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Synthetic Approaches to Either Homochiral or Achiral Derivatives of 3-Hydroxy-2(5*H*)-furanone (Isotetronic Acid)

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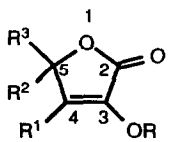
Abstract. *Several title compounds were synthesized according to new methods based either on the use of D-ribonolactone as a chiral precursor or on the cyclization of 2,4-dioxopentanoic acid as a suitable achiral precursor. Base-induced elimination and subsequent acid-promoted ring contraction is an efficient protocol for the preparation of isotetronic acids from 2-O-alkyl-3,4-O-benzylidene-D-ribono-1,5-lactone derivatives.*

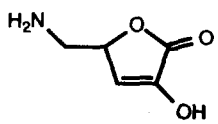
INTRODUCTION

The isotetronic acid derivatives possess the general structure **1** and have been isolated from a variety of natural sources.[1-3] Properties leading to their use as flavouring agents,[1] anti-depressants,[4] and perfumes[5] have been described, and analgesic[6] and antifungal[7] activity has been reported. Furthermore, the compound **2** has been synthesized as a GABA analogue.[8] All these products have as a common feature the presence of a chiral center at the *C-5* position of the furanone ring. On the other hand, achiral methylene isotetronic acids merit also to be considered. For instance, 3-hydroxy-5-methylene-2(5*H*)-furanone, **4**, is an undescribed interesting product whose formation has been postulated as a result of the oxidative degradation of RNA.[9a] This hypothesis may be sustained by the fact of detecting protoanemonin, **3**, among the degradation products from DNA.[9b]

Chart 1



1



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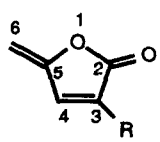
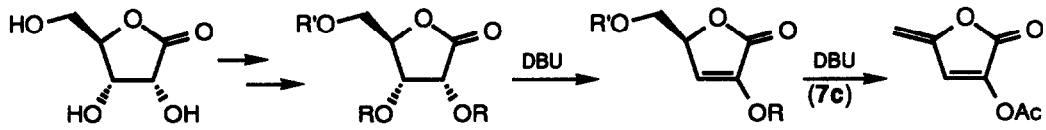


3 R = H
4 R = OH

Only few methods are reported in the literature for the synthesis of molecules such **1**, and **4** and their *O*-derivatives. The protocol affording the largest number and variety of such compounds has been published by Barrett[10] starting from D-ribonolactone, **5**, and is depicted in Scheme 1.



5 **6** **7a**: R=Ac, R'=Ph_3C **8**

7b: R=Ac, R'=Ph_2Bu^tSi

7c: R=R'=Ac

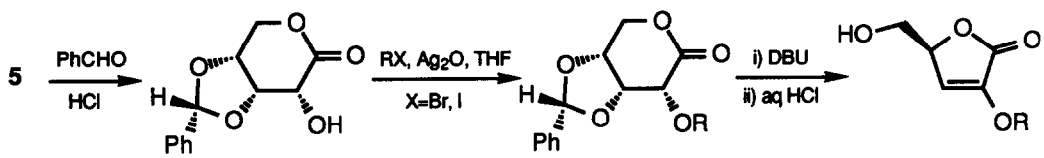
Scheme 1

In this paper we report and discuss our results on the synthesis of the title molecules. The methods employed are based on two main approaches: (a) Use of D-ribonolactone as a chiral cyclic precursor. (b) Cyclization of 2,4-dioxopentanoic acid as a suitable acyclic precursor.

RESULTS AND DISCUSSION

Synthesis of (S)-3-Hydroxy-5-hydroxymethyl-2(5H)-furanone and O-Derivatives.

The synthesis of several homochiral molecules with general structure **7** have been accomplished starting from D-ribonolactone as a source of chirality. The key step involves an elimination-rearrangement process from 2-*O*-alkyl-3,4-*O*-benzylidene derivatives **10a-c** to afford butenolides **11a-c** (Scheme 2).



9 **10a**: R=Bn **11a**: R=Bn

10b: R=Me **11b**: R=Me

10c: R=Bu **11c**: R=Bu

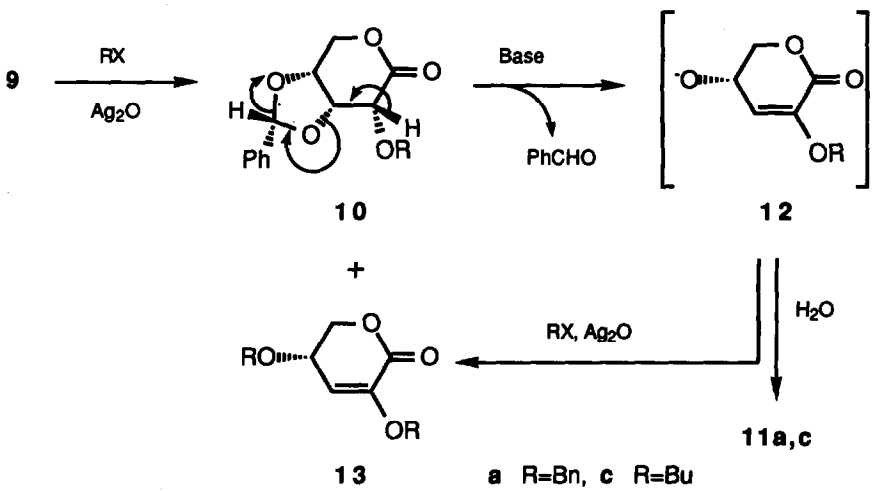
Scheme 2

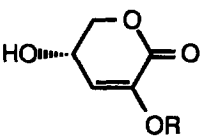
Lactone **11a** had previously been obtained by Weidmann through treatment of 5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone with sodium borohydride.[11]

The new ethers **10a-c** were obtained by reaction of **9**[12] with benzyl bromide, methyl iodide, and butyl iodide respectively in the presence of silver oxide, and using tetrahydrofuran as a solvent. The reaction with butyl iodide was much slower than the others: after eight days ether **10c** had been produced in only 32% yield. Remaining starting material and an unidentified by-product were also detected in the reaction mixture. The use of longer reaction times resulted in a lower recovery of unreacted **9** while the yield in **10c** was not substantially increased.

