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A SHORT AND EFFICIENT SYNTHESIS OF THE C-3 TO C-10 PORTION OF THE MAYTANSINOIDS

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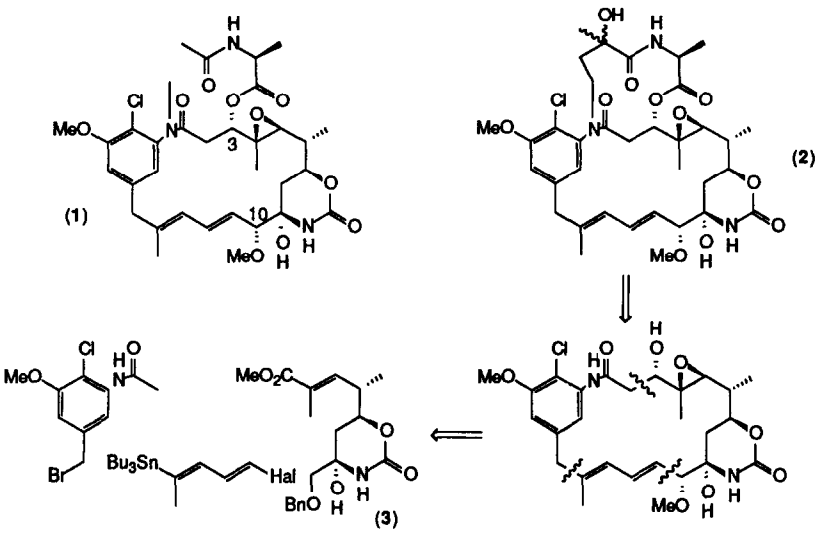
Abstract: The cyclic carbamate (**3**), a key intermediate in our projected synthesis of trenudine (**2**), has been synthesised from 3,4-epoxycyclohexene (**4**) by ozonolytic cleavage of the cyclopentene (**9**) as a key step.

The maytansinoids are a class of biologically active and richly functionalised macrocyclic amides which, since their discovery by Kupchan *et al.* in 1972, have been the subject of much synthetic interest.[1] Total syntheses of the key member of the class, maytansine (**1**), have been reported from research groups led by Corey, Meyers and Isobe.[2] Our work is directed towards the synthesis of trenudine (**2**) which was isolated from the seeds of *Trewia nudiflora* in 1982[3] and possesses exceedingly potent insect antifeedant activity.[4]



Scheme 1

In this paper we disclose in full our route to the cyclic carbamate (**3**), which is a key intermediate in our projected synthesis of trenudine (**2**) (Scheme 1).[5]

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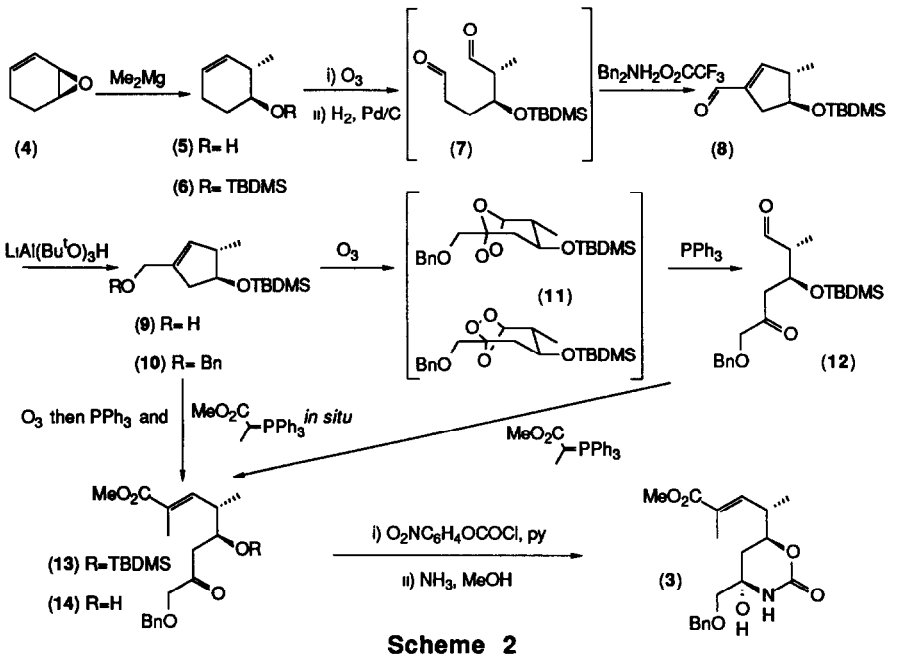
The synthesis of the cyclic carbamate (**3**) began with formation of the *trans*-homoallylic alcohol (**5**) (87%) from 3,4-epoxycyclohexene (**4**) and dimethylmagnesium (Scheme 2).[6] This alcohol (**11**) was protected as its silyl ether (**6**) (90%)[7] and was then subjected to ozonolysis followed by work-up with Pd/C under an atmosphere of hydrogen to give the intermediate dialdehyde (**7**) (40%), which was best used immediately in the next step without purification. Regioselective aldol ring formation was facilitated using dibenzylammonium trifluoroacetate to yield the enal (**8**) (47%, or 57% directly from silyl ether (**6**)).[8] The concise route to this functionalised cyclopentene is worthy of note. Reduction of the enal (**8**) with $LiAl(Bu^tO)_3H$ afforded the allylic alcohol (**9**) (82%), which was protected as its benzyl ether to give the cyclopentene (**10**) (90%).



