Approach to the synthesis of 4-demethylforskolin (19-norforskolin)

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Two synthetic routes to the methyl ketone **30** from the dione **2** are described. Compound **30** is a potential precursor of 4-demethylforskolin.

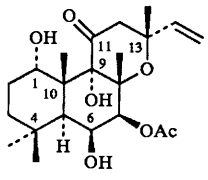
Introduction

There has been interest in recent years in the synthesis of the diterpene forskolin **1** because of its significant biological properties.[1] A number of transformation products have been prepared from the natural product and their activities measured. Three total syntheses have been reported[2] so we have investigated the synthesis of the 4-demethyl (19-nor) compound since it is not readily prepared by modification of the natural product, and comparison of its biological properties with those of forskolin is of interest. The starting material chosen was the dione **2** which had been prepared previously by us.[3]

Results and discussion

Oxidation of dione **2** with SeO_2–1,4-dioxane–water gave the alcohol **3** (78%), which was converted into the acetate **4** (95%) with Ac_2O–pyridine. On reduction of acetate **4** with H_2/10% Pd on C–EtOAc the dione **6** was obtained (95%); its ^1H NMR spectrum exhibited a triplet at δ 5.33 (J 2.5 Hz) establishing the regio- and stereo-chemistry of the oxidation **2** ⟶ **3**. The dione **2** undergoes regiospecific addition of $RCCCeCl_2$ reagents to the C-9 carbonyl group (forskolin numbering scheme),[3] but reaction of compound **6** under similar conditions gave only a low yield of addition product to the C-6 carbonyl group (forskolin numbering). Reduction of the acetate **6** with $NaBH_4$–Pr^iOH gave the alcohol **10** (86%); spectroscopic data [λ_{max} 266 nm; δ_H 4.76 (1 H, d, J 2.5 Hz)] established the regio- and stereo-chemistry of the reduction. Attempts to force the alcohol **10** to react with a variety of nucleophilic acetylides failed, as did reactions with the derived tetrahydropyran (THP) ethers **11** (prepared from alcohol **10** and dihydropyran). With the failure of the intermolecular reactions (presumably due to steric hindrance caused by the axial acetoxy group) we turned to intramolecular cyclisations utilising the anion derived from the latter group. Reaction of the acetate **6** with $LiNPr^i_2$ (LDA)–tetrahydrofuran (THF) gave the lactone **8** (72%); however, on reduction with $NaBH_4$ a compound was obtained whose spectroscopic properties were not consistent with those of the required alcohol. Under similar conditions the diastereoisomeric ethers **11** cyclised to the lactones **14** (86%); the unexpected stability of the hydroxy enol ether is likely to be due to the equatorial disposition of the hydroxy group. On acid hydrolysis the lactones **14** were converted into the enone **16** (95%) [ν_{max} 3460, 1750, 1670 and 1620 cm^{-1}; δ_H 4.23 (1 H, t, J 2 Hz), 4.13 (1 H, t, J 6 Hz), 3.60 (1 H, d, J 15 Hz), 3.42 (1 H, d, J 15 Hz), 1.86 (3 H, s), 1.22 (3 H, s) and 1.08 (3 H, d, J 6 Hz)]. Reduction of the enone **16** with $NaBH_4$–MeOH at 0 °C formed the *cis*-diol **18** which, in accordance with the postulated stereochemistry, gave the ether **19** on reaction with 2-methoxypropene.

A number of approaches were now investigated to cleave and transform the lactone ring into an appropriate functional group which could lead to the fabrication of ring C. That which was eventually successful required reduction of the lactone **19** with



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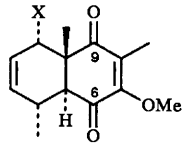
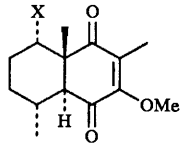
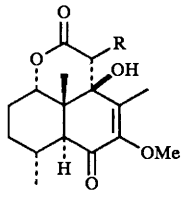


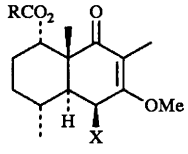
2 X = H
3 = OH
4 X = OAc



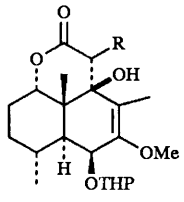
5 X = OH
6 X = OAc
7 X = OCOEt



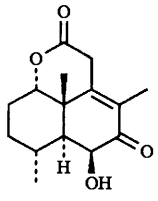
8 R = H
9 R = Me



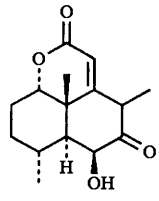
10 X = OH, R = Me
11 X = OTHP, R = Me
12 X = OH, R = Et
13 X = OTHP, R = Et



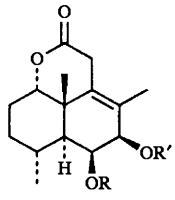
14 R = H
15 R = Me



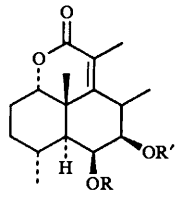
16



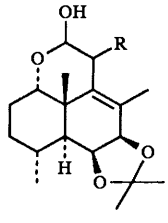
17



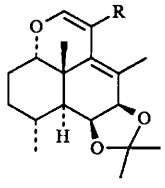
18 R = R′ = H
19 RR′ = CMe_2



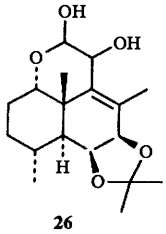
20 R = R′ = H
21 RR′ = CMe_2



22 R = H
23 R = β Me



24 R = H
25 R = Me



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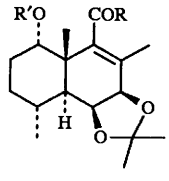
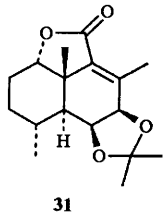


