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Synthesis of New Potential Aminopeptidase Inhibitors by Lewis Acid Induced Rearrangement of 2,3-Epoxy Amines and Regiospecific Nucleophilic Trapping of Aziridinium Ion Intermediates with α-Amino Esters.

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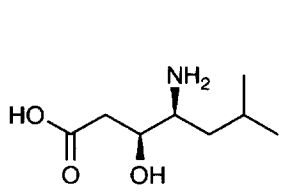
Abstract: Optically active 2,3-epoxy alcohols, prepared using the Sharpless asymmetric epoxidation, are readily converted into 2,3-epoxy amines which, upon treatment with TMSOTf, undergo stereospecific rearrangement to the corresponding 3-trimethylsilyloxy-1,2-aziridinium triflates. These electrophilic species undergo efficient regiospecific nucleophilic ring opening at C-1 using α-amino esters with full control of absolute and relative stereochemistry. The products are structurally related to the known potent aminopeptidase inhibitor bestatin and other biologically active molecules. © 1997 Elsevier Science Ltd.

Enantiomerically pure β-amino alcohols are found in many important biologically active compounds and natural products. Examples are the peptide mimetic statin (**1**)[1] and the protein kinase C inhibitor balanol (**2**).[2] As part of our research programme involving the generation and reactions of 3-membered ring heterocycles (*vide infra*), we became particularly interested in the potent aminopeptidase inhibitor bestatin (**3**)[3] and the development of novel methodology for the synthesis of analogues (e.g. **4**) and related peptide isosteres.



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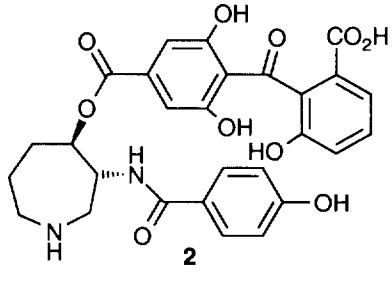

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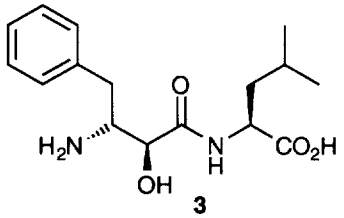

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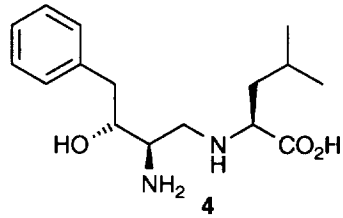

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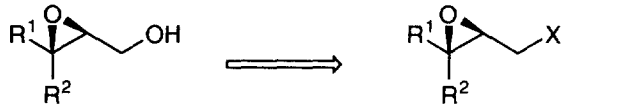
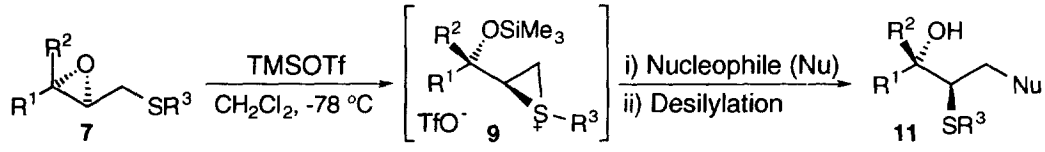
We have recently developed new synthetic methodology based on the chemistry of derivatives of 2,3-epoxy alcohols (**5**), readily available in an optically active form using the Sharpless asymmetric epoxidation,

where the alcohol moiety is replaced by some other heteroatom functionality such as sulfur or nitrogen (**6**).[4]

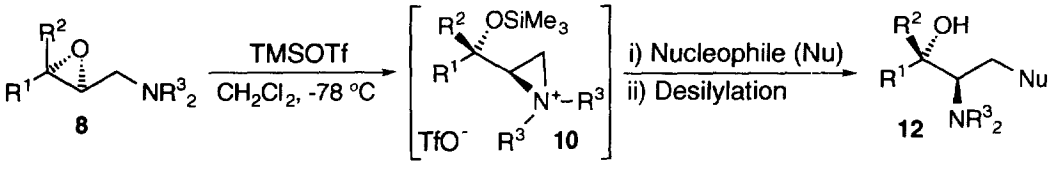


They represent new homochiral building blocks for use in asymmetric synthesis, and have a rich and varied chemistry. Thus under Lewis acidic conditions, a 2,3-epoxy sulfide (**7**) or a 2,3-epoxy amine (**8**) generates reactive thiiranium (**9**)[5] or aziridinium (**10**)[6] ions respectively, which can be regiospecifically trapped with nucleophiles at *C*-1 (scheme 1). They thus allow the preparation of β-hydroxy sulfides (**11**) and β-amino alcohols (**12**) in an optically active form, with full control over both absolute and relative stereochemistry.[4-6]

Thiiranium ion generation and trapping:



Aziridinium ion generation and trapping:



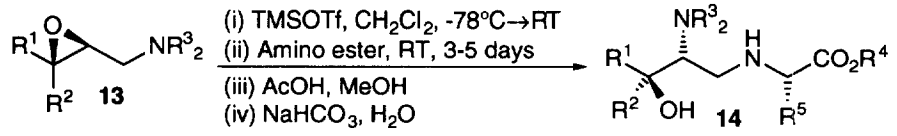
Scheme 1.

In the course of these studies, we became interested in the synthesis of structural analogues of the potent aminopeptidase inhibitor bestatin (**3**).[3] Such compounds are of considerable importance, having activity as immune response modifiers,[7] analgesics by enkephalinase inhibition,[8] and antitumour and antimicrobial properties believed to be associated with their ability to inhibit cell surface aminopeptidases.[9] We therefore felt it would be of interest to embark on a programme to synthesise related potential novel aminopeptidase inhibitors [e.g. (**4**)], to further probe the structural requirements for aminopeptidase inhibitory activity, and in addition provide access to novel peptide isosteres.[11]

We thus needed to develop methodology which would allow the use of α-amino esters as nucleophiles in this rearrangement-nucleophilic trapping sequence (scheme 1). We have previously reported the use of simple amine nucleophiles in this reaction, however only moderate yields of the desired products (40-50%) were obtained along with significant quantities of products resulting from polyalkylation at nitrogen.[6a] We had previously observed in related systems that α-amino ester nucleophiles were much less prone to such polyalkylation reactions,[5a] and hence we began to investigate their reaction with our aziridinium salts (table 1).

The 2,3-epoxy amine substrates were prepared *via* the corresponding homochiral 2,3-epoxy alcohols obtained using a Sharpless asymmetric epoxidation[12] and have been reported previously.[6] Note that diallyl-[13] and dibenzyl-amine[14] derived systems were chosen to allow for ready conversion to the primary amine, which is usually the desired target. The desilylation/workup procedure has been modified from our original conditions[6a] to

avoid problems of ester hydrolysis and/or racemisation. Deprotection of the initially formed *O*-trimethylsilyl ether was achieved using AcOH/MeOH followed by neutralisation using $NaHCO_3$ (aq.).



Entry	R^1	R^2	R^3	Amino ester	Product	Yield (%)
1	^{n}Pr	H	Bn	Ala(OMe)	**14a**	86
2	^{n}Pr	H	allyl	Ala(OMe)	**14b**	79
3	$CH_2OTBDMS$	H	allyl	Ala(OMe)	**14c**	74
4	^{n}Pr	H	Bn	Ala(O^tBu)	**14d**	88
5	^{n}Pr	H	allyl	Ala(O^tBu)	**14e**	84
6	^{n}Pr	H	Bn	Val(OMe)	**14f**	90
7	^{n}Pr	H	allyl	Val(OMe)	**14g**	85
8	^{n}Pr	H	Bn	Phe(OMe)	**14h**	88
9	^{n}Pr	H	allyl	Phe(OMe)	**14i**	81
10	^{n}Pr	H	Bn	Pro(OMe)	**14j**	87
11	H	^{n}Pr	allyl	Ala(OMe)	**14k**	57
12	H	^{n}Pr	Bn	Ala(OMe)	**14l**	62

Table: Coupling of α-amino esters with aziridinium salts derived from 2,3-epoxy amines.