In the next synthetic step, base-induced elimination of benzaldehyde followed by hydrolysis afforded the alkoxy furanones **11a-c** in 75-85% yield. Several bases such as lithium trimethylsilyl amide, LDA, or NaH were tested, the optimal conditions being the use of DBU (1.2 eq) at room temperature. Lactone **11a** could also be prepared through elimination of acetone when the isopropylidene ketal, instead of the benzylidene ketal protection, was used.[13]

When alkylation reactions of **9** were performed in a large excess of alkylating agent, avoiding the use of a solvent, a mixture of δ-lactones was produced. Thus, we observed that a 3 : 2 mixture of benzyl ethers **10a** and **13a** was obtained in 90% total yield from **9** (Scheme 3). This fact can be attributed to the action of the slightly basic silver oxide. A similar result was obtained when **9** was reacted with butyl iodide and silver oxide,





13'b R=Me

13'c R=Bu

Scheme 3

affording ethers **10c** and **13c** in a 3.5 : 1 ratio, along with unreacted **9**. Thereby, base-induced elimination of benzaldehyde could lead to the formation of the alkoxy anion **12** which was trapped giving **13a** or **13c**, under the reaction conditions.

When isolated **10a** was treated with a base however, the final hydrolysis of the reaction mixture, containing **12**, could provoke the rearrangement of the 1,5-lactone to the 1,4-lactone **11a**. This hypothesis agrees with the isolation of pyrone **13'b** as the only identified product from reaction between lactone **10b** and DBU, when hydrolysis of the reaction mixture was omitted (see Experimental Section). This product was characterized by its spectral data; for instance, the ^{1}H NMR spectrum shows a characteristic signal at δ 5.76 (d, J=5.6 Hz) for vinylic H_4, while furanone **11b** gives a signal at δ 6.03 (d, J=2.1 Hz) for H_4. Similarly, pyrone **13'c** was detected in the reaction mixture from **10c**, previous to hydrolysis. Therefore, all these findings seem to corroborate the above mechanistic outcome for the overall process.

Attempts to obtain butenolide **14** (Scheme 4) directly from **9** failed since treatment of **9** with LDA under several conditions, and subsequent acid hydrolysis, led always to the formation of unidentified materials.

This method is not of general application to other D-ribonolactone benzylidene derivatives, bearing ester, halide or azido substituents at the *C-2* position. In such cases, butenolides were obtained in very poor yields, or they were not detected. On the contrary, when a carbamoyl amino group was the substituent at such a position, the corresponding butenolide was obtained in 55% yield by using NaH as a base.[14]

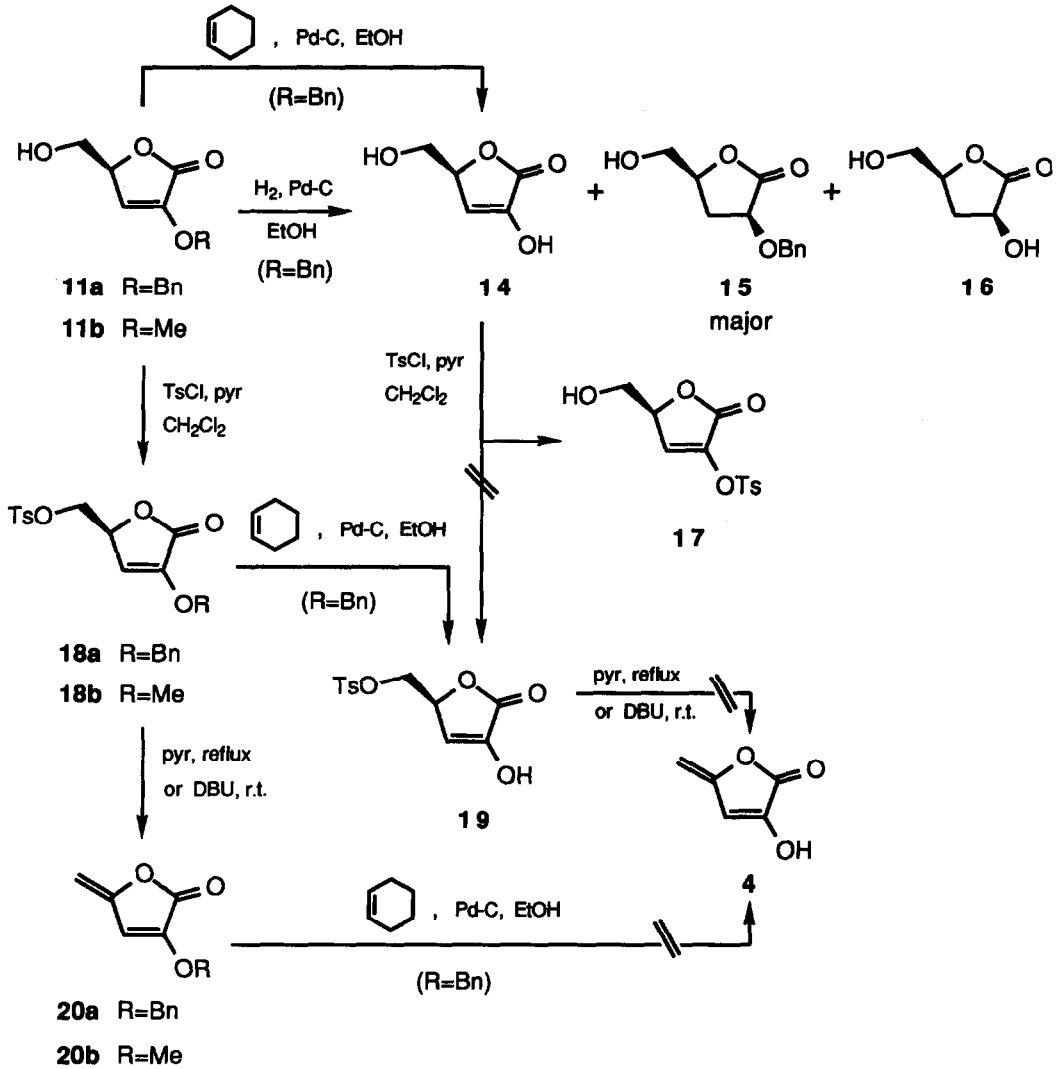
Several transformations were performed on compounds **11a,b** in order to synthesize other isotetronic acids (Scheme 4). For instance, hydrogenation of **11a** at atmospheric pressure in the presence of 5% Pd-C furnished a mixture of lactones **14-16** in which **15** was the major product (23% yield). Butyrolactone **16** was a known compound and its spectral data compared well with those reported previously.[15] Products **14** and **15** were new; although butenolide **14** could not be conveniently purified for microanalysis, it was completely identified by means of spectroscopic techniques (^{1}H and ^{13}C NMR, IR and MS, see Experimental Section). Compound **15** was fully characterized and gave satisfactory microanalysis. These results revealed a competition between the reduction of the C-C double bond and the hydrogenolysis of the benzyl ether in **11a**, despite of the results described by Caine on the chemoselective reaction of a benzyl ether group as substituent in an unsaturated lactone.[16]

The use of ammonium formate and 10% Pd-C[17] did not give indeed satisfactory results, and attempts to remove the benzyl group by using BCl_3[18] also failed. However, reaction of **11a** with cyclohexene and 10% Pd-C in ethanol[19] afforded quantitatively dihydroxybutenolide **14**.