Scheme 2

The best yields of the desired labile 1,5-ketoaldehyde (**12**) were obtained from ozonolysis of the cyclopentene (**10**) if the intermediate diastereomeric pair of inseparable, stable ozonides (**11**) were purified by chromatography (87%) before cleavage with PPh_3 (50%, 44% overall from cyclopentene (**10**)). At this point, we envisaged *E*-double bond and allylic oxygen functionality being introduced into the 1,5-ketoaldehyde (**12**) in one step using a carbonyl-stabilised Wittig reagent. Such ylids are known to react with aldehydes, but are generally inert towards ketones. There are also many examples of α-methyl carbonyl-stabilised ylids reacting with aldehydes to selectively form *E*-trisubstituted double bonds, as we required.[9] The 1,5-keto-aldehyde (**12**) reacted with methyl 2-(triphenylphosphoranylidene) propanoate to give mainly the desired *E*-ketoester (**13**) as the only isolated material (55% yield, pure by high field ^1H n.m.r. (>90% pure by ^{13}C n.m.r.; 8% of *Z*-

isomer, or methyl epimer present by =CH integration)). The best yields of the *E*-ketoester (**13**) (79% *directly* from cyclopentene (**10**)) were obtained by decomposing the crude ozonides (**11**) with PPh_3 *in the presence of* the ylid.[10] This procedure removed problems associated with handling the somewhat unstable 1,5-ketoaldehyde (**12**).

Aqueous HF in MeCN was used to remove the silyl protecting group of the *E*-ketoester (**12**) to give the β-hydroxyketone (**14**) (84%) without concomitant elimination.[11] The cyclic carbamate (**3**) was successfully formed by applying conditions Isobe used in his total synthesis of (-)-*N*-methylmaysenine.[12] Thus, the β-hydroxyketone (**14**) was reacted with *p*-nitrophenyl chloroformate and pyridine at 0°C, followed by dry ammonia-saturated MeOH at -80°C to give the cyclic carbamate (**3**) as a 6:1 anomeric mixture (50% in total, 66% based on recovered β-hydroxyketone (**14**)).

There has been some debate in the literature concerning the cyclic/acyclic nature of carbamates which are structurally similar to (**3**).[13] It is known that the proton chemical shift of the 7-H (maytansine (**1**) numbering) of cyclic carbamates is always less than 5.0 p.p.m., whereas in acyclic carbamates it is always greater than 5.0 p.p.m. Spectral data for the carbamate (**3**) were consistent with having obtained cyclic, as opposed to acyclic, material, since this proton was observed at δ 4.50 (major anomer) and 4.01 (minor anomer)). Furthermore, the ketonic carbon in the ^{13}C n.m.r. spectrum of the β-hydroxyketone (**14**) (δ 209.4) was replaced in the spectrum of the carbamate (**3**) by two quaternary centres (δ 79.7 (major anomer) and 81.0 (minor anomer)).

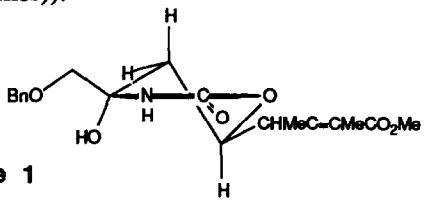


Figure 1

The cyclic carbamate (**3**) is likely to exist in a half-chair conformation (Figure 1), as in maytansine (**1**) and other cyclic carbamates.[14] Coupling constants between the ring methine and methylene protons were 12.5 Hz and 2 Hz, indicating the ester side chain to be equatorial. The OH would be expected to be pseudoaxial in the major isomer due to the anomeric effect.[15] Interestingly, minor isomers have never been reported in any other cyclic carbamate studies.[16] The reason why only one anomer is reported for the maytansinoids may be due to a combination of the preferred macrocyclic conformation together with the fixed orientation of the C-10 methoxy. However, 9-epimaytansine (**1**) (C-9 β-OH) has recently been tentatively identified as a decomposition product of clinically formulated maytansine (**1**).[17]

