The 3,4-Dihydro-2*H*-pyran Approach to (+)-Milbemycin β_3. Part 2.[1] An Improved Synthesis of (2*R*,4*S*,6*S*, 8*R*, 9*S*)-2-[(5*R*)-(2*E*)-3-Methyl-5-formyl-hex-2-en-1-yl]-8,9-dimethyl-4-(dimethyl-t-butylsilyloxy)-1,7-dioxa-spiro[5.5]undecane

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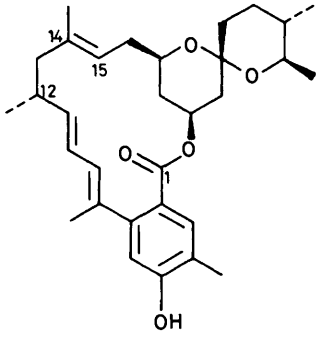
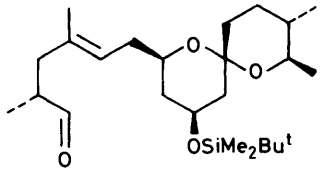
A more efficient synthesis of the title compound (**2**), previously used in a total synthesis of (+)-milbemycin β_3 (**1**), is described. The key step in the sequence involves a nucleophilic cleavage of the oxirane (**4**) by the organocuprate derived from metallation of (2*R*,3*S*)-2,3-dimethyl-3,4-dihydro-2*H*-pyran (**5**).

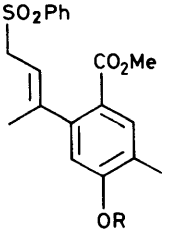
We recently described a synthesis of (+)-milbemycin β_3 (**1**) from the aldehyde (**2**) and the sulphone (**3**).[1,2] This synthesis was marred by the inefficiency of 2 steps: the novel intramolecular directed aldol condensation used to construct the 1,7-dioxaspiro[5.5]undecane moiety and the Fe^{I}-catalysed coupling of a Grignard reagent and a vinyl sulphone used to construct the C(14)–C(15) trisubstituted double bond. We now give details[3] of a more practical synthesis of (**2**) which is highly convergent and uses cheap chiral precursors. Once again stereoselective synthesis of the spiroacetal moiety and the C(14)–C(15) trisubstituted double bond are premier considerations which, in the pivotal step, exploits the reaction of a metallated derivative of the 3,4-dihydro-2*H*-pyran (**5**)[4] with the oxirane (**4**).



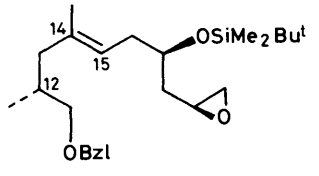
(**1**)



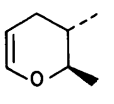
(**2**)



(**3**)



(**4**)



(**5**)

The oxirane (**4**) contains the remote chiral centre at C(12)-(milbemycin numbering) and the trisubstituted double bond of (+)-milbemycin β_3. The crucial step in the preparation of compound (**4**) was the nucleophilic cleavage of the oxirane (**7**) by the aluminate (**8**) derived from the carboalumination[5] of acetylene (**6**) (Scheme 1). The conversion of compounds (**6**) and (**7**) to compound (**9**) was clean and efficient and could easily be performed on a 10 g scale. Analysis of the product (**9**) by ^{13}C n.m.r. spectroscopy and high performance liquid chromatography showed that the key carbometallation reaction had occurred with high *syn*-stereoselectivity. Routine transformations were used to convert the dioxolane (**9**) to the desired oxirane (**4**).

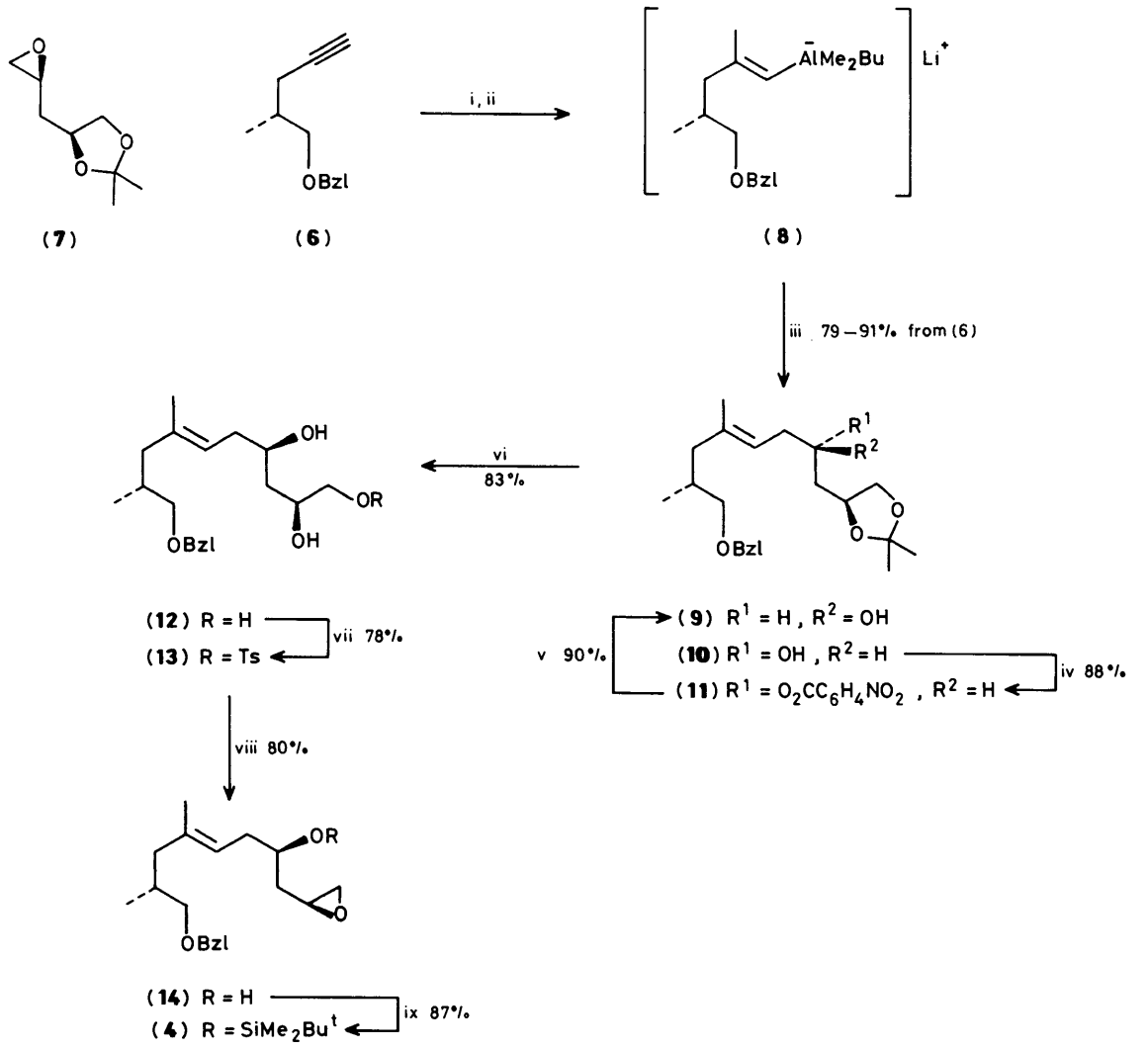
The synthesis of the acetylene (**6**) was achieved from methyl (*R*)-(−)-3-hydroxy-2-methylpropionate (**15**) by standard procedures as shown in Scheme 2. All of the reactions in the sequence could be performed on a substantial scale and gave products which were easily purified. Unfortunately, the nucleophilic displacement of the bromide from (**19**) by lithium acetylide was accompanied by elimination to the olefin (**20**). However, olefin (**20**) and acetylene (**6**) were easily separated by spinning band distillation.

