# Synthesis of the Germination Stimulant (±)-Strigol [1]

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Two synthetic routes to the octahydroindeno[1,2-*b*]furanone derivative strigol (1), a germination stimulant of witchweed seeds, and its stereoisomers are described.

THE wide-spread witchweed (*Striga lutea* Lour.) is a semi-parasitic plant which damages numerous gramineous crops, including corn, rice, and sugar cane.[2] It is a difficult pest to control by conventional means as the host–parasite relationship is both subtle and highly effective. The seeds of the witchweed can lie dormant in the soil for many years; their germination is triggered by contact with a stimulant exuded from the rootlets of the growing 'victim' plant. Much attention has been focused on the chemical nature of the stimulant, with the aim of producing a synthetic substitute. This would render possible witchweed seed germination in the absence of standing crops, when the growing parasite could be effectively controlled.

Considerable effort has thus been concentrated on the isolation and identification of the stimulant(s).[3] A pure crystalline highly potent stimulant, active at concentrations of less than $10^{-5}$ p.p.m., was isolated in 1966 from cotton root exudates.[4] This stimulant, termed strigol, was assigned the structure (1; relative configuration) on the basis of chemical, spectroscopic, and *X*-ray studies.[5] We now report the synthesis by two routes of (±)-strigol and three diastereoisomeric racemates of the same gross structure. While this work was in progress a

[1] Preliminary communication, G. A. MacAlpine, R. A. Raphael, A. Shaw, A. W. Taylor, and H.-J. Wild, *J.C.S. Chem. Comm.*, 1974, 834.

[2] W. C. Shaw, D. R. Shepherd, E. L. Robinson, and P. F. Sands, *Weeds*, 1962, **10**, 182.

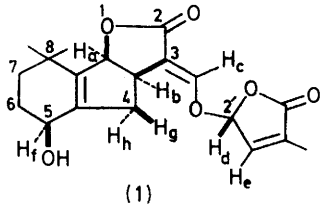
[3] R. Brown, A. W. Johnson, E. Robinson, and A. R. Todd, *Proc. Roy. Soc.* 1949, *B*, **136**, 1.

[4] C. E. Cook, L. P. Whichard, B. Turner, M. E. Wall, and G. H. Egley, *Science*, 1966, **154**, 1189.

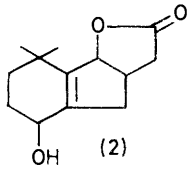
[5] C. E. Cook, L. P. Whichard, M. E. Wall, G. H. Egley, P. Coggon, P. A. Luhan, and A. T. McPhail, *J. Amer. Chem. Soc.*, 1972, **94**, 6198; P. Coggon, P. A. Luhan, and A. T. McPhail, *J.C.S. Perkin II*, 1973, 465.

preliminary communication appeared reporting another synthesis of strigol by a completely different approach.[6]

Retrosynthetic examination of structure (1) leads inevitably to the two key building blocks (2) and (3; X = Br). It is reasonable to suppose that base-catalysed interaction of (2) and ethyl formate would yield the corresponding hydroxymethylene derivative, alkylation of which by the bromo-lactone (3; X = Br) would produce the gross structure of strigol. The bromo-lactone * (3; X = Br) was readily obtainable by treatment of 2-methylbut-2-en-4-olide[7] (3; X = H) with *N*-bromosuccinimide, allylic bromination occurring exclusively on the methylene group.



(1)



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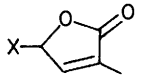

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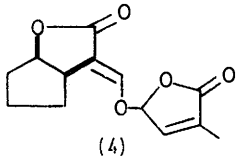

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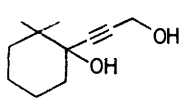

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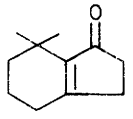
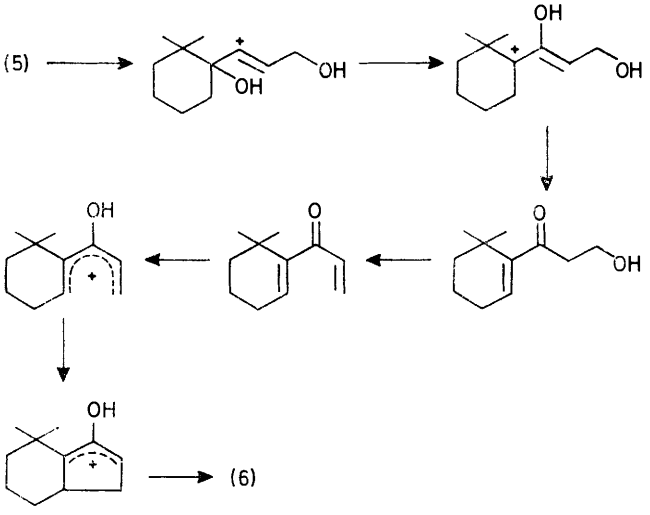


(6)

As it was apparent that elaboration of the required *E*-configuration about the side-chain double bond of strigol might present problems, it was decided to explore this process by means of a closely related model series. Accordingly the easily obtainable analogous *cis*-fused lactone, perhydrocyclopenta[*b*]furan-2-one, was treated with lithium di-isopropylamide and ethyl formate to give the corresponding hydroxymethylene derivative as a tautomeric *E*–*Z*-mixture. Alkylation of the sodium salt of this product with the bromo-lactone (3; X = Br) gave two separable crystalline diastereoisomers (4), *both* of which had the desired *E*-stereochemistry as shown by n.m.r. spectra. In particular the resonance for the exocyclic vinyl proton of both isomers occurred as a doublet (*J* 2.4 Hz) centred at τ 2.62 [the comparable proton in strigol resonates at τ 2.58 (d, *J* 2.5 Hz)]. It is plausible that the *E*-isomer of the hydroxymethylene-lactone anion would be thermodynamically more favoured because of the maximised separation of the two negative oxygen centres. To underpin this assignment each of the *E*-isomers (4) was separately stereomutated with u.v. light to produce a photoequilibrium mixture from which the corresponding *Z*-isomers could be separated. As expected from its removal from the deshielding zone of the lactone carbonyl group, the exocyclic vinylic proton now resonated upfield in the spectra of both *Z*-isomers, at τ 3.26 (d, *J* 1.8 Hz).

