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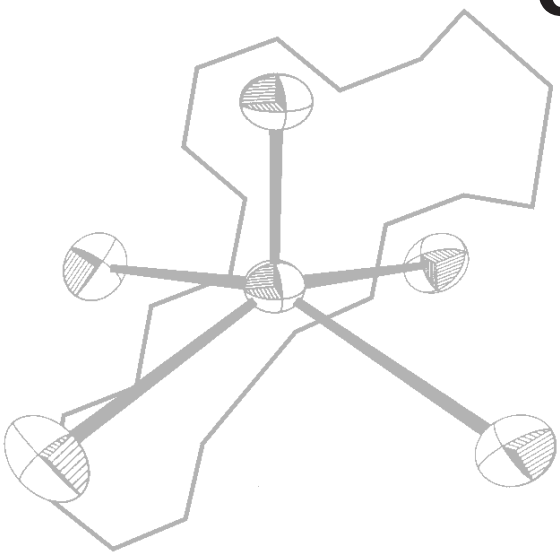

Volume 53, 2000

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Aust. J. Chem., 2000, **53**, 845–851

Synthesis of an Oxaspirolactone Intermediate for the Synthesis of Spirolides

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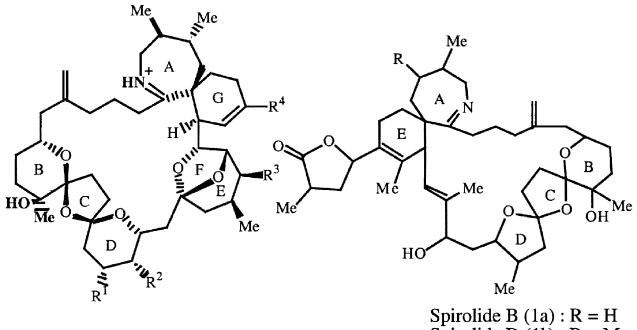
A new method has been established for the preparation of C2-oxidized 5,5-spiroacetals, which are key intermediates for the synthesis of the *bis*-spiroacetal moiety of the spirolides. A bridged orthoester was used as a masked carboxylic acid in the preparation of these bicyclic oxaspirolactones. The synthesis of chiral lactone (12), a building block for the synthesis of the spirolides, is also reported. The two chiral centres in lactone (12) were assembled by addition of a chiral crotyl borane to an aldehyde. The structure of lactone (12) was determined by single-crystal X-ray diffraction; orthorhombic space group $P2_12_12_1$(No. 19), *a* 12.437(2), *b* 23.881(4), *c* 7.545(1) Å, *V* 2240.9(5) Å^3, *R*(*F*) 0.0460, and $R_w(F)$ 0.0458.

Keywords: Spirolides, oxaspirolactones; spirolactones.

Introduction

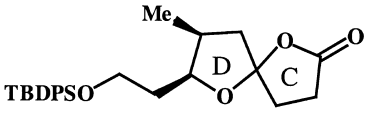
Spirolides B (1a) and D (1b) were isolated in 1995 by Wright *et al.*[1] and were found to be structurally related to the pinnatoxins (2a–d) in that they contain a 6,5,5-*bis*-spiroacetal system, whereas the pinnatoxins contain a 6,5,6-spiroacetal system. The spiro bicyclic imine is common to both the spirolides and the pinnatoxins. To date no synthesis of the spirolides has been reported and the stereochemistry of the spirolides has yet to be determined. We herein report the synthesis of oxaspirolactone (3), which is a key intermediate for the synthesis of the *bis*-spiroacetal moiety of the spirolides.

The syntheses of 6,6-, 5,6- and 5,5-oxaspirolactones have been reported by either a mercury(II) oxide promoted cyclization of a hydroxy alkynoic acid,[2] or an analogous palladium(II)-induced cyclization.[3] DeShong generated a manganese complex from tetrahydrofuran, which, after regiospecific insertion of methyl acrylate and photodemetallation, afforded an oxaspirolactone on acid treatment.[4] A common approach has also involved the addition of organocerium reagents to succinic anhydride.[5] Furyl alcohols have also provided useful precursors to α,β-unsaturated spirolactones.[6,7]

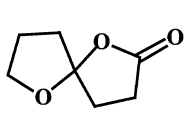


Spirolide B (1a) : R = H
Spirolide D (1b) : R = Me

Pinnatoxin A (2a) : $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = COO^-$
Pinnatoxin B (2b) : $R^1 = R^2 = H$, $R^3 = OH$, $R^4 =$ C*H(OH)COO
Pinnatoxin C (2c) : $R^1 = R^2 = H$, $R^3 = OH$, $R^4 =$ C*H(OH)COO-
Pinnatoxin D (2d) : $R^1 = Me$, $R^2 = OH$, $R^3 = H$, $R^4 = CO(CH_2)_2COO^-$



(3)



(4)

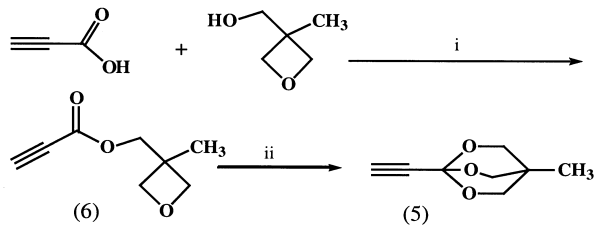
We herein report a new method for the synthesis of 5,5-oxaspirolactones which makes use of a bridged orthoester as a masked carboxylic acid.

Results and Discussion

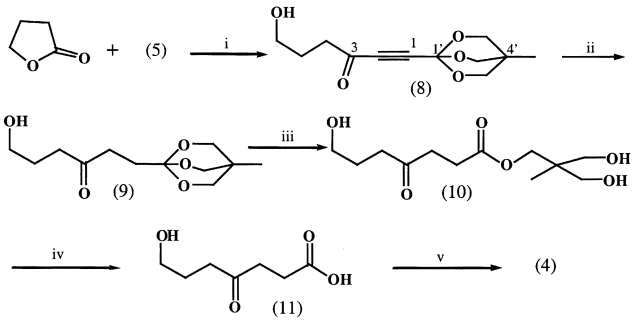
Our retrosynthesis adopted for the *bis*-spiroacetal moiety of the spirolides involved initial assembly of the C,D ring, spirolactone (3), followed by attachment of the B ring. The lactone functionality in oxaspirolactone (3) would be used to append the B ring and the protected hydroxy group would provide a handle for further elaboration of the left-hand side of the molecule. The synthesis of bicyclic lactone (3) requires flexibility in the introduction of the two substituents on the D ring so that a number of stereoisomers can be prepared for comparison with the natural product. For the present study, we decided to introduce substituents on the D ring which have the same stereochemistry as that found in the pinnatoxins (2a–d).