The oxirane (**7**) was prepared from (*S*)-(−)-malic acid (**21**) as shown in Scheme 3. Reaction of the sensitive aldehyde (**22**)[6] with phenylthiomethyl-lithium[7] gave a diastereomeric mixture of adducts (**23**) and (**24**) which were difficult to separate by column chromatography. In fact, this is the only stage in the entire synthesis in which chromatographic purification was problematic. Subsequently it was found that separation of diastereoisomers at this stage was unnecessary (*vide infra*).

The stereochemistry of the adducts (**23**) and (**24**) could not be ascertained by spectroscopic methods alone. Similarly the stereochemistry of the oxiranes (**25**) and (**7**) derived from the pure thioethers by routine methods could not be distinguished by n.m.r. methods so a chemical correlation was required as shown in Scheme 4.

Reaction of the oxiranes (**25**) and (**7**) with vinylmagnesium bromide in the presence of 10 mol % CuI gave the diastereoisomeric alcohols (**26**) and (**27**) which were prepared by Hanessian and co-workers[8] while this work was in progress. Alcohol (**26**) had been converted to acetal (**29**) which was synthesized independently from D-glucose (**28**) thus proving the absolute and relative stereochemistry of (**7**).

In the early stages of the synthesis, the diastereoisomeric adducts (**23**) and (**24**) were subjected to a tedious separation and



Scheme 1. *Reagents and conditions:* i, Me_3Al, $(C_5H_5)_2ZrCl_2$, $ClCH_2CH_2Cl$–hexane, 20 °C, 3 d; ii, Bu^nLi–hexane, −70 °C; iii, add (7), −30 to −10 °C; iv, *p*-nitrobenzoic acid, $EtO_2CN{=}NCO_2Et$–toluene, 0 °C; v, KOH, THF–H_2O, 20 °C; vi, Amberlite IR 120 (H^+), THF–H_2O, 20 °C, 3d; vii, TsCl–pyridine, 0 °C, 10 h; viii, K_2CO_3–MeOH, 20 °C, 25 min; ix, Bu^tMe_2SiCl, 4-(*N*,*N*-dimethylamino)pyridine, NEt_3–DMF, 20 °C, 5 h

individually converted into the pure oxiranes (**25**) and (**7**). The desired oxirane (**7**) was thus available in limited quantity not only because of the difficulty in separation, but also because the addition of phenylthiomethyl-lithium to aldehyde (**22**) proceeded with poor diastereoselectivity to give the adducts (**23**) and (**24**) in a ratio of 3:1 with the desired (**24**) being the minor component. Fortunately it was subsequently found that the mixture of (**23**) and (**24**) could be converted to a mixture of oxiranes (**25**) and (**7**) which were then allowed to react with the aluminate (**8**) to give a more easily separable mixture of alcohols (**9**) and (**10**). Furthermore, the undesired isomer (**10**) was easily converted to the desired product by Mitsunobu inversion.[9]

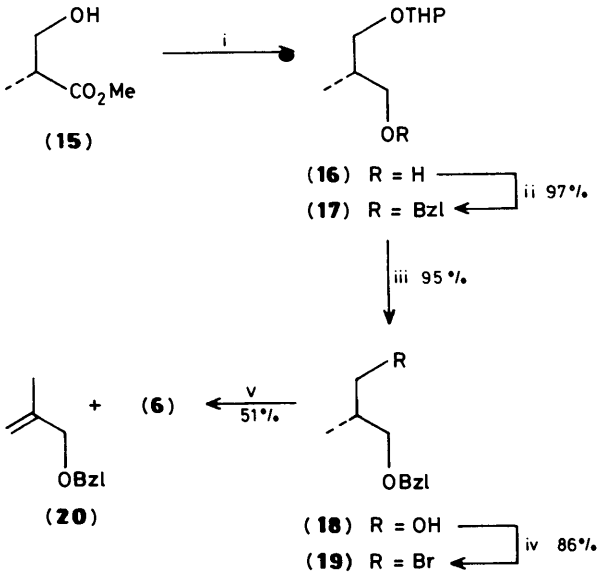
The fulcrum of our synthesis of spiroacetal (**2**) was the nucleophilic cleavage of the oxirane (**4**) by the mixed cuprate (**31**) prepared from (2*S*,3*S*)-dimethyloxirane[10] (Scheme 5). This is a sluggish reaction which was only made possible by the relative thermal stability of the mixed cuprate (**31**) thereby allowing the reaction to proceed at an appreciable rate at or near room temperature. The reaction cleanly gave the alkylation product (**32**) which, without further purification, was converted to the spiroacetal (**33**) on treatment with a trace of camphorsulphonic acid in methanol. As expected from the well-established thermodynamically controlled cyclisation, a single diastereoisomer was obtained in which the configuration of the acetal carbon was governed by the anomeric effect.[11] Three further routine steps were then used to prepare the aldehyde (**2**) which we have converted to (+)-milbemycin β_3.[1]

