A stereoselective remote homochiral boronate ester-mediated aldol reaction

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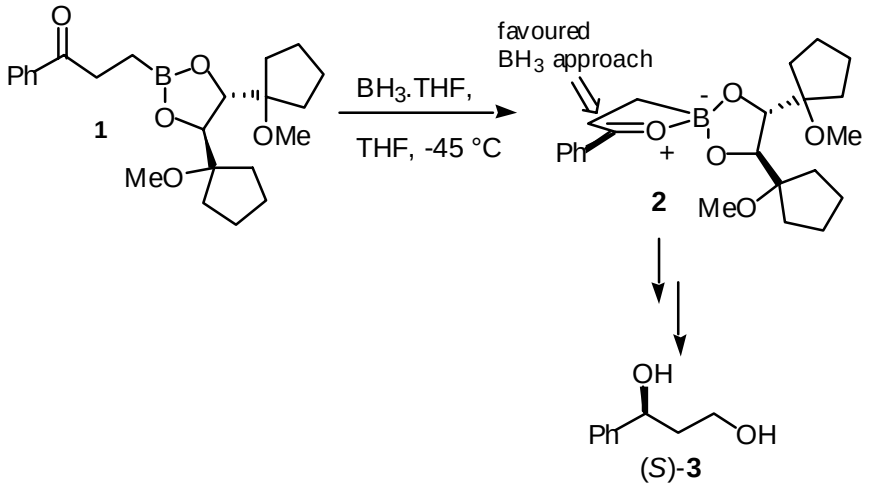
Abstract
As part of a program aimed at exploring the utility of remote asymmetric centres to control the addition of nucleophiles to carbonyl functions, it was discovered that homochiral ester derivatives of β-boronate carbonyl compounds do not control the addition of alkyllithium, Grignard or cuprate-based nucleophiles. However, use of a lithium ester enolate nucleophile exhibits medium to high remote diastereocontrol in aldol additions to carbonyl functions.

Keywords: Remote asymmetric induction, boronate, auxiliary, aldol reaction

Introduction

The application of remote chiral centres for controlling asymmetric transformations is difficult,[1] though beginning to attract greater attention due to the range over which diastereocontrol may be effected.[2] We were attracted to the use of remote asymmetric methodology due to the possibility of using a single asymmetric element for controlling multiple stereogenic centres at several remote sites. In particular, we were interested in the use of a remote stereo-controlling group to effect stereoselective reactions involving an intramolecular carbonyl group, such as α-alkylations, aldol and addition reactions. Our initial studies in this area involved the development of an achiral intramolecular boronate function to control the relative stereochemistry of aldol reactions.[3] Subsequently, parallel studies were conducted by Molander *et al.* on 1,7-asymmetric induction[4] and by ourselves on 1,6-asymmetric induction[5] involving the use of a homochiral boronate unit for controlling remote asymmetric reduction of an intramolecular carbonyl function.[6] MM2 parameterisation of the boronate moiety and subsequent molecular modelling[7] reinforced the original hypothesis of Molander[4] that the mechanism of the remote asymmetric reduction process[8] involved the intervention of an intramolecularly activated boronate Lewis acid complex, such as **2**, in **Scheme 1**.

