# A new route to furanoeremophilane sesquiterpenoids. Synthesis of *Senecio* metabolites (±)-6-hydroxyeuryopsin, (±)-1,10-epoxy-6-hydroxyeuryopsin, (±)-toluccanolide A and (±)-toluccanolide C

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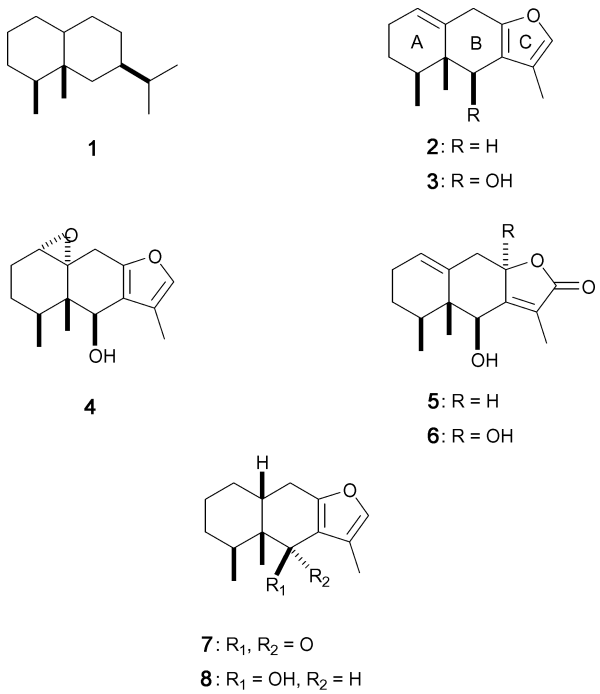
A new strategy for the synthesis of sesquiterpenoids of the furanoeremophilane family was developed in which the tricyclic nucleus was assembled in an A + C → A–C → A–B–C sequence. The A–C connection was made *via* coupling of a cyclohexenylmethyl bromide with a stannylfuran under "ligandless" Stille conditions, and the key cyclization which closed ring B was accomplished with complete stereocontrol by intramolecular formylation of a 2-silylfuran in the presence of trimethylsilyl triflate. This route was used to complete the first total syntheses of the furanoeremophilane 6-hydroxyeuryopsin and the eremophilenolides toluccanolide A and toluccanolide C, as well as a formal synthesis of 1,10-epoxy-6-hydroxyeuryopsin.

## Introduction

Plants of the *Senecio* family are a rich source of secondary metabolites with structures based on the eremophilane skeleton **1**.[1] Furanoeremophilanes and eremophilenolides constitute two major subsets of this group of sesquiterpenoids in which the isopropyl substituent of **1** is oxidized and a third ring, either a furan or a butenolide, is appended to the bicyclic framework. Representative examples of the furanoeremophilanes include euryopsin (**2**), isolated from *Senecio othonal*,[2] 6-hydroxyeuryopsin (**3**), isolated from the aerial part of *Senecio toluccanus*,[3] and 1,10-epoxy-6-hydroxyeuryopsin (**4**), isolated from the roots of *S. toluccanus*.[4] These and other *Senecio* species are also the source of eremophilenolides including toluccanolide A (**5**) and toluccanolide C (**6**).[5,6] Furanoeremophilanes are known to undergo facile oxidation to eremophilenolides, a transformation that has proven useful in the structure determination of these materials and which is believed to interconnect them biogenetically.[7]

Exploration of synthetic routes to furanoeremophilanes and eremophilenolides began with the pioneering studies of Piers[8] and have generally followed a pathway in which the five-membered heterocycle (ring C) is joined to a preformed decalin platform (rings A and B).[9–11] An alternative approach, exemplified in Bohlmann's[12] and Yamakawa's[13] syntheses of ligularone (**7**), has been annulation of ring A on a furanoquinonoid template representing rings B and C. The only exception to this general pattern is Jacobi's synthesis of petasalbine (**8**),[14] where rings B and C were created simultaneously from a monocyclic (ring A) precursor *via* intramolecular cycloaddition of an alkyne to an oxazole. An attractive but thus far untested route to sesquiterpenes of this family would be one in which the cyclohexene nucleus of ring A is first linked to a furan surrogate for ring C, leading to a substrate in which an intramolecular process would assemble the complete tricyclic framework of a furanoeremophilane. This A + C → A–C → A–B–C sequence is depicted in Scheme 1 and implies an A–C connection through coupling of a cyclohexenylmethyl halide **9** with a 2-metallo substituted furan **10**. Closure to the tricyclic skeleton of **3** is envisioned in this scenario *via* an intramolecular formylation of **11**. With Scheme 1 as the blueprint, construction of the ring A and ring C modules, **9** and **10**, therefore became our first objective.




**1**

**2**: R = H
**3**: R = OH

**4**

**5**: R = H
**6**: R = OH

**7**: $R_1$, $R_2$ = O
**8**: $R_1$ = OH, $R_2$ = H

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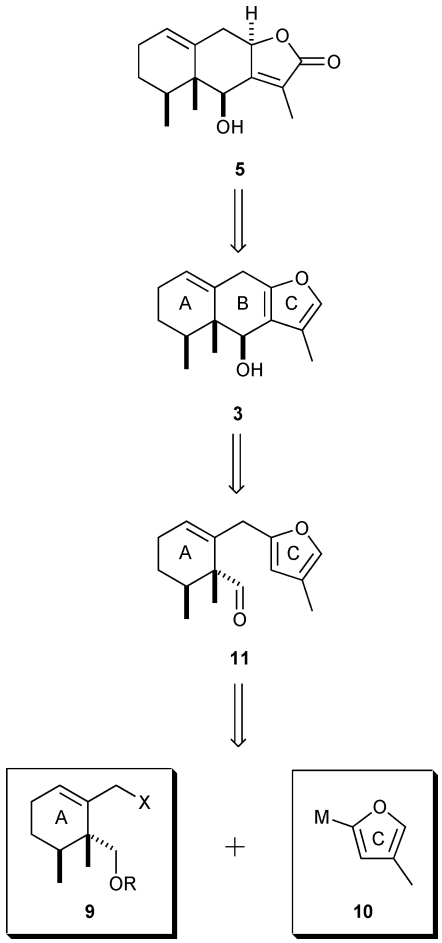
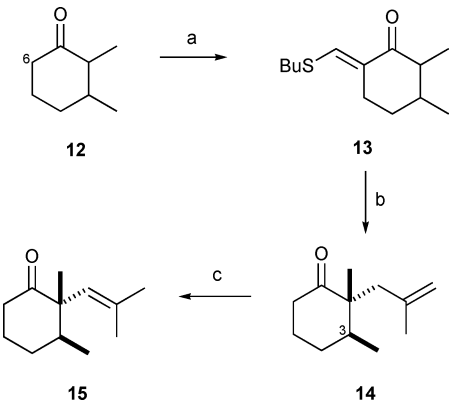


**Scheme 1** The A + C strategy for synthesis of furanoeremophilanes and eremophilenolides.

## Results and discussion

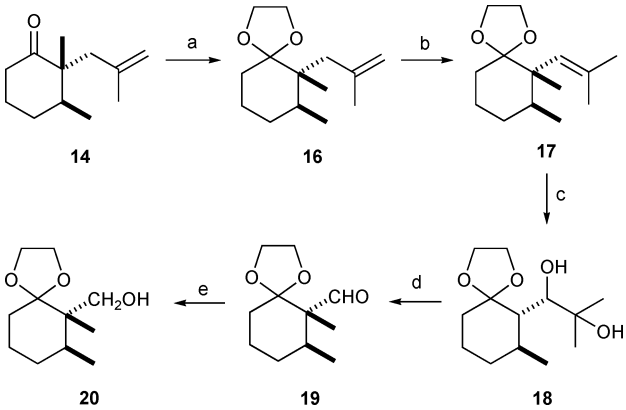
The synthesis of **9** commenced from 2,3-dimethylcyclohexanone **12**, obtained as a 4 : 1 mixture of *trans* : *cis* isomers from cyclohex-2-enone by conjugate addition of methylmagnesium bromide and subsequent *in situ* trapping of the magnesium enolate with methyl iodide,[15] or more directly by oxidation of commercially available 2,3-dimethylcyclohexanol with pyridinium chlorochromate. Following a procedure due to Piers,[8] the 6-position of **12** was blocked by reaction with ethyl formate in the presence of freshly prepared sodium methoxide and then treatment of the intermediate hydroxymethylene ketone with *n*-butanethiol (Scheme 2). The potassium enolate of thiomethylene ketone **13** was alkylated with methallyl bromide at low temperature; subsequent alkaline hydrolysis of the thiomethylene group yielded a mixture of **14** and its stereoisomer in which methallylation had occurred *cis* to the C3 methyl substituent. The 4 : 1 ratio of stereoisomers in favour of **14** contrasts with results reported by Halcomb[16] who obtained a 15 : 1 ratio of products in the allylation of **13**. The major stereoisomer **14** could not be separated from this mixture which was subjected directly to isomerization of the exo olefin through the agency of tristriphenylphosphinechlororhodium.[17] The resulting trisubstituted alkene **15** was isolated and purified in moderate yield on a small scale, but the isomerization of **14** to **15** proved to be capricious on a large scale and an alternative



**Scheme 2** Reagents and conditions: (a) (i) $HCO_2Et$, NaOMe, $Et_2O$, 0 °C to rt, 95%, (ii) *n*-BuSH, $C_6H_6$, Δ, 80%; (b) (i) KHMDS, THF, −78 °C to 0 °C, (ii) $CH_2{=}C(CH_3)CH_2Br$, −78 °C to rt, 87%, (iii) KOH (25% aq), $(HOCH_2CH_2)_2O$, Δ, 97%; (c) $RhCl(PPh_3)_3$, EtOH, Δ. 55%.

route to the functionalized cyclohexene **9** was therefore sought which avoided this troublesome step.

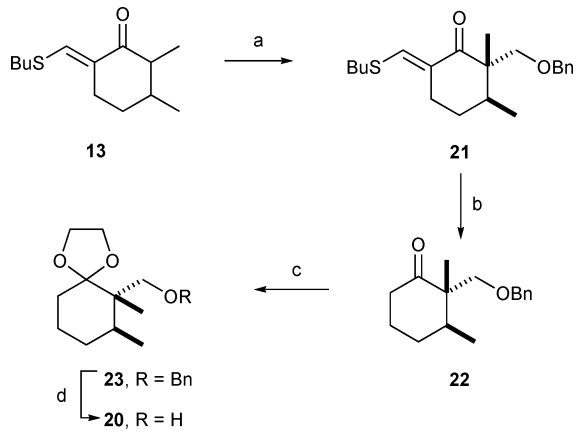
Protection of ketone **14** as its ethylene ketal **16** was the first operation in this new sequence (Scheme 3), and although this transketalization[18] proceeded in low yield, it was found that acid-catalyzed conversion of olefin **16** to its in-chain isomer **17** consistently gave a high yield of product. Alkene **17** was not purified but was transformed directly to vicinal diol **18** by osmylation using Tsuji's procedure.[19] Cleavage of **18** with periodate then led cleanly to aldehyde **19** which was reduced to primary alcohol **20**.



**Scheme 3** Reagents and conditions: (a) 2-ethyl-2-methyl-1,3-dioxolane, $(CH_2OH)_2$, *p*-TsOH, 76 h, 28%; (b) *p*-TsOH, $C_6H_6$, reflux, 24 h; (c) $K_2OsO_4$, $K_3Fe(CN)_6$, $K_2CO_3$, quinuclidine, $MeSO_2NH_2$, $H_2O$, *t*-BuOH, rt, 48 h, 80% (2 steps); (d) $NaIO_4$, THF, $H_2O$, rt, 12 h; (e) $NaBH_4$, NaOH, MeOH, $H_2O$, rt, 12 h, 95% (2 steps).

