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Photoinduced Addition of Methanol to 5(*S*)-5-Triisopropylsiloxymethyl-N-boc-dihydropyrrole-2(5*H*)-one: a New Route to 4(*S*), 5(*S*)-Disubstituted Pyrrolidin-2-ones

Michael G. B. Drew, R. John Harrison, John Mann*, Allen J. Tench, and Robert J.Young#

Department of Chemistry, Reading University, Whiteknights, Reading, RG6 6AD, UK.

#Glaxo-Wellcome Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK

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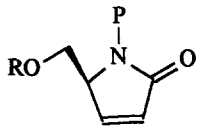
Abstract: We describe the photoinduced addition of methanol to 5(*S*)-5-triisopropylsiloxymethyl--N-boc-dihydropyrrole-2(5*H*)-one to produce 5(*S*)-5-triisopropylsiloxymethyl-4(*S*)-hydroxymethyl-pyrrolidine-2-one, and conversion of this into a variety of 4(*S*), 5(*S*)-pyrrolidine-2-ones. Photo-induced addition of methanol to 5(*R*)-N-boc-5-amino-dihydropyran-2(5*H*)-one yielded the unexpected product 4(*S*)-1'-[2'-hydroxy, 1'-(*R*)-N-boc-amino]ethyl-tetrahydrofuran-2-one via rearrangement of the initial photoadduct.

During the past five years, we have demonstrated the synthetic utility of photoinduced additions of alcohols and amines to 5-substituted-dihydrofuran-2(5*H*)-ones (butenolides),[1] but had not explored the potential of the corresponding dihydropyrrole-2(5*H*)-one analogues **1**. For example, addition of methanol to this species would be expected to yield adducts of general structure **2**. Such homochiral products could be of use in the synthesis of analogues of glutamate **3**[2] and of the kainoids, eg kainic acid[3] **4**. Glutamate is a major excitatory neurotransmitter, active at around half of all neurones in the brain[2]. Over-excitation of glutamate receptors is implicated in various neurological disorders such as epilepsy, spasticity and neuropathic pain; and in a variety of neurodegenerative diseases including stroke, schizophrenia, Huntington's chorea, and Alzheimer's disease. Compounds that act at these receptors to moderate the activity of glutamate, eg kainoids, are thus of considerable interest.



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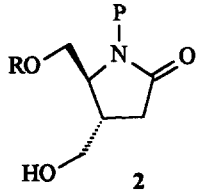

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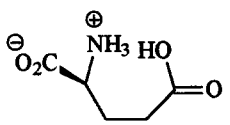

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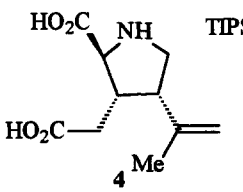

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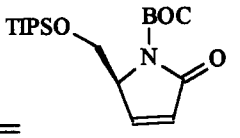

5

Our chosen substrate **5** is readily available via the route shown in **Scheme One**. Thus 5(*S*)-5-hydroxymethyl-tetrahydropyrrolidine-2-one **6** was prepared from (*S*)-glutamic acid via the known route,[4] and converted sequentially into its triisopropylsilyl-ether derivative **7**, and N-boc-derivative **8**, neither of which had been reported previously. It is worth noting, that all of our initial experiments were carried out with a *tert*-butyldimethylsilyl ether, but this gave lower yields in the photochemical step and proved to be incompatible with DAST (see **Scheme Two**). Reaction of **8** with lithium *bis*-trimethylsilylamide and phenylselenenyl

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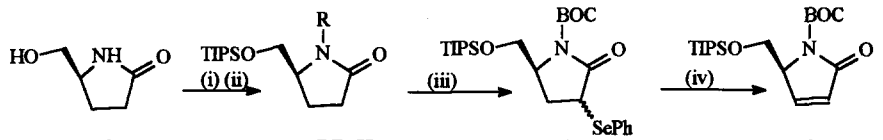
bromide provided the expected phenylselenenyl-derivative **9**, and this was easily converted into the desired dihydropyrrole-2(5*H*)-one **5** using MCPBA in DCM at -30° C. The overall yield for the four-stage process was around 55%.



