The 3,4-Dihydro-2*H*-pyran Approach to (+)-Milbemycin β_3. Part 1. An Alternative Synthesis of (2*S*,4*S*,6*R*,8*R*,9*S*)-2-Formylmethyl-4-(dimethyl-t-butylsilyloxy)-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane

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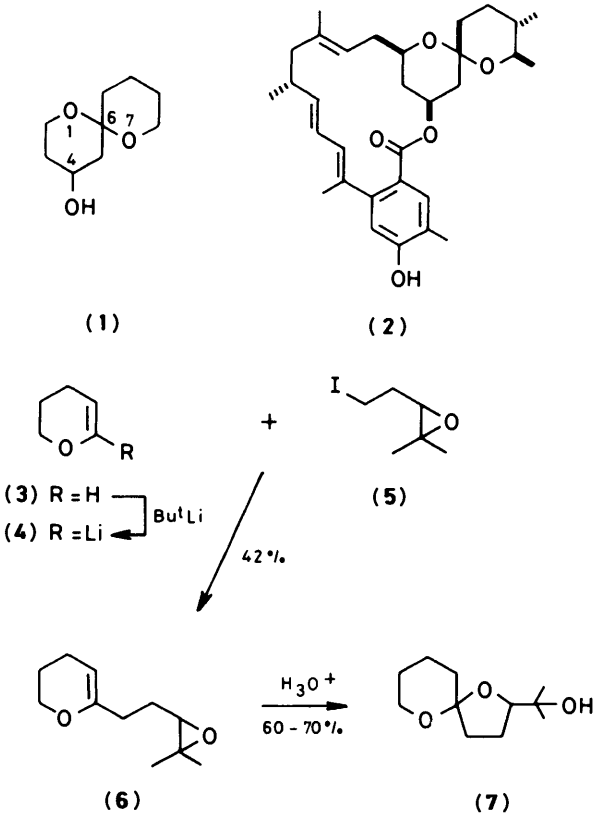
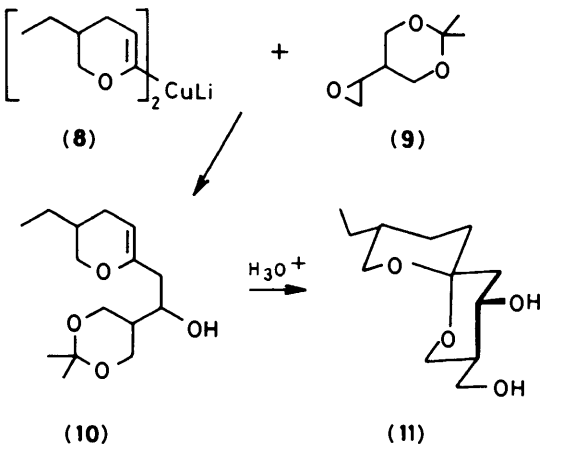
A more efficient synthesis of the title compound (**12**), previously used in a total synthesis of (+)-milbemycin β_3 (**2**), is described. The key step in the sequence involves a nucleophilic cleavage of the oxirane (**33**) by the organocuprate (**28**) derived from metallation of (2*R*,3*S*)-2,3-dimethyl-3,4-dihydro-2*H*-pyran (**26**).

The 4-hydroxy-1,7-dioxaspiro[5.5]undecane moiety (**1**) is a key structural feature of the milbemycins and avermectins which are prized for their pesticidal activity.[1] As part of a programme directed toward the synthesis of milbemycin β_3 (**2**), the simplest member of the milbemycin family, we noted the transformations depicted in Scheme 1 reported by Boeckman and coworkers[2] in



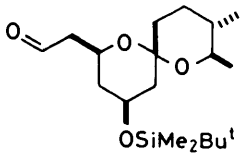
Scheme 1.

which a metallated dihydropyran (**4**) was used as a nucleophile[3] in an S_N2 reaction to give an intermediate (**6**) which then underwent an acid-catalysed cyclisation involving a proximate hydroxy function to generate the 1,6-dioxaspiro[4,5]decane ring system (**7**). In order to adapt the tandem donor–acceptor properties of the dihydropyran moiety to the synthesis of a 4-hydroxy-1,7-dioxaspiro[5.5]undecane[4] ring system, we required as a pivotal step the nucleophilic scission of an oxirane by a metallated dihydropyran. Although meagre precedent was available[4,5] which cast doubt on the feasibility of such a step using organolithium derivatives, we were able to effect the desired reaction by using a suitable organocuprate[6] as shown in Scheme 2 for the synthesis of the avian toxin talaromycin B



