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A Stereodivergent Synthesis of 3,4-Disubstituted-2-Azetidinones

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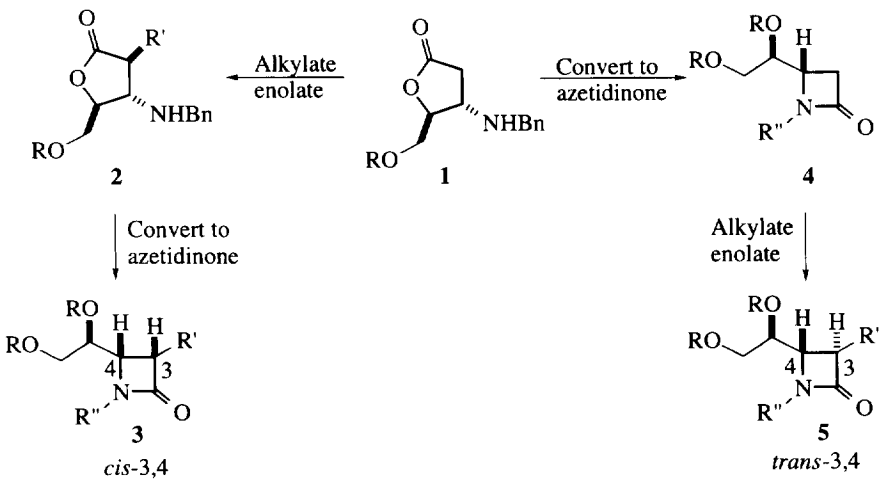
Abstract: The synthesis of a new aminolactone **1**, using a highly diastereoselective conjugate addition of benzylamine to the unsaturated lactone **6** derived from D-mannitol, is described. The enantiospecific transformation of this aminolactone into either cis- or trans-3,4-disubstituted azetidinones, β-amino esters as well as some aldol reactions are described.

INTRODUCTION.

The development of new methods for the preparation of 2-azetidinones is still an area of intense interest due to the critical role played by 2-azetidinones in the activity of many important antibiotics.[1-5] We recently reported the preparation of the carbohydrate-derived aminolactone **1**.[6] In this paper we provide full experimental details for the preparation of *cis*- or *trans*-3,4-azetidinones using aminolactone **1** as a common intermediate. In addition, we show how **1** may be transformed into highly-substituted β-amino esters and also how it undergoes high-yielding aldol reactions with aldehydes and ketones.

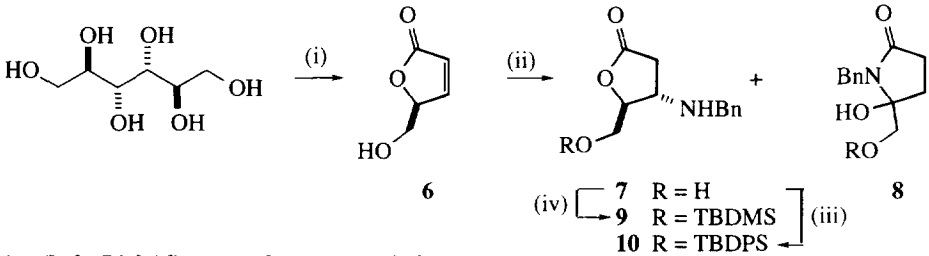
RESULTS AND DISCUSSION.

The strategy developed in this work is outlined in Scheme 1. As shown in this Scheme, alkylation of the enolate of aminolactone **1** should lead to *cis*-azetidinones (via **2**) whereas alkylation *after* azetidinone formation should afford *trans*-azetidinones (via **4**).



Scheme 1. Stereodivergent strategy for the synthesis of 3,4-disubstituted-2-azetidinones.

The synthesis of the key intermediates, aminolactones **9** and **10** is outlined in Scheme 2.[6] Thus lactone **6**, prepared from D-mannitol in five steps,[7,8] was reacted with benzylamine in methanol at 0°C. The crude conjugate adduct **7**[9,10] was very difficult to purify and was directly silylated providing **9** or **10**. Also isolated was by-product **8**, arising from 1,2-addition. We have reported the X-ray crystal structure determination of **10** elsewhere.[6]

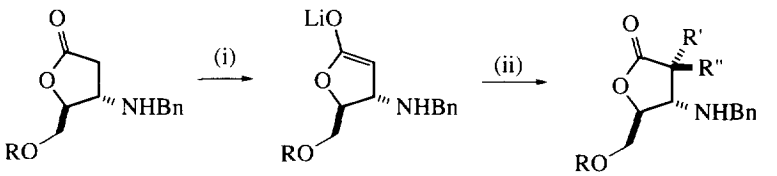


(i) Refs. 7&8 (five steps from D-mannitol)
(ii) $BnNH_2$, MeOH, 0°C, 24 h
(iii) TBDMSCl, Im., DMF, r.t., 48 h, 30% from (**7**)
(iv) TBDPSCl, Im., DMF, r.t., 48 h, 35% from (**7**)

Scheme 2. Synthesis of key intermediates **9** and **10**.

*Preparation of 3,4-*cis*-azetidinones.*

In order to demonstrate the efficacy of our approach we chose ethyl as the group to be introduced at C3 as this is the side chain found in the antibiotic (+)-PS-5.[11] Thus alkylation of the lithium enolate of **9** with ethyl iodide gave the desired product **11** in 45% yield. Similar alkylation of **10** afforded a 12 : 4 : 0.6 mixture of lactones **12a**, **12b** and **12c** (equation (1)). The desired diastereomer **12a** could be isolated by flash chromatography on silica.



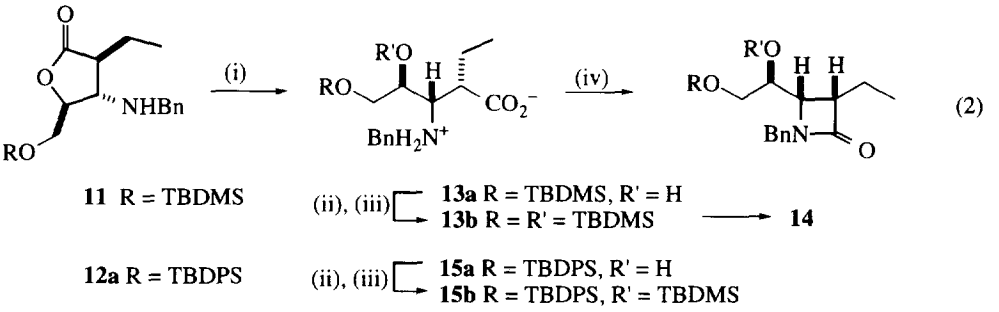
(1)

9 R = TBDMS
10 R = TBDPS

(i) LiHMDS, THF
(ii) EtI, DMPU

11 R = TBDMS, R' = H, R" = Et
12a R = TBDPS, R' = H, R" = Et
12b R = TBDPS, R' = Et, R" = H
12c R = TBDPS, R' = R" = Et

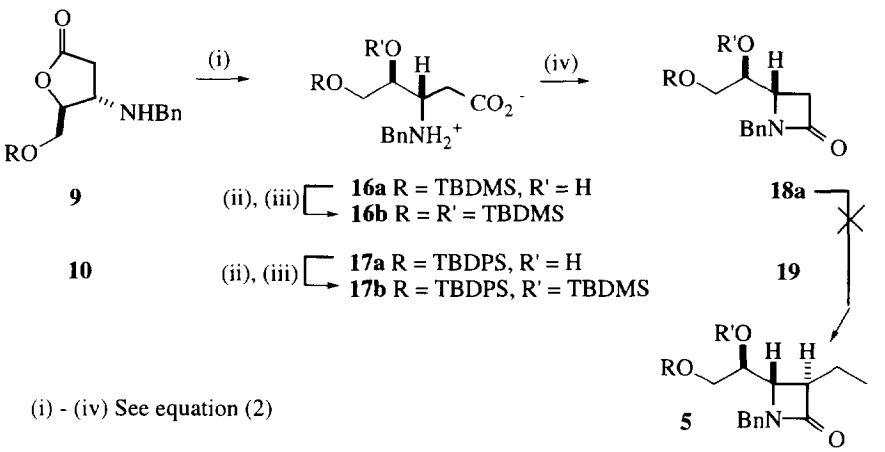
Processing **11** through to *cis*-3,4-azetidinones was relatively straightforward. Thus hydrolysis of **11** with aqueous sodium hydroxide followed by acidification gave amino acid **13a**. Silylation of the crude amino acid followed by ester hydrolysis gave the doubly protected amino acid **13b**. Ring closure, using Ohno's procedure,[12] provided enantiomerically pure *cis*-3,4-azetidinone **14** in 24% overall yield from **11**.



