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Stereoselective Syntheses and Reactions of Chiral Oxygenated α,β-Unsaturated-γ- and δ-lactones

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This paper is dedicated to the memory of Professor William S. Johnson

Abstract: The syntheses of the chiral α,β-unsaturated lactones (+)-**5**, (-)-**6**, (+)-**8**, (+)-**9**, and (+)-**10** have been efficiently achieved from readily available starting materials. The lactone (+)-**5** has been synthesized in 7 steps from (*R*,*R*)-dimethyl tartrate (38-43% overall yield). The use of (+)-**5** in formal syntheses of natural (+)-asperlin **4** and advanced intermediates for (+)-olguine **2** are also reported. The lactone (-)-**6** has been prepared in 5 steps from (*R*)-malic acid (44-50% overall yield). It can be a useful precursor for the syntheses of branched chain and deoxy nucleoside analogues. The preparation of (-)-**6** constitues formal syntheses of natural (+)-eldanolide **53** and the (+)-Geissman-Waiss lactone **54** (an intermediate for the syntheses of a variety of pyrrolizidine alkaloids). The lactones (+)-**8**, (+)-**9** and (+)-**10** have been synthesized from 3,4-di-O-acetyl-L-rhamnal **58**. The highly diastereoselective transformations of (+)-**9** and (+)-**10**, through sequential conjugate nucleophilic addition and enolate reaction, into densely functionalized chiral γ-lactones **12** are also reported.

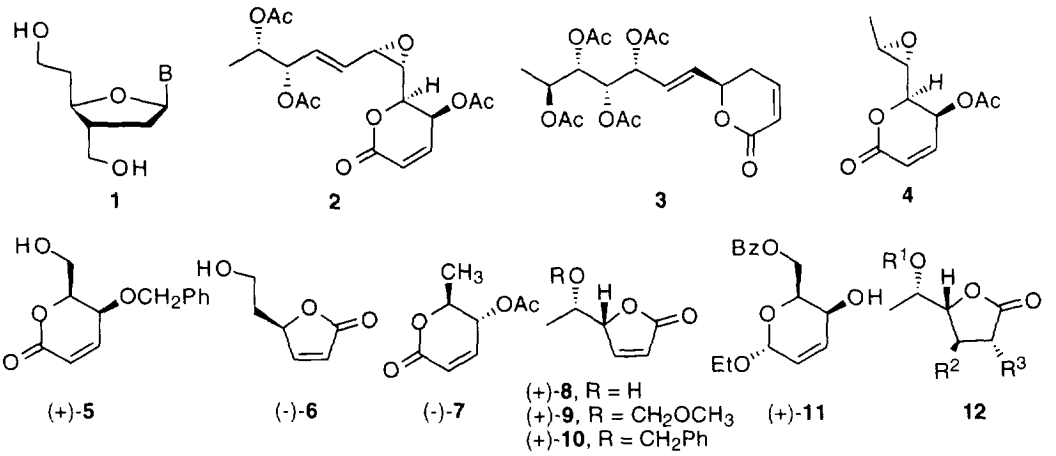
INTRODUCTION

α,β-Unsaturated-γ- and δ-lactones and their saturated counterparts are found as structural subunits in a wide variety of natural products and analogs[1] with diverse biological activities.[2] Furthermore, simple lactones have been used as intermediates for the syntheses of biologically active compounds[3] and materials with interesting technological properties.[4] Due to the known dependence between the biological activity of a molecule and its absolute configuration,[5] there is a necessity to obtain these lactones in enantiomerically pure form (EPC-synthesis[6]).[7]

In connection with projects on the syntheses of branched nucleoside analogues (e. g.; **1**, Chart 1),[8] and biologically active natural products, such as (+)-olguine **2**,[9] (+)-anamarine **3**,[10] and (+)-asperlin **4**,[11]

and analogues, we have required practical routes to the chiral oxygen-substituted unsaturated lactones **5**, **6**, **9**, and **10** (Chart 1).

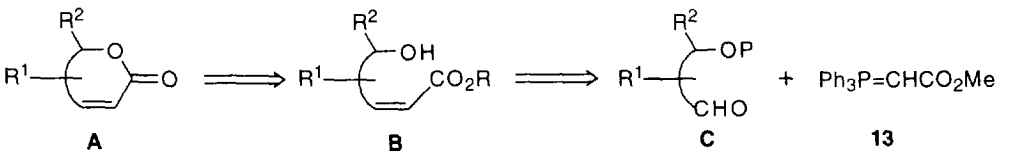
Chart 1



Although some chiral α,β-unsaturated lactones has been prepared by oxidative rearrangement of the cognate acylated glycal,[12] some of these are not readily available.[13]

In order to overcome this inconvenience, we have developed a method for the syntheses of these α,β-unsaturated lactones **A** based on the direct lactonization of the corresponding γ- or δ-hydroxy-α,β-unsaturated esters **B** (Scheme 1), which are prepared through a olefination reaction from the chiral protected hydroxy aldehydes **C**, which in turn are synthesized from readily available starting materials from the pool of chiral edducts (mainly amino acids, carbohydrates, and hydroxy acids)[14] (Scheme 1).

Scheme 1



To achieve efficient syntheses of our target molecules **A**, it is necessary to obtain the *Z*-isomer of the α,β-unsaturated esters **B** (Scheme 1) in a stereoselective manner. We have achieved this goal through a Wittig reaction of a α- or β-alkoxy or -acyloxy aldehyde (**C**, Scheme 1) and methoxycarbonylmethylen-triphenylphosphorane **13** in methanol as solvent. It is well known that the Wittig reaction of aldehydes with stabilized phosphoranes is highly *E*-stereoselective.[15] House proved that the use of an alcoholic solvent afforded lower levels of *E*-stereoselectivity,[16] but the use of an alcohol as solvent in the Wittig reaction had not been extensively used.[17] We previously showed that the reaction of α- or β-oxygenated aldehydes **C** and the phosphorane **13** in methanol afforded the *Z*-isomer of the α,β-unsaturated ester with moderate to excellent levels of diastereoselectivity.[18] We demonstrated that the combination of both factors, namely the presence of a carbon-oxygen bond in α- or β-position to the formyl group in the edduct and methanol as solvent, made the reaction Z-stereoselective.[19]

In the present paper, we report:

1) Full details of the successful application of the strategy indicated in Scheme 1 to the synthesis of the α,β-unsaturated-δ-lactone (+)-**5** from (*R,R*)-dimethyl tartrate,[20] which is a potentially useful intermediate for the syntheses of the polyoxygenated natural lactones pointed out above (Chart 1).[9-11]

2) The transformation of (+)-**5** to the *L*-ethyl glycoside (+)-**11** (Chart 1) and to advanced intermediates for the synthesis of (+)-olguine (**2**). Previously,[11d] we employed the enantiomer of (+)-**11** in the synthesis of the enantiomer of natural (+)-asperlin **4**; the preparation of (+)-**11** constitutes, therefore, a formal synthesis of the antibiotic (+)-asperlin **4**.

3) The synthesis of the α,β-unsaturated-γ-lactone (-)-**6** from (*R*)-malic acid.[21] Besides the potential for the syntheses of the nucleoside analogues[8] indicated above, the racemic form of the lactone **5** has been used as intermediate in the syntheses of the pheromone (±)-eldanolide,[22,23] 11-deoxyprostaglandins,[24] and the (±)-Geissman-Waiss lactone[25] (an intermediate in the synthesis of a variety of pyrrolizidine alkaloids).[26] Consequently, the preparation of (-)-**6** constitutes formal syntheses of these secondary metabolites in their natural absolute configurations.

4) We describe the efficient synthesis of the α,β-unsaturated-γ-lactone (+)-**8** (Chart 1) from 3,4-di-O-acetyl-L-rhamnal through sequential oxidative rearrangement (to the α,β-unsaturated-δ-lactone (-)-**7**),[12b] deacetylation and translactonization. The lactone (+)-**8** is a natural product isolated from *Osmunda japonica* possessing antifeedant activity.[27] In this paper, we report the transformation of (+)-**8** into the differently protected derivatives (+)-**9** and (+)-**10**. The functionality and the stereochemical features present in the lactones **9** and **10** make them interesting precursors for the stereocontrolled syntheses of a variety of modified carbohydrates,[28] as well as the side-chain of (+)-anamarine (**3**).[10] In this paper, we also report the synthesis of the densely functionalized γ-lactones of type **12** (Chart 1) through the diastereoselective sequential conjugate additions of carbo-nucleophiles and reaction with electrophiles from the protected α,β-unsaturated-γ-lactones (+)-**9** and (+)-**10**.

RESULTS AND DISCUSSION

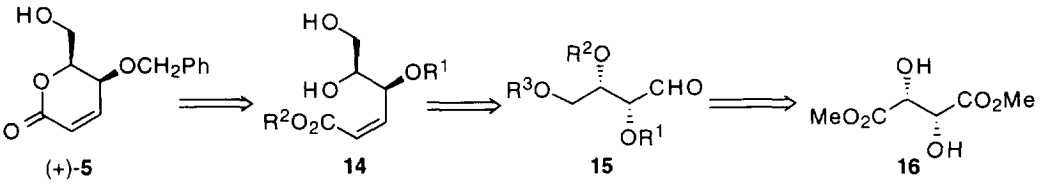
Synthesis of (*S,S*)-5-Benzyloxy-6-hydroxymethyl-5,6-dihydro-2H-pyran-2-one (+)-5.

The retrosynthetic analysis of the target lactone (+)-**5** is depicted in Scheme 2. This compound can be obtained by cyclization of the corresponding (*Z*)-δ-hydroxy-α,β-unsaturated acid derivative **14**, which in turn can be prepared from the protected aldehyde **15** through a stereoselective Wittig reaction as mentioned above. The sense of the chirality in the two stereogenic centers of **15** is the same as in commercial (*R,R*)-dimethyl tartrate **16**, which is a suitable starting material for the synthesis of (+)-**5**.

The synthesis is indicated in Scheme 3. In our hand, the reported synthesis[29] of the benzylidene acetal of (*R,R*)-dimethyl tartrate using zinc chloride as catalyst was low yielding and quite capricious. We obtained better results when *p*-toluenesulfonic acid was used as catalyst in refluxing benzene using a Dean-Stark device to remove water; the benzylidene acetal **17** was formed in high yield (91% isolated yield).[30] Although the method was satisfactory, the reaction time depended on the scale used. More reproducible results regarding the reaction time, and also in good yield, was obtained when the reaction was performed by refluxing a toluene solution containing (*R,R*)-dimethyl tartrate, a slight excess of benzaldehyde and a catalytic amount of *p*-

toluenesulfonic acid under a Soxhlet charged with 4 Å molecular sieves.[31] Under these experimental conditions, the acetal **24** was obtained in 83-88% isolated yield working in up to 0.1 mol scale.

Scheme 2



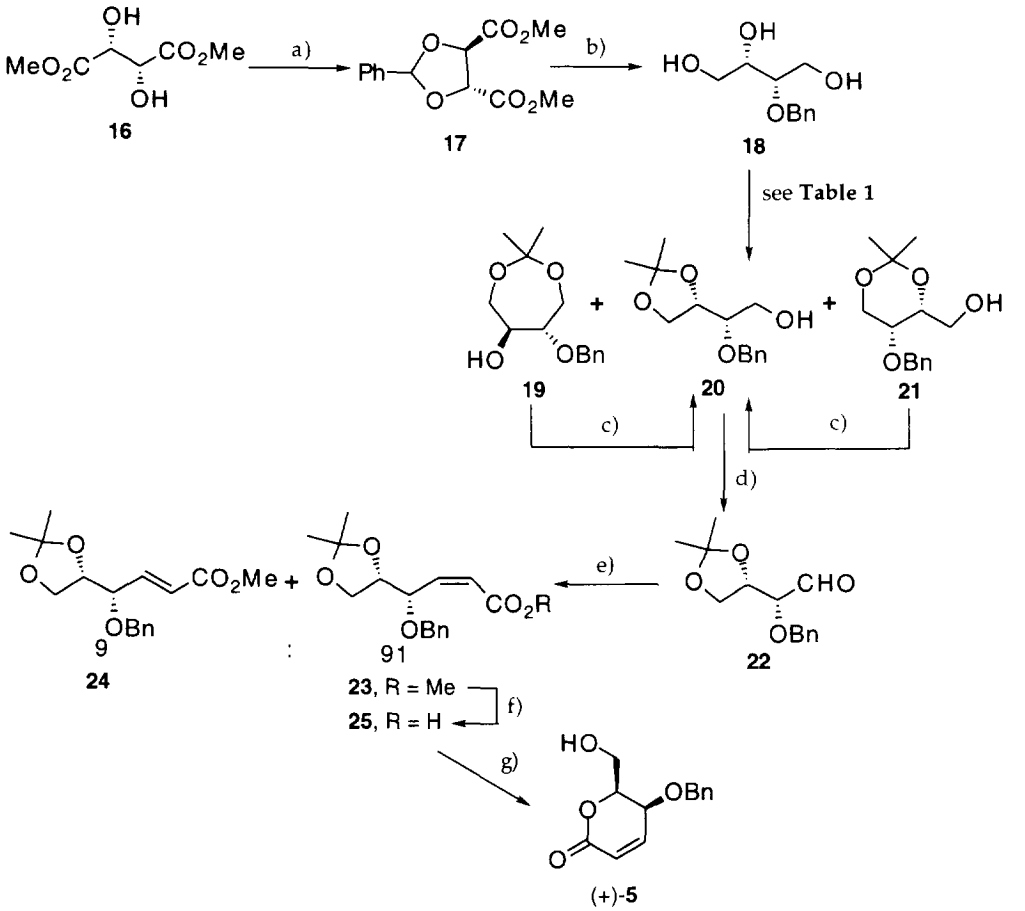
The reduction of **17** using a mixture of lithium aluminium hydride and aluminium chloride[32] under the conditions reported by Seebach and Hungerbühler[33] for the analogous ethyl ester afforded the monoprotected tetraol **18** in high yield.[34] To convert **18** to our target molecule it was necessary to selectively protect the secondary hydroxy group and one of the primary hydroxy groups, leaving the other primary hydroxy group free,[35] which would be oxidized to the aldehyde; which, by a Wittig reaction, would serve to elongate the chain. A suitable protection plan for two hydroxy groups is the isopropylidene acetal.[36] With the objective to optimize this transformation, we carried out a study of the influence of experimental conditions (reagents, catalysts, solvents and temperatures) on the selectivity and yield of the process. The results are indicated in Table 1.

Under most of the experimental conditions, mixtures of the three possible acetals **19**, **20** and **21** (as indicated by the elution order in chromatography) were obtained. The acetals were separated by flash-chromatography.[37] The three acetals were easily distinguished by the chemical shift of the acetalic and methyl carbons in ^{13}C-NMR spectroscopy: 101.4, 24.9, and 24.3 ppm for the 1,3-dioxepane (**19**), 109.4, 26.4, and 25.4 ppm for the 1,3-dioxolane (**20**), and 98.7, 28.9, and 19.0 ppm for the 1,3-dioxane (**21**) as previously found with model compounds.[38] The use of 2-methoxypropane (entries 1-3, Table 1), a well known reagent for kinetic acetonization,[39] afforded nearly equimolecular amounts of the three acetals, regardless of the amount of reagent and the nature of the catalyst. Better result were obtained when the triol **18** was reacted with 2,2-dimethoxypropane in refluxing benzene using *p*-toluenesulfonic acid as catalyst (entries 4-6), giving the dioxolane **20** as the major product. The use of a limited amount of reagent and short reaction time resulted in moderate selectivity (entry 4). Better selectivity and conversions were achieved with higher amounts of 2,2-dimethoxypropane and longer reaction times (entries 5 and 6).

The selectivity of the acetonization of **18** using acetone as reagent was dependent on the acidic catalyst used. Thus, the reaction of **18** with acetone using sulfuric acid as catalyst was very sluggish, and the selectivity was moderate (entry 7). The dioxolane **20** was obtained in high yield as a single isomer when the triol **18** and a high amount of *p*-toluenesulfonic acid were dissolved in a high excess of acetone and stirred at room temperature (entry 8, Table 1); but this transformation was efficient only at low scale; when the reaction was carried out at higher scale, we observed that the reaction was much slower than indicated in the entry 8 of Table 1. Fortunately, we found that concentrated perchloric acid was also a good catalyst for this reaction (entry 9); being possible to obtain reproducible results (reaction time, isolated yields, and selectivity) when the reaction was scaled-up (up to 40 mmol). Although under these conditions small amounts of **19** and **21** were also formed, they were readily separated by flash-chromatography. We found that undesired **19** and **21** were isomerized to **20** when submitted to the conditions reported in entry 9 of Table 1 (see Scheme 3). Combining

the two transformations (acetalation as reported in entry 9 and the isomerizations of the undesired acetals) allowed us to convert the triol **18** into the alcohol **20** in high yield (> 90%) and in multigram scale (> 8 grams).[40]

Scheme 3



a) PhCHO, TsOH, benzene, reflux, Dean-Stark water separator; or PhCHO, TsOH, toluene, 4Å ms, reflux (83-91%); b) $LiAlH_4$, $AlCl_3$, Et_2O, CH_2Cl_2, from rt to reflux (90-95%); c) acetone (xs), $HClO_4$, 4Å ms, rt (> 92%); d) PCC, NaOAc, 3Å or 4Å ms, CH_2Cl_2 rt; or NCS, SMe_2, toluene, -20°; e) $Ph_3P{=}CHCO_2CH_3$ (**13**), MeOH, rt (70-85%, 2 steps); f) LiOH, THF, MeOH, H_2O, rt; g) CF_3CO_2H, H_2O, CH_2Cl_2, rt (86%, 2 steps); or TsOH, toluene, rt (85%, 2 steps).