Methodology was initially developed for the preparation of unsubstituted oxaspirolactone (4). This synthetic strategy was then applied to the synthesis of the chiral oxaspirolactone (3).

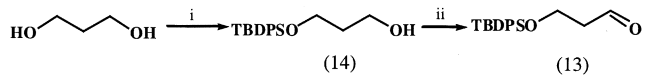
Manuscript received 21 August 2000 10.1071/CH00111 0004-9425/00/100845



Scheme 1. Reagents and conditions : (i) DCC, DMAP, CH_2Cl_2, 0°C, 2h, 51%; (ii) $BF_3.Et_2O$, CH_2Cl_2, RT, 24h, 56%.



Scheme 2. Reagents and conditions : (i) ^nBuLi, THF, -10°C, 71%; (ii) H_2, 10% Pd-C, EtOAc; (iii) PPTS, MeOH-H_2O (4: 1), RT, 1h; (iv) LiOH, H_2O, 25 min, followed by 2 M HCl; (v) *p*-TSA, Et_2O, $MgSO_4$, 30 min, 51% overall.



Scheme 3. Reagents and conditions : (i) NaH, THF, TBDPSCl, 67%; (ii) PCC, CH_2Cl_2, 80%.

In our approach to oxaspirolactones, we focused on the addition of an acetylide anion to butyrolactone, followed by (after hydrogenation) an acid-catalysed cyclization of a protected carboxylic acid. One requirement of this approach is that the carboxylic acid must be protected before the acetylide addition. The use of an orthoester (e.g. triethyl orthopropiolate) as a protected carboxylic acid is hampered by the lability of these acyclic orthoesters.[8] We therefore decided to protect the carboxylic acid as a more stable bridged orthoester.

Orthoester (5) (Scheme 1) has been used in the synthesis of several natural products including retgeranic acid,[9] ginkolide[10] and prostaglandins E_1 and D_2,[11,12] but its use in the synthesis of spirolactones has not been reported. Bridged orthoester (5) was prepared according to the procedure described by Ducray *et al.*,[8] starting from 3-(hydroxymethyl)-3-methyloxetane and propiolic acid (Scheme 1), affording 3-(hydroxymethyl)-3-methyloxetane ester (6) in 51% yield. Rearrangement to orthoester (5) then took place upon exposure of (6) to a catalytic quantity of boron trifluoride diethyl ether complex. Orthoester (5) was isolated in 56% yield as a crystalline solid.

The acetylide generated from orthoester (5) was used in reactions with electrophiles such as aldehydes and ketones to provide the corresponding alcohols.[8] Lactones have not been used as electrophiles and added to the acetylide generated from orthoester (5).

With orthoester (5) in hand, the addition of the corresponding acetylide to γ-butyrolactone could now be investigated. Addition of γ-butyrolactone as a solution in tetrahydrofuran to a solution of the lithium acetylide generated from orthoester (5), by using n-butyllithium at –10°C in tetrahydrofuran, afforded hydroxy ketone (8) in 71% yield (Scheme 2). The appearance of a strong carbonyl group absorbance at 1686 cm^{-1} and a strong absorbance at 3445 cm^{-1} due to an hydroxy group, in the infrared spectrum, supported formation of this product. In the ^{13}C n.m.r. spectrum a quaternary carbon due to the carbonyl group was observed at δ 186.3 and another quaternary resonance at δ 82.7 was assigned to C 1′, the orthoester carbon.

Hydrogenation of (8) over 10% Pd/C in ethyl acetate gave the saturated keto alcohol (9), which was not isolated. The carboxylic acid was then regenerated from the orthoester in two steps. First, orthoester (9) was treated with a catalytic quantity of pyridinium *p*-toluenesulfonate in MeOH-H_2O (4 : 1) to afford the intermediate diol ester (10). *In situ* treatment of this latter ester (10) with an aqueous solution of lithium hydroxide (LiOH) gave a carboxylate salt which was then acidified to pH 3 with 2 M hydrochloric acid solution to give keto acid (11).

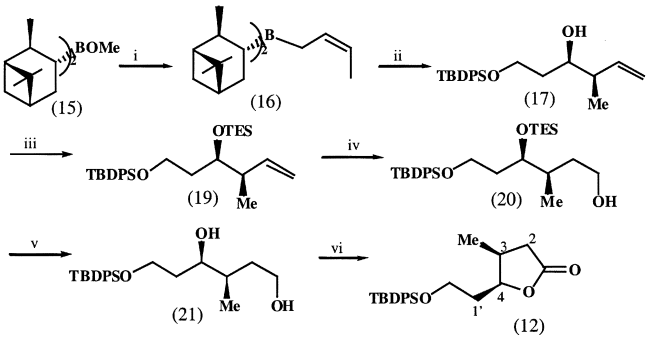
Cyclization to the spirolactone was then effected upon treatment of a solution of keto acid (11) in ether with a catalytic quantity of *p*-toluenesulfonic acid in the presence of anhydrous magnesium sulfate. Spirolactone (4) was isolated in 51% yield (over four steps) after 30 min at room temperature. The relatively low yield was attributed to the volatility and instability of the product.[3] In the ^{13}C n.m.r. spectrum for (4) the resonance due to the spiro carbon appeared at δ 116.2 and the quaternary resonance at δ 176.6 was assigned to the carbonyl carbon.

The synthesis of spirolactone (4) was originally reported by Kitching and coworkers[3] by using a palladium(II)-induced cyclization of hydroxyalkynoic acid. The alkynoic acid in turn was prepared in four steps.

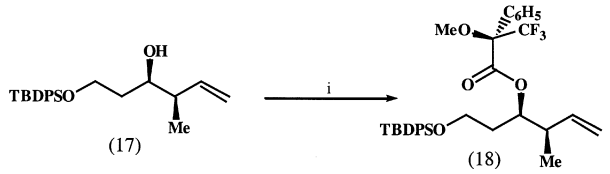
Having successfully prepared the model spirolactone (4), we next decided to prepare spirolactone (3) by using the same strategy. Spirolactone (3) is a key building block for the synthesis of the *bis*-spiroacetal moiety (the BCD ring systems) of the spirolides (1a) and (1b).

In order to prepare spirolactone (3) enantioselectively, a synthesis of lactone (12) was initially required. The route to lactone (12) is summarized in Scheme 4, in which the key step involves the addition of a chiral crotyl borane (α-B-methoxydiisocampheylborane)[13] to an aldehyde.

