Desymmetrization of 3-dimethyl(phenyl)silyl glutaric anhydride with Evans' oxazolidinone: an application to stereocontrolled synthesis of the antifungal agent (+)-preussin

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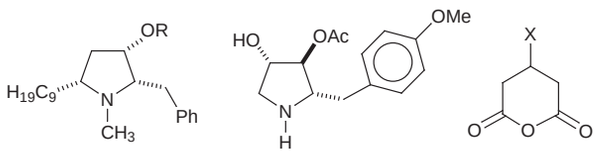
A stereoselective total synthesis of (+)-preussin (**1**) has been achieved from the σ-symmetric 3-dimethyl(phenyl)silyl substituted glutaric anhydride **4** featuring its desymmetrization using Evans' oxazolidinone **10**. The first homochiral intermediate, the glutarate half-ester **9** was obtained from both the diastereoisomeric acids **11a** and **12a** in a convergent fashion. The dimethyl(phenyl)silyl group is not only acting as a masked hydroxy group but also restricts elimination reactions and facilitates Curtius reaction. It also stereodirects ester enolate alkylation of **18** and hydrogenation of intermediate Δ^1-pyrroline **5**.

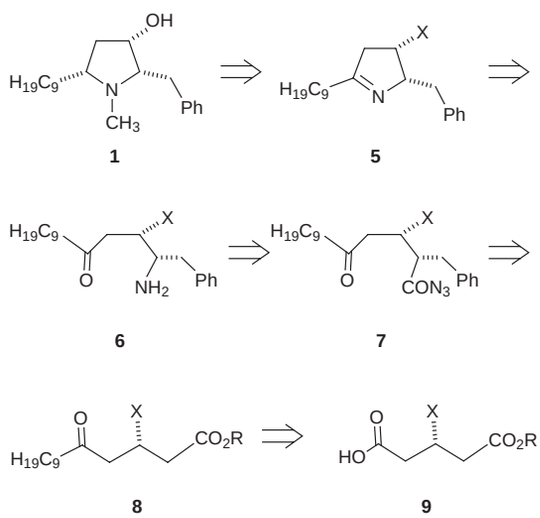
Introduction

(+)-Preussin, (2*S*,3*S*,5*R*)-1-methyl-5-nonyl-2-benzylpyrrolidin-3-ol (also known as L-657,398) (**1**) was isolated from the



fermentation broth of *Aspergillus ochraceus* ATCC 22947 and *Preussia* sp. by scientists at Squibb and Merck.[1] This structurally novel pyrrolidine alkaloid antibiotic and its acetate ester **2** show a broader spectrum antifungal activity against both filamentous fungi and yeasts than the structurally related antibiotic anisomycin (**3**).[1c] The first synthesis was reported by Pak and Lee[2] using D-glucose as a substrate. A few more syntheses based on the chiral pool have been published subsequently using D-mannose,[3] D-arabinose,[4] (*S*)-phenylalanine[5] and its enantiomer, (*R*)-phenylalanine[6] as starting materials. Recently, a chiral induction based strategy for **1** has also been reported by Greene.[7]

Our interest was to develop a versatile route for preussin by which either enantiomer could be synthesized from the same starting material as well as having inherent flexibility to produce its analogs with different substituents at positions 1, 2 and 5 for biological screening. In the preceding paper,[8] we have discussed a methodology for desymmetrization of σ-symmetric anhydrides. In a sequel, we envisioned a retrosynthetic analysis for **1** from 3-hydroxyglutaric anhydride (**4**; X = OH; Scheme 1). Preussin could be prepared *via* stereoselective reductive methylation of Δ^1-pyrroline **5** preceded by the amino ketone **6** which in turn could be obtained from the δ-keto acyl azide **7** *via* a Curtius reaction. The latter could be obtained from the keto-ester **8**, synthesis of which might be accomplished from **4** (X = OH) *via* the glutarate half-ester **9**. The *O*-silyl/alkyl protected intermediates like **8** tend to undergo elimination during ester enolate alkylation[9] reaction, thereby making the alkylation rather difficult. Alternatively, β-hydroxy acids are known to undergo dianion alkylation with very high *anti*-selectivity,[10] but, as pointed out by Livinghouse,[5a] an intermediate like **5** is unable to provide a tetrahydropyrrole derivative due to ease of elimination of either a protected or unprotected OH group. Therefore,



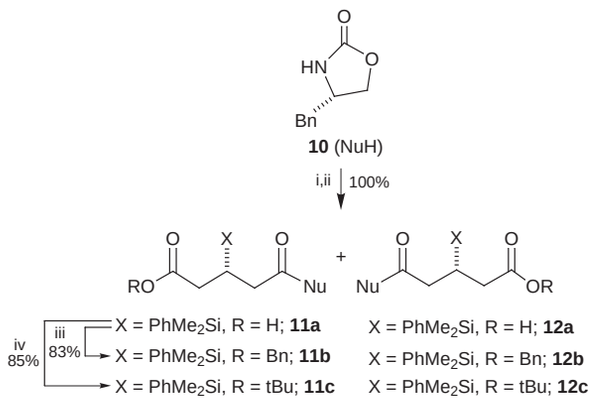
Scheme 1

this retrosynthesis in the present form probably could not be applicable for preussin synthesis. Hence, a suitable substitute for the OH group in the retrosynthetic sequence is desirable which would resist elimination, could stereospecifically be converted to a hydroxy group when desired, could possibly stereodirect both saturation of the Δ^1-pyrroline system and introduction of the benzyl group in **8** and possibly facilitate the Curtius reaction of **7**. Considering all these requirements, we envisaged that a dimethyl(phenyl)silyl ($PhMe_2Si$) group can be an ideal substitute for the OH group. It is known to be a poor leaving group and as shown by Fleming,[11] it could be stereospecifically converted into a hydroxy group with retention of configuration. It has further been shown that the β-silyl ester enolate alkylations occur with high *anti* stereoselectivity.[12] Also, it is expected that the steric bulk of a $PhMe_2Si$ group is large enough to stereodirect the hydrogenation in intermediate **5**. Moreover, we have recently shown that a silicon group at the β-position facilitates the Curtius reaction of acyl azides.[13] Based on the above factors, a retrosynthetic analysis was conceived as shown in Scheme 1 (X = $PhMe_2Si$). A communication on this report has already been published by us.[14]