With a ready supply of **20**, we carried out the final steps of the synthesis of the lactone (+)-**5** as indicated in the Scheme 3. Whereas Collins oxidation[41] afforded the aldehyde **22** in low yield (27%), both Corey-Kim oxidation[42] and PCC oxidation[43] (in the presence of sodium acetate and molecular sieves[44]) furnished the corresponding aldehyde **22**. Although in low to moderate scale (up to 8 mmol), the Corey-Kim oxidation gave excellent result (90% yield), the reaction at higher scale was more problematic, producing complex crude reaction mixtures.[45] Because that, PCC oxidation proved to be the most practical method in larger scale (70-90% yield, > 8 mmol).

Table 1. Results of the acetonization reactions of **18**.

Entry	Experimental conditions[a)]	Products (isolated yields)
1	2-MP (2.5 mol equiv), TsOH (0.02 mol equiv), DMF, 0°, 0.75 hours	**19** (31%), **20** (34%), **21** (28%)
2	2-MP (1.1 mol equiv), PPTS (0.025 mol equiv), DMF, from -78° to r. t., 5 hours	**19** (33%), **20** (27%), **21** (20%)
3	2-MP (1.25 mol equiv), PPTS (0.08 mol equiv), DMF, from -20° (5 hours) and r. t., 1 hour	**19** (26%), **20** (31%), **21** (38%)
4	2,2-DMP (1.05 mol equiv), TsOH (0.03 mol equiv), benzene, 4 Å molecular sieves (2 mass equiv, 1 time)[b)], reflux, 0.5 hours	**19** (2%), **20** (45%), **21** (16%)
5	2,2-DMP (1.1 mol equiv), TsOH (0.03 mol equiv), benzene, 4 Å molecular sieves (1.6 mass equiv each time, 2 times)[c)], reflux, 3.25 + 3.75 hours	**19** (1.5%), **20** (70%), **21** (< 1%)
6	2,2-DMP (1.3 mol equiv), TsOH (0.01 mol equiv), benzene, 4 Å molecular sieves (0.5 mass equiv. each time, 2 times)[d)], reflux, 3 + 4 hours	**19** (8%), **20** (78%), **21** (4%)
7	acetone (30 mL/mmol), H_2SO_4 (1.0 + 1.0 mol equiv), 4 Å molecular sieves (2.0 + 2.0 mass equiv)[e)], r. t., 120 hours	**19** (20%), **20** (56%), **21** (10%)[f)]
8	acetone (110 mL/mmol), TSOH (0.4 mol equiv), r. t., 12 hours	**20** (94%)[g)]
9	acetone (25 mL/mmol), $HClO_4$ (1.0 mol equiv), 4 Å molecular sieves (3.0 mass equiv), r. t. , 28 hours[h)]	**19** (4%), **20** (89%), **21** (4%)

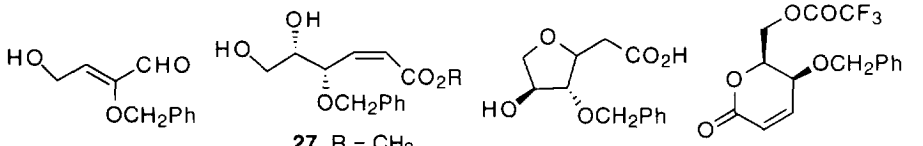
[a)] Abbreviations: 2-MP for 2-methoxypropane, 2,2-DMP for 2,2-dimethoxypropane, TsOH for *p*-toluenesulfonic acid, PPTS for pyridinium *p*-toluenesulfonate. Crude reaction product was analyzed by ^{13}C-NMR spectroscopy. The ratio of products found by NMR agreed with the isolated yield. [b)] The mixture was refluxed under a Soxhlet extractor charged with molecular sieves. Only one batch of molecular sieves was used. [c)] After 3.25 hours, a second batch of freshly activated molecular sieves was added. The mixture was additionally heated at reflux by 3.75 hours. d) After 3 hours, a second batch of freshly activated molecular sieves was added. The mixture was additionally heated at reflux by 4 hours. [e)] After 60 hours, 1.0 mol equiv of concentrated H_2SO_4 and a second batch of freshly activated 4Å molecularr sieves was added. [f)] *ca* 10% of starting material (**18**) was recovered. [g)] This result is for small scale (0.5-2 mmol) reaction. For medium scale reaction (2-5 mmol), reproducible results were obtained if the reaction was carried out in the presence of molecular sieves (1 mass equiv). [h)] The reaction was carried out from 1 mmol to 40 mmol, the results were reproducible.

Although the aldehyde **22** could be purified by rapid flash-chromatography, it was found to be easily hydratable and unstable,[46] eliminating acetone to give the α,β-unsaturated aldehyde **26** (Chart 2).[47] Due to this inconvenience, it was more appropriate to use crude aldehyde **22** in the Wittig reaction with the phosphorane **13** in methanol to obtain the (Z)-α,β-unsaturated ester **23** and its *E*- isomer **24** in a *ca* 91:9 ratio in 70-85% overall yield from the alcohol **20** (Scheme 3). These two isomers, which were separated by careful flash-chromatography, were identified by the chemical shifts and coupling constant of the olefinic protons [6.20 ppm (dd, J = 11.8, 9.1 Hz) and 6.01 ppm (dd, J = 11.8, 1.0 Hz) for the Z-isomer **23**, and 6.87 ppm (dd, J = 15.8, 6.1 Hz) and 6.13 ppm (dd, J = 15.8, 1.2 Hz) for the E-isomer **24**].[48]

Although it was expected that acid treatment of **23** would cause acetal cleavage (to **27**, Chart 2) and intramolecular transesterification to give the lactone (+)-**5** directly; this was not the case, and under a variety of experimental conditions,[49] the only isolated product was the diol **27** (Chart 2). Considering that the cyclization of the corresponding dihydroxy acid **28** (Chart 2) would be very smooth, sequential basic (KOH/MeOH) and acidic (HCl/THF) treatment from the ester **27** were tried; but under these conditions the crude reaction product

was a complex mixture; where, by ^{1}H-NMR analysis, no olefinic protons were observed, but a characteristic signal corresponding to the protons of the CH_2 group geminal to COOH (multiplet at *ca* 2.7 ppm), which indicated the presence of the tetrahydrofuran **29** (as a mixture of epimers) formed through intramolecular Michael addition from **27** (Chart 2).

Chart 2



26 **27**, R = CH_3 **28**, R = H **29** **30**

It was found that, on changing the sequence of hydrolyses, the target lactone (+)-**5** was obtained in good yield. Thus, basic hydrolysis (and further neutralization) of the ester **23** gave the corresponding acid **25** (Scheme 3), that, without purification, was dissolved in 9:1 (v/v) trifluoroacetic/water to give the lactone (+)-**5** in 86% isolated yield from the ester **23**, along with a small amount of the trifluoroacetyl derivative **30** (Chart 2). Similar isolated yield was obtained when the crude acid **25** was treated with *p*-toluenesulfonic acid in dry toluene.

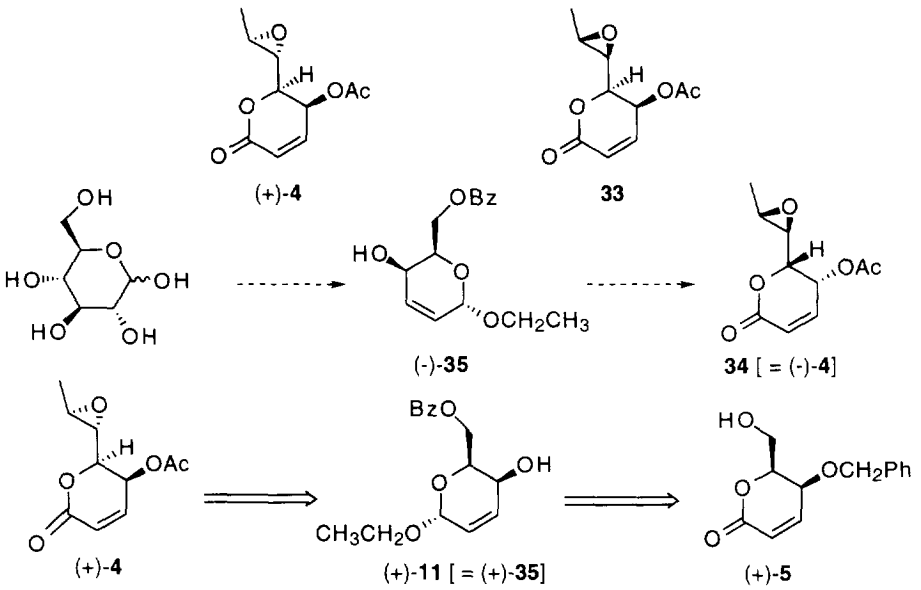
Summarizing, the α,β-unsaturated-δ-lactone (+)-**5** has been synthesized, in seven steps, from (*R,R*)-dimethyl tartrate in 43-49% overall yield.[50] The synthesis required only three chromatographic separations and it is amenable to be carry out at relatively large scale. The structural and stereochemical features of the lactone (+)-**5** make it a useful chiral building block for the synthesis of a variety of compounds. Some of these synthetic applications have already realized, such as in the lactone portion of (+)-anamarine,[10e] branched-chain sugars,[51] and in formal syntheses of (+)-asperlin and the C_1-C_8 fragment of (+)-olguine (as indicated below). Furthermore, because the lactone (+)-**5** is formally a sugar of the *L*-series, this compound can be a useful intermediate for the synthesis of these non-readily available and biologically important compounds.[52]

Synthetic Applications of the Lactone (+)-5: Formal Syntheses of (+)-Asperlin and Advanced Intermediates to (+)-Olguine.

(+)-Asperlin **4** is an antibiotic isolated from a culture of *Aspergillus nidulans*.[11] At the outset of our work on natural oxygenated α,β-unsaturated lactones, the absolute configurations at the oxiranyl carbons of (+)-asperlin were unknown: two structures (as indicated by **4** and **33** in Chart 3) were possible at that time. We carried out a stereoselective synthesis of the enantiomer of (+)-asperlin (i. e., compound **34**) starting from D-glucose, being the D-hex-2-enopiranoside (-)-**35** a key intermediate. Our former synthesis, although of the enantiomer of natural (+)-asperlin, served to assign the absolute configurations of all the stereogenic centers of the natural product.[11d] Because the lactone (+)-**5**, whose synthesis has been indicated above, has the same sense of absolute configurations in its two stereogenic centres than those of the lactonic fragment of (+)-asperlin; (+)-**5** would be a suitable chiral building block for the EPC-synthesis of (+)-asperlin. Due that our previous synthetic studies established (-)-**35** as a convenient intermediate for the preparation of (-)-asperlin **34**, we decided to prepare the *L*-hex-2-enopiranoside (+)-**11**, the enantiomer of (-)-**35**, constituting, therefore, a formal synthesis of natural (+)-asperlin. The transformation of (+)-**5** into (+)-**11** (Chart 3) would

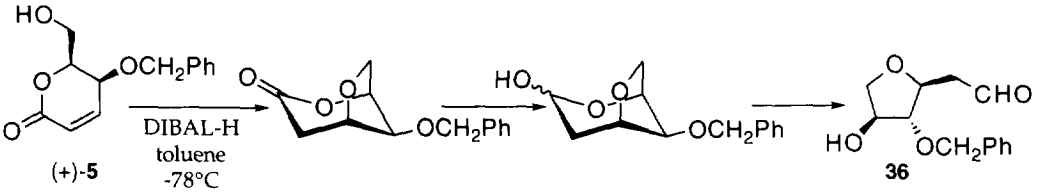
require the reduction of the lactone functionality to lactol, the subsequent masking of this, and the manipulation of protecting groups.

Chart 3



When the lactone (+)-**5** was treated with di(isobutyl)aluminium hydride (DIBAL-H), the expected unsaturated lactol was not formed, but compound **36** was obtained in moderate yield (50%) as the only product.[53] A plausible reaction course would involve the deprotonation of the hydroxy group, intramolecular Michael addition, reduction to the lactol, and tautomerization, as indicated in Scheme 4. Although, not useful for our purpose, it is worth to mention that the smooth and stereocontrolled intramolecular Michael addition to α,β-unsaturated lactones, such as (+)-**5**, could constitute a suitable synthetic method for the EPC-synthesis of functionalized heterocycles.[54]

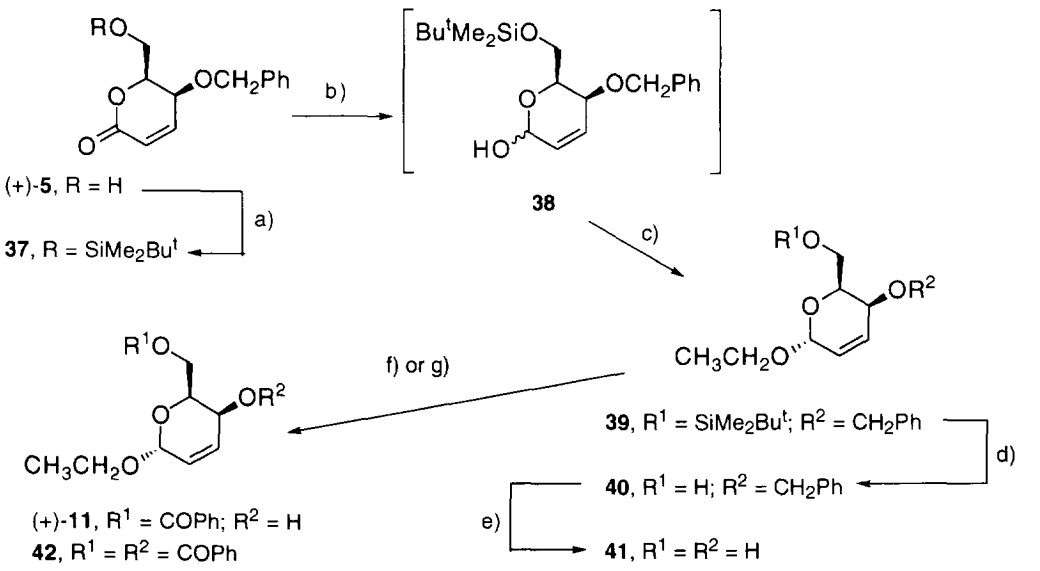
Scheme 4



From this preliminary result it was evident the necessity to protect the primary alcohol previous to any basic or reductive treatment. It was achieved in an efficient manner by silylation with *tert*-butyldimethylsilyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) as catalyst[55] to give the silyl ether **37** (Scheme 5). Although the reduction of **37** with DIBAL-H in toluene at -78°C yielded the lactol **38**, this compound was unstable at room temperature. Therefore, it was necessary to transform the lactone **37** into the glycoside **39** in a two-reactions, one-pot process. The lactone **37** was reduced at -78°C with DIBAL-H using toluene as

solvent and the reaction was quenched with an ethanolic solution of hydrogen chloride at -78°C. The mixture was left to reach room temperature and then was stirred at this temperature for 20 hours. In this way, the α-glycoside **39** was obtained as a single anomer in 58% overall yield from the lactone **37**. Compound **39** was desilylated with tetrabutylammonium fluoride to afford a product **40** that, without purification, was dissolved in THF and reacted with a solution of lithium in liquid ammonia at -78°C. The diol **41** was, in this way, obtained in 71% overall yield from **43**. This compound was benzoylated using phase transfer conditions[56] to afford the monobenzoylated product (+)-**11** (42% yield) along with the dibenzoylated product **42** (30% yield). Alternatively, a more efficient monoprotection of the diol **41** was achieved by a two steps procedure consisting on the dibenzoylation (excess benzoyl chloride/pyridine) of **41** to give the dibenzoate **42**, that, without purification, was dissolved in methanol and treated with a catalytic amount of potassium hydroxide at -20°C, to furnish the monobenzoate (+)-**11** in 67% overall yield from the diol **41** (Scheme 5). This efficent mono-alcoholysis of the dibenzoate **42** was probably achieved through the reaction of the primary benzoate and migration of the benzoyl group on C-4, a fact known in hex-2-enopiranosides with threo configuration.[57,58] Because the enantiomer of (+)-**11** [compound (-)-**35**, Chart 3] was previously transformed to (-)-asperlin,[11d] the synthesis of (+)-**11** is, hence, a formal synthesis of natural (+)-asperlin **4**.

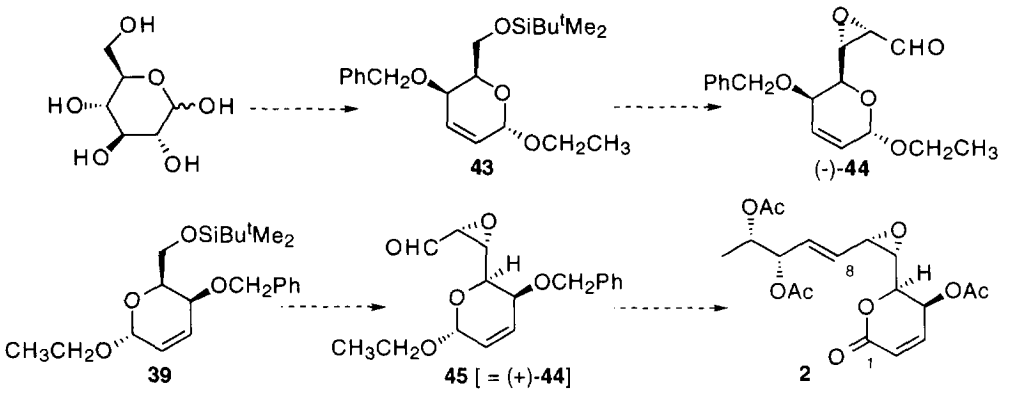
Scheme 5



a) ^{t}BuMe$_2$SiCl, Et$_3$N, DMAP, CH_2Cl_2, rt (93%); b) DIBAL-H, toluene, -78°; c) HCl, EtOH, toluene, from -78° to rt (58%, 2 steps); d) ^{n}Bu$_4$NF•3H$_2$O, THF, rt; e) Li, NH_3 (l), THF, from -78° to -20° (71%, 2 steps); f) PhCOCl, ^{n}Bu$_4$NHSO$_4$, NaOH, CH_2Cl_2, H_2O, rt (42%); g) 1) PhCOCl (xs),C_5H_5N, from 0° to rt; KOH, MeOH, -20° (67%, 2 steps).