Although the pathway in Scheme 3 enabled us to prepare alcohol **20** in quantities sufficient to continue our route towards **9**, the need to isomerize and then degrade a methallyl side chain in this sequence was clearly a wasteful exercise. A more direct method for introducing the hydroxymethyl substituent of **20** was therefore sought, and for this purpose we returned to ketone **13**. Enolate alkylation with benzyl chloromethyl ether has been found to be a valuable tactic for introducing a hydroxymethyl substituent[20] but our initial results with this reagent using potassium hexamethyldisilazide as the base in a hexane–THF mixture were unpromising, the major product from **13** being *O*-alkylated material. A similar

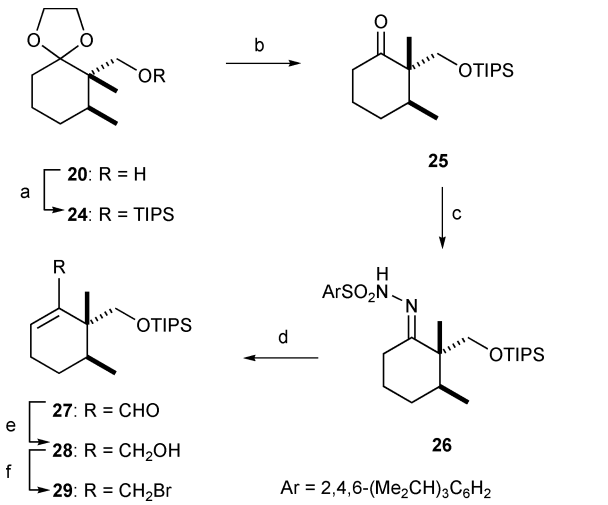
outcome prevailed when lithium hexamethyldisilazide in THF was used as a base, but when the solvent was changed to toluene a dramatic reversal took place and *C*-alkylation of **13** was the sole result. This afforded **21** in good yield (Scheme 4). A further consequence of the reaction of **13** with benzyl chloromethyl ether was that, in contrast to the alkylation of **13** with methallyl bromide, the desired product **21** was virtually the sole stereoisomer. This feature allowed clean chromatographic separation of **21** so that it could be carried forward in pure form.




**Scheme 4** Reagents and conditions: (a) (i) LiHMDS, hexanes–toluene, (ii) $BnOCH_2Cl$ (75%); (b) KOH, $H_2O$, $(HOCH_2CH_2)_2O$, reflux (73%); (c) $(TMSOCH_2)_2$, TMSOTf, $CH_2Cl_2$, −78 °C, 4 h, then rt, 14 h, 99%; (d) Li, $NH_3$, THF, −78 °C, 1 h, 96%.

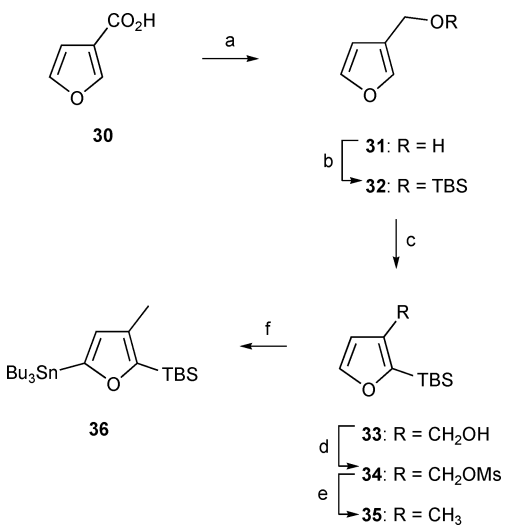
Alkaline hydrolysis of **21** in hot diethylene glycol led to ketone **22** which was protected as its ethylene ketal **23**. It was necessary to carry out the latter step before liberating the primary alcohol from its benzyl ether in order to avoid retroaldol fragmentation. Ketal **23** presented sufficient steric obstruction towards hydrogenolysis that no reaction occurred when this benzyl ether was exposed to a hydrogen atmosphere in the presence of a palladium catalyst, but the problem was circumvented very effectively by removing the benzyl group with lithium–ammonia.[21] At this juncture, the routes in Schemes 3 and 4 converged upon alcohol **20**, with the latter sequence being clearly preferred for moving this substance towards a suitable coupling partner for **10**.

In order to advance **20** towards **9**, it was first necessary to protect the primary alcohol with a group which would be inert to the strongly basic conditions needed for elaborating the alkene functionality of **9**, yet could be cleaved after coupling **9** with **10** in order to reach the precyclization substrate **11**. A triisopropylsilyl (TIPS) ether was selected for this purpose, and **20** was therefore converted to its ether **24** (Scheme 5). With the hydroxyl group blocked, it was now possible to cleave the ketal of **24** to ketone **25** without fear of retroaldol fragmentation. Introduction of an allylic halide function at the ketone site of **25** was envisioned by means of a Shapiro reaction[22] with hydrazone **26**, and the modification of this process due to Chamberlin and Bond[23] was found to be an efficient means for transforming the 2,4,6-triisopropylbenzenesulfonylhydrazone **26** to aldehyde **27** if four equivalents of *tert*-butyllithium were used as the base. Aldehyde **27** was reduced without purification to alcohol **28** which was then converted to bromide **29** *via* displacement of its mesylate with anhydrous lithium bromide.




**Scheme 5** Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 to −20 °C, 4 h, 100%; (b) PPTS, $Me_2CO$–$H_2O$ (9 : 1), 65 °C, 18 h, 93%; (c) $H_2NNHSO_2Ar$, THF, rt, 14 h, 78%; (d) (i) *t*-BuLi (4 eq.), hexanes–TMEDA (9 : 1), (ii) DMF; (e) DIBAL-H, $CH_2Cl_2$, 75%, (2 steps); (f) (i) $Ms_2O$, $Et_3N$, $CH_2Cl_2$, (ii) LiBr, THF, 92%.

The furan subunit required for coupling with **29** and represented as **10** appeared to be accessible through a series of straightforward transformations from 3-furoic acid (**30**), and to this end the carboxyl group of **30** was first reduced to alcohol **31** (Scheme 6). Our initial plan was to continue the reduction of **31** to 3-methylfuran, then introduce a tin substituent at C5 *via* halogen–metal exchange of 2-bromo-4-methylfuran. In practice, this plan confronted two obstacles, one being poor site selectivity in the functionalization of 3-methylfuran with bromine and the other being complications in coupling attempts with **29** arising from a furan partner that was inherently too reactive. These difficulties led us to consider placing a substituent, ideally a silyl group, at C2 of **31** which could direct further substitution to C5 of

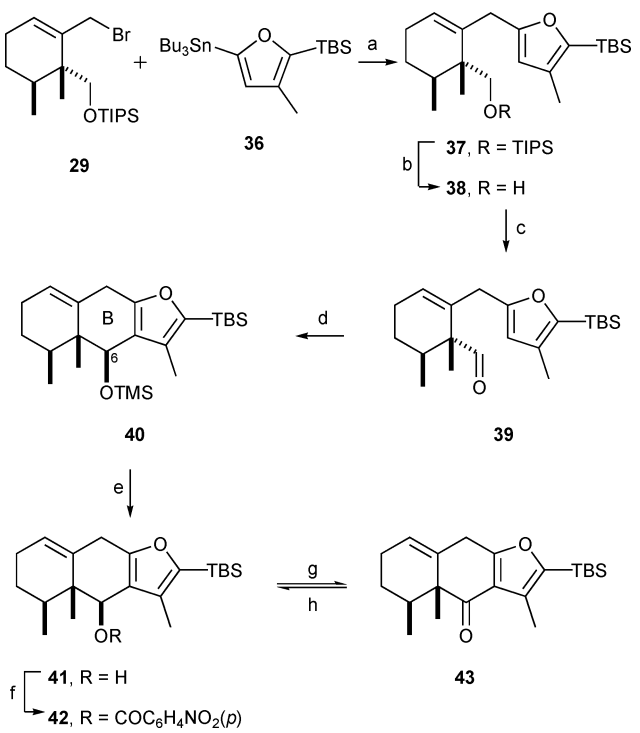



**Scheme 6** Reagents and conditions: (a) $BH_3.SMe_2$, THF, 0 °C to rt, 24 h, 80%; (b) TBSCl, imidazole, $CH_2Cl_2$, 0 °C, 10 min, then rt, 2 h, 100%; (c) *n*-BuLi, HMPA–hexane, −78 °C to rt, 6 h, then rt, 12 h, 79%; (d) $Ms_2O$, *i*-$Pr_2NEt$, PhMe, 0 °C (e) $LiBHEt_3$, THF, 0 °C, 1 h, 93%, (2 steps); (f) (i) *t*-BuLi, hexanes–TMEDA (9 : 1), −78 °C to rt, 6 h, (ii) $Bu_3SnCl$, 95%.

the furan, which would moderate its reactivity in a coupling process, and which could be removed after the tricycle framework had been established. The *tert*-butyldimethylsilyl (TBS) ether **32** was prepared for this purpose and, as was hoped, exposure of **32** to *n*-butyllithium promoted its rearrangement to **33**.[23] This *O*-to-*C* silyl migration,[24] an example of a 1,3-retro-Brook rearrangement[25] initiated in this case by deprotonation at C2 of **32**, required quite specific conditions for its success. For example, HMPA was essential for this process, and its replacement by other additives such as DMPU resulted in complete failure of the rearrangement. With alcohol **33** in hand, its conversion to a 3-methylfuran was completed *via* conversion to mesylate **34** and reduction with lithium triethylborohydride to **35**. The latter underwent clean lithiation at C5, after which transmetallation with tri-*n*-butylchlorostannane led to the trisubstituted furan **36**.

Coupling of furan **36** with bromide **29** was most conveniently effected with palladium(0) dibenzylideneacetone as the catalyst under "ligandless" conditions (Scheme 7).[26] For the coupling to give a consistent yield of product, it was important to rigorously degas the solvent before adding the catalyst. The alkylated furan **37** could be obtained in high yield if this were done, but difficulty in separating **37** from stannane residues caused us to advance this silyl ether to the more polar alcohol **38**. This was accomplished with tetra-*n*-butylammonium fluoride under controlled conditions that left the TBS substituent in place. Alcohol **38** was easily purified by chromatography and was oxidized to aldehyde **39** with tetra-*n*-propylammonium perruthenate (TPAP).[27]




**Scheme 7** Reagents and conditions: (a) $Pd_2(dba)_3$, THF, 36 h, rt; (b) TBAF, THF, 5 h, rt, 97%, (2 steps); (c) TPAP, NMO, 4 Å molecular sieves, $CH_2Cl_2$, rt, 1 h; (d) TMSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, 16 h, 93%, (2 steps); (e) TBAF, THF, rt, 53%; (f) *p*-$O_2NC_6H_4COCl$, $CH_2Cl_2$, pyr, DMAP, 80 °C, 12 h, 80%; (g) TPAP (cat), NMO, 4 Å sieves, 80%; (h) DIBAL-H, $CH_2Cl_2$, −78 °C → −20 °C, 70%.

In anticipation that the furan of **39** would undergo intramolecular formylation to produce the tricyclic framework of a furanoeremophilane, this aldehyde was treated with several Lewis acids under a wide variety of conditions. Initial experiments were discouraging, however. For example, exposure of **39** to boron trifluoride etherate or to diethylaluminum chloride resulted in rapid decomposition of the furan moiety with no evidence for formation of a cyclization product. After several unsuccessful efforts, it was found that trimethylsilyl triflate (TMSOTf) in the presence of 2,6-lutidine at low temperature accomplished the transformation of **39** to **40** in remarkably high yield. At −78 °C, two stereoisomeric TMS ethers were formed from **39** in the ratio 10 : 1, the major product being the 6β isomer **40** as shown by X-ray crystallographic analysis of a derivative (*vide infra*). The clean, nearly quantitative cyclization of **39** with TMSOTf, in contrast to the extensive decomposition of **39** seen with traditional Lewis acids, is noteworthy and is probably due to the high affinity of the silicon reagent for complexation with the aldehyde carbonyl together with its diminished propensity to cause polymerization of the furan moiety.

