Synthesis of Conformationally Restricted Chiral γ-Aminobutyric Acid (GABA) Analogues

Dionissios Papaioannou,[a] George Stavropoulos,[a] Manolis Sivas,[a] Kleomenis Barlos,[a] George W. Francis,[b] Dagfinn W. Aksnes[b] and Knut Maartmann-Moe[b]

[a]Department of Chemistry, University of Patras, Patras, Greece and [b]Department of Chemistry, University of Bergen, N-5007 Bergen, Norway

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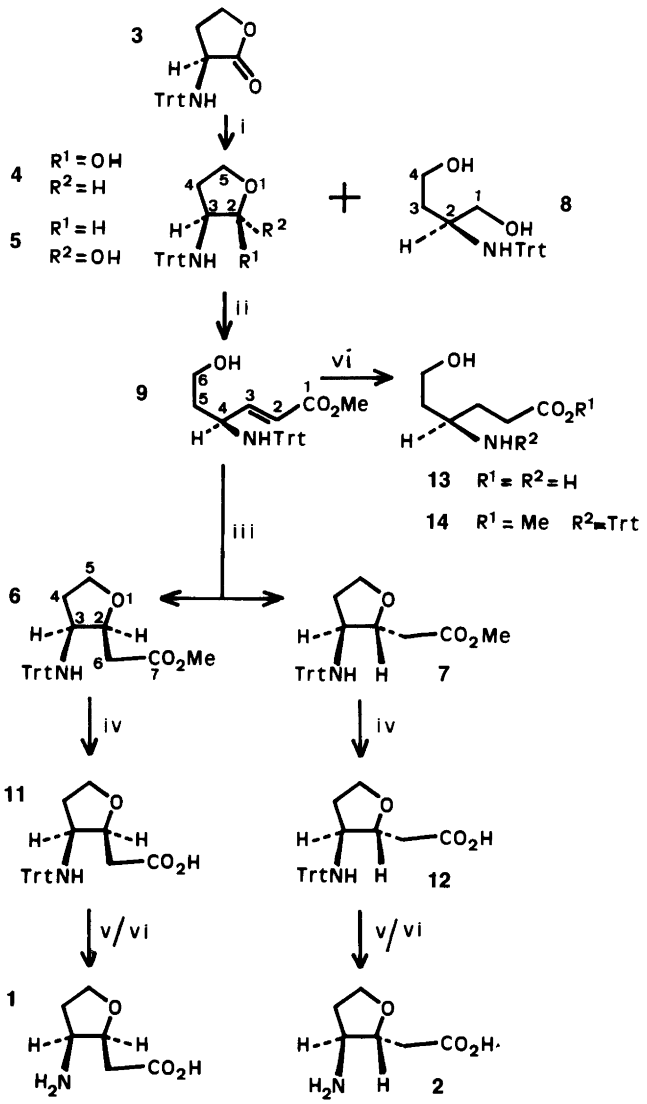
The epimeric (2*S*, 3*S*)- and (2*R*, 3*S*)-3-amino-2-(carboxymethyl)oxolanes have been synthesised from (*S*)-*N*-tritylhomoserine lactone. The lactone was first reduced with diisobutylaluminium hydride to a diastereomeric mixture of the corresponding lactols which underwent Wittig olefination to give methyl (4*S*)-(*E*)-6-hydroxy-4-tritylamino-hex-2-enoate. Fluoride-ion induced ring-closure gave a mixture of (2*S*, 3*S*)- and (2*R*, 3*S*)-oxolanes. After chromatographic separation and deprotection these yielded the required products. Application of the initial reduction to the bicyclic *cis*-*N*-trityl-4-hydroxyproline lactone failed to provide the corresponding lactol mixture, although this could be obtained indirectly by way of the corresponding methyl ester. While the lactol did indeed undergo olefination to yield (2*S*, 4*S*)-4-hydroxy-2-[(*E*)-2-(methoxycarbonyl)]ethenyl-1-tritylpyrrolidine, this latter could not be cyclised.