(i) (a) NaOH, H_2O (b) HCl (ii) TBDMSCl, Et_3N, DMAP, DMF (iii) (a) HCl, MeOH (b) NaOH, H_2O (iv) $(PyS)_2$, PPh_3, CH_3CN, reflux 4 h

*Preparation of 3,4-*trans*-azetidinones.*

Preparation of the *trans*-isomer of **14**, i.e. **5** in Scheme 1, required azetidinone formation *prior to* alkylation. Thus aminolactones **9** and **10** were taken through the same sequence developed for **14** yielding azetidinones **18a** and **19** in 48 and 40% yield respectively (Scheme 3). Unfortunately, all attempts to alkylate



Scheme 3.

the lithium enolate of **18a** failed, and starting material was usually recovered in high yield. Examination of the presumed enolate structure revealed that the N-benzyl group, forced to adopt a *trans* orientation relative to the C4 substituent, most likely blocks approach of the electrophile (Figure 1). Access to the "lower" face (as drawn in Figure 1) is hindered by the C4 substituent. To overcome this problem the N-benzyl group was replaced by a

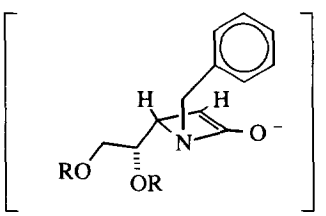
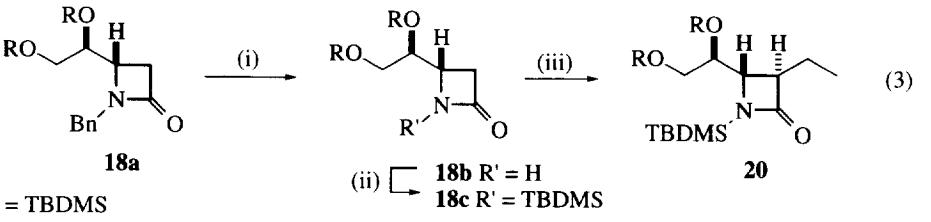


Figure 1.

TBDMS group (equation (3)). Subsequent alkylation of the lithium enolate of **18c** was successful, yielding the *trans*-3,4-azetidinone **20** as a single diastereomer.



18a

R = TBDMS

18b R' = H
18c R' = TBDMS

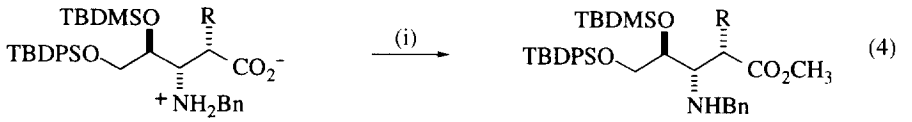
20

(3)

(i) Na, NH_3, -78°C (ii) TBDMSCl, Et_3N, DMF (iii) (a) LHMDS, DMPU, THF, -78°C (b) EtI, 20°C

Other transformations of aminolactone **10**.

Amino acids[13] **15b** and **21**, (the latter obtained by hydrolysis of **10** and subsequent silylation), were converted to the corresponding methyl esters **22** and **23** respectively by treatment with diazomethane (equation (4)).



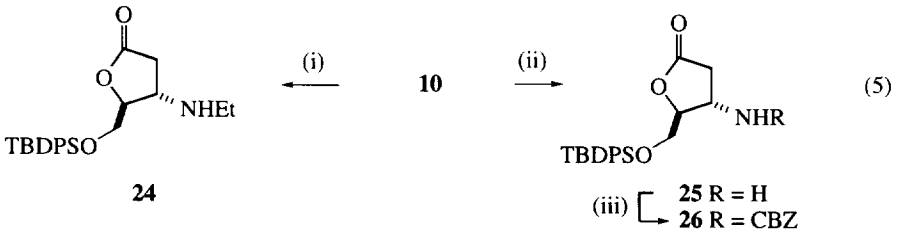
(4)

21 R = H
15b R = Et

(i) CH_2N_2, CH_2Cl_2

22 R = H
23 R = Et

Catalytic hydrogenation of **10** in ethanol provided the N-ethylamino derivative **24** rather than the expected aminolactone **25** (equation (5)). This may have been due to the palladium catalysing the dehydrogenation of ethanol to acetaldehyde, which could then reductively alkylate the amine. In any event, switching solvents to ethyl acetate provided **25** in 67% yield. This product was then readily protected as its N-carbobenzyloxy-(CBZ)-derivative **26**.



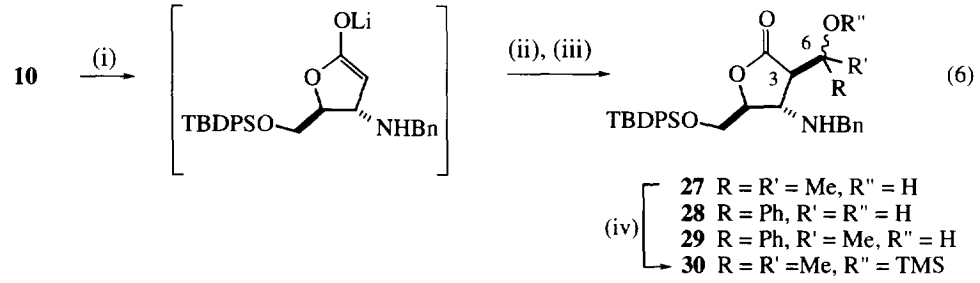
24

25 R = H
26 R = CBZ

(5)

(i) 10% Pd/C, H_2, EtOH, 41% (ii) 10% Pd/C, H_2, EtOAc, 68% (iii)CBZCl, Et_3N, DMAP, 67%

Alternatively, aminolactone **10** underwent aldol reactions with several ketones and aldehydes (equation (6)). In all cases stereocontrol at C3 was complete, however additions to benzaldehyde or acetophenone showed no stereoselectivity at the newly-formed carbinol centre (equation (6) and Table). All attempts to convert these aldol adducts into the corresponding azetidinones, using the methods outlined above (and also O-protection of **27** to give **30** prior to hydrolysis), have so far been unsuccessful.



(i) LiHMDS, THF, -78°C, 30 min. (ii) RCOR' (iii) Aq. NH_4Cl. (iv) TMSCl, $(i\text{-}Pr)_2EtN$, CH_2Cl_2

Table. Results for aldol reactions with enolate **10** (equation (6)).

Electrophile	Product	Yield%	C3/C4 (*trans/cis*)	Ratio C6 epimers
Acetone	**27**	89	>98:2	-
Benzaldehyde	**28**	77	>98:2	1:1.1
Acetophenone	**29**	60	>98:2	1:1.4

Conclusions

Aminolactones **9** and **10** are versatile intermediates for the enantiospecific synthesis of either *cis*- or *trans*-3,4-disubstituted azetidinones as well as β-amino esters.

Acknowledgement

We are grateful to the Australian Research Council for financial support through the award of an ARC Indicative Grant.

EXPERIMENTAL[14]

(4*S*,5*S*)-4-Benzylamino-5-[(*t*-butyldimethyl)silyloxymethyl]dihydro-2(*3H*)furanone 9.

A solution of lactone **6** (0.892 g, 7.82 mmol) in methanol (6 mL) was cooled to 0°C and treated with benzylamine (0.838 g, 855 μL, 7.82 mmol). The resulting solution was left at 0°C for 48 hrs. The mixture was then concentrated and the residue dissolved in DMF (5 mL). To the solution was then added *t*-butyldimethylsilylchloride (1.77 g, 11.74 mmol) and imidazole (0.85 g, 24.48 mmol). The mixture was then stirred at room temperature for two days. After this time the mixture was partitioned between water (20 mL) and dichloromethane (20 mL) and the phases separated. The aqueous phase was extracted further with dichloromethane (3x20 mL). The extract was washed with water (40 mL) and then dried, filtered and evaporated to give an orange oil which was purified by flash chromatography (eluant, 2:1, Et_2O, hexanes). Fractions containing material Rf=0.4 were combined and concentrated to give as a pale yellow oil (909 mg, 35%). A sample of this material was recrystallised from hexanes, to give **9**, mp 52-53°C, $[\alpha]_D^{20}$ +6.75 (*c*=

0.875, $CHCl_3$). ^1H NMR (300 MHz) δ 7.37-7.27 (m, 5H), 4.36 (dd, *J*=3.1, 6.6 Hz, 1H, H5), 3.85-3.73 (m, 4H, 2xH6, NCH_2Ph), 3.59 (m, 1H, H4), 2.85 (dd, *J*=7.8, 17.7 Hz, 1H, H3), 2.38 (dd, *J*=3.9 Hz, 17.8 Hz, 1H, H3), 2.07 (bs, 1H, NH), 0.87 (s, 9H, $C(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (50 MHz) δ 176.0 (C=O), 138.8, 128.9, 128.4, 128.2, 85.1, 63.9, 56.0, 36.5, 26.0. IR (film) 3328, 2955, 2929, 2857, 1773, 1255, 1194, 1124, 837, 780 cm^{-1}. MS (CI, methane) *m/z* 336 (M+1, 100), 236 (25), 91 (13). HRMS $C_{18}H_{30}NO_3Si$ (M+1) requires 336.199; found 336.197 $\pm$0.003.

(4*S*,5*S*)-4-Benzylamino-5-((*t*-butyldiphenylsilyl)oxymethyl)dihydro-2-(*3H*)furanone 10.

