Synthetic Studies on the Ophiobolane Sesterterpenes: Construction of an Optically Pure, Advanced Tricyclic Intermediate for the Synthesis of Ceroplasteric Acid

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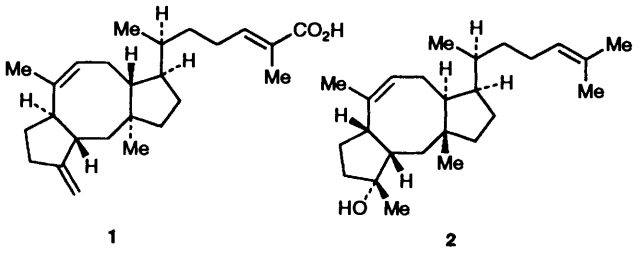
Tropone has been transformed into an optically pure tricyclic system that could serve as an advanced intermediate in the synthesis of ceroplasteric acid. The sequence features a stereoselective Ireland ester enolate Claisen rearrangement followed by an intramolecular nitrile oxide cycloaddition for assembly of an ABC-ring precursor of the target molecule. Efforts to homologate the seven-membered B ring to the requisite eight-membered system were unsuccessful.

The ophiobolane sesterterpenes represent a numerically small but structurally elaborate class of natural products characterized by a core 5-8-5 ring architecture[1] and many of these materials exhibit potent biological and phytological activities.[2] Typical examples include ceroplasteric acid **1** [1e] and ophiobolin



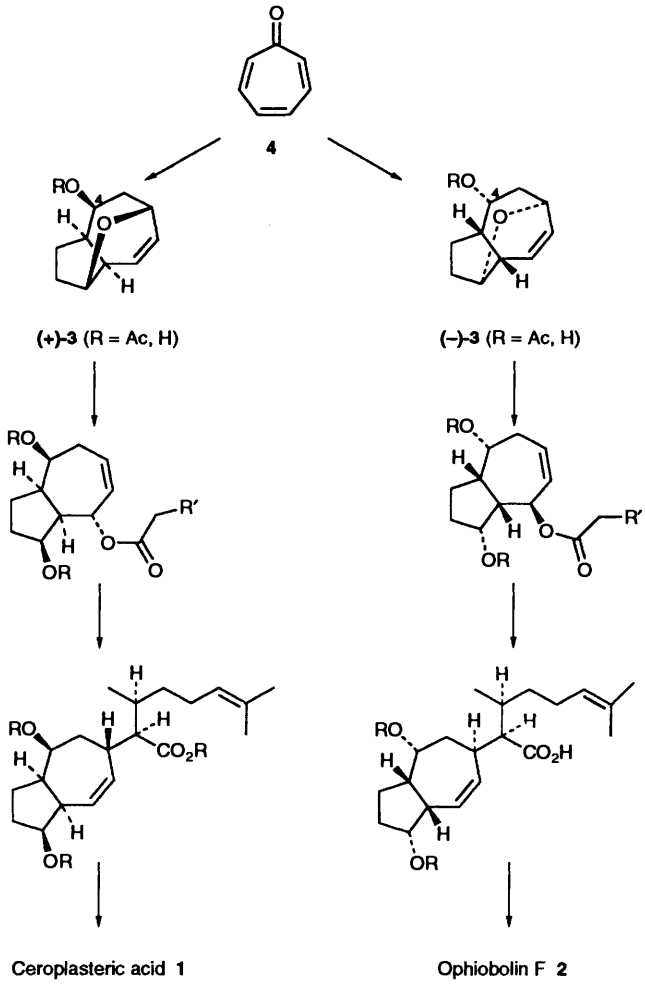
1 **2**

F **2**,[1f] both of which possess the characteristic, richly substituted dicyclopenta[*a*,*d*]cyclooctene ring system.

The challenges associated with the construction of the eight-membered B-ring sub-structure has prompted numerous synthetic approaches into the ophiobolane system as well as into related structures.[3] Successful total syntheses of several members of the ophiobolin and ceroplastin families have recently been recorded by Kato and Takeshita,[4] Kishi,[5] Boeckman[6] and Paquette.[7]

Results and Discussion

Our approach into the ophibolane system features an ester enolate Claisen rearrangement[8] on an appropriately functionalized *cis*-hydroazulene building block that incorporates most of the dicyclopenta[*a*,*d*]cyclooctene carbon skeleton as well as setting much of the requisite C-ring stereochemical information found in these sesterterpene targets. It was envisioned that this objective could be achieved by employing an appropriate ester derivative of (*S*)-citronellic acid in the projected sigmatropic rearrangement step. This approach would incorporate the entire C-ring side chain with the correct relative and absolute stereochemistry typical of both series of ophiobolane sesterterpenes as well as introducing all but one of the carbon atoms required for assembly of the C-ring portion of the molecule. Cyclopentannulation and ring expansion of the B-ring unit from a seven-membered to an eight-membered carbocycle would complete the synthesis (Scheme 1). In addition, recognition of the particular relationships extant between the stereogenic centres present in the AB ring units of the ceroplastin and ophiobolin series suggested that each family could be accessed independently by employing the enantiomeric, rigid *cis*-hydroazulenes (+)-**3** and (−)-**3**, respectively.

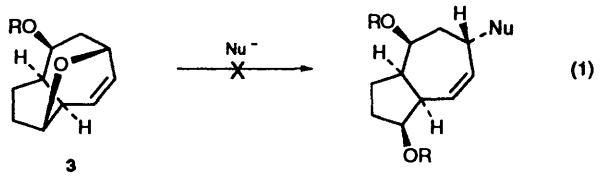


Scheme 1 Strategy for the synthesis of ceroplastin and ophiobolin sesterterpenes

The synthetic plan originally called for preparation of a racemic hydroazulene precursor, (±)-**3**, which would be resolved and the enantiomers processed separately toward the representative sesterterpenes, ceroplasteric acid **1** and ophiobolin F **2**. The synthesis of the readily available 1,6-epoxyhydroazulene (±)-**3** from tropone **4** has been detailed previously,[9] however, efforts to resolve (±)-**3** *via* derivatization of the free C_4 alcohol were surprisingly ineffectual. After considerable experimentation, esterification with 3β-acetoxy-Δ^5-etienic acid[10] permitted moderately efficient separation of

(+)-**3** and (−)-**3** (R = H). However, this particular protocol was clearly incapable of delivering optically pure **3** in sufficient quantities for successful synthesis of targets as structurally complex as **1** and **2**. As a consequence of these difficulties, the resolution step was postponed until the oxatricyclic system had been opened to a *cis*-hydroazulenol at a later stage in the synthesis.

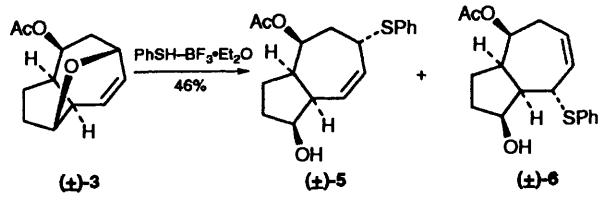
Conceptually, the most direct strategy for stereocontrolled installation of the requisite C-ring elements would be *via* nucleophilic displacement of the allylically activated bridging oxygen in **3** with an appropriate carbon nucleophile as depicted in eqn. (1) and our initial synthetic plan exploited this



3 (1)

advantage. However, very little strain appears to be associated with the ring system of **3** and, as a consequence, no ring-opened products could be isolated using a range of carbon nucleophiles.[11]

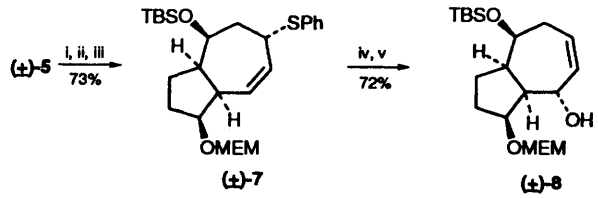
Alternatively, the introduction of an appropriate heteroatom substituent could be exploited in a somewhat less direct sequence for elaboration of the C-ring. It was envisioned that Lewis acid-mediated C–O bond cleavage with an appropriate heteroatom nucleophile could offer an attractive route to the required carbon–carbon bond formation *via* subsequent sigmatropic bond reorganization. Efforts to introduce oxygen directly at one of the allylic positions in **3** using conditions developed in another system were not successful.[12] A sulfur-based nucleophilic process was regarded as a useful alternative to oxygen since the former could be allylically transposed into the latter *via* suprafacial 2,3-sigmatropic rearrangement of the corresponding sulfoxide. In the event, treatment of (±)-**3** with BF_3·Et_2O in thiophenol afforded a 2:1 mixture of the hydroazulenes **5** and **6**, respectively, and the unwanted regioisomer could be recycled to **5** by re-exposure to the reaction conditions (Scheme 2). As a result, reasonable supplies of the required hydroazulene isomer could be accessed and the stage was set to explore the ester enolate Claisen process.



(±)-**3** (±)-**5** (±)-**6**

Scheme 2

Previous experience with these systems indicated that an acetoxy group (or related esters) in the seven-membered ring would not survive the projected ester enolate Claisen operation,[3n] so the alcohol protecting groups in compound **5** were adjusted accordingly. Protection of the A-ring hydroxy group as a MEM ether and replacing the acetoxy group with a TBS ether proceeded without incident to deliver the hydroazulene **7** in good yield (Scheme 3). In addition to producing a substrate for sigmatropic rearrangement, it was envisioned that transposition of the sulfide into the requisite allylic alcohol would also afford a compound amenable to resolution *via* esterification with an appropriate chiral carboxylic acid. Heteroatom exchange was achieved by *m*-chloroperbenzoic acid oxidation of **7** followed by *room temperature* 2,3-



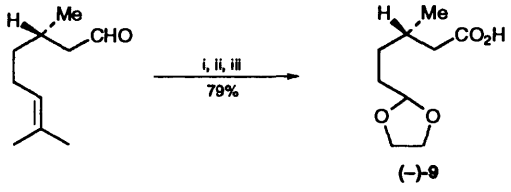
(±)-**7** (±)-**8**

Scheme 3 *Reagents:* i, MEMCl–Pr^i_2EtN; ii, K_2CO_3–MeOH; iii, TBSCl–imidazole; iv, MCPBA; v, $(MeO)_3P$, MeOH

sigmatropic rearrangement of the resultant mixture of sulfoxide diastereoisomers in the presence of $(MeO)_3P$, affording the requisite allylic alcohol **8** as a single diastereoisomer. It is noteworthy that the minor sulfoxide isomer was resistant to rearrangement. The structure assigned to intermediate **8** was supported by extensive ^1H homonuclear spin-decoupling experiments.

