Use of *S*-t-Butyl Acetothioacetate in the Preparation of Milbemycin Seco-Analogues

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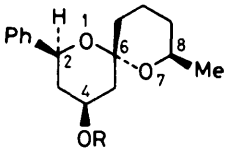
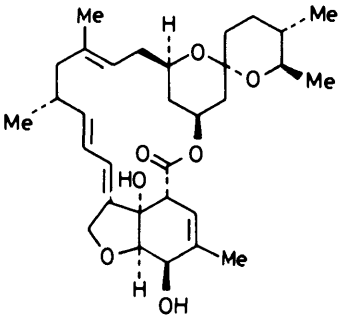
The preparation of milbemycin seco-analogues are described in which the key step involves alkylation of the γ-carbon atom by acrylaldehyde, or methacrylaldehyde of dianions generated from *S*-t-butyl acetothioacetate (**6**). Subsequent protection and transesterification of the products of these reactions with a model spiro acetal unit (**1**) gave acetoacetate derivatives. These compounds upon reaction with sodium borohydride and deprotection afforded the seco-species.

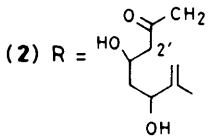
Since the discovery of the extremely potent antiparasitic agents the milbemycins [1] and avermectins,[2] there has been considerable interest in their preparation and mode of action. We have recently developed a short route to a spiro acetal derivative (**1**) displaying some of the structural features common to the milbemycins.[3] Here we show how this unit may be converted into a compound (**2**) which incorporates an acyclic seco side-chain that should mimic the dihydroxylated southern region of these molecules, for example in milbemycin α_1 (**3**).



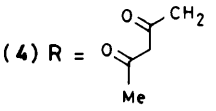
(**1**) R = H



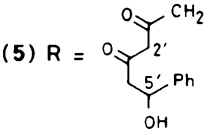
(**3**)



(**2**) R =



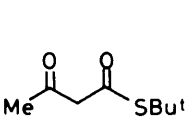
(**4**) R =



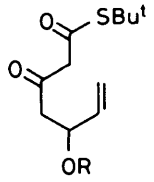
(**5**) R =

Reaction of compound (**1**) with diketene proceeds well to give the corresponding acetoacetate derivative (**4**). However problems arose in attempts to generate and quench the dianion from (**4**) to give homologated derivatives using the standard Weiler conditions.[4] For example, we found that upon quenching at the γ-carbon position with benzaldehyde only low yields (35%) of the 1,2-product (**5**) could be obtained. We ascribed this problem to the competitative benzylic deprotonation during the addition of butyl-lithium necessary for the formation of the acetoacetate dianion. Other attempts to form the dianion from (**4**) with lithium di-isopropylamide were also disappointing.

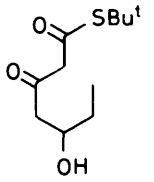
For these reasons it was decided to use an alternative strategy employing *S*-t-butyl acetothioacetate (**6**) as a diketene equivalent.* In a model study, the dianion from (**6**) was treated with acrylaldehyde to give compound (**7**) in 83% yield. Protection of the hydroxy group in (**7**) as its dimethyl-t-butylsilyl ether to give (**8**) was straightforward. Transesterification of (**8**) with cyclohexanol, as a model alcohol for compound (**1**), in the presence of silver(I) trifluoroacetate[5] in THF at room temperature gave the ester (**9**) in 67% yield after 18 h. Selective reduction of the ketone carbonyl group in (**9**) with sodium borohydride gave compound (**10**) as a mixture of diastereoisomers, which were not separated or individually characterised. These were deprotected to give the diol (**11**), using tetrabutylammonium fluoride in the normal way, in 92% overall yield from (**9**). The dianion from (**6**) was also reacted at the γ-carbon atom with propionaldehyde and methacrylaldehyde to give compounds (**12**) and (**13**) in excellent yields. The dione



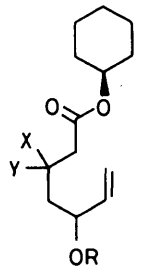
(**6**)



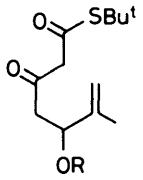
(**7**) R = H
(**8**) R = $SiBu^tMe_2$



(**12**)



(**9**) X,Y = =O; R = $SiBu^tMe_2$
(**10**) X,Y = H,HO; R = $SiBu^tMe_2$
(**11**) X,Y = H,HO; R = H



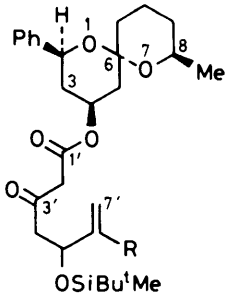
(**13**) R = H
(**14**) R = $SiBu^tMe_2$

* See the preceding paper for the preparation of *S*-t-butyl acetothioacetate for acyltetronic acid synthesis.