27 R′ = CHO, R = H
28 R′ = R = H
29 R′ = CHO, R = Me
30 R′ = H, R = Me



31

Bu^i_2AlH(DIBAL)–CH_2Cl_2 at −78 °C to yield the diastereomeric lactols **22**. Dehydration of compound **22** to give the diene **24** in satisfactory yield proved unexpectedly difficult, but was achieved in 47% yield using $MeSO_2Cl$–Et_3N–CH_2Cl_2; alternatively the diene could be prepared by reduction of the ketone **16** with DIBAL–CH_2Cl_2 at −78 °C followed by treatment of the crude product with 2-methoxypropene–toluene-*p*-sulfonic acid (PTSA)–CH_2Cl_2 (27%). Cleavage of the enol ether double bond was achieved by hydroxylation [OsO_4–*N*-methylmorpholine *N*-oxide (NMMNO)–Bu^tOH][4] to the diol **26** followed by oxidation with $NaIO_4$–MeOH–water to give the formate **27** (82% over two steps), ν_{max} 1725 and 1675 cm^{-1}; δ_H 10.08 (1 H, s), 7.94 (1 H, s) and 5.72 (1 H, t, *J* 2 Hz). Methanolysis of compound **27** with K_2CO_3–MeOH yielded the aldehyde **28** (97%) which, in solution, was in equilibrium with the lactol isomer. Oxidation of the mixture with Pr_4NRuO_4–NMMNO[5] formed the lactone **31** (70%), ν_{max} 1750 cm^{-1}; δ_H 4.02 (1 H, dd, *J* 11.5 and 6 Hz); the latter signal suggests that ring A has a twist-boat conformation. MM2 calculations predicted that the model with the twist-boat conformation was ~6 kcal mol^{-1}† more stable than that with a highly distorted chair; application of the Altona equation to the torsion angles found in the models gave *J*-values of 10.8 and 4.8 Hz for the former and 6.6 and 0.8 Hz for the latter. Reaction of the lactone **31** with MeMgI–Et_2O gave the methyl ketone **30** (88%), ν_{max} 1685 cm^{-1}; δ_H 2.38 (3 H, s). These experiments provided three potential precursors (**26**, **27** and **30**) for the construction of ring C.

An alternative route to the methyl ketone **30** was also established. Catalytic reduction of the alcohol **3** gave the dihydro compound **5** (87%) which, on reaction with $(EtCO)_2O$–pyridine, formed the propionate **7** (93%). Cyclisation of propionate **7** to the lactone **9** (53%) was effected with LDA–THF at −78 °C, but again $NaBH_4$ reduction to form the alcohol was unsuccessful. However, an approach similar to the previous strategy gave the lactone **15**: reduction of **7** to alcohol **12** (87%), conversion of alcohol **12** into the diastereoisomeric ethers **13** (90%) and their cyclisation to the diastereoisomeric lactones **15** (69%). Hydrolysis of the enol ether **15** gave an unsaturated ketone (74%) whose spectroscopic properties, ν_{max} 1750 and 1705 cm^{-1}, left the position (endo- or exo-cyclic) of the double bond in doubt. Structure **17** was supported by the reduction with $NaBH_4$–Pr^iOH to the alcohol **20** [δ_H 4.23 (1 H, t, *J* 3 Hz), 3.98 (1 H, t, *J* 2.5 Hz) and 3.56 (1 H, dd, *J* 7 and 4 Hz)] which gave the 7-monoacetate of diol **20** [δ_H 4.60 (1 H, dd, *J* 6.8 and 3.5 Hz), 4.25 (1 H, t, *J* 3 Hz) and 3.97 (1 H, t, *J* 3 Hz)] on acetylation. Reaction of the diol **20** with 2-methoxypropene gave the ether **21** (89%), which was reduced with DIBAL to a 4:1 mixture of lactols **23** (89%) in which the double bond had migrated into an endocyclic position. Reduction with $LiAlH_4$ gave the same lactols, but in a reversed (1:9) ratio. As in the previous case, dehydration to the diene proved difficult, with the molecule showing a pronounced tendency to formation of a dimeric ether rather than elimination. However, if the $LiAlH_4$ reduction was carried out at −78 °C, $MeSO_2Cl$–Et_3N added at that temperature, and the mixture allowed to warm up to ambient temperature slowly, the diene **25** was formed and could be isolated (49%) by flash chromatography of the reaction mixture (λ_{max}/nm 255; δ_H 6.57 (1 H, q, *J* 1.5), 3.27 (1 H, t, *J* 3.5) and 1.95 (3 H, d, *J* 1.5). Oxidation with OsO_4–NMMNO–Bu^tOH gave the crude diol which, without purification, was oxidised with $NaIO_4$–MeOH–water to the formate **29** (33%). Methanolysis (MeOH–K_2CO_3) of ester **29** gave the methyl ketone **30**, identical with that prepared previously.

† 1 cal = 4.184 J.

Experimental

All ^1H NMR spectra were measured in $CDCl_3$ at 300 MHz using a Bruker AC300 spectrometer; *J*-values are given in Hz; and UV spectra in EtOH using a Shimadzu UV–visible spectrophotometer. Low-resolution mass spectra were measured on a Kratos MS25 instrument in the EI and CI modes, the latter with NH_3 as carrier gas. Accurate mass measurements were determined using a Kratos MS30 instrument with a DS55 data system, and IR spectra as thin films using a Perkin-Elmer 1710 FT IR spectrometer. The term 'work-up in the usual way' implies washing of the organic extract with brine, drying of the solution with $MgSO_4$, filtration and concentration of the extract under reduced pressure. Light petroleum refers to the fraction with distillation range 40–60 °C.