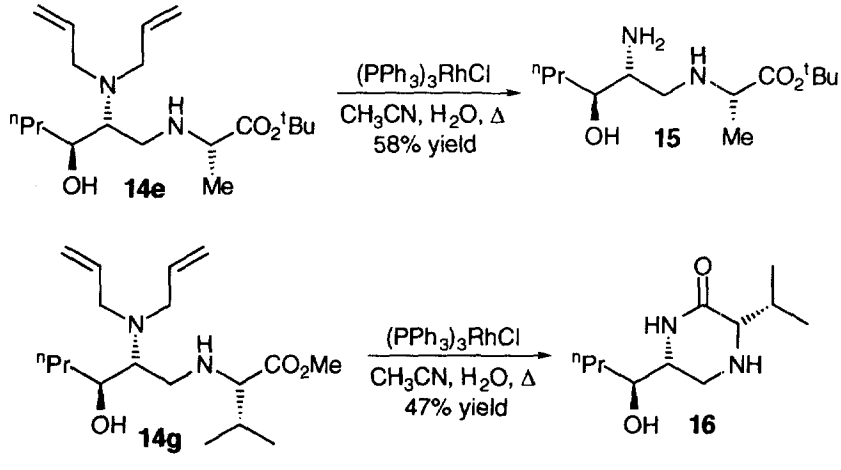
The reported yields are after chromatography, and are for the 3 step process, *viz.* aziridinium ion generation, nucleophilic trapping and deprotection. Note that in all cases, good to excellent overall yields are obtained of diastereomerically pure products (by ^1H and ^{13}C NMR), resulting from regiospecific ring opening of

the aziridinium ion at *C*-1, with no sign of poly-*N*-alkylation. Although there are relatively few synthetic studies on the regioselectivity of aziridinium ion ring opening,[6] in general, ring opening by nucleophilic attack at a primary position is favoured over competing secondary sites, although selectivity is nucleophile dependent. In our case, the likely electronic deactivating effect of the *C*-3 ether substuent with respect to attack at *C*-2, along with considerable steric crowding, leads to exclusive ring opening at *C*-1.

Note that the relative stereochemical configuration at *C*-2 and *C*-3 is controlled by the initial epoxide geometry, and that epoxides derived from *Z*-allylic alcohols give the required relative stereochemical configuration (entries 11 and 12) for bestatin-like products (e.g. 4). The reaction is equally successful for both methyl and *tert*-butyl α-amino esters (*cf.* entries 1 and 4), which has important consequences for subsequent synthetic manipulation (*vide infra*).

This new methodology allows for the coupling of amino acid equivalents with adjacent amino alcohol functionality, under very mild conditions. The aziridinium salt intermediates are sufficiently reactive to couple with relatively weak nucleophiles such as primary amines, whereas procedures involving less reactive aziridine derivatives (e.g. *N*-acyl- and *N*-sulfonyl-aziridines) would require harsher reaction conditions which could compromise the stereochemical integrity of the amino acid moiety.[14]

The main drawback of this procedure is that primary amines are usually the eventual target molecules, and so the tertiary amine groups in our products must be deprotected. We have recently reported the efficient deprotection of diallyl groups under acidic conditions ($MeSO_3H$, Pd/C)[6a] in related products which do not contain readily epimerisable chiral centres, however milder conditions were envisaged as being desirable for amino ester-containing substrates. Thus the allyl groups of typical products (**14e**) and (**14g**) are readily deprotected to give the primary amine (scheme 2), under mild, essentially neutral conditions using $(PPh_3)_3RhCl$ in CH_3CN/H_2O.[13] Note again, that much harsher reaction conditions would be required to deprotect the initial amide and sulfonamide products available using related aziridine chemistry, which again would be likely to compromise the stereochemical integrity of the amino acid moiety.[14] So far we have seen no indication that this is a problem in our systems. Interestingly the *tert*-butyl ester (**14e** from entry 5, table 1) is cleanly deprotected to give the required primary amine (**15**), whereas the methyl ester (**14g** from entry 7, table 1) is deprotected but cyclises under the reaction conditions to give the 2-ketopiperazine (**16**). Further studies on improving the yield and generality of these and other deprotection strategies are currently underway and will be reported in due course.[16]



Scheme 2.

In conclusion, we have developed a mild and efficient method for the coupling of aziridinium salts derived from homochiral 2,3-epoxy amines, with α-amino ester nucleophiles, and have demonstrated in principle that the products of such reactions can be converted into amino alcohol-substituted α-amino esters with full stereochemical control. We are currently exploiting this methodology for the synthesis of molecules of biological importance, and this and information on biological activity of the products will be reported in due course.

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Experimental Section.

General Procedures and Instrumentation.

Melting points were determined on a Reichert Hot Stage apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a General Electric QE 300 spectrometer or a Bruker AM400 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield of tetramethylsilane for ^{1}H resonances, and referenced to the central peak of the deuterated chloroform triplet for ^{13}C resonances. Infrared spectra were recorded on a Philips PU 8706 infrared spectrophotometer and signals were referenced to the polystyrene 1601 cm^{-1} absorbtion. Mass spectra were recorded on a VG Autospec mass spectrometer. Optical rotations were measured on an Optical Activity AA-1000 polarimeter and calibrated using a solution of camphor in ethanol of known rotation, $[\alpha]_D^{20}$ +44.1° (*c* 10, ethanol). Microanalyses were carried out at the University of Leeds Microanalytical Laboratory. All C, H, N, and S analytical figures are percentage values. Flash chromatography signifies column chromatography on Merck silica gel (230-400) or equivalent according to the method of Still.[17] Thin layer chromatography was carried out using precoated aluminium (or plastic) backed silica plates which were visualised using either ultraviolet light, permanganate or anisaldehyde stain. All glassware was washed with acetone, oven dried overnight at 125°C and allowed to cool under a stream of dry nitrogen prior to use. Reactions were carried out under a positive pressure of dry oxygen - free nitrogen. Solvents were removed under reduced pressure using a Buchi rotary evaporator at water aspirator pressure, followed by drying under high vacuum at 0.5 mm Hg. Solvents were purified prior to use by established procedures[18] and other reagents used as received. Trimethylsilyl trifluoromethanesulfonate was obtained from Aldrich Chemical Company Ltd. and used immediately upon opening. Petroleum ether refers to petroleum ether (b.p. 40-60°C) unless otherwise stated. α-Amino esters were liberated from commercial samples of their hydrochloride salts by treatment with saturated aqueous sodium hydrogen carbonate solution, extraction into chloroform, drying with magnesium sulfate and concentration as previously reported.[5a] The 2,3-epoxy amine substrates (>96% e.e.) have been reported previously.[6a] Enantiomeric excesses were determined using $Eu(hfc)_3$ on the acetate derivatives of the 2,3-epoxy alcohols prepared by Sharpless epoxidation. The products of coupling with homochiral amino esters were single diastereoisomers, which provides further evidence of enantiomeric purity.

Experimental details.

Table: Coupling of α-amino esters with aziridinium salts derived from 2,3-epoxy amines.

(-)-*N*-[(2*R*, 3*S*)-2-*N*, *N*-Dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a).

