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Diastereoselective borono-Mannich reactions on cyclic *N*-acyliminium ions

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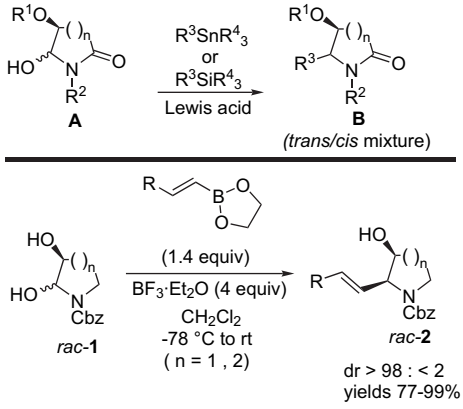
Abstract

The addition of boronic acids to five- and six-membered ring *N*-acyliminium ions has been employed to prepare 5- and 6-substituted 4-hydroxypyrrolidin-2-ones and 5-hydroxypiperidin-2-ones, respectively, in a diastereoselective fashion.

1. Introduction

As part of a project aimed at the synthesis of bioactive polyhydroxylated pyrrolidine, piperidine, indolizidine and pyrrolizidine alkaloids and their analogues,[1] we have examined the addition of organoboronic acids to five- and six-membered ring *N*-acyliminium ions. The synthesis of *trans* 5-substituted-4-hydroxypyrrolidin-2-ones and 6-substituted-5-hydroxypiperidin-2-ones is relatively easily achieved from the addition of tin or silicon based nucleophiles to five- and six-membered ring *N*-acyliminium ions (Scheme 1).[2–7] *cis*-Diastereoselective additions to *N*-acyliminium ions have been reported by Batey.[5] He has shown that the racemic hemi-aminal derivatives, *rac*-**1** (n=1 or 2), having an *exo*-cyclic *N*-acyl group, react with 2-substituted vinyl- and arylboronate ethylene glycol esters, in the presence of $BF_3{\cdot}Et_2O$, to give products *rac*-**2** in a highly diastereoselective manner (Scheme 1).[5] This work, however, has not been extended to enantiomerically enriched cyclic hemi-aminals of the type **A** (n=1, 2) having an *endo*-cyclic *N*-acyl group. Here we report our work on the borono-Mannich reactions of the cyclic *N*-acyliminium ions generated in situ from the enantiomerically enriched cyclic hemi-aminals **A** (n=1, 2).



Scheme 1.

2. Results and discussion

The six-membered ring hemi-aminal (5*S*)-**3** (dr=3:1) was prepared from the known *N*-PMB-(3*S*)-hydroxyglutarimide[2m,6] by $NaBH_4$ reduction. Under the conditions described by Batey[5] the diol (5*S*)-**3** when treated with (*E*)-2-styrylboronic acid **4** (X=OH, n=2), in the presence of $BF_3{\cdot}Et_2O$, failed to produce the desired product, even at elevated temperatures. However, when the more polar solvent MeCN was used this modification gave rise to the desired *cis*-adduct **5** in a yield of 77% and with high diastereoselectivity (>98:<2) as determined by ^1H NMR analysis at 500 MHz (Scheme 2). The

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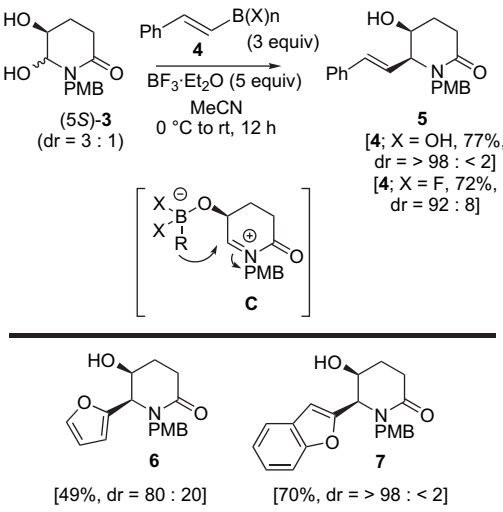
Table 1
Products from the reactions of $RB(OH)_2$ with (4*S*)-**18**

Entry	R	Product	Yield (%)	dr (*trans*/*cis*)
1	(*E*)-PhCH=CH	**19a**	47	91:9
2	(*E*)-PhCH=CH[a]	**19a**	59	92:8
3	2-Furyl	**19b**	79	71:29
4	2-Benzofuranyl	**19c**	55	89:11
5	2-Thienyl	**19d**	72	38:62
6	Phenyl	**19e**	0	—
7	4-$MeOC_6H_4$	**19f**	48	72:28
8	3,4-$(MeO)_2C_6H_3$	**19g**	74	74:26

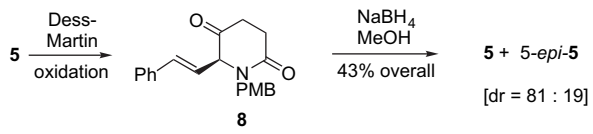
[a] The corresponding RBF_3K was used.

corresponding potassium trifluoroborate **4** (X=F, *n*=3) also provided the *cis*-adduct **5** but with a reduced yield (72%) and a lower, but good diastereoselectivity (dr=92:8). We have examined the reactions of (5*S*)-**3** with other boronic acids and boronates as shown in Table 1. Only the electron-rich boronic acids, 2-furylboronic acid and 2-benzofuranylboronic acid, gave the desired adducts, **6** and **7**, respectively (Scheme 2). The other boronic acids and boronates did not react or gave mixtures that were not readily characterised. The use of $MeNO_2$ as an alternative, less nucleophilic solvent to MeCN did not provide increased yields of the desired products.



Scheme 2.

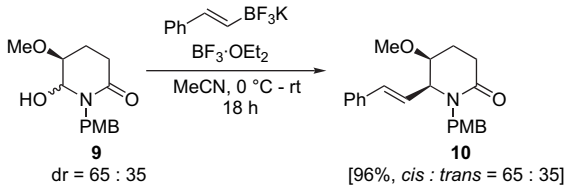
To determine the stereochemistry of **5**, the alcohol was oxidised using the Dess–Martin periodinane reagent to its corresponding ketone **8**, which upon sodium borohydride reduction gave the carbinol **5** as the major isomer in an 81:19 mixture of two carbinol isomeric products (Scheme 3). From literature precedence[7] the major isomer from reduction of **8** was expected to be the *cis*-isomer **5**, thus we have assigned the major isomers of **5**–**7**, prepared according to Scheme 2, as the 5,6-



Scheme 3.

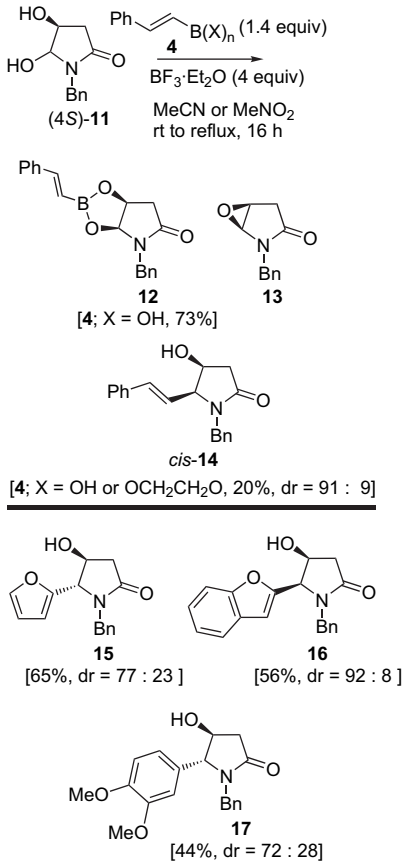
cis isomers. The $J_{5,6}$ values for all the major diastereomers of these compounds were 5.1–6.0 Hz, and is consistent with that of the known *cis*-6-phenyl analogue of these compounds, which had $J_{5,6}$=5.2 Hz.[7]

The stereochemical outcomes of the major products in Scheme 2 are consistent with the formation of an initial boronate complex **C** (Scheme 2) to the 5-hydroxy group of (5*S*)-**3** followed by the intramolecular delivery of the sp^2 hybridised boron ligand to the same face of the iminium ion intermediate. A similar mechanism has been proposed for the borono-Mannich reaction involving acyclic iminium ions.[1e,8] Further support for such boronate intermediates being responsible for the high *cis*-diastereoselectivity came from the result of treating **9**, the *O*-methyl derivative of (5*S*)-**3**, with potassium (*E*)-2-styryltrifluoroborate in the presence of $BF_3\cdot Et_2O$. This reaction was high yielding (96%) but poorly diastereoselective in favour of the *cis*-adduct **10** (Scheme 4).[9]



Scheme 4.

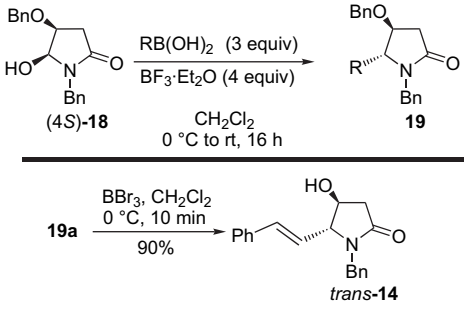
Similarly, (4*S*)-**11**[10,11] was also unreactive under Batey's conditions but, in contrast to (5*S*)-**3**, treatment of (4*S*)-**11** with (*E*)-2-styrylboronic acid **4** (X=OH, *n*=2) and $BF_3\cdot Et_2O$ in MeCN, under similar reaction conditions to that of (5*S*)-**3**, did not result in the desired product **14**. Instead this reaction resulted in formation of the cyclic boronate ester **12** that was readily isolated (73% yield) and characterised. Repeating this reaction with heating at reflux temperature gave rise to the epoxide **13** (Scheme 5). Attempts to purify this epoxide by column chromatography were unsuccessful due to its instability on silica gel.[11b] While further treatment of this epoxide mixture in MeCN at reflux with fresh **4** (X=OH, *n*=2 or X=F, *n*=3, as the K^+ salt) and $BF_3\cdot Et_2O$ gave none of the desired product **14**. When $MeNO_2$ was used as solvent in the reaction of (4*S*)-**11** then the desired adduct *cis*-**14** was isolated in 20% yield using either (*E*)-2-styrylboronic acid **4** (X=OH, *n*=2) or its ethylene glycol boronate ester **4** (*n*=2, X=OCH_2CH_2O). The 4,5-*cis*-stereochemistry of **14** was based on the magnitude of $J_{4,5}$ (6.0 Hz) for this compound.[2a,b] In related literature examples, $J_{4,5}$ is typically 0–2.5 Hz for *trans* isomers and 6.0–7.5 Hz for the corresponding *cis* isomers.[2a,b] Under similar reaction conditions and using $MeNO_2$ as solvent, the electron-rich boronic acids, 2-furyl-, 2-benzofuranyl- and 3,4-dimethoxyphenylboronic acid, also reacted with (4*S*)-**11**, furnishing the adducts **15**–**17**, respectively, (Scheme 5) and in higher yields than **14**. Interestingly, both adducts **15** and **17** favoured formation of the 4,5-*trans*-adduct, while the 2-benzofuranyl-adduct **16** favoured the 4,5-*cis*-diastereomer in high diastereoselectivity (dr=92:8). The stereochemical outcomes of **14** and **16** are consistent with the formation of an initial boronate complex similar to **C** (Scheme 2). While that of **15** and



Scheme 5.