Enedione 3

The enedione **2** (8.65 g), SeO_2 (12.31 g) and water (1 cm^3) in 1,4-dioxane (150 cm^3) were heated under reflux for 2 days under N_2. The mixture was then cooled and filtered through Celite. The filtrate was concentrated under reduced pressure to give a brown oily solid, which upon SiO_2 60 flash column chromatography (4:6; EtOAc–hexane) yielded the *dione* **3** as an off-white solid (7.26 g, 78%), mp 123–124 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 3485 and 1700; δ_H 5.75 (2 H, m), 4.33 (1 H, d, *J* 3), 3.99 (3 H, s), 3.08 (1 H, d, *J* 10), 1.86 (3 H, s), 1.17 (3 H, d, *J* 7) and 1.02 (3 H, s); *m/z* (EI) 250, (CI) 251 (Found: C, 67.7; H, 7.3. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%).

Acetate 4

Ac_2O (3.3 cm^3), pyridine (4.2 cm^3) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) were added successively to a solution of the hydroxy dione **3** (0.87 g) in CH_2Cl_2 (30 cm^3). After the mixture had been stirred at room temp. under N_2 for 12 h the solvent was removed under reduced pressure to give a viscous brown oil, which was purified by SiO_2 60 flash column chromatography (4:6 to 6:4; EtOAc–hexane) to afford the *acetate* **4** (1.045 g, 95%), mp 73–75 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 1740 and 1700; δ_H 5.86 (1 H, ddd, *J* 10, 5 and 2), 5.79 (1 H, dd, *J* 10 and 2), 5.38 (1 H, d, *J* 5), 4.00 (3 H, s), 3.10 (1 H, d, *J* 10), 2.75 (1 H, m), 1.98 (3 H, s), 1.88 (3 H, s), 1.18 (3 H, d, *J* 7) and 1.05 (3 H, s); *m/z* (EI) 292, (CI) 293 (Found: C, 65.3; H, 6.9. $C_{16}H_{20}O_5$ requires C, 65.8; H, 6.9%).

Acetate 6

The acetate **4** (3.35 g) and 10% Pd–C (200 mg) in EtOAc (40 cm^3) under H_2 were stirred vigorously at room temp. After 40 min the mixture was filtered through Celite to afford a pale yellow solution. Concentration under reduced pressure and SiO_2 60 flash column chromatography (3:7 to 4:6; EtOAc–hexane) gave the *acetate* **6** (3.2 g, 95%), ν_{max}/cm^{-1} 1745, 1705, 1670 and 1620; δ_H 5.33 (1 H, t, *J* 2.5), 3.97 (3 H, s), 3.06 (1 H, d *J* 10.5), 2.00 (3 H, s), 1.82 (3 H, s), 1.09 (3 H, d, *J* 6) and 1.08 (3 H, s); *m/z* (EI) 294, (CI) 295 (Found: 65.6; H, 7.7. $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.5%).

Alcohol 10

(*a*) $NaBH_4$ (0.8 g) was added portionwise to a stirred solution of the dione **6** (3.0g) in dry Pr^iOH (60 cm^3). Saturated aq. NH_4Cl was added carefully to quench the reaction after 30 min. The mixture was extracted with CH_2Cl_2 (3 × 50 cm^3) and worked up in the usual way. SiO_2 60 flash chromatography (4:6 to 1:1; EtOAc–hexane) of the product yielded the *alcohol* **10** as a solid (2.59 g, 86%), mp 200–203 °C (from EtOAc–hexane); λ_{max}/nm 266; ν_{max}/cm^{-1} 3385 and 1730; δ_H 5.25 (1 H, t, *J* 2.5), 4.76 (1 H, d, *J* 2.5), 4.00 (3 H, s), 2.01 (1 H, t, *J* 2.5), 1.94 (3 H, s), 1.73 (3 H, s), 1.24 (3 H, s) and 1.10 (3 H, d, *J* 6); *m/z* (EI) 296, (CI) 297 (Found: C, 64.9; H, 8.4. $C_{16}H_{24}O_5$ requires C, 64.9; H, 8.1%).

(*b*) $NaBH_4$ (130 mg) was added portionwise to a stirred suspension of the dione **6** (340 mg) and $CeCl_3 \cdot 6H_2O$ (290 mg) in dry Pr^iOH (20 cm^3). The resulting mixture was stirred at room temp. for a further 4 h and was then poured into saturated aq. NH_4Cl (10 cm^3). The mixture was stirred at room temp. for 30 min and was then extracted with CH_2Cl_2 (3 × 20 cm^3) and worked up in the usual way. SiO_2 60 flash chromatography (4:6; EtOAc–hexane) gave the title alcohol (292 mg, 85%).

Lactone 8

A solution of acetoxy dione **6** (100 mg) in THF (5 cm^3) was added dropwise to a solution of LDA (1.5 mol dm^{-3} in cyclohexane; 340 mm^3) in THF (2 cm^3) at −78 °C under N_2. After 5 h saturated aq. NH_4Cl (10 cm^3) was added to quench the reaction at −78 °C and the mixture was warmed to room temp., and extracted with Et_2O (3 × 10 cm^3). Work-up in the usual way, followed by SiO_2 60 flash chromatography (6 : 4 to 7 : 3; EtOAc–hexane) gave the lactone **8** as an off-white solid (72 mg, 72%), mp 124–125 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 3440 and 1730; δ_H 4.65 (1 H, t, *J* 3), 3.53 (3 H, s), 3.03 (1 H, d, *J* 18.5), 2.93 (1 H, d, *J* 18.5), 2.22 (1 H, d, *J* 8.5), 1.92 (3 H, s), 1.12 (3 H, d, *J* 6) and 1.02 (3 H, s); *m/z* (CI) 312.