Experimental: All reactions requiring anhydrous conditions were conducted in flame dried apparatus under an atmosphere of nitrogen. Syringes and needles for the transfer of reagents were dried at 90°C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl, (chlorinated) hydrocarbons, DMF, and MeCN

from CaH_2, and alcohols from their magnesium alkoxides. Internal reaction temperatures are reported unless stated otherwise. All reactions were monitored by tlc using commercially available (Camlab) glass backed plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator. Organic layers were evaporated with a Buchi rotary evaporator by using water aspirator reduced pressure, followed by drying on a static oil pump (1 mm Hg). Column chromatography was carried out on Kieselgel 60 (0.04-0.063 nm) using light petroleum (bp 40-60°C) (PE) and EtOAc.

Melting points were determined with an electrothermal melting point apparatus and are uncorrected. Microanalyses were performed at Queen Mary College, London. I.r. spectra were recorded as thin films unless stated otherwise, using a Perkin-Elmer 298 spectrophotometer with polystyrene film for calibration (1602 and 1029 cm^{-1}). Peak intensities are specified as strong (s), medium (m) or weak (w). ^1H n.m.r. spectra of literature compounds were recorded in $CDCl_3$ with Me_4Si as internal standard, using a Perkin-Elmer R-24B spectrometer at 60 MHz. ^1H n.m.r. spectra of new compounds were recorded in $CDCl_3$ with a Bruker AM360 spectrometer operating at 360.134 MHz. Chemical shifts are reported relative to residual $CHCl_3$ (δ 7.27) in sample. Coupling constants (J) are given in Hz. ^{13}C n.m.r. spectra were recorded in $CDCl_3$ on the Bruker at 90.556 MHz. Chemical shifts are reported relative to $CDCl_3$ (centre line of triplet, δ 77.15). A mixture of off-resonance, DEPT 135, and DEPT 90 pulse sequences were used to aid spectral interpretation. Mass spectra were obtained either from a VG Analytical 70-250-E spectrometer or from the SERC Mass Spectrometry Centre, Swansea, with a VG Micromass ZAB-E instrument.

trans-(±)-2-Methyl-3-cyclohexen-1-ol (**5**).[6] Dimethylmagnesium[18] (324 ml, 0.77 M in ether, 0.249 mol) was added dropwise over 45 min to a stirred solution of 3,4-epoxycyclohexene (**4**)[19] (21.8 g, 0.227 mol) in dry ether (400 ml) such that the reaction temperature was maintained between -33°C and -30°C ($MeCN/N_2$ bath), and was then allowed to reach room temperature overnight. The reaction mixture was carefully poured into 1 M HCl, extracted with ether (x2), dried ($MgSO_4$), and evaporated *in vacuo* to give a pale yellow oil, pure by t.l.c. and ^1H n.m.r., *alcohol* (**5**) (22.15 g, 87%); $\nu_{max.}$ 3400s, 3020m, 2940s, 1650w, 1460m, 1440m, and 1070s cm^{-1}; δ_H 5.4 (2H, m, =CHx2), 3.3 (2H, m, CHOH), 2.0 (5H, m, CHMe and CH_2x2), and 1.1 (3H, d, J 6, Me).

trans-(±)-[(2-Methyl-3-cyclohexen-1-yl)oxy](1,1-dimethylethyl)dimethylsilane (**6**). Imidazole (8.92 g, 0.131 mol) in dry DMF (10 ml), TBDMSCl (19.80 g, 0.131 mol) in dry DMF (25 ml), and DMAP (4.00 g, 0.03 mol) in dry DMF were added in turn to a stirred solution of alcohol (**5**) (12.24 g, 0.110 mol) in dry DMF (60 ml) at room temperature and then left overnight. The reaction mixture was poured into aqueous 1 M $CuSO_4$ solution and extracted with pentane (x2). The combined organic layers were washed with water and then saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo*. The crude material may be purified by column chromatography (PE) or, as in this case, distilled (care, froths) to give a colourless oil, *silyl ether* (**6**) (22.13 g, 90%), b.p. 106°C/19 mm Hg. Found: C, 68.9; H, 11.5. $C_{13}H_{26}OSi$ requires C, 69.0; H, 11.6%. Also found (NH_3 CI): $(M+H)^+$, 227.1835 (100%). $C_{13}H_{27}OSi$ requires M, 227.18312; $\nu_{max.}$ (CCl_4) 3030 cm^{-1}; δ_H 5.59 and 5.42 (1H and 1H,

m and m, =CHx2), 3.44 (1H, ddd, *J* 10, 7 and 3, CHOSi), 2.14 (3H, m, C*H*Me and =CH*CH*$_2$), 1.84 and 1.64 (2H, m and m, CH_2)), 1.05 (3H, d, *J* 7, CH*Me*), 0.96 (9H, s, Bu^t), and 0.13 (6H, s, $SiMe_2$); δ_C 131.7 and 125.6 (=CHx2), 74.8 (CHOSi), 39.6 (*C*HMe), 31.3 (=CH*C*H$_2$), 26.1 (C*Me*$_3$), 24.8(CH_2), 19.3 (CH*Me*), 18.3 (SiC), and -3.9 and -4.4 ($SiMe_2$); *m/z* (EI) 138 (17%), 111 (26), 95 (25), 94 (44), 83 (37), 82 (56) and 68 (100).