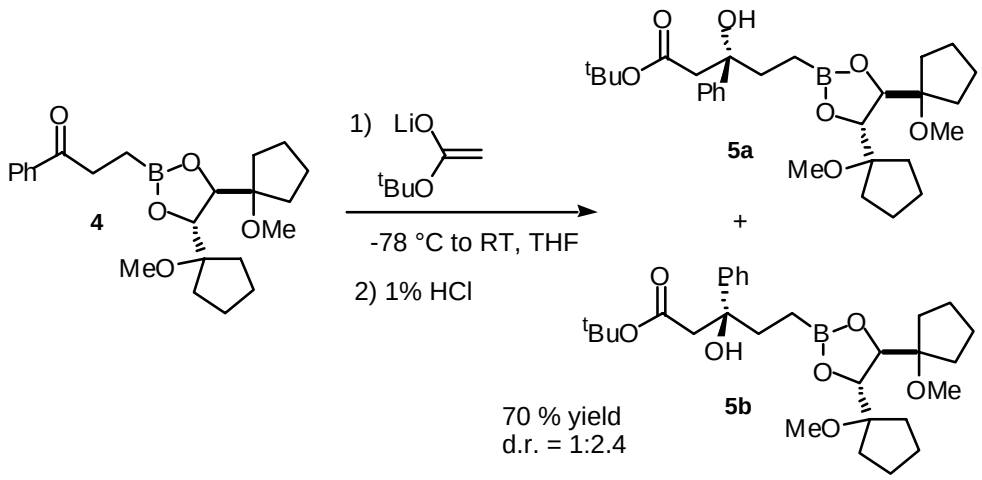


Scheme 1. Mechansim of remote asymmetric reduction in a β-ketoboronate.

We therefore undertook an investigation to determine whether the remote boronate function of systems such as **1** could be used to control the asymmetric addition of nucleophiles other than hydride equivalents to the carbonyl group. In this communication, we report preliminary results on the diastereoselective addition of enolate nucleophiles to homochiral β-boronate ester carbonyl compounds.

Results and Discussion

In order to study the addition of carbon based nucleophiles to homochiral β-boronate carbonyl, we chose the ketone **4** as an initial substrate, which can either be prepared using previously reported methods, or using more recently developed hydrazone-based chemistry.[9] Treatment of ketone **4** with a variety of organo-lithium, magnesium and copper(I) reagents predominantly resulted in ring opening of the boronate ester. However, treatment of ketone **4** with lithium *tert*-butyl acetate resulted in the formation of a highly elimination-prone tertiary alcohol **5** (**Equation 1**).



Equation 1. Aldol addition of lithium *tert*-butyl acetate to chiral ketone **4**.

Initial examination of the ^{1}H NMR (300 MHz) spectrum of product **5** suggested that product could be a single diastereoisomer, however ^{13}C NMR clearly showed doubling of most signals, betraying a 1:2.4 ratio of diastereoisomers (48% d.e.). This moderate remote diastereoselectivity seemed to be reasonable on the basis of likely models[7,3] for the addition reaction, *i.e.* assuming the intervention of an activated complex of type **6** in the formation of **5** from **4** and an acyclic transition state[10] for the aldol addition, due to prior boron-ketone chelation in the activated complex (**Figure 1**). Thus, one might expect the enolate to approach in preference from the *Si*-face of **4**, by either addition modes **A** or **B** (**Figure 1**), to provide the (*S*)-alcohol **5b**. However, as shown in **Figure 1**, additions to both carbonyl faces of **4** could be hampered by the presence of the phenyl group. We therefore argued that replacing the phenyl group in **4**, with a smaller functional group would result in increased remote diastereoselectivity. This was tested by preparation of the aldehyde **10**, which was prepared by the sequence shown in **Scheme 2**.

