Short Enantioselective Approach to Heteroyohimbine Alkaloids from *meso*-Bicyclo[3.3.0]octane-3,7-dione: Synthesis of Methyl 2-Epielenolate

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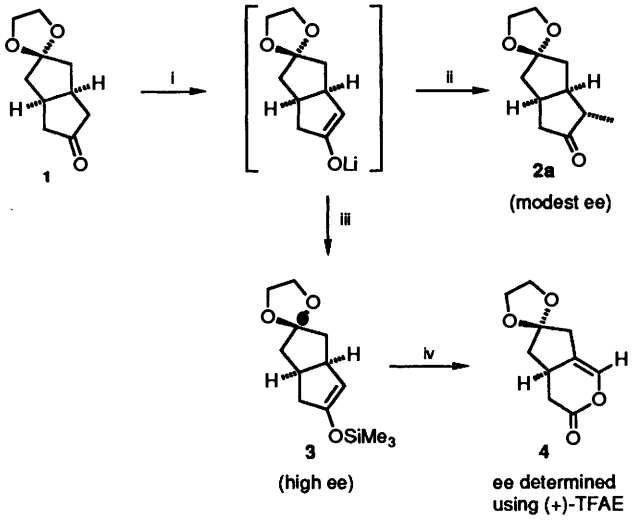
meso-Bicyclo[3.3.0]octane-3,7-dione mono ethylene ketal **1** has been converted into chiral enol derivatives with good enantioselectivity. In this paper we report the efficient stereoselective transformation of *meso*-bicyclo[3.3.0]octane-3,7-dione mono ethylene ketal into methyl 2-epielenolate **15**, a direct precursor to the heteroyohimbine alkaloid tetrahydroalstonine. The synthetic work described shows that each ring of the bicyclic ketone can be functionalized independently with good regio- and stereo-control. A new procedure for installing the alkoxyacrylate function of monoterpenoids is described and it has been shown that the cyclopentanone ring of methyl (1αH,6αH)-2α-methyl-8-oxo-3-oxabicyclo[4.3.0]non-4-ene-5-carboxylate **11** can be regioselectively converted into enol derivatives which are cleaved to give D/E-ring precursors of *Corynanthé* alkaloids.

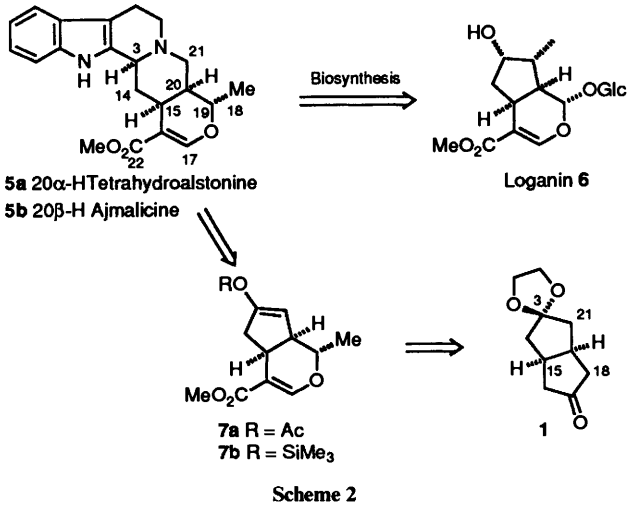
The mono ketal of *meso*-bicyclo[3.3.0]octane-3,7-dione, compound **1**, is an attractive starting material for the stereoselective synthesis of a broad range of polyfunctional compounds.[2] One of the main attractions of using this *meso* ketone as a synthetic starting material is the possibility of breaking its symmetry in an asymmetrically controlled manner, thus providing access to advanced synthetic intermediates in either chiral form. We[3] and others[4,5] have been investigating processes whereby the symmetry of the *meso* bicyclic system can be broken in an enantioselective manner.

In early studies we attempted to break the symmetry of the system in an enantioselective manner by enolization using chiral lithium amide bases, followed by direct alkylation of the chiral enolates with methyl iodide. The methylated product obtained by this method had only a modest degree of enantiomeric enrichment.[1] Taking into account the results of similar studies,[5] we felt sure that some loss of enantiomeric integrity was occurring during the alkylation step and we therefore turned our attention to trapping the enolate *in situ* as its trimethylsilyl ether.[3] This immediately led to products with much higher enantiomeric enrichment. In our study we converted the silyl enol ether into enelactone **4** (Scheme 1), the enantiomeric ^{1}H NMR signals of which were resolved in the presence of the chiral solvating agent trifluoroanthrylethanol (TFAE).[3a] The highest e.e. we obtained was 72%, but in an independent study Koga and co-workers used a broader range of bases and reported enantioselectivities up to 94% e.e., as determined by comparison of optical-rotation measurements.[4a]

The functionality of ketone **1** is quite flexible and it is clear from our work and that of others that a variety of useful chiral synthons can be derived from it. In order to expand the utility of such chiral synthons we have, in parallel with our methodology work, been pursuing synthetic targets bases on derivatives of ketone **1**. In particular we have been exploring methods for independently derivatizing or cleaving either one or both rings so that cyclopentane derivatives, 6-membered heterocycles, or acyclic compounds can be formed. A vast array of iridoids and indole alkaloids are biosynthesized from the bicyclic cyclopentanoid monoterpene loganin **6** and we were intrigued by the similarity of this flexible biosynthetic synthon to the bicyclic ketone **1**. It was this comparison which influenced us to investigate routes by which compound **1** could be converted into iridoids and monoterpenoid indole alkaloids, as a vehicle for developing general selective methods for functionalization of the symmetrical ketone.