(R,S*)-(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methylhexan-1.6-dial* (**7**). A mixture of O_2 and O_3 was bubbled through a solution of silyl ether (**6**) (1.37 g, 6.05mmol) in dry MeOH (100 ml) at -80°C until a blue colour just formed. The solution was degassed with N_2, then Pd/C (100 mg, 10% w/w) was added and the reaction vessel flushed out with H_2. The reaction mixture was allowed to warm to room temperature overnight under H_2. The mixture was filtered through celite, evaporated *in vacuo*, and purified by column chromatography (20% EtOAc/PE) to give a colourless oil, *dialdehyde* (**7**) (630 mg, 40%), b.p. 65-70°C/0.6 mm Hg. Found (NH_3 CI): $(M+NH_4)^+$, 276.1995 (68%). $C_{13}H_{30}NO_3Si$ requires *M*, 276.19950; $\nu_{max.}$ 2960s, 2940s, 2860s, 2730w, 1730s, 1460m, 1390m, 1260s, 1105s, 1040s, 840s, and 780s cm^{-1}; δ_H 9.69 (2H, s, CHOx2), 4.02 (1H, m, CHOSi), 2.40 (3H, m, C*H*Me and C*H*$_2$CHO), 1.70 (2H, m, CH_2), 0.96 (3H, d, *J* 7, CH*Me*), 0.76 (9H, s, Bu^t), and -0.03 and -0.05 (6H, s and s, $SiMe_2$); δ_C 204.2 and 201.1 (CHOx2), 71.5 (CHOSi), 51.5 (CHMe), 40.0 (*C*H$_2$CHO), 26.8 (CH_2), 25.8 (C*Me*$_3$), 18.1 (SiC), 8.5 (CH*Me*), and -4.3 and -4.5 ($SiMe_2$); *m/z* (EI) 171 (19%), 159 (14), 143 (16), 85 (16), and 75 (100).

trans-(±)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methyl-1-cyclopentenecarboxaldehyde (**8**). (a) Dialdehyde (**7**) (440 mg, 1.7 mmol), dibenzylammonium trifluoroacetate (16 mg, 0.05 mmol), and $MgSO_4$ (1 g) in dry CH_2Cl_2 (40 ml) were heated to reflux overnight. Further $MgSO_4$ (2 g) was added and the reaction mixture filtered, evaporated *in vacuo*, and purified by column chromatography (5% EtOAc/PE) to give a light red oil, *enal* (**8**) (193 mg, 47%), b.p. 55-60°C/0.5 mm Hg. Found (NH_3 CI): $(M+NH_4)^+$, 258.1893 (100%). $C_{13}H_{28}NO_2Si$ requires *M*, 258.18893; $\nu_{max.}$ (CCl_4) 1690s cm^{-1}; δ_H 9.67 (1H, s, CHO), 6.64 (1H, dd, *J* 4 and 2, =CH), 4.02 (1H, dt, *J* 7 and 5, CHOSi), 2.77 (2H, m, C*H*Me and CH of CH_2), 2.35 (1H, ddt, *J* 16, 5, and 12, CH of CH_2), 1.10 (3H, d, *J* 7, CH*Me*), 0.86 (9H, s, Bu^t), and 0.05 (6H, s, $SiMe_2$); δ_C 189.8 (CHO), 154.2 (=CH), 143.7 (=C), 80.0 (CHOSi), 50.1 (CHMe), 37.8 (CH_2), 25.9 (C*Me*$_3$), 18.1 (SiC), 16.7 (CH*Me*), and -4.6 and -4.7 ($SiMe_2$); *m/z* (EI) 240 (1%, *M*$^+$), 199 (13), 183 (31, *M*-Bu^t), 171 (34) and 75 (100).