Attention was then turned to the second key building block, the tricyclic lactone (2). Our first synthesis of this compound started from the readily available 2,2-dimethylcyclohexanone, which was condensed with either the Grignard or the lithio-derivative of 3-tetrahydropyran-2-yloxypropyne to produce, after acidic hydrolysis, the crystalline diol (5). Brief treatment of the diol (5) at room temperature with phosphorus pentaoxide in methanesulphonic acid furnished directly, in acceptable yield, the bicyclic enone (6). This transformation [8] may be rationalised as in the illustrated Scheme, which blends the Newman mechanism [9] for the Rupe rearrangement with a consequent Nazarov-type conrotatory electrocyclisation.[10] The reaction of the ketone (6) with sodium hydride and diethyl oxalate followed by treatment with methyl bromoacetate and subsequent removal of the oxalyl grouping [11] gave the crystalline ester (7). This was treated sequentially with *N*-bromosuccinimide and silver acetate in acetic acid and the resulting acetoxy-esters were hydrolysed to give a mixture of the two epimeric hydroxy-acids (8). That the initial allylic bromination had ensued in the cyclohexene ring of (7) as desired was proven at a later stage. Reduction of the hydroxy-acid mixture with di-isobutylaluminium hydride [12] or of the corresponding acetoxy-acids with zinc borohydride [13] followed by hydrolysis



SCHEME

* Racemates are illustrated as one enantiomer throughout.

[6] J. B. Heather, R. S. D. Mittal, and C. J. Sih, *J. Amer. Chem. Soc.*, 1974, **96**, 1976.

[7] M. Frank-Neumann and C. Berger, *Bull. Soc. chim. France*, 1968, 4067.

[8] *Cf.* A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 1953, 2247.

[9] M. S. Newman, *J. Amer. Chem. Soc.*, 1953, **75**, 4740.

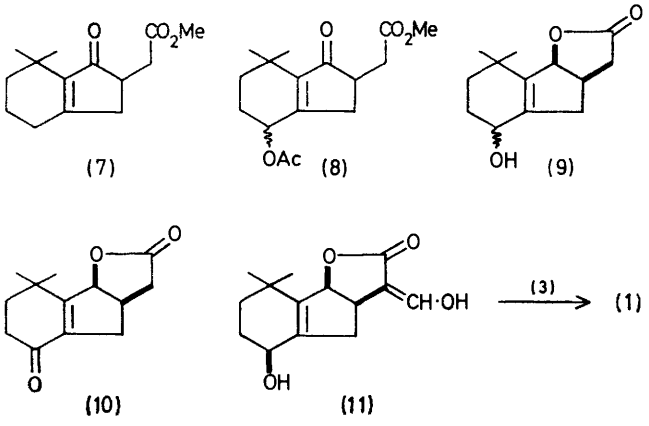
[10] R. B. Woodward and R. Hoffmann, ' The Conservation of Orbital Symmetry,' Academic Press, 1970, p. 58.

[11] E. Brown, M. Ragault, and J. Touet, *Tetrahedron Letters*, 1971, 1043.

[12] S. C. Welch and R. Y. Wong, *Tetrahedron Letters*, 1972, 1853; J. A. Marshall and N. H. Andersen, *J. Org. Chem.*, 1966, **31**, 667.

[13] E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. Winter, *J. Amer. Chem. Soc.*, 1968, **90**, 3245.

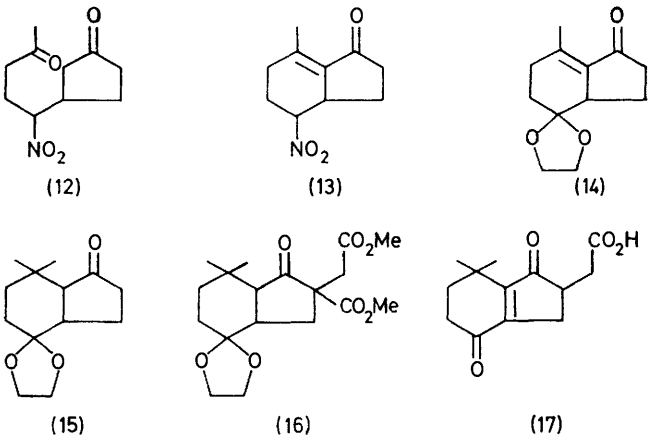
gave two epimeric γ-lactones (9). The spontaneous formation of the γ-lactone rings indicated that they pos-




sessed the required *cis*-fusion to the cyclopentane ring. These isomeric hydroxy-γ-lactones were readily separable to give a solid and a liquid epimer. Jones oxidation of these isomeric hydroxy-γ-lactones gave a homogeneous keto-γ-lactone (10); the spectroscopic properties of this showed that it was a cyclohexenone, thus rigorously proving the initial point of attack of the allylic bromination.

The solid isomer of the hydroxy-γ-lactone (9) was converted in the usual manner by methyl formate into the corresponding hydroxymethylene compound (11), the potassium salt of which was alkylated with the bromolactone (3; X = Br) to give a separable mixture of (±)-strigol, m.p. 202—205° (decomp.), and (±)-2′-*epi*-strigol, m.p. 178—180°. The spectroscopic properties of these two products were indistinguishable from each other and from those of naturally occurring strigol. However the chromatographic properties of the higher melting racemate tallied precisely with those of strigol. Application of the same processes to the liquid hydroxy-lactone (9) produced a separable mixture of (±)-5-*epi*-strigol and (±)-2′-*epi*,5-*epi*-strigol, m.p.s (not necessarily respectively) 156—158 and 188—190°. Although these two isomers showed virtually identical spectroscopic properties, there were significant differences in the n.m.r. spectra as compared with strigol and 2′-*epi*-strigol. All four strigol isomers are now being tested for their comparative germination stimulant activity by Professor A. W. Johnson's group (A.R.C. Unit of Invertebrate Chemistry and Physiology, University of Sussex). Initial results using the seeds of *Striga hermonthica* show that (±)-strigol and the isomer of m.p. 156—158° are highly active to almost an identical degree; (±)-2′-*epi*-strigol and the isomer of m.p. 188—190° both have considerably less activity.

