with Brine (2 x 1 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 2 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 99:1, to give 23a as an oil (80 mg, 68%). FT-IR νmax (film)/cm⁻¹: 2977, 1722, 1270, 710. ¹H NMR (400 MHz, CDCl₃): δ = 8.03 (2H, d, J 7.4 Hz, H⁴), 7.56 (1H, t, J 7.4 Hz, H⁵), 7.35 (2H, t, J 7.4 Hz, H⁶), 4.44 (1H, dd, J 11.0, 7.3 Hz, H⁷), 4.39 (1H, dd, J 11.0, 5.9 Hz, H⁸), 2.84 (1H, ap. sext., J 6.8 Hz, H⁹), 1.44 (9H, s, H₁₀), 1.25 (3H, d, J 6.8 Hz, H₁₁). ¹³C NMR (100 MHz, CDCl₃): δ = 173.0 (C=O), 166.2 (C=O), 132.9 (CH), 130.1 (C), 129.6 (2 x CH), 128.3 (2 x CH), 80.8 (C), 66.4 (CH₂), 40.2(CH), 28.0 (3 x CH₃), 13.8 (CH₃). HRMS (ESI) Found: [M+Na]⁺, 287.1259. C₁₅H₂₀NaO₄ requires [M+Na]⁺, 287.1254.

Resolution of the enantiomers of 23 was achieved using chiral HPLC analysis (IA column, hexane:IPA 99:1 (10% of 10% IPA in hexane), 1 mL/min, 273 nm, tᵣ 8.020 min (S), 9.058 (R).

(R)-3-(tert-Butoxy)-2-methyl-3-oxopropyl benzoate [(R)-23a]

Following a modified literature procedure,[¹⁴] a solution of (R)-23 (30 mg, 0.20 mmol, 1.00 equiv.) in CH₂Cl₂:pyridine 2:1 (0.5 M, 0.3 mL) was cooled to 0 °C and benzoyl chloride (40 mg, 0.033 mL, 0.30 mmol, 1.50 equiv.) was added dropwise. The solution was warmed to room temperature and stirred for 6 h. Aqueous NH₄Cl (0.5 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 1 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 2 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with
petrol:EtOAc 99:1, to give \((R)-23a\) as an oil (40 mg, 81%, 95:5 e.r.). \([\alpha]_D\) (20 °C, CHCl₃, c 1.0) = -9. Other data as above.

Chiral HPLC analysis (IA column, hexane:IPA 99:1 (10% of 10% IPA in hexane), 1 mL/min, 273 nm, \(t_R\) 8.020 min [(S), minor], 9.058 [(R), major]:

\[
\begin{align*}
&\text{BzO} \quad \text{Ot-Bu} \\
&23a \quad \text{BzO} \quad \text{Ot-Bu}
\end{align*}
\]

\(\alpha\)D (20°C, CHCl₃, c 1.0) = -9.

Other data as above.

Chiral HPLC analysis (IA column, hexane:IPA 99:1 (10% of 10% IPA in hexane), 1 mL/min, 273 nm, \(t_R\) 8.020 min [(S), minor], 9.058 [(R), major]:

\[
\begin{align*}
&\text{BzO} \quad \text{Ot-Bu} \\
&(R)-23a \quad \text{BzO} \quad \text{Ot-Bu}
\end{align*}
\]

\(\alpha\)D (20°C, CHCl₃, c 1.0) = -12.

FT-IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2976, 1727, 1457, 1367, 1144, 846. \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) = 3.33 (1H, dd, \(J\ 9.6, 6.5\) Hz, \(H^A\)), 3.22 (1H, dd, \(J\ 9.6, 6.5\) Hz, \(H^A\)), 2.65 (1H, ap. sext., \(J\ 6.5\) Hz, \(H^B\)), 1.45 (9H, s, \(H^C\)), 1.22 (3H, d, \(J\ 6.5\) Hz, \(H^D\)). \(^13\)C NMR (100 MHz, CDCl₃): \(\delta\) = 170.9 (C=O), 79.5 (C), 41.3 (CH), 26.3 (3 x CH₃), 16.4 (CH₃), 6.1 (CH₂). HRMS (ESI) could not be obtained.

