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The Enantiocontrolled Synthesis of a Highly Functionalized Cyclohexenone Related to the A-Ring of the Furanosteroid Viridin

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A seven-step reaction sequence has been used to convert the enantiomerically pure *cis*-1,2-dihydrocatechol **10** into the cyclohexenone **17a**. A near equivalent sequence involving the same starting material has allowed for the synthesis of the regioisomeric system **17b**. Compound **17a** is related to the A-ring of *ent*-viridin (*ent*-**1**), the non-natural enantiomer of the furanosteroid viridin (**1**).

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Introduction

The viridins are a well known but structurally unusual class of steroids produced by various microorganisms.[1] They feature a furan ring fused between C-4 and C-6 of the normal steroidal framework and have thus been labelled as furanosteroids. These compounds display, among other things, potent anti-fungal, anti-proliferative, as well as immunosuppressive properties. As such they have considerable potential as therapeutic agents.[1] A prominent and representative member of the class is viridin (**1**, Fig. 1) which was first isolated from the mould *Gliocladium virens* in 1945.[2] Biogenetically speaking, the compound is derived by the tail-to-tail condensation of two farnesyl residues with the non-ring-fused furan carbon thought likely to arise from the methyl group of mevalonate.[3] On this basis the illustrated absolute configuration of viridin was assigned. Its structure, including relative configuration, was confirmed by single-crystal X-ray analysis in 1972.[4] It is related to wortmannin (another furanosteroid), which was first isolated from culture filtrates of *Penicillium wortmanni* Klocker and which interacts with a range of important biological targets. In vitro it binds most strongly to PI-3 kinase.[1b,5]

The fascinating structural and biological features of furanosteroids has prompted significant effort, over the past decade or so, directed towards the total synthesis of these systems as well as certain analogues.[6–8] Nevertheless, and despite a range of elegant studies conducted by various groups, the first and thus far single total synthesis of virdin was only reported in 2004.[7] It was obtained in racemic form. Thus, Sorensen and coworkers first constructed the CD-ring subunit of virdin (**1**) using a Vollhardt-type cyclotrimerization process that involved an open-chain triyne. Their end-game involved assembly of the A-ring through a ring-closing metathesis reaction and then exploiting the ensuing cyclohexene double bond for the purposes of introducing the relevant oxygenation pattern within this part of viridin (**1**).

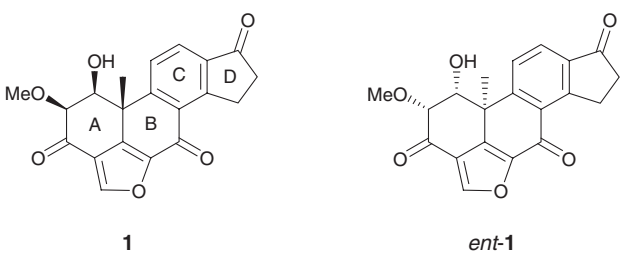

Fig. 1. Structures of viridin (**1**) and *ent*-viridin (*ent*-**1**).

As part of an ongoing program within our laboratories that has been directed towards the exploitation of microbially-derived and enantiomerically pure *cis*-1,2-dihydrocatechols in the synthesis of biologically active systems,[9] we have sought to prepare compounds related to the A-ring of viridin (**1**) and the same ring of its enantiomer *ent*-**1** (Fig. 1). The outcomes of some of our preliminary efforts in this area are now described.

The approach we have been taking as part of our effort to develop total syntheses of both viridin and its enantiomer is shown in retrosynthetic form in Fig. 2. The pivotal final step that leads to *ent*-viridin would require an intramolecular Friedel–Crafts acylation reaction of compound **2** and thus lead to the formation of the non-aromatic B-ring of *ent*-**1**. Subsequent and selective deprotection and oxidation steps should then deliver the target. In what is likely to be the most challenging aspect of the synthesis, the tetracyclic system **2** would, itself, be assembled through the diastereoselective conjugate addition of a metallated indanone of the general form **4** to a β-methoxylated and trioxygenated cyclohexenone such as **3**. Furannulation of the resulting enolate using protocols of the type introduced by Garst and Spencer[10] should then deliver substrate **2**. The indan-1-one-based building block **4**, which incorporates a suitable directed metallating group (DMG), was expected to be accessible from the known indan-1-one-4-carboxylic acid **5**,[11] while enone **3** was considered likely to be available through manipulation of

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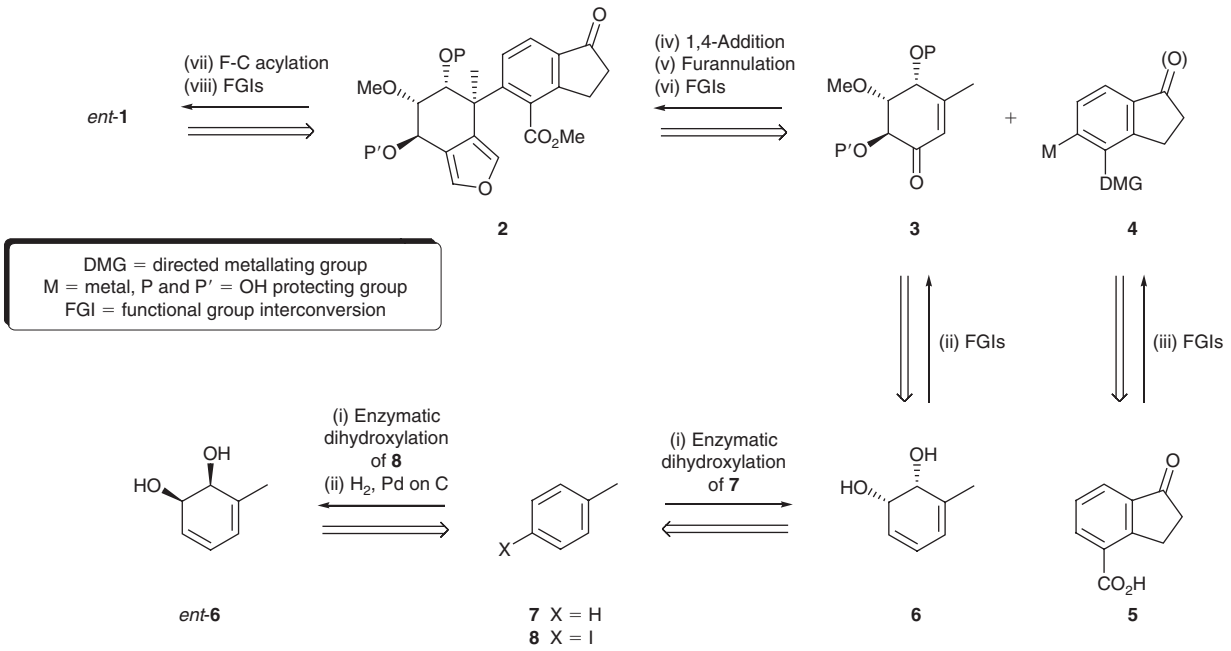