Trimethylsilyl trifluoromethanesulfonate (0.24 g, 0.21 cm^3, 1.10 mmol) was added to a solution of (-)-(2*S*, 3*S*)-1-*N*,*N*-dibenzylamino-2,3-epoxyhexane (0.27 g, 0.92 mmol) in dichloromethane (6 cm^3) at -78°C under nitrogen. After 10 mins, *L*-alanine methyl ester (0.19 g, 1.83 mmol) was added to the solution which was then allowed to warm to room temperature and stirred for 96 h. Methanol (4 cm^3) and acetic acid (0.22 g, 0.21

cm^3, 3.68 mmol) were added to it and the mixture stirred for a further 5 h. The solvents were then removed *in vacuo*. Sodium hydrogen carbonate (0.62 g, 7.36 mmol) in water (20 cm^3) and chloroform (15 ml) were then added to the residue which was stirred for 20 mins. The organic layer was separated and the aqueous layer was extracted with chloroform (3 x 15 cm^3). The organic extracts were combined and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by column chromatography on flash silica [2:1 ethyl acetate:light petroleum] to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (0.31 g, 0.78 mmol, 86% yield) as a colourless oil: $[\alpha]_D^{20}$ -80.7° (*c* 1.2 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.92 (3 H, t, J 6.9, CH_2CH_3,), 1.21-1.40 (3 H, m, CH_2CH_3 and one of $CH_2CH_2CH_3$). 1.26 (3 H, d, J 6.9, $CHCH_3$), 1.83-1.90 (1 H, m, one of $CH_2CH_2CH_3$), 2.51 (1 H, dt, J 9.3, 3.3, $CHN(Bn)_2$), 2.92 (1 H, dd, J 12.0, 9.3, one of CH_2NH), 3.04 (1 H, dd, J 12.0, 3.3, one of CH_2NH), 3.31 (1 H, q, J 6.9, $CHCH_3$), 3.46 (2 H, d, J 13.5, benzylic CH_2), 3.77 (2 H, d, J 13.5, benzylic CH_2), 3.80 (3 H, s, CO_2CH_3), 3.95 (1H, dt, J 8.4, 3.3, CHOH), 7.21-7.40 (10 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 14.21 (1 C, CH_2CH_3), 18.31 (1 C, CH_2CH_3), 18.84, (1 C, $CHCH_3$), 37.31 (1 C, $CH_2CH_2CH_3$), 45.16 (1 C, CH_2NH), 52.02 (1 C, CO_2CH_3), 54.46 (2 C, benzylic CH_2), 55.38 (1 C, $CHCH_3$), 58.40 (1 C, $CHN(Bn)_2$), 73.91(1 C, CHOH), 127.02, 128.26, 128.79, 139.60 (12 C, Ar), 175.46 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3300 (m, br.), 3080 (w), 3050 (w), 3020 (w), 2940 (s, CH), 2910 (m), 2850 (m), 1730 (s, C=O), 1590 (w), 1485 (m), 1440 (s), 1360 (m), 1320 (w), 1190 (m), 1150 (w), 1110 (w), 1060 (m), 1020 (w), 960 (w), 900 (w), 735 (s), 690 (s); MS (EI) m/z 399 (M^++1, 9%), 339 (17), 325 (37), 307 (19), 282 (91), 265 (19), 236 (24), 223 (19), 210 (10), 190 (26), 132 (37), 118 (7), 106 (9), 91(100), 65 (23), 56 (36), 43 (12); (Found, C, 72.35, H, 8.55, N, 7.0. Calc. for $C_{24}H_{34}N_2O_3$: C, 72.36, H, 8.54, N, 7.04%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Diallylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14b).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*, 3*S*)-1-*N*,*N*-diallylamino-2,3-epoxyhexane (0.38 g, 1.95 mmol), trimethylsilyl trifluoromethanesulfonate (0.52 g, 0.45 cm^3, 2.34 mmol), *L*-alanine methyl ester (0.40 g, 3.90 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-trimethylsilyloxyhexyl]-*L*-alanine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.47 g, 0.45 cm^3, 7.80 mmol), methanol (6 cm^3), sodium hydrogen carbonate (1.31 g, 15.6 mmol), and water (20 cm^2). The product was purified by column chromatography on flash silica [2:1 ethyl acetate:light petroleum] to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (0.46 g, 1.54 mmol, 79% yield) as a colourless oil: $[\alpha]_D^{20}$ -54.5° (*c* 1.13 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, t, J 7.2, CH_2CH_3), 1.28 (3 H, d, J 7.0, $CHCH_3$), 1.34-1.41 (2 H, m, CH_2CH_3), 1.51-1.58 (1 H, m, one of $CH_2CH_2CH_3$), 1.66-1.71 (1 H, m, one of $CH_2CH_2CH_3$), 2.57 (1 H, dt, J 6.9, 5.4, $CHN(allyl)_2$), 2.81 (2 H, d, J 6.7, CH_2NH), 3.01 (2 H, dd, J 14.4, 7.6, allylic CH_2), 3.25 (2 H, dd, J 14.3, 5.0, allylic CH_2), 3.39, (1 H, q, J 7.0, $CHCH_3$), 3.74 (3 H, s, CO_2CH_3), 3.83 (1 H, dt, J 8.1, 3.1, CHOH), 5.09-5.14 (4 H, m, $CH=CH_2$ x 2), 5.72-5.82 (2 H, m, $CH=CH_2$ x 2); δ_C(75 MHz; $CDCl_3$) 14.23 (1 C, CH_2CH_3), 18.76 (1 C, CH_2CH_3), 18.93 (1 C, $CHCH_3$), 37.66 (1 C, $CH_2CH_2CH_3$), 45.24 (1 C, CH_2NH), 51.91 (1 C, CO_2CH_3), 53.21 (2 C, $CH_2CH=CH_2$ x 2), 55.57 (1 C, $CHCH_3$), 59.67 (1 C, $CHN(allyl)_2$), 73.77 (1 C, CHOH), 116.72 (2 C, $CH=CH_2$ x 2), 136.80 (2 C, $CH=CH_2$ x 2), 175.49 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3300 (m, br.), 3060 (w), 2940 (s, CH), 2910 (s), 2850 (m), 1735 (s, C=O), 1630 (w), 1440 (s), 1410 (m), 1360 (w), 1250 (w), 1190 (s), 1150 (m), 1065 (m), 990 (w), 910 (s), 840 (w), 775 (w). MS (EI) m/z 298 (M^+, 6%), 269 (5), 257 (16), 239 (7), 225 (13), 182(100), 140 (31), 122 (11), 110 (12), 96 (8), 81 (7), 70 (22), 56 (24), 41 (36). (Found, C, 64.35, H, 10.00, N, 9.40. Calc. for $C_{16}H_{30}N_2O_3$: C, 64.43, H, 10.07, N, 9.40%).