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter and diminished levels can lead to the development of certain neurological and psychiatric disorders.[1-2] Stimulation of GABA receptors by administration of GABA agonists, inhibition of GABA uptake or inactivation of GABA transaminase, the enzyme responsible for GABA biodegredation, can thus be used as a means of treating such diseases.[3-4]

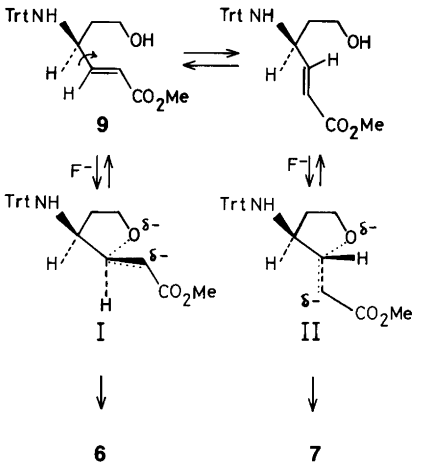
We report here on a simple asymmetric synthesis of (2*S*, 3*S*)- and (2*R*, 3*S*)-3-amino-2-(carboxymethyl)oxolane, **1** and **2** respectively, GABA analogues, in which rotation around the C3–C4 bond has been restricted by incorporation into a tetrahydrofuran ring. GABA analogues of restricted conformation have been widely used to identify 'active conformations'.[5] The triphenylmethyl (trityl, Trt) group was chosen for α-amino group protection in all synthetic transformations for the following reasons: (a) it is easily introduced, and readily removed by mild acid treatment in excellent yields,[6,7] (b) it offers excellent resistance to racemisation,[8] and (c) in contrast with groups of the urethane type,[9] it is compatible with complex metal hydrides.[10]

Our synthetic route to the projected analogues (Scheme 1) initially involved a diisobutyalumium hydride (DIBAH) reduction,[11] using a 50 % molar excess of reagent in THF, of the readily available[12] *N*-tritylhomoserine lactone **3** for 30 min at −65 °C. This gives an excellent yield of the non-separable (TLC) lactols **4** and **5** in the ratio 1:5. The stereochemical assignment was based on the same chemical shift arguments as used below for the diastereomeric pair **6** and **7**. A small quantity of the diol **8** was formed as a by-product. Wittig reaction of the mixture of lactols with 2 mol equiv. of methoxycarbonylmethylenetriphenylphosphorane (MCMP) in DMF,[13] for 12 h at 90 °C, followed by flash chromatography (FC), gave an 80 % yield of the pure *E*-olefin **9**.

Treatment of **9** with 1 mol equiv. of tetrabutylammonium fluoride trihydrate (TBAF),[14] in THF, for 15 min at room temperature produced an almost quantitative yield of the two diastereomeric esters **6** and **7**, in the ratio ca. 1:3 (NMR). The major reaction product **7** is presumably derived through the transition state II (Scheme 2) of the ring-closure reaction which places the bulky tritylamino and methoxycarbonylmethyl groups in a *trans* relationship in order to minimise steric crowding. Separation of these esters by preparative HPLC provided crystalline **6**, and **7** as an oil. The stereochemical assignment of these compounds was based initially on the chemical shift of the methine proton (H-2). This resonated at 4.439 ppm for the *cis*-ester and at 3.896 ppm for the *trans*-ester, indicating shielding due to the vicinal trityl group in the latter case. This phenomenon has also been observed in the structurally related diastereomeric pair *cis*- (**10**) and *trans*-4-hydroxy-*N*-tritylproline methyl esters,[15] where the methine proton H-4, being shielded by the trityl group, resonates at 3.871 ppm for the *cis*-isomer and at 4.374 ppm for the *trans*-isomer. Similar shielding is observed in the NMR spectrum of **8** where the chemical shift difference of the protons H-1 and H-1′ is of the order of 3.5 Hz. Furthermore, the chemical shift difference of the methylene protons on C-1 and C-4 is of the order of 0.5 Hz, suggesting shielding in the former case by the trityl group and thus implying that the preferred



Scheme 1. Synthetic route to GABA analogues from (*S*)-*N*-tritylhomoserine lactone. Key to the reagents used: i, DIBAH; ii, $Ph_3P{=}CHCO_2Me$; iii, Bu_4NF; iv, NaOH; v, glacial ACOH; vi, H_2, Pd–C.



Scheme 2. Transition states for the conversion of the conformers of the olefin **9** into the diastereomeric esters **6** and **7**.

conformation of **8** has the bulky tritylamino and (C-4)-hydroxymethyl groups in an *anti* arrangement. Conclusive evidence in favour of the stereochemical assignment of **6** was obtained by X-ray analysis.[16]

Saponification of the esters **6** and **7** with 2 M NaOH/MeOH for 3 h at room temperature produced the corresponding *N*-tritylamino acids **11** (an oil) and **12** (crystalline), respectively. Finally, detritylation at room temperature with either 9:1 glacial acetic acid/H_2O (3 h) or catalytic hydrogenolysis with 10% Pd-on-C in MeOH (2 h) produced the GABA analogues **1** and **2**, respectively, in good overall yields.