Bearing in mind a possible synthesis of **4**, compound **14** was treated with tosyl chloride (1 eq) in order to get a primary tosylate, with a view to obtaining **4** under elimination conditions. Instead of the desired product **19**, only the enol tosylate **17** was obtained in 30% yield, showing that reactivity of the enol towards tosylation clearly predominates over that of the primary alcohol. Preparation of **19** was achieved following an alternative route depicted in Scheme 4: alcohol **11a** was tosylated affording butenolide **18a** which by treatment with cyclohexene and 10% Pd-C afforded tosylate **19** in 64% yield (two steps).

On the other hand, tosylate **18b** was prepared from alcohol **11b**. The use of compounds **11a,b** and **19** as potential synthetic precursors of 5-methylenefuranones **20a,b** and **4**, respectively, is discussed below.

Therefore, the method described herein to synthesize tetronic acids from 1,5-D-ribonolactone ketal derivatives **10a,c** shows more verstility than that described by Barrett[10] in the sense that the elimination-



Scheme 4

rearrangement process affords a butenolide with the desired alkoxy susbstituent at *C-2*, while the hydroxyl group at *C-4* remains free. Thereby, this functional group can be submitted to later transformations in order to furnish other homochiral or achiral lactones.

Synthetic Approaches to 3-Hydroxy-5-methylene-2(5H)-furanone and Derivatives.

Four strategies were envisaged in order to accomplish the synthesis of the title compounds: (i) Base-promoted elimination of *p*-toluenesulfonic acid from butenolides **18a,b**. (ii) Cyclization of 2,4-dioxopentanoic

acid **21a** or its ethyl ester **21b**. (iii) Deprotection of the hydroxyl group at *C-3* in *O*-acetyl isotetronic acid, **8**, in order to obtain the parent compound **4**. (iv) Hydroxylation at *C-3* in protoanemonin, **3**.

According to the first methodology, reaction between tosylate **18a** and anhydrous refluxing pyridine afforded the new compound **20a** in 71% yield. In a similar manner, **18b** gave **20b**. Nevertheless, attempts to obtain **4** from **19**, through an elimination process, failed. Furthermore, treatment of the benzyl derivative **20a** with cyclohexene and Pd-C to try the hydrogenolysis of the benzyl ether was also fruitless (Scheme 4).

On the other hand, the synthesis of methylene isotetronic acids from an acyclic precursor was very attractive because of the commercial availability and low price of ethyl 2,4-dioxopentanoate, **21b** (Scheme 5). Moreover, 2,4-dioxopentanoic acid **21a** was easily prepared according to the method described by Guthrie, who determined the enol form represented in Scheme 5 to be the major tautomer for this comopund in organic solvents.[20]

There are some methods described in the bibliography to obtain 4-hydroxy-2-pyrones from β,δ-diketoacids. Ohta *et al.* used successfully 1,1'-carbonyldiimidazole as a dehydrating agent,[21] but a mixture of unidentified materials was obtained by applying this method to **21a**. Moreno-Mañas *et al.* achieved the cyclization of β,δ-diketoesters by using DBU in refluxing benzene.[22] Nevertheless, ester **21b** remained unaltered under these conditions, and only polymers were formed at higher temperature.

In contrast, reaction between acid **21a** and excess acetic anhydride in the presence of catalytic sulfuric acid at room temperature for 20 minutes afforded lactone **8** in 50% yield (Scheme 5). These reaction conditions were similar, although milder, to those employed by Shaw in the synthesis of protoanemonin, **3**, from β-acetylacrylic acid.[23] This one-pot synthesis of **8** is interesting due to its simplicity and low economic cost.

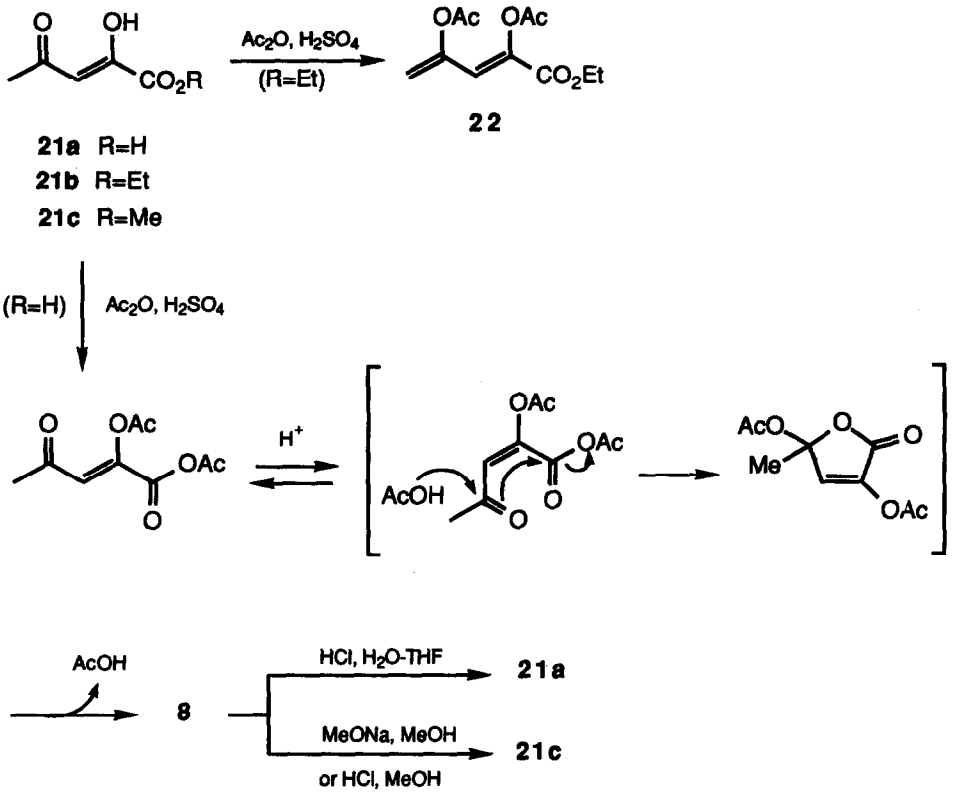
Instead, dienoate **22** was produced in 21% when the reaction was performed on the ethyl ester **21b** at 80 °C, the starting material remaining unaltered at lower temperature. The new oily product **22** was mainly identified from its ^{1}H NMR spectrum. It shows significant signals for the two vinyl protons, as an AB system centered at 5.27 ppm, and for H_3 as a singlet at 6.83 ppm. The fact that cyclization occurred from the free acid and did not from the ester **21b** agrees with the accepted mechanism for the formation of **3** according to the method reported by Shaw.[23,24] By analogy, acid **21a** could react with acetic anhydride in the presence of sulfuric acid to produce a mixed anhydride which must evolve towards the cyclic final product (Scheme 5).

