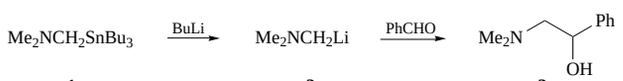
Preparation of β-amino alcohols by carbon–carbon bond formation using substituted lithiomethylpyrrolidines

Iain Coldham,*[a] Stuart Holman[b] and Maria M. S. Lang-Anderson[a]

[a] *Department of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD*
[b] *Glaxo-Wellcome, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, UK SG1 2NY*

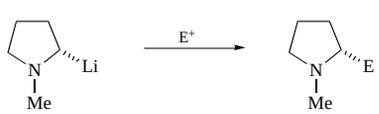
***N*-Thiomethylation or stannylmethylation of prolinol derivatives, followed by sulfur–lithium or tin–lithium exchange is used for the formation of α-amino-organolithiums. Condensation with aldehydes gives β-amino alcohols in good yield but modest diastereoselectivity.**

There has been considerable recent interest in the use of α-amino-organolithiums in synthesis. The formation of the organolithium is normally achieved either by proton abstraction or tin–lithium exchange, the latter based on early work by Peterson.[1] Quenching the organolithium **2** (prepared from **1**) with benzaldehyde resulted in the formation of the β-amino alcohol **3**. An alternative method from sulfur–lithium exchange



1 **2** **3**

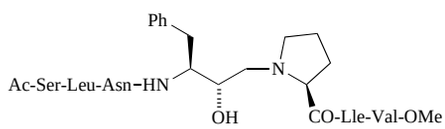
is known.[2] The α-amino-organolithiums may undergo cyclization,[3] rearrangement[4] or external electrophilic quench.[5–7] The use of secondary α-amino-organolithiums has allowed the investigation of the stereoselectivity at the carbanionic centre. For example, the organolithium **4** reacts with carbonyl electrophiles such as cyclohexanone, Bu^{t}COCl and benzaldehyde with retention of configuration at the carbanionic centre, to give the products **5**.[6] With the electrophile benzaldehyde, the product



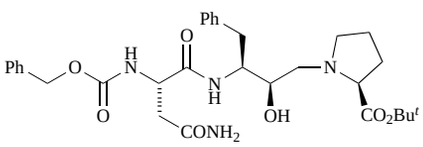
4 **5**

β-amino alcohol **5** [E = CH(OH)Ph] contains a chiral centre at the carbon atom bearing the hydroxy group. However, no control of the stereochemistry at this carbon centre, originating from the electrophile, is observed.

The β-amino alcohol unit is an important functional arrangement, present in many biologically-active compounds. In particular, the unit can act as a peptide isostere, mimicking the transition state in protease action. As a result, there are a number of potent inhibitors of enzymes such as the HIV proteases and renin proteases which incorporate a β-amino alcohol at the position needed for interaction at the active site of these enzymes. Two such inhibitors are the β-amino alcohols **6** and **7**.[8] We were interested in investigating a new approach to such targets by carbon–carbon bond formation, using attack by an α-amino-organolithium onto an aldehyde. In addition to providing a route to such bio-isosteres, we were interested in the possibility of asymmetric induction in the formation of the β-amino alcohol. As an approach to such β-amino alcohol targets, we report here some studies with model systems based on prolinol (pyrrolidine-2-methanol) as the chiral directing group. Alkylation of the organolithium from (prolinolyl-



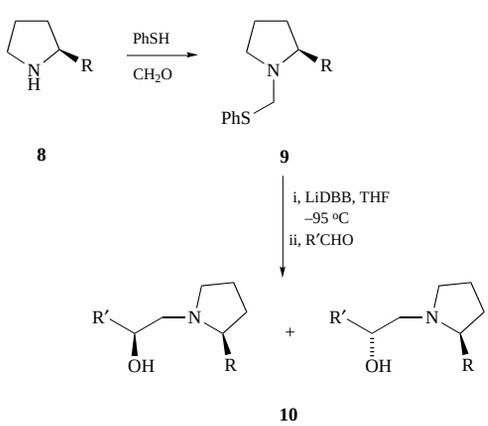
6



7

methyl)oxazoles and oxadiazoles has been reported recently to give rise to high selectivities at the α-centre, although no selectivity at the β-centre.[9]

Initial work centred on the use of sulfur–lithium exchange in order to prepare the α-amino-organolithium species. Pyrrolidine **8**, R = H, and (*S*)-(+)-2-(methoxymethyl)pyrrolidine **8**, R = CH_2OMe, were converted to the sulfides **9** by treatment with paraformaldehyde and thiophenol in a flask fitted with a Dean-Stark trap. The sulfides **9** could be purified by column chromatography on neutral alumina, but were prone to decomposition over time. Exchange of sulfur for lithium, using lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB),[2,10] followed by electrophilic quench with a range of aldehydes was performed to give the β-amino alcohols **10**. The results of this study are



8 **9**

10

given in Table 1. The characteristic deep green colour of LiDBB changed to a red colour on addition to the sulfide, which decolourised on addition of the aldehyde. The product β-amino

Table 1 Formation of β-amino alcohols **10** using sulfur–lithium exchange

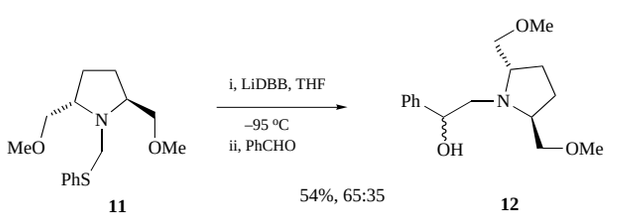
Entry	R	R′	Product	Yield (%)	Diastereoisomer ratio
1	H	Ph	**10a**	53	—
2	CH_2OMe	Ph	**10b**	57	65:35
3	CH_2OMe	*p*-BrC_6H_4	**10c**	49	61:39
4	CH_2OMe	*p*-MeC_6H_4	**10d**	29	64:36
5	CH_2OMe	*p*-$MeOC_6H_4$	**10e**	39	78:22
6	CH_2OMe	Pr^i	**10f**	50	54:46
7	CH_2OMe	Bu^t	**10g**	51	50:50

