Synthesis of 4-Hydroxy-2,5-dimethylfuran-3(2H)-one (Furaneol) from (2R,3R)-Tartaric Acid

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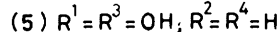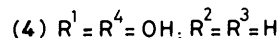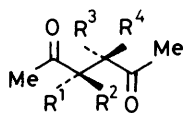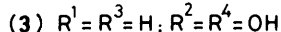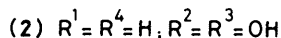*School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ*
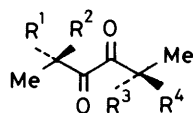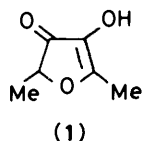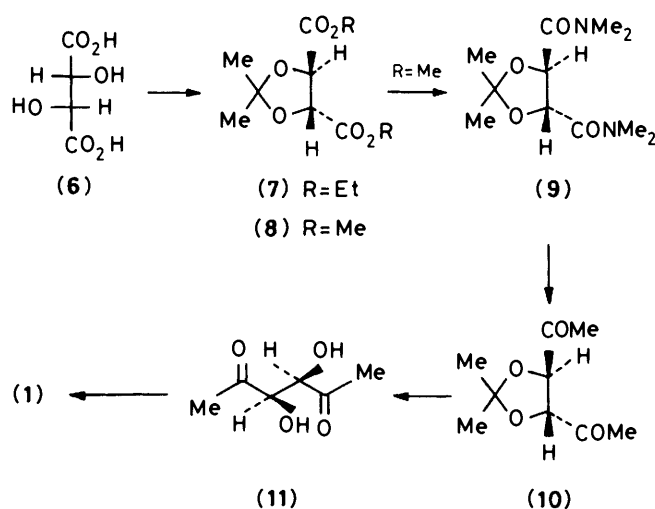**Haydn F. Jones**
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(2R,3R)-Tartaric acid (6) has been converted through a five-step sequence into the important volatile flavour and aroma component 4-hydroxy-2,5-dimethylfuran-3(2H)-one (furaneol) (1) in 18.5% overall yield. The key step involves the formation of (4R,5R)-4,5-diacetyl-2,2-dimethyl-1,3-dioxolane (10) by reaction of methylmagnesium chloride with the corresponding 4,5-bis(dimethyl-amide). The same dioxolane (10) was also prepared via a related reaction sequence involving a Grignard type reaction on the corresponding dinitrile.

The fact that 4-hydroxy-2,5-dimethylfuran-3(2H)-one † (1) is an important volatile flavour and aroma component of a range of fruits, such as pineapple,[1] strawberry,[2] and mango,[3] and of food products such as beef broth,[4] sponge-cake,[5] and roasted coffee,[6] has made it an attractive target for synthesis, since the furanone clearly has a considerable number of applications in the food industry. Syntheses of the furanone have been reported from a diverse range of starting materials, including L-rhamnose,[7] dimethyl diglycolate,[8] methylglyoxal,[9,10] 2,5-di-methylfuran,[10] hexane-3,4-dione,[10] and hex-3-yne-2,5-diol,[11] and there are a large number of patents covering its preparation from readily available starting materials.[12]

Retrosynthetic analysis indicates a variety of possible approaches for synthesis of the ring system in (1), one of the most general of which involves cyclization of a suitable six-carbon, 2,5-oxygenated acyclic precursor. Thus, treatment of a mixture of *erythro*- and *threo*-2,5-dihydroxy-hexane-3,4-dione ‡ [(2) and (3), respectively] with aqueous oxalic acid,[11] and treatment of

(1)

(2) R¹ = R⁴ = H; R² = R³ = OH

(3) R¹ = R³ = H; R² = R⁴ = OH

(4) R¹ = R⁴ = OH; R² = R³ = H

(5) R¹ = R³ = OH; R² = R⁴ = H

erythro- and *threo*-3,4-dihydroxyhexane-2,5-dione ‡ [(4) and (5), respectively] with aqueous disodium hydrogen phosphate[10] afforded the furanone (1) in reasonable yields; cyclization of (4) also occurred smoothly to (1) in aqueous sodium hydrogen carbonate.[10] Here, we report the preparation of (4R,5R)-4,5-diacetyl-2,2-dimethyl-1,3-dioxolane (10) from (2R,3R)-tartaric acid (6), and its conversion, via (3R,4R)-3,4-dihydroxyhexane-2,5-dione (11) into the furanone (1) (Scheme 1). Although this

Scheme 1.

synthetic approach might be currently regarded as unfashionable, since it involves destruction of chirality, the favourably low cost of (2R, 3R)-tartaric acid relative to other useful starting materials makes a synthetic process based upon it attractive, if an efficient and simple process for the CO_2H to COMe conversion can be developed for the dicarboxylic acid.