Several methods were tried to remove the acetyl group in order to obtain hydroxylactone **4** from **8**. Acid **21a** was the only product formed however, when **8** was treated with HCl in$THF-H_2O$. Furthermore, the metyl ester **27c** was almost quantitatively obtained when lactone **8** was treated with sodium methoxide in methanol or with HCl saturated methanol, but compound **4** was never detected.

To sum up, when the *C-3* hydroxyl group in methylene isotetronic acid was protected as an acetate or an ether function, the resultant derivatives were fairly stable and they were synthesized in rather satisfactory yields. However, removal of the acetate function in **8** was always accompanied by lactone-ring-opening to give an acyclic acid or ester, depending on the reaction conditions (*vide supra*). These results led to conclude that hydroxylactone **4** should be much less stable than the related dioxoacid **21a** or its ester derivatives. Consequently, this relative stability must be the driving force that induces the rapid conversion of **4** into open-chain products, thus precluding the detection of that compound.

Finally, direct hydroxylation at the *C-3* position in protoanemonin, **3**, was attempted. LDA-induced formation of a vinyl anion and subsequent oxidation with trimethyl borate and hydrogen peroxide is a method

successfully applied to the hydroxylation of tetronic acids.[25] Unfortunately, the only identified product obtained in our case was β-acetylacrylic acid.



Scheme 5

EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240-400 mesh). Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (o.t.) being reported. Electron-impact (EI) mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale).

General procedure for the alkylation of the hydroxylactone 9: Ethers 10a-c, 13a and 13c. *Method (a): use of tetrahydrofuran as a solvent.* A typical experiment was run as follows. A light-protected mixture of compound **9**[12] (750 mg, 3.2 mmol), methyl iodide (2 mL, 32.1 mmol), and silver oxide (2.2 g, 9.6 mmol), in anhydrous tetrahydrofuran, was stirred at room temperature for four days. Then dichloromethane (300 mL) was added and the suspension was filtered through celite and evaporated to dryness giving a white solid which was purified by crystallization to afford pure ether **10b.** *Method (b): whithout solvent.* A typical

experiment was run as follows. A light-protected mixture of compound **9** (197 mg, 0.83 mmol), benzyl bromide (25 mL), and silver oxide (1.28 g, 5.52 mmol) was stirred at room temperature for six days. The suspension was subsequently diluted with dichloromethane (100 mL), filtered, and evaporated to dryness. The residue was chromatographed (mixtures of hexane-ethyl acetate) to afford compounds **10a** and **12a**.

2-*O*-Benzyl-3,4-*O*-(*R*)-benzylidene-δ-D-ribonolactone, 10a. *Method (a)*: 1.6 g, 60% yield; *method (b)*: 143 mg, 53% yield. Crystals, m.p. 178-180 °C (from acetone-hexane); $[\alpha]_D$ -123.1 (c 1.17, DMF); IR (KBr) 1745 cm^{-1}; MS (CI, isobutane), *m/e* 327 (M+1); MS (EI), *m/e* 220 (12), 129 (15), 105 (28), 97 (42), 91 (100), 77 (27), 66 (22),; 400-MHz ^1H NMR (DMSO-d_6) 4.35 (d, $J_{5,5'}$=13.2 Hz, H_5), 4.43 (dd, $J_{5'5}$=13.2 Hz, $J_{5',4}$=1.7 Hz, $H_{5'}$), 4.58 (d, $J_{7,7'}$=11.5 Hz, H_7), 4.68 (m, H_2 and H_4), 4.83 (d, $J_{7',7}$=11.5 Hz, $H_{7'}$), 4.85 (dd, $J_{3,4}$=8.2 Hz, $J_{3,2}$=3.2 Hz, H_3), 5.74 (s, H_6), 7.36 (m, 10 H, H_{Ar}); 62.5-MHz ^{13}C NMR (DMSO-d_6) 169.6 (C_1), 137.9 and 136.1 (C_{Ar} *ipso*), 129.9, 128.4, 127.8, and127.3 (C_{Ar}), 103.0 (C_6), 75.4, 74.9, and 73.6 (C_2, C_3, and C_4), 72.1 (C_7), 67.2 (C_5). Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.64; H, 5.63.

2-*O*-Methyl-3,4-*O*-(*R*)-benzylidene-δ-D-ribonolactone, 10b. *Method (a)*: 646 mg, 81% yield . Crystals, m.p. 189-191 °C; $[\alpha]_D$ -143.3 (c 1.34, acetone); IR (KBr) 1764 cm-1; MS, *m/e* 250 (M, 10), 144 (100), 106 (46), 105 (81), 85 (29), 78 (22), 77 (80), 71 (57), 51 (37); 400-MHz ^1H NMR (DMSO-d_6) 3.45 (s, 3 H, CH_3), 4.33 (d, $J_{5,5'}$=13.1 Hz, H_5), 4.41 (d, $J_{5',5}$=13.1 Hz, $H_{5'}$), 4.46 (d, $J_{2,3}$=3.1 Hz, H_2), 4.66 (d, $J_{4,3}$=8.1 Hz, H_4), 4.82 (dd, $J_{3,4}$=8.1 Hz, $J_{3,2}$=3.1 Hz, H_3), 5.74 (s, H_6), 7.40 (s, 5 H, H_{Ar}); 100-MHz ^{13}C NMR (DMSO-d_6) 169.4 (C_1), 136.1 (C_{Ar} *ipso*), 129.9, 128.3, and 127.2 (C_{Ar}), 102.9 (C_6), 76.2, 74.9, and 73.5 (C_2, C_3, and C_4), 67.0 (C_5), 58.1 (CH_3). Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.46; H, 5.64. Found: C, 62.37; H, 5.68.

2-*O*-Butyl-3,4-*O*-(*R*)-benzylidene-δ-D-ribonolactone, 10c. *Method (a)*: 32% yield; *method (b)* 35% yield. Crystals, m.p. 98-99 °C (from ethyl acetate-pentane); $[\alpha]_D$ -91.5 (c 3.52, $CHCl_3$); IR (KBr) 1771 cm^{-1}; MS, *m/e* 292 (M, 4), 220 (12), 186 (85), 141 (31), 130 (77), 106 (66), 105 (100), 77 (85), 57 (76), 41 (47); 250 ^1H NMR ($CDCl_3$) 0.89 (t, J=7.3 Hz, 3 H, CH_3), 1.39 (m, 2 H), 1.65 (m, 2 H), 3.50 (dt , J=9.0 Hz, J'=6.7 Hz, 1 H), 4.00 (dt, J=9.0 Hz, J'=6.7 Hz, 1 H), 4.08 (d, $J_{2,3}$=3.0 Hz, H_2), 4.21 (d, $J_{5,5'}$=13.3 Hz, H_5), 4.50 (d, $J_{5',5}$=13.3 Hz, $H_{5'}$), 4.60 (d, $J_{4,3}$=8.0 Hz, H_4), 4.83 (dd, $J_{3,4}$=8.0 Hz, $J_{3,2}$=3.0 Hz, H_3), 5.74 (s, H_6), 7.39 (m, 5 H, H_{Ar}); 62.5-MHz ^{13}C NMR ($CDCl_3$) 168.5 (C_1), 134.8 (C_{Ar} *ipso*), 130.0, 128.3, and 127.3 (C_{Ar}), 104.4 (C_6), 75.6, 75.1, and 73.3 (C_2, C_3, and C_4), 71.8 (OCH_2), 67.2 (C_5), 31.4, 19.0, 13.7 (CH_3). Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.65; H, 6.99.