Table 2 Formation of β-amino alcohols **10** using tin–lithium exchange

Entry	R	R′	Product	Yield (%) in THF	Ratio	Yield (%) in hexane–Et_2O	Ratio
1	CH_2OMe	Ph	**10b**	88	60:40	76	63:37
2	CH_2OMe	*p*-BrC_6H_4	**10c**	81	56:44	83	60:40
3	CH_2OMe	*p*-$MeOC_6H_4$	**10e**	74	57:43	89	61:39
4	CH_2OMe	Pr^i	**10f**	81	60:40	87	63:37
5	CH_2OMe	Bu^t	**10g**	78	55:45	94	64:36
6	CH_2OH	Ph	**10h**	29	50:50	64	50:50
7	$CH_2OSiMe_2Bu^t$	Ph	**10i**	70	50:50	—	—

alcohols were formed in yields up to 57%. Using the sulfide **9**, R = CH_2OMe, some asymmetric induction was observed with aromatic aldehydes. Products **10b–d** were formed as mixtures of diastereoisomers (up to 65:35) and product **10e** had significant diastereoselection (78:22). However, essentially no diastereoselectivity was observed using aliphatic aldehydes. Using acetaldehyde or acetone as electrophiles gave the proto-desulfurised product rather than the β-amino alcohol **10**.

In an attempt to improve the diastereoselectivity of this reaction, the C_2-symmetric diamine **11** was prepared and subjected to the same conditions as above. The product β-amino alcohol **12** was obtained in reasonable yield (54%), but with the same level of stereocontrol at the new chiral centre (65:35). This suggests that, in the formation of the alcohols **10**, the aldehyde approaches from the side of the methoxymethyl group, probably with coordination of the methoxy and aldehyde oxygen atoms to the lithium atom. The presence of the additional chiral centre and substituent pointing in the opposite direction therefore has no influence on the diastereoselectivity.



11 54%, 65:35 **12**

As an alternative approach to the α-amino-organolithium, we investigated the use of tin–lithium exchange. Direct alkylation of the pyrrolidines **8** with iodomethyltributyltin[11] was low yielding, so the stannanes **13** were prepared from the amines **8** using methodology described by Pearson and Stevens and Katritzky *et al*.[12] Treatment of pyrrolidines **8**, R = CH_2OH or CH_2OMe, with paraformaldehyde and benzotriazole, gave intermediate *N*-(benzotriazolylmethyl)pyrrolidines, from which the benzotriazole group was displaced by tributylstannyllithium. Stannane **13**, R = $CH_2OSiMe_2Bu^t$ was prepared by *O*-silylation of the alcohol **13**, R = CH_2OH with *tert*-butyldimethylsilyl chloride. Tin–lithium exchange with butyllithium was successful in either the polar solvent THF (−78 °C) or the non-polar hexane–Et_2O (10:1, on warming to room temperature). Addition of aldehydes resulted in the formation of the β-amino alcohols **10** in excellent yields (Table 2). This protocol was cleaner as well as giving improved yields over the sulfur–lithium route.

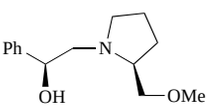
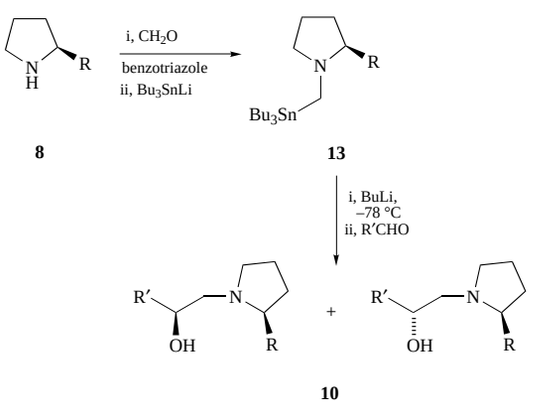


Fig. 1



In contrast to the sulfur–lithium route, the use of tin–lithium exchange resulted in β-amino alcohols **10** with some diastereoselectivity from aliphatic aldehydes (up to 64:36), but without significant improvement in the diastereoselectivity from aromatic aldehydes. In general, the use of the less polar hexane–Et_2O solvent system rather than THF gave slightly higher yields and selectivities. The diastereoselectivities are, however, similar to those from sulfur–lithium exchange (as expected) and differences may be due to the variation in the temperature of the addition reaction and/or slight changes in the lithium aggregate structure on changing from sulfur–lithium to tin–lithium exchange and on altering the solvent. The major diastereoisomer from either the sulfur–lithium or tin–lithium exchange route (R = CH_2OMe), has the stereochemistry as shown in Fig. 1, as determined by the addition of (*S*)-(+)-2-(methoxymethyl)-pyrrolidine **8**, R = CH_2OMe, to (*R*)-styrene oxide (methanol, room temperature).[13]

We have looked briefly at the effect of modifying the R group on the diastereoselectivities of the addition reaction. Transmetallation of the stannane **13**, R = CH_2OH, with three equivalents of butyllithium and quenching with benzaldehyde, resulted in a 50:50 mixture of alcohols **10h**. With the stannane **13**,

R = $CH_2OSiMe_2Bu^t$, transmetallation and addition to benzaldehyde resulted in the formation of the alcohols **10i** also with no diastereoselectivity.

In summary, tin–lithium exchange methodology offers a clean transmetallation and efficient carbon–carbon bond forming process for the preparation of β-amino alcohols. The development of a method for highly selective addition of an α-amino-organolithium to one prochiral face of an aldehyde electrophile is clearly not a trivial exercise and requires further research.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 881 spectrophotometer, using a polystyrene reference (1602 cm^{-1}). ^1H Nuclear magnetic resonance (NMR) spectra were run on a Bruker AM250 (250 MHz) or AM300 (300 MHz) instrument, with $SiMe_4$ as the reference; *J* values are given in Hz. ^{13}C NMR Spectra were run on a Bruker AM250 (62.9 MHz) or AM300 (75.5 MHz) instrument. Mass spectra were run on a Kratos Profile instrument. Microanalyses were carried out by Butterworth Microanalytical Consultancy Ltd., Teddington, Middlesex. Gas chromatography (GC) was performed with a Shimadzu GC-14A gas chromatograph equipped with a capillary column, BPI (25 m), using helium as the carrier gas. Gas liquid chromatography (GLC) was performed with a 15 m × 0.5 mm id × 0.25 μm MPS column (or for **10f**,**g** a 15 m × 0.25 mm id × 0.25 μm MPS-5 column), using a temperature gradient of 50 to 230 °C at 3 °C min^{-1}, and a pressure gradient of 50 to 140 kPa at 1.5 kPa min^{-1}.