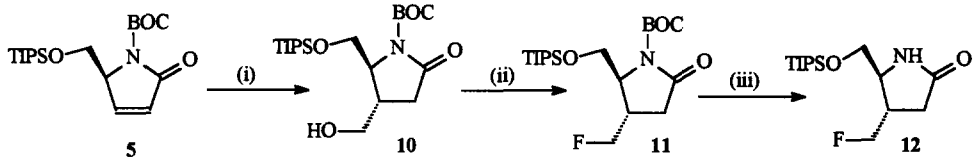
6 **7 R=H** **8 R=BOC** **9** **5**

Scheme One

(i) TIPSCl, imidazole, DCM (quant); (ii) Bu^{t}OCO.OBu^t, DMAP, MeCN (quant); (iii) Li *bis*-TMS-amide, THF, PhSeBr (76%); (iv) MCPBA, DCM (72%).

Irradiation of a solution of **5** in methanol containing one equivalent of benzophenone as photoexcitant, using medium pressure mercury vapour lamps and an irradiation time of around 30 hours, provided a 51% yield of photoadduct **10**, after flash column chromatography. There was no evidence for other regio- or stereoisomers, though around 30% of the adduct of **5** and the diphenylmethanol radical was produced. This was anticipated from our previous work.[1] The stereochemical purity of **10** was established through the formation of the Mosher's ester, [5] and the stereochemistry was assigned through extensive NOE experiments.

Given the current interest in compounds containing fluorine atoms in place of hydrogens,[6] the photoadduct was also converted into the corresponding fluoromethyl derivative **11** by reaction with diethylaminosulphur trifluoride (DAST). The N-BOC group could then be selectively removed using acid to provide the fluoromethyl-lactam **12**.



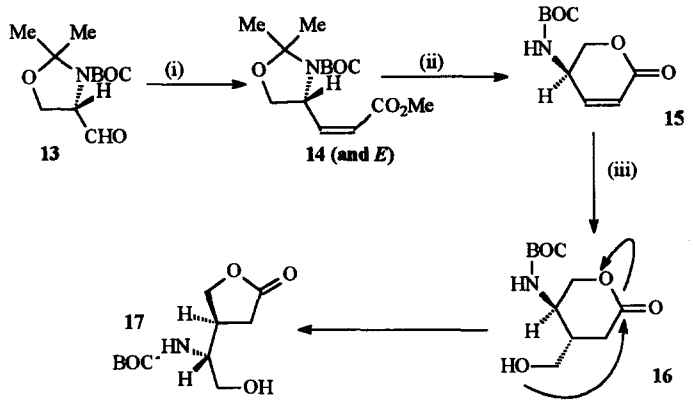
5 **10** **11** **12**

Scheme Two

(i) hv, Ph_2CO, MeOH (51%); (ii) DAST, DCM (56%); (iii) aq. HCl (52%)

Finally, an alternative route to the photochemical substrate **5** , that avoided the use of selenium chemistry, was explored. This involved the chemistry shown in **Scheme Three**. The known Garner aldehyde[7] **13** was prepared from (*S*)-serine via the literature procedure, but with the use of hypervalent iodine (Dess-Martin) oxidation[8] for the final oxidation of alcohol to aldehyde. This consistently provided excellent (>85%) yields of

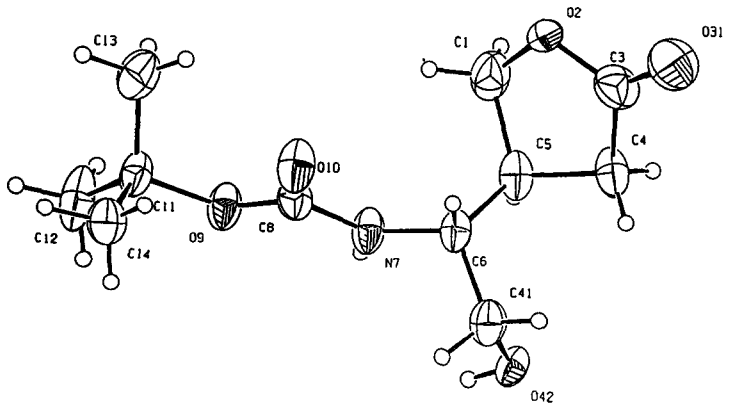
13. Reaction of this with carbomethoxymethylidene triphenylphosphorane in methanol produced a mixture of *Z*- and *E*-alkenes in ratio of 1:3. The *Z*-alkene **14** [9] was treated with acid in the hope of obtaining the alcohol-unprotected form of **5**, but the only product was in fact the dihydropyran-2-one **15** [9] in 75% yield. Irradiation of this compound in methanol in the presence of one equivalent of benzophenone provided not the anticipated photoadduct **16**, but the tetrahydrofuranone **17**, which presumably arises via rearrangement of the initial photoadduct **16**. An X.ray structural study of compound **17**, was in full agreement with the structure proposed. An ORTEP plot is shown below.