A solution of lactone **6** (500 mg, 4.39 mmol) in dry methanol was cooled to 0°C. Benzylamine (480µL, 4.39 mmol) was added dropwise and the mixture stirred at 0°C for 36 hours. The methanol was then evaporated at reduced pressure. The crude residue was dissolved in DMF (10 mL) and *t*-butyldiphenylsilyl chloride (1.5 mL, 6.45 mmol) and imidazole (470 mg, 6.90 mmol) were added. The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 days. After this time the DMF was removed at reduced pressure and the residue dissolved in CH_2Cl_2 (30 mL). Water (30 mL) was added and the phases separated. The aqueous phase was extracted further with CH_2Cl_2 (2x20 mL) and the combined organic phases then washed with water (2x40 mL), dried ($MgSO_4$) and concentrated at reduced pressure. The residue was purified by MPLC (2:1, Et_2O, hexanes). Fractions containing material R_f=0.3 were combined and concentrated to afford an oil which crystallised slowly on standing (856 mg, 43%) and was recrystallised from hexanes, to give (4*S*,5*S*)-4-benzylamino-5-((*t*-butyldiphenylsilyl)oxymethyl)dihydro-2-(*3H*)furanone **10**, mp 78-79°C, $[\alpha]_D^{20}$ +15.3 (*c*=1.08, $CHCl_3$). Anal. calc'd for $C_{28}H_{33}NO_3Si$: C, 73.2; H, 7.4; N, 3.0. Found C, 73.2; H, 7.2; N, 2.9%. ^1H NMR (200 MHz) δ 7.7-7.5 (m, 4H), 7.4-7.3 (m, 11H), 4.35 (q, *J*=3.4 Hz, 1H, H5), 3.85 (dd, *J*=3.8, 11.3 Hz, 1H, H4), 3.76 (d, *J*=1.7 Hz, 2H, CH_2Ph). 3.7-3.6 (m, 2H, OCH_2), 2.92 (dd, *J*=7.8, 17.7 Hz, 1H, H3), 2.40 (dd, *J*=4.0, 17.7 Hz, 1H, H3), 1.03 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 175.9 (C=O), 139.0, 135.6, 135.5, 132.7, 132.2, 130.0, 128.6, 128.4, 128.1, 127.9 (2Cs), 127.4, 85.1 (C5), 64.2 (C6), 55.7 (C4), 51.6 (NCH_2Ph), 36.5 (C3), 26.7 ($C(\underline{C}H_3)_3$), 19.1 ($\underline{C}(CH_3)_3$). IR (film) 2931, 2857, 1780, 1428, 1113, 702 cm^{-1}. MS (CI, methane) *m/z* 460 (M+1, 22), 361 (36), 360 (100), 340 (15), 282 (15), 178 (17), 120 (19), 91 (94). Fractions containing material R_f=0.1 were combined and concentrated to afford **8** (237 mg, 12%). ^1H NMR (200 MHz) δ 7.5-7.2 (m, 15H), 4.45 (AB quartet, *J*=15.5 Hz, 2H, NCH_2Ph), 3.56 (AB quartet, *J*=10.6 Hz, 2H, 2xH6), 2.7-2.5 (m, 2H, 2xH3), 2.4-2.2 (m, 1H, H4), 1.99 (m, 1H, H4), 1.04 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 175.4, 138.2, 135.5, 135.5, 132.4, 132.2, 129.92, 128.3, 127.8, 127.7, 127.0, 9.53, 42.4, 31.2, 29.2, 26.8, 19.1. MS (CI, methane) *m/z* 460 (M+1, 18), 442 (22), 91 (100).

General procedure for alkylation/hydroxyalkylation of benzylaminolactones 9 and 10.

A THF solution of lactone was transferred by cannula to a solution of lithiumhexamethyldisilazide (2.2 equiv) in THF (cooled to -78°C). The mixture was then stirred for 30 mins at -78°C and the electrophile (either neat or in solution) was then cannulated into the enolate solution. The mixture was then stirred for the specified time and the reaction quenched by the addition of saturated aqueous ammonium chloride solution. The mixture was then extracted several times with CH_2Cl_2, washed once with water, dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude products were purified by chromatography as individually described.

(3*S*,4*S*,5*S*)-4-Benzylamino-5-(*t*-butyldimethylsilyl)oxymethyl-3-ethyldihydro-2-(3*H*)furanone 11.

A solution of the lithium enolate prepared from lactone **9** (597 mg, 1.78 mmol) at -78°C was treated with a solution of iodoethane (1.42 mL, 17.8 mmol) in DMPU (2 mL). The resulting mixture was stirred at -78°C for 20 mins and the solution then allowed to warm to 0°C, at which temperature stirring was maintained for 2.5 hours. The reaction was then quenched at 0°C to afford after work-up a yellow oil. The crude product was purified by flash chromatography (2:1, Et_2O, hexanes). Fractions containing material R_f=0.2 were combined and concentrated to afford **11** (292 mg, 45%), $[\alpha]_D^{20}$ +12.9 (*c*=1.345, $CHCl_3$). ^1H NMR (200 MHz) δ 7.34-7.26 (m, 5H), 4.18 (m, 1H, H5), 3.9-3.85 (m, 3H, H6, NCH_2Ph), 3.77 (ddd, *J*=0.6, 3.4, 12.1 Hz, 1H, H6), 3.43 (dd, *J*=6.6, 7.3 Hz, 1H, H4), 2.46 (q, *J*=6.9 Hz, 1H, H3), 1.87-1.73 (m, 2H, $C\underline{H}_2CH_3$), 0.99 (t, *J*=7.4 Hz, 3H, CH_3), 0.87 [s, 9H, $C(CH_3)_3$], 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$) . ^{13}C NMR (50 MHz) δ 177.2 (C=O), 139.5, 128.5, 128.0, 127.4, 83.9 (C5), 62.9 (C6), 58.6 (C4), 51.8 (NCH_2Ph), 48.8 (C3), 25.8 ($C(\underline{C}H_3)_3$), 22.3 ($\underline{C}H_2CH_3$), 18.3 ($\underline{C}(CH_3)_3$), 11.0 (CH_3), -5.4, -5.5 (2x$SiCH_3$). IR (film) 3332, 2930, 2858, 1771, 1463, 1255, 1175, 1131, 837cm^{-1}. HRMS $C_{20}H_{34}NO_3Si$ (M+1) requires 364.231; found 364.231±0.004.

(3*S*,4*S*,5*S*)-4-Benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-ethyldihydro-2-(3*H*)furanone 12a, (3*R*,4*S*,5*S*)-4-benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-ethyldihydro-2-(3*H*)furanone 12b and (4*S*,5*S*)-4-benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3,3-diethyldihydro-2-(3*H*)furanone 12c.

A solution of the lithium enolate prepared from lactone **10** (350 mg, 0.762 mmol) at -78°C was treated with a solution of ethyl iodide (0.61 mL, 7.62 mmol) in DMPU (1 mL). The resulting mixture was stirred at -78°C for 15 mins and the solution then allowed to warm to 0°C, at which temperature stirring was maintained for 2.5 hours. The reaction was then quenched at 0°C to afford after work-up a yellow oil. The crude product was

