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REACTIONS OF SOME D-RIBONOLACTONE DERIVATIVES WITH ALKYL CUPRATES

SYNTHESIS OF (+)-ELDANOLIDE AND (+)-trans-COGNAC LACTONE

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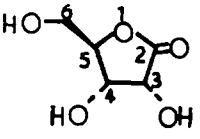
Summary.- Reactions of some D-ribonolactone derivatives with alkyl cuprates have been investigated in order to obtain molecules with a (4S,5R)-4,5-dialkyldihydro-2(3H)-furanone type constitution. As a direct application, (+)-eldanolide and (+)-trans-cognac lactone have been synthetized.

INTRODUCTION

Chirality of D-ribonolactone, 1, has been transferred into a variety of natural product molecules by using this lactone as a chiral starting material in enantioselective synthesis.[1] For this purpose, transformations meaning hydroxyl manipulations,[2] lactone ring opening,[3] and ring carbon alkylations,[4] have been made. Preparation of compounds having a 5-alkyldihydro-2(3H)-furanone constitution, such as (+)-pelargonolactone, 2, (+)-trans-cognac lactone, 3a, and (+)-eldanolide, 4, needs mainly chain elongation at C-6 position of the D-ribonolactone molecule.



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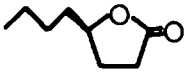

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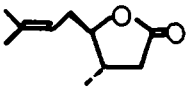

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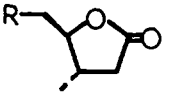
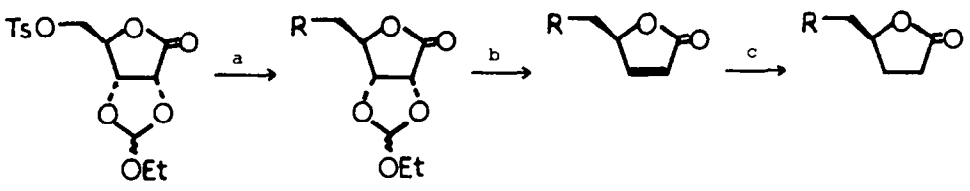


R = Bu, 3a
Pr, 3b
Me, 3c

We have recently described[5] a facile and general entry to optically active 5-alkylbutenolides and 5-alkylbutanolides, involving chain extension in 1 by means of the reaction of the tosylorthoester derivative 5,[6] with lithium dialkyl cuprates. (Scheme 1).



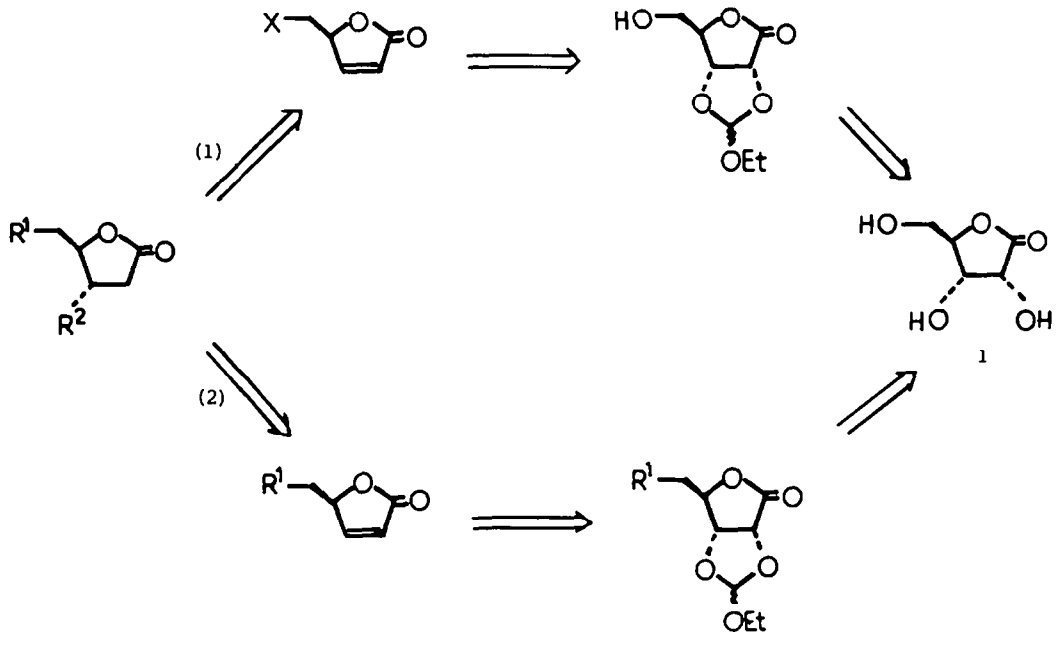
5

a: R_2CuLi; b: heat; c: H_2, Pd/C.