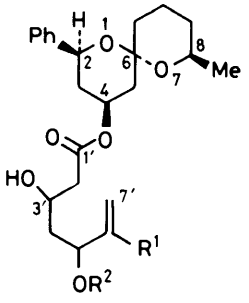
(**13**) was subsequently protected as its t-butyldimethylsilyl ether (**14**) (96%) prior to coupling studies with compound (**1**).

Transesterification of compounds (**8**) or (**14**) with the milbemycin model spiro acetal (**1**) gave the acetoacetates (**15**) and (**16**) in 77 and 76% yield respectively. The remaining steps in the syntheses involved reduction of the β-carbonyl group and a final deprotection. While the reduction of (**15**) and (**16**) with sodium borohydride proceeded in essentially quantitative yields, to (**17**) and (**18**), the deprotection using tetrabutylammonium fluoride was poor, typically < 40%. This was readily overcome using the HF–acetonitrile procedure[6] which afforded the deprotected seco-model compounds (**19**) and (**2**)* In virtually quantitative yields.

The above study has shown that milbemycin acyclic seco-analogues may be prepared in good yield by the use of *S*-t-butyl acetothioacetate (**6**) as a diketene equivalent when use of more conventional methods for their preparation are less successful.



(**15**) R = H
(**16**) R = Me



(**17**) $R^1 = H$; $R^2 = SiBu^tMe_2$
(**18**) $R^1 = Me$; $R^2 = SiBu^tMe_2$
(**19**) $R^1 = R^2 = H$
(**2**) $R^1 = Me$; $R^2 = H$

Experimental

I.r. spectra were recorded with a Perkin-Elmer 983 G spectrophotometer and ^1H n.m.r. spectra with a Bruker WH250 spectrometer, for solutions in deuteriochloroform with tetramethylsilane as the internal standard. Mass spectra were obtained using a V.G. Micromass 7070 B spectrometer. Petroleum refers to the fraction boiling in the range 40—60 °C. Solutions were dried over anhydrous magnesium sulphate, and solvents by standard methods. Chromatography was performed on MN-Silica gel 60, 230—400 mesh, under pressure.

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl Acetoacetate* (**4**).—To a solution of compound (**1**) (98.4 mg, 0.375 mmol) in THF (5 ml) was added Et_3N (20 mg, 0.198 mmol) and the mixture was heated at reflux for 10 min. Diketene (41.0 mg, 0.488 mmol) was then added and the mixture heated at reflux for a further 2 h before being poured into 1M-HCl solution (2 ml). The product was extracted into Et_2O (3 × 10 ml) and the combined organic extracts were dried, evaporated under reduced pressure and chromatographed (20% Et_2O–petroleum) to give the *title compound* (**4**) (116 mg, 89%) as a colourless oil, $\nu_{max.}$(film) 2 935, 1 742, and 1 717 cm^{-1}; δ (16% enol form) 1.05—2.00 (8 H, m), 1.13 (3 H, d, *J* 7.2 Hz, 8-Me), 2.12 (1 H, dd, *J* 3.6, 12.6 Hz, 11-*H*), 2.25 (3 H, s, COMe), 2.36 (1 H, m, 5-H), 3.41 (1.68 H, s, 2-H keto), 3.71 (1 H, m, 8-H), 4.71 (1 H, dd, *J* 2.2, 11.5 Hz, 2-H), 4.94 (0.16 H, s, 2′-H enol), 5.47 (1 H, m, 4-H), and 7.36 (5 H, m, Ph); *m/z* 244 ($M^+ - 102$) (Found: C, 69.55; H, 7.75. $C_{20}H_{26}O_5$ requires C, 69.33; H, 7.58%).

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 5-*Hydroxy*-3-*oxo*-5-*phenylpentanoate* (**5**).—To a stirred suspension of sodium hydride (12 mg, 0.25 mmol; 50% dispersion in oil), prewashed with sodium-dried petroleum (1 × 1 ml) in THF (2 ml) at 0 °C under argon, was added the β-keto ester (**4**) (58.5 mg, 0.169 mmol). The solution was stirred at 0 °C for 10 min, cooled to −20 °C, and BuLi (139 μl of a 1.3M solution in hexane; 0.186 mmol) added dropwise. The resulting deep yellow solution of the dianion was stirred at −20 °C for 30 min, cooled to −78 °C, and benzaldehyde (26.9 mg, 0.254 mmol) was added dropwise. The mixture was allowed to warm to 0 °C over 30 min, poured into saturated aqueous NH_4Cl (3 ml), and extracted with Et_2O (3 × 10 ml), each extract being washed with water (5 ml) and brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residual oil chromatographed (30% Et_2O–petroleum) to give the β-keto ester (**5**) (26.8 mg, 35%) as a colourless oil, $\nu_{max.}$(film) 3 428, 2 934, 1 736, and 1 710 cm^{-1}; δ (10% enol form) 1.13 (2 H, d, *J* 6.8 Hz, 8-Me), 1.15—2.00 (8 H, m), 2.09 (1 H, ddd, *J* 1.6, 5.0, 12.6 Hz, 11-H), 2.34 (1 H, m, 5-H), 2.87 (1 H, dd, *J* 3.6, 17.3 Hz, 4′-H), 2.97 (1 H, dd, *J* 8.5, 17.3 Hz, 4′-H), 2.98 (1 H, s, OH), 3.45 (1.8 H, s, 2′-H), 3.70 (1 H, m, 8-H), 4.69 (1 H, dd, *J* 2.5, 11.8 Hz, 2-H), 5.0 (0.1 H, s, 2′-H enol), 5.17 (1 H, m, 5′-H), 5.43 (1 H, m, 4-H), and 7.32 (10 H, m, Ph); *m/z* 452 (M^+).