purified by flash chromatography (2:1, Et_2O, hexanes). Fractions containing material R_f=0.4 were combined and concentrated to afford (3*S*,4*S*,5*S*) 4-benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-ethyldihydro-2-(*3H*)furanone **12a** (121 mg, 33%), $[\alpha]_D^{20}$ +11.89 (*c*=0.90, $CHCl_3$). Anal. calc'd for $C_{30}H_{37}NO_3Si$: C, 73.9; H, 7.7; N, 2.9. Found C, 73.8; H, 7.8 ; N, 2.5%. ^1H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.5-7.2 (m, 11H), 4.22 (m, 1H, H5), 3.95 (dd, *J*=11.6, 3.5 Hz, 1H, H6), 3.9-3.6 (m, 3H, H6, NCH_2Ph), 3.52 (dd, *J*=8.0, 6.7 Hz, 1H, H4), 2.5 (ddd, *J*=6.1, 6.2, 8.1 Hz, 1H, H3), 1.9-1.7 (m, 2H, $C\underline{H}_2CH_3$), 1.08 (s, 9H, $C(CH_3)_3$), 1.04 (t, *J*=7.5 Hz, 3H, CH_3). ^{13}C NMR (50 MHz) δ 177.0 (C=O), 139.4, 135.6, 135.5, 132.8, 132.5, 129.8, 128.4, 127.8, 127.7, 127.2, 83.8 (C5), 63.4 (C6), 58.4 (C4), 51.6 (NCH_2Ph), 48.7 (C3), 25.7 ($C(\underline{C}H_3)_3$), 22.3 ($\underline{C}H_2CH_3$), 19.1 ($\underline{C}(CH_3)_3$), 11.0 (CH_3). IR (film) 2962, 2931, 2858, 1770, 1428, 1173, 1113, 701 cm^{-1}. MS (CI, methane) *m/z* 488 (M+1, 58), 360 (88), 340 (28), 91 (100), 79(34). Fractions containing material R_f=0.5 were combined and concentrated to afford (3*R*,4*S*,5*S*)-4-benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-ethyldihydro-2-(*3H*)furanone **12b** (40 mg, 11%), $[\alpha]_D^{20}$ -0.65, (*c*=0.92, $CHCl_3$). ^1H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.6-7.2 (m, 11H), 4.34 (dd, *J*=3.8, 6.7 Hz, 1H, H5), 3.88-3.66 (m, 4H, 2xH6, NCH_2Ph), 3.55 (dd , *J*=2.6, 7.2 Hz, 1H, H4), 2.75 (ddd, *J*=6.9, 6.9, 8.5 Hz, 1H, H3), 1.82-1.55 (m, 2H, $C\underline{H}_2CH_3$), 1.03 (s, overlapping t, 12H, $C(CH_3)_3$ and CH_3). ^{13}C NMR (50 MHz) δ 178.03 (C=O), 139.3, 135.6, 135.5, 132.7, 132.4, 130.0, 128.5, 128.1, 127.9, 127.3, 82.5 (C5), 63.9 (C6), 57.3 (C4), 51.6 ($N\underline{C}H_2Ph$), 44.7 (C3), 26.8 ($C(\underline{C}H_3)_3$), 19.1 ($\underline{C}(CH_3)_3$), 17.5 ($\underline{C}H_2CH_3$), 12.2 (CH_3). IR (film) 2960, 2932, 2858, 1772, 1428, 1184, 1114, 702 cm^{-1}. MS (CI, methane) *m/z* 488 (M+1, 96), 360 (95), 340 (44), 91 (100). Fractions containing material R_f=0.8 were combined and concentrated to afford the diethyl compound **12c** (24 mg, 6%), $[\alpha]_D^{20}$ +27.84 (*c*=0.905, $CHCl_3$). ^1H NMR (200 MHz) δ 7.76-7.72 (m, 4H), 7.5-7.3 (m, 11H), 4.05 (m, 6H), 1.96 (m, 1H), 1.72-1.42 (m, 4H), 1.03 (s, overlapping t, 12H, $C(CH_3)_3$ and CH_3), 0.89 (t, *J*=7.4 Hz, CH_3). ^{13}C NMR (50 MHz) δ 178.5 (C=O), 139.9, 135.7, 135.6, 133.0, 132.6, 129.8, 128.4, 127.9, 127.8, 127.3, 82.1 (C5), 62.5 (C6), 57.6 (C4), 52.7, 51.0 (C3, NCH_2Ph), 27.3 (CH_2), 26.7 ($C(\underline{C}H_3)_3$), 25.0 (CH_2), 19.1 ($\underline{C}(CH_3)_3$), 9.1, 9.0 (2xCH_3). IR (film) 2962, 2930, 2858, 1770, 1114, 702 cm^{-1}. MS (CI, methane) *m/z* 516 (M+1, 100), 360 (85), 340 (40), 91 (66).

General Hydrolysis Procedure for the Conversion of Aminolactones to β-Amino-Acids.

A solution of aminolactone in methanol was treated with one equivalent of 1M aqueous sodium hydroxide. The mixture was then left to stir at room temperature until TLC indicated the complete disappearance of starting material (approx. 24 hours). After this time one equivalent of aqueous 1M HCl was added. The mixture was cooled to 0°C and the precipitated product collected by filtration. The filtrate could be concentrated and the residual water removed by freeze drying to give further product in essentially quantitative yield. Due to the

zwitterionic nature of the product it was used in the next step without further purification. A solution of crude amino acid in DMF (8 mL/mmol) was treated with *t*-butyldimethylsilyl chloride (5 equivalents), triethylamine (10 equivalents), and dimethylaminopyridine. The mixture was stirred at room temperature for 24 hours. After this time the DMF was removed at reduced pressure. The residue was partitioned between CH_2Cl_2 and water. The aqueous phase was extracted further with CH_2Cl_2 (x4). The combined organic extracts were then washed with water then dried, filtered and concentrated. The residue was then dissolved in MeOH (5mL/mmol) and cooled to 0°C. To the mixture was then added HCl (one equivalent of a 1M aqueous solution) and the solution then stirred for 30 mins. NaOH (one equivalent of a 1M aqueous solution) was then added and the mixture concentrated to afford an oil which was used without purification in the subsequent reaction.

(2*S*,3*S*,4*S*)-3-Benzylamino-4,5-bis(*t*-butyldimethyl)silyloxy-2-ethylpentanoic acid 13b.

A solution of aminolactone **9** (0.93 g, 2.8 mmol) in methanol (10 mL) was treated with 1M NaOH (2.8 mL, 2.8 mmol). The mixture was stirred for 20 h at room temperature. 1M Aqueous HCl (2.8 mL, 2.8 mmol) was then added and the mixture cooled in an ice bath for 30 min. The resulting precipitate was collected by filtration to afford (2*S*,3*S*,4*S*)-3-benzylamino-4-hydroxy-5-(*t*-butyldimethyl)silyloxy-2-ethylpentanoic acid **13a** as a white solid (0.442 g, 45%). The filtrate was then concentrated to give a pale yellow solid which was also product (combined mass 0.96g, 98%). Due to the zwitterionic character of this product it was used in the subsequent reaction without purification . A solution of amino acid **13a** (0.44 g, 1.25 mmol) in DMF (6 mL) was treated with *t*-butyldimethylsilylchloride (754 mg, 5.00 mmol), triethylamine (379mg, 523 mL, 3.75 mmol), and dimethylaminopyridine (20 mg). The mixture was stirred at room temperature for two days. It was then concentrated at reduced pressure to remove the DMF. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2x10 mL). The combined organic phases were then dried, filtered and concentrated to give an orange oil (0.759 g). The residue was dissolved in methanol (10 mL) and the solution cooled to 0°C. 1M aqueous HCl (1.25 mL) was added to the solution and the mixture was stirred at 0°C for 15 minutes. 1M Aqueous NaOH (1.25 mL) was then added and the mixture concentrated to remove the solvent and water, leaving **13b** as a viscous oil. This residue was used in the next reaction.

(3*S*,4*S*,1'*R*)-1-Benzyl-4-(1,2-bis(*t*-butyldimethyl)silyloxy)-1-ethyl)-3-ethylazetidin-2-one 14.

A solution of amino acid **13b** (0.114 mmol, crude from hydrolysis and silylation) in acetonitrile (15 mL) was treated with 2,2-dipyridyldisulfide (33 mg, 0.148 mmol) and triphenylphosphine (39 mg, 0.148 mmol). The

mixture was heated at reflux for 4 hours and then the solvent was removed at reduced pressure and the residue dissolved in CH_2Cl_2. The solution was then cooled to 0°C and then treated with triethylamine (40 μL) and iodomethane (140 μL). The mixture was left to stand overnight and then concentrated. The residue was purified by preparative t.l.c. (eluant 3:1 hexanes, Et_2O). The faintly chromophoric band, R_f=0.3 was extracted to give **14** as a colourless oil (13 mg, 24% 3 steps), $[\alpha]_D^{20}$ -0.58 (*c*=0.345) ($CHCl_3$). ^1H NMR (300 MHz) δ 7.35-7.21 (m, 5H), 4.81 (d, *J*=15.1 Hz, 1H, NCHPh), 3.89 (td, *J*=2.6, 5.8 Hz, 1H, H5), 3.85 (d, *J*=15.1 Hz, 1H, NCHPh), 3.59 (dd, *J*=2.6, 5.4 Hz, 1H, H4), 3.53 (d, *J*=5.9 Hz, 2H, H6), 3.07 (dt, *J*=5.5, 10.0 Hz, 1H, H3), 2.09-1.98 (m, 1H, $C\underline{H}_2CH_3$), 1.74-1.61 (m, 1H, $C\underline{H}_2CH_3$), 1.09 (t, *J*=7.4 Hz, 3H, $CH_2C\underline{H}_3$), 0.89 (s, 9H, $C(CH_3)_3$), 0.83 (s, 9H, $C(CH_3)_3$), 0.104 (s, 3H, $SiCH_3$), 0.097 (s, 3H, $SiCH_3$), -0.005 (s, 3H, $SiCH_3$), -0.009 (s, 3H, $SiCH_3$). ^{13}C NMR (100 MHz) δ 171.3, (C=O), 136.1, 128.8, 128.303 127.6, 71.9 (C5), 65.3 (C6), 56.3, 54.5 (C4, NCH_2Ph), 44.6 (C3), 25.9, 25.8 (2x$C(\underline{C}H_3)_3$), 19.3 ($\underline{C}H_2CH_3$), 18.3, 18.1 (2x$\underline{C}(CH_3)_3$), 13.4 ($CH_2\underline{C}H_3$), -3.9, -4.9, -5.4, -5.4. (4x$SiCH_3$). IR (film) 2956, 2930, 2858, 1750, 1254, 1091, 835, 778 cm^{-1}. HRMS $C_{26}H_{48}NO_3Si_2$ (M+1) requires 478.328 ; found 478.319±0.005.

(3*S*,4*S*)-3-Benzylamino-4-((*t*-butyldimethyl)silyl)oxy)-5-((*t*-butyldiphenyl)silyl)oxypentanoic acid 17b.