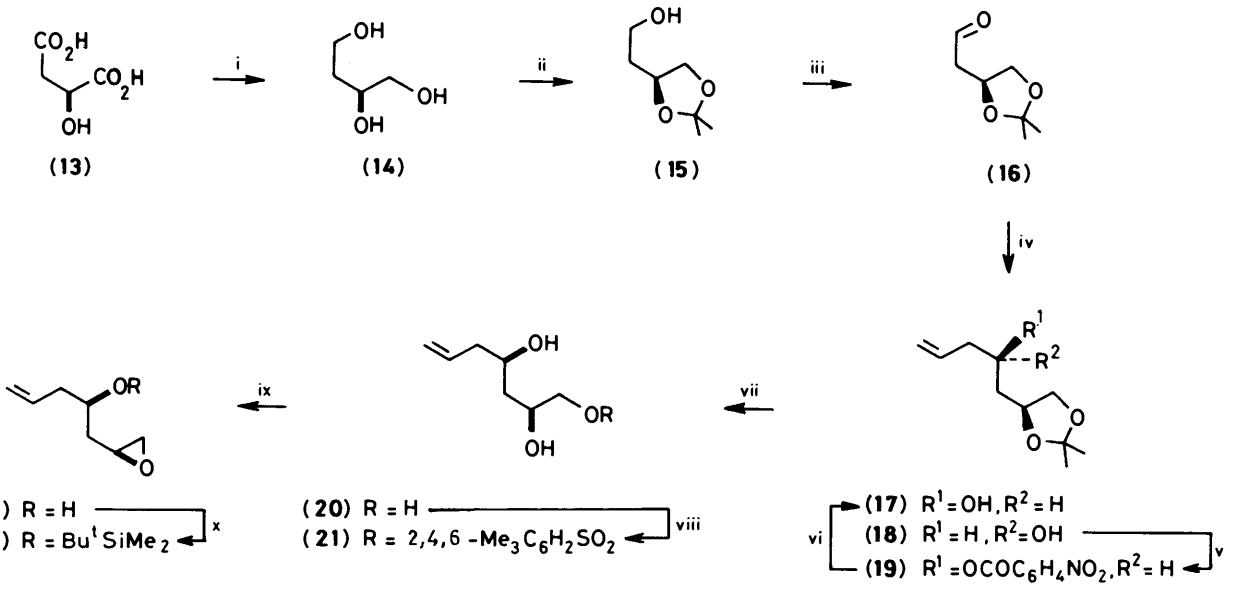
Scheme 2.

(**11**).[7] The moderate thermal stability of the organocuprate (**8**) was a crucial factor in the success of the desired transformation. We now report a further, more demanding example of the use of a metallated 3,4-dihydro-2*H*-pyran as a masked acyl anion equivalent[8] in the synthesis of the 4-hydroxy-1,7-dioxaspiro-[5.5]undecane fragment (**12**) which we have used as an intermediate in a synthesis of (+)-milbemycin β_3.[9]



(**12**)

Two key chiral intermediates were required for the synthesis of (**12**): the oxirane (**23**) (Scheme 3) and the dihydropyran (**26**) (Scheme 4). The oxirane (**23**) was prepared from (−)-(*S*)-malic acid (**13**) in 8 steps. Borane reduction of (**13**) gave (**14**) in 84% yield provided the reduction was performed in the presence of *freshly distilled* trimethyl borate[10] and the scale did not exceed 0.25 mol. Larger scale reactions invariably gave substantially lower yields. Two further trivial steps gave the sensitive