Preparation of S-*t-Butyl* 5-*Hydroxy*-3-*oxohept*-6-*enethioate* (**7**).—To a stirred suspension of sodium hydride (228 mg, 4.74 mmol; 50% dispersion in oil), prewashed with sodium-dried petroleum (2 × 2 ml), in THF (2 ml) at 0 °C under argon, was added *S*-t-butyl acetothioacetate (**6**) (531 mg, 3.05 mmol). The solution was stirred at 0 °C for 10 min, cooled to −20 °C, and BuLi (2.44 ml of a 1.50M solution; 3.66 mmol) added dropwise. The resulting deep yellow solution of the dianion was stirred at −20 °C for 10 min, cooled to −78 °C, and freshly distilled acrolylaldehyde (224 mg, 4.00 mmol) added dropwise. The mixture was allowed to warm to 0 °C over 30 min, poured into saturated aqueous NH_4Cl (5 ml) and extracted with Et_2O (3 × 10 ml), each extract being washed with water (5 ml) and brine (5 ml). The combined organic extracts were dried, the solvent evaporated under reduced pressure, and the residue chromatographed (25% Et_2O petroleum) to give S-*t-butyl* 5-*hydroxy*-3-*oxohept*-6-*enethioate* (**7**) (584 mg, 83%) as a colourless oil, $\nu_{max.}$(film) 3 560, 2 850, 1 708, 1 670, and 1 620 cm^{-1}; δ (19% enol form) 1.48 (7.29 H, s, Bu^t, enol), 2.78 (3 H, m, 4-H_2 and OH), 3.61 (1.62 H, s, 2-H), 4.60 (1 H, m, 5-H), 5.15 (1 H, ddd, *J* 2.9, 2.9, 10.6 Hz, 7-H), 5.31 (1 H, ddd, *J* 2.9, 2.9, 17.1 Hz, 7-H *Z*), 5.40 (0.19 H, s, 2-H enol), and 5.86 (1 H, ddd, *J* 5.5, 10.6, 17.1 Hz, 6-H); *m/z* 230 (M^+) (Found: C, 57.15; H, 7.7. $C_{11}H_{18}O_3S$ requires C, 57.35; H, 7.89%).

Preparation of S-*t-Butyl* 5-*Dimethyl*-t-*butylsilyloxy*-3-*oxohept*-6-*enethioate* (**8**).—A solution of the allylic alcohol (**7**) (765 mg, 3.33 mmol), dimethyl-t-butylsilyl chloride (602 mg, 3.99 mmol) and imidazole (566 mg, 8.31 mmol) in dry DMF (2.5 ml) was stirred overnight at room temperature. The mixture was poured into Et_2O (50 ml) and washed with water (3 × 10 ml), followed by brine (10 ml). After drying of the extract and evaporation of solvent under reduced pressure, the residue was chromatographed (3% Et_2O–petroleum) to give the *title compound* (**8**) (1.06 g, 93%) as a colourless oil, $\nu_{max.}$(film) 2 855, 1 720, 1 670, 1 618, and 1 360 cm^{-1}; δ (30% enol form) 0.05 (6 H, s, $SiMe_2$), 0.87 (9 H, s, $SiBu^t$), 1.47 (6.3 H, s, SBu^t), 1.51 (2.7 H, s, SBu^t enol), 2.62 (1 H, dd, *J* 5.0, 15.1 Hz, 4-H), 2.80 (1 H, dd, *J* 7.6, 15.1 Hz, 4-H), 3.58 (1.4 H, s, 2-H), 4.47 (0.3 H, m, 5-H enol), 4.61

* None of the analogues prepared in this programme showed any significant biological activity.

(0.7 H, m, 5-H keto), 5.07 (1 H, ddd, *J* 2.5, 2.5, 10.3 Hz, 7-H *E*), 5.22 (1 H, ddd, *J* 2.5, 2.5, 17.0 Hz, 7-H *Z*), 5.37 (0.3 H, s, 2-H enol), and 5.82 (1 H, ddd, *J* 6.7, 10.3, 17.0 Hz, 6-H); *m/z* 287 (M^+ − Bu^t) (Found: C, 59.47; H, 9.40. $C_{17}H_{32}O_3SSi$ requires C, 59.24; H, 9.38%).