(b) In a separate experiment, dibenzylammonium trifluoroacetate (800 mg, 123 mmol) and $MgSO_4$ (30 g) were added directly to a solution of crude dialdehyde (**7**) obtained by ozonolysis of silane (**6**) (20.05 g, 0.088 mol) in dry MeOH (1 L) at -80°C, Pd/C (800 mg, 10% w/w) work-up, celite filtration and evaporation *in vacuo*) in dry CH_2Cl_2 (1 L) to give product (12.2 g, 57% from silyl ether (**6**)) with identical characteristics (t.l.c. mobility and ^{1}H n.m.r. spectrum) to enal (**8**) obtained in (a) above.

trans-(±)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methyl-1-cyclopentene-1-methanol (**9**). $LiAl(Bu^tO)_3H$ (prepared by adding dry Bu^tOH (67.5 ml, 69 mmol) in dry THF (30 ml) to $LiAlH_4$ (77 ml, 0.30 M in THF,[20] 23 mmol) at -15°C) was added dropwise over 30 min to a stirred solution of enal (**8**) (3.96 g, 16 mmol) in dry THF (150 ml) at -80°C and then allowed to reach room temperature. The reaction mixture was diluted with ether, an equivalent of water added and filtered through celite. The separated aqueous layer was saturated with NaCl and extracted with ether. The combined organic layers were dried ($MgSO_4$), evaporated *in vacuo*, and purified by column chromatography (25% EtOAc/PE) to give a colourless oil, *allylic alcohol* (**9**) (3.19 g, 82%), b.p. 50-60°C/0.2 mm Hg. Found (NH_3 CI): $(M+NH_4)^+$, 260.2050 (100%). $C_{13}H_{30}NO_2Si$ requires *M*, 260.20458; $\nu_{max.}$ 2400br cm^{-1}; δ_H 5.41 (1H, br d, *J* 2, =CH), 4.06 (2H, br s, CH_2OH), 3.96 (1H, dt, *J* 7 and 5, CHOSi), 2.75 (2H, m, C*H*Me and H of ring CH_2), 2.23 (1H, m, H of ring CH_2), 1.00 (3H, d, *J* 7, CH*Me*), 0.86 (9H, s, Bu^t), and 0.004 (6H, s, $SiMe_2$); δ_C 140.6(=C), 129.0 (=CH), 80.9 (CHOSi), 62.1 (CH_2OH), 48.8 (*C*HMe), 41.9 (ring CH_2), 26.0 (C*Me*$_3$), 18.2 (SiC), 18.1 (CH*Me*), and -4.5 and -4.6 ($SiMe_2$); *m/z* (EI) 185 (26%, *M*-Bu^t), 93 (15) and 75 (100).

trans-(±)-(1,1-Dimethylethyl)dimethyl[[2-methyl-4-[(phenylmethoxy)methyl]-3-cyclopenten-1-yl]silane (**10**). Allylic alcohol (**9**) (2.45 g, 10.1 mmol) in dry DME (40 ml) was added to a stirred slurry of pentane washed NaH (486 mg, 60% w/w dispersion in mineral oil, 12.1 mmol) in dry DME (150 ml) at room temperature. After 10 min, freshly distilled benzyl bromide (1.5 ml, 12.6 mmol) and NaI (750 mg, 5.0 mmol) were added and the reaction mixture heated to 60°C overnight. The cooled reaction mixture was diluted with ether, washed with water and the aqueous layer was saturated with NaCl and re-extracted with ether. The combined organic layers were dried (MgSO4), evaporated *in vacuo*, and purified by column chromatography (55 EtOAc/PE) to give a colourless oil, *cyclopentene* (**10**) (3.04 g, 90%), b.p. 100°C/0.03 mm Hg. Found (NH_3 CI): $(M+NH_4)^+$, 350.2519 (100%). $C_{20}H_{36}NO_2Si$ requires *M*, 350.25253; $\nu_{max.}$ 3040w, 2970s, 2940s, and 2870s cm^{-1}; δ_H 7.409 (5H m, Ph), 5.57(1H, br s, =CH), 4.56 (2H, 2d's, *J* 12, $PhCH_2$), 4.08(3H, m, CHOSi and CH_2O), 2.70 (2H, m, C*H*Me and H of ring CH_2), 2.37 (1H, m, H of ring CH_2), 1.12 (3H, d, *J* 7, CH*Me*), 0.99 (9H, s, Bu^t), and 0.15 (6H, s, $SiMe_2$); δ_C 138.7 and 137.8 (=C and quat. aromatic), 131.1 (=CH), 128.4-127.5 (aromatics), 80.9 (CHOSi), 72.1 and 69.2 ($PhCH_2OCH_2$), 48.8 (*C*Me), 42.3(ring CH_2), 26.0 C*Me*$_3$), 18.1 (SiC and CH*Me*), and -4.4 and -4.6 ($SiMe_2$); *m/z* (EI) 275 (18%, *M*-Bu^t), 183 (16), 169 (11), 165 (13), 135 (10), 92 (11), and 91 (100, C_7H_7).