\(t\)-Butyl (S)-3-iodo-2-methylpropanoate (33)

Following a modified literature procedure,[15] 23 (86 mg, 0.54 mmol, 1.00 equiv.) was dissolved in CH₂Cl₂ (6 mL). The flask was protected from light and triphenylphosphine (247 mg, 0.94 mmol, 1.50 equiv.), imidazole (73 mg, 1.08 mmol, 2.00 equiv.) and iodine (238 mg, 0.94 mmol, 1.50 equiv.) were added. The solution was stirred for 4 h at room temperature, then saturated aqueous Na₂S₂O₃ (5 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtO 95:5, to give 33 as a colourless oil (130mg, 89%). \([\alpha]_D\) (20 °C, CHCl₃, c 1.0) = -12. FT-IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 2976, 1727, 1457, 1367, 1144, 846. \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) = 3.33 (1H, dd, \(J\ 9.6, 6.5\) Hz, \(H^A\)), 3.22 (1H, dd, \(J\ 9.6, 6.5\) Hz, \(H^A\)), 2.65 (1H, ap. sext., \(J\ 6.5\) Hz, \(H^B\)), 1.45 (9H, s, \(H^C\)), 1.22 (3H, d, \(J\ 6.5\) Hz, \(H^D\)). \(^13\)C NMR (100 MHz, CDCl₃): \(\delta\) = 170.9 (C=O), 79.5 (C), 41.3 (CH), 26.3 (3 x CH₃), 16.4 (CH₃), 6.1 (CH₂). HRMS (ESI) could not be obtained.
**tert-Butyl (R)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (4)**

To a solution of 33 (110 mg, 0.41 mmol, 1.00 equiv.) in Et$_2$O (4 mL) was added $i$-PrOB(pin) (91 mg, 0.10 mL, 0.49 mmol, 1.20 equiv.). The solution was cooled to $-105 \, ^\circ\text{C}$ and $t$-BuLi (1.6 M in pentane, 0.51 mL, 0.82 mmol, 2.00 equiv.) was added dropwise. The solution was stirred for 10 min at $-105 \, ^\circ\text{C}$, then it was slowly warmed to room temperature. Water (5 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with Et$_2$O (3 x 5 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography, eluting with petrol:Et$_2$O 95:5, to give 4 as a colourless oil (75 mg, 69%, 94:6 e.r.). $[\alpha]_D$ (20 °C, CHCl$_3$, c 1.0) = –3. **FT-IR** $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2977, 1725, 1367, 1140, 846, 755. **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ = 2.54 (1H, ap. sext, $J$ 7.0 Hz, H$^A$), 1.42 (9H, s, H$^B$), 1.22 (6H, s, H$^C$), 1.21 (6H, s, H$^C$), 1.14 (3H, d, $J$ 7.0 Hz, H$^D$), 1.07 (1H, dd, $J$ 15.8, 7.0 Hz, H$^E$), 0.85 (1H, dd, $J$ 15.8, 7.0 Hz, H$^E$). **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ = 176.8 (C=O), 83.1 (2 x C), 79.6 (C), 36.4 (CH), 28.1 (3 x CH$_3$), 24.9 (4 x CH$_3$), 19.6 (CH$_3$). **$^{11}$B NMR** (96 MHz, CDCl$_3$): $\delta$ = 33. **HRMS** (ESI) Found: [M+Na]$^+$, 293.1904. C$_{14}$H$_{27}$BNaO$_4$ requires [M+Na]$^+$, 293.1897.