At this juncture in the synthetic plan, the elements of the C-ring and the C-14 side-chain (ophiobolane numbering) were to be introduced *via* an Ireland ester enolate Claisen rearrangement of the (*S*)-citronellate ester of the alcohol **8**. At the outset, it was hoped that simple esterification of racemic **8** with optically pure (*S*)-citronellic acid would afford a convenient opportunity for resolution into the two stereochemical series as outlined in Scheme 1. Unfortunately, the resulting diastereoisomeric mixture of esters was not separable by either chromatography or selective crystallization. Effective separation of (±)-**8**, however, was achieved using (−)-(1*S*,4*R*)-camphanic acid[13] as the resolving agent. The absolute configurations of the resultant alcohols were initially assigned *via* the corresponding *O*-methyl mandelate ester protocol[14] and later confirmed by single-crystal X-ray analysis.

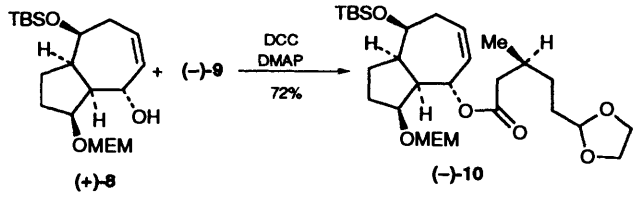
It was reasoned that a modified citronellic acid derived precursor would be a more useful and versatile species in the latter stages of the synthesis for the introduction of the C-14 side-chain α,β-unsaturated acid unit. To this end (*S*)-citronellal was efficiently modified as shown in Scheme 4 to afford the acetal acid (−)-**9**.



(−)-**9**

Scheme 4 *Reagents:* i, $AgNO_3$–KOH; ii, O_3–DMS; iii, $(CH_2OH)_2$–H^+

Coupling of optically pure (+)-**8** with optically pure (−)-**9** using DCC in the presence of 4-pyrrolidinylpyridine[15] afforded the key Claisen substrate (−)-**10** in 75% yield (Scheme 5). The

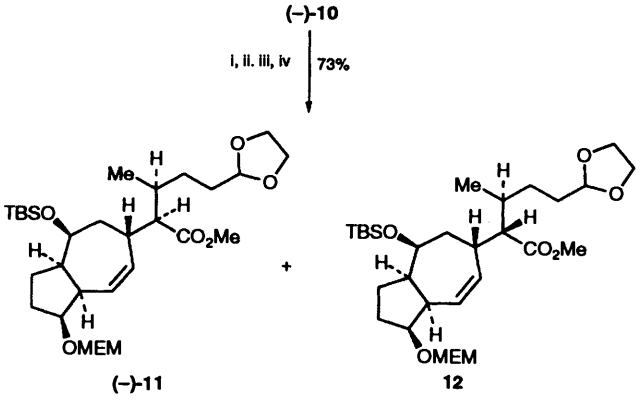


(+)-**8** (−)-**10**

Scheme 5

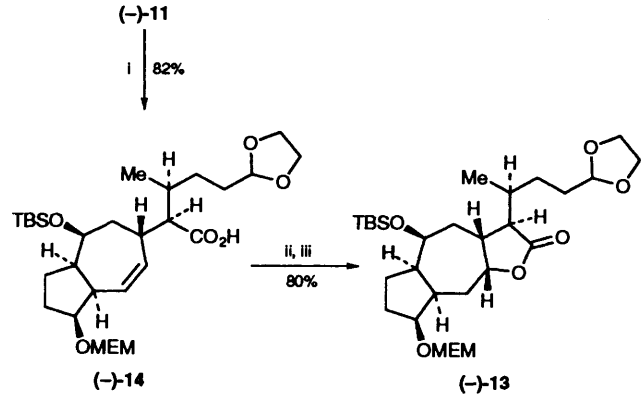
particular ester enolate Claisen rearrangement in this synthesis was designed specifically to set the relative configurations at three contiguous centres and instal most of the C-ring elements in one operation. Treatment of (−)-**10** with lithium diisopropylamide (LDA) in THF at −78 °C followed by silylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)

afforded a mixture of silyl ketene acetals, which was immediately heated to reflux to yield rearranged products (−)-**11** and **12** in a ratio of 4:1, respectively, after silyl ester cleavage and esterification with diazomethane (Scheme 6).



Scheme 6 *Reagents and conditions:* i, LDA, TBSOTf; ii, 67 °C; iii, Bu_4NF; iv, CH_2N_2

While previous observations on related systems suggested that these conditions would deliver products exhibiting the correct relative stereochemistry at the incipient vicinal stereogenic centres,[3n] this fact was confirmed by obtaining a single-crystal X-ray structure on the lactone (−)-**13*** derived from the Claisen product. This material was prepared by lithium thiopropoxide-mediated demethylation of (−)-**11**[16] to afford acid (−)-**14** followed by selenolactonization and subsequent removal of the phenyl selenide substituent (Scheme 7).[17]

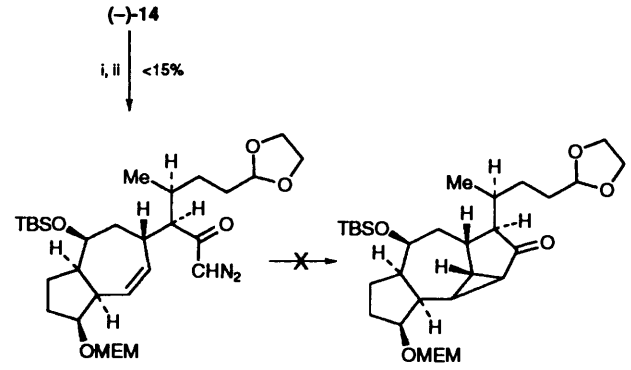


Scheme 7 *Reagents:* i, PrSLi–HMPA; ii, PhSeCl; Bu_3SnH

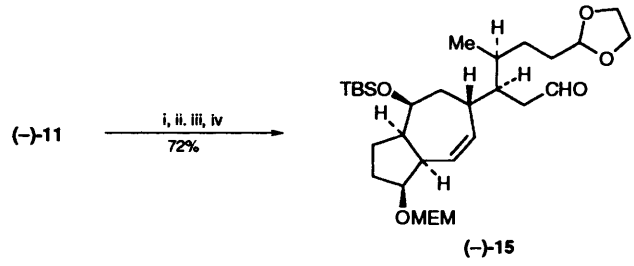
Attention then turned to elaborating the C-ring substructure. In earlier studies a copper-mediated diazo ketone insertion protocol efficiently delivered a C-ring species;[3n] however, efforts to achieve this objective by employing a similar cyclopropanation in the present context failed (Scheme 8). Alternatively, an intramolecular nitrile oxide cycloaddition protocol was examined for this purpose.[18] Implementation of this approach, however, necessitated a one-carbon homologation of the ester function in (−)-**11**. This structural modification was achieved employing a routine series of transformations, which afforded the requisite aldehyde (−)-**15** in 72% yield for four steps (Scheme 9).

Treatment of the aldehyde (−)-**15** with an excess of hydroxylamine hydrochloride in the presence of triethylamine afforded an oxime that underwent spontaneous cycloaddition *via* the corresponding nitrile oxide upon treatment with a biphasic mixture of 30% aqueous sodium hypochlorite in

* Details of the X-ray determination will be reported elsewhere.



Scheme 8 *Reagents:* i, $(COCl)_2$; ii, CH_2N_2



Scheme 9 *Reagents:* i, LAH; ii, MsCl–TEA; iii, KCN–DMSO; iv, DIBALH

dichloromethane at room temperature.[19] The resultant isoxazoline (−)-**16** was isolated in 41% yield as a single diastereoisomer.

Functional group manipulation of the heterocyclic moiety in (−)-**16** was envisioned to afford an α,β-unsaturated ketone *via* the corresponding β-hydroxy carbonyl species.[20] Reductive alkylation of the enone would provide a means for introducing the angular methyl group required at the B–C ring fusion of ceroplasteric acid. After considerable experimentation, the requisite β-hydroxy ketone was obtained from **16** by exposure to Ra-Ni under sonication conditions (Scheme 10).[20]

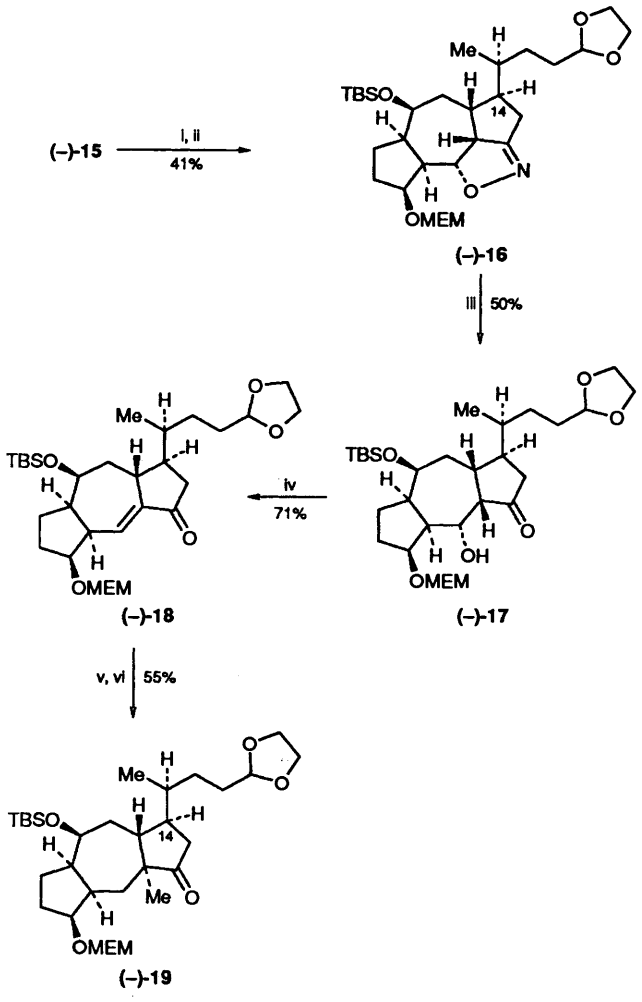
Introduction of the angular methyl group required at the B–C ring junction was accomplished in stereoselective fashion by careful dehydration of (−)-**17** with $SOCl_2$/py at 0 °C to afford the key enone (−)-**18**. Reductive alkylation of this species was conveniently achieved by exposure to dissolving metal conditions followed by addition of an excess of MeI. A single diastereoisomeric product resulted and was tentatively assigned structure (−)-**19** based on models indicating that the preferred approach of the alkylating agent would occur from the enolate face distal to the large C-14 substituent (ophiobolane numbering).

The tricycle **19** embodies a nearly complete skeleton of the target ceroplasteric acid, lacking only the *eight*-membered B-ring. Unfortunately, all efforts to induce one-carbon ring expansion of the corresponding B-ring carbonyl derivatives of **19** and **16** met with complete failure. Interestingly, facile one-carbon insertion could be achieved on various hydroazulenones related to **11** but the resultant 5-8 systems failed to undergo the necessary intramolecular nitrile oxide cycloaddition, thus limiting their utility for ohphiobolane synthesis.