Initially, we hoped that treatment of (6) with an excess of methyl-lithium might achieve its direct conversion[13] into (11). Reaction of dipotassium (4R,5R)-2,2-dimethyl-1,3-dioxolane 4,5-dicarboxylate § [prepared by saponification of the corresponding diethyl ester (7)[14] with aqueous potassium hydroxide] with methyl-lithium gave a complex mixture of products in which the hexane-2,5-dione derivative could not be detected. The difficulty of controlling the reaction of an ester with an organometallic reagent to afford a ketone in reasonable yield[15] weighed against the direct use of a suitably protected ester such as (4R,5R)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (8)[16,17] in the chain-lengthening step.¶ On the other hand,

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† Furaneol is the registered trade mark of Firmenich S.A., Switzerland, for this furanone.

‡ Only one enantiomer of the *threo*-isomer is depicted.

§ The salt of the protected derivative of (2R,3R)-tartaric acid was chosen, rather than that of the free acid, to obtain maximum solubility of the substrate in the organic medium.

¶ A procedure[18] for the synthesis of alkyl ketones from carboxylic esters by reaction of the ester with a Grignard reagent in the presence of triethylamine is only satisfactory, generally, when the ester does not have an enolizable α-hydrogen atom; the methyl ester (8) readily forms an enolate on treatment with lithium di-isopropylamide in tetrahydro-furan–hexamethylphosphoric triamide solvent.[19]

the necessity of minimising the costs and maintaining the simplicity of a potentially useful route to (1) led us to avoid several established, and some newer but seemingly useful methods for the conversion of acid derivatives into ketones; examples of such methods are the reaction of organometallic compounds with acyl halides,[20,21]* with imidazolides,[24] with pyridine-2-thiol esters,[25,26] with mixed anhydrides,[27] with N-methyl-N-methoxyamides,[28] with N-methyl-N-(2-pyridyl)-amides,[29] and with N-acylaziridines.[30] However, the readily prepared[17] bis-amide (9) did appear to warrant investigation as a possible precursor of the dione (10). There is ample indication in the literature† that N,N-dialkylamides react with alkyl-lithiums[32–34] and Grignard reagents[35] to give carbonyl compounds, and particularly relevant is the reported synthesis[36] of 1,4- and 1,5-diketones from N,N,N',N'-tetramethylsuccinimide and N,N,N',N'-tetramethylglutaramide, respectively, and organolithium reagents. It was noted,[36] however, that although the tetramethyldiamides [(12), Scheme 2] reacted instantly with
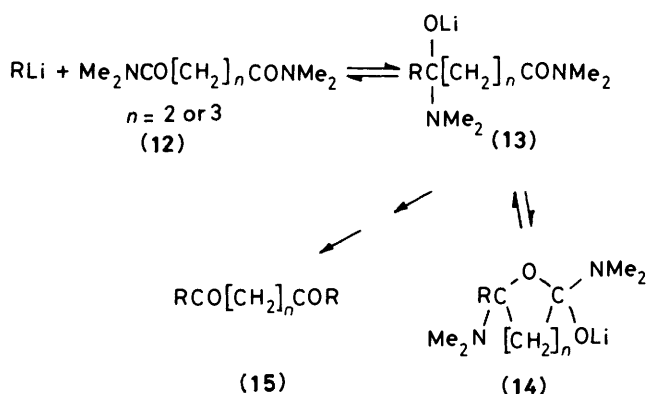
Scheme 2.

the organolithium reagent, the appearance of the diketone (15) often took a considerable time, a fact that was attributed to cyclization of the mono-addition product (13) to give a relatively stable intermediate (14). A related result[37] is the formation of 3-oxo-N,N-diethylhexanamide (EtCO·CH₂CH₂·-CONEt₂) in 63% yield and octane-3,6-dione in only 3% yield on reaction of N,N,N',N'-tetraethylsuccinimide with an excess of ethylmagnesium bromide. Clearly, the trans-relationship of the N,N-dimethylcarboxamide groups about the 1,3-dioxolane ring in (9) would be expected to disfavour cyclization compared with an acyclic analogue, suggesting that the diketone formation might be particularly favoured in such derivatives of (2R,3R)-tartaric acid on reaction with organometallic reagents.