Preparation of Cyclohexyl 5-Dimethyl-t-butylsilyloxy-3-oxohept-6-enoate (**9**).—To a solution of the thio ester (**8**) (201.7 mg, 0.585 mmol) and cyclohexanol (70.5 mg, 0.704 mmol) in THF (3 ml) was added silver(I) trifluoroacetate (155 mg, 0.705 mmol). The mixture was stirred at room temperature for 18 h. The solution was diluted with Et_2O (50 ml), filtered through a short pad of silica, and washed with saturated aqueous $NaHCO_3$ (2 × 20 ml) followed by brine (10 ml). After drying of the extract and evaporation of the solvent under reduced pressure, the residue was chromatographed (5% Et_2O–petroleum) to give the *title compound* (**9**) (137.9 mg, 67%) as a colourless oil, $\nu_{max.}$(film) 2 915, 2 850, 1 735, 1 712, and 1 635 cm^{-1}; δ (22% enol form) 0.04 (4.68 H, s, $SiMe_2$), 0.05 (1.32 H, s, $SiMe_2$), 0.87 (7.02 H, s, SiBu^t), 0.88 (1.98 H, s, SiBu^t), 1.10—1.60 (6 H, m), 1.70 (2 H, m, 2′-H and 6′-H), 1.85 (2 H, m, 2′-H and 6′-H), 2.31 (0.44 H, m, 4-H enol), 2.60 (0.78 H, dd, *J* 4.4, 15.0 Hz, 4-H), 2.80 (0.78 H, dd, *J* 6.1, 15.0 Hz, 4-H), 3.45 (1.56 H, s, 2-H), 4.47 (0.22 H, m, 5-H enol), 4.61 (0.78 H, m, 5-H), 4.81 (1 H, m, 1′-H), 4.99 (0.22 H, s, 2-H enol), 5.07 (1 H, ddd, *J* 2.9, 10.5 Hz, 7-H *E*), 5.22 (1 H, ddd, *J* 2.9, 2.9, 16.8 Hz, 7-H *Z*), and 5.82 (1 H, ddd, *J* 5.9, 10.5, 16.8 Hz, 6-H); *m/z* 354 (M^+) (Found: C, 64.4; H, 9.7. $C_{19}H_{34}O_4Si$ requires C, 64.35; H, 9.7%).

Preparation of Cyclohexyl 5-Dimethyl-t-butylsilyloxy-3-hydroxyhept-6-enoate (**10**).—To a solution of the β-keto ester (**9**) (99.2 mg, 0.28 mmol) in MeOH (2 ml) was added sodium borohydride (27.0 mg, 0.714 mmol). The mixture was stirred at 20 °C for 20 min when it was poured into saturated aqueous NH_4Cl (10 ml). The product was extracted into Et_2O (4 × 20 ml), and the combined organic extracts were dried, evaporated under reduced pressure, and finally passed through a short pad of silica to give the *title compound* (**10**) (95.7 mg, 96%) as a colourless oil, $\nu_{max.}$(film) 3 480, 2 935, 2 860, 1 725, and 1 450 cm^{-1}; δ (2:1 mixture of diastereoisomers) 0.05 (4 H, s, $SiMe_2$), 0.06 (2 H, s, $SiMe_2$), 0.88 (6 H, s, SiBu^t), 0.89 (3 H, s, SiBu^t), 1.15—1.90 (12 H, m), 2.45 (1 H, dd, *J* 3.0, 7.4 Hz, 2-H), 2.47 (1 H, dd, *J* 1.0, 7.4 Hz, 2-H), 4.15 (1 H, m, 3-H), 4.37 (1 H, br s, OH), 4.48 (1 H, m, 5-H), 4.79 (1 H, m, 1′-H), 5.07 (0.66 H, ddd, *J* 1.4, 2.1, 10.1 Hz, 7-H *E*), 5.09 (0.33 H, ddd, *J* 1.6, 1.6, 10.1 Hz, 7-H *E*), 5.17 (0.33 H, ddd, *J* 1.5, 1.5, 17.2 Hz, 7-H *Z*), 5.24 (0.66 H, ddd, *J* 1.5, 1.5, 17.2 Hz, 7-H *Z*), and 5.74—5.92 (1 H, m, 6-H); *m/z* 356 (M^+).