Scheme 1

We describe herein alternative methods that permit an easy access to 4,5-dialkylsubstituted dihydro-2-furanones in an enantioselective manner, using the chirality of D-ribonolactone, 1. Syntheses of products 3a and 4 have been achieved employing these methodologies.

RESULTS AND DISCUSSION

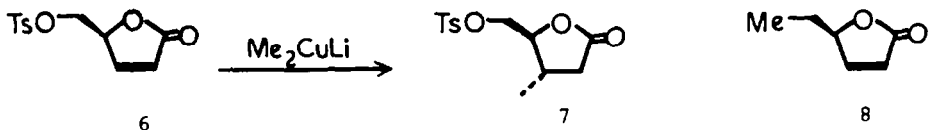


1

Scheme 2

Scheme 2 shows two retrosynthetic pathways that connect the target molecules with D-ribonolactone derivatives as chiral precursors through suitable butenolides as intermediates. In way 1 the R^2 group can be introduced by a stereoselective Michael addition, while R^1 would be the result of a substitution reaction, X being a good leaving group. The order of events must be

addition previously to substitution, since reaction of the tosyl butenolide **6** with lithium dimethyl cuprate lead to the Michael adduct **7**, although in low yield, instead of the ethyl butenolide **8** along with undesired by-products.[5] (Scheme 3).



6 7 8

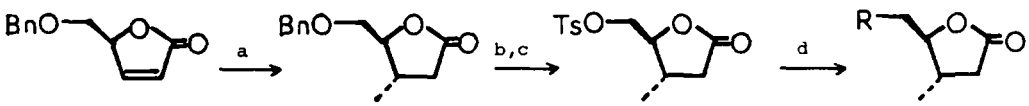
Scheme 3

On the other hand, way 2 (Scheme 2) means that the alkyl chain at C-6 has been extended prior to the C-C double bond creation. Then, conjugate addition of an organocuprate to a 5-alkylbutenolide should give the final products.

Route 1: trans-Cognac lactone, 3a.

According to retrosynthetic sequence 1 we envisaged the preparation of products **3a** and **3c**. Compound **3a**, known as trans-cognac lactone, is a constituent of brandy and is one of the nicknamed "quercus lactones" or "oak lactones", **3a** and **3b** (cis and trans isomers), that are extracted by alcoholic beverages like whisky or brandy from oak barrels in which they are kept for maturing.[7] In spite of several published syntheses of whisky lactones (**3b**, trans isomer shown) in both racemic and enantiomeric forms,[8] as far as we know the trans cognac lactone (+)-**3a** had never been synthetized. The homologous (4S,5R)-4-methyl-5-ethyldihydro-2(3H)-furanone, **3c**, is precursor of 4-methyl-3-heptanol, the main constituent of the aggregation pheromone of Scolytus multistriatus Marsh.[9]

The synthesis of compound **3a** is shown in Scheme 4 and consists in Michael addition of Me_2CuLi to the easily accessible butenolide **9**[6] to give **10**, followed by hydrogenolysis of the benzyl ether and subsequent tosylation to afford **11**, $\{\alpha\}^{20}_D$ = +54.6° (c = 2.8, methylene chloride).[10] Reaction of the tosylate **11** with lithium dibutyl cuprate allowed the obtention of compound **3a** as a liquid, b.p. 115°/11 torr, $\{\alpha\}^{20}_D$ = +48.3° (c = 0.79, CH_2Cl_2).



9 10 11 R = Bu, 3a

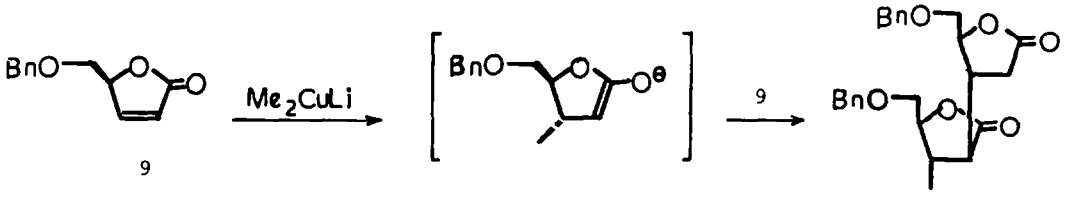
a: Me_2CuLi; b: H_2, Pd/C; c: TsCl, pyr; d: R_2CuLi.

Scheme 4

Although this route is very simple and would also lead to lactone **3c**, we have been unable to obtain it. To explain this fact some features affecting the reactions of these substances with cuprates must be mentioned.