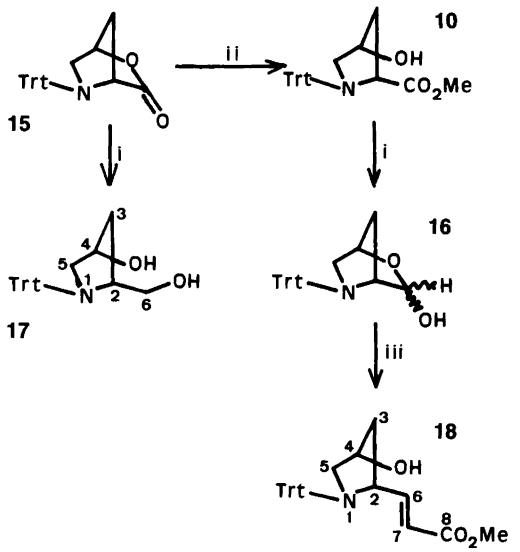
The olefin **9** appeared to be an interesting intermediate for the synthesis of (*R*)-4-amino-6-hydroxyhexanoic acid (**13**), which represents the next higher homologue of 4-amino-5-hydroxypentanoic acid. The *S*-enantiomer of the

latter has been reported to be a competitive inhibitor of GABA-transaminase.[17] Initial attempts to convert the olefin into the amino acid in a two-step process, involving saponification followed by hydrogenation/hydrogenolysis, were unsuccessful owing to the much faster rate of ring-closure than of saponification. As a result, a mixture of the *N*-trityl amino acids **11** and **12** was produced from the olefin **9** in an one-pot procedure.

It was thus evident that reduction of the double bond of the olefin **9** should precede saponification. However, hydrogenation of **9** with 10% Pd-on-C in ethyl acetate for 2.5 h produced the ester **14** in a mixture with a less polar by-product (TLC). Simultaneous detritylation by hydrogenolysis also took place, albeit to a small extent, as evidenced by the presence of a singlet resonance at 5.546 ppm assignable to the methine proton of triphenylmethane. The reaction mixture was subjected to FC to provide a 60% yield of pure **14** and a significant amount of the major by-product, tritylamine. The latter presumably arises by hydrogenolysis of the allylic C–N bond, a reaction which effectively competes with hydrogenation of the double bond. In a final step, the desired product **13** could be obtained pure and in good yield by sequential saponification and detritylation of the purified ester **14**.

Extension of the present methodology to the bicyclic lactone **15**, obtained by Mitsunobu intramolecular esterification[15] of the readily available *trans*-4-hydroxy-*N*-tritylproline, was however problematical (Scheme 3). Treatment of lactone **15** with DIBAH, under a variety of conditions, produced only a trace of the desired lactol **16** and gave almost exclusively the diol **17**. However when the ester **10**, easily obtained by Mitsunobu transesterification of the lactone **15** with methanol,[15] was subjected to reduction with 2.4 equiv. of DIBAH for 3 h at −65 °C, the corresponding lactol **16** was obtained as the main product (NMR) with some diol **17** and unchanged starting material. Treatment of the reaction mixture with MCMP, as for **4** and **5**, followed by FC produced the olefin **18** in 30% overall yield. Treatment of the olefin **18** with TBAF, as for the olefin **9**, for 24 h at room temperature failed to produce any cyclised products, and the starting material was recovered unchanged. This result is in accordance with the observation that the structurally related ester **10** does not cyclise to the lactone **15** on treatment with bases such as NH_3 or pyridine,[15] and this may be attributed to unfavourable stereoelectronic effects.

The present methodology can be utilised for the synthesis of the enantiomers of amino acids **1** and **2** by starting with (*R*)-*N*-tritylhomoserine lactone.



Scheme 3. Initial steps in the synthetic route to GABA analogues from *cis*-4-hydroxy-*N*-tritylproline lactone. Key to the reagents used: i, DIBAH; ii, MeOH, Ph_3P, $EtO_2CN{=}NCO_2Et$; iii, $Ph_3P{=}CHCO_2Me$.