(2*S*)-2-(Methoxymethyl)-*N*-(phenylthiomethyl)pyrrolidine 9, R = CH_2OMe

Paraformaldehyde (0.08 g, 2.6 mmol), thiophenol (0.11 cm^3, 0.97 mmol) and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol were added to (*S*)-2-(methoxymethyl)pyrrolidine **8**, R = CH_2OMe (0.12 g, 1 mmol) in toluene (5 cm^3). After stirring at room temperature for 24 h with 4 Å molecular sieves, the mixture was filtered, evaporated and the residue was purified by column chromatography on neutral aluminium oxide, eluting with light petroleum to give the *sulfide* **9**, R = CH_2OMe (0.13 g, 0.56 mmol, 56%) as an oil; $[\alpha]_D^{25}$ −19.35 (*c* 2.06 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1580 (Ph); δ_H($CDCl_3$) 1.16–1.95 (4H, m, $NCH_2CH_2CH_2$), 2.84–2.93 (2H, m, $NCH_2CH_2CH_2O$), 3.15–3.22 (1H, m, $NCHCH_2O$), 3.25–3.30 (2H, m, $NCHCH_2O$), 3.26 (3H, s, OCH_3), 4.68 (1H, d, *J* 13, NCH^AH^BS), 4.77 (1H, d, *J* 13, NCH^AH^BS), 7.05–7.54 (5H, m, Ph); δ_C($CDCl_3$) 23.57 (NCH_2CH_2), 28.37 ($NCH_2CH_2CH_2$), 52.02 (NCH_2CH_2), 58.98 (NCH), 59.05 (OCH_3), 62.42 (OCH_2), 76.33 (NCH_2S), 127.11, 128.18 and 128.24 (CH aromatic), 138.12 (C aromatic) (Found: M^+, 237.1186. $C_{13}H_{19}NOS$ requires *M*, 237.1187); *m/z* 237 (M^+, 0.2%), 206 (M − OCH_3, 0.7), 192 (M − CH_2OCH_3, 24), 84 (M − SPh, 100) (Found: C, 65.71; H, 7.92; N, 5.59; S, 13.75. $C_{13}H_{19}NOS$ requires C, 65.78; H, 8.07; N, 5.90; S, 13.51%).

General method for sulfur–lithium exchange

Lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB), prepared from 4,4′-di-*tert*-butylbiphenyl (1.5 g, 6.0 mmol) in THF (15 cm^3) and excess lithium metal (0 °C, 4 h), was cooled to −95 °C and added to the sulfide **9** (1.0 mmol) in dry THF (2 cm^3) under argon until the blue–green colour persisted. After 2 min the aldehyde (2.0 mmol) in THF (1 cm^3) was added. The mixture was allowed to warm slowly to room temperature, acidified with HCl (15 cm^3; 2 M) and extracted into diethyl ether (3 × 15 cm^3). The aqueous layer was basified with NaOH (20 cm^3; 2 M) and extracted with diethyl ether (3 × 15 cm^3). The combined organic extracts were dried ($MgSO_4$), evaporated and purified by column chromatography on silica gel, eluent 1% MeOH in CH_2Cl_2, to give the β-amino alcohol **10**.

General method for tin–lithium exchange

Butyllithium (0.6 mmol) was added to the stannane **13** (0.3 mmol) in THF (1 cm^3) at −78 °C. After 40 min the aldehyde (0.6 mmol) in THF (1 cm^3) was added and the mixture was allowed to warm to room temperature. The mixture was quenched with MeOH (1 cm^3), evaporated and purified by column chromatography on silica gel, eluent 1% MeOH in CH_2Cl_2, to give the β-amino alcohol **10**. When hexane–diethyl ether (10:1) was used as solvent, the mixture was allowed to warm to room temperature (2 h) before addition of the aldehyde at −78 °C.

(2*S*,2′*S*)- and (2*S*,2′*R*)-*N*-(2′-Hydroxy-2′-phenylethyl)-2-(methoxymethyl)pyrrolidine 10b. Diastereoselectivities were determined by ^1H NMR spectroscopy and GC (column temp. 170 °C, detector and injector temp. 280 °C), retention times, t_r, 11.30 and 11.54 min; using sulfur–lithium exchange, 57% (ratio of diastereoisomers 65:35); using tin–lithium exchange in THF, 88% (60:40); in hexane–Et_2O (10:1), 76% (63:37); ν_{max}($CHCl_3$)/cm^{-1} 3430 (OH), 1605 and 1495 (Ph); δ_H($CDCl_3$) 1.50–2.00 (4H, m, $NCH_2CH_2CH_2$), 2.30–3.00 (4H, m, CH_2NCH_2CHOH), 3.24–3.59 (3H, m, $NCHCH_2O$), 3.38 (3H, s, OCH_3), 4.64 (0.6H, dd, *J* 10 and 7, NCH_2CHOH), 4.72 (0.4H, dd, *J* 10 and 7, NCH_2CHOH), 7.20–7.60 (5H, m, C_6H_5); δ_C($CDCl_3$) 23.58 and 23.79 (NCH_2CH_2), 28.31 and 28.36 ($NCH_2CH_2CH_2$), 53.41 and 54.19 (NCH_2CH_2), 58.99 and 59.05 (OCH_3), 63.27 and 63.66 (NCH), 64.25 (NCH_2CHOH), 70.99 (CHOH), 76.31 and 76.48 (CH_2O), 125.80 and 125.96, 127.12 and 127.36, 128.19 and 128.25 (CH, aromatic), 142.43 (C, aromatic) (Found: M^+, 235.1571. $C_{14}H_{21}NO_2$ requires *M*, 235.1572); *m/z* 235 (M^+, 0.1%), 190 (M − CH_2OCH_3, 11), 128 (M − CHOHPh, 100).