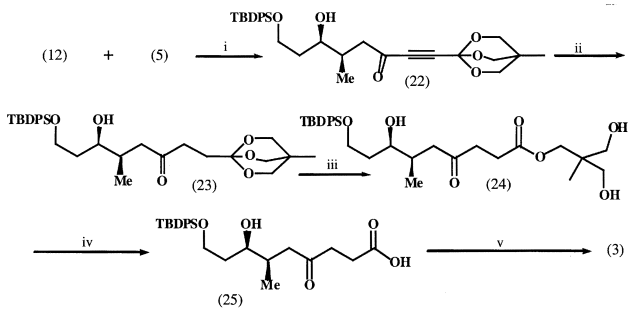
The known aldehyde (13)[14,15] required for the synthesis of lactone (12) was prepared in two steps from commercially available propane-1,3-diol (Scheme 3). Thus propane-1,3-diol was first monosilylated with sodium hydride and t-butyldiphenylsilyl chloride in tetrahydrofuran in 67% yield, according to the method reported by McDougal *et al.*[14] Oxidation of the remaining hydroxy group afforded aldehyde



Scheme 4. Reagents and conditions: (i) (*Z*)-but-2-ene, ^{n}BuLi, potassium *tert*-butoxide, $BF_3.Et_2O$; (ii) aldehyde (13), then NaOH, H_2O_2, 89%; (iii) $SiEt_3OTf$, Et_3N, CH_2Cl_2, 97%; (iv) $BH_3.Me_2S$, 5h, then H_2O_2, NaOH, 73%; (v) CSA, MeOH, 10 min, 88%; (vi) NMO, $(Ph_3P)_3RuCl_2$, acetone, RT, 18h, 72%.



Scheme 5. Reagents and conditions: (i) (*R*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl chloride, Et_3N, CH_2Cl_2, 69%.



Scheme 6. Reagents and conditions : (i) ^{n}BuLi, THF, -10 °C, 64%; (ii) H_2, 10% Pd-C, EtOAc; (iii) PPTS, MeOH-H_2O (4: 1), RT, 1h; (iv) LiOH, H_2O, 25 min, followed by 2 M HCl; (v) *p*-TSA, Et_2O, $MgSO_4$, 30 min, 10% overall.

(13) in 80% yield by using pyridinium chlorochromate (PCC) in dichloromethane.

Aldehyde (13) then underwent Brown crotylmetallation[13] with crotyl borane (16). Thus, treatment of the (–)-β-methoxydiisopinocampheylborane (15) (derived from (+)-α-pinene) with the organometallic reagent generated by treatment of *cis*-but-2-ene with n-butyllithium and potassium t-butoxide gave (*Z*)-but-2-enyl diisopinocampheylborane (16) (Scheme 4) which was reacted *in situ* with aldehyde (13) to give the *syn* homoallylic alcohol (17)[15] in 89% yield.

A protonated molecular ion at *m/z* 369.2250 in the high-resolution mass spectrum for (17) supported the molecular formula $C_{23}H_{30}O_2Si$. The infrared spectrum exhibited a hydroxyl absorbance at 3502 cm^{-1}, while vinylic protons were evident at δ 5.11 and 5.86 in the ^{1}H n.m.r. spectrum.

Upon examination by ^{1}H and ^{13}C n.m.r. spectroscopy, alcohol (17) appeared to be essentially a single diastereomer. This diastereomer was shown to exhibit an enantiomeric excess of >97% by conversion to the corresponding Mosher[16] ester (18) by treatment with (*R*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl chloride (Scheme 5). The ^{1}H n.m.r. spectrum of the derived Mosher ester (18) displayed a three-proton singlet at δ 3.46, assigned to the methoxy group, and a doublet at δ 0.98 (*J* 6.9 Hz), assigned to the methyl group.

Two new chiral carbon atoms are formed in this crotyl metallation step; hence four isomeric alcohols could be obtained. Under the reaction conditions adopted ((+)-α-pinene as chiral auxiliary with a (*Z*)-alkene) one diastereomer (17) was formed. This approach is flexible in that it provides access to all four possible stereoisomers of (12) by selecting either the (*Z*)- or (*E*)-alkene for use with the appropriate enantiomer of α-pinene.

Alcohol (17) was then protected as a triethylsilyl ether (19) in 97% yield by using triethylsilyl trifluoromethanesulfonate and triethylamine in dichloromethane. Hydroboration of alkene (19) with borane–dimethyl sulfide complex in tetrahydrofuran, followed by alkaline peroxide oxidation, afforded the primary alcohol (20) in 72% yield. A protonated molecular ion at *m/z* 501.3211 in the high-resolution mass spectrum supported the molecular formula $C_{29}H_{48}O_3Si_2$. The absence of any vinylic protons in the ^{1}H n.m.r. spectrum and the appearance of a hydroxy group at 3613 and 3409 cm^{-1} in the infrared spectrum confirmed the formation of alcohol (20).

Selective cleavage of the triethylsilyl protecting group by camphorsulfonic acid (CSA) in methanol afforded diol (21) in 88% yield. Conversion of diol (21) to lactone (12) was then achieved by using tris(triphenylphosphine)ruthenium(II) chloride as catalyst and *N*-methylmorpholine-*N*-oxide as oxidant in acetone[17,18] to give an intermediate lactol which was further oxidized to lactone (12) in 72% yield. Disappearance of the hydroxyl absorbance and appearance of a lactone carbonyl absorbance at 1773 cm^{-1} in the infrared spectrum was the preliminary evidence for formation of lactone (12). This was confirmed by the ^{13}C n.m.r. spectrum which exhibited a characteristic resonance at δ 176.6, assigned to the carbonyl carbon.

The two substituents at C3 and C4 were expected to be *syn* to each other, on the basis of the relative stereochemistry of the diol precursor (21). In the ^{1}H n.m.r. spectrum of lactone (12) the two geminal protons H_{2A} and H_{2B} resonated at δ 2.71 and 2.18, respectively, with geminal coupling constant *J* 16.9 Hz. H4 appeared as a double triplet at δ 4.73 ($J_{4,3}$ 8.2 and $J_{4,1'\text{-CH2}}$ 5.6 Hz), while H3 appeared as a multiplet at δ 2.51–2.63. The methyl group resonated as a doublet (*J* 6.9 Hz) at δ 0.99. The expected relative stereochemistry of lactone (12) was confirmed with a single-crystal X-ray diffraction analysis (Fig. 1).