Experimental

General. Capillary melting points were taken on a Buchi SMP-20 apparatus and are uncorrected. Optical rotations were determined with a Carl-Zeiss precision polarimeter. IR spectra were recorded,as Nujol mulls unless otherwise indicated, on a Perkin-Elmer 457 grating spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained at 400.13 and 100.63 MHz, respectively, on a Bruker AM 400 spectrometer, using either $CDCl_3$ or D_2O as solvent with tetramethylsilane or $Me_3SiCD_2CD_2CO_2Na$ as the respective internal standards. Chemical shifts are reported in δ (ppm) downfield from the internal standard. Data for the aromatic region (trityl group) are omitted from both ^1H and ^{13}C NMR spectra of the *N*-tritylated compounds for the sake of brevity. The values observed for compound **17** are typical: ^1H NMR ($CDCl_3$): δ 7.583–7.553 (6 H, m, *o*-H), 7.266–7.225 (6 H, m, *m*-H), 7.183–7.141 (3 H, m, *p*-H). ^{13}C NMR ($CDCl_3$): δ 144.339 (*ipso*-C), 129.493 (*o*-C), 127.650 (*m*-C), 126.319 (*p*-C).

Mass spectra for amino- and carboxy-protected compounds were recorded by means of the direct insertion probe on a JEOL JMS D-100 instrument operating at 70 eV with a source temperature of 180 °C and the minimum sample temperature required to ensure volatilisation. Flash chromatography (FC) was performed on silica gel 60 (230–400 mesh, Merck) whereas preparative HPLC separations were carried out on a Jobin-Yvon Miniprep LC, using silica gel 60H (15 μm, Merck) as the stationary phase, and TLC on silica gel $60F_{254}$ films (0.2 mm, Merck) precoated on plastic sheets. The solvent systems used were: (A) toluene/PE/acetone (7:3:2), (B) toluene/acetone (7:3), (C) EtAc/PE/toluene (1:8:1), (D) $CHCl_3$/MeOH (9:1), (E) BuOH/AcOH/H_2O (4:1:1), and (F) Et_2O/PE/acetone (1:3:1). PE represents here as elsewhere petroleum ether b.p. 60–80 °C. Spots were visualised by 254 nm UV irradiation, with ninhydrin, and chlorine/KI/starch reagent.

In general all reactions were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen and *N,N*-dimethylformamide (DMF) from calcium hydride under

reduced pressure. Amino acids used in this work as starting materials had the *S*-configuration.

Diisobutylaluminium hydride reduction of N-*tritylhomoserine lactone* (**3**). *Preparation of* cis- *and* trans-N-*tritylhomoserine lactols* (**4** and **5**). To a cooled (−65 °C) solution of the lactone **3** (3.43 g, 10 mmol) in THF (10 ml) were added, by means of a syringe over a period of 15 min, 15 ml of a solution of DIBAH in THF (1.0 M; Aldrich). The resulting solution was kept at that temperature for an additional 30 min and the excess of reagent was then destroyed by the dropwise addition of methanol. The mixture was then allowed to attain room temperature, diluted with diethyl ether (50 ml) and vigorously stirred with a saturated aqueous solution of Rochelle's salt (50 ml). The organic layer was collected and the aqueous layer re-extracted with diethyl ether (30 ml). The combined ether phases were washed twice with water and once with brine, dried (Na_2SO_4), and evaporated to leave an oily residue (3.4 g). A small quantity of this product was subjected to FC. The inseparable diastereomeric pair of lactols **4** and **5** were first eluted with solvent system A and thereafter the diol **8** with solvent system B (R_f values for TLC with solvent system A were as follows **3**, 0.65; **4/5**, 0.40; **8**, 0.10). The fractions were obtained as thick oils in the ratio lactol:diol = 95:5. The NMR spectrum of the lactols showed the absence of an aldehydic proton and allowed the relative quantities (**4**:**5** = 1:5) of the two stereoisomeric lactols to be calculated on the basis of the abundances of the H-2 protons. Partial ^1H and ^{13}C NMR for H-2 and C-2 were as follows: **4** [δ 4.534 (d, *J* 5.2 Hz, H-2); δ 102.565 (C-2)] and **5** [δ 4.005 (d, *J* 4.3 Hz, H-2); δ 94.756 (C-2)]. MS for the **4/5** mixture [*m/z* (% rel. int.)]: 345 (*M*, absent), 316 (7, [*M*−CHO]), 268 (22, [*M*−Ph]), 258 (18, [TrtNH]), 243 (100, [Trt]), 228 (18), 215 (16), 202 (13), 165 (60).