Results and discussion

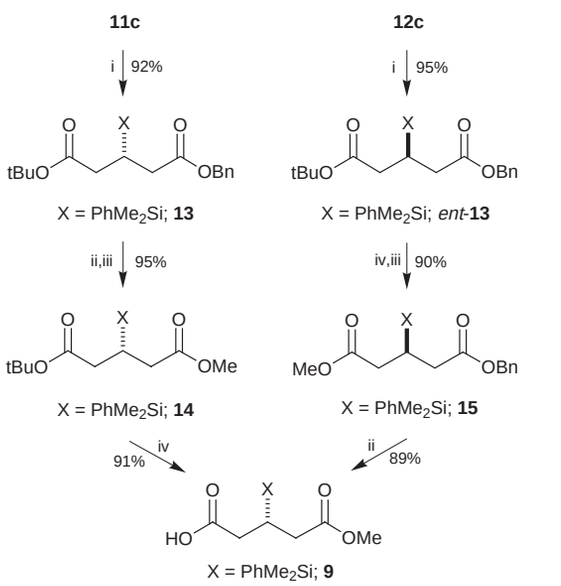
The anhydride **4** (X = $PhMe_2Si$) was opened up[8] using the

lithium anion of the Evans oxazolidinone **10**[15] to provide a mixture of diastereoisomeric acids **11a** and **12a** which were separated as their benzyl (**11b** and **12b**) and *tert*-butyl (**11c** and **12c**) esters (Scheme 2). The diastereoisomerically pure *tert*-



Scheme 2 *Reagents*: i, *n*-BuLi, THF; ii, **4**; iii, Et_3N, Piv-Cl, then BnOH, DMAP; iv, $(COCl)_2$, DMF, then t-BuOH, DMAP.

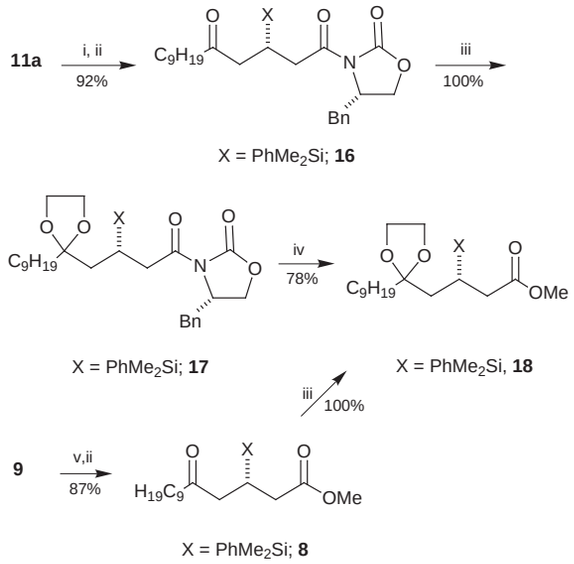
butyl esters were separately subjected to oxazolidinone removal conditions[15c] (Scheme 3) to provide the benzyl *tert*-butyl



Scheme 3 *Reagents*: i, $Ti(OBn)_4$, BnOH; ii, H_2, Pd/C; iii, CH_2N_2; iv, PhOH, TMS-Cl.

diesters **13** and *ent*-**13**, respectively. The former on hydrogenolysis and esterification gave methyl ester **14**, and the latter under *tert*-butyl ester removal conditions with phenol–chlorotrimethysilane[16] followed by esterification yielded methyl ester **15**. The ester **14** was now subjected to *tert*-butyl ester removal conditions while **15** underwent hydrogenolysis to provide the same half-ester **9** (X = $PhMe_2Si$; R = Me). The overall yield of **9** from the anhydride **4** (X = $PhMe_2Si$) was 68%. The oxazolidinone **10** was also isolated in almost quantitative yield without any loss of optical purity.

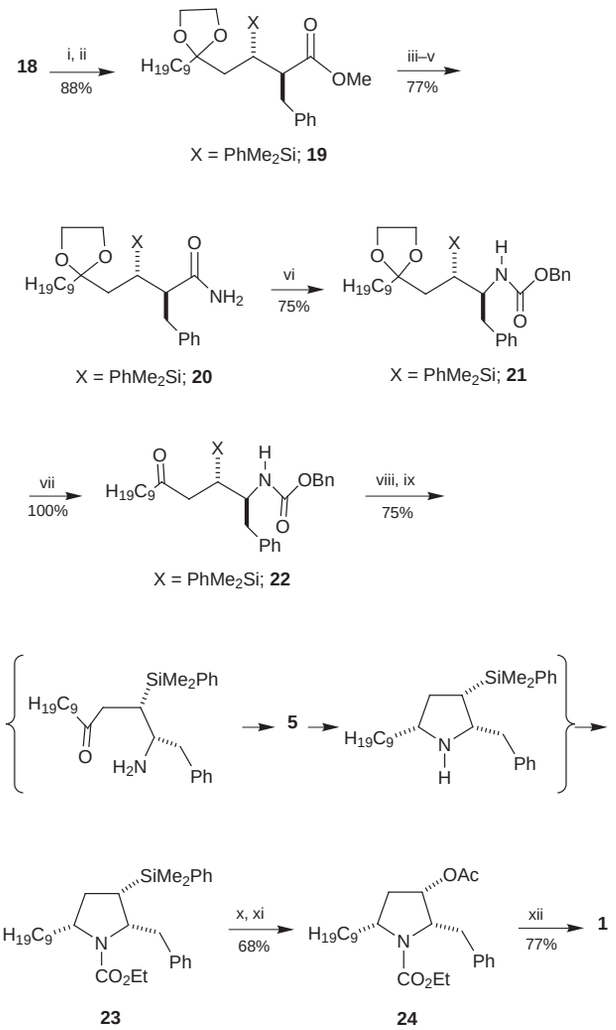
As communicated earlier by us,[14] the major acid **11a** (obtained from **11b**) was converted to its mixed pivaloic anhydride which *in situ* was treated with nonylmagnesium bromide at −25 °C to provide the ketone **16** in 60% yield (92% based on 35% recovery of **11a**) (Scheme 4). The ketone was quantitatively protected[17] as acetal **17** and the oxazolidinone was removed with methoxymagnesium bromide[15c] to give the homochiral methyl ester **18** in 78% yield. During the process an undesired product (about 22%) was also formed probably due