Furthermore, the preparation of the intermediate **39** constitutes also a formal synthesis of the C_1-C_8 fragment of (+)-olguine. Previously,[9c] we employed the enantiomer of **39** (i. e.; compound **43**, Chart 4) in the synthesis of the epoxialdehyde (-)-**44**. Analougously, the glycoside **39** (Scheme 5) might be transformed into **45** [the enantiomer of (-)-**44**], which is a synthetic equivalent of the C_1-C_8 fragment of (+)-olguine **2**.

Chart 4

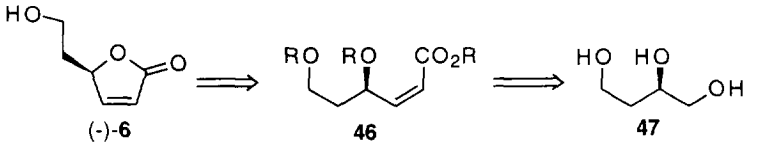


Summarizing, it has been shown that the lactone (+)-**5** is a useful chiral building block for the preparation of advanced intermediates for natural polyoxygenated α,β-unsaturated-δ-lactones, as demonstrated in the formal syntheses of (+)-asperlin and the C_1-C_8 fragment of (+)-olguine.

Synthesis of (*R*)-5-(2-Hydroxyethyl)-2(5H)-furanone (-)-6.

The retrosynthetic analysis for (-)-**6** is shown in Scheme 6. The sense of the chirality of the stereogenic centre in the target molecule is the same as in (*R*)-1,2,4-butanetriol (**47**). To convert **47** to the butenolide (-)-**6**, it is necessary to selectively protect the hydroxy groups of C-2 and C-4 and to elongate the chain to the α,β-unsaturated ester with *Z*-configuration (compound **46**). These two goals have been efficiently achieved by the known tendency of polyhydroxylated compounds to give six-membered cyclic acetals when reacted with aromatic aldehydes under thermodinamically controlled conditions,[59] and the *Z*-stereoselective Wittig reaction between alkoxy aldehydes and methoxycarbonylmethylentriphenylphosphorane **13** as discussed above.[18]

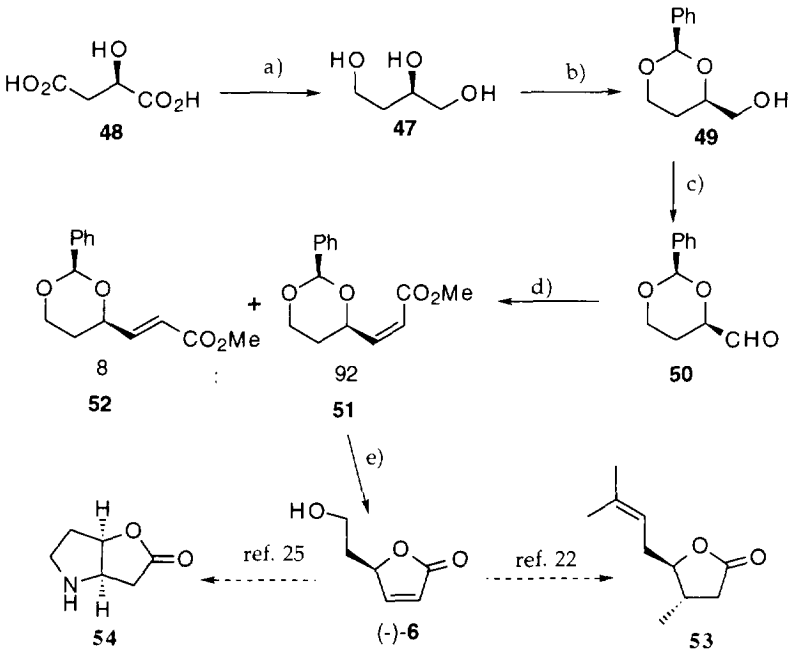
Scheme 6



The synthesis is indicated in Scheme 7. Reduction of (*R*)-malic acid **48** with borane-dimethyl sulfide complex according to the method of Hanessian[60] afforded (*R*)-1,2,4-butanetriol **47** in 97% yield after chromatography. The hydroxy groups of C-2 and C-4 of the triol **47** were protected as benzylidene acetal by heating at reflux a toluene solution of **47** with a slight excess of benzaldehyde or benzaldehyde dimethyl acetal and a catalytic amount of *p*-toluenesulfonic acid under a Soxhlet extractor charged with 4 Å molecular sieves[31] to give regio- and stereo-selectively the *cis*-1,3-dioxane **49** in good yield,[61,62] along with a trace amount of its epimer (the *trans*-1,3-dioxane) and a small amount of the regioisomeric 1,3-dioxolanes (as a *ca.* 1:1 mixture of *cis*- and *trans*-diastereoisomers in *ca* 10% overall yield). PCC/molecular sieves oxidation of the alcohol **49** gave the corresponding aldehyde **50**, although only in moderate yield (57%). Better results were obtained by

Swern oxidation,[63] which gave the aldehyde **50** in high yield (> 85%). Although this aldehyde could be purified by rapid flash-chromatography, it proved to be relatively unstable and easily hydratable,[46] and it was used in the next step without purification. Thus, crude Swern oxidation product was dissolved in dry methanol and treated with 1.5 molar equivalents of methoxycarbonylmethylentriphenylphosphorane (**13**) at low temperature to give a 92:8 mixture of the (*Z*)-α,β-unsaturated ester **51** and its *E*-isomer **52** in 60-65% overall yield from **49**.[64] These two isomers, which were separated by careful flash-chromatography, were identified by the chemical shifts and coupling constant of the olefinic protons [6.36 ppm (dd, J = 11.7, 7.2 Hz) and 5.83 ppm (dd, J = 11.7, 1.4 Hz) for the *Z*-isomer **51**, and 6.97 ppm (dd, J = 15.7, 4.1 Hz) and 6.17 ppm (dd, J = 15.7, 1.9 Hz) for the *E*-isomer **52**].[48] The acetal **51** was hydrolyzed with acetic acid/water to give the target lactone (-)-**6** in quantitative yield.

Scheme 7



a) BH_3•SMe_2, $B(OMe)_3$, THF, r.t. (97%); b) PhCHO or $PhCH(OMe)_2$, TsOH, 4Å ms, toluene, reflux (> 85%); c) $(COCl)_2$, DMSO, CH_2Cl_2, -60°; Et_3N; d) $Ph_3P{=}CHCO_2CH_3$ **13**, MeOH, -78° to r. t. (60-65%, 2 steps); e) AcO/$H_2$0 (4:1, v/v), r.t. (99%).

Summarizing, the preparation of (-)-**6** from (*R*)-malic acid is quite efficient, requiring only 5 steps, the overall yield being 48-53%. Moreover, as it has been mentioned above, the preparation of the (-)-**6** constitutes formal syntheses of (+)-eldanolide **53**[22] and the (+)-Geissman-Waiss lactone **54**[25] (Scheme 7).

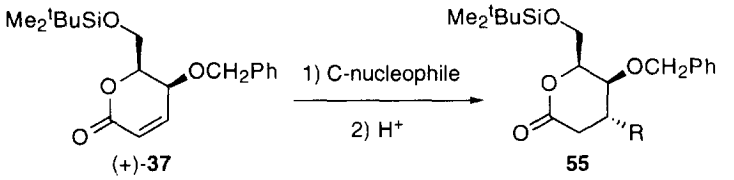
Stereoselective Transformations from Derivatives of (5*R*,1'*S*)-5-(1-Hydroxyethyl)-2(5H)-furanone.

Although a likely mechanism of the biological activity of the natural polyoxygenated α,β-unsaturated-γ- and δ-lactones indicated above (e. g.; **2**, **3**, and **4**) is through the conjugate addition of some nucleophilic

biomolecule (probably an amino or thiol protein),[65] it is surprising that the stereocontrolled conjugate addition of nucleophiles to simpler oxygenated α,β-unsaturated-γ- and δ-lactones has been scarcely studied.[66]

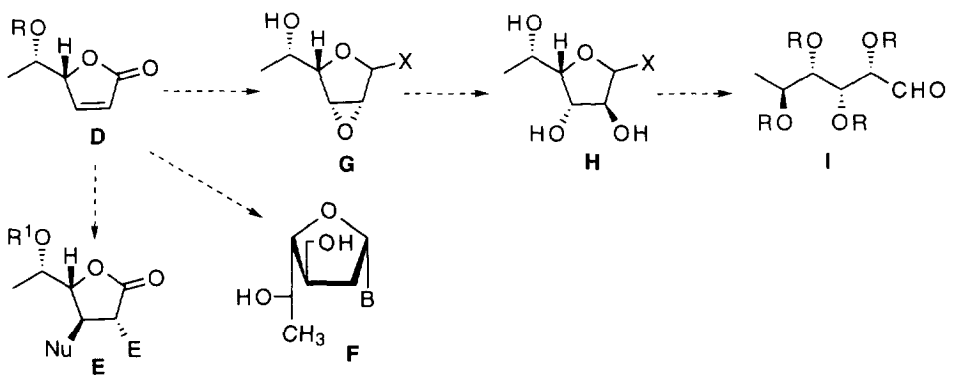
In connection with our interest on the stereocontrolled carbon-carbon bond formation on lactone templates, we have recently reported[51] the conjugate addition of both copper reagents and soft carbo-nucleophiles to the unsaturated lactone (+)-**37**, finding that the reaction was highly diastereoselective, giving **55** as single isomers at the heterocyclic stereogenic center (Scheme 8).

Scheme 8



On continuing our studies on the stereoselective transformations from chiral α,β-unsaturated lactones, we have used derivatives of (5*R*,1'*S*)-5-(1-hydroxyethyl)-2(5H)-furanone (**D**, Chart 5) to perform sequential conjugate addition and reaction with electrophile to afford the densely functionalized butanolide **E**. Aditionally, **D** would be a suitable chiral building block for the synthesis of branched-chain nucleoside analogues (e. g. **F**, Chart 5).[8] Also, the lactone **D** might be a useful precursor for the synthesis of (+)-anamarine (**3**, see Chart 1);[67] the planned work would involve the hydroxy-directed diastereoselective epoxidation (to **G**),[68] and regioselective opening of the epoxide (to **H**), which is a synthetic equivalent of 6-deoxy-*L*-glucose (**I**, Chart 5), which constitutes the side chain of natural (+)-anamarine **3**.

Chart 5

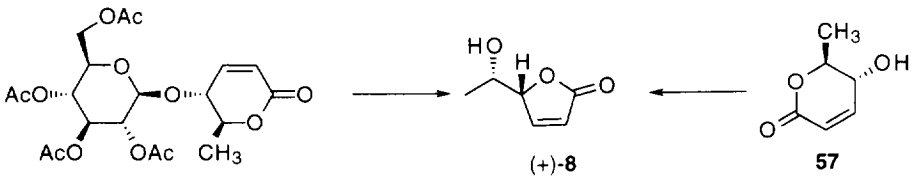


The α,β-unsaturated-γ-lactone (+)-**8** is a natural product with antifeedant activity.[27] Also it was obtained, albeit in low yield and small scale, during the hydrolytic cleavage of tetra-O-acetylosmundalin **56** and by isomerization of osmundalactone **57** (Scheme 9).[69] The lactone (+)-**8** was also prepared in 8 steps from 1-bromo-2,3-butanedione using a chemoenzymatic approach.[70,71]

In order to find a practical synthesis of our target lactone (+)-**8**, we decided to investigate further the isomerization of **57**. Although considerable experimentation was required to optimize the process,[72] we were pleased to find that treatment of (-)-**7** with barium hydroxyde was chemoselective, causing the hydrolysis of

the acetate and translactonization to give (+)-**8** in 91% isolated yield (Scheme 10). The substrate of the hydrolysis, compound (-)-**7**, was prepared by oxidative rearrangement of 3,4-di-O-acetyl-L-rahmnal **58**, according to the method reported by Lichtenthaler.[12b] With a convenient access to the lactone (+)-**8**, we protected the hydroxy group to obtain derivatives suitable for the planned transformations (to **E**, Chart 5). Due to the sensitivity of the lactone **8** to basic conditions, it was essential to protect the hydroxyl group under slightly acidic conditions. Thus, the methoxymethyl acetal (+)-**9** was obtained by reaction of **8** with dimethoxymethane promoted by phosphorus pentoxide;[73] and the benzyl ether (+)-**10** was prepared by reaction of **8** with benzyl trichloroacetimidate under acidic catalysts (Scheme 10).[74]

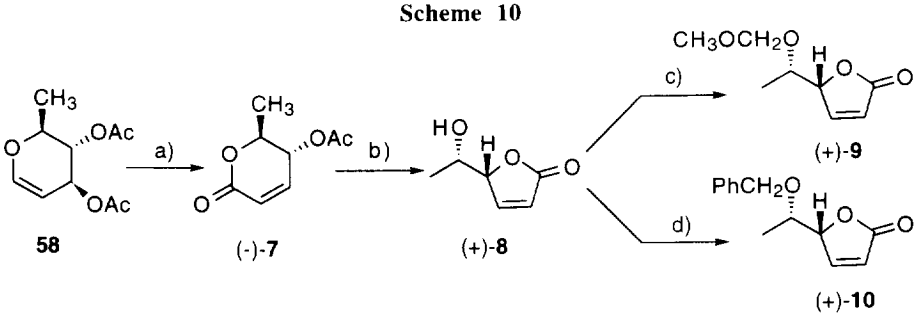
Scheme 9



56 (+)-**8** **57**

The conjugate additions of lithium dialkylcuprates, in the presence of trimethylsilyl chloride,[75] and the anion generated from diethyl malonate to the unsaturated lactones (+)-**9** and (+)-**10** were realized as previously reported with the lactone **37** (Scheme 11).[51] The results, along with some experimental details are indicated in Table 2. It was observed that, in all the cases examined a single diastereoisomer was detected by ^{1}H-NMR (diastereoselectivity > 90%), to give compunds **59-64**. Although ^{1}H-NMR spectra of crude products indicated that the reaction were quite clean, the isolated yield of the conjugate addition product was only modest, probably reflecting a relatively high volatility of these compounds, as it has been observed before.[76]

Scheme 10



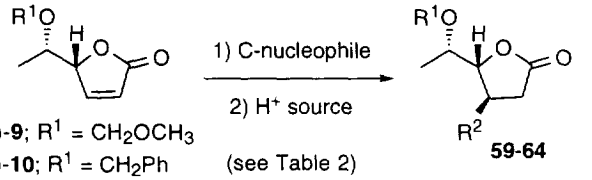
58 (-)-**7** (+)-**8** (+)-**9** (+)-**10**

a) mCPBA, $BF_3.OEt_2$, CH_2Cl_2, -20° (82%); b) $Ba(OH)_2$, THF/H_2O (1:1), rt (91%); c) $(MeO)_2CH_2$ (xs), P_2O_5, $CHCl_3$, rt (80%); d) $Cl_3C(=NH)$-OBn; CF_3SO_3H, cyclohexane/CH_2Cl_2 (2:1), rt (53%).

The relative stereochemistry of the new stereogenic centre was assigned as indicated in structures **59-64** considering the most likely course of the nucleophilic attack (*trans*-addition to the substituent on the heterocyclic ring);[77] and confirmed by analysis of the coupling constant in the ^{1}H-NMR spectra of these compounds as well as NOESY and NOE experiments. All these lactones showed the same coupling pattern in H-3, H-4, H-5, and H-6 in the ^{1}H-NMR spectra, which indicated the same stereochemical course of all the conjugate additions to both α,β-unsaturated-γ-lactones **9** and **10** (see Experimental Part). Additional proves of the proposed structure of the conjugate addition products came from a NOESY spectrum of **59** and a NOE

experiment on **61**, which showed the existence of NOEs between H-4 and the methyl group of the substituent at C-5 of the 2(5H)-furanone in both compounds, as well as the absence of NOE between H-4 and H-5 in the NOESY spectrum of **59**.[78]

Scheme 11



(+)-**9**; $R^1 = CH_2OCH_3$
(+)-**10**; $R^1 = CH_2Ph$
(see Table 2)

Table 2. Results of the Michael addition to the α,β-unsaturated-δ-lactones (+)-**9** and (+)-**10**.