The diol **8** was characterised as follows. Oil, $[\alpha]_D^{25}$ +14.2° (*c* 1, $CHCl_3$). R_f (TLC, system A) = 0.10. Anal. $C_{23}H_{25}NO_2$; C, H. MS [*m/z* (% rel. int.)]: 347 (*M*, absent), 316 (24, [*M*−CH_2OH]), 270 (22, [*M*−Ph]), 258 (10, [TrtNH]), 243 (100, [Trt]), 228 (21), 215 (18), 182 (18), 165 (66), 104 (23), 77 (17).

^1H NMR ($CDCl_3$) δ 3.689 (1 H, ddd, *J* −10.5, 8.5 and 3.5 Hz, H-4), 3.566 (1 H, ddd, *J* −10.5, 6.0 and 3.5 Hz, H-4′), 3.172 (1 H, dd, *J* −12.0 and 1.7 Hz, H-1), 2.807 (1 H, m, H-2), 2.782 (1 H, dd, *J* −12.0 and 5.0 Hz, H-1′), 2.550 (2 H, br, OH), 1.570 (1 H, m, H-3), 1.385 (1 H, m, H-3′). ^{13}C NMR ($CDCl_3$): δ 71.379 (Ph_3C), 64.402 (C-1), 59.533 (C-4), 51.731 (C-2), 36.789 (C-3). IR: 3500–3200 cm^{-1}.

Wittig reaction of the lactols **4** *and* **5** *with MCMP. Preparation of* (4S)-(E)-6-hydroxy-4-tritylaminohex-2-enoate (**9**). Crude lactols **4** and **5**, as obtained above, and MCPP (6.18 g; 18.5 mmol) in DMF (25 ml) were heated at 100 °C for 12 h, thereafter diluted to 100 ml with 5 % aqueous citric acid and extracted with ethyl acetate (2×50 ml). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated to dryness. The resulting residue was subjected to FC, using solvent system A as the eluant, to give the pure *E*-olefin **9**.

Yield 3 g (80 % based on lactone **3**). Foam, $[\alpha]_D^{25}$ −43.4° (*c* 1, $CHCl_3$). R_f (TLC, system A) = 0.31. Anal $C_{26}H_{27}NO_3$; C, H. MS [*m/z* (% rel. int.)]: 401 (7, *M*), 324 (56, [*M*−Ph]), 258 (24, [TrtNH]), 243 (100, [Trt]), 228 (20), 215 (17), 202 (11), 182 (25), 165 (54), 158 (23). ^1H NMR ($CDCl_3$): δ 6.491 (1 H, dd, *J* 15.7 and 7.8 Hz, H-3), 5.472 (1 H, dd, *J* 15.7 and 1.0 Hz, H-2), 3.654 (3 H, s, OMe), 3.618 (1 H, m, *J* −11.1, 6.1 and 5.2 Hz, H-6), 3.519 (1 H, m, *J* −11.1, 7.5 and 4.9 Hz, H-6′), 3.415 (1 H, dtd, *J* 7.8, 4.9 and 1.0 Hz, H-4), 2.000 (1 H, br, NH), 1.370 (1 H, m, *J* −14.1, 7.5, 6.1 and 4.9 Hz, H-5), 1.502 (1 H, m, *J* −14.1, 7.8, 5.2, 4.9 Hz, H-5′). ^{13}C NMR ($CDCl_3$): δ 166.823 (C-1), 151.187 (C-3), 118.757 (C-2), 71.453 (Ph_3C), 59.862 (C-6), 53.656 (OCH_3), 51.336 (C-4), 38.430 (C-5). IR ($CHCl_3$): 3500–3200, 1715, 1655 cm^{-1}.

Tetrabutylammonium fluoride induced ring-closure of the olefin **9**. *Preparation of* (2S, 3S)- *and* (2R, 3S)-2-*methoxycarbonyl-3-(tritylamino)oxolanes* (**6** *and* **7**, *respectively*). TBAF (1,83 g, 5.8 mmol) was added at room temperature to a stirred solution of the olefin **9** (2.25 g, 5.6 mmol) in THF (40 ml). When the reaction was complete (TLC, 15 min) the resulting solution was diluted with 5 % aqueous citric acid (100 ml) and extracted twice with diethyl ether (2×100 ml). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated to yield a mixture (2.18 g) of the pure (TLC) diastereomeric oxolanes **6** and **7** (R_f [system C] = 0.13). Preparative HPLC, with system C as the eluant, provided **6** (0.45 g, 20 %) and **7** (1.22 g) as oils.