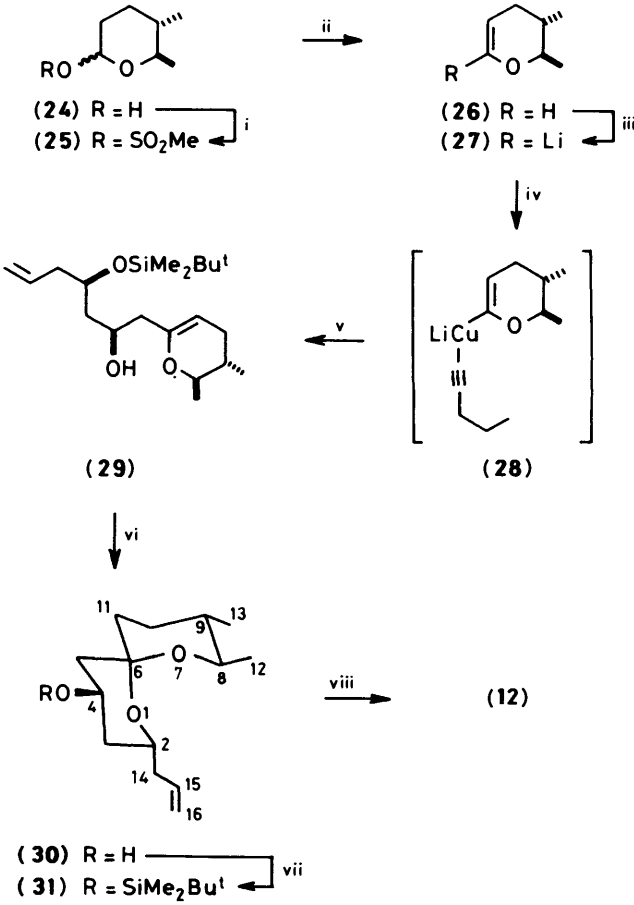
Scheme 3. *Reagents:* i, BH_3–SMe_2; $B(OMe)_3$–THF, (84%); ii, *p*-TsOH–$CuSO_4$–acetone, (85%); iii, pyridinium chlorochromate–CH_2Cl_2, (75%); iv, allylmagnesium chloride–Et_2O, (91%); v, *p*-$NO_2C_6H_4CO_2H$–$EtO_2CN{=}NCO_2Et$–Ph_3P–toluene, (90%); vi, KOH–MeOH, (99%); vii, Amberlite IR-120(H^+) resin–MeOH, (100%); viii, Mesitylenesulphonyl chloride–pyridine, (78%); ix, K_2CO_3–MeOH, (92%); x, Bu^tMe_2SiCl–DMF–NEt_3–trace 4-(dimethylamino)pyridine (DMAP), (85%)

aldehyde (**16**) which was stable in the cold in the absence of acid or base, but decomposed rapidly when warmed in an impure state. Variations in yield in the oxidation of (**15**) were the result of β-elimination reactions of the aldehyde (**16**). Rapid distillation of (**16**) using a Kugelrohr apparatus under high vacuum is recommended for purification.

The reaction of allylmagnesium chloride with (**16**)[11] gave a *ca.* 1:1 mixture of the diastereoisomers (**17**) and (**18**) which were separable by column chromatography. Fortunately the undesired isomer (**18**) could be converted to the desired isomer (**17**) *via* a Mitsunobu inversion[12] thereby giving (**17**) stereoconvergently in 85% overall yield from (**16**). Purification of (**17**) as the crystalline *p*-nitrobenzoate ester (**19**) was easily achieved. Thus pure samples of the chiral oxirane (**23**) were readily accessible on a substantial scale from cheap, readily available starting materials.

The lactol (**24**), previously prepared[9] from (+)-(2*R*,3*R*)-tartaric acid was dehydrated to the dihydropyran (**26**) in 55% yield as shown in Scheme 4. Metallation[4] of (**26**) with Bu^tLi in tetrahydrofuran (THF) at 0 °C was clean and efficient giving the 6-lithio derivatives (**27**) in quantitative yield as a clear, colourless solution which formed the bright yellow heterogeneous 'ate' complex (**28**) on addition to a suspension of pentynylcopper(I) in THF. Addition of the oxirane (**23**) to 2 equivalents of the mixed cuprate (**28**) at −30 °C led to negligible reaction; however, on gradual warming to room tempeature, clean nucleophilic scission of the oxirane took place to give the intermediate (**29**). Two equivalents of (**28**) were necessary for complete consumption of the oxirane and made most efficient use of the expensive ligand. However, with two equivalents of the corresponding homocuprate [from 4 equivalents of dihydropyran (**27**)] comparable yields were obtained. The mixed cuprates prepared from CuCN and PhSCu also gave the desired product (**29**) but in diminished yield.