With chiral lactone (12) in hand, efforts were then directed towards its reaction with orthoester (5) in an attempt to synthesize lactone (3). The optimum results were obtained by treating orthoester (5) with n-butyllithium (1.2 equivalents) in tetrahydrofuran at –10°C to generate the acetylide, followed by addition of lactone (12) (1.2

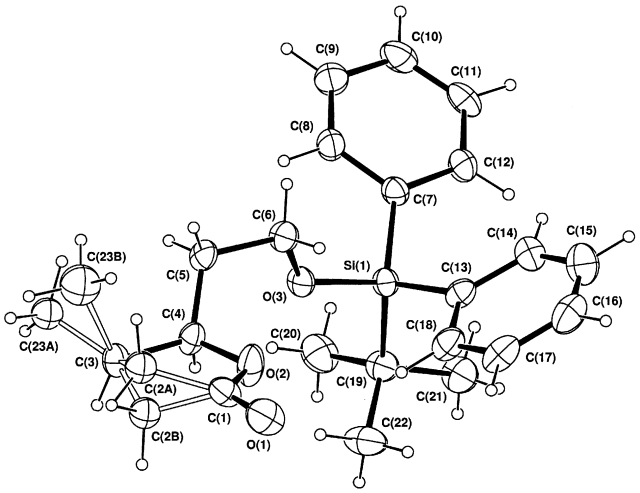


Fig. 1. ORTEP Projection of (12) with thermal ellipsoids at the 20% level. There is configurational disorder with A and B populations of 0.6 and 0.4 respectively.

equivalents) in tetrahydrofuran (Scheme 6). A mixture of the desired coupled product (22) (64%) was obtained together with unreacted lactone (12) (10%) and orthoester (5) (8%).

Examination of the infrared spectrum of the coupled product (22) showed a large absorbance at 3494 cm^{-1} assigned to a hydroxy group and a strong absorbance at 1745 cm^{-1} due to the carbonyl group. This provided strong evidence that the product is the open-chain keto acetylene (22) and not the hemiacetal.

Hydrogenation of keto acetylene (22) over 10% palladium on charcoal (Pd/C) in ethyl acetate gave the desired saturated ketone (23), which was not isolated. Release of the latent carboxylic acid was then achieved in two steps in methodology analogous to that used for the preparation of lactone (4) via diol ester (24). *In situ* hydrolysis of diol ester (24) gave carboxylic acid (25), which, upon treatment with a catalytic quantity of *p*-toluenesulfonic acid in the presence of anhydrous magnesium sulfate in diethyl ether, cyclized to give the desired spirolactone (3), albeit in low yield (10% yield).

An ion at *m/z* 381.1522 (M^+–^{t}Bu) in the high-resolution mass spectrum for spirolactone (3) supported the molecular formula $C_{26}H_{34}O_4Si$. An infrared absorbance at 1772 cm^{-1} indicated successful formation of a lactone. The ^{1}H n.m.r. spectrum exhibited a doublet (*J* 6.8 Hz) at δ 0.95, assigned to the methyl group, and two multiplets (integrating for a total of 10 protons) in the aromatic region provided strong evidence that the protecting group (TBDPS) was intact. The ^{13}C n.m.r. spectrum exhibited a characteristic resonance at δ 115.1, assigned to the newly formed spiro centre, and a quaternary carbon due to the lactone carbonyl was observed at δ 176.1.

Unfortunately, the ^{1}H n.m.r. spectrum did not provide any stereochemical information, since both key protons (H 7 and H 8) resonated as part of a multiplet. Hence the key coupling constant $J_{7,8}$ could not be used to assign the relative stereochemistry at these chiral centres. The stereochemistry at the two contiguous chiral centres C 7 and C 8 was assigned as *syn* by analogy with the simpler lactone (12).

The successful completion of the synthesis of spirolactone (3) constitutes a synthesis of the CD rings of spirolides. It now remains to append the B ring to the CD fragment. One advantage of this strategy is that it allows the synthesis of stereoisomers of spirolactone (3) by the appropriate choice of chiral crotyl borane used. One limitation to the synthesis of spirolactone (3) is the low yield observed in the final deprotection-cyclization step.

Experimental

General Details

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a PolAAR 2001 polarimeter at room temperature in the indicated solvent. Infrared spectra were recorded on a Perkin–Elmer 1600 Fourier-transform infrared spectrophotometer as thin film between sodium chloride plates. ^{1}H and ^{13}C n.m.r. spectra were obtained by using a Bruker AC 200 spectrometer. ^{13}C n.m.r. spectra were interpreted with the aid of DEPT 135 experiments. Low-resolution mass spectra were recorded on a VG 70-SE, VG 70-250S, VG 70-SD or AEI MS902 double-focusing magnetic-sector mass spectrometer operating with an ionization potential of 70 eV. High-resolution mass spectra were recorded at a nominal resolution of 5000 or 10 000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionization methods employed were (i) electron impact (EI), (ii) chemical ionization with ammonia or methane as reagent gas (CI) and (iii) electrospray chemical ionization (ESI). Flash chromatography was performed by using Merck Kieselgel 60 or Riedel-de-Haen Kieselgel S silica gel (both 230–400 mesh) with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine or vanillin in methanolic sulfuric acid.

Propiolic Acid 3-Methyl-3-(hydroxymethyl)oxetane Ester (6)

To a mixture of 3-(hydroxymethyl)-3-methyloxetane (3.7 g, 36 mmol), DCC (10 g, 50 mmol) and 4-dimethylaminopyridine (220 mg, 1.8 mmol) in dry dichloromethane (10 ml) at 0°C was added propiolic acid (2.55 g, 36 mmol) over 2.5 h, and the mixture was stirred for another 2 h. After filtration the mixture was washed with 1% ammonium chloride solution (50 ml) and 5% sodium hydrogen carbonate solution (50 ml), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude oil was distilled under reduced pressure to give the title compound (6) (2.87g, 51%) as a colourless oil, b.p. 56°C/0.4 mmHg (lit.[8] b.p. 50°C/0.3 mmHg). The spectroscopic data were in good agreement with those reported in the literature.[8]

1-Ethynyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (5)

Ester (6) (2.00 g, 13 mmol) was dissolved in dichloromethane (5 ml) and stirred with boron trifluoride–diethyl ether complex (30 µl) at room temperature under argon for 24 h. After treatment with triethylamine (0.5 ml) the mixture was diluted with diethyl ether and filtered through Celite to remove the boron trifluoride–triethylamine complex, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with dichloromethane (containing 1% triethylamine) as eluant to give the title compound (5) (1.17 g, 56%). The spectroscopic data were in good agreement with those reported in the literature.[8]

6-Hydroxy-1-(4'-methyl-2',6',7'-trioxabicyclo[2.2.2]octyl)hex-1-yn-3-one (8)