The oxolane **6** could be crystallised from Et_2O/PE to give colourless prisms, m.p. 150 °C. $[\alpha]_D^{25}$ −111.5° (*c* 1, $CHCl_3$). R_f (TLC, system C) = 0.16. Anal. $C_{26}H_{27}NO_3$: C, H. MS [*m/z* (% rel. int.)]: 401 (12, *M*), 328 (20, [*M*−CH_2CO_2Me]), 324 (32, [*M*−Ph]), 258 (24, [TrtNH]), 243 (100, [Trt]), 228 (21), 215 (16), 202 (13), 165 (43). ^1H NMR ($CDCl_3$): 4.432 (1 H, dt, *J* 5.1 and 8.0 Hz, H-2), 3.770 (3 H, s, OMe), 3.665 (1 H, td, *J* −8.8 and 3.4 Hz, H-5), 3.341 (1 H, dt, *J* −8.8 and 7.2 Hz, H-5′), 3.320 (1 H, ddd, *J* 9.3, 8.0 and 7.3 Hz, H-3), 2.844 (1 H, dd, *J* −15.1 and 5.1 Hz, H-6), 2.557 (1 H, dd, *J* 15.1 and 8.0 Hz, H-6′), 0.893 (1 H, m, *J* −12.5, 9.3, 9.1 and 8.6 Hz, H-4), 0.817 (1 H, m, *J* 12.5, 7.3, 7.2 and 3.4 Hz, H-4′). ^{13}C NMR ($CDCl_3$): 172.495 (C-7), 76.541 (C-2), 71.369 (CPh_3), 65.585 (C-5), 56.172 (OCH_3), 51.740 (C-3), 36.759 (C-6), 32.114 (C-4). IR: 3300, 1730 cm^{-1}.

Catalytic reduction of the olefin **9**. *Preparation of methyl* (4R)-6-*hydroxy-4-(tritylamino)hexanoate* (**14**). Hydrogen gas was bubbled through a stirred suspension of 10 % Pd-on-C (0.1 g) in ethyl acetate (20 ml) containing the olefin **9** (1.0 g, 2.5 mmol) for 2.5 h at room temperature when hydrogenation was found to be complete (NMR, disappearance of olefinic protons). Filtration and evaporation of the solvent afforded the crude ester **14** as an oil, which was

subjected to FC with solvent system F as the eluant to give the major by-product (0.21 g), tritylamine (R_f [TLC, system F] = 0.42) which was identical in all respects with the genuine material, and **14** (0.59 g). Compound **14**, which was used as such in the following deprotection procedures, was obtained as an oil and had R_f (TLC, system F) = 0.28. ^{13}C NMR ($CDCl_3$): δ 174.011 (C-1), 71.574 (Ph_3C), 60.057 (C-6), 51.459 (OCH_3), 50.381 (C-4), 35.344 (C-2), 30.302 (C-5), 29.315 (C-3).

General procedure for saponification of the esters **6**, **7** *and* **14**. To 2 mmol substrate in MeOH (20 ml) was added 2 M NaOH (4 ml) and the resulting mixture was stirred at room temperature until reaction was complete (3 h, TLC). A brief period (15 min) of reflux was required for complete saponification in the case of **6**. Solvents were removed under reduced pressure and the residue dissolved in water. The resulting solution was brought to pH 6 by the dropwise addition of glacial acetic acid, and extracted twice with diethyl ether. The combined ether phases were washed twice with brine, dried and evaporated to dryness to give the corresponding *N*-tritylated amino acids as foams. TLC R_f values for the *N*-tritylamino acids **11** and **14** (R^1 = H, R^2 = Trt) were 0.53 and 0.19, respectively, with system A.