**e.r. Determination:** A solution of 4 (50 mg, 0.19 mmol, 1.0 equiv.) in THF (1 mL) was cooled to 0 °C, then aqueous NaOH 2M:H$_2$O$_2$ 30% (2:1, 1 mL) was added dropwise. The biphasic solution was stirred vigorously for 1 h. Water (5 mL) and Et$_2$O (5 mL) were added and the layers were separated. The organic layer was washed with Brine (2 x 3 mL) and the combined aqueous layers were extracted with Et$_2$O (2 x 5 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel, eluting with petrol:EtOAc 3:1, to give (R)-23 as a colourless oil (70%). (R)-23 was then converted into benzoate (R)-23a following the procedure described above (98%).
Chiral HPLC analysis (IA column, hexane:IPA 99:1 (10% of 10% IPA in hexane), 1 mL/min, 273 nm, \( t_R \) 8.020 min [(S), minor], 9.058 [(R), major]:

![Chiral HPLC peaks](image)

- **BzO**
- **Ot-Bu**
- **23a**

- **BzO**
- **Ot-Bu**
- **(R)-23a**

  (after asymmetric reduction, e.r. 95:5)

- **BzO**
- **Ot-Bu**
- **(R)-23a**

  (after B(pin) oxidation, e.r. 94:6)
8.1. Model Lithiation-Borylation with Boronic Ester 4

(2R,4S)-tert-Butyl 6-(4-methoxyphenyl)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoate (34)

TIB ester 8a[4] (see TIB ester 8, section 2 for synthesis) (50 mg, 0.13 mmol, 1.30 equiv.) and (+)-sparteine (28 mg, 0.03 mL, 0.12 mmol, 1.20 equiv.) were dissolved in CPME (1.3 mL). The solution was cooled to –78 °C and s-BuLi (1.3 M in hexanes, 0.09 mL, 0.12 mmol, 1.20 equiv.) was added dropwise. The solution was stirred at –78 °C for 3 h, then a solution of 4 (26 mg, 0.1 mmol, 1.00 equiv.) in CPME (0.3 mL) was added dropwise. The solution was stirred for 45 min at –78 °C, after which $^{11}$B NMR analysis of the crude mixture showed complete boronate complex formation [$^{11}$B NMR (92.6 MHz, no solvent) δ = 7]. The solution was warmed to 105 °C and stirred for 3 h. $^{11}$B NMR analysis of the crude mixture showed full product formation [$^{11}$B NMR (92.6 MHz, no solvent) δ = 33]. Water (5 mL) and Et$_2$O (5 mL) were added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with Et$_2$O (3 x 5 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3 to 95:5, to give 34 as an oil (25 mg, 61%). $[^\alpha]$(D) (20 °C, CHCl$_3$, c 1.0) = +2. FT-IR ν$_{\text{max}}$ (film)/cm$^{-1}$: 2926, 1725, 1512, 1244, 1142, 1037, 753. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.10 (2H, d, J 8.2 Hz, H$^A$), 6.82 (2H, d, J 8.2 Hz, H$^B$), 3.79 (3H, s, H$^C$), 2.54 (2H, m, H$^D$), 2.39 (1H, sext, J 7.0 Hz, H$^E$), 1.83 (1H, m, H$^F$), 1.69 (2H, m, H$^G$), 1.49-1.37 (10H, m, H$^H$ & H$^I$), 1.27 (12H, s, H$^J$), 1.08 (3H, d, J 7.0 Hz, H$^K$), 0.87 (1H, m, H$^K$). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 176.3 (C=O), 157.6 (C), 135.0 (C), 129.2 (2 x CH), 113.7 (2 x CH), 83.0 (2 x C), 79.6 (C), 55.2 (CH$_3$), 39.3 (CH), 34.9 (CH$_2$), 34.6 (CH$_2$), 33.4 (CH$_2$), 28.1 (3 x CH$_3$), 24.9 (2 x CH$_3$), 24.8 (2 x CH$_3$), 16.9 (CH$_3$). $^{11}$B NMR (96 MHz, CDCl$_3$): δ = 33. HRMS (ESI) Found: [M+Na]$^+$, 441.2779. C$_{24}$H$_{39}$BNaO$_5$ requires [M+Na]$^+$, 441.2787.
9. Synthesis of Building Block 26