To a solution of orthoester (5) (200 mg, 1.3 mmol) in dry tetrahydrofuran (5 ml) cooled to –10°C under argon was added n-butyllithium (1.12 ml of a 1.4 M solution in hexanes, 1.56 mmol)

dropwise under argon. After stirring at –10°C for 1 h, a solution of γ-butyrolactone (134 mg, 1.56 mmol) in dry tetrahydrofuran (4 ml) was added in one portion and the mixture was stirred at –10°C for 1 h. Saturated aqueous ammonium chloride solution (3 ml) was added and the reaction mixture was extracted with ethyl acetate (3 × 10 ml), washed with brine (7 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure gave a colourless oil which was purified by flash chromatography with hexane/ethyl acetate (1 : 1) as eluant to give the *title compound* (8) (221 mg, 71%) as a colourless solid, m.p. 57–59°C (Found: MH^+, 241.1072. $C_{12}H_{17}O_5$ requires MH, 241.1076). υ_{max} ($CHCl_3$)/cm^{-1} 3445 (OH), 2935, 2886m (CH), 1686s (C=O), 1467, 1395, 1304, 1044. ^{1}H n.m.r. δ_H (200 MHz, $CDCl_3$) 0.84, s, CH_3; 1.70–1.95, 3H, m, C**H**$_2$CH$_2$C=O and OH; 2.71, t, *J* 7.1 Hz, CH_2C=O; 3.62, t, *J* 6.2 Hz, C**H**$_2$OH; 3.98, 6H, s, 3 × CH_2O. ^{13}C n.m.r. δ_C (50 MHz, $CDCl_3$) 14.2, CH_3, Me; 26.4, CH_2, **C**H$_2$CH$_2$OH; 30.3, quat., **C**Me; 42.0, CH_2, **C**H$_2$C=O; 61.5, CH_2, CH_2OH; 73.1, CH_2, 3 × CH_2O; 78.2, quat., **C**≡C–CO_3; 82.7, quat., C≡**C**–CO_3; 101.9, quat., CO_3; 186.3, quat., C=O. *m/z* (EI) 240 (M^+, 5%), 181 ($C_9H_9O_4$, 29), 142 (13), 113 (61), 89 (63), 70 (100).

1,6-Dioxaspiro[4.4]nonan-2-one (4)

A solution of alkyne (8) (180 mg, 0.75 mmol) in ethyl acetate (25 ml) was stirred with 10% Pd/C catalyst (10–15 mg) at room temperature under a balloon of hydrogen for 1 h. Removal of the catalyst by filtration through a short pad of Celite followed by removal of the solvent at reduced pressure afforded a colourless oil which was dissolved in methanol (4 ml) and H_2O (1 ml). Pyridinium *p*-toluenesulfonate (10 mg) was added and the mixture was stirred at room temperature for 1 h. Lithium hydroxide (60 mg) in water (3 ml) was then added, followed by water (4 ml) after 25 min, and the methanol was removed under reduced pressure. The reaction mixture was acidified with 2 M HCl, extracted with diethyl ether (3 × 10 ml) and dried over $MgSO_4$. Fresh $MgSO_4$ was then added, followed by *p*-toluenesulfonic acid (10 mg), and the mixture was stirred at room temperature for 30 min. After filtration the solvent was evaporated at 0°C to give a pale yellow oil which was purified by flash chromatography with pentane/diethyl ether (1 : 1) to give the unstable and volatile title compound (4) as a colourless oil (55 mg, 51%). The spectroscopic data were in good agreement with those reported in the literature.[3]

3-(t-Butyldiphenylsilyloxy)propan-1-ol (14)

Sodium hydride (60%, 1.0 g, 25 mmol) was washed with dry pentane (3 × 6 ml) and suspended in dry tetrahydrofuran (45 ml) under argon. A solution of propane-1,3-diol (1.9 g, 0.025 mol) in dry tetrahydrofuran (5 ml) was then added dropwise at room temperature and the mixture was stirred for 1 h, resulting in formation of a white precipitate. t-Butyldiphenylsilyl chloride (6.78 g, 6.5 ml, 25 mmol) was then added dropwise and the reaction was stirred vigorously for 18 h. The reaction mixture was poured into diethyl ether (200 ml) then washed with 10% aqueous K_2CO_3 (50 ml) and brine (50 ml). After drying over Na_2SO_4, concentration under reduced pressure afforded an oil which was purified by flash chromatography with hexane/ethyl acetate (3 : 1) as eluant, to afford the title compound (14) (5.23 g, 67%) as a colourless oil. The spectroscopic data were in good agreement with those reported in the literature.[19]

3-(t-Butyldiphenylsilyloxy)propanal (13)

Activated powdered molecular sieves (4 Å, 420 mg) and sodium acetate (21 mg, 0.26 mmol) were added to a solution of the alcohol (14) (200 mg, 0.6 mmol) in dry dichloromethane (10 ml) at room temperature under argon. To the suspension was added pyridinium chlorochromate (276 mg, 1.28 mmol), and the dark mixture was stirred for 2 h then filtered through silica gel. The filtrate was concentrated under reduced pressure and purified by flash chromatography with hexane/diethyl ether (9 : 1) as eluant to afford the title compound (13) (159 mg, 80%) as a colourless oil. The spectroscopic data were good in agreement with those reported in the literature.[15,20]

(+)-(3R,4R)-6-(t-Butyldiphenylsilyloxy)-3-methylhex-1-en-4-ol (17)

To a stirred mixture of potassium t-butoxide (1.69 g, 15 mmol) and *cis*-but-2-ene (2.8 ml, 30 mmol) in tetrahydrofuran (12 ml) at –78°C, was added dropwise n-butyllithium (6 ml, 15 mmol, 2.5 M solution in hexanes). The resulting mixture was stirred at –45°C for 10 min, then the orange solution was recooled to –78°C and (–)-β-methoxydiisopinocampheylborane (5.1 g, 16 mmol) in tetrahydrofuran (18 ml) was added dropwise. After the reaction mixture was stirred at –78°C for 30 min, boron trifluoride etherate (2.33 ml, 19.9 mmol) was added dropwise, followed by a solution of the aldehyde (13) (6.54 g, 21 mmol) in tetrahydrofuran (15 ml). The mixture was stirred for a further 3 h at –78°C then treated with 3 N sodium hydroxide (8 ml) and 30% hydrogen peroxide (3.5 ml) and heated under reflux for 1 h. The tetrahydrofuran was partially evaporated and the residue extracted with diethyl ether (3 × 40 ml). The combined organic layers were washed with water (25 ml) and brine (25 ml) and then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a yellow oil which was purified by flash chromatography with hexane/ethyl acetate (4 : 1) as eluant, to give the title compound (17) (3.26 g, 89%) as a colourless oil, $[\alpha]_D$ +17.0° (*c*, 1.23, acetone), lit.[15] $[\alpha]_D$ +3.3° (*c*, 1.06, $CHCl_3$). The spectroscopic data were in good agreement with those reported in the literature.[15]

Mosher Ester (18)