Diastereoisomeric ethers 11

3,4-Dihydro-2*H*-pyran (1.1 cm^3) and PTSA (10 mg) were added to a solution of the hydroxy dione **10** (1.15 g) in CH_2Cl_2 (30 cm^3). After 12 h the solvent was removed under reduced pressure to give a crude product, which was purified by SiO_2 60 flash chromatography (3:7 to 4:6; EtOAc–hexane) to give the diastereoisomeric *ethers* **11** (1.31 g, 89%), ν_{max}/cm^{-1} 1735 and 1660; *m/z* (EI) 380, (CI) 381 (Found: C, 66.7; H, 8.8. $C_{21}H_{32}O_6$ requires C, 66.3; H, 8.4%).

Diastereoisomeric lactones 14

BuLi (1.6 mol dm^{-3} in hexane; 45 cm^3) was added dropwise to a solution of Pr^i_2NH (10.5 cm^3) in THF (60 cm^3) at −78 °C under N_2. The resulting mixture was stirred −78 °C for 10 min, and was then warmed up to 0 °C during 20 min. The mixture was then cooled down to −78 °C, a solution of the ethers **11** (6.30 g) in THF (60 cm^3) was added dropwise and the mixture was stirred at − 78 °C for 3.5 h. Saturated aq. NH_4Cl (50 cm^3) was added to quench the reaction at −78 °C. The mixture was then warmed to room temp. and was extracted with CH_2Cl_2 (3 × 50 cm^3). Work-up in the usual way, followed by SiO_2 60 flash chromatography (1:1; EtOAc–light petroleum) afforded the diastereoisomeric *lactones* **14** as an oil (4.90 g, 86%), ν_{max}/cm^{-1} 3450 and 1725; δ_H(isomer A) 4.76 (1 H, t, *J* 3), 4.53 (1 H, t, *J* 1.5), 4.29 (1 H, d, *J* 4), 4.02 (1 H, ddd, *J*, 15, 7 and 4), 3.55 (3 H, s), 3.52 (1 H, m), 2.90 (1 H, d, *J* 18), 2.59 (1 H, d, *J* 18), 1.75 (3 H, s), 1.12 (3 H, s) and 0.98 (3 H, s); δ_H(isomer B) 4.94 (1 H, t, *J* 2), 4.52 (1 H, t, *J* 3), 4.29 (1 H, d, *J* 4.5), 3.91 (1 H, m), 3.52 (3 H, s), 3.52 (1 H, m), 2.89 (1 H, d, *J* 18), 2.58 (1 H, d, *J* 18), 1.74 (3 H, s), 1.12 (3 H, s) and 0.97 (3 H, s); *m/z* (CI) 381 (Found: C, 66.0; H, 8.5. $C_{21}H_{32}O_6$ requires C, 66.3; H, 8.4%).

Lactone 16

10 Mol dm^{-3} HCl (0.1 cm^3) was added dropwise to a solution of the diastereoisomeric lactone **14** (66 mg) in MeOH (5 cm^3) at room temp. After 1 h the mixture was neutralised with 1 mol dm^{-3} NaOH. Water (10 cm^3) and CH_2Cl_2 (10 cm^3) were then added. Extraction with CH_2Cl_2 (3 × 10 cm^3) and work-up in the usual way followed by flash chromatography (1:1; EtOAc–light petroleum) on silica gel 60 furnished the *lactone* **16** as a white solid (44 mg, 95%), mp 163–164 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 3460, 1750 and 1670; δ_H 4.23 (1 H, t, *J* 2), 4.13 (1 H, d, *J* 3), 3.60 (1 H, d, *J* 15), 3.42 (1 H, br d, *J* 15), 2.59 (1 H, m), 1.86 (3 H, s), 1.22 (3 H, s) and 1.08 (3 H, d, *J* 6) (Found: C, 68.4; H, 7.7%; M^+, 264.1352. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%; M, 264.1361).

Isopropylidenelactone 19

$NaBH_4$ (69 mg) was added portionwise to a solution of the lactone **16** (242 mg) in MeOH at 0 °C. After being stirred at 0 °C for 40 min the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with CH_2Cl_2 (3 × 15 cm^3). Work-up in the usual way followed by flash chromatography (EtOAc) on silica gel 60 gave the diol **18** as a viscous oil (195 mg, 80%), ν_{max}/cm^{-1} 3420 and 1735; δ_H 4.35 (1 H, dd, *J* 7 and 3.5), 4.17 (1 H, br d, *J* 7), 4.07 (1 H, t, *J* 3.5), 3.40 (1 H, d, *J* 14), 3.18 (1 H, br d, *J* 14), 1.82 (3 H, s), 1.30 (3 H, s) and 1.10 (3 H, s); *m/z* (EI) 266.

PTSA was added to a solution of the diol (10 mg) in CH_2Cl_2 (2 cm^3) at room temp. 2-Methoxypropene (27 mg) was added and the mixture was stirred at room temp. under N_2 for 2 h. The solvent was removed under reduced pressure to give a crude product, which was purified by flash column chromatography (3:7; EtOAc–hexane) on silica gel 60 to give the *acetal* **19** as a solid (10 mg, 91%), mp 80–82 °C (EtOAc–hexane); ν_{max}/cm^{-1} 1745; δ_H 4.50 (2 H, m), 4.08 (1 H, t, *J* 3), 3.43 (1 H, d, *J* 15), 3.19 (1 H, dq, *J* 15 and 1.5), 1.85 (3 H, d, *J* 1.5), 1.50 (3 H, s), 1.37 (3 H, s), 1.24 (3 H, s) and 1.05 (3 H, d, *J* 6) (Found: M^+, 3.06.1831. $C_{18}H_{26}O_4$ requires M, 306.1831).