Scheme Three

(i) $Ph_3P{=}CHCO_2Me$, MeOH (78%, *E*:*Z* 3:1); (ii) TFA, DCM (75%); (iii) hv, Ph_2CO, MeOH (22%).

We are currently exploring the potential of compounds **10**, **12** and **17** for the construction of novel analogues of glutamic acid and kainic acid. In addition, while the yield of the photo-induced addition to produce **10** is reasonable for this type of process [1] (the yield is around 70% if isopropanol is used), the reaction that produces the rearranged product **17** is rather poor. Work to explore the full scope of these processes is underway.



Experimental

IR spectra were recorded using a Perkin-Elmer 881 series double beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low resolution and accurate mass data were recorded on a VG Autospec spectrometer. Elemental analyses were carried out by Medac Ltd., Brunel University. NMR spectra were recorded using JEOL EX400, Bruker DPX 250 or Bruker WM250 spectrometers. Solvents were dried by distillation from calcium hydride (DCM, toluene, benzene) or from sodium-benzophenone (THF and diethyl ether). Petrol refers to the fraction boiling at 40-60° C, and ether refers to diethyl ether.

Crystallographic data was collected with Mo-Kα radiation using the MARresearch Image Plate System. The crystals were positioned at 75 mm from the Image Plate and 95 frames were measured at 2° intervals with a counting time of 2 minutes. Data analysis was carried out with the XDS programme[10]. The structure was solved using direct methods with the SHELX86 programme[11], and the structure was then refined on F2 using SHELX1[12]. All calculations were carried out on a Silicon Graphics R4000 Workstation at the University of Reading. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre.

(S)-(+)-5-(Triisopropylsilyloxymethyl)-pyrrolidin-2-one (7).

A solution of (S)-(+)-5-(hydroxymethyl)-pyrrolidin-2-one **(6)** (15.79g, 137 mmol) was cooled to 0° C, and a mixture of imidazole (12.07 g, 177 mmol) and TIPSCl (31.85 g, 165 mmol) in dry dichloromethane (150ml) was added. The mixture was then stirred over night and allowed to warm to room temperature. The reaction was quenched with water (30 ml), the dichloromethane was removed by evaporation and the residue dissolved in ethyl acetate. This was washed with 2 x 70 ml portions of cold 10% aqueous citric acid, water, brine and dried ($MgSO_4$). Filtration and evaporation provided 42.64 g, 157 mmol (quant.) of the protected alcohol (as the monohydrate) as a pale yellow oil, which was used in the next reaction without further purification.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 21H, H-TIPS), 2.10-2.20, 1.75-1.83 (m, 2H, H-4), 2.30-2.40 (m, 2H, H-3), 3.55-3.60 (m, 1H, H-5), 3.70-3.80 (m, 2H, H-6), 6.20 (s, 1H, NH); ^{13}C N.M.R. (100 MHz, $CDCl_3$) δ: 12.30, 12.62, 18.26 (C-TIPS); 23.18 (C-4); 30.10 (C-3); 56.33 (C-5); 67.67 (C-6); 178.24 (C=O of lactam); IR (thin film) Umax. 3215 (NH st); 2968, 2943 (C-H st); 1699 (C=0 st of lactam) cm^{-1}; analysis calcd. for $C_{14}H_{29}O_2NSi.H_2O$ C 58.13, H 10.81, N 4.84, found C 58.46, H 10.53, N 4.73.