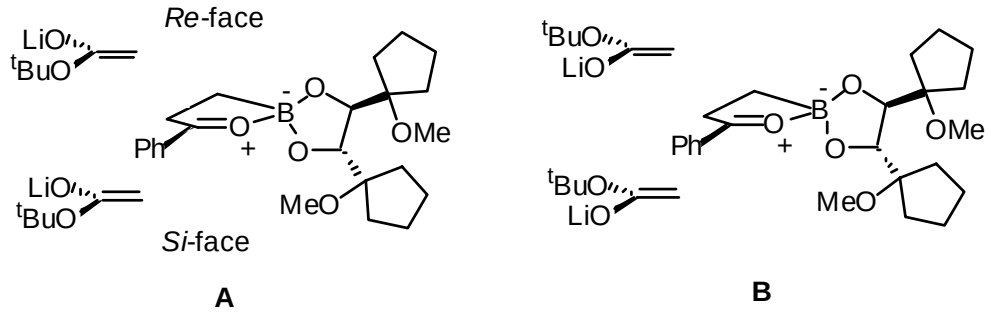
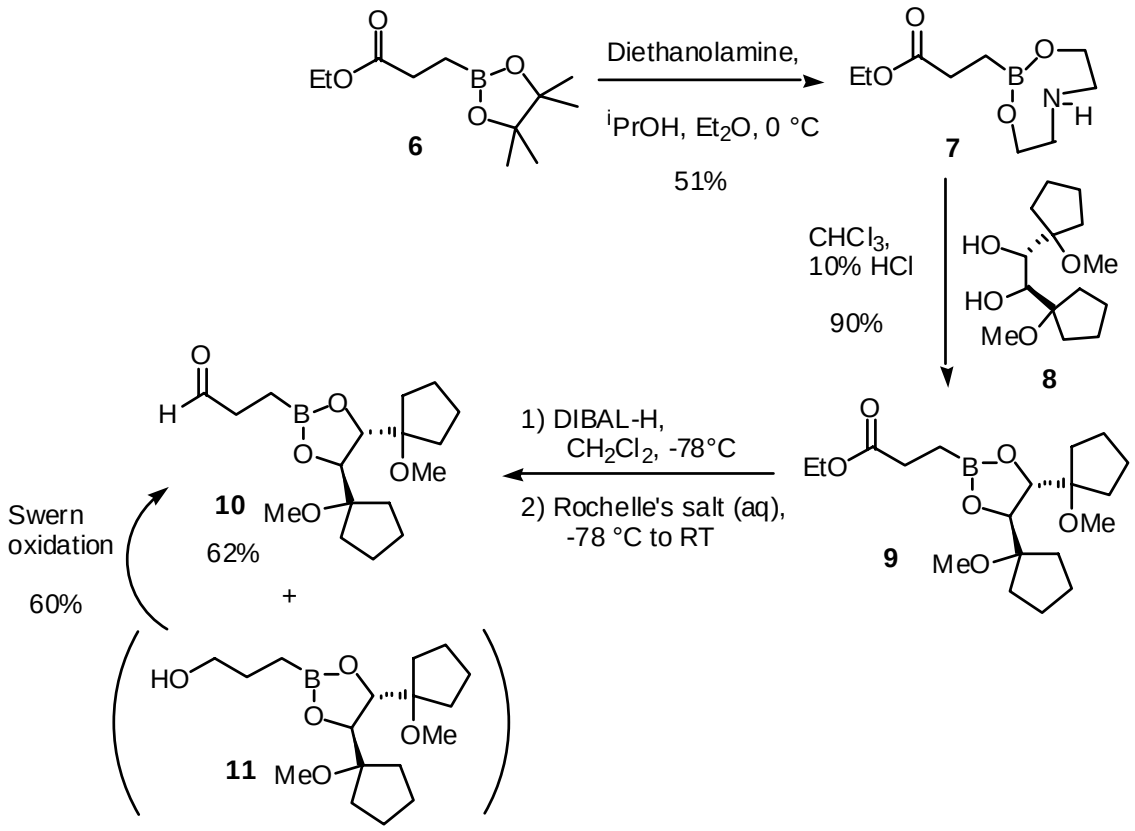