(2*S*,2′*S*)- and (2*S*,2′*R*)-*N*-[2′-(*p*-Bromophenyl)-2′-hydroxyethyl]-2-(methoxymethyl)pyrrolidine 10c. Diastereoselectivities were determined by GLC (t_r 43.70 and 43.96 min) or GC (column temp. 200 °C, detector and injector temp. 280 °C), t_r 11.74 and 12.04 min; using sulfur–lithium exchange, 49% (61:39); using tin–lithium exchange in THF, 81% (56:44); in hexane–Et_2O (10:1), 83% (60:40); ν_{max}($CHCl_3$)/cm^{-1} 3410 (br, OH), 1595 (Ar); δ_H($CDCl_3$) 1.49–2.00 (4H, m, $NCH_2CH_2CH_2$), 2.29–3.00 (4H, m, CH_2NCH_2CHOH), 3.23–3.42 (3H, m, $NCHCH_2OCH_3$), 3.34 (3H, s, OCH_3), 4.10 (1H, br s, OH), 4.67 (0.6H, dd, *J* 9 and 5, NCH_2CHOH), 4.62 (0.4H, dd, *J* 9 and 5, NCH_2CHOH), 7.25–7.40 (4H, m, C_6H_4Br); δ_C($CDCl_3$) 23.59 and 23.60 (NCH_2CH_2), 28.24 and 28.31 ($NCH_2CH_2CH_2$), 54.22 and 56.54 (NCH_2CH_2), 58.92 and 58.98 (CH_3O), 63.26 and 63.72 (NCH), 64.11 (NCH_2CH), 70.49 and 70.55 (CHOH), 76.33 and 76.55 (CH_2O), 120.90 and 121.09 (CBr, aromatic), 127.57 and 127.67, 131.22 and 131.15 (CH, aromatic), 141.13 and 142.63 (C, aromatic) (Found: M^+, 313.0674. $C_{14}H_{20}NO_2{}^{79}Br$ requires *M*, 313.0677. Found: M^+, 315.0668. $C_{14}H_{20}NO_2{}^{81}Br$ requires *M*, 315.0659); *m/z* 313 (M^+, 0.1%), 270 (M − CH_2OCH_3, 22.6), 128 (M − $CHOHC_6H_4Br$, 100).

(2*S*,2′*S*)- and (2*S*,2′*R*)-*N*-[2′-Hydroxy-2′-(*p*-methylphenyl)ethyl]-2-(methoxymethyl)pyrrolidine 10d. (2*S*)-2-(methoxymethyl)-*N*-(phenylthiomethyl)pyrrolidine **9**, R = CH_2OMe (0.16 g, 0.66 mmol) and *p*-methylbenzaldehyde (0.25 g, 1.74 mmol) gave the alcohols **10d** (0.05 g, 29%) as an oil; ratio of diastereoisomers 64:36 [determined by GLC, t_r 38.24 (62.76%) and 38.62 min (34.08%)]; ν_{max}($CHCl_3$)/cm^{-1} 3420 (br, OH), 1605 and 1590 (Ar); δ_H($CDCl_3$) 1.54–2.03 (4H, m, $NCH_2CH_2CH_2$), 2.31–3.05 (4H, m, CH_2NCH_2CHOH), 2.35 (3H, s, $C_6H_4CH_3$), 3.25–3.42 (3H, m, $NCHCH_2O$), 3.39 (3H, s, OCH_3), 4.64 (0.65H, dd, *J* 10 and 4, NCH_2CHOH), 4.67 (0.35H, dd, *J* 10 and 4, NCH_2CHOH), 7.04–7.31 (4H, m, C_6H_4); δ_C($CDCl_3$) 21.07 and 21.40 ($C_6H_4CH_3$), 23.59 and 23.78 ($NCH_2CH_2CH_2$), 28.34 and 28.41 ($NCH_2CH_2CH_2$), 54.17 and 56.47 (NCH_2CH_2), 58.15 and 59.01 (OCH_3), 63.31 and 63.34 (NCH), 64.26 and 64.34 (NCH_2CHOH), 70.83 and 71.01 (CHOH), 76.33 and 76.34 (CH_2O), 122.91 and 123.06 (C, aromatic), 126.58 and

126.59, 128.13 and 128.93 (CH, aromatic), 137.04 and 137.83 (C, aromatic) (Found: M^+, 249.1724. $C_{15}H_{23}NO_2$ requires *M*, 249.1729); *m/z* 249 (M^+, 0.2%), 218 (M − OCH_3, 0.2), 128 (M − $CHOHC_6H_4CH_3$, 100).

(2*S*,2′*R*)- and (2*S*,2′*R*)-*N*-[2′-Hydroxy-2′-(*p*-methoxyphenyl)-ethyl]-2-(methoxymethyl)pyrrolidine 10e. Diastereoselectivities were determined by GLC (t_r 42.89 and 43.17 min) or GC (column temp. 200 °C, detector and injector temp. 280 °C), t_r 10.37 and 10.74 min; using sulfur–lithium exchange, 39% (78:22); using tin–lithium exchange in THF, 74% (57:43); in hexane–Et_2O (10:1), 89% (61:39); ν_{max}(neat)/cm^{-1} 3430 (OH), 1610 and 1585 (Ar); δ_H($CDCl_3$) 1.60–2.00 (4H, m, $NCH_2CH_2CH_2$), 2.30–3.10 (4H, m, CH_2NCH_2CHOH), 3.30–3.50 (3H, m, NCH-CH_2O), 3.35 (3H, s, OCH_3), 3.80 (3H, s, $C_6H_4OCH_3$), 4.10 (1H, br s, OH), 4.67 (0.65H, d, *J* 9 and 4, NCH_2CHOH), 4.70 (0.35H, dd, *J* 9 and 4, NCH_2CHOH), 6.39–7.45 (4H, m, $C_6H_4OCH_3$) (Found: M^+, 265.1679. $C_{15}H_{23}NO_3$ requires *M*, 265.1678); *m/z* 265 (M^+, 3.8%), 251 (M − CH_3, 9.3), 137 (M − $CH_2NC_4H_7$·CH_2OCH_3, 48.8), 128 (M − $CHOHC_6H_4$·OCH_3, 100).