A solution of lactone **10** (400 mg, 0.871 mmol) in MeOH was treated with NaOH (0.88 mL of a 1M aqueous solution) and the mixture stirred overnight at room temperature. After this time HCl (0.88 mL of a 1M aqueous solution) was added. The mixture was left at room temperature for 2 hours and the product precipitated as a white solid (244 mg). The filtrate was concentrated and the residue dissolved in MeOH. A further 75 mg of product precipitated to give an overall yield for (3*S*,4*S*)-3-benzylamino-4-hydroxy-5-(t-butyldiphenylsilyl)oxypentanoic acid **17a** of 319 mg, 77%. ^1H NMR (200 MHz) δ 7.6-7.5 (m, 4H), 7.4-7.2 (m, 11H), 4.20 (m, 1H, H4), 3.99 (AB quartet, *J*=13.5 Hz, 2H, NCH_2Ph), 3.75 (m, 1H, H5), 3.47 (m, 2H, H5, H3), 2.61 (dd, *J*=9.5, 17.3 Hz, 1H, H2), 2.33 (m, 1H, H2) 0.95 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 178.2 (C=O), 135.4, 132.8, 131.4, 131.2, 129.8, 129.4, 129.1, 127.8, 66.8 (C4), 63.7 (C5), 56.2 (C3), 48.4 (NCH_2Ph), 29.8 (C2), 26.8 ($C(\underline{C}H_3)_3$), 19.0 ($\underline{C}(CH_3)_3$). A solution of amino acid **17a** (834 mg, 1.748 mmol) in DMF (12 mL) was treated with *t*-butyldimethylsilyl chloride (1.33 g, 8.82 mmol), triethylamine (1.21 mL, 1.66 g, 16.47 mmol), and dimethylaminopyridine (50 mg) was stirred at room temperature for 20 hours. The DMF was removed at reduced pressure. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous phase was extracted further with CH_2Cl_2 (4x20 mL). The combined organic extracts were then washed with water (30 mL) then dried, filtered and concentrated to give a pinkish oil. ^1H NMR of the crude product indicated a 1.1:1 ratio of silyl ester and acid. The residue was then dissolved in MeOH (10 mL)

and cooled to 0°C. To the mixture was then added HCl (0.92 mL of a 1M aqueous solution) and the solution then stirred for 30 mins. NaOH (0.92 mL of a 1M aqueous solution) was then added and the mixture concentrated to afford **17b** as a brownish/pink oil (1.155 g, 90%) (yield based on purity from NMR spectrum). This material was used without purification in subsequent reactions. ^{1}H NMR (200 MHz) δ 7.7-7.1 (m, 11H), 3.8-3.7 (m, 3H, NCH_2Ph, H4), 3.57 (dd, *J*=4.8, 10.5 Hz, 1H, H5), 3.5-3.4 (m, 1H, H5), 3.27 (m, 1H, H3), 2.37 (bd, *J*=6.9 Hz, 2H, 2xH2), 0.93 (s, 9H, $C(CH_3)_3$), 0.71 (s, 9H, $C(CH_3)_3$), -0.11 (s, 3H, CH_3), -0.24 (s, 3H, CH_3).

(3*S*,4*S*,1'*R*)-4-[1-(*t*-butyldimethylsilyl)oxy-2-*t*-(butyldiphenylsilyl)oxy-1-ethyl]-1-phenylmethylazetidin-2-one 19.

A mixture of crude amino acid **17b** (670 mg, 0.927 mmol), triphenylphosphine (316 mg, 1.205 mmol) and 2,2-dipyridyldisulfide (265 mg, 1.205 mmol) in acetonitrile (100 mL) was heated at reflux for 4 hours. The mixture was cooled to room temperature and then concentrated. Dichloromethane (3 mL) was then added and to the cooled solution (0°C) was added triethylamine (0.3 mL) and methyl iodide (1.0 mL). The mixture was left overnight and then concentrated. The residue was purified by flash chromatography (1:1 Et_2O, hexanes) to give **19** as a colourless oil, R_f=0.5, (304 mg, 57%) $[\alpha]_D^{20}$ -7.48, (*c*=1.11, $CHCl_3$). Anal. calc'd for $C_{34}H_{47}NO_3Si_2$: C, 71.2; H, 8.3; N, 2.4. Found C, 71.0; H, 8.3; N, 2.5%. ^{1}H NMR (200 MHz) δ 7.6-7.5 (m, 4H), 7.5-7.2 (m, 11H), 4.84 (d, *J*=15 Hz, 1H, CH_2Ph), 3.89-3.74 (m, 3H, CH_2Ph, H4, H5), 3.55 (dd, *J*=4.5, 10.4 Hz, 1H, H6), 3.38 (dd, *J*=8.0, 10.4 Hz, 1H, H6), 3.01 (dd, *J*=1.6, 14.1 Hz, 1H, H3), 2.64 (dd, *J*=5.1, 14.1 Hz, 1H, H3), 0.96 (s, 9H, $C(CH_3)_3$), 0.83 (s, 9H, $C(CH_3)_3$), -0.01 (s, 3H, $SiCH_3$), -0.12 (s, 3H, $SiCH_3$). ^{13}C NMR (50 MHz) δ 167.9 (C=O), 135.7, 135.5, 134.5, 133.0, 132.9, 129.9, 129.9, 128.8, 128.3, 127.8, 127.7, 68.8 (C5), 65.1 (C6), 52.1 (C4), 44.5 (CH_2Ph), 36.5, (C3), 26.7, 25.59 (2 x $C(\underline{C}H_3)_3$), 19.0, 17.9 (2 x $\underline{C}(CH_3)_3$), -4.3, -5.1 (2 x $SiCH_3$). IR (film) 3071, 2955, 2930, 2857, 1755, 1113, 837, 703 cm^{-1}. MS (CI, methane) *m/z* 574 (M+1, 10), 516 (22), 474 (22), 91 (100).

(4*S*,1'*R*)-4-[1,2-Bis-(*t*-butyldimethyl)silyloxy-1-ethyl]-1-phenylmethylazetidin-2-one 18a.

A solution of amino acid **16b** (1.25 mmol, prepared from lactone **9** according to the general procedure described earlier) in acetonitrile (125 mL) was treated with 2,2-dipyridyldisulfide (359 mg, 1.63 mmol) and triphenylphosphine (426 mg, 1.63 mmol). The mixture was then heated at reflux for 4 hours. After this time the solvent was removed at reduced pressure and the residue dissolved in CH_2Cl_2. The solution was cooled to 0°C and then treated with triethylamine (0.4 mL) and iodomethane (1.4 mL). The mixture was left to stand overnight and then concentrated. The residue was purified by flash chromatography (eluant 2:1 hexanes, Et_2O).

Fractions containing material R_f=0.5 were combined and concentrated to give **18a** as a pale yellow oil (271 mg, 48%, 3 steps). $[\alpha]_D^{20}$ -0.65 (*c*=0.775, $CHCl_3$). ^1H NMR (200 MHz) δ 7.33-7.20 (m, 5H), 4.79 (d, *J*=15 Hz, 1H, NCHPh), 3.83 (m, 2H, NCHPh, H5), 3.63 (m, 1H, H6), 3.48 (dd, *J*=4.7, 10.3 Hz, 1H, H6), 3.33 (dd, *J*=5.1, 14.1 Hz, 1H, H4), 3.01 (dd, *J*=1.6, 14.1 Hz, 1H, H3), 2.70 (dd, *J*=5.1, 14.1 Hz, 1H, H3), 0.86 (s, 9H, $C(CH_3)_3$), 0.79 (s, 9H, $C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$), -0.04 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (50 MHz) δ 167.9 (C=0), 135.8 128.7, 128.3, 127.6, 69.5 (C5), 64.7 (C6), 52.3 (C4), 44.5 (NCH_2Ph), 36.9 (C3), 25.7 , 25.7 (2x$C\underline{C}H_3)_3$), 18.1, 18.0 (2x$\underline{C}(CH_3)_3$), -4.1, -4.9, -5.6 (4x$SiCH_3$). IR (film) 2956, 2929, 2857, 1759, 1254, 1120, 838, 778cm^{-1}. MS (CI, methane) *m/z* 450 (M+1, 100), 408 (75), 392 (53), 350 (27), 91 (25), 57 (24). HRMS $C_{24}H_{44}NO_3Si_2$ (M+1) requires 450.286; found 450.284±0.004.

(4*S*,1'*R*)-4-[1,2-Bis-(*t*-butyldimethyl)silyloxy-1-ethyl]azetidin-2-one 18b.