Scheme 4 *Reagents*: i, Et_3N, Piv-Cl; ii, $C_9H_{19}MgBr$; iii, 1,2-bis-(trimethylsilyloxy)ethane, TMS-OTf; iv, MeOMgBr; v, $(COCl)_2$, DMF.

to the attack of the methoxide ion on the wrong carbonyl of the oxazolidinone. We could recover the oxazolidinone **10** in 78% yield (>99% considering the wrong attack on the oxazolidinone). A better *modus operandi* subsequently employed for the preparation of this methyl ester **18** was from the half-ester **9**. Thus, the latter was converted to its acid chloride and then reacted with nonylmagnesium bromide at −78 °C to provide the keto ester **8** (X = $PhMe_2Si$; R = Me) in very good yield. This was quantitatively protected[17] as the acetal to give the same intermediate **18**. The overall yield of the acetal **18** from the anhydride **4** (X = $PhMe_2Si$) was considerably high (58%) and no side products were detected.

As expected, alkylation of **18** with benzyl bromide took place with high *anti* selectivity[12] (93 : 7) to give **19** (Scheme 5) which was found to be resistant to hydrazinolysis. Alternatively, the methyl ester **19** was hydrolyzed and converted to a primary amide **20** *via* the acid imidazolide in 77% yield. On treatment with lead tetraacetate[18] and benzyl alcohol, the expected benzyloxycarbonyl protected amine **21** was isolated in good yield. The rearrangement was smooth and probably facilitated by the presence of the β-silyl group.[13] The acetal protection was subsequently removed to give the ketone **22**. At this stage we could easily separate the unwanted minor diastereoisomer by chromatography. The ketone **22** was subjected to hydrogenolysis where upon removal of the benzyloxycarbonyl group took place. The generated amine group condensed intramolecularly with the carbonyl group spontaneously to provide the Δ^1-pyrroline **5** (X = $PhMe_2Si$) which was hydrogenated *in situ* with hydrogens coming from the least hindered surface, *i.e.* away from the silicon and benzyl groups to provide the pyrrolidine derivative with all three substituents having *cis* stereochemistry. Subsequently, the NH group was protected as ethoxycarbonyl derivative **23** and the silyl group in the molecule was converted to a hydroxy group[11] and then to its acetate **24**. The NMR spectra of the products **23** and **24** were complex and could not be fully interpreted as these are known to be mixtures of amide isomers. Lithium aluminium hydride reduction of **24** provided (+)-preussin (**1**) in 77% yield. Since we started with the homochiral half-ester **9**, and the synthetic sequence does not involve any epimerization, the enatiomeric purity of (+)-preussin should undoubtedly be very high (>99%). It was further confirmed from the specific rotation value ($[\alpha]_D^{25}$ +31.1, *c* 1, $CHCl_3$) measured for **1** and also, the spectral data which were in good agreement with the reported values[2] for synthetic (+)-preussin. The overall yield of (+)-preussin from the homochiral methyl ester **18** is 17.2%.



Scheme 5 *Reagents*: i, Li-TMP; ii, BnBr; iii, KOH; iv, Im_2CO; v, NH_3; vi, $Pb(OAc)_4$, BnOH; vii, TsOH, Me_2CO–H_2O; viii, H_2, Pd/C; ix, EtOCOCl, Et_3N; x, KBr, AcOOH, NaOAc; xi, Ac_2O, DMAP; xii, $LiAlH_4$.

Experimental

All mps are recorded with a Fisher-Johns apparatus. The ^1H NMR and ^{13}C NMR spectra are recorded on a Bruker (model AC200) 200 MHz or Varian (model VXR300) 300 MHz instrument. ^1H NMR chemical shifts (δ) are given in ppm downfield from internal tetramethylsilane ($\delta = 0.00$) or from residual chloroform ($\delta = 7.26$) and J (coupling constant) values in Hz. The IR spectra are recorded on a Perkin-Elmer 783 spectrophotometer or Nicolet Impact 410 FT IR spectrometer. Optical rotations are measured in a JASCO DIP polarimeter. Mass spectra are recorded on a Shimadzu GCMS-QP 1000A instrument. Air sensitive reactions were carried under Ar or N_2 atmosphere. Solvents were freshly dried and distilled prior to use. The preparations of **4**, **11a**–**c** and **12a**–**c**, described in the preceding paper,[8] are not included in the experimental.