(S)-(+)-N-*tert*-Butyloxycarbonyl-5-(triisopropylsilyloxymethyl)-pyrrolidin-2-one (8).

A solution of the protected alcohol **(7)** (42.64 g, 157 mmol) and 4-dimethylaminopyridine (1.9 g, 15.55 mmol) in acetonitrile (250 ml) was cooled to -30 °C. Di-*tert*-butyl dicarbonate (33.89 g, 155 mmol) was added under

nitrogen and the mixture stirred for 30 mins. at -30 ^{0}C, and then allowed to warm to room temperature. After stirring overnight, the mixture had turned black, and as TLC indicated no starting material remained, the acetonitrile was removed by evaporation. Purification by column chromatography on silica gel eluting with 20% ethyl acetate / hexane gave 50.51 g, 136 mmol (99% yield) of a colourless oil which crystallised as a white solid. M.p.79-82 ^{0}C; $[\alpha]^{22}_D$ -52 (c 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 21H, H-TIPS), 1.52 (s, 9H, H-BOC), 2.12 (m, 2H, H-4), 2.33-2.4, 2.69-2.77 (2m, 2H, H-3), 3.77-3.81, 3.99-4.16 (2dd, 2H, H-6, J_{gem} 10.1 Hz, $J_{6a/5}$ 2.2 Hz, and $J_{6b/5}$ 4.1 Hz), 4.19 (m, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.32, 18.27, 28.45 (C-TIPS); 21.33 (C-4); 32.58 (C-3); 59.54 (C-5); 64.98 (C-6); 82.95 (Cquarternary of BOC); 150.53 (C=O of BOC); 174.87 (C=O of lactam). Umax (thin film) 2945, 2863 (C-H st); 1790 (C=0 st of lactam); 1753, 1715 (C=O st of BOC group); 1367, 1315 (CH_3 δ sy); 1161, 1115, 1034 (Si-O st, C-O st) cm^{-1}; analysis calcd. for $C_{19}H_{37}O_4NSi$ .0.5 H_2O C 60.10, H 10.06, N 3.69; found C 59.81, H 9.79, N 3.57.

(S)-(+)-N-*tert*-Butyloxycarbonyl-5-(triisopropylsilyloxymethyl)-3-phenylselenenyl-pyrrolidin-2-one (9).

The protected alcohol **(8)** (26 g, 70.22 mmol) in dry THF (250 ml) was added dropwise via a pressure equalising dropping funnel to a 1M solution of lithium *bis*(trimethylsilyl)amide in THF (77.0 ml, 77 mmol) at -78 ^{0}C under nitrogen. After stirring for 1 hour, phenylselenenyl bromide (15.27 g) in dry THF (25 ml) was added dropwise to the mixture via a pressure equalising dropping funnel, and the reaction was stirred overnight. After quenching with saturated aqueous ammonium chloride, the THF was removed by evaporation, the residue redissolved in ethyl acetate, washed with water (2 x 30 ml), brine (30 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography on silica gel and eluted with 10% ethyl acetate / hexane to give 28.06 g (76% yield) of an orange oil.

$[\alpha]^{22}_D$ -43 (c 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$)δ: 1.00 (s, 21H, H-TIPS), 1.50 (s, 9H, H-BOC), 2.20 (m, 1H, H-4), 2.50-2.71(m, 1H, H-4), 3.65-4.40 (m, 4H, H-3, H-5, H-6), 7.25-7.80 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.78 (CH-TIPS); 17.87, 28.02 (CH_3-TIPS); 30.16 (C-4); 42.25 (C-5); 57.71 (C-3); 64.38 (C-6); 83.02 (Cquarternary of BOC); 128.21-135.14 (5C-Ar); 150.01 (C=O of BOC); 173.0 (C=O of lactam); Umax 2966, 2943 (C-H st); 1786 (C=0 st of lactam); 1745, 1715 (C=O st of BOC group); 1367, 1256, 1308 (CH_3 δ sy); 1153, 1111 (Si-O st, C-O st) cm^{-1}; analysed for $C_{25}H_{42}O_4NSiSe$ C 56.88, H 8.02, N 2.65; found C 56.85, H 7.89, N 2.44.

