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Synthesis of Chiral, Nonracemic Methyleneaziridines Derived From β-Amino Alcohols

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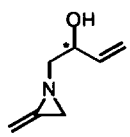
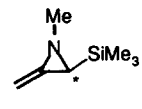
Abstract: An efficient three step process for the synthesis of chiral, nonracemic methyleneaziridines derived from homochiral β-amino alcohols is described. Methyleneaziridines **4a-e** produced using this chemistry have been shown to possess high enantiomeric purities (≥ 95%ee).

As part of a general programme directed towards developing new synthetic methods for organic chemistry based upon methyleneaziridines, we have begun to explore the utility of homochiral methyleneaziridines in asymmetric synthesis. Prior to our studies, only two reports concerning the preparation of chiral, nonracemic methyleneaziridines had appeared in the literature. In 1962, Bottini and Dev reported the preparation of (-)-**1**, an analogue of tetramin, although the enantiomeric purity of this methyleneaziridine was not determined (Figure 1).[2] In a second study, Quast and Vélez described the synthesis of methyleneaziridine (-)-**2** in 12% enantiomeric excess from 1-methyl-2-methyleneaziridine using an asymmetric deprotonation / alkylation process.[3] Our work in this area initially focused on the preparation of homochiral (*S*)-(-)-**3** from (*S*)-α-methylbenzylamine.[4] While (*S*)-(-)-**3** and its enantiomer may prove to be useful compounds for asymmetric synthesis, we required access to a more diverse range of homochiral methyleneaziridines to explore the relative merits of such compounds in organic chemistry. With this objective in mind, we chose to prepare compounds based upon general structure **4**. By using a variety of commercially available homochiral β-amino alcohols as starting materials, we hoped to make a range of such compounds possessing different groupings attached to the asymmetric centre and the oxygen atom (*ie* R^1, R^2). In this paper, we disclose efficient routes to such methyleneaziridines in enantiomerically enriched form.



(-)-**1**



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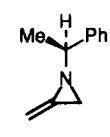

(*S*)-(-)-**3**

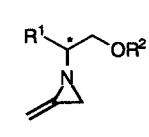

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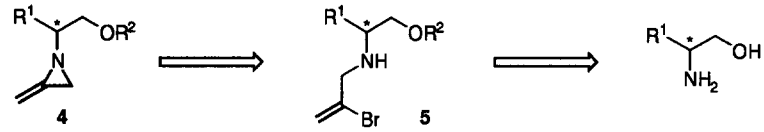
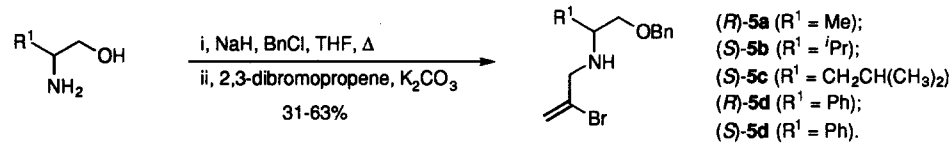
Figure 1

Synthesis of Precursors. We chose to employ the cyclisation methodology originally described by Pollard and Parcell for the preparation of the desired methyleneaziridines.[5] This chemistry involves ring closure of the corresponding *N*-(2-bromoallyl)-alkylamines **5** by treatment with sodium amide in liquid ammonia (Scheme 1). It was anticipated that these cyclisation precursors could, in turn, be derived from the corresponding chiral β-amino alcohols. If this strategy could be successfully implemented, the wide availability of homochiral β-amino alcohols[6] would enable a large number of methyleneazidines to be prepared and subsequently evaluated in asymmetric synthesis.



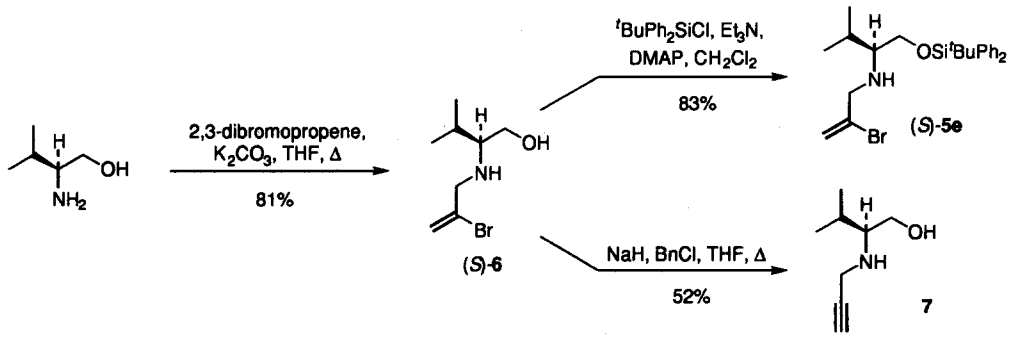
Scheme 1

Efficient general methods for the selective *O*- and *N*-alkylation of chiral β-amino alcohols were required for the preparation of the cyclisation precursors. *O*-Benzylation was successfully accomplished on a range of chiral β-amino alcohols using the methodology recently described by Hu and Cassady.[7] Subsequent *N*-alkylation of these compounds with 2,3-dibromopropene furnished a range of chiral, nonracemic cyclisation precursors **5a-d** in moderate to good overall yields (Scheme 2).