Following a literature procedure,\textsuperscript{[15]} to a solution of methyl (S)-3-hydroxy-2-methylpropanoate (24) (1.00 g, 0.934 mL, 8.47 mmol, 1.00 equiv.) in dichloromethane (40 mL) was added imidazole (1.15 g, 16.94 mmol, 2.00 equiv.) followed by tert-butylidimethylsilyl chloride (1.53 g, 10.16 mmol, 1.20 equiv.). The solution was stirred at room temperature for 16 h, then aqueous NH\textsubscript{4}Cl (30 mL) was added. The layers were separated, the organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over MgSO\textsubscript{4} and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 97:3, to give 35 as a colourless oil (1.97 g, 99%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 3.77\) (1H, dd, \(J = 9.7, 6.8\) Hz), 3.67 (3H, s), 3.64 (1H, dd, \(J = 9.7, 6.3\) Hz), 2.65 (1H, sextet, \(J = 6.9\) Hz), 1.13 (3H, d, \(J = 6.9\) Hz), 0.87 (9H, s), 0.03 (6H, s). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 175.5\) (C=O), 65.2 (CH\textsubscript{2}), 51.5 (CH\textsubscript{3}), 42.5 (CH), 25.8 (3 x CH\textsubscript{3}), 18.2 (CH\textsubscript{3}), 13.5 (C), −5.5 (2 x CH\textsubscript{3}). Data in accordance with the literature.\textsuperscript{[15]}

(R)-3-((tert-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (36)

Following a literature procedure,\textsuperscript{[15]} a solution of 35 (2.0 g, 8.60 mmol, 1.00 equiv.) in dichloromethane (40 mL) was cooled down to −78 °C. DIBAL-H (1.0 M in CH\textsubscript{2}Cl\textsubscript{2}, 25.8 mL, 25.8 mmol, 3.00 equiv.) was added dropwise to the solution, which was then stirred for 1 h at −78 °C. The solution was warmed to room temperature. Et\textsubscript{2}O (51.6
mL) was added, followed by water (2.3 mL), dropwise, while stirring vigorously. The solution was stirred for 30 min, then 1.3 M NaOH (7.0 mL) was added. The aluminium salts were filtered, washing with EtOAc. The solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 90:10 to 85:15, to give 36 as a colourless oil (1.65 g, 94%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.73 (1H, dd, $J$ = 9.7, 4.5 Hz), 3.67-3.59 (2H, m), 3.54 (1H, dd, $J$ = 9.7, 8.0 Hz), 1.94 (1H, m), 0.90 (9H, s), 0.83 (3H, d, $J$ = 7.4 Hz), 0.07 (6H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 68.8 (CH$_2$),68.3 (CH$_2$), 37.0 (CH), 25.9 (3 x CH$_3$), 18.2 (CH$_3$), 13.1 (C), −5.5 (2 x CH$_3$). Data in accordance with the literature.\footnote{15}

(S)-$t$-Butyl(3-iodo-2-methylpropoxy)dimethylsilane (25)

To a solution of 36 (200 mg, 0.98 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (10 mL), covered in Al foil, were added imidazole (133 mg, 1.96 mmol, 2.0 equiv.), triphenylphosphine (385 mg, 1.47 mmol, 1.5 equiv.) and iodine (373 mg, 1.47 mmol, 1.5 equiv.). The solution was stirred at room temperature for 4 h, then aqueous Na$_2$S$_2$O$_3$ (10 mL) was added. The layers were separated, the organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with CH$_2$Cl$_2$ (2 x 10 mL). The organic layers were combined, dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with neat pentane to pentane:Et$_2$O 97:3, to give 26 as a colourless oil (280 mg, 91%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.53 (1H, dd, $J$ = 10.1, 5.1 Hz), 3.40 (1H, dd, $J$ = 10.1, 6.9 Hz), 3.31 (1H, dd, $J$ = 9.5, 5.1 Hz), 3.25 (1H, dd, $J$ = 9.3, 5.6 Hz), 1.65 (1H, m), 0.95 (3H, d, $J$ = 6.8 Hz), 0.90 (9H, s), 0.07 (6H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 66.7 (CH$_2$), 37.4 (CH), 25.9 (3 x CH$_3$), 18.2 (CH$_3$), 17.2 (C), 13.7 (CH$_2$), -5.4 (2 x CH$_3$). Data in accordance with the literature.\footnote{15}