The *N*-tritylamino acid **12** could be crystallised from Et_2O/PE to give colourless prisms, m.p. 148–149 °C. $[\alpha]_D^{25}$ −45.9° (*c* 1, $CHCl_3$). R_f (TLC, system D) = 0.53. Anal. $C_{25}H_{25}NO_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.845 (1 H, ddd, *J* 9.1, 5.1 and 3.7 Hz, H-2), 3.769 (1 H, dt, *J* −8.5 and 7.4 Hz, H-5), 3.685 (1 H, dt, *J* −8.5 and 6.1 Hz, H-5′), 2.993 (1 H, dt, *J* 5.1 and 7.3 Hz, H-3), 2.410 (1 H, dd, *J* −15.6 and 3.7 Hz, H-6), 2.272 (1 H, dd, *J* −15.6 and 9.1 Hz, H-6′), 1.437 (1 H, m, *J* −14.7, 8.5, 7.4 and 7.3 Hz, H-4), 1.165 (1 H, m, *J* −14.7, 7.4, 6.1 and 5.1 Hz, H-4′). ^{13}C NMR ($CDCl_3$): δ 175.770 (C-7), 81.443 (C-2), 71.247 (CPh_3), 66.941 (C-5), 58.775 (C-3), 38.679 (C-6), 34.016 (C-4). IR: 3100–2400, 1705 cm^{-1}.

General procedure for detritylation. Detritylation could be effected either by treating the *N*-tritylamino acids with 9:1 AcOH/H_2O (4 ml per mmol substrate) for 3 h at room temperature, or by bubbling hydrogen gas through a stirred suspension of 10 % Pd-on-C (40 mg per mmol substrate) in MeOH (20 ml per mmol substrate) containing the *N*-tritylamino acid, for 3 h at room temperature. Work-up was carried out by dilution with water (in the case of hydrogenolysis, the catalyst was removed by filtration and the solvent by evaporation prior to work-up) and washing twice with diethyl ether. Evaporation of the aqueous layer under reduced pressure and crystallisation from EtOH/Et_2O gave final products **1**, **2** and **13** in yields of 70–80 %.

(2S, 3S)-3-Amino-2-(carboxymethyl)oxolane (**1**). Colourless prisms, m.p. 160 °C, $[\alpha]_D^{25}$ +25.5° (*c* 1, H_2O). R_f (TLC, system E) = 0.13. Anal. $C_6H_{11}NO_3$: C, H. ^{1}H NMR (D_2O): 4.201 (1 H, ddd, *J* 7.5, 6.3 and 4.8 Hz, H-2), 4.083 (1 H, dt, *J* −8.8 and 5.8 Hz, H-5), 3.955 (1 H, ddd, *J* 7.5, 4.5 and 2.6 Hz, H-3), 3.701 (1 H, dt, *J* −8.8 and 6.5 Hz, H-5′), 2.626–2.466 (3 H, m, H-4, H-6 and H-6′), 2.055 (1 H, m, *J* −14.5, 8.8, 6.5 and 2.6 Hz, H-4′). ^{13}C NMR (D_2O): δ 180.711 (C-7), 80.027 (C-2), 68.314 (C-5), 55.662 (C-3), 40.107 (C-6), 33. 281 (C-4). IR: 3200–2300, 2190, 1650, 1610–1510 cm^{-1}.

(2R, 3S)-3-Amino-2-(carboxymethyl)oxolane (**2**). Colourless prisms, m.p. 233 °C (softens at 210 °C), $[\alpha]_D^{25}$ +11.8°(*c* 1, H_2O). R_f (TLC, system E) = 0.18. Anal. $C_6H_{11}NO_3$; C, H. ^{1}H NMR (D_2O): 4.251 (1 H, dt, *J* 7.0 and 4.6 Hz, H-2), 4.053–3.937 (2 H, m, H-3 and H-5), 3.713 (1 H, apparent quintet, *J* 4.3 Hz, H-5′), 2.598 and 2.540 (2 H, ABqd, *J* −15.7 and 7.0 Hz, H-6 and H-6′), 2.483 (1 H, ddd, *J* −15.0, 14.1 and 8.8 Hz, H-4), 2.078 (1 H, m, *J* −15.0, 7.7, 4.8 and 4.3 Hz, H-4′). ^{13}C NMR (D_2O): δ 181.283 (C-7), 82.085 (C-2), 68.776 (C-5), 57.746 (C-3), 43.583 (C-6), 32.531 (C-4). IR: 3200–2300, 2190, 1650, 1610–1510 cm^{-1}.

(R)-4-Amino-6-hydroxyhexanoic acid (**13**). Colourless prisms, m.p. 154–157 °C $[\alpha]_D^{25}$ −4.4° (*c* 1, H_2O). R_f (TLC, system E) = 0.25. Anal. $C_6H_{13}NO_3$: C, H. ^{1}H NMR (D_2O): δ 3.765–3.656 (2 H, m, H-6 and H-6′), 3.362 (1 H, quintet, *J* 6.6 Hz, H-4), 2.280 (2 H, td, *J* 7.6 and 1.0 Hz, H-2 and H-2′), 1.932–1.754 (4 H, m, H-3, H-3′, H-5 and H-5′). ^{13}C NMR (D_2O): δ 183.820 (C-1), 61.256 (C-6), 53.203 (C-4), 36.457 (C-2), 35.883 (C-5), 31.461 (C-3). IR: 3230, 3100–2200, 2100, 1660, 1620, 1580–1510 cm^{-1}.