In conclusion we have developed methodology which permits the stereoconvergent synthesis of advanced intermediates in the milbemycin-avermectin series on a gram scale. The absence of arduous chromatographic separations is particularly noteworthy. The key step provides a cogent illustration of the value of metallated enol ethers for the formation of C–C bonds.[6,12]

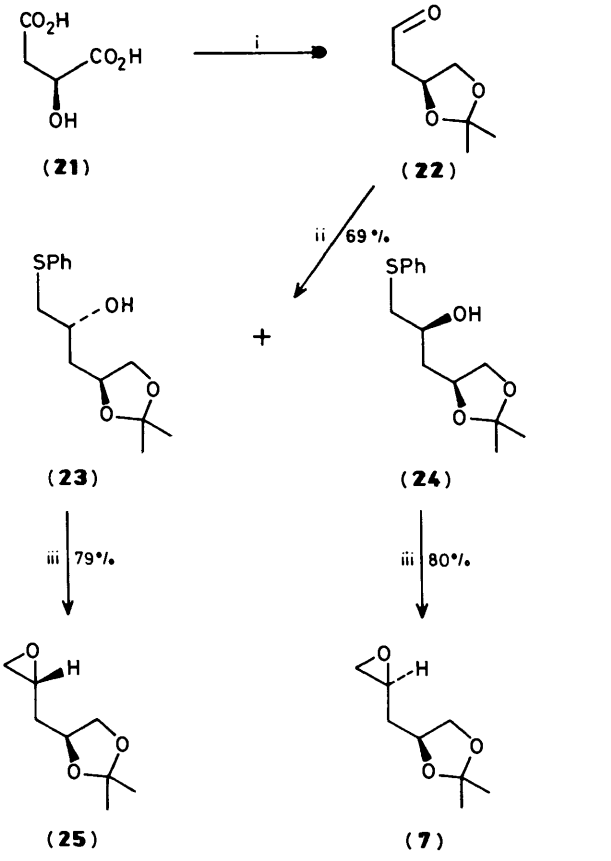
Experimental

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

Diethyl ether (referred to as ether) and tetrahydrofuran (THF) were distilled from sodium wire; dichloromethane and

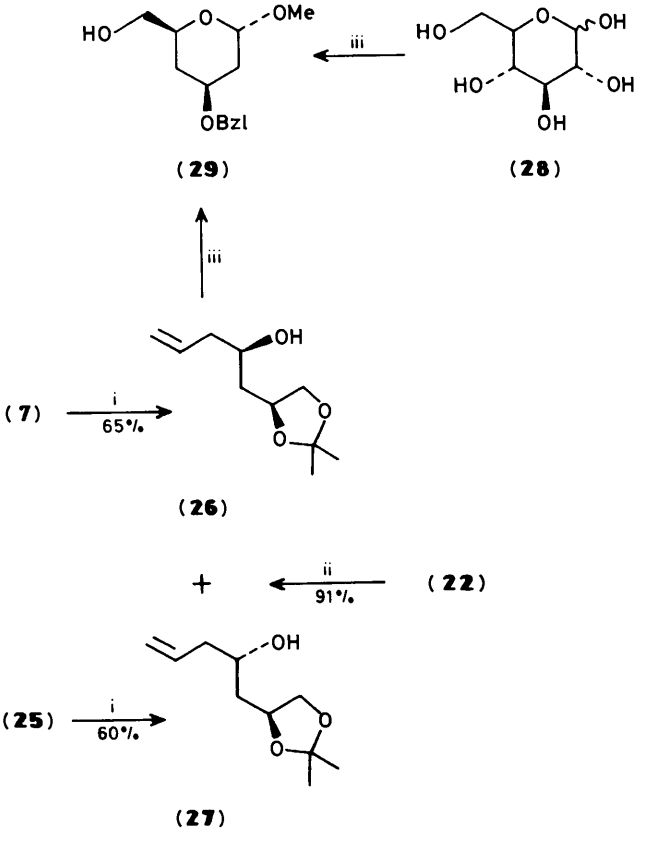


Scheme 2. *Reagents and conditions:* i, ref. 13; ii, benzyl bromide, NaH, THF–HMPA, 20 °C, 4 h; iii, Amberlite IR 120 (H^+)–MeOH, 20 °C, 16 h; iv, *N*-bromosuccinimide, Ph_3P–CH_2Cl_2, 10 to 20 °C; v, HC≡CLi–DMSO, 8 °C, 40 min



Scheme 3. *Reagents and conditions:* i, ref. 6; ii, $PhSCH_2Li$–THF, −70 °C; iii, Me_3OBF_4, 2,6-di-t-butylpyridine–CH_2Cl_2, 20 °C, 2 h followed by NaOH–H_2O, 20 °C, 16 h

1,2-dichloroethane from phosphorus pentaoxide; pyridine, triethylamine, dimethyl sulphoxide (DMSO), dimethyl formamide (DMF), and hexamethylphosphoric triamide (HMPA) from calcium hydride at 20 mmHg; and methanol (MeOH) from magnesium dimethoxide.

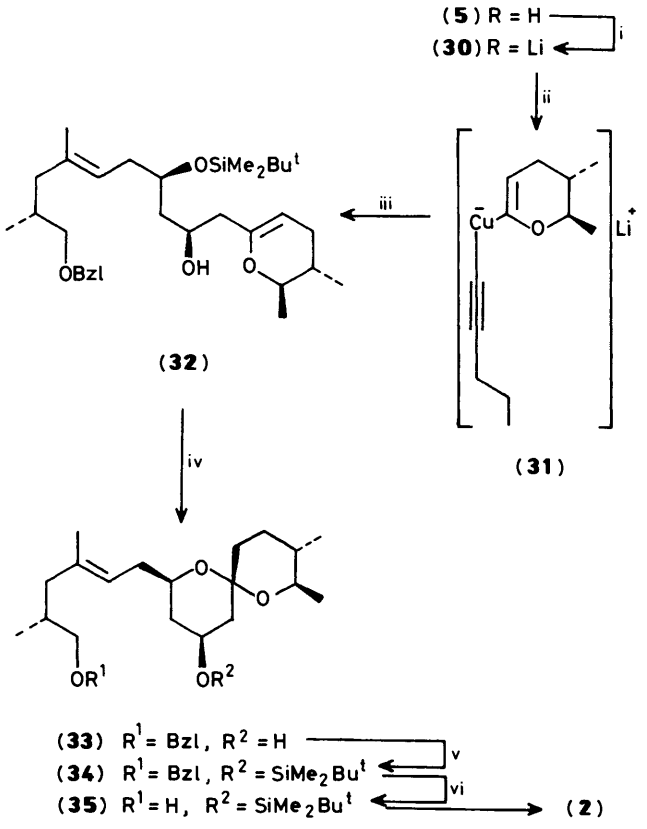


Scheme 4. *Reagents and conditions:* i, H_2C=CHMgBr, 10 mol % CuI–THF, −40 °C, 1 h; ii, allylmagnesium chloride–Et_2O, −78 °C, 1 h; iii, ref. 8