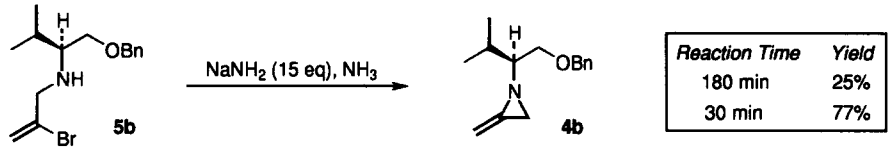
Scheme 2

In order to probe further the generality of the cyclisation methodology, we prepared *tert*-butyldiphenylsilyl ether (*S*)-**5e** (Scheme 3). This compound was synthesised in two steps from (*S*)-valinol by alkylation with 2,3-dibromopropene and subsequent silylation with *tert*-butyldiphenylsilyl chloride. Interestingly, attempts to prepare precursor **5b** by *O*-benzylation of **6** using the Hu and Cassady procedure failed completely and instead led to the formation of acetylene **7** in 52% yield. We speculate that this product arises from intermolecular elimination of HBr by alkoxide anion generated *in situ* from sodium hydride and alcohol **6**.



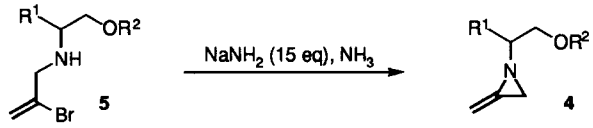
Scheme 3

Cyclisation Studies. Our initial attempts at facilitating the cyclisation of homochiral *N*-(2-bromoallyl)-alkylamines **5a-e** to the corresponding methyleneaziridines met with only limited success. For example, treatment of **5b** with 15 equivalents of sodium amide in liquid ammonia for 3 hours gave the desired methyleneaziridine **4b** in a disappointing 25% yield after column chromatography (Scheme 4).[8] While reducing the quantity of sodium amide in the reaction had little effect,[9] we did find that the reaction time had a significant impact on the efficiency of the cyclisation. Indeed, reducing the reaction time for this cyclisation from 180 to 30 minutes led to a threefold increase in the yield of methyleneaziridine **4b**.



Scheme 4

Having established the importance of the reaction time, we were quickly able to optimise this parameter for each precursor **5a-e**. In this way, we have been able to prepare all the methyleneaziridines **4a-e** in good yields (Table 1). At the outset of this work, we were concerned that the strongly basic conditions required for the formation of the methyleneaziridines might cause racemisation at the stereogenic centre. We anticipated that methyleneaziridine **4d** possessing a benzylic hydrogen atom may be particularly prone to this problem. However, we were delighted to discover that in all the cases we have examined, no significant racemisation occurs under the cyclisation conditions.



Entry	Product	R^1	R^2	Yield[§]	ee[¶]
1	(*R*)-**4a**	CH_3	CH_2Ph	73%	≥95%
2	(*S*)-**4b**	^iPr	CH_2Ph	77%	≥95%
3	(*S*)-**4c**	$CH_2CH(CH_3)_2$	CH_2Ph	93%	≥95%
4	(*S*)-**4d**	Ph	CH_2Ph	68%	≥95%
5	(*R*)-**4d**	Ph	CH_2Ph	68%	≥95%
6	(*S*)-**4e**	^iPr	Si^tBuPh_2	73%	≥95%

Table 1. [§]Isolated yields after column chromatography. [¶] Determined using chiral shift NMR experiments and/or chiral HPLC analysis (see Experimental). Racemic compounds were prepared and used for comparison purposes in these analyses (except for **4d**).

In summary, we have devised a simple three step protocol for the preparation of a range of chiral, nonracemic methyleneaziridines from commercially available β-amino alcohols. Studies to evaluate the utility of such methyleneaziridines in novel enantioselective transformations are ongoing and will be disclosed in due course.

EXPERIMENTAL

General. ^{1}H and ^{13}C nmr spectra were recorded at 250 MHz and 62.5 MHz on a Bruker ACF-250 instrument and at 400 MHz and 100 MHz on a Bruker DPX 400 instrument with either tetramethylsilane or residual protic solvent as the internal standard. Infrared spectra were recorded on a Nicolet FT-205 spectrometer. Mass Spectra were recorded on a Kratos MS80 or VG analytical ZAB-E instrument under EI conditions unless otherwise stated. All solvents and reagents were purified by standard means. All reactions were performed using oven dried glassware under an atmosphere of nitrogen unless otherwise stated.

Preparation of (*R*)-1-phenylmethoxy-2-propylamine 8a. To a stirred suspension of sodium hydride (60% dispersion, 2.0 g, 51.0 mmol) in THF (40 ml) at 0°C was added (*R*)-2-amino-1-propanol (5.0 g, 65.7 mmol) dropwise. The reaction mixture was refluxed for 90 minutes then benzyl chloride (7.5 g, 59.1 mmol) was added dropwise and the mixture refluxed for a further 14 hours. On cooling to room temperature, water (10 ml) was added and solvent removed under reduced pressure. The residue was dissolved in dichloromethane (100 ml) and the product extracted into the aqueous phase by washing with 1M HCl (3 x 100 ml). The aqueous phase was basified with 10% sodium hydroxide (400 ml) and re-extracted into dichloromethane (6 x 100 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure to give **8a** (7.2 g, 73%) as a yellow oil which was used without further purification. $[\alpha]_D$ -17.8 (*c* 1.0, $CHCl_3$), literature $[\alpha]_D$ +16.4 (*c* 0.85, MeOH) for (*S*)-enantiomer;[10] ν_{max} (film) 3362, 3030, 2962, 2859, 1453, 1369, 1098, 738, 699 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.33-7.26 (5H, m, Ph), 4.51 (2H, s, OCH_2Ph), 3.39-3.33 (1H, m, CH_2OBn), 3.21-3.15 (2H, m, NCH, CHOBn), 1.37 (2H, s, NH_2), 1.03 (3H, d, 5.9 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 138.3 (s), 128.2 (d), 127.53 (d), 127.49 (d), 77.1 (t), 73.1 (t), 46.4 (d), 19.7 (q); *m/z* 165, 134, 91; Observed (M^+): 165.1134; $C_{10}H_{15}NO$ requires 165.1154.