Sodium (13 mg, 0.579 mmol) was added to distilled ammonia (3 mL) at -78°C. The dark blue mixture was treated with a solution of **18a** (104 mg, 0.232 mmol) in THF (1 mL). The mixture was stirred at -78°C for 1 hour. Solid ammonium chloride was then carefully added, followed by Et_2O (5 mL). The mixture was warmed to room temperature, filtered and concentrated. The residue was purified by preparative TLC (eluant, 2:1, Et_2O, hexanes) to afford **18b** as a colourless oil (65 mg, 78%). $[\alpha]_D^{20}$ -20.80 (*c*=1.37, $CHCl_3$). ^1H NMR (200 MHz) δ 5.93 (bs, 1H, NH), 3.73 (m, 2H, H4, H5), 3.61 (dd, *J*=4.1, 10.1 Hz, 1H, H6), 3.42 (dd, *J*=7.4, 10.0 Hz, 1H, H6), 2.92 (d, with further fine splitting, *J*=14.7 Hz, 1H, H3), 2.84 (ddd, *J*=1.8, 4.3, 14.6 Hz, 1H, H3), 0.88 (s, 9H, $C(CH_3)_3$), 0.87 (s, 9H, $C(CH_3)_3$), 0.59 (s, 6H, $Si(CH_3)_2$), 0.44 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (50 MHz) δ 168.4 (C=O), 72.4 (C5), 65.8 (C6), 50.2 (C4), 39.2 (C3), 25.8, 25.7 (2x$C\underline{C}H_3)_3$), 18.2, 18.0 (2x$\underline{C}(CH_3)_3$), -4.5, -4.9, -5.5 (4x$SiCH_3$). IR (film) 3250, 2956, 2858, 1766, 1472, 1483, 1254, 1124, 1088, 1004, 836, 778 cm^{-1}. MS (CI, methane) *m/z* 360 (M+1, 100), 344 (23), 302 (43), 260 (23), 202 (40), 73 (20), 57 (23). HRMS $C_{17}H_{38}NO_3Si_2$ (M+1) requires 360.238; found 360.238±0.004.

(4*S*,1'*R*)-4-[1,2-Bis-(*t*-butyldimethyl)silyloxy-1-ethyl]-1-((*t*-butyldimethyl)silyl)azetidin-2-one 18c.

A solution of **18b** (64 mg, 0.178 mmol) in DMF (1 mL) was cooled to 0°C. *t*-Butyldimethylsilylchloride (35 mg, 0.232 mmol) was then added followed by triethylamine (27 mg, 37 µL, 0.276 mmol). The mixture was stirred at 0°C for 1 hour and then at room temperature for 20 min. The mixture was partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The aqueous phase was extracted further with CH_2Cl_2 (3x10 mL). The combined organic extracts were then washed with water (15 mL), dried ($MgSO_4$), filtered and concentrated to give a colourless oil (90 mg). The crude material was purified by preparative t.l.c. (3:1, hexanes, Et_2O) to give **18c**

(53 mg, 63%). $[\alpha]_D^{20}$ -44.2 (*c*=0.31, $CHCl_3$). ^1H NMR (200 MHz) δ 3.87 (m, 2H, H4, H5), 3.54 (dd, *J*=2.6, 14.9 Hz, 1H, H6), 3.28 (dd, *J*=8.3, 10.0 Hz, 1H, H6), 3.11 (dd, *J*=2.6, 14.9 Hz, 1H, H3), 2.86 (dd, *J*=5.6, 14.8 Hz, 1H, H3), 0.95 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.88)s, 9H, $C(CH_3)_3$), 0.34 (s, 3H, $SiCH_3$), 0.17 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.04 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (50 MHz) δ 173.8 (C=O), 71.8 (C5), 64.7 (C6), 51.2 (C4), 37.8 (C3), 26.3, 25.7, 25.7 ($3xC(\underline{C}H_3)_3$), 19.4, 18.0, 18.0 ($3x\underline{C}(CH_3)_3$), -4.0, -4.8, -5.2, -5.4, -5.6, -5.7 ($6xSiCH_3$). IR (film) 2930, 2858, 1751, 1472, 1254, 836, 776 cm^{-1}.

(3*R*,4*S*,1'*R*)-4-(1,2-Bis-(*t*-butyldimethyl)silyloxy-1-ethyl)-1-((*t*-butyldimethyl)silyl)-3-ethylazetidin-2-one 20.

18c (40 mg, 0.085 mmol) in THF (1 mL) was added to a solution of LDA (0.101 mmol) in THF (1mL) at -78°C. The mixture was stirred at -78°C for 15 min after which time DMPU (20 µL) was added to the mixture, followed by iodoethane (49 mg, 0.315 mmol). The mixture was warmed to -20°C at which temperature stirring was maintained for 3 hours. Aqueous ammonium chloride was added and the mixture extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were washed with water, dried ($MgSO_4$), filtered and concentrated. The residue was purified by preparative t.l.c. (eluant 3:1, hexanes/Et_2O) to give **20** as a colourless oil (18 mg, 59% based on recovered starting material), $[\alpha]_D^{20}$ -22.4 (*c*= 0.50) ($CHCl_3$). ^1H NMR (300 MHz) δ 3.87 (dd, *J*=5.2, 8.9 Hz, 1H, H5), 3.60-3.53 (m, 2H, H4, H6), 3.28 (dd, *J*=8.8, 9.9 Hz, 1H, H6), 3.20 (ddd, *J*=2.3, 6.2, 8.8, 1H, H3), 1.84-1.74 (m, 1H, $C\underline{H}_2CH_3$), 1.67-1.54 (m, 1H, $C\underline{H}_2CH_3$), 1.01 (t, *J*=7.4 Hz, 3H, $CH_2C\underline{H}_3$), 0.89 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$), 0.34 (s, 9H, $C(CH_3)_3$), 0.16 (s, 3H, $SiCH_3$), 0.084, (s, 3H, $SiCH_3$) 0.077 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$). ^{13}C NMR (50 MHz) δ 177.0 (C=O), 72.0 (C5), 64.6 (C6), 57.9 (C4), 52.2 (C3), 26.4, 25.8, 25.8 ($3xC(\underline{C}H_3)_3$), 22.5 (CH_2), 19.4, 18.1, 18.1 ($3x\underline{C}(CH_3)_3$), 11.8 (CH_3), -3.9, -5.2, -5.5 ($3xSi(CH_3)_2$). (IR (film) 2956, 2930, 2884, 2839, 1747, 1471, 1464, 1254, 1118, 836, 777 cm^{-1}. HRMS $C_{25}H_{56}NO_3Si_3$ (M+1) requires 502.357; found 502.356±0.005.

(3*S*,4*S*) Methyl 3-benzylamino-4-(*t*-butyldimethylsilyl)oxy-5-(*t*-butyldiphenylsilyl)-oxypentanoate 22.

Diazomethane was bubbled through a solution of amino acid **21** (74 mg, 0.103 mmol, prepared from lactone **10** according to the general procedure described earlier) in CH_2Cl_2 (10 mL) until yellow colouration persisted. The solution was concentrated and the residue purified by preparative t.l.c. to afford **22** in quantitative yield. $[\alpha]_D^{20}$ -9.9 (*c*=0.565, $CHCl_3$). Anal. calc'd for $C_{35}H_{51}NO_4Si_2$: C, 69.3; H, 8.6; N, 2.3. Found C, 69.4; H, 8.5; N,

1.9%. ^{1}H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.5-7.2 (m, 11H), 3.96 (m, 1H, H4), 3.81 (m, 2H, NCH_2Ph), 3.66 (s, 3H, CH_3), 3.64 -3.51 (m, 2H, H5), 3.38 (m, 1H, H3), 2.54 (dd, J=4.5, 15.1 Hz, 1H, H2), 2.39 (dd, J=8.4, 15.1 Hz, 1H, H2), 1.81 (bs, 1H, NH), 1.02 (s, 9H, $C(CH_3)_3$), 0.82 (s, 9H, $C(CH_3)_3$), 0.01 (s, 3H, $SiCH_3$), -0.10 (s, 3H, $SiCH_3$). ^{13}C NMR (50 MHz) δ 173.3 (C=O), 135.6, 133.1, 129.7, 129.7, 127.7, 126.9, 72.5 (C4), 65.2 (C5), 59.3 (C3), 51.5 ($CO_2\underline{C}H_3$), 51.3 (NCH_2Ph), 26.8, 25.7 (2x$C(\underline{C}H_3)_3$), 19.1, 17.9 (2x$\underline{C}(CH_3)_3$), -4.6, -4.9 (2x$SiCH_3$). IR (film) 3453, 2954, 2930, 2857, 1738, 1253, 1113, 701 cm^{-1}. MS (CI, methane) *m/z* 606 (M+1, 20), 192 (100), 91 (82), 79 (23), 59 (36).

(2*S*,3*S*,4*S*) Methyl 3-benzylamino-4-(*t*-butyldimethylsilyl)oxy-5-(*t*-butyldiphenylsilyl)oxy)-2-ethylpentanoate 23.