(2*S*,2′*S*)- and (2*S*,2′*R*)-*N*-(2′-Hydroxy-3′-methylbutyl)-2-(methoxymethyl)pyrrolidine 10f. Diastereoselectivities were determined by GLC (t_r 8.59 and 8.69 min) or GC (column temp. 130 °C, detector and injector temp. 280 °C), t_r 10.46 and 10.88 min; using sulfur–lithium exchange, 50% (54:46); using tin–lithium exchange in THF, 81% (60:40); in hexane–Et_2O (10:1), 87% (63:37); ν_{max}(neat)/cm^{-1} 3455 (OH); δ_H($CDCl_3$) 1.90 (3H, d, *J* 8, $CHMe^AMe^B$), 1.97 (3H, d, *J* 8, $CHMe^AMe^B$), 1.55–2.00 (4H, m, $NCH_2CH_2CH_2$), 2.20–3.10 (4H, m, CH_2NCH_2CHOH), 3.21–3.61 (5H, m, $NCH_2CHOHCH$ and $NCHCH_2O$), 3.34 (3H, s, OCH_3), 4.36 (1H, br s, OH); δ_C($CDCl_3$) 17.98 and 18.16 ($CHMe^AMe^B$), 18.27 and 18.41 ($CHMe^AMe^B$), 23.21 (NCH_2CH_2), 27.80 and 28.13 (NCH_2-CH_2CH_2), 32.29 and 32.26 ($CHMe_2$), 54.31 and 56.93 (NCH_2CH_2), 59.00 and 59.64 (OCH_3), 63.52 and 63.93 (NCH), 64.08 and 65.15 (NCH_2CHOH), 72.48 (CHOH), 75.62 (OCH_2) (Found: M^+, 201.1728. $C_{11}H_{23}NO_2$ requires *M*, 201.1729); *m/z* 201 (M^+, 0.7%), 156 (M − CH_2OCH_3, 100).

(2*S*,2′*S*)- and (2*S*,2′*R*)-*N*-(3′,3′-Dimethyl-2′-hydroxybutyl)-2-(methoxymethyl)pyrrolidine 10g. Diastereoselectivities were determined by GLC (t_r 21.75 and 21.99 min) or GC (column temp. 130 °C, detector and injector temp. 280 °C), t_r 9.17 and 9.35 min; using sulfur–lithium exchange, 51% (50:50); using tin–lithium exchange in THF, 78% (55:45); in hexane–Et_2O (10:1), 94% (64:36); ν_{max}(neat)/cm^{-1} 3465 (OH); δ_H($CDCl_3$) 0.95 [9H, s, $C(CH_3)_3$], 1.50–2.00 (4H, m, $NCH_2CH_2CH_2$), 2.30–3.00 (4H, m, CH_2NCH_2CHOH), 3.00–3.70 (4H, m, NCH-CH_2OCH_3 and $CHOH$), 3.36 (3H, s, OCH_3); δ_C($CDCl_3$) 23.51 (NCH_2CH_2), 25.99 [$C(CH_3)_3$], 28.52 ($NCH_2CH_2CH_2$), 33.63 [$C(CH_3)_3$], 54.10 (NCH_2CH_2), 58.70 (OCH_3), 63.97 (NCH), 67.75 (NCH_2CHOH), 75.03 (CHOH), 76.49 (OCH_2) (Found: M^+, 215.1841. $C_{12}H_{25}NO_2$ requires *M*, 215.1848); *m/z* 216 (M^+, 0.2%), 170 (M − CH_2OCH_3, 18), 128 [M − $CHOHC(CH_3)_3$, 100].

(2*S*,2′*S*)- and (2*S*,2′*R*)-*N*-(2′-Hydroxy-2′-phenylethyl)pyrrolidine-2-methanol 10h. (2*S*)-*N*-(tributylstannylmethyl)pyrrolidine-2-methanol **13**, R = CH_2OH (0.11 g, 0.27 mmol) in THF (1 cm^3), butyllithium (2.5 M in hexanes; 0.3 cm^3, 0.07 mmol) and benzaldehyde (0.075 g, 0.75 mmol) in THF (1 cm^3), gave the alcohols **10 h** (0.02 g, 29%) as an oil; ratio of diastereoisomers 50:50 (determined by GC, column temp. 200 °C, detector and injector temp. 280 °C, t_r 12.10 and 12.87 min); δ_H($CDCl_3$) 1.59–2.00 (4H, m, $NCH_2CH_2CH_2$), 2.36–2.69 (2H, m, NCH_2CH_2), 2.71–3.08 (3H, m, $NCHCH_2O$ and NCH_2CHOH), 3.31–3.77 (2H, m, CH_2OH), 4.75 (0.5H, dd, *J* 8 and 5, NCH_2CHOH), 4.81 (0.5H, dd, *J* 8 and 5, NCH_2CHOH), 7.23–7.49 (5H, m, Ph); δ_C($CDCl_3$) 23.75 and 24.09 (NCH_2CH_2), 27.22 and 27.44 ($NCH_2CH_2CH_2$), 56.35 and 54.44 (NCH_2CH_2), 63.38 and 63.75 (NCH), 65.41 and 66.04 (NCH_2CHOH), 71.49 and 72.33 (CHOH), 76.58 and 76.98 (CH_2O), 125.85, 125.89, 127.63, 128.37 and 128.40 (CH, aromatic), 142.82 (C, aromatic) (Found: M^+, 221.1417. $C_{13}H_{19}NO_2$ requires *M*, 221.1415); *m/z* 221 (M^+, 0.2%), 190 (M − CH_2OH, 21.4), 114 (M − CHOHPh, 100).