(*S*)-3,5-Dibenzyloxy-5,6-dihydro-2-pyrone, 13a: *Method (b)*: 91 mg, 35% yield. Oil, $[\alpha]_D$ +55.0 (c 1.38, $CHCl_3$); IR (film) 1740, 1635 cm^{-1}; MS, *m/e* 310 (M, 1.3), 219 (14), 91 (100), 65 (35); 80-MHz ^1H NMR ($CDCl_3$) 4.11-4.61 (complex absorption, H_5 and 2xH_6), 4.53 (s, 2 H, CH_2Ph), 4.90 (s, 2 H, CH_2Ph'), 7.40 (m, 10 H, H_{Ar}); 20-MHz ^{13}C NMR 68.0, 69.6, 70.3, 70.5, 109.5, 127.3, 127.7, 128.0, 128.2, 128.5, 128.6, 135.2, 137.6. Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.49; H, 6.01.

(*S*)-3,5-Dibutoxy-5,6-dihydro-2-pyrone, 13c: *Method (b)*: 10% yield. Oil. 250-MHz ^1H NMR ($CDCl_3$) 0.89 (m, 6 H, 2xCH_3), 1.24-1.80 (complex absorption, 8 H, 4xCH_2), 3.46 (t, J=6.5 Hz, OCH_2), 3.74 (m, 2 H, OCH_2), 4.09 (dt, $J_{5,4}$=5.5 Hz, $J_{5,6}$=3.4 Hz, H_5), 4.32 (dd, $J_{6,6'}$=12.1 Hz, $J_{6,5}$=3.4 Hz, H_6), 4.43 (dd, $J_{6',6}$=12.1 Hz, $J_{6',5}$=3.4 Hz, $H_{6'}$), 5.67 (d, $J_{4,5}$=5.5 Hz, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 160.0 (C_2), 145.9 (C_3), 107.6 (C_4), 68.6 (C_5), 69.3, 68.5, 68.1 , 31.8, 30.4, 191.1, 13.6 (2C).

General procedure for the elimination of benzaldehyde: furanones 11a-c and pyrone 13'b. A typical experiment was run as follows. DBU (0.52 mL, 3.4 mmol) was added for 25 min to a stirred solution of ketal **10b** (700 mg, 2.8 mmol) in anhydrous tetrahydrofuran (45 mL), and the resultant mixture was stirred at room temperature for 6 h. *Wok-up (a).* Then water (15 mL) was added and the resultant solution was stirred for 30 min, diluted with dichloromethane (50 mL) and washed with 2N HCl (2x25 mL). The combined aqueous layers were continously extracted with dichloromethane for 15 h. The combined organic phases were dried and the solvents were removed. The residue was chromatographed (1:3 hexane-ethyl acetate) to afford furanone **11b**. *Work-up (b).* The solvent was removed and the residue was poured into dichloromethane. The resultant solution was washed with 2N HCl (2x25 mL) and the combined organic phases were exhaustively extracted with dichloromethane. The combined organic solutions were dried and the solvent was evaporated to give lactone **13'b** in a very low yield (*c.f.* 5%).

(*S*)-3-Benzyloxy-5-hydroxymethyl-2(5*H*)-furanone, 11a: 96 mg, 74%. Crystals, m.p. 99-101 °C, $[\alpha]_D$ +9.4 (c 0.85, MeOH) (lit.[11] m.p. 100-101 °C; $[\alpha]_D$ +11.4 (c 1.0, MeOH)); previously undescribed spectra follow: 20-MHz ^{13}C NMR ($CDCl_3$) 63.6, 73.0, 79.3, 114.8, 127.7, 128.6, 128.7, 134.8, 146.9, 167.4; MS, *m/e* 220 M, (0.3), 91 (100).

(*S*)-5-Hydroxymethyl-3-methoxy-2(5*H*)-furanone, 11b: 342 mg, 84% yield. Crystals, m.p. 84-85 °C (from ethyl acetate-pentane); $[\alpha]_D$; IR (KBr) 3480 (broad), 1764, 1666 cm^{-1}; MS, *m/e* 144 (M, 7), 114 (100), 113 (27), 99 (37), 85 (23), 71 (16); 400-MHz ^1H NMR ($CDCl_3$) 2.02 (s, O*H*), 3.67 (dd, $J_{6,6'}$=12.2 Hz, $J_{6,5}$=5.5 Hz, H_6), 3.79 (s, 3 H, OCH_3), 3.91 (dd, $J_{6',6}$=12.2 Hz, $J_{6',5}$=3.7 Hz, $H_{6'}$), 5.02 (m, H_5), 6.03 (d, $J_{4,5}$=2.1 Hz, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 167.8 (C_2), 147.9 (C_3), 113.5 (C_4), 79.6 (C_5), 63.3 (C_6), 58.1 (CH_3). Anal. Calcd. for $C_6H_8O_4$: C, 50.05; H, 5.60. Found: C, 50.12; H, 5.62.

(S)-5-Hydroxymethyl-3-butoxy-2(5H)-furanone, 11c: 114 mg, 82% yield. Crystals, m.p. 36-39 °C (from ethyl acetate-pentane); $[\alpha]_D$ +11.4 (c 1.24, chloroform); IR (film) 3431 (broad), 1757, 1652 cm^{-1}; MS, *m/e* 186 (M, 7), 156 (33), 100 (100), 99 (45), 85 (24), 57 (41), 41 (33); 250-MHz ^1H NMR ($CDCl_3$) 0.92 (t, J=7.3 Hz, 3 H, CH_3), 1.45 (m, 2 H), 1.74 (m, 2 H), 2.26 (s, OH), 3.65 (dd, $J_{6,6'}$=12.3 Hz, $J_{6,5}$=5.6 Hz, H_6), 3.89 (m, 3 H), 5.00 (m, H_5), 5.98 (d, $J_{4,5}$=2.1 Hz, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 168.1 (C_2), 146.8 (C_3), 113.7 (C_4), 79.6 (C_5), 71.0 (C_7), 63.2 (C_6), 30.4 (C_8), 18.9 (C_9), 13.5 (C_{10}). Anal. Calcd. for $C_9H_{14}O_4$: C, 58.12; H, 7.59. Found: C, 58.11; H, 7.64.