(3*R*)-Benzyl *tert*-butyl 3-[dimethyl(phenyl)silyl]pentane-1,5-dioate 13

Titanium tetrakis(benzyl oxide)[15c] (0.375 M in benzyl alcohol) (2.25 cm^3, 0.85 mmol) was added to the ester **11c** (272 mg, 0.585 mmol) and the mixture was heated at 75 °C for 24 h under argon. Water (5 cm^3) was added to the reaction mixture with stirring and filtered through a pad of Celite. The filtrate was evaporated under reduced pressure and then under high vacuum to remove the benzyl alcohol. The residue was chromatographed to give ester **13** (225 mg, 94%) and oxazolidinone **10** (92 mg, 92%). For ester **13**: R_f(hexane–EtOAc; 95 : 5) 0.64; $[a]_D^{24}$ +1.2 (*c* 4.46, MeOH); ν_{max}(film)/cm^{-1} 1731, 1252, 1113; δ_H(200 MHz, $CDCl_3$) 0.30 (6 H, s), 1.40 (9 H, s), 1.80–2.00 (1 H, m), 2.10–2.52 (4 H, m), 5.00 (2 H, s), 7.29–7.52 (10 H, m) (Found: C, 69.7; H, 7.9. $C_{24}H_{32}O_4Si$ requires C, 69.9; H, 7.8%).

(3*R*)-*tert*-Butyl methyl 3-[dimethyl(phenyl)silyl]pentane-1,5-dioate 14

A mixture of benzyl ester **13** (446 mg, 1.08 mmol) and Pd/C (10% in Pd) (20 mg) in ethyl acetate (5 cm^3) was stirred under a hydrogen atmosphere for 15 h. The mixture was passed through a Celite pad and the residue was washed thoroughly with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was esterified with ethereal diazomethane to give the methyl ester **14** (370 mg, 95%); R_f(hexane–EtOAc; 95 : 5) 0.51; $[a]_D^{23}$ +1.0 (*c* 2.28, $CHCl_3$); ν_{max}(film)/cm^{-1} 1731, 1252, 1112; δ_H(200 MHz, $CDCl_3$) 0.31 (6 H, s), 1.41 (9 H, s), 1.81–1.93 (1 H, m), 2.10–2.51 (4 H, m), 3.56 (3 H, s), 7.32–7.52 (5 H, m) (Found: C, 64.0; H, 8.6. $C_{18}H_{28}O_4Si$ requires C, 64.2; H, 8.4%).

(3*S*)-Methyl hydrogen 3-[dimethyl(phenyl)silyl]pentane-1,5-dioate 9

Chlorotrimethylsilane[16] (1 molar solution in CH_2Cl_2, 2 cm^3, 2 mmol) was added to a stirred solution of *tert*-butyl ester **14** (110 mg, 0.327 mmol), phenol (188 mg, 2 mmol) in CH_2Cl_2 (2 cm^3) at room temperature. After 24 h, solvent and phenol were removed under high vacuum to give the acid **9** (83 mg, 91%); $[a]_D^{21}$ +1.3 (*c* 0.92, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400–2400 (br), 1733, 1712, 1260, 1112; δ_H(200 MHz, $CDCl_3$) 0.33 (6 H, s), 1.79–1.93 (1 H, m), 2.17–2.52 (4 H, m), 3.57 (3 H, s), 7.34–7.52 (5 H, m); δ_C(50 MHz, $CDCl_3$) 178.6, 173.5, 136.7, 133.9, 129.3, 127.9, 51.2, 34.5, 18.8, −4.5 (Found: C, 59.7; H, 7.4. $C_{14}H_{20}O_4Si$ requires C, 60.0; H, 7.2%).

This compound was also prepared in 89% yield from **15** following the procedure described for the preparation of **14** without CH_2N_2 treatment.

(3*S*)-Benzyl *tert*-butyl 3-[dimethyl(phenyl)silyl]pentane-1,5-dioate *ent*-13

This compound was prepared in 95% yield from **12c** following the procedure described for the preparation of **13**; $[a]_D^{24}$ −1.8 (*c* 2.88, MeOH); ν_{max}(film)/cm^{-1} 1731, 1252, 1112; δ_H(200 MHz, $CDCl_3$) 0.30 (6 H, s), 1.40 (9 H, s), 1.80–2.00 (1 H, m), 2.10–2.55 (4 H, m), 5.00 (2 H, s), 7.29–7.52 (10 H, m).

(3*R*)-Benzyl methyl 3-[dimethyl(phenyl)silyl]pentane-1,5-dioate 15

This compound was prepared in 90% yield from *ent*-**13** following the procedure described for the preparation of **9** from **14** followed by esterification with CH_2N_2; $[a]_D^{23}$ +1.0 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 1737, 1252, 1113; δ_H(200 MHz, $CDCl_3$) 0.31 (s, 6 H), 1.85–1.99 (1 H, m), 2.23–2.54 (4 H, m), 3.55 (3 H, s), 5.02 (2 H, s), 7.29–7.51 (10 H, m); δ_C(50 MHz, $CDCl_3$) 173.4, 172.9, 136.9, 136.2, 134.0, 129.3, 128.5, 128.2, 128.1, 127.9, 66.3, 51.3, 34.8, 34.6, 19.0, −4.4 (Found: C, 68.0; H, 7.2. $C_{21}H_{26}O_4Si$ requires C, 68.1; H, 7.1%).

(3*S*)-Methyl 3-[dimethyl(phenyl)silyl]-5-oxotetradecanoate 8

Oxalyl chloride (0.5 cm^3, 5.2 mmol) was added to a stirred solution of acid **9** (370 mg, 1.32 mmol) and DMF (0.02 cm^3) in dichloromethane (4 cm^3) at 0 °C. After 2 h at room temperature, the solvent and excess oxalyl chloride were removed under vacuum. The residue was dissolved in dry ether (5 cm^3) and nonylmagnesium bromide (0.5 M in ether) (3 cm^3, 1.5 mmol) was added to it at −78 °C under argon atmosphere. The reaction mixture was slowly brought to room temperature (20 h). The reaction mixture was diluted with ether, washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by chromatography (SiO_2,