Diastereoisomeric lactols 22

DIBAL (1.0 mol dm^{-3} in THF; 1 cm^3) was added dropwise to a solution of the lactone **19** (131 mg) in CH_2Cl_2 (10 cm^3) at −78 °C. After 1 h the reaction was quenched with saturated aq. NH_4Cl at −78 °C and then was warmed to room temp. The mixture was extracted with CH_2Cl_2 (3 × 10 cm^3). Work-up in the usual way followed by flash chromatography on silica gel 60 (1:1; EtOAc–hexane) yielded the diastereoisomeric lactols **22** as a solid (113 mg, 86%), ν_{max}/cm^{-1} 3415; δ_H 5.15 (1 H, dd, *J* 8 and 6), 4.50 (2 H, m), 3.82 (1 H, t, *J* 3), 2.85 (1 H, dd, *J* 14 and 6), 1.82 (3 H, d, *J* 1.5), 1.51 (3 H, s), 1.37 (3 H, s), 1.12 (3 H, s) and 1.03 (3 H, d, *J* 6).

Diene 24

(*a*) Et_3N (51 mg) was added dropwise to a solution of the lactol (50 mg) and $MeSO_2Cl$ (37 mg) in CH_2Cl_2 (3 cm^3) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 30 min and at room temp. for 4.5 h. The solvent was then removed under reduced pressure to give a crude product, which was purified by flash column chromatography (2:8; EtOAc–hexane) on silica gel 60 to give the *diene* **24** as an oil (22 mg, 47%), λ_{max}/nm 254; δ_H 6.63 (1 H, d, *J* 6), 5.84 (1 H, d, *J* 6), 4.52 (1 H, d, *J* 8), 4.48 (1 H, dd, *J* 8 and 4), 3.47 (1 H, t, *J* 3), 1.82 (3 H, s), 1.54 (3 H, s), 1.38 (3 H, s), 1.26 (3 H, s) and 1.07 (3 H, d, *J* 6) (Found: M^+, 290.1874. $C_{18}H_{26}O_3$ requires M, 290.1881).

(*b*) DIBAL (1.0 mol dm^{-3} in THF; 7.5 cm^3) was added dropwise to a solution of lactone **16** (500 mg) in CH_2Cl_2 (30 cm^3) at −78 °C under N_2. The resulting mixture was stirred at −78 °C for 1 h. The reaction was quenched with saturated aq. NH_4Cl at −78 °C and the mixture was warmed to room temp. 1 Mol dm^3 HCl was added, followed by CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3). Work-up of the combined organic phases in the usual way gave a *triol* as a solid (490 mg, 89%) (Found: M^+, 268.1672. $C_{15}H_{24}O_4$ requires M, 268.1674).

Anhydrous PTSA (5 mg) was added to a solution of the triol [crude sample (490 mg)] in CH_2Cl_2 (30 cm^3), at room temp. under N_2, followed by addition of 2-methoxypropene (0.70 cm^3). The resulting mixture was stirred at room temp. for 14 h. 10% Aq. $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3 × 10 cm^3). Work-up in the usual way gave a crude product, which upon SiO_2 60 flash chromatography (2:8; EtOAc–light petroleum) afforded the title diene (159 mg, 27%).

Aldehyde 27

OsO_4 (5 mg) was added to a solution of the diene **24** (145 mg), NMMNO hydrate (101 mg) and water (5 drops) in Bu^{t}OH (5 cm^3). The resulting mixture was stirred at room temperature under N_2 for 4.5 h. Sodium metabisulfite (30 mg) was then added and the mixture was stirred at room temp. for 30 min. The mixture was filtered through a pad of SiO_2 60, which was then washed with CH_2Cl_2 (3 × 10 cm^3). The filtrate was concentrated and dried under reduced pressure to give the diol **26** as a viscous oil (169 mg).

$NaIO_4$ (324 mg) was added to a solution of the above diol (163 mg) in MeOH (15 cm^3)–water (7.5 cm^3) The resulting mixture was stirred at room temp. for 1 h. Water (50 cm^3) and CH_2Cl_2 (100 cm^3) were then added. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 cm^3). Work-up in the usual way, followed by SiO_2 60 flash chromatography (2:8; EtOAc–light petroleum) gave the formate **27** as a solid (131 mg, 82% from **24**), mp 137–139 °C (from EtOAc–light petroleum); ν_{max}/cm^{-1} 1725, 1675 and 1620; δ_H 10.08 (1 H, s), 7.94 (1 H, s), 5.72 (1 H, t, *J* 2), 4.62 (1 H, dd, *J* 6.5 and 2.5), 4.45 (1 H, d, *J* 6.5), 2.18 (3 H, s), 1.42 (3 H, s), 1.40 (3 H, s), 1.38 (3 H, s) and 1.05 (3 H, d, *J* 6) (Found: M^+, 322.1792. $C_{18}H_{26}O_5$ requires M, 322.1780).

Aldehyde 28

K_2CO_3 (230 mg) was added to a solution of the aldehydo formate **27** (270 mg) in MeOH (20 cm^3) at room temp. The mixture was stirred at room temp. for 1 h and was then filtered through Celite. Removal of the solvent under reduced pressure gave a residue to which CH_2Cl_2 (80 cm^3) and water (80 cm^3) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3). Work-up in the usual way, followed by SiO_2 60 flash chromatography (3:7 to 1:1; EtOAc–light petrolum) gave a 1:2 mixture (240 mg, 97%) of aldehyde **28**, δ_H 10.20 (1 H, s), 4.62 (1 H, dd, *J* 7 and 3), 4.45 (2 H, m), 2.40 (3 H, s), 1.41 (3 H, s), 1.38 (3 H, s), 1.34 (3 H, s), 1.04 (3 H, d, *J* 7), and the isomeric lactol, δ_H 5.82 (1 H, d, *J* 3.5), 4.55 (1 H, d, *J* 7), 4.45 (1 H, m), 4.03 (1 H, dd, *J* 10 and 7), 2.62 (1 H, m), 1.90 (3 H, s), 1.51 (3 H, s), 1.39 (3 H, s), 1.29 (3 H, s) and 1.07 (3 H, d, *J* 7); *m/z* (EI) 294, (CI) 295.