In order to prove the structure of cyclization product **40**, the TMS ether was cleaved and alcohol **41** was esterified with *p*-nitrobenzoyl chloride. X-Ray analysis of the crystalline *p*-nitrobenzoate **42** (Fig. 1) established that cyclization of **39** had yielded the 6β silyl ether **40**, a result that can be rationalized by the precyclization conformation of **39** shown in Fig. 2. Steric factors operating in this conformation suggest that attack by the furan at the silyl-complexed pseudoequatorial aldehyde should occur along a trajectory that closes ring B of **40** at the *re* face of the carbonyl group. Subsequent to the separation of **40** from its minor (6α) stereoisomer, it was found that the mixture of **41** and its C6 epimer could be oxidized to ketone **43** in high yield with Ley's reagent.[27] Reduction of **43** with DIBAL-H then led cleanly to **41** as the sole product.

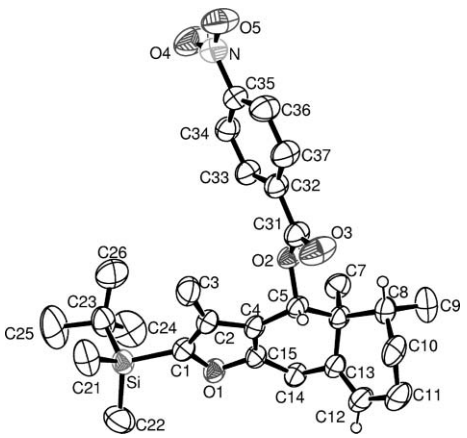



**Fig. 1** Crystal structure of **42**.

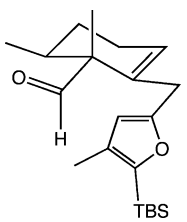
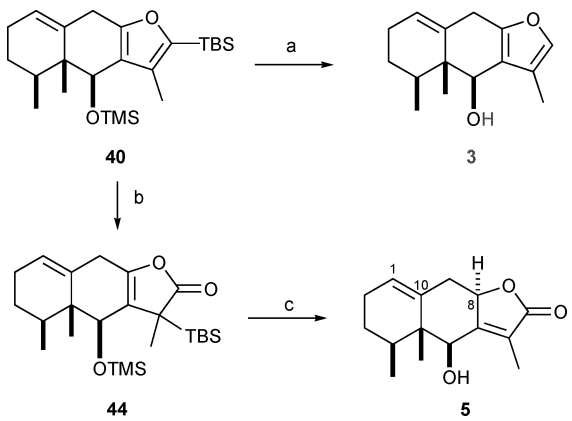



**Fig. 2** Conformation of **39** leading to **40**.

With the cyclization of **39** to the furanoeremophilane skeleton accomplished, the TBS substituent which had played a pivotal role in directing the cyclization and stabilizing the furan moiety against polymerization during closure to **40** needed to be removed. This required quite strenuous conditions, but after some experimentation it was found that a concentrated solution of TBAF in THF at reflux removed both the TBS and TMS group from **40** (Scheme 8). The product, (±)-6-hydroxyeuryopsin (**3**), had spectral properties that exactly matched data in the literature for the natural substance,[3] thus confirming the assignment made by Romo de Vivar to this sesquiterpene.




**Scheme 8** Reagents and conditions: (a) TBAF, THF, 60 °C, 24 h, 60%; (b) *m*-CPBA, $CH_2Cl_2$, rt, 5 min 99%; (c) TBAF, THF, rt, 30 min, 84%.

The furanoeremophilane derivative **40** also provided a platform from which related eremophilenolides, *e.g.* toluccanolides A (**5**) and C (**6**) could be accessed. Treatment of 40 with *m*-chloroperbenzoic acid yielded γ-lactone **44** as a 1 : 1 mixture of stereoisomers *via* a process assumed to involve epoxidation of the furan followed by epoxide opening which was accompanied by a 1,2-silyl shift.[28] Exposure of **44** to TBAF led to (±)-toluccanolide A (**5**) with spectral data in accord with those reported by Romo de Vivar[5] and Niemeyer[6] for the natural product. The structure of synthesized **5** was established by X-ray crystallographic analysis (Fig. 3) which confirmed that, after cleavage of the TBS substituent from **44**, protonation at C8 had occurred from the rear face. Kitagawa has shown that epoxidation of tolucannolide A (**5**) with *m*-chloroperbenoic acid results in a 10 : 1 mixture of α and β epoxides at C1–C10, and that reduction of the lactone of the major α epoxide with diisobutylaluminum hydride gives **4**.[7] Hence our route to (±)-**5** constitutes a formal synthesis of (±)-1,10-epoxy-6-hydroxyeuryopsin. The tricycle **40** also afforded entry to toluccanolide C (**6**) *via* singlet oxygenation of the furan (Scheme 9).

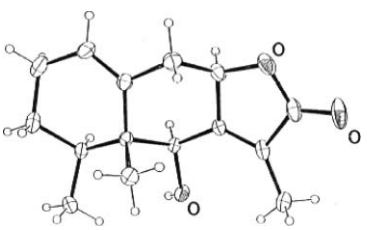
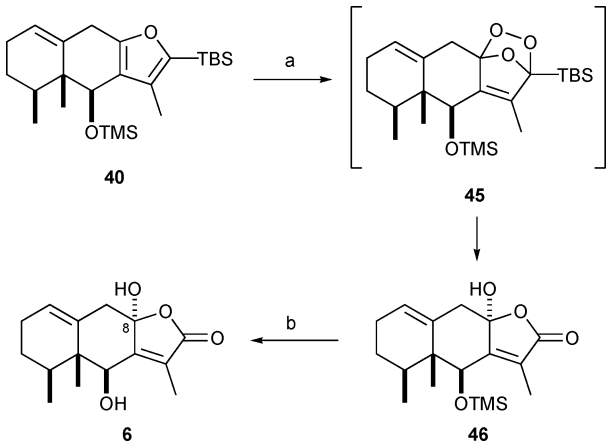


**Fig. 3** Crystal structure of tolucannolide A (**5**).




**Scheme 9** Reagents and conditions: (a) (i) $O_2$, Rose Bengal, *hv*, $CH_2Cl_2$, (ii) PPTS, THF–$H_2O$ (1 : 1), quant; (b) HCl, $H_2O$, THF, 97%.

The intermediate ozonide **45** from this cycloaddition collapsed under acid catalysis to the butenolide **46**,[29] and subsequent silyl ether cleavage with dilute acid then furnished crystalline (±)-**6**, identical by comparison of NMR data with natural toluccanolide C.[4,5] X-Ray crystallographic analysis was used to assign relative stereochemistry to **6** (Fig. 4), the angular hydroxyl group at C8 being shown to have the more stable α configuration.

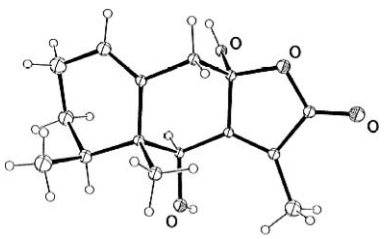


**Fig. 4** Crystal structure of tolucannolide C (**6**).

In summary, a new construction of the furanoeremophilane system has been developed in which mild intramolecular formylation of a TBS substituted furan mediated by trimethylsilyl triflate is a key step. Efficient coupling of furan and cyclohexene modules *via* a Stille reaction permits access to a precyclization substrate from which the central (B) ring of the furanoeremophilane structure is then elaborated. This approach illustrates a new strategy for entry into a class of broadly distributed sesquiterpenoids which includes the eremophilenolides.

## Experimental

### General

Reagents were obtained from commercial sources and were used without purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were distilled from sodium and benzophenone under an argon atmosphere. Acetonitrile (MeCN), dichloromethane ($CH_2Cl_2$), diisopropylamine and triethylamine ($Et_3N$) were distilled from calcium hydride under argon. Moisture and air sensitive reactions were carried out under an atmosphere of argon.

Analytical thin layer chromatography (TLC) was performed using precoated aluminum or glass TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light or by heating the plate after dipping in a 3% solution of vanillin in 0.2 M $H_2SO_4$ in EtOH or a 1% solution of $KMnO_4$ in 0.02% 1 N NaOH in $H_2O$. Flash chromatography was performed on E. Merck silica gel 60 (230–400 mesh ASTM).

Melting points were measured using a Büchi melting point apparatus, and are uncorrected. Infared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300 or a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) using the $\delta$ scale.

Chemical ionization (CI) high and low resolution mass spectra (HRMS and MS) were obtained using a Kratos MS-50 spectrometer with a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtain using a Varian MAT311 or a Siemens P4 spectrometer.

**2,3-Dimethylcyclohexanone (12).** Method A: To a suspension of copper(I) iodide (1.22 g, 6.4 mmol, 3.2 mol%) in THF (185 mL) at −78 °C under argon was added dimethyl sulfide (30 mL), followed by a solution of methylmagnesium bromide in $Et_2O$ (3 M, 74 mL, 0.22 mol). A solution of 2-cyclohexen-1-one (19.22 g, 0.20 mol) in THF (30 mL) was added dropwise to the solution at −50 °C over 80 min, and the mixture was stirred for 6 h at −50 °C. The resulting suspension was cooled to −78 °C and MeI (63 mL, 1.0 mol) was added rapidly followed by freshly distilled DMPU–THF (1 : 1, 120 mL). The suspension was warmed to 0 °C over 6 h and was stirred at room temperature for 18 h. The mixture was poured into 20% aqueous $NH_4OH$ (200 mL) and the suspension was filtered through Celite. The filtrate was extracted with $Et_2O$ (5 × 100 mL) and the combined extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (1500 g, $Et_2O$–hexanes, 1 : 4) afforded 18.65 g (74%) of **12** as a colourless oil. A sample of the pure *trans* isomer was isolated for spectroscopic purposes: IR (neat) 2958, 2930, 2871, 1709, 1455, 1373 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.98 (d, $J$ = 7 Hz, 3H), 1.01 (d, $J$ = 7 Hz, 3H), 1.35–1.48 (m, 2H), 1.54–1.66 (m, 1H), 1.77–1.82 (m, 1H), 1.94–2.04 (m, 2H), 2.24 (dddd, $J$ = 2, 3, 5, 14 Hz, 1H), 2.33 (dddd, $J$ = 1, 1, 6, 13 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 12.1, 21.1, 26.5, 34.6, 41.5, 41.9, 52.2, 213.6; MS (CI) $m/z$ 126 $(M)^+$, 111, 95, 81; HRMS (CI) $m/z$ 126.1043 (calcd for $C_8H_{14}O$ 126.1044).

Method B: Pyridinium chlorochromate (24.7 g, 115 mmol) was added to a solution of 2,3-dimethylcyclohexan-1-ol (12.3 g, 95.8 mmol) in $CH_2Cl_2$ (160 mL) and the mixture was stirred at room temperature for 16 h. The mixture was diluted with $Et_2O$ (450 mL) and filtered through a pad of Celite. The filtrate was concentrated and the residue was distilled to yield 11.1 g (92%) of **12** (mixture of *cis* and *trans* isomers) as a colourless liquid: bp 185–187 °C.