Diazomethane was bubbled through a solution of amino acid **15b** (0.154 mmol, prepared from lactone **12a** in CH_2Cl_2 (5 mL) and ethanol (10 mL) until yellow colouration of the solution persisted. The solution was then concentrated and the residue purified by preparative t.l.c. to afford **23** (41 mg, 42%, 3 steps). ^{1}H NMR (200 MHz) δ 7.68-7.63 (m, 4H), 7.42-7.21 (m, 11H), 3.79 (AB quartet, J=13.0 Hz, 2H, NCH_2Ph), 3.83 (obscured multiplet, 1H, H4), 3.64 (obscured multiplet, 2H, H5), 3.59 (s, 3H, CO_2CH_3), 3.17 (dd, J= 3.6, 5.8 Hz, 1H, H3), 2.58 (m, 1H, H2), 1.90-1.75 (m, 1H, $C\underline{H}_2CH_3$), 1.72-1.58 (m, 1H, $C\underline{H}_2CH_3$), 1.00 (s, 9H, $C(CH_3)_3$), 0.84 (s and overlapping t, 12H, $C(CH_3)_3$ and $CH_2C\underline{H}_3$). ^{13}C NMR (50 MHz) δ 176.0 (C=O), 140.9, 135.7, 133.3, 126.697 128.3, 128.2, 127.7, 126.7, 73.8 (C4), 65.4 (C5), 60.9 (C3), 53.1 (NCH_2Ph), 51.2 (CO_2CH_3), 48.5 (C2), 26.7 ($C(\underline{C}H_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 20.6 ($\underline{C}H_2CH_3$), 19.1 ($C(\underline{C}H_3)_3$), 18.0 ($C(\underline{C}H_3)_3$), 12.4 ($CH_2\underline{C}H_3$), -4.4 ($SiCH_3$), -4.9 ($SiCH_3$). IR (film) 2931, 2857, 1733, 1471, 1428, 1256, 1113, 701cm^{-1}. MS (CI, methane) *m/z* 634 (M+1, 6), 510 (22), 220 (100), 91 (40), 71 (22), 57 (34). HRMS, $C_{37}H_{56}NO_4Si_2$ (M+1) requires 634.375, found 634.374$\pm$0.003.

(4*S*,5*S*)-4-Ethylamino-5-(*t*-butyldiphenylsilyl)oxymethyldihydro-2-(3*H*)furanone 24.

A solution of lactone **10** (157 mg, 0.342 mmol) in ethanol (5 mL) containing palladium on carbon (10%) (200 mg) was stirred under an atmosphere of hydrogen for 2 days. The mixture was filtered through a pad of celite and the filtrate concentrated at reduced pressure. The residue was purified by flash chromatography (19:1, $CHCl_3$/MeOH). The less polar fractions were combined and concentrated to give starting material (21 mg, 13%). The more polar fractions contained **24** (56 mg, 41%), $[\alpha]_D^{20}$ +15.44, (c=1.19, $CHCl_3$). Anal. calc'd for $C_{23}H_{31}NO_3Si$: C, 69.5; H, 7.9; N, 3.5. Found C, 69.3; H, 8.0; N, 3.5%. ^{1}H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.5-7.4 (m, 6H), 4.30 (m, 1H, H5), 3.86 (dd, J=3.9, 11.3 Hz, 1H, H6), 3.76 (dd, J=3.1, 11.3 Hz, 1H, H6), 3.59 (m, 1H, H4), 2.92 (dd, J=7.8, 17.8 Hz, 1H, H3), 2.61 (q, J=7.1 Hz, 2H, $NC\underline{H}_2CH_3$),

2.36 (dd, *J*=4.0, 17.8 Hz, 1H, H3), 1.11 (t, *J*=7.1 Hz, 3H, $NCH_2C\underline{H}_3$), 1.05 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 175.9 (C=O), 135.6, 135.5, 132.7, 132.2, 129.0, 127.9, 85.1 (C5), 64.4 (C6), 56.4 (C4), 41.7 ($N\underline{C}H_2CH_3$), 36.5 (C3), 26.7 ($C(\underline{C}H_3)_3$), 19.1 ($\underline{C}(CH_3)_3$), 15.2 (CH_3). IR (film) 2961, 2932, 2858, 1777, 1428, 1178, 1114, 703 cm^{-1}. MS (CI, methane) *m/z* 398 (M+1, 7), 298 (32), 144 (28), 116 (100), 58 (48).

(4*S*,5*S*)-4-Amino-5-(*t*-butyldiphenylsilyl)oxymethyldihydro-2-(*3H*)furanone 25.

A solution of lactone **10** (926 mg, 2.02 mmol) in ethyl acetate (50 mL) containing palladium on carbon (10%) (600 mg) was stirred under an atmosphere of hydrogen for 2 days. The mixture was then filtered through a pad of celite and the filtrate concentrated at reduced pressure. The residue was purified by flash chromatography. The column was first eluted with Et_2O to remove the unreacted starting material (217 mg, 23%), and then with 19:1, $CHCl_3$/MeOH to give **25**, R_f=0.4, (500 mg, 68%), $[\alpha]_D^{20}$ +19.44, (*c*=0.72, $CHCl_3$). Anal. calc'd for $C_{23}H_{31}NO_3Si$: C, 68.3; H, 7.4; N, 3.8. Found C, 68.1; H, 7.5; N, 4.0%. ^1H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.5-7.4 (m, 6H), 4.18 (q, *J*=3.5 Hz, 1H, H5), 3.83 (m, 3H, 2xH6, H4), 2.98 (dd, *J*=7.7, 17.6 Hz, 1H, H3), 2.29 (dd, *J*=4.8, 17.6 Hz, 1H, H3), 1.60 (bs, 2H, NH_2), 1.05 (s, 9H, $C(CH_3)_3$). IR (film) 2932, 2858, 1774, 1472, 1427, 1114, 703 cm^{-1}. MS (CI, methane) *m/z*, 370 (M+1, 3), 250 (22), 121 (58), 116 (26), 97 (20), 88 (100), 79 (23), 77 (34), 75 (44), 57 (39).

(4*S*,5*S*)-4-Benzyloxycarbonylamino-5-((*t*-butyldiphenylsilyl)oxymethyl)dihydro-2-(*3H*)furanone 26.

A solution of aminolactone **25** in CH_2Cl_2 (14 mL) was cooled to 0°C and treated with benzylchloroformate (413 µL, 2.89 mmol), triethylamine (402 µL, 2.88 mmol) and DMAP (10 mg). The reaction mixture was stirred at 0°C for 1.5 hours, until TLC showed that the starting material had been consumed. The reaction mixture was then partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The aqueous phase was further extracted with CH_2Cl_2 (3x10 mL). The combined organic extract was then washed with water (20 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (2:1, Et_2O, hexanes) to afford (**26**) R_f=0.5, (453 mg, 67%), $[\alpha]_D^{20}$ +18.99, (*c*=0.695, $CHCl_3$). Anal. calc'd for $C_{29}H_{33}NO_5Si$: C, 69.2; H, 6.6; N, 2.8. Found C, 68.9; H, 6.8; N, 2.4%. ^1H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 6H), 5.18 (d, *J*=6.6 Hz, 1H, NH), 5.10 (s, 2H, NCH_2Ph), 4.47 (bm, 2H, H4, H5), 3.87 (bs, 2H, 2xH6), 3.15 (dd, *J*=8.6, 18.0 Hz, 1H, H3), 2.44 (dd, *J*=3.0, 18.1 Hz, 1H, H3), 1.04 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 175.5 (C=O, lactone), 155.7 (C(O)OBn), 135.9, 135.48, 135.4, 132.4, 132.0, 129.9, 128.5, 128.2, 128.0, 127.8, 86.0 (C5), 66.9 (OCH_2Ph), 64.1 (C6), 49.7 (C4), 35.80 (C3), 26.6 ($C(\underline{C}H_3)_3$), 19.0

($\underline{C}(CH_3)_3$). IR (film) 3330, 2958, 2932, 2859, 1782, 1719, 1528, 1264, 1114, 740, 702 cm^{-1}. MS (FAB) *m/z* 504 (M+1, 26), 197 (83), 135 (100).

(3*R*,4*S*,5*S*)-4-Benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-((1-hydroxy-1-methyl)-1-ethyl)dihydro-2-(*3H*)furanone 27.

Using the general method described above lactone **10** (120 mg, 0.261 mmol) was treated with acetone (200 µL, 2.30 mmol). The resulting mixture was stirred at -78°C for 1.5 hours to afford, after work-up and flash chromatography (2:1, Et_2O, hexanes), **27** as a colourless oil, R_f=0.4, (119 mg, 89%), $[\alpha]_D^{20}$ +5.07 (*c*=0.69, $CHCl_3$). ^1H NMR (200 MHz) δ 7.7 (m, 4H), 7.5-7.1 (m, 11H), 4.24 (ddd, *J*=3.5, 3.5, 7.1 Hz, 1H, H5), 4.01 (dd, *J*=3.0, 11.0 Hz, 1H, H4), 3.9-3.5 (m, 4H, NCH_2Ph, 2xH6), 2.68 (d, *J*=9.8 Hz, 1H, H3), 1.36 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.06 [s, 9H, $C(CH_3)_3$]. ^{13}C NMR (50 MHz) δ 175.3 (C=O), 139.0, 135.7, 136.6, 132.8, 132.4, 130.0, 128.5, 127.9, 127.8, 127.4, 83.7 (C5), 71.3 (C1'), 63.3 (C6), 56.7 (C4), 55.7 (C3), 51.1 (NCH_2Ph), 27.5 (CH_3), 26.8 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}(CH_3)_3$). IR (film) 3422, 2931, 2858, 1764, 1428, 1113, 701 cm^{-1}. MS (CI, methane) *m/z* 518 (M+1, 16), 360 (30), 309 (20), 199 (20), 91 (100). HRMS $C_{31}H_{40}O_4NSi$ (M+1) requires 518.273, found 518.270 ±0.006.