Preparation of (*S*)-3-methyl-1-phenylmethoxy-2-butylamine 8b. To a stirred solution of (*S*)-valinol (5.0 g, 48.5 mmol) in THF (50 ml) was added sodium hydride (60% dispersion, 1.6 g, 48.5 mmol) in portions and the resultant suspension heated under reflux for 30 minutes. Benzyl chloride (5.39 g, 42.6 mmol) was added and the mixture refluxed for a further 48 hours. On cooling, water (10 ml) was added and the solvent removed under reduced pressure. The residue was partitioned between 1M hydrochloric acid (pH<1) and dichloromethane. The organic phase was collected and re-extracted with 1M hydrochloric acid (2 x 10 ml). The combined aqueous extracts were washed with dichloromethane (2 x 10 ml), and the pH of the aqueous phase adjusted to pH 10 with 10% sodium hydroxide. The aqueous phase was extracted with dichloromethane (3 x 30 ml). These combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to give **8b** (6.77 g, 84%) as a yellow oil which was used without further purification. ν_{max} (film) 3400, 2959, 1467 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.35-7.27 (5H, m, Ph), 4.53 (2H, s, CH_2Ph), 3.53 (1H, dd, 9.1, 3.8 Hz, CHOBn), 3.33-3.26 (1H, dd, 9.1, 8.0 Hz, CHOBn), 2.82-2.75 (1H, m, NCH), 2.42 (2H, bs, NH_2), 1.69-1.61 (1H, m, $C\underline{H}(CH_3)_2$), 0.93 (3H, d, 6.7 Hz, CH_3), 0.90 (3H, d, 6.7 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 138.0 (s), 128.1 (d), 127.5 (d), 127.4 (d), 73.9 (t), 73.1 (t), 56.2 (d), 30.8 (d), 19.3 (q), 18.3 (q); *m/z* 193 (M^+), 162, 91; Observed (M^+): 193.1459; $C_{12}H_{19}NO$ requires 193.1467.

Preparation of (*S*)-4-methyl-1-phenylmethoxy-2-pentylamine 8c. To a stirred suspension of sodium hydride (60% dispersion, 2.0 g, 51.0 mmol) in THF (50 ml) at 0°C was added (*R*)-leucinol (5.0 g, 43.0 mmol) dropwise. The reaction mixture was refluxed for 30 minutes then benzyl chloride (4.9 g, 38.7 mmol) was added and the mixture refluxed for a further 14 hours. On cooling to room temperature, water (10

ml) was added and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (100 ml) and the product extracted into the aqueous phase by washing with 1M HCl (3 x 100 ml). The aqueous phase was then basified with 10% sodium hydroxide (400 ml) and the product re-extracted into dichloromethane (6 x 100 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure to give **8c** (4.80 g, 60%) as a yellow oil which was used without further purification. $[\alpha]_D$ +5.0 (*c* 1.0, $CHCl_3$), lit $[\alpha]_D$ +6.7 (c 1.3, $CHCl_3$);[11] ν_{max} (film) 3372, 3030, 2954, 2867, 568, 1102, 698 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.32-7.29 (5H, m, Ph), 4.51 (2H, s, CH_2Ph), 3.44 (1H, dd, 9.0, 3.6 Hz, CHOBn), 3.20 (1H, dd, 8.8, 8.0 Hz, CHOBn), 3.10-3.03 (1H, m, NCH), 1.76-1.66 (1H, m, $C\underline{H}(CH_3)_2$), 1.40 (2H, bs, NH_2), 1.25-1.14 (2H, m, CH_2), 0.91 (3H, d, 6.5 Hz, CH_3), 0.89 (3H, d, 6.6 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 138.0 (s), 128.3 (d), 127.6 (d) 127.5 (d), 76.9 (t), 73.1 (t) 48.7 (d), 43.3 (t), 24.5 (d) 23.4 (q), 21.9 (q); Observed (MH^+): 208.1700; $C_{13}H_{22}NO$ requires 208.1701.