(R)-$t$-Butyldimethyl(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane (26)

A solution of 25 (530 mg, 1.69 mmol, 1.0 equiv.) and $i$-PrOB(pin) (377 mg, 0.42 mL,
2.03 mmol, 1.20 equiv.) in Et₂O (10 mL) was cooled down to −105 °C, then t-BuLi (1.9 M in pentane, 1.78 mL, 3.37 mmol, 2.00 equiv.) was added. The solution was stirred at −105 °C for 10 min, then slowly let warm to room temperature. Aqueous NH₄Cl (10 mL) was added and the layers were separated. The organic layer was washed with Brine (2 x 5 mL) and the combined aqueous layers were extracted with Et₂O (3 x 5 mL). The organic layers were combined, dried over MgSO₄ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with petrol:EtOAc 99.5:0.5, to give 26 as a colourless oil (435 mg, 82%). [α]D (20 °C, CHCl₃, c 1.0) = +4. FT-IR νmax (film)/cm⁻¹: 2929, 1370, 1145, 1082, 834, 773.

¹H NMR (400 MHz, CDCl₃): δ = 3.43 (1H, dd, J = 9.6, 5.8 Hz, Hᴬ), 3.31 (1H, dd, J = 9.6, 7.0 Hz, Hᴬ), 1.84 (1H, m, Hᴮ), 1.24 (12H, s, Hᶜ), 0.92 (3H, d, J = 6.5 Hz, Hᴰ), 0.89 (9H, s, Hᴱ), 0.86 (1H, dd, J = 15.4, 5.8 Hz, Hᴱ), 0.58 (1H, dd, J = 15.4, 8.8 Hz, Hᴱ), 0.03 (6H, s, Hᴳ). ¹³C NMR (100 MHz, CDCl₃): δ = 100.0 (C), 82.8 (2 x C), 70.0 (CH₂), 32.2 (CH), 26.0 (3 x CH₃), 24.9 (2 x CH₃), 24.8 (2 x CH₃), 19.0 (CH₃), 18.0 (C) −5.33 (2 x CH₃). ¹¹B NMR (96.2 MHz, CDCl₃): δ = 33.4. HRMS (ESI) Found: [M+H]^+, 315.2515. C₁₆H₃₅BO₃Si requires [M+H]^+, 315.2525.
10. Endgame

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
\]

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
\]

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
\]

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
\]

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
\]

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
\]

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
\]

\[
\begin{align*}
(i) \quad \text{s-BuLi, (+)-sps} & \quad \text{OTBS} \\
(ii) \quad \text{B(pin)} & \quad \text{26} \\
(iii) \quad \text{H}_2\text{O}_2/\text{NaOH} & \quad \text{52\%} \\
\end{align*}
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(2R,4S,6R)-1-((tert-Butyldimethylsilyl)oxy)-2-methyl-6-((9R,9aS)-octahydro-1H-pyrrolo[1,2-a]azepin-9-yl)heptan-4-ol (21)