17 suggest that direct addition of the arylboronic acid to the cyclic iminium ion intermediate had occurred.

The results of the reactions of (4*S*)-**18**,[12] the 4-*O*-benzyl ether of (4*S*)-**11**, with boronic acids and trifluoroboronates[13] are shown in Scheme 6 and Table 1. In contrast to the reaction of (4*S*)-**11**, these reactions were successful under Batey's conditions (CH_2Cl_2 solution) but at a slightly elevated temperature (rt).

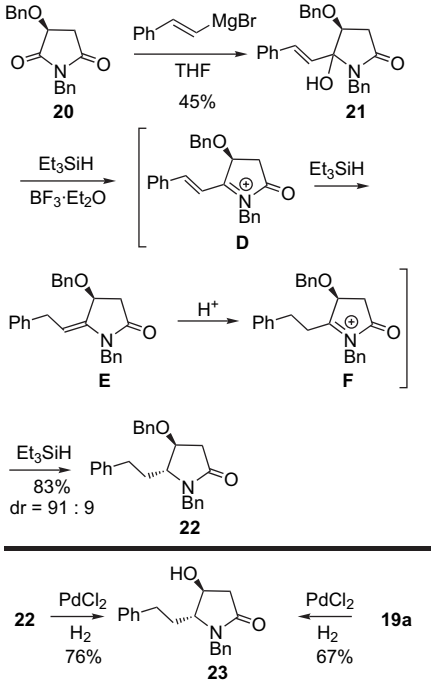


Scheme 6.

The reaction of (4*S*)-**18** with (*E*)-2-styrylboronic acid **4** (X=OH, n=2) in CH_2Cl_2 at rt gave the 5-(2-styryl)-adduct **19a** in 47% yield and as a 91:9 mixture of the *trans* and *cis* isomers, respectively (Table 1, entry 1). This product **19a** was obtained in a slightly higher yield (59%) and diastereoselectivity (92:8) when potassium (*E*)-2-styryltrifluoroborate was used (entry 2). The electron-rich heteroaromatic boronic acids (entries 3–5) gave the adducts **19b** and **19c** in which the major diastereoisomers had the *trans* stereochemistry, while the 2-thienyl adduct **19e** favoured the unexpected *cis*-adduct. The reaction of (4*S*)-**18** with furan itself in the presence of $BF_3\cdot Et_2O$ also gave **19b** (40% yield) as a 55:45 mixture of *trans* and *cis* isomers, respectively. In contrast, phenylboronic acid was unreactive (entry 6), while its more electron-rich analogues, 4-methoxyphenylboronic acid and 3,4-dimethoxyphenylboronic, acid gave their respective adducts **19f** and **19g**, in yields (48 and 74%, respectively) that reflected their electron-richness and associated nucleophilicities. The latter two reactions favoured formation of the *trans* isomer (entries 7 and 8).

The stereochemistry of these adducts **19** was readily determined from examination of the coupling constant $J_{4,5}$, which was typically 0–2.5 Hz for the *trans* isomers and 6.0–7.5 Hz for the corresponding *cis* isomers, consistent with literature examples.[2a,b] Furthermore, O-debenzylation of **19a** with BBr_3 gave *trans*-**14** (Scheme 6), identical to the minor isomer formed from the reaction of (4*S*)-**11** and (*E*)-2-styrylboronic acid (Scheme 5).

In an attempt to prepare the compound **19a** in higher yield and diastereoselectivity via an alternative route, the succinimide **20**[11] was treated with 2-phenylvinylmagnesium bromide[14] to give a diastereomeric mixture of tertiary carbinols **21** (Scheme 7). Reduction of this mixture with $Et_3SiH/BF_3\cdot Et_2O$ gave the *trans*-5-(2-phenylethyl)-2-pyrrolidinone **22** in 83% yield (dr=91:9). A plausible mechanism for this transformation is shown in Scheme 7. The intermediate iminium ion **D** undergoes 1,4-addition of hydride to give the *N*-acyl enamine **E**, which upon protonolysis gives the iminium ion **F** that is further reduced to the *trans*-product **22**. The reduction of alkenes with $Et_3SiH/BF_3\cdot Et_2O$ in the absence of a transition metal catalyst has precedence[15] as also does the formation of 4,5-



Scheme 7.

trans-pyrrolidinones from the reduction of hemi-aminals related to **21**.[2r]

To prove the stereochemistry of **22**, it was converted to the alcohol **23** by hydrogenolysis over $PdCl_2$. The same compound **23** was obtained from **19a** after treatment under similar reductive conditions, thus indicating the *trans* stereochemistry of **22** (Scheme 7).

In conclusion, we have demonstrated that boronic acids and boronates add to five- and six-membered ring *N*-acyliminium ions having an *endo*-cyclic *N*-acyl group to provide 5- and 6-substituted 4-hydroxypyrrolidin-2-ones and 5-hydroxypiperidin-2-ones, respectively, in a diastereoselective fashion. The six-membered rings adducts can be obtained with good to high *cis*-diastereoselectivities but are limited to reactive, electron-rich, boronic acids. Nevertheless, such 5,6-*cis*-substituted compounds are difficult to access using current methods.[2c]

3. Experimental

3.1. General

Unless stated, $CDCl_3$ was used as a solvent for all ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) measurements. All IR spectra were determined as neat samples. All solutions were dried over anhydrous $MgSO_4$. Petrol refers to the hydrocarbon fraction of boiling point 40–60 °C.

3.1.1. (5*S*)-1-(4-Methoxybenzyl)-5,6-dihydroxypiperidin-2-one (**3**)

To a solution of (5*S*)-1-(4-methoxybenzyl)-6-hydroxypiperidin-2,6-dione[2m,6] (2.00 g, 8.02 mmol) in MeOH/CH_2Cl_2 (80:40 mL) at −15 °C was added $NaBH_4$ (1.52 g, 40.12 mmol) and the reaction was monitored by TLC. After 40 min the reaction was carefully quenched with acetone (30 mL). Saturated $NaHCO_3$ solution (30 mL) and then brine (30 mL) were added and the volatiles were removed in vacuo. The crude residue was taken up in EtOAc (150 mL) and washed with brine (1×100 mL). The aqueous portions were then combined and re-extracted with EtOAc (1×50 mL) and then the combined organic extracts were dried and concentrated to yield the crude diol as a colourless solid. The crude product was purified by column chromatography (10% MeOH/EtOAc) yielding the diol **3** (0.972 g, 3.87 mmol, 48%, R_f=0.30 EtOAc) as a colourless solid and as a mixture of diastereoisomers (3:1) showing: mp 120–122 °C; ν_{max}/cm^{-1} 3263, 2935, 1614, 1562, 1244, 1029, 964, 818.

Major isomer: δ_H 7.25 (2H, app, d, *J*=8.6 Hz, 2-, 6-ArCH), 6.86 (2H, app d, *J*=8.6 Hz, 3-, 5-ArCH), 4.89 (1H, d, *J*=14.7 Hz, C*H*HPMP), 4.73 (1H, dd, *J*=4.9, 4.4 Hz, 6-CH), 4.45 (1H, d, *J*=14.7 Hz, C*H*HPMP), 3.93 (1H, m, 5-H), 3.79 (3H, s, OMe), 2.68 (1H, ddd, *J*=17.9, 9.8, 6.7 Hz, 3-CH*H*), 2.47 (1H, ddd, *J*=17.9, 6.5, 4.7 Hz, 3-C*H*H), 2.40 (1H, d, *J*=5.9 Hz, OH), 2.15–2.17 (1H, m, 4-CH*H*), 1.82–1.86 (1H, m, 4-C*H*H); δ_C (CD_3OD) 172.3, 160.6, 130.5, 130.4, 115.0, 80.7, 68.4, 55.7, 47.5, 30.7, 24.1.

Minor isomer: δ_H 7.26 (2H, app, d, *J*=8.6 Hz, 2-, 6-ArCH), 6.87 (2H, app d, *J*=8.6 Hz, 3-, 5-ArCH), 5.00 (1H, d, *J*=14.6 Hz, C*H*HPMP), 4.80 (1H, dd, *J*=5.4, 2.9 Hz, 6-H), 4.29 (1H, d, *J*=14.6 Hz, CH*H*PMP), 3.87 (1H, m, 5-H), 3.79 (3H, s, OMe), 2.64 (1H, ddd, *J*=18.0, 6.0, 4.2 Hz, 3-C*H*H), 2.40–2.48 (1H, m, 3-CH*H*), 2.07–2.14 (1H, m, 4-C*H*H), 1.82–1.87 (1H, m, 4-CH*H*); δ_C (CD_3OD) 171.1, 160.4, 132.4, 129.8, 114.9, 72.7, 62.8, 55.7, 43.1, 32.4, 29.3; MS (ESI^-) *m*/*z* 285.8 $(M+Cl)^-$ 100%; HRMS (ESI^+) calcd for $C_{13}H_{18}NO_4$ $(M+H)^+$: 252.1236, found: 252.1246.

3.1.2. (5*S*,6*S*)-1-(4-Methoxybenzyl)-5-hydroxy-6-styrylpiperidin-2-one (**5**)

To a suspension of the diol **3** (0.150 g, 0.597 mmol) and (*E*)-2-styrylboronic acid (0.265 g, 1.791 mmol) in anhydrous MeCN (10 mL) at 0 °C was added $BF_3 \cdot OEt_2$ (0.375 mL, 2.985 mmol) and the resulting solution was stirred at rt overnight (ca. 15 h). The reaction was quenched by careful addition of saturated $NaHCO_3$ solution (5 mL), brine (5 mL) and diluted with EtOAc (20 mL). The organic layer was separated and the aqueous portion was further extracted with EtOAc (2×20 mL). The combined organics were washed with brine (60 mL), dried and the solvent removed. Column chromatography (EtOAc to 1% MeOH/EtOAc) of the crude residue yielded the olefin **5** (0.156 g, 0.463 mmol, 77%, R_f=0.51, 1% MeOH/EtOAc) essentially, as a single diastereoisomer. $[\alpha]_D^{23}$ +12.4 (*c* 1.93, $CHCl_3$); ν_{max}/cm^{-1} 3360, 2925, 2848, 1612, 1512, 1455, 1245, 1173, 1025, 749; δ_H 7.28–7.41 (5H, m), 7.16 (2H, d, *J*=8.6 Hz), 6.84 (2H, d, *J*=8.6 Hz), 6.53 (1H, d, *J*=16.0 Hz), 6.19 (1H, dd, *J*=16.0, 7.4 Hz), 5.40 (1H, d, *J*=14.6 Hz), 4.04 (1H, dd, *J* ca. 7, 6 Hz), 3.98 (1H, app dt, *J*=10.0, 5.2 Hz), 3.79 (3H, s), 3.73 (1H, d, *J*=14.6 Hz), 2.69 (1H, ddd, *J*=18.3, 6.1, 4.1 Hz), 2.55 (1H, ddd, *J*=18.3, 8.2, 9.6 Hz), 1.90–1.97 (2H, m). δ_C 168.8, 158.8, 135.8, 134.4, 129.3, 128.8, 128.5, 128.0, 126.5, 124.4, 113.4, 67.7, 61.8, 55.2, 47.3, 29.3, 26.0; MS (ESI^-) *m*/*z* 371.9 $(M+Cl)^-$ 100%; HRMS (ESI^+) calcd for $C_{21}H_{24}NO_3$ $(M+H)^+$, 338.1756, found: 338.1766.