(2*S*,2′*S*)- and (2*S*,2′*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)-*N*-(2′-hydroxy-2′-phenylethyl)pyrrolidine 10i. Stannane **13**, R = $CH_2OSiMe_2Bu^t$ (0.14 g, 0.28 mmol) in THF (2 cm^3), butyllithium (2.5 M in hexanes; 0.25 cm^3, 0.56 mmol) and benzaldehyde (0.07 g, 0.56 mmol) in THF (1 cm^3), gave the alcohols **10i** (0.065 g, 70%) as an oil; ratio of diastereoisomers 50:50 (determined by GC, column temp. 150 °C, detector and injector temp. 280 °C, t_r 3.01 and 3.19 min); ν_{max}(neat)/cm^{-1} 3440 (OH), 1495 (Ph); δ_H($CDCl_3$) 0.08 [6H, s, $Si(CH_3)_2$], 0.89 [9H, s, $SiC(CH_3)_3$], 1.50–1.93 (4H, m, $NCH_2CH_2CH_2$), 2.29–3.02 (4H, m, CH_2NCH_2CHOH), 3.31 (1H, m, $NCHCH_2O$), 3.41–3.66 (2H, m, $NCHCH_2O$), 3.94 (1H, br s, OH), 4.66 (0.5H, dd, *J* 9 and 4, NCH_2CHOH), 4.70 (0.5H, dd, *J* 9 and 4, NCH_2CHOH), 7.18–7.35 (5H, m, Ph); δ_C($CDCl_3$) −5.38 and −5.37 [$Si(CH_3)_2$], 18.31 and 18.35 [$SiC(CH_3)_3$], 23.58 and 23.79 (NCH_2CH_2), 25.95 and 25.97 [$SiC(CH_3)_3$], 27.90 and 28.02 ($NCH_2CH_2CH_2$), 54.09 and 56.31 (NCH_2CH_2), 64.11 and 64.24 (NCH_2CHOH), 65.18 and 65.98 (NCH), 66.26 and 66.37 (CH_2O), 70.78 and 71.27 (CHOH), 125.81 and 125.93, 127.12 and 127.29, 128.14 and 128.21 (CH, aromatic), 142.48 and 143.09 (C, aromatic) (Found: M^+, 335.2288. $C_{19}H_{33}NO_2Si$ requires *M*, 335.2280); *m/z* 335 (M^+, 0.1%), 278 (M − Bu, 8), 228 (M − CHOHPh, 100), 190 (M − $CH_2OSiMe_2Bu^t$, 41).

(2*S*,5*S*)-2,5-Bis-(methoxymethyl)-*N*-(phenylthiomethyl)-pyrrolidine 11

(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidine (0.20 g, 1.25 mmol), paraformaldehyde (0.038 g, 1.25 mmol), thiophenol (0.125 cm^3, 1.22 mmol) and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol in toluene (5 cm^3) were stirred at room temperature over 4 Å molecular sieves. After 48 h the mixture was filtered, evaporated and the residue was purified by column chromatography on neutral aluminium oxide, eluting with light petroleum–EtOAc (20:1) to give the sulfide **11** (0.17 g, 47%) as an oil; $[\alpha]_D^{25}$ −38.90 (*c* 0.63 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2960, 2930 and 2860 (CH), 1585 (Ph); δ_H($CDCl_3$) 1.84–2.00 (4H, m, CH_2CH_2), 3.17–3.46 (6H, m, 2 × $CHCH_2O$), 3.34 (6H, s, 2 × OCH_3), 4.76 (1H, d, *J* 7, NCH^AH^BS), 4.89 (1H, d, *J* 7, NCH^AH^BS), 7.14–7.40 (5H, m, Ph) (Found: M^+, 218.1560. $C_{15}H_{23}NO_2S$ requires *M*, 218.1449); *m/z* 281 (M^+, 3.3%), 172 (M − SPh, 75.8), 114 (M − $CH_2SC_6H_5$ − CH_2OCH_3, 100).

(2*S*,5*S*,2′*S*)- and (2*S*,2*R*,2′*R*)-*N*-(2′-Hydroxy-2′-phenylethyl)-2,5-bis (methoxymethyl)pyrrolidine 12

Sulfide **11** (0.17 g, 0.6 mmol) in THF (1 cm^3), LiDBB and benzaldehyde (0.10 g, 1.0 mmol) in THF (1 cm^3) gave the alcohols **12** (0.09 g, 54%) as an oil; ratio of diastereoisomers 65:35 (determined by ^1H NMR spectroscopy); δ_H($CDCl_3$) 0.90–1.10 (2H, m, $CH^AH^BCH^AH^B$), 1.15–1.75 (2H, m, $CH^AH^BCH^AH^B$), 2.50–2.70 (2H, m, NCH_2), 3.10–3.44 (6H, m, 2 × $NCHCH_2O$), 3.48 (6H, s, 2 × OCH_3), 3.80 (1H, br s, OH), 4.68–4.42 (0.35H, dd, *J* 6 and 2, NCH_2CHOH), (0.65H, dd, *J* 6 and 2, NCH_2-$CHOH$), 7.13–7.43 (5H, m, Ph); δ_C($CDCl_3$) 27.29 and 27.37 ($NCHCH_2$), 56.05 and 57.09 (NCH_2), 58.91 and 58.95 (OCH_3), 59.72 and 62.87 (NCH), 70.03 and 72.12 (CHOH), 74.13 and 74.60 (OCH_2), 125.74 and 125.86, 127.09 and 127.21, 128.20 and 128.45 (CH, aromatic), 142.83 and 143.39 (C, aromatic) (Found: M^+, 279.1841. $C_{16}H_{25}NO_3$ requires *M*, 279.1834); *m/z* 279 (M^+, 0.1%), 234 (M − CH_2OCH_3, 26), 172 (M − CHOHPh, 100).