Preparation of (*R*)-1-phenyl-2-(phenylmethoxy)ethylamine 8d. To a stirred solution of (*R*)-2-amino-2-phenylethanol (4.0 g, 29.2 mmol) in THF (50 ml) was added sodium hydride (60% dispersion, 0.98 g, 29.2 mmol) in portions and the suspension refluxed for 30 minutes. Benzyl chloride (3.25 g, 25.7 mmol) was added and the mixture refluxed for a further 48 hours. On cooling, water (10 ml) was added and the solvent removed under reduced pressure. The residue was partitioned between 1M hydrochloric acid (pH<1) and dichloromethane. The organic phase was collected and re-extracted with 1M hydrochloric acid (2 x 20 ml). The aqueous phase was washed with dichloromethane (2 x 10 ml) and the pH of this layer adjusted to pH 10 with 10% sodium hydroxide. The aqueous phase was extracted with dichloromethane (3 x 20 ml) and the combined organic extracts dried over Na_2SO_4. Removal of the solvent under reduced pressure and subsequent column chromatography (50% ethyl acetate / petroleum ether pretreated with triethylamine) gave (*R*)-**8d** (3.7 g, 64%) as a pale yellow oil. $[\alpha]_D$ -28.3 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3379, 1603, 1494, cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.38-7.24 (10H, m, Ph), 4.54 (2H, s, CH_2Ph), 4.22 (1H, dd, 8.7, 3.7 Hz, NCH), 3.60 (1H, dd, 9.2, 3.7 Hz, CHOBn), 3.44 (1H, t, 8.8 Hz, CHOBn), 1.73 (2H, bs, NH_2); δ_C (62.9 MHz, $CDCl_3$) 142.1 (s), 138.0 (s), 128.3 (d), 127.6 (d), 127.5 (d), 127.3 (d), 126.7 (d), 126.5 (d), 76.5 (t), 73.2 (t), 55.5 (d); *m/z* 228 (MH^+), 107, 91, 77; Observed (MH^+): 228.1388; $C_{15}H_{18}NO$ requires 228.1388.

Preparation of (*S*)-1-phenyl-2-(phenylmethoxy)ethylamine 8d.[12] To a stirred solution of (*S*)-2-amino-2-phenylethanol (5.0 g, 36.4 mmol) in THF (60 ml) was added sodium hydride (60% dispersion, 1.22 g, 36.4 mmol) in portions and the suspension refluxed for 30 minutes. Benzyl chloride (4.06 g, 32.1 mmol) was added and the mixture heated for a further 48 hours. Work-up and purification as described above gave (*S*)-**8d** (3.7 g, 51%) as a pale yellow oil. $[\alpha]_D$ +30.1 (*c* 1.1, $CHCl_3$). Spectroscopic data identical with (*R*)-enantiomer.

Preparation of (*R*)-*N*-(2-bromo-2-propenyl)-2-[1-(phenylmethoxy)]propylamine 5a. To a stirred suspension of **8a** (12.0 g, 72.2 mmol) and potassium carbonate (3.8 g, 36.1 mmol) in THF (100 ml) was added 2,3-dibromopropene (7.2 g, 36.1 mmol) dropwise and the mixture stirred for 2 days. The mixture was filtered, concentrated under reduced pressure then redissolved in dichloromethane (200 ml). The organic layer was washed with 10% NaOH (3 x 70 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (30% diethyl ether / petroleum ether) gave **5a** (7.0 g, 68%) as a pale yellow oil. $[\alpha]_D$ +19.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3328, 2858, 1635, 1099, 8945, 698 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.34-7.25 (5H, m, Ph), 5.81 (1H, bs, =CH), 5.55 (1H, bs, =CH) 4.55 (1H, d, 12.0 Hz, A of AB, CH_2Ph), 4.52 (1H, d, 12.0 Hz, B of AB, CH_2Ph), 3.56-3.46 (2H, m, NCH_2), 3.43 (1H, dd, 9.4, 4.4 Hz, CHOBn), 3.35 (1H,

dd, 9.4, 7.6 Hz, CHOBn), 3.03-2.95 (1H, m, NCH), 2.36 (1H, bs, NH), 1.02 (3H, d, 6.4 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 138.0 (s), 133.3 (s), 128.3 (d), 127.52 (d), 127.50 (d) 117.5 (t), 74.6 (t), 73.0 (t), 54.7 (t), 50.3 (d), 16.7 (q); Observed (M^+): 283.0580; $C_{13}H_{18}BrNO$ requires 283.0571.

Preparation of (*S*)-*N*-(2-bromo-2-propenyl)-2-[3-methyl-1-(phenylmethoxy)]butylamine 5b. To a stirred solution of **8b** (6.0 g, 31.1 mmol) in THF (50 ml) was added 2,3-dibromopropene (3.10 g, 15.5 mmol) dropwise and the resulting solution heated under reflux for 12 hours. Potassium carbonate (8.5 g, 62.2 mmol) was then added and the mixture heated for a further 48 hours. On cooling, the mixture was filtered and the precipitate washed with diethyl ether. The filtrate was washed with 10% sodium hydroxide (2 x 10 ml) then the aqueous phase was back extracted with diethyl ether (3 x 15 ml). The combined organic extracts were washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (15% ethyl acetate / petroleum ether using silica pretreated with triethylamine) gave **5b** (3.60 g, 75%) as an orange oil. $[\alpha]_D$ -4.7 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3400, 2925, 1635, 1466, 1102 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.35-7.29 (5H, m, Ph), 5.80 (1H, m, =CH), 5.51 (1H, d, 1.7 Hz, =CH), 4.52 (2H, s, CH_2Ph), 3.53 (1H, dd, 9.5, 4.1 Hz, CHOBn), 3.48 (2H, s, CH_2N), 3.39 (1H, dd, 9.5, 6.6 Hz, CHOBn), 2.61-2.59 (1H, m, NCH), 1.8 (1H, m, $C\underline{H}(CH_3)_2$), 1.75 (1H, s, NH), 0.93 (3H, d, 6.9 Hz, CH_3), 0.90 (3H, d, 6.9 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) 138.0 (s), 133.9 (s), 128.3 (d), 127.5 (d), 117.1 (t), 73.1 (t), 70.4 (t), 60.3 (d), 56.6 (t), 29.0 (d), 18.8 (q), 18.3 (q), two aromatic carbons coincident; *m/z* 314/312 (MH^+), 190, 91; Observed (M^+) 311.0884; $C_{15}H_{22}BrNO$ requires 311.0885.