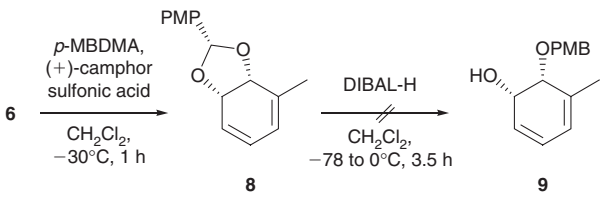
Fig. 2. Retrosynthetic analysis of approaches to developing total syntheses of viridin and its enantiomer.

the *cis*-1,2-dihydrocatechol **6**. This last compound is readily obtained on a large scale and in the illustrated enantiomeric form through the whole-cell-mediated biotransformation of toluene (**7**) using a genetically engineered microorganism that overexpresses the responsible enzyme, toluene dioxygenase (TDO).[12] Significantly, it is possible to obtain the enantiomer of diol **6** (i.e., *ent*-**6**) by subjecting *p*-iodotoluene (**8**) to dihydroxylation with TDO and then subjecting the ensuing metabolite to de-iodination with dihydrogen in the presence of palladium on carbon.[13] Accordingly, any preparation of a compound such as **3** would also constitute a synthesis of its enantiomer, as would be required in developing approaches to the natural enantiomeric form of viridin. The syntheses of a suitably protected form of compound **3** as well as a regio-isomeric system are detailed in the following section.

Results and Discussion

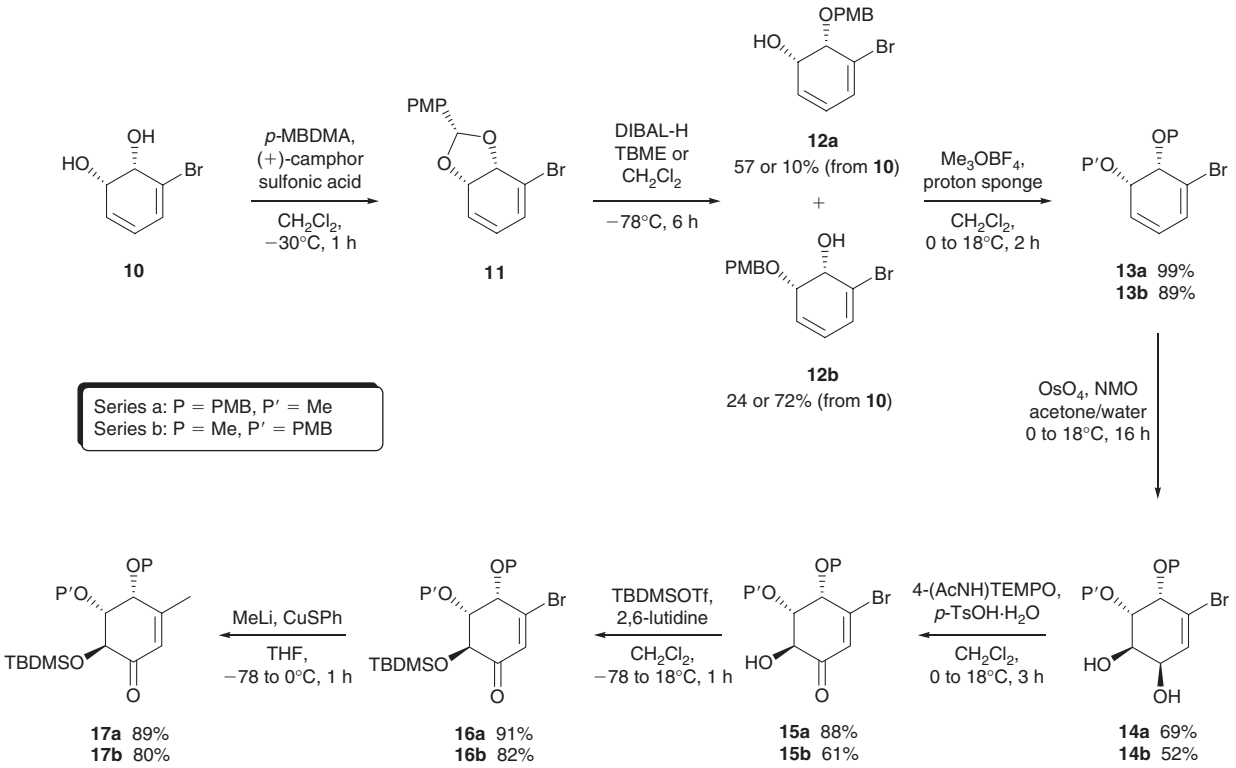
In seeking to follow the retrosynthetic analysis shown in Fig. 2, which would involve the methyl group of toluene ultimately becoming the angular substituent between and the A- and B-rings of *ent*-viridin, metabolite **6** was converted into the corresponding *p*-methoxyphenyl (PMP)-acetal **8** (Scheme 1) by reacting the former compound with *p*-methoxybenzaldehyde dimethyl acetal (*p*-MBDMA) in the presence of catalytic quantities of (+)-camphor sulfonic acid. Unfortunately, and despite our positive experiences with related systems,[14] this unstable acetal failed to engage in the hoped-for reductive cleavage reaction with diisobutylaluminium hydride (DIBAL-H) such that none of the required *cis*-1,2-dihydrocatechol monobenzyl ether **9** was observed. Rather, a complex mixture of products, which included aromatized ones, was obtained.