(3-endo,4-exo)- and (3-exo,4-endo)-(±)-3-[[(Dimethylethyl)dimethylsilyl]oxy]-4-methyl-1-[(phenylmethoxy)methyl]-6,7,8-trioxabicyclo[3.2.1]octanes (**11**). A mixture of O_2 and O_3 was bubbled through a solution of cyclopentene (**10**) (1.130 g, 3.40 mmol) in dry CH_2Cl_2 (100 ml) at -80°C until a blue colour just formed. The solution was degassed with N_2, allowed to warm to room temperature, evaporated *in vacuo*, and purified by column chromatography (5% EtOAc/PE) to give a colourless oil, the pair of diastereomeric *ozonides* (**11**) (1.13 g,

87%); $\nu_{max.}$ 2965s, 2940s, 1460s, 1365m, 1260m, and 1095s cm^{-1}; δ_H (major isomer (mj): minor (mn), 3:1 by CHO_3 integration, data for mj) 7.37 (m, Ph), 5.56 (s, CHO_3), 4.65 (2d's, *J* 12, PhCH_2), 4.03 (dt. *J* 9 and 6, CHOSi), 3.70 (2d's, *J* 11, CH_2O), 2.31 (dd, *J* 13 and 6, H of ring CH_2), 1.70 (m, H of ring CH_2 and C*H*Me), 1.09 (d, *J* 7, CH*Me*), 0.94 (s, Bu^t), and 0.13 and 0.,11 (s and s, $SiMe_2$); δ_H (discernible data for mn) 5.53 (s, CHO_3), 2.24 (dd, H of ring CH_2), 1.12 (d, CHMe), 0.95 (s, Bu^t), and 0.10 and 0.09 (s and s, $SiMe_2$); δ_C (data for mj) 137.6 (quat. aromatic), 128.0 and 127.8 (*o*- and *m*-aromatics), 127.9 (*p*-aromatic), 108.3 (CO_3), 106.0 (CHO_3), 73.8 and 70.1 (PhCH_2OCH_2), 69.5 (CHOSi), 43.5 (*C*HMe), 40.2 (ring CH_2), 25.8 (C*Me*$_3$), 18.0 (SiC), 15.4 (CH*Me*), and -4.1 and -4.7 ($SiMe_2$); δ_C (discernible data for mn) 105.3 (CHO_3), 43.1 (*C*HMe), 37.9 (ring CH_2) and 15.7 (CH*Me*).

(R,S*)-(±)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methyl-5-oxo-6-(phenylmethoxy)-hexanal* (**12**). PPh_3 (312 mg, 1.19 mmol) was added to stirred solution of the ozonides (**11**) (453 mg, 1.19 mmol) in dry CH_2Cl_2 (50 ml) at room temperature. After 3 h. the reaction mixture was evaporated *in vacuo*, preabsorbed onto silica gel (60-120 mesh), and purified by column chromatography (10% EtOAc/PE) to give a colourless oil, *1,5-ketoaldehyde* (**12**) (218 mg, 50%). Found (NH_3 CI): $(M+NH_4)^+$, 383.2419 (20%). $C_{20}H_{36}NO_4Si$ requires *M*, 383.24190; $\nu_{max.}$ 2980s, 1940s, 2870s, 2720w, 1730s, 1465m, and 1265s cm^{-1}; δ_H 9.80 (1H, s, CHO), 7.35 (5H, m, Ph), 4.72 (1H, m. CHOSi), 4.60 (2H, s, PhCH_2), 4.05 (2H, s, CH_2O), 2.72 (1H, dd, *J* 16 and 7, H of CH_2), 2.58 (1H, dd, *J* 17 and 5, H of CH_2), 2.55 (1H, m, C*H*Me), 1.05 (3H, d, *J* 7, CH*Me*), 0.85 (9H, s, Bu^t) and 0.05 and 0.01 (6H, s and s, $SiMe_2$); δ_C 206.4 (C=O), 203.8 (CHO), 137.2 (quat. aromatic), 128.6 and 1127.9 (*o*- and *m*-aromatics), 128.1 (*p*-aromatic), 75.7 and 73.5(PhCH_2OCH_2), 68.0 (CHOSi), 51.7 (*C*HMe), 43.9 (CH_2), 27.8 (C*Me*$_3$), 18.0 (SiC), 8.0 (CH*Me*), and -4.5 and -4.8 ($SiMe_2$); *m/z* (EI) 215 (11%), 92 (9) and 91 (100).