hexane–EtOAc) to give ketone **8** (450 mg, 87%); R_f(hexane–EtOAc; 98:2) 0.17; $[\alpha]_D^{21}$ −0.8 (*c* 0.79, $CHCl_3$); ν_{max}(film)/cm^{-1} 1738, 1715, 1250, 1112; δ_H(200 MHz, $CDCl_3$) 0.30 (6 H, s), 0.87 (3 H, t, *J* 6.7), 1.20–1.24 (12 H, br), 1.41–1.50 (2 H, m), 1.88–2.01 (1 H, m), 2.13–2.44 (6 H, m), 3.56 (3 H, s), 7.34–7.63 (5 H, m); δ_C(50 MHz, $CDCl_3$) 209.9, 173.7, 137.3, 134.0, 129.2, 127.9, 51.2, 42.9, 42.7, 34.7, 31.9, 29.4, 29.3, 23.9, 22.6, 17.7, 13.9, −4.2, −4.4 (Found: C, 70.5; H, 10.0. $C_{23}H_{38}O_3Si$ requires C, 70.7; H, 9.8%).

(3′*S*,4*S*)-3-{3-[Dimethyl(phenyl)silyl]-1,5-dioxotetradecyl}-4-benzyloxazolidin-2-one 16

A solution of pivaloyl chloride (0.41 cm^3, 3.3 mmol) in THF (1 cm^3) was added to a stirred solution of acid **11a** (1.40 g, 3.29 mmol) and triethylamine (0.46 cm^3, 3.3 mmol) in THF (17 cm^3) at −78 °C. The reaction mixture was stirred at 0 °C for 1 h and cooled to −78 °C followed by an addition of nonyl magnesium bromide (0.9 M in THF) (4.4 cm^3, 4 mmol). The reaction mixture was slowly allowed to attain to −25 °C and stirred for 48 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by chromatography (SiO_2, hexane–EtOAc) to give ketone **16** (1.04 g, 60%). Also, the starting acid **11a** (500 mg, 35%) was also recovered. For **16**: R_f(hexane–EtOAc; 90:10) 0.65; $[\alpha]_D^{25}$ +22.8 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1784, 1701, 1249, 1112; δ_H(200 MHz, $CDCl_3$) 0.34 (6 H, s), 0.87 (3 H, t, *J* 6.7), 1.23 (12 H, br), 1.45 (2 H, t, *J* 6.6), 2.05–2.10 (1 H, m), 2.26–2.37 (3 H, m), 2.41–2.45 (2 H, m), 2.68 (1 H, dd, *J* 10, 14), 3.23 (1 H, dd, *J* 3.2, 14), 3.37 (1 H, dd, *J* 3.7, 14), 4.09 (1 H, dd, *J* 2.4, 8.8), 4.25 (1 H, t, *J* 8.5), 4.34–4.54 (1 H, m), 7.15–7.53 (10 H, m) (Found: C, 71.5; H, 8.7; N, 2.6. $C_{32}H_{45}O_4NSi$ requires C, 71.7; H, 8.5; N, 2.6%).

(3′*S*,4*S*)-3-{3-[Dimethyl(phenyl)silyl]-5,5-(ethylenedioxy)-1-oxotetradecyl}-4-benzyloxazolidin-2-one 17

Trimethylsilyl trifluoromethanesulfonate[17] (0.03 cm^3, 0.155 mmol) was added to a stirred solution of ketone **16** (3.85 g, 7.2 mmol) and 1,2-bis(trimethylsilyloxy)ethane (7 cm^3, 29 mmol) in dry dichloromethane (7 cm^3) at −78 °C under argon atmosphere. The reaction mixture was stirred at −20 °C for 48 h, quenched with sodium bicarbonate solution and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the acetal **17** (4.1 g, 100%); R_f(hexane–EtOAc; 95:5) 0.43; $[\alpha]_D^{28}$ +43.8 (*c* 1.74, EtOAc); ν_{max}(film)/cm^{-1} 1782, 1698, 1250, 1110; δ_H(300 MHz, $CDCl_3$) 0.32 (3 H, s), 0.33 (3 H, s), 0.88 (3 H, t, *J* 7), 1.23 (15 H, br), 1.58–1.63 (2 H, m), 1.76–1.82 (1 H, dd, *J* 2.5, 15), 1.84–1.89 (1 H, m), 2.60 (1 H, dd, *J* 10, 14), 3.09 (2 H, dd, *J* 1.1, 6), 3.27 (1 H, dd, *J* 3, 13), 3.82–3.90 (4 H, m), 3.99–4.07 (2 H, m), 4.32–4.40 (1 H, m), 7.17–7.31 (2 H, m), 7.32–7.36 (6 H, m), 7.51–7.55 (2 H, m) (Found: C, 70.4; H, 8.6; N, 2.2. $C_{34}H_{49}O_5NSi$ requires C, 70.4; H, 8.5; N, 2.4%).

(3*S*)-Methyl 3-[dimethyl(phenyl)silyl]-5,5-(ethylenedioxy)tetradecanoate 18

Ethylmagnesium bromide[15c] (2.5 M in ether) (1.38 cm^3, 3.45 mmol) was added to methanol (25 cm^3) at 0 °C. After attaining room temperature, a solution of the oxazolidinone **17** (1 g, 1.72 mmol) in methanol (3 cm^3) was added to it and the reaction mixture was stirred for 15 h. The solvent was evaporated and the residue was diluted with benzene. The reaction mixture was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed to give the acetal **18** (590 mg, 78%); R_f(hexane–EtOAc; 70:30) 0.25; $[\alpha]_D^{23}$ −2.1 (*c* 2.04, EtOAc); ν_{max}(film)/cm^{-1} 1737, 1698, 1249, 1112; δ_H(300 MHz, $CDCl_3$) 0.28 (3 H, s), 0.29 (3 H, s), 0.88 (3 H, t, *J* 6.4), 1.22–1.25 (14 H, m), 1.49–1.59 (4 H, m), 1.75 (1 H, d, *J* 12), 2.40 (1 H, dd, *J* 6.6, 16), 2.55 (1 H, dd, *J* 5, 16), 3.54 (3 H, s), 3.79–3.90 (4 H, m), 7.31–7.38 (3 H, m), 7.49–7.52 (2 H, m) (Found: C, 68.9; H, 10.0. $C_{25}H_{42}O_4Si$ requires C, 69.1; H, 9.7%).