(*R*)-2-Methoxy-2-trifluoromethyl-2-phenylacetyl chloride (32 μl, 0.17 mmol) was added to a solution of alcohol (17) (52 mg, 0.14 mmol) in carbon tetrachloride/pyridine (1 ml of a 1 : 1 mixture). The mixture was stirred at room temperature for 24 h and water (1 ml) was added. The mixture was diluted with diethyl ether (20 ml), washed with aqueous hydrogen chloride (0.1 M, 5 ml), saturated aqueous sodium hydrogen carbonate (5 ml), water (5 ml) and brine (5 ml), and dried ($MgSO_4$). After concentration of the organic extracts under reduced pressure, chromatography of the residue with hexane/ethyl acetate (9 : 1) as eluant afforded ester (18) (57 mg, 69%) as a colourless oil. ^{1}H n.m.r. δ_H (200 MHz, $CDCl_3$) 0.98, d, *J* 6.9 Hz, CH_3; 1.07, s, $(CH_3)_3$; 1.72–1.94, m, C**H**$_2$CH$_2$OSi; 2.50–2.62, m, C**H**Me; 3.46, s, OCH_3; 3.65–3.72, m, CH_2OSi; 4.88–5.01, m, HC=C**H**$_2$, 5.31–5.39, m, CHOC=O; 5.65, ddd, *J* 6.8, 10.5, 17.0 Hz, C**H**=CH_2; 7.32–7.55, 11H, m, ArH; 7.63–7.68, 4H, m, ArH. *m/z* (ESI) 607 [$(M+Na)^+$, 100%], 1190 [$(2M+Na)^+$, 15].

(+)-(3R,4R)-6-(t-Butyldiphenylsilyloxy)-4-(triethylsilyloxy)-3-methylhex-1-ene (19)

To a solution of alcohol (17) (988 mg, 2.7 mmol) in tetrahydrofuran (35 ml) at room temperature was added dry triethylamine (542 mg, 747 μl, 5.4 mmol) followed by chlorotriethylsilane (485 mg, 540 μl, 3.2 mmol). The reaction mixture was stirred at room temperature for 24 h, whereupon a white precipitate formed. Water (7 ml) was added and the reaction mixture was extracted with diethyl ether (3 × 40 ml). The organic extract was washed with water (30 ml) and brine (30 ml) and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a pale yellow liquid which was purified by flash chromatography with hexane/ethyl acetate (95 : 5) as eluant to give the *title compound* (19) (1.25 g, 97%) as a colourless oil. $[\alpha]_D$ +19.1° (*c*, 2.1, acetone). (Found: MH^+, 483.3115. $C_{29}H_{47}O_2Si_2$ requires MH, 483.3114). υ_{max} ($CHCl_3$)/cm^{-1} 2958s, 2876m, 1589w, 1472w, 1427w, 1240w, 1110s, 1007m, 940w, 823m. ^{1}H n.m.r. δ_H (200 MHz, $CDCl_3$) 0.59, q, *J* 8.0 Hz, 3 × CH_2Si; 0.90–0.98, m, 3 × C**H**$_3$CH$_2$Si and C**H**$_3$; 1.07, br s, $(CH_3)_3$; 1.52–1.79, m, C**H**$_2$CH$_2$OSi; 2.21–2.39, m, C**H**CH=CH_2; 3.74, t, *J* 6.3 Hz, CH_2OSi; 3.81–3.89, m, CHOSi; 4.96–5.04, m, HC=C**H**$_2$; 5.80–5.97, m, C**H**=CH_2; 7.38–7.45, 6H, m, ArH; 7.65–7.72, 4H, m, ArH. ^{13}C n.m.r. δ_C (50 MHz, $CDCl_3$) 5.2, CH_2, 3 × CH_2Si; 7.0, CH_3, 3 × CH_3CH_2Si; 14.7, CH_3, Me; 19.2, quat., $C(CH_3)_3$; 26.8, CH_3, $C(CH_3)_3$; 36.6, CH_2, C 5; 43.2, CH, $CHCH_3$; 60.9, CH_2, CH_2OSi; 72.8; CH, CHOSi; 114.1, CH_2, CH=CH_2; 127.6, 129.5, 135.6, 3 × CH, ArC; 134.0; quat., ArC; 141.1, CH, CH=CH_2. *m/z* (CI, CH_4) 483 (MH^+, 100%), 453 (M–C_2H_5, 60), 405 (M–C_6H_6, 32), 351 (M–$OSiEt_3$, 29).

*(+)-(3*R*,4*R*)-6-(t-Butyldiphenylsilyloxy)-4-(triethylsilyloxy)-3-methylhexan-1-ol (20)*

To a solution of (19) (299 mg, 0.62 mmol) in dry tetrahydrofuran (8 ml) at 0°C and under argon was added dropwise a solution of borane–dimethylsulfide complex (2.0 M in tetrahydrofuran, 0.93 ml, 1.86 mmol), and the mixture was stirred at room temperature until all the alkene had been consumed (t.l.c.). The mixture was cooled to 0°C and treated with aqueous sodium hydroxide (3 M, 10 ml). Oxidation was then carried out by slow dropwise addition of hydrogen peroxide (35%, 5 ml), the temperature being maintained below 40°C. After stirring for 1 h, the solvent was evaporated and the residue extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with brine (20 ml), dried over sodium sulfate and concentrated under reduced pressure to give a colourless oil which was purified by flash chromatography with hexane/ethyl acetate (9 : 1) as eluant to afford the *title compound* (20) (224 mg, 73%) as a colourless oil. $[\alpha]_D$ + 21.4° (*c*, 0.45, CH_2Cl_2) (Found: MH^+, 501.3211. $C_{29}H_{49}O_3Si_2$ requires MH, 501.3220). υ_{max} ($CHCl_3$)/cm^{-1} 3613, 3406 (OH), 3072w, 2957s, 2933s, 2876s, 1589w, 1472m, 1427m, 1390m, 1111s, 1081s, 1006m, 940w, 822m. ^{1}H n.m.r. δ_H (200 MHz, $CDCl_3$) 0.63, q, *J* 7.9 Hz, 3 × CH_2Si; 0.90, d, *J* 6.8 Hz, CH_3; 0.97, t, *J* 7.9 Hz, 3 × C**H**$_3$$CH_2$Si; 1.10, br s, $(CH_3)_3$; 1.63–1.84, m, 2-CH_2 and 5-CH_2; 2.20–2.38, m, C**H**CH_3; 3.07, br s, OH; 3.57–3.69, m, C**H**$_2$OH; 3.76, t, *J* 6.3 Hz, CH_2OSi; 3.89–3.97, m, CHOSi; 7.34–7.45, 6H, m, ArH; 7.67–7.74, 4H, m, ArH. ^{13}C n.m.r. δ_C (50 MHz, $CDCl_3$) 4.9, CH_2, 3 × CH_2Si; 6.8, CH_3, 3 × **C**H_3CH_2Si; 17.2, CH_3, Me; 19.1, quat., $C(CH_3)_3$; 26.8, CH_3, $C(CH_3)_3$; 34.8 and 35.3, 2 × CH_2, C 5 and C 2; 37.8, CH, $CHCH_3$; 60.8, CH_2, CH_2OSi; 62.1, CH_2, CH_2OH; 72.8, CH, CHOSi; 127.5, 129.5, 135.5, 3 × CH, ArC; 133.8, 133.9, quat., ArC. *m/z* (CI, CH_4) 501 (MH^+, 53%), 483 (M–H_2O, 8), 387 (M–$SiEt_3$, 89), 291 (M–2 × C_6H_5–^{t}Bu, 100), 175 (M–$SiPh_2$^{t}Bu–Me, 74).