Methyl [R,R*-(E)]-(±)-5-[[(dimethylethyl)dimethylsilyl]oxy]-2,4-dimethyl-7-oxo-8-(phenyl methoxy)-2-octenoate* (**13**). A mixture of O_2 and O_3 was bubbled through a solution of cyclopentene (**10**) (4.820 g, 0.014 mol), in dry CH_2Cl_2 (100 ml) at -80°C until a blue colour just formed. The solution was degassed with N_2 and allowed to warm to -50°C. PPh_3 (3.81 g, 0.014 mol) was added, followed after 5 min. by methyl 2-(triphenylphosphoranylidene)-propanoate[21] (10.10 g, 0.029 mol) and the mixture heated to reflux for 2 d. Further ylid (5.05 g, 0.014 mol) was added and refluxing continued for another 24 h. The reaction mixture was cooled, preabsorbed onto silica gel (60-120 mesh), and purified by column chromatography (20% EtOAc/PE) to give a pale yellow oil (5.39 g), a 13:1 mixture (by ^{13}C =CH integrations) of E-*ketoester* (**13**) (79%) and Z-isomer, or methyl epimer (6%, only discernible in ^{13}C n.m.r. spectrum). Found (NH_3 CI): $(M+NH_4)^+$, 452.2328 (100%). $C_{24}H_{42}NO_5Si$ requires *M*, 452.28323; $\nu_{max.}$ 2960s, 2940s, 1900m, 2860s, 1720s, 1710s, 1650w, 1460m, 1430m, 1250s, 1100s, 835a, 780s, 750s, and 700m cm^{-1}; δ_H 7.35 (5H, m, Ph), 6.63 (1H, dq, *J* 10.1 and 1.5, =CH), 4.59 (2H, 2d's, *J* 12, PhCH_2), 4.18 (1H, dt, *J* 7 and 5, CHOSi), 4.04 (2H, s, CH_2O), 3.73 (3H, s, CO_2Me), 2.60 (3H, m, C*H*Me and CH_2), 1.86

(3H, s, *J* 12, =CMe), 0.99 (3H, d, *J* 7, CH*Me*), 0.86 (9H, s, Bu^t), and 0.06 and -0.01 (6H, s and s, $SiMe_2$); δ_C (data for *E*-ketoester (**13**)) 206.4 (C=O), 168.4 (CO_2Me), 144.2 (=CH), 137.2 (quat. aromatic), 128.4, 127.9 and 127.8 (aromatics), 127.5 (=CMe), 75.7 and 63.4 ($PhCH_2OCH_2$), 71.1 (CHOSi), 51.5 (CO_2Me), 44.6 (CH_2), 39.2 (*C*HMe), 25.8 (CMe_3), 18.0 (SiC), 14.6 and 12.6 (=C*Me* and CH*Me*), and -4.6 and -4.9 ($SiMe_2$); δ_C (discernible data for *Z*-isomer, or Me epimer) 143.0 (=CH), 74.2 (CH_2), 70.9 (CHOSi), 44.1 (CH_2), 39.0 (*C*HMe), 25.7 (Bu^t), and 15.6 (Me); *m/z* (EI) 307 (4%), 22 (6), 105 (9), 101 (7), 92 (9) and 91 (100).

*Methyl [*R**,*R**-(*E*)]-(±)-5-hydroxy-2,4-dimethyl-7-oxo-8-(phenylmethoxy)-2-octenoate* (**14**). HF (0.1 ml, 60% w/w in water, 3.0 mmol) was added to a stirred solution of *E*-ketoester (**13**) (629 mg, 1.45 mmol) in MeCN (2 ml) at room temperature. After 1 h., $CHCl_3$ and water were added and the mixture was extracted with $CHCl_3$ (x3), dried ($MgSO_4$), evaporated *in vacuo*, and purified by column chromatography (35% EtOAc/PE) to give a colourless oil, *β-hydroxyketone* (**14**) (390 mg, 84%). Found (NH_3 CI): $(M+NH_4)^+$, 338.1971 (100%). $C_{18}H_{28}NO_5$ requires *M*, 338.19675; $\nu_{max.}$ 3480br, 2950m, 2929m, 2870m, 1720s, 1710, 1650m, 1450m, 1440m, 1390m, 1270s, 1120s, 1100s, 750s, 740s, and 700s cm^{-1}; δ_H 7.34 (5H, m, Ph), 6.56 (1H, d, *J* 10, =CH), 4.58 (2H, s, $PhCH_2$), 4.05 (2H, s, CH_2O), 3.93 (1H, br t, *J* 8, *C*HOH), 3.73 (3H, s, CO_2Me), 3.14 (1H, br d, *J* 4, OH), 2.60 (3H, m, C*H*Me and CH_2), 1.86 (3H, d, *J* 1.5, =CMe), and 1.08 (3H, d, *J* 6.7, CH*Me*); δ_C (major isomer (mj): minor (mn), 15:1 by =CH integration, data for mj) 209.4 (C=O), 168.5 (CO_2Me), 143.2 (=CH), 137.1 (quat. aromatic), 128.6, 128.2, and 128.0 (aromatics), 128.4 (=*C*Me), 75.4 and 73.6 ($PhCH_2OCH_2$), 71.0 (CHOH), 51.8 (CO_2Me), 43,7 (CH_2), 39.2 (*C*HMe), and 15.6 and 12.3 (=C*Me* and CH*Me*); δ_C (discernible data for mn (*Z*-isomer, or Me epimer)) 143.0 (=CH), 75.5 (CH_2), 70.8 (CHOSi), 43.6 (CH_2), and 39.0 (*C*HMe); *m/z* (EI) 321 (0.9%, *M*+H), 196 (11), 128 (50), 125 (12), 96 (14) and 91 (100).