Preparation of Cyclohexyl 3,5-Dihydroxyhept-6-enoate (**11**).—To a solution of the dimethyl-t-butylsilyloxy derivative (**10**) (42.0 mg, 0.118 mmol) in THF (2 ml) at 0 °C was added tetrabutylammonium fluoride (130 μl of a 1.0M solution in THF; 0.130 mmol). After 1 h the mixture was poured into 1M-HCl solution (2 ml). The product was extracted into ether (3 × 15 ml), each extract being washed with brine (5 ml). The combined organic extracts were dried, the solvent was evaporated under reduced pressure, and the residue chromatographed (50% E_2O–petroleum) to give cyclohexyl 3,5-dihydroxyhept-6-enoate (**11**) (27.4 mg, 96%) as a colourless oil, $\nu_{max.}$(film) 3 420, 2 950, 2 870, 1 725, and 1 470 cm^{-1}; δ (2:1 mixture of diastereoisomers) 1.15—1.97 (12 H, m), 2.50 (2 H, m, 2-H), 2.75 (1 H, br s, OH), 3.51 (1 H, br s, OH), 4.22—4.52 (2 H, m, 3- and 5-H), 4.81 (1 H, m, 1′-H), 5.12 (0.33 H, ddd, *J* 1.5, 1.5, 9.6 Hz, 7-H *E*), 5.16 (0.66 H, ddd, *J* 1.5, 1.5, 9.6 Hz, 7-H *E*), 5.28 (0.33 H, ddd, *J* 1.5, 1.5, 16.3 Hz, 7-H *Z*), 5.32 (0.66 H, ddd, *J* 1.5, 1.5, 16.3 Hz, 7-H *Z*), and 5.80—6.00 (1 H, m, 6-H); *m/z* 242 (M^+).

Preparation of S-t-Butyl 5-Hydroxy-3-oxoheptanethioate (**12**).—Using the procedure described for the preparation of compound (**7**), the dianion of (**6**) (96.6 mg, 0.555 mmol) was reacted with propionaldehyde (39.0 mg, 0.671 mmol) to give S-*t-butyl 5-hydroxy-3-oxoheptanethioate* (**12**) (108.5 mg, 84%) as a colourless oil, $\nu_{max.}$(film) 3 570, 2 920, 1 710, 1 670, and 1 620 cm^{-1}; δ (18% enol form) 0.95 (3 H, t, *J* 7.6 Hz, CH_2Me), 1.48 (7.38 H, s, Bu^t), 1.49 (2 H, m, CH_2Me), 1.51 (1.62 H, s, Bu^t enol), 2.63 (1 H, dd, *J* 8.6, 17.9 Hz, 4-H), 2.75 (1 H, dd, *J* 2.8, 17.9 Hz, 4-H), 2.81 (1 H, br s, OH), 3.61 (2 H, s, 2-H), and 3.99 (1 H, m, 5-H); *m/z* 232 (M^+) (Found: C, 56.75; H, 8.7. $C_{11}H_{20}O_3S$ requires C, 56.85; H, 8.69%).

Preparation of S-t-Butyl 5-Hydroxy-6-methyl-3-oxohept-6-enethioate (**13**).—Using the procedure described for the preparation of compound (**7**), the dianion of compound (**6**) (2.0 g, 11.48 mmol) was treated with the methacrylaldehyde (886 mg, 12.64 mmol) to give the *title compound* (**13**) (2.50 g, 88%) as a colourless oil, $\nu_{max.}$(film) 3 500, 2 940, 1 725, 1 675, 1 625, and 1 370 cm^{-1}; δ (19% enol form) 1.47 (7.29 H, s, Bu^t), 1.51 (1.71 H, s, Bu^t enol), 1.74 (3 H, s, 6-Me), 2.73 (1 H, br s, OH), 2.78 (2 H, d, *J* 5.5 Hz, 4-H_2), 3.63 (1.62 H, s, 2-H), 4.52 (1 H, m, 5-H), 4.88 (1 H, br s, 7-H), 5.02 (1 H, br s, 7-H), and 5.41 (0.19 H, s, 2-H enol); *m/z* 244 (M^+) (Found: C, 59.1; H, 8.55. $C_{12}H_{20}O_3S$ requires C, 58.97; H, 8.27%).

Preparation of S-t-Butyl 5-Dimethyl-t-butylsilyloxy-6-methyl-3-oxohept-6-enethioate (**14**).—A solution of the β-keto ester (**13**) (1.01 g, 4.14 mmol), dimethyl-t-butylsilyl chloride (781 mg, 5.18 mmol), and imidazole (721 mg, 10.59 mmol) in dry DMF (3 ml) was stirred overnight at room temperature. The mixture was poured into Et_2O (50 ml) and washed with water (3 × 10 ml), followed by brine (10 ml). After drying of the extract, and evaporation of the solvent under reduced pressure, the residue was chromatographed (3% Et_2O–petroleum) to give the *title compound* (**14**) (1.425 g, 96%) as a colourless oil, $\nu_{max.}$(film) 2 930, 1 730, 1 680, 1 625, and 1 370 cm^{-1}; δ (52% enol form) 0.04 (6 H, s, $SiMe_2$), 0.86 (9 H, s, SiBu^t), 1.47 (4.3 H, s, SBu^t), 1.51 (4.7 H, s, SBu^t enol), 1.70 (3 H, br s, 6-Me), 2.19 (0.52 H, ddd, *J* 1.4, 9.8, 4.7 Hz, 4-H enol), 2.29 (0.52 H, dd, *J* 4.6, 14.7 Hz, 4-H enol), 2.56 (0.48 H, dd, *J* 4.2, 16.8 Hz, 4-H), 2.84 (0.48 H, dd, *J* 9.2, 16.8 Hz, 4-H), 3.58 (0.96 H, d, *J* 2.8 Hz, 2-H), 4.40 (0.52 H, dd, *J* 4.6, 9.8 Hz, 5-H enol), 4.56 (0.48 H, dd, *J* 4.6, 9.8 Hz, 5-H), 4.79 (1 H, br s, 7-H), 4.95 (1 H, br s, 7-H), and 5.34 (0.52 H, s, 2-H enol); *m/z* 301 (M^+ − Bu^t) (Found: C, 60.2; H, 9.6. $C_{18}H_{34}O_3SSi$ requires C, 60.27; H, 9.57%).