Scheme 1 *Reagents and conditions:* i, chiral lithium amide base (RR*NLi), THF; ii, MeI; iii, Me_3SiCl added *in situ* in step i; iv, *m*-chloroperbenzoic acid (MCPBA) (excess), CH_2Cl_2



Scheme 2

Enol derivatives such as **7a** and **7b** were proposed as suitable D/E-ring precursors for the heteroyohimbine alkaloids tetrahydroalstonine **5a** and ajmalicine **5b** (Scheme 2). These were

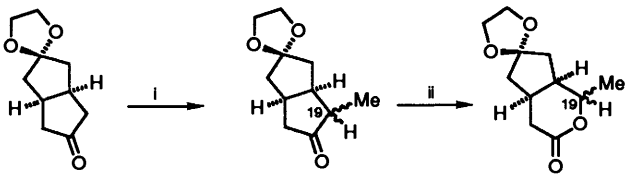
chosen as representative targets for our initial investigation, since several regioselective and stereoselective transformations of compound **1** would be required in order to attain the objective.

Results and Discussion

The first reaction of the synthetic scheme is the introduction of the C-18 * methyl group and is perhaps the most important step, since the *meso* ketone becomes chiral during this stage. In fact, asymmetry is introduced at the enolization stage and, as outlined above, this has been achieved with high selectivity. Although direct methylation of the initially generated chiral enolate has not been achieved with such a high degree of selectivity, development of new alkylation conditions by Koga and co-workers might make this more effective.[6] For the purpose of this synthetic study it was the diastereoisomeric selectivity of the process which was of importance and all the synthetic work described was carried out on racemic material. Because of its *cis* ring junction ketone **1** has a distinct folded shape and its enolate should therefore be alkylated from the convex α-face, as required for most natural heteroyohimbine alkaloids. Methylation of the enolate formed by reaction of the ketone with lithium diisopropylamide (LDA) (1 mol equiv.) in tetrahydrofuran (THF) proceeded in low yield, but under Seebach's modified conditions (3 mol equiv. of LiCl + 1 mol equiv. of butyllithium added),[7] a very high yield of methylated products was obtained. The major methylated product **2a** (79%) could be separated from the minor isomer **2b** (15%), which could be equilibrated to a mixture containing mainly isomer **2a** by being refluxed in sodium methoxide/methanol. However, separation at the next stage was much easier and from a practical point of view it was more convenient to use the crude methylation product for the next step.

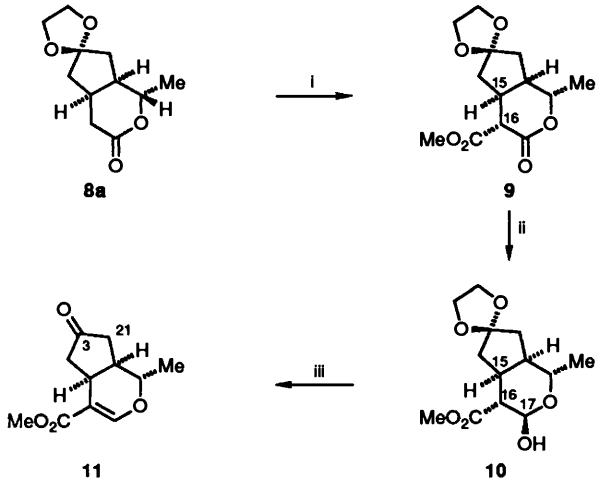
Baeyer–Villiger oxidation of the methyl ketone **2** was the obvious method for introduction of the oxygen required for the heteroyohimbine E-ring. It is well established that unsymmetrical ketones such as **2** react in a regioselective manner, with retention of stereochemistry at the secondary centre.[8] Careful control of the reaction conditions was necessary in order to achieve oxidation and to retain the acid-sensitive ketal group during the reaction. After experimenting with a range of oxidizing agents and conditions we finally accomplished the required oxidation, without hydrolysis of the ketal, by portionwise addition of *m*-chloroperbenzoic acid (MCPBA) (1.3 mol equiv.) to a methylene dichloride solution of compound **2** over solid sodium hydrogen carbonate (1.3 mol equiv.). The amount of sodium hydrogen carbonate used is important, since the ketal was hydrolysed if less was used and larger amounts caused a reduction in the rate of oxidation. A mixture of δ-lactones, epimeric at C-19, was obtained in 90% yield, with no trace of regioisomers, and the desired 19β-H isomer **8a** was isolated in 60% yield by flash chromatography (Scheme 3). In an independent study Winterfeldt prepared *cis*-bicyclo[3.3.0]octane-3,7-dione systems by a different route to that described here, and similar Baeyer–Villiger oxidations were employed, to prepare the same lactone system, but in unprotected form.[9]