3 (250 mg, 0.57 mmol, 1.00 equiv.) and (+)-sparteine surrogate (330 mg, 0.33 mL, 1.70 mmol, 3.00 equiv.) were dissolved in CPME (6 mL). The solution was cooled to −78 °C and s-BuLi (1.3 M in hexanes, 1.30 mL, 3.00 equiv.) was added dropwise. The solution was stirred at −78 °C for 1 h, then a solution of 26 (534 mg, 1.70 mmol, 3.00 equiv.) in CPME (1 mL) was added dropwise. The solution was stirred for 45 min at −78 °C, after which \(^{11}\)B NMR analysis of the crude mixture showed complete boronate complex formation \[^{11}\text{B NMR (92.6 MHz, no solvent)} \delta = 7\]. The solution was warmed to 60 °C and stirred for 16 h. \(^{11}\)B NMR analysis of the crude mixture showed full product formation \[^{11}\text{B NMR (92.6 MHz, no solvent)} \delta = 33\]. CPME was removed under vacuum and THF (6 mL) was added. The solution was cooled to 0 °C and an aqueous solution of 2 M NaOH and 30% \(\text{H}_2\text{O}_2\) (2:1 v/v, 6 mL) was added dropwise. The solution was stirred vigorously for 2 h at 0 °C, then it was warmed to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The layers were separated, the organic layer was washed with Brine (2 x 10 mL) and the combined aqueous layers were extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over MgSO\(_4\) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with CHCl\(_3\):MeOH:NH\(_2\)OH 99.9:0:0.1 to 94.9:5:0.1, to give 21 as an oil (117 mg, 52%). \([\alpha]_D\) (20 °C, CHCl\(_3\),
c 1.0) = −2. FT-IR νmax (film)/cm−1: 3367, 2926, 1461, 1250, 1087, 834. 1H NMR (500 MHz, CDCl3): δ = 3.77 (1H, m, H^A), 3.54 (1H, dd, J 10.1, 5.3 Hz, H^B), 3.44 (1H, dd, J 10.1, 7.4 Hz, H^D), 3.14-2.95 (3H, m, H^E & H^F & H^G), 2.69-2.51 (2H, m, H^D & H^F), 1.89-1.78 (3H, m, H^E & H^G & H^H), 1.76-1.62 (6H, m, H^G & H^H & H^I & H^J & H^K), 1.52 (2H, m, H^I), 1.44-1.28 (6H, m, H^M & H^N & H^O), 0.97 (3H, d, J 6.1 Hz, H^P), 0.94-0.90 (12H, m, H^O & H^R), 0.09 (6H, s, H^S). 13C NMR (125 MHz, CDCl3): δ = 69.3 (CH2), 68.6 (CH), 54.3 (CH2), 52.4 (CH2), 46.0 (CH), 43.1 (CH2), 42.2 (CH2), 34.1 (CH), 29.7 (CH2), 28.3 (CH2), 28.0 (CH2), 26.0 (CH2), 25.9 (3 x CH3), 23.8 (CH2), 20.0 (CH3), 18.3 (C), 17.8 (CH3), −5.4 (2 x CH3). HRMS (ESI) Found: [M+H]^+, 398.3450. C23H48NO2Si requires [M+H]^+, 398.3449.

(2R,4S,6R)-2-Methyl-6-((9R,9aS)-octahydro-1H-pyrrolo[1,2-a]azepin-9-yl)heptane-1,4-diol (37)

21 (150 mg, 0.38 mmol, 1.0 equiv.) was dissolved in MeOH (4 mL). 1% aqueous HCl (0.5 mL) was added and the solution was stirred for 2 h at room temperature. Solid NaHCO3 was added, the solids were filtered washing with CH2Cl2 and the solvent was evaporated under vacuum, to give 37 as an oil (105 mg, quantitative crude yield), which was used in the next step without further purification.