Rather than suffer the loss of acid-sensitive (**29**) sustained on chromatographic purification, the crude product was treated with a trace of camphorsulphonic acid in anhydrous MeOH at room temperature to give the alcohol (**30**) as a single diastereoisomer. The configuration of the acetal centre in (**30**) was governed by the anomeric effect[13] and the equatorial



Scheme 4. *Reagents:* i, $MeSO_2Cl$–NEt_3–CH_2Cl_2; ii, NEt_3–CH_2Cl_2, reflux, [55% overall from (**24**)]; iii, Bu^tLi–THF, −78→0 °C; iv, pentynylcopper(I)–THF, −78 °C; v, the oxirane (**23**)–THF, −30→20 °C; vi, camphorsulphonic acid (trace)–MeOH, [70% overall from (**23**) and (**26**)]; vii, Bu^tMe_2SiCl–DMF–NEt_3–DMAP, (87%); viii, O_3–MeOH–pyridine, −78 °C, followed by SMe_2, (59%)

disposition of the four substituents. The overall yield of (**30**) from (**26**) was 70% based on the oxirane (**23**) as the limiting reagent. The desired aldehyde (**12**), prepared in two trivial steps from (**30**), was identical by mass spectrometry, high field ^1H and ^{13}C n.m.r. spectroscopy, and thin layer chromatography mobility with a sample prepared by an alternative route.[9]

There are several noteworthy aspects of the synthesis reported herein: there are no arduous chromatographic separations required and the one diastereoisomeric separation is easy; there is compensation for the regrettable stereorandom Grignard reaction of aldehyde (**16**) in the ease with which the undesired isomer (**18**) is converted to the desired isomer (**17**); the yields were generally good; and the reactions could be run on a substantial scale. The dihydropyran* approach to (+)-milbemycin β_3 intermediate (**12**)[14] is, therefore, far more practical than the previously reported directed aldol approach.

Experimental

Column chromatography was carried out on Kieselgel 60 (0.04—0.063 mm) with the eluant specified in parentheses. All reactions requiring anhydrous conditions were conducted in a flame-dried apparatus under a static atmosphere of dry nitrogen. Organic extracts were dried over $MgSO_4$ and evaporated at aspirator pressure using a rotary evaporator. Distillations in which the bath temperature is specified were performed with a Kugelrohr apparatus.

Diethyl ether (referred to as ether), tetrahydrofuran (THF), and dioxane were distilled from sodium wire; CH_2Cl_2 from P_2O_5; pyridine, triethylamine, and dimethylformamide (DMF) from CaH_2; MeOH from $Mg(OMe)_2$.

Chemical shifts are reported as δ values relative to Me_4Si as an internal standard. ^1H N.m.r. and ^{13}C n.m.r. spectra were recorded in $CDCl_3$ unless otherwise indicated on JEOL FX90Q or Bruker WH400 spectrometers. All coupling constants (*J*) are given in Hz. Peak intensities in the i.r. spectra are specified as a s (strong), m (medium), or w (weak). Accurate mass determinations were made on compounds estimated to be >95% pure by ^1H or ^{13}C n.m.r. spectroscopy and thin layer chromatography.

(2S)-*Butane*-1,2,4-*triol* (**14**).—Borane–methyl sulphide (10M; 30 cm^3, 0.3 mol) was added over 50 min to a solution of (−)-(*S*)-malic acid (13.4 g, 0.1 mol) and trimethyl borate (45.7 g, 0.44 mol) in THF (100 cm^3) at 0 °C. The reaction was allowed to warm to room temperature where it was stirred for 22 h before being quenched at 0 °C by the dropwise addition of MeOH (100 cm^3) followed by 30 min stirring at room temperature and then concentration. After two similar MeOH additions (100 cm^3 and 50 cm^3) the product was distilled to yield (**14**) (8.51 g, 84%), b.p. 130 °C (bath)/0.15 mmHg: $[\alpha]_D^{22}$ −28.2° (*c* 2.8 in EtOH) [lit.,[15] +22.5° (*c* 2.3 in EtOH for the *R*-isomer)]; $\nu_{max.}$(film) 3 350br,s, 2 950s, 1 420m, and 1 060s cm^{-1}.