Treatment[17] of the diester (8) with dimethylamine in methanol afforded the crystalline diamide (9) in 94% yield, and this was allowed to react in tetrahydrofuran solution, at room temperature with commercially available methylmagnesium

chloride to afford, after column chromatography, the dioxolane (10) in 50% yield. A minor product, identified solely on its spectral properties was the dioxolane (16).

(16)   (17)
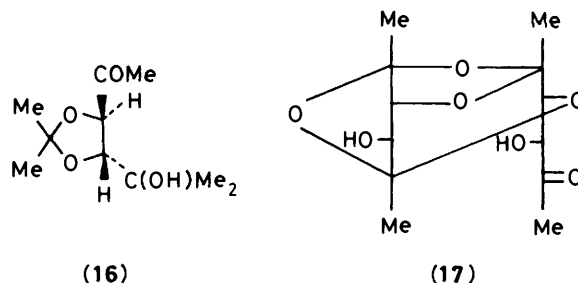
We have reported previously[38] on the acidic hydrolysis of the acetal (10) in 9:1 (v/v) trifluoroacetic acid–water, which afforded the highly crystalline self-condensation product (17), m.p. 199—201 °C, rather than the expected (3R,4R)-3,4-dihydroxyhexane-2,5-dione (11), on attempted crystallisation of the crude hydrolysis product from ethyl acetate or methanol. Subsequently, we found that trituration of this crude hydrolysis product with dry, cold diethyl ether left, as residual crystalline material, the crude dihydroxy dione (11), m.p. 75—78 °C, which on attempted recrystallisation was rapidly converted into the relatively insoluble self-condensation product (17). Although ¹H and ¹³C n.m.r. spectra consistent with the structure (11) could be obtained by rapid measurement in deuteriochloroform solution, precipitation of (17) occurred rapidly at probe temperature. In view of this relative instability,‡ the crude dihydroxy dione (11) was used directly for further transformation.

Several catalysts have been used to bring about cyclization of 3,4-dihydroxy-2,5-diones to the furanone (1), but a preferred one appears to be piperidinium acetate.[40] When an aqueous solution of the crude dihydroxy dione (11) containing piperidinium acetate was heated under reflux for 7 days, the furanone (1) was the major product, as indicated by g.l.c. Extraction of the aqueous solution with diethyl ether, and sublimation of the product so obtained, afforded the furanone (1) in 48% yield, which gave an i.r. spectrum indistinguishable from that of an authentic sample made from L-rhamnose.[7]

Since ketones may be prepared by addition of Grignard reagents to nitriles[41] and subsequent hydrolysis of the reaction product, and since precedent exists for the preparation of diketones from α,ω-dicyanoalkanes,[42] we investigated the use of the dinitrile (18) as a precursor of the dihydroxy dione (10). The highly crystalline dinitrile (18) was readily prepared in good yield by dehydration of the diamide (19)§ through treatment of

(18)   (19)
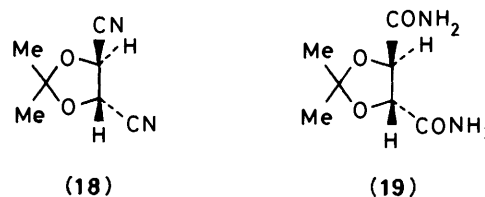
* A recently reported[22] improvement in the synthesis of ketones by reaction of Grignard reagents with acyl chlorides involves the use of tetrahydrofuran as solvent in a low temperature (−78 °C) reaction. The method has been used in a slightly modified form for the preparation of functionalised ketones.[23] In our hands, the reaction between n-hexylmagnesium bromide and n-butyryl chloride, which was reported[22] to afford decan-4-one in 95% isolated yield, consistently gave this ketone in yields (estimated by g.l.c.) of approximately 40%.