The second synthetic route had the advantage that the required functionality at C-5 was built in from the start. Interaction of but-3-en-2-one and nitromethane gave 5-nitropentan-2-one. Michael addition of this to cyclopentenone gave the expected adduct (12), which readily underwent acid-catalysed cyclisation to the bicyclic nitro-ketone (13). The next step envisaged involved conjugate addition to this ketone with lithium dimethylcuprate [14] to generate the *gem*-dimethyl grouping. Surprisingly this reagent left the ketone (13) substantially unchanged under a variety of conditions. The nitro-ketone was accordingly transformed by treatment with titanium trichloride [15] into the corresponding diketone, which was selectively converted into the crystalline monoacetal (14) by acid-catalysed interaction with ethylene glycol. Conjugate addition to this monoacetal proceeded smoothly with the production of the saturated ketone (15). Reaction of the ketone (15) with methoxymethylmagnesium carbonate,[16] esterification with diazomethane, and subsequent base-catalysed alkylation with methyl bromoacetate gave the saturated keto-diester (16). Treatment of (16) with acid in an atmosphere of oxygen not only hydrolysed the acetal and ester groups, with concomitant monodecarboxylation, but also induced autoxidation,[17] which introduced a double bond




in the desired position between the two carbonyl groups. The resulting unsaturated diketo-acid (17) was then readily reduced [6] by di-isobutylaluminium hydride to the two epimers of the key tricyclic lactone (9) identical with those obtained by the first route.

## EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. T.l.c. was carried out on Merck plates pre-coated with Kieselgel 60 $F_{254}$. Preparative layer chromatography (p.l.c.) was carried out on plates (20 × 20 cm; 1.3 mm thick) prepared from Kieselgel $PF_{254}$ or on plates (20 × 20 cm; 1.5 mm thick) pre-coated with aluminium oxide $F_{254}$ (type T). Mass spectra were determined on an A.E.I. MS 9 spectrometer. U.v. absorption spectra (solutions in 95% ethanol) were measured with a Unicam SP 800 or 1 800 instrument. I.r. spectra were determined on a Perkin-Elmer 257 spectrophotometer. $^1H$ N.m.r. spectra were measured on a Varian HA-100 or Perkin-Elmer R12B 60 MHz instrument, with tetramethylsilane as internal reference; reported

[14] G. H. Posner, *Org. Reactions*, 1972, **19**, 1.
[15] J. E. McMurry and J. Melton, *J. Org. Chem.*, 1973, **38**, 4367.
[16] M. Stiles, *J. Amer. Chem. Soc.*, 1959, **81**, 2598.
[17] *Cf.* W. G. Dauben, G. A. Boswell, and W. Templeton, *J. Org. Chem.*, 1960, **25**, 1853.

values for multiplets refer to the apparent centres of these signals. Light petroleum refers to that fraction of boiling range 40—60°. Extracts were dried over magnesium sulphate.

*4-Bromo-2-methylbut-2-en-4-olide* (3; X = Br).—Freshly recrystallised *N*-bromosuccinimide (1.95 g) and benzoyl peroxide (10 mg) were added to a solution of 2-methylbut-2-en-4-olide [7] (0.98 g) in AnalaR carbon tetrachloride (25 ml). The mixture was stirred and heated under reflux for 1.5 h with exclusion of moisture. Cooling, filtration, evaporation, and distillation gave the *bromo-lactone* (1.45 g, 82%), b.p. 40—44° at 0.15 mmHg [Found: $M^+$, 175.9489/177.9437 (1 : 1). $C_5H_5BrO_2$ requires $M$ 175.9472/177.9453], $\nu_{max.}$ (film) 1 785 and 1 650 $cm^{-1}$, $\tau$ ($CCl_4$) 2.80 (1 H, m, CH=C), 3.19 (1 H, m, methine H), and 8.00 (3 H, m, $CH_3$).

*3-Hydroxymethyleneperhydrocyclopenta[b]furan-2-one*—To a cooled (0 °C) stirred solution of di-isopropylamine (2.42 g) in anhydrous tetrahydrofuran (25 ml) under nitrogen was added (syringe) n-butyl-lithium in hexane (15%; 10 ml) over 5 min. After a further 10 min a solution of perhydrocyclopenta[*b*]furan-2-one [18] (2.52 g) in tetrahydrofuran (20 ml) was added. After 30 min at −78 °C the cooling bath was removed and ethyl formate (1.78 g) added. The mixture was allowed to warm to room temperature, stirred for a further 2 h, and then poured into an excess of ice-cold hydrochloric acid (10%). Brine was added and the mixture thoroughly extracted with chloroform. Washing with water, drying, and evaporation yielded an oil which rapidly solidified. Crystallisation from acetone–petroleum (b.p. 60—80°) gave the *hydroxymethylenelactone* (1.96 g, 65%), m.p. 115—117°; although the product is sharp-melting and homogeneous by t.l.c. the spectra are complicated by tautomeric equilibria (Found: $M^+$, 154. $C_8H_{10}O_3$ requires $M$, 154.2), $\nu_{max.}$ (Nujol) 1 720s, 1 680s, and 1 630br $cm^{-1}$, $\tau$ ($CDCl_3$) 0.00br (exchangeable, OH), 0.22 (s, CHO), 2.33 (d, $J$ 1.5 Hz, CH:), and 2.98 (d, $J$ 1.5 Hz, CH:) (geometrical isomers), 5.00 (m, CH·O), 6.60 (m, CH·C=), and 8.50—9.20 (complex).