The crude product could also be purified by reverse phase flash chromatography (tr 7 min) to give 37 as the formate salt, as an oil (79 mg, 73%). [α]D (20 °C, CHCl3, c 1.0) = −21. FT-IR νmax (film)/cm−1: 3319, 2926, 1594, 1456, 1337, 1036, 761. 1H NMR (500 MHz, CDCl3): δ = 8.63 (1H, s, HCO2) 4.00 (1H, m, H^A), 3.90 (1H, m, H^B), 3.66 (1H, dd, J 14.5, 6.6 Hz, H^C), 3.56 (1H, m, H^D), 3.40-3.30 (2H, m, H^E & H^F), 3.14 (1H, ap. dd, J 14.5, 6.6 Hz, H^F), 2.94 (1H, m, H^E), 2.41 (1H, m, H^F), 2.08 (1H, m, H^G), 2.03-1.83 (7H, m, H^G & H^H & H^I & H^J & H^K), 1.76-1.57 (4H, m, H^I & H^M), 1.53-1.37 (4H, m, H^N & H^O), 0.90 (3H, d, J 6.8 Hz, H^P), 0.89 (3H, d, J 7.3 Hz, H^P). 13C NMR (125 MHz, CDCl3): δ = 169.3 (formate HCO2) 68.9 (CH2), 67.9 (CH), 64.4 (CH), 52.2 (CH2), 51.5 (CH2), 44.6 (CH2), 42.0 (CH2), 39.1 (CH), 34.7 (2 x CH), 28.4 (CH2), 28.1 (CH2), 27.8 (CH2), 23.7 (CH2), 22.9 (CH2), 18.6 (CH3), 17.7 (CH3). HRMS (ESI) Found: [M+H]^+, 284.2594. C17H34NO2 requires [M+H]^+, 284.2584.
To a solution of 37 (6 mg, 0.021 mmol, 1.0 equiv.) in toluene (2 mL) was added RuCl₂(PPh₃)₃ [16] (30 mg, 0.032 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 16 h, then it was filtered through silica washing with CH₂Cl₂:MeOH:Et₂NH 98.8:1.0:0.2. The crude product was purified by preparative TLC in an aluminium-backed plate pre-coated (0.25 mm) with Merck Silica Gel 60 F254. To visualise the product on the preparative TLC plate, a reference sample was run on the same plate, then cut and stained with KMnO₄ (see picture below). 1 was obtained as an oil (4 mg, 67%). [α]D (20 °C, CHCl₃, c 0.2) = –31 [lit. [17] for (–)-1, [α]D (20 °C, CHCl₃, c 0.54) = –36.7]. FT-IR ν_max (film)/cm⁻¹: 2928, 1767, 1667, 1454, 1376, 1173, 1001, 927. ¹H NMR (600 MHz, CDCl₃): δ = 4.40 (1H, m, H¹₂), 3.01 (1H, m, H³), 2.94 (1H, m, H⁵), 2.89 (1H, m, H⁹a), 2.64 (1H, m, H¹⁴), 2.53-2.44 (3H, m, H³ & H⁵ & H¹₃), 2.01 (1H, m, H¹₁), 1.82-1.74 (3H, m, H¹ & H⁷), 1.72-1.63 (4H, m, H² & H¹⁰ & H¹¹), 1.61-1.42 (6H, m, H⁶ & H⁸ & H⁹ & H¹₃), 1.32 (1H, m, H⁷), 1.26 (3H, d, J 7.2 Hz, H¹₆), 0.99 (3H, d, J 6.6 Hz, H¹⁷). ¹³C NMR (150 MHz, CDCl₃): δ = 179.8 (C¹⁵), 78.8 (CH¹₂), 65.1 (CH⁹a), 54.8 (CH³), 52.6 (CH⁵), 46.8 (CH⁹), 39.6 (CH¹₄), 38.0 (CH²), 36.0 (CH¹⁴), 32.5 (CH¹⁰), 28.9 (CH⁶), 28.5 (CH¹), 27.9 (CH²), 26.0 (CH⁶), 24.0 (CH³), 19.6 (CH³), 15.2 (CH³). HRMS (ESI) Found: [M+H]⁺, 280.2276. C₁₇H₃₄NO₂ requires [M+H]⁺, 280.2271. Data in accordance with the literature [17] (See Table 3 for NMR data comparison between natural and synthetic (–)-1).
**NOTE:** Substantial degradation of the natural product was observed when it was kept as a solution in CDCl$_3$ for several days. The following $^1$H NMR spectra correspond to the same sample of (−)-1; the bottom one was taken 72 h after the top one.
Table 3. Comparison of $^1$H and $^{13}$C NMR spectra between natural$^{[17]}$ and synthetic (−)-stemaphylline [(−)-1].