Completion of the E-ring functionality required installation of the C-22 methoxycarbonyl group and introduction of the alkoxyacrylate chromophore. In early approaches to *Corynanthé* alkaloids this has been achieved by formylation, followed by acid-catalysed rearrangement and methanolysis.[10] In our case, although formylation of lactone **8a** could be achieved, albeit in low yield, the methanolysis step was almost totally



Scheme 3 *Reagents and conditions:* i, (a) LDA, THF, LiCl (3 mol equiv.), −78 °C; (b) BuLi (1 mol equiv.); (c) MeI; ii, MCPBA (1.3 mol equiv.), CH_2Cl_2, $NaHCO_3$ (1.3 mol equiv.)

ineffective and the overall yield of the required alkoxyacrylate was very low. We therefore decided to devise a more efficient procedure for installing this functionality, based on Mander's methoxycarbonylation procedure.[11] In the event the C-16 position of lactone **8a** could be methoxycarbonylated in excellent yield to give ester **9**. The ^1H NMR spectrum of product **9** indicated the presence of one major C-16 diastereoisomer (~10:1 ratio) and the coupling constant between 15-H and 16-H was found to be 12 Hz. This indicates that there is an approximate *trans*-diaxial relationship between these protons and the methoxycarbonyl group is therefore on the sterically less encumbered α-face of the molecule. We required reducing conditions which would selectively reduce the lactone to a lactol without affecting the methyl ester, and after some experimentation it was found that this could be accomplished by careful, slow addition of diisobutylaluminium hydride (DIBAH) (1 mol equiv.) to ester **9**. Interestingly, this reaction was also stereoselective (~9:1) and the product **10** was a quite stable β-hydroxy ester. There was again a pseudo-*trans*-diaxial relationship between 15-H and 16-H, as indicated by a coupling constant of 11 Hz. A 7 Hz coupling constant between 16-H and 17-H indicated that reduction had taken place from the axial face of the carbonyl, to give an alcohol with the hydroxy group on the β-face. The ammonia CI mass spectrum of compound **10** was interesting, showing only one major ion, with the same mass as the molecule itself (*m/z* 272) rather than M + 1 or M + 18. Mass measurement showed that the ion in fact corresponded to $[(M - H_2O)NH_4]^+$ and given this we anticipated that the next synthetic step would be straightforward. Indeed, simple treatment of the crude reduction product with methylene dichloride containing a catalytic quantity of toluene-*p*-sulfonic acid (PTSA) brought about dehydration as well as cleavage of the ketal, to provide alkoxyacrylate **11** in 72% yield, over two steps from lactone **9** (Scheme 4).



Scheme 4 *Reagents and conditions:* i, (a) LDA, THF, −78 °C; (b) MeO_2CCN; ii, DIBAH (1 mol equiv.), toluene, −78 °C; iii, PTSA (cat.), CH_2Cl_2

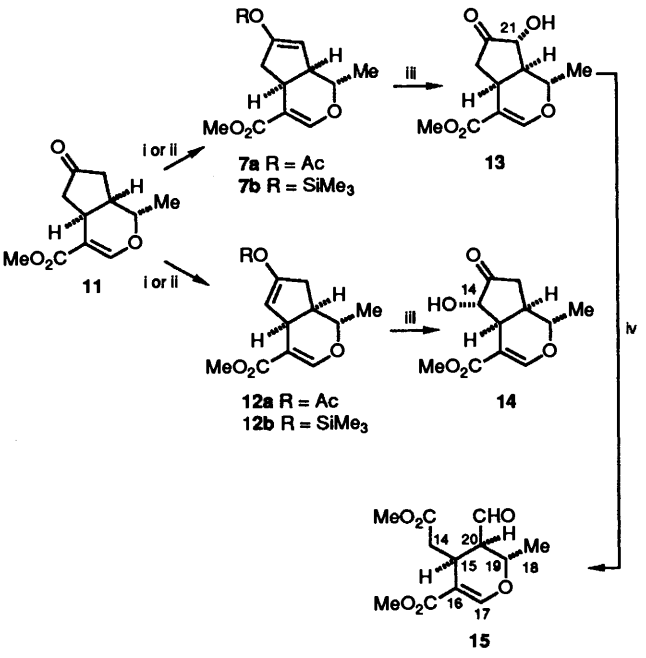
* Biogenetic monoterpenoid alkaloid numbering is used throughout the Discussion section, as illustrated in structure **5**.

The heteroyohimbine E-ring having been completed, one major obstacle remained to completion of a D/E-ring synthon, and that was regioselective cleavage of the cyclopentanone ring between C-3 and C-21. With this in mind we explored the possibility of generating an enol acetate **7a** or enol ether **7b** regioselectively. When the ketone **11** was heated with isopropenyl acetate and acetic anhydride, the corresponding enol acetates were obtained as 2:1 mixture of regioisomers in 75% yield. The major isomer was **7a**, indicating that there is a slight thermodynamic preference for the desired geometry. Alternatively, the lithium enolates were trapped as silyl enol ethers by *in situ* reaction with trimethylsilyl chloride (TMSCl).[12] This provided a 4:1 mixture of siloxy compound **7b** and its regioisomer **12b** in 75% yield, indicating a kinetic as well as a thermodynamic preference for the desired enolate geometry. Although the regioisomers of the enol ethers and enol acetates could not be separated easily by chromatography, their relative proportions could be estimated from decoupled ^{1}H NMR spectra.