**6-Hydroxymethylene-2,3-dimethylcyclohexanone.** To an ice-cold suspension of freshly-prepared NaOMe (5.40 g, 100.0 mmol) in $Et_2O$ (80 mL) under argon was added **12** (5.05 g, 40.0 mmol) and the mixture was stirred for 10 min. Ethyl formate (5.50 mL, 68.0 mmol) was added, and the mixture was allowed to warm to room temperature and was stirred for 12 h. The mixture was diluted with $H_2O$ (50 mL), the phases were separated and the ethereal layer was extracted with 10% aqueous NaOH (2 × 20 mL). The combined aqueous layer and alkaline extract was cooled, acidified with 6 M HCl, and extracted with $Et_2O$ (5 × 20 mL). The combined extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting oil (5.92 g, 96%) was used for the next step without further purification. A small sample was purified for spectroscopic analysis: IR (neat) 2960, 2930, 2855, 1639, 1590, 1455, 1365, 1329, 1229, 1179, 1150 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (major isomer) $\delta$ 1.00 (d, $J$ = 7 Hz, 3H), 1.20 (d, $J$ = 7 Hz, 3H), 1.23–1.35 (m, 1H), 1.39–1.53 (m, 1H), 1.74–1.80 (m, 1H), 2.01 (q, $J$ = 7 Hz, 1H), 2.24–2.39 (m, 2H), 8.62 (d, $J$ = 3 Hz, 1H), 14.59 (d, $J$ = 3 Hz, 1H); (minor isomer) $\delta$ 0.91 (d, $J$ = 7 Hz, 3H), 1.08 (d, $J$ = 7 Hz, 3H), 1.46–1.53 (m, 1H), 1.55–1.63 (m, 1H), 1.82–1.95 (m, 1H), 2.31–2.47 (m, 3H), 8.66 (d, $J$ = 3 Hz, 1H), 14.44 (d, $J$ = 3 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (major isomer) $\delta$ 16.1, 20.5, 22.7, 30.2, 35.5, 43.5, 108.3, 187.8, 188.1; (minor isomer) $\delta$ 12.8, 17.0, 22.4, 26.8, 31.3, 40.3, 107.6, 188.4, 188.5.

**6-(*n*-Butylthio)methylene-2,3-dimethylcyclohexanone (13).** A solution of 6-hydroxymethylene-2,3-dimethylcyclohexanone prepared above (5.92 g, 38.4 mmol), *n*-butyl mercaptan (5.22 mL, 48.8 mmol) and *p*-TsOH (20 mg) in anhydrous benzene (90 mL) was refluxed under an argon atmosphere for 3 h using a Dean–Stark separator. The cooled solution was diluted with $Et_2O$ (100 mL), washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (800 g, $Et_2O$–hexanes, 1 : 200) gave 7.58 g (87%) of **13** as a yellow oil: IR (neat) 2957, 2929, 2872, 1544, 1456, 1434 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (major isomer) $\delta$ 0.88 (d, $J$ = 7 Hz, 3H), 0.90 (t, $J$ = 7 Hz, 3H), 1.02 (t, $J$ = 7 Hz, 3H), 1.14 (d, $J$ = 7 Hz, 2H), 1.39 (q, $J$ = 7 Hz, 3H), 1.54–1.71 (m, 3H), 1.80–1.89 (m, 1H), 2.21–2.30 (m, 1H), 2.35–2.43 (m, 1H), 2.45–2.53 (m, 1H), 2.80 (t, $J$ = 7 Hz, 2H), 7.45 (bs, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (major isomer) $\delta$ 13.5, 14.3, 20.7, 21.5, 26.5, 30.2, 32.6, 34.1, 36.1, 49.9, 130.1, 141.6, 198.6; (minor isomer) $\delta$ 12.3, 15.2, 24.9, 27.5, 33.2, 47.2, 129.9, 141.3, 199.4; MS (FAB) $m/z$ 227 $(M + H)^+$, 211, 197, 169; HRMS (CI) $m/z$ 227.1465 (calcd for $C_{13}H_{23}OS$ 227.1469).

**6-(*n*-Butylthio)methylene-2,3-dimethyl-2-(2-methylallyl)cyclohexanone.** To a solution of **13** (6.79 g, 30.0 mmol) in THF (54 mL) at −78 °C under argon was added a solution of KHMDS in toluene (0.5 M, 66 mL, 33.0 mmol) and the mixture was stirred for 1 h at 0 °C. The red solution was cooled to −78 °C and 3-bromo-2-methylpropene (7 mL, 70 mmol) was added. The mixture was allowed to warm slowly to room temperature and was stirred for 12 h, then was diluted with saturated aqueous $NH_4Cl$ and extracted with $Et_2O$ (3 × 100 mL). The combined extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (800 g, $Et_2O$–hexanes, 1 : 4) afforded 7.40 g (88%) of the title compound as a colourless oil: IR (neat) 3071, 2960, 2930, 2874, 1660, 1541, 1451, 1296, 1151, 890, 810 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (major diastereomer) $\delta$ 0.90 (d, $J$ = 7 Hz, 3H), 0.90 (t, $J$ = 7 Hz, 3H), 0.95 (s, 3H), 1.40 (sextet, $J$ = 7 Hz, 2H), 1.49

(s, 3H), 1.50–1.68 (m, 4H), 1.90–1.98 (m, 1H), 2.09 (d, $J = 14$ Hz, 1H), 2.12–2.31 (m, 1 H), 2.44–2.51 (m, 1H), 2.79–2.87 (m, 3H), 4.61 (m, 1H), 4.72 (m, 1H), 7.54 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) (major diastereomer) $\delta$ 13.9, 16.4, 21.0, 22.0, 24.3, 26.7, 27.1, 33.0, 34.2, 34.7, 45.5, 49.7, 114.7, 130.2, 143.5, 143.6, 201.3; MS (FAB) $m/z$ 281 $(M + H)^+$, 265, 223, 211, 191, 161; HRMS (FAB) $m/z$ 281.1937 (calcd for $C_{17}H_{29}OS$ 281.1939).

**2,3-Dimethyl-2-(2-methylallyl)cyclohexanone (14).** To a solution of 6-(*n*-butylthio)methylene-2,3-dimethyl-2-(2-methylallyl)-cyclohexanone (9.81 g, 35.0 mmol) in diethylene glycol (60 mL) under argon was added a solution of 25% aqueous KOH (56 mL) and the solution was heated at reflux for 24 h. The cooled solution was diluted with $Et_2O$ (100 mL) and $H_2O$ (100 mL), the phases were separated and the aqueous phase was extracted with $Et_2O$ (2 × 100 mL). The combined extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (800 g, $Et_2O$–hexanes, 1 : 9) gave 5.68 g (90%) of **14** (4 : 1 mixture of diastereomers) as a colourless oil: IR (neat) 3073, 2939, 2876, 1704, 1458, 1380, 890 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) (major diastereomer) $\delta$ 0.89 (d, $J = 7$ Hz, 3H), 0.97 (s, 3H), 1.45–1.53 (m, 1H), 1.59 (s, 3H), 1.71–1.78 (m, 1H), 1.84–1.96 (m, 3H), 2.29–2.36 (m, 2H), 2.45–2.52 (m, 1H), 2.63 (d, $J = 14$ Hz, 1H), 4.63 (m, 1H), 4.77 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) (major diastereomer) $\delta$ 16.2, 20.1, 23.9, 24.6, 29.2, 38.7, 38.8, 44.7, 52.4, 114.9, 143.3, 216.1; (minor diastereomer) $\delta$ 16.1, 20.6, 24.2, 27.0, 29.9, 39.4, 40.28, 45.4, 52.9, 114.8, 142.5, 216.5; MS (CI) $m/z$ 181 $(M + H)^+$, 165, 147, 137, 125, 109; HRMS (CI) $m/z$ 180.1513 (calcd for $C_{12}H_{20}O$ 180.1514).

**2,3-Dimethyl-2-(2-methylprop-1-enyl)cyclohexanone (15).** To a solution of **14** (2.16 g, 12.0 mmol) in 10% aqueous EtOH (80 mL) under argon was added $RhCl(PPh_3)_3$ (1.12 g, 1.21 mmol, 10 mol% *vs* substrate) and the red solution was heated at reflux for 72 h. The solvent was removed by distillation and the residue was diluted with $Et_2O$ (100 mL). The ethereal solution was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (250 g, $Et_2O$–hexanes, 1 : 20) gave 1.18 g (55%) of **15** as a colourless oil: IR (neat) 2965, 2929, 2874, 1704, 1451, 1384, 1371, 1308 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.78 (d, $J = 7$ Hz, 3H), 1.03 (s, 3H), 1.36 (dddd, $J = 2$, 4, 4, 4 Hz, 1H), 1.38 (d, $J = 1$ Hz, 3H), 1.67 (d, $J = 1$ Hz, 3H), 1.78–1.87 (m, 1H), 2.00–2.09 (m, 1H), 2.09–2.16 (m, 1H), 2.59–2.67 (m, 1H), 5.35 (t, $J = 1$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 14.6, 18.7, 21.0, 24.1, 27.3, 29.0, 39.5, 45.2, 54.8, 132.6, 134.0, 216.6; MS (CI) $m/z$ 180 $(M)^+$, 165, 137, 109, 95; HRMS (CI) $m/z$ 180.1513 (calcd for $C_{12}H_{20}O$ 180.1514).

**6,7-Dimethyl-6-(2-methylallyl)-1,4-dioxaspiro[4.5]decane (16).** To a solution of **14** (18.02 g, 0.10 mol) in 2-ethyl-2-methyl-1, 3-dioxolane (580.0 g, 5.0 mol) at room temperature under argon was added ethylene glycol (62.0 g, 1.0 mmol) and *p*-TsOH (19.0 g, 0.1 mol) and the mixture was stirred for 76 h. The mixture was diluted with $Et_2O$ (300 mL), washed with saturated $NaHCO_3$, and concentrated under reduced pressure. Chromatography of the residue on silica (600 g, $Et_2O$–hexanes, 1 : 20) afforded 6.40 g (28%) of **16** as a colourless oil: IR (neat) 3070, 2952, 2882, 1638, 1463, 1442, 1382, 1212, 1182 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.91 (d, $J = 7$ Hz, 3H), 1.01 (s, 3H), 1.23–1.31 (m, 1H), 1.46–1.61 (m, 5H), 1.78–1.86 (m, 1H), 1.82 (s, 3H), 2.20 (d, $J = 14$ Hz, 1H), 2.28 (d, $J = 14$ Hz, 1H), 3.82–3.95 (m, 4H), 4.63 (m, 1H), 4.73 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.4, 16.6, 22.1, 25.2, 30.2, 30.4, 38.4, 44.4, 45.6, 64.1, 64.4, 113.3, 113.7, 146.3; MS (CI) $m/z$ 224 $(M)^+$, 209, 181, 163, 153, 139, 121; HRMS (CI) $m/z$ 224.1771 (calcd for $C_{14}H_{24}O$ 224.1776).

**6,7-Dimethyl-6-(2-methyl)propenyl-1,4-dioxaspiro[4.5]decane (17).** To a solution of **16** (0.531 g, 2.37 mmol) in anhydrous benzene (100 mL) at room temperature under argon was added *p*-TsOH.$H_2O$ (0.27 g) and the solution was heated at 60 °C for 24 h. The cooled solution was diluted with $Et_2O$ (100 mL), washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford 0.305 g (59%) **17** as a colourless oil: IR (neat) 3070, 2953, 2880, 1639, 1543, 1460, 1373, 1189, 1059 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.77 (d, $J = 7$ Hz, 3H), 1.14 (s, 3H), 1.21–1.27 (m, 1H), 1.35–1.49 (m, 2H), 1.51–1.59 (m, 3H), 1.70 (d, $J =$ 1 Hz, 3H), 1.76 (d, $J = 1$ Hz, 3H), 1.82–1.92 (m, 1H), 3.78–3.86 (m, 4H), 4.99 (t, $J = 1$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 15.8, 16.8, 19.7, 23.0, 29.0, 29.5, 32.0, 40.0, 48.2, 65.4, 65.8, 114.8, 131.9, 132.9; MS (CI) $m/z$ 224 $(M^+)$, 209, 181, 163, 153, 139, 121; HRMS (CI) $m/z$ 224.1771 (calcd for $C_{14}H_{24}O$ 224.1776). This material was used for the next step without further purification.