Thus, the conjugate addition of Me_2CuLi to lactone **9** in several conditions (Table 1) afforded always a by-product, **12**, that was identified by their spectral characteristics and elemental analysis (see experimental part). Formation of this compound in the reaction conditions can be explained by attack of the enolate of **10** to a molecule of unreacted butenolide **9**, process that competes with the addition of the cuprate. (Scheme 5). Although Vigneron et al have reported

this same reaction to occur in similar conditions affording 10 in 80% yield without mention of the dimeric compound 12,[10] Fariña et al have also described the production of this type of molecules in the reactions of pseudoesters with carbanions.[11]



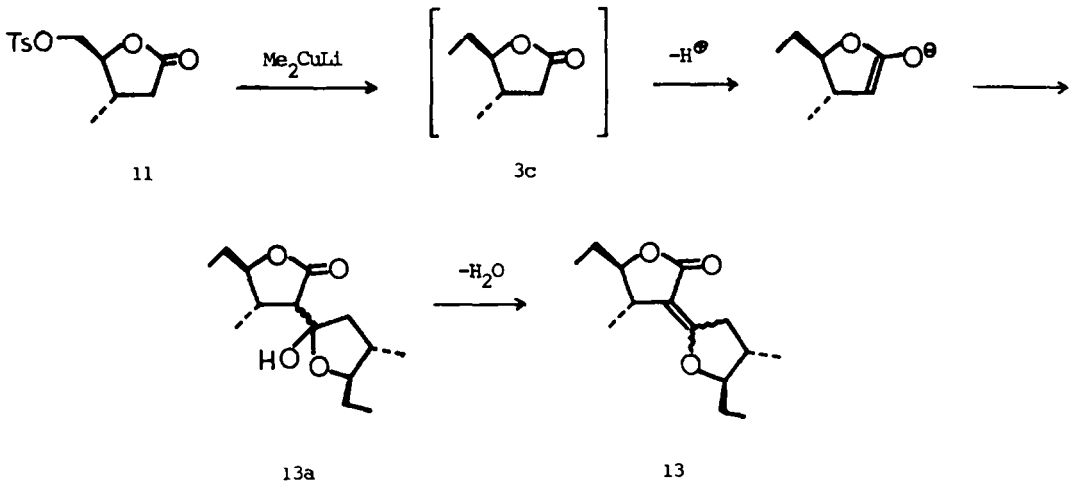
9 12

Scheme 5

Table 1. Reactions of lactones 9 and 11 with lithium dimethyl cuprate

Lactone	Moles of cuprate	Temperature (°C)	Time (h)	Normal product (%)	By-product (%)	% Starting material
9	1.1	- 40	0.5	10 (49)	12 (24)	13
9	1.1	- 40	1	10 (30)	12 (27)	3
9	1.1	- 15	0.5	10 (52)	12 (25)	5
9	3	- 15	0.5	10 (48)	12 (14)	--
9	3	+ 15	0.5	10 (50)	12 (9)	--
11	3	- 40	2	-------	-------	80
11	3	- 15	2	-------	13 (29)	13
11	4	- 10	2	-------	13 (33)	18
11	3	0	2	-------	13 (30)	7

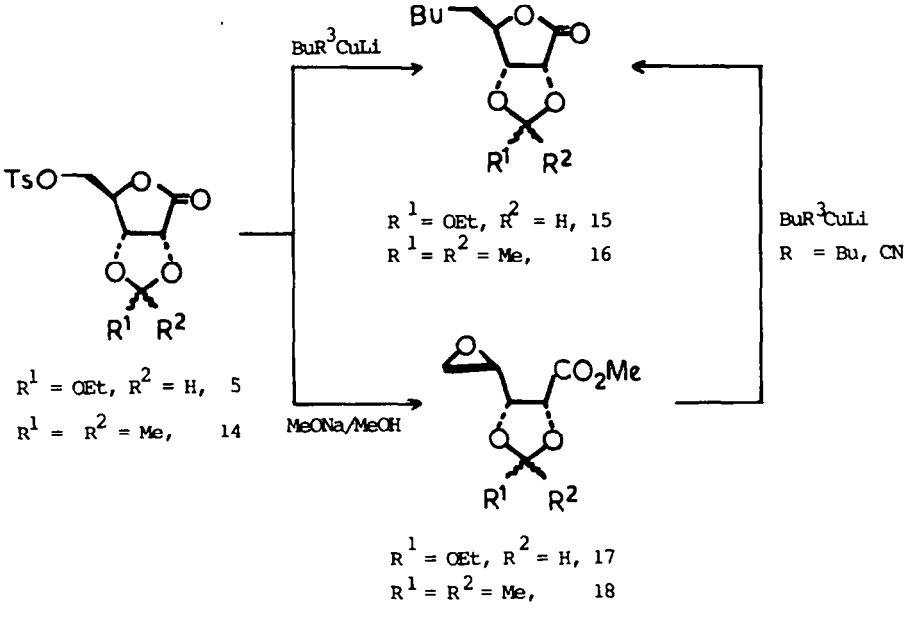
Moreover, while the substitution reaction in tosylate 11 with Bu_2CuLi at -25° gave good yields of 3a as the only identified substance, when Me_2CuLi was used in order to prepare lactone 3c, the aldolic condensation product, 13, was always obtained instead of 3c in the reaction conditions. (Table 1). The compound 13 was identified by its spectral characteristics and the presence of the aldol adduct 13a in the reaction crude was also detected in some experiments. This transformation can be rationalized as shown in Scheme 6, assuming the formation of the enolate of 3c in spite of the weakly basic reaction medium. A similar condensation process is described in the literature[12] referred to the reaction of γ-butyrolactone with ethyl cinnamate using LDA as the base: in that case the lactone self-condensation compound was obtained and the alkylation product was not detected. This behaviour of tosylate 11 towards alkyl cuprates differs from that of its homologous without a methyl group in C-4 position, since Silverstein[13] and ourselves[5] have reported its reaction to occur in good yields.