Although rapid access to stereochemically elaborate tricycles resembling ophiobolane sesterterpenes is easily achieved using the above approach, modifications of current methodology are required to prepare the natural products themselves and studies in this direction are currently underway.

Experimental

^1H and ^{13}C NMR spectra were obtained on a GE-QE-300 spectrometer at 300 MHz and 75 MHz, respectively. Chemical



Scheme 10 *Reagents:* i, H_2NOH–TEA; ii, NaOCl–TEA; ii, Raney Ni–H_2, $B(OH)_3$, MeOH–H_2O; iv, $SOCl_2$–pyridine; v, Li–NH_3; vi, MeI

shifts are reported relative to $CDCl_3$ as an internal standard and *J*-values are recorded in Hz. Optical rotations were recorded on a Perkin-Elmer polarimeter using the Na_D line at a temperature of 25 °C and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Ether refers to diethyl ether.

4-*Acetoxy*-6-*phenylsulfanyl*-1α,2,3,3aα,4α,5,6β,8aα-*octahydroazulen*-1-*ol* (+)-**5** *and* 4-*Acetoxy*-8-*phenylsulfanyl*-1α,2,3,3aα,4a,5,8β,8aα-*octahydroazulen*-1-*ol* (±)-**6**.—The cyclic ether (±)-**3** (30 g, 0.14 mol) and freshly distilled thiophenol (100 cm^3, 0.91 mol) were mixed in a flask (500 cm^3) and to the stirred solution was added freshly distilled boron trifluoride–diethyl ether *via* a syringe at room temperature. The dark orange solution was stirred for 6 h and then quenched carefully with saturated aqueous sodium hydrogen carbonate and then solid sodium hydrogen carbonate until the foaming ceased. The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (4 × 200 cm^3). After the combined extracts had been washed first with 5% aqueous sodium hydroxide (5 × 200 cm^3) to remove excess of thiophenol and then with brine (1 × 300 cm^3), they were dried ($MgSO_4$) and evaporated under reduced pressure to afford a crude pale yellow oil. Flash chromatography[21] of this on silica gel (500 g; eluting with 1:5 ethyl acetate–hexanes) provided **5** (15.5 g) and **6** (4.17 g) in a combined yield of 46%.

Compound **5**: m.p. 118–119 °C; R_F 0.15 (1:5 ethyl acetate–hexanes); $\nu_{max}(CCl_4)$/cm^{-1} 3636, 3561, 3063, 3022, 2961, 1740, 1585, 1368, 1240 and 1025; $\delta_H(CDCl_3$; 300 MHz) 1.60–1.90 (m, 5 H), 2.06 (s, 3 H), 2.10 (m, 1 H), 2.60 (m, 2 H), 2.89 (m, 1 H), 3.90 (m, 1 H), 5.33 (ddd, *J* 2.1, 4.4, 12.4, 1 H), 5.67 (ddd, *J* 1.6, 4.8, 12.4, 1 H), 5.91 (ddd, *J* 2.1, 4.4, 12.4, 1 H), 7.19–7.31 (m, 3 H) and 7.42–7.45 (m, 2 H); $\delta_C(CDCl_3$; 75 MHz) 21.04, 25.28, 32.84, 33.84, 43.39, 44.89, 46.89, 72.52, 75.37, 127.39, 127.71, 128.92, 131.62, 132.57 and 169.88; *m*/*z* (rel. int.) 318 (1), 258 (5), 209 (5), 167 (6), 149 (59) and 131 (100) (Found: C, 67.5; H, 7.0%; M, 318.1287. Calc. for $C_{18}H_{22}SO_3$: C, 67.89; H, 6.97%. M^+, 318.1289).

Compound **6**: pale yellow oil: R_F 0.25 (1:5 ethyl acetate–hexanes): ν_{max}(neat)/cm^{-1} 3536, 3073, 3057, 3021, 1739, 1655 and 1587; $\delta_H(CDCl_3$; 300 MHz) 1.60–1.90 (m, 3 H), 2.10 (s, 3 H), 2.40–2.78 (m, 6 H), 4.37 (m, 1 H), 4.60 (m, 1 H), 5.29 (m, 1 H), 5.43 (m, 1 H), 5.86 (m, 1 H), 7.20–7.35 (m, 3 H) and 7.44–7.48 (m, 2 H); $\delta_C(CDCl_3$; 75 MHz) 27.21, 33.62, 34.36, 39.00, 43.32, 45.04, 51.41, 72.67, 75.08, 126.60, 126.83, 129.10, 130.92, 132.86, 135.39 and 170.41; *m*/*z* (rel. int.) 318 (1), 251 (18), 149 (87), 130 (11) (Found: *m*/*z* 318.1287. Calc. for $C_{18}H_{22}SO_3$: *m*/*z* 318.1289).

Additional sulfide **5** could be obtained by re-exposing **6** to reaction conditions identical with those described above. A mixture (≈1:1) of the two isomers was produced from which pure **5** could be isolated.

4-[(tert-*Butyldimethyl*)*siloxy*]-1-[(2-*methoxyethoxy*)*methoxy*]-6-*phenylsulfanyl*-1α,2,3,3aα,4α,5,6b,8aα-*hexahydroazulene* **7**.—A flask (500 cm^3) was charged with the alcohol **5** (14.16 g, 44.5 mmol) and dichloromethane (50 cm^3). After the solution had been placed under a blanket of nitrogen and cooled to 0 °C, ethyldiisopropylamine (10.1 cm^3, 57.9 mmol) was syringed into the flask followed by (2-methoxyethoxy)methyl chloride (MEMCl) (6.6 cm^3, 57.9 mmol). The solution was allowed to warm to room temperature and stirred for 6 h. At this time it was quenched with 5% aqueous hydrochloric acid and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 300 cm^3) and the combined organic layer and extracts were washed with 5% aqueous hydrochloric acid (2 × 50 cm^3), saturated aqueous sodium hydrogen carbonate (1 × 100 cm^3), and brine (1 × 200 cm^3) and then dried ($MgSO_4$) and evaporated under reduced pressure to provide a pale yellow oil. Flash chromatography of this on silica gel (500 g; eluting with 1:5 ethyl acetate–hexanes) provided the MEM ether (18.0 g, 99%), R_F 0.5 (1:5 ethyl acetate–hexanes); $\nu_{max}(CCl_4)$/cm^{-1} 3025, 2942, 2885, 2818, 1738, 1586 and 1025; $\delta_H(CDCl_3$; 300 MHz) 1.50–1.90 (m, 6 H), 1.99 (s, 3 H), 2.27 (m, 1 H), 2.45 (m, 1 H), 2.90 (m, 1 H), 3.39 (s, 3 H), 3.55 (m, 1 H), 3.68 (m, 2 H), 3.96 (m, 1 H), 4.08 (m, 1 H), 4.71 (m, 2 H), 5.76 (ddd, *J* 2.9, 4.7, 10.8, 1 H), 5.80 (dd, *J* 12.0, 3.2, 1 H), 5.93 (ddd, *J* 12.0, 6.8, 2.5, 1 H), 7.30 (m, 3 H) and 7.50 (m, 2 H); $\delta_C(CDCl_3$; 75 MHz) 20.32, 21.14, 28.16, 31.77, 41.98, 45.06, 58.99, 67.00, 71.31, 71.74, 79.56, 94.77, 102.309, 127.39, 128.86, 129.23, 130.29, 132.96, 134.82 and 169.90; *m*/*z* (rel. int.) 406 (1), 330 (3), 302 (7), 257 (8) and 179 (4) [Found: *m*/*z* 302.1347. Calc. for $C_{22}H_{30}SO_5$ (406.1813) − $C_4H_8O_3$: *m*/*z* 302.1340].

The MEM ether (18 g, 44 mmol) and anhydrous methanol (300 cm^3) were mixed in a flask (500 cm^3) and anhydrous potassium carbonate (18.4 g, 133 mmol) was added in one portion to the stirred solution at room temperature. The solution turned orange and the reaction was complete in 3 h. Water (100 cm^3) was added to the methanolic solution and the methanol was removed under reduced pressure to afford a brown oil and residual water. The residue was taken up into ethyl acetate (1 dm^3) and the organic layer was separated; the aqueous layer was extracted again with ethyl acetate (2 × 50 cm^3). The combined organic layer and extracts were washed with brine (300 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford a crude orange oil, filtration of which

through a plug of silica gel provided the alcohol (13.7 g, 85%), R_F 0.2 (1:3 ethyl acetate–hexanes); $\nu_{max}(CCl_4)/cm^{-1}$ 3452, 3079, 2882, 1581 and 1060; $\delta_H(CDCl_3$; 300 MHz) 1.55–1.97 (m, 6 H), 2.43–2.51 (m, 2 H), 2.79–2.84 (m, 1 H), 3.37 (s, 3 H), 3.52 (m, 2 H), 3.60–3.74 (m, 2 H), 3.95 (m, 1 H), 4.16 (m, 2 H), 4.73 (dd, *J* 12.6, 6.9, 1 H), 4.74 (d, *J* 6.9, 1 H), 5.60 (m, 1 H), 5.79–5.80 (m, 1 H), 7.19–7.31 (m, 3 H) and 7.42–7.45 (m, 2 H); $\delta_C(CDCl_3$; 75 MHz) 20.13, 26.52, 30.47, 43.70, 46.11, 59.10, 67.29, 70.44, 71.75, 73.44, 81.12, 93.92, 126.99, 127.27, 128.95, 132.00, 132.15 and 135.25; *m/z* (rel. int.) 364 (1), 259 (50) and 155 (20) (Found: *m/z* 364.1712. Calc. for $C_{20}H_{28}O_4S$: *m/z* 364.1708).