Chemical shifts are reported in p.p.m. relative to Me_4Si as an internal standard. ^1H and ^{13}C N.m.r. spectra were recorded in $CDCl_3$ unless otherwise indicated. All coupling constants *J* are given in Hz. Peak intensities in the i.r. spectra are specified as 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.

(2R,S)-[(2S)-3-*Benzyloxy*-2-*methylpropoxy*]*tetrahydropyran* (**17**).—A solution of alcohol (**16**)[13] (19.34 g, 0.11 mmol) in THF (32 ml) was added to an ice-cooled suspension of NaH (5.8 g, 0.24 mol) in THF (200 ml) and HMPA (3.1 g, 0.017 mol). After 30 min benzyl bromide (20.5 g, 0.12 mol) was added and the reaction mixture was allowed to warm to room temperature. After 4 h the mixture was quenched with ice water (300 ml) and the product extracted into hexane, washed with brine, dried, and concentrated to yield (**17**) (28.3 g, 97%); $\nu_{max.}$(film) 3 075w, 3 040w, 2 950s, 2 880s, 1 455m, 1 205m, 1 120s, 1 035s, 740s, and 700s cm^{-1}; δ_H (90 MHz) 7.3 (5 H, s), 4.55 (1 H, m), 4.5 (2 H, s), 4.1—3.2 (6 H, m), 2.1 (1 H, m), 2.0—1.3 (6 H, m) and 1.0 (3 H, d, *J* 7) (Found M^+ 264.1720. $C_{16}H_{24}O_3$ requires *M*, 264.1725).

(2R)-3,3-*Benzyloxy*-2-*methylpropan*-1-*ol* (**18**).—A suspension of Amberlite 120 acidic ion exchange resin (28 g) in a solution of (**17**) (28.3 g, 0.107 mol) and MeOH (400 ml) was stirred at room temperature for 16 h before being filtered, concentrated and distilled to yield (**18**) (18.3 g, 95%) as a colourless oil; b.p. 95 °C (bath)/0.1 mmHg; $[\alpha]_D$ −4.4° (*c* 1.02 in EtOH) [lit.,[14] −4° (*c* 1.07 in EtOH)]; $\nu_{max.}$(film) 3 420m, 2 960s, 2 930s, 2 880s, 1 500m, 1 455s, 1 365m, 1 100s, 1 040s, 740s, and 700s cm^{-1}; δ_H (90 MHz) 7.3 (5 H, s), 4.5 (2 H, s), 3.7—3.3 (4 H, m), 2.6 (1 H, br



Scheme 5. *Reagents and conditions:* i, Bu^{t}Li, pentane–THF, −70 to 0 °C; ii, pentynylcopper(I)–THF, −70 °C; iii, oxirane (**4**)–THF, −30 to 20 °C, 6 h; iv, H^+–MeOH, 20 °C, 1 h followed by K_2CO_3; v, Bu^{t}Me$_2$SiCl, 4-(*N*,*N*-dimethylamino)pyridine, NEt_3–CH_2Cl_2, 20 °C, 3.5 h; vi, ref. 6

s, OH), 2.05 (1 H, m), and 0.9 (3 H, d, *J* 7) (Found: M^+ 180.1149; $C_{11}H_{16}O_2$ requires *M*, 180.1150).

(2S)-3-*Benzyloxy*-1-*bromo*-2-*methylpropane* (**19**).—*N*-Bromosuccinimide (16.75 g, 0.095 mol) was added to a solution of PPh_3 (24.7 g, 0.095 mol) and alcohol (**18**) (16.95 g, 0.095 mol) in dichloromethane (160 ml) at a rate sufficient to maintain the internal temperature over a range of 10—18 °C. After 45 min at room temperature, the solvent was evaporated, and the residue dissolved in ether, washed with water, dried and concentrated. The crude product was treated with hexane and filtered; the filtrate was concentrated and the residue distilled to give the bromide (**19**) (19.65 g, 86%) as a colourless oil, b.p. 65—68 °C/0.05 mmHg; $[\alpha]_D$ +12.1° (*c* 1.06 in EtOH) [lit.,[14] +12.5° (*c* 0.98 in EtOH)]; $\nu_{max.}$(film) 2 970s, 2 860s, 1 495m, 1 455s, 1 365m, 1 235m, 1 100s, 740m, and 700m cm^{-1}; δ_H (90 MHz) 7.3 (5 H, s), 4.5 (2 H, s), 3.47 (2 H, d, *J* 6), 3.39 (2 H, d, *J* 6), 2.15 (1 H, m), and 1.05 (3 H, d, *J* 7) (Found: M^+, 188.1174; $C_{13}H_{16}O$ requires *M*, 188.1201).

(4R)-5-*Benzyloxy*-4-*methylpent*-1-*yne* (**6**).—A solution of bromide (**19**) (20 g, 0.08 mol) in DMSO (5 ml) was added to a suspension of lithium acetylide ethylenediamine complex (8.85 g, 0.087 mol) in DMSO (40 ml) at 8 °C. After 20 min at room temperature the reaction was quenched with water and the product extracted into hexane, washed with brine, dried and the solvent evaporated. Spinning band distillation of the residue gave the olefin (**20**) (5 g, 38%), b.p. 68 °C/2.5 mmHg and the acetylene (**6**) (7.7 g, 51%); b.p. 75 °C/0.01 mmHg, $[\alpha]_D$ +16.3° (*c* 0.95 in $CHCl_3$); $\nu_{max.}$(film) 2 970m, 2 920m, 2 860m, 2 120w, 1 100s, 740s, and 700s cm^{-1}; δ_H (90 MHz) 7.3 (5 H, s), 4.47 (2 H, s), 3.36 (2 H, d, *J* 7), 2.5—1.85 (4 H, m), and 1.05 (3 H, d, *J* 7) (Found: M^+, 188.1174; $C_{13}H_{16}O$ requires *M*, 188.1201).