† After completion of our work, an important preparation of aldehydes and ketones from N,N-dimethylamides and Grignard reagents was reported.[31]

‡ It seems astonishing, in view of the extremely facile condensation of (11) to (17), that a similar reaction was not encountered by previous workers, who prepared the racemic form of the 3,4-dihydroxy dione,[10] or what appears to be the (3S,4S)-isomer of (11).[39] However, it is clear that under suitable conditions (11) and (17) may be readily interconverted. Thus, the ¹H n.m.r. spectrum of the solution obtained by dissolving (17) in trifluoroacetic acid and then adding deuterium oxide to give a 9:1 (v/v) CF₃CO₂H–D₂O mixture, showed only signals attributable to (11).

§ This chiral diamide has not, to our knowledge, been reported, although the racemic and meso forms of 2,3-O-isopropylidene-tartaramide are known.[43]

the latter with benzenesulphonyl chloride.[44] Surprisingly, the dinitrile (18) did not show an absorption in or near the region 2 240—2 260 cm^{-1} in its i.r. spectrum, but its laser Raman spectrum showed a strong peak at 2 250 cm^{-1}. Another noteworthy property of (18) was its resistance to hydrolysis by trifluoroacetic acid–water, an acidic medium which normally brings about ready hydrolysis of the type of acetal group present in this compound.[45]

Reaction of the dinitrile (18) with a suspension of methylmagnesium iodide in toluene containing 1 molar equivalent of diethyl ether with respect to the Grignard reagent, afforded the dione (10) in 43% yield. It should be noted that the use of benzene containing 1 equivalent of diethyl ether as a solvent in Grignard reactions on nitriles has been reported[46] to lead to increased yields of ketones compared with similar reactions performed in diethyl ether.

Of the two routes to the furanone (1) from (2R,3R)-tartaric acid reported here, the higher yielding, shorter one proceeding via the bis(dimethylamide) (9) (18.5% overall yield in five steps) is clearly preferable to that proceeding via the dinitrile (18) (9.3% over six steps).

Experimental

[13]C N.m.r. spectra were recorded at ca. 27 °C using a JEOL FX-100 spectrometer at 25.05 MHz in [²H]chloroform unless stated otherwise; generally, the spectra were recorded at a sweep width of 6 024 Hz and chemical shifts (δ_C) are measured from SiMe$_4$. [1]H N.m.r. spectra were recorded at 60 MHz on a Perkin-Elmer R12 spectrometer or a JEOL PMX60SI spectrometer in [²H]chloroform unless indicated otherwise, and chemical shifts (δ_H) are from SiMe$_4$. Rotations were measured with a Perkin-Elmer 141 polarimeter, for chloroform solutions, except that for (19), which was measured in water. The Raman spectrum was run on a Spex 1401 double monochromator spectrometer using 568.2 nm (Kr) excitation from a Coherent Radiation mixed gas laser.

Column chromatography was performed on Merck Kieselgel (70—230 mesh). Light petroleum refers to the fraction b.p. 60—80 °C. (4R,5R)-Diethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (7)[16,17] and (4R,5R)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (8)[16,17] (94% yield) were prepared from (2R,3R)-tartaric acid, and (4R,5R)-2,2N,N,N',N'-hexamethyl-1,3-dioxolane-4,5-dicarboxamide (9)[17] was prepared from the dimethyl ester (8), according to literature procedures. An authentic specimen of the furanone (1) was made[7] by treatment of L-rhamnose with piperidinium acetate in ethanol at 70—75 °C. Methylmagnesium chloride was purchased as an approximately 3M-solution in tetrahydrofuran from Aldrich Chemical Company Ltd or from Alfa Inorganics. Tetrahydrofuran was dried by heating under reflux with calcium hydride for 48h, followed by distillation from the hydride. Organic solutions were dried over anhydrous sodium sulphate.

(4R,5R)-4,5-*Diacetyl-2,2-methyl*-1,3-*dioxolane* (10).—A solution of (4R,5R)-2,2,N,N,N',N'-hexamethyl-1,3-dioxolane-4,5-dicarboxamide (4.88 g, 20 mmol) in dry tetrahydrofuran (25 ml) and a solution of methylmagnesium chloride (80 mmol) in tetrahydrofuran (30 ml) were added dropwise and simultaneously to a three-necked flask containing dry tetrahydrofuran (20 ml), at room temperature and under an atmosphere of dry nitrogen. The mixture was stirred throughout the addition, which was made over 10 min, and stirring was continued for a further 50 min. After this time the mixture was poured onto ice–water (100 g). Sufficient ammonium chloride was added to the slurry, with stirring, to dissolve the precipitate which had formed. The aqueous solution so obtained was extracted with dichloromethane (3 × 50 ml) and the combined extracts were washed, dried, and concentrated to give an oil, which was