Selective cleavage of the enol ester bond of acetate **7a** or enol ether bond of siloxy compound **7b** was the final synthetic challenge and was by no means as straightforward as we had anticipated. Various ozonolysis conditions were tried, but none was selective enough and the alkoxyacrylate was always attacked to some extent. We therefore turned our attention to two-step procedures for cleavage of the alkene moiety. In early attempts to convert silyl enol ether **7b** into an α-hydroxy ketone, epoxidizing conditions were explored with very little success. For example, with MCPBA under very carefully buffered conditions, followed by work-up with fluoride, only a very small quantity of an α-hydroxy ketone could be isolated from a complex reaction product. Finally, the regioisomeric mixture of silyl enol ethers **7b** and **12b** was oxidized smoothly by using a catalytic quantity of osmium tetraoxide with *N*-methylmorpholine *N*-oxide (NMO) in aqueous acetone, to give a mixture of regioisomeric hydroxy ketones **13** and **14**, which were readily separated by flash chromatography. Although it is not relevant for the progress of the synthesis, it was interesting that each of the hydroxy ketones was formed in a highly stereoselective manner. Both compounds had an 11 Hz coupling constant between the proton at the alcohol centre and the adjacent ring-junction proton. In each of the molecules the large coupling constant was found to be consistent with an α-orientation of the alcohol, according to molecular modelling calculations.*

We wanted to form a methyl ester and an aldehyde by cleavage of the hydroxy ketone and this was conveniently brought about in one step (65% yield) by treatment of compound **13** with lead tetraacetate (LTA) in methanol. The product was methyl 2-epielenolate **15** (Scheme 5) which has aldehyde and ester residues ideally positioned for elaboration of the heteroyohimbine D-ring.† Procedures for the conversion of elenolic acid derivatives into heteroyohimbine alkaloids are already well established.[13] Methyl 2-epielenolate[15] can be converted directly into tetrahydroalstonine **5a**, which has a *cis* D/E ring junction. It has also been shown that 2-epielenolic acid derivatives are easily epimerized, providing precursors for alkaloids with *trans* D/E ring stereochemistry, such as ajmalicine **5b**.[14,15]

In summary, through the synthesis of methyl 2-epielenolate **14**, we have shown that the two rings of *meso*-bicyclo-[3.3.0]octane-3,7-dione mono ethylene ketal **1** can be manipulated independently with good control of stereochemistry and regiochemistry. We have established new methodology for



Scheme 5 *Reagents and conditions:* i, isopropenyl acetate, Ac_2O, PTSA, reflux; ii, LDA, THF, TMSCl, −78 °C; iii, OsO_4, NMO, acetone–water (8:1); iv, LTA, MeOH

installation of the alkoxyacrylate functionality of monoterpenes and for regioselective cleavage of the cyclopentanone ring of methyl (1αH,6αH)-2α-methyl-8-oxo-3-oxabicyclo[4.3.0]non-4-ene-5-carboxylate **11** *alpha* to the carbonyl.

Experimental

M.p.s were determined on an electrothermal apparatus and were recorded uncorrected. IR absorption spectra were run either neat (for liquids) or as Nujol mulls (for solids) on a Perkin-Elmer 1710 FT-IR instrument. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC-300 instrument, as solutions in deuteriochloroform. Chemical shifts are referenced to tetramethylsilane and *J*-values are given in Hz. Mass spectra were recorded at low resolution on a Finnigan 4500 instrument. High-resolution mass spectra were run on a Kratos concept 1-S instrument. Figures in parenthesis refer to the relative intensity as a percentage of the base peak. Mass spectra were recorded under chemical ionization conditions, using ammonia unless stated otherwise. TLC was carried out using Merck Kieselgel 60 F_{254} glass-backed plates. The plates were visualized by the use of a UV lamp, or by dipping into a solution of vanillin in ethanolic sulfuric acid, followed by heating. Silica gel 60 (particle sizes 40–63 μ) supplied by E. M. Merck was employed for flash chromatography. Light petroleum refers to the fraction boiling in the range 40–60 °C.

(1αH,5αH)-7-Ethylenedioxy-2α-methylbicyclo[3.3.0]*octan-3-one* **2a** *and (1αH,5αH)-7-Ethylenedioxy-2β-methylbicyclo*[3.3.0]*octan-3-one* **2b**.—BuLi (5.1 cm^3, 7.14 mmol; 1.39 mol dm^3) was added to a solution of diisopropylamine (1.08 cm^3, 7.69 mmol) and lithium chloride (0.69 g, 16.5 mmol) in THF (40 cm^3) at 0 °C under nitrogen. After 30 min the solution was cooled to −78 °C and a solution of the monoketal **1** (1.0 g, 5.49 mmol) in THF (20 cm^3) was added. Another portion of BuLi (3.9 cm^3, 5.49 mmol; 1.39 mol dm^{-3}) was added after 30 min, and methyl iodide (480 mm^3, 7.69 mmol) was added after a further 15 min. After 1 h the solution was warmed to room temperature and was stirred for 3 h. The reaction mixture was then diluted with diethyl ether (80 cm^3) and washed with saturated aq. sodium

* We thank Professor W. C. Still for Macromodel III which was used for molecular-modelling calculations.