Entry	Starting Material	Experimental Conditions	R^1	R^2	Product (Yield)[a]
1	(+)-**9**	Me_2CuLi (4 mol equiv) TMSCl (10 mol equiv) Et_2O, -20°, 18.5 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	CH_2OCH_3	CH_3	**59** (50%)
2	(+)-**9**	Bu_2CuLi (4 mol equiv) TMSCl (10 mol equiv) Et_2O, -20°, 5 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	CH_2OCH_3	$(CH_2)_3CH_3$	**60** (58%)
3	(+)-**9**	$CH_2(CO_2Et)_2$ (2 mol equiv) $KOBu^t$ (2 mol equiv) THF, r. t., 19 hours; NH_4Cl/H_2O, 0° to r. t.	CH_2OCH_3	$CH(CO_2Et)_2$	**61** (30%)
4	(+)-**10**	Me_2CuLi (4 mol equiv) TMSCl (10 mol equiv) Et_2O, -20°, 5.25 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	CH_2Ph	CH_3	**62** (40%)
5	(+)-**10**	Bu_2CuLi (4 mol equiv) TMSCl (10 mol equiv) Et_2O, -20°, 4.25 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	CH_2Ph	$(CH_2)_3CH_3$	**63** (43%)
6	(+)-**10**	$CH_2(CO_2Et)_2$ (2 mol equiv) $KOBu^t$ (2 mol equiv) THF, r. t., 19.5 hours; NH_4Cl/H_2O, 0° to r. t.	CH_2Ph	$CH(CO_2Et)_2$	**64** (45%)

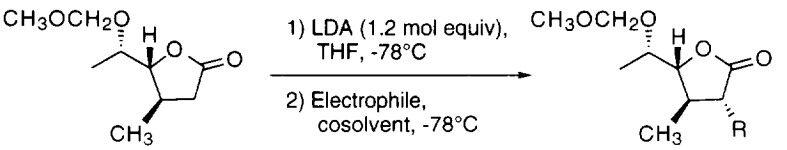
[a] Isolated yields after flash chromatography.

In order to further extend the synthetic potential of these chiral lactones, we have performed some preliminary studies on the reaction with carbo- and hetero-electrophiles of the enolate generated from the lactone (+)-**59** (Scheme 12). The results are indicated in Table 3.

In all the cases, the major product of this reaction came from attack of the electrophile on the 3*Re*-face of the enolate to give the 3,4-*trans*-diastereoisomers. In the reaction with methyl iodide, a sterically undemanding electrophile, a moderate selectivity was achieved, giving **65** and its epimer as a 3:1 inseparable mixture (Table 3, entry 1). Excellent selectivity, albeit in lower yield, was obtained in the reaction of the lithium enolate of (+)-**59** with allyl bromide (entry 2), giving **66** (30%), along with 30% of unreacted starting

material. The aldol reaction of the enolate of (+)-**59** with *p*-chlorobenzaldehyde afforded an inseparable mixture of three diastereoisomers in a *ca* 47:35:18 ratio (entry 3); although not rigorously proved, we assume that the two majors diastereoisomers **67a** and **67b** (Chart 6) came from the attack on the *Re*-face of the enolate, these two compounds being epimeric at the exocyclic stereogenic center; the third diastereoisomer (**67c**) must result from the attack on the *Si*-face of the enolate; therefore the facial diastereoselectivity of attack to the enolate is *ca* 82%. The reaction with the hetero-electrophile, di-*tert*-butyl azodicarboxylate,[79] proceeded with good diastereoselectivity and yield, giving the α-hydrazino lactone **68**, which can be a useful intermediate for the synthesis of modified amino acids and peptidomimetics.[80]

Scheme 12



(+)-**59** **65-68**

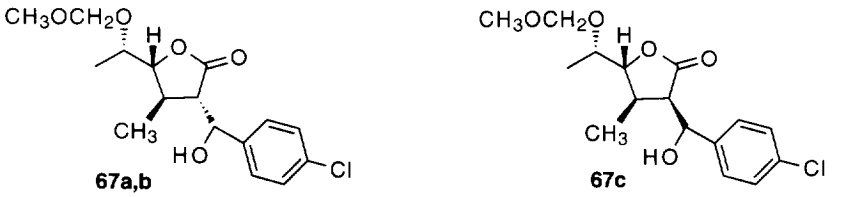
Table 3. Results of the alkylation of the enolate generated from the lactone (+)-**59**.

Entry	Electrophile (Amount)	Cosolvent[a]	Reaction Time	Ratio of isomers	R	Product (Yield)[b]
1	CH_3I (10 mol equiv)	DMPU	3 h	3:1[c],[d]	CH_3-	**65** (75%)[e]
2	CH_2=CH-CH_2Br (5 mol equiv)	DMPU	3 h	25:1[c],[d]	CH_2=CH-CH_2-	**66** (30%)
3	*p*-Cl-C_6H_4-CHO (3 mol equiv)	DMPU	4 h	47:35:18[c]	*p*-Cl-C_6H_4-C(OH)H-	**67** (80%)[e]
4	BOC-N=N-BOC (1.25 mol equiv)	--	0.5 h	> 10:1[c]	BOC-NH-N(BOC)-	**68** (87%)

[a] In the cases indicated, a 3:2 mixture (v/v) of THF:DMPU was used. [b] Isolated yields after flash-chromatograpy. [c] The ratio of diastereoisomers was determined by ^{1}H- and ^{13}C-NMR spectroscopy analysis of the crude reaction product. [d] The ratio of diastereoisomers was determined by capillary g. l. c. of the crude reaction product. [e] Obtained as an inseparable mixture of diastereoisomers.

The configuration of the major diastereoisomer of each reaction was tentatively assigned as indicated in structure **65-68**, based on the most likely steric course: *trans*-attack to the sustituent in C-4,[81] and corroborated[78] by the observation of a strong NOE between H-3 and C$\underline{H}_3$-C(4) in the NOESY spectrum of the allyl derivative **66**. The absence of NOE between H-4 and H-5 in the NOESY spectrum of **66** is also significant, which indicates a trans relationship between the substituents at C-4 and C-5, confirming the stereochemistry of the starting material [(+)-**59**].

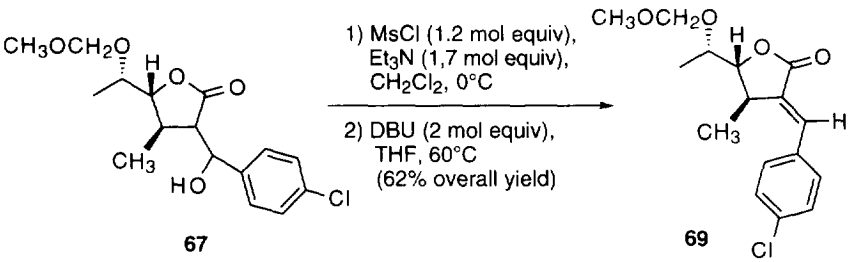
Chart 6



67a,b **67c**

The aldol products **67** are also good edducts for the preparation of more highly functionalized derivatives. Thus, water elimination from the mixture of diastereoisomers **67** gave selectively (*ca* 95% ds, g. l. c. analysis) the exocyclic unsaturated lactone **69** (Scheme 13),[82] which can be a useful chiral building block for further synthetic applications.

Scheme 13



67 **69**

Summarizing, the preliminary results of the conjugate addition to the α,β-unsaturated-γ-lactones (+)-**9** and (+)-**10** and the reactions of the enolate generated from (+)-**59** show good stereoselectivity. Our improvements in the synthesis of the lactone (+)-**8**, combined with the diastereoselective transformations indicated above, allow us to obtain densely functionalized chiral building blocks, which can be useful for organic synthesis.

CONCLUSION

It has been demonstrated that the strategy indicated in Scheme 1 is suitable for achieving practical EPC-syntheses of oxygenated α,β-unsaturated-γ- and δ-lactones. These compounds are useful chiral building blocks for a variety of purposes, some of them have been shown in the present paper. Additional synthetic applications of these and other related chiral compounds are in progress.

EXPERIMENTAL PART

All the reactions with sensitive materials were carried out using dry solvents under argon or nitrogen atmosphere. All the solvents and chemicals were commercially available and, unless otherwise indicated, were used as received. When necessary, tetrahydrofuran, diethyl ether and toluene were freshly dried over sodium-benzophenone ketyl. Methylene chloride and pyridine were dried over CaH_2 under argon and kept over molecular sieves. Acetone was distilled over anhydrous K_2CO_3 under argon. Dimethylformamide was distilled from anhydrous $MgSO_4$ under a reduced pressure of argon. Benzaldehyde was freshly distilled under a reduced pressure of argon. Copper(I) iodide was purified by continuous extraction with refluxing dry THF. ^{1}H-NMR and ^{13}C-NMR spectra were measured in *Varian-XL-300*, *Varian-Gemini-200*, or *Bruker AM-200*; chemical shift are reported in parts per million (δ), and the coupling constants are indicated in Hz. ^{1}H-NMR spectra were referenced to either the residual proton in the deuterated solvent or TMS. ^{13}C-NMR spectra were referenced to the chemical shifts of the deuterated solvent. The multiplicity of the signals in the ^{13}C-NMR spectra were determined by APT or DEPT experiments. The IR spectra were taken in a *Perkin Elmer-657 spectrometer*, the frequencies in the IR spectra are indicated in cm^{-1}. Unless otherwise indicated, all the mass spectra are low-resolution electron-impact

(70 eV) mass spectra, and were recorded in a *RMU-GMG* spectrometer from *Hitachi-Perkin-Elmer*. Microanalysis were realized by E. Barbero (*Instituto de Química Orgánica, C. S. I. C.*) in a *Carlo Erba EA 1180-Elemental Analyzer*. The optical rotations were measured in a *Perkin-Elmer 241 MC* polarimeter; all the optical rotations were measured at room temperature (21-24°C), using $CHCl_3$ as solvent. Unless otherwise indicated, all the preparative chromatographies were done with silica gel (40-63 mm) using the technique of flash-chromatography.[37]

Synthesis of (*R,R*)-4,5-Dimethoxycarbonyl-2-phenyl-1,3-dioxolane 17.

Method A. A mixture of benzaldehyde (4.3 mL, 42 mmol), (*R,R*)-dimethyl tartrate (6.0 g, 34 mmol) and $TsOH{\cdot}H_2O$ (200 mg, 0.1 mmol) in dry benzene (60 mL) was heated at reflux, under an argon atmosphere using a Dean-Stark device for removing water, for 45 hours. After this time, the mixture was concentrated up to a volume of 15 mL by distillation under argon. On cooling at room temperature, a precipitate was obtained which was filtered and washed with aqueous 2% Na_2CO_3, water, 40% aqueous $NaHSO_3$, and water. The solid was dried and crystallized from hexane to give pure **17** (8.2 g, 91% yield). M. p. 70°C (lit[29]: 69-70°C) $[\alpha]_D$ -42 (c = 0.5) (lit[29]: -40°). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.53-7.23 (m, 5H), 6.08 (s, 1H), 4.90 (d, *J* = 4.0, 1H), 4.75 (d, *J* = 4.0, 1H), 3.80 (s, 3H), 3.72 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 169.8 (s), 169.2 (s), 135.1 (s), 129.8 (d), 128.2 (2C, d), 127.0 (2C, d), 106.6 (d), 77.3 (d), 77.0 (d), 52.7 (2C, d). IR (KBr) ν 2420, 1760, 1465, 1435, 1400, 1265, 1240, 1220, 1110, 1085, 980, 925, 765, 710.

Method B. A mixture of (*R,R*)-dimethyl tartrate (53.4 g, 0.3 mol), $TsOH{\cdot}H_2O$ (5.7 g, 0.03 mol), and benzaldehyde (39.6 mL, 0.39 mol) in dry toluene (900 mL) was heated at reflux under a Soxhlet charged with 4Å molecular sieves (53 g) for 7 hours under argon. After cooling at room temperature, K_2CO_3 (20 g) was added, and the mixture was stirred for 30 minutes. After this time, the solid was filtered off and washed with CH_2Cl_2. The organic solvent was removed under vacuum, and the solid residue was crystallized from hexane/ethyl acetate to give pure **17** (65.4 g, 83% yield).

Synthesis of (*S,S*)-2-Benzyloxy-1,3,4-butanetriol 18.

A solution of $AlCl_3$ (106.7 g, 0.8 mol) in diethyl ether (360 mL) was added dropwise to a suspension of $LiAlH_4$ (30.4 g, 0.8 mmol) in diethyl ether (600 mL) at -20°C. The mixture was diluted with CH_2Cl_2 (1 L) and a solution of **17** (53.2 g, 0.2 mmol) in CH_2Cl_2 (600 mL) was added dropwise. Once the addition was finished, the mixture was stirred for 1 hour at room temperature and heated at reflux for 3 hours. The mixture was cooled at -20°C, and sequentially treated with water (60 mL) and 10N aqueous solution of KOH (230 mL). After removing the cooling bath, the mixture was stirred at room temperature overnight, diluted with THF (350 mL), and stirred at 30-35°C for 2 hours. After cooling at room temperature, the mixture was filtered over celite. The solvents were removed under vacuum to give one batch of **18** (27 g). The residue was extracted with CH_2Cl_2 in a Soxhlet for 4 days, evaporation of the solvent gave additional **18** (11.7 g, 93% yield), identical to the reported in the literature.[33] ^{1}H-NMR (200 MHz, acetone-d_6) δ 7.42-7.20 (m, 5H), 4.76 (d, *J* = 11.7, 1H), 4.63 (d, *J* = 11.7, 1H), 3.87-3.70 (m, 4H), 3.70-3.55 (m, 5H). ^{13}C-NMR (50.3 MHz, acetone-d_6) δ 139.8 (s), 129.0 (2C, d), 128.7 (2C, d), 128.3 (d), 80.5 (d), 73.02 (t), 72.96 (d), 63.8 (t), 61.6 (t).

Reaction of (*S,S*)-2-Benzyloxy-1,3,4-butanetriol 18 with 2-Methoxypropene (Table 1, Entries 1-3).

A solution of 2-methoxypropene (2.5 mL, 27 mmol) in dry DMF (15 mL) was dropwise added to a solution of the triol **18** (2.3 g, 10.8 mmol) and $TsOH{\cdot}H_2O$ (25 mg, 0.13 mmol) in DMF (20 mL) at 0°C. After stirring at this temperature for 45 minutes, the mixture was treated with K_2CO_3 (25 mg), and allowed to reach room

temperature. Then, DMF was distilled off under reduced pressure (1 mm Hg). The residue was taken up with $CHCl_3$ and washed with aqueous saturated solution of borax ($Na_2B_4O_7$), water, and brine. After drying (Na_2SO_4), the solvent was evaporated, and the residue was carefully flash-chromatographed (3:2, 1:1, and 2:3 hexane/AcOEt mixtures) to give **19** (831 mg, 31% yield), **20** (904 mg, 34% yield), and **21** (743 mg, 28% yield).

Note: The experiments reported in entries 2 and 3 of Table 1 were caried out analogously, but changing the acid catalyst, the temperature, and the reaction time, as indicated in Table 1.

(*S,S*)-5-Benzyloxy-6-hydroxy-2,2-dimethyl-1,3-dioxepane 19. Thick oil. $[\alpha]_D$ +49 (c = 0.7). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 4.70 (d, *J* = 12.0, 1H), 4.58 (d, *J* = 12.0, 1H), 3.93 (dd, *J* = 11.9, 1.5, 1H), 3.74-3.50 (m, 4H), 3.34 (m, 1H), 2.50 (d, *J* = 6.7, 1H), 1.37 (s, 3H), 1.34 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 138.2 (s), 128.4 (3C, d), 127.8 (2C, d), 101.4 (s), 80.0 (d), 71.3 (t), 71.0 (d), 61.2 (t), 58.7 (t), 24.9 (q), 24.3 (q). MS *m/z* 237 (M-15, 2), 194 (8), 92 (95), 91 (100), 69 (90). Anal. calcd. for $C_{14}H_{20}O_4$: C, 66.64%; H, 7.99%. Found: C, 66.49%; H, 8.06%.

(*S,S*)-4-(1'-Benzyloxy-2'-hydroxy)ethyl-2,2-dimethyl-1,3-dioxolane 20. Thick oil. $[\alpha]_D$ -17 (c = 0.2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 4.77 (d, *J* = 11.7, 1H), 4.68 (d, *J* = 11.7, 1H), 4.30 (distorted q, *J* = 6.6, 1H), 4.01 (dd, *J* = 8.3, 6.7, 1H), 3.80 (dd, *J* = 8.3, 7.2, 1H), 3.75 (m, 1H), 3.72 (m, 1H), 3.57 (m, 1H), 2.25 (broad s, 1H), 1.46 (s, 3H), 1.38 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 139.4 (s), 128.5 (2C, d), 127.9 (2C, d), 127.8 (d), 109.4 (s), 79.5 (d), 76.7 (d), 72.9 (t), 65.7 (t), 61.8 (t), 26.4 (q), 25.4 (q). MS *m/z* 237 (M-15, 5), 194 (13), 134 (10), 101 (95), 91 (75), 61 (39), 43 (100). Anal. calcd. for $C_{14}H_{20}O_4$: C, 66.64%; H, 7.99%. Found: C, 66.83%; H, 8.07%

(*S,S*)-5-Benzyloxy-4-hydroxymethyl-2,2-dimethyl-1,3-dioxane 21. M. p. 60-61°C (AcOEt-hexane). $[\alpha]_D$ +64 (c = 0.3). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.77 (d, *J* = 12.3, 1H), 4.43 (d, *J* = 12.3, 1H), 4.09-3.92 (m, 3H), 3.91-3.78 (m, 1H), 3.65 (m, 1H), 3.31 (q, *J* = 2.2, 1H), 1.47 (s, 3H), 1.46 (s, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 137.9 (s), 128.4 (2C, d), 127.8 (2C, d), 127.7 (d), 98.7 (s), 71.9 (d), 70.7 (t), 69.9 (d), 62.5 (t), 61.2 (t), 28.9 (q), 19.0 (q). MS *m/z* 252 (M^+, < 1), 237 (1), 194 (25), 131 (25), 92 (90), 91 (100). Anal. calcd. for $C_{14}H_{20}O_4$: C, 66.64%; H, 7.99%. Found: C, 66.71%; H, 8.11%.