Lactone 31

NMMNO monohydrate (35 mg) and 4 Å molecular sieves (powdered, 50 mg) were added to a solution of the aldehyde **28** (50 mg) in CH_2Cl_2 (3.5 cm^3). The mixture was stirred at room temp. under N_2 for 10 min. Tetrapropylammonium perruthenate (TPAP) (5 mg) was then added to the mixture, which was then stirred at room temp. for 14 h. The mixture was filtered through a pad of SiO_2 60 and concentrated to give a mixture, which upon SiO_2 60 flash column chromatography (3:7; EtOAc–light petroleum) gave the *lactone* **31** as a viscous oil (35 mg, 70%), ν_{max}/cm^{-1} 1750 and 1675; δ_H 4.65 (1 H, d, *J* 7.5), 4.49 (1 H, dd, *J* 7.5 and 4), 4.02 (1 H, dd, *J* 11.5 and 6), 2.32 (3 H, s), 1.52 (3 H, s), 1.40 (3 H, s), 1.28 (3 H, s) and 1.11 (3 H, d, *J* 7); *m/z* (CI) 310 (Found: M^+, 292.1665. $C_{17}H_{24}O_4$ requires M, 292.1674).

Methyl ketone 30

(*a*) MeMgI (3.0 mol dm^{-3} in Et_2O; 200 mm^3) was added dropwise to a solution of the γ-lactone **31** (35 mg) in THF (5 cm^3) at 0 °C under N_2. The mixture was stirred at 0 °C for 2 h. Saturated aq. NH_4Cl (5 cm^3) was added to quench the reaction at 0 °C and then the mixture was warmed to room temp. and extracted with Et_2O (5 × 5 cm^3). Work-up in the usual way, followed by SiO_2 60 flash chromatography (3:7 to 4:6; EtOAc–hexane) gave the ketone **30** as an oil (32 mg, 88%), ν_{max}/cm^{-1} 3495 and 1685; δ_H 4.59 (1 H, dd, *J* 6.5 and 2.5), 4.33 (1 H, d, *J* 6.5), 3.37 (1 H, t, *J* 3), 3.28 (1 H, m), 2.38 (3 H, s), 1.71 (3 H, s), 1.45 (3 H, s), 1.38 (3 H, s), 1.32 (3 H, s) and 1.03 (3 H, d, *J* 6); *m/z* (Cl) 326.

(*b*) K_2CO_3 (12 mg) was added to a solution of the formate **29** (14 mg) in AnalaR MeOH (6 cm^3) the mixture was stirred under N_2 for 2 h at room temp. Water (10 cm^3) and CH_2Cl_2 (50 cm^3) were added and the mixture was stirred for an additional 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 cm^3). Work-up in the usual way, followed by SiO_2 60H dry column chromatography, gave the ketone **30** as an oil (11 mg), identical with the material obtained previously.

Propionate 7

The dione **5** (439 mg) was added portionwise to a mixture of CH_2Cl_2 (5 cm^3), pyridine (2.1 cm^3), propionic anhydride (2.25 cm^3), and DMAP (5 mg) under N_2. After the mixture had been stirred at room temp. for 15 h the solvents were removed under reduced pressure, the residue was azeotroped with PhMe (3 × 15 cm^3) and was then purified by dry column chromatography on SiO_2 60H (1:4; EtOAc–hexane) to yield the *ester* **7** as an oil (500 mg, 93%), ν_{max}/cm^{-1} 1740, 1705 and 1670; δ_H 5.35 (1 H, t, *J* 3), 3.97 (3 H, s), 3.07 (1 H, d, *J* 11), 2.28 (2 H, q, *J* 7.5), 2.08 (1 H, m), 1.82 (3 H, s), 1.12 (3 H, t, *J* 7.5), 1.09 (3 H, d, *J* 7) and 1.05 (3 H, s) (Found: M^+, 308.1620. $C_{17}H_{24}O_5$ requires M, 308.1624).

Lactone 9

The propionate **7** (100 mg) as a solution in THF (4 cm^3) was added dropwise to a solution of LDA (1.5 mol dm^{-3} in cyclohexane; 500 mm^3) in THF (2 cm^3) at −78 °C. The mixture was stirred at −78 °C for 3 h and was then quenched with saturated aq. NH_4Cl, and after warming to room temp. was extracted with CH_2Cl_2 (3 × 25 cm^3). Work-up in the usual way, followed by SiO_2 60H dry column chromatography gave the *lactone* **9** as a solid in 53% yield, mp 125–127 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 3440, 1735, 1690 and 1635; δ_H 4.65 (1 H, t, *J* 2.5), 3.65 (3 H, s), 2.95 (1 H, q, *J* 7), 2.25 (1 H, d, *J* 10.2), 1.90 (3 H, s), 1.45 (3 H, d, *J* 7), 1.12 (3 H, d, *J* 6) and 1.01 (3 H, s) (Found: C, 66.4; H, 7.5%; M^+, 308.1626. $C_{17}H_{24}O_5$ requires C, 66.2; H, 7.8%; M, 308.1624).

Alcohol 12

$NaBH_4$ (482 mg) was added in small portions to a solution of the propionate ester **7** (1.57 g) in dry Pr^{i}OH (20 cm^3) under N_2 at 0 °C. After the mixture had been stirred for 1 h, saturated aq. NH_4Cl was added and the solution was extracted with CH_2Cl_2 (5 × 50 cm^3). Work-up in the usual way, followed by SiO_2 60H dry column chromatography gave the *alcohol* **12** as a crystalline solid (1.378 g, 87%), mp 150–151 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 3380, 1725 and 1605; δ_H 5.25 (1 H, t, *J* 3), 4.78 (1 H, br d, *J* 2), 4.00 (3 H, s), 2.20 (2 H, q, *J* 7.5), 2.00 (1 H, m), 1.73 (3 H, s), 1.24 (3 H, s), 1.09 (3 H, d, *J* 7) and 1.06 (3 H, t, *J* 7.5) (Found: C, 65.4; H, 8.4%; M^+, 310.1775. $C_{17}H_{26}O_5$ requires C, 65.8; H, 8.4%; M, 310.1780).