† We thank Dr. R. T. Brown for a comparison sample and spectra of methyl elenolate.

chloride (40 cm^3). The organic layer was dried over magnesium sulfate, concentrated in a rotary evaporator, and purified by chromatography [light petroleum–ethyl acetate (4:1)] to give *compound* **2a** (850 mg, 79%); ν_{max}/cm^{-1} 1730, 1320 and 1110; δ_H(300 MHz) 0.97 (3 H, d, *J* 6, Me), 1.58 (1 H, m), 1.78 (1 H, m), 2.05–2.20 (5 H, m), 2.35 (1 H, dd), 2.66 (1 H, m, C*H*Me) and 3.79 (4 H, br s, OCH_2CH_2O); *m/z* (CH_4, Cl) 197 [$(M + H)^+$, 100%], 196 (29) and 87 (22); (Found: M^+ [EI], 196.2481. $C_{11}H_{16}O_3$ requires *M*, 196.2485); and *isomer* **2b** (160 mg, 15%); ν_{max}/cm^{-1} 1730 and 1320; δ_H(300 MHz) 0.95 (3 H, d, *J* 7, Me), 1.54 (1 H, m), 1.77 (1 H, m), 2.07–2.25 (5 H, m), 2.39 (1 H, m), 2.68 (1 H, m) and 3.81 (4 H, br s, OCH_2CH_2O); *m/z* (CH_4, Cl): 197 [$(M + H)^+$, 100%] and 196 (10) (Found: M^+ [EI], 196.2483).

Equilibration of Ethylenedioxy-2β-methylbicyclo[3.3.0]*octan-3-one* **2b**.—To a solution of ketone **2b** (28 mg, 0.143 mmol) in methanol (2 cm^3), under nitrogen was added a small quantity of sodium metal. The solution was stirred for 24 h, then solid carbon dioxide was added to the reaction mixture and the solution was diluted with methylene dichloride (2 cm^3) and washed with saturated aq. sodium chloride (1 cm^3). The organic layer was dried, then concentrated, and the residue was purified by flash chromatography [light petroleum–ethyl acetate (4:1)] to give isomer **2a** (26 mg, 93%).

(1α*H*6α*H*)-8-*Ethylenedioxy-2α-methyl-3-oxabicyclo*[4.3.0]-*nonan-4-one* **8a** *and* (1α*H*,6α*H*)-8-*Ethylenedioxy-2β-methyl-3-oxabicyclo*[4.3.0]*nonan-4-one* **8b**.—To a solution of the ketone mixture **2a**/**2b** (as prepared above) (500 mg, 2.55 mmol) in methylene dichloride (50 cm^3) was added sodium hydrogen carbonate (279 mg, 2.32 mmol), followed by portionwise addition of MCPBA (571 mg, 2.64 mmol, 85%), during several hours. After the mixture had been stirred for 5 days, saturated aq. sodium 'metabisulfite' ($Na_2S_2O_5$) (10 cm^3) was added. After 15 min the solution was diluted with water (20 cm^3) and extracted with methylene dichloride (3 × 30 cm^3). The organic extracts were combined, dried over magnesium sulfate, and filtered, and the organic solvent was evaporated off. Purification of the residue by chromatography [light petroleum–ethyl acetate (1:1)] gave the lactones.

Lactone **8a** (367 mg, 68%); m.p. 92–94 °C; ν_{max}/cm^{-1} 2977, 1741 and 1252; δ_H(300 MHz) 1.27 (3 H, d, *J* 6, Me), 1.5 (2 H, m), 1.95 (1 H, ddd, *J* 13, 10 and 2), 2.05 (1 H, m), 2.19 (1 H, m, 1-H), 2.50 (3 H, m, 5-H_2 and 6-H), 3.89 (4 H, br s, OCH_2CH_2O) and 4.19 (1 H ~sextuplet, $J_{1,2}$ 10, $J_{2,10}$ 6, C*H*Me); *m/z* (NH_3, Cl) 230 ($[M + NH_4]^+$, 100%) and 213 (11) (Found: $[M + NH_4]^+$, 230.1393. $C_{11}H_{20}NO_4$ requires *m/z* 230.1391); and *lactone* **8b** 147 mg (27%) as an oil; ν_{max}/cm^{-1} 2935, 1752 and 1294; δ_H(300 MHz) 1.24 (3 H, d, *J* 6.5, Me), 1.47 (1 H, dd, *J* 13, 10, C*H*H), 1.74 (1 H, m, CH*H*), 1.83 (1 H, ~t, *J* 11, C*H*H), 1.95 (1 H, m, CH*H*), 2.34 (1 H, dd, $J_{5\alpha,5\beta}$ 15, $J_{5,6}$ 1.5, 5α-H), 2.48 (1 H, ~dq, 1-H), 2.58 (1 H, dd, $J_{5\alpha,5\beta}$ 15, $J_{5,6}$ 8, 5β-H), 2.74 (1 H, ~quint., *J* ~9, 6-H), 3.90 (4 H, br s, OCH_2CH_2O) and 4.45 [1 H, ~dq, CH(Me)C*H*O]; *m/z* (NH_4, Cl) 230 ($[M + NH_4]^+$, 100%), 213 (83) and 212 (76) (Found: $[M + NH_4]^+$, 230.1393).