To a stirred solution of the alcohol (10 g, 27.5 mmol) and imidazole (2.81 g, 41.3 mmol) in dry DMF (20 cm^3) was added *tert*-butyldimethylsilyl chloride (6.19 g, 41.3 mmol). The reaction mixture was stirred at room temperature for 10 h after which saturated aqueous sodium hydrogen carbonate (200 cm^3) was added to it and the whole extracted with ether (3 × 200 cm^3). The combined extracts were washed with saturated aqueous hydrogen carbonate (3 × 100 cm^3) and brine (200 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure to provide a crude yellow oil. Flash chromatography of this on silica gel (300 g; eluting with 1:5 ethyl acetate–hexanes) afforded the silyl ether **7** (10.4 g, 85%): R_F 0.8 (1:3 ethyl acetate–hexanes); ν_{max}(neat)/cm^{-1} 3063, 3026, 2818, 1660, 1546 and 1054; $\delta_H(CDCl_3$; 300 MHz) −0.09 (s, 3 H), 0.0 (s, 3 H), 0.82 (s, 9 H), 1.49–1.74 (m, 3 H), 1.78–1.93 (m, 2 H), 2.15–2.32 (m, 2 H), 2.85 (m, 1 H), 3.41 (s, 3 H), 3.56 (t, *J* 4.7, 2 H), 3.70 (m, 2 H), 4.07 (m, 2 H), 4.57 (m, 2 H), 4.69 (d, *J* 3.9, 1 H), 4.77 (d, *J* 3.9, 1 H), 5.79 (dd, *J* 9.1, 2.9, 1 H), 5.90 (ddd, *J* 9.3, 6.8, 2.4, 1 H), 7.22–7.32 (m, 3 H) and 7.41–7.44 (m, 2 H); $\delta_C(CDCl_3$; 75 MHz) −4.85, −4.70, 18.09, 19.86, 25.87, 28.00, 35.10, 41.74, 44.66, 45.67, 59.17, 67.10, 68.97, 71.90, 80.02, 94.91, 126.87, 129.02, 129.81, 130.53 and 131.50; *m/z* (rel. int.) 478 (1), 364 (1) and 259 (50) (Found: *m/z* 478.2570. Calc. for $C_{26}H_{42}O_4SSi$: *m/z* 478.2573).

4-[(tert-*Butyldimethyl*)*siloxy*]-1-[(2-*methoxyethoxy*)*methoxy*]-1α,2,3,3aα,4α,5,8β,8aα-*octahydroazulen*-8-*ol* **8**.—To a solution of the sulfide **7** (10.4 g, 21.7 mmol) in dichloromethane (450 cm^3) cooled to −78 °C was added, in small portions, *m*-chloroperbenzoic acid (50%, w/w) (8.3 g, 23.9 mmol) over 1 h. The solution was stirred for an additional 1 h at −78 °C and was then allowed to warm slowly to room temperature (*ca.* 30 min), when it was quenched with 5% aqueous sodium hydroxide (100 cm^3) and stirred for an additional 30 min. The biphasic solution was transferred to a separatory funnel and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 × 100 cm^3) and the combined organic layer and extracts were then washed with 5% aqueous sodium hydroxide (100 cm^3) and brine (200 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford a crude oil comprised of a 3:1 mixture of diastereoisomeric sulfoxides (8.58 g, 80%). The two sulfoxides were separated by flash chromatography on silica gel (400 g; eluting with 1:4 ethyl acetate–hexanes) to provide the major isomer (6.43 g) and the minor isomer (2.15 g). The former was used in the next step.

To a solution of the major sulfoxide isomer (6.0 g, 12.1 mmol) in freshly distilled methanol (60 cm^3), was added freshly distilled trimethyl phosphite (15.0 g, 121.0 mmol) at room temperature. The solution was stirred at this temperature for 10 h, at which time saturated aqueous sodium hydrogen carbonate (200 cm^3) was added to it. The resulting mixture was stirred for 30 min after which the methanol was removed under reduced pressure to leave a white oily material which was taken up in ethyl acetate (500 cm^3). The organic layer was washed with water (200 cm^3) and the aqueous layer then back-extracted with ethyl acetate (2 × 100 cm^3). The combined organic layer and extracts were washed with brine (200 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to leave a clear oil. Flash chromatography of this on silica gel (150 g; eluting with 1:3 ethyl acetate–hexanes) provided the allylic alcohol (±)-**8** (4.24 g, 91%); R_F 0.5 (1:3 ethyl acetate–hexanes); ν_{max}(neat)/cm^{-1} 3500, 3017, 2942, 1583, 1463, 1253 and 1171; $\delta(CDCl_3$; 300 MHz) 0.04 (s, 3 H), 0.06 (s, 3 H), 0.91 (s, 9 H), 1.53–1.69 (m, 2 H), 1.81–2.02 (m, 2 H), 2.07–2.23 (m, 2 H), 2.38–2.48 (m, 3 H), 3.41 (s, 3 H), 3.59 (t, *J* 3.7, 2 H), 6.69 (dt, *J* 10.8, 4.3, 1 H), 3.81 (dt, *J* 3.9, 5.4, 1 H), 3.94 (m, 1 H), 4.25 (q, *J* 9.4, 1 H), 4.73 (d, *J* 6.7, 1 H), 4.78 (d, *J* 6.7, 1 H), 5.08 (dt, *J* 10.5, 2.3, 1 H), 5.38 (m, 1 H), and 5.69 (dq, *J* 12.1, 2.1, 1 H); $\delta_C(CDCl_3$; 75 MHz) −5.16, −4.47, 25.68, 26.39, 30.03, 36.69, 44.56, 53.03, 59.02, 66.95, 67.53, 70.71, 71.70, 78.16, 81.35, 94.45, 122.63 and 136.05; *m/z* (rel. int.) no M^+, 369 (5), 253 (47), 223 (100) and 178 (13) [Found: *m/z* 369.2466. Calc. for $C_{20}H_{38}O_5Si$ (386.2488) − OH: *m/z* 369.2461] (Found: C, 61.8; H, 10.2. Calc. for $C_{20}H_{38}O_5Si$: C, 62.13; H, 9.91%).

Resolution of (±)-**8** *and Isolation of* (+)-**8**.—To a stirred solution of the allylic alcohol (±)-**8** (7.0 g, 18.2 mmol) in dry diethyl ether (100 cm^3) was added (−)-camphanic acid (5.6 g, 28 mmol), DCC (4.5 g, 21.8 mmol) and DMAP (500 mg, 4 mmol) at room temperature. The solution was stirred until TLC analysis showed that the starting material had been consumed. The resultant slurry was vacuum filtered to remove the dicyclohexylurea by-product and the filter cake was washed several times with ether (4 × 50 cm^3). The combined filtrate and washings were evaporated under reduced pressure to give a colourless semi-solid consisting of two diastereoisomeric camphanoate esters. These were separated by careful flash chromatography on silica gel (250 g; eluting with 1:4 ethyl acetate–hexanes) to provide the (+)-camphanoate ester (4.12 g) and (−)-camphanoate ester (4.00 g), 80% combined yield.

To a vigorously stirred solution of the (+)-camphanoate ester (4.12 g, 7.27 mmol) in absolute methanol, cooled to 0 °C in an ice-bath, was added potassium hydroxide (2.3 g, 41.2 mmol). Upon complete dissolution of the potassium hydroxide the ice-bath was removed and the mixture stirred at room temperature for 10 h. At this point the ice-bath was returned and the solution cooled to 0 °C. A 1 mol dm^{-3} solution of HCl was added to the cool solution until it reached pH 6.0 (pH paper). The methanol was then removed from it under reduced pressure to give a biphasic mixture which was taken up into ethyl acetate (500 cm^3). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 cm^3). The combined organic layer and extracts were washed with saturated aqueous sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford a colourless viscous oil. Column chromatography of this on silica gel (50 g; eluting with 1:3 ethyl acetate–hexanes) provided the (+)-allylic alcohol **8** (2.65 g, 95%); $[\alpha]^{25}$ +53 (*c* 0.1 in $CHCl_3$).

(S)-3-*Methyl*-5-(1,3-*dioxolan*-2-*yl*)*pentanoic Acid* (−)-**9**.—A flask (2 dm^3) was charged with absolute ethanol (1 dm^3), silver nitrate (100 g, 0.588 mol), water (160 cm^3) and (*S*)-citronellal (42.8 g, 0.278 mol) and the mixture was stirred at room temperature whilst aqueous potassium hydroxide (82 g, 1.46 mol in 1 dm^3 of water) was added dropwise to it over 1.5 h. After the mixture had been stirred an additional 0.5 h it was vacuum filtered. The ethanol was removed from the filtrate under reduced pressure to leave a concentrated aqueous layer containing the potassium salt of the acid. After careful acidification of the solution with 1 mol dm^{-3} HCl to pH 2.0 (pH paper) it was extracted with ether (3 × 500 cm^3). The combined extracts were washed with brine (300 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to afford a clear colourless liquid (42.2 g). The unpurified liquid was

transferred to a flask (2 dm^3) and diluted with dichloromethane (1 dm^3). The solution was cooled to −78 °C with a solid CO_2–acetone bath and then stirred whilst O_3 (generated by an electrical discharge-tube ozonator) was bubbled through it until the solution turned pale blue. At this point the ozonator was turned off and dry nitrogen was bubbled into the solution to remove the excess of O_3 (indicated by solution becoming colourless). To decompose the ozonides, dimethyl sulfide (30.45 g, 0.496 mol) was added in one portion to the cold solution, which was then allowed to warm to room temperature. After the mixture had been stirred for 8 h, it was evaporated under reduced pressure to afford a clear oil (34.7 g, 98%) which was used without further purification. The oil was transferred to a flask (1 dm^3) and benzene (600 cm^3) was added to it along with an excess of ethylene glycol. The solution was heated gently under reflux for 8 h after which it was allowed to cool. Benzene was then removed from the mixture under reduced pressure and the biphasic residue was dissolved into ether (800 cm^3) and the solution washed with brine (3 × 300 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to afford the acetal (−)-**9** (41.1 g, 90%), $[\alpha]^{25}$ −75.5 (*c* 0.1 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3114, 2959, 1708 and 1047; δ_H($CDCl_3$; 300 MHz) 0.95 (d, *J* 6.6, 3 H), 1.22–1.36 (m, 1 H), 1.42–1.52 (m, 1 H), 1.57–1.70 (m, 2 H), 1.93–2.00 (m, 1 H), 2.11 (dd, *J* 15.0, 8.2, 1 H), 2.33 (dd, *J* 15.0, 5.7, 1 H), 3.81 (m, 2 H), 3.94 (m, 2 H), 4.82 (t, *J* 4.5, 1 H) and 11.50 (br s, 1 H); δ_C($CDCl_3$; 75 MHz) 19.45, 29.91, 30.57, 31.18, 41.36, 64.78, 104.43 and 179.13; *m/z* (rel. int.) 188 (1), 113 (1) and 98 (2) [Found: *m/z* 187.0967. Calc. for $C_9H_{15}O_4$ (188.1048) − H: *m/z* 187.0970].