Scheme 6

Route 2: (+)-Eldanolide, 4.

With these results in hand, we decided to explore the alternative way 2 shown in Scheme 2. An efficient synthesis of (+)-eldanolide, 3, was realized following this strategy.[13] Compound 3 is a sex attractant pheromone, isolated from the male wing glands of the African sugar cane borer Eldana Saccharina (Wlk).[14]



Scheme 7

First of all, a study was carried out to compare the behaviour of some D-ribonolactone derivatives towards cuprates, using Bu_2CuLi and BuCNCuLi as available models. (Table 2). Reactions of tosylate

orthoester 5 and tosylate acetonide 14[15] in several conditions (entries 1-5) afforded the expected products **15** and **16**, respectively, but in yields lower than 40% (Scheme 7). The orthoester **15** had been converted into (R)-5-pentyl-2(5H)-furanone[5], being a virtual precursor of (+)-trans-cognac lactone, **3a**.

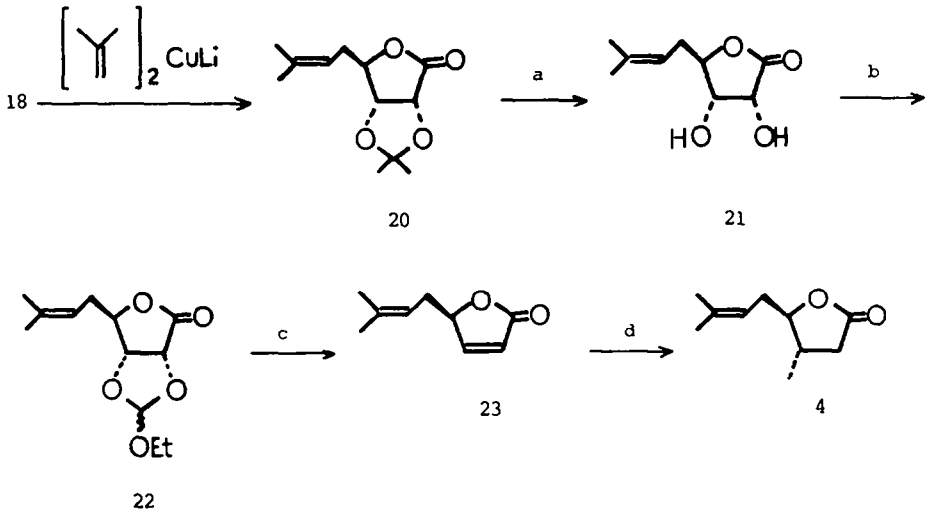
Table 2. Reactions of tosylates 5 and 14, and epoxides 17 and 18 with cuprates

Entry	Substrate	Cuprate	Molar ratio	Temperature (°C)	Time (h)	Product	Yield (%)	% Starting material
1	**5**	Bu_2CuLi	3	- 20	2	**15**	22	5
2	**14**	Bu_2CuLi	3	- 25	2	**16**	36	6
3	**14**	BuCNCuLi	3	- 30	2	**16**	13	40
4	**14**	BuCNCuLi	3	r.t.	2	**16**	31	8
5	**14**	BuCNCuLi	3	r.t.	6	**16**	32	--
6	**17**	Bu_2CuLi	3	- 25	1.5	**15**	12	--
7	**17**	Bu_2CuLi	1	- 15	1.5	**15**	20	10
8	**17**	Bu_2CuLi	1.1	- 15	2	**15**	34	--
9	**17**	Bu_2CuLi	1.1	- 40	1.5	**15**	7	40
10	**17**	BuCNCuLi	3	r.t.	6	**15**	30	--
11	**17**	**19**	1.1	-40 (-10)	0.5 (0.25)	**22**	31	--
12	**18**	BuCuCNLi	3	r.t.	6	**16**	63	--
13	**18**	**19**	1.1	-40 (-25)	1 (0.5)	**20**	67	--