3.1.3. (5*S*,6*R*)-1-(4-Methoxybenzyl)-6-(furan-2-yl)-5-hydroxypiperidin-2-one (**6** and 6-epi-**6**)

Prepared in a similar fashion to **5** above, from the diol **3** (150 mg, 0.597 mmol), 2-furanboronic acid (100 mg, 0.894 mmol) and $BF_3 \cdot OEt_2$ (375 μL, 2.985 mmol) with stirring at rt overnight. Column chromatography (EtOAc) of the crude residue furnished *trans*-**6** (7 mg, 0.023 mmol, 4%, R_f=0.42), *cis*-**6** (63 mg, 0.209 mmol, 35%, R_f=0.36) and a *cis*/*trans*-mixture (19 mg, 0.063 mmol, 10%) as pale yellow oils (*cis*/*trans* 80:20). The *trans* isomer: $[\alpha]_D^{24}$ +13.1 (*c* 0.265, $CHCl_3$); ν_{max}/cm^{-1} 3345, 2935, 2827, 1609, 1516, 1465, 1245, 1173; δ_H 7.39 (1H, br, 5-Ar′CH), 7.13 (2H, app d, *J*=8.3 Hz, 2-, 6-ArCH), 6.83 (2H, app d, *J*=8.3 Hz, 3-, 5-ArCH), 6.37 (1H, dd, *J*=3.1, 1.8 Hz, 4-Ar′CH), 6.22 (1H, d, *J*=3.1 Hz, 3-Ar′CH), 5.51 (1H, d, *J*=14.8 Hz, C*H*H–PMP), 4.38 (1H, d, *J*=3.2 Hz, 6-H), 4.17–4.20 (1H, m, 5-H), 3.79 (3H, s, OMe), 3.46 (1H, d, *J*=14.8 Hz, CH*H*–PMP), 2.75 (1H, ddd, *J*=18.0, 10.2, 7.1 Hz, 3-C*H*H), 2.54 (1H, ddd, *J*=18.0, 6.6, 4.0 Hz, 3-CH*H*), 2.05–2.13 (1H, m, 4-C*H*H), 1.80–1.87 (1H, m, 4-CH*H*); δ_C 142.8 (2-Ar′CH), 129.4 (2-, 6-ArCH), 128.8 (ArC), 114.1 (3-, 5-ArC), 110.4 and 108.6 (3-, 4-Ar′CH), 67.3 (5-C), 60.7 (6-C), 55.2 (OMe), 46.9 (CH_2–PMP), 27.3 (3-CH_2), 24.8

(4-CH_2); *m/z* (ESI^-) 299.8 $(M-H)^-$ 75%; HRMS (ESI^+) calcd for $C_{17}H_{20}NO_4$ $(M+H)^+$: 302.1392, found: 302.1384.

The *cis* isomer: $[\alpha]_D^{23}$ −10.4 (*c* 2.16, $CHCl_3$); ν_{max}/cm^{-1} 3309, 2919, 2848, 1610, 1513, 1475, 1246, 1177, 747; δ_H 7.46 (1H, dd, *J*=1.6, 0.6 Hz, 5-Ar′CH), 7.09 (2H, app d, *J*=8.6 Hz, 2-Ar′CH), 6.83 (2H, app d, *J*=8.6 Hz, 3-, 5-ArCH), 6.42 (2H, dd, *J*=3.2, 1.8 Hz, 4-Ar′CH), 6.32 (2H, d, *J*=3.2 Hz, 3-Ar′CH), 5.40 (1H, d, *J*=14.6 Hz, C*H*H−PMP), 4.49 (1H, d, *J*=5.2 Hz, 6-CH), 3.98−4.04 (1H, m, 5-CH), 3.80 (3H, s, OMe), 3.42 (1H, d, *J*=14.6 Hz, CH*H*−PMP), 2.75 (1H, ddd, *J*=18.2, 6.4, 3.2 Hz, 3-C*H*H), 2.57 (1H, ddd, *J*=18.2, 10.0, 8.0 Hz, 3-CH*H*), 1.94−1.97 (2H, m, 4-CH_2); δ_C 169.4 (C=O), 159.0 (ArC), 149.7 (5-Ar′CH), 143.3 (2-Ar′CH), 129.6 (2-, 6-ArCH), 128.6 (ArC), 114.0 (3-, 5-ArCH), 110.9, 110.5 (3-, 4-Ar′CH), 67.2 (5-CH), 57.7 (6-CH), 55.2 (OMe), 47.4 (CH_2−PMP), 29.6 (3-CH_2), 26.1 (4-CH_2); *m/z* (ESI^-) 299.8 $(M-1)^-$ 70%; HRMS (ESI^+) calcd for $C_{17}H_{20}NO_4$ $(M+H)^+$: 302.1392, found: 302.1393.

3.1.4. (5S,6R)-1-(4-Methoxybenzyl)-6-(benzofuran-2-yl)-5-hydroxypiperidin-2-one (7)

Prepared in a similar fashion to **5** above, from the diol **3** (150 mg, 0.597 mmol), 2-benzofuranboronic acid (193 mg, 1.194 mmol) and $BF_3{\cdot}OEt_2$ (375 μL, 2.985 mmol) with stirring at rt overnight. Column chromatography (EtOAc, R_f= 0.5) of the crude residue furnished **7** (146 mg, 0.415 mmol, 70%) as a pale yellow oil. $[\alpha]_D^{23}$ +21.6 (*c* 1.11, $CHCl_3$); ν_{max}/cm^{-1} 3365, 2960, 1614, 1512, 1454, 1248, 1175, 1030, 820, 752; δ_H 7.58 (1H, d, *J*=7.4 Hz, 4-Ar′CH), 7.49 (1H, d, *J*=8.2 Hz, 7-Ar′CH), 7.32 (1H, ddd, *J*=8.2, 7.9, 1.3 Hz, 6-Ar′CH), 7.25−7.29 (1H, m, 5-Ar′CH), 7.11 (2H, app d, *J*=8.5 Hz, 2-, 6-ArCH), 6.82 (2H, app d, *J*=8.5 Hz, 3-, 5-ArCH), 6.70 (1H, s, 3-Ar′CH), 5.46 (1H, d, *J*=14.7 Hz, C*H*H−PMP), 4.63 (1H, d, *J*=5.1 Hz, 6-CH), 4.08−4.15 (1H, m, 5-CH), 3.78 (3H, s, OMe), 3.52 (1H, d, *J*=14.7 Hz, CH*H*−PMP), 2.83 (1H, ddd, *J*=18.3, 6.7, 2.7 Hz, 3-CH*H*), 2.63 (1H, ddd, *J*=18.3, 10.6, 7.7 Hz, 3-C*H*H), 2.00−2.10 (1H, m, 4-CH*H*), 1.94−2.00 (1H, m, 4-C*H*H), 1.76 (1H, d, *J*=7.9 Hz, OH); δ_C 169.6 (C=O), 159.0 (ArC), 155.1 (2-Ar′C), 152.6 (3-Ar′CH), 129.5 (2-, 6-ArCH), 128.4 (ArC), 127.7 (Ar′C), 124.5 (6-Ar′CH), 123.0 (5-Ar′CH), 120.9 (4-Ar′CH), 114.0 (3-, 5-ArCH), 111.3 (7-Ar′CH), 107.5 (3-Ar′CH), 67.1 (5-CH), 58.1 (6-CH), 55.1 (OMe), 47.6 (CH_2−PMP), 29.6 (3-CH_2), 26.0 (4-CH_2); *m/z* (ESI^-) 299.8 $(M-H)^-$ 70%; HRMS (ESI^+) calcd for $C_{21}H_{21}NO_4Na$ $(M+Na)^+$: 374.1368, found: 374.1379.

3.1.5. Synthesis of (5S,6S)-1-(4-methoxybenzyl)-5-hydroxy-6-styrylpiperidin-2-one (5) from (6S)-1-(4-methoxybenzyl)-6-styrylpiperidin-2,5-dione (8)

To a solution of the olefin **5** (170 mg, 0.505 mmol) in anhydrous CH_2Cl_2 (15 mL) was added Dess−Martin periodinane (0.30 g, 0.707 mmol) and the mixture was stirred at rt. After 1 h TLC analysis indicated a complete reaction and the excess oxidant was quenched with saturated sodium thiosulfate (10 mL) then this mixture was allowed to stir vigorously for 30 min. The resulting mixture was extracted with EtOAc (3×25 mL) and the combined organic extracts were washed with brine (50 mL) and the solvent evaporated to yield the ketone **8** as pale yellow oil, which was used without any further purification. δ_H 7.28−7.35 (5H, m), 7.19 (2H, d, *J*=8.6 Hz), 6.85 (2H, d, *J*=8.6 Hz), 6.50 (1H, dd, *J*=16.0, 1.7 Hz), 6.05 (1H, dd, *J*=16.0, 5.6 Hz), 5.41 (1H, d, *J*=14.6 Hz), 4.42 (1H, dd, *J*=5.6, 1.7 Hz), 3.85 (1H, d, *J*=14.6 Hz), 3.79 (3H, s), 2.77−2.85 (2H, m), 2.69−2.74 (2H, m); δ_C 203.3, 170.5, 159.0, 136.3, 135.1, 127.9, 129.7, 129.6, 128.6, 128.4, 126.6, 114.2, 67.1, 55.2, 47.4, 35.0, 28.8. To a solution of the crude ketone **8** (assumed quantitative yield, 0.505 mmol) in MeOH (3 mL) at 0 °C was added $NaBH_4$ (57.3 mg, 1.515 mmol) and the reaction mixture was stirred for 45 min at which time TLC analysis indicated that the reaction was complete. The reaction was quenched with saturated $NaHCO_3$ solution (2 mL) and then the MeOH was removed in vacuo. The crude residue was diluted with EtOAc (50 mL), washed with saturated K_2CO_3 (10 mL), brine (20 mL), dried, concentrated and finally subjected to column chromatography yielding a mixture of **5** and 5-*epi*-**5** (74 mg, 0.219 mmol, 43%, R_f=0.1, 90:10 Et_2O/EtOAc, **5**/5-*epi*-**5**, 81:19), with the major isomer showing analytical data in full accordance with an analytically pure sample of compound **5**.