(4S)-4-[(2R)-2-*Hydroxy*-3-*phenylthiopropyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**23**) *and* (4S)-4-[(2S)-2-*Hydroxy*-3-*phenylthiopropyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**24**).—A solution of aldehyde (**22**) (4.36 g, 30 mmol) in THF (10 ml) was added at −70 °C to a solution of phenylthiomethyl-lithium[7] in THF (50 ml) prepared by the reaction of BuLi (1.2M, 27 ml, 32.3 mmol) and thioanisole (3.9 g, 31.5 mmol) in the presence of 1,4-diazabicyclo[2.2.2]octane (3.6 g, 31.5 mmol) at 0 °C for 1 h. After 15 min at −70 °C the reaction was quenched with saturated aqueous ammonium chloride and the product extracted into ether. The organic layer was dried, the solvent evaporated, and the residue chromatographed (2% dioxane in benzene) to give (**23**) (3.0 g, 38%) which crystallised in the refrigerator, m.p. 15—20 °C; $[\alpha]_D$ +4.8° (*c* 1 in $CHCl_3$); $\nu_{max.}$(film) 3 450br, 2 990s, 2 940m, 2 880m, 1 585m, 1 480m, 1 440m, 1 375s, 1 250s, 1 220s, 1 155s, 1 085s, 875m, 830m, 740m, and 690m cm^{-1}, δ_H (90 MHz) 7.5—7.1 (5 H, m), 4.25 (1 H, m), 4.05 (1 H, dd, *J* 7, *J*′ 6.5), 3.95 (1 H, m), 3.55 (1 H, dd, *J* 7, *J*′ 7), 3.35 (1 H, br s, OH), 3.05 (2 H, d, *J* 7), 1.85 (2 H, m), and 1.4 and 1.35 (3 H each, s) (Found: C, 62.35; H, 7.45; S, 11.95. $C_{14}H_{20}O_3S$ requires C, 62.6; H, 7.5; S, 11.95%), mixed fractions containing (**23**) and (**24**) (1.21 g, 15%); and pure (**24**) (1.21 g, 16%), b.p. 115 °C (bath)/0.01 mmHg; $[\alpha]_D$ +12.35° (*c* 1 in $CHCl_3$); $\nu_{max.}$(film) 3 450br, 2 990s, 2 940m, 2 880m, 1 585m, 1 480m, 1 440m, 1 375s, 1 250s, 1 220s, 1 155s, 1 065s, 875m, 830m, 740m, and 690m cm^{-1}, δ_H (90 MHz) 7.5—7.1 (5 H, m), 4.3 (1 H, m), 4.05 (1 H, dd, *J* 7, *J*′ 6.5), 3.9 (1 H, m), 3.55 (1 H, dd, *J* 7, *J*′ 7), 3.18 (1 H, dd, *J* 14, *J*′ 5), 2.93 (1 H, dd, *J* 14, *J*′ 8), 2.9 (1 H, br s, OH), 1.8 (2 H, m), and 1.4 and 1.35 (3 H each, s) (Found: M^+, 268.1136; $C_{14}H_{20}O_3S$ requires *M*, 268.1133).

(4S)-4-[(2R)-2,3-*Epoxypropyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**7**).—Trimethyloxonium tetrafluoroborate (2.2 g, 14.6 mmol) was added to a solution of (**24**) (3.55 g, 13.25 mmol) and 2,6-di-t-butylpyridine (0.51 g, 2.65 mmol) in dichloromethane (30 ml) at room temperature. After 2 h NaOH solution (0.15M, 100 ml) was added and the two-phase mixture efficiently stirred for 16 h. The organic layer was separated and dried before chromatography (5 to 20% ether–hexane) gave the oxirane (**7**) (1.65 g, 80%) as a colourless oil, b.p. 105 °C (bath)/15 mmHg; $[\alpha]_D$ −15.7° (*c* 1 in $CHCl_3$); $\nu_{max.}$(film) 2 990s, 2 940s, 2 880s, 1 370s, 1 364s, 1 260s, 1 220s, 1 160s, and 855s cm^{-1}; δ_H (400 MHz) 4.30 (1 H, dddd, *J* 7.5, 7.1, 6.0, 5.4), 4.11 (1 H, dd, *J* 8.1, *J*′ 6), 3.58 (1 H, dd, *J* 8.1, *J*′ 7.1), 3.04 (1 H, dddd, *J* 7.62, 4.0, 4.0, 2.7), 2.81 (1 H, dd, *J* 5, *J*′ 4), 2.51 (1 H, dd, *J* 5, *J*′ 2.7), 1.97 (1 H, ddd, *J* 14, *J*′ 7.6, *J*″ 4), 1.54 (1 H, ddd, *J* 14, *J*′ 7.6, and *J*″ 5.4), and 1.41 and 1.37 (3 H, each, s) [Found: $(M + 1)^+$, 159.1022; $C_8H_{15}O_3$ requires $(M + 1)$, 159.1021].

(4S)-4-[(2S)-2,3-*Epoxypropyl*]-2,2-*dimethyl*-1,3-*dioxolane* (**25**).—Thioether (**23**) (6 g, 22.4 mmol), trimethyloxonium tetrafluoroborate (3.65 g, 24.6 mmol), and 2,6,-di-t-butylpyridine (0.56 g, 4.5 mmol) reacted in dichloromethane as described above to give the oxirane (**25**) (2.77 g, 79%) as a colourless oil, b.p. 105 °C (bath)/15 mmHg; $[\alpha]_D$ +15° (*c* 1.2 in $CHCl_3$); $\nu_{max.}$(film) 2 990s, 2 940s, 2 880s, 1 370s, 1 364s, 1 260s, 1 220s, 1 160s, and 855s cm^{-1}; δ_H (400 MHz) 4.22 (1 H, dddd, *J* 7.4, 6.0, 5.75, 5.0), 4.07 (1 H, dd, *J* 8.1, *J*′ 6.0), 3.65 (1 H, dd, *J* 8.1, *J* 7.4), 3.05 (1 H, dddd, *J* 5.7, 5.0, 4.0, 2.7), 2.78 (1 H, dd, *J* 5, *J*′ 4.1), 2.54 (1 H, dd, *J* 5, *J*′ 2.7), 1.89 (1 H, ddd, *J* 14.4, *J*′ 6, *J*″ 6.1), 1.82 (1 H, ddd, *J* 14.4, *J*′ 5.2, *J*″ 5.2), and 1.42 and 1.36 (3 H each, s) [Found: $(M + 1)^+$, 159.1022; $C_8H_{15}O_3$ requires $(M + 1)$, 159.1021].