(-)-*N*-[(2*R*,3*R*)-2-*N*,*N*-Diallylamino-3-hydroxy-4-*tert*-butyldimethylsilyloxybutyl]-*L*-alanine methyl ester (14c).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (2*S*,3*S*)-1-*N*,*N*-diallylamino-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutane (0.20 g, 0.67 mmol), trimethylsilyl trifluoromethanesulfonate (0.18 g, 0.16 cm^3, 0.81 mmol), *L*-alanine methyl ester (0.14 g, 1.35 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*R*)-2-*N*,*N*-diallylamino-4-*tert*-butyldimethylsilyloxy-3-trimethylsilyloxy-butyl]-*L*-alanine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.16 g, 0.15 cm^3, 2.68 mmol), methanol (4 cm^3), sodium hydrogen carbonate (0.45 g, 5.36 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica [1:1 ethyl acetate:light petroleum] to give *N*-[(2*R*,3*R*)-2-*N*,*N*-diallylamino-3-hydroxy-4-*tert*-butyldimethylsilyloxybutyl]-*L*-alanine methyl ester (0.20 g, 0.50 mmol, 74% yield) as a colourless oil: $[\alpha]_D^{20}$ -23.6° (*c* 1.00 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.07 (6 H, s, $Si(CH_3)_2$), 0.90 (9 H, s, $C(CH_3)_3$), 1.29 (3 H, d, J 7.0, $CHCH_3$), 2.74-2.83 (3 H, m, CH_2NH, and $CHN(allyl)_2$), 3.11 (2 H, dd, J 14.4, 6.9, allylic CH_2), 3.22 (2 H, dd, J 14.5, 5.5, allylic CH_2), 3.37 (1 H, q, J 7.0, $CHCH_3$), 3.60 (1 H, dd, J 10.2, 6.4, one of $TBDMSOCH_2$), 3.71 (1 H, dd, J 10.0, 4.0, one of $TBDMSOCH_2$), 3.73 (3 H, s, CO_2CH_3), 3.83 (1 H, dt, J 6.2, 4.2, CHOH), 5.08-5.14 (4 H, $CH=CH_2$ x 2), 5.71-5.81 (2 H, m, $CH=CH_2$ x 2); δ_C(75 MHz; $CDCl_3$) 5.26 (2 C, $Si(CH_3)_2$), 18.34 (1 C, $C(CH_3)_3$), 18.84 (1 C, $CHCH_3$), 25.95 (3 C, $C(CH_3)_3$), 44.96 (1 C, CH_2NH), 51.79 (1 C, CO_2CH_3), 53.34 (2 C, $CH_2CH=CH_2$ x 2), 56.13 (1 C, $CHCH_3$), 57.67 (1 C, $CHN(allyl)_2$), 65.77 (1 C, $TBDMSOCH_2$), 72.95 (1 C, CHOH), 116.55 (2 C, $CH=CH_2$ x 2), 136.94 (2 C, $CH=CH_2$ x 2), 175.63 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3300 (m, br.), 3060 (w), 2940 (s, CH), 2920 (s), 2840 (s), 1730 (s, C=O), 1635 (w), 1450 (s), 1350 (w), 1245 (m), 1195 (m), 1100 (s), 1060 (w), 980 (m), 910 (m), 830 (s), 770 (s). MS (EI) m/z 400 (M^+, 8%), 385 (17), 371 (42), 359 (25), 341 (92), 298 (5), 284 (85), 256 (7), 225 (7), 122 (7), 110 (100), 89 (20), 73 (46), 56 (19), 41 (47). (Found, C, 60.25, H, 10.25, N, 6.90. Calc. for $C_{20}H_{40}N_2O_4Si$: C, 60.00, H, 10.00, N, 7.00%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Dibenzylamino-3-hydroxy]hexyl-*L*-alanine *tert*-butyl ester (14d).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (2*S*,3*S*)-1-*N*,*N*-dibenzylamino-2,3-epoxyhexane (0.34 g, 1.15 mmol), trimethylsilyl trifluoromethanesulfonate (0.31 g, 0.27 cm^3, 1.38 mmol), *L*-alanine *tert*-butyl ester (0.33 g, 2.30 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-trimethylsilyloxy]hexyl-*L*-alanine *tert*-butyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.28 g, 0.26 cm^3, 4.60 mmol), methanol (5 cm^3), sodium hydrogen carbonate (0.77 g, 9.20 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica [1:1 ethyl acetate:light petroleum] to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine *tert*-butyl ester. (0.45 g, 1.02 mmol, 88% yield) as a colourless oil: $[\alpha]_D^{20}$ -78.3° (*c* 1.14 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.90 (3 H, t, J 7.0, CH_2CH_3), 1.19 (3 H, d, J 7.0, $CHCH_3$), 1.22-1.38 (3 H, m, CH_2CH_3, one of $CH_2CH_2CH_3$), 1.54 (9 H, s, $C(CH_3)_3$), 1.83-1.90 (1 H, m, one of $CH_2CH_2CH_3$), 2.47 (1 H, ddd, J 9.9, 8.3, 2.8, $CHN(Bn)_2$), 2.93 (1 H, dd, J 12.3, 9.9, one of CH_2NH), 3.06 (1 H, dd, J 12.4, 2.8, one of CH_2NH), 3.17 (1 H, q, J 7.0, $CHCH_3$), 3.42 (2 H, d, J 13.5, benzylic CH_2), 3.78 (2 H, d, J 13.5, benzylic CH_2), 3.94 (1 H, dt, J 8.4, 3.1, CHOH), 7.21- 7.35 (10 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 14.23 (1 C, CH_2CH_3), 18.20 (1 C, CH_2CH_3), 18.95 (1 C, $CHCH_3$), 28.18 (3 C, $C(CH_3)_3$), 37.19 (1 C, $CH_2CH_2CH_3$), 45.00 (1 C, CH_2NH), 54.44 (2 C, benzylic CH_2), 55.86 (1 C, $CHCH_3$), 57.78 (1 C, $CHN(Bn)_2$), 74.22 (1 C, CHOH), 81.41 (1 C, $C(CH_3)_3$), 127.02, 128.24, 128.84, 139.64 (12 C, Ar), 174.56 (1 C, $CO_2C(CH_3)_3$); ν_{max}(thin film)/cm^{-1} 3310 (m, br.), 3075 (w), 3050 (w), 3020 (w), 2950 (s, CH), 2930 (s), 2870 (m), 1725 (s, C=O), 1605 (w), 1490 (w), 1450 (s), 1390 (w), 1360 (s), 1325 (w), 1250 (w), 1215 (w), 1150 (w), 1115 (m), 1065 (m), 1025 (w), 960 (w), 910 (w), 845 (m), 740 (s), 695 (s). MS (EI) m/z 440 (M^+, 6%), 339 (9), 282 (100), 265 (7), 236 (7), 190 (6), 132 (10), 91 (96), 57 (10). (Found, C, 73.65, H, 9.15, N, 6.1. Calc. for $C_{27}H_{40}N_2O_3$: C, 73.64, H, 9.09, N, 6.36%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Diallylamino-3-hydroxyhexyl]-*L*-alanine *tert*-butyl ester (14e).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*,3*S*)-1-*N*,*N*-diallylamino-2,3-epoxyhexane (0.28 g, 1.44 mmol), trimethylsilyl trifluoromethanesulfonate (0.38 g, 0.33 cm^3, 1.72 mmol), *L*-alanine *tert*-butyl ester (0.42 g, 2.88 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-trimethylsilyloxyhexyl]-*L*-alanine *tert*-butyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.35 g, 0.33 cm^3, 5.76 mmol), methanol (5 cm^3), sodium hydrogen carbonate (0.97 g, 11.5 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica [1:1 ethyl acetate:light petroleum] to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-hydroxyhexyl]-*L*-alanine *tert*- butyl ester (0.41 g, 1.21 mmol, 84% yield) as a colourless oil: $[\alpha]_D^{20}$ -46.7° (*c* 1.07 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, t, J 7.2, CH_2CH_3), 1.22 (3 H, d, J 7.0, $CHCH_3$), 1.33-1.42 (2 H, m, CH_2CH_3), 1.48 (9 H, s, $C(CH_3)_3$), 1.51-1.57 (1 H, m, one of $CH_2CH_2CH_3$), 1.69-1.74 (1 H, m, one of $CH_2CH_2CH_3$), 2.55 (1 H, dt, J 7.6, 4.3, $CHN(allyl)_2$), 2.80-2.82 (2 H, m, CH_2NH), 2.97 (2 H, dd, J 14.3, 7.7, allylic CH_2), 3.22-3.27 (3 H, m, allylic CH_2, and $CHCH_3$), 3.82 (1 H, dt, J 7.8, 3.0, CHOH), 5.09-5.15 (4 H, m, $CH=CH_2$ x 2), 5.72-5.82 (2 H, m, $CH=CH_2$ x 2); δ_C(75 MHz; $CDCl_3$) 14.26 (1 C, CH_2CH_3), 18.68 (1 C, CH_2CH_3), 18.96 (1 C, $CHCH_3$), 28.10 (3 C, $C(CH_3)_3$), 37.62 (1 C, $CH_2CH_2CH_3$), 45.21 (1 C, CH_2NH), 53.20 (2 C, $CH_2CH=CH_2$ x 2), 56.10 (1 C, $CHCH_3$), 59.17 (1 C, $CHN(allyl)_2$), 74.19 (1 C, CHOH), 81.25 (1 C, $C(CH_3)_3$), 116.66 (2 C, $CH=CH_2$ x 2), 136.93 (2 C, $CH=CH_2$ x 2), 174.52 (1 C, $CO_2C(CH_3)_3$); ν_{max}(thin film)/cm^{-1} 3300 (m, br.), 3070 (m), 2960 (s, CH), 2920 (s), 2860 (m), 1725 (s, C=O), 1635 (m), 1450 (m), 1410 (w), 1390 (w), 1365 (m), 1250 (w), 1210 (w), 1150 (s), 1070 (w), 990 (m), 910 (s), 840 (m). MS (EI) m/z 340 (M^+, 35%), 325 (5), 311 (19), 299 (77), 283 (15), 267 (10), 239 (28), 211 (12), 182 (100), 165 (6), 140 (26), 123 (17), 110 (16), 96 (9), 82 (8), 70 (23), 56 (26). (Found, C, 67.25, H, 10.8, N, 8.1. Calc. for $C_{19}H_{36}N_2O_3$: C, 67.06, H, 10.59, N, 8.24%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Dibenzylamino-3-hydroxyhexyl]-*L*-valine methyl ester (14f).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*,3*S*)-1-*N*,*N*-dibenzylamino-2,3-epoxyhexane (0.34 g, 1.15 mmol), trimethylsilyl trifluoromethanesulfonate (0.31 g, 0.27 cm^3, 1.38 mmol), *L*-valine methyl ester (0.30 g, 2.30 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-trimethylsilyloxy]hexyl-*L*-valine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.28 g, 0.26 cm^3, 4.60 mmol), methanol (6 cm^3), sodium hydrogen carbonate (0.77 g, 9.20 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica (1:1 ethyl acetate:light petroleum) to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-valine methyl ester (0.44 g, 1.03 mmol, 90% yield) as a colourless oil: $[\alpha]_D^{20}$ -70.6° (*c* 1.11 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.87-0.92 (9 H, m, CH_2CH_3, $CH(CH_3)_2$), 1.25-1.35 (3 H, m, CH_2CH_3 and one of $CH_2CH_2CH_3$), 1.80-1.94 (2 H, m, $CH(CH_3)_2$ and one of $CH_2CH_2CH_3$), 2.49 (1 H, dt, J 8.6, 3.1, $CHN(Bn)_2$), 2.90 (1 H, dd, J 12.4, 3.0, one of the CH_2NH), 2.97-3.02 (2 H, m, $CH(CO_2Me)$ and one of CH_2NH), 3.45 (2 H, d, J 13.5, benzylic CH_2), 3.79 (2 H, d, J 13.5, benzylic CH_2), 3.82 (3 H, s, CO_2CH_3), 3.94 (1H, dt, J 7.8, 2.7, CHOH), 7.22-7.26 (2 H, m, ArH), 7.29-7.35 (8 H, m, ArH); (75 MHz; $CDCl_3$) 14.21 (1 C, CH_2CH_3), 18.17 (1 C, CH_2CH_3), 18.49 (1 C, one of $CH(CH_3)_2$), 19.29 (1 C, one of $CH(CH_3)_2$), 31.42 (1 C, $CH(CH_3)_2$), 37.22 (1 C, $CH_2CH_2CH_3$), 45.86 (1 C, CH_2NH), 51.71 (1C, CO_2CH_3), 54.51 (2 C, benzylic CH_2), 58.01 (1 C, $CHN(Bn)_2$), 66.21 (1 C, $CH(CO_2Me)$ 73.90 (1 C, CHOH), 127.01, 128.22, 128.83, 139.64 (12 C, Ar), 174.89 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3320 (m, br.), 3080 (w), 3060 (w), 3025 (w), 2960 (s, CH), 2930 (m), 2870 (m), 2840 (m), 1730 (s, C=O), 1605 (w), 1495 (m), 1455 (s), 1430 (m), 1365 (m), 1310 (w), 1245 (w), 1200 (s), 1180 (w), 1160 (w), 1110 (m), 1070 (m), 1025 (m), 990 (w), 960 (w), 905 (w), 845 (w), 750 (s), 700 (s). MS (EI) m/z 427 (M^++1, 6%), 383 (23), 353 (12), 335 (6), 282 (89), 223 (6), 190 (8), 132 (16), 91 (100), 65 (9), 55