3.1.6. (S)-1-(4-Methoxybenzyl)-6-hydroxy-5-methoxypiperidin-2-one (9)

Step 1: into an oven-dried flask under an atmosphere of dry nitrogen were added (5*S*)-1-(4-methoxybenzyl)-6-hydroxypiperidin-2,6-dione[2m,6] (0.75 g, 3.01 mmol), silver oxide (2.09 g, 9.03 mmol), anhydrous EtOAc (4 Å molecular sieve dried, 20 mL), methyl iodide (0.56 mL, 9.03 mmol) and then the resulting heterogeneous mixture was stirred at rt overnight. The methyl iodide was quenched by slow addition of triethylamine (10 mL) and the mixture was allowed to stir for 30 min at rt. The solids were removed by filtration through a short plug of silica (ca. 5 cm×5 cm) using ethyl acetate as the eluent and then the solvent was removed yielding the crude product. Subsequent column chromatography (20:80 petrol/EtOAc, R_f=0.54) afforded (5*S*)-6-methoxy-1-(4-methoxybenzyl)piperidin-2,6-dione (0.629 g, 2.39 mmol, 79%) as a colourless oil. $[\alpha]_D^{22}$ +13.0 (*c* 1.56, $CHCl_3$); δ_H 7.32 (2H, app d, *J*= 8.4 Hz, 2-, 6-ArCH), 6.81 (2H, app d, *J*=8.4 Hz, 3-, 5-ArCH), 4.87 (2H, br s, CH_2PMP), 3.89 (1H, dd, *J*=7.0, 4.1 Hz, 3-CH), 3.77 (3H, s, OMe), 3.50 (3H, s, OMe), 2.89 (1H, ddd, *J*=17.7, 8.2, 5.6 Hz, 5-C*H*H), 2.60 (1H, app dt, *J*=17.7, 6.2 Hz, 5-CH*H*), 2.04−2.10 (2H, m, 4-CH_2); δ_C 171.5 (C=O), 171.2 (C=O), 158.9 (ArCOMe), 103.3 (2-, 6-ArCH), 129.2 (ArC), 113.7 (3-, 5-ArCH), 76.4 (3-CH), 58.5 (OMe), 55.2 (OMe), 42.3 (CH_2PMP), 29.1 (5-CH_2), 23.6 (4-CH_2); *m/z* (ESI^-) 279.8 $(M+17)^-$ 100%; HRMS (ESI^+) calcd for $C_{14}H_{18}NO_4$ $(M+H)^+$: 264.1236, found: 264.1246.

Step 2: the title compound was prepared from (5*S*)-6-methoxy-1-(4-methoxybenzyl)piperidin-2,6-dione (0.600 g, 2.28 mmol) in a similar fashion to **3** above using sodium borohydride (0.26 g, 6.84 mmol) at −20 °C to −5 °C for 1 h. Column chromatography (30:70 petrol/EtOAc to 100%

EtOAc) yielded the title alcohol **9** (0.448 g, 1.69 mmol, 74% R_f=0.24 EtOAc) as a colourless oil and as a mixture of diastereoisomers (*trans*/*cis* 65:35); ν_{max}/cm^{-1} 3309, 2935, 2827, 1614, 1513, 1245, 1175, 1107, 1065, 1032.

The major *trans* alcohol: δ_H 7.23 (2H, app d, *J*=8.6 Hz, 3-, 5-ArCH), 6.85 (2H, d, *J*=8.6 Hz, 2-, 6-ArCH), 4.89 (1H, d, *J*=14.8 Hz, C*H*HPMP), 4.84–4.86 (1H, m, 6-CH), 4.42 (1H, d, *J*=14.8 Hz, CH*H*PMP), 3.78 (3H, s, ArOMe), 3.45–3.48 (1H, m, 5-CH), 3.27 (3H, s, OMe), 2.55–2.64 (1H, m, 1×C*H*H), 2.34–2.43 (1H, m, 1×CH*H*), 2.08–2.19 (1H, m, 1×C*H*H), 1.78 (1H, m, 1×CH*H*); δ_C 170.5 (C=O), 158.6 (ArC), 129.1 (ArC), 129.0 (2×ArCH), 113.7 (2×ArCH), 79.0 (6-CH), 76.2 (5-CH), 56.2 (OMe), 55.0 (OMe), 46.1 (CH_2PMP), 27.1 (3-CH_2), 19.7 (4-CH_2).

The minor *cis* alcohol: δ_H 7.24 (2H, d, *J*=8.8 Hz, 3-, 5-ArCH), 6.84 (2H, d, *J*=8.8 Hz, 2-, 6-ArCH), 5.13 (1H, d, *J*=14.5 Hz, C*H*HPMP), 4.82 (1H, dd, *J*=5.8, 3.6 Hz, 6-CH), 4.18 (1H, d, *J*=14.5 Hz, CH*H*PMP), 3.79 (3H, ArOMe), 3.45–3.48 (1H, m, 5-CH), 3.39 (3H, s, OMe), 2.55–2.64 (1H, m, 1×C*H*H), 2.34–2.43 (1H, m, 1×CH*H*), 2.08–2.19 (1H, m, 1×C*H*H), 1.91–1.97 (1H, m, 1×CH*H*); δ_C 169.9 (C=O), 129.2 (ArC), 129.2 (2×ArCH), 113.8 (2×ArCH), 77.7 (6-CH), 75.4 (5-CH), 56.4 (OMe), 55.1 (OMe), 45.9 (CH_2PMP), 28.6 (3-CH_2), 19.9 (4-CH_2); *m*/*z* (ESI^-) 263.8 $(M-1)^-$ 100%; HRMS (ESI^+) calcd for $C_{14}H_{20}NO_4$ $(M+H)^+$: 266.1392, found: 266.1396.

3.1.7. (*S*)-1-(4-Methoxybenzyl)-5-methoxy-6-styrylpiperidin-2-one (**10**)

Prepared in a similar fashion to **5** above, using **9** (0.118 g, 0.445 mmol), potassium *trans*-styryltrifluoroborate (0.286 g, 1.36 mmol), acetonitrile (8 mL) and $BF_3\cdot OEt_2$ (0.279 mL, 2.225 mmol) with stirring at rt overnight. Column chromatography (EtOAc/petrol, 70:30–100:0) of the crude residue yielded the adduct **10** (0.150 g, 0.427 mmol, 96%, R_f=0.56, EtOAc) as a mixture of diastereoisomers (*cis*/*trans*, 65:35). ν_{max}/cm^{-1} 2925, 1638, 1512, 1460, 1245, 1175, 1105, 1032, 751; δ_H 7.14–7.44 (14H, 14×ArCH), 6.85–6.87 (4H, m, 2×3-, 5-ArCH), 6.49 (1H, d, *J*=16.0 Hz, α-CH *trans*), 6.43 (1H, d, *J*=16.0 Hz, α-CH *cis*), 6.21 (1H, dd, *J*=16.0, 6.5 Hz, β-CH *cis*), 6.01 (1H, dd, *J*=15.0, 6.8 Hz, β-CH *trans*), 5.53 (1H, d, *J*=14.9 Hz, C*H*HPMP *trans*), 5.45 (1H, d, *J*=14.6 Hz, C*H*HPMP *cis*), 4.12–4.18 (2H, m, 6-CH *cis* and *trans*), 3.80 (3H, s, OMe *cis*), 3.79 (3H, s, OMe *trans*), 3.72 (1H, d, *J*=14.8 Hz, CH*H*PMP *cis*), 3.69 (1H, d, *J*=14.9 Hz, CH*H*PMP *trans*), 3.49–3.54 (1H, m, 5-CH *cis*), 3.45–3.48 (1H, m, 5-CH *trans*), 3.32 (3H, s, OMe *cis*), 3.18 (3H, s, OMe *trans*), 2.63–2.72 (2H, m, 2×3-C*H*H), 2.42–2.56 (2H, m, 2×3-CH*H*), 1.89–2.02 (4H, m, 2×4-CH_2).

The *trans* isomer: δ_C 169.7 (C=O), 158.7 (ArCOMe), 135.7 (ArC), 132.9 (α-CH), 129.1 (2×ArCH), 129.0 (ArC), 128.5 (2×ArCH), 128.0 (ArCH), 126.6 (β-CH), 126.3 (2×ArCH), 113.7 (3-, 5-ArCH), 76.1 (5-CH), 60.0 (6-CH), 55.8 (OMe), 55.0 (OMe), 46.7 (CH_2PMP), 27.0 (3-CH_2), 21.3 (4-CH_2).

The *cis* isomer: δ_C 169.7 (C=O), 158.8 (ArCOMe), 136.0 (ArC), 133.0 (α-CH), 129.3 (2×ArCH), 128.9 (ArC), 128.4 (2×ArCH), 127.8 (ArCH), 126.4 (2×ArCH), 124.6 (β-CH), 76.7 (6-CH), 59.3 (5-CH), 56.4 (OMe), 55.0 (OMe), 47.2 (CH_2PMP), 29.0 (3-CH_2), 22.2 (4-CH_2); *m*/*z* (ESI^+) 351.9 $(M+H)^+$ 100%; HRMS (ESI^+) calcd for $C_{22}H_{26}NO_3$ $(M+H)^+$: 352.1907, found: 352.1905.

3.1.8. (4*S*)-1-Benzyl-4,5-dihydroxypyrrolidin-2-one (**11**)

(*S*)-1-Benzyl-3-hydroxypyrrolidin-2,5-dione[10] (1.0 g, 4.87 mmol) was dissolved in a mixture of EtOH and CH_2Cl_2 (40 mL, 1:1), and the solution cooled to −20 °C. $NaBH_4$ (0.92 g, 24.3 mmol) was added portionwise and the resulting suspension was stirred at −20 °C for 30 min. The mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 mL) and was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried and concentrated in vacuo. The crude product was purified by flash column chromatography (increasing polarity from 1:1, EtOAc/petrol as eluent to EtOAc) to give the title compound (0.725 g, 72%) as a white solid. R_f: 0.22 (1:1, EtOAc/petrol); Mp 109–111 °C; ν_{max}/cm^{-1} 3477, 1644, 1449, 1332, 1178, 1081; δ_H (CD_3OD) 7.32–7.24 (5H, m), 4.85 (1H, d, *J*=15.5 Hz, H1′), 4.76 (1H, br d, *J*=1.0 Hz, H5), 4.12 (1H, dd, *J*=1.5, 6.5 Hz, H4), 4.08 (1H, d, *J*=15.5 Hz, H1′), 2.86 (1H, dd, *J*=6.5, 17.0 Hz), 2.22 (1H, dd, *J*=1.5, 17.0 Hz); δ_C (CD_3OD) 175.7, 137.6, 129.6, 129.6, 128.9, 128.4, 90.1, 72.3, 43.9, 39.3; MS (EI) *m*/*z* 207 (100%); HRMS (EI) calcd for $C_{11}H_{13}NO_3$ ($M^{+\bullet}$): 207.0895, found: 207.0902.

3.1.9. (3a*S*,6a*S*,*E*)-1-Benzyl-5-styryl-hexahydroborolo-[3,4-b]pyrrol-2(1*H*)-one (**12**)

To a solution of **11** (0.10 g, 0.482 mmol) and *trans*-styrylboronic acid (0.214 g, 1.45 mmol) in dry MeCN (5.0 mL) at 0 °C under N_2 was added dropwise $BF_3\cdot OEt_2$ (0.273 g, 1.927 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated $NaHCO_3$ solution (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The title product was obtained without further purification (0.113 g, 73%). ν_{max}/cm^{-1} 1685, 1449, 1367, 1065. δ_H 7.42 (1H, d, *J*=18.5 Hz, H2′), 7.35–7.20 (10H, m, ArH), 6.14 (1H, d, *J*=18.5 Hz, H1′), 5.59 (1H, d, *J*=6.0 Hz, H5), 5.02 (1H, d, *J*=14.5 Hz, H3′), 4.93 (1H, dd, *J*=6.0, 7.0 Hz, H4), 4.15 (1H, d, *J*=14.5 Hz, H3′), 2.83 (1H, dd, *J*=7.0, 18.0 Hz, H3), 2.71 (1H, d, *J*=18.0 Hz, H3); δ_C 171.2 (C2), 151.5 (ArC), 136.9 (ArC), 135.6 (ArC), 129.4 (C2′), 128.7 (ArC), 128.7 (ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 127.8 (ArC), 127.2 (C1′), 89.4 (C5), 73.1 (C4), 43.9 (C3′), 38.1 (C3); MS (EI) *m*/*z* 319 (100%); HRMS (EI) calcd for $C_{19}H_{18}BNO_3$ ($M^{+\bullet}$): 319.1379, found: 319.1376.