(1S,3aR,4R,8S,8aR)-4-[(tert-*Butyldimethyl*)*siloxy*]-1-[(2-*methoxyethoxy*)*methoxy*]-8-[5-(1,3-*dioxolan*-2-*yl*)-(3S)-3-(*methyl*)*pentanoyl*]-1,2,3,3a,4,5,8,8a-*octahydroazulene* (−)-**10**.—To a flask (250 cm^3) was added a solution of the allylic alcohol (+)-**8** (3.56 g, 9.25 mmol) in ether, the carboxylic acid (−)-**9** (2.6 g, 13.9 mmol), DCC (2.8 g, 13.9 mmol) and a catalytic quantity of 4-pyrrolidinylpyridine (*ca.* 300 mg). The cloudy solution was stirred at room temperature until TLC analysis indicated the reaction to be complete (*ca.* 24 h). At this point, the reaction mixture, a very thick suspension of the white urea side-product along with the ester, was vacuum filtered and the filter cake was washed several times with ether (4 × 100 cm^3). The filtrate was then evaporated under reduced pressure to afford a mixture of the desired product and traces of the urea side-product. Flash chromatography on silica gel (50 g; eluting with 1:15 ethyl acetate–hexanes) provided the ester (−)-**10** (3.70 g, 72%): $[\alpha]^{25}$ −99.5 (*c* 0.1 in $CHCl_3$); R_F 0.8 (1:10 ethyl acetate–hexanes); ν_{max}($CDCl_3$)/cm^{-1} 3020, 2957, 1718 and 1048; δ_H($CDCl_3$; 300 MHz) 0.04 (s, 6 H), 0.92 (s, 9 H), 0.95 (d, *J* 6.6, 3 H), 1.32–1.47 (m, 3 H), 1.62–1.67 (m, 4 H), 1.88–2.47 (m, 6 H), 2.54–2.59 (m, 1 H), 3.37 (s, 3 H), 3.5 (m, 4 H), 3.70–3.73 (m, 1 H), 3.80–3.85 (m, 2 H), 3.93–3.95 (m, 2 H), 3.97–4.05 (m, 2 H), 4.61 (d, 6.9, 1 H), 4.62 (d, *J* 6.9, 1 H), 4.83 (t, *J* 4.5, 1 H), 5.29–5.34 (m, 1 H), 5.41–5.45 (m, 1 H) and 6.10 (d, *J* 10.8, 1 H); δ_C($CDCl_3$; 75 MHz) −4.98, −4.19, 18.11, 19.73, 25.75, 28.68, 30.21, 30.88, 31.42, 32.48, 38.50, 42.17, 44.34, 51.41, 59.11, 64.96, 66.11, 70.74, 77.16, 77.59, 82.03, 95.89, 104.69, 124.15, 132.10 and 172.11; *m/z* (rel. int.) 499 (1), 369 (3), 223 (100) and 171 (25) [Found: *m/z* 499.2731. Calc. for $C_{29}H_{52}O_8Si$ (556.3431) − C_4H_9: *m/z* 499.2727].

(1S,3aR,4R,6S,8aR)-4-[(tert-*Butyldimethyl*)*siloxy*]-1-[(2-*methoxyethoxy*)*methoxy*]-6-[(1S,2S)-1-*methoxycarbonyl*-4-(1,3-*dioxolan*-2-*yl*)-2-*methylbutyl*]-1,2,3,3a,4,5,6,8a-*hexahydroazulene* (−)-**11**.—In a flame-dried 3-necked flask (250 cm^3) fitted with a reflux condenser and nitrogen inlet, dry THF (50 cm^3) and distilled diisopropylamine (1.01 g, 10 mmol) were mixed under nitrogen and cooled to 0 °C. To the cool solution was added a solution of 2.5 mol dm^{-3} butyllithium in pentane (4 cm^3, 10 mmol) and the resulting mixture was stirred for 30 min. The thus prepared solution of LDA was cooled further to −78 °C and a solution of the ester (−)-**10** (3.7 g, 6.7 mmol) in dry THF (50 cm^3) was added dropwise to it over the course of 5 min. After the mixture had been stirred for an additional 1 h, it was quenched with *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.96 g, 7.3 mmol) and stirred for a further 1 h. The mixture was then warmed to room temperature over 30 min and finally brought to reflux and was maintained at this temperature for 15 h. The reaction mixture was then cooled to room temperature and a solution of 1.0 mol dm^{-3} tetrabutylammonium fluoride in THF (10 cm^3, 10 mmol) was added to it. After the mixture had been stirred for 1 h it was diluted with ether (400 cm^3), washed with 5% aqueous hydrochloric acid (3 × 200 cm^3) and brine (200 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to provide the crude carboxylic acids. Without further purification the crude mixture was treated with a solution of diazomethane in ether to provide the methyl esters. Flash chromatography of the resulting crude mixture on silica gel (60 g; eluting with 1:5 ethyl acetate–hexanes) provided the major ester (−)-**11** (2.20 g, 58%): $[\alpha]^{25}$ −89.1 (*c* 0.1 in $CHCl_3$); R_F 0.6 (1:3 ethyl acetate–hexanes); ν_{max}($CDCl_3$)/cm^{-1} 3020, 2964, 1725, 1647, 1436 and 1379; δ_H($CDCl_3$; 300 MHz) −0.002 (s, 6 H), 0.83 (s, 9 H), 0.89 (d, *J* 6, 3 H), 1.47–1.81 (m, 11 H), 2.15–2.17 (m, 1 H), 2.48 (dd, *J* 10.5, 4.8, 1 H), 2.75–2.79 (m, 2 H), 3.37 (s, 3 H), 3.52 (t, *J* 4.2, 2 H), 3.58 (s, 3 H), 3.65 (t, *J* 4.8, 2 H), 3.79–3.83 (m, 2 H), 3.91–3.93 (m, 2 H), 4.03–4.05 (m, 2 H), 4.67 (d, *J* 6.7, 1 H), 4.71 (d, *J* 6.7, 1 H), 4.81 (t, *J* 4.8, 1 H) and 5.57–5.70 (m, 2 H); δ_C($CDCl_3$; 75 MHz) −4.58, −4.82, 14.46, 15.21, 17.95, 20.06, 25.72, 28.17, 29.68, 31.84, 32.14, 32.69, 33.41, 41.59, 45.27, 50.85, 51.80, 58.93, 65.79, 66.83, 69.13, 71.71, 80.15, 94.77, 104.48, 127.45, 133.24 and 174.07; *m/z* (rel. int.) 513 (16), 437 (13), 407 (6), 332 (7) and 271 (6) [Found: *m/z* 513.2892. Calc. for $C_{30}H_{54}O_8Si$ (570.3588) − C_4H_9: *m/z* 513.2883].

(1S,3aR,4R,6S,8aR)-4-[(tert-*Butyldimethyl*)*siloxy*]-1-[(2-*methoxyethoxy*)*methoxy*]-6-[1-*carboxy*-4-(1,3-*dioxolan*-2-*yl*)-2-*methylbutyl*)]-1,2,3,3a,4,5,6,8a-*hexahydroazulene* (−)-**14**.—To a dry flask (100 cm^3) flushed with nitrogen was added a stir bar and the methyl ester (−)-**11** (2.2 g, 3.8 mmol). The flask was cooled to 0 °C with an ice-bath and a solution of freshly prepared 0.5 mol dm^{-3} lithium propanethiolate–HMPA solution (8.5 cm^3) was added to it. The mixture was allowed to warm to room temperature and was stirred until TLC analysis showed the reaction to be complete. The reaction mixture was then diluted with water (100 cm^3) and extracted with ether (4 × 100 cm^3). The combined extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford a viscous oil which was passed through a plug of silica gel (eluting with 1:2 ethyl acetate–hexanes) to provide the acid (−)-**14** (1.82 g, 85%); $[\alpha]^{25}$ −115 (*c* 0.1 in $CHCl_3$); R_F 0.1 (1:3 ethyl acetate–hexanes); ν_{max}(neat)/cm^{-1} 3400, 2955, 2932, 1702, 1463 and 1123; δ_H($CDCl_3$; 300 MHz) 0.007 (s, 6 H), 0.85 (s, 9 H), 0.95 (d, *J* 7.2, 3 H), 1.24–1.26 (m, 2 H), 1.53–1.83 (m, 9 H), 2.22 (dd, *J* 7.2, 3.6, 2 H), 2.70–2.80 (m, 1 H), 2.92–3.00 (m, 1 H), 3.38 (s, 3 H), 3.51–3.54 (m, 2 H), 3.63–3.66 (m, 2 H), 3.84 (dd, *J* 4.5, 2.4, 2 H), 3.94 (m, 2 H), 4.04–4.10 (m, 2 H), 4.67 (dd, *J* 14.7, 6.9, 2 H), 4.81–4.84 (m, 1 H), 5.60–5.75 (m, 2 H) and 9.63 (br s, 1 H); δ_C($CDCl_3$; 75 MHz) −4.70, −4.47, 14.59, 18.06, 20.18, 25.85, 28.30, 29.80, 31.96, 32.26, 33.54, 41.73, 45.41, 50.96, 51.80, 59.06, 64.92, 66.97, 69.26, 71.85, 80.15, 94.93, 104.62, 127.60, 133.40 and 174.197; *m/z* (rel. int.) no M^+, 467 (1), 409 (7), 335 (3), 291 (2) and 273 (3).

(1S,3aR,4R,6S,7R,8aR)-4-[(tert-*Butyldimethyl*)*siloxy*]-1-[(2-*methoxyethoxy*)*methoxy*]-6-[4′-(1,3-*dioxolan*-2-*yl*)-(2′S)-2′-

methylbutyl]-1,2,3,3a,4,5,6,8a-*octahydroazulene*-(1'R)-1',7-*carbolactone* (−)-**13**.—In a flask (25 cm^3) cooled to −30 °C (acetonitrile–solid CO_2 bath), the carboxylic acid (−)-**14** (985 mg, 1.77 mmol) and triethylamine (545 mm^3,* 4.0 mmol) in dichloromethane (5.0 cm^3) were mixed and then stirred during the addition of benzeneselenenyl chloride. The resultant orange solid was allowed to dissolve over a 1 h period at which point the cooling bath was removed and the solution was allowed to warm to room temperature. After 1 h at room temperature, the reaction was complete and the solution was diluted with dichloromethane (50 cm^3), washed with 5% aqueous hydrochloric acid (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude selenolactone which, without further purification, was used for the next step. In a flask (25 cm^3) fitted with a reflux condenser distilled toluene (10 cm^3), tributyltin hydride (483 mm^3, 1.80 mmol), the selenolactone, and a catalytic amount of AIBN (4 mg), were mixed and then stirred whilst being brought to reflux. The reaction, monitored with TLC, was complete in *ca.* 30 min. The reaction mixture was then cooled to room temperature and evaporated under reduced pressure to provide a crude slurry of the product and tin species. Flash chromatography of the residue on silica gel (eluting with 1:5 ethyl acetate–hexanes) provided the lactone (787 mg, 80%): m.p. 96–97 °C; $[\alpha]^{25}$ −109 (*c* 0.1 in $CHCl_3$); R_F 0.9 (1:5 ethyl acetate–hexanes); ν_{max}($CDCl_3$)/cm^{-1} 2950, 2936, 1766, 1471 and 1119; δ_H($CDCl_3$; 300 MHz) 0.03 (s, 6 H), 0.90 (s, 9 H), 0.93 (d, *J* 7.5, 3 H), 1.20–1.41 (m, 5 H), 1.58–1.80 (m, 6 H), 1.85–2.05 (m, 2 H), 2.09–2.13 (m, 2 H), 2.25–2.35 (m, 1 H), 2.42 (dd, *J* 10.2, 4.2, 1 H), 2.72–2.78 (m, 1 H), 3.38 (s, 3 H), 3.55 (dd, *J* 4.8, 3.0, 2 H), 3.66 (t, *J* 4.8, 2 H), 3.80–3.84 (m, 2 H), 3.93–3.97 (m, 2 H), 3.97–3.99 (m, 1 H), 4.03–4.07 (m, 1 H), 4.54 (d, *J* 3.0, 1 H), 4.58 (d, *J* 6.9, 1 H), 4.59 (d, *J* 6.9, 1 H) and 4.85 (t, *J* 4.8, 1 H); δ_C($CDCl_3$; 75 MHz) −5.38, −4.23, 17.75, 18.02, 23.29, 25.10, 25.82, 28.01, 29.22, 29.82, 30.30, 31.01, 35.17, 38.85, 47.17, 51.40, 58.99, 64.80, 66.86, 68.60, 71.76, 79.69, 80.35, 94.55, 104.72 and 177.37; *m/z* (rel. int.) 556 (1), 499 (1), 423 (5), 393 (35), 257 (5), 211 (52) and 163 (6) [Found: *m/z* 499.2731. Calc. for $C_{29}H_{52}O_8Si$ (556.3431) − C_4H_9: *m/z* 499.2727].