(4S)-4-(2-*Hydroxyethyl*)-2,2-*dimethyl*-1,3-*dioxolane* (**15**).—Anhydrous $CuSO_4$ (30 g) and toluene-*p*-sulphonic acid (0.3 g) were added to a mechanically stirred solution of (**14**) (27.7 g, 0.26 mol) in acetone (500 cm^3) at room temperature and the reaction was stirred for 62 h before an excess of solid K_2CO_3 was added. After a further 2 h, the $CuSO_4$ and the excess of base were filtered off and the product was concentrated and distilled to yield (**15**) (25.4 g, 85%), b.p. 60—62 °C/0.3 mmHg; $\nu_{max.}$(film) 3 450br, 2 900s, 2 940s, 2 880s, 1 370s, 1 250s, 1 220s, 1 160s, and 855s cm^{-1}; δ_H(90 MHz) 4.6—3.5 (5 H, m), 3.1 (1 H, s, OH), 1.8 (2 H, q, *J* 6), and 1.4 and 1.35 (2 × 3 H, s); *m/z* 131 (M^+ − 15, 74), 72 (48), 71 (100), 59 (36), 43 (97), and 41 (22%) (Found: M^+, 146.094 02. $C_7H_{14}O_3$ requires *M*, 146.094 287).

(4S)-4-*Formylmethyl*-2,2-*dimethyl*-1,3-*dioxolane* (**16**).—Pyridinium chlorochromate (8.87 g, 41.12 mmol) was added to a mechanically stirred solution of (**15**) (3 g, 20.5 mmol) in CH_2Cl_2 (85 cm^3) with ground 3 Å molecular sieves (10.3 g). After 25 min the reaction was diluted with ether (120 cm^3) and passed through Florisil to yield, after distillation, [b.p. 90 °C (bath)/15 mmHg] (**16**) (2.22 g, 75%), $\nu_{max.}$(film) 2 990m, 2 880w, 2 840w, 1 725s, 1 375s, 1 222s, 1 160m, 1 065s, and 855w cm^{-1}; δ_H (90 MHz) 9.8 (1 H, t, *J* 1.5), 4.52 (1 H, tdd, *J* 7, 7, 6), 4.18 (1 H, dd, *J* 8, 6.5), 3.60 (1 H, dd, *J* 8, 7), 2.88 (1 H, dd, *J* 17, 7), 2.61 (1 H, dd, *J* 17, 7), and 1.41 (2 × 3 H).

(4S)-4-[(2R)-2-*Hydroxypent*-4-*enyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**17**) *and* (4S)-4-[(2S)-2-*Hydroxypent*-4-*enyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**18**).—To a stirred solution of allylmagnesium chloride [prepared from magnesium turnings (4.25 g, 0.175 mol) and allyl chloride (7.2 cm^3, 87.5 mmol) in ether (50 cm^3)] was added over 5 min, a solution of the freshly prepared aldehyde (**16**) (4.2 g, 29.2 mmol) in ether (25 cm^3). After having been stirred at room temperature for 30 min, the mixture was poured into saturated aqueous NH_4Cl containing 10% ammonia (50 cm^3). The mixture was filtered and the organic phase separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 cm^3) and the combined organic layers were dried and concentrated to a colourless oil (4.96 g), which was purified by chromatography [ether–benzene (1:9)] to give, in order of elution, (**18**) (2.58 g, 14.4 mmol, 49%), b.p. 85 °C (bath)/0.2 mmHg; $\nu_{max.}$(film) 3 480s, 1 640m, 1 250s, 1 220s, 1 160s, 1 062s, 1 000s, and 918s cm^{-1}; δ_C (22.6 MHz) 134.7, 117.5, 109.3, 75.3, 69.9, 69.72, 42.0, 40.0, 26.9, and 25.8 (Found: M^+ + 1, 187.133 61. $C_{10}H_{18}O_3$ requires *M* + 1, 187.133 41) and (**17**) (2.30 g, 12.4 mmol, 42%), b.p. 85 °C (bath)/0.2 mmHg; $[\alpha]_D^{21}$ −8.5° (*c* 2.6 in $CHCl_3$); δ_C (22.6 MHz) 134.6, 117.8, 108.8, 73.8, 69.7, 68.1, 42.2, 40.1, 27.0, and 25.8 (Found: M^+ + 1, 187.133 22).

Quantitative analysis of the mixture was performed by gas chromatography on a Carbowax 20M capillary (47 m) at 130 °C.