As a result of the difficulties outlined immediately above, we turned to using the bromo-analogue, **10** (Scheme 2) of compound **6** as the starting point for the synthesis on the basis that the halogen could be replaced by a methyl group at some point in the reaction sequence. A further motivation for pursuing this approach was our observation that derivatives of



Scheme 1.

compound **10** are often more stable than the equivalent systems derived from congener **6**. As a result, it also seemed prudent to delay the methyl-for-bromine substitution process for as long as possible. Accordingly, compound **10** was converted, under standard conditions, into the previously reported acetal **11**.[14a] A solution of the latter compound in *t*-butyl methyl ether (TBME) was cooled to −78°C and then treated with a 1.0 M solution of DIBAL-H in hexane. After workup a ~2:1 and chromatographically separable mixture of the desired mono-ether **12a** (57%) and its regio-isomer **12b** (24%) was obtained. The assignment of structures to each of these mono-ethers follows from 2D NMR experiments and from a single-crystal X-ray analysis (see below) of a derivative of compound **12b**. *O*-Methylation of the free hydroxy group within compound **12a** was readily effected with trimethyloxonium tetrafluoroborate in the presence of 1,8-bis(dimethylamino)naphthalene (Proton Sponge)[15] and the resulting bis-ether **13a** (99%) was then subjected to *cis*-1,2-dihydroxylation using the UpJohn protocol.[16] In keeping with expectations, this second reaction took place with good levels of regio- and diastereocontrol and such that the diol **14a** was obtained as the major product (69%). Selective oxidation of the allylic hydroxy group within compound **14a** was best effected by using the sterically demanding oxoammonium salt derived from the *p*-toluenesulfonic acid (*p*-TsOH)-promoted disproportionation of the 4-acetamido-TEMPO (TEMPO = 2,2,6,6-tetramethyl-l-piperidyloxyl) radical.[17] The remaining hydroxy group within



Scheme 2.

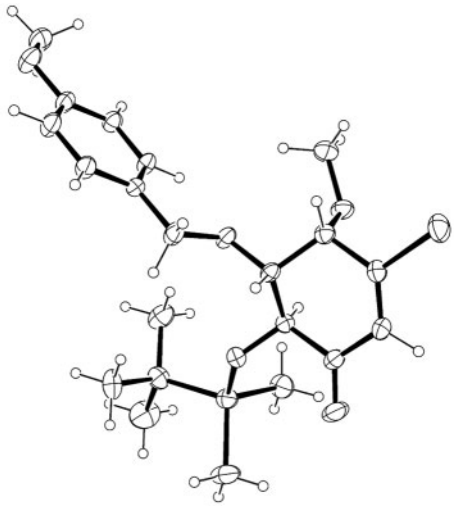


Fig. 3. *ORTEP* plot derived from the single-crystal X-ray analysis of compound **16b** (thermal ellipsoids shown at 30% probability level).

the product enone **15a** (88%) was converted into the corresponding *t*-butyldimethylsilyl (TBDMS)-ether **16a** (91%) using *t*-butyldimethylsilyl triflate (TBDMSOTf) in the presence of 2,6-lutidine. In the final step of the reaction sequence, compound **16a** was reacted with the cuprate derived from methyl lithium (MeLi) and CuSPh.[18] By such means, a nucleophilic addition/elimination reaction took place that effected the required methyl-for-bromine exchange and thus resulted in the formation of the target β′-methoxylated enone **17a**. This was obtained in 89% yield as a pale-yellow oil.

Interestingly, essentially the same reaction sequence as just described can be used to prepare the regioisomeric compound **17b**. Thus, by treating acetal **11** with DIBAL-H in CH_2Cl_2, rather than TBME as used before, a ∼1:6 mixture of the mono-*p*-methoxybenzyl (mono-PMB) ether **12a**[19] and regio-isomer **12b**[19] was obtained (see Series b, Scheme 2). This change in regioselectivity of the reductive cleavage of acetal **11** as a function of reaction medium is attributed to the co-ordinating or non-co-ordinating effects of the relevant solvent. Thus, in the reductive cleavage reaction carried out in TBME that leads to mono-ether **12a** as the major product of reaction, it is presumed that the solvent coordinates to the reducing agent and that steric effects thus direct, in a preferential but not an exclusive sense, the complexed DIBAL-H to the acetal oxygen of substrate **11** that is remote from the bulky bromine. As a result the C–O bond remote from this same bromine undergoes preferential cleavage and thus leads to a predominance of mono-ether **12a**. In contrast, when the weakly co-ordinating CH_2Cl_2 is used as solvent, the bromine within substrate **11** now has a capacity to coordinate with the DIBAL-H and thereby direct acetal cleavage so as to deliver regio-isomer **12b** preferentially.[20] Now, following the previously established synthetic sequence, compound **12b** was *O*-methylated using trimethyloxonium tetrafluoroborate in the presence of Proton Sponge and thus afforded the mixed bis-ether **13b** (89%). Reaction of this last compound under the UpJohn conditions[16] then gave diol **14b** in 52% yield. Selective oxidation of compound **14b** under conditions essentially identical to those applied to congener **14a** gave α′-hydroxyenone **15b** (61%) that was *O*-silylated using TBDMSOTf in the presence of 2,6-lutidine. In this manner the tris-ether **16b** was obtained in 82% yield. The crystalline nature of this material allowed it to be subjected to a single-crystal X-ray analysis that served to confirm the illustrated structure (including absolute stereochemistry) and, thereby, those of all of its precursors. The derived *ORTEP* plot is shown in Fig. 3.

In the final step of the reaction sequence, β-bromoenone **16b** was subjected to the same type of methyl-for-halogen exchange reaction as used for the conversion of **16a** into **17a**, and in this way compound **17b** was obtained as a light-yellow oil in 80% yield.