We had already reported[5] that the orthoester function could be no compatible with the cuprate alkylation conditions, leading to the formation of polymeric material. However, since reaction of the tosylate acetonide **14** gave similar yields of coupling products, steric hindrance due to rigidity of the bicycle seems to be another negative factor in these transformations. Therefore, in order to release ring-strain epoxides **17** and **18**[16] were prepared in 85% yield by treating tosylates **5** and **14**, respectively, with sodium methoxide in methanol. The new epoxy orthoester **17** is the key precursor to obtain the intermediate butenolide **23**,[10] since opening of the oxirane ring by nucleophilic attack of a cuprate and subsequent lactonization should lead to the isopentenyl side-chain formation, while pyrolysis of the orthoester would allow the creation of the conjugate C-C double bond of **23**.

Reactions of the epoxyorthoester **17** with Bu_2CuLi, BuCNCuLi, as well as with lithium diisobutenyl cuprate, **19**,[17] (Table 2, entries 6-11) afforded adducts with yields similar to those of tosylates, but the epoxy acetonide **18** gave yields two-fold higher. (Entries 12,13). These results clearly confirm that orthoesters are unstable in the conditions involved in these kind of transformations.

At this step, synthesis of (+)-eldanolide, **4**, was easily accomplished.[18] (Scheme 8). Thus, the alkyl acetonide **20**, $\{\alpha\}^{20}_D$ = -34.1° (c = 1.7, CH_2Cl_2) was prepared from epoxide **18** and cuprate **19** in 67% yield. Compound **20** was quantitatively hydrolyzed[19] to the diol **21**, m.p. 103-104°, $\{\alpha\}^{20}_D$ = +33.5° (c = 1.0, MeOH), that was converted to the orthoester **22**. Pyrolysis of **22** afforded the butenolide **23**, $\{\alpha\}^{20}_D$ = -132.8° (c = 1.56, MeOH) in 85% yield, and finally Michael addition of Me_2CuLi allowed the obtention of (+)-eldanolide, **4**, as a liquid, b.p. 120°/12 torr, $\{\alpha\}^{20}_D$ = +50.7° (c = 2.8, MeOH), in 63 % yield. (Lit.[10] $\{\alpha\}^{20}_D$ = +51.5° (c = 1.15, MeOH)). Although product **4** has been prepared by other authors,[10,20] the synthesis described herein competes advantageously, since the overall yield is 30% from D-ribonolactone, being the best yield reported till now, starting from a commercial available product.



a: CF_3CO_2H - H_2O (9:1); b: $HC(OEt)_3$; c: 120°/12 torr; e: Me_2CuLi.

Scheme 8

EXPERIMENTAL SECTION

Melting points have been determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained on a Propol polarimeter, model Dr. Kernchen. Distillation of small amounts were effected on a rotational distillator Büchi, model KRV 65/30 (only external or oven temperature given). The 70 eV electron impact mass spectra were recorded with a Hewlett-Packard apparatus, model 5985 B. The infrared spectra were recorded on a Perkin-Elmer spectrophotometer, model 1310. The 80 MHz pmr and 20 MHz cmr spectra were recorded on a Bruker spectrometer model WP 80 SY, from chloroform-d_3 solutions , unless otherwhise indicated; chemical shifts are given in parts per million relative to TMS (δ scale). Microanalyses were performed at the Instituto de Química Bio-Orgánica, C.S.I.C., Barcelona.

Reaction of (S)-5-benzyloxymethyl-2(5H)-furanone, 9, with lithium dimethyl cuprate. A typical experiment was run as follows:

To a stirred solution of cuprous iodide (1.85 g, 9.7 mmol) in anh ether (30 ml) at -15°, under argon, 12.1 ml (19.4 mmol) of a 1.6 M solution of methyllithium in anh ether was slowly added. After 30 min a solution of butenolide 9 (1.8 g, 8.8 mmol) in anh ether (10 ml) was added dropwise. After stirring for 30 min at -15° the mixture was hydrolyzed with sat aq ammonium chloride (15 ml), stirred to reach r.t. and then filtered. The layers were separated and the aqueous phase was extracted with 3x30 ml portions of ethyl acetate. The combined organic layers were washed with sat aq sodium chloride and dried over sodium sulfate. The solvents were removed under reduced pressure to give 1.74 g of a crude that was chromatographed through silica gel (mixtures of ethyl acetate-hexane as eluents) to afford 1.0 g (52% yield) of (4S,5S)-5-benzyloxymethyl-4-methyl-2(5H)-furanone, 10, and 0.5 g (25% yield) of dimer 12.