Methyl (1α*H*,6α*H*)-8-*Ethylenedioxy-2α-methyl-4-oxo-3-oxabicyclo*[4.3.0]*nonane-5α-carboxylate* **9**.—BuLi (3.73 cm^3, 5.19 mmol; 1.39 mol dm^{-3}) was added to a stirred solution of diisopropylamine (754 mm^3, 5.43 mmol) in THF (20 cm^3) at 0 °C under nitrogen. After 30 min, the temperature was lowered to −78 °C, a solution of the lactone **8a** (500 mg, 2.36 mmol) in THF (10 cm^3) was added, and the mixture was stirred for 1 h at 0 °C. The temperature was lowered again to −78 °C, hexamethylphosphoric triamide (407 mm^3, 2.30 mmol) was added, followed by methyl cyanoformate (223 mm^3, 2.83 mmol) and the mixture was stirred for 1 h at −78 °C. The reaction mixture was then poured into cold water (20 cm^3) and the product was extracted into diethyl ether (2 × 20 cm^3). After drying, filtration, and concentration of the ethereal layers, the residue was chromatographed [light petroleum–ethyl acetate (3:2)] to give the *ester* **9** (588 mg, 92%); ν_{max}/cm^{-1} 2957, 1741, 1739 and 1648; δ_H(300 MHz) 1.31 (3 H, d, *J* 6, Me), 1.47–1.56 (2 H, m, 7α- and 9α-H), 2.03–2.11 (2 H, m, 7β- and 9β-H), 2.31 (1 H, ~dq, $J_{5,6}$ 12, $J_{1,6}$ 10, $J_{7\alpha,6}$ 5, 6-H), 2.93 (1 H, m, 1-H), 3.58 (1 H, d, *J* 12, 5-H), 3.76 (3 H, s, CO_2Me), 3.87 (4 H, m, OCH_2CH_2O) and 4.26 (1 H, ~sextuplet, *J* 10 and 6, 2-H); *m/z* (NH_3, Cl) 288 ([M + $NH_4]^+$, 20%), 271 ($[M + H]^+$, 100) and 245 (60) (Found: $[M + H]^+$, 271.1185. $C_{13}H_{19}O_6$ requires *m/z*, 271.1181).

Methyl (1α*H*,6α*H*)-8-*Ethylenedioxy-4-hydroxy-2α-methyl-3-oxabicyclo*[4.3.0]*nonane-5α-carboxylate* **10**.—To a solution of the lactone **9** (500 mg, 1.85 mmol) in toluene (25 cm^3) at −78 °C under nitrogen was added a solution of DIBAH (1.35 cm^3, 2.03 mmol; 1.5 mol dm^{-3}) in toluene. After 1 h saturated aq. sodium sulfate (5 cm^3) was added and the mixture was stirred for a further 10 min before being diluted with water (10 cm^3) and extracted into diethyl ether (3 × 20 cm^3). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. TLC examination of the residue revealed it to be essentially one compound, which was subsequently purified by column chromatography [light petroleum–ethyl acetate (1:1)] to afford *lactol* **10** (480 mg, 95%), ν_{max}/cm^{-1} 3400, 1730, 1430 and 1320; δ_H(300 MHz) 1.16 (3 H, d, *J* 6, Me), 1.53 (1 H, dd, $J_{9\alpha,9\beta}$ 13, $J_{1,9\beta}$ 8, 9β-H), 1.78 (1 H, dd, $J_{7\alpha,7\beta}$ 14, $J_{7\beta,6}$ 7, 7β-H), 1.82–2.02 (2 H, m, 7α- and 9α-H), 2.08 (1 H, m, 1-H), 2.42 (1 H, m, 6-H), 2.66 (1 H, dd, $J_{5,6}$ 11, $J_{4,5}$ 7, 5-H), 3.25 (1 H, br m, OH), 3.68 (3 H, s, CO_2Me), 3.80 (1 H, m, *J* 10 and 6, 2-H), 3.87 (4 H, s, OCH_2CH_2O) and 5.30 (1 H, dd, $J_{4,5}$ 7, $J_{4,OH}$ 3, 4-H); *m/z* (NH_3, Cl) 290 ($[M + NH_4]^+$, 21%), 272 (100) and 187 (82) (Found: $[M + NH_4]^+$ 290.1604. $C_{13}H_{24}NO_6$ requires *m/z* 290.1603).