This compound was also prepared in 100% yield from **8** following the procedure described for the preparation of acetal **17**.

(2*R*,3*S*)-Methyl 3-[dimethyl(phenyl)silyl]-5,5-(ethylenedioxy)-2-benzyltetradecanoate 19

Butyllithium (1.54 M in hexane) (4.3 cm^3, 6.6 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine in THF (18 cm^3) at −78 °C under argon atmosphere. After 20 min at 0 °C, the reaction mixture was cooled to −78 °C and DMPU (9 cm^3) was added followed by a solution of the acetal **18** (1.92 g, 4.41 mmol) in THF (25 cm^3 THF). The reaction mixture was stirred for 1 h and slowly allowed to attain −50 °C and stirred for 10 min. Benzyl bromide (1.05 cm^3, 8.82 mmol) was added to this at −78 °C and stirred for 12 h. After further stirring at −50 °C for 48 h, the reaction mixture was quenched with citric acid solution and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed to give the acetal **19** (2 g, 88%); R_f(hexane–EtOAc; 95:5) 0.46; $[\alpha]_D^{22}$ +24.2 (*c* 1.36, EtOAc); ν_{max}(film)/cm^{-1} 1732, 1248, 1110; δ_H(300 MHz, $CDCl_3$) 0.38 (3 H, s), 0.45 (3 H, s), 0.89 (3 H, t, *J* 7), 1.26 (16 H, br), 1.41–1.47 (1 H, m), 1.70 (1 H, dd, *J* 3.3, 15), 1.92 (1 H, dd, *J* 8, 15), 2.55 (1 H, dd, *J* 6, 13.8), 2.95 (1 H, dd, *J* 9, 13.8), 3.18–3.25 (1 H, m), 3.51 (3 H, s), 3.67–3.85 (4 H, m), 7.02–7.60 (10 H, m) (Found: C, 73.3; H, 9.4. $C_{32}H_{48}O_4Si$ requires C, 73.2; H, 9.2%).

(2*R*,3*S*)-3-[Dimethyl(phenyl)silyl]-5,5-(ethylenedioxy)-2-benzyltetradecanamide 20

The methyl ester **19** (1.868 g, 3.56 mmol) was dissolved in potassium hydroxide solution (2.5 M) in MeOH–THF–H_2O (3:5:2) and heated under reflux for 32 h. The solvent was removed, the residue was acidified with citric acid solution and extracted with ethyl acetate. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give (2*R*,3*S*)-3-[dimethyl(phenyl)-silyl]-5,5-(ethylenedioxy)-2-benzyltetradecanoic acid (1.8 g, 100%); ν_{max}(film)/cm^{-1} 3500–2400 (br), 1703, 1249, 1110; δ_H(300 MHz, $CDCl_3$) 0.37 (3 H, s), 0.47 (3 H, s), 0.89 (3 H, t, *J* 7), 1.25 (15 H, br), 1.44–1.55 (2 H, m), 1.72 (1 H, dd, *J* 3.4, 15.3), 1.92 (1 H, dd, *J* 9.3, 15), 2.53 (1 H, dd, *J* 6.4, 14), 2.98 (1 H, dd, *J* 8.4, 13.7), 3.23 (1 H, m), 3.71–3.86 (5 H, m), 7.05–7.58 (10 H, m). A solution of 1,1-carbonyldiimidazole (710 mg, 4.4 mmol) in dichloromethane (5 cm^3) was added to a stirred solution of the above acid (1.477 g, 2.89 mmol) in dichloromethane (10 cm^3) under argon atmosphere. After 30 min at room temperature, liquid ammonia (10 cm^3) was introduced into the same flask and the mixture was stirred until the ammonia evaporated. The mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed to give the amide **20** (1.13 g, 77%); R_f(hexane–EtOAc; 70:30) 0.5; $[\alpha]_D^{22}$ +20.5 (*c* 1.02, EtOAc); ν_{max}(film)/cm^{-1} 3422, 3339, 3178, 1682, 1600, 1454, 1246, 1108; δ_H(300 MHz, $CDCl_3$) 0.37 (3 H, s), 0.57 (3 H, s), 0.64–0.70 (1 H, m), 0.90 (3 H, t, *J* 7), 0.94–1.33 (16 H, br), 1.71–1.74 (2 H, m), 2.61 (1 H, dd, *J* 5.5, 12), 2.97–3.12 (2 H, m), 3.78–3.94 (4 H, m), 5.38 (1 H, br s), 6.12 (1 H, br s), 7.15–7.36 (8 H, m), 7.55–7.58 (2 H, m) (Found: C, 72.8; H, 9.5; N, 2.6. $C_{31}H_{47}O_3NSi$ requires C, 73.0; H, 9.3; N, 2.7%).