Reaction of (*S,S*)-2-Benzyloxy-1,3,4-butanetriol (18) with 2,2-Methoxypropane (Table 1, Entries 4-6).

Method A (entry 4). A mixture of the triol **18** (4.8 g, 22.6 mmol), 2,2-dimethoxypropane (2.9 mL, 23.6 mmol) and $TsOH{\cdot}H_2O$ (144 mg, 0.76 mmol) in dry benzene (100 mL) was heated at reflux under a Soxhlet charged with 4Å molecular sieves (9.5 g) for 30 minutes. After cooling at room temperature, anhydrous K_2CO_3 (300 mg) was added, and the mixture was stirred at room temperature for 6 hours. The solid residue was filtered off, the solution was diluted with Et_2O, and sequentially washed with saturated solution of borax, water and brine. The organic phase was dried (Na_2SO_4), and the solvent was removed. The residue was chromatographed to give **19** (114 mg, 2% yield), **20** (2.57 g, 45% yield), and **21** (912 mg, 16% yield).

Method B (entry 5). A mixture of the triol **18** (2.85 g, 13.4 mmol), 2,2-dimethoxypropane (1.9 mL, 14.7 mmol) and $TsOH{\cdot}H_2O$ (86 mg, 0.45 mmol) in dry benzene (60 mL) was heated at reflux under a Soxhlet charged with 4Å molecular sieves (4.5 g) for 3.25 hours. After this time, another batch of 4Å molecular sieves (4.5 g) was added, and the mixture was heated at reflux for 3.75 hours. Although starting material (**18**) was detected by t. l. c., the reaction did not progress anymore. Work up and purification as in the precedent procedure gave **19** (50 mg, < 2% yield) and **20** (2.37 g, 70% yield). Traces of **21** were detected by t. l. c., although not isolated.

Method C (entry 6). A mixture of the triol **18** (11.1 g, 52.4 mmol), 2,2-dimethoxypropane (8.4 mL, 68.1 mmol) and $TsOH{\cdot}H_2O$ (125 mg, 0.66 mmol) in dry benzene (250 mL) was heated at reflux under a Soxhlet charged

with 4Å molecular sieves (5 g) for 3 hours. After this time, another batch of 4Å molecular sieves (5 g) was added, and the mixture was heated at reflux for 4 hours. Work up and purification as in the precedent procedures gave **19** (1.06 g, 8% yield), **20** (10.3 g, 78% yield), and **21** (528 mg, 4% yield).

Reaction of (*S,S*)-2-Benzyloxy-1,3,4-butanetriol 18 with Acetone (Table 1, Entries 7-9).

Method A (entry 8). A solution of the triol **18** (114 mg, 0.54 mmol) and $TsOH \cdot H_2O$ (33 mg, 0.19 mmol) in dry acetone (60 mL) was stirred at room temperature under argon for 12 hours. After this time, anhydrous K_2CO_3 (100 mg) was added, and the mixture was stirred at room temperature for 2 hours. The solid residue was filtered off and washed with acetone. The solvent was removed to give a crude product, which consisted of **20** as the only ketalic product (g. l. c. evidence). Flash-chromatography of the residue gave pure **20** (127 mg, 94% yield).

Method B (entry 9). A slurry of the triol **18** (8.4 g, 39.6 mmol) and 4Å molecular sieves (25.2 g) in dry acetone (950 mL) was treated with concentrated $HClO_4$ (4.1 mL, 41 mmol). The mixture was stirred at room tempearture under argon for 29 hours. After this time, anhydrous K_2CO_3 (40 g) was added at 0°C, and the mixture was allowed to reach room temperature in one hour. The solid residue was removed by filtration and washed with acetone. The solvent was evaporated, and the residue, whose ^{13}C-NMR spectrum showed mostly a single peak in the acetalic region (at 109.9 ppm), was flash-chromatographed to give **19** (434 mg, 4% yield), **20** (8.9 g, 89% yield), and **21** (360 mg, 4% yield).

Note: The reaction promoted by sulfuric acid (Table 1, entry 7) was carried out analogously to the method B, but using concentrated H_2SO_4 instead of $HClO_4$ as acid catalyst.

Isomerization of (*S,S*)-5-Benzyloxy-6-hydroxy-2,2-dimethyl-1,3-dioxepane 19 to (*S,S*)-4-(1'-Benzyloxy-2'-hydroxy)ethyl-2,2-dimethyl-1,3-dioxolane 20.

A slurry of the 1,3-dioxepane **19** (550 mg, 2.18 mmol) and freshly activated 4 Å molecular sieves (1.5 g) in dry acetone (70 mL) was treated with concentrated aqueous $HClO_4$ (0.22 mL, 2.2 mmol) under argon. The mixture was stirred at room temperature for 28 hours. The reaction was quenched by the addition of excess anhydrous K_2CO_3 at 0°C. After stirring for 30 minutes, the solid was filtered off and washed with CH_2Cl_2. Evaporation of the solvents and flash chromatography, as indicatefd above, gave **19** (14 mg, 3% yield), **20** (511 mg, 93% yield), and **21** (17 mg, 3% yield).

Isomerization of (*S,S*)-5-Benzyloxy-4-hydroxymethyl-2,2-dimethyl-1,3-dioxane 21 to (*S,S*)-4-(1'-Benzyloxy-2'-hydroxy)ethyl-2,2-dimethyl-1,3-dioxolane 20.

A slurry of the 1,3-dioxane **21** (172 mg, 0.68 mmol) and freshly activated 4 Å molecular sieves (420 mg) in dry acetone (30 mL) was treated with concentrated aqueous $HClO_4$ (70 μL, 0.7 mmol) under argon. The mixture was stirred at room temperature for 23 hours. The reaction was quenched by the addition of excess anhydrous K_2CO_3 at 0°C. After stirring for 30 minutes, the solid was filtered off and washed with CH_2Cl_2. Evaporation of the solvents and chromatography, as indicated above, gave **19** (4 mg, 2% yield), **20** (158 mg, 92% yield), and **21** (5 mg, 3% yield).

Synthesis of (2*R*,3*S*)-2-O-Benzyl-3,4-di-O-isopropylidene-2,3,4-trihydroxybutanal 22.

By PCC oxidation. A mixture of the alcohol **20** (5.0 g, 19.8 mmol) and 3Å molecular sieves (4 g) in dry CH_2Cl_2 (200 mL) was stirred at room temperature for 2 hours (mixture A).

A slurry of NaOAc (11.5 g, 140 mmol), PCC (15.8 g, 73.3 mmol), and 3Å molecular sieves (4 g) in CH_2Cl_2 (200 mL) was stirred at room temperature for 2 hours (mixture B).

The mixture B was added over the mixture A, and stirred at room temperature. When all the starting material was consumed (*ca* 8 hours), dry diethyl ether (400 mL) was added, and stirring was continued for 30 minutes. The resulting precipitate was filtered off over a short pad of silica gel 60 G and thoroughly washed with diethyl ether. It is important that during the filtration the silica gel does not become dry, because the Cr(III) salts are not retained in the silica gel. The solvents were removed to give the aldehyde **22** and its hydrate (4.9 g, > 95% crude yield), which could be used in the next reaction without further purification. A purer sample of aldehyde **22** was obtained by fast flash-chromatography (3:1 hexane/AcOEt). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1.6, 1H), 7.36 (m, 5H), 4.80 (d, *J* = 11.9, 1H), 4.66 (d, *J* = 11.9, 1H), 4.38 (distorted q, *J* = 6.1, 1H), 4.07 (dd, *J* = 8.8, 6.5, 1H), 3.95 (dd, *J* = 8.8, 6.1, 1H), 3.86 (dd, *J* = 5.4, 1.6, 1H), 1.43 (s, 3H), 1.35 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 202.0 (s), 137.0 (s), 128.6 (2C, d), 128.2 (d), 128.1 (2C, d), 109.8 (s), 82.8 (d), 75.3 (d), 73.3 (t), 65.3 (t), 26.1 (q), 25.1 (q).

By Corey-Kim oxidation. Dimethyl sulfide (1.2 mL, 16.4 mmol) was dropwise added to a solution of N-chlorosuccinimide (1.60 g, 12 mmol) in dry toluene (50 mL) at 0°C under argon. After stirring at this temperature for 30 minutes, the mixture was cooled at -25°C and dropwise treated with a solution of the alcohol **20** (1.96 g, 7.8 mmol) in toluene (8 mL). After stirring at -25°C for 6 hours, Et_3N (1.7 mL) was added. Then, the mixture was allowed to evolve to room temperature. The solution was diluted with ether and washed with 1% aqueous HCl and water and dried over Na_2SO_4. Evaporation of the solvent afforded the aldehyde **22** (1.75 g, 90% yield).

Wittig Reaction of the Aldehyde 22 and Methoxycarbonylmethylentriphenylphosphorane 13 in Methanol.

A mixture of $Ph_3P{=}CHCO_2Me$ (9.8 g, 29.3 mmol) and the crude aldehyde **22** (as obtained by either PCC or Corey-Kim oxidations, 2.67 g) in dry methanol (42 mL) was stirred at room temperature for 20 hours. The solvent was removed and the residue was dissolved in the minimum amount of CH_2Cl_2 and added to the top of a column of silica gel and carefully flash-chromatographed (9:1 hexane/AcOEt) to give the *Z* olefin **23** (2.31 g, 71% overall yield from the alcohol **20**) and the *E* olefin (205 mg, 7% yield overall yield from the alcohol **20**).

(*Z*,*S*,*S*)-Methyl 4-O-Benzyl-5,6-di-O-isopropylidene-4,5,6-trihydroxy-2-hexenoate 23. Thick oil. $[\alpha]_D$ +32 (c = 0.9). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 6.20 (dd, *J* = 11.8, 9.1, 1H), 6.01 (dd, *J* = 11.8, 1.0, 1H), 5.16 (ddd, *J* = 9.1, 5.2, 1.0, 1H), 4.62 (d, *J* = 12.0, 1H), 4.50 (d, *J* = 12.0, 1H), 4.24 (dd, *J* = 6.7, 5.2, 1H), 3.94 (m, 2H), 3.70 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 166.1 (s), 146.2 (d), 138.1 (s), 128.3 (2C, d), 127.8 (2C, d), 127.6 (d), 123.1 (d), 109.8 (s), 77.7 (d), 74.4 (d), 71.5 (t), 65.3 (t), 51.5 (q), 26.2 (q), 25.6 (q). IR (neat) ν 1725, 1650, 1200, 1070, 825, 695. Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.67%; H, 7.19%. Found: C, 67.02%; H, 7.29%.

(*E*,*S*,*S*)-Methyl 4-O-Benzyl-5,6-di-O-isopropyliden-4,5,6-trihydroxy-2-hexenoate 24. M. p. 48-50°C (hexane). $[\alpha]_D$ +28 (c = 1.4). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.87 (dd, *J* = 15.8, 6.1, 1H), 6.13 (dd, *J* = 15.8, 1.2, 1H), 4.69 (d, *J* = 12.1, 1H), 4.48 (d, *J* = 12.1, 1H), 4.24 (q, *J* = 6.1, 1H), 4.10 (m, 1H), 4.03-3.95 (m, 1H), 3.82-3.75 (m, 1H), 3.77 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 166.2 (s), 143.8 (d), 137.6 (s), 128.5 (2C, d), 127.9 (d), 127.8 (2C, d), 124.0 (d), 109.8 (s), 78.2 (d), 76.7 (d), 71.5 (t), 65.3 (t), 51.7 (q), 26.3 (q), 25.1 (q). IR (neat) ν 1730, 1660, 1210, 1070, 845, 695. Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.67%; H, 7.19%. Found: C, 66.59%; H, 7.28%.

(*Z*,*S*,*S*)-4-O-Benzyl-5,6-di-O-isopropyliden-4,5,6-trihydroxy-2-hexenoic Acid 25.

A 0.5N aqueous solution of LiOH (260 mL, 130 mmol) was added to a solution of the ester **23** (5.0 g, 16.3 mmol) in 2:1 (v/v) THF-MeOH (450 mL). The mixture was stirred at room temperature for one hour and then concentrated under vacuum. The solution was acidified up to pH 2-3 with 2N HCl, saturated with NaCl and extracted with ether. This process was repeated once more. The combined ethereal extracts were dried ($MgSO_4$) and the solvents were evaporated to give the crude acid **25** (4.36 g, 92% yield), which was used, without further purification, in the next step. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.80 (broad s, 1H), 7.37-7.27 (m, 5H), 6.30 (dd, *J* = 11.8, 9.0, 1H), 6.06 (dd, *J* = 11.8, 1.1, 1H), 5.09 (ddd, *J* = 9.0, 4.9, 1.1, 1H), 4.64 (d, *J* = 11.9, 1H), 4.50 (d, *J* = 11.9, 1H), 4.29 (td, *J* = 6.6, 4.9, 1H), 3.97 (m, 2H), 1.43 (s, 3H), 1.36 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 169.9 (s), 147.9 (d), 137.9 (s), 128.3 (d), 127.9 (d), 127.7 (d), 123.0 (d), 109.9 (s), 77.5 (d), 74.3 (d), 71.6 (t), 65.2 (t), 26.1 (q), 25.4 (q).

Synthesis of (*S*,*S*)-5-Benzyloxy-6-hydroxymethyl-5,6-dihydro-2H-pyran-2-one (+)-5.

Method A. A solution of the acid **25** (436 mg, 1.49 mmol) in 9:1 (v/v) CF_3CO_2H/H_2O (8 mL) was stirred from 0°C to room temperature for 2 hours, stirring was continued at this temperature for 5 hours. The mixture was cooled at 0°C, diluted with CH_2Cl_2, and neutralized with anhydrous K_2CO_3. The solid was filtered off and washed with CH_2Cl_2 leading to a solution, that was evaporated under vacuum to yield a residue that was chromatographed (6:4 hexane/AcOEt) to give the lactone (+)-**5** (300 mg, 86% yield). M. p. 83°C. $[\alpha]_D$ +284 (c = 0.2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 6.94 (dd, *J* = 9.9, 5.2, 1H), 6.20 (d, *J* = 9.9, 1H), 4.68 (d, *J* = 11.8, 1H), 4.57 (d, *J* = 11.8, 1H), 4.51 (ddd, *J* = 6.7, 5.2, 3.3, 1H), 4.13 (dd, *J* = 5.2, 3.3, 1H), 4.07 (distorted dd, *J* = 12.0, 6.8, 1H), 3.91 (dd, *J* = 12.0, 5.3, 1H), 2.05 (broad s, exchange with D_2O, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 162.9 (s), 142.6 (d), 137.2 (s), 128.6 (2C, d), 128.3 (d), 127.9 (2C, d), 123.8 (d), 80.4 (d), 71.6 (t), 66.2 (d), 61.0 (t). IR (KBr) ν 3290, 1740, 1730, 1625, 1260, 1065, 825, 695. MS *m/z* 234 (M^+, 2), 174 (5), 107 (10), 97 (30), 91 (100). Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65%; H, 6.02%. Found: C, 66.72%; H, 6.15%.

Method B. A solution of the acid **25** (1.30 g, 4.45 mmol) and $TsOH{\cdot}H_2O$ (200 mg, 1.05 mmol) in dry toluene (250 mL) was stirred at room temperature for 20 hours. Then, anhydrous K_2CO_3 (500 mg) was added at 0°C and the mixture was warmed at room temperature. The solid was filtered and washed with CH_2Cl_2. Evaporation of the solvent and chromatography of the residue gave the lactone (+)-**5** (885 mg, 85% yield).

Synthesis of (*S*,*S*)-5-Benzyloxy-6-(*tert*-butyldimethylsilyloxy)methyl-5,6-dihydro-2H-pyran-2-one 37.

A mixture of the hydroxy lactone **5** (410 mg, 1.75 mmol), DMAP (33 mg, 0.26 mmol), Et_3N (0.32 mL, 2.3 mmol) and ^{t}BuMe$_2$SiCl (320 mg, 2.13 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 5 hours under argon. Then, the solution was washed with water and saturated aqueous solution of NH_4Cl. The organic phase was dried over Na_2SO_4. The solvent was removed under vacuum and the residue was chromatographed to give the pure protected lactone **37** (563 mg, 93% yield). Thick oil. $[\alpha]_D$ +129 (c = 0.2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.87 (dd, *J* = 9.7, 5.5, 1H), 6.13 (d, *J* = 9.7, 1H), 4.67 (d, *J* = 11.5, 1H), 4.62 (d, *J* = 11.5, 1H), 4.40 (ddd, *J* = 8.4, 5.5, 2.9, 1H), 4.11 (dd, *J* = 5.5, 2.9, 1H), 4.07 (dd, *J* = 10.1, 8.4, 1H), 3.91 (dd, *J* = 10.1, 5.5, 1H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 162.6 (s), 142.8 (d), 137.8 (s), 128.5 (2C, d), 128.1 (d), 127.8 (2C, d), 123.9 (d), 80.1 (d), 72.1 (t), 65.8 (d), 60.5 (t), 25.4 (3C, q), 18.2 (s), -5.4 (2C, q). Anal. Calcd. for $C_{19}H_{28}O_4Si$: C, 71.27%; H, 8.81%. Found: C, 71.42%; H, 9.06%.