Compound 10. $[\alpha]_D^{20}$ = +33.9° (c = 2.3, methylene chloride).(Lit $[\alpha]_D^{21}$ = -35.9° (c = 2.2, dioxane) for the enantiomer); ir (film) 1775 cm^{-1} (C=O); pmr 1.11 (d, J = 6.3 Hz, 3H); 2.0-3.0 (complex abs, 3H); 3.60 (m, 2H); 4.14 (m, 1H); 4.51 (s, 2H); 7.26 (s, 5H); cmr 176.2, 137.7, 128.3, 127.6, 127.4, 85.5, 73.4, 70.3, 36.6, 32.0, 18.1; ms, m/e 220 (M, 2), 114 (34), 107 (19), 105 (26), 99 (34), 92 (18), 91 (100), 77 (21), 71 (36), 65 (82), 55 (11), 43 (59).

Compound 12. B.p. 240°/0.04 torr; ir (film) 1760 cm^{-1} (broad, C=O); pmr 1.14 (d, J = 6.3 Hz, 3H); 2-3.1 (complex abs, 5H); 3.62 (complex abs, 4H); 4.07 (m, 1H); 4.49 (s, 2H); 4.54 (s, 2H); 4.67 (m, 1H); 7.31 (s, 10 H); cmr 175.7, 175.4, 137.4, 128.2, 127.6, 127.5, 127.4, 127.3, 83.4, 80.7, 73.3, 71.0, 68.8, 49.7, 36.1, 34.7, 32.0, 16.8; ms, m/e 424 (M, 0.2), 333 (27), 92 (18), 91 (100), 65 (17). Anal. Calcd. for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.84; H, 6.43.

Reaction of tosylate 11 with lithium dimethyl cuprate. A typical experiment was run as follows:

Lithium dimethyl cuprate (2.9 mmol) prepared as described above, was made to react with tosylate 11 (206 mg, 0.7 mmol), obtained according to ref 10, for 2 h at -10°. After hydrolysis, conventional working-up and chromatography of the crude through silica gel (mixtures of ethyl acetate-hexane as eluents) 37 mg of unreacted 11 was recovered and compound 13 (29 mg, 33% yield)

was obtained as a liquid, b.p. 150°/11 torr; ir (film): 1730 (C=O), 1665 (C=C) cm^{-1}; pmr 0.82-1.28 (complex abs, 2H); 1.43-1.93 (complex abs, 8H); 3.36-4.03 (complex abs, 2H); cmr 172.6, 169.5, 99.8, 91.9, 86.0, 38.2, 37.8, 36.6, 28.5, 26.5, 18.6, 16.8, 10.0, 9.2; ms, m/e 238 (M, 33), 223 (64), 152 (79), 137 (54), 125 (18), 123 (21), 113 (21), 111 (33), 97 (21), 79 (24), 77 (26), 69 (100), 68 (24), 67 (36).

(4S,5R)-4-Methyl-5-butyl-2(5H)-furanone ((+)-trans-cognac lactone), **3a**.
To a stirred solution of cuprous iodide (419 mg, 2.2 mmol) in anh ether (10 ml) at -40°, under argon, 2.8 ml (4.5 mmol) of a 1.6 M solution of butyllithium in hexane was slowly added. After 30 min a solution of tosylate **11**,(208mg, 0.7 mmol) in anh DME (3 ml) was added dropwise. After stirring for 2 h at -25° the mixture was hydrolyzed and worked-up in the conventional manner, to afford 126 mg of a crude that was chromatographed through silica gel (1:9 ethyl acetate-hexane as eluent) to give 62 mg of **3a** (50% yield) and 24 mg of unreacted **11**. (+)-trans-Cognac lactone, **3a**, is a liquid, b.p. 115°/11 torr, $[\alpha]_D^{20}$ = +48.3° (c = 0.79, methylene chloride); ir (film) 1770 cm^{-1} (C=O); pmr 0.74-1.82 (complex abs, 11H), 1.14 (d, J = 6.2 Hz, 3H); 1.94-2.95 (complex abs, 3H); 4.03 (m, 1H); cmr 176.2, 87.4, 37.1, 36.0, 34.0, 31.6, 25.3, 22.4, 17.5, 13.8; ms, m/e 170 (M, 0.4), 142 (3), 128 (7), 110 (7), 99 (100), 83 (11), 71 (23). Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.32; H, 10.40.