(12), 43 (8). (Found, C, 73.0, H, 8.95, N, 6.4. Calc. for $C_{26}H_{38}N_2O_3$: C, 73.24, H, 8.92, N, 6.57%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Diallylamino-3-hydroxyhexyl]-*L*-valine methyl ester (14g).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*,3*S*)-1-*N*,*N*-diallylamino-2,3-epoxyhexane (0.28 g, 1.44 mmol), trimethylsilyl trifluoromethane sulfonate (0.38 g, 0.33 cm^3, 1.72 mmol), *L*-valine methyl ester (0.38 g, 2.87 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-trimethylsilyloxyhexyl]-*L*-valine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.35 g, 0.33 cm^3, 5.76 mmol), methanol (6 cm^3), sodium hydrogen carbonate (0.97 g, 11.5 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica (1:1 ethyl acetate:light petroleum) to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-hydroxyhexyl]-*L*-valine methyl ester (0.40 g, 1.23 mmol, 85% yield) as a colourless oil: $[\alpha]_D^{20}$ -41.8° (*c* 1.09 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.86-0.93 (9 H, m, CH_2CH_3, $CH(CH_3)_2$), 1.33-1.39 (2 H, m, CH_2CH_3), 1.48-1.57 (1 H, m, one of $CH_2CH_2CH_3$), 1.63-1.67 (1 H, m, one of $CH_2CH_2CH_3$), 1.86-1.93 (1 H, m, $CH(CH_3)_2$), 2.54 (1 H, dt, J 8.1, 2.1, $CHN(allyl)_2$), 2.69 (1 H, dd, J 12.6, 2.7, one of CH_2NH), 2.85 (1 H, dd, J 12.6, 8.7, one of CH_2NH), 2.97 (2 H, dd, J 14.1, 7.8, allylic CH_2), 3.04 (1 H, d, J 6.0, $CH(CO_2Me)$), 3.25 (2 H, dd, J 14.1, 4.5, allylic CH_2), 3.74 (3 H, s, CO_2CH_3), 3.81 (1 H, dt, J 8.1, 3.6, *CH*OH), 5.09-5.14 (4 H, m, $CH=CH_2$ x 2), 5.69-5.81 (2 H, m, $CH=CH_2$ x 2); δ_C(75 MHz; $CDCl_3$) 14.24 (1 C, CH_2CH_3),18.56 (1 C, one of $CH(CH_3)_2$), 18.72 (1 C, CH_2CH_3), 19.37 (1 C, one of $CH(CH_3)_2$), 31.44 (1 C, $CH(CH_3)_2$), 37.65 (1 C, $CH_2CH_2CH_3$), 45.92 (1 C, CH_2NH), 51.56 (1 C, CO_2CH_3), 53.19 (2 C, $CH_2CH=CH_2$ x 2), 59.19 (1 C, $CHN(allyl)_2$), 66.37 (1 C, $CH(CO_2Me)$), 73.81 (1 C, CHOH), 116.66 (2 C, $CH=CH_2$ x 2), 136.86 (2 C, $CH=CH_2$ x 2), 174.86 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3310 (m, br.), 3075 (m), 2950 (s, CH), 2920 (s), 2860 (m), 1735 (s, C=O), 1637 (m), 1455 (s), 1430 (m), 1410 (w), 1385 (w), 1365 (w), 1345 (w), 1310 (w), 1260 (w), 1190 (m), 1170 (m), 1145 (m), 1090 (m), 990 (s), 910 (s), 840 (w), 790 (w). MS (EI) m/z 326 (M^+, 4%), 297 (14), 285 (15), 267 (4), 253 (7), 229 (10), 212 (19), 205 (9), 196 (19), 182 (100), 164 (5), 152 (8), 136 (12), 123 (18), 110 (14), 96 (11), 84 (14), 70 (14), 55 (25), 41 (54). (Found, C, 66.0, H, 10.7, N, 8.45. Calc. for $C_{18}H_{34}N_2O_3$: C, 66.26, H, 10.43, N, 8.59%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Dibenzylamino-3-hydroxyhexyl]-*L*-phenylalanine methyl ester (14h).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*,3*S*)-1-*N*,*N*-dibenzylamino-2,3-epoxyhexane (0.37 g, 1.25 mmol), trimethylsilyl trifluoromethane sulfonate (0.33 g, 0.29 cm^3, 1.51 mmol), *L*-phenylalanine methyl ester (0.45 g, 2.51 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-trimethylsilyloxyhexyl]-*L*-phenylalanine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.30 g, 0.29 cm^3, 5.00 mmol), methanol (6 cm^3), sodium hydrogen carbonate (0.84 g, 10.0 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica (1:1 ethyl acetate:light petroleum) to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-phenylalanine methyl ester (0.52 g, 1.10 mmol, 88% yield) as a colourless oil: $[\alpha]_D^{20}$ -43.0° (*c* 1.20 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, J 7.2, CH_2CH_3), 1.17-1.32 (3 H, m, CH_2CH_3, and one of $CH_2CH_2CH_3$), 1.73-1.77 (1 H, m, one of $CH_2CH_2CH_3$), 2.39 (1 H, dt, J 6.9, 6.9, $CHN(Bn)_2$), 2.81-2.99 (4 H, m, CH_2NH and $CHCH_2(C_6H_5)$), 3.39 (2 H, d, J 13.5, *N*-benzylic CH_2), 3.47 (1 H, t, J 6.9, $CH(CO_2Me)$), 3.73 (2 H, d, J 13.5, *N*-benzylic CH_2), 3.75 (3 H, s, CO_2CH_3), 3.90 (1 H, dt, J 7.8, 3.0, *CH*OH), 7.08-7.11 (2 H, m, ArH), 7.14-7.33 (13 H, m, ArH); (75 MHz; $CDCl_3$) 14.18 (1 C, CH_2CH_3), 18.26 (1 C, CH_2CH_3), 37.33 (1 C, $CH_2CH_2CH_3$), 39.38 (1 C, $CHCH_2(C_6H_5)$), 45.44 (1 C, CH_2NH), 51.94 (1 C, CO_2CH_3), 54.50 (2 C, *N*-benzylic CH_2), 58.79 (1 C, $CHN(Bn)_2$), 61.87 (1 C, $CH(CO_2Me)$), 73.40 (1 C, CHOH), 126.91, 126.99, 128.25, 128.57, 128.79, 129.12, 136.61, 139.59 (18 C, Ar), 174.24 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1}