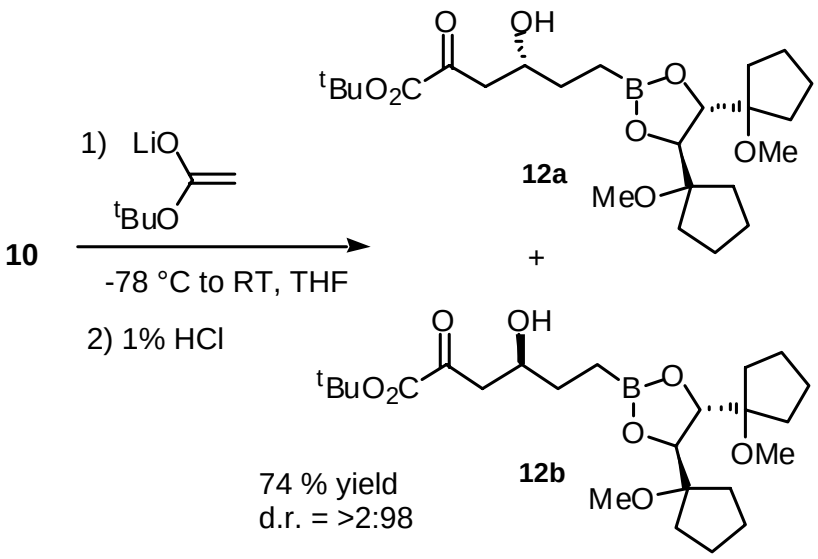
Figure 1. Diagram to show the possible mode of addition of an ester enolate to chiral ketone **4**.



Scheme 2. Preparation of aldehyde **7**.

Ethyl ester **6**[11] was transesterified with diethanolamine to provide **7**, then re-transesterified with homochiral diol[3] under biphasic acidic conditions to provide chiral boronate ester **9**. DIBAL-H reduction of ester **9** produced aldehyde **10** in 62% yield after silica gel chromatography, together with variable small quantities (5-10%) of alcohol **11**, which could be recycled by Swern oxidation to aldehyde **10** (**Scheme 2**).

Having accessed aldehyde **10**, subsequent reaction with lithium *tert*-butyl acetate at –78 °C proceeded smoothly to provide secondary alcohol **12** as a single diastereoisomer by both ^{1}H and ^{13}C NMR, *i.e.* >96% d.e. (**Equation 2**).



Equation 2. Ester enolate addition to homochiral boronate aldehyde **10**.

On the basis of our previous models, we can propose that the single diastereoisomer **12** should have the (*R*)-absolute stereochemistry, **12a**, *i.e.* derived from *Si*-face addition of the enolate to aldehyde **10**, as shown in **Figure 2**. In this addition mode, the ester enolate can approach the aldehyde carbon with minimised (compared to ketone **4**) steric repulsion between the *tert*-butoxy function and the aldehyde H, thus optimising 1,6-asymmetric induction, controlled by the chiral boronate ester moiety of **10**.

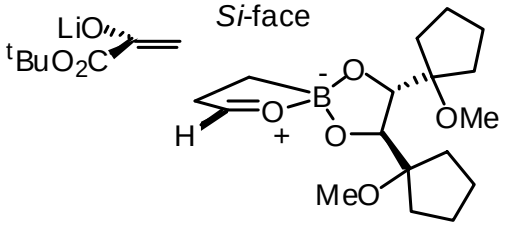


Figure 2. Mode of addition of lithium *tert*-butyl acetate to aldehyde **10**.

In order to prove the absolute stereochemistry of the major diastereoisomer of tertiary alcohol **5** and the single diastereoisomeric secondary alcohol **12** have to date proved unsuccessful, due to the extreme sensitivity of both compounds towards elimination under a range of B-C bond cleavage conditions, such as basic hydrogen peroxide. However, we have shown that the homochiral boronate ester of carbonyl systems such as **4** and **10** can exert moderate to high 1,6-asymmetric induction with a lithium ester enolate nucleophile. It is expected that this type of remote asymmetric induction methodology could find application for

the synthesis of multiple stereogenic centres in carbon frameworks using a single chirality-controlling motif. Further studies are underway in this area.