*(2S, 4S)-2-[(*trans*)-4-Hydroxy-2-(methoxycarbonyl)]ethenyl-1-tritylpyrrolidine* (**18**). The ester **10** (1.94 g, 5 mmol) in THF (30 ml) was treated with DIBAH (12 mmol) for 5 h at −65 °C. The resulting reaction mixture was worked-up as for the lactone **3** to give the crude lactol **16** (1.75 g) in admixture with the starting material **10** and the diol **17** (R_f [TLC, system A] **16** = 0.33, **10** = 0.39 and **17** = 0.07). An analytical sample of diol **17** was obtained from a small quantity of this mixture by FC (eluant system B) and recrystallisation from acetone/PE.

Diol **17** had m.p. 154–155 °C, $[\alpha]_D^{25}$ +53.9° (*c* 1, $CHCl_3$). Anal. $C_{24}H_{25}NO_2$; C, H. MS [*m/z* (% rel. int.)]: 359 (*M*, absent), 328 (10, [*M*−CH_2OH]), 282 (6, [*M*−Ph]), 243 (100, [Trt]), 228 (13), 215 (11), 202 (8), 165 (48). ^{1}H NMR ($CDCl_3$): δ 3.964 (1 H, dd, *J* 9.9 and 4.7 Hz, H-4), 3.632 (2 H, br, OH), 3.519 (1 H, dd, *J* −10.8 and 2.0 Hz, H-6), 3.462 (1 H, m, *J* 9.5, 7.1, 4.0 and 2.0 Hz, H-2), 3.298–3.205 (3 H, m, H-5, H-5′ and H-6′), 1.323 (1 H, d, *J* −14.0 Hz, H-3), 0.982 (1 H, ddd, *J* −14.0, 9.9 and 7.1 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 77.777 (C-4), 71.808 (Ph_3C), 67.251 (C-6), 60.991 (C-2), 60.474 (C-5), 39.688 (C-3). IR: 3450–3100 cm^{-1}.

The NMR of the first fraction from the above FC, containing the ester **10** and the lactol **16**, did indeed confirm the absence of aldehydic protons. Treatment of the crude lactol **16** with MCMP (3.34 g, 10 mmol) in DMF (15 ml) for

12 h at 100 °C, followed by work-up as for **9** and FC (eluant system A) gave the pure olefin **18** (0.60 g; 30 % based on **10**) which solidified on standing.

Compound **18** had m.p. 79–81 °C, $[\alpha]_D^{25}$ −80.5° (*c* 1, $CHCl_3$). R_f (system A) = 0.26. Anal. $C_{27}H_{27}NO_3$; C, H. MS [*m/z* (% rel. int.)]: 413 (*M*, 1.4), 382 (1.3, [*M*−31]), 336 (6, [*M*−Ph]), 328 (4, [*M*−CH=CH·CO_2Me]), 243 (100, [Trt]), 228 (14), 215 (12), 202 (9), 165 (63). ^{1}H NMR ($CDCl_3$): δ 7.113 (1 H, dd, *J* 15.7 nd 6.9 Hz, H-6), 5.973 (1 H, dd, *J* 15.7 and 1.3 Hz, H-7), 3.782 (1 H, m, H-4), 3.748 (3 H, s, OCH_3), 3.562 (1 H, m, H-2), 3.221 (1 H, dd, *J* −13.3 and 4.0 Hz, H-5), 3.148 (1 H, dd, *J* −13.3 and 6.5 Hz, H-5′), 1.565 (1 H, br, OH), 1.291 (1 H, dt, *J* −14.0 and 3.1 Hz, H-3), 1.231 (1 H, ddd, *J* −14.0, 8.5 and 7.0 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 167.278 (C-8), 152.711 (C-6), 118.506 (C-7), 77.216 (C-4), 71.932 (Ph_3C), 60.910 (OCH_3), 58.921 (C-2), 51.504 (C-5), 30.332 (C-3). IR: 3600, 1710, 1650 cm^{-1}.

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