Diastereoisomeric tetrahydropyranyl ethers 13

A mixture of ester **12** (2.57 g), 3,4-dihydro-2*H*-pyran (3.78 g), CH_2Cl_2 (60 cm^3) and PTSA (15 mg) was stirred for 10 h. After removal of solvent under reduced pressure the black oil residue was purified by SiO_2 60H dry column chromatography (1:4; EtOAc–hexane) to give the diastereoisomeric *ethers* **13** as a yellow oil (2.945 g, 90%), ν_{max}/cm^{-1} 1735, 1660 and 1630; δ_H(isomer A) 5.25 (1 H, t, *J* 2.5), 4.88 (1 H, br s), 4.78 (1 H, d, *J* 3), 3.95 (1 H, m), 3.92 (3 H, s), 3.52 (1 H, m), 2.20 (2 H, q, *J* 7.5), 1.73 (3 H, s), 1.09 (3 H, d, *J* 6) and 1.03 (3 H, t, *J* 7.5); δ_H(isomer B) 5.25 (1 H, t, *J* 2.5), 4.88 (1 H, br s), 4.74 (1 H, br s), 3.87 (1 H, m), 3.84 (3 H, s), 3.52 (1 H, m), 2.18 (2 H, q, *J* 7.5), 1.72 (3 H, s), 1.096 (3 H, d, *J* 6) and 1.03 (3 H, t, *J* 7.5) (Found: M^+, 394.2357. $C_{22}H_{34}O_6$ requires M, 394.2355).

Diastereoisomeric lactones 15

A solution of the ethers **13** (1.725 g) in THF (20 cm^3) was added dropwise to a stirred solution of LDA (1.5 mol dm^{-3} in cyclohexane; 30 cm^3) in THF (10 cm^3) at −78 °C. After 5 h the mixture was quenched at −78 °C with saturated aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2 (3 × 50 cm^3). Work-up in the usual way followed by SiO_2 60H dry column chromatography (3:7; EtOAc–hexane) gave the diastereoisomeric *lactones* **15** (1.20 g, 69%), ν_{max}/cm^{-1} 3455 and 1715. The diastereoisomeric mixture could be separated by fractional crystallisation (from EtOAc–hexane) into a pale yellow oil, δ_H 4.95 (1 H, t, *J* 2.5), 4.57 (1 H, br s), 4.38 (1 H, d, *J* 4.5), 3.99 (1 H, m), 3.58 (3 H, s), 3.50 (1 H, m), 2.80 (2 H, q, *J* 7.5), 1.40 (1 H, dd, *J* 11 and 4.5), 1.27 (3 H, d, *J* 7.5), 1.10 (3 H, s) and 1.03 (3 H, d, *J* 6) (Found: M^+, 394.2357. $C_{22}H_{34}O_6$ requires M, 394.2355) and a crystalline solid, mp 169–171 °C (from EtOAc–hexane); δ_H 4.75 (1 H, t, *J* 3), 4.3 (1 H, d, *J* 3.8), 3.90 (1 H, m), 3.55 (3 H, s), 3.50 (1 H, m), 1.70 (3 H, s), 1.40 (1 H, dd, *J* 11 and 4.5), 1.27 (3 H, d, *J* 7.5), 1.09 (3 H, s), 0.95 (3 H, d, *J* 6) (Found: C, 67.0; H, 8.7. $C_{22}H_{34}O_6$ requires C, 67.0; H, 8.7%).

Hydroxy ketone 17

Anhydrous PTSA (20 mg) was added to a solution of the ethers **15** (4.6 g) in 10% aq. MeOH (100 cm^3) at room temp. After 12 h the MeOH was removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (100 cm^3) and worked up in the usual way. The residue was purified by dry column SiO_2 H chromatography (1:1; EtOAc–hexane) to afford the *alcohol* **17** as a crystalline solid (2.4 g, 74%), mp 139–141 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 3480, 1750 and 1705; δ_H 3.65 (1 H, d, *J* 6.5), 3.36 (1 H, br t, *J* 2.5), 3.02 (1 H, m), 2.86 (1 H, s), 1.89 (3 H, s), 1.44 (3 H, d, *J* 7), 1.21 (1 H, dd, *J* 11.5 and 6.5), 0.96 (3 H, d, *J* 6) and 0.80 (3 H, s) (Found: C, 68.8; H, 8.0%; M^+, 278.1514. $C_{16}H_{22}O_4$ requires C, 69.1; H, 8.0%; M, 278.1518).

Diol 20

$NaBH_4$ (155 mg) was added in small portions to a stirred solution of the lactone **17** (380 mg) in Pr^iOH (40 cm^3) under N_2 at 0 °C. After 2 h saturated aq. NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (3 × 60 cm^3). Work-up in the usual way followed by SiO_2 60H dry column chromatography (1:1; EtOAc–hexane) gave the *diol* **20** as a solid (306 mg, 80%), ν_{max}/cm^{-1} 3425 and 1685; δ_H 4.23 (1 H, t, *J* 3), 3.98 (1 H, br t, *J* 2.5), 3.56 (1 H, dd, *J* 7 and 4), 3.37 (1 H, m), 1.94 (3 H, s), 1.47 (3 H, s), 1.45 (3 H, d, *J* 7.5), 1.20 (1 H, dd, *J* 11 and 3), 0.96 (3 H, d, *J* 6.5) and 0.80 (3 H, s) (Found: M^+, 280.1684. $C_{16}H_{22}O_4$ requires M, 280.1675).