Experimental Section

General Procedures. All reagents were obtained from Acros, Aldrich or Lancaster. Dimethylsulfoxide and ethanolamine were stored under argon, over activated 3 Å molecular sieves. Dry tetrahydrofuran was freshly distilled from sodium and benzophenone immediately prior to use. Dry dichloromethane was distilled from calcium hydride. Bromobenzene and triethylamine were distilled from calcium hydride before use. Distillations were carried out under an argon atmosphere. Flash column chromatography was achieved using Acros silica gel, pore size 60 Å, or Lancaster silica gel 60, 0.060 – 0.2 mm (70 – 230 mesh). Thin layer chromatography was performed on Merck plastic or aluminium sheets coated with silica gel 60 F_{254} (Art. 5735). Chromatograms were initially examined under UV light and then developed by spraying with either phosphomolybdic acid (6 g in 125 ml of ethanol) or aqueous potassium permanganate, followed by heating. All anhydrous reactions were carried out in oven-dried (120 ^{o}C) glassware which was cooled under a stream of argon. Organic extracts were dried over $MgSO_4$ before evaporation. Evaporations were achieved using a Büchi rotary evaporator followed by drying at *ca.* 5 mmHg using a vacuum pump. Bulb-to-bulb distillations were carried out using a Büchi GKR-51 Kugelrohr apparatus. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded using Bruker NMR spectrometers. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CHCl_3$ and $CDCl_3$ respectively, as internal standards. Resonances for ^{11}B NMR spectra are quoted relative to $BF_3.Et_2O$ (δ ^{11}B = 0.00 ppm) as external standard. Chemical shift values (δ) are given in ppm, coupling constants (*J*) are given in Hz, and NMR peaks are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Infra-red (IR) spectra were recorded on a Perkin-Elmer 298 spectrophotometer or a Matson Unicam FTIR spectrometer. Electron impact (EI) (70 eV) and chemical ionisation (CI) were recorded with a Kratos MS50 or a Finnigan MAT 95S spectrometer. Fast atom bombardment (FAB) spectra were recorded on a Kratos MS50 using a *m*-nitrobenzylalcohol matrix. Accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Microanalyses were performed using a Carlo-Erba 1106 elemental analyser. Optical rotation values [α] were determined using a Perkin Elmer Model 241 or an Optical Activity AA-1000 polarimeter, and are recorded in units of 10^{-1} deg cm^2 g^{-1}. High performance liquid chromatography (HPLC) was carried out using a Shimadzu Class VP model equipped with an autosampler and UV detector, or a Gilson SF3 instrument. Chiralpak (AD, AS) and Chiralcel (OD, OB, OJ) columns, dimensions 250 x 4.6 mm, were used.

Preparation of 3-(1,3,2,6-dioxazaborocan-2-yl)propionic acid ethyl ester 7. To a solution of boronate ester 6 (0.87 g, 3.81 mmol) in diethyl ether (20 ml), diethanolamine (1.91 ml of a 2.0 M solution in isopropanol, 3.82 mmol) was added dropwise. The solution was refrigerated,

yielding title compound ester 7 (0.418 g, 1.94 mmol, 51 %) as a white solid, after filtration: Mp 130 - 131 ^{o}C; ν_{max} (KBr) / cm^{-1} 3050, 2960, 2880 – 2840, 1710 – 1690, 1360, 1240, 1095, 1055; δ_H (300 MHz; $CDCl_3$) 0.66 – 0.71 (2 H, m, CH_2B), 1.26 (3 H, t, *J* 7.2, CH_3), 2.46 – 2.50 (2 H, m, CH_2C:O), 2.76 – 2.83 (2 H, m, CH_2N), 3.15 – 3.26 (2 H, m, CH_2N), 3.83 – 3.90 (2 H, m, $CH_2\underline{C}H_2O$), 3.96 – 4.04 (2 H, m, $CH_2\underline{C}H_2O$), 4.09 (2 H, q, *J* 7.2, $CH_3\underline{C}H_2O$), 6.48 (1 H, br s, NH) (addition of D_2O caused peak at δ 6.48 to disappear); δ_C (75.5 MHz; $CDCl_3$) 11.5 (br, CH_2B), 14.0 (CH_3), 29.6 ($\underline{C}H_2C$:O), 51.1 (CH_2N), 60.2 ($CH_3\underline{C}H_2O$), 62.9 ($CH_2\underline{C}H_2O$), 178.9 (C:O); δ_B (64.2 MHz; $CDCl_3$) +12.5; *m/z* (FAB) 216 $(M + H)^+$ [Found (HRMS): *m/z* 215.1335. $C_9H_{18}BNO_4$ requires M^+ 215.1329].

