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Asymmetric Synthesis of Substituted Cyclopentanes via Michael Initiated Ring Closure Reactions[1]

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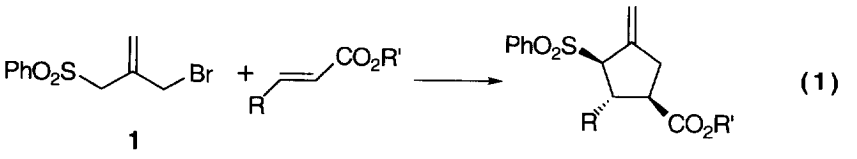
Abstract: Michael initiated ring closure reactions of bromosulfone **1** and γ-oxygenated (E)-α,β-unsaturated esters, which lead stereohomogeneously to trisubstituted methylenecylopentanes, proceed also with good facial selectivity. The use of nonracemic enoate **14** in these reactions led to the synethesis of enantiomerically pure cylcopentanone **17**. The reason for the preferred *anti*-selective Michael addition of enoate **14** with allyl and alkyl α-phenylsulfonyl lithiated reagents is discussed.

INTRODUCTION

Cyclopentanoid natural products (e.g., prostaglandins, prostacyclines, various sesquiterpenoids, di- and tricyclopentanoids) display a variety of biological properties and therefore much interest has been recently focused on the preparation of enantiomerically pure cyclopentane derivatives, with particular emphasis on the synthesis of optically active cyclopentanones as valuable synthetic intermediates.

In recent developments the chirality in five-membered carbocycles has been achieved by different means such as chiral auxiliary groups,[2a] dynamic kinetic resolution,[2b] chiral catalysts,[2c] enzymatic methods,[2d] rearrangements of other chiral compounds,[2e] chemical transformation from sugars[2f] and amino acids.[2g] A tandem asymmetric cyclopentanation, by Pd-catalyzed cycloaddition of a conjunctive reagent to a chiral (E) enoate was reported by Trost to give a 3-4:1 diastereofacial selectivity.[3] Asymmetric Michael additions are an object of recent research interest[4] but few successful asymmetric Michael initiated ring closure (MIRC) reactions involving acyclic olefins and leading to cyclopentanes have been reported. An exceptionally high diastereomeric and enantiomeric excess was achieved by Enders in an intramolecular cyclopentanation by reacting SAMP/RAMP hydrazones with an (E)-6-bromohex-2-enoate,[5] while less successful attempts of an asymmetric MIRC cyclopentane formation were recently reported by Little.[6]

We have recently investigated [3+2] MIRC cyclopentanations which were carried out by reacting a bifunctional conjunctive reagent, namely 2-bromomethyl-3-phenylsulfonyl-1-propene **1** with various electrophilic olefins as the acceptors.[7,8] Utilization of acyclic (E)-enoates in these reactions resulted in high yields (>90%) of stereohomogeneous *trans-trans* trisubstituted methylenecyclopentanes (eq 1).[8b] The exclusive



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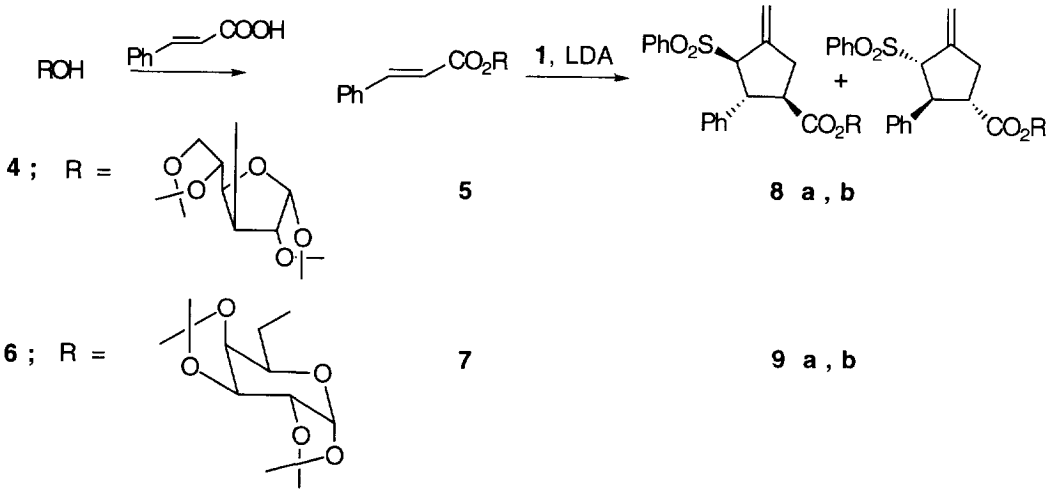
formation of a single diastereomer in these reactions prompted us to investigate the possibility of stereofacial selectivity in the conjugate addition step, to result eventually in asymmetric cyclopentanation when chiral substrates are involved. We report herewith our successful results obtained in this direction.