*Methyl[4a,6b(2*E*,4*R**)]-(±)-4-[tetrahydro-4-hydroxy-2-oxo-4-[(phenylmethoxy)methyl]-2H-1,3-oxazin-6-yl]-2-pentenoate* (**3**). *p*-Nitrophenyl chloroformate (490 mg, 97% w/w pure, 2.36 mmol) in dry THF (5 ml) was added dropwise to a stirred solution of β-hydroxyketone (**14**) (629 mg, 1.96 mmol) and dry pyridine (206 ml, 2.55 mmol) in dry THF (7 ml) at 0°C. After 15 min. at 0°C, the reaction mixture was cooled to -80°C and dry MeOH (30 ml), which had been saturated at 0°C with Na dried NH_3, was added in one portion and the reaction mixture was allowed to warm to room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc (x3). The combined organic layers were washed successively with water, 10% w/v aqueous Na_2CO_3 (x4), and then saturated aqueous NaCl, dried (Na_2SO_4), evaporated *in vacuo*, preabsorbed onto silica gel (60-120 mesh), and purified by column chromatography (50% EtOAc/PE then 2% MeOH/EtOAc) to give a white solid, *cyclic carbamate* (**3**) (358 mg, 50%, 66% based on recovered β-hydroxy-ketone (**14**), m.p. 130-132°C (from EtOAc/PE). Found: C, 62.7; H, 6.95; N, 3.9. $C_{19}H_{25}NO_6$ requires C, 62.8; H, 6.95; N, 3.85%. Also found (NH_3 CI): $(M-H_2O-HNCO+NH_4)^+$, 320.1864 (100%). $C_{18}H_{26}NO_4$ requires *M*, 320.18618; $\nu_{max.}$ 3400br(NH), 3060m

(sharp, OH), 3000m, 1720s, 1440m, 1270s, 1000m, 750s, and 710s cm^{-1}; δ_H (major isomer (mj): minor (mn), 6:1 by NH integration, data for mj) 7.30 (m, Ph), 6.73 (br s, NH), 6.56 (d, *J* 10, =CH), 4.57 (s, PhCH_2), 4.50 (ddd, *J* 12.2, 7.3 and 2.1, ring CH), 4.20 (br s, OH), 3.71 (s, CO_2Me), 3.48 (d, *J* 9.2, H of CH_2O), 3.42 (d, *J* 9.1, H of CH_2O), 2.77 (dt, *J* 10 and 7, C*H*Me), 1.86(dd, *J* 12.8 and 1.4, H_{eq} of ring CH_2), 1.86 (d, *J* 1.3, =CMe), 1.59 (dd, *J* 13.4 and 12.5, H_{ax} of ring CH_2), and 1.14 (d, *J* 6.7, CH*Me*); δ_H (discernible data for mn) 6.51 (d, =CH), 6.46 (br s, NH), 4.01 (m, ring CH), 2.17 (dd, H_{eq} of ring CH_2), and 1.10 (d, *J* 6.7, CH*Me*); δ_C (data for mj) 168.2 (*C*O_2Me), 153.2 (OCONH), 141.0 (=CH), 137.1 (=*C*Me), 129.2 (quat. aromatic), 128.6, 128.1 and 127.9 (aromatics), 79.7 (COH), 76.6 (ring CH), 75.6 and 73.8 (Ph*C*H_2O*C*H_2), 51.7 (CO_2*Me*), 37.7 (*C*HMe), 33.6 (ring CH_2), and 15.5 and 12.8 (=C*Me* and CH*Me*); δ_C (discernible data for mn) 81.0 (COH), 77.9 (ring CH), 75.4 and 73.7 (Ph*C*H_2O*C*H_2), 37.6 (*C*HMe), 34.9 (ring CH_2), and 15.6 (Me); *m/z* (EI) 346 (2%), 345 (4, M-H_2O), 301 (5, M-H_2O-CO_2), 210 (10), 128 (10), and 91 (100).

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