Preparation of 3-[(4*S*,5*S*)-*bis*(1-methoxycyclopentyl)-1,3,2-dioxaborolan-2-yl]propionic acid ethyl ester 9. A solution of diethanolamine derivative **7** (0.335 g, 1.56 mmol) and diol **8** (0.375 g, 1.45 mmol) in chloroform (20 ml) was treated with 10 % HCl (aq) (20 ml). The biphasic solution was stirred at room temperature for 1 hour then separated. The organic extracts were combined, dried and evaporated to yield the title compound **9** (0.480 g, 1.30 mmol, 90 %) as a colourless oil: $[\alpha]_D^{26}$ +33 (*c* 2.50, $CHCl_3$); ν_{max} (film) / cm^{-1} 2960, 1735, 1395, 1370, 1195, 1075; δ_H (300 MHz; $CDCl_3$) 1.09 – 1.14 (2 H, m, CH_2B), 1.24 (3 H, t, *J* 7.0, $C\underline{H}_3CH_2$), 1.57 – 1.80 (16 H, m, CH_2 cyclopentyl), 2.42 (2 H, t, *J* 7.5, CH_2C:O), 3.23 (6 H, s, 2 x OCH_3), 4.11 (2 H, q, *J* 7.0, CH_2O), 4.31 (2 H, s, 2 x CHO); δ_C (75.5 MHz; $CDCl_3$) 14.2 ($\underline{C}H_3CH_2$), 24.5 (CH_2 cyclopentyl), 28.7 ($\underline{C}H_2C$:O), 30.7, 31.2 (CH_2 cyclopentyl), 50.3 (OCH_3), 60.2 (CH_2O), 79.1 (CHO), 87.9 (COMe), 174.4 (C:O); δ_B (64.2 MHz; $CDCl_3$) +35.9; *m/z* (FAB) 369 $(M + H)^+$ [Found (HRMS): *m/z* 369.2450. $C_{19}H_{33}BO_6$ requires $(M + H)^+$ 369.2448].

Preparation of 3-[(4*S*,5*S*)-*bis*(1-methoxycyclopentyl)-1,3,2-dioxaborolan-2-yl]propionaldehyde 10. To a solution of boronate ester **9** (0.052 g, 0.14 mmol) in dry dichloromethane (10 ml) at -78 ^{o}C under argon, diisobutylaluminium hydride (0.21 ml of a 1.0 M solution in dichloromethane, 0.21 mmol) was added very slowly. The reaction was stirred at -78 ^{o}C for a further 6 hours then quenched with methanol (1 ml) and allowed to warm to room temperature. The solution was treated with a saturated aqueous solution of potassium sodium L-tartrate tetrahydrate (10 ml) for 1 hour, then extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried and evaporated, yielding the title compound aldehyde **10** (0.028 g, 0.086 mmol, 62 %) after column chromatography [1 : 20, ethyl acetate : petroleum ether (40 - 60 ^{o}C) as eluent]: $[\alpha]_D^{26}$ +28 (*c* 1.35, $CHCl_3$); ν_{max} (film) / cm^{-1} 2980 – 2820, 1720, 1390 – 1360, 1090 – 1070, δ_H (300 MHz; $CDCl_3$) 1.07 (2 H, t, *J* 7.3, CH_2B), 1.53 – 1.83 (16 H, m, CH_2 cyclopentyl), 2.55 – 2.60 (2 H, m, CH_2C:O), 3.23 (6 H, s, 2 x OCH_3), 4.30 (2 H, s, 2 x CHOB), 9.78 (1 H, s, HC:O); δ_C (75.5 MHz; $CDCl_3$) 24.5, 24.7, 29.7, 31.1 (CH_2 cyclopentyl), 38.6 ($\underline{C}H_2C$:O), 50.3 (OCH_3), 81.4 (CHOB), 87.9 ($\underline{C}OCH_3$), 202.6 (C:O); δ_B (64.2 MHz; $CDCl_3$) +37.6; *m/z* (CI, NH_3) 324 M^+ [Found (HRMS): *m/z* 324.2104. $C_{17}H_{29}BO_5$ requires M^+ 324.2108]; and by-product alcohol **11**: $[\alpha]_D^{26}$ +28 (*c* 5.0, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 0.89 (2 H, t, *J* 7.7, CH_2B), 1.50 – 1.95 (19 H, m, CH_2 cyclopentyl, $C\underline{H}_2CH_2O\underline{H}$), 3.24 (6 H, s, 2 x OCH_3), 3.63 (2 H, t, *J* 6.2, $C\underline{H}_2OH$), 4.30 (2 H, s, 2 x CHO); δ_C (75.5 MHz; $CDCl_3$) 7.1 (br, CH_2B), 24.7 (CH_2 cyclopentyl), 27.1 ($\underline{C}H_2CH_2B$), 30.7, 31.2 (CH_2 cyclopentyl), 50.3 (OCH_3),