Preparation of (*S*)-N-(2-bromo-2-propenyl)-2-[4-methyl-1-(phenylmethoxy)]pentylamine 5c. To a stirred suspension of **8c** (8.0 g, 41.0 mmol) and potassium carbonate (0.80 g, 20.5 mmol) in THF (160 ml) was added 2,3-dibromopropene (5.10 g, 20.5 mmol) dropwise and the mixture refluxed for 24 hours. The mixture was filtered, concentrated under reduced pressure then redissolved in dichloromethane (150 ml). The organic layer was washed with 10% NaOH (3 x 50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (30% diethyl ether / petroleum ether) gave **5c** (3.40 g, 51%) as a pale yellow oil. $[\alpha]_D$ +1.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3030, 2955, 1454, 1366, 1101, 698 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.34-7.25 (5H, m, Ph), 5.81 (1H, m, =CH), 5.54 (1H, m, =CH), 4.55 (1H, d, 12.0 Hz, A of AB, CH_2Ph), 4.51 (1H, d, 12.0 Hz, B of AB, CH_2Ph), 3.55-3.47 (3H, m, NCH_2, CHOBn), 3.36 (1H, dd, 9.6, 6.8 Hz, CHOBn), 2.90-2.84 (1H, m, NCH), 2.60 (1H, bs, NH), 1.65 (1H, m, $C\underline{H}(CH_3)_2$), 1.36-1.23 (2H, m, CH_2), 0.89 (6H, d, 6.5 Hz, 2 x CH_3); δ_C (62.9 MHz; $CDCl_3$) 138.0 (s), 134.0 (s), 128.3 (d) 127.5 (d), 127.3 (d), 117.3 (t), 73.1 (t), 72.9 (t), 54.9 (t), 53.2 (d), 41.2 (t), 24.9 (d), 23.0 (q), 22.9 (q); *m/z* 328/326 (MH^+), 206/204; Observed (MH^+): 326.1120; $C_{16}H_{25}BrNO$ requires 326.1119.

Preparation of (*R*)-*N*-(2-bromo-2-propenyl)-1-phenyl-2-(phenylmethoxy)ethylamine 5d. To a stirred solution of (*R*)-**8d** (3.50 g, 15.4 mmol) in THF (50 ml) was added 2,3-dibromopropene (1.54 g, 7.70 mmol) dropwise and the resulting solution refluxed for 12 hours. Potassium carbonate (4.20 g, 30.8 mmol) was added and the mixture heated for a further 48 hours. On cooling, the mixture was filtered and the precipitate washed with diethyl ether. The filtrate was washed with 10% sodium hydroxide (2 x 10 ml) and the aqueous phase back extracted with diethyl ether (3 x 15 ml). The combined organic extracts were washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (10% ethyl acetate / petroleum ether using silica pretreated with triethylamine) gave (*R*)-**5d** (2.2 g, 82%) as an orange oil. $[\alpha]_D$ -22.3 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3400, 2924, 1635, 1465 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.25 (10H, m, Ph), 5.66 (1H, bs, =CH), 5.53 (1H, bs, =CH), 4.58 (1H, d, 12.0 Hz, A of AB, CH_2Ph), 4.54

(1H, d, 12.0 Hz, B of AB, CH_2Ph), 4.0 (1H, dd, 8.5, 4.6 Hz, NCH), 3.56-3.46 (2H, m, CH_2OBn), 3.38 (1H, d, 15.3 Hz, A of AB, NCH_2), 3.25 (1H, d, 15.3 Hz, B of AB, NCH_2), 2.56 (1H, bs, NH); δ_C (62.9 MHz, $CDCl_3$) 139.7 (s), 138.0 (s), 133.3 (s), 128.4 (d), 128.3 (d), 127.8 (d), 127.65 (d), 127.61 (d), 127.5 (d), 117.5 (t), 75.2 (t), 73.0 (t), 60.0 (d), 54.7 (t); *m/z* 346 (MH^+), 224, 148, 91; Observed (MH^+): 346.0807; $C_{18}H_{21}NOBr$ requires 346.0807.

Preparation of (*S*)-*N*-(2-bromo-2-propenyl)-1-phenyl-2-(phenylmethoxy)ethylamine 5d. To a stirred solution of (*S*)-**8d** (3.0 g, 13.2 mmol) in THF (50 ml) was added 2,3-dibromopropene (1.32 g, 6.61 mmol) dropwise and the resulting solution refluxed for 12 hours. Potassium carbonate (3.65 g, 26.4 mmol) was added and the mixture heated for a further 48 hours. Work-up and purification as described above gave (*S*)-**5d** (1.95 g, 85%) as an orange oil. $[\alpha]_D$ +24.2 (*c* 1.1, $CHCl_3$). Spectroscopic data for this compound were identical with the (*R*)-enantiomer.