(*S*)-5-Hydroxy-3-methoxy-5,6-dihydro-2-pyrone, 13'b: 250-MHz ^1H NMR ($CDCl_3$) 2.88 (s, O*H*), 3.64 (s, 3 H, OCH_3), 4.40 (m, 2 H, H_6), 4.45 (m, H_5), 5.76 (d, $J_{4,5}$=5.6 Hz, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 160.4 (C_2), 146.2 (C_3), 109.4 (C_4), 72.6 (C_6), 61.9 (C_5), 55.5 (OCH_3).

Reduction of butenolide 11a with cyclohexene/Pd-C: compound 14. A mixture of butenolide **11a** (220 mg, 1.0 mmol), 10% Pd-C (220 mg) and cyclohexene (2 mL) in absolute ethanol was heated to reflux for 30 min. The suspension was filtered through celite and the solvent was evaporated to give **(*S*)-3-hydroxy-5-hydroxymethyl-2(5*H*)-furanone, 14** as an unstable oil, unsuitable for microanalysis, which was identified by its spectroscopic data. IR (film) 3376 (broad), 1757, 1659 cm^{-1}; MS, *m/e* 130 (M, 4), 103 (27), 100 (79), 85 (20), 71 (20), 55 (31), 54 (20), 44 (16), 43 (100), 42 (24); 400-MHz ^1H NMR (acetone-d_6) 3.62 (d, $J_{6,6'}$=11.5 Hz, H_6), 3.78 (d, $J_{6',6}$=11.5 Hz, $H_{6'}$), 4.14 (s, 1 H, C_6-O*H*), 4.92 (m, H_5), 6.21 (d, $J_{4,5}$=2.1 Hz, H_4), 8.98 (s, 1 H, C_3-O*H*); 20-MHz ^{13}C NMR (acetone-d_6) 169.9 (C_2), 144.5 (C_3), 116.9 (C_4), 80.2 (C_5), 63.6 (C_6).

Hydrogenation of butenolide 11a: (*S*)-3-benzyloxy-5-hydroxymethyl-2(5*H*)-furanone, 15. A mixture of butenolide **11a** (203 mg, 0.9 mmol) and 5% Pd-C (48 mg) in absolute ethanol (15 mL) was hydrogenated at atmospheric pressure for 3.5 h. The suspension was filtered through celite and the solvent was removed. The residue was chromatographed (mixtures of hexane-ethyl acetate) to give the butyrolactone **15** (47 mg, 23% yield) along with the butenolide **14** (8 mg) and the lactone **16** which was identified by comparing its ^{1}H NMR data with those previously described for this product.[14]

Compound 15: crystals, m.p. 78-80 °C (from ethyl acetate-pentane); $[\alpha]_D$ -34.38 (c 0.48, $CHCl_3$); IR (KBr) 3459 (broad), 1785 cm^{-1}; MS, *m/e* 116 (59), 91 (100), 73 (22), 65 (17),; 400-MHz ^{1}H NMR ($CDCl_3$) 2.07 (m, 2 H, H4 and O*H*), 2.42 (m, H4'), 3.62 (dd, $J_{6,6'}$=12.7 Hz, $J_{6,5}$=5.2 Hz, H6), 3.83 (dd, $J_{6',6}$=12.7 Hz, $J_{6',5}$=2.8 Hz, H6'), 4.24 (dd, $J_{3,4}$=8.8 Hz, H3), 4.41 (m, H5), 4.80 (d, J=11.9 Hz, 2H, C*H*$_2$Ph), 7.34 (m, 5 H, *H*$_{Ar}$); 100-MHz ^{13}C NMR ($CDCl_3$) 174.7 (C_2), 136.8 (C_{Ar} *ipso*), 128.5 and 128.1 (C_{Ar}), 77.2, 73.3, 72.3 and 63.6 (C_3, C_5, C_6 and *C*H$_2$Ph), 30.6 (C_4). Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.93; H, 6.36. Found: C, 64.81, H, 6.33.

General procedure for the tosylation of the lactones 11a, 11b and 14: tosylates 18a, 18b and 17. A typical experiment was run as follows.Tosyl chloride (1.0 g, 5.5 mmol) was added to a stirred an ice-cooled solution of butenolide **11a** (400 mg, 1.8 mmol) and anhydrous pyridine (0.44 mL, 1.8 mmol) in dry dichloromethane (7 mL). The resultant solution was stirred at room temperature for 48 h. Then the reaction mixture was subsequently washed with 1M H_2SO_4 (2x5 mL) and with brine (5 mL), and dried. The solvent was removed and the residue was chromatographed (1:1 hexane-ethyl acetate) to afford tosylate **18a.**

(*S*)-3-Benzyloxy-5-*p*-toluenesulfonyloxymethyl-2(5*H*)-furanone, 18a: 624 mg, 92% yield. Oil, $[\alpha]_D$ +44.1 (c 1.28, $CHCl_3$); IR (film) 3107 (broad), 1778, 1659, 1595 cm^{-1}; MS (CI, NH_3), *m/e* 392 (M+18); 400-MHz ^{1}H NMR ($CDCl_3$) 2.45 (s, 3 H, CH_3), 4.09 (dd, $J_{6,6'}$=11.0 Hz, $J_{6,5}$=5.5 Hz, H6), 4.13 (dd, $J_{6',6}$=11.0 Hz, $J_{6',5}$=4.3 Hz, H6'), 4.97 (d, J=11.9 Hz, 2 H, C*H*$_2$Ph), 5.02 (m, H5), 6.00 (d, $J_{4,5}$=1.8 Hz, H4), 7.33 (m, 7H, H_{Ar}), 7.73 (d, J=8.6 Hz, 2 H, H_{Ar}); 100-MHz ^{13}C NMR ($CDCl_3$) 166.6 (C_2), 146.9 (C_3), 145.3, 134.2 and 131.9 (C_{Ar} *ipso*), 129.8, 128.5, 128.4, 127.7 and 127.5 (C_{Ar}), 112.9 (C_4), 75.3, 72.9 and 68.4 (C_5, C_6 and *C*H$_2$Ph), 21.4 (*C*H$_3$). Anal. Calcd. for $C_{19}H_{18}O_6S$: C, 61.02; H, 4.85; S, 8.57. Found: C, 60.78; H, 5.16; S, 8.10.