(4S)-2,2-*Dimethyl*-4-[(2R)-2-(*p*-*nitrobenzoyloxy*)*pent*-4-*enyl*]-1,3-*dioxolane* (**19**).—To a stirred suspension of Ph_3P (5.41 g, 20.6 mmol) and *p*-nitrobenzoic acid (3.45 g, 20.6 mmol) in toluene (60 cm^3) cooled to −30 °C was added a solution of the alcohol (**18**) (3.2 g, 17.2 mmol) in toluene (10 cm^3). A solution of diethyl azodicarboxylate (3.3 cm^3, 20.6 mmol) in toluene (30 cm^3) was added dropwise over 15 min to the vigorously stirred mixture during which the temperature was maintained at −30 °C. When the addition was complete, the mixture was allowed to warm gradually to 0 °C over 1 h whereupon saturated aqueous $NaHCO_3$ (75 cm^3) was added. The aqueous phase was separated and extracted with ether (2 × 75 cm^3). The organic extracts were combined, dried, and concentrated. To the residue was added ether (25 cm^3) and hexane (75 cm^3) whereupon the bulk of the triphenylphosphine oxide was filtered off. Concentration of the residue gave a viscous oil which was purified by chromatography [ether–hexane (1:4)] to give the *p*-nitrobenzoate ester (**19**) (5.23 g, 90%) as colourless needles from cold hexane, m.p. 28—30 °C; $[\alpha]_D^{21}$ −44.8° (*c* 2.5 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 725, 1 608, 1 530, 1 352, 1 275, 920, 874, and 840 (all s) cm^{-1}; δ_H (90 MHz) 8.1—8.4 (4 H, m), 5.5—6.1 (1 H, m), 5.35 (1 H, m), 5.18 (1 H, m), 5.05 (1 H, m), 3.9—4.35 (1 H, m), 4.0 (1 H, dd, *J* 6, 6), 3.55 (1 H, dd, *J* 5, 7.7), 2.05 (2 H, m), and 1.32 and 1.38 (3 H each, s) (Found: C, 60.75; H, 6.35; N, 4.2. $C_{17}H_{21}O_6N$ requires C, 60.88; H, 6.31; N, 4.17%).

Hydrolysis of the *p*-nitrobenzoate ester (**19**) (3.45 g, 10.3 mmol) in methanolic KOH in the usual way gave (**17**) (1.84 g, 99%) after distillation, $[\alpha]_D^{21}$ −9.7° (*c* 2.6 in $CHCl_3$).

* Smith and co-workers also used the racemic aldehyde (**12**) in their synthesis of (±)-milbemycin-β_3.[14]

(2S,4R)-1-(*Mesitylsulphonyloxy*)*hept*-6-*ene*-2,4-*diol* (**21**).—To a solution of the acetonide (**17**) (1.35 g, 7.26 mmol) in a mixture of MeOH (15 cm^3) and water (0.5 cm^3) was added Amberlite IR-120 (H^+) resin (0.2 g). After having been stirred for 18 h at room temperature the mixture was filtered and concentrated and the residue was distilled to give the triol (**20**) (1.06 g, 100%) as a colourless viscous oil, b.p. 125 °C (bath)/0.2 mmHg.

The triol (**20**) was dissolved in pyridine (15 cm^3) and cooled to 0 °C. Mesitylenesulphonyl chloride (1.86 g, 8.5 mmol) was added portionwise over 30 min. When the addition was complete the mixture was allowed to warm gradually to room temperature over 6 h. The bulk of the pyridine was removed under reduced pressure and the residue was partitioned between ether and dilute H_2SO_4 (20 cm^3). The ether layer was separated and the aqueous layer extracted with ether (3 × 20 cm^3). The combined organic layers were washed with aqueous $NaHCO_3$, dried, and evaporated. Chromatography [EtOAc–hexane 1:1)] of the residue gave the mesitylsulphonate (**21**) as a colourless oil which crystallised from cold ether–hexane to give (**21**) (1.99 g, 78%) as colourless needles, m.p. 76—76.5 °C, $[\alpha]_D^{22}$ −7.0° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$(Nujol) 3 350s, 1 640m, 1 605s, 1 568m, 1 355s, 1 175s, 1 040s, 968s, 910s, and 828s cm^{-1}; δ_H (90 MHz) 7.0 (2 H, s), 5.5—6.0 (1 H, m), 5.2 (1 H, m), 5.05 (1 H, m), 3.9—4.3 (1 H, m), 3.8—4.0 (3 H, m), 2.6 (6 H, s), 2.3 (3 H, s), 2.1—2.35 (4 H, m), and 1.5—1.7 (2 H, m) (Found: C, 58.55; H, 7.45; S, 9.8. $C_{16}H_{24}O_5S$ requires C, 58.51; H, 7.36; S, 9.76%).