Preparation of (*S*)-2-(2-bromo-2-propenyl)amino-3-methylbutan-1-ol 6. To a stirred solution of (*S*)-valinol (4.0 g, 38.8 mmol) in THF (50 ml) was added 2,3-dibromopropene (3.87 g, 19.4 mmol) dropwise and the resulting solution refluxed for 12 hours. Potassium carbonate (10.7 g, 77.5 mmol) was added and the mixture heated for a further 48 hours. On cooling, the mixture was filtered and the precipitate washed with diethyl ether. The filtrate was washed with 10% sodium hydroxide solution (2 x 10 ml) and the aqueous phase back extracted with diethyl ether (3 x 10 ml). The combined organic extracts were washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (60% ethyl acetate / petroleum ether using silica pretreated with triethylamine) gave **6** (3.47 g, 81%) as a yellow oil. $[\alpha]_D$ +24.6 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3400, 2958, 1630, 1467 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.79 (1H, d, 1.3 Hz, =CH), 5.55 (1H, d, 1.3 Hz, =CH), 3.62 (1H, dd, 10.7, 4.0 Hz, C<u>H</u>OH), 3.54 (1H, d, 14.4 Hz, NCH), 3.42 (1H, d, 14.4 Hz, NCH), 3.36 (1H, dd, 10.7, 6.4 Hz, C<u>H</u>OH), 2.41-2.37 (1H, m, NCH), 2.10 (2H, bs, OH, NH), 1.84-1.76 (1H, m, C<u>H</u>$(CH_3)_3$), 0.98 (3H, d, 6.8 Hz, CH_3), 0.92 (3H, d, 6.8 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) 135.4 (s), 117.7 (t), 62.6 (d), 60.4 (t), 56.1 (t), 28.9 (d), 19.4 (q), 18.5 (q); *m/z* 224/222 (MH^+), 190, 70, 39; Observed (MH^+): 222.0449; $C_8H_{17}BrNO$ requires 222.0489.

Preparation of (*S*)-*N*-(2-bromo-2-propenyl)-2-[1-(*tert*-butyldiphenylsilyloxy)-3-methyl]butylamine 5e. To a stirred solution of **6** (3.0 g, 13.5 mmol), triethylamine (4.1 g, 40.6 mmol) and a catalytic amount of 4-dimethylaminopyridine in dichloromethane (10 ml) was added *tert*-butyldiphenylsilyl chloride (4.08 g, 14.9 mmol). After 4 days, the mixture was diluted with water (15 ml), washed with saturated ammonium chloride (10 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure. Column chromatography (5% ethyl acetate / petroleum ether using silica pretreated with triethylamine) gave **5e** (5.2 g, 83%) as a yellow oil. $[\alpha]_D$ -4.29 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3350, 3100, 2900, 1640, 1466 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.69-7.65 (4H, m, Ph), 7.43-7.35 (6H, m, Ph), 5.77 (1H, d, 1.3 Hz, =CH), 5.50 (1H, d, 1.3 Hz, =CH), 3.69 (1H, dd, 10.3, 4.7 Hz, $CHOSiR_3$), 3.58 (1H, dd, 10.3, 6.3 Hz, $CHOSiR_3$), 3.41 (2H, m, NCH_2), 2.48 (1H, m, NCH) 1.82 (1H, m, C<u>H</u>$(CH_3)_2$) 1.79 (1H, bs, NH), 1.05 (9H, s, ^tBu), 0.88 (3H, d, 6.9 Hz, CH_3), 0.85 (3H, d, 6.9 Hz, CH_3); δ_C (100.9 MHz, $CDCl_3$) 135.5 (d), 134.2 (s), 134.0 (s), 129.6 (d), 127.6 (d), 117.0 (t), 63.3 (t), 62.2 (d), 55.5 (t), 28.4 (d), 26.8 (q), 19.7 (s), 18.6 (q), 18.3 (q); *m/z* 461/459 (M^+), 190, 77; Observed (M^+): 459.1593; $C_{24}H_{34}BrNOSi$ requires 459.1593.

General Method for the Synthesis of Methyleneaziridines 4a-4e. To a three necked flask fitted with a dry ice condenser and gas inlet was added sodium amide (15 equivalents) and the system flushed with

ammonia. A dry ice / acetone mixture was added to the condenser and ammonia was condensed into the flask. The substrate was added to this mixture in a small volume of diethyl ether and the resultant solution stirred for the stated period of time. The reaction mixture was diluted with diethyl ether (20 ml) and quenched by the dropwise addition of water (15 ml) (CAUTION). After the ammonia had evaporated, water (15 ml) and diethyl ether (15 ml) were added and the mixture stirred for 2 minutes. The organic phase was separated and the aqueous phase extracted with diethyl ether. The combined organic extracts were washed with 10% sodium hydroxide, then water, dried over $MgSO_4$ and the solvent removed under reduced pressure to give the crude product which was purified by column chromatography.