Methyl (1α*H*,6α*H*)-2α-*Methyl-8-oxo-3-oxabicyclo*[4.3.0]*non-4-ene-5-carboxylate* **11**.—To a solution of the lactol **10** (500 mg, 1.84 mmol) in methylene dichloride (50 cm^3) was added PTSA monohydrate (386 mg, 2.03 mmol). After 1 h the reaction mixture was washed with saturated aq. sodium hydrogen carbonate. The organic layer was dried over anhydrous sodium sulfate, then filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography [light petroleum–ethyl acetate (1:1)] to give the title compound **11** (208 mg, 72%—based on ketal **9** when reactions are run consecutively); m.p. 66–68 °C; ν_{max}/cm^{-1} 2925, 1745, 1702 and 1634; δ_H(300 MHz) 1.32 (3 H, d, *J* 6, Me), 2.03 (1 H, ddd, $J_{7\alpha,7\beta}$ 18, $J_{6,7\beta}$ 8, $J_{7\beta,9}$ 2, 7β-H), 2.1 (1 H, ~dd, *J* 19 and 3, 9β-H), 2.25 (1 H, m, 1-H), 2.53 (1 H, ddd, $J_{9\alpha,9\beta}$ 18, $J_{1,9\alpha}$ 8, $J_{9\alpha,7}$ 2, 9α-H), 2.74 (1 H, ddd, $J_{7\alpha,7\beta}$ 18, $J_{6,7\alpha}$ 8, $J_{7\alpha,9}$ 2, 7α-H), 3.14 (1 H, ~dq, 6-H), 3.69 (3 H, s, CO_2Me), 3.74 (1 H, m, $J_{1,2}$ 10, $J_{2,10}$ 6, 2-H) and 7.60 (1 H, s, 4-H); *m/z* (NH_3, Cl) 228 ([M + $NH_4]^+$, 100%) (Found: $[M + NH_4]^+$, 228.1235. $C_{11}H_{18}NO_4$ requires *m/z*, 228.1235).

Methyl (1α*H*,6α*H*)-8-*Acetoxy-2α-methyl-3-oxabicyclo*[4.3.0]-*nona-4,8-diene-5-carboxylate* **7a** *and Methyl* (1α*H*,6α*H*)-8-*Acetoxy-2α-methyl-3-oxabicyclo*[4.3.0]*nona-4,7-diene-5-carboxylate* **12a**.—A solution of the ketone **11** (25 mg, 0.12 mmol), isopropenyl acetate (100 mm^3, 0.91 mmol), acetic anhydride (100 mm^3, 1.06 mmol) and a catalytic amount of PTSA (1 mg, 0.012 mmol) was heated at reflux for 1 h. The solution was then allowed to cool and the solvents were removed under reduced pressure. The resulting oily residue was chromatographed [light petroleum–ethyl acetate (4:1)] to afford a *mixture of the enol acetates* **7a** and **12a** (27 mg, 90%) in the ratio 2:1 as observed by ^1H NMR spectroscopy; ν_{max}/cm^{-1} 1760, 1710 and 1630; δ_H(300

MHz) 1.29 (3 H, d, *J* 7, Me), 2.09 [3 H × $\frac{1}{3}$, s, OAc (minor)], 2.11 [3 H × $\frac{2}{3}$, s, OAc (major)], 2.30 (1 H, m, 7β-H), 2.35 (1 H, m, 1-H), 2.82 (1 H, dd, *J* 15 and 10, 7α-H), 3.10 (1 H, dq, *J* 10, 10 and 10, 6-H), 3.50 (1 H, dd, *J* 10 and 7, 2-H), 3.68 (3 H, s, CO_2Me), 5.43 ($\frac{2}{3}$ H, br s, 9-H), 5.54 ($\frac{1}{3}$ H, br s, 7-H) and 7.62 (1 H, s, 4-H); *m/z* (NH_3, CI) 270 ($[M + NH_4]^+$, 100%), 221 (22) and 102 (22) (Found: $[M + NH_4]^+$, 270.1345. $C_{13}H_{20}NO_5$ requires *m/z*, 270.1341).

Methyl (1α*H*,6α*H*)-2α-*Methyl*-8-*trimethylsiloxy*-3-*oxabicyclo*[4.3.0]*nona*-4,8-*diene*-5-*carboxylate* **7b** *and Methyl* (1α*H*,6α*H*)-2α-*Methyl*-8-*trimethylxiloxy*-3-*oxabicyclo*[4.3.0]*nona*-4,7-*diene*-5-*carboxylate* **12b**.—BuLi (2.27 cm^3, 0.36 mmol, 1.39 mol dm^{-3}) was added to a solution of diisopropylamine (59 mm^3, 0.42 mmol) in THF (2 cm^3) at 0 °C under N_2. After 30 min the solution was cooled to −78 °C and TMSCl (98 mm^3, 0.769 mmol) was added. A solution of ketone **11** (25 mg, 0.12 mmol) in THF (2 cm^3) was then added and the reaction mixture was stirred for 30 min, allowed to warm to room temperature, diluted with diethyl ether (6 cm^3) and washed with saturated aq. sodium chloride. The organic layer was dried and filtered, and the solvents were removed under reduced pressure. The oily residue was then chromatographed (Et_2O) to afford a mixture of silyl enol ethers **7b** and **12b** (26 mg, 74%) in the ratio 4:1, as observed by ^1H NMR spectroscopy, ν_{max}/cm^{-1} 3050, 1755, 1710 and 1640; δ_H(300 MHz) 0.18 (9 H, br s, $SiMe_3$), 1.31 (3 H, d, *J* 6, Me), 2.32 (1 H, m), 2.38 (1 H, m), 2.85 (1 H, m), 3.15 (1 H, m), 3.72 (3 H, s, CO_2Me), 3.75 (1 H, m, $J_{1,2}$ 10, $J_{2,10}$ 6, 2-H), 4.49 [0.2 H, br s, 7-H (minor)], 4.58 [0.8 H, d, 9-H (major)] and 7.65 (1 H, s, 4-H).