*Isomers of 3-(2,5-Dihydro-4-methyl-5-oxo-2-furyloxymethylene)perhydrocyclopenta[b]furan-2-one* (4).—Anhydrous tetrahydrofuran (10 ml) was syringed through a septum on to sodium hydride (60% dispersion in oil; 0.22 g, 5.5 mmol) contained under nitrogen in a dry 250 ml three-necked flask. After 10 min stirring the tetrahydrofuran was removed by syringe and the washing repeated. More tetrahydrofuran (50 ml) was then added and, to the stirred suspension, was introduced, over 10 min, a solution of the foregoing hydroxymethylene-lactone (0.8 g) in tetrahydrofuran (10 ml). A gelatinous precipitate formed with rapid evolution of hydrogen. After a further 15 min a solution of the distilled bromolactone (3; X = Br) (0.98 g) in tetrahydrofuran (10 ml) was added, and the stirred mixture was heated under reflux for 90 min. At this point the gel had disappeared and was replaced by a fine precipitate. The cooled mixture was poured into water (150 ml) and extracted with chloroform (3 × 75 ml). The combined extracts were washed (2N-HCl, 5% $NaHCO_3$, and water), dried, and evaporated to give a clear gum (1.3 g), shown by t.l.c. (1 : 1 ethyl acetate–toluene) to comprise two major products of similar $R_F$ values (*ca.* 0.4). These were quantitatively separated by the ' short column ' technique [19] [Kieselgel $GF_{254}$ and ethyl acetate–toluene (1 : 3) with Propyl Red as marker]. The higher $R_F$ *lactone*, termed isomer A*E*, was obtained as an oil (450 mg, 35%) which crystallised slowly; m.p. 86—87.5° (Found: $M^+$, 250.0837. $C_{13}H_{14}O_5$ requires $M$, 250.0840), $\nu_{max.}$ ($CHCl_3$) 1 780, 1 740, and 1 680 $cm^{-1}$, $\tau$ ($CDCl_3$) 2.62 (1 H, d, $J$ 2.4 Hz, =CH·O), 3.07 (1 H, m, =CH), 3.84 (1 H, m, O·CH·O), 5.06 (1 H, m, CH·O), 6.53 (1 H, m, CH·C=C), 8.01 (3 H, t, $J$ 1.5 Hz, $CH_3$), and 7.8—8.5 (6 H, complex).

The diastereoisomeric *lactone*, B*E*, (420 mg, 33%) of lower $R_F$ value rapidly solidified and was recrystallised from acetone–cyclohexane; m.p. 116—117.5°, $M^+$,250.0839. The n.m.r. and solution i.r. spectra of this isomer were superimposable on those of isomer A*E*.

A solution of the lactone A*E* (280 mg) and benzophenone (150 mg) in dry benzene (80 ml) was thoroughly degassed and irradiated through Pyrex with a medium-pressure Hanovia lamp for 20 min. Preparative t.l.c. (ethyl acetate–toluene, 1 : 1) gave starting material ($R_F$ 0.4) and the geometrically isomeric *lactone* A*Z* ($R_F$ 0.19; 20 mg), m.p. 160—161° [from acetone–petroleum (b.p. 60—80°)], $M^+$ 250.0843. Similar treatment of B*E* (145 mg) gave the geometrically isomeric *lactone* B*Z* ($R_F$ 0.24; 15 mg), m.p. 149—150°, $M^+$ 250.0839. The n.m.r. and solution i.r. spectra of these two *Z*-lactones were identical: $\nu_{max.}$ ($CHCl_3$) 1 780, 1 750, and 1 675 $cm^{-1}$, $\tau$ ($CDCl_3$) 3.00 (1 H, m, =CH), 3.26 (1 H, d, $J$ 1.8 Hz, =CH·O), 3.89 (1 H, m, O·CH·O), 5.05 (1 H, m, CH·O), 6.62 (1 H, m, CH·C=C), 8.02 (3 H, t, $J$ 1.5 Hz, $CH_3$), and 7.8—8.5 (6 H, complex).

*2,2-Dimethyl-1-(3-tetrahydropyran-2-yloxyprop-1-ynyl)-cyclohexanol*.—To a stirred solution of ethylmagnesium bromide [from magnesium (11.18 g) and ethyl bromide (62.6 g)] in dry tetrahydrofuran (100 ml) at room temperature under nitrogen was added, over 20 min, a solution of 3-tetrahydropyran-2-yloxypropyne (67.2 g) in tetrahydrofuran (200 ml), and the mixture was heated under reflux for 4 h. A solution of 2,2-dimethylcyclohexanone (50 g) in tetrahydrofuran (100 ml) was added over 30 min and the mixture was heated under reflux for 2 h. The cooled mixture was poured into saturated ammonium chloride solution and extracted with ether (3 × 300 ml). Washing (brine), drying, evaporation, and distillation gave the *alcohol* (86 g, 82%) as a viscous liquid, b.p. 134—140° at 0.5 mmHg (Found: C, 72.0; H, 10.1%; $M^+$, 266. $C_{16}H_{26}O_3$ requires C, 72.1; H, 9.9%; $M$, 266), $\nu_{max.}$ (film) 3 440, 1 450, 1 360, 1 200, 1 120, and 1 025 $cm^{-1}$, $\tau$ ($CDCl_3$) 9.03 and 8.96 (2 × 3 H, 2s, $CMe_2$), 8.6—8.1 (14 H, complex), 7.94 (1 H, s, OH), 6.6—6.0 (2 H, m, $CH_2O$), 5.72 (2 H, s, C≡C·$CH_2O$), and 5.17 (1 H, m, O·CH·O).

Use of the lithio-derivative of tetrahydropyranyloxypropyne in tetrahydrofuran (made by use of n-butyl-lithium) gave a lower yield (74%) of the alcohol.

*1-(3-Hydroxyprop-1-ynyl)-2,2-dimethylcyclohexanol* (5).—The above alcohol (30.7 g) was added to a solution of sulphuric acid (6 ml) in methanol (300 ml) and the mixture kept at room temperature under nitrogen for 2 days. It was then neutralised by slow addition of solid sodium hydrogen carbonate (18 g). After 2 h stirring the mixture was filtered and the solids were washed with methanol. Evaporation of the filtrate and washings at room temperature under reduced pressure gave a solid which was dissolved in chloroform (100 ml); the solution was filtered through Celite and evaporated at room temperature under reduced pressure. The resulting solid was crystallised from chloroform–hexane to give the *diol* (5) as needles (18.65 g, 89%), m.p. 92° (Found: C, 72.4; H, 9.7%; $M^+$, 182. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.9%; $M$, 182), $\nu_{max.}$ ($CHCl_3$) 3 600

[18] R. P. Linstead and A. M. Meade, *J. Chem. Soc.*, 1934, 942.
[19] B. J. Hunt and W. Rigby, *Chem. and Ind.*, 1967, 1868.

3 400br, 1 450, and 1 385 cm$^{-1}$, τ ($CDCl_3$) 9.00 and 8.93 (2 × 3 H, 2s, $CMe_2$), 8.7—8.1 (8 H, complex), 7.8—7.5 (2 H, m, 2 OH; removed by $D_2O$ treatment), and 5.69 (2 H, s, C≡C·$CH_2$O).