3.1.10. (1*S*,5*S*)-2-Benzyl-6-oxa-2-aza-bicyclo[3.1.0]-hexan-3-one (**13**)

To a solution of **11** (0.10 g, 0.482 mmol) in nitromethane (5 mL) at 0 °C was added $BF_3\cdot OEt_2$ (0.273 g, 1.93 mmol). The mixture was stirred at 80 °C for 5 h. A saturated solution of $NaHCO_3$ (5 mL) was added, and aqueous layer was

extracted with dichloromethane (3×10 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The title compound was unstable to silica gel and was obtained as an oil without further purification (0.071 g, 78%). R_f: 0.31 (EtOAc); ν_{max}/cm^{-1} 1690, 1449, 1362, 1214, 1081, 1019; δ_H 7.33–7.22 (5H, m, ArH), 5.41 (1H, d, J=7.0 Hz, H5), 5.03 (1H, d, J=14.5 Hz, H1′), 4.89 (1H, dd, J=7.0, 8.0 Hz, H4), 4.07 (1H, d, J=14.5 Hz, H1′), 2.85 (1H, dd, J=8.0, 18.5 Hz, H3), 2.68 (1H, d, J=18.5 Hz, H3); δ_C 171.1 (C2), 136.2 (ArC), 128.9 (ArC), 128.8 (ArC), 128.7 (ArC), 128.6 (ArC), 128.4 (ArC), 128.1 (ArC), 83.5 (C5), 75.0 (C4), 44.7 (C1′), 37.7 (C3); MS (EI) *m/z* 189 (75%); HRMS (EI) calcd for $C_{11}H_{11}NO_2$ ($M^{+\bullet}$) 189.0789, found: 189.0783.

3.1.11. (4S,5S,E)-1-Benzyl-4-hydroxy-5-styrylpyrrolidin-2-one (**14**)

To a solution of **11** (0.10 g, 0.482 mmol) in anhydrous $MeNO_2$ (5 mL), at 0 °C was added *trans*-styrylboronic acid (0.214 g, 1.4 mmol) and then $BF_3\cdot OEt_2$ (0.273 g, 1.93 mmol). The mixture was stirred at 80 °C for 5 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried and concentrated in vacuo. The crude product was purified by column chromatography (1:1, EtOAc/petrol as eluent) to give the title compound (0.027 g, 20%, dr=91:9) as a white solid. R_f: 0.32 (1:1, EtOAc/petrol); mp 128–130 °C; ν_{max}/cm^{-1} 3334, 1669, 1444, 1426, 1262, 1176, 1071; δ_H (major isomer): 7.35–7.18 (10H, m, ArH), 6.51 (1H, d, J=16.5 Hz, H2′), 6.15 (1H, dd, J=16.5, 8.5 Hz, H1′), 4.93 (1H, d, J=15.5 Hz, H3′), 4.43 (1H, ddd, J=3.5, 6.0, 7.0 Hz, H4), 4.10 (1H, dd, J=6.0, 8.5 Hz, H5), 3.96 (1H, d, J= 15.5 Hz, H3′), 2.73 (1H, dd, J=7.0, 17.5 Hz, H3), 2.54 (1H, dd, J=3.5, 17.5 Hz, H3), 2.45 (1H, br s, OH); δ_C 172.9 (C2), 136.5 (ArC), 136.3 (C2′), 135.7 (ArC), 128.6 (ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 127.4 (ArC), 126.6 (ArC), 123.3 (C1′), 67.5 (C4), 65.2 (C5), 44.3 (C3′), 39.9 (C3); MS (EI) *m/z* 293 (100%); HRMS (EI) calcd for $C_{19}H_{19}NO_2$ ($M^{+\bullet}$): 293.1417, found: 293.1415.

3.1.12. (4S,5S)-1-Benzyl-5-(furan-2-yl)-4-hydroxypyrrolidin-2-one (**15**)

Prepared in a similar fashion to **14** above, from **11** (0.150 g, 0.725 mmol), 2-furanboronic acid (0.243 g, 2.17 mmol), $MeNO_2$ (5.0 mL) and $BF_3\cdot OEt_2$ (0.411 g, 2.90 mmol), except that the reaction mixture was warmed to rt and stirred for 16 h. The crude product was purified by flash column chromatography (1:1, EtOAc/petrol as eluent) to give the title compound (0.126 g, 65%, dr=77:23) as an oil. R_f: 0.53 (1:1, EtOAc/petrol); MS (EI) *m/z* 257 (100%); HRMS (EI) calcd for $C_{15}H_{15}NO_3$ ($M^{+\bullet}$): 257.1049, found: 257.1049; ν_{max}/cm^{-1} 3365, 1669, 1447, 1253, 1149, 1070, 1012.

Major *trans* isomer: δ_H 7.38 (1H, d, J=1.5 Hz, H5′), 7.30–7.17 (5H, m, ArH), 6.34 (1H, dd, J=1.5, 3.0 Hz, H4′), 6.21 (1H, d, J=3.0 Hz, H3′), 4.92 (1H, d, J=15.5 Hz, H6′), 4.42 (1H, ddd, J=2.0, 2.5, 6.0 Hz, H4), 4.31 (1H, d, J=2.0 Hz, H5), 3.58 (1H, d, J=15.5 Hz, H6′), 3.00 (1H, dd, J=6.5, 17.0 Hz, H3), 2.48 (1H, dd, J=2.5, 17.0 Hz, H3); δ_C 172.9 (C2), 150.1 (ArC), 143.1 (ArC), 135.8 (ArC), 128.7 (ArC), 128.6 (ArC), 128.5 (ArC), 128.3 (ArC), 128.1 (ArC), 128.0 (ArC), 127.4 (C5′), 110.3 (C4′), 109.0 (C3′), 69.5 (C4), 63.9 (C5), 44.2 (C6′), 39.8 (C3). Minor *cis* isomer: δ_H 7.46 (1H, d, J=1.5 Hz, H5′), 7.30–7.17 (5H, m, ArH), 6.42 (1H, dd, J=1.5, 3.0 Hz, H4′), 6.17 (1H, d, J=3.0 Hz, H3′), 4.98 (1H, d, J=15.0 Hz, H6′), 4.57 (1H, d, J=7.0 Hz, H5), 4.53 (1H, ddd, J=7.5, 7.0, 2.5 Hz, H4), 3.60 (1H, d, J=15.0 Hz, H6′), 2.70 (1H, dd, J=7.5, 17.0 Hz, H3), 2.65 (1H, dd, J=2.5, 17.0 Hz, H3); δ_C 172.5 (C2), 148.3 (ArC), 143.6 (ArC), 135.7 (ArC), 128.7 (ArC), 128.7 (ArC), 128.5 (ArC), 128.1 (ArC), 128.0 (ArC), 127.6 (C5′), 111.1 (C4′), 110.5 (C3′), 66.9 (C4), 59.8 (C5), 44.6 (C6′), 39.1 (C3).

3.1.13. (4S,5R)-5-(Benzofuran-2-yl)-1-benzyl-4-hydroxypyrrolidin-2-one (**16**)

Prepared in a similar fashion to **15** above, from **11** (0.05 g, 0.241 mmol), 2-benzofuranboronic acid (0.117 g, 0.724 mmol), $MeNO_2$ (3.0 mL) and $BF_3\cdot OEt_2$ (0.137 g, 0.966 mmol). The crude product was purified by flash column chromatography (Et_2O as eluent) to give the title compound (0.041 g, 56%, dr=92:8) as an oil. R_f: 0.47 (Et_2O); MS (EI) *m/z* 307 (100%); HRMS (EI) calcd for $C_{19}H_{17}NO_3$ ($M^{+\bullet}$): 307.1208, found: 307.1207; ν_{max}/cm^{-1} 3308, 1670, 1454, 1417, 1355, 1306, 1255, 1167, 1108, 1086.

Major *cis* isomer: δ_H 7.51 (1H, d, J=8.0 Hz, ArH), 7.41 (1H, d, J=8.0 Hz, ArH), 7.24 (6H, m, ArH), 7.08 (1H, d, J=8.0 Hz, ArH), 6.64 (1H, s, H1′), 5.06 (1H, d, J=15.0 Hz, H2′), 4.64 (1H, d, J=7.0 Hz, H5), 4.57 (1H, app br q, J ca. 7 Hz, H4), 3.61 (1H, d, J=15.0 Hz, H2′), 2.74 (2H, m, H3); δ_C 172.5 (C2), 155.3 (ArC), 151.3 (ArC), 135.7 (ArC), 128.4 (ArC), 128.2 (ArC), 127.7 (ArC), 127.6 (ArC), 124.8 (ArC), 123.1 (ArC), 121.2 (ArC), 111.5 (ArC), 108.1 (ArC), 107.7 (C1′), 67.0 (C4), 60.2 (C5), 44.5 (C2′), 39.1 (C3).

Minor *trans* isomer: δ_H 7.54 (1H, d, J=8.0 Hz, ArH), 7.42 (1H, d, J=8.0 Hz, ArH), 7.25 (7H, m, ArH), 6.58 (1H, s, H1′), 5.12 (1H, d, J=15.0 Hz, H2′), 4.57 (1H, br dd, J=7.0, 2.5 Hz, H4), 4.48 (1H, s, H5), 3.71 (1H, d, J=15.0 Hz, H2′), 3.07 (1H, dd, J=7.0, 17.5 Hz, H3), 2.52 (1H, dd, J=2.5, 17.5 Hz, H3); δ_C 172.8 (C2), 155.2 (ArC), 152.6 (ArC), 135.7 (ArC), 128.6 (ArC), 128.1 (ArC), 127.6 (ArC), 125.5 (ArC), 124.8 (ArC), 123.1 (ArC), 121.1 (ArC), 111.4 (ArC), 105.9 (C1′), 69.6 (C4), 64.3 (C5), 44.4 (C2′), 39.9 (C3).

3.1.14. (4S,5R)-1-Benzyl-5-(3,4-dimethoxyphenyl)-4-hydroxypyrrolidin-2-one (**17**)

Prepared in a similar fashion to **15** above, from **11** (0.05 g, 0.241 mmol), 3,4-dimethoxyphenylboronic acid (0.132 g, 0.724 mmol) and $BF_3\cdot OEt_2$ (0.137 g, 0.966 mmol). The desired product (0.035 g, 44%, dr=72:28) was obtained as an oil after purification by column chromatography (EtOAc as eluent). R_f: 0.23 (EtOAc); MS (EI) *m/z* 327 (100%); HRMS (EI) calcd for $C_{19}H_{21}NO_4$ ($M^{+\bullet}$): 327.1470, found: 327.1468; ν_{max}/cm^{-1} 3352, 1699, 1505, 1463, 1272, 1257, 1149, 1016.