(*R*)-1-[2-(1-phenylmethoxy)propyl]-2-methyleneaziridine 4a. Treatment of **5a** (6.30 g, 22.0 mmol) with sodium amide (12.8 g, 330 mmol) in liquid ammonia (120 ml) for 30 minutes as described in the General Method and subsequent column chromatography (30% diethyl ether / petroleum ether) gave **4a** (3.3 g, 73%) as a colourless oil. $[\alpha]_D$ +17.6 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2970, 2857, 1768, 1190, 1101, 698 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.41-7.23 (5H, m, Ph), 4.75 (1H, d, 1.4 Hz, =CH), 4.66 (1H, d, 0.8 Hz, =CH), 4.55 (2H, s, OCH_2Ph), 3.59 (1H, dd, 9.5, 6.4 Hz, CHOBn), 3.48 (1H, dd, 9.5, 5.3 Hz, CHOBn), 2.11-2.10 (3H, m, aziridine CH_2, NCH), 1.20 (3H, d, 6.5 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 138.3 (s), 136.1 (s), 128.(d), 127.5 (d), 127.5 (d), 83.2 (t), 74.6 (t), 73.2 (t), 62.9 (d), 29.6 (t), 17.1 (q); Observed (M^+): 203.1302; $C_{13}H_{17}NO$ requires 203.1310.

(*S*)-1-[2-(3-methyl-1-phenylmethoxy)butyl]-2-methyleneaziridine 4b. Treatment of **5b** (2.25 g, 7.21 mmol) with sodium amide (4.22 g, 108 mmol) in liquid ammonia (100 ml) for 30 minutes as described in the General Method and subsequent column chromatography (15% ethyl acetate / petroleum ether using silica pretreated with triethylamine) gave **4b** (1.28 g, 77%) as a colourless oil. $[\alpha]_D$ -27.1 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2961, 1770, 1467, 1104 cm^{-1}; δ_H (400 MHz, C_6D_6) 7.29-7.11 (5H, m, Ph), 4.77 (1H, m, =CH), 4.67 (1H, bs, =CH), 4.30 (2H, s, CH_2Ph), 3.58 (1H, dd, 9.8, 6.0 Hz, CHOBn), 3.49 (1H, dd, 9.8, 4.4 Hz, CHOBn), 2.06 (1H, d, 0.6 Hz, aziridine CH), 2.04-1.96 (2H, m, $C\underline{H}(CH_3)_2$ and NCH), 1.90 (1H, d, 0.6 Hz, aziridine CH), 1.01 (3H, d, 6.9 Hz, CH_3), 0.98 (3H, d, 6.9 Hz, CH_3); δ_C (100.6 MHz, C_6D_6) 139.1 (s), 136.5 (s), 128.5 (d), 127.3 (d), 127.0 (d), 82.1 (t), 73.3 (t), 71.7 (d), 71.0 (t), 30.9 (d), 29.7 (t), 19.0 (q), 18.6 (q); *m/z* 232 (MH^+), 182, 91; Observed (MH^+) 232.1701, $C_{15}H_{22}NO$ requires 232.1701.

(*S*)-1-[2-(4-methyl-1-phenylmethoxy)pentyl]-2-methyleneaziridine 4c. Treatment of **5c** (2.0 g, 6.14 mmol) with sodium amide (3.60 g, 92.1 mmol) in liquid ammonia (40 ml) for 5 minutes as described in the General Method and subsequent column chromatography (20% diethyl ether / petroleum ether) gave **4c** (1.4 g, 93%) as a colourless oil. $[\alpha]_D$ -10.6 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3090, 3031, 2956, 2868, 1765, 1453, 1366, 1182, 1111, 736, 697 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.37-7.26 (5H, m, Ph), 4.73 (1H, bs, =CH), 4.65 (1H, bs, =CH), 4.58 (1H, d, 12.2 Hz, A of AB, CH_2Ph), 4.55 (1H, d, 12.2 Hz, B of AB, CH_2Ph), 3.57 (2H, *pseudo* d, 4.8 Hz, CH_2OBn), 2.17 (1H, s, aziridine CH), 2.15-2.10 (1H, m, NCH), 2.10 (1H, s, aziridine CH), 1.74-1.64 (1H, m, $C\underline{H}(CH_3)_2$), 1.61-1.54 (1H, m, CH_2),1.49-1.42 (1H, m, CH_2), 0.92 (3H, d, 6.5 Hz, CH_3), 0.88 (3H, d, 6.5 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 136.0 (s) 135.0 (s), 128.3 (d), 127.5 (d), 127.4 (d), 83.1 (t), 73.2 (t), 72.9 (t), 65.1 (d), 41.2 (t), 29.5 (t), 24.7 (d), 23.3 (q), 22.6 (q); *m/z* 246 (MH^+); Observed (MH^+): 246.1858; $C_{16}H_{24}NO$ requires 246.1858.