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 5-*Dimethyl*-t-*butylsilyloxy*-3-*oxohept*-6-*enoate* (**15**).—To a solution of the thio ester (**8**) (255.8 mg, 0.742 mmol) and compound (**1**) (230.0 mg, 0.878 mmol) in THF (5 ml) was added silver(I) trifluoroacetate (463 mg, 1.765 mmol). The mixture was stirred at room temperature for 18 h. The solution was diluted with Et_2O (50 ml), filtered through a short pad of silica, and washed with saturated aqueous $NaHCO_3$ (2 × 20 ml) followed by brine (10 ml). After drying of the filtrate and evaporation of the solvent under reduced pressure, the residue was chromatographed (10% Et_2O–petroleum) to give the *title ester* (**15**) (295.4 mg, 77%) as a colourless oil, $\nu_{max.}$(film) 2 940, 2 870, 1 740, 1 715, 1 653, and 1 375 cm^{-1}; δ (28% enol form) 0.04 (4.32 H, s, $SiMe_2$), 0.05 (1.68 H, s, $SiMe_2$), 0.86 (6.48 H, s, SiBu^t), 0.87 (2.52 H, s, SiBu^t), 1.14 (3 H, d, *J* 7.2 Hz, 8-Me), 1.10—2.35 (10 H, m), 2.51 (1 H, dd, *J* 2.4, 7.6 Hz, 4-H), 2.76 (1 H, dd, *J* 3.7, 7.6 Hz, 4′-H), 3.45 (1.44 H, s, 2′-H), 3.71 (1 H, m, 8-H), 4.47 (0.28 H, m, 5′-H), 4.60 (0.72 H, m, 5′-H), 4.70 (0.72 H, dd, *J* 1.1, 5.8 Hz, 2-H), 4.72 (0.28 H, dd, *J* 1.1, 5.8 Hz, 2-H), 4.97 (0.28 H, s, 2′-H enol), 5.07 (1 H, ddd, *J* 1.5, 1.5, 5.3 Hz, 7′-H *E*), 5.22 (1 H, ddd, *J* 1.5, 1.5, 8.4 Hz, 7′-H *Z*), 5.46 (1 H, m, 4-H), 5.81 (1 H, m, 6′-H), 7.36 (5 H, m, Ph), and 10.7 (0.28 H, s, OH enol); *m/z* 459 (M^+ −

Bu^t) (Found: C, 67.35; H, 8.7. $C_{29}H_{44}O_6Si$ requires C, 67.39; H, 8.60%).

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 5-*Dimethyl*-t-*butylsilyloxy*)-6-*methyl*-3-*oxo*-*hept*-6-*enoate* (**16**).—To a solution of the thio ester (**14**) (470.3 mg, 1.311 mmol) and compound (**1**) (354.1 mg, 1.352 mmol) in THF (5 ml) was added silver(I) trifluoracetate (575.8 mg, 2.617 mmol). The mixture was stirred at room temperature for 18 h before dilution with Et_2O (50 ml) and filtration through a short pad of silica gel. The ether layer was washed with saturated aqueous $NaHCO_3$ (2 × 20 ml), water (10 ml), and brine (10 ml). After drying of the extract and removal of the solvent under reduced pressure, the residue was chromatographed (10% Et_2O–petroleum) to give the *title compound* (**16**) (529 mg, 76%) as a colourless oil, $\nu_{max.}$(film) 2 940, 2 860, 1 745, 1 720, 1 650, and 1 385 cm^{-1}; δ (20% enol form) 0.02 (4.8 H, s, $SiMe_2$), 0.04 (1.2 H, s, $SiMe_2$), 0.84 (1.8 H, s, SiBu^t), 0.86 (7.2 H, s, SiBu^t), 1.14 (3 H, d, *J* 7.1 Hz, 8-Me), 1.06—1.64 (8 H, m), 1.69 (3 H, s, 6′-Me), 2.12 (1 H, m, 11-H), 2.35 (1 H, m, 5-H), 2.50 (1 H, dd, *J* 3.5, 14.3 Hz, 4′-H), 2.80 (1 H, dd, *J* 8.4, 14.3 Hz, 4′-H), 3.46 (1.6 H, s, 2′-H), 3.71 (1 H, m, 8-H), 4.41 (0.2 H, m, 5′-H enol), 4.54 (0.8 H, dd, *J* 3.5, 8.4 Hz, 5′-H), 4.70 (1 H, dd, *J* 2.1, 11.8 Hz, 2-H), 4.80 (1 H, br s, 7′-H *E*), 4.94 (0.2 H, s, 2′-H enol), 4.96 (1 H, br s, 7′-H *Z*), 5.46 (1 H, m, 4-H), 7.36 (5 H, m, Ph), and 11.8 (0.2 H, s, OH enol); *m/z* 473 (M^+ − Bu^t) (Found: C, 67.95; H, 8.75. $C_{30}H_{46}O_6Si$ requires C, 67.87; H, 8.75%).