(2*S*)-2-(Methoxymethyl)-*N*-(tributylstannylmethyl)pyrrolidine 13, R = CH_2OMe

(2*S*)-2-(Methoxymethyl)pyrrolidine **8**, R = CH_2OMe (0.54 g, 4.7 mmol), paraformaldehyde (0.14 g, 4.7 mmol) and benzotriazole (0.56 g, 4.7 mmol) in toluene (10 cm^3) were stirred at

room temperature over 4 Å molecular sieves for 24 h. The mixture was filtered and evaporated to give the *N*-benzotriazolylmethyl derivatives (1.18 g, 100%) as an oil; 4:1 mixture of benzotriazol-1- and -2-yl isomers (determined by ^{1}H NMR spectroscopy).

Butyllithium (2.5 M in hexanes; 8.4 cm^3, 21 mmol) was added to diisopropylamine (2.89 g, 28.6 mmol) in THF (20 cm^3) at 0 °C. After 2 min, tributyltin hydride (2.69 g, 9.26 mmol) in THF (10 cm^3) and then the *N*-benzotriazolylmethyl derivatives (0.93 g, 3.7 mmol) in THF (10 cm^3) were added at 0 °C. The mixture was stirred at 0 °C for 2 h. Diethyl ether (50 cm^3) was added and the mixture was washed with sat. aqueous NH_4Cl (50 cm^3), NaOH (50 cm^3; 2 M) and sat. aqueous NaCl (50 cm^3). The solution was dried ($MgSO_4$), evaporated and purified by column chromatography on basic aluminium oxide, eluting with light petroleum–EtOAc (50:1) to give the stannane **13**, R = CH_2OMe (1.13 g, 2.7 mmol, 73%) as an oil; $[\alpha]_D^{25}$ −47.76 (*c* 1.12 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2955, 2920 and 2875 (CH); δ_H($CDCl_3$) 0.76–1.00 (15H, m, 3 × CH_2CH_3), 1.21–1.80 [16H, m, $Sn(CH_2CH_2)_3$ and $NCH_2CH_2CH_2$], 1.82–2.00 (2H, m, NCH_2CH_2), 2.13 (1H, q, *J* 8, $NCHCH_2$), 2.63 (1H, d, *J* 12, NCH^AH^BSn), 2.93 (1H, d, *J* 12, NCH^AH^BSn), 3.25 (1H, dd, *J* 9 and 6, $NCHCH^AH^BO$), 3.34 (3H, s, OCH_3), 3.42 (1H, dd, *J* 9 and 4, $NCHCH^AH^BO$); δ_C($CDCl_3$) 10.31 ($SnCH_2CH_2CH_2CH_3$), 13.53 and 13.63 ($SnCH_2CH_2CH_2CH_3$), 22.82 (NCH_2CH_2), 27.37 ($SnCH_2CH_2CH_2CH_3$), 28.81 ($NCH_2CH_2CH_2$), 29.21 ($SnCH_2CH_2CH_2CH_3$), 41.29 (NCH_2CH_2), 58.36 (NCH_2Sn), 59.08 (OCH_3), 66.45 (NCH), 75.89 (CH_2O) (Found: M$^+$, 419.2222. $C_{19}H_{41}NO^{120}Sn$ requires *M*, 419.2210); *m/z* 419 (M$^+$, 0.5%), 374 (M − CH_2OCH_3, 0.1), 362 (M − Bu, 0.3), 128 (M − $SnBu_3$, 100).

(2*S*)-*N*-(Tributylstannylmethyl)pyrrolidine-2-methanol 13, R = CH_2OH

In the same way as for **13**, R = CH_2OMe, (2*S*)-pyrrolidine-2-methanol **8**, R = CH_2OH (0.51 g, 5.0 mmol), paraformaldehyde (0.16 g, 5.2 mmol) and benzotriazole (0.63 g, 5.3 mmol) gave the *N*-benzotriazolylmethyl derivatives (1.1 g, 91%) as an oil; 3:1 mixture of benzotriazol-1- and -2-yl isomers, which were added to diisopropylamine (1.2 g, 11.9 mmol), butyllithium (2.5 M in hexanes; 4.8 cm^3, 12 mmol) and tributyltin hydride (2.67 g, 9.2 mmol) to give the stannane **13**, R = CH_2OH (0.93 g, 50%) as an oil; $[\alpha]_D^{21}$ −27.00 (*c* 1.2 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450 (OH); δ_H($CDCl_3$) 0.69–1.00 (15H, m, 3 × CH_2CH_3), 1.12–1.93 [18H, m, $NCH_2CH_2CH_2$ and $Sn(CH_2CH_2)_3$], 2.31 (1H, d, *J* 12, NCH^AH^BSn), 2.53 (1H, br s, OH), 2.78 (1H, d, *J* 12, NCH^AH^BSn), 3.03 (1H, m, $NCHCH_2OH$), 3.37 (1H, dd, *J* 10 and 3, $NCHCH^AH^BOH$), 3.65 (1H, dd, *J* 10 and 4, $NCHCH^AH^BOH$); δ_C($CDCl_3$) 10.31 ($SnCH_2CH_2CH_2CH_3$), 13.53 and 13.63 ($SnCH_2CH_2CH_2CH_3$), 23.42 (NCH_2CH_2), 27.37 ($SnCH_2CH_2CH_2CH_3$), 27.42 ($NCH_2CH_2CH_2$), 29.21 ($SnCH_2CH_2CH_2CH_3$), 40.16 (NCH_2CH_2), 58.26 (NCH_2Sn), 63.41 (NCH), 70.95 (OCH_2) (Found: M$^+$, 405.2027. $C_{18}H_{39}NO^{120}Sn$ requires *M*, 405.2054); *m/z* 374 (M − CH_2OH, 0.1%), 348 (M − Bu, 0.4), 114 (M − $SnBu_3$, 100).