Major *trans* isomer: δ_H 7.28–7.21 (5H, m, ArH), 7.02 (1H, s, ArH), 6.89 (1H, d, J=8.0 Hz, ArH), 6.72 (1H, d, J=8.0 Hz, ArH), 4.88 (1H, d, J=2.5 Hz, H5), 4.82 (1H, d, J=14.5 Hz,

H1′), 4.23 (1H, br dd, J=6.5, 2.5 Hz, H4), 4.10 (1H, d, J=14.5 Hz, H1′), 3.89 (3H, s, OMe), 3.80 (3H, s, OMe), 2.58 (1H, dd, J=6.5, 17.0 Hz, H3), 2.46 (1H, d, J=17.0 Hz, H3); δ_C 172.4 (C2), 149.3 (ArC), 136.0 (ArC), 128.6 (ArC), 128.5 (ArC), 128.5 (ArC), 128.4 (ArC), 128.2 (ArC), 127.9 (ArC), 127.6 (ArC), 127.5 (ArC), 127.4 (ArC), 125.2 (ArC), 121.0 (ArC), 111.6 (ArC), 111.2 (ArC), 81.8 (C4), 65.13 (C5), 55.8 (OMe), 43.2 (C1′), 38.3 (C3).

Minor *cis* isomer: δ_H 7.28–7.21 (5H, m, ArH), 6.99 (1H, s, ArH), 6.86 (1H, d, J=8.0 Hz, ArH), 6.70 (1H, d, J=8.0 Hz, ArH), 5.06 (1H, d, J=14.5 Hz, H1′), 4.47 (1H, d, J=5.5 Hz, H5), 4.43–4.45 (1H, br m H4), 3.87 (3H, s, OMe), 3.77 (3H, s, OMe), 3.63 (1H, d, J=14.5 Hz, H1′), 2.70 (1H, dd, J=6.5, 17.0 Hz, H3), 2.54 (1H, d, J=17.0 Hz, H3); δ_C 174.1 (C2), 149.2 (ArC), 135.7 (ArC), 128.6 (ArC), 128.5 (ArC), 128.5 (ArC), 128.4 (ArC), 128.2 (ArC), 127.9 (ArC), 127.6 (ArC), 127.5 (ArC), 127.4 (ArC), 125.2 (ArC), 121.0 (ArC), 111.6 (ArC), 66.7 (C5), 66.3 (C4), 55.9 (OMe), 44.6 (C1′), 39.5 (C3).

*3.1.15. (4S,5R,E)-1-Benzyl-4-(benzyloxy)-5-styrylpyrrolidin-2-one (**19a**)*

To a solution of **18**[11] (0.150 g, 0.504 mmol) and potassium (*E*)-2-styryltrifluoroborate (0.315 g, 1.49 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under N_2 was added dropwise $BF_3{\cdot}OEt_2$ (0.286 g, 2.06 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated $NaHCO_3$ solution (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (1:4, EtOAc/petrol as eluent) to give the title compound (0.113 g, 59%, dr=92:8) as an oil. R_f: 0.32 (1:2, EtOAc/petrol); MS (EI) *m/z* 383 (80%); HRMS (EI) calcd for $C_{26}H_{25}NO_2$ ($M^{+\bullet}$): 383.1881, found: 383.1885; ν_{max}/cm^{-1} 1692, 1495, 1451, 1261, 1096, 1071, 1028.

δ_H (major isomer) 7.58–7.15 (15H, m, ArH), 6.45 (1H, d, J=15.7 Hz, H2′), 5.91 (1H, dd, J=15.7, 8.0 Hz, H1′), 5.07 (1H, d, J=14.7 Hz, H3′), 4.50 (2H, s, H4′), 4.10 (1H, d, J=7.2 Hz, H4), 3.99 (1H, d, J=8.0 Hz, H5), 3.91 (1H, d, J=14.7 Hz, H3′), 2.82 (1H, dd, J=7.2, 17.5 Hz, H3), 2.58 (1H, d, J=17.5 Hz, H3); δ_C (major isomer) 172.4 (C2), 137.3 (ArC), 136.2 (ArC), 135.7 (ArC), 133.9 (C7), 128.7 (ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 128.1 (ArC), 127.8 (ArC), 127.6 (ArC), 127.4 (ArC), 126.5 (ArC), 125.6 (C6), 77.0 (C4), 71.2 (C8), 65.9 (C5), 44.0 (C9), 37.2 (C3).

*3.1.16. (4S,5R)-1-Benzyl-4-(benzyloxy)-5-(furan-2-yl)-pyrrolidin-2-one (**19b**)*

Method A: prepared in a similar fashion to **19a** above, from **18** (0.150 g, 0.504 mmol), 2-furanboronic acid (0.169 g, 1.51 mmol), $BF_3{\cdot}OEt_2$ (0.286 g, 2.06 mmol) and CH_2Cl_2 (5 mL). The desired product (0.140 g, 79%, dr=71:29) was obtained as an oil after purification by column chromatography (1:3, EtOAc/petrol as eluent). R_f: 0.44 (1:3, EtOAc/petrol).

Method B: to a solution of **18** (0.10 g, 0.336 mmol) in CH_2Cl_2 (5 mL) at 0 °C under N_2 was added furan (0.068 g, 1.00 mmol) and then $BF_3{\cdot}OEt_2$ (0.168 g, 1.34 mmol). The reaction mixture was stirred at rt for 2 h. Saturated aqueous $NaHCO_3$ solution (5 mL) was added and aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The desired product (0.045 g, 40%, dr=55:45) was obtained as an oil after purification by column chromatography (1:3, EtOAc/petrol. as eluent). R_f: 0.44 (1:3, EtOAc/petrol); MS (EI) *m/z* 347 (100%); HRMS (EI) calcd for $C_{22}H_{21}NO_3$ ($M^{+\bullet}$): 347.4078, found: 347.4079; ν_{max}/cm^{-1} 1673, 1452, 1263, 1154, 1072, 1027.

Major *trans* isomer: δ_H 7.35 (1H, d, J=1.2 Hz, H5′), 7.29–7.05 (10H, m, ArH), 6.32 (1H, dd, J=1.2, 3.2 Hz, H4′), 6.16 (1H, d, J=3.2 Hz, H3′), 5.07 (1H, d, J=15.0 Hz, H6′), 4.51 (1H, d, J=1.5 Hz, H5), 4.45 (2H, s, H7′), 4.24–4.20 (1H, m, H4), 3.64 (1H, d, J=15.0 Hz, H6′), 2.93 (1H, dd, J=7.0, 17.5 Hz, H3), 2.59 (1H, dd, J=2.5, 17.5 Hz, H3); δ_C 172.4 (C2), 150.3 (C2′), 143.0 (C5′), 137.1 (ArC), 135.7 (ArC), 128.4 (ArC), 128.2 (ArC), 128.2 (ArC), 127.8 (ArC), 127.7 (ArC), 127.6 (ArC), 127.5 (ArC), 127.4 (ArC), 127.3 (ArC), 110.2 (C3′), 108.6 (C4′), 76.1 (C4), 71.0 (C7′), 60.85 (C5), 44.0 (C6′), 37.3 (C3).

Minor *cis* isomer: δ_H 7.45 (1H, d, J=1.2 Hz, H5′), 7.29–7.05 (10H, m, ArH), 6.38 (1H, dd, J=1.2, 3.0 Hz, H4′), 6.29 (1H, d, J=3.0 Hz, H3′), 5.07 (1H, d, J=14.7 Hz, H6′), 4.67 (1H, d, J=7.5 Hz, H5), 4.32 (2H, s, H7′), 4.30–4.28 (1H, m, H4), 3.58 (1H, d, J=14.7 Hz, H6′), 2.84 (1H, dd, J=8.5, 16.5 Hz, H3), 2.71 (1H, dd, J=8.5, 16.5 Hz); δ_C 171.8 (C2), 148.8 (C2′), 143.0 (C5′), 137.0 (ArC), 135.9 (ArC), 128.4 (ArC), 128.2 (ArC), 128.2 (ArC), 127.8 (ArC), 127.7 (ArC), 127.6 (ArC), 127.5 (ArC), 127.4 (ArC), 127.3 (ArC), 110.3 (C3′), 110.2 (C4′), 73.2 (C4), 71.4 (C7′), 57.8 (C5), 44.3 (C6′), 36.6 (C3).

*3.1.17. (4S, 5R)-5-(Benzofuran-2-yl)-1-benzyl-4-(benzyloxy)-pyrrolidin-2-one (**19c**)*

Prepared in a similar fashion to **19a** above, from **18** (0.10 g, 0.336 mmol), benzofuranboronic acid (0.163 g, 1.0 mmol), $BF_3{\cdot}OEt_2$ (0.190 g, 1.34 mmol) and CH_2Cl_2 (5 mL). The desired product (0.110 g, 55%, dr=89:11) was obtained as an oil after purification by column chromatography (1:3, EtOAc/petrol as eluent). R_f: 0.47 (1:2, EtOAc/petrol); MS (EI) *m/z*: 397 (75%); HRMS (EI) calcd for $C_{26}H_{23}NO_3$ ($M^{+\bullet}$): 397.1676, found: 397.1677; ν_{max}/cm^{-1} 1684, 1454, 1417, 1253, 1109, 1093.

Major *trans* isomer: δ_H 7.53 (1H, d, J=8.0 Hz, ArH), 7.42 (1H, d, J=8.0 Hz, ArH), 7.28–7.18 (12H, m, ArH), 6.55 (1H, s, H1′), 5.15 (1H, d, J=15.2 Hz, H2′), 4.63 (1H, d, J=2.0 Hz, H5), 4.49 (2H, s, H3′), 4.30–4.28 (1H, m, H4), 3.71 (1H, d, J=15.2 Hz, H2′), 3.01 (1H, dd, J=7.0, 17.2 Hz, H3), 2.65 (1H, dd, J=2.5, 17.2 Hz, H3); δ_C 172.6 (C2), 155.1 (ArC), 152.9 (ArC), 137.0 (ArC), 135.6 (ArC), 128.5 (ArC), 128.3 (ArC), 127.9 (ArC), 127.8 (ArC), 127.5 (ArC), 127.4 (ArC), 124.7 (ArC), 123.0 (ArC), 121.0 (ArC), 111.3 (ArC), 105.4 (C1′), 76.1 (C4), 71.2 (C3′), 61.3 (C5), 44.2 (C2′), 37.4 (C3).

Minor *cis* isomer: δ_H 7.56 (1H, d, J=8.0 Hz, ArH), 7.48 (1H, d, J=8.0 Hz, ArH), 7.29–7.02 (12H, m, ArH), 6.67 (1H, s, H1′), 5.16 (1H, d, J=15.0 Hz, H2′), 4.78 (1H, d, J=7.5 Hz, H5), 4.49 (1H, d, J=12.0 Hz, H3′), 4.43–4.39 (1H, m, H4), 4.39 (1H, d, J=12.0 Hz, H3′), 3.65 (1H, d, J=15.0 Hz, H2′), 2.93 (1H, dd, J=8.0, 16.5 Hz, H3), 2.76 (1H, dd, J=8.0, 16.5 Hz, H3); δ_C 172.0 (C2), 155.3 (ArC), 152.0 (ArC), 137.0 (ArC), 135.9 (ArC), 128.7 (ArC), 128.3 (ArC), 127.8 (ArC), 127.7 (ArC), 127.5 (ArC), 124.5 (ArC), 122.9 (ArC), 120.9 (ArC), 111.5 (ArC), 107.1 (C1′), 73.4 (C4), 71.8 (C3′), 58.3 (C5), 44.5 (C2′), 36.6 (C3).