(S)-(+)-N-*tert*-Butyloxycarbonyl-5-(triisopropylsilyloxymethyl)pyrrolid-3-en-2-one (5).

M-Chloroperbenzoic acid (1.61 g, 9.3 mmol) was added to the phenylselenenyl compound **(9)** (2.46 g, 4.67 mmol) in dry DCM (30 ml) at -30 ^{0}C. The orange reaction mixture became colourless and a white precipitate

developed. After stirring for an hour at -30°C, the reaction was quenched by the addition of pyridine (0.735 g, 0.75 ml) and the reaction stirred for a further hour. The white precipitate disappeared leaving a pale yellow solution, which was evaporated and the residue dissolved in ethyl acetate. Pyridine was removed by washing with aqueous copper sulfate solution (3 x 50 ml). The organic layer became green and was washed with water, brine, dried ($MgSO_4$) and purified by column chromatography, eluting with 20% ethyl acetate / hexane to yield 1.24 g (72% yield) of a colourless oil.

$[\alpha]^{22}_D$ -138 (c 0.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 21H, H-TIPS), 1.55 (s, 9H, H-BOC), 3.83, 4.27 (2dd, 2H, J_{gem} 9.4 Hz, $J_{6b/5}$ 6.8 Hz, $J_{6a/5}$ 3.6 Hz, H-6), 4.62 (m, 1H, H-5), 6.11 (dd, 1H, $J_{3/5}$ 1.7 Hz, $J_{3/4}$ 6.2 Hz, H-3), 7.28 (dd, 1H, $J_{4/5}$ 2.1 Hz, $J_{4/3}$ 6.2 Hz, H-4); Umax_2943, 2893, 2866 (C-H st), 1784 (C=0 st of lactam), 1745, 1713 (C=O st of BOC group) 1621(C=C st), 1163, 1122, 1103 (Si-O st, C-O) cm^{-1}; analysed for $C_{19}H_{35}O_4NSi$ C 61.75, H 9.55, N 3.79, found C 61.54, H 9.78, N 3.85.

(4S,5S)-(+)-N-*tert*-Butyloxycarbonyl-4-hydroxymethyl-5-(triisopropylsilyloxymethyl) pyrrolidin-2-one (10).

The pyrrolidin-2(5*H*)-one **(5)** (4.41 g, 11.94 mmol) and benzophenone (2.176 g, 11.94 mmol), were dissolved in 2 litres of HPLC grade methanol and degassed for 1.5 hours by bubbling nitrogen through the mixture, using a 2 litre quartz vessel. The UV source was a large Rayonet UV reactor using medium pressure mercury vapour lamps at 254 nm. The reaction mixture was irradiated for 30 hours and stirred with a magnetic stirrer. After evaporation of the methanol, the residue was purified by column chromatography using silica gel and eluting with 40% ethyl acetate / hexane to yield 2.46 g (51% yield) of a yellow oil.

$[\alpha]^{22}_D$ -71 (c 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04- 1.06 (s, 21H, H-TIPS), 1.521 (s, 9H, H-BOC), 2.17-2.22, 2.45-2.48 (2dd, 2H, J_{gem} 17.8 Hz, $J_{3b/4}$ 1.9 Hz, $J_{3a/4}$ 4.0 Hz, H-3), 2.85 (m, 1H, H-4); 3.61 (d, 2H, J_{gem} 10.1 Hz, CH_2OH), 3.83 (dd, 1H, J 4.4 Hz, 12.1 Hz, H-6), 4.06 (m, 2H, H-6, H-5);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.309, 18.295, 28.46 (TIPS, tBOC CH & CH_3); 35.80 (C-3); 36.31 (C-4); 61.96 (C-5); 65.08 (C-1'); 65.34 (C-6); 83.25 (Cquarternary of BOC); 151.0 (C=O of BOC); 172.58 (C=O of lactam); Umax (thin film) 3450 (OH st), 2943, 2891, 2866 (C-H st), 1776 (C=0 st of lactam), 1715 (C=O st of BOC group) 1462 (CH_3 δ), 1155, 1117, 1047 (Si-O st, C-O st) cm^{-1}; high resolution MS calculated for $C_{20}H_{39}O_5NSi$ 401.2587, found 401.2593.