(*R*)-1-[1-(1-phenyl-2-phenylmethoxy)ethyl]-2-methyleneaziridine 4d. Treatment of (*R*)-**5d** (0.80 g, 2.21 mmol) with sodium amide (1.29 g, 33.2 mmol) in liquid ammonia (20 ml) for 90 seconds as described

in the General Method and subsequent column chromatography (5% ethyl acetate / petroleum ether pretreated with triethylamine) gave (*R*)-**4d** (0.40 g, 68%) as a colourless oil. $[\alpha]_D$ -76.9 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2923, 1745, 1427 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.25 (10H, m, Ph), 4.64 (1H, s, =CH), 4.59 (1H, m, =CH), 4.58 (1H, d, 12.0 Hz, A of AB, CH_2Ph), 4.53 (1H, d, 12.0 Hz, B of AB, CH_2Ph), 3.85 (1H, dd, 9.8, 7.6 Hz, CHOBn), 3.69 (1H, dd, 9.8, 4.6 Hz, CHOBn), 3.11 (1H, dd, 7.6, 4.6 Hz, NCH), 2.23 (1H, bs, aziridine CH), 2.12 (1H, bs, aziridine CH); δ_C (62.9 MHz, $CDCl_3$) 139.7 (s), 138.5 (s), 136.2 (s), 128.2 (d), 127.8 (d), 127.7 (d), 127.5 (d), 84.0 (t), 75.2 (t), 73.2 (t), 72.1 (d), 30.2 (t); *m/z* 266 (MH^+), 144, 117, 91, 77; Observed (MH^+) 266.1545; $C_{18}H_{20}NO$ requires 266.1545.

(*S*)-1-[1-(1-phenyl-2-phenylmethoxy)ethyl]-2-methyleneaziridine 4d. Treatment of (*S*)-**5d** (2.0 g, 5.52 mmol) with sodium amide (3.23 g, 82.9 mmol) in liquid ammonia (50 ml) for 90 seconds as described in the General Method and subsequent column chromatography (5% ethyl acetate / petroleum ether pretreated with triethylamine) gave (*S*)-**4d** (1.0 g, 68%) as a colourless oil. $[\alpha]_D$ +80.8 (*c* 1.1, $CHCl_3$). Spectroscopic data for this compound were identical with the (*R*)-enantiomer.

(*S*)-1-[2-[1-(*tert*-butyldiphenylsilyloxy)-3-methyl]butyl]-2-methyleneaziridine 4e. Treatment of **5e** (1.0 g, 2.17 mmol) with sodium amide (1.27 g, 32.6 mmol) in liquid ammonia (30 ml) for 15 minutes as described in the General Method and subsequent column chromatography (15% ethyl acetate / petroleum ether using silica pretreated with triethylamine) gave **4e** (0.60 g, 73%) as a colourless oil. $[\alpha]_D$ +3.2 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2960, 1770, 1464, 1112 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.69-7.66 (4H, m, Ph), 7.42-7.25 (6H, m, Ph), 4.60 (2H, m, $=CH_2$), 3.80 (1H, dd, 10.7, 6.0 Hz, CHOBn), 3.74 (1H, dd, 10.7, 5.0 Hz, CHOBn), 2.17 (1H, bs, aziridine CH), 2.15 (1H, bs, aziridine CH), 2.11-2.03 (1H, m, $C\underline{H}(CH_3)_2$), 1.87 (1H, m, NCH), 1.03 (9H, s, ^{t}Bu) 0.96 (3H, d, 7.0 Hz, CH_3), 0.93 (3H, d, 7.0 Hz, CH_3); δ_C (100.9 MHz, $CDCl_3$) 135.3 (d), 133.2 (s), 133.1 (s), 129.3 (d), 127.2 (d), 82.4 (t), 73.5 (d), 64.0 (t), 29.9 (t), 29.8 (d), 26.7 (q), 18.8 (s), 18.7 (q), 18.2 (q); *m/z* 380 (MH^+), 256, 110; Observed (MH^+) 380.2410 requires $C_{24}H_{34}NOSi$ 380.2410.

Enantiomeric Purity of Methyleneaziridines 4a-e. With the exception of **4d** for which both enantiomers were already available, the corresponding racemic compounds were prepared for comparison purposes using identical procedures to those described above. The enantiomeric purity of methyleneaziridines (*R*)-**4a**, (*S*)-**4b**, (*S*)- and (*R*)-**4d**, and (*S*)-**4e** were determined by ^{1}H NMR (400 MHz, $CDCl_3$) using 4.2-6.8 molar equivalents of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The following resonances resolved in the presence of the shift reagent for the racemic compounds: **4a** [1.17 (1.5H, d, 6.5 Hz, (*S*)-CH_3), 1.16 (1.5H, d, 6.5 Hz, (*R*)-CH_3)]; **4b** [4.32 (1H, s, (*R*)-OCH_2Ph), 4.30 (1H, s, (*S*)-OCH_2Ph)]; *pseudo* racemate **4d** [3.88 (0.5H, dd, 9.9, 7.9 Hz, (*R*)-CHOBn), 3.87 (0.5H, dd, 9.7, 7.6 Hz, (*S*)-CHOBn)]; **4e** [3.79 (0.5H, d, 10.7 Hz, CHOSi), 3.78 (0.5H, d, 10.7 Hz, CHOSi), 3.75 (0.5H, d, 10.7 Hz, CHOSi), 3.74 (0.5H, d, 10.7 Hz, CHOSi)]. To simplify the analysis of **4e**, the spectra for this compound were acquired with simultaneous selective decoupling at δ1.89 (CHN). Using the chiral methyleneaziridines only one set of resonances could be detected. Addition of known quantities of the racemate to these compounds established that they were all ≥ 95% ee. The enantiomeric purity of methyleneaziridine **4c** was determined to be ≥95% ee by chiral HPLC analysis using a Chiralcel OD column (1% ^{i}PrOH in hexane; 0.4 ml min^{-1}; (*R*)-minor: 11.9 min, (*S*)-major: 13.1 min). The racemate was again used for spiking purposes in this analysis.

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