| Position | Natural $\delta$H | Synthetic $\delta$H | Natural $\delta$C | Synthetic $\delta$C |
|----------|-------------------|---------------------|------------------|-------------------|
| 1        | 1.79 (m)          | 1.82-1.74 (m)       | 28.1             | 28.5             |
| 2        | 1.72 (m)          | 1.72-1.63 (m)       | 23.8             | 24.0             |
| 3        | 3.01 (m)          | 3.01 (m)            | 54.3             | 54.8             |
|          | 2.51 (m)          | 2.53-2.44 (m)       |                  |                  |
| 5        | 2.94 (m)          | 2.94 (m)            | 52.3             | 52.6             |
|          | 2.51 (m)          | 2.53-2.44 (m)       |                  |                  |
| 6        | 1.50 (m)          | 1.61-1.42 (m)       | 25.9             | 26.0             |
| 7        | 1.80 (m)          | 1.82-1.74 (m)       | 27.7             | 27.9             |
|          | 1.33 (m)          | 1.32 (m)            |                  |                  |
| 8        | 1.58 (m)          | 1.61-1.42 (m)       | 28.2             | 28.9             |
| 9        | 1.62 (m)          | 1.61-1.42 (m)       | 45.9             | 46.7             |
| 9a       | 2.93 (m)          | 2.94 (m)            | 64.8             | 65.1             |
| 10       | 1.70 (m)          | 1.72-1.63 (m)       | 32.5             | 32.5             |
| 11       | 2.00 (m)          | 2.01 (m)            | 39.5             | 39.6             |
|          | 1.64 (m)          | 1.72-1.63 (m)       |                  |                  |
| 12       | 4.39 (m)          | 4.40 (m)            | 78.4             | 78.8             |
| 13       | 2.51 (m)          | 2.53-2.44 (m)       | 37.8             | 38.0             |
|          | 1.48 (m)          | 1.61-1.42 (m)       |                  |                  |
| 14       | 2.61 (m)          | 2.64 (m)            | 35.8             | 36.0             |
| 15       | -                 | -                   | 179.6            | 179.8            |
| 16       | 1.26 (d, J 7.0)   | 1.26 (d, J 7.0)     | 15.0             | 15.2             |
| 17       | 0.98 (d, J 6.5)   | 0.99 (d, J 6.4)     | 19.2             | 19.6             |

SI-65
11. $^1$H-NMR and $^{13}$C-NMR Spectra

500 MHz, DMSO-$d_6$, 90 °C
$\text{(S, R)-11}$

500 MHz, DMSO-$d_6$, 90 °C
500 MHz, DMSO-$d_6$, 90 °C
SI-69

400 MHz, CDCl$_3$
500 MHz, DMSO-$d_6$, 90 °C
500 MHz, DMSO-$_d_6$, 90 °C
$\text{500 MHz, DMSO-$d_6$, 90 \degree C}$
500 MHz, DMSO-$d_6$, 90 °C
500 MHz, DMSO-$d_6$, 90 °C
400 MHz, CDCl$_3$
SI-77
500 MHz, CDCl₃
500 MHz, CDCl$_3$
$^1$H NMR (400 MHz, CDCl$_3$)
(pin)B₂Ot-Bu

400 MHz, CDCl₃
SI-83

$\text{MeO}$

$\text{B(pin)}$

$\text{O}^\text{t-Bu}$

400 MHz, CDCl$_3$
500 MHz, CDCl₃
SI-86
600 MHz, CDCl$_3$
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