(*S*)-3-Methoxy-5-*p*-toluenesulfonyloxymethyl-2(5*H*)-furanone, 18b: 500 mg, 90% yield. Crystals, m.p. 108-109 °C (from ethyl acetate-pentane), $[\alpha]_D$ +43.4 (c 1.22, $CHCl_3$); IR (KBr) 1771, 1659 cm^{-1}; MS (CI, NH_3), *m/e* 316 (M+18, 100), 299 (M+1, 2); MS (EI), *m/e* 155 (32), 126 (47), 113 (100), 91 (53); 250-MHz ^{1}H NMR ($CDCl_3$) 2.42 (s, 3 H, Ar-C*H*$_3$), 3.78 (s, 3 H, OC*H*$_3$), 4.10 (dd, $J_{6,6'}$=11.0 Hz, $J_{6,5}$=5.1 Hz, H6), 4.16 (dd, $J_{6',6}$=11.0 Hz, $J_{6',5}$=4.8 Hz, H6'), 5.06 (m, H5), 6.00 (d, $J_{4,5}$=2.2 Hz, H4), 7.34 (d, J=8.1 Hz, 2 H, H_{Ar}), 7.74 (d, J=8.1 Hz, 2 H, H_{Ar}); 62.5-MHz ^{13}C NMR ($CDCl_3$) 166.2 (C_2), 148.5 (C_3), 145.4 and 132.1 (C_{Ar} *ipso*), 130.0 and 127.8 (4xC_{Ar}), 11.5 (C_4), 75.3 (C_5), 68.5 (OCH_3), 58.2 (C_6), 21.5 (Ar-*C*H$_3$). Anal. Calcd. for $C_{13}H_{14}O_6S$: C, 52.40; H, 4.74; S, 10.76. Found: C, 52.35; H, 4.67; S, 10.68.

(*S*)-3-*p*-Toluenesulfonyloxy-5-hydroxymethyl-2(5*H*)-furanone, 17: 53 mg, 30% yield. Crystals, m.p. 74-77 °C (from ethyl acetate-pentane); $[\alpha]_D$ -68.4 (c 0.38, $CHCl_3$); IR (KBr) 3480 (broad), 1743, 1645, 1595 cm^{-1}; 80-MHz ^{1}H NMR ($CDCl_3$) 2.13 (s, O*H*), 2.48 (s, 3 H, C*H*$_3$), 3.76 (dd, $J_{6,6'}$=12.1 Hz, $J_{6,5}$=4.8 Hz, H6), 4.00 (dd, $J_{6',6}$=12.1 Hz, $J_{6',5}$=3.6 Hz, H6'), 5.07 (m, H5), 7.17 (d, $J_{4,5}$=2.1 Hz, H4),

7.38 (d, J=10 .0 Hz, 2H, H_{Ar}), 7.88 (d, J=10.0 Hz, 2 H, H_{Ar}); 20-MHz ^{13}C NMR ($CDCl_3$) 165.6 (C_2), 146.6 (C_3), 138.0 ($C_{Ar\ ipso}$), 133.0 (C_4), 131,5 ($C_{Ar\ ipso}$), 130.1 and 128.6 (C_{Ar}), 79.4 (C_5), 62.3 (C_6), 21.7 (CH_3). Anal. Calcd. for $C_{12}H_{12}O_6S$: C, 50.75; H, 4.26; S, 11.29. Found: C, 50.49; H, 4.22; S, 11.15.

Reduction of the butenolide 18a: compound 19. Following a similar procedure than that described above for butenolide **11a**, **(*S*)-3-hydroxy-5-*p*-toluenesulfonyloxymethyl-2(5*H*)-furanone, 19**, (203 mg, 70% yield) was obtained as an oil, unsuitable for microanalysis, which was identified by its spectroscopic data. IR (film) 3381 (broad), 1778, 1659, 1595 cm^{-1}; MS (CI, NH_3), *m/e* 302 (M+18); 400-MHz ^1H NMR (acetone-d_6) 2.44 (s, 3 H, CH_3), 4.11 (dd, $J_{6,6'}$=11.3 Hz, $J_{6,5}$=5.5 Hz, H_6), 4.39 (dd, $J_{6',6}$=11.3 Hz, $J_{6',5}$=3.0 Hz, $H_{6'}$), 5.15 (m, H_5), 6.18 (d, $J_{4,5}$=2.1 Hz, H_4), 7.44 (d, J=8.5 Hz, 2 H, H_{Ar}), 7.79 (d, J=8.5 Hz, 2 H, H_{Ar}), 9.20 (s, OH); 100-MHz ^{13}C NMR (acetone-d_6) 168.6 (C_2), 146.1 (C_3), 145.3 and 133.6 ($C_{Ar\ ipso}$), 130.8 and 128.6 (C_{Ar}), 114.6 (C_4), 76.4 (C_5), 70.0 (C_6), 21.4 (CH_3).

Elimination reactions from tosylates 18a and 18b: furanones 20a and 20b. *Method (a): Use of pyridine as a base.* A typical experiment was run as follows. A solution of tosylate **18a** (308 mg, 0.8 mmol) in anhydrous pyridine (8 mL) was heated to reflux for 3 h. The mixture was cooled to room temperature and diluted with dichloromethane (15 mL). The resultant solution was washed with 1M H_2SO_4 (3x15 mL) and dried. The solvent was removed and the residue was chromatographed (3:1 hexane-ethyl acetate) to afford furanone **20a**. *Method (b): Use of DBU as a base.* A solution of tosylate **18b** (600 mg, 2.0 mmol) and DBU (0.4 mL, 2.7 mmol) in anhydrous THF (35 mL) was stirred at room temperature for 3.5 h.The reaction mixture was diluted with dichloromethane (100 mL) and washed with 2N HCl (2x50 mL). The aqueous phase was extracted with dichloromethane (2x30 mL) and the combined organic phases were dried. The solvents were removed and the residue was chromatographed (2:1 hexane-ethyl acetate) to afford pure **20b**.

3-Benzyloxy-5-methylene-2(5*H*)-furanone, 20a. *Method (a)*: 118 mg, 71% yield. Oil unsuitable for microanalysis. IR (film) 1792, 1652, 1623 cm^{-1}; MS, *m/e* 202 (M, 2), 91 (100); 400-MHz ^1H NMR ($CDCl_3$) 4.80 (d, J=2.7 Hz, 2xH_6), 5.04 (s, 2 H, CH_2Ph), 6.27 (s, H_4), 7.35 (m, 5 H, H_{Ar}); 100 MHz ^{13}C NMR ($CDCl_3$) 164.1 (C_2), 151.4 (C_3 or C_5), 148.0 (C_5 or C_3), 134.1 ($C_{Ar\ ipso}$), 128.7, 127.6 and 127.5 (C_{Ar}), 109.4 (C_4), 94.3 (C_6), 73.3 (CH_2Ph).