A comparison of the ^{1}H and ^{13}C NMR spectroscopic data obtained for regioisomers **17a** and **17b** is provided in Table 1. This clearly indicates that the compounds are distinct but, nevertheless, closely related in a structural sense. Furthermore, the infrared and mass spectra obtained for each of these compounds were very similar and fully consistent with the illustrated structures. As such, and given the X-ray analysis carried out on compound **16b**, the structure assigned to target enone **17a** appears quite secure. Accordingly, investigations into establishing a total synthesis of *ent*-virdin by the pathway defined in Fig. 2 have begun. The results of such efforts will be reported in due course.

Table 1. Comparison of the ^{1}H and ^{13}C NMR spectroscopic datasets derived from the isomeric enones 17a and 17b

δ_H[A]		δ_C[B]	
17a	**17b**	**17a**	**17b**
7.32 (2H, d, *J* 8.7)	7.29 (2H, d, *J* 8.4)	196.6	196.7
6.89 (2H, d, *J* 8.7)	6.88 (2H, d, *J* 8.4)	159.5	159.2
5.79 (1H, s)	5.80 (1H, d, *J* 1.2)	156.7	156.7
4.76 (2H, ABq, *J* 11.1)	4.68 (2H, ABq, *J* 12.0)	130.1	130.3
4.44 (1H, d, *J* 8.4)	4.41 (1H, d, *J* 8.4)	130.1	129.4
4.26 (1H, d, *J* 3.0)	3.87 (1H, d, *J* 3.3)	126.2	126.1
3.81 (3H, s)	3.81 (3H, s)	113.8	113.7
3.54 (3H, s)	3.75 (1H, dd, *J* 8.4 and 3.3)	83.0	79.4
3.53 (1H, dd, *J* 9.0 and 3.3)	3.58 (3H, s)	75.2	79.2
1.93 (3H, s)	2.00 (3H, d, *J* 1.2)	74.1	74.3
0.92 (9H, s)	0.92 (9H, s)	73.9	73.1
0.14 (3H, s)	0.14 (3H, s)	59.5	60.6
0.12 (3H, s)	0.08 (3H, s)	55.3	55.2
		25.8	25.8
		21.6	21.8
		18.5	18.5
		−4.7	−4.7
		−5.3	−5.2

[A] Spectrum recorded in $CDCl_3$ at 300 MHz.
[B] Spectrum recorded in $CDCl_3$ at 75 MHz.

Experimental

General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian Mercury or Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) (relative integral, multiplicity, coupling constant(s) *J* (Hz)) where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations of the above. The residual $CHCl_3$ peak (δ 7.26) was used as a reference for ^{1}H NMR spectra, and the central peak (δ 77.0) of the $CDCl_3$ 'triplet' was used as a reference for proton-decoupled ^{13}C NMR spectra. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on NaCl plates. A VG Fisons AutoSpec three-sector (E/B/E) double-focusing mass spectrometer was used to obtain both low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in positive ionization mode.

Optical rotations were measured at 20–25°C with a Perkin–Elmer 241 polarimeter at the sodium-D line (589 nm) and the concentrations (*c*) (g per 100 mL) indicated using spectroscopic grade solvents. The measurements were carried out in a cell with a path length (*l*) of 1 dm. Specific rotations, $[\alpha]_D$, were calculated using the equation $[\alpha]_D = 100 \cdot \alpha/(c \cdot l)$ and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on an Optimelt automated melting point system or a Reichert hot-stage microscope apparatus and are uncorrected.

Analytical TLC was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g/7.5 g/37.5 g/720 mL) or potassium permanganate/potassium carbonate/5% w/v sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL). The retention factor (R_F) was quoted to the nearest 0.1. Flash column chromatography[21] was performed using silica gel 60 (0.040–0.0063 mm) as the stationary phase and the analytical reagent (AR) or HPLC grade solvents indicated.

Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem, or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX, BDH, or Unilab Chemical Companies. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from its magnesium alkoxide salt. CH_2Cl_2 was distilled from calcium hydride. Triethylamine was distilled from and stored over potassium hydroxide pellets.

Specific Chemical Conversions

Compound *11*

A solution of (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol (**10**)[12] (1.00 g, 5.26 mmol) in CH_2Cl_2 maintained under a nitrogen atmosphere at −35°C was treated with *p*-MBDMA (0.99 mL, 1.07 mmol) and (+)-camphorsulfonic acid (61 mg, 0.26 mmol). The resulting solution was stirred at this temperature for 0.33 h and then quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution). The phases were separated and the aqueous one was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were then washed with NaOH (1 × 50 mL of 2 M aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give acetal **11**[14a] (~1.30 g, 80%) as a clear, colourless oil, R_F 0.5 (in 3/7, v/v, ethyl acetate/hexanes), $[\alpha]_D$ +193.8 (*c* 1.53, $CHCl_3$). (Found: $[M + Na]^+$, 330.9919. $C_{14}H_{13}{}^{79}BrO_3$ requires $[M + Na]^+$: 330.9946.) δ_H (300 MHz, $CDCl_3$) 7.41 (2H, d, *J* 8.1), 6.88 (2H, d, *J* 8.1), 6.41 (1H, d, *J* 6.0), 6.03 (1H, dd, *J* 9.6 and 3.3), 5.93 (1H, dd, *J* 9.6 and 6.0), 5.72 (1H, s), 4.77 (2H, s), 3.80 (3H, s). δ_C (75 MHz, $CDCl_3$) 160.7, 128.5, 128.1, 125.9, 124.2, 123.4, 123.1, 113.7, 99.4, 76.0, 73.4, 55.3. ν_{max} (NaCl)/cm^{-1} 1612, 1517, 1439, 1310, 1251, 1057, 1027, 1000. *m*/*z* (ESI) 333 and 331 $[M + Na]^+$ (45 and 40%), 257 (37), 239 (34), 213 (58), 199 (98), 185 (100), 171 (50).

The sample of acetal **11** obtained as described immediately above was used without purification in the next step of the reaction sequence.