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 5-*Dimethyl*-t-*butylsilyloxy*)-3-*hydroxyhept*-6-*enoate* (**17**).—To a solution of the β-keto ester (**15**) (200 mg, 0.387 mmol) in MeOH (3 ml) was added borohydride (38 mg, 1.004 mmol). After stirring at room temperature for 25 min the solution was diluted with Et_2O (50 ml) and washed with water (3 × 10 ml) and brine (10 ml). The organic phase was dried, the solvent evaporated under reduced pressure, and the resulting oil filtered through a short column of silica to give the *title ester* (**17**) (200 mg, 100% as a colourless oil, $\nu_{max.}$(film) 3 520, 2 950, 2 870, 1 740, and 1 385 cm^{-1}; δ (2:1 mixture of diastereoisomers) 0.05 (4 H, s, $SiMe_2$), 0.07 (2 H, s, $SiMe_2$), 0.89 (6 H, s, SiBu^t), 0.90 (3 H, s, SiBu^t), 1.13 (3 H, d, *J* 7.1 Hz, 8-Me), 1.14—2.00 (10 H, m), 2.10 (1 H, m, 11-H), 2.35 (1 H, m, 5-H), 2.44 (2 H, m, 2′-H), 3.72 (1 H, m, 8-H), 4.15 (0.66 H, m, 3′-H), 4.28 (0.33 H, m, 3′-H), 4.36 (0.66 H, m, 5′-H), 4.48 (0.33 H, m, 5′-H), 4.70 (1 H, dd, *J* 1.9, 11.6 Hz, 2-H), 5.07 (0.66 H, ddd, *J* 2.0, 2.0, 10.1 Hz, 7′-H *E*), 5.10 (0.33 H, ddd *J* 2.0, 2.0, 10.1 Hz, 7′-H *E*), 5.17 (0.66 H, ddd, *J* 2.0, 2.0, 17.1 Hz, 7′-H *Z*), 5.23 (0.33 H, ddd, *J* 2.0, 2.0, 17.1 Hz, 7′-H *Z*), 5.43 (1 H, m, 4-H), 5.72—5.93 (1 H, m, 6′-H), and 7.38 (5 H, m, Ph); *m/z* 461 (M^+ − Bu^t) (Found: C, 67.2; H, 9.0. $C_{29}H_{46}O_6Si$ requires C, 67.13; H, 8.9%).

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 5-*Dimethyl*-t-*butylsilyloxy*-3-*hydroxy*-6-*enoate* (**18**).—To a solution of the β-keto ester (**16**) (203.8 mg, 0.384 mmol) in MeOH (3 ml) was added sodium borohydride (36.0 mg, 0.951 mmol). After having been stirred at room temperature for 30 min, the solution was poured into water (5 ml) and extracted into Et_2O (4 × 10 ml). The combined organic extract was dried, evaporated under reduced pressure, and filtered through a short column of silica to give the *title compound* (**18**) (199 mg, 97%) as a colourless oil, $\nu_{max.}$(film) 3 520, 2 940, 2 870, 1 732, and 1 375 cm^{-1}; δ (2:1 mixture of diastereoisomers) 0.04 (4 H, s, $SiMe_2$), 0.09 (2 H, s, $SiMe_2$), 0.89 (6 H, s, SiBu^t), 0.90 (3 H, s, SiBu^t), 1.14 (3 H, d, *J* 7.1 Hz, 8-Me), 1.16—1.98 (10 H, m), 1.68 (3 H, s, 6′-Me), 2.09 (1 H, m, 11-H), 2.35 (1 H, m, 5-H), 2.44 (2 H, m, 2′-H), 3.71 (1 H, m, 8-H), 4.12 (0.66 H, m, 3′-H), 4.20 (0.33 H, m, 3′-H), 4.33 (1 H, m, 5′-H), 4.70 (1 H, dd, *J* 2.0, 11.8 Hz, 2-H), 4.81 (0.66 H, br s, 7′-H *E*), 4.84 (0.33 H, br s, 7′-H *E*), 4.93 (0.66 H, br s, 7′-H *Z*), 5.00 (0.33 H, br s, 7′-H *Z*), 5.43 (1 H, m, 4-H), and 7.38 (5 H, m, Ph); *m/z* 475 (M^+ − Bu^t) (Found: C, 67.8; H, 9.2. $C_{30}H_{48}O_6Si$ requires C, 67.62; H, 9.10).