(2S,4R)-1,2-*Epoxy*-4-(*dimethyl-t-butylsilyloxy*)*hept*-6-*ene* (**23**).—To a solution of the mesitylsulphonate (**21**) (2.0 g, 6.33 mmol) in dry MeOH (30 cm^3) was added anhydrous K_2CO_3 (1.75 g, 12.66 mmol). The mixture was stirred for 1 h at room temperature before being filtered through Celite and concentrated. The residue was partitioned between CH_2Cl_2 (30 cm^3) and water (10 cm^3). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated to give the crude epoxy alcohol (**22**) (0.75 g, *ca.* 92%) which was used immediately in the next step.

The crude epoxy alcohol (**22**) (0.75 g) was converted to the dimethyl-t-butylsilyl ether (**23**) in the usual way. Chromatography [ether–hexane (5:95)] gave the epoxide (**23**) (1.2 g, 85%) as a colourless oil. $\nu_{max.}$(film) 1 640s, 1 470m, 1 258s, 1 090s, 1 070s, 915s, 838s, 810s, and 778s cm^{-1}; δ_H (90 MHz) 1 H multiplets at 5.6—6.1, 5.14, 5.0, 4.0, 3.05, and 2.8, 2.3 (2 H, m), 1.5—1.8 (2 H, m), 0.92 (9 H, s), and 0.08 (6 H, s) (Found: M^+, 242.170 45. $C_{13}H_{26}O_2Si$ requires *M*, 242.170 198).

(2R,3S)-2,3-*Dimethyl*-3,4-*dihydro*-2H-*pyran* (**26**).—Methanesulphonyl chloride (4.3 g, 37.5 mmol) was added dropwise to a solution of the lactol (**24**)[9] (4.0 g, 30.7 mmol) and NEt_3 (6.33 g, 63 mmol) in CH_2Cl_2 (30 cm^3) at −5 °C. After 2.5 h, a further portion of NEt_3 (6.33 g) was added and the reaction was refluxed for 8 h. After having been cooled to room temperature, the reaction was diluted with water, washed with saturated aqueous NaCl, dried, and the crude product fractionally distilled with a spinning band column to give (**26**) (1.9 g, 55%) as a colourless oil, b.p. 135—136 °C/760 mmHg; δ_H (90 MHz) 6.35 (1 H, m), 4.65 (1 H, m), 3.55 (1 H, dq, *J* 7, 7), 2.1—1.4 (3 H, m), 1.25 (3 H, d, *J* 7), and 0.95 (3 H, d, *J* 7); *m/z* 112 (M^+, 28%), 97 (24), 83 (36), 69 (50), 57 (40), 56 (100), 55 (50), 43 (31), and 41 (63) (Found: M^+, 112.0889. $C_7H_{12}O$ requires *M*, 112.088 87).

(2R,4S,6R,8R,9S)-2-*Allyl*-8,9-*dimethyl*-4-(*dimethyl-t-butylsilyloxy*)-1,7-*dioxaspiro*[5.5]*undecane* (**31**).—To a solution of the dihydropyran (**26**) (0.90 g, 8 mmol) in THF at −78 °C was added dropwise Bu^tLi (2.2M in pentane; 3.6 cm^3, 8 mmol). The mixture was stirred at 0 °C for 45 min and then cooled to −78 °C and added rapidly *via* cannula to a rapidly stirred suspension of pentynylcopper(I) (1.05 g, 8 mmol) in THF at −78 °C. The resultant yellow suspension was then stirred at 0 °C for 30 min, cooled to −30 °C, and the oxirane (**23**) (0.97 g, 4 mmol) in THF (3 cm^3) added rapidly *via* syringe. The mixture was allowed to warm gradually to 20 °C whereat it was stirred for 10 h. The mixture was poured into a 1:1 mixture of saturated aqueous NH_4Cl and 10% ammonia (30 cm^3), diluted with Et_2O (50 cm^3) and filtered through Celite. The organic phase was separated and the aqueous layer extracted with Et_2O (2 × 25 cm^3). The combined organic layers were dried and concentrated to give crude (**29**) (1.66 g) which was dissolved in anhydrous MeOH (20 cm^3). After the addition of camphorsulphonic acid (50 mg), the mixture was stirred at room temperature for 1 h after which anhydrous K_2CO_3 (0.25 g) was added and stirring was continued for 15 min. The mixture was filtered and concentrated and the residue was dissolved in CH_2Cl_2 (50 cm^3), washed with saturated aqueous $NaHCO_3$, dried and concentrated to a yellow oil which was chromatographed on Kieselgel (4 × 8 cm; 25% EtOAc in hexane) to give the spiroacetal (**30**) (0.68 g, 70%) as an oil which was used directly in the next step without further purification.