3300 (m, br.), 3080 (w), 3060 (w), 3025 (m), 2945 (s, CH), 2920 (m), 2860 (m), 1735 (s, C=O), 1600 (w), 1490 (m), 1450 (s), 1360 (w), 1200 (m), 1165 (w), 1110 (w), 1065 (w), 1025 (w), 740 (s), 690 (s); MS (EI) m/z 475 (M^++1, 7%), 415 (16), 401 (49), 383 (32), 282 (85), 265 (21), 252 (9), 236 (29), 210 (19), 190 (49), 181 (40), 164 (14), 149 (11), 132 (71), 120 (31), 104 (48), 91 (100), 77 (23), 65 (59), 55 (39), 41 (34). (Found, C, 76.2, H, 8.1, N, 6.15. Calc. for $C_{30}H_{38}N_2O_3$: C, 75.95, H, 8.02, N, 5.91%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Diallylamino-3-hydroxyhexyl]-*L*-phenylalanine methyl ester (14i).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*,3*S*)-1-*N*,*N*-diallylamino-2,3-epoxyhexane (0.29 g, 1.49 mmol), trimethylsilyl trifluoromethane sulfonate (0.40 g, 0.34 cm^3, 1.78 mmol), *L*-phenylalanine methyl ester (0.53 g, 2.97 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-trimethylsilyloxyhexyl]-*L*-phenylalanine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.36 g, 0.34 cm^3, 5.96 mmol), methanol (6 cm^3), sodium hydrogen carbonate (1.00 g, 11.9 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica [1:1 ethyl acetate:light petroleum] to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-hydroxyhexyl]-*L*-phenylalanine methyl ester (0.45 g, 1.20 mmol, 81% yield) as a colourless oil: $[\alpha]_D^{20}$ -24.7° (*c* 1.36 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.91(3 H, t, J 7.1, CH_2CH_3), 1.27-1.35 (2 H, m, CH_2CH_3), 1.45-1.57 (1 H, m, one of $CH_2CH_2CH_3$), 1.58-1.62 (1 H, m, one of $CH_2CH_2CH_3$), 2.52 (1 H, dt, J 6.8, 3.9, $CHN(allyl)_2$), 2.70 (1 H, dd, J 12.1, 3.9, one of CH_2NH), 2.80 (1 H, dd, J 12.1, 7.9, one of CH_2NH), 2.87-3.01 (4 H, m, allylic CH_2 and $CH_2(C_6H_5)$), 3.18 (2 H, dd, J 14.4, 5.2, allylic CH_2), 3.53 (1 H, dd, J 7.3, 6.2, $CH(CO_2Me)$), 3.69 (3 H, s, CO_2CH_3), 3.76 (1 H, dt, J 6.8, 3.2, CHOH), 5.04-5.10 (4 H, m, $CH=CH_2$ x 2), 5.63-5.73 (2 H, m, $CH=CH_2$ x 2), 7.14 (2 H, m, ArH), 7.23-7.31 (3 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 14.19 (1 C, CH_2CH_3), 18.76 (1 C, CH_2CH_3), 37.64 (1 C, $CH_2CH_2CH_3$), 39.47 (1 C, $CH_2(C_6H_5)$), 45.55 (1 C, CH_2NH), 51.80 (1 C, CO_2CH_3), 53.22 (2 C, allylic CH_2), 60.05 (1 C, $CHN(allyl)_2$), 62.12 (1 C, $CH(CO_2Me)$), 73.20 (1 C, CHOH), 116.61 (2 C, $CH=CH_2$ x 2), 126.86, 128.51, 129.11, 136.68 (6 C, Ar), 136.86 (2 C, $CH=CH_2$ x 2), 174.21 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3300 (m, br.), 3070 (w), 3020 (w), 2990 (w), 2940 (s, CH), 2915 (m), 2855 (m), 1735 (s, C=O), 1630 (w), 1490 (w), 1450 (s), 1345 (w), 1265 (w), 1190 (s), 1160 (s), 1100 (w), 1070 (w), 1020 (w), 990 (m), 910 (s), 735 (m), 690 (s). MS (EI) m/z 374 (M^+, 10%), 359 (10), 345 (57), 315 (8), 301 (20), 182 (100), 164 (7), 152 (11), 140 (28), 122 (16), 110 (19), 91 (22), 81 (9), 70 (22), 55 (16), 41 (41). (Found, C, 70.35, H, 9.1, N, 7.55. Calc. for $C_{22}H_{34}N_2O_3$: C, 70.59, H, 9.09, N, 7.49%).