(4S,5S)-(+)-N-*tert*-Butyloxycarbonyl-4-fluoromethyl-5-(triisopropylsilyloxymethyl) pyrrolidin-2-one (11).

The alcohol **(10)** (250 mg, 0.623 mmol) was dissolved in freshly dried DCM (2 ml) and cooled to -78 °C in flame dried apparatus. DAST (83 μl, 0.623 mmol) was added slowly via a syringe to the cooled reaction mixture. After

stirring for 30 minutes, a further portion of DAST (40 μl) was added to enable the reaction to go to completion. The reaction was warmed to room temperature and quenched with water (10 ml). The aqueous layers were extracted with DCM, the DCM fractions washed with water, brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography, eluting with 20% ethyl acetate / hexane to yield 125 mg (56%) of **(11)** as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.02-1.09(m, 21H, H-TIPS), 1.53 (s, 9H, H-BOC), 2.16-2.21 (dd, 1H, J_{gem} 18.0 Hz, $J_{3b/4}$ 1.8 Hz, H-3b), 2.87-2.95 (1H, dd, J_{gem} 18.0 Hz, $J_{3a/4}$ 8.1 Hz, H-3a), 2.64-2.73 (m, $J_{4/3a}$ 8.1 Hz, H-4), 3.79-3.82 (dd, 1H, J_{gem} 10.1 Hz, $J_{6a/5}$ 2.0 Hz, H-6a), 4.09-4.12 (dd, 1H, J_{gem} 10.1 Hz, $J_{6b/5}$ 3.5 Hz, H-6b), 4.07-4.08 (m, 1H, H-5), 4.40-4.45 (2m, 2H, J_{gem} 5.9 Hz, $J_{H,F}$ 45.9 Hz, CH_2F); ^{13}C N.M.R. (100 MHz, $CDCl_3$) δ: 11.85 (C-CH TIPS); 17.94 (C-CH_3 TIPS); 28.05 (C-BOC); 34.05, 34.25 (C-4); 34.35 (C-3); 60.75, 60.81 (C-5); 64.48 (C-6); 83.19 (Cquarternary of BOC); 83.54, 85.29 (d, $J_{C,F}$ 167.4, CH_2F) 149.94 (C=O of BOC); 173.04 (C=O of lactam); Umax (tin film) 2945, 2868 (CH st); 1785, 1752, 1718, 1696 (C=O of BOC and lactam); 1118, 1015 (C-F st) cm^{-1}; high resolution MS calculated for $C_{20}H_{38}O_4NSiF$ 404.2544, found 404.2548.

(4S,5S)-(+)-N-*tert*-Butyloxycarbonyl-4-fluoromethyl-5-(hydroxymethyl) pyrrolidin-2-one (12).

The protected alcohol **(11)** (51 mg, 0.124 mmols) was stirred with 0.01N HCl (1drop of conc. HCl in 100 ml of water / ethanol 1:1). After 1 hour, the compound **(11)** had not reacted, therefore the reaction was heated to 90 ^0C and left for 6 hours. Analysis by TLC, revealed that no starting material remained, only a spot on TLC that was much more polar than the starting material. The mixture was neutralised to pH7 using IRA-93 ion exchange resin, filtered and evaporated to remove the ethanol. The residual aqueous fraction was extracted with ethyl acetate (3 x 20 ml) and purified by column chromatography, eluting with 40% ethyl acetate / hexane to give 19 mg (52%) of the product **(12)** as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.04-1.06 (m, 21H, H-TIPS), 2.03-2.18 (m, 1H, J_{gem} 10.2 Hz, H-3b), 2.51-2.58 (m, 2H, J_{gem} 10.2 Hz, H-3a, H-4), 3.64 (m, 1H, H-5), 3.59-3.81 (2m, 2H, H-6), 4.36-4.53 (2m, 2H, $J_{H,F}$ 44.7 Hz, CH_2F); ^{13}C N.M.R. (100 MHz, $CDCl_3$) δ: 12.10 (C-TIPS-CH); 18.20 (C-TIPS-CH_3); 32.18 (C-3); 37.15, 37.35 (C-4); 58.27, 58.31 (C-5); 66.87 (C-6); 83.67, 85.38 (d, $J_{C,F}$, 166.9 Hz, CH2F); 176.39 (C=O); Umax (thin film) 3282 (NH st); 2943, 2866 (CH st); 1703 (C=O lactam); high resolution MS, calculated for $C_{15}H_{30}O_2NFSi$ 303.2022, found M+H 304.2190.