(4S)-4-[(2R,7R)-(4E)-8-*Benzyloxy*-2-*hydroxy*-5,7-*dimethyl*-*oct*-4-*en*-1-*yl*]-2,2-*dimethyl*-1,3-*dioxolane* (**9**).—Me_3Al (2.4M in hexane, 20 ml, 48 mmol) was added to a solution of $(C_5H_5)_2ZrCl_2$ (2.4 g, 8.2 mmol) in 1,2-dichloroethane (20 ml) followed by acetylene (**6**) (2.95 g, 16 mmol) in 1,2-dichloroethane (25 ml). The mixture was left to stir at room temperature for 3 days whereupon the solvent was removed under reduced pressure and the residue evacuated for 4 h at 0.3 mmHg. The resultant alane was extracted into hexane (3 × 25 ml) and the solution cooled to −70 °C. Butyl-lithium in hexane (1.9M, 8.4 ml, 15.8 mmol) was added with mechanical stirring and the mixture was allowed to warm to −30 °C. To the resultant complex (**8**), the oxirane (**7**) (1.65 g, 9 mmol) in hexane (5 ml) was added. The mixture was then stirred at −10 °C for 25 min and the reaction quenched by the careful addition of water (34 ml) followed by 3M HCl (10 ml). After a further 10 min of vigorous stirring, the mixture was filtered through Celite, and the organic layer separated, washed with brine, dried, and evaporated. The residue was chromatographed (8% ethyl acetate–hexane) to give unchanged (**7**) (0.5 g, 35%) and alcohol (**9**) (1.98 g, 61%); $[\alpha]_D$ *ca.* 1° (*c* 1 in $CHCl_3$); $\nu_{max.}$(film) 3 470br, 2 990s, 2 940s, 2 875s, 1 455m, 1 370s, 1 250m, 1 215s, 1 158m, 1 070s, 740m, and 700m cm^{-1}; δ_H (90 MHz) 7.3 (5 H, s), 5.15 (1 H, t, *J* 7), 4.5 (2 H, s), 4.35 (1 H, ddt, *J* 6.5, *J'* 7, *J''* 7), 4.05 (1 H, dd, *J* 7, *J'* 6.5), 3.8 (1 H, s, OH), 3.8 (1 H, m), 3.56 (1 H, dd, *J* 7, *J'* 7), 3.3 (2 H, dd, *J* 5.5, *J'* 2), 2.35-1.6 (7 H, m), and 1.61, 1.41, 1.36, and 0.9 (3 H each, s); δ_C (22.5 MHz) 138.9(s), 136.9(s), 128.3(d), 127.5(d), 121.5(d), 108.5(s), 75.8(t), 73.9(d), 73.1(t), 69.72(t), 68.96(d), 44.4(t), 40.0(t), 36.7(t), 31.7(d), 26.98(q), 25.73(q), 17.1(q), and 16.4(q) (Found: M^+, 362.2457; $C_{22}H_{34}O_4$ requires *M*, 362.2457). Isomer (**9**) had a retention time of 14 min on Spherisorb Si 5, 10% ethyl acetate–hexane at 2 ml min^{-1}.

(4S)-4-[(2S,7R)-(4E)-8-*Benzyloxy*-2-*hydroxy*-5,7-*dimethyl*-*oct*-4-*en*-1-*yl*]-2,2-*dimethyl*-1,3-*dioxolane* (**10**).—From acetylene (**6**) (5.75 g, 31.5 mmol), 1,2-dichloroethane (80 ml), Me_3Al (95 mmol), $(C_5H_5)_2ZrCl_2$ (4.6 g, 15.75 mmol), BuLi (31.5 mmol), and oxirane (**25**) was obtained by the procedure outlined above unchanged (**25**) (0.4 g, 15%), and compound (**10**) (4.61 g, 73%); $[\alpha]_D$ −8.1° (*c* 1 in $CHCl_3$); $\nu_{max.}$(film) 3 470br, 2 990s, 2 940s, 2 875s, 1 455m, 1 370s, 1 250m, 1 215s, 1 158m, 1 070s, 740m, and 700m cm^{-1}; δ_H (90 MHz) 7.31 (5 H, s), 5.15 (1 H, t, *J* 7), 4.49 (2 H, s), 4.25 (1 H, ddt, *J* 7, *J'* 6.5, *J''* 7), 4.06 (1 H, dd, *J* 7, *J'* 6.5), 3.78 (1 H, m), 3.54 (1 H, dd, *J* 7, *J'* 7), 3.27 (2 H, dd, *J* 5.5, *J'* 2), 2.9 (1 H, br s, OH), 2.35—1.5 (7 H, m), and 1.6, 1.42, 1.36, and 0.87 (3 H each, s); δ_C (22.5 MHz) 138.8(s), 136.4(s), 128.4(d), 128.7(d), 127.4(d), 121.6(d), 109.2(s), 75.8(t), 75.4(d), 73.0(t), 70.7(d), 69.7(t), 44.4(t), 39.9(t), 36.1(t), 31.6(d), 26.9(q), 25.7(q), 17.06(q), and 16.25(q) (Found: M^+, 362.2457; $C_{22}H_{34}P_4$ requires *M*, 362.2457).

Isomer (**10**) had a retention time of 10 min on Spherisorb Si 5, 10% ethyl acetate–hexane at 2 ml min^{-1}.