(-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-Dibenzylamino-3-hydroxyhexyl]-*L*-proline methyl ester (14j).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*,3*S*)-1-*N*,*N*-dibenzylamino-2,3-epoxyhexane (0.33 g, 1.12 mmol), trimethylsilyl trifluoromethane sulfonate (0.30 g, 0.26 cm^3, 1.34 mmol), *L*-proline methyl ester (0.29 g, 2.24 mmol), and dichloromethane (6 cm^3) gave *N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-trimethylsilyloxyhexyl]-*L*-proline methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.27 g, 0.26 cm^3, 4.48 mmol), methanol (6 cm^3), sodium hydrogen carbonate (0.75 g, 8.96 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica (1:1 ethyl acetate:light petroleum) to give (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-proline methyl ester (0.41 g, 0.97 mmol, 87% yield) as a colourless oil: $[\alpha]_D^{20}$ -111.6° (*c* 1.19 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, t, J 7.0, CH_2CH_3), 1.25-1.48 (3 H, m, CH_2CH_3, and one of $CH_2CH_2CH_3$), 1.74-1.97 (4 H, m, one of $CH_2CH_2CH_3$, $NCH_2CH_2CH_2$ and one of $NCH_2CH_2CH_2$), 2.09-2.20 (2 H, m, one of NCH_2CH_2 and one of $NCH_2CH_2CH_2$), 2.65 (1 H, ddd, J 10.8, 8.2, 2.3, $CHN(Bn)_2$), 2.88 (1 H, dd, J 11.5, 2.2, one of 1'-CH_2), 3.06-3.14 (2 H, m, one of 1'-CH_2, and one of NCH_2CH_2), 3.19 (1 H, dd, J 8.9, 6.9, $CH(CO_2Me)$), 3.46 (2 H, d, J 13.6, benzylic CH_2), 3.76 (3 H, s, CO_2CH_3), 3.79 (2 H, d, J 13.6, benzylic CH_2), 3.98 (1 H, dt, J

8.5, 3.0, *CH*OH), 5.84 (1 H, s, OH), 7.20-7.35 (10 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 14.31 (1 C, CH_2CH_3), 18.30 (1 C, CH_2CH_3), 23.04, 28.95, 36.94 (1 C, $CH_2CH_2CH_3$), 52.04 (1 C, CO_2CH_3), 53.21 and 53.36, 54.23 (2 C, benzylic CH_2), 57.25 (1 C, CHN(Bn)$_2$), 66.30 (1 C, CH(CO_2Me)), 74.57 (1 C, CHOH), 126.96, 128.19, 128.76, 139.69 (12 C, Ar), 173.77 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3300 (m, br.), 3070 (w), 3045 (w), 3020 (w), 2940 (s, CH), 2860 (m), 2810 (m), 1730 (s, C=O), 1600 (w), 1490 (w), 1445 (s), 1355 (w), 1335 (w), 1270 (w), 1200 (s), 1170 (m), 1110 (m), 1060 (w), 1020 (w), 960 (w), 970 (w), 940 (w), 740 (s), 690 (s); MS (EI) m/z 424 (M$^+$, 1%), 351 (7), 282 (100), 252 (7), 223 (8), 210 (6), 190 (10), 154 (6), 142 (3), 114 (7), 91 (92), 55 (9). MS (EI) (Found, (M$^+$) 424.269. Calc. for $C_{26}H_{36}N_2O_3$, m/z 424.268).

(+)-*N*-[(2*R*, 3*R*)-2-*N*, *N*-Diallylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14k).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (-)-(2*S*,3*R*)-1-*N*,*N*-diallylamino-2,3-epoxyhexane (0.30 g, 1.55 mmol), trimethylsilyl trifluoromethanesulfonate (0.41 g, 0.36 cm^3, 1.86 mmol), *L*-alanine methyl ester (0.32 g, 3.10 mmol), and dichloromethane (7 cm^3) gave *N*-[(2*R*,3*R*)-2-*N*,*N*-diallylamino-3-trimethylsilyloxy]hexyl-*L*-alanine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.37 g, 0.35 cm^3, 6.20 mmol), methanol (6 cm^3), sodium hydrogen carbonate (1.04 g, 12.4 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica (1:1 ethyl acetate:light petroleum) to give (+)-*N*-[(2*R*,3*R*)-2-*N*,*N*-diallylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (0.26 g, 0.88 mmol, 57% yield) as a colourless oil: $[\alpha]_D^{20}$ +2.6° (*c* 1.23 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, t, J 7.0, CH_2CH_3), 1.29 (3 H, d, J 7.0, $CHCH_3$), 1.31-1.43 (2 H, m, CH_2CH_3), 1.51-1.62 (2 H, m, $CH_2CH_2CH_3$), 2.53-2.67 (3 H, m, CH_2NH, CHN(allyl)$_2$), 3.13 (2 H, dd, J 14.0, 8.0, allylic CH_2), 3.28 (1 H, q, J 7.0, $CHCH_3$), 3.31-3.39 (3 H, m, allylic CH_2, CHOH), 3.73 (3 H, s, CO_2CH_3), 5.11-5.20 (4 H, m, CH=CH_2 x 2), 5.74-5.84 (2 H, m, CH=CH_2 x 2); δ_C(75 MHz; $CDCl_3$) 14.27 (1 C, CH_2CH_3), 19.15 (1 C, $CHCH_3$), 19.29 (1 C, CH_2CH_3), 36.69 (1 C, $CH_2CH_2CH_3$), 45.34, 51.77 (1 C, CO_2CH_3), 53.45, 56.88 (1 C, $CHCH_3$), 63.73 (1 C, CHN(allyl)$_2$), 68.83 (1 C, CHOH), 117.31 (2 C, CH=CH_2 x 2), 136.62 (2 C, CH=CH_2 x 2), 176.08 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3550-3250 (br. m), 2900 (s), 2850 (m), 2830 (m), 1730 (s), 1630 (w), 1440 (s), 1360 (w), 1300 (w), 1200 (m), 1150 (m), 1100 (w), 1060 (w), 980 (m), 910 (s), 840 (m), 740 (m); MS (EI) m/z 298 (M$^+$, 9), 271 (12), 255 (4), 239 (14), 225 (24), 188 (10), 182 (100), 140 (37), 128 (7), 122 (13), 116 (6), 110 (31), 96 (11), 88 (6), 82 (9), 70 (32), 56 (34), 41 (56). (Found, C, 64.55, H, 10.40, N, 9.50. Calc. for $C_{16}H_{30}N_2O_3$: C, 64.43, H, 10.07, N, 9.40%).

(-)-*N*-[(2*R*, 3*R*)-2-*N*, *N*-Dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14l).

A procedure similar to that for the preparation of (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (14a) using (+)-(2*S*,3*R*)-1-*N*,*N*-dibenzylamino-2,3-epoxyhexane (0.31g, 1.04mmol), trimethylsilyl trifluoromethanesulfonate (0.28 g, 0.24 cm^3, 1.25 mmol), *L*-alanine methyl ester (0.22 g, 2.08 mmol), and dichloromethane (7 cm^3) gave *N*-[(2*R*,3*R*)-2-*N*,*N*-dibenzylamino-3-trimethylsilyloxyhexyl]-*L*-alanine methyl ester. Deprotection of trimethylsilyl group and neutralisation of product were performed by using acetic acid (0.25 g, 0.24 cm^3, 4.16 mmol), methanol (5 cm^3), sodium hydrogen carbonate (0.70 g, 8.32 mmol), and water (20 cm^3). The product was purified by column chromatography on flash silica (1:1 ethyl acetate:light petroleum) to give (-)-*N*-[(2*R*,3*R*)-2-*N*,*N*-dibenzylamino-3-hydroxyhexyl]-*L*-alanine methyl ester (0.25 g, 0.64 mmol, 62% yield) as a colourless oil: $[\alpha]_D^{20}$ -50.2° (*c* 1.10 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.89 (3 H, t, J 7.2, CH_2CH_3), 1.17-1.33 (2 H, m, CH_2CH_3), 1.34 (3 H, d, J 7.0, $CHCH_3$), 1.44-1.51 (2 H, m, $CH_2CH_2CH_3$), 2.53 (1 H, dt, J 8.9, 5.4, CHN(Bn)$_2$), 2.75-2.77 (2 H, m, CH_2NH), 3.33 (1 H, q, J 7.0, $CHCH_3$), 3.52 (1 H, dt, J 8.8, 1.6, CHOH), 3.63 (2 H, d, J 13.2, benzylic CH_2), 3.77 (3 H, s, CO_2CH_3), 3.91 (2 H, d, J 13.2, benzylic CH_2), 7.21-7.33 (10 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 14.22 (1 C, CH_2CH_3), 19.16 (1 C, CH_2CH_3), 19.28, (1 C, $CHCH_3$), 36.4 (1 C, $CH_2CH_2CH_3$), 45.10, 51.83 (1 C, CO_2CH_3), 54.36, 57.03 (1 C, $CHCH_3$),