*(+)-(3*R*,4*R*)-6-(t-Butyldiphenylsilyloxy)-3-methylhexan-1,4-diol (21)*

A solution of alcohol (20) (195 mg, 0.39 mmol) in methanol (25 ml) was cooled to 0°C and treated with solid camphorsulfonic acid (21 mg) in one portion. The reaction mixture was stirred for 10 min then quenched with solid $NaHCO_3$ (30 mg) and concentrated under reduced pressure. Purification by flash chromatography with hexane/ethyl acetate (1 : 1) as eluant afforded the *title compound* (21) (133 mg, 88%) as a colourless oil, $[\alpha]_D$ +10.3° (*c*, 1.63, acetone) (Found: MH^+, 387.2358. $C_{23}H_{35}O_3Si$ requires MH, 387.2355). υ_{max} ($CHCl_3$)/cm^{-1} 3687w, 3608w, 3501 (OH), 3072w, 2959s, 2931s, 2859m, 2364w, 1605w, 1472m, 1427m, 1390w, 1111s, 1077s, 822m. ^{1}H n.m.r. δ_H (200 MHz, $CDCl_3$) 0.94, d, *J* 6.7 Hz, CH_3; 1.07, br s, $(CH_3)_3$; 1.44–1.59, m, 2-CH_2; 1.67–1.92, m, H 3 and 5-CH_2; 3.25, br s, OH; 3.61–3.95, m, CH_2OSi, C**H**$_2$OH and CHOSi; 7.36–7.46, 6H, m, ArH; 7.65–7.74; 4H, m, ArH. ^{13}C n.m.r. δ_C (50 MHz, $CDCl_3$) 14.9, CH_3, Me; 18.9, quat., $C(CH_3)_3$; 26.7, CH_3, $C(CH_3)_3$; 34.4 and 35.9, 2 × CH_2, C 5 and C 2; 36.3, CH, $CHCH_3$; 60.7, CH_2, CH_2OSi; 64.0, CH_2, CH_2OH; 75.0, CH, CHOH; 127.7, 129.8, 135.5, 3 × CH, ArC; 132.8, 132.9, quat., ArC. *m/z* (CI, CH_4) 387 (MH^+, 55%), 329 (M–^{t}Bu, 15), 309 (MH–C_6H_6, 15), 291 (M–C_6H_6–H_2O), 231 (MH–2 × C_6H_6, 82) and 175 (M–2 × C_6H_6–^{t}Bu, 82).

(+)-(3S,4S)-4-[(2'-t-Butyldiphenylsilyloxy)ethyl]-3-methyl-γ-butyrolactone (12)

To a stirred suspension of the diol (21) (131 mg, 0.34 mmol) and molecular sieves (4 Å, 300 mg) in dry acetone (10 ml) were added *N*-methylmorpholine *N*-oxide (118 mg, 1.0 mmol) and tris(triphenylphosphine)ruthenium(II) chloride (12 mg). The gold suspension was stirred under argon for 18 h then filtered through Celite. The filtrate was concentrated under reduced pressure and purified by flash chromatography with hexane/ethyl acetate (9 : 1) as eluant to afford the *title compound* (12) (95 mg, 72%) as a colourless solid (from hexane, m.p. 93–94°C). $[\alpha]_D$ +49.6° (*c*, 0.24, acetone) (Found: MH^+, 383.2018. $C_{23}H_{31}O_3Si$ requires MH, 383.2042). υ_{max} ($CHCl_3$)/cm^{-1} 3051w, 2961, 2931m, 2858w, 1773s (C=O, lactone), 1472w, 1427m, 1210w, 1169m, 1112s, 1090m, 935w and 823w. ^{1}H n.m.r. δ_H (200 MHz, $CDCl_3$) 0.99, d, *J* 6.9 Hz, CH_3; 1.08, s, $(CH_3)_3$; 1.78–1.88, m, C**H**$_2$$CH_2$OSi; 2.18, dd, $J_{2A,2B}$ 16.9, $J_{2A,3}$ 3.9 Hz, H_A 2; 2.51–2.63, m, C**H**CH_3; 2.71, dd, $J_{2B,2A}$ 16.9, $J_{2B,3}$ 7.8 Hz, H_B 2; 3.82–3.88, m, CH_2OSi; 4.73, dt, $J_{4,3}$ 8.2, $J_{4,1'}$ 5.6 Hz, H 4; 7.34–7.46, 6H, m, ArH; 7.65–7.72, 4H, m, ArH. ^{13}C n.m.r. δ_C (50 MHz, $CDCl_3$) 14.0, CH_3, Me; 19.0, quat., $C(CH_3)_3$; 26.8, CH_3, $C(CH_3)_3$; 32.8, CH_2, **C**H_2CH_2OS; 32.8, CH, C 3; 37.4, CH_2, C 2; 60.3, CH_2, CH_2OSi; 80.1, CH, C 4; 127.6, 129.6, 135.4, 3 × CH, ArC; 133.3 and 133.5, quat., ArC; 176.6, quat., C=O. *m/z* (CI, CH_4) 383 (MH^+, 3%), 325 (M–^{t}Bu, 10), 305 (MH–C_6H_6, 100).