Synthesis of Ethyl 4-O-Benzyl-6-O-*tert*-butyldimethylsilyl-2,3-dideoxy-α-*L-threo*-hex-2-enopyranoside 39.

A 1.2 M solution of DIBAL-H in toluene (1.85 mL, 2.2 mmol) was dropwise added to a cooled (-78°C) solution of the protected lactone **37** (400 mg, 1.5 mmol) in dry toluene (20 mL) under argon atmosphere. The mixture was stirred at that temperature for 3.5 hours, and treated with a saturated solution of HCl in EtOH (60 mL). The mixture was slowly allowed to reach room temperature, and, then, stirred for 20 hours. After this time, the solution was neutralized with resin Amberlite IRA-400 at 0°C. The solids were filtered off and washed with ethanol. Evaporation of the solvents and flash-chromatography of the residue gave isomerically pure α-glycoside **39** (250 mg, 58% yield). Thick oil. $[\alpha]_D$ +126 (c = 0.4). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.10 (dd, *J* = 9.9, 5.0, 1H), 5.97 (dd, *J* = 9.9, 3.1, 1H), 5.06 (d, *J* = 3.1, 1H), 4.65 (d, *J* = 12.0, 1H), 4.59 (d, *J* = 12.0, 1H), 4.07 (td, *J* = 6.6, 2.4, 1H), 3.86 (m, 3H), 3.72 (m, 1H), 3.54 (m, 1H), 1.23 (t, *J* = 7.1, 3H), 0.91 (s, 9H), 0.08 (s, 6H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 138.9 (s), 129.9 (d), 128.4 (2C, d), 127.8 (2C, d), 127.6 (d), 127.3 (d), 94.0 (d), 71.4 (d), 71.2 (t), 67.3 (d), 63.5 (t), 62.5 (t), 26.0 (3C, q), 18.3 (s), 15.3 (q), -5.3 (2C, q). MS *m/z* 235 (2), 174 (4), 128 (10), 94 (32), 91 (100). Anal. Calcd. for $C_{21}H_{34}O_4Si$: C, 66.63%; H, 9.06%. Found: C, 66.22%; H, 9.08%.

Synthesis of Ethyl 4-O-Benzyl-2,3-dideoxy-α-*L-threo*-hex-2-enopyranoside 40.

A solution of **39** (378 mg, 1 mmol) and ^{n}Bu$_4$NF•3H$_2$O (947 mg, 3 mmol) in THF (5 mL) was stirred at room temperature for one hour. The solution was diluted with Et_2O and washed with water. After drying (Na_2SO_4) and evaporation of the solvents, chromatographically homogeneous alcohol **40** was obtained, which was used in the next step without further purification. An analytical pure sample was obtained by flash-chromatography (3:2 hexane/AcOEt). M. p. 77°C. $[\alpha]_D$ +238 (c = 0.2). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.09 (m, 2H), 5.10 (d, *J* = 2.0, 1H), 4.66 (d, *J* = 11.0, 1H), 4.46 (d, *J* = 11.0, 1H), 4.27-3.33 (m, 6H), 1.73 (broad s, 1H, exchange with D_2O), 1.23 (t, *J* = 7.0, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 138.2 (s), 130.2 (d), 128.5 (2C, d), 127.8 (2C, d), 126.3 (d), 94.0 (d), 70.7 (d), 70.5 (t), 68.1 (d), 63.7 (t), 62.7 (t), 15.3 (q). Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16%; H, 7.63%. Found: C, 68.29%; H, 8.00%.

Synthesis of Ethyl 2,3-Dideoxy-α-*L-threo*-hex-2-enopyranoside (41).

Crude alcohol **40**, as obtained in the preceding experiment, was taken up in dry THF (10 mL). This solution was added to a cooled (-78°C) flask (equipped with a low temperature cooler) containing liquid ammonia (*ca* 30 mL) and lithium (56 mg, 8 atom-gram). After maintaining this mixture at -78°C for 4 hours, the temperature was slowly raised to -20°C. Solid NH_4Cl was then added, and the mixture was allowed to reach room temperature. The solids were filtered off and washed with Et_2O. The solvents were removed, and the residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH) to give pure diol **41** (122 mg, 71% overall yield for two steps), which was identical, except in the sign of the optical rotation, to the enantiomer.[83] $[\alpha]_D$ +80 (c = 1.0) (lit.[83] for the enantiomer: -78°).

Synthesis of Ethyl 6-O-Benzoyl-2,3-dideoxy-α-*L-threo*-hex-2-enopyranoside (+)-11.

Method A. A solution of the diol **41** (100 mg, 0.57 mmol) in CH_2Cl_2 (3 mL) was sequentially treated with ^{n}Bu$_4$NHSO$_4$ (19 mg, 0.058 mmol), 25% aqueous NaOH (0.1 mL, 0.63 mmol), and PhCOCl (190 mg, 0.63 mmol). The mixture was stirred at room temperature for one hour. The two phases were separated, the aqueous one was extracted with CH_2Cl_2. The combined oganic extracts were washed with aqueous saturated $NaHCO_3$ and

brine, and dried ($NaSO_4$). After removing the solvent, the residue was chromatographed to give the dibenzoate **42** (65 mg, 30% yield)[84] and the monobenzoate (+)-**11** (66 mg, 42% yield).

Method B. The diol **41** (100 mg, 0.57 mmol) in pyridine (2 mL) was treated with excess PhCOCl (*ca* 1 mL) at 0°C. The mixture was allowed to reach room temperature, and stirred overnight. The reaction mixture was poured over a saturated aqueous solution of $NaHCO_3$. After stirring for 30 minutes, the mixture was thoroughly extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, half saturated $CuSO_4$, and H_2O. The organic phase was dried ($MgSO_4$), and the solvent evaporated to give the dibenzoate **42**, which was dissolved in dry MeOH (3 mL). A catalytic amount of KOH (5.5 mg, 0.1 mmol) was added to this solution at -20°C, and stirred at this temperature for 12 hours. The mixture was neutralized with 5% aqueous HCl. The solvents were removed and the residue was purified by chromatography to give the monobenzoate (+)-**11** (111 mg, 67% overall yield for the two steps). M. p. 122-4°C (hexane). $[\alpha]_D$ +25 (c = 0.2). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.45 (m, 3H), 6.13 (dd, *J* = 10.0, 5.0, 1H), 5.87 (dd, *J* = 10.0, 3.0, 1H), 4.98 (d, *J* = 3.0, 1H), 4.54 (m, 2H), 4.33 (m, 1H), 4.00-3.35 (m, 3H), 1.80 (broad s, exchange with D_2O, 1H), 1.20 (t, *J* = 6.0, 3H). ^{13}C-NMR (50.3 MHz, CDCl3) δ 166.5 (s), 133.0 (s), 130.1 (d), 129.6 (2C, d), 129.2 (2C, d), 128.8 (d), 128.4 (d), 93.9 (d), 69.9 (d), 64.3 (d), 63.6 (t), 61.6 (t), 15.2 (q). Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73%; H, 6.52%. Found: C, 64.50%; H, 6.14%.

Synthesis of (*R*)-1,2,4-Butanetriol 47.

Borane/dimethyl sulfide complex (0.98 mol, 98 mL) was added dropwise to a mixture of $B(OMe)_3$ (100 mL) and THF (300 mL) at 0°C. After stirring for 5 minutes, a solution of (*R*)-malic acid **48** (32.2 g, 0.246 mol) in THF (200 mL) was added dropwise. After stirring at 0°C for 5 minutes, the cooling bath was removed and the mixture was stirred at room temperature for 24 hours. The reaction was quenched by the slow addition of MeOH (300 mL) at 0°C. All the volatile were removed [in order to facilitate the evaporation of all $B(OMe)_3$ more MeOH was added portionwise, the process being repeated three times] to give a residue which was chromatographed (85:15 CH_2Cl_2/MeOH) to afford **47** (25.1 g, 97% yield), identical to the reported in the literature.[60]

Synthesis of (*R,R*)-4-Hydroxymethyl-2-phenyl-1,3-dioxane 49.

Method A. A mixture of the triol **47** (13.1 g, 124 mmol), PhCHO (15.0 mL, 136 mmol), and $TsOH{\cdot}H_2O$ (274 mg, 1.3 mmol) in dry toluene (700 mL) was heated at reflux under a Soxhlet containing freshly activated powered 4Å molecular sieves (40 g) under an argon flow for 7 hours. After cooling, 38% aqueous $NaHSO_3$ (100 mL) was added and the mixture was stirred at room temperature for 1 hour, followed by extraction with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and water. After drying ($MgSO_4$), evaporation of the solvents gave crude **49**, which contained *ca* 5-10% of the regioisomeric dioxolanes (as a *ca* 1:1 mixture of *trans*- and *cis*-diastereoisomers) and a trace amount of the *cis*- diastereoisomer of **49** (^{1}H-NMR evidence). Pure acetal **49** (10.16 g, 87% yield) was obtained by flash-chromatography (hexane/AcOEt, from 55:45 to 40:60). Thick oil. $[\alpha]_D$ -10 (c = 1.2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.33 (m, 5H), 5.56 (s, 1H), 4.31 (ddd, *J* = 11.4, 5.2, 1.3, 1H), 4.09-3.92 (m, 2H), 3.72-3.65 (m, 2H), 2.10 (broad s, exchange with D_2O, 1H), 2.04-1.83 (m, 1H), 1.51-1.41 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 138.4 (s), 128.9 (d), 128.4 (2C, d), 126.1 (2C, d), 101.3 (d), 77.6 (d), 66.6 (t), 65.6 (t), 26.8 (t). MS *m/z* 194 (42), 193 (65), 163 (73), 123 (8), 107 (45), 106 (18), 105 (100), 91 (48), 79 (75), 78 (25), 77 (69), 71 (48), 57 (36), 43 (25). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02%; H, 7.27%. Found: C, 67.78%; H, 7.60%.

Method B. A mixture of the triol **47** (23.2 g, 219 mmol), benzaldehyde dimethyl acetal (42.7 mL, 283 mmol), and $TsOH \cdot H_2O$ (2.09 g, 11.0 mmol) in dry toluene (900 mL) was heated at reflux under a Soxhlet containing freshly activated powered 4Å molecular sieves (36 g) under an argon flow for 4.75 hours. After this time, another batch of 4Å molecular sieves (32 g) was placed in the Soxhlet extractor and the reflux was continued for another 4 hours. After cooling, excess anhydrous Na_2CO_3 was added and the mixture was stirred at room temperature for 1 hour. The solid was filtered off, and the solution was diluted with CH_2Cl_2/H_2O. The phases were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with water. After drying ($MgSO_4$), evaporation of the solvents gave crude **49**, which contained *ca* 9% of the regioisomeric dioxolanes (as a *ca* 1:1 mixture of *trans*- and *cis*-diastereoisomers; ^{1}H-NMR evidence). Pure acetal **49** (32.9 g, 80% yield) was obtained by flash-chromatography as indicated above.

Synthesis of (*R,R*)-4-Formyl-2-phenyl-1,3-dioxane 50.

A solution of dry DMSO (18 mL, 0.25 mol) in CH_2Cl_2 (65 mL) was dropwise added to a solution of oxalyl chloride (9.8 mL, 0.11 mol) in CH_2Cl_2 (250 mL) at -60°C (internal temperature) under argon. After stirring for 12 minutes, a solution of the alcohol **49** (20 g, 0.10 mol) in CH_2Cl_2 (110 mL) was dropwise added. The mixture was stirred at -60°C for 30 minutes and treated with Et_3N (72 mL, 0.52 mol). After 5 minutes, the cooling bath was removed. Water was added, and the mixture was allowed to reach room temperature. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with saturated aqueous NH_4Cl and water and dried over $MgSO_4$. Evaporation of the solvents afforded crude aldehyde **50** (19.7 g, 99% crude yield), which was a single spot on t. l. c. ^{1}H-NMR of the crude mixture showed single peaks for the formyl and acetalic protons. The crude material was used in the next reaction. A purer sample (> 90% purity) was obtained by flash-chromatography (2:1 hexane/AcOEt). Thick oil. $[\alpha]_D$ -4 (c = 1.0). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.57-7.46 (m, 2H), 7.44-7.36 (m, 3H), 5.61 (s, 1H), 4.40-4.32 (m, 2H), 4.01 (td, *J* = 11.7, 2.9, 1H), 2.06-1.76 (m, 2H). IR (neat) ν 3010, 2890, 1705, 1595, 1585, 1455, 1280, 1115, 1070, 1055, 915. MS *m/z* 193 (10), 192 (M^+, 65), 191 (76), 163 (20), 145 (8), 133 (7), 123 (13), 121 (73), 117 (18), 115 (59), 107 (43), 106 (82), 105 (100), 91 (19), 90 (30), 89 (19), 87 (32), 77 (90), 70 (81), 51 (65).

Wittig FReaction of the Aldehyde 50 and Methoxycarbonylmethylentriphenylphosphorane 13.

A solution of crude aldehyde **50** (17.6 g, 91 mmol) in dry MeOH (140 mL) was rapidly added to a suspension of the phosphorane **13** (50 g, 150 mmol) in MeOH (220 mL) at -78°C under argon. The mixture was allowed to warm up to room temperature for 8 hours. Then, the solvent was evaporated, without heating, to give a residue which was dissolved in the minimum amount of CH_2Cl_2 and added to the top of a column of silica gel and flash-chromatographed using hexane/ethyl acetate mixtures (a gradient from 97:3 to 65:35) to give the (*Z*)-α,β-unsaturated ester **51** (12.9 g, 57% overall yield from the alcohol **49**) and its *E*-isomer **52** (1.13 g, 5% yield).

(*Z,R,R*)-Methyl 4,6-Di-O-benzylidene-4,6-dihydroxy-2-hexenoate 51. M. p. 68-78°C. $[\alpha]_D$ -63 (c = 1.2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.43 (m, 2H), 7.40-7.32 (m, 3H), 6.36 (dd, *J* = 11.7, 7.2, 1H), 5.83 (dd, *J* = 11.7, 1.4, 1H), 5.62 (s, 1H), 5.53 (m, 1H), 4.30 (m, 1H), 4.11 (td, *J* = 11.4, 3.3, 1H), 3.75 (s, 3H), 1.95-1.76 (m, 2H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 166.5 (s), 149.5 (d), 138.9 (s), 129.3 (d), 128.7 (2C, d), 126.6 (2C, d), 119.4 (d), 101.4 (d), 75.2 (d), 67.3 (t), 51.9 (q), 30.1 (t). MS *m/z* 249 (2), 248 (M^+, 3), 247 (15), 217 (5), 171 (4), 170 (5), 163 (2), 143 (21), 142 (24), 134 (9), 126 (15), 125 (43), 114 (53), 111 (36), 106 (35), 105 (100), 98 (43), 83 (37), 82 (22), 77 (49). Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73%; H, 6.50%. Found: C, 67.72%; H, 6.68%.

(*E*,*R*,*R*)-Methyl 4,6-Di-O-benzylidene-4,6-dihydroxy-2-hexenoate 52. M. p. 59-61°C. $[\alpha]_D$ +19 (c = 2.0). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.39-7.36 (m, 3H), 6.97 (dd, *J* = 15.7, 4.1, 1H), 6.17 (dd, *J* = 15.7, 1.9, 1H), 5.61 (s, 1H), 4.57 (ddt, *J* = 11.3, 4.1, 2.0, 1H), 4.32 (ddd, *J* = 11.5, 4.9, 1.2, 1H), 4.03 (td, *J* = 11.9, 2.6, 1H), 3.76 (s, 3H), 1.94 (distorted qd, *J* = 12.4, 4.9, 1H), 1.70 (distorted ddd, *J* = 13.5, 4.1, 2.6, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 167.3 (s), 146.8 (d), 138.8 (s), 129.4 (d), 128.7 (2C, d), 126.6 (2C, d), 120.7 (d), 101.5 (d), 75.7 (d), 67.2 (t), 52.1 (q), 31.1 (t).

Synthesis of (*R*)-5-(2-Hydroxyethyl)-2(5H)-furanone (-)-6.

A solution of the acetal **51** (7.0 g, 28.2 mmol) in 4:1 (v/v) AcOH/H_2O (410 mL) was stirred at room temperature for 4.5 hours. The solvents were removed by coevaporation with toluene to give chromatographically pure (-)-**6** (4.3 g, 99% yield). An analytical pure sample was obtained by flash-chromatography using hexane/ethyl acetate mixtures (gradient from 22:75 to 10:90). Thick oil. $[\alpha]_D$ -48 (c = 2.2). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 5.7, 1.5, 1H), 6.13 (dd, *J* = 5.7, 2.0, 1H), 5.25 (m, 1H), 3.87 (distorted broad t, *J* = 5.4, 2H), 2.06 (m, 1H), 1.86 (m, 1H). 1.80 (very broad s, exchange with D_2O, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 173.5 (s), 157.5 (d), 120.6 (d), 81.2 (d), 58.1 (t), 35.6 (t), IR ($CHCl_3$) ν 3620, 3480, 3010, 2960, 2890, 1755, 1165, 1105, 1065, 1050, 815. MS *m/z* 129 (24), 128 (M^+, 4), 111 (10), 110 (60), 101 (10), 99 (67), 98 (33), 97 (61), 84 (82), 83 (99), 82 (100), 81 (29), 73 (78), 71 (29), 70 (35), 69 (50), 68 (85), 56 (45), 55 (97), 54 (67), 53 (48), 45 (46), 43 (69), 42 (52), Anal. Calcd. for $C_6H_8O_3$: C, 56.25%; H, 6.29%. Found: C, 56.29%; H, 6.43%.