62.57 (1 C, CHN(Bn)$_2$), 69.03 (1 C, CHOH), 127.13, 128.41, 129.10, 139.10, 176.12 (1 C, CO_2CH_3); ν_{max}(thin film)/cm^{-1} 3500-3280 (br. m), 3010 (m), 2940 (s), 2900 (m), 2850 (m), 1730 (s), 1600 (w), 1480 (m), 1440 (s), 1360 (m), 1300 (w), 1190 (s), 1150 (m), 1130 (w), 1110 (w), 1090 (w), 1060 (m), 1015 (m), 970 (m), 900 (w), 840 (m), 740 (s), 690 (s); MS (EI) m/z 399 (M$^+$+1, 5%), 355 (6), 339 (20), 325 (40), 307 (25), 282 (78), 265 (6), 238 (15), 223 (113), 210 (23), 190 (31), 147 (5), 132 (31), 116 (13), 105 (9), 91(100), 65 (24), 56 (38), 43 (16). (Found, C, 72.40, H, 8.75, N, 7.05. Calc. for $C_{24}H_{34}N_2O_3$: C, 72.36, H, 8.54, N, 7.04%).

Deprotection of diallylamine-derived products (scheme 2).

(-)-*N*-[(2*R*, 3*S*)-2-Amino-3-hydroxyhexyl]-*L*-alanine *tert*-butyl ester (15).[13]

A mixture of *N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-hydroxyhexyl]-*L*-alanine *tert*-butyl ester (0.128 g, 0.376 mmol), and tris(triphenylphosphine)rhodium(I) chloride (0.045 g, 0.037 mmol) in mixed acetonitrile and water (20 ml, 84:16) was prepared in a magnetically stirred 50 ml flask. A Claisen adapter fitted with reflux condenser and addition funnel on one arm and with short path distillation head on the other was then attached to the reaction vessel. The addition funnel was charged with excess acetonitrile and water (84:16), the system flushed with N_2 and brought to vigorous boiling. Fresh solvents were added to replace the volume of liquid distilled out. After 5 hours, the solvents were removed *in vacuo*, the product was separated by column chromatography on flash silica (eluent 1:1 ethyl acetate:methanol) to give *N*-[(2*R*,3*S*)-2-amino-3-hydroxyhexyl]-*L*-alanine *tert*-butyl ester (0.058 g, 0.223 mmol, 59% yield) as an oil: $[\alpha]_D^{20}$ -30.1° (*c* 1.17 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, t, J 7.2, CH_2CH_3), 1.24 (3 H, d, J 7.0, $CHCH_3$), 1.37-1.59 (4 H, m, CH_2CH_2), 1.46 (9 H, s, $(CH_3)_3$), 2.46 (2 H, s, br., NH_2), 2.58 (1 H, dt, J 11.4, 5.2, $CHNH_2$), 2.75 (1 H, dd, J 10.1, 5.2, one of CH_2NH), 2.80 (1 H, dd, J 11.4, 5.2, one of CH_2NH), 3.20 (1 H, q, J 7.0, $CHCH_3$), 3.54 (1 H, dt, J 11.7, 4.9, CHOH); δ_C(75 MHz; $CDCl_3$) 14.18 (1 C, CH_2CH_3), 19.06 (1 C, CH_2CH_3), 19.21 (1 C, $CHCH_3$), 28.05 (3 C, $C(CH_3)_3$), 36.41 (1 C, $CH_2CH_2CH_3$), 50.85 (1 C, CH_2NH), 53.59 (1 C, $CHCH_3$), 57.33 (1 C, $CHNH_2$), 75.58 (1 C, CHOH), 81.21 (1 C, $C(CH_3)_3$), 174.65 (1 C, $CO_2C(CH_3)_3$); ν_{max}(thin film)/cm^{-1} 3550-3100 (br. s), 2940 (s), 2900 (m), 2850 (m), 1720 (s), 1630 (s), 1460 (s), 1560 (m), 1240 (w), 1220 (w), 1150 (s), 1070 (w), 1055 (w), 1030 (w), 840 (m), 745 (m); MS (EI) m/z 261 (M$^+$+1, 7%), 229 (9), 215 (2), 203 (8), 185 (6), 159 (65), 131 (29), 102 (100), 90 (14), 85 (49), 74 (7), 68 (11), 56 (71), 44 (32). MS (EI) (Found, (M$^+$) 260.209. Calc. for $C_{13}H_{28}N_2O_3$, m/z 260.210).

(-)-(3*S*, 6*R*)-6-[(1*S*)-1-Hydroxybutyl]-3-isopropyl-2-ketopiperazine (16).[13]

A procedure similar to that for (-)-*N*-[(2*R*,3*S*)-2-amino-3-hydroxyhexyl]-*L*-alanine *tert*-butyl ester (15) using (-)-*N*-[(2*R*,3*S*)-2-*N*,*N*-diallylamino-3-hydroxyhexyl]-*L*-valine methyl ester (0.098 g, 0.300 mmol) and tris-(triphenylphosphine)rhodium(I) chloride (0.014 g, 0.030 mmol) gave (-)-(3*S*,6*R*)-6-[(1*S*)-1-hydroxybutyl]-3-isopropyl-2-ketopiperazine (0.030 g, 0.140 mmol, 47% yield) as a colourless solid: m.p. 138-139.5°C; $[\alpha]_D^{20}$ -74.6° (*c* 0.96 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.87-1.02 (9 H, m, $CH(CH_3)_2$ and CH_2CH_3), 1.35-1.60 (4 H, m, $CH_2CH_2CH_3$), 2.52-2.58 (1 H, m, $CH(CH_3)_2$), 3.03 (1 H, dt, J 12.3, 4.2, $CHCH_2NH$), 3.19 (1 H, d, J 3.3, one of CH_2NH), 3.32 (1 H, d, J 2.7, one of CH_2NH), 3.48 (1 H, d, J 12.6, $CHCH(CH_3)_2$), 3.72 (1 H, dt, J 4.8, 3.9, CHOH), 6.70 (1 H, s, OH); δ_C(75 MHz; $CDCl_3$) 14.08 (1 C, CH_2CH_3), 16.66 (1 C, one of $CH(CH_3)_2$), 19.27 (1 C, CH_2CH_3), 19.39 (1 C, one of $CH(CH_3)_2$), 29.04 (1 C, $CH(CH_3)_2$), 36.76 (1 C, $CH_2CH_2CH_3$), 42.75 (1 C, CH_2NH), 54.49 (1 C, $CHCH_2NH$), 64.20 (1 C, $CHCH(CH_3)_2$), 74.22 (1 C, CHOH), 171.84 (1 C, CONH); ν_{max}(CH_2Cl_2)/cm^{-1} 3440-3080 (s, br.), 2860 (s), 2480 (m), 2010 (m), 1620 (s), 1460 (m), 1250 (m), 980 (m), 700 (m); MS (EI) m/z 214 (M$^+$+1%) (9), 197 (36), 171 (100), 154 (18), 143 (27), 128 (29), 113 (98), 102 (11), 96 (37), 84 (28), 72 (60), 55 (50), 43 (52). MS (EI) (Found, (M$^+$) 214.168. Calc. for $C_{11}H_{22}N_2O_2$, m/z 214.168).

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