*7,7-Dimethyl-*$\Delta^{3a(7a)}$*-hexahydroinden-1-one* (6).—A mixture of phosphorus pentaoxide (17.0 g) and methanesulphonic acid (120 ml) was stirred at 80 °C until dissolution was effected.[20] The solution was then cooled to −15 °C under nitrogen and the diol (5) (21.3 g) was added over 10 min; the cooling bath was then removed and stirring continued for 15 min. The solution was poured into ice–water (500 ml) and extracted with ether (3 × 300 ml). Washing (water followed by aqueous $NaHCO_3$), drying, and evaporation gave a dark oil (19.0 g) which was purified by co-distillation with ethylene glycol at 14 mmHg pressure until no further product was detected in the distillate (2.8 l). The glycol distillate was diluted with water (700 ml) and extracted with ether (3 × 500 ml). Washing (water), drying, and evaporation gave almost pure crystalline *enone* (6) (10.14 g, 53%). Distillation gave a liquid, b.p. 100—105° at 0.4 mmHg, which solidified to a crystalline mass, m.p. 45° (Found: C, 80.2; H, 9.8%; $M^+$, 164. $C_{11}H_{16}O$ requires C, 80.4; H, 9.8%; $M$, 164), $\nu_{max.}$ (film) 1 690, 1 635, 1 322, 1 385, 1 215, and 980 cm$^{-1}$, $\lambda_{max.}$ 237 nm (log ε 4.07), τ ($CDCl_3$) 8.89 (6 H, s, $CMe_2$), 8.7—8.2 (4 H, m), and 7.9—7.5 (6 H, m).

*Methyl 7,7-Dimethyl-1-oxo-*$\Delta^{3a(7a)}$*-hexahydroinden-2-ylacetate* (7).—The enone (6) (1.31 g), diethyl oxalate (1.2 g), and sodium hydride (60% suspension; 0.4 g) were sequentially added to dry benzene (100 ml), and the mixture was stirred under argon at room temperature for 3 days. The resulting viscous yellow liquid was evaporated to dryness at room temperature under reduced pressure and dry acetone (400 ml) was added, followed by methyl bromoacetate (5 g). The stirred mixture was heated under reflux for 5 h under nitrogen, cooled, and concentrated under reduced pressure (50 ml); water (500 ml) was then added. Extraction with ether, washing (brine), and evaporation gave a residue which was heated under reflux under nitrogen for 3 h with methanolic sodium methoxide [from sodium (8 g) and methanol (500 ml)]. Concentration under reduced pressure (100 ml), dilution with ice–water (200 ml), acidification to pH 2 (2N-HCl), extraction with ether, washing (brine), drying, and evaporation under reduced pressure gave a dark red oil. Elution from a silica column with light petroleum (b.p. 60—80°)–ethyl acetate (15 : 1) gave the *enone ester* (7) (0.99 g, 52%), needles, m.p. 64—65° (from light petroleum). (Found: C, 71.9; H, 8.4%; $M^+$, 236. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%; $M$, 236), $\nu_{max.}$ ($CCl_4$) 1 745, 1 705, 1 640, 1 440, 1 390, 1 360, 1 320, 1 220, and 1 170 cm$^{-1}$, $\lambda_{max.}$ 238 nm (log ε 4.31), τ ($CDCl_3$) 8.87 (6 H, s, $CMe_2$), 8.7—8.0 (4 H, m), 8.0—7.0 (7 H, m), and 6.37 (3 H, s, $CO_2Me$). On a larger scale (nine-fold) it proved more convenient to purify the crude ester by direct crystallisation from methanol at −15 °C.

*Methyl 4-Acetoxy-7,7-dimethyl-1-oxo-*$\Delta^{3a(7a)}$*-hexahydroinden-2-ylacetate* (8).—A mixture of the enone ester (7) (4.02 g), *N*-bromosuccinimide (3.21 g), and αα′-azobisisobutyronitrile (38 mg) in carbon tetrachloride (75 ml) was heated under reflux under nitrogen for 20 min. Cooling, filtration, and evaporation gave the crude allylic bromide (5.9 g). To a solution of this product in glacial acetic acid (125 ml) was added silver acetate (3.72 g), and the mixture was heated under reflux in the dark under argon for 30 min. Cooling, filtration, and washing of the solids with ether precipitated further solids which were again filtered off and washed. Evaporation of the filtrates under reduced pressure gave a thick yellow oil (5.2 g) which was chromatographed on silica (540 g) in light petroleum–ethyl acetate (10 : 1 to 8 : 1) to give a mixture of the two diastereoisomers of the *acetate* (8) as an oil (3.2 g, 64%) (Found: $M^+$, 294. $C_{16}H_{22}O_5$ requires $M$, 294) $\nu_{max.}$ ($CCl_4$) 1 750, 1 710, and 1 640 cm$^{-1}$, $\lambda_{max.}$ 235 nm, τ ($CDCl_3$) 8.95 (6 H, s, $CMe_2$), 7.93 (3 H, s, OAc), 8.7—7.0 (9 H, m), 6.36 (3 H, s, $CO_2Me$), and 4.6—4.3 (1 H, m, C*H*·OAc).

*5-Hydroxy-8,8-dimethyl-*$\Delta^{4a(8a)}$*-octahydroindeno*[1,2-b]*furan-2-one* (9).—The diastereoisomeric mixture of acetates (8) (0.724 g) in methanol (30 ml) was treated at 0 °C with sodium hydroxide (6N; 15 ml), dropwise with stirring at such a rate that the temperature rose to 20 °C during the addition. After 5 h at room temperature the mixture was taken to pH 4 with hydrochloric acid (10N). Removal of most of the methanol under reduced pressure, extraction with chloroform (3 × 200 ml), drying, and evaporation gave a semi-solid mass of the two hydroxy-acid epimers (0.7 g). This product was dissolved in dry dichloromethane (120 ml) in an argon-flushed sealed flask with stirrer and cooled to −70 °C. A solution of di-isobutylaluminium hydride in toluene (1.9M; 6.2 ml) was slowly added by argon-flushed syringe. After 3 h, methanol (60 ml), pre-cooled to −70 °C, was added and the mixture was allowed to warm to room temperature. The methanol was removed under reduced pressure and sulphuric acid (2N; 30 ml) and chloroform (200 ml) were added sequentially. Further extraction with chloroform (2 × 200 ml), washing (brine), drying, and evaporation gave a gummy product which was chromatographed on four aluminium oxide plates with chloroform–dichloromethane (1 : 1) to give a slower moving solid component (122 mg, 22%) and a faster moving liquid component (127 mg, 23%). Crystallisation from benzene–light petroleum (b.p. 60—80°) of the slower moving component gave the *hydroxy-lactone* [6] (9) as needles, m.p. 146—147° (Found: C, 70.3; H, 8.3%; $M^+$, 222. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%; $M$, 222), $\nu_{max.}$ ($CHCl_3$) 3 600, 3 460 (removed on dilution), 1 765, and 1 175 cm$^{-1}$, τ($CDCl_3$–$D_2O$) 8.93 and 8.86 (6 H, 2s, $CMe_2$), 8.6—6.8 (9 H, m), 5.87 (1 H, ' t ', ' *J* ' 5.5 Hz, C*H*·OH), and 4.53 (1 H, ' d ', ' *J* ' 6.8 Hz, CH·O·CO). Further chromatography of the faster moving component on silica (chloroform–acetone, 4 : 1) gave the liquid 4-epimer of (9), $M^+$ 222, $\nu_{max.}$ ($CHCl_3$) 3 600, 3 470 (removed on dilution), 1 768, and 1 175 cm$^{-1}$, τ($CDCl_3$–$D_2O$) 8.96 and 8.92 (6 H, 2s), 8.6—6.8 (9 H, m), 5.86 (1 H, ' t ', ' *J* ' 4.8 Hz), and 4.48 (1 H, ' d ', ' *J* ' 6.5 Hz).