Inversion of configuration of the alcohol (**10**) was achieved under standard Mitsunobu conditions[9] using *p*-nitrobenzoic acid to give the *p*-nitrobenzoate ester (**11**) in 88% yield; $[\alpha]_D$ −15.8° (*c* 1 in $CHCl_3$); $\nu_{max.}$(film) 2 990m, 2 930m, 2 870m, 1 725s, 1 530s, 1 370m, 1 350m, 1 275s, 1 105s, 875m, and 720s cm^{-1}; δ_H (90 MHz) 8.2 (4 H, m), 7.3 (5 H, s), 5.2 (2 H, m), 4.5 (2 H, s), 4.18 (1 H, tt, *J* 7, *J'* 7), 4.0 (1 H, dd, *J* 7, *J'* 7), 3.54 (1 H, dd, *J* 7, *J'* 7), 3.24 (2 H, dd, *J* 5.5, *J'* 1), 2.6—1.65 (7 H, m), and 1.6, 1.38, 1.3, and 0.8 (3 H each, s) (Found: M^+, 511.2566; $C_{29}H_{37}NO_7$ requires *M*, 511.2570).

Basic hydrolysis of the ester (**11**) in the usual way in aqueous THF gave the desired alcohol (**9**) (90%) which was identical in all respects with the sample prepared as described above.

(2S,4R,9R)-(6E)-10-*Benzyloxy*-7,9-*dimethyldec*-6-*ene*-1,2,4-*triol* (**12**).—Amberlite 120 acidic exchange resin (1.8 g) was added to a solution of the dioxolane (**9**) (4.75 g, 13.1 mmol) in MeOH (85 ml) and water (1.7 ml) and the mixture was stirred at room temperature for 3 d before the resin was filtered off. The filtrate was stirred with an excess of K_2CO_3 for 3 h, then filtered through Celite, diluted with $CHCl_3$, filtered again and the bulk of the solvent evaporated. The residue was chromatographed (1% MeOH–$CHCl_3$) to give the triol (**12**) (2.93 g, 69%) and recovered (**9**) (0.83 g, 17%) which on recycling, as described, afforded another 0.57 g of the triol (**12**) to give a total yield of 83%; $\nu_{max.}$(film) 3 450s, 2 930s, 2 860m, 1 455m, 1 095s, 1 075s, 1 030m, 740m, and 700m cm^{-1}; δ_H (90 MHz) 7.3 (5 H, s), 5.13 (1 H, t, *J* 7), 4.45 (2 H, s), 4.2—3.1 (9 H, m), 2.35—1.35 (7 H, m), and 1.6, 0.88 (3 H each, s) (Found: M^+, 322.2146; $C_{19}H_{30}O_4$ requires *M*, 322.2144).

(2S,4R,9R)-(6E)-10-*Benzyloxy*-1,2-*epoxy*-7,9-*dimethyldec*-6-*en*-4-*ol* (**14**).—Toluene-*p*-sulphonyl chloride (2 g, 10.5 mmol) was added to a solution of the triol (**12**) (2.93 g, 9.1 mmol) in pyridine (45 ml) and the mixture stirred at 0 °C for 10 h. The mixture was diluted with ether and washed with dilute HCl and saturated aqueous $NaHCO_3$ before drying and evaporation of the solvent. The crude tosylate (**13**) (3.4 g, 78%) and K_2CO_3 in MeOH (60 ml) were stirred at room temperature for 25 min. The reaction mixture was filtered through Celite, the bulk of the MeOH evaporated and the residue partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane and the combined organic layers dried and concentrated. Chromatography (10% ethyl acetate–hexane) of the residue gave the oxirane (**14**) (1.616 g, 80%) as a colourless oil; $[\alpha]_D$ −10.1° (*c* 1.1 in $CHCl_3$); $\nu_{max.}$(film) 3 450br, 2 960s, 2 920s, 2 860s, 1 450m, 1 365m, 1 090s, 1 030m, 740s, and 700s cm^{-1}; δ_H (90 MHz) 7.3 (5 H, s), 5.18 (1 H, t, *J* 7), 4.5 (2 H, s), 3.85 (1 H, ddt, *J* 6.5, *J'* 4, *J''* 8 Hz), 3.27 (2 H, dd, *J* 5.7, *J'* 1.6), 3.13 (1 H, ddt, *J* 3, *J'* 4, *J''* 6.5), 2.83 (1 H, dd, *J* 5, *J'* 4), 2.59 (1 H, dd, *J* 5, *J'* 3), 2.4—1.5 (8 H, m), 1.62 (3 H, s), 0.88 (3 H, d, *J* 6.5) (Found: M^+, 304.2041; $C_{19}H_{28}O_3$ requires *M*, 304.2038).

(2S,4R,9R)-(6E)-1,2-*Epoxy*-10-*benzyloxy*-7,9-*dimethyl*-4-(*dimethyl*-*t*-*butylsilyloxy*)*dec*-6-*ene* (**4**).—A solution of the alcohol (**14**) (1.62 g, 5.32 mmol), 4-(*N*,*N*-dimethylamino)pyridine (0.195 g, 1.59 mmol), Bu^tMe_2SiCl (0.922 g, 6.12 mmol), and NEt_3 (0.7 g, 4.7 mmol) in DMF (5 ml) was stirred at room temperature for 5 h whereupon the reaction mixture was diluted with ether, washed with dilute HCl followed by saturated aqueous $NaHCO_3$ and brine, dried, and the solvent evaporated. The residue was chromatographed (5% ether–hexane) to give the silylether (**4**) (1.93 g, 87%) as a colourless oil; $[\alpha]_D$ −27° (*c* 1 in hexane); $\nu_{max.}$(film) 2 960s, 2 930s, 2 860s, 1 255m, 1 090s, 840s, and 780s cm^{-1}; δ_H (90 MHz) 7.32 (5 H, s), 5.13 (1 H, t, *J* 7), 4.49 (2 H, s), 3.90 (1 H, dt, *J* 6.5, *J'* 6.5), 3.27 (2 H, dd, *J* 5.2, *J'* 2.3), 3.0 (1 H, m), 2.78 (1 H, dd, *J* 5.2, *J'* 4), 2.46 (1 H, dd, *J* 5.2, *J'* 2.75), 2.35—1.5 (7 H, m), 1.58 (3 H, s), 0.86 (9 H and 3 H, overlapping s), and 0.09 (6 H, s); δ_C (100.6 MHz) 138.8(s), 135.5(s), 128.3(d), 127.5(d), 127.4(d), 121.6(d), 47.9(t), 44.3(t), 40.0(t), 36.7(t), 31.5(d), 25.8(q), 18.0(s), 17.1(q), and 16.2(q) (Found: M^+, 418.2904; $C_{25}H_{42}O_3Si$ requires *M*, 418.2903).