**1-(6,7-Dimethyl-1,4-dioxaspiro[4.5]dec-6-yl)-2-methylpropan-1,2-diol (18).** To a mixture of $K_2OsO_4$ (8 mg, 0.02 mmol), $K_3Fe(CN)_6$ (0.494 g, 1.50 mmol), $K_2CO_3$ (0.208 g, 1.50 mmol), quinuclidine (0.168 g, 1.50 mmol) and methanesulfonamide (0.142 g, 1.50 mmol) in $H_2O$ (2.5 mL) at room temperature under argon was added a solution of **17** prepared above (0.112 g, 0.50 mmol) in *t*-BuOH (2.5 mL). The mixture was stirred for 48 h, then was treated with $Na_2SO_3$ (0.756 g, 6.0 mmol) and was stirred for 1 h. The mixture was diluted with $Et_2O$ (10 mL) and $H_2O$ (10 mL), the phases were separated, and the aqueous phase was extracted with $Et_2O$ (2 × 10 mL). The combined extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (30 g, $Et_2O$–hexanes, 1 : 1) yielded 0.104 g (80%) of **18** as a colourless oil: IR (neat) 3485, 2932, 1466, 1177, 1097, 1039, 921 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.88 (d, $J = 7$ Hz, 3H), 1.03 (s, 3H), 1.26 (s, 3H), 1.31–1.49 (m, 4H), 1.33 (s, 3H), 1.50–1.56 (m, 1H), 1.69–1.73 (m, 1H), 2.47–2.56 (m, 1H), 3.36 (d, $J = 11$ Hz, 1H), 3.51–3.54 (m, 2H), 3.91–3.95 (m, 1H), 3.97–4.07 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.0, 22.3, 28.6, 29.6, 29.8, 30.3, 36.2, 48.7, 62.7, 62.9, 74.9, 82.6, 116.0; MS (CI) $m/z$ 257 $(M + H)^+$, 240, 199, 170, 155, 138, 109; HRMS (CI) $m/z$ 257.1751 (calcd for $C_{14}H_{25}O_4$ 257.1752).

**6,7-Dimethyl-1,4-dioxaspiro[4.5]decane-6-carboxaldehyde (19).** To a solution of **18** (1.29 g, 5.0 mmol) in THF–$H_2O$ (1 : 1, 50 mL) under argon was added solid $NaIO_4$ (10.69 g, 50.0 mmol) and the solution was stirred for 12 h at room temperature. The mixture was diluted with $Et_2O$ (100 mL) and $H_2O$ (100 mL), the phases were separated and the aqueous phase was extracted with $Et_2O$ (3 × 20 mL). The combined extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 1.00 g (100%) of virtually pure **19** as a colourless oil: IR (neat) 2956, 2933, 2883, 1725, 1181, 1104, 1064 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.73 (d, $J = 7$ Hz, 3H), 1.05 (s, 3H), 1.17–1.25 (m, 1H), 1.52–1.60 (m, 1H), 1.60–1.68 (m, 1H), 2.35–2.44 (m, 1H), 3.89–3.97 (m, 4H),

9.70 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 9.7, 14.5, 16.7, 22.6, 28.8, 30.7, 33.1, 56.8, 64.9, 65.1, 113.3, 207.6; MS (CI) *m/z* 199 $(M + H)^+$, 185, 169, 141, 127, 113, 99; HRMS (CI) *m/z* 199.1337 (calcd for $C1_{11}H_{19}O_3$ 199.1334).

**(6,7-Dimethyl-1,4-dioxaspiro[4.5]dec-6-yl)methanol (20).**

*From **19***. To a solution of **19** (0.49 g, 2.5 mmol) in MeOH (25 mL) under argon was added a solution of $NaBH_4$ (0.07 g, 1.85 mmol) in 2 M NaOH (5 mL) and $H_2O$ (45 mL) and the mixture was stirred at room temperature for 12 h. The mixture was diluted with $Et_2O$ (100 mL), washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (180 g, $Et_2O$–hexanes, 2 : 3) afforded 0.40 g (95% from **18**) of **20** as a colourless oil: IR (neat) 3537, 2931, 2881, 1461, 1412, 1185, 1122, 1051 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.79 (s, 3H), 0.87 (d, $J = 7$ Hz, 3H), 1.21–1.33 (m, 1H), 1.42–1.61 (m, 5H), 2.08–2.15 (m, 1H), 3.17 (d, $J = 7$ Hz, 1H), 3.30 (dd, $J = 7$, 11 Hz, 1H), 3.76 (d, $J = 11$ Hz, 1H), 3.91–4.07 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 13.3, 15.8, 23.0, 29.5, 30.3, 32.7, 45.1, 64.3, 64.8, 65.8, 115.4; MS (CI) *m/z* 200, 183, 169, 157, 141, 127, 113; HRMS (CI) *m/z* 200.1412 (calcd for $C_{11}H_{20}O_3$ 200.1412).

*From **23***. Lithium metal (0.702 g, 100 mmol) was added to liquid $NH_3$ (300 mL) at −78 °C and to the deep blue solution thus formed was added **23** (2.95 g, 10 mmol) in THF (60 mL). The solution was stirred for 1 h, after which isoprene (5 mL) and $H_2O$ (100 mL) were added. The $NH_3$ was allowed to evaporate and the resulting mixture was extracted with $Et_2O$ (3 × 50 mL). The combined extract was dried ($MgSO_4$) and concentrated, and the residue was purified by flash column chromatography (silica, 20% EtOAc in hexanes) to give 1.96 g (96%) of **20**, identical with material prepared from **19**.

**2-Benzyloxymethyl-6-(*n*-butylthio)methylene-2,3-dimethylcyclohexanone (21).** To a solution of **13** (1.47 g, 6.47 mmol) in toluene (14 mL) at −78 °C was added a solution of LiHMDS in hexanes (1.0 M, 8.5 mL, 8.50 mmol) and the mixture was stirred at 0 °C for 1 h. The solution was cooled to −78 °C, benzyl chloromethyl ether (2.5 mL, 18.0 mmol) was added, and the solution was allowed to warm to room temperature over 14 h. Saturated aqueous $NH_4Cl$ (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with $Et_2O$ (2 × 30 mL) and the combined organic extract was dried ($MgSO_4$) and concentrated. The residue was purified by repeated gradient flash column chromatography (silica, 50 to 75% toluene in hexanes) to yield 1.68 g (75%) of **20** as a pale yellow oil: IR (neat) 2958, 2929, 2972, 1662, 1542, 1496, 1454, 1162, 1100, 814, 736, 698 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.90 (s, 3H), 0.93 (d, $J = 7$ Hz, 3H), 0.97 (t, $J = 7$ Hz, 3H), 1.42–1.51 (m, 2H), 1.60–1.76 (m, 5H), 2.33–2.55 (m, 2H), 2.88 (t, $J = 7$ Hz, 2H), 3.31 (d, $J = 9$ Hz, 1H), 3.91 (d, $J = 9$ Hz, 1H), 4.43 (d, $J = 12$ Hz, 1H), 4.59 (d, $J = 12$ Hz, 1H), 7.20–7.38 (m, 5H), 7.63–7.64 (br, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.8, 16.0, 16.0, 21.9, 26.2, 26.8. 32.3, 32.9, 34.5, 51.3, 73.5, 73.5, 125.5, 127.5, 127.7, 128.4, 138.9, 143.4, 200.1; MS (CI) *m/z* 347 $(M + H)^+$, 255; HRMS (CI) *m/z* 347.2052 (calcd for for $C_{21}H_{31}O_2S$ 347.2045).

**2-Benzyloxymethyl-2,3-dimethylcyclohexanone (22).** A solution of **21** (4.93 g, 14.2 mmol) in 10% aqueous KOH (24.2 mL) and diethylene glycol (25.6 mL) was heated at reflux for 24 h. The solution was cooled to room temperature and saturated aqueous NaCl (25 mL) was added. The mixture was extracted with $Et_2O$ (3 × 50 mL) and the combined extract was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, 75% toluene in hexanes followed by 5% $Et_2O$ in hexanes) to yield 2.55 g (73%) of **22** as a pale yellow oil: IR (neat) 3088, 3063, 3030, 2931, 2865, 1709, 1454, 1099, 737, 698 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.90 (d, $J = 7$ Hz, 3H), 0.95 (s, 3H), 1.44–1.61 (m, 1H), 1.69–1.80 (m, 2H), 1.87–1.96 (m, 1H), 2.23–2.32 (m, 1H), 2.33–2.45 (m, 2H), 3.37 (d, $J = 9$ Hz, 1H), 3.71 (d, $J = 9$ Hz, 1H), 4.47 (d, $J = 12$ Hz, 1H), 4.60 (d, $J = 12$ Hz, 1H), 7.26–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 214.3, 138.9, 128.5, 127.7, 127.6, 73.5, 72.6, 53.3, 38.7, 35.6, 29.1, 24.1, 15.8, 15.6; HRMS (ES) *m/z* 247.1699 (calcd for $C_{16}H_{23}O_2$ 247.1698).

**6-Benzyloxymethyl-6,7-dimethyl-1,4-dioxaspiro[4.5]decane (23).** To a solution of **22** (0.502 g, 2.00 mmol) in $CH_2Cl_2$ (20 mL) at −78 °C was added bis(trimethylsilyl)ethylene glycol (2.5 mL, 10 mmol) and trimethylsilyl trifluoromethanesulfonate (74 μl, 0.41 mmol). The solution was stirred at −78 °C for 4 h and allowed to warm to room temperature over 14 h. Pyridine (5 drops) was added followed by $H_2O$ (15 mL), and the mixture was extracted with $Et_2O$ (3 × 25 mL). The combined extract was dried ($MgSO_4$) and concentrated, and the residue was purified by flash column chromatography (silica, 2.5% $Et_2O$ in hexanes) to give 0.590 g (99%) of **23** as a colourless oil: IR (neat) 3029, 2932, 2876, 1497, 1454, 1361, 1378, 1336, 1285, 1191, 1101, 1067, 735, 697 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.95 (s, 3H), 0.93 (d, $J = 7$ Hz, 3H), 1.25–1.34 (m, 1H), 1.42–1.47 (br, 1H), 1.55–1.67 (m, 4H), 2.02–2.11 (m, 1H), 3.32 (d, $J = 10$ Hz, 1H), 3.51 (d, $J = 10$ Hz, 1H), 3.84–3.96 (m, 4H), 4.50 (d, $J = 12$ Hz, 1H), 4.53 (d, $J = 12$ Hz, 1H), 7.29–7.39 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.0, 16.5, 22.5, 29.8, 31.0, 35.5, 45.9, 64.7, 64.7, 73.6, 73.7, 113.2, 127.4, 127.7, 128.3, 139.2; HRMS: (ES) *m/z* 291.1937 (calcd for $C_{18}H_{27}O_3$ 291.1960).

**(6,7-Dimethyl-1,4-dioxaspiro[4.5]dec-6-ylmethoxy)triisopropylsilane (24).** To a solution of **20** (1.96 g, 9.80 mmol) in $CH_2Cl_2$ (20 mL) at −78 °C under argon was added 2,6-lutidine (5.7 mL, 44.5 mmol) and triisopropylsilyl triflate (2.99 mL, 97%, 10.7 mmol) and the mixture was warmed to room temperature over 4 h. The solution was diluted with $Et_2O$ (100 mL), washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica ($Et_2O$–hexanes, 3 : 97) gave 3.49 g (100%) of **24** as a colourless oil: IR (neat) 2942, 2866, 1463, 1381, 1189, 1090, 1056 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.90–1.00 (m, 6H), 1.00–1.12 (m, 18H), 1.19–1.31 (m, 1H), 1.38–1.61 (m, 8H), 1.85–1.19 (m, 1H), 3.75 (s, 2H), 3.80–3.98 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 12.3, 12.4, 17.2, 18.2, 22.5, 30.5, 31.0, 37.5, 46.9, 64.8, 67.6, 113.6; MS (FAB) *m/z* 357, 313, 295, 283, 269, 241, 227, 199; HRMS (FAB) *m/z* 357.2824 (calcd for $C_{20}H_{41}O_3Si$ 357.2825).