*Compound **12a***

A magnetically stirred solution of acetal **11** (500 mg, 1.62 mmol) in TBME (17 mL) maintained under a nitrogen atmosphere at −78°C was treated with DIBAL-H (3.25 mL of a 1 M solution in hexanes, 3.25 mmol) in TBME (8 mL). The ensuing mixture was stirred at −78°C for 2 h and then treated with a further aliquot of DIBAL-H (3.25 mL of a 1 M solution in hexanes) in TBME (8 mL). The resulting mixture was stirred at −78°C for 2 h and then yet another aliquot of DIBAL-H (3.25 mL of 1 M solution in hexanes) in TBME (8 mL) was added. The ensuing solution was stirred at −78°C for a further 2 h before being quenched by the careful addition (**CAUTION!**) of sodium potassium tartrate (50 mL of a saturated aqueous solution). The resulting mixture was stirred vigorously at 18°C for 1 h and then the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash column chromatography (15/85, v/v, ethyl acetate/hexanes) afforded two fractions, A and B.

Concentration of fraction A (R_F 0.24 in 3/7, v/v, ethyl acetate/hexanes) yielded *ether **12a*** (284 mg, 57%) as a clear, colourless oil, $[\alpha]_D$ −61.6 (*c* 1.67, $CHCl_3$). (Found: $[M + Na]^+$, 333.0101. $C_{14}H_{15}{}^{79}BrO_3$ requires $[M + Na]^+$: 333.0102.) δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.7), 6.89 (2H, d, *J* 8.7), 6.45 (1H, d, *J* 5.7), 5.90 (1H, dm, *J* 9.6), 5.77 (1H, ddd, *J* 9.6, 5.7, and 2.1), 4.73 (2H, ABq, *J* 11.1), 4.59–4.51 (1H, complex m), 4.10 (1H, d, *J* 6.9), 3.81 (3H, s), 2.59 (1H, d, *J* 9.3). δ_C (75 MHz, $CDCl_3$) 159.5, 131.4, 129.9, 129.5, 128.5, 122.6, 122.2, 113.9, 78.4, 73.1, 69.6, 55.2. ν_{max} (NaCl)/cm^{-1} 3410, 1611, 1513, 1248, 1173, 1098, 1034, 823. *m/z* (ESI) 335 and 333 $[M + Na]^+$ (51 and 53%), 121 (100).

Concentration of fraction B (R_F 0.26 in 3/7, v/v, ethyl acetate/hexanes) yielded ether **12b**[19] (76 mg, 24%) as a clear, colourless oil. The ^1H NMR spectroscopic data derived from this material matched those reported for an authentic sample.[19]

*Compound **13a***

A magnetically stirred solution of alcohol **12a** (570 mg, 1.84 mmol) in CH_2Cl_2 (35 mL) maintained at 0°C under a nitrogen atmosphere was treated with 1,8-bis(dimethyamino) naphthalene (Proton Sponge, 1.18 g, 5.52 mmol) followed by trimethyloxonium tetrafluoroborate (406 mg, 2.76 mmol). The resulting solution was stirred at ∼18°C for 1 h and then quenched by the addition of $NaHCO_3$ (40 mL of a saturated aqueous solution). The phases were separated and the aqueous one was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were then washed with citric acid (80 mL of a 1/9, w/v, aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (1/10/89, v/v/v, triethylamine/ethyl acetate/hexane elution) and thus yielded, after concentration of the appropriate fractions (R_F 0.45 in 3/7, v/v, ethyl acetate/hexane), *bis-ether **13a*** (588 mg, 99%) as a clear, colourless oil, $[\alpha]_D$ −85.7 (*c* 1.50, $CHCl_3$). (Found: $[M + Na]^+$, 347.0259. $C_{15}H_{17}{}^{79}BrO_3$ requires $[M + Na]^+$: 347.0259.) δ_H (300 MHz, $CDCl_3$) 7.33 (2H, d, *J* 8.7), 6.87 (2H, d, *J* 8.7), 6.50 (1H, d, *J* 5.7), 5.99 (1H, dm, *J* 9.6), 5.82 (1H, ddd, *J* 9.6, 5.7, and 2.4), 4.63 (2H, s), 4.26–4.19 (2H, complex m), 3.80 (3H, s), 3.44 (3H, s). δ_C (75 MHz, $CHCl_3$) 159.2, 130.2, 129.9, 129.3, 129.1, 122.7, 122.6, 113.6, 79.1, 75.2, 71.0, 57.3, 55.2. ν_{max} (NaCl)/cm^{-1} 2932, 1612, 1513, 1249, 1106, 1063, 1034, 823. *m/z* (ESI) 349 and 347 $[M + Na]^+$ (6 and 6%), 215 (100), 121 (50).

*Compound **14a***

A magnetically stirred solution of diene **13a** (930 mg, 2.87 mmol) in acetone (1.8 mL) maintained under a nitrogen atmosphere at 0°C was treated with a solution of *N*-methylmorpholine *N*-oxide (504 mg, 4.31 mol) in water (2.0 mL). OsO_4 (0.58 mL of a 0.2 M solution in *t*-BuOH, 0.11 mmol) was then added dropwise to the reaction mixture. The resulting solution was allowed to warm to 18°C and stirred at this temperature for 16 h before being quenched with $Na_2S_2O_3$ (4 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (5 × 4 mL) and the combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (1/1, v/v, ethyl acetate/hexanes elution) and concentration of the appropriate fractions (R_F 0.13) then afforded *diol **14a*** (709 mg, 69%) as a clear, colourless oil, $[\alpha]_D$ −136.4 (*c* 2.71, $CHCl_3$). (Found: $M^{+\bullet}$, 358.0419. $C_{15}H_{19}{}^{79}BrO_5$ requires $M^{+\bullet}$: 358.0416.) δ_H (300 MHz, $CDCl_3$) 7.35 (2H, d, *J* 8.7), 6.88 (2H, d, *J* 8.7), 6.23 (1H, d, *J* 5.1), 4.78 (2H, ABq, *J* 11.1), 4.33 (1H, d, *J* 3.9), 4.30–4.27 (1H, complex m), 4.10–4.05 (1H, complex m), 3.80 (3H, s), 3.63 (1H, dd, *J* 10.2 and 3.9), 3.45 (3H, s), 3.04–3.00 (2H, m). δ_C (75 MHz, $CDCl_3$) 159.4, 131.1, 129.9(1), 129.8(7), 125.2, 113.7, 79.3, 77.0, 74.5, 66.9, 66.5, 58.3, 55.2. ν_{max} (NaCl)/cm^{-1} 3418, 2933, 1612, 1514, 1463, 1302, 1249, 1115, 1094, 818. *m/z* (EI, 70 eV) 360 and 358 $M^{+\bullet}$ (5 and 5%), 206 and 204 (19 and 21), 137 (80), 121 (100).