Each of the epimeric hydroxy-lactones (7 mg) was separately dissolved in acetone (2 ml), and a few drops of Jones reagent were added. After a few min ether was added and the organic layer washed (sodium hydrogen carbonate solution), dried, and evaporated. Both hydroxy-lactones gave the same *enone lactone* (10) (6 mg), which crystallised from carbon tetrachloride–light petroleum at −15 °C in prisms, m.p. 86—87° (Found: $M^+$, 220.1092. $C_{13}H_{16}O_3$ requires $M$, 220.1099), $\nu_{max.}$ ($CHCl_3$) 1 775, 1 675, 1 290, and 1 165 cm$^{-1}$, $\nu_{max.}$ 245 nm (log ε 4.016), τ ($CDCl_3$) 8.73 and 8.70 (6 H, 2s, $CMe_2$), 8.10 (2 H, dd, *J* 6.7 and 5.8 Hz, C*H*$_2$·$CMe_2$), 7.8—6.8 (7 H, m), and 4.37 (1 H, d, *J* 7.6 Hz, CH·O·CO).

An alternative preparation of (9) involved reduction of the acetoxy-acid corresponding to (8) with zinc borohy-

[20] P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, 1972, **94**, 1015.

dride [13] followed by lactonisation, but the overall yield of the epimers of (9) was less.

*Strigol Diastereoisomers.*—To a solution of the crystalline lactone (9) (240 mg) and methyl formate (0.6 ml) in dry ether (30 ml) was added sodium hydride (60% suspension; 120 mg) and the mixture was stirred under nitrogen in the dark at room temperature for 40 h. Chloroform (240 ml) and ice-cold brine (160 ml) were carefully added and the solution was acidified to pH 5 with aqueous phosphoric acid (5%). Extraction with chloroform (4 × 240 ml), washing (brine), drying, and evaporation under reduced pressure gave the crude hydroxymethylene-lactone. This product and the bromobutenolide (3; X = Br) (192 mg) were dissolved in hexamethylphosphoramide (8 ml) and potassium carbonate (150 mg) was added; the mixture was stirred under argon in the dark at room temperature for 18 h. Addition of brine (60 ml), extraction with ether (3 × 150 ml), washing (brine), drying, and evaporation gave a residue from which hexamethylphosphoramide was removed by heating at 60 °C and 2 mmHg for 2 min. Chromatography on silica plates with chloroform–acetone (10 : 1) gave three mobile components. The fastest moving ($R_F$ 0.34 in 4 : 1 chloroform–acetone) was crystallised from ethyl acetate–light petroleum to give (±)-2′-epi-*strigol* [6] (58 mg) as needles, m.p. 178–180° (Found: $M^+$, 346.1434. $C_{19}H_{22}O_6$ requires $M$, 346.1415), $\nu_{max.}$ ($CHCl_3$) 3 590, 1 790, 1 745, and 1 684 $cm^{-1}$, $\lambda_{max.}$ 238 nm (log ε 4.20), τ ($CDCl_3$–$D_2O$) 8.95 and 8.88 (6 H, 2s, $CMe_2$), 8.48 (4 H, m), 8.03 (3 H, t, $J$ 1.4 Hz, $CH_3$·C=C), 7.32 (2 H, d, $J$ 6.1 Hz, cyclopentene $CH_2$), 6.37 ($H_b$, m), 5.93 ($H_f$, m), 4.51 ($H_a$, ' d ', ' $J$ ' 8 Hz), 3.85 ($H_d$, m), 3.10 ($H_e$, m), and 2.59 ($H_c$, d, $J$ 2.4 Hz). The component of intermediate mobility proved to be the lactone (9) (10 mg). The slowest moving component had t.l.c. properties identical with those of natural strigol ($R_F$ 0.18 in 4 : 1 chloroform–acetone). Crystallisation from ethyl acetate–light petroleum gave (±)-*strigol* [6] (58 mg) as needles, m.p. 202—205° (decomp.) (Found: C, 65.7; H, 6.25%; $M^+$, 346. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%; $M$, 346), $\nu_{max.}$ ($CHCl_3$) 3 590, 1 787, 1 740, and 1 682 $cm^{-1}$, $\lambda_{max.}$ 238 nm (log ε 4.20), τ ($CDCl_3$–$D_2O$) 8.93 and 8.86 (6 H, 2s, $CMe_2$), 8.48 (4 H, m), 8.01 (3 H, t, $J$ 1.4 Hz, $CH_3$·C=C), 7.30 (2 H, d, $J$ 6.5 Hz, cyclopentene $CH_2$), 6.36 ($H_b$, m), 5.90 ($H_f$, m), 4.50 ($H_a$, ' d ', ' $J$ ' 8 Hz), 3.87 ($H_d$, m), 3.09 ($H_e$, m), and 2.58 ($H_c$, d, $J$ 2.5 Hz).