**2,3-Dimethyl-2-(triisopropylsilyloxymethyl)cyclohexanone (25).** To a solution of **24** (1.04 g, 2.91 mmol) in acetone–$H_2O$ (9 : 1, 36 mL) at 0 °C under argon was added pyridinium *p*-toluenesulfonate (0.076 g, 0.30 mmol) and the solution was heated at 65 °C for 18 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with $Et_2O$ (3 × 30 mL) and

the combined extract was washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography of the residue (silica, 1% $Et_2O$ in hexanes) yielded 0.85 g (93%) of **25** as a colourless oil: IR (neat) 2941, 2866, 1712, 1463, 1104, 1068 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.88 (s, 3H), 0.90 (d, $J = 7$ Hz, 3H), 0.97–1.10 (m, 21H), 1.43–1.61 (m, 1H), 1.67–1.91 (m, 4H), 2.22–2.42 (m, 4H), 3.60 (d, $J = 7$ Hz, 1H), 3.98 (d, $J = 7$ Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 12.4, 15.8, 16.0, 18.0, 18.4, 23.8, 29.2, 35.0, 39.1, 54.6, 66.7, 214.7; MS (CI) $m/z$ 313, 295, 269, 239, 227, 199; HRMS (CI) $m/z$ 313.2562 (calcd for $C_{18}H_{37}O_2Si$ 313.2562).

**Hydrazone 26.** To a solution of **25** (0.51 g, 1.60 mmol) in THF (11 mL) under argon was added 2,4,6-triisopropylbenzenesulfonylhydrazine (0.58 g, 2.0 mmol) and the solution was stirred at room temperature for 12 h. Silica was added and the mixture was concentrated under reduced pressure while keeping the bath temperature below 30 °C. Gradient chromatography of the material dry-loaded on silica ($Et_2O$–hexanes, 1 : 19, then EtOAc–hexanes, 3 : 97) afforded 0.75 g (78%) of **26** as a colourless foam: IR (neat) 3243, 2958, 2866, 1600, 1563, 1462, 1425 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.78 (d, $J = 7$ Hz, 3H), 0.88 (s, 3H), 0.91–1.05 (m, 21H), 1.28 (m, 21H), 1.57–1.71 (m, 2H), 1.75–1.85 (m, 1H), 1.98–2.12 (m, 2H), 2.32–2.42 (m, 1H), 2.90 (q, $J = 5$ Hz, 1H), 3.48 (d, $J = 7$ Hz, 1H), 3.78 (d, $J = 7$ Hz, 1H), 4.20 (m, 1H), 7.11 (s, 2H), 7.45 (bs, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 12.3, 12.9, 15.9, 18.0, 18.4, 19.5, 20.9, 23.5, 24.0, 25.2, 28.4, 30.2, 34.5, 34.6, 48.6, 69.5, 123.8, 131.9, 151.5, 153.3, 161.8; MS (CI) $m/z$ 593, 549, 482, 392, 325, 295, 236; HRMS (CI) $m/z$ 593.4174 (calcd for $C_{33}H_{61}O_3N_2SSi$ 593.4172). There was also isolated 0.052 g (10%) of **25**.

**[(5,6-Dimethyl-6-triisopropylsilyloxymethyl)cyclohex-1-enyl]-methanol (28).** To a solution of **26** (1.86 g, 3.10 mmol) in hexane (1 : 9, 39 mL) under argon at −78 °C was added *tert*-butyllithiumhexane (1.3 M, 9.6 mL, 13 mmol) and the solution was warmed to 0 °C for 15 min, after which gas evolution had ceased. The orange solution was cooled to −78 °C, DMF (1.25 mL, 16 mmol) was added, and the mixture was allowed to warm to room temperature over 2 h. $Et_2O$ (10 mL) and $H_2O$ (10 mL) were added, and the mixture was extracted with $Et_2O$ (3 × 20 mL). The combined extract was washed with saturated aqueous NaCl (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield crude **27** as a yellow oil. This material was taken up in $CH_2Cl_2$ (31 mL) and the solution was cooled to −78 °C. A solution of DIBAL-H in $CH_2Cl_2$ (1 M, 6.3 mL, 6.3 mmol) was added and the mixture was allowed to warm to −20 °C over 30 min. After cooling the mixture to −78 °C, saturated aqueous potassium sodium tartrate (2 mL) was added and the mixture was allowed to warm to room temperature over 14 h. The mixture was dry-loaded on silica and subjected to gradient flash column chromatography (silica, hexanes to 5% $Et_2O$ in hexanes) to give 0.768 g (75% from **26**) of **28** as a colourless oil: IR (neat) 3354, 2942, 2866, 1659, 1463, 1433, 1383 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.85 (d, $J = 7$ Hz, 3H), 0.87 (s, 3H), 1.05–1.15 (m, 21H), 1.30–1.42 (m, 1H), 1.52–1.62 (m, 1H), 1.82–1.95 (m, 1H), 2.00–2.08 (m, 2H), 3.05 (m, 1H), 3.65 (s, 2H), 3.9 (m, 1H), 4.2 (d, $J = 4$ Hz, 1H), 5.82 (t, $J = 3$ Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 12.4, 16.3, 17.7, 18.4, 24.7, 26.8, 33.0, 42.8, 65.3, 69.2, 129.1, 142.0; MS (CI) $m/z$ 327 $(M + H)^+$, 309, 283, 239; HRMS (CI) $m/z$ 326.2637 (calcd for $C_{19}H_{38}O_2Si$ 326.2641).

**(2-Bromomethyl-1,6-dimethylcyclohex-2-enylmethoxy)triisopropylsilane (29).** To a solution of **28** (0.060 g, 0.18 mmol) in $CH_2Cl_2$ (1.9 mL) under argon at 0 °C was added methanesulfonic anhydride (0.050 g, 0.29 mmol) and $Et_3N$ (0.09 mL, 0.65 mmol) and the solution was stirred for 1.5 h. The mixture was diluted with hexanes (6 mL) and filtered through Celite. The filtrate was concentrated to yield the crude mesylate which was taken up into THF (2.4 mL). To the solution at room temperature under argon was added freshly dried LiBr (0.081 g, 0.93 mmol) and the solution was stirred at room temperature for 1 h, at which time a white suspension had formed. The mixture was diluted with hexane (10 mL) and filtered through a pad of basic alumina (Activity IV). The filtrate was concentrated under reduced pressure to leave a residue, which was purified by passage through a pad of basic alumina (Activity IV, hexanes) to yield 0.066 g, (92%) of **29** as a colourless oil: IR (neat) 2959, 2941, 2865, 1463, 1098, 1066 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.85 (d, $J = 7$ Hz, 3H), 0.95–1.15 (m, 21H), 1.30–1.42 (m, 1H), 1.52–1.62 (m, 1H), 1.82–1.95 (m, 1H), 2.00–2.2 (m, 2H), 3.72 (m, 2H), 4.15 (q, $J = 7$ Hz, 2H), 6.02 (t, $J = 3$ Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 12.4, 16.3, 19.7, 24.6, 26.0, 30.0, 32.2, 36.0, 43.6, 68.8, 133.2, 148.2; MS (CI) $m/z$ 389, 347, 309, 182; HRMS (CI) $m/z$ 387.1718 (calcd for $C_{19}H_{36}BrOSi$ 387.1718).

**3-(Hydroxymethyl)furan (31).** To a solution of 3-furoic acid (**30**, 2.24 g, 20.0 mmol) in THF (10 mL) at 0 °C under argon was added a solution of borane–dimethyl sulfide in THF (2 M, 12 mL, 24.0 mmol) and the mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was diluted carefully with $H_2O$ (20 mL), and solid NaCl and $Na_2CO_3$ (1 : 1, 20 g) were added. The mixture was extracted with $Et_2O$ (2 × 10 mL), and the combined extract was washed with saturated NaCl, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (300 g, $Et_2O$–hexanes, 1 : 1) afforded 1.56 g (80%) of **31** as a colourless oil: IR (neat) 3335, 2928, 2880, 1504, 1388, 1157, 1023 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.08 (bs, 1H), 4.44 (s, 2H), 6.37 (m, 1H), 7.34–7.36 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 56.6, 110.2, 125.6, 140.3, 143.8; MS (CI) $m/z$ 98 $(M^+)$, 95; HRMS (CI) $m/z$ 98.0366 (calcd for $C_5H_6O_2$ 98.0368).

**3-(*tert*-Butyldimethylsilyloxy)methylfuran (32).** To a solution of **31** (2.94 g, 30.0 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C under argon was added imidazole (2.45 g, 36.0 mmol). After the imidazole had dissolved, solid *tert*-butyldimethylsilyl chloride (5.43 g, 36.0 mmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was diluted with a mixture of $Et_2O$ and $H_2O$ (1 : 1, 100 mL), the layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 25 mL). The combined extract was washed with saturated aqueous NaCl, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (300 g, $Et_2O$–hexanes, 1 : 19) afforded 6.36 g (100%) of **31**: IR (neat) 2956, 2930, 2858, 1502, 1472, 1463, 1255, 1093, $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.10 (s, 6H), 0.93 (s, 9H), 4.61 (d, $J = 1$ Hz, 2H), 6.37 (m, 1H), 7.35–7.38 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 18.8, 26.3, 57.8, 110.0, 126.1, 139.7, 143.5; MS (CI) $m/z$ 212 $(M)^+$, 197, 155, 137,

125, 111, 99, 89; HRMS (CI) $m/z$ 212.1235 (calcd for $C_{11}H_{20}O_2Si$ 212.1232).

**2-(*tert*-Butyldimethylsilyl-)3-(hydroxymethyl)furan (33).** To a solution of **32** (4.24 g, 20.0 mmol) in THF (40 mL) under argon at −78 °C was added *n*-butyllithium (1.0 M in hexanes, 12.5 mL, 22.0 mmol) and hexamethylphosphoramide (HMPA, 3.94 mL, 22.0 mmol). The mixture was allowed to warm to room temperature over 6 h and was stirred at room temperature for 12 h. The mixture was diluted with a mixture of $Et_2O$ and $H_2O$ (1 : 1, 100 mL), the layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 25 mL). The combined extract was washed with saturated aqueous NaCl, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification of the residue by flash chromatography (300 g silica EtOAc–hexanes 2 : 3) gave 3.35 g (79%) of **33** as a colourless solid: mp 44–45 °C; IR (neat) 3322, 2953, 2929, 2857, 1471, 1412, 1390, 1252 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.28 (s, 6H), 0.90 (s, 9H), 2.12 (bs, 1H), 4.55 (s, 2H), 6.46 (d, $J = 1$ Hz, 1H), 7.57 (d, $J = 1$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.3, 17.7, 26.7, 57.4, 110.9, 136.3, 147.1, 155.2; MS (CI) $m/z$ 213 $(M + H)^+$, 195, 155, 127, 99; HRMS (CI) $m/z$ 195.1207 (calcd for $C_{11}H_{19}OSi$ 195.1205).

**2-(*tert*-Butyldimethylsilyl)-3-methylfuran (35).** To a solution of **33** (0.252 g, 1.19 mmol) in toluene (12 mL) at 0 °C was added methanesulfonic anhydride (0.413 g, 2.37 mmol) and diisopropylethylamine (1.01 mL, 5.85 mmol) and the mixture was stirred for 1 h at 0 °C. The mixture was diluted with hexanes (25 mL) and filtered, and the filtrate was concentrated to yield crude mesylate **34**: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.32 (s, 6H), 0.91 (s, 9H), 2.95 (s, 3H), 5.19 (s, 2H), 6.51 (m, 1H), 7.63 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.4, 17.7, 26.7, 38.8, 64.2, 111.6, 129.2, 147.6, 158.9.