To a solution of a spiroacetal (**30**) (0.65 g, 2.7 mmol) in a mixture of dimethylformamide (5 cm^3) and NEt_3 (0.45 cm^3, 3.5 mmol) was added 4-(*N*,*N*-dimethylamino)pyridine (0.11 g, 0.9 mmol) followed by dimethyl-t-butylsilyl chloride (0.45 g, 3 mmol). After having been stirred at room temperature for 2 h, the mixture was poured into saturated aqueous $NaHCO_3$ (10 cm^3) and extracted with Et_2O (3 × 25 cm^3). The combined organic extracts were dried and concentrated to a yellow oil which was chromatographed (2% Et_2O in hexane) to give the silyl ether (**31**) (0.83 g, 87%) as a colourless oil, $[\alpha]_D^{21}$ +68.3° (*c* 2.5 in hexane); $\nu_{max.}$(film) 1 640m, 1 385s, 1 252s, 1 196s, 1 075s, 990s, 838s and 778s cm^{-1}; δ_H (400 MHz) 5.84 (1 H, dddd, *J* 17, 10, 7.5, 6.5, 15-H), 5.07 (1 H, dm, *J ca.* 17, 16-H), 5.02 (1 H, dm, *J ca.* 10, 16-H), 4.04 (1 H, dddd, *J* 11, 11, 4.5, 4.5, 4-H), 3.5 (1 H, m, 2-H), 3.2 (1 H, dq, *J* 9.5, 6, 8-H), 2.2 (2 H, dm, 14-H_2), 1.7—1.9 (2 H, m, 3-H_{eq} and 5-H_{eq}), 1.4—1.7 (4 H, m, 10-H_2, 11-H_2), 1.25 (1 H, dd, *J* 11, 11, 5-H_{ax}), 1.1—1.3 (1 H, 9-H_{ax}), 1.15 (1 H, ddd, *J* 11, 11, 11, 3-H_{ax}), 1.07 (3 H, d, *J* 6, 8-Me), 0.84 (9 H, s), 0.79 (3 H, d, *J* 6, 9-Me), and 0.03 (6 H, s); δ_C (22.6 MHz) 135.3 (C-15), 116.4 (C-16), 97.5 (C-6), 71.0 (C-8), 67.7 (C-2), 65.6 (C-4), 45.3 (C-5), 41.2 (C-3), 40.5 (C-14), 36.8 (C-9), 36.1 (C-11), 28.0 (C-10), 25.9 (Me_3C), 19.4 (C-13), 18.1 (C-12), 18.0 (Me_3C), and −4.4 (Me_2Si); *m/z* 297 (24%), 221 (21), 172 (15), 171 (100), 145 (14), 143 (23), 129 (89), 127 (16), 115 (12), 113 (90), 105 (40), 95 (18), 79 (31), and 73 (51) (Found: M^+, 354.259 45. $C_{20}H_{38}O_3Si$ requires *M*, 354.259 008).

(2S,4S,6R,8R,9S)-2-*Formylmethyl*-8,9-*dimethyl*-4-(*dimethyl-t-butylsilyloxy*)-1,7-*dioxaspiro*[5.5]*undecane* (**12**).—A stream of ozone was bubbled through a solution of the alkene (**31**) (0.71 g, 2 mmol) in a mixture of MeOH (20 cm^3) and pyridine (1 cm^3) at −70 °C until the blue colour persisted. The excess of ozone was then discharged in a stream of nitrogen. Dimethyl sulphide (3 cm^3) was added, the cooling bath was removed, and the mixture was allowed to stand at ambient temperature for 2 h. Evaporation followed by chromatography of the residue [ether–hexane (1:4)] gave the aldehyde (**12**) (0.42 g, 59%) identical in every detail with a sample prepared by an alternative route.[9]

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