N-(*tert*-Butoxycarbonyl)-2,2-Dimethyl-4(R)-[2'-Carboxymethylethenyl]-oxazolidine. (14) To a solution of the aldehyde **(13)** (4.00 g, 17.5 mmol) in methanol (30 mL) at 0 °C was added methoxycarbonylmethylene(triphenyl)phosphorane (5.8 g, 17.5 mmol) and the solution stirred for 1 h. The solvent was removed under vacuum and the residue extracted with hot petrol. After cooling the combined extracts were filltered and the filtrate evaporated to dryness. Purification by flash chromatography (hexane : Et_2O 7:3) furnished the *cis* and *trans* isomers (ratio 1:3) as colourless crystals in an overall of yield 78%. ***Cis* Isomer** mpt 56.2-57.3 °C; NMR data ^1H [$CDCl_3$, 400 MHz] δ 1.39 & 1.48 (2xs rotamers, 9H, 3xCH_3), 1.51 &1.53 (2xs rotamers, 3H, 2-Me), 1.59 & 1.63 (2xs rotamers, 3H, 2-Me), 3.71 (s, 3H, OMe), 3.77 (dd, 1H, J_{gem} 9.8 Hz, J_{vic} 2.9Hz, 5-H), 4.25 (dd, 1H, J_{gem} 9.8 Hz, J_{vic} 7.3 Hz, 5-H), 5.31 (m, 1H, 4-H), 5.84 (d, 2H, J_{cis} 10.3 Hz, 7-H), 6.23 (dd, 1H, J_{cis}10.3 Hz, J_{vic} 7.5 Hz, 6-H); ^{13}C [$CDCl_3$, 100 MHz] δ 23.54 (2-Me), 26.38 (2-Me), 28.32 (Boc-^{t}Bu), 51.59 (OCH_3), 57.97 (4-C), 67.29 (5-C), 80.18 (quat. Boc), 94.48 (2-C), 121.82 (6-C), 146.3 (7-C), 151.51 (C=O Boc), 166.52 (C=O ester).IR ($CDCl_3$); IR (nujol mull) ν_{max} 1720, 1708, 1610, 1256, 1173, 665cm^{-1}; High resolution MS (CI^+) calcd $(C_{14}H_{24}NO_5)^+$ 286.1654, found 286.1649; Analysis calcd C 58.91 H 8.13 N 4.91, found C 58.98 H 7.90 N 4.85; $[\alpha]_D$ +33 (c = 1.0, $CHCl_3$). ***Trans* Isomer** mpt 50.1-50.9 °C; NMR data: ^1H [$CDCl_3$, 400 MHz] δ 1.42 & 1.48 (2xs rotamers, 9H, Boc), 1.51 & 1.53 (2xs rotamers, 3H, 2-Me), 1.60 & 1.64 (2xs rotamers, 3H, 2-Me), 3.75 (s, 3H, OMe), 3.79 (dd, 1H, J_{gem} 9.2 Hz, J_{vic} 2.2 Hz, 5-H), 4.09 (dd, 1H, J_{gem} 9.2 Hz, J_{vic} 6.6 Hz, 5-H), 4.41 & 4.55 (m, 1H, 4-H), 5.90 (d, 1H, J_{trans} 15.4 Hz, 7-H), 6.83 (dd, 1H, J_{trans} 15.4 Hz, J_{vic} 5.7 Hz, 6-H); ^{13}C [$CDCl_3$, 100 MHz] δ 23.54(2-Me), 26.38 (2-Me), 28.32 (Boc-^{t}Bu), 51.59 (OCH_3), 57.97 (4-C), 67.29 (5-C), 80.18 (quat. Boc), 94.48 (2-C), 121.82 (6-C), 146.3 (7-C), 151.51 (C=O Boc), 166.52 (C=O ester) IR ($CDCl_3$); IR (nujol mull) ν_{max} 1760, 1725, 1698, 1256, 1173, 976 cm^{-1}; High resolution MS (FAB) calcd $(C_{14}H_{24}NO_5)^+$ 286.1654, found 286.1652; $[\alpha]_D$ -60 (c = 1.0 $CHCl_3$).