(1S,3aR,4R,6S,8aR)-4-[(tert-*Butyldimethyl*)*siloxy*]-1-[(2-*methoxyethoxy*)*methoxy*]-6-[6-(1,3-*dioxolan*-2-*yl*)-5-*formyl*-(3R,4S)-4-*methylpentan*-3-*yl*]-1,2,3,3a,4,5,6,8a-*hexahydroazulene* (−)-**15**.—To a solution of the methyl ester (−)-**11** (990 mg, 1.80 mmol) in dry ether (10 cm^3) cooled to 0 °C with an ice-bath, was added, in small portions, solid lithium aluminium hydride (242 mg, 7.12 mmol). After addition of the reducing agent, the solution was warmed to room temperature and stirred overnight. Once the reaction was complete (TLC) the reaction mixture was again cooled to 0 °C with an ice-bath and the reaction carefully quenched by the addition of 10% aqueous NaOH (*ca.* 2 cm^3); the mixture was stirred vigorously until a fine white precipitate was formed (initially a grey paste). The ethereal solution when vacuum filtered to remove the aluminate salts left a clear colourless filtrate which upon evaporation under reduced pressure provided the alcohol (879 mg, 90%); this was used for the next step without further purification: $[\alpha]^{25}$ −85.4 (*c* 0.1 in $CHCl_3$); R_F 0.1 (1:3 ethyl acetate–hexanes); ν_{max}(neat)/cm^{-1} 3464, 2950, 2929, 1647, 1407 and 1253; δ_H($CDCl_3$; 300 MHz) 0.03 (s, 6 H), 0.87 (s, 9 H), 0.87 (d, *J* 6.9, 3 H), 1.40–1.80 (m, 13 H), 2.15–2.30 (m, 1 H), 2.50–2.65 (m, 1 H), 2.84–2.89 (m, 1 H), 3.39 (s, 3 H), 3.55 (t, *J* 4.8, 2 H), 3.63–3.72 (m, 4 H), 3.83–3.87 (m, 2 H), 3.95–3.99 (m, 2 H), 4.08–4.11 (m, 2 H), 4.69 (d, *J* 6.8, 1 H), 4.73 (d, *J* 6.8, 1 H), 4.86 (t, *J* 4.8, 1 H), 5.70 (dd, *J* 7.5, 4.2, 1 H) and 5.87 (ddd, *J* 11.7, 6.9, 1.5, 1 H); δ_C($CDCl_3$; 75 MHz) −4.73, −4.43, 15.24, 18.13, 20.78, 25.91, 28.88, 32.32, 32.56, 33.92, 42.31, 45.72, 47.49, 59.14, 61.97, 64.97, 65.94, 67.13, 69.58, 71.89, 80.59, 95.07, 104.83, 127.58 and 135.07; *m/z* (rel. int.) no M^+, 436 (2.8), 409 (10.3), 225 (16.2), 171 (16.3), 133 (38.4), 99 (32.5), 89 (80.9) and 73 (100) [Found: *m/z* 436.3018. Calc. for $C_{29}H_{54}O_7Si$ (542.3638) − $C_4H_{10}O_3$: *m/z* 436.3009].

In a flask (10 cm^3), dichloromethane (5 cm^3) and the alcohol (714 mg, 1.32 mmol) were mixed and then stirred whilst triethylamine (360 mm^3, 2.64 mmol) followed by methanesulfonyl chloride (204 mm^3, 2.64 mmol) were added at room temperature. The reaction, monitored by TLC and complete in 2 h was quenched by the addition of saturated aqueous sodium hydrogen carbonate to the mixture. The mixture was extracted with dichloromethane (3 × 20 cm^3) and the combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford a crude orange oil. Flash chromatography of this on silica gel (eluting with 1:5 ethyl acetate–hexanes) afforded the mesylate (765 mg, 94%): $[\alpha]^{25}$ −120 (*c* 0.1 in $CHCl_3$); R_F 0.5 (1:5 ethyl acetate–hexanes); ν_{max}(neat)/cm^{-1} 3014, 2950, 2852, 1471, 1175 and 1126; δ_H($CDCl_3$; 300 MHz) 0.01 (s, 6 H), 0.85 (s, 9 H), 0.92 (d, *J* 6.9, 3 H), 1.40–1.90 (m, 12 H), 2.19–2.25 (m, 1 H), 2.50–2.65 (m, 1 H), 2.75–2.80 (m, 1 H), 2.96 (s, 3 H), 3.37 (s, 3 H), 3.51–3.54 (m, 2 H), 3.57–3.68 (m, 2 H), 3.80–3.85 (m, 2 H), 3.92–3.97 (m, 2 H), 4.05–4.11 (m, 2 H), 4.23–4.24 (m, 2 H), 4.69 (dd, *J* 12.9, 6.0, 2 H), 4.83 (t, *J* 4.5, 1 H) and 5.65–5.73 (m, 2 H); δ_C($CDCl_3$; 75 MHz) −4.85, −4.57, 15.02, 17.96, 20.27, 25.73, 28.21, 29.57, 32.08, 32.51, 33.32, 33.61, 37.13, 41.68, 44.12, 45.33, 58.96, 64.81, 66.95, 68.97, 69.10, 71.73, 80.07, 94.78, 102.28, 104.38, 127.69 and 133.24; *m/z* (rel. int.) no M^+, 535 (4), 494 (17) and 296 (100).

The mesylate (765 mg, 1.23 mmol) was mixed in a flask (10 cm^3) with distilled DMSO (5 cm^3) and the solution then stirred whilst potassium cyanide (dried in a vacuum oven overnight; 401 mg, 6.17 mmol) was added to it. The mixture was stirred at room temperature for 1 h and then warmed in an oil-bath to 80 °C, at which temperature it was maintained for 20 h. The mixture was then cooled to room temperature, diluted with water (20 cm^3) and extracted with ether (3 × 20 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue when subjected to flash chromatography (eluting with 1:3 ethyl acetate–hexanes) provided the nitrile (579 mg, 85%): $[\alpha]^{25}$ −102.7 (*c* 0.1 in $CHCl_3$); R_F 0.85 (1:3 ethyl acetate–hexanes); ν_{max}(neat)/cm^{-1} 3014, 2950, 2929, 2239 and 1471; δ_H($CDCl_3$; 300 MHz) 0.024 (s, 6 H), 0.86 (s, 9 H), 0.95 (d, *J* 6.6, 3 H), 1.42–1.83 (m, 12 H), 2.15–2.26 (m, 1 H), 2.30 (d, *J* 4.2, 1 H), 2.34 (d, *J* 5.7, 1 H), 2.58–2.67 (m, 1 H), 2.76–2.81 (m, 1 H), 3.39 (s, 3 H), 3.55 (t, *J* 4.5, 2 H), 3.67–3.71 (m, 2 H), 3.83–3.87 (m, 2 H), 3.95–3.99 (m, 2 H), 4.07–4.13 (m, 2 H), 4.72 (dd, *J* 13.2, 6.3, 2 H), 4.86 (t, *J* 4.5, 1 H) and 5.72–5.82 (m, 2 H); δ_C($CDCl_3$; 75 MHz) −4.71, −4.44, 14.19, 15.71, 18.09, 20.34, 25.86, 28.29, 29.50, 32.06, 33.45, 33.59, 35.67, 41.93, 45.48, 59.12, 65.00, 67.15, 69.20, 71.93, 80.29, 95.03, 104.41, 120.12, 128.63 and 133.02; *m/z* (rel. int.) 551 (1), 494 (45), 418 (13), 388 (16), 252 (15) and 211 (11) (Found: *m/z* 551.3650. Calc. for $C_{30}H_{53}NO_6Si$: *m/z* 551.3642).

The nitrile (579 mg, 1.05 mmol) was mixed with dry ether (10 cm^3) in a flask (20 cm^3) and the solution cooled to −30 °C. Diisobutylaluminium hydride (1.0 mol dm^{-3}; 1.26 cm^3, 1.26 mmol) was added to the cooled and stirred solution and stirring was continued at this temperature for 1 h. The reaction mixture was then warmed to room temperature and, after a further 1.5 h, quenched with cold (*ca.* 0 °C) 10% aqueous sulfuric acid solution (9 cm^3) and stirred for 30 min. The mixture was extracted with ether (3 × 20 cm^3) and the combined extracts were washed with 5% aqueous hydrochloric acid (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated to provide the

* 1 mm^3 = 1 μl.

crude aldehyde. Flash chromatography of this on silica gel (eluting with 1:3 ethyl acetate–hexanes) provided the aldehyde (−)-**15** (580 mg, 98%); $[\alpha]^{25}$ −99.5 (*c* 0.1 in $CHCl_3$); R_F 0.65 (1:3 ethyl acetate–hexanes); ν_{max}(neat)/cm^{-1} 3018, 2950, 2711, 1725 and 1471; δ_H($CDCl_3$; 300 MHz) −0.01 (s, 6 H), 0.76 (d, *J* 6.9, 3 H), 0.82 (s, 9 H), 1.29–1.33 (m, 1 H), 1.44–1.78 (m, 10 H), 2.11–2.25 (m, 4 H), 2.30–2.35 (m, 1 H), 2.67 (t, *J* 6.0, 1 H), 3.34 (s, 3 H), 3.51 (t, *J* 3.9, 2 H), 3.63 (t, *J* 4.2, 2 H), 3.77–3.82 (m, 2 H), 3.90–3.94 (m, 2 H), 4.02–4.06 (m, 1 H), 4.09–4.13 (m, 1 H), 4.94 (dd, *J* 12.6, 5.7, 2 H), 4.79 (t, *J* 4.5, 1 H), 5.61–5.64 (m, 2 H) and 9.60 (s, 1 H); δ_C($CDCl_3$; 75 MHz) −4.78, −4.53, 13.71, 17.93, 19.86, 25.61, 25.72, 27.91, 29.57, 31.96, 33.04, 36.80, 39.02, 41.59, 41.96, 43.30, 45.15, 58.95, 64.80, 67.04, 69.13, 71.72, 80.09, 94.89, 104.40, 128.72, 134.52 and 202.55; *m/z* (rel. int.) no M^+, 497 (3), 133 (2) [Found: *m/z* 497.2944. Calc. for $C_{30}H_{54}O_7Si$ (554.3638) − C_4H_9: *m/z* 497.2934].