Isopropylidenelactone 21

PTSA (5 mg) was added to a solution of diol **20** (142 mg) and 2-methoxypropene (200 mm^3) in freshly distilled CH_2Cl_2 (10 cm^3) at 0 °C under N_2. After 10 h at room temp. the mixture was evaporated to dryness and the residue was purified by SiO_2 H dry column chromatography (1:4; EtOAc–hexane) to give the *ketal* **21** (145 mg, 89%), ν_{max}/cm^{-1} 1710; δ_H 4.54 (1 H, m), 4.45 (1 H, dd, *J* 8 and 5), 4.00 (1 H, t, *J* 2.5), 3.17 (1 H, m), 1.88 (3 H, s), 1.52 (3 H, s), 1.32 (3 H, d, *J* 8), 1.27 (3 H, s) and 0.98 (3 H, d, *J* 6) (Found: M^+, 320.1980. $C_{18}H_{26}O_5$ requires M, 320.1987).

Diastereoisomeric lactols 23

(*a*) DIBAL (1 mol dm^{-3} in THF; 1.82 cm^3) was added dropwise to a solution of the lactone **21** (145 mg) in CH_2Cl_2 (15 cm^3) at −78 °C under Ar. After 30 min the reaction was quenched with saturated aq. NH_4Cl at −78 °C. Work-up in the usual way followed by SiO_2 60H dry column chromatography (1:3; EtOAc–hexane) gave a mixture (4:1) of diastereoisomeric *lactols* **23** (118 mg, 89%), ν_{max}/cm^{-1} 3405; δ_H(major isomer) 5.24 (1 H, d, *J* 7), 4.30 (2 H, m), 3.32 (1 H, t, *J* 3), 2.95 (1 H, m), 1.73 (3 H, s), 1.57 (3 H, s), 1.40 (3 H, d, *J* 7.5), 1.27 (3 H, s), 1.24 (3 H, s) and 1.15 (3 H, d, *J* 6) and δ_H(minor isomer) 5.06 (1 H, d, *J* 4.5), 4.30 (2 H, m), 4.02 (1 H, t, *J* 3), 2.95 (1 H, m), 1.68 (3 H, s), 1.57 (3 H, s), 1.42 (3 H, d, *J* 7.5), 1.33 (3 H, s), 1.24 (3 H, s) and 1.12 (3 H, d, *J* 6) (Found: M^+, 322.2155. $C_{19}H_{30}O_4$ requires M, 322.2144).

(*b*) $LiAlH_4$ (1 mol dm^{-3} in THF; 310 mm^3) was added dropwise to a solution of the lactone **21** (44 mg) in THF at −78 °C under Ar. The cooling bath was removed and after 10 h saturated aq. NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (3 × 20 cm^3) and worked up in the usual way. SiO_2 60H dry column chromatography (1:3; EtOAc–hexane) gave the lactols (1:9) (25 mg, 57%).

Diene 25

$LiAlH_4$ (1 mol dm^{-3} in THF; 180 mm^3) was added dropwise to a solution of the lactone **21** (52 mg) in dry THF (5 cm^3) at −78 °C under Ar. $MeSO_2Cl$ (40 mm^3) was added carefully, followed by Et_3N (230 mm^3) at −78 °C. The mixture was allowed to warm to room temp. overnight and was then filtered through a short pad of SiO_2 60H. After evaporation of the solvent the residue was purified by SiO_2 60H dry column chromatography (1:9; EtOAc–hexane) to afford the *diene* **25** as an oil (24 mg, 49%), λ_{max}/nm 255; δ_H 6.57 (1 H, q, *J* 1.5), 4.52 (2 H, m), 3.27 (1 H, t, *J* 3.5), 1.99 (3 H, s), 1.95 (3 H, d, *J* 1.5), 1.53 (3 H, s), 1.37 (3 H, s), 1.21 (3 H, s) and 1.06 (3 H, d, *J* 7) (Found: M^+, 304.2035. $C_{19}H_{28}O_3$ requires M, 304.2037).

Formate 29

NMMNO hydrate (16 mg) was added to a solution of the diene **25** (67 mg) in Bu^tOH (3 cm^3) containing water (4 drops). OsO_4 (4 mg) was added to the stirred solution. After 12 h, $Na_2S_2O_5$ (~1 g) was added, and after 30 min the mixture was filtered through a short pad of SiO_2 60H. The solvents were removed under reduced pressure to afford crude diol (70 mg), which was dissolved in MeOH (8 cm^3)–water (4 cm^3). $NaIO_4$ (128 mg) was added to the solution. After 3 h, water (10 cm^3) and CH_2Cl_2 (30 cm^3) were added and the mixture was stirred for an additional 10 min. The organic phase was then separated and the aqueous phase was washed with CH_2Cl_2 (3 × 15 cm^3). Work-up in the usual way, followed by SiO_2 60H flash column chromatography (3:7; EtOAc–hexane), gave *formate* **29** as an oil (24 mg, 33%), ν_{max}/cm^{-1} 1725 and 1690; δ_H 8.00 (1 H, s), 5.88 (1 H, br t, *J* 2.5), 4.59 (1 H, dd, *J* 7 and 3), 4.43 (1 H, d, *J* 7), 2.25 (3 H, s), 1.77 (3 H, s), 1.44 (3 H, s), 1.37 (3 H, s), 1.26 (3 H, s) and 1.06 (3 H, d, *J* 6); *m/z* (CI) 354 (Found: M^+, 336.1929. $C_{19}H_{28}O_5$ requires M, 336.1937).

Acknowledgements

We thank the Sino-British Friendship Scholarship Scheme, the SERC, and the University of Manchester for financial support.

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Paper 4/07503J
Received 8th *December* 1994
Accepted 3rd *February* 1995