*Compound **15a***

A magnetically stirred solution of diol **14a** (160 mg, 0.45 mmol) in CH_2Cl_2 (6 mL) maintained under a nitrogen atmosphere at 0°C was treated with *p*-TsOH·H_2O (127 mg, 0.67 mmol). The ensuing mixture was then treated, in four equal portions over 0.5 h, with 4-acetamido-TEMPO (143 mg, 0.67 mmol). The resulting solution was allowed to warm to 18°C and stirred at this temperature for 2 h before being re-cooled to 0°C and then treated with more *p*-TsOH·H_2O (127 mg, 0.67 mmol). The ensuing mixture was then treated, yet again and now in four equal portions over 0.5 h, with 4-acetamido-TEMPO (143 mg, 0.67 mmol). The resulting solution was again allowed to warm to 18°C, stirred at this temperature for 1 h, and then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution). The phases were separated and the aqueous one was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (3/7, v/v, ethyl acetate/hexane) and concentration of the appropriate fractions (R_F 0.07) afforded *α′-hydroxyenone **15a*** (141 mg, 88%) as a clear, colourless oil, $[\alpha]_D$ −100.3 (*c* 2.03, $CHCl_3$). (Found: $[M + Na]^+$, 379.0162. $C_{15}H_{17}{}^{79}BrO_5$ requires $[M + Na]^+$: 379.0157.) δ_H (300 MHz, $CDCl_3$) 7.37 (2H, d, *J* 8.7), 6.90 (2H, d, *J* 8.7), 6.55 (1H, d, *J* 0.6, H2), 4.88 (2H, ABq, *J* 10.8), 4.64 (1H, dd, *J* 10.5 and 1.8), 4.56 (1H, dd, *J* 3.6 and 0.6), 3.81 (3H, s), 3.57 (3H, s), 3.54 (1H, dd, *J* 10.5 and 3.6), 3.32–3.31 (1H, complex m). δ_C (75 MHz, $CDCl_3$) 195.2, 159.6, 146.5, 131.4, 130.2, 129.3, 113.8, 82.6, 78.2, 75.1, 73.0, 59.1, 55.2. ν_{max} (NaCl)/cm^{-1} 3440, 2933, 1689, 1611, 1514, 1248, 1117, 1062, 1031, 822. *m/z* (ESI) 381 and 379 $[M + Na]^+$ (65 and 63%), 121 (100).

*Compound **16a***

A magnetically stirred solution of compound **15a** (132 mg, 0.37 mmol) in CH_2Cl_2 (6 mL) maintained under a nitrogen atmosphere at −78°C was treated with 2,6-lutidine (129 μL, 1.11 mmol). The ensuing mixture was stirred at −78°C for 5 min and then treated with TBDMSOTf (128 μL, 0.56 mmol). After stirring the reaction mixture at −78°C for 10 min it was allowed to warm to 0°C and stirred at this temperature for 1 h then quenched with NH_4Cl (2 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (hexane → 1/9, v/v, ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_F 0.26 in 1/9, v/v, ethyl acetate/hexane) then gave the title *tris-ether **16a*** (158 mg, 91%) as a clear, pale-yellow oil, $[\alpha]_D$ −97.5 (*c* 3.02, $CHCl_3$). (Found: $[M + Na]^+$, 493.1021. $C_{21}H_{31}{}^{79}BrO_5Si$ requires $[M + Na]^+$: 493.1022.) δ_H (300 MHz, $CDCl_3$) 7.37 (2H, d, *J* 8.7), 6.90 (2H, d, *J* 8.7), 6.41 (1H, s), 4.84 (2H, ABq, *J* 10.8), 4.52 (1H, d, *J* 3.3), 4.46 (1H, d, *J* 9.0), 3.81 (3H, s), 3.54 (1H, dd, *J* 8.7 and 3.3), 3.52 (3H, s), 0.92 (9H, s), 0.13 (3H, s), 0.10 (3H, s). δ_C (75 MHz, $CDCl_3$) 194.1, 159.5, 145.5, 132.1, 130.1, 129.4, 113.7, 82.7, 77.9, 74.7, 74.0, 59.5, 55.2, 25.6, 18.4, −4.9, −5.3. ν_{max} (NaCl)/cm^{-1} 2952, 2930, 2856, 1698, 1612, 1514, 1463, 1250, 1150. *m/z* (ESI) 495 and 493 $[M + Na]^+$ (25 and 23%), 121 (100).

*Compound **17a***

A magnetically stirred solution of thiophenyl copper[22] (17 mg, 96 μmol) in THF (0.8 mL) maintained under a nitrogen atmosphere at 18°C was treated with MeLi (59 μL of a 1.6 M solution in hexanes, 96 μmol). The resulting solution was stirred at this temperature for 10 min by which time a clear, red solution had formed. This solution was cooled to −78°C and then a solution of bromide **16a** (30 mg, 64 μmol) in THF (1 mL) was added dropwise. The resulting mixture was allowed to warm to 0°C and stirred at this temperature for 1 h before being treated with methanol (1 mL) followed by NH_4Cl (2 mL of a saturated aqueous solution). The two phases so-formed were separated and the aqueous one was extracted with diethyl ether (3 × 2 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (1/9, v/v, ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.07) afforded the *β-methylenone **17a*** (23 mg, 89%) as a clear, pale-yellow oil, $[\alpha]_D$ −71.1 (*c* 1.10, $CHCl_3$). (Found: $[M + Na]^+$, 429.2072. $C_{22}H_{34}O_5Si$ requires $[M + Na]^+$: 429.2073.) δ_H (300 MHz, $CDCl_3$) see Table 1. δ_C (75 MHz, $CDCl_3$) see Table 1. ν_{max} (NaCl)/cm^{-1} 2930, 2856, 1690, 1612, 1514, 1250, 1154, 1109, 1065, 1039, 881, 837. *m/z* (ESI) 445 $[M + K]^+$ (56%), 429 $[M + Na]^+$ (35), 121 (100).