(2*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-*N*-(tributylstannylmethyl)pyrrolidine 13, R = $CH_2OSiMe_2Bu^t$

tert-Butyldimethylsilyl chloride (0.19 g, 1.20 mmol) in CH_2Cl_2 (3 cm^3) was added to (2*S*)-*N*-(tributylstannylmethyl)pyrrolidine-2-methanol **13**, R = CH_2OH (0.25 g, 0.60 mmol) and imidazole (0.14 g, 2.10 mmol) in CH_2Cl_2 (6 cm^3). After 24 h at room temperature, the solvent was evaporated and the residue was purified by column chromatography on neutral aluminium oxide, eluting with light petroleum–EtOAc (20:1) to give the stannane **13**, R = $CH_2OSiMe_2Bu^t$ (0.06 g, 19%) as an oil; ν_{max}(neat)/cm^{-1} 2965, 2935, 2885 and 2860 (CH); δ_H($CDCl_3$) 0.06 [6H, s, $Si(CH_3)_2$], 0.91 [9H, s, $SiC(CH_3)_3$], 0.76–1.00 (15H, m, 3 × CH_2CH_3), 1.24–1.42 [6H, m, $Sn(CH_2CH_2)_3$], 1.42–1.97 [10H, m, $NCH_2CH_2CH_2$ and $Sn(CH_2CH_2)_3$], 2.11–2.29 (2H, m, NCH_2CH_2), 2.53 (1H, d, *J* 13, NCH^AH^BSn), 2.97 (1H, m, $NCHCH_2O$), 2.99 (1H, d, *J* 13, NCH^AH^BSn), 3.39 (1H, dd, *J* 10 and 7, $NCHCH^AH^BO$), 3.66 (1H, dd, *J* 10 and 5, $NCHCH^AH^BO$); δ_C($CDCl_3$) −5.32 and −5.34 ($SiCH_3$), 10.28 ($SnCH_2CH_2CH_2CH_3$), 13.64 ($SnCH_2CH_2CH_2CH_3$), 18.31 [$SiC(CH_3)_3$], 22.95 (NCH_2CH_2), 25.95 [$SiC(CH_3)_3$], 27.41 ($SnCH_2CH_2CH_2CH_3$), 29.11 ($SnCH_2CH_2CH_2CH_3$), 29.37 ($NCH_2CH_2CH_2$), 42.00 (NCH_2CH_2), 58.68 (NCH_2Sn), 67.50 (NCH), 68.90 (CH_2O) (Found: M$^+$, 519.2933. $C_{24}H_{53}NOSi^{120}Sn$ requires *M*, 519.2918); *m/z* 519 (M$^+$, 0.2%), 228 (M − $SnBu_3$, 100).

Acknowledgements

We thank the SERC for a grant (to M. M. S. L.-A.) and Glaxo-Wellcome for a CASE award (to M. M. S. L.-A.).

References

1 D. J. Peterson, *J. Am. Chem. Soc.*, 1971, **93**, 4027.
2 T. Tsunoda, K. Fujiwara, Y. Yamamoto and S. Ito, *Tetrahedron Lett.*, 1991, **32**, 1975; C. A. Broka and T. Shen, *J. Am. Chem. Soc.*, 1989, **111**, 2981; C. Strohmann and B. C. Abele, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2378.
3 I. Coldham, R. Hufton and D. J. Snowden, *J. Am. Chem. Soc.*, 1996, **118**, 5322; I. Coldham and R. Hufton, *Tetrahedron*, 1996, **52**, 12 541.
4 I. Coldham, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1275; R. E. Gawley, Q. Zhang and S. Campagna, *J. Am. Chem. Soc.*, 1995, **117**, 11 817.
5 B. Elissondo, J.-B. Verlhac, J.-P. Quintard and M. Pereyre, *J. Organomet. Chem.*, 1988, **339**, 267; W. H. Pearson and A. C. Lindbeck, *J. Am. Chem. Soc.*, 1991, **113**, 8546; J. M. Chong and S. B. Park, *J. Org. Chem.*, 1992, **57**, 2220; E. Vedejs and W. O. Moss, *J. Am. Chem. Soc.*, 1993, **115**, 1607; W. H. Pearson, A. C. Lindbeck and J. W. Kampf, *J. Am. Chem. Soc.*, 1993, **115**, 2622; A. F. Burchat, J. M. Chong and S. B. Park, *Tetrahedron Lett.*, 1993, **34**, 51; P. Beak, S. T. Kerrick, S. Wu and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231; R. E. Gawley and Q. Zhang, *Tetrahedron*, 1994, **50**, 6077; T. R. Elworthy and A. I. Meyers, *Tetrahedron*, 1994, **50**, 6089; M. E. Kopach and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 6764.
6 R. E. Gawley and Q. Zhang, *J. Org. Chem.*, 1995, **60**, 5763.
7 I. M. P. Huber and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1944; R. E. Gawley and K. Rein, *Comprehesive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 3, p. 65; A. I. Meyers, *Tetrahedron*, 1992, **48**, 2589; P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109; D. J. Gallagher and P. Beak, *J. Org. Chem.*, 1995, **60**, 7092; Y. S. Park, M. L. Boys and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 3757.
8 N. A. Roberts, J. A. Martin, D. Kinchington, A. V. Broadhurst, J. C. Craig, I. B. Duncan, S. A. Galpin, B. K. Handa, J. Kay, A. Kröhn, R. W. Lambert, J. H. Merrett, J. S. Mills, K. E. B. Parkes, S. Redshaw, A. J. Ritchie, D. L. Taylor, G. J. Thomas and P. J. Machin, *Science*, 1990, **248**, 358; D. H. Rich, C.-Q. Sun, J. V. N. V. Prasad, A. Pathiasseril, M. V. Toth, G. R. Marshall, M. Clare, R. A. Mueller and K. Houseman, *J. Med. Chem.*, 1991, **34**, 1222.
9 M. Pohl, M. Thieme, P. G. Jones and J. Liebscher, *Liebigs Ann.*, 1995, 1539.
10 P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924; T. Cohen and M. Bhupathy, *Acc. Chem. Res.*, 1989, **22**, 152.
11 D. Seyferth and S. B. Andrews, *J. Organomet. Chem.*, 1971, **30**, 151.
12 W. H. Pearson and E. P. Stevens, *Synthesis*, 1994, 904; A. R. Katritzky, H.-X. Chang and J. Wu, *Synthesis*, 1994, 907.
13 M. Chini, P. Crotti, L. Favero, F. Macchia and M. Pineschi, *Tetrahedron Lett.*, 1994, **35**, 433.

Paper 6/08576H
Received 23rd *December* 1996
Accepted 7th *February* 1997