Synthesis of (5*R*,6*S*)-5-Acetoxy-6-methyl-5,6-dihydro-2H-pyran-2-one (-)-7.

A solution of anhydrous *m*-chloroperoxybenzoic acid (MCPBA, containing *ca* 5% *m*-chorobenzoic acid) (4.5 g, 26 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise to a stirred solution of the glycal **58** (4.7 g, 22 mmol) in CH_2Cl_2 (60 mL) at -20°C under argon. Subsequently, BF_3•Et_2O (1.35 mL, 11 mmol) was added dropwise and the mixture was stirred at -20°C for 45 minutes (during this time, the solution became clear). Then, the reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (70 mL) containing $Na_2S_2O_3$ (25 mg). The mixture was diluted with CH_2Cl_2, the phases were separated, and the aqueous one was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residual solid [a mixture of the product and *m*-chlorobenzoic acid (MCBA)] was dissolved in $CHCl_3$ and washed first with a 2N solution of $NaHCO_3$ (3 times) and then with water (once). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. When a solid was still obtained, it was necessary to repeat the washing with $NaHCO_3$ in order to remove the MCBA in excess. The resulting syrup was purified by flash chromatography to obtain pure (-)-**7** (3.05 g, 82% yield). Thick oil. $[\alpha]_D$ -158 (c = 1.5) (lit.[12b]: $[\alpha]_D$ -179; lit.[69]: $[\alpha]_D$ -160). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 9.9, 3.3, 1H), 6.11 (dd, *J* = 9.9, 1.4, 1H), 5.25 (ddd, *J* = 6.7, 3.3, 1.4, 1H), 4.60 (quint, *J* = 6.7, 1H), 2.11 (s, 3H), 1.41 (d, *J* = 6.6, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 169.6 (s), 161.8 (s), 142.8 (d), 122.4 (d), 76.1 (d), 67.4 (d), 20.5 (q), 18.0 (q). IR (neat) ν 2990, 2940, 1730, 1635, 1450, 1430, 1375, 1275, 1235, 1115, 1050, 970, 850, 815. MS *m/z* 171 (M+1, 2), 155 (2), 126 (27), 115 (3), 95 (11), 84 (85), 55 (10), 43 (100).

Synthesis of (5*R*,1'*S*)-5-(1'-Hydroxyethyl)-2(5H)-furanone (+)-8.

$Ba(OH)_2$ (4 g, 21.2 mmol) was added to a solution of the α,β-unsaturated-δ-lactone (-)-**7** (1.8 g, 10.6 mmol) in 1:1 (v/v) THF/H_2O (25 mL) at room temperature. The mixture was stirred for 45 minutes and acidified by the addition of 5% aqueous HCl until pH 2. The aqueous phase was saturated with NaCl and extracted with AcOEt.

After drying ($MgSO_4$), the organic solvent was evaporated to give (+)-**8** (1.23 g, 91% yield), that could be used in the next reactions without further purification. A pure sample was obtained by flash chromatography (1:1 hexane/AcOEt). Thick oil. $[\alpha]_D$ +177 (c = 1.5).[85] ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 5.8, 1.6, 1H), 6.17 (dd, *J* = 5.8, 2.0, 1H), 4.92 (ddd, *J* = 4.7, 2.0, 1.6, 1H), 4.05 (qd, *J* = 6.5, 4.7, 1H), 3.40 (broad s, 1H), 1.29 (d, *J* = 6.5, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 173.5 (s), 154.2 (d), 122.1 (d), 87.0 (d), 67.0 (d), 18.4 (q). IR (neat) ν 3700-3200, 2980, 2920, 1790, 1750, 1600, 1380, 1340, 1300, 1170, 1100, 1060, 1040, 1015, 980, 900, 850, 820, 800, 700. MS *m/z* 129 (M^++1, 3), 84 (90), 56 (13), 55 (21), 45 (100), 43 (12). Anal. Calcd. for $C_6H_8O_3$: C, 56.25%; H, 6.29%. Found: C, 55.99%; H, 6.45%.

Synthesis of (5*R*,1'*S*)-5-[1'-((Methoxy)methoxy)ethyl]-2(5H)-furanone (+)-9.

Excess dimethoxymethane (30 mL) and P_2O_5 (6 g, 35 mmol) were added to a solution of the butenolide (+)-**8** (1.35 g, 10.54 mmol) in dry $CHCl_3$ (25 mL) under argon. The mixture was stirred at room temperature for 15 minutes, cooled at 0°C and quenched by the slow addition of a saturated aqueous solution of Na_2CO_3. The aqueous phase was extracted with AcOEt. The combined organic phase was washed with saturated aqueous Na_2CO_3 and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded (+)-**9** (1.43 g, 80% yield), that could be used without further purification. An analytical pure sample was obtained after flash chromatography (3:2 hexane/AcOEt). $[\alpha]_D$ +127 (c = 1.0). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 5.8, 1.5, 1H), 6.19 (dd, *J* = 5.8, 2.0, 1H), 4.95 (ddd, *J* = 4.9, 2.0, 1.5, 1H), 4.67 (d, *J* = 7.0, 1H), 4.62 (d, *J* = 7.0, 1H), 3.94 (qd, *J* = 6.4, 4.9, 1H), 3.36 (s, 3H), 1.30 (d, *J* = 6.4, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 172.5 (s), 153.1 (d), 122.3 (d), 95.3 (t), 85.3 (d), 72.3 (d), 55.2 (q), 16.3 (q). IR (neat) ν 2940, 1790, 1760, 1160, 1100, 1040, 820. MS *m/z* 172 (M^+, < 1), 128 (2), 126(4), 112 (2), 111 (3), 99 (14), 89 (11), 84 (13), 55 (11), 45 (100). Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81%; H, 7.02%. Found: C, 56.15%; H, 7.10%.

Synthesis of (5*R*,1'*S*)-5-[1'-(Benzyloxy)ethyl]-2(5H)-furanone (+)-10.

Benzyl trichloroacetimidate (0.83 mL, 4.44 mmol) was added to a solution of the butenolide (+)-**8** (474 mg, 3.70 mmol) in 2:1 (v/v) cyclohexane/CH_2Cl_2 (24 mL) at 0°C under argon. Then, CF_3SO_3H (0.1 mL, 1.0 mmol) was added dropwise. The mixture was allowed to reach room temperature and it was stirred for 2h. The solid residue was filtered off, and the solution was washed with a saturated aqueous solution of $NaHCO_3$, H_2O, and brine, and dried over $MgSO_4$. The solvent was evaporated to give a crude product, which, after chromatography and further distillation under vacuum (to remove the residual trichloroacetamide), afforded pure benzyl ether (+)-**10** (428 mg, 53% yield). Thick oil. $[\alpha]_D$ +126 (c = 1.3). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 5.8, 1.5, 1H), 7.31 (m, 5H), 6.18 (dd, *J* = 5.8, 2.0, 1H), 4.94 (m, 1H), 4.63 (d, *J* = 11.7, 1H), 4.50 (d, *J* = 11.7, 1H), 3.70 (distorted quint, *J* = 6.9, 1H), 1.35 (d, *J* = 6.4, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 172.8 (s), 153.8 (d), 137.6 (s), 128.4 (2C, d), 128.0 (d), 127.6 (d), 122.3 (d), 85.7 (d), 74.7 (d), 71.6 (t), 16.6 (q). IR (neat) ν 2980, 2940, 2880, 1785, 1750, 1730, 1600, 1495, 1450, 1380, 1340, 1270, 1160, 1100, 1020, 890, 820, 795, 740, 700. MS *m/z* 218 (M^+, < 1), 167 (7), 141 (36), 135 (4), 123 (6), 112 (3), 91 (100), 65 (13), 55 (13).

Conjugate Addition of Lithium Dialkylcuprates to the α,β-Unsaturated-γ-lactones (+)-9 and (+)-10. General Procedure for the Synthesis of the Lactones 59, 60, 62, and 63.

A solution of the organolithium reagent (2.9 mmol) was added dropwise to a stirred suspension of CuI (300 mg, 1.57 mmol) in diethyl ether (5 mL) at 0°C. After stirring for 10 minutes, Me_3SiCl (0.44 mL, 3.52 mmol) was added to the copper reagent. The mixture was cooled at -20°C and a solution of the corresponding α,β-unsaturated-γ-lactone (0.35 mmol) in diethyl ether (2 mL) was added. The reaction mixture was stirred at -20°C

for the time indicated in Table 2 and then quenched with a NH_3/NH_4Cl solution (pH 8). The mixture was diluted with diethyl ether and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent and flash chromatography led to the corresponding pure product. The spectroscopic and analytical data of the conjugate addition products are indicated below.

(4*R*,5*R*,1'*S*)-5-[1'-((Methoxy)methoxy)ethyl]-4-methyl-2(5H)-furanone 59. It was obtained from (+)-**9** in 50% yield after chromatography (7:3 hexane/AcOEt). Thick oil. $[\alpha]_D$ +10 (c = 0.1). ^{1}H-NMR (300 MHz, C_6D_6) δ 4.39 (d, *J* = 6.9, 1H), 4.34 (d, *J* = 6.9, 1H), 3.59 (qd, *J* = 6.5, 3.7, 1H), 3.39 (distorted t, *J* = 4.1, 1H), 3.11 (s, 3H), 2.33 (dd, *J* = 17.4, 9.2, 1H), 2.00 (m, 1H), 1.60 (dd, *J* = 17.4, 5.6, 1H), 0.80 (d, *J* = 6.5, 3H), 0.55 (d, *J* = 6.8, 3H). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.68 (d, *J* = 6.9, 1H), 4.61 (d, *J* = 6.9, 1H), 3.98 (m, 2H), 3.36 (s, 3H), 2.81 (dd, *J* = 17.3, 9.1, 1H), 2.60 (m, 1H), 2.11 (dd, *J* = 17.3, 5.2, 1H), 1.22 (d, *J* = 6.4, 3H), 1.20 (d, *J* = 6.8, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 177.0 (s), 95.5 (t), 89.2 (d), 73.5 (d), 55.7 (q), 37.0 (t), 30.0 (d), 20.6 (q), 16.1 (q). IR (neat) ν 2980, 2940, 2900, 2825, 1775, 1460, 1380, 1210, 1150, 1100, 1040, 920, 850. MS *m/z* 188 (M^+, <1), 157 (2), 155 (2), 144 (8), 135 (37), 99 (39), 71 (23), 57 (21), 45 (100). Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43%; H, 8.57%. Found: C, 57.21%; H, 8.79%.

(4*R*,5*R*,1'*S*)-4-Butyl-5-[1'-((methoxy)methoxy)ethyl]-2(5H)-furanone 60. It was obtained from (+)-**9** in 58% yield after chromatography (9:1 hexane/AcOEt). Thick oil. $[\alpha]_D$ +8 (c = 1.0). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.67 (d, *J* = 6.8, 1H), 4.60 (d, *J* = 6.8, 1H), 4.05 (distorted t, *J* = 3.4, 1H), 3.90 (qd, *J* = 6.4, 3.2, 1H), 3.33 (s, 3H), 2.76 (dd, *J* = 17.5, 9.2, 1H), 2.43 (m, 1H), 2.12 (dd, *J* = 17.5, 4.2, 1H), 1.60-1.19 (m, 6H), 1.17 (d, *J* = 6.4, 3H), 0.88 (t, *J* = 6.9, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 177.1 (s), 95.4 (t), 87.5 (d), 73.5 (d), 55.5 (q), 34.9 (t), 34.81 (t), 34.75 (d), 29.2 (t), 22.4 (t), 15.8 (q), 13.9 (q). IR (neat): 2940, 2860, 1780, 1460, 1380, 1210, 1175, 1150, 1100, 1040, 915, 850. MS *m/z* 230 (M^+, < 1), 186 (4), 169 (3), 141 (48), 123 (10), 95 (28), 81 (15), 69 (19), 55 (20), 45 (100). Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58%; H, 9.63%. Found: C, 62.37%; H, 9.53%.

(4*R*,5*R*,1'*S*)-5-[1'-(Benzyloxy)ethyl]-4-methyl-2(5H)-furanone 62. It was obtained from (+)-**10** in 40% yield after chromatography (3:1 hexane/AcOEt). Thick oil. $[\alpha]_D$ = +17 (c = 0.4, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.62 (d, *J* = 11.5, 1H), 4.48 (d, *J* = 11.5, 1H), 3.99 (distorted t, *J* = 4.1, 1H), 3.74 (qd, *J* = 6.4, 3.9, 1H), 2.78 (dd, *J* = 17.2, 9.1Hz, 1H), 2.61 (m, 4.9, 1H), 2.10 (dd, *J* = 17.2, 4.9Hz, 1H), 1.21 (d, *J* = 6.4, 3H), 1.18 (d, *J* = 7.0, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 176.9 (s), 138.1 (s), 128.7 (d), 128.4 (2C, d), 127.7 (2C, d), 89.4 (d), 75.6 (d), 71.6 (t), 36.9 (t), 30.2 (d), 20.5 (q), 15.6 (q). IR (neat) ν 2970, 2940, 2880, 1780, 1605, 1500, 1450, 1380, 1300, 1210, 1180, 1070, 1030, 930, 740, 700. MS *m/z* 234 (M^+, < 1), 190 (4), 162 (3), 128 (12), 107 (5), 99 (67), 91(100), 71 (25), 65 (15).

(4*R*,5*R*,1'*S*)-5-[1'-(Benzyloxy)ethyl]-4-butyl-2(5H)-furanone 63. It was obtained from (+)-**10** in 43% yield after chromatography (85:15 hexane/AcOEt). Thick oil. $[\alpha]_D$ +10 (c = 1.7). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.61 (d, *J* = 11.5, 1H), 4.47 (d, *J* = 11.5, 1H), 4.07 (distorted t, *J* = 3.5, 1H), 3.75 (qd, *J* = 6.5, 3.6, 1H), 2.77 (dd, *J* = 17.7, 9.3, 1H), 2.45 (m, 1H), 2.12 (dd, *J* = 17.7, 4.2, 1H), 1.60-1.20 (m, 6H), 1.21 (d, *J* = 6.5, 3H), 0.90 (t, *J* = 6.9, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 177.2 (s), 138.0 (s), 128.4 (2C, d), 128.3 (d), 127.7 (2C, d), 87.8 (d), 75.8 (d), 71.6 (t), 35.0 (t), 34.9 (t), 34.7 (d), 29.2 (t), 22.4 (t), 15.4 (q), 13.9 (q). IR (neat) ν 2960, 2940, 2860, 1780, 1600, 1500, 1470, 1455, 1415, 1375, 1175, 1070, 1030, 1010, 735, 700. MS *m/z* 232 (M-44, 2), 141 (35), 123 (6), 91 (100), 81 (16), 69 (16).

Conjugate Addition of Diethyl Malonate to the α,β-Unsaturated-γ-lactones (+)-9 and (+)-10. General Procedure for the Synthesis of the Lactones 61 and 64.

A solution of diethyl malonate (0.7 mmol) in dry THF (2 mL) was added dropwise to a stirred suspension of $KOBu^t$ (0.7 mmol) in THF (2 mL) at room temperature under argon. After stirring for 20 minutes, the corresponding α,β-unsaturated-γ-lactone (0.35 mmol) dissolved in THF (2 mL) was added dropwise. The mixture was stirred at room temperature for the time indicated in Table 2. Then, a saturated aqueous NH_4Cl was added. The aqueous phase was extracted with AcOEt and the organic layer was dried over $MgSO_4$. After evaporating the solvent and flash chromatography, pure compound (**61** or **64**) was obtained. The spectroscopic and analytical data of the conjugate addition products are indicated below.

(4*S*,5*R*,1'*S*)-4-Di(ethoxycarbonyl)methyl-5-[1'-((methoxy)methoxy)ethyl]-2(5H)-furanone 61. It was obtained from (+)-**9** in 30% yield after chromatography (3:2 hexane/AcOEt). Thick oil. $[\alpha]_D$ +20 (c = 0.9). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.67 (d, *J* = 6.9, 1H), 4.58 (d, *J* = 6.9, 1H), 4.32 (distorted t, *J* = 3.0, 1H), 4.21 (m, 4H), 3.96 (qd, *J* = 6.4, 3.1, 1H), 3.51 (d, *J* = 7.4, 1H), 3.34 (s, 3H), 3.14 (m, 1H), 2.89 (dd, J = 18.2, 10.0, 1H), 2.41 (dd, *J* = 18.2, 2.8, 1H), 1.27 (t, *J* = 7.0, 6H), 1.22 (d, *J* = 6.5, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 176.1 (s), 167.6 (2C), 95.2, 84.3, 74.0, 62.0, 61.9, 55.6, 54.7, 34.5, 32.9, 15.7, 13.9 (2C). IR (neat) ν 2980, 2940, 2900, 1785, 1750, 1730, 1170, 1150, 1100, 1040, 920, 860. MS *m/z* 287 (M-45, < 1), 243 (11), 242 (13), 197 (31), 169 (26), 151 (14), 123 (10), 85 (10), 55 (11), 45 (100). Anal. Calcd. for $C_{15}H_{24}O_8$: C, 54.21%; H, 7.28%. Found: C, 53.97%; H, 7.01%.