*Compound **12b***

A magnetically stirred solution of acetal **11** (1.12 g, 3.64 mmol) in CH_2Cl_2 (25 mL) maintained at −78°C under a nitrogen atmosphere was treated with DIBAL-H (14.5 mL of a 1 M solution in hexanes, 14.5 mmol). The resulting solution was stirred at −78°C for 1 h and then quenched (**CAUTION!**) with sodium potassium tartrate (30 mL of a saturated aqueous solution). The resulting mixture was stirred vigorously at 18°C for 1 h and then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. Subjection of this material to flash chromatography (15/85, v/v, ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_F 0.24 in 3/7, v/v, ethyl acetate/hexane) afforded the ether **12a** (117 mg, 10%) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample obtained as described above.

Concentration of fraction B (R_F 0.26 in 3/7, v/v, ethyl acetate/hexane) afforded ether **12b** (818 mg, 72%) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample obtained as described above.

*Compound **13b***

A magnetically stirred solution of alcohol **12b** (150 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) maintained at 0°C under a nitrogen atmosphere was treated with 1,8-bis(dimethylamino)naphthalene (Proton Sponge, 311 g, 1.45 mmol) followed by trimethyloxonium tetrafluoroborate (107 mg, 0.73 mmol). The resulting solution was stirred at 18°C for 2 h before being quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were then washed with citric acid (50 mL of a 10% w/v aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (1/10/89, v/v/v, Et_3N/ethyl acetate/hexane elution) to yield, after concentration of the appropriate fractions (R_F 0.2 in 15/85, v/v, ethyl acetate/hexane), *methyl ether **13b*** (139 mg, 89%) as a clear, colourless oil, $[\alpha]_D$ −95.1 (*c* 2.18, $CHCl_3$). (Found: $[M + Na]^+$, 347.0260. $C_{15}H_{17}{}^{79}BrO_3$ requires $[M + Na]^+$: 347.0259.) δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.7), 6.90 (2H, d, *J* 8.7), 6.47 (1H, d, *J* 5.7), 5.99 (1H, ddt, *J* 9.6, 2.4, and 0.9), 5.78 (1H, ddd, *J* 9.6, 5.7, and 2.7), 4.63 (2H, ABq, *J* 11.7), 4.43–4.37 (1H, complex m), 4.04 (1H, dd, *J* 6.9 and 0.9), 3.81 (3H, s), 3.51 (3H, s). δ_C (75 MHz, $CDCl_3$) 159.3, 129.9, 129.7, 129.4, 129.0, 122.4, 121.9, 113.8, 78.2, 76.1, 70.8, 57.8, 55.2. ν_{max} (NaCl)/cm^{-1} 2930, 1612, 1513, 1248, 1172, 1111, 1074, 1033, 822. *m/z* (ESI) 349 and 347 $[M + Na]^+$ (9 and 9%), 229 (48), 215 (100).

*Compound **14b***

A magnetically stirred solution of diene **13b** (418 mg, 1.29 mmol) in acetone (10.8 mL) maintained at 0°C was treated with a solution of *N*-methylmorpholine *N*-oxide (334 mg, 2.84 mmol) in H_2O (1.2 mL) then dropwise, with OsO_4 (0.33 mL of 0.197 M solution in *t*-BuOH, 64.4 μmol). The ensuing mixture was allowed to warm to 18°C and stirred at this temperature for 16 h before being treated with $Na_2S_2O_3$ (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL) and the combined organic phases were then washed with brine (1 × 70 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash column chromatography (1/1, v/v, ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.2) afforded *diol **14b*** (238 mg, 52%) as a clear, colourless oil, $[\alpha]_D$ −110.5 (*c* 2.25, $CHCl_3$). (Found: $[M + Na]^+$, 381.0310. $C_{15}H_{19}{}^{79}BrO_5$ requires $[M + Na]^+$: 381.0314.) δ_H (300 MHz, $CDCl_3$) 7.29 (2H, d, *J* 9.0), 6.90 (2H, d, *J* 9.0), 6.22 (1H, d, *J* 5.4), 4.62 (2H, ABq, *J* 11.1), 4.30 (1H, dd, *J* 5.4 and 4.5), 4.02 (1H, dd, *J* 9.9 and 4.2), 4.01 (1H, d, *J* 3.9), 3.87 (1H, dd, *J* 10.2 and 3.6), 3.81 (3H, s),

3.64 (3H, s), 2.86 (2H, br s). δ_C (75 MHz, $CDCl_3$) 159.6, 130.9, 129.7, 129.4, 125.2, 114.0, 80.6, 76.8, 72.6, 67.0, 66.6, 61.2, 55.3. ν_{max} (NaCl)/cm^{-1} 3412, 2930, 2834, 1612, 1514, 1249, 1107, 1037, 822. *m/z* (ESI) 383 and 381 $[M + Na]^+$ (55 and 54%), 121 (100).