(2*R*,3*S*)-3-[Dimethyl(phenyl)silyl]-5,5-(ethylenedioxy)-1-phenyl-2-(benzyloxycarbonylamino)tetradecane 21

Lead tetraacetate[18] (5 g, 11.5 mmol) was added to a stirred

solution of amide **20** (1.13 g, 2.22 mmol) and benzyl alcohol (2.3 cm^3, 22.2 mmol) in DMF (20 cm^3) at 40 °C under argon atmosphere. After 15 h at 100 °C, the reaction mixture was passed through a silica gel pad and eluted with ether. The solvent was evaporated under reduced pressure and the excess DMF was removed under high vacuum. The residue was chromatographed to give the urethane **21** (930 mg, 75%); R_f(hexane–EtOAc; 90:10) 0.6; $[\alpha]_D^{24}$ −7.4 (*c* 1, EtOAc); ν_{max}(film)/cm^{-1} 3381, 1721, 1504, 1249, 1110; δ_H(300 MHz, $CDCl_3$) 0.44 (6 H, s), 0.89 (3 H, t, *J* 6.6), 0.94–1.08 (1 H, m), 1.15–1.31 (14 H, br), 1.44–1.54 (2 H, m), 1.75–1.85 (2 H, m), 2.48–2.61 (2 H, m), 3.84–3.98 (4 H, m), 4.26–4.34 (1 H, m), 4.95 (2 H, AB quartet, *J* 12.6), 5.98 (1 H, d, *J* 10), 6.93–7.60 (15 H, m) (Found: C, 73.9; H, 8.9; N, 2.6. $C_{38}H_{53}O_4NSi$ requires C, 74.1; H, 8.7; N, 2.3%).

(2*R*,3*S*)-3-[Dimethyl(phenyl)silyl]-1-phenyl-2-(benzyloxycarbonylamino)tetradecan-5-one 22

A solution of acetal **21** (924 mg, 1.62 mmol) and toluene-4-sulfonic acid (100 mg, 0.6 mmol) in acetone–water (98:2) (70 cm^3) was heated under reflux for 2.5 h. The acetone was removed and the residue was dissolved in ethyl acetate. The solution was washed with sodium bicarbonate solution and with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the ketone **22** (816 mg, 100%); R_f(hexane–EtOAc; 90:10) 0.37; $[\alpha]_D^{22}$ −22.2 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3348, 1712, 1251, 1111; δ_H(300 MHz, $CDCl_3$) 0.36 (3 H, s), 0.38 (3 H, s), 0.87 (3 H, t, *J* 6.4), 1.24–1.29 (12 H, br), 1.46 (2 H, br t), 1.96–2.08 (1 H, m), 2.27–2.35 (2 H, m), 2.37–2.41 (1 H, m), 2.46 (1 H, dd, *J* 4.5, 17), 2.59–2.75 (2 H, m), 4.05 (1 H, br s), 4.36 (1 H, d, *J* 8), 4.91 (2 H, s), 6.93–7.53 (15 H, m) (Found: C, 75.5; H, 8.7; N, 2.2. $C_{36}H_{49}O_3SiN$ requires C, 75.6; H, 8.6; N, 2.5%).

(2*S*,3*S*,5*R*)-3-[Dimethyl(phenyl)silyl]-1-ethoxycarbonyl-2-benzyl-5-nonylpyrrolidine 23

A solution of the ketone **22** (800 mg, 1.4 mmol) in ethanol (285 cm^3) and acetic acid (15 cm^3) was hydrogenated in a Parr apparatus (53 psi) in the presence of Pd/C (10% Pd) (200 mg) over 7 h. The reaction mixture was passed through a Celite pad and washed with ethanol. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 followed by addition of ethyl chloroformate (0.27 cm^3, 2.8 mmol) and triethylamine (0.42 cm^3, 3 mmol). After 18 h at room temperature, the reaction mixture was diluted with benzene, washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the pyrrolidine **23** as a mixture (about 2:1) of geometrical and/ or atropisomers (518 mg, 75%); R_f(EtOAc–hexane; 2:98) 0.2; $[\alpha]_D^{22}$ −85.9 (*c* 0.61, $CHCl_3$); ν_{max}(film)/cm^{-1} 1694, 1252, 1112; δ_H(300 MHz, $CDCl_3$) 0.41 (6 H, s, from major), 0.45 (6 H, s, from minor), 0.67 (3 H, t, *J* 7 major), 0.89 (3 H, t, *J* 6.8), 1.20–1.40 (16 H, m), 1.57–1.78 (1 H, m, in addition to that an overlapped triplet from minor accounting for 3 H), 2.25–2.44 (3 H, m), 2.68 (1 H, br d, *J* 11), 3.30–3.38 (1 H, m), 3.56–3.70 (2 H, m, from major), 3.82–3.92 (2 H, m, from minor), 4.18–4.24 (1 H, m, from major), 4.39–4.52 (1 H, m, from minor), 6.95–7.21 (5 H, m), 7.35–7.57 (5 H, m); *m*/*z* (EI) 493 ($M^{\cdot+}$, 0.9%), 403 (M + H − Bn, 100), 402 (M + H − Bn, 71.4), 340 (5.6), 326 (19.2), 135 (Me_2PhSi, 41.8), 91 (Bn, 14.5) (Found: C, 75.3; H, 9.9; N, 2.6. $C_{31}H_{47}O_2NSi$ requires C, 75.4; H, 9.6; N, 2.8%).

(2*S*,3*S*,5*R*)-3-Acetoxy-1-ethoxycarbonyl-2-benzyl-5-nonylpyrrolidine 24

Peracetic acid[11] (about 30% solution in acetic acid) (4 cm^3) was added to a stirred mixture of pyrrolidine **23** (160 mg, 0.324 mmol), potassium bromide (45 mg, 0.38 mmol) and sodium acetate (200 mg) at 0 °C. The reaction mixture was stirred for 1 day at room temperature and evaporated under vacuum. The residue was diluted with water and extracted with ethyl acetate. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in Et_3N (1 cm^3) and acetic anhydride (0.5 cm^3, 5.25 mmol) was added followed by a catalytic amount of DMAP. After 1 day at room temperature, water was added, stirred for 0.5 h and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed to give the acetate **24** (78 mg, 68%); R_f(EtOAc-hexane; 10:90) 0.58; $[\alpha]_D^{23}$ −48.2 (*c* 0.66, $CHCl_3$); ν_{max}(film)/cm^{-1} 1744, 1703, 1698, 1234; δ_H(300 MHz, at 70° C in C_6D_6) 0.82–1.02 (6 H, m), 1.20–1.40 (16 H, m), 1.50–1.80 (1 H, m), 1.58, 1.60 and 1.65 (3 H, three singlets overlapping with preceding multiplet), 1.96–2.40 (2 H, m), 2.70–3.32 (2 H, m), 3.62–4.10 (3 H, m), 4.28–4.38 (1 H, m from one isomer), 4.44–4.52 (1 H, m, from one isomer), 4.68–4.78 (1 H, m, from one isomer), 4.90–5.00 (1 H, m, from one isomer), 5.00–5.07 (1 H, m, from one isomer), 6.85–7.50 (5 H, m); *m*/*z* (EI) 341 (1.9%), 326 (100), 284 (15.7) (Found: C, 71.7; H, 9.5; N, 3.2. $C_{25}H_{39}O_4N$ requires C, 71.9; H, 9.4; N, 3.4%).