(4*S*,5*R*,1'*S*)-5-[1'-(Benzyloxy)ethyl]-4-di(ethoxycarbonyl)methyl-2(5H)-furanone 64. It was obtained from (+)-**10** in 45% yield after chromatography (3:1 hexane/AcOEt). Thick oil. $[\alpha]_D$ +15° (c = 0.3). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 4.60 (d, *J* = 11.5, 1H), 4.45 (d, *J* = 11.5, 1H), 4.33 (distorted t, *J* = 3.1, 1H), 4.19 (m, 4H), 3.78 (qd, *J* = 6.4, 3.3, 1H), 3.53 (d, *J* = 7.3, 1H), 3.13 (m, 1H), 2.89 (dd, *J* = 18.1, 9.9, 1H), 2.40 (dd, *J* = 18.1, 3.0 1H), 1.27 (t, *J* = 7.0, 6H), 1.25 (d, *J* = 6.4, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 176.2, 167.7, 167.6, 137.8, 128.4 (2C), 127.8 (2C), 127.5, 84.5, 78.7, 71.7, 62.04, 61.97, 54.7, 34.9, 33.0, 15.4, 13.9 (2C). IR (neat) ν 2990, 2940, 2880, 1785, 1750, 1730, 1600, 1495, 1465, 1455, 1415, 1370, 1180, 1025, 860, 750, 700 cm^{-1}. MS *m/z* 272 (M-106, 2), 254 (3), 243 (20), 197 (40), 169 (31), 151 (13), 141 (11), 123, (8) 91 (100).

Alkylation of the Lactone (+)-59. General Procedure for the Synthesis of the Lactones 65, 66, and 67.

A solution of the saturated lactone (+)-**59** (0.48 mmol) in dry THF (2 mL) was added dropwise, via cannula, to a stirred solution of LDA (0.58 mmol, prepared from a 2M solution in heptane/THF/ethylbenzene) in THF (1 mL) at -78°C under argon. After stirring for 15 minutes, DMPU (1.4 mL) was added, and stirring was continued for additional 15 minutes. Then, a solution of the electrophile (3-10 molar equivalents, as indicated in Table 3) in dry THF (2 mL) was added via cannula. The temperature was mantained at -78°C until completion of the reaction (as shown by t. l. c.). Then, a saturated aqueous solution of NH_4Cl was added. After stirring for *ca* 20 minutes (until room temperature is reached), H_2O and Et_2O were added. The phases were separated, the aqueous phase was extracted with Et_2O (twice) and AcOEt (twice). The combined organic extracts were washed with H_2O and brine. After drying and solvent evaporation, a crude product was obtained, that was purified by chromatography to give compounds **65-67**.

(3*R*,4*R*,5*R*,1'*S*)- and (3*S*,4*R*,5*R*,1'*S*)-5-[1'-((Methoxy)methoxy)ethyl]-3,4-di-methyl-2(5H)-furanone 65 (as a 3:1 inseparable mixture of epimers). It was obtained following the general procedure using 10 molar equivalents of MeI as electrophile. The product was obtained as a 3:1 mixture of epimers (3*R*:3*S*), as determined by NMR and capillary g. l. c. analysis. This mixture could not be separated by flash chromatography (7:3

hexane/AcOEt). Yield = 75%. Thick oil. $[\alpha]_D$ +4 (c = 1.0). ^{1}H-NMR (300 MHz, C_6D_6) δ 4.45 (d, *J* = 6.8, 1H, **M**), 4.42 (d, *J* = 6.8, 1H, **M**), 4.38 (d, *J* = 6.8, 1H, **m**), 4.33 (d, *J* = 6.8, 1H, **m**), 3.62 (qd, *J* = 6.5, 4.3, 1H, **both epimers**), 3.42 (dd, *J* = 4.0, 2.7, 1H, **m**), 3.38 (dd, *J* = 8.3, 4.3, 1H, **M**), 3.13 (s, 3H, **M**), 3.12 (s, 3H, **m**), 2.62 (dq, *J* = 9.0, 7.6, 1H, **m**), 2.15 (dqd, *J* = 9.0, 6.3, 2.7, 1H, **m**), 1.75-1.55 (m, 2H, **M**), 1.00 (d, *J* = 6.7, 3H, **M**), 0.96 (d, *J* = 6.5, 3H, **M**), 0.92 (d, *J* = 7.6, 3H, **m**), 0.83 (d, *J* = 6.4, 3H, **m**), 0.65 (d, *J* = 6.2, 3H, **M**), 0.55 (d, *J* = 6.3, 3H, **m**) (**m** = minor epimer; **M** = major epimer). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 179.9 (**m**), 178.5 (**M**), 95.5 (**M**) 95.4 (**m**), 87.6 (**m**), 86.7 (**M**), 73.4 (**m**), 73.1 (**M**), 55.6 (**m** and **M**), 43.2 (**M**), 39.6 (**M**), 37.7 (**m**), 33.1 (**m**), 17.5 (**M**), 16.3 (**M**), 16.2 (**m**), 15.5 (**m**), 13.5 (**M**), 10.3 (**m**) (**m** = minor epimer; **M** = major epimer). IR (neat) ν 2980, 2930, 2880, 1775, 1460, 1380, 1315, 1250, 1150, 1040, 920. MS *m/z* 171 (M-31, 1), 158 (5), 142 (5), 141 (14), 140 (90), 139 (25), 113 (28), 92 (100), 91 (60), 81 (31), 65 (11), 57 (29), 55 (43), 43 (45). MS (FAB) *m/z* 203 (M+1, 15), 171 (64), 141 (100), 93 (90), 45 (97).

(3*R*,4*R*,5*R*,1'*S*)-3-Allyl-5-[1'-((methoxy)methoxy)ethyl]-4-methyl-2(5H)-furanone 66. It was obtained as a single isomer (> 25:1 ratio of isomers by capillary g. l. c.) following the general procedure using 5 molar equivalents of allyl bromide as electrophile. Flash chromatography (4:1 hexane/AcOEt) afforded pure compound **66** in 30% yield [along with 30% of recovered starting material **59**]. Thick oil. $[\alpha]_D$ -14, (c = 0.5). ^{1}H-NMR (300 MHz, C_6D_6) δ 5.66 (m, 1H), 4.88 (m, 2H), 4.43 (d, *J* = 6.8, 1H), 4.40 (d, *J* = 6.8, 1H), 3.65 (qd, *J* = 6.5, 4.1, 1H), 3.44 (dd, *J* = 8.0, 4.1, 1H), 3.13 (s, 3H), 2.33 (m, 2H), 1.99 (ddq, *J* = 10.0, 8.0, 6.6, 1H), 1.76 (ddd, *J* = 10.0, 7.1, 5.1, 1H), 0.94 (d, *J* = 6.5, 3H), 0.71 (d, *J* = 6.6, 3H). ^{13}C-NMR (50.3 MHz, C_6D_6) δ 177.0, 135.3, 117.4, 95.4, 86.2, 73.4, 55.2, 47.6, 36.1, 33.7, 18.3, 16.2. IR ν 3090, 2980, 2940, 2815, 1780, 1645, 1450, 1385, 1310, 1150, 1110, 1100, 1040, 920. MS *m/z* 228 (M^+, < 1), 197 (1), 152 (3), 139 (10), 121 (13), 97 (43), 95 (30), 81 (17), 55 (38), 45 (100). MS (FAB) 229 (M+1, 38), 197 (84), 167 (90), 45 (100).

Diastereoisomers of (4*R*,5*R*,1'*S*)-3-[(4-Chlorophenyl)hydroxymethyl]-5-[1'-((methoxy)methoxy)ethyl]-4-methyl-2(5H)-furanone 67. They were obtained as a 47:35:18 mixture of diastereoisomers (^{1}H-NMR evidence) using 3 molar equivalents of 4-chlorobenzaldehyde as electrophile. The diastereoisomers could not be separated by flash chromatography (4:1 hexane/AcOEt) and were obtained in 80% combined yield. Thick oil. $[\alpha]_D$ -47 (c = 1.0). ^{1}H-NMR (300 MHz, C_6D_6) δ 7.12 (m), 6.93 (m), 5.15 (distorted t, *J* = 3.1), 4.66 (d, *J* = 8.3), 4.40 (m, 2H), 3.69 (qd, *J* = 6.4, 3.7), 3.64, (qd, *J* = 6.5, 3.7), 3.58 (qd, *J* = 6.3, 4.5), 3.50 (dd, *J* = 7.2, 3.7), 3.44 (dd, *J* = 4.3, 3.7), 3.36 (dd, *J* = 7.4, 4.5), 3.15 (s), 3.13, (s), 2.46-2.35 (m), 2.10 (dd, *J* = 9.0, 3.0), 2.02 (t, *J* = 8.7), 1.98-1.87 (m), 1.63 (dd, *J* = 17.5, 5.9), 1.01 (d, *J* = 6.5), 0.85 (d, *J* = 6.7), 0.81 (d, *J* = 7.0), 0.61 (d, *J* = 6.4), 0.35 (d, *J* = 6.5), 0.27 (d, *J* = 6.3). ^{13}C-NMR (50.3 MHz, C_6D_6) δ 177.9, 176.5, 176.3, 141.1, 139.9, 134.0, 133.1, 128.8, 128.7, 128.6, 127.2, 126.8, 95.3, 88.5, 87.2, 87.0, 74.1, 73.9, 73.6, 73.0, 70.2, 56.1, 55.3, 54.7, 36.6, 33.1, 30.9, 30.0, 19.9, 19.4, 18.9, 16.2, 15.9. IR (neat) ν 3600-3200, 2970, 2930, 2880, 2720, 1770, 1600, 1495, 1460, 1405, 1385, 1320, 1220, 1190, 1150, 1095, 1040, 990, 920, 840, 760, 735. MS *m/z* 283 (M-45, 6), 196 (7), 194 (8), 165 (13), 141 (48), 128 (35), 99 (47), 77 (55), 69 (37), 45 (100). MS (FAB) *m/z* 329 (M+1, 10), 311 (26), 267 (28), 165 (31), 141 (33), 139 (30), 69 (32), 45 (100).

Synthesis of (3*R*,4*R*,5*R*,1'*S*)-3-[1,2-Di-*tert*-butoxycarbonylhydrazino]-5-[1'-((methoxy)methoxy)ethyl]-4-methyl-2(5H)-furanone 68.

A solution of the lactone (+)-**59** (0.40 mmol) in dry THF (3 mL) was added dropwise, via cannula, to a stirred solution LDA (0.48 mmol, prepared from a 2M solution in heptane/THF/ethylbenzene) in THF (1 mL) at -78°C under argon. After stirring for 20 minutes, a solution of di-*tert*-butyl azodicarboxylate (0.5 mmol) was added, via cannula. Stirring was continued at -78°C until completion of the reaction (as shown by t. l. c., *ca* 30 minutes).

Then, a saturated aqueous solution of NH_4Cl was added at -78°C, and the mixture was allowed to reach room temperature. The mixture was diluted with H_2O and Et_2O; the phases were separated, the aqueous phase was extracted with Et_2O (twice) and AcOEt (twice). The combined organic extracts were washed with H_2O and brine. After drying ($MgSO_4$), and solvent evaporation, the crude product consisted mainly of a single diastereoisomer (ds > 10:1, ^{1}H-NMR evidence). Flash chromatography (4:1 hexane/AcOEt) afforded the pure product in 87% yield. Thick oil. $[\alpha]_D$ -14 (c = 1.1). ^{1}H-NMR (300MHz, C_6D_6, as a mixture of rotamers, at 40°C) δ 6.50 (broad s, 1H), 4.85 (broad m, 1H), 4.42 (m, 2H), 3.65 (m, 1H), 3.45 (m, 1H), 3.15 (s, 3H), 2.65 (broad s), 1.40 (s, 9H), 1.33 (s, 9H), 1.10-0.85 (m, 6H). ^{1}H-NMR (300MHz, C_6D_6, as a mixture of rotamers, at 22°C) δ 6.47 (broad s, 1H), 4.85 (broad m, 1H), 4.65 (m, 2H), 4.03 (m, 1H), 3.89 (m, 1H), 3.34 (s, 3H), 2.79 (dd, *J* = 17.6, 9.2, 1H), 2.55 (m, 1H), 2.09 (dd, *J* = 17.6, 5.4, 1H), 1.44 (s, 18H), 1.22 (d, *J* = 6.4, 3H), 1.20 (d, *J* = 6.6, 3H). ^{1}H-NMR (300MHz, $CDCl_3$, as a mixture of rotamers, at 22°C) δ 6.43 (broad s, 1H), 4.88 (broad m, 1H), 4.71 (d, *J* = 6.8, 1H), 4.63 (d, *J* = 6.8, 1H), 4.00 (m, 1H), 3.89 (m, 1H), 3.37 (s, 3H), 2.70-2.45 (very broad s, 1H), 1.47 (s, 18H), 1.37 (d, *J* = 6.5, 3H), 1.25 (d, *J* = 6.5, 3H). ^{13}C-NMR (50.3 MHz, C_6D_6, as a mixture of rotamers) δ 172.1, 155.9, 155.1, 95.2, 85.0, 81.6 (broad), 80.6 (broad), 73.4, 64.8 (broad), 55.2, 35.8, 28.4, 28.3, 28.1, 16.3, 16.2. IR (neat) ν 3400-3200, 2990, 2950, 1790, 1750, 1720, 1480, 1460, 1370, 1310, 1250, 1150, 1040, 970, 920, 860, 760. MS *m/z* 363 (M-55, < 1), 262 (3), 257 (3), 218 (4), 186 (11), 158 (3), 143 (4), 102 (7), 85 (10), 69 (6), 57 (100). MS (FAB) *m/z* 419 (M+1, 100), 363 (100), 307 (95), 275 (35), 263 (57), 231 (100), 203 (33), 177 (47), 121 (46), 41 (43).

Synthesis of (3*E*,4*R*,5*R*,1'*S*)-3-[(4-Chlorophenyl)methylene]-5-[1'-((methoxy)methoxy)-ethyl]-4-methyl-2(5H)-furanone 69.

Triethyl amine (0.06 mL, 0.46 mmol) and methanesulfonyl chloride (0.02 mL, 0.32 mmol) were sequentially added to a solution of the hydroxy lactone **67** (as a mixture of three diastereoisomers) (90 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) at 0°C. The reaction was followed by t. l. c. until all the starting material was consumed (*ca* 2.5 hours). Water was then added at 0°C; the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic extracts were washed with brine. After drying ($MgSO_4$) and solvent evaporation, the crude product was dissolved in dry THF (2 mL), and treated with DBU (0.08 mL, 0.54 mmol) under argon. The mixture was heated at 60°C for 2h and, then, cooled to room temperature. After addition of H_2O, extraction with AcOEt (twice), drying (Na_2SO_4) and solvent evaporation, the crude product was purified by flash chromatography (4:1 hexane/AcOEt) to give the olefin **69** (53 mg, 62% overall yield), along with a small amount of its Z-isomer (*ca* 5%, g. l. c. evidence). Thick oil. $[\alpha]_D$ -94 (c = 0.4). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 5H), 4.66 (d, *J* = 6.9), 4.58 (d, *J* = 6.9, 1H), 4.08 (dd, *J* = 3.9, 2.2, 1H), 3.89 (qd, *J* = 6.5, 3.9, 1H), 3.58 (distorted qt, *J* = 6.8, 2.2, 1H), 3.13 (s, 3H), 1.29 (d, *J* = 6.8, 3H), 1.26 (d, *J* = 6.5, 3H). ^{1}H-NMR (300 MHz, C_6D_6) δ 7.51 (d, *J* = 2.2, 1H), 6.97-6.90 (m, 4H), 4.38 (d, *J* = 6.7, 1H), 4.35 (d, *J* = 6.7, 1H), 3.63 (m, 2H), 3.36 (distorted qt, *J* = 7.1, 2.1, 1H), 3.10 (s, 3H), 0.87 (d, *J* = 6.2, 3H,), 0.83 (d, *J* = 7.1, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 174.7 (s), 135.6 (s), 134.8 (d), 132.5 (s), 131.3 (d), 131.1 (2C, d), 129.2 (2C, d), 95.4 (t), 87.0 (d), 73.4 (d), 55.6 (q), 33.2 (d), 18.5 (q), 16.0 (q). MS *m/z* 310 (M^+, 1), 280 (5), 278 (15), 250 (13), 248 (46), 234 (11), 233 (10), 223 (30), 222 (16), 221 (84), 220 (12), 193 (18), 165 (28), 149 (12), 130 (16), 129 (30), 128 (24),127 (19), 125 (11), 89 (15), 57 (27), 45 (100).[86]

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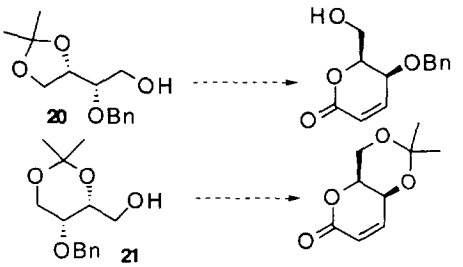

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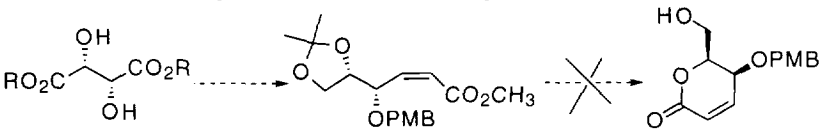
(50) Analougosly to the synthesis of (+)-**5**, the preparation of **31**, bearing a more labile protecting group, was tried. Although the α,β-unsaturated ester **32** was uneventfully prepared from either (*R,R*)-dimethyl tartrate or (*R,R*)-diethyl tartrate, we were unable to selectively deblock the terminal glycol unity without affecting the *p*-methoxybenzyloxy group [Bao, R.; Herradón, B.; unpublished observations]



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