Crude **34** was taken up in THF (4.7 mL) and the solution was stirred at 0 °C as lithium triethylborohydride (1.0 M, 2.4 mL, 2.4 mmol) was added. The solution was allowed to warm to room temperature over 1 h, by which time the initially clear solution had turned cloudy. $H_2O$ (10 mL) was added cautiously and the mixture was extracted with $Et_2O$ (3 × 20 mL). The combined extract was washed with saturated aqueous NaCl (30 mL), dried ($Na_2SO_4$), and concentrated, and the crude product was purified by flash column chromatography (silica, hexanes) to yield 0.245 g (93%) of **35** as a volatile, colourless oil: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.28 (s, 6H), 0.91 (s, 9H), 2.13 (s, 3H), 6.23 (m, 1H), 7.54 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.4, 11.8, 18.2, 26.8, 113.1, 131.1, 146.3, 153.7; MS (CI) $m/z$ 196 $(M)^+$, 181, 139, 125, 111; HRMS (CI) $m/z$ 196.1277 (calcd for $C_{11}H_{20}OSi$ 196.1283).

**2-(Tri-*n*-butylstannyl)-5-(*tert*-butyldimethyl)silyl-4-methylfuran (36).** *tert*-Butyllithiumhexene (0.88 M, 3.12 mL, 2.75 mmol) was added to a solution of **35** (0.451 g, 2.29 mmol) in hexane (4.14 mL) containing TMEDA (0.46 mL) at −78 °C and the solution was allowed to warm to room temperature over 6 h. The resulting yellow suspension was cooled to −78 °C and tri-*n*-butyltin chloride (0.75 mL, 2.76 mmol, dried by passage through a short pad of basic alumina) was added after which the mixture was allowed to warm to room temperature over 14 h. $H_2O$ (10 mL) was added and the mixture was extracted with $Et_2O$ (3 × 20 mL). The organic extracts were combined, washed with saturated aqueous NaCl (30 mL), dried ($Na_2SO_4$) and concentrated. The crude product was purified by flash column chromatography (basic alumina, hexanes) to yield 1.06 g, (95%) of **36** as a volatile, colourless oil: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.26 (s, 6H), 0.86–0.92 (m, 6H), 0.90 (s, 9H), 1.04 (t, $J =$ 8 Hz, 6H), 1.26–1.39 (m, 9H), 1.51–1.59 (m, 6H), 2.12 (s, 3H), 6.38 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.4, 10.5, 11.6, 14.1, 18.3, 27.3, 28.0, 29.4, 124.9, 131.0, 158.4, 164.9; MS (CI) $m/z$ 486 $(M + H)^+$, 429, 373, 315, 291; HRMS (CI) $m/z$ 486.2349 (calcd for $C_{23}H_{46}OSiSn$ 486.2340).

**2-(*tert*-Butyldimethyl)silyl-5-[(5,6-dimethyl-6-hydroxymethyl)-cyclohex-1-enylmethyl)]-3-methylfuran (38).** A solution of **29** (0.0779 g, 0.20 mmol) in THF (1 mL) and **36** (0.290 g, 0.60 mmol) in THF (1 mL) were each purified by passage through a short pad of alumina, eluting with THF (5 mL). Each solution was transferred to a base-washed flask, the mixture was concentrated and THF (2 mL) was added. The solution was degassed by two freeze–pump–thaw cycles and stirred at room temperature under argon. Palladium dibenzylideneacetone (0.037 g, 0.039 mmol) was added and the solution was stirred at room temperature for 36 h. The solution was diluted with $CH_2Cl_2$ (20 mL), dry-loaded on silica, and subjected to flash column chromatography (silica, hexanes) to give crude **37** (0.147 g) contaminated with a small quantity of tin residues as a colourless oil: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.29 (s, 6H), 0.88 (s, 3H), 0.90 (d, $J = 7$ Hz, 3H), 0.92 (s, 9H), 1.01–1.15 (m, 21H), 1.32–1.52 (m, 2H), 1.60–1.70 (m, 2H), 1.95–2.05 (m, 3H), 2.12 (s, 3H), 3.31–3.36 (m, 2H), 3.44–3.52 (m, 1H), 3.61–3.69 (m, 1H), 5.34 (m, 1H), 5.91 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.9, 12.5, 13.1, 13.9, 16.2, 17.6, 18.2, 18.5, 19.3, 24.6, 26.8, 31.9, 32.1, 43.4, 67.6, 67.9, 110.3, 125.8, 132.6, 139.3, 151.5, 159.4; MS (CI) $m/z$ 504 $(M)^+$, 461, 317, 273; HRMS (FAB) $m/z$ 504.3810 (calcd for $C_{30}H_{56}O_2Si_2$: 504.3818).

To a solution of crude **37** in THF (5.8 mL) was added a solution of TBAF in THF (1 M, 2.90 mL, 2.9 mmol) and the solution was stirred for 5 h at room temperature. The solution was dry loaded on silica and purified by chromatography (silica, 5% $Et_2O$ in hexanes) to give 0.0677 g (97% from **29**) of **38** as a colourless oil: IR (neat) 3383, 2954, 2926, 2856, 1599, 1470, 1462, 1249, 1108 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.30 (s, 6H), 0.81 (s, 3H), 0.90 (s, 9H), 0.95 (d, $J = 7$ Hz, 1H), 1.36–1.50 (m, 2H), 2.05–2.13 (m, 3H), 2.13 (s, 3H), 3.32 (s, 2H), 3.45 (dd, $J = 10$, 7 Hz, 1H), 3.66 (dd, $J = 8$, 2 Hz, 1H), 5.69 (t, $J = 2$ Hz, 1H), 5.96 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ −5.6, 12.2, 16.4, 17.1, 18.0, 25.6, 26.9, 27.1, 31.2, 32.8, 43.9, 66.1, 110.1, 130.1, 133.1, 138.1, 138.1, 152. 8, 158.8; MS (CI) $m/z$ 348 $(M)^+$, 317, 291, 273, 261, 245, 215, 199, 183, 169; HRMS (CI) $m/z$ 348.2483 (calcd for $C_{21}H_{36}O_2Si$ 348.2484).

**2-(*tert*-Butyldimethyl)silyl-3,4*a*,5-trimethyl-4-trimethylsilyloxy-4,4*a*,5,6,7,9-hexahydronaphtho[2,3-*b*]furan (40).** To a solution of **38** (0.0415 g, 0.12 mmol) in $CH_2Cl_2$ (1.2 mL) was added powdered 4 Å molecular sieves (0.261 g), TPAP (0.0045 g, 0.013 mmol) and NMO (0.262 g, 1.9 mmol) and the mixture was stirred at room temperature for 45 min. The mixture was diluted with $Et_2O$ (10 mL) and filtered through a pad of basic alumina (Activity IV). The pad was washed with a further quantity of $Et_2O$ and the filtrate was concentrated to give crude aldehyde **39** (0.0391 g) as a pale yellow oil: IR (neat) 2954, 2927, 2856, 1725, 1470, 1461, 1249 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.25 (s, 6H), 0.81 (d, $J = 7$ Hz, 1H), 0.94 (s, 9H), 1.05 (s, 3H), 1.40 (m, 1H), 1.56 (m, 1H), 1.95 (m, 1H), 2.10 (s, 3H), 2.18 (m, 2H), 3.12 (q, $J = 7$ Hz,

2H), 5.69 (t, $J = 2$ Hz, 1H), 5.96 (s, 1H), 9.21 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −5.3, 11.9, 13.5, 16.5, 18.1, 25.6, 25.7, 26.8, 32.5, 55.8, 110.8, 128.9, 132.6, 134.3, 152.3, 157.3, 204.9; MS (CI) $m/z$ 346 $(M)^+$, 331, 317, 289, 261, 245, 215, 205, 183, 167; HRMS (CI) $m/z$ 346.2323 (calcd for $C_{21}H_{34}O_2Si$ 348.2328).

To a solution of crude **39** (0.0391 g) obtained above in $CH_2Cl_2$ (3.7 mL) at −78 °C under argon were added 2,6-lutidine (0.10 mL, 0.88 mmol) and trimethylsilyl triflate (81 μL, 0.45 mmol), and the solution was stirred for 16 h at −78 °C. $H_2O$ (5 mL) was added and the mixture was warmed to room temperature and extracted with $Et_2O$ (3 × 20 mL). The combined extract was washed with saturated aqueous NaCl (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica, 0.25% $Et_2O$ in hexanes) to yield 0.0464 g (93%) of **40** as a colourless solid: mp 112–114 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (major isomer) 0.25 (s, 3H), 0.28 (s, 3H), 0.30 (s, 6H), 0.96 (s, 9H), 1.04 (d, $J = 7$ Hz, 3H), 1.08 (s, 3H), 1.46–1.60 (m, 1H), 1.80–1.95 (m, 2H), 2.15 (s, 3H), 2.95 (d, $J =$ 7 Hz, 1H), 3.45 (d, $J = 7$ Hz, 1H), 4.86 (s, 1H), 5.62 (d, $J = 2$ Hz, 1H).

**2-(*tert*-Butyldimethyl)silyl-4,4*a*,5,6,7,9-hexahydro-3,4*a*,5-trimethylnaphtho[2,3-*b*]furan-4-ol (41).**

*From **40**.* To a solution of **40** (0.0057 g, 0.014 mmol) in THF (1.3 mL) was added a solution of TBAF in THF (1 M, 0.03 mL, 0.03 mmol) and the mixture was stirred at room temperature for 5 min. The mixture was dry-loaded on silica and purified by column chromatography (5% $Et_2O$ in hexanes) to yield 0.0067 g (83%) of **41** as a colourless oil: IR (neat) 3423, 2951, 2926, 2855, 1461, 1248 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.27 (s, 6H), 0.94 (s, 9H), 1.03 (s, 3H), 1.06 (d, $J = 7$ Hz, 3 H), 1.43–1.53 (m, 2H), 1.70–1.78 (m, 1H), 1.89–1.95 (m, 1H), 2.02–2.16 (m, 2H), 2.18 (s, 3H), 3.02 (d, $J = 7$ Hz, 1H), 3.45 (d, $J = 7$ Hz, 1H), 4.69 (d, $J =$ 8 Hz, 1H), 5.65 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 11.1, 15.7, 16.2, 18.1, 22.5, 26.9, 27.3, 30.1, 32.0, 33.6, 43.5, 73.7, 120.3, 123.9, 132.2, 137.4, 152.9, 154.6; MS (CI) $m/z$ 346 $(M^+)$, 329, 289, 259, 229, 219, 197; HRMS (CI) $m/z$ 346.2325 (calcd for $C_{21}H_{34}O_2Si$ 346.2328).

*From **43**.* To a solution of **43** (0.0160 g, 0.046 mmol) in $CH_2Cl_2$ (0.4 mL) at −78 °C under argon was added a solution of DIBALH (1.0 M in $CH_2Cl_2$, 0.096 mL, 0.096 mmol) and the mixture was allowed to warm to −20 °C over 4 h. The solution was recooled to −78 °C and was quenched with Rochelle's salt (0.5 M). The layers were separated, the aqueous layer was extracted with $Et_2O$ (3 × 5 mL) and the combined extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (10 g, $Et_2O$–hexanes, 1 : 9) afforded 0.011 g (70%) of **41** identical with material prepared from **40**. A solution of **41** in $CH_2Cl_2$ and pyridine containing a catalytic quantity of DMAP was reached with *p*-nitrobenzoyl chloride at 80 °C for 12 h to give *p*-nitrobenzoate **42** (80%) as a crystalline solid, mp 117–120 °C (decomp.).