(3*R*,4*S*,5*S*)-4-Benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-(1-hydroxy-1-phenyl)methyldihydro-2-(*3H*)furanone 28.

Using the general method described earlier, lactone **10** (83 mg, 0.181 mmol) was treated with benzaldehyde (96 µL, 0.905 mmol). The resulting mixture was allowed to warm to -50°C, at which temperature stirring was maintained for 2 hours. The reaction was quenched at -50°C to afford after work-up a yellow oil. ^1H NMR of the crude product indicated a 1:1 mixture of diasteromeric products. The crude product was purified by preparative TLC (2:1, Et_2O, hexanes). Extraction of the chromophoric band R_f=0.5 gave pure *diastereomer (A)*, (42 mg, 41%), as a colourless oil, $[\alpha]_D^{20}$ 34.11, (*c*=0.475, $CHCl_3$). ^1H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.6-7.3 (m, 12H), 7.24-7.18 (m, 2H), 6.9-6.8 (m, 2H), 5.42 (d, *J*=3.2 Hz, 1H, H1'), 4.27 (m, 1H, H5), 3.95 (dd, *J*=4.0, 11.4 Hz, 1H, H6), 3.79 (m, 2H, H6, H4), 3.18 (AB quartet, *J*=12.6 Hz, 2H, NCH_2Ph), 2.95 (dd, *J*=3.2, 7.6 Hz, 1H, H3), 1.08 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 175.8 (C=O), 140.9, 139.1, 135.7, 135.7, 133.0, 132.9, 129.9, 128.8, 128.3, 127.8, 127.1, 125.3, 84.7 (C5), 70.7 (C1'), 63.7 (C6), 54.8, 54.7 (C3, C4), 51.0 (NCH_2Ph), 26.8 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}(CH_3)_3$). IR (film) 3462, 3069, 2931, 2857, 1770, 1428, 1113, 739, 701 cm^{-1}. MS (CI, methane) *m/z* 566 (M+1, 4), 402 (24), 360 (20), 199 (52), 107 (71), 106 (100), 105 (52), 79 (38), 77 (58). HRMS, $C_{35}H_{40}NO_4Si$ (M+1) requires 566.2726, found 566.2729. *Diastereomer (B)* could not be obtained pure.

(1'*S*,3*R*,4*S*,5*S*)-4-Benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-(1-hydroxy-1-methyl)benzyldihydro-2-(*3H*)furanone and (1'*R*,3*R*,4*S*,5*S*)-4-benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-(1-hydroxy-1-methyl)benzyldihydro-2-(*3H*)furanone 29.

Using the general method described above lactone **10** (92 mg, 0.200 mmol) was treated with acetophenone (120 μL, 0.965 mmol). The resulting mixture was stirred at -78°C for 2.5 hours. The temperature was allowed to slowly rise to -20°C and was stirred at this temperature for a further 1 hour. The reaction was then quenched at -20°C to afford after work-up an orange oil (173 mg) which was purified by preparative TLC (2:1, Et_2O, hexanes). Extraction of the chromophoric band R_f=0.4 gave pure *diastereomer (A)* as a colourless oil which crystallised on standing (41 mg, 35%), $[\alpha]_D^{20}$ +20.9, (*c*=0.635, $CHCl_3$), mp 122-123°C (from Et_2O/hexanes). Anal. calc'd for $C_{36}H_{41}NO_4Si$: C, 74.6; H, 7.1. Found C, 74.6; H, 7.4%. ^1H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.5 -7.2 (m, 16H), 7.0-6.9 (m, 2H), 4.24 (m, 1H, H5), 3.80 (dd, *J*=4.0, 11.5 Hz, 1H, H6), 3.67 (dd, *J*=5.1, 11.5 Hz, 1H, H6), 3.49 (dd, *J*=5.9, 7.2 Hz, 1H, H4), 3.26 (AB quartet, *J*=12.6 Hz, 2H, NCH_2Ph), 3.00 (s, 1H, OH), 2.89 (d, *J*=7.4 Hz, 1H, H3), 1.91 (s, 3H, CH_3), 1.08 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 175.0 (C=O), 144.9, 139.0, 135.6, 135.6, 132.9, 132.8, 129.8, 128.5, 128.3, 127.798 127.7, 127.3, 127.1, 125.0, 83.9 (C5), 74.3 (C1'), 63.8 (C6), 57.1, 56.8, (C3, C4), 51.0 (NCH_2Ph), 28.1 (CH_3), 26.7 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}(CH_3)_3$). IR (film) 3474, 2931, 2858, 1762, 1428, 1113, 702 cm^{-1}. MS (CI, methane) *m/z* 580 (M+1, 8), 488 (56), 460 (100), 121 (95). Chromophoric band, R_f=0.3 was extracted and concentrated to give *diastereomer (B)* as a colourless oil (30 mg, 25%), $[\alpha]_D^{20}$ +8.9, (*c*=0.46, $CHCl_3$). ^1H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.5-7.2 (m, 14H), 6.7-6.9 (m, 2H), 4.16 (m, 1H, H5), 3.88 (dd, *J*=12.1, 2.8 Hz, 1H, H6), 3.63 (dd, *J*=12.0, 3.6 Hz, 1H, H6), 3.49 (dd, *J*=10.0, 7.5 Hz, 1H, H4), 3.33 (AB quartet, *J*=12.5 Hz, 2H, NCH_2Ph), 2.97 (d, *J*=10.0 Hz, 1H, H3), 1.78 (s, 3H, CH_3), 1.00 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz) δ 175.0 (C=O), 144.1, 138.7, 135.7, 135.6, 132.8, 132.4, 130.0, 128.6, 128.5, 127.9, 127.8, 127.4, 125.5, 83.9 (C5), 74.6 (C1'), 63.0 (C6), 56.9, 56.8 (C3, C4), 51.0 (NCH_2Ph), 26.8 ($C(\underline{C}H_3)_3$), 25.3 (CH_3), 19.2 ($\underline{C}(CH_3)_3$). IR (film) 3318, 3070, 2831, 2858, 1762, 1428, 1113, 701 cm^{-1}. MS (FAB) *m/z* 580 (M+1, 100), 199 (88), 197 (86), 162 (55), 146 (94), 145 (100), 137 (59), 135 (100), 121 (100), 106 (100). HRMS, $C_{36}H_{41}NO_4Si$ (M+1) requires 580.288, found 580.290±0.006.

(3*R*,4*S*,5*S*)-4-Benzylamino-5-(*t*-butyldiphenylsilyl)oxymethyl-3-(1-trimethylsilyoxy-1-methyl)ethyldihydro-2-(*3H*)furanone 30.

A solution of lactone (**29**) (267 mg, 0.516 mmol) in CH_2Cl_2 (5 mL) was treated with trimethylsilyl chloride (98 μL, 0.774 mmol) and diisopropylethylamine (153 μL, 0.877 mmol). The mixture was stirred at room temperature for 20 hours and then concentrated at reduced pressure. To the residue was added Et_2O (5 mL), a

white precipitate formed and the mixture was then filtered through a pad of celite using Et_2O as eluant. The filtrate was then concentrated at reduced pressure to afford a pale yellow oil (323 mg). The crude product was purified by flash chromatography (2:1, Et_2O/hexanes) to give **30**, R_f=0.7, (264 mg, 87%), $[\alpha]_D^{20}$ +3.5, (*c*=0.46, $CHCl_3$). Anal. calc'd for $C_{34}H_{47}NO_4Si_2$: C, 69.2; H, 8.0; N, 2.4. Found C, 69.2; H, 8.0; N, 2.2%. ^{1}H NMR (200 MHz) δ 7.7-7.6 (m, 4H), 7.4-7.2 (m, 11H), 4.26 (ddd, *J*=4.0, 4.2, 6.1 Hz, 1H, H5), 3.91 (dd, *J*=4.0, 12.0 Hz, 1H, H6), 3.8-3.6 (m, 4H, NCH_2Ph, H4 and H6), 2.59 (d, *J*=8.0 Hz, 1H, H3), 1.53 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.06 (s, 9H, $C(CH_3)_3$), 0.05 (s, 9H, Si $(CH_3)_3$). ^{13}C NMR (50 MHz) δ 174.5 (C=O), 139.5, 135.7, 135.6, 132.9, 132.8, 129.9, 128.5, 128.0, 127.8, 127.2, 83.8 (C5), 75.1 (C1'), 64.3 (C6), 58.2, 57.8 (C3, C4), 52.1 (NCH_2Ph), 30.0 (CH_3), 26.8 ($C(\underline{C}H_3)_3$), 25.7 (CH_3), 19.2 ($\underline{C}(CH_3)_3$), 2.4 ($Si(CH_3)_3$). IR (film) 2957, 2932, 2858, 1773, 1252, 1113, 1029, 811, 701 cm^{-1}. MS (CI, methane) *m/z* 590 (M+1, 20), 500 (45), 91 (100).

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