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 3,5-*Dihydroxyhept*-6-*enoate* (**19**).—To a solution of the dimethyl-t-butylsilyloxy derivative (**17**) (137.6 mg, 0.265 mmol) in THF (2 ml) at 0 °C was added tetrabutylammonium fluoride (292 μl of a 1.0M solution in THF; 0.292 mmol). After 30 min the mixture was poured into 1M-HCl solution (5 ml), the product extracted into Et_2O (3 × 20 ml) and the combined organic extracts were dried, and evaporated under reduced pressure. Chromatography of the residue (50% Et_2O–petroleum) gave the spiroacetal (**1**) (32.9 mg) and the *title compound* (**19**) (40.4 mg, 38%) as a colourless oil, $\nu_{max.}$(film) 3 430, 2 940, 2 870, 1 730, and 1 385 cm^{-1}; δ (2:1 mixture of diastereoisomers) 1.13 (3 H, d, *J* 7.1 Hz, 8-Me), 1.14—2.00 (10 H, m), 2.10 (1 H, dd, *J* 4.6, 11.5 Hz, 11-H), 2.34 (1 H, m, 5-H), 2.48 (2 H, m, 2′-H), 2.68 (1 H, br s, OH), 3.15 (1 H, br s, OH), 3.70 (1 H, m, 8-H), 4.20—4.50 (2 H, m, 3′-H and 5′-H), 4.70 (1 H, dd, *J* 1.9, 11.6 Hz, 2-H), 5.08—5.18 (1 H, m, 7′-H *E*), 5.45 (1 H, m, 4-H), 5.79—6.00 (1 H, m, 6′-H), and 7.35 (5 H, m, Ph); *m/z* 404 (M^+) (Found: C, 68.2; H, 8.05%. $C_{23}H_{32}O_6$ requires C, 68.28; H, 7.99%).

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 3,5-*Dihydroxyhept*-6-*enoate* (**19**) *using* CH_3CN–HF.—To a solution of the dimethyl-t-butylsilyloxy derivative (**17**) (23.2 mg, 0.048 mmol) in THF (1 ml) at 0 °C was added HF (100 μl of a 0.70M solution of 40% HF in acetonitrile; 0.072 mmol). After 15 min the mixture was poured into saturated aqueous $NaHCO_3$ (2 ml). The product was extracted into CH_2Cl_2 (4 × 10 ml), the combined organic extracts were dried, and evaporated under reduced pressure, and the residue was chromatographed (50% Et_2O–petroleum) to give the diol (**19**) (17.6 mg, 97%) identical to the previously prepared sample.

Preparation of (2S,4S,8R)-8-*Methyl*-2-*phenyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*yl* 3,5-*Dihydroxy*-6-*methylhept*-6-*enoate* (**2**).—To a solution of dimethyl-t-butylsilyloxy derivative (**18**) (179.0 mg, 0.336 mmol) in THF (2 ml) at 0 °C was added HF (500 μl of a 0.7M solution of 40% HF in acetonitrile; 0.35 mmol). After 10 min the reaction was complete by t.l.c. and the mixture was poured into saturated $NaHCO_3$ solution (5 ml). The product was extracted into CH_2Cl_2 (4 × 10 ml), and the combined organic extracts dried and evaporated under reduced pressure, and *title residue* chromatographed (50% Et_2O–petroleum) to give the *title ester* (**2**) (140.2 mg, 100%) as a colourless oil, $\nu_{max.}$(film) 3 420, 2 940, 2 870, 1 732, and 1 375 cm^{-1}; δ (2:1 mixture of diastereoisomers) 1.12 (3 H, d, *J* 7.1 Hz, Me), 1.13—2.02 (10 H, m), 1.72 (3 H, s, 6′-Me), 2.10 (1 H, dd, *J* 5.0, 11.9 Hz, 11-H), 2.34 (1 H, m, 5-H), 2.48 (2 H, m, 2′-H), 3.14 (1 H, br s, OH), br s, OH), 3.73 (1 H, m, 8-H), 4.22—4.40 (2 H, m, 3′- and 5′-H), 4.64 (0.33 H, dd, *J* 2.0, 11.8 Hz, 2-H), 4.71 (0.66 H, dd, *J* 2.0, 11.8 Hz, 2-H), 4.84 (0.66 H, br s, 7′-H *E*), 4.88 (0.33 H, br s, 7′-H *E*), 5.00 (0.66 H, br s, 7′-H *Z*), 5.05 (0.33 H, br s, 7′-H *Z*), 5.45 (1 H, m, 4-H), and 7.38 (5 H, m, Ph); *m/z* 418 (M^+) (Found: C, 68.65; H, 8.2. $C_{24}H_{34}O_6$ requires C, 68.86; H, 8.20%).

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