**2-(*tert*-Butyldimethyl)silyl-3,4*a*,5-trimethyl-4,4*a*,5,6,7,9-hexahydronaphtho[2,3-*b*]furan-4-one (43).** To a solution of **41** (8.0 mg, 0.01 mmol) in $CH_2Cl_2$ (1 mL) at room temperature under argon were added 4 Å mol sieves (25 mg), TPAP (1 mg) and NMO (10 mg). The green suspension was stirred for 2 h, then was filtered and concentrated under reduced pressure. Chromatography of the residue on silica (10 g, EtOAc–hexanes, 1 : 19) afforded 5.0 mg (80%) of **43** as a colourless oil: IR (neat) 2953, 2928, 2856, 1679, 1650, 1607, 1431, 1412, 1251, 836, 824 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.26 (s, 6H), 0.91 (s, 9H), 1.15 (d, $J = 7$ Hz, 3H), 1.21 (s, 3H), 1.39–1.55 (m, 2H), 1.90–2.07 (m, 2H), 2.26 (s, 3H), 2.36–2.43 (m, 1H), 3.32 (d, $J = 8$ Hz, 1H), 3.71 (dq, $J = 8$, 1 Hz, 1H), 5.70 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.3, 10.8, 17.8, 18.1, 19.9, 24.0, 26.8, 29.0, 31.9, 32.7, 51.3, 119.3, 126.7, 131.3, 135.9, 154.8, 168.0, 200.2; MS (CI) $m/z$ 344 $(M^+)$, 329, 287, 259, 217, 189, 97; HRMS (CI) $m/z$ 344.2174 (calcd for $C_{21}H_{32}O_2Si$ 344.2172).

**6β-Hydroxyeuryopsin (3).** To a solution of **40** (2.0 mg, 0.006 mmol) in THF (0.2 mL) under argon was added solid TBAF (0.060 g, 0.23 mmol) and the red solution was heated at 55 °C for 24 h. The solution was diluted with $Et_2O$ and $H_2O$, the layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The combined extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (1 g, $Et_2O$–hexanes, 1 : 9) afforded 0.8 mg (60%) of **3**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (s, 3H), 1.06 (d, $J =$ 7 Hz, 3 H), 1.40–1.50 (m, 2H), 1.70–1.78 (m, 1H), 1.89–1.95 (m, 1H), 2.02–2.16 (m, 2H), 2.05 (s, 3H), 2.97 (d, $J = 7$ Hz, 1H), 3.42 (d, $J = 7$ Hz, 1H), 4.67 (d, $J = 8$ Hz, 1H), 5.65 (m, 1H), 7.05 (s, 1H); MS (CI) $m/z$ 232 $(M^+)$, 220, 215, 199, 191, 177, 163, 149, 135; HRMS (CI) $m/z$ 232.1460 (calcd for $C_{15}H_{20}O_2$ 232.1463).

**3-(*tert*-Butyldimethyl)silyl-3,4*a*,5-trimethyl-4-trimethylsilyloxy-4*a*,5,6,7-tetrahydro-4*H*-naphtho[2,3-*b*]furan-2-one (44).** *m*-Chloroperbenzoic acid (0.0073 g, 0.042 mmol) was added to a solution of **40** (0.0148 g, 0.035 mmol) in $CH_2Cl_2$ (1.4 mL) and the solution was stirred for 5 min at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$ (2 × 2 mL) and filtered through a pad of basic alumina (Activity IV). The pad was washed with $CH_2Cl_2$ (5 mL) and the filtrate was concentrated to yield crude **44** as a mixture of two diastereomers. The mixture was separated by column chromatography (silica, 25% $CH_2Cl_2$ in hexanes) to yield a less polar diastereomer (0.0064 g, 42%) and a more polar isomer (0.0085 g, 55%). Less polar isomer: IR (neat) 2929, 2858, 1776, 1251, 1076, 1062 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.27 (s, 9H), 0.97 (d, $J = 7$ Hz, 3H), 1.04 (s, 9H), 1.11 (s, 3H), 1.42–1.47 (m, 1H), 1.56 (s, 3H), 1.66–1.74 (m, 1H), 1.90 (dt, $J = 18$, 6 Hz, 1H), 2.08–2.17 (m, 2H), 2.65 (d, $J = 17$ Hz, 1H), 3.18 (br, 1H), 4.53 (dd, $J = 4$, 1.3 Hz, 1H), 5.59 (d, $J = 6$ Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −5.5, −4.8, 2.1, 15.1, 15.5, 17.2, 20.7, 21.1, 26.6, 28.2, 30.2, 31.4, 44.7, 45.7, 74.6, 121.2, 123.6, 135.2, 145.6, 183.3; HRMS (ES) $m/z$ 435.2736 (calcd for $C_{24}H_{43}O_3Si_2$ 435.2751). More polar isomer: IR (neat) 2927, 2859, 1776, 1251, 1078, 1068, 869, 838 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.21 (s, 3H), 0.24 (s, 12H), 0.97 cm$^{-1}$ (d, $J = 7$ Hz, 3H), 1.00 (s, 3H), 1.37–1.25 (m, 1H), 1.51 (s, 3H), 1.76–1.67 (m, 1H), 1.86 (dt, $J =$ 18, 6 Hz, 1H), 2.03–2.19 (m, 2H), 2.66 (dd, $J = 17$, 1 Hz, 1H), 3.21 (br, 1H), 4.66 (dd, $J = 3$, 2 Hz, 1H), 5.60 (d, $J = 5$ Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ −7.5, −5.8, 1.8, 14.6, 17.0, 19.4, 19.9, 20.9, 26.3, 27.4, 30.7, 31.0, 43.4, 44.1, 75.7, 120.2, 123.5, 134.5, 147.1, 183.1; HRMS (CI) $m/z$ 435.2743 (calcd for $C_{24}H_{43}O_3Si_2$ 435.2751).

**Toluccanolide A (5).** To a solution of **44** (0.0035 g, 0.0081 mmol) in THF (0.08 mL) was added TBAF (0.08 mL, 0.08 mmol) and the mixture was stirred at room temperature for 30 min. $Et_2O$ (5 mL) was added, and the resulting suspension was filtered through a

pad of basic alumina (Activity IV). The alumina was washed with EtOAc and the filtrate was concentrated to dryness. The residue was purified by column chromatography (silica, 15% EtOAc in hexanes) to give 0.0016 g (84%) of **5** as a colourless solid: mp 153–155 °C; IR (neat) 3444, 2925, 1733, 1675, 1447, 1380, 1339, 1286, 1152, 1080, 1040, 1003 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.92 (s, 3H), 1.11 (d, $J = 7$ Hz, 3H), 1.40–1.49 (m, 1H), 1.56–1.63 (m, 1H), 2.07 (t, $J = 2$ Hz, 3H), 1.90–2.19 (m, 3H), 2.76 (dd, $J =$ 12, 7 Hz, 1H), 4.44–4.50 (m, 2H), 5.77 (td, $J = 4$, 2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 9.4, 14.1, 17.7, 23.9, 27.8, 35.9, 40.3, 45.9, 78.5, 78.7, 122.8, 129.3, 134.3, 161.1, 175.0; HRMS (CI) $m/z$ 249.1491 (calcd for $C_{15}H_{21}O_3$ 249.1491).

**Ozonide 45.** A solution of **40** (0.0072 g, 0.017 mmol) in $CH_2Cl_2$ (1.14 mL) containing a small quantity of Rose Bengal was flushed with $O_2$, then was cooled to −78 °C and irradiated with a 300 W tungsten lamp. After 30 min, charcoal was added, the reaction was warmed to room temperature and the mixture was filtered through a pad of Celite. The filtrate was evaporated to dryness to yield crude **45**, which was used without further purification: IR (neat) 2957, 2928, 2858, 1713, 1310, 1261, 1252, 1232, 1155, 1069, 1050, 880, 842, 825, 794, 604 $cm^{-1}$;$^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.10 (s, 3H), 0.38 (s, 6H), 0.93 (s, 3H), 0.98–0.94 (m, 1H), 1.02 (d, $J = 7$ Hz, 3H), 1.04 (s, 3H), 1.36 (dtd, $J = 18$, 7, 4 Hz, 1H), 1.58–1.64 (m, 1H), 1.99 (s, 3H), 2.02–2.06 (m, 2H), 2.73 (d, $J =$ 16 Hz, 1H), 3.51 (ddd, $J = 16$, 5, 3 Hz, 1H), 4.58 (s, 1H), 5.41 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ −5.1, −4.9. 0.1, 15.4, 16.7 (×2), 17.8, 25.0, 25.6, 26.9, 34.1, 44.6, 46.2, 69.6, 125.6, 135.2, 135.6, 138.5, 170.7, 199.6; HRMS (CI) $m/z$ 451.2720 (calcd for $C_{24}H_{43}O_4Si_2$ 451.2700).

**9*a*-Hydroxy-3,4*a*,5-trimethyl-4-trimethylsilyloxy-4*a*,5,6,7,9,9*a*-hexahydro-4*H*-naphtho[2,3-*b*]furan-2-one (46).** A solution of **40** (0.0079 g, 0.019 mmol) in $CH_2Cl_2$ (1.3 mL) containing a small quantity of Rose Bengal was flushed with $O_2$, then was cooled to −78 °C and irradiated with a 300 W tungsten lamp. After 30 min, a small quantity of pyridinium *p*-toluenesulfonate in THF (1 mL) and water (1 mL) was added, and the mixture was stirred at room temperature for 3 h. The mixure was extracted with $Et_2O$ (3 × 5 mL) and the combined extract was concentrated to dryness. The residue was purified by column chromatography (silica, 10% EtOAc in hexanes) to yield 0.0072 mg (100%) of **46** as a colourless solid: mp 192–196 °C; IR (neat) 3347, 2957, 2922, 2852, 1740, 1694, 1435, 1306, 1253, 1232, 1204, 1121, 1086, 1062, 1013, 954, 909, 882, 840, 753 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.17 (s, 9H), 0.88 (s, 3H), 1.10 (d, $J = 7$ Hz, 3H), 1.36 (dddd, $J = 14$, 10, 7, 7 Hz, 1H), 1.51–1.59 (m, 1H), 1.82 (dtd, $J = 16$, 7, 3 Hz, 1H), 2.02 (d, $J = 2$ Hz, 3H), 2.00–2.07 (m, 2H), 2.54 (dd, $J = 14$, 2 Hz, 1H), 2.65 (d, $J = 14$ Hz, 1H), 2.76 (s, 1H), 4.47 (d, $J = 2$ Hz, 1H), 5.75 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ − 0.2, 9.2, 12.8, 18.5, 24.7, 28.6, 36.7, 46.2, 47.5, 78.4, 102.5, 124.4, 129.8, 134.8, 159.7, 172.0; MS (CI) $m/z$ 337 $(M + H)^+$, 319, 247, 229; HRMS (CI) $m/z$ 337.1820 (calcd for $C_{18}H_{29}O_4Si$ 337.1835).

**Toluccanolide C 6.** To a stirred solution of **46** (0.0025 g, 0.0074 mmol) in THF (1 mL) was added HCl (1 M, 2 drops) and the solution was stirred for 16 h. The solution was concentrated to dryness and the residue was purified by column chromatography (30% EtOAc in hexanes) to give 0.0019 g (97%) of **6** as a colourless solid: mp 159–161 °C; IR (neat) 3444, 2922, 2850, 1739, 1684, 1456, 1434, 1380, 1311, 1231, 1189, 1118, 1078, 1058, 1040, 1010, 975, 942, 909, 752, 733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.93 (s, 3H), 1.16 (d, $J = 7$ Hz, 3H), 1.44 (dddd, $J = 14$, 10, 8, 7 Hz, 1H), 1.54–1.57 (m, 1H), 1.93 (dtd, $J = 17$, 7, 3 Hz, 1H), 2.06 (d, $J = 2$ Hz, 3H), 2.03–2.09 (m, 2H), 2.55 (dd, $J = 14$, 2 Hz, 1H), 2.67 (d, $J = 14$ Hz, 1H), 3.09 (s, 1H), 4.62–4.64 (m, 1H), 5.75 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 9.0, 12.9, 18.5, 24.7, 28.5, 37.4, 45.3, 47.0, 78.4, 102.4, 124.5, 129.6, 134.7, 158.8, 172.1; MS, (ES) $m/z$ 265 $(M + H)^+$, 247; HRMS (ES) $m/z$ 265.1435 (calcd for $C_{15}H_{21}O_4$ 265.1440).

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