3.1.18. (4S,5R)-1-Benzyl-4-(benzyloxy)-5-(2-thienyl)-pyrrolidin-2-one (**19d**)

Prepared in a similar fashion to **19a** above, from **18** (0.10 g, 0.336 mmol), 2-thiopheneboronic acid (0.127 g, 1.0 mmol), $BF_3\cdot OEt_2$ (0.190 g, 1.34 mmol) and CH_2Cl_2 (5 mL). The desired product (0.088 g, 72%, dr=62:38) was obtained as an oil after purification by column chromatography (1:4, EtOAc/petrol as eluent). R_f: 0.33 (1:3, EtOAc/petrol); MS (EI) *m/z* 363 (100%); HRMS (EI) calcd for $C_{22}H_{21}NO_2S$ ($M^{+\bullet}$): 363.1296, found: 363.1293; ν_{max}/cm^{-1} 1685, 1451, 1434, 1269, 1111, 1072.

Minor *trans* isomer: δ_H 7.39–7.12 (10H, m, ArH), 7.03 (1H, m, H5′), 6.98 (1H, dd, J=3.2, 4.7 Hz, H4′), 6.84 (1H, d, J=3.2 Hz, H3′), 5.17 (1H, d, J=15.5 Hz, H6′), 4.72 (1H, d, J=2.0 Hz, H5), 4.47 (2H, s, H7′), 4.11–4.07 (1H, m, H4), 3.65 (1H, d, J=15.5 Hz, H6′), 2.93 (1H, dd, J=7.0, 17.5 Hz, H3), 2.59 (1H, dd, J=2.5, 17.5 Hz, H3); δ_C 172.3 (C2), 141.6 (C2′), 137.1 (ArC), 135.7 (ArC), 128.6 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 127.8 (ArC), 127.5 (ArC), 127.4 (ArC), 127.1 (C5′), 125.9 (C4′), 125.7 (C3′), 79.5 (C4), 71.3 (C6′), 63.0 (C5), 44.0 (C7′), 37.0 (C3).

Major *cis* isomer: δ_H 7.29–7.22 (9H, m, ArH), 7.13 (1H, d, J=7.0 Hz, ArH), 7.03 (2H, m, H5′, H4′), 6.95 (1H, d, J=3.5 Hz, H3′), 5.13 (1H, d, J=15.0 Hz, H6′), 4.89 (1H, d, J=7.0 Hz, H5), 4.33 (1H, d, J=12.0 Hz, H7′), 4.33–4.29 (1H, m, H4), 4.28 (1H, d, J=12.0 Hz, H7′), 3.58 (1H, d, J=15.0 Hz, H6′), 2.79 (1H, dd, J=7.5, 17.5 Hz, H3), 2.72 (1H, dd, J=7.5, 17.5 Hz, H3); δ_C 171.1 (C2), 137.7 (C2′), 136.0 (ArC), 128.6 (ArC), 128.6 (ArC), 128.4 (ArC), 128.2 (ArC), 128.0 (ArC), 128.0 (ArC), 127.7 (ArC), 127.6 (ArC), 127.4 (C5′), 126.8 (C4′), 126.4 (C3′), 73.3 (C4), 71.7 (C6′), 60.2 (C5), 44.1 (C7′), 36.8 (C3).

3.1.19. (4S,5R)-1-Benzyl-4-(benzyloxy)-5-(4-methoxy-phenyl)pyrrolidin-2-one (**19f**)

Prepared in a similar fashion to **19a** above, from **18** (0.10 g, 0.336 mmol), *p*-methoxyphenylboronic acid (0.214 g, 1.00 mmol), $BF_3\cdot OEt_2$ (0.190 g, 1.34 mmol) and CH_2Cl_2 (5 mL). The desired product (0.063 g, 48%, dr=72:28) was obtained as an oil after purification by column chromatography (1:3, EtOAc/petrol. as eluent). R_f: 0.42 (1:3, EtOAc/petrol); MS (EI) *m/z* 387 (100%); HRMS (EI) calcd for $C_{25}H_{25}NO_3$ ($M^{+\bullet}$): 387.1833, found: 387.1834; ν_{max}/cm^{-1} 1690, 1512, 1442, 1408, 1248, 1175, 1072.

Major *trans* isomer: δ_H 7.29–7.12 (10H, m, ArH), 7.00 (2H, d, J=8.0 Hz, ArH), 6.89 (2H, d, J=8.0 Hz, ArH), 5.10 (1H, d, J=15.0 Hz, H1′), 4.37 (2H, s, H2′), 4.34 (1H, d, J=2.5 Hz, H5), 3.90–3.87 (1H, m, H4), 3.74 (3H, s, OMe), 3.44 (1H, d, J=15.0 Hz, H1′), 2.87 (1H, dd, J=6.5, 17.0 Hz, H3), 2.60 (1H, dd, J=2.5, 17.0 Hz, H3); δ_C 172.9 (C2), 159.5 (ArC), 137.3 (ArC), 135.8 (ArC), 130.0 (ArC), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 128.1 (ArC), 128.0 (ArC), 127.8 (ArC), 127.7 (ArC), 127.5 (ArC), 127.4 (ArC), 127.3 (ArC), 127.1 (ArC), 114.4 (ArC), 79.4 (C4), 71.1 (C5), 67.0 (C2′), 55.2 (OMe), 43.9 (C1′), 37.2 (C3). Minor *cis* isomer: δ_H 7.28–7.12 (14H, m, ArH), 7.10 (2H, d, J=8.5 Hz, ArH), 6.93 (2H, d, J=8.5 Hz, ArH), 5.15 (1H, d, J=14.5 Hz, H1′), 4.53 (1H, d, J=6.5 Hz, H5), 4.25–4.23 (1H, m, H4), 4.17 (1H, d, J=12.0 Hz, H2′), 4.12 (1H, d, J=12.0 Hz, H2′), 3.76 (3H, s, OMe), 3.48 (1H, d, J=14.5 Hz, H1′), 2.73 (2H, m, H3); δ_C 172.6 (C2), 159.6 (ArC), 137.2 (ArC), 136.0 (ArC), 129.6 (ArC), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 128.1 (ArC), 128.0 (ArC), 127.8 (ArC), 127.7 (ArC), 127.5 (ArC), 127.4 (ArC), 127.3 (ArC), 127.1 (ArC), 113.8 (ArC), 73.5 (C4), 71.6 (C5), 64.4 (C2′), 55.2 (OMe), 44.1 (C1′), 37.6 (C3).

3.1.20. (4S,5R)-1-Benzyl-4-(benzyloxy)-5-(3,4-dimethoxy-phenyl)pyrrolidin-2-one (**19g**)

Prepared in a similar fashion to **19a** above, from **18** (0.10 g, 0.336 mmol), 3,4-dimethoxyphenylboronic acid (0.182 g, 1.0 mmol), $BF_3\cdot OEt_2$ (0.190 g, 1.34 mmol), and CH_2Cl_2 (5 mL). The desired product (0.103 g, 74%, dr=74:26) was obtained as an oil after purification by column chromatography (1:2, EtOAc/petrol as eluent). R_f: 0.47 (1:3, EtOAc/petrol); MS (EI) *m/z* 417 (80%); HRMS (EI) calcd for $C_{26}H_{27}NO_4$ ($M^{+\bullet}$): 417.1941, found: 417.1940; ν_{max}/cm^{-1} 1689, 1515, 1453, 1413, 1260, 1237, 1139, 1072, 1026.

Major *trans* isomer: δ_H 7.28–7.12 (10H, m, ArH), 6.85 (1H, d, J=8.0 Hz, ArH), 6.66 (1H, dd, J=2.0, 7.7 Hz, ArH), 6.48 (1H, d, J=2.0 Hz, ArH), 5.14 (1H, d, J=15.5 Hz, H1′), 4.45 (2H, s, H2′), 4.40 (1H, d, J=2.5 Hz, H5), 4.00–3.97 (1H, m, H4), 3.88 (3H, s, OMe), 3.79 (3H, s, OMe), 3.58 (1H, d, J=15.5 Hz, H1′), 2.88 (1H, dd, J=7.0, 17.0 Hz, H3), 2.60 (1H, dd, J=3.5, 17.0 Hz, H3); δ_C 172.7 (C2), 149.4 (ArC), 148.8 (ArC), 137.2 (ArC), 135.8 (ArC), 128.3 (ArC), 128.2 (ArC), 128.0 (ArC), 128.0 (ArC), 127.4 (ArC), 127.4 (ArC), 118.9 (ArC), 111.3 (ArC), 109.3 (ArC), 79.1 (C4), 71.0 (C2′), 67.3 (C5), 55.7 (OMe), 43.9 (C1′), 37.0 (C3).

Minor *cis* isomer: δ_H 7.28–7.12 (10H, m, ArH), 6.87 (1H, d, J=8.0 Hz, ArH), 6.72 (1H, d, J=8.0 Hz, ArH), 6.71 (1H, s, ArH), 5.10 (1H, d, J=15.0 Hz, H1′), 4.51(1H, d, J=7.0 Hz, H5), 4.22–4.20 (1H, m, H4), 4.19 (1H, d, J=11.5 Hz, H2′), 4.08 (1H, d, J=11.5 Hz, H2′), 3.91 (3H, s, OMe), 3.78 (1H, d, J=15.0 Hz, H1′), 3.73 (3H, s, OMe), 2.73 (2H, m, H3); δ_C 172.8 (C2), 149.5 (ArC), 148.9 (ArC), 137.3 (ArC), 136.0 (ArC), 128.3 (ArC), 128.2 (ArC), 128.0 (ArC), 127.6 (ArC), 127.3 (ArC), 127.2 (ArC), 127.1 (ArC), 126.6 (ArC), 121.2 (ArC), 111.9 (ArC), 110.6 (ArC), 73.6 (C4), 71.5 (C2′), 64.9 (C5), 55.6 (OMe), 44.1 (C1′), 37.7 (C3).