The liquid 5-epimer of the lactone (9) was converted in precisely the same manner into a 1 : 1 mixture of (±)-5-epi-*strigol* and (±)-2′-epi,5-epi-*strigol*, separated by chromatography on silica plates with chloroform–acetone (30 : 1). The faster moving epimer ($R_F$ 0.33 in 4 : 1 chloroform–acetone) crystallised from ethyl acetate–light petroleum in needles, m.p. 188–190° (Found: $M^+$, 346.1415. $C_{19}H_{22}O_6$ requires $M$, 346.1415), $\nu_{max.}$ ($CHCl_3$) 3 600, 1 788, 1 742, and 1 684 $cm^{-1}$, $\lambda_{max.}$ 237 nm (log ε 4.19), τ ($CDCl_3$–$D_2O$) 8.92 and 8.88 (6 H, 2s, $CMe_2$), 8.6—7.6 (5 H, m), 8.00 (3 H, t, $J$ 1.6 Hz, $CH_3$·C=C), 6.96 (1 H of cyclopentene $CH_2$, dd, $J$ 17 and 9 Hz), 6.40 ($H_b$, m), 5.86 ($H_f$, ' t ', ' $J$ ' 5 Hz), 4.48 ($H_a$, dd, $J$ 8 and 2.2 Hz), 3.88 ($H_d$, m), 3.08 ($H_e$, m), and 2.56 ($H_c$, d, $J$ 3 Hz). The slower-moving epimer ($R_F$ 0.29 in 4 : 1 chloroform–acetone) crystallised from ethyl acetate–light petroleum in needles, m.p. 156—158° (Found: C, 65.7; H, 6.4%; $M^+$, 346), $\nu_{max.}$ ($CHCl_3$) 3 600, 1 787, 1 743, and 1 684 $cm^{-1}$, $\lambda_{max.}$ 237 nm (log ε 4.18), τ ($CDCl_3$–$D_2O$) 8.92 and 8.88 (6 H, 2s, $CMe_2$), 8.6—7.6 (5 H, m), 8.00 (3 H, t, $J$ 1.6 Hz, $CH_3$·C=C), 6.94 (1 H of cyclopentene $CH_2$, dd, $J$ 17 and 9 Hz), 6.39 ($H_b$, m), 5.88 ($H_f$, ' t ', ' $J$ ' 5 Hz), 4.49 ($H_a$, dd, $J$ 8 and 2.2 Hz), 3.87 ($H_d$, m), 3.10 ($H_e$, m), and 2.58 ($H_c$, d, $J$ 3 Hz).

3-(1-*Nitro*-4-*oxopentyl*)*cyclopentanone* (12).—A solution of 5-nitropentan-2-one (7.24 g; made as described [21] in 35% yield) and cyclopent-2-enone [22] (6.8 g) in chloroform (50 ml) containing di-isopropylamine (3 ml) was heated and stirred at 60 °C under nitrogen for 54 h. The cooled mixture was washed sequentially with water, N-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, dried, and evaporated. Chromatography of the residue through silica gel (150 g) with light petroleum–ether (9:1) yielded the two diastereoisomers of the diketone (12) as a yellow oil (8.8 g, 75%), which was used directly for the next step; $\nu_{max.}$ (film) 1 740, 1 715, and 1 545 $cm^{-1}$, τ ($CDCl_3$) 7.86 (3 H, s, MeCO), 7.2—8.5 (15 H, m), and 5.5 (1 H, m, CH·$NO_2$).

7-*Methyl*-4-*nitro*-Δ⁷-*hexahydroinden*-1-*one* (13).—A solution of the diketone (12) (5.4 g) in benzene (100 ml) containing toluene-*p*-sulphonic acid (380 mg) was heated under reflux for 5 h with continuous separation of water. Pouring into saturated aqueous sodium hydrogen carbonate, extraction with ether (3 × 50 ml), washing (brine), drying, and evaporation gave the two diastereoisomers of the ketone (13) (4.9 g, 94%) as a semi-solid mass suitable for direct use in the next stage. The two diastereoisomers could be separated by p.l.c. on silica with ether–light petroleum (3 : 2). The faster moving isomer ($R_F$ 0.26) was obtained as an oil, $\nu_{max.}$ ($CHCl_3$) 1 705, 1 640, and 1 540 $cm^{-1}$, τ ($CDCl_3$) 7.9 (3 H, d, $J$ 1.5 Hz, $CH_3$·C=C), 7.4—8.6 (8 H, m), 6.8 (1 H, m, CH), and 5.7 (1 H, m, CH·$NO_2$). The more polar *ketone* ($R_F$ 0.086 in 2 : 1 ether–light petroleum) had m.p. 87—88° (from ether–light petroleum) (Found: C, 61.4; H, 6.9; N, 7.1. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%), $\nu_{max.}$ ($CHCl_3$) 1 705, 1 640, and 1 540 $cm^{-1}$, $\lambda_{max.}$ 250 nm (log ε 3.996), τ ($CDCl_3$) 7.82 (3 H, d, $J$ 1.5 Hz, $CH_3$·C=C), 7.2—8.6 (8 H, m), 6.94 (1 H, m, CH), and 5.92 (1 H, m, CH·$NO_2$).

4,4-*Ethylenedioxy*-7-*methyl*-Δ⁷-*hexahydroinden*-1-*one* (14).—A solution of the nitro-ketone (13) (4.9 g) in methanol (50 ml) was treated sequentially with sodium methoxide (1.35 g) and a buffered solution of titanium trichloride (15% w/v; 140 ml) in ammonium acetate (47 g in 145 ml of water). The mixture was stirred under nitrogen for 30 min with external cooling and then extracted with ether (5 × 100 ml). Washing (sodium hydrogen carbonate solution), drying, and evaporation gave the oily diketone (2.16 g), which was heated under reflux in benzene (100 ml) containing ethylene glycol (4.3 ml) and toluene-*p*-sulphonic acid (300 mg) with continuous removal of water for 1.5 h. Pouring into saturated aqueous sodium hydrogen carbonate extraction with ether, drying, and evaporation gave a product which was chromatographed on neutral alumina (75 g; grade II) with ether–light petroleum (1 : 9) to give the *acetal enone* (14) (1.68 g), m.p. 100–103° (from ether) (Found: C, 69.2; H, 7.9%; $M^+$, 208. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%; $M$, 208), $\nu_{max.}$ ($CHCl_3$) 1 710, 1 645, and 1 060 $cm^{-1}$, $\lambda_{max.}$ 255 nm (log ε 3.98), τ ($CDCl_3$) 7.91 (3 H, d, $J$ 1.5 Hz, $CH_3$·C=C), 7.6—8.6 (8 H, m), 7.12 (1 H, m, CH), and 6.1 (4 H, s, O·$[CH_2]_2$O).