*(5*R*,6*R*)-8-(t-Butyldiphenylsilyloxy)-6-hydroxy-5-methyl-1-(4'-methyl-2',6',7'-trioxabicyclo[2.2.2]octyl)hex-1-yn-3-one (22)*

To a solution of orthoester (5) (77 mg, 0.5 mmol) in dry tetrahydrofuran (6 ml) cooled to –10°C under argon was added n-butyllithium (0.4 ml of a 1.5 M solution in hexanes, 0.6 mmol) dropwise under argon. After stirring at –10°C for 1 h, a solution of lactone (12) (246 mg, 0.64 mmol) in dry tetrahydrofuran (5 ml) was added in one portion. The mixture was stirred at –10°C for 3 h and then saturated aqueous ammonium chloride solution (3 ml) was added. The reaction mixture was extracted with ethyl acetate (3 × 20 ml), washed with brine (15 ml) and dried over magnesium sulfate. Removal of solvent at reduced pressure gave a colourless oil which was purified by flash chromatography with hexane/ethyl acetate (7 : 3) as eluant to give (22) (172 mg, 64%) as a colourless oil (Found: MH^+, 537.2668. $C_{31}H_{41}O_6Si$ requires MH, 537.2672). υ_{max} ($CHCl_3$)/cm^{-1} 3494w, 3069w, 2961s, 2884s, 1745m, 1471m, 1428m, 1191m, 1111s, 900s, 822m. ^{1}H n.m.r. δ_H (200 MHz, $CDCl_3$) 0.75, s, CH_3CO_3; 0.96, d, *J* 6.8 Hz, CH_3; 1.07, s, $(CH_3)_3$; 1.38–1.97, m, C**H**$_2$$CH_2$OSi; 3.73–4.01, m, 3 × CH_2O, CH_2OSi and CHO; 2.43–2.53, m, CH_2CO; 7.33–7.40, 6H, m, ArH; 7.62–7.75; 4H, m, ArH. *m/z* (ESI) 559 [$(M + Na)^+$, 39%], 1095 [$(2M + Na)^+$, 100].

*(7*S*,8*S*)-7-[(2'-t-Butyldiphenylsilyloxy)ethyl]-8-methyl-1,6-dioxaspiro[4.4]nonan-2-one (3)*

A solution of alkyne (22) (167 mg, 0.31 mmol) in ethyl acetate (10 ml) was stirred with 10% Pd/C (15 mg) at room temperature under a balloon of hydrogen for 18 h. The progress of the reaction was monitored by ^{1}H n.m.r. spectroscopy. Removal of the catalyst by filtration through a short pad of Celite, followed by removal of the solvent at reduced pressure, afforded a colourless oil which was dissolved in methanol (8 ml) and water (1 ml). Pyridinium *p*-toluenesulfonate (10 mg) was added and the mixture was stirred at room temperature for 1 h. Lithium hydroxide (60 mg) in water (3 ml) was then added. After stirring for 30 min, water (4 ml) was added and the methanol was removed under reduced pressure. The aqueous solution was acidified with 2 M hydrochloric acid, extracted with diethyl ether (3 × 20 ml) and dried over $MgSO_4$. After filtration, fresh $MgSO_4$ was added, followed by *p*-toluenesulfonic acid (10 mg), and the mixture was stirred at room temperature for 30 min. The $MgSO_4$ was removed by filtration and the solvent evaporated to give a yellow oil which was purified by flash chromatography with hexane/ethyl acetate (4 : 1 containing 1% triethylamine) to give the *title compound* (3) as a colourless oil (13 mg, 10%) (Found: M^+–^{t}Bu, 381.1522. $C_{22}H_{25}O_4Si$ requires M–^{t}Bu, 381.1661. υ_{max} ($CHCl_3$)/cm^{-1} 2958w, 2930s, 2857s, 1772s, 1463m, 1428s, 1209m, 1111s, 900w, 822. ^{1}H n.m.r. δ_H (200 MHz,; $CDCl_3$) 0.95, d, *J* 6.8 Hz, CH_3; 1.05, s, $(CH_3)_3$; 1.7–2.83, m, 4 × CH_2 and C**H**CH_3; 3.72–3.82, m, CH_2OSi; 4.31–4.34, m, CHO; 7.35–7.41, 6H, m, ArH; 7.65–7.71, 4H, m, ArH. ^{13}C n.m.r. δ_C (50 MHz, $CDCl_3$) 14.2, CH_3, Me; 18.1, quat., $C(CH_3)_3$; 26.6, CH_3, $C(CH_3)_3$; 29.2, CH, $CHCH_3$; 32.9, 33.4, 34.1, 3 × CH_2, C 4, C 6 and **C**H_2CH_2OSi; 41.5, CH_2, CH_2C=O; 61.0, CH_2, CH_2OSi; 79.6, CH, CHO; 115.1, quat., C 5; 127.6, 129.5, 135.5, 3 × CH, ArC; 133.8, quat., ArC; 176.1, quat., C=O. *m/z* (ESI) 461 [$(M + Na)^+$, 100%], 898 [$(2M + Na)^+$, 92].

Crystal Structure Determination for Lactone (12)

A colourless prismatic crystal was attached to a thin glass fibre and mounted on a Rigaku AFC7R diffractometer employing graphite monochromatized Cu Kα radiation generated from a rotating anode. Cell constants were obtained from a least squares refinement against 25

reflections located between 66.00 and 78.80° 2θ. Data were collected at 294.2 K with ω – 2θ scans to 135.46° 2θ. The intensities of three standard reflections measured every 150 reflections did not change significantly during the data collection. An empirical absorption correction based on azimuthal scans of three reflections was applied and the data were also corrected for Lorentz and polarization effects. Processing and calculations were undertaken with teXsan.[21] The structure was solved in the space group $P2_12_12_1$(No. 19) by direct methods with SIR92[22], and extended with difference maps generated by DIRDIF.[23] In general the non-hydrogen atoms were modelled with anisotropic displacement parameters, and the hydrogen atoms were included in the model at calculated positions with group thermal parameters. The C(2) and C(23) atoms are both disordered about two sites, with occupancies of 0.6 for C(2A) and C(23A) and 0.4 for C(2B) and C(23B). The partially occupied sites were modelled with isotropic displacement parameters. The Flack[24] parameter refined to 0.12(4). An ORTEP[25] projection of the molecule with 20% displacement ellipsoids is provided in Fig. 1.

Crystallographic data. Formula $C_{23}H_{30}O_3Si$, M 382.57, orthorhombic, space group $P2_12_12_1$(No. 19), a 12.437(2), b 23.881(4), c 7.545(1) Å, V 2240.9(5) Å^3, D_c 1.134 g cm^{-3}, Z 4, crystal size 0.40 by 0.21 by 0.15 mm, colourless, habit prism, λ(Cu Kα) 1.5418 Å, μ(Cu Kα) 1.067 mm^{-1}, T(psi scans)$_{min,max}$ 0.850, 0.970, $2\theta_{max}$ 135.46, *hkl* range 0 14, 0 28, 0 8, N 2310, N_{obs} 1688 ($I > 3.00\sigma(I)$), N_{var} 242, residuals* $R(F)$ 0.0460, $R_w(F)$ 0.0458, GoF(all) 2.880, $\Delta\rho_{min,max}$ –0.19, 0.23 e$^-$ Å^{-3}.

*$R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = (\Sigma w(F_o - F_c)^2/\Sigma(wF_c)^2)^{1/2}$
$w = 1/\sigma^2(F_o)$

Crystallographic details for (12) have been deposited and copies are available from the Australian Journal of Chemistry, P.O. Box 1139, Collingwood, Vic. 3066, until 31 December 2005.

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