(2*S*,3*S*,5*R*)-1-Methyl-5-nonyl-2-benzylpyrrolidin-3-ol 1

A solution of the acetate **24** (125 mg, 0.29 mmol) in THF (3 cm^3) was added to a stirred suspension of $LiAlH_4$ (100 mg, 2.5 mmol) in THF (3 cm^3) and the mixture was stirred at room temp. for 24 h. The reaction was decomposed with a saturated solution of sodium sulfate in water and triturated with ethyl acetate. The solvent was removed to give **1** (74 mg, 77%); R_f(hexane–EtOAc; 90:10) 0.32; $[\alpha]_D^{25}$ 31.1 (*c* 1, $CHCl_3$); lit.,[2] $[\alpha]_D^{25}$ 31.08 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3406; δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.9), 1.20–1.46 (16 H, m), 1.65–1.80 (1 H, m), 2.00–2.33 (4 H, m), 2.34 (3 H, s), 2.80–2.94 (2 H, AB multiplet), 3.80–3.83 (1 H, m), 7.16–7.32 (5 H, m); ^{13}C NMR δ_C(50 MHz, $CDCl_3$) 139.5, 129.3, 128.3, 125.9, 73.6, 70.3, 65.8, 39.4, 38.5, 34.7, 33.6, 31.8, 29.6, 29.2, 26.2, 22.6, 13.9.

References

1 (*a*) R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity and R. A. Fromtling, *J. Antibiot.*, 1988, **41**, 1774; (*b*) R. E. Schwartz, J. C. Onishi, R. L. Monaghan, J. M. Liesch and O. D. Hensens, US Patent 4 847 284, 1989; (*c*) J. H. Johnson, D. W. Phillipson and A. D. Kahle, *J. Antibiot.*, 1989, **42**, 1184.

2 C. S. Pak and G. H. Lee, *J. Org. Chem.*, 1991, **56**, 1128.

3 P. de-Armas, F. García-Tellado, J. J. Marrero-Tellado and J. Robles, *Tetrahedron Lett.*, 1998, **39**, 131.

4 H. Yoda, M. Yamazaki and K. Takabe, *Tetrahedron: Asymmetry*, 1996, **7**, 373.

5 (*a*) P. L. McGrane and T. Livinghouse, *J. Am. Chem. Soc.*, 1993, **115**, 11485; (*b*) M. Overhand and S. M. Hecht, *J. Org. Chem.*, 1994, **59**, 4721; (*c*) W. Deng and L. E. Overman, *J. Am. Chem. Soc.*, 1994, **116**, 11241; (*d*) C. Beier and E. Schaumann, *Synthesis*, 1997, 1296.

6 M. Shimazaki, F. Okazaki, F. Nakajima, T. Ishikawa and A. Ohta, *Heterocycles*, 1993, **36**, 1823.

7 A. Kanazawa, S. Gillet, P. Delair and A. E. Greene, *J. Org. Chem.*, 1998, **63**, 4660.

8 R. Verma, S. Mithran and S. K. Ghosh, please see the preceding article 8/08838A.

9 (*a*) T. Rosen and C. H. Heathcock, *J. Am. Chem. Soc.*, 1985, **107**, 3731; (*b*) D. S. Karanewsky, M. F. Malley and J. Z. Gougoutas, *J. Org. Chem.*, 1991, **56**, 3744.

10 For stereoselective α-alkylation of β-hydroxy acids; see: G. Fr'ater, *Helv. Chim. Acta*, 1979, **62**, 2825; D. Seebach and D. Wasmuth, *Helv. Chim. Acta*, 1980, **63**, 197.

11 For a review, see: I. Fleming, A. Barbero and D. Walter, *Chem. Rev.*, 1997, **97**, 2063. See also: I. Fleming, R. Henning, D. C. Parker, H. E. Plaut and P. E. J. Sanderson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 317.

12 R. A. N. C. Crump, I. Fleming, J. H. M. Hill, D. Parker, N. L. Reddy and D. Waterson, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3277.

13 R. Verma and S. K. Ghosh, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2377.
14 R. Verma and S. K. Ghosh, *Chem. Commun.*, 1997, 1601.
15 (*a*) D. A. Evans and A. S. Kim, in *Encyclopedia of reagents for organic synthesis*, ed. L. A. Paquette, Wiley, NY, 1995, vol. 11, p. 345; (*b*) D. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835; (*c*) D. A. Evans, T. C. Briton, J. A. Ellman and R. L. Dorow, *J. Am. Chem. Soc.*, 1990, **112**, 4011.
16 E. Kaiser, Sr., F. Pickart, T. Kubiak, J. P. Tam and R. B. Merrifield, *J. Org. Chem.*, 1993, **58**, 5167.
17 T. H. Chan, M. A. Brook and T. Chaly, *Synthesis*, 1983, 203.
18 H. E. Baumgarten, H. L. Smith and A. Staklis, *J. Org. Chem.*, 1975, **40**, 3555.

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