subjected to column chromatography. Elution with toluene–ethyl acetate (20:1 v/v) afforded, as an oil, the major product, the dioxolane (10) (1.85 g, 50%), b.p. 44 °C at 0.025 mmHg; [α]$_D$ + 26° (c, 1.53) (Found: C, 58.3; H, 7.3. C$_9$H$_{14}$O$_4$ requires C, 58.0; H, 7.6%); δ_H 1.45 (6 H, s, CMe$_2$), 2.30 (6 H, s, 2 × MeCO), and 4.60 (2 H, s, 2 × HCOR); δ_C 26.2 (CMe$_2$), 26.4 (MeCO), 81.8 (HCOR), 112.5 (CMe$_2$), 206.3 (CO); ν$_{max}$.(film) 1 720 cm^{-1} (CO).

Further elution of the column gave, as a liquid, a second product (0.338 g), tentatively identified on the basis of its spectral properties as (4R,5R)-4-acetyl-5-(2-hydroxypropan-2-yl)-2,2-dimethyl-1,3-dioxolane (16); δ_H 1.15, 1.25, 1.30, 1.50 (4 × 3H, 4 × s, 4 × MeC), 2.30 (3 H, s, MeCO), 4.05 (1 H, d, HCOR); δ_C 25.6*, 26.2, 26.6 (5 × MeC), 70.1 (R$_3$COH), 81.5, 83.2 (HCOR), 110.3 (OCMe$_2$O), and 209.8 (CO); ν$_{max}$.(film) 3 500 (OH), and 1 725 cm^{-1} (CO).

Acidic Hydrolysis of (4R,5R)-4,5-*Diacetyl-2,2-dimethyl*-1,3-*dioxolane* (10).—A mixture of trifluoroacetic acid–water (9:1 v/v) (10 ml) was added to the acetal (10) (1 g, 5.4 mmol) at 0 °C. After storage of the mixture at this temperature for 10 min, the aqueous acid was removed under reduced pressure (bath temperature <30 °C) and the residue was triturated with diethyl ether (5 ml). The mixture was cooled to ca. −15 °C and the supernatant liquid was removed by means of a Pasteur pipette. The remaining solid was washed with diethyl ether (3 × 5 ml) at 0 °C, leaving as a crystalline solid, the major portion of the hydrolysis product (11). The ethereal supernatant liquid and the washings were combined, concentrated under reduced pressure, and the residue so obtained triturated and washed with diethyl ether, in a similar manner to that used for the initial residue, to afford a second crystalline portion of the hydrolysis product (11). The two portions were combined to give crude (3R,4R)-3,4-dihydroxyhexane-2,5-dione (11) (0.702 g, 89%), m.p. 75—78 °C; δ_H 2.35 (6 H, s, 2 × MeCO), 3.75 (2 H, s, OH), and 4.60 (2 H, s, HCOH); δ_C 23.4 (CMe), 77.4 (HCOH), and 205.3 (CO).† Attempted recrystallisation of this crude material from either ethyl acetate–light petroleum or from methanol gave the self-condensation product (17).[38]

4-*Hydroxy-2,5-dimethylfuran*-3(2H)-*one* (*Furaneol*) (1).— Piperidine (0.45 ml, 4.6 mmol) was added dropwise to a stirred solution of glacial acetic acid (0.37 g, 6.2 mmol) in distilled water (10 ml) at 20 °C, and crude (3R,4R)-3,4-dihydroxyhexane-2,5-dione (11) (0.73 g) was added. The mixture was heated under reflux in an atmosphere of nitrogen for 7 days and was then neutralised by the addition of 15% aqueous sodium hydroxide. The solution was extracted continuously with diethyl ether for 3 days and the dried extract was concentrated to afford a residue ‡ which was subjected to sublimation (bath temp. 85 °C/1 mmHg) to give the title product (0.306 g, 48%), m.p. 73—78 °C (lit, m.p. 70 °C,[1] 71 °C,[9] 75—78 °C,[8] 77—79 °C,[11] 78—80 °C,[10] 79.5—80.5 °C,[4] and 82—84 °C,[7]); δ_H 1.45 (3 H, d, J 7 Hz, MeCH), 2.25 (3 H, s, MeC=C), 4.45 (1 H, q, MeCH), and 6.45 (1 H, s, OH). The [1]H n.m.r. spectrum was identical with that of an authentic sample of (1) prepared from L-rhamnose, and agreed with the reported[10] spectrum. The i.r. spectrum was indistinguishable from that of an authentic sample made from L-rhamnose.