N-(*tert*-Butoxycarbonyl)-4(R)-amino-2-penten-5-olide. (15) To a solution of the *cis* unsaturated ester **(14)** (500 mg, 1.75 mmol) in DCM (10 mL), TFA (2 equiv.) was added and the solution stirred for 24 h. The reaction was quenched by addition of sat. $NaHCO_3$ (10 mL) and diluted with DCM (10 mL), the organic phase was collected and the aqueous phase washed with DCM (2x15 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated to dryness to give a brown solid. Purification by flash chromatography hexane : EtOAc 2:1 gave the lactone **(15)** colourless crystals yield 320 mg, 75% mpt 127-130 °C; NMR data: ^1H [$CDCl_3$, 400 MHz] δ 1.45 (s, 9H, 3xCH_3), 4.38 (m, 1H, 5-H), 4.48 (m, 1H, 4-H),

4.49 (m, 1H, 6-H), 4.76 (sbr, 1H, NH), 6.08 (dd, 1H, J_{cis} 9.9 Hz, J 1.1 Hz, 3-H), 6.88 (dd, 1H, J_{cis} 9.9 Hz, J_{vic} 4.8 Hz, 4-H), ^{13}C [$CDCl_3$, 100 MHz] δ 28.27 (Boc-^{t}Bu), 42.81 (4-C), 70.42 (5-C), 80.65 (quat. Boc), 1.22 (3-C), 144.75 (2-C), 154.94 (C=O Boc), 162 (1-C), IR ($CDCl_3$); IR (nujol mull) ν_{max} 3333, 1721, 1686, 831cm^{-1}; High resolution MS (CI^+) calcd $(C_{10}H_{15}NO_4)^+$ requires 213.0977, found $(M+H)^+$ 214.1075; $[\alpha]_D$ -61 (c = 1.0, $CHCl_3$).

4(S)-[1'-(N-(*tert*-butoxycarbonyl)-1'(R)-amino-2'-hydroxyethyl]-tetrahydrofuran-2-one. (17). A solution of the unsaturated lactone **(15)** (400 mg, 1.89 mmol) and benzophenone (344 mg, 1.89 mmol) in methanol (350 mL) was degassed with a stream of nitrogen for 1 h, before irradiation using a medium pressure mercury lamp, for 4 h. On completion of the reaction the solvent was removed under vacuum. Purification by flash chromatography 3:7 petrol : EtOAc to give the furanone **(17)** as a crystalline compound. Yield 102 mg, 22.4%, mpt 121-124 °C; NMR data: ^1H [$CDCl_3$, 400 MHz] δ 1.46 (s, 9H, 3xCH_3), 2.39 (dd, J_{gem} 17.2 Hz, J_{vic} 9.2 Hz, 1H, 3-H) 2.60 (dd, J_{gem} 17.2 Hz, J_{vic} 8.4 Hz 1H, 3-H), 2.84 (m, 1H, 4-H), 3.67 (m, 1H, 1'-H), 3.74 (d, J_{vic} 8.1 Hz, 2H, 2'-H), 4.18 (t, J_{vic} 8.1 Hz, 1H, 5-H), 4.42 (t, J_{vic} 8.1 Hz, 1H, 5-H), 5.10 (sbr, 1H, OH); IR (nujol mull) ν_{max} 3353, 1768, 1686, 1687 cm^{-1}; analysis calcd. for $C_{11}H_{19}NO_5$ C 53.87 H 7.81 N 5.71, found C 53.54 H 7.92 N 5.58; $[\alpha]_D$ +18.2 (c = 1.0, $CHCl_3$).

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