5-Deoxy-2,3-O-isopropylidene-5-butyl-D-ribonolactone, **16**.
To a stirred solution of cuprous cyanide (403 mg, 4.5 mmol) in anh ether (20 ml) at -40°, under argon, 2.8 ml (4.5 mmol) of a 1.6 M solution of butyllithium in hexane was slowly added. After 1 h a solution of epoxide **18**, prepared according to ref 16, (366 mg, 1.5 mmol) in anh ether (6 ml) was added dropwise. After stirring for 15 min at -40° the reaction mixture was allowed to warm-up to r.t. and stirred for an additional 6 h period. The mixture was hydrolyzed with sat aq ammonium chloride (20 ml), stirred for 30 min and then filtered. The layers were separated and the aqueous phase was extracted with 3x20 ml portions of ethyl acetate. The combined organic layers were washed with sat aq sodium chloride (25 ml) and dried over sodium sulfate. The solvents were removed under reduced pressure giving 280 mg of a residue that was chromatographed through silica gel (mixtures of methylene chloride-hexane as eluents) to afford 237 mg (63% yield) of compound **16** as a liquid, b.p. 110°/0.6 torr; $[\alpha]_D^{20}$ = -42.5° (c = 0.68, methylene chloride); ir (film) 1775 cm^{-1} (C=O); pmr 0.70-1.85 (complex abs, 17H); 4.48 (complex abs, 2H); 4.56 (d, J = 6.1 Hz, 1H); cmr 173.4, 113.6, 82.9, 79.4, 74.7, 33.5, 31.1, 26.6, 25.4, 24.2, 22.1, 13.6; ms, m/e 213 (29), 169 (5), 85 (16), 83 (18), 59 (57), 43 (100). Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.19; H, 8.68.

Methyl (2R,3R,4R)-4,5-epoxy-2,3-ethoxymethylenedioxypentanoate, **17**.
To an ice-cooled solution of tosylate **5** (2.6 g, 7.3 mmol) in anh THF (60 ml), 5.9 ml (7.7 mmol) of a 1.3 M solution of sodium methoxide in anh methanol was added dropwise. After stirring for 2 h at 0° the solvent was removed and the residue poured into water and extracted with ether. The combined organic extracts were dried over sodium sulfate and the solvent was evaporated giving a crude that, by distillation at 89°/0.5 torr, afforded 1.3 g (85% yield) of the diastereoisomeric mixture of epoxyesters **17**; ir (film) 1760 cm^{-1} (C=O); pmr 1.22 (t, J= 7.1 Hz, 3H); 1.26 (t, J = 7.1 Hz, 3H); 2.58-2.95 (complex abs, 3H); 3.08-3.35 (complex abs, 3H); 3.48-4.34 (complex abs, 6H), 3.84 (s, 6H); 4.79 (d, J = 7.4 Hz, 1H); 4.94 (d, J = 7.4 Hz, 1H); 5.92 (s, 1H); 6.08 (s, 1H); ms, m/e 217 (M, 2), 175 (34), 173 (100), 159(82), 99 (39), 85 (42), 83 (41), 71 (38), 59 (46). Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.66; H, 6.64.

5-Deoxy-2,3-O-isopropylidene-5-isobutenyl-D-ribonolactone, **20**.
To a stirred solution of cuprous iodide (808 mg, 4.2 mmol) in anh ether (20 ml) at -50°, under argon, 17 ml (8.5 mmol) of a 0.5 M solution of isobutenyllithium[17] in ether was added. After 1 h at -40° a solution of epoxide **18** (780 mg, 3.9 mmol) in anh ether (5 ml) was slowly added. After stirring for 1 h at -40° the mixture was allowed to warm-up to -25° for 15 min and maintained at -25° for an additional 30 min period. The reaction mixture was hydrolyzed with sat aq ammonium chloride (10 ml), stirred for 20 min and then filtered. After conventional working-up a crude (730 mg) was obtained and chromatographed through silica gel (mixtures of methylene chloride-hexane as eluents) affording compound **20** (585 mg, 67% yield) as a liquid, b.p. 134°/0.8 torr, $[\alpha]_D^{20}$ = -34.1° (c = 1.7, methylene chloride); ir (film) 1780 cm^{-1} (C=O); pmr 1.35 (s, 3H); 1.43 (s, 3H); 1.62 (s, 3H); 1.71 (s, 3H); 2.41 (m, 2H); 4.41-4.79 (complex abs, 3H); 5.02 (m, 1H); cmr 173.5, 138.0, 115.7, 113.3, 82.6, 78.8, 74.9, 31.6, 26.6, 25.6, 25.5, 17.8; ms, m/e 226 (M, 1.8), 211 (6), 168 (27), 129 (54), 125 (36), 109 (36), 85 (49), 69 (100), 55 (58). Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.39; H, 7.74.