(1R,3aR,4S,4aR,5S,7aR,8S)-8-[(tert-*Butyldimethyl*)*siloxy*]-1-[3-(1,3-*dioxolan*-2-*yl*)-(1S)-1-(*methyl*)*propyl*]-5-[2-(*methoxyethoxy*)*methoxy*]-2,3a,4,4a,5,6,7,7a,8,9,9a-*undecahydro*-4,3-(*epoxynitrilo*)-1H-*cyclopent*[f]*azulene* (−)-**16**.—To a solution of the aldehyde (−)-**15** (580 mg, 1.04 mmol) in dichloromethane (5 cm^3) was added at room temperature triethylamine (545 mm^3, 4.0 mmol). Hydroxylamine hydrochloride (145 mg, 2.09 mmol) was then added with vigorous stirring to the mixture. The reaction, monitored by TLC, was complete in 2.5 h, at which time the mixture was diluted with dichloromethane (50 cm^3). It was then washed quickly with cold 5% aqueous hydrochloric acid (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to provide a crude mixture of the oximes (565 mg). To the mixture of oximes was added dichloromethane (3 cm^3) and then, with vigorous stirring, 5% aqueous sodium hypochlorite (2 cm^3). The biphasic solution was stirred at room temperature until the reaction was complete (*ca.* 6 h). The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (3 × 10 cm^3). The combined organic layer and extracts were washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to provide a pale yellow oil. Flash chromatography of this on silica gel (eluting with 1:3 ethyl acetate–hexanes) provided the isoxazoline (−)-**16** (242 mg, 41%): $[\alpha]^{25}$ −130 (*c* 0.1 in $CHCl_3$); R_F 0.75 (1:3 ethyl acetate–hexanes); ν_{max}($CDCl_3$)/ cm^{-1} 3380, 2957, 2887 and 1379; δ_H($CDCl_3$; 300 MHz) 0.02 (s, 3 H), 0.03 (s, 3 H), 0.84 (d, *J* 6.3, 3 H), 0.89 (s, 9 H), 1.20–1.50 (m, 4 H), 1.60–1.76 (m, 4 H), 1.77–1.90 (m, 2 H), 2.00–2.25 (m, 4 H), 2.35–2.50 (m, 2 H), 3.37 (s, 3 H), 3.51–3.57 (m, 2 H), 3.72–3.75 (m, 2 H), 3.80–3.85 (m, 2 H), 3.92–4.00 (m, 3 H), 4.20–4.25 (m, 1 H), 4.75 (dd, *J* 2.8, 1 H), 4.79 (d, *J* 2.8, 1 H), 4.82 (t, *J* 4.8, 3 H) and 5.16 (t, *J* 10.2, 1 H); δ_C($CDCl_3$; 75 MHz) −5.10, −4.42, 14.27, 18.12, 24.74, 25.90, 26.46, 30.34, 31.49, 32.06, 33.15, 33.77, 36.90, 41.65, 48.06, 56.28, 56.66, 59.12, 64.99, 66.88, 68.86, 72.02, 83.15, 94.89, 104.40 and 169.75; *m/z* (rel. int.) no M^+, 499 (0.1), 369 (4), 293 (16), 251 (2) and 207 (0.4).

(1R,3aR,4S,4aR,5S,7aR,8S)-8-[(tert-*Butyldimethyl*)*siloxy*]-1-[3-(1,3-*dioxolan*-2-*yl*)-4-*hydroxy*-5-[2-*methoxyethoxy*)*methoxy*]-(1S)-1-(*methyl*)*propyl*]-2,3a,4,4a,5,6,7,7a,8,9,9a-*undecahydro*-1H-*cyclopent*[f]*azulen*-3-*one* (−)-**17**.—Methanol–water (5:1; 10 cm^3), boric acid (500 mg) and the isoxazoline (−)-**16** (242 mg, 0.428 mmol) were mixed in a flask (50 cm^3) and then stirred whilst a spatula tip full of W-5 Raney nickel (pre-washed several times with water to remove basic material) was added to the mixture; a three-way stopcock fitted with a balloon filled with hydrogen gas was then placed on the flask. The flask was evacuated and refilled with hydrogen from the balloon several times. The flask was then submerged into a Branson ultrasonicator so that the level of the reaction was just beneath the surface of the water in the unit. The reaction was monitored for 4 h, during which time the temperature of the water was regulated so that the reaction mixture was not heated > 40 °C. After 6 h, sonication was terminated and the reaction mixture was stirred overnight at room temperature. The Raney nickel and excess of boric acid were filtered off and the methanol removed under reduced pressure to provide a biphasic mixture of organic products and water. The aqueous layer was extracted with ether (3 × 20 cm^3) and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford a clear oil. Flash chromatography of this on silica gel (eluting with 1:2 ethyl acetate–hexanes) provided (−)-**17** (115 mg, 50%); $[\alpha]^{25}$ −111 (*c* 0.1 in $CHCl_3$); R_F 0.45 (1:2 ethyl acetate–hexanes); ν_{max}($CDCl_3$)/cm^{-1} 3468, 2955, 1718 and 1457; δ_H($CDCl_3$; 300 MHz) −0.015 (s, 3 H), −0.012 (s, 3 H), 0.79 (d, *J* 6.6, 3 H), 0.88 (s, 9 H), 1.13 (t, *J* 12.9, 2 H), 1.23–1.35 (m, 4 H), 1.58–1.70 (m, 4 H), 1.78–1.99 (m, 6 H), 2.02–2.06 (m, 1 H), 2.18–2.29 (m, 2 H), 3.37 (s, 3 H), 3.51–3.55 (m, 2 H), 3.64–3.70 (m, 2 H), 3.80–3.85 (m, 2 H), 3.92–3.97 (m, 2 H), 4.25–4.35 (m, 2 H), 4.68 (d, *J* 10.2, 1 H), 4.73 (d, *J* 10.2, 1 H), 4.81 (t, *J* 4.5, 1 H) and 5.34 (s, 1 H); δ_C($CDCl_3$; 75 MHz) −4.87, −3.71, 13.16, 18.10, 25.94, 29.15, 30.61, 30.83, 31.37, 32.10, 37.50, 39.49, 43.73, 44.89, 54.56, 59.08, 60.17, 65.00, 66.48, 69.69, 70.03, 72.01, 79.10, 94.48, 104.55 and 222.44; *m/z* (rel. int.) 571 [$(M + H)^+$ 0.7], 495 (12), 333 (7), 255 (12), 211 (6) and 155 (3).

(1R,4aR,5S,7aR,8S)-8-[(tert-*Butyldimethyl*)*siloxy*]-1-[3-(1,3-*dioxolan*-2-*yl*)-(1S)-1-(*methyl*)*propyl*]-5-[2-(*methoxyethoxy*)-*methoxy*]-2,4a,5,6,7,7a,8,9,9a-*nonahydro*-1H-*cyclopent*[f]*azulen*-3-*one* (−)-**18**.—The β-hydroxy ketone (−)-**17** (36 mg, 0.063 mmol) and dichloromethane (3 cm^3) were mixed in a flask (5 cm^3) and the solution was cooled to 0 °C. Pyridine (200 mm^3, 2.5 mmol) and thionyl chloride (11 mm^3, 0.15 mmol) were added to the mixture which was then stirred for 30 min. Since at this point, TLC analysis indicated that the reaction had slowed greatly, further thionyl chloride (11 mm^3) and pyridine (50 mm^3) were added to the mixture which was then allowed to warm to room temperature. The reaction was complete in 3 h at which point it was quenched with saturated aqueous sodium hydrogen carbonate (5 cm^3). The aqueous layer was extracted with dichloromethane (3 × 5 cm^3) and the combined extracts were washed with brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Preparatory thin layer chromatography of the residue on glass plates coated with silica gel (0.5 mm; eluting with 1:3 ethyl acetate–hexanes) provided the enone (−)-**18** (24.9 mg, 71%); $[\alpha]^{25}$ −153 (*c* 0.1 in $CHCl_3$); R_F 0.6 (1:3 ethyl acetate–hexanes); ν_{max}($CDCl_3$)/cm^{-1} 3014, 2929, 1717, 1647, 1470 and 1252; δ_H($CDCl_3$; 300 MHz) 0.025 (s, 6 H), 0.85 (d, *J* 2.7, 3 H), 0.87 (s, 9 H), 1.36–1.41 (m, 2 H), 1.52–1.83 (m, 10 H), 2.03–2.13 (m, 3 H), 2.21–2.33 (m, 2 H), 2.87–2.96 (m, 2 H), 3.38 (s, 3 H), 3.52–3.55 (m, 2 H), 3.53–3.65 (m, 2 H), 3.82–3.87 (m, 2 H), 4.04–4.10 (m, 1 H), 4.17–4.22 (m, 1 H), 4.65 (d, *J* 6.7, 1 H), 4.69 (d, *J* 6.7, 1 H), 4.84 (t, *J* 4.5, 1 H) and 6.71 (dd, *J* 4.8, 1.8, 1 H); δ_C($CDCl_3$; 75 MHz) −4.85, −4.45, 13.82, 18.18, 24.47, 25.91, 30.01, 30.56, 32.06, 32.15, 38.00, 38.09, 38.17, 44.56, 45.02, 45.37, 59.14, 65.00, 67.00, 69.20, 71.89, 80.90, 94.62, 104.69, 132.77, 143.60 and 208.01; *m/z* (rel. int.) 552 (9.0), 133 (20) (Found: *m/z* 552.4389. Calc. for $C_{30}H_{52}O_7Si$: *m/z* 552.3482).