*3.1.21. (4S,5R,E)-1-Benzyl-4-hydroxy-5-styrylpyrrolidin-2-one (trans-**14**)*

To a solution of **19a** (0.080 g, 0.208 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added dropwise BBr_3 (0.209 g, 0.835 mmol). The mixture was stirred for 10 min, and then water (15 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (increasing polarity from 1:1, EtOAc/petrol to EtOAc as eluent) to give the title compound (0.055 g, 90%) as an oil. R_f: 0.62 (EtOAc); ν_{max}/cm^{-1} 3334, 1664, 1511, 1449, 1253, 1058; δ_H 7.32–7.21 (10H, m, ArH), 6.47 (1H, d, J=15.5 Hz, H2′), 5.90 (1H, dd, J=8.5, 15.5 Hz, H1′), 4.90 (1H, d, J=15.0 Hz, H3′), 4.23 (1H, br dd, J=6.5, 2.5 Hz, H4), 3.94 (1H, d, J=15.0 Hz, H3′), 3.92 (1H, d, J=8.5 Hz, H5), 2.84 (1H, dd, J=6.5, 17.0 Hz, H3), 2.63 (1H, br s., OH), 2.45 (1H, dd, J=2.5, 17.0 Hz, H3); δ_C 172.6 (C2), 136.2 (ArC), 135.6 (C2′), 134.2 (ArC), 128.7 (ArC), 128.6 (ArC), 128.3 (ArC), 128.1 (ArC), 127.5 (ArC), 126.5 (ArC), 125.09 (C1′), 70.6 (C4), 68.9 (C5), 44.2(C3′), 39.4 (C3); MS (EI) *m/z* 293 (100%); HRMS (EI) calcd for $C_{19}H_{19}NO_2$ ($M^{+\bullet}$): 293.1415, found: 293.1409.

*3.1.22. (4S)-1-Benzyl-4-(benzyloxy)-5-hydroxy-5-styrylpyrrolidin-2-one (**21**)*

Magnesium turnings (0.302 g, 12.6 mmol) were stirred overnight under N_2, and anhydrous THF (5 mL) was added to the flask. Neat *trans*-β-bromostyrene (0.461 g, 2.52 mmol) was added dropwise at rt. The reaction mixture was stirred at 40 °C for 1 h. The pyrrolidine-2,5-dione **20** (0.50 g, 1.68 mmol) was dissolved in dry THF (10 mL) and the solution was cooled to −78 °C. 2-Phenylvinylmagnesium bromide was then transferred to the solution via syringe. The reaction mixture was stirred at −78 °C for 4 h, and then warmed slowly to −10 °C. Saturated aqueous NH_4Cl solution (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1:1, EtOAc/petrol as eluent) to give the title compound as an oil (0.306 g, 45%, dr=58:42). R_f: 0.54 (1:1, EtOAc/petrol); MS (EI) *m/z* 399 (100%); HRMS (EI) calcd for $C_{26}H_{25}NO_3$ ($M^{+\bullet}$): 399.1834, found: 399.1819.

Major diastereomer: δ_H 7.31–7.17 (15H, m, ArH), 6.79 (1H, d, J=16.0 Hz, H2′), 5.86 (1H, d, J=16.0 Hz, H1′), 4.60 (2H, s, H4′), 4.85 (1H, d, J=15.0 Hz, H3′), 4.42 (1H, d, J=15.0 Hz, H3′), 4.03 (1H, br s, OH), 4.00–3.98 (1H, m, H4), 2.70 (1H, dd, J=7.0, 17.0 Hz, H3), 2.58 (1H, dd, J=4.5, 17.0 Hz, H3); δ_C 171.6 (C2), 138.3 (ArC), 135.3 (ArC), 132.4 (C2′), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 128.2 (ArC), 128.2 (ArC), 128.2 (ArC), 128.1 (ArC), 128.0 (ArC), 127.7 (ArC), 127.6 (ArC), 127.3 (ArC), 126.8 (ArC), 126.7 (C1′), 90.5 (C5), 77.2 (C4), 72.3 (C4′), 43.0 (C3′), 35.5 (C3). Minor diastereomer: δ_H 7.30–7.19 (15H, m, ArH), 6.85 (1H, d, J=16.5 Hz, H2′), 6.25 (1H, d, J=16.5 Hz, H1′), 4.57–4.49 (3H, m, H4′, H3′), 4.31 (1H, d, J=15.0 Hz, H3′), 3.99–3.96 (1H, m, H4), 2.87 (1H, dd, J=6.5, 17.5 Hz, H3), 2.52 (1H, dd, J=3.0, 17.5 Hz, H3); δ_C 173.1 (C2), 138.1 (ArC), 137.3 (ArC), 135.7 (C2′), 128.5 (ArC), 128.5 (ArC), 128.5 (ArC), 128.3 (ArC), 128.3 (ArC), 128.2 (ArC), 128.1 (ArC), 127.8 (ArC), 127.7 (ArC), 127.5 (ArC), 127.4 (ArC), 127.3 (ArC), 126.8 (C1′), 93.7 (C5), 81.7 (C4), 72.1 (C4′), 42.8 (C3′), 36.6 (C3).

*3.1.23. (4S,5R)-1-Benzyl-4-(benzyloxy)-5-phenethylpyrrolidin-2-one (**22**)*

To a solution of **21** (0.98 g, 2.45 mmol) in CH_2Cl_2 (7 mL) at −78 °C was added dropwise Et_3SiH (1.42 g, 12.25 mmol) and then $BF_3{\cdot}OEt_2$ (1.03 g, 7.35 mmol). The mixture was stirred at −78 °C for 6 h and then allowed to warm slowly to rt and stirred overnight. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (increasing polarity from 1:1, EtOAc/petrol to EtOAc as eluent) to give the title compound as an oil (0.781 g, 83%, dr=91:9). R_f: 0.26 (1:1, EtOAc/petrol); MS (EI) *m/z* 385 (100%); HRMS (EI) calcd for $C_{26}H_{27}NO_2$ ($M^{+\bullet}$): 385.2041, found: 385.2039; δ_H 7.32–7.02 (15H, m, ArH), 4.9 (1H, d, J=15.5 Hz, H3′), 4.45 (1H, d, J=11.5 Hz, H4′), 4.36 (1H, d, J=11.5 Hz, H4′), 3.97 (1H, d, J=15.5 Hz, H3′), 3.93 (1H, d, J=6.5 Hz, H4), 3.52 (1H, br d, J=8.5 Hz, H5), 2.74 (1H, dd, J=6.5, 17.5 Hz, H3), 2.55–2.52 (2H, m, H3, H1′), 2.48–2.45 (1H, m, H1′), 1.94–1.93 (1H, m, H2′), 1.67–1.69 (1H, m, H2′); δ_C 172.5 (C2), 140.5 (ArC), 137.3 (ArC), 136.0 (ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 128.0 (ArC), 127.9 (ArC), 127.8 (ArC), 127.6 (ArC), 127.4 (ArC), 126.1 (ArC), 76.7 (C4), 70.5 (C4′), 62.8 (C5), 44.1 (C3′), 37.2 (C3), 32.2 (C3), 31.0 (C1′).

*3.1.24. (4S, 5R)-1-Benzyl-4-hydroxy-5-phenethylpyrrolidin-2-one (**23**)*

To a solution of **22** (0.050 g, 0.130 mmol) in MeOH (3 mL) was added $PdCl_2$ (0.018 g, 0.10 mmol). The mixture was stirred at rt under an atmosphere of H_2 for 1 h, then the flask was flushed with N_2 before the mixture was filtered through Celite® and the solids were washed with MeOH (2×10 mL). The filtrate was evaporated in vacuo and the crude product was purified by column chromatography (1:1, EtOAc/petrol as eluent) to give the title product as an oil (0.030 g, 76%). R_f: 0.19 (1:1, EtOAc/petrol); MS (EI) *m/z* 295 (80%); HRMS (EI) calcd for $C_{19}H_{21}NO_2$ ($M^{+\bullet}$): 295.1572, found: 295.1556; ν_{max}/cm^{-1} 3359, 1663, 1474, 1451, 1244, 1081; δ_H 7.26–7.04 (10H, m, ArH), 4.94 (1H, d, J=15.0 Hz, H3′), 4.21 (1H, d, J=6.0 Hz, H4), 3.99 (1H, d, J=15.0 Hz, H3′), 3.35 (1H, br d, J=7.0 Hz, H5), 2.80 (1H, dd, J=6.0, 17.5 Hz, H3), 2.64–2.62 (1H, m, H1′), 2.53–2.50 (1H, m, H1′), 2.39 (1H, d, J=17.5 Hz, H3), 1.95–1.52 (1H, m, H2′), 1.63–1.60 (1H, m, H2′); δ_C 171.9 (C2), 141.0, 136.4 (ArC), 128.9 (ArC), 128.8 (ArC), 128.4 (ArC), 128.2 (ArC), 127.8

(ArC), 126.4 (ArC), 69.3 (C4), 66.4 (C5), 44.6 (C3′), 40.4 (C3), 32.4 (C2′), 31.4 (C1′).

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3. The addition of allyltrimethylsilane or tributylstannane to five- and six-membered ring *N*-acyliminium ions derived from precursors **C** or **D** (Scheme 1), gives product mixtures that favour the cis isomer, however, this selectivity is only modest. For five-membered ring examples see Refs. 2a (*cis*/*trans*=77:23), 2b (*cis*/*trans*=80:20), 2f (*cis*/*trans*=83:17), 2g (*cis*/*trans* 83:17), 2h (*cis*/*trans*=66:34), 2i (*cis*/*trans*=80:20) and 2l (*cis*/*trans*=57:43). For six-membered ring examples see Refs. 2l (*cis*/*trans*=76:24) and 2o (*cis*/*trans*=63:27). For the *cis*-selective allylation (*cis*/*trans*=77:23) of the *O*-TBS, methylcarbamate analogue of **1** (*n*=1, Scheme 2) see Ref. 2a.
4. For the synthesis of *cis*-adducts from aryl or alkynyl migration from a C-3 silyl ether to C-2 iminium ion see: (a) Tomooka, K.; Nakazaki, A.; Nakai, T. *J. Am. Chem. Soc.* **2000**, *122*, 408–409; (b) Huang, J.-M.; Hong, S.-C.; Wu, K.-L.; Tsai, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 3047–3050.
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9. The 5-*O*-methyl, *N*-benzyl analogue of **12** was also poorly diastereoselective with silicon based nucleophiles, except propargyl trimethylsilane (100% *trans* selective).[2o]
10. Prepared from the known (3*S*)-hydroxysuccinimide (Kočalka, P.; Pohl, R.; Rejmam, D.; Rosenberg, I. *Tetrahedron* **2006**, *62*, 5763–5774) by $NaBH_4$ reduction.
11. (a) Compound **11** was formed as a single isomer. The ^{1}H NMR spectrum of **11** showed a very small $J_{4,5}$ coupling constant, $J_{4,5}$=1.0 Hz, consistent with the 4,5-*trans*-stereochemistry. However, obtaining $J_{4,5}$ for its C-5 epimer (see (b) below) from NMR analysis of a mixture of **11** and its C-5 epimer was difficult and therefore we are not 100% confident of the stereochemistry at C-5 in **11**. (b) A referee has suggested that compound **13** may be 5-*epi*-**11** rather than the epoxide. We have made a mixture (80:20, respectively) of **11** and 5-*epi*-**11** by treating **11** with 10% HCl/THF at rt for 16 h. This mixture could not be separated by TLC, however, the ^{1}H NMR resonances for 5-*epi*-**11** (δ_H (d^4-MeOH) (in part) 4.24 (1H, app q, *J* ca. 6 Hz, H4), 2.62 (1H, dd, *J*=7.0, 16.5 Hz, H3), 2.42 (1H, dd, *J*=5.5, 16.5 Hz, H3)) were different to that of **13**. Furthermore, **13** was much less polar (much higher R_f value) than the mixture of **11** and 5-*epi*-**11**, again consistent with the epoxide structure for **13**.
12. Prepared according to Ref. 2r and references cited therein.
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