*Compound **15b***

A magnetically stirred a solution of diol **14b** (69 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) maintained at 0°C under a nitrogen atmosphere was treated, in portions over 0.5 h, with *p*-TsOH·H_2O (55 mg, 0.29 mmol) followed by 4-acetamido-TEMPO (62 mg, 0.29 mmol). The resulting solution was allowed to warm to 18°C and then stirred at this temperature for 2 h. The reaction mixture was then re-cooled to 0°C and further aliquots of *p*-TsOH·H_2O (55 mg, 0.29 mmol) and 4-acetamido-TEMPO (62 mg, 0.29 mmol) were added in portions over 0.5 h. The resulting solution was, once again, allowed to warm to 18°C. After 1 h at this temperature, the reaction mixture was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and the separated aqueous phase extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (3/7, v/v, ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.16 in 1/4, v/v, ethyl acetate/hexane) afforded *hydroxy enone **15b*** (41 mg, 61%) as a clear, colourless oil, $[\alpha]_D$ −42.7 (*c* 2.05, $CHCl_3$). (Found: $[M + Na]^+$, 379.0151. $C_{15}H_{17}{}^{79}BrO_5$ requires $[M + Na]^+$: 379.0157.) δ_H (300 MHz, $CDCl_3$) 7.32 (2H, d, *J* 8.7), 6.90 (2H, d, *J* 8.7), 6.52 (1H, d, *J* 0.6), 4.78 (2H, ABq, *J* 11.7), 4.61 (1H, dd, *J* 10.5 and 1.5), 4.13 (1H, dd, *J* 3.9 and 0.6), 3.81 (3H, s), 3.73 (3H, s), 3.72 (1H, dd, *J* 10.5 and 3.6), 3.33 (1H, d, *J* 1.5). δ_C (75 MHz, $CDCl_3$) 195.4, 159.4, 146.3, 131.2, 129.6(5), 129.5(7), 113.9, 82.5, 79.2, 73.3, 73.1, 62.0, 55.2. ν_{max} (NaCl)/cm^{-1} 3460, 2931, 2834, 1689, 1611, 1514, 1248, 1119, 827. *m/z* (ESI) 381 and 379 $[M + Na]^+$ (37 and 38%), 121 (100).

*Compound **16b***

A magnetically stirred solution of alcohol **15b** (41 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) maintained at −78°C under a nitrogen atmosphere was treated with 2,6-lutidine (40 μL, 0.35 mmol). The ensuing mixture was stirred at −78°C for 5 min and then TBDMSOTf (40 μL, 0.17 mmol) was added. The reaction mixture was then stirred at −78°C for 10 min before being allowed to warm to 0°C and then stirred at this temperature for 1 h before being quenched by the addition of NH_4Cl (4 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic phases were then dried ($MgSO_4$) before being filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (hexane → 5/95, v/v, ethyl acetate/hexane gradient elution) and concentration of the relevant fractions (R_F 0.3 in 1/9, v/v, ethyl acetate/hexane) then gave *ether **16b*** (46 mg, 82%) as a pale-yellow oil, $[\alpha]_D$ −50.2 (*c* 1.84, $CHCl_3$). (Found: $[M + Na]^+$, 493.1021. $C_{21}H_{31}{}^{79}BrO_5Si$ requires $[M + Na]^+$: 493.1022.) δ_H (300 MHz, $CDCl_3$) 7.27 (2H, d, *J* 8.7), 6.88 (2H, d, *J* 8.7), 6.40 (1H, s), 4.68 (2H, ABq, *J* 11.7), 4.42 (1H, d, *J* 9.3), 4.08 (1H, d, *J* 3.6), 3.81 (3H, s), 3.78 (1H, dd, *J* 9.3 and 3.6), 3.67 (3H, s), 0.92 (9H, s), 0.13 (3H, s), 0.07 (3H, s). δ_C (75 MHz, $CDCl_3$) 194.4, 159.4, 145.1, 132.2, 129.8, 129.5, 113.8, 81.9, 79.0, 74.3, 73.4, 61.3, 55.2, 25.7, 18.5, −4.8, −5.2. ν_{max} (NaCl)/cm^{-1} 2952, 2930, 2856, 1697, 1613, 1514, 1249, 1147, 1121, 827, 780. *m/z* (ESI) 495 and 493 $[M + Na]^+$ (21 and 20%), 121 (100).

A sample of this compound could be crystallized from hexane/$CHCl_3$ to give material (mp 71–72°C) suitable for single-crystal X-ray analysis.

*Compound **17b***

A magnetically stirred solution of thiophenyl copper[22] (25 mg, 0.15 mmol) in THF (1.2 mL) maintained at 18°C under a nitrogen atmosphere was treated with methyllithium (92 μL of a 1.6 M solution in diethyl ether, 0.15 mmol). The resulting solution was stirred at 18°C for 10 min at which point a clear, red solution had formed. The reaction mixture was cooled to −78°C and then a solution of bromide **16b** (46 mg, 98 μmol) in THF (1.8 mL) was added dropwise. The resulting solution was allowed to warm to 0°C, stirred at this temperature for 1 h, and then treated with methanol (1 mL) followed by NH_4Cl (2 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (3 × 2 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash column chromatography (1/9, v/v, ethyl acetate/hexane elution) and concentration of the relevant fractions (R_F 0.09 in 1/9, v/v, ethyl acetate/hexane) gave *enone **17b*** (32 mg, 80%) as a clear, pale-yellow oil, $[\alpha]_D$ −20.9 (*c* 1.60, $CHCl_3$). (Found: $[M + Na]^+$, 429.2072. $C_{22}H_{34}O_5Si$ requires $[M + Na]^+$: 429.2073.) δ_H (300 MHz, $CDCl_3$) see Table 1. δ_C (75 MHz, $CDCl_3$) see Table 1. ν_{max} (NaCl)/cm^{-1} 2952, 2929, 2886, 2856, 1688, 1514, 1249, 1152, 1092, 837. *m/z* (ESI) 429 $[M + Na]^+$ (38%), 121 (100).

X-Ray Crystallographic Study

*Crystal Data for Compound **16b***

$C_{21}H_{31}O_5Si$, *M* 471.46, *T*200(1) K, orthorhombic, space group $P2_12_12_1$, *Z* 4, *a* 7.3920(1), *b* 10.6998(2), *c* 29.7883(5) Å, *V* 2356.04(7) Å^3, D_x 1.329 g cm^{-3}, 5393 unique data ($2\theta_{max}$ 55°), 4044 with $I > 2.0\sigma(I)$; *R* 0.040, *Rw* 0.095, *S* 0.88, Flack parameter = 0.010.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ 0.71073 Å) and data extracted using the *DENZO* package.[23] Structure solution was by direct methods (SIR92)[24] and the refinement was carried out using the *CRYSTALS* program package.[25] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 715994). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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