3-Methoxy-5-methylene-2(5*H*)-furanone, 20b. *Method (a)*: 32 mg, 52% yield; *method (b)*: 230 mg, 90% yield. Crystals, m.p. 61-63 °C; IR (KBr) 1785, 1659, 1631 cm^{-1}; MS, m/e 126 (M, 100), 97 (98), 69 (70), 55 (56), 42 (38); 250-MHz ^1H NMR ($CDCl_3$) 3.77 (s, 3 H, OCH_3), 6.13 (dd, $J_{6,6'}$=7.3 Hz, $J_{6,4}$=5.1 Hz, H_6), 6.41 (dd, $J_{6',6}$=7.3 Hz, $J_{6',4}$=1.8 Hz, $H_{6'}$), 7.13 (dd, $J_{4,6}$=5.1 Hz, $J_{4,6'}$=1.8 Hz, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 158.8 (C_2), 146.1/142.6 (C_3/C_5), 111.9/105.4 (C_4/C_6), 55.9 (OCH_3).Anal. Calcd. for $C_6H_6O_3$: C, 57.20; H, 4.80. Found: C, 57.33; H, 4.88.

Reaction of 2,4-dioxopentanoic acid, 21a, with acetic anhydride: 3-acetoxy-5-methylene-2(5*H*)-furanone, 8. A mixture of acid **21a** (500 mg, 3.8 mmol), acetic anhydride (5 mL) and concentrated H_2SO_4 (two drops) was stirred at room temperature for 20 min. Then water (30 mL) was added and the solution was neutralized with solid sodium bicarbonate and extracted with ether (3x30 mL). The combined organic extracts were dried and the solvent was removed. The residue was chromatographed (1:1 hexane-methylene chloride) to afford furanone 8 (300 mg, 51% yield) as a solid, m.p. 75-76 °C (lit.[10a] m.p. 75-76 °C) whose spectroscopic data were in accordance with those previously described for this product.[10a]

Reaction of ethyl 2,4-dioxopentanoate, 21b, with acetic anhydride: ethyl 2,4-diacetoxy-2,4-pentadienoate, 22. A mixture of ester **21b** (450 mg, 2.7 mmol), acetic anhydride (5 mL) and concentrated H_2SO_4 (three drops) was heated at 80 °C for 90 min. The reaction mixture was cooled to room temperature and water (40 mL) was added. The resultant solution was neutralized with solid sodium bicarbonate and extracted with ether (3x30 mL). The combined organic extracts were dried and the solvent was evaporated. The residue was chromatographed (1:1 hexane-ethyl acetate) to afford compound **22** (138 mg, 21% yield) as an oil, o.t. 105 °C (0.2 Torr); IR (film) 1771, 1729, 1659 cm^{-1}; MS, *m/e* 242 (M, 2), 158 (37), 85 (17), 84 (42), 43 (100); 80-MHz ^1H NMR ($CDCl_3$) 1.29 (t, J=7.4 Hz, 3 H, OCH_2CH_3), 2.20 (s, 3 H, $OCOCH_3$), 2.24 (s, 3 H, $OCOCH_3$), 4.23 (q, J=7.4 Hz, 2 H, OCH_2CH_3), 5.27 (d, J=2.5 Hz, 2xH_5), 6.83 (s, 3H); 20-MHz ^{13}C NMR ($CDCl_3$) 168.1 and 167.7 (2x$OCOCH_3$), 161.5 (*C*OOEt), 147.7, 137.3, 121.2 and 112.9 (C_2, C_3, C_4 and C_5), 61.8 (OCH_2CH_3), 20.4 and 20.1 (2x$OCOCH_3$), 13.9 (OCH_2CH_3). Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.60; H, 5.83. Found: C, 54.54; H, 5.78.

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REFERENCES

1. Sulser, H.; De Pizzol, J.; Büchi, W. *J. Food Sci.* **1967**, *32*, 611.
2. Anderson, R. C.; Calder, A. British Patent 1,364,103 (21 August 1974); Chem. Abs. **1975**, *82*, 14177t.
3. Takahashi, K.; Tadenuma, M.; Sato, S. *Agric. Biol. Chem.* **1976**, *40*, 325.
4. Galantay, E. US Patent 3,474,112 (21 October 1969); *Chem. Abs.* **1970**, *72*, 31254b.
5. Batchelor, D. W. H. Clark; Tuey, G. A. P. Germ. Patent 1,955,390 (9 July 1970); *Chem. Abs.* **1970**, *73*, 77034d.
6. Couquelet, J.; Bastide, J. *Trav. Pharm. Montpellier* **1973**, *33*, 299; *Chem. Abs.* **1974**, *80*, 128370q.
7. Sakurai, K.; Matsumoto, H.; Adachi, J. *Yakugaku Zasshi*, **1968**, *88*, 919; *Chem. Abs.* **1968**, *69*, 94729j.
8. Allan, R. D.; Johnston, G. A. R.; Kazlauskas, R.; Tran, H. *Aust. J. Chem.* **1983**, *36*, 977.
9. (a) Sigman, D. S. private communication. (b) Goyne, T. E.; Sigman, D. S. *J. Am. Chem. Soc.* **1987**, *109*, 2846.
10. (a) Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017. (b)Attwood, S. V.; Barrett, A. G. M. *J. Chem. Soc. Perkin Trans. I*, **1984**, 1315.
11. Weidmann, H.; Timpe, W.; Wolf, N. *Carbohyd. Res.*, **1972**, *25*, 67.
12. Chen, S.; Joulliée, M. M. *J. Org. Chem.* **1984**, *49*, 2168.
13. Corbera, J. *Ph. D. Dissertation*, Universitat Autònoma de Barcelona, **1990**.
14. Ariza, J.; Font, J.; Ortuño, R. M. *Tetrahedron Lett.* **1991**, *32*, 1979.
15. Uchikawa, O.; Okukado, N.; Sakata, T.; Arase, K.; Terada, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2025.
16. Caine, D.; Forbese, A. S.; Ukachukwu, V. C. *J. Org. Chem.* **1983**, *48*, 740.
17. Ram, S.; Ehrennkaufer, R. E. *Synthesis*, **1988**, 91.
18. Seela, F.; Menkhoff, *Liebigs Ann. Chem.* **1982**, 813.
19. (a) Anantharamaiah, G. M.; Sivanandaiah, K. M. *J. Chem. Soc. Perkin Trans. 1*, **1976**, 490. (b) Hanessian, S. Liak, T. J.; Vanasse, B. *Synthesis*, **1981**, 396. (c) Witiak, D. T.; Tehim, A. K. *J. Org. Chem.* **1987**, *52*, 2324.
20. Guthrie, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 7020.
21. Ohta, S.; Tsujimura, A.; Okamoto, M. *Chem. Pharm. Bull.* **1981**, *29*, 2762.
22. Cervelló, J.; Marquet, J.; Moreno-Mañas, M. *Tetrahedron*, **1990**, *46*, 2035.
23. Shaw, E. *J. Am. Chem. Soc.* **1946**, *68*, 2510.
24. Calderón, A.; Font, J.; Ortuño, R. M. *An. Quím.* **1985**, *81, C*, 83.
25. (a) Miyata, O.; Schimdt, R. R. *Tetrahedron Lett.* **1982**, *23*, 1793. (b) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1989**, *30*, 2233.