4,4-*Ethylenedioxy*-7,7-*dimethylperhydroinden*-1-*one* (15).—An oven-dried 250 ml, three-necked flask with a serum cap and perforated dropping funnel (also with a serum

[21] W. D. S. Bowering, V. M. Clark, R. S. Thakur, and Lord Todd, *Annalen*, 1963, **669**, 106.

[22] C. H. De Puy and K. L. Eilers, *Org. Synth.*, Coll. Vol. 5, 1973, p. 326.

cap) was cooled to 20 °C in a stream of argon. Copper(I) iodide (4.56 g) was introduced and the flask placed under a static argon atmosphere. Dry ether (50 ml) was added by syringe and the stirred suspension was cooled to −5 °C. Ethereal methyl-lithium (2M; 24 ml) was added dropwise by syringe to give a clear tan-coloured solution. The acetal enone (14) (4.16 g) in dry ether (80 ml) was syringed into the dropping funnel and added dropwise over 30 min to the stirred lithium dimethylcuprate solution. The funnel was washed through with dry ether (20 ml) and the yellow suspension stirred at −5 °C for a further 2 h. Pouring into stirred saturated aqueous ammonium chloride (400 ml), extraction with ether (4 × 200 ml), washing (brine), drying, and removal of solvent gave a yellow oil which slowly solidified. Crystallisation from light petroleum followed by chromatography of the mother liquors (silica gel; 1 : 9 ether–light petroleum) gave the *acetal ketone* (15) (3.49 g, 78%), m.p. 90—93° (Found: C, 69.7; H, 9.1%; $M^+$, 224. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%; $M$, 224), $\nu_{max.}$ ($CHCl_3$) 1 745 and 1 040 $cm^{-1}$, $\tau$ ($CDCl_3$) 8.76 and 9.07 (6 H, 2s, $CMe_2$), 7.6—8.6 (10 H, m), and 6.07 (4 H, s, O·$[CH_2]_2$O).

*Methyl 4,4-Ethylenedioxy-2-methoxycarbonyl-7,7-dimethyl-1-oxoperhydroinden-2-ylacetate* (16).—A solution of the acetal ketone (15) (1.12 g) in dimethylformamide (15 ml) and methoxymethylmagnesium carbonate (1.94M in dimethylformamide; 30 ml) was heated at 150 °C (bath temp.) under nitrogen for 6 h. The mixture was cooled to 20 °C and the solvent removed under reduced pressure to give a brown powder. This was cooled to −5 °C and N-hydrochloric acid was added slowly (to pH 2). The β-keto-acid was extracted with chilled ether (3 × 200 ml) and the extract treated with an excess of diazomethane. Washing (brine), drying, and evaporation gave the crude β-keto-ester, which was heated under reflux in acetone (30 ml) with methyl bromoacetate (0.8 g) and potassium carbonate (0.7 g) for 5 h. More methyl bromoacetate (0.8 g) was then added and the mixture heated for a further 3 h. The acetone was removed under reduced pressure, water (20 ml) was added, and the mixture was extracted with dichloromethane (3 × 100 ml). Washing with water, drying, and evaporation gave the two diastereoisomers of the diester (16) as a semi-solid mass (1.5 g) suitable for submitting directly to the following stage. The two isomers could be separated by p.l.c. on silica with ether–light petroleum (7 : 3). The faster-moving *diester* isomer ($R_F$ 0.34) had m.p. 180—181° (from ethyl acetate–light petroleum) (Found: C, 61.3; H, 7.3%; $M^+$, 354. $C_{18}H_{26}O_7$ requires C, 61.0; H, 7.4%; $M$, 354), $\nu_{max.}$ ($CHCl_3$) 1 735 $cm^{-1}$, $\tau$ ($CDCl_3$) 8.8 and 9.09 (6 H, 2s, $CMe_2$), 6.88—8.68 (10 H, m), 6.3 and 6.36 (6 H, 2s, 2 × $CO_2Me$), 6.01 (4 H, m, O·$[CH_2]_2$O). The slower moving *diester* isomer ($R_F$ 0.26) had m.p. 120—122° (from ethyl acetate–light petroleum) (Found: C, 61.0; H, 7.4%; $M^+$, 354), $\nu_{max.}$ ($CHCl_3$) 1 735 $cm^{-1}$, $\tau$ ($CDCl_3$) 8.94 (6 H, s, $CMe_2$), 6.88—8.50 (10 H, m), 6.17 and 6.25 (6 H, 2s, 2 × $CO_2Me$), and 6.05 (4 H, m, O·$[CH_2]_2$O).

*7,7-Dimethyl-1,4-dioxo-$\Delta^{3a(7a)}$-hexahydroinden-2-ylacetic Acid* (17).—A solution of the crude diester (16) (1.5 g) in 1,2-dimethoxyethane (30 ml) and sulphuric acid (5%; 30 ml) was heated under reflux for 96 h under a static oxygen atmosphere. The cooled mixture was poured into water (50 ml) and extracted with ether (4 × 50 ml). The ether layer was washed with aqueous sodium hydrogen carbonate (4 × 25 ml), and the washings were taken to pH 2 with sulphuric acid (5%) and then extracted with dichloromethane (4 × 60 ml). Washing (water), drying, and evaporation gave a product which was crystallised, first from toluene at −5 °C then from benzene, to give the *diketo-acid* [6] (17) (450 mg), m.p. 136—138° (Found: C, 66.2; H, 6.9%; $M^+$, 236. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%; $M$, 236), $\nu_{max.}$ ($CHCl_3$) 3 600—2 500, 1 710, and 1 685 $cm^{-1}$, $\lambda_{max.}$ 260 nm (log $\varepsilon$ 4.08), $\tau$ ($CDCl_3$) 8.69 and 8.71 (6 H, 2s, $CMe_2$), 8.07 (2H, m), 6.80—7.74 (7 H, m), and −0.6br (1 H, removed by $D_2O$, $CO_2H$). Reduction [6] of this diketo-acid with di-isobutylaluminium hydride gave the two epimers of the hydroxy-lactone (9) identical with those obtained by the above synthetic route.

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