(2R,4R,6S,8R,9S)-2-[(5R)-(2E)-6-*Benzyloxy*-3,5-*dimethyl*-*hex*-2-*en*-1-*yl*]-8,9-*dimethyl*-4-(*dimethyl*-*t*-*butylsilyloxy*)-1,7-*dioxaspiro*[5.5]*undecane* (**34**).—Bu^tLi (1.4M in pentane, 10.4 ml, 14 mmol) was added to a solution of dihydropyran (**5**) (1.83 g, 14 mmol) in THF (3.5 ml) at −70 °C to form a yellow suspension which was immediately warmed to 0 °C. After 45 min the now clear yellow solution was re-cooled to −70 °C and added to a suspension of pentynylcopper(I) (1.93 g, 14 mmol) in THF (17 ml) at −70 °C and then left to warm to 0 °C. After 30 min the cuprate solution was cooled to −30 °C, a solution of the oxirane (**4**) (1.812 g, 4.34 mmol) in THF (3.2

ml) was added, and the reaction was allowed to warm to room temperature where it was stirred for 6 h before being quenched with a mixture of saturated NH_4Cl (27 ml) and aqueous NH_3 (15M, 3 ml). The mixture was filtered through Celite, the organic layer was separated, and the aqueous layer extracted with several portions of ether. The combined organic layers were washed with water, dried, and the solvent evaporated. The crude product (**32**) was dissolved in MeOH (25 ml) and camphorsulphonic acid (100 mg) added. After 1 h at room temperature an excess of finely powdered K_2CO_3 was added and the mixture was stirred for 30 min whereupon it was filtered and the solvent evaporated. The residue was dissolved in dichloromethane and washed with saturated aqueous $NaHCO_3$ and brine, dried, and the solvent evaporated. The residue was chromatographed (25% ethyl acetate–hexane) to give the spiroacetal (**33**) (1.5 g) which was used immediately in the next step.

To a solution of the spiroacetal (**33**) (1.5 g) in DMF (3.5 ml) was added Bu^tMe_2SiCl (0.61 g, 4 mmol), 4-(*N*,*N*-dimethylamino)pyridine (0.13 g, 1 mmol), and NEt_3 (0.46 g, 4.6 mmol). After having been stirred at room temperature for 3.5 h, the mixture was diluted with ether, washed with saturated $NaHCO_3$, dried, and concentrated. The residue was chromatographed (3% ether–hexane) to give the spiroacetal (**34**) (1.3 g) in 57% overall yield from the oxirane (**4**). The product gave high field ^1H n.m.r., ^{13}C n.m.r., i.r., and mass spectra identical with a sample previously prepared by a different route.[1]

The 2-step conversion of (**34**) to the desired aldehyde (**2**) was carried out as described.[1]

Proof of Stereochemistry in Oxiranes (**7**) *and* (**25**).—The copper(I)-catalysed cleavage of the oxirane (**7**) by vinylmagnesium bromide according to the procedure of Linstrumelle and co-workers[15] gave the alcohol (**26**) (65%); $[\alpha]_D$ −9.5° (*c* 2.6 in dichloromethane) [lit.,[8] $[\alpha]_D$ −8.4° (*c* 1.6 in dichloromethane)].

Similar cleavage of oxirane (**25**) gave alcohol (**27**) (60%); $[\alpha]_D$ +8.0 (*c* 1 in dichloromethane) [lit.,[8] $[\alpha]_D$ +8.3° (*c* 1.25 in dichloromethane)]. For ^1H n.m.r. and ^{13}C n.m.r. data of both isomers prepared by the reaction of aldehyde (**22**) with allylmagnesium bromide see reference 6.

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References

1 P. Kocieński, S. D. A. Street, C. Yeates, and S. F. Campbell, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
2 The aldehyde (**2**) has been used in an alternative synthesis of (+)-milbemycin β_3: S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenburg, and A. B. Smith, *J. Am. Chem. Soc.*, 1986, **108**, 2662.
3 Preliminary communication: C. Yeates, S. D. A. Street, P. Kocieński, and S. F. Campbell, *J. Chem. Soc., Chem. Commun.*, 1985, 1388.
4 The use of metallated cyclic enol ethers for the synthesis of spiroacetals is precedented: R. K. Boeckman, K. J. Bruza, and G. R. Heinrich, *J. Am. Chem. Soc.*, 1978, **100**, 7101; P. Kocieński and C. Yeates, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1879; P. Kocieński and C. Yeates, *Tetrahedron Lett.*, 1983, **24**, 3905; R. Amouroux, *Heterocycles*, 1984, **22**, 1489.
5 M. Kobayashi, C. F. Valente, and E. Negishi, *Synthesis*, 1980, 1034.
6 P. Kocieński, C. Yeates, S. D. A. Street, and S. F. Campbell, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2171.
7 E. J. Corey and D. Seebach, *J. Org. Chem.*, 1966, **31**, 4097.
8 S. Hanessian, U. Ugolini, and M. Thérien, *J. Org. Chem.*, 1983, **48**, 4427.
9 O. Mitsunobu, *Synthesis*, 1981, 1.
10 V. Schürig, B. Koppenhoeffer, and W. Bürkle, *J. Org. Chem.*, 1980, **45**, 538; P. Kocieński and S. D. A. Street, *Synth. Commun.*, 1984, **14**, 1087.
11 P. Deslongchamps, R. D. Rowan, N. Pothier, T. Sauvé, and J. K. Saunders, *Can. J. Chem.*, 1981, **59**, 1105; P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry,' Pergamon, Oxford, 1983, pp. 4—47.
12 P. Lesimple, J.-M. Beau, G. Jaurand, and P. Sinaÿ, *Tetrahedron Lett.*, 1986, **27**, 6201; A. B. Smith and M. Fukui, *J. Am. Chem. Soc.*, 1987, **109**, 1269.
13 K. Mori, *Tetrahedron*, 1983, **39**, 3107.
14 Q. Branca and A. Fischli, *Helv. Chim. Acta*, 1977, **60**, 925.
15 C. Huynh, F. Derguini, and G. Linstrumelle, *Tetrahedron Lett.*, 1979, 1503.

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