(4R,5R)-2,2-*Dimethyl*-1,3-*dioxolane*-4,5-*dicarboxamide* (19).—A mixture of the dimethyl ester (8) (20 g, 91 mmol), methanol (40 ml) and concentrated aqueous ammonia (200 ml)

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* This signal is of greater intensity than others in the group.

† On removal from the n.m.r. probe, the solution contained a precipitate, which was collected as a crystalline solid m.p. 199—201 °C, and identified as the self-condensation product (17).[38]

‡ Analysis of the residue by g.l.c. (Carbowax column at 220 °C) confirmed that the furanone (1) was the major product.

was stirred for 3 days at room temperature. The solution was then concentrated to dryness under reduced pressure and the solid residue was recrystallised from ethanol to give the diamide (19) (11.45 g, 66%), m.p. 157—160 °C, $[\alpha]_D$ −3.5° (c, 0.26 in H_2O) (Found: C, 44.7; H, 6.4; N, 14.6. $C_7H_{12}N_2O_4$ requires C, 44.7; H, 6.4; N, 14.9%); $\delta_H(D_2O$–$SiMe_4$ as external standard) 1.45 (6 H, s, CMe_2), 4.58 (2 H, s, 2 × HCOR); $\delta_C(D_2O$–$SiMe_4$ as external standard) 26.3 (CMe_2), 78.1 (HCOR), 114.7 (CMe_2), and 175.2 (CO).

(4R,5R)-2,2-*Dimethyl*-1,3-*dioxolane*-4,5-*dicarbonitrile* (18).— Benzenesulphonyl chloride (55 ml, 0.43 mol) was added dropwise to a stirred solution of the dicarboxamide (19) (9.4 g, 50 mmol) in dry pyridine at 0 °C. After 1 h, the cooling bath was removed and the reaction was stirred at room temperature for 7 days. The reaction mixture was then poured onto ice, and the resulting slurry was stirred for a further 2 h. The solid which formed was collected and recrystallised from ethanol to give the nitrile (6.12 g, 80.5%), m.p. 163—164 °C (sublimes above 120 °C); $[\alpha]_D$ −83° (c, 0.6) (Found: C, 55.2; H, 5.3; N, 18.2. $C_7H_8N_2O_2$ requires C, 55.3; H, 5.3; N, 18.4%); δ_H 1.65 (6 H, s, CMe_2) and 5.30 (2 H, s, 2 × HCOR); δ_C [(CD_3)$_2$CO] 26.6 (CMe_2), 68.7 (HCOR), and 117.1 (CN); $v_{max.}$(Nujol) no absorption near 2 260 or 1 690 cm^{-1}; the Raman spectrum shows absorption at 2 250 cm^{-1}.

Treatment of Dipotassium (4R,5R)-2,2-*Dimethyl*-1,3-*dioxolane*-4,5-*dicarboxylate with Methyl-lithium*.—A solution of potassium hydroxide (2.9 g, 52 mmol) in water (20 ml) was added to a stirred solution of (4R,5R)-diethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (4.92 g, 20 mmol) in ethanol (5 ml). The mixture was stirred for 24 h at room temperature, after which it was concentrated to dryness. Methanol was added to, and evaporated from the residue, and the latter was then extracted several times with absolute ethanol, and finally dried over phosphorous pentaoxide, *in vacuo*, to give the dipotassium salt.

To a stirred suspension of the dipotassium salt (0.532 g, 2 mmol) in diethyl ether (20 ml) at −78 °C, under nitrogen, was added a solution of methyl-lithium (8 mmol) in diethyl ether (10 ml), over a 2 h period. The reaction mixture was allowed to warm to room temperature over 3 h and it was then poured into ice–water. Sufficient 2M-hydrochloric acid was added to the mixture to dissolve the precipitate which had formed, and the aqueous solution was extracted with dichloromethane (3 × 100 ml). The combined organic extracts were washed with sodium hydrogen carbonate solution, dried, and concentrated. Examination of the product by t.l.c. indicated a number of products to be present, but the hexane-2,5-dione derivative (10) could not be detected.

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