5-Deoxy-5-isobutenyl-D-ribonolactone, **21**.
A 9:1 trifluoroacetic acid-water solution (2 ml) was slowly added with stirring to the acetonide **20** (300 mg, 1.33 mmol) at 0°. The resultant solution was stirred for 1 h at 0° and then the solvents were removed at r.t. at reduced presure. The residue was purified by flash chromatography (silica gel, methylene chloride as eluent) affording quantitatively 239 mg of lactone **21** as a white solid, m.p. 103-104°; $[\alpha]_D^{20}$ = +33.5° (c = 1.0, methanol); ir (KBr) 3440 and 3270 (broad, OH), 1750 (C=O) cm^{-1}; pmr (acetone-d_6) 1.61 (s, 3H); 1.73 (s, 3H); 2.38 (m, 2H); 3.2-3.6 (broad, 2H); 4.22 (d, J = 5 Hz, 1H); 4.35-4.62 (complex abs, 2H); 5.08 (m, 1H); cmr (acetone-d_6) 175.8, 136.1, 119.0, 85.4, 71.1, 69.3, 31.6, 25.8, 18.0; ms, m/e 186 (M, 2.8), 168 (3), 140 (12), 123 (10), 112 (14), 97 (18), 81 (20), 69 (100), 61 (75), 41 (78). Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.16; H, 7.77.

5-Deoxy-2,3-O-ethoxymethylene-5-isobutenyl-D-ribonolactone, **22**, from hydroxylactone **21**.
A mixture of **21** (400 mg, 2.1 mmol) and ethyl orthoformate (643 mg, 4.3 mmol) in 25 ml of anh THF was heated to reflux for 48 h. The solvent and the excess ethyl orthoformate were removed under vacuo to afford quantitatively 518 mg of orthoester **22** as a diastereoisomeric mixture that was

purified by distillation at 120°/1 torr; ir (film) 1785, 1725, 1670, 1630 cm^{-1}; pmr 1.18 (t, J = 7.0 Hz, 3H); 1.65 (s, 3H); 1.73 (s, 3H); 2.43 (m, 2H); 3.58 (q, J = 7.0 Hz, 2H); 4.37-4.86 (complex abs, 3H); 5.05 (m, 1H); 5.96 (s, 1H); ms, m/e 196 (12), 145 (18), 125 (17), 109 (12), 107 (11), 95 (13), 89 (18), 81 (21), 71 (32), 69 (65), 68 (30), 53 (23), 41 (100). Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.66; H, 7.62.

(R)-5-(3-Methyl-2-butenyl)-2(5H)-furanone, 23.
A 25 ml flask containing orthoester 22 (495 mg, 2.05 mmol) was connected to a rotary microdistillation apparatus and heated at 240°/18 torr to give a crude that was chromatographed through silica gel (mixtures of ether-hexane as eluents) affording 23 (263 mg, 85% yield); $[\alpha]_D^{20}$ -132.8° (c = 1.56, methanol). (Lit[10] $[\alpha]_D^{21}$ = -130°, c = 0.80, methanol); pmr 1.65 (s, 3H); 1.72 (s, 3H); 2.45 (m, 2H); 4.75-5.30 (complex abs, 3H); 6.10 (d, J = 6 Hz, 1H); 7.45 (d, J = 6 Hz, 1 H); cmr 172.8, 156.0, 136.4, 121.6, 116.4, 83.0, 31.8, 25.5, 17.7; ms, m/e 152 (M, 6.5), 97 (7), 84 (16), 83 (15), 69 (100), 55 (29).

(4S,5R)-4-Methyl-5-(3-methyl-2-butenyl)-2(5H)-furanone ((+)-Eldanolide), 4.
To a solution of lithium dimethyl cuprate (3.7 mmol), prepared as described above, in 20 ml of anh ether , a solution of butenolide 23 (228 mg, 1.5 mmol) in 4 ml of anh ether was added dropwise at -35°. After stirring for 30 min at -20° the reaction mixture was hydrolyzed and worked-up in the usual manner to afford 180 mg of a crude that was chromatographed on silica gel (ethyl acetate-hexane as eluents) to afford (+)-eldanolide, 4 (159 mg, 63% yield) as a liquid, b.p. 120°/12 torr; $[\alpha]_D^{20}$ = +50.7° (c = 2.8, methanol).(Lit[10] $[\alpha]_D^{20}$ = +51.5°(c = 1.15, methanol); ir (film) 1775 and 1765 cm^{-1} (C=O); pmr 1.12 (d, J = 6.1 Hz, 3H); 1.63 (s, 3H); 1.72 (s, 3H); 1.95-2.90 (complex abs, 6H); 4.05 (q, J = 6.1 Hz, 2H); 5.16 (m, 1H); cmr 176.0, 135.1, 117.9, 86.8, 36.8, 34.9, 32.1, 25.5, 17.7, 17.5; ms, m/e 168 (M, 39), 99 (100), 71 (51), 69 (13), 43 (22), 41 (20).

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NOTES AND REFERENCES

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