64.7 (CH_2OH), 81.0 (CHO), 87.9 (COMe); δ_B (64.2 MHz; $CDCl_3$) +39.6; *m/z* (FAB) 327 $(M + H)^+$ [Found (HRMS): *m/z* 327.2330. $C_{17}H_{31}BO_5$ requires $(M + H)^+$ 327.2343].

Swern oxidation of 3-[(4*S*,5*S*)-*bis*(1-methoxycyclopentyl)-1,3,2-dioxaborolan-2-yl]propan-1-ol 11. To a solution of oxalyl chloride (0.14 ml, 1.58 mmol) in dry dichloromethane (7 ml) at –78 ^oC under argon, dimethylsulfoxide (0.29 ml, 4.02 mmol) was added dropwise. After 10 minutes, a solution of alcohol **11** (0.116 g, 0.36 mmol) in dichloromethane (2 ml) was slowly added. Triethylamine (0.180 ml, 1.29 mmol) was added after 30 minutes. The reaction was allowed to warm to room temperature after 5 minutes then partitioned between dichloromethane and water. The combined organic phases were washed with 1 % HCl (aq) (25 ml), water (25 ml), saturated $NaHCO_3$ (aq) (25 ml), then water (25 ml), and dried. Evaporation yielded aldehyde **10** (0.070 g, 0.22 mmol, 60 %) as a colourless oil after column chromatography [1 : 10, ethyl acetate : petroleum ether (40 - 60 ^oC) as eluent]: all spectroscopic and analytical properties were as reported above.