(1R,3aS,4aR,5S,7aR,8S)-8-[(tert-*Butyldimethyl*)*siloxy*]-1-[3-(1,3-*dioxolan*-2-*yl*)-(1S)-1-(*methyl*)*propyl*]-5-[2-(*methoxyethoxy*)*methoxy*]-3a-*methyl*-2,4,4a,5,6,7,7a,8,9,9a-*decahydro*-1H-*cyclopent*[f]*azulen*-3-*one* (−)-**19**.—A flame-dried flask (50 cm^3) with a solid CO_2 condenser, ammonia tank inlet and pressure-equalizing bubbler was flushed with nitrogen and then

cooled to −78 °C by placing acetone and solid CO_2 in the condenser. Ammonia was passed through a drying tower filled with potassium hydroxide and calcium carbonate to ensure absolute dryness prior to condensation into the reaction vessel. Liquid ammonia (3 cm^3) was condensed into the flask which was also cooled to −78 °C with a solid CO_2–acetone bath. Lithium wire (*ca.* 5 mg, 0.7 mmol) was rinsed with pentane and then quickly placed into the ammonia and stirred at −78 °C for 10 min. A persistent deep blue colour was observed. A solution of enone (−)-**18** (26.5 mg, 0.048 mmol) in ether (700 mm^3) was syringed into the dissolving metal solution, the colour of which was retained. The solution was stirred for 30 min, at which point freshly distilled methyl iodide (100 mm^3, 1.6 mmol) was syringed into the reaction vessel. Immediately the blue colour disappeared to give a clear and colourless solution. This was allowed to warm to room temperature when the ammonia evaporated to leave a pale yellow oil. This was taken up into ether (20 cm^3) and the solution washed with 5% aqueous hydrochloric acid (5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to afford a clear oil. This, when subjected to preparatory thin layer chromatography on glass plates coated with silica gel (0.5 mm; eluted with 1:3 ethyl acetate–hexanes) provided the ketone (−)-**19** (15 mg, 55%); $[\alpha]^{25}$ −108 (*c* 0.1 in $CHCl_3$); R_F 0.65 (1:3 ethyl acetate–hexanes); $\nu_{max}(CDCl_3)/cm^{-1}$ 2957, 2929 and 1731; $\delta_H(CDCl_3$; 300 MHz) 0.02 (s, 3 H), 0.03 (s, 3 H), 0.85 (s, 9 H), 0.92 (d, *J* 7, 3 H), 1.02 (s, 3 H), 1.15–1.50 (m, 4 H), 1.55–1.80 (m, 10 H), 1.90–2.05 (m, 2 H), 2.12–2.13 (m, 3 H), 3.39 (s, 3 H), 3.56 (t, *J* 4.8, 2 H), 3.65–3.74 (m, 2 H), 3.84–3.88 (m, 2 H), 3.96–4.00 (m, 3 H), 4.10–4.12 (m, 1 H), 4.67 (d, *J* 6.8, 1 H), 4.71 (d, *J* 6.8, 1 H) and 4.85 (t, *J* 4.5, 1 H); $\delta_C(CDCl_3$; 75 MHz) −4.79, −4.68, 0.97, 13.30, 18.01, 19.58, 25.57, 25.77, 28.78, 29.11, 29.57, 30.27, 30.77, 32.13, 32.49, 37.79, 38.03, 41.50, 44.64, 44.91, 50.38, 63.87, 66.96, 68.64, 71.87, 78.97, 94.21, 104.45 and 222.90; *m/z* (rel. int.) 568 (1), 463 (31) and 331 (36) (Found: *m/z* 568.3798. Calc. for $C_{31}H_{56}O_7Si$: *m/z* 568.3795).

Acknowledgements

The authors thank the National Institutes of Health for their support of this research through Grant GM-30771 and Dr. A. Kutagawa of the Takasago Research Institute for generous supplies of (*S*)-citronellal.

References

1 (*a*) S. Nozoe, M. Morisaki, K. Tsuda, Y. Iitaka, N. Takahashi, S. Tamura, K. Ishibashi and M. Shirasaka, *J. Am. Chem. Soc.*, 1965, **87**, 4968; (*b*) T. Rios and F. Colunga, *Chem. Ind. (London)*, 1965, 1184; (*c*) S. Nozoe, K. Hirai and K. Tsuda, *Tetrahedron Lett.*, 1966, 2211; (*d*) A. Ital, S. Nozoe, K. Tsuda, S. Okuda, Y. Iitka and Y. Nakayama, *Tetrahedron Lett.*, 1967, 4111; (*e*) Y. Itake, I. Watanabe, I. T. Harrison and S. Harrison, *J. Am. Chem. Soc.*, 1968, **90**, 1092; (*f*) S. Nozoe, M. Morisaki, K. Fukushima and S. Okuda, *Tetrahedron Lett.*, 1968, 4457; (*g*) S. Nozoe and M. Morisaki, *J. Chem. Soc., Chem. Commun.*, 1969, 1319; (*h*) T. Rios and L. Quijano, *Tetrahedron Lett.*, 1969, 1317; (*i*) T. Rios and G. F. Gomez, *Tetrahedron Lett.*, 1969, 2929.

2 (*a*) K. Ishibashi, *J. Agr. Chem. Soc. Jpn.*, 1969, **36**, 649; (*b*) S. Nozoe, A. Itai, K. Tsuda and S. Okuda, *Tetrahedron Lett.*, 1967, 4113; (*c*) P. C. Leung, W. A. Taylor, J. H. Wang and C. L. Tipton, *J. Biol. Chem.*, 1984, **259**, 2742.

3 T. K. Das, A. D. Gupta, P. K. Ghosal and P. C. Dutta, *Indian J. Chem., Sect. B*, 1976, **14**, 238; (*b*) T. K. Das and P. C. Dutta, *Synth. Commun.*, 1976, **6**, 253; (*c*) T. K. Das, P. C. Dutta, G. Kartha and J. M. Bermassan, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1287; (*d*) R. K. Boeckman, Jr., J. P. Bershas, J. Clardy and B. Solheim, *J. Org. Chem.*, 1977, **42**, 3630; (*e*) W. G. Dauben and D. J. Hart, *J. Org. Chem.*, 1977, **42**, 922; (*f*) W. R. Baker, P. D. Senter and R. M. Coates, *J. Chem. Soc., Chem. Commun.*, 1980, 1011; (*g*) R. M. Coates, P. D. Senter and W. R. Baker, *J. Org. Chem.*, 1982, **47**, 3597; (*h*) L. A. Paquette, D. R. Andrews and J. P. Springer, *J. Org. Chem.*, 1983, **48**, 1147; (*i*) H. Takeshita, N. Kato and K. Nakanishi, *Chem. Lett.*, 1984, 1495; (*j*) R. M. Coates, J. W. Muskopf and P. A. Senter, *J. Org. Chem.*, 1985, **50**, 3541; (*k*) L. A. Paquette, J. A. Colapret and D. R. Andrews, *J. Org. Chem.*, 1985, **50**, 201; (*l*) G. Metha and N. Krishnamurthy, *J. Chem. Soc., Chem. Commun.*, 1986, 1319; (*m*) N. Kato, K. Nakanishi and H. Takeshita, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 1109; (*n*) J. H. Rigby and C. Senanayake, *J. Org. Chem.*, 1987, **52**, 4634; (*o*) M. Rowley and Y. Kishi, *Tetrahedron Lett.*, 1988, **29**, 4909; (*p*) W. G. Dauben and A. M. Warshawsky, *J. Org. Chem.*, 1990, **55**, 3075; (*q*) L. A. Paquette, S. Liang and P. Galatsis, *Synlett*, 1990, 663; (*r*) G. Jommi, F. Orsini, M. Resmini and M. Sisti, *Tetrahedron Lett.*, 1991, **32**, 6969; (*s*) S. M. Sieburth and J.-L. Chen, *J. Am. Chem. Soc.*, 1991, **113**, 8163; (*t*) B. B. Snider and K. Yang, *J. Org. Chem.*, 1992, **57**, 3615.

4 (*a*) N. Kato, H. Kataoka, S. Ohbushi, S. Tanaka and H. Takeshita, *J. Chem. Soc., Chem. Commun.*, 1988, 354; (*b*) N. Kato, H. Takeshita, H. Kataoka, S. Ohbuchi and S. Tanaka, *J. Chem. Soc., Perkin Trans. 1*, 1989, 165; (*c*) N. Kato, X. Wu, S. Tanaka and H. Takeshita, *Chem. Lett.*, 1989, 91.

5 M. Rowley, M. Tsukamoto and Y. Kishi, *J. Am. Chem. Soc.*, 1989, **111**, 2735.

6 R. K. Boeckman, Jr., A. Arvantis and M. E. Voss, *J. Am. Chem. Soc.*, 1989, **111**, 2737.

7 L. A. Paquette, T.-Z. Wang and N. H. Vo, *J. Am. Chem. Soc.*, 1993, **115**, 1676.

8 (*a*) R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868; (*b*) R. E. Ireland, P. Wipf and J. P. Armstrong, III, *J. Org. Chem.*, 1991, **57**, 650; (*c*) R. E. Ireland, P. Wipf and J.-N. Xiang, *J. Org. Chem.*, 1991, **56**, 3572 and references cited therein.

9 (*a*) J. H. Rigby, *Tetrahedron Lett.*, 1982, **23**, 1863; (*b*) J. H. Rigby and J. Z. Wilson, *J. Am. Chem. Soc.*, 1984, **106**, 8217; (*c*) J. H. Rigby and J. Z. Wilson, *J. Org. Chem.*, 1987, **52**, 34.

10 C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, 1961, **83**, 736.

11 Carbon nucleophile opening of bridging ethers is well-precedented in more strained ring systems: (*a*) M. Lautens, C. DiFelice and A. Huboux, *Tetrahedron Lett.*, 1989, **30**, 6817; (*b*) M. Lautens, A. S. Abd-El-Aziz and A. Lough, *J. Org. Chem.*, 1990, **55**, 5305.

12 J. H. Rigby and C. Senanayake, *J. Org. Chem.*, 1988, **53**, 440.

13 H. Gelrach, D. Kappes, R. K. Boeckmann and N. M. Graham, *Org. Synth.*, 1992, **71**, 48.

14 (*a*) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512; (*b*) B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal and J. M. Balkovec, *J. Org. Chem.*, 1986, **51**, 2370.

15 A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 1978, 4475.

16 F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.

17 K. C. Nicolaou, *Tetrahedron*, 1981, **37**, 4097.

18 For a recent review of this subject, see: P. A. Wade in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, vol. 4, Pergamon, Oxford, 1991, pp. 1124–1133.

19 (*a*) K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schole and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880; (*b*) R. Annunziata, M. Cinquini, F. Cozzi, C. Gennari and L. Raimondi, *J. Org. Chem.*, 1987, **52**, 4674.

20 (*a*) D. P. Curran, *J. Am. Chem. Soc.*, 1983, **105**, 5826; (*b*) A. P. Kozikowski and Y. Y. Chen, *Tetrahedron Lett.*, 1982, **23**, 2081.

21 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

Paper 4/03899A
Received 27*th June* 1994
Accepted 15*th August* 1994