Methyl (1α*H*,6α*H*)-9α-*Hydroxy*-2α-*methyl*-8-*oxo*-3-*oxabicyclo*[4.3.0]*non*-4-*ene*-5-*carboxylate* **13** *and Methyl* (1α*H*,6α*H*)-7α-*Hydroxy*-2α-*methyl*-8-*oxo*-3-*oxabicyclo*[4.3.0]*non*-4-*ene*-5-*carboxylate* **14**.—To a stirred solution of trimethylsilyl enol ethers **7b** and **12b** (200 mg, 0.7 mol) and a catalytic amount of osmium tetraoxide in acetone–water (8:1) at −10 °C was added portionwise NMO (100 mg, 0.84 mmol; 97%). After 40 min, the solution was allowed to warm up to room temperature and was stirred for 21 h. A small amount of silica and aq. sodium metabisulfite, ($Na_2S_2O_5$) were added, and after 15 min the suspension was filtered through Celite to remove osmium-containing material. The filtrate was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (15 cm^3) and washed successively with hydrochloric acid (1 mol dm^{-3}; 2 cm^3) and saturated aq. sodium chloride. The organic layer was dried, concentrated under reduced pressure then subjected to flash column chromatography [light petroleum–ethyl acetate (1:1)] to give α-*hydroxy ketone* **13** (100 mg, 47%), ν_{max}/cm^{-1} 3403, 2952, 1753, 1703 and 1626; δ_H(300 MHz) 1.33 (3 H, d, *J* 6, Me), 2.17 (1 H, ddd, $J_{1,9}$ 11, $J_{1,6}$ 8, $J_{1,2}$ 3, 1-H), 2.65 (2 H, m, 7-H_2), 2.96 (1 H, br s, OH), 3.13 (1 H, m, 6-H), 3.68 (3 H, s, CO_2Me), 3.91 (1 H, d, *J* 11, 9-H), 4.58 (1 H, dq, *J* 6, 3, 2-H) and 7.53 (1 H, fine d, 4-H); *m/z* (NH_3, CI) 244 ($[M + NH_4]^+$, 100%), 227 and 148 (Found: *m/z*, 244.1177. $C_{11}H_{18}NO_5$ requires *m/z* 244.1185); and *compound* **14** (20 mg, ~10%), ν_{max}(neat)/cm^{-1} 3400, 1750, 1706 and 1620; δ_H(300 MHz) 1.36 (3 H, d, *J* 6, Me), 2.15–2.59 (2 H, m, 9β- and 1-H), 2.64 (1 H, dd, $J_{9\alpha,9\beta}$ 20, $J_{1,9}$ 10, 9α-H), 2.90 (1 H, dd, $J_{6,7}$ 10.5, $J_{1,6}$ 7, 6-H), 3.69 (1 H, m, 2-H), 3.76 (3 H, s, CO_2Me), 3.90 (dd, $J_{6,7}$ 10.5, $J_{7,9}$ 1.5, 7-H) and 7.69 (1 H, s, 4-H); *m/z* (NH_3, CI) 244 ($[M + NH_4]^+$, 100%) and 147 (Found: *m/z*, 244.1184).

Methyl 2-*Epielenolate* **15**.—To a stirred solution of α-hydroxy ketone **13** (30 mg, 0.132 mmol) in methanol (3 cm^3) at −20 °C was added LTA (117 mg, 0.265 (mmol) in two portions. The mixture was stirred at −20 °C for 10 min, then at room temperature for 2 h. The mixture was then diluted with methylene dichloride (6 cm^3) and washed with saturated aq. sodium hydrogen carbonate (3 cm^3). The organic extracts were dried over anhydrous sodium sulfate, the solvents were evaporated off under reduced pressure, and the residue was subjected to column chromatography [light petroleum–ethyl acetate (1:1)] to give the title aldehydo ester **15** (22 mg, 65%); ν_{max}(neat)/cm^{-1} 2950, 1730, 1720br and 1650; δ_H(300 MHz) (biosynthetic numbering) 1.34 (3 H, d, *J* 6, Me), 2.20 (1 H, dd, *J* 17 and 9, 14-H), 2.58 (1 H, m, 20-H), 3.14 (1 H, dd, *J* 17 and 5, 14-H), 3.54 (1 H, m, 15-H), 3.66 (1 H, m, 19-H), 3.69 (3 H, s, CO_2Me), 3.70 (s, CO_2Me), 7.58 (1 H, d, *J* 2, 17-H) and 9.55 (1 H, *J* 5.5, CHO); *m/z* (NH_3, CI) 274 ($[M + NH_4]^+$), 257 and 225.

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