Preparation of 5-[(4*R*,5*R*)-*bis*(1-methoxycyclopentyl)-1,3,2-dioxaborolan-2-yl]-3-hydroxy-3-phenyl-pentanoic acid *tert*-butyl ester 5. To a stirred solution of diisopropylamine (0.023 ml, 0.16 mmol) in THF (1 ml) at 0 ^oC under argon, butyllithium (0.064 ml of a 2.5 M solution in hexanes, 0.16 mmol) was added dropwise. After 30 minutes the reaction was cooled to -78 ^oC and *tert*-butyl acetate (0.017 ml, 0.13 mmol) was added. This solution was stirred for a further 1 hour, then β-boronate ketone (*R*,*R*)-**4** (0.045 g, 0.11 mmol) in THF (1 ml) was added dropwise. After 4 hours the reaction was allowed to warm to room temperature overnight. The yellow solution formed was partitioned between 1 % HCl (aq) and ethyl acetate. The combined organic phases were washed with water (20 ml) and dried. Evaporation yielded the crude title compound **5** (0.040 g, 0.077 mmol, 70 %) as a pale yellow oil: ν_{max} (film) / cm^{-1} 3500, 3050, 2950, 2860, 2820, 1700, 1375, 1360, 1260, 1140, 1170; δ_H (300 MHz; $CDCl_3$) 0.79 – 2.05 [31 H, m, CH_2 cyclopentyl, $(CH_2)_2B$, $(CH_3)_3C$, $CH_2C{:}O$], 3.22 (6 H, s, 2 x OCH_3), 4.27 - 4.28 (2 H, m, 2 x CHO), 7.17 – 7.38 (5 H, m, H aromatic); δ_C (75.5 MHz; $CDCl_3$), 1 : 2.4 mixture of diastereomers, 24.5, 24.6, 24.7, 24.9 (CH_2 cyclopentyl), 27.7 (major isomer), 28.2 (minor isomer) [($\underline{C}H_3)_3C$], 30.7, 31.1, 31.2, 31.3 (CH_2 cyclopentyl), 33.2 (major isomer), 37.3 (minor isomer) ($\underline{C}H_2CH_2B$), 46.2 ($\underline{C}H_2C{:}O$), 50.3, 50.8 (OCH_3), 75.4 (PhCOH), 80.7 (CHOB), 81.5 [$(CH_3)_3\underline{C}$], 87.9 ($\underline{C}OCH_3$), 125.8, 126.9, 127.2, 128.3, 128.7, 128.8, 145.7 (C aromatic), 166.3 (C:O); *m/z* (CI, NH_3) 517 $(M + H)^+$ [Found (HRMS): *m/z* 517.3322. $C_{29}H_{45}BO_7$ requires $(M + H)^+$ 517.3336].

Preparation of 5-[(4*S*,5*S*)-*bis*(1-methoxycyclopentyl)-1,3,2-dioxaborolan-2-yl]-3-hydroxyl pentanoic acid *tert*-butyl ester 12. To a stirred solution of diisopropylamine (0.018 ml, 0.125 mmol) in dry THF (1 ml) at 0 ^oC under argon, butyllithium (0.050 ml of a 2.5 M solution in hexanes, 0.125 mmol) was added dropwise. After 30 minutes the reaction was cooled to -78 ^oC and *tert*-butyl acetate (0.013 ml, 0.10 mmol) was added. The solution was stirred at -78 ^oC for a further 1 hour, then aldehyde 10 (0.027 g, 0.083 mmol) in THF (1 ml) was slowly added. After 1 hour the reaction was allowed to warm to room temperature overnight, then treated with aqueous ammonium chloride (0.125 ml of a 1.0 M solution, 0.125 mmol). The mixture was partitioned

between ethyl acetate and water. The combined organic phases were then combined and dried. Evaporation yielded the crude title compound 12 (0.027 g, 0.061 mmol, 74 %) as a colourless oil: ν_{max} (film) / cm^{-1} 2960 – 2840, 1710, 1460, 1390 – 1370, 1260; δ_H (300 MHz; $CDCl_3$) 0.85 – 2.02 [29 H, m, CH_2 cyclopentyl, $(CH_2)_2B$, $(CH_3)_3C$], 2.26 – 2.53 (2 H, m, CH_2C:O), 3.23 (6 H, s, 2 x OCH_3), 3.87 – 3.40 (1 H, m, C<u>H</u>OH), 4.29 (2 H, s, 2 x CHOB); δ_C (75.5 MHz; $CDCl_3$) 24.6, 24.7 (CH_2 cyclopentyl), 28.1 [(<u>C</u>$H_3)_3$C], 30.7, 31.1 (CH_2 cyclopentyl), 33.2 (<u>C</u>H_2CH_2B), 42.0 (<u>C</u>H_2C:O), 50.4 (OCH_3), 69.6 (CHOH), 80.9 (CHOB), 81.0 [$(CH_3)_3$<u>C</u>], 87.9 (<u>C</u>OCH_3), 172.4 (C:O); *m/z* (CI, NH_3) 441 $(M + H)^+$ [Found (HRMS): *m/z* 441.3024. $C_{23}H_{41}BO_7$ requires $(M + H)^+$ 441.3023].

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