RESULTS AND DISCUSSION

Sugar auxiliaries

First we investigated the possibility of stereofacial control by introducing a sugar-derived auxiliary in

Scheme 1



the ester group of the enoate. Asymmetric 1,4-additions to enoates having bulky chiral ester auxiliaries have been successfully explored by Oppolzer.[9] We assumed that the readily available sugar-derived ester groups could promote a facially discriminating conjugate attack assisted by chelation of the lithium counterion with the oxygens of the stereodemanding chiral moiety. Esterification of cinnamic acid with 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **4**[10a] and respectively, with 1,2:3,4-di-O-isopropylidene-D-galactose **6**[10b] (DCC, DMAP, CH_2Cl_2)[11] afforded the enoates **5** and **7**. Low temperature reactions of lithiated **1** with each of these esters resulted indeed in a high-yielding MIRC cyclopentanation with complete stereoselectivity at the cyclopentane stereocenters but the stereofacial selectivity of the conjugate addition was disappointing: an inseparable mixture of two stereomers was obtained in both reactions with insufficient preference for one of the isomers (3:1 for **8a,b** and 2:1 for **9a,b**, Scheme 1).

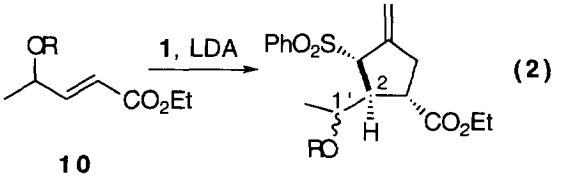
γ-Oxygenated acceptors.

Next we explored γ-oxygenated-α,β-unsaturated-(E)-enoates as acceptors for eventual asymmetric

cyclopentanation. Extensive studies conducted in recent years have shown that γ-oxygen substitution in acyclic α,β-unsaturated carbonyl derivatives can sometimes exert a high degree of stereocontrol in conjugate additions. Among the factors influencing the stereochemical outcome, the structure of the organometallic reagent seems of utmost importance. Reversal of the stereochemical outcome in these reactions has often been observed and the rationalization of sometimes confusing results is not yet conclusive. For instance, utilization of allyllithium reagents[12] as well as of alkyl-[12,13,14] and vinylcopper reagents[14,15] resulted predominantly in *anti*-adducts whereas alkyllithium reagents[12,16,17] and allylic cuprates[12,14,18] afforded mostly *syn*-adducts.

In this context we examined first the possibility of obtaining stereofacial selective cyclopentanation in reactions of **1** with racemic γ-oxygenated α,β-unsaturated (E) esters. The protected 4-hydroxy-2-pentenoate[19] **10** smoothly reacted with lithiated **1** at low temperature (-95 °C, 15 min) to afford in 85% yield two diastereomeric methylenecyclopentanes **11a,b** (eq 2). The stereomeric ratio 85:15 was determined by integration of the corresponding vinylic proton signals in the ^{1}H NMR spectrum of the crude product mixture which on chromatography provided the major component **11a** in pure form. On the basis of NOE data (for **11a**) and in analogy with previous MIRC cyclopentanations[8] a *trans-trans* substitution in the ring is assigned for both diastereomers of **11**. An *anti*-configuration assignment[20] involving the C-2 and C-1′ centers in **11a** is based on a "gauche" interaction between the corresponding hydrogens (J=3 Hz) as well as on NOE data (Fig. 1). While there was strong NOE enhancement between C<u>H</u>-OR and the α-sulfonyl hydrogen, none was observed between -C<u>H</u>-OR and C<u>H</u>CO_2Et.

We then reasoned that the introduction of additional rigidity in the acceptor by bonding the γ-oxygenated and the δ-carbons should improve the stereofacial selectivity. The epoxy enoate **12** was thus prepared[21] and reacted with **1**, under identical conditions to those used above to afford this time a single methylenecyclopentane derivative **13**, stereohomogeneous at the five stereogenic centers (eq. 3). The conformations **13A,B**, (Fig. 2) are consistent with a "gauche" arrangement of H-2 and H-1′ (J=4.5 Hz) but the obtained NOE data were not sufficient to differentiate between the *anti*-(**13A**) and *syn*-(**13B**) configuration because of overlap of ^{1}H NMR signals. However, on the basis of the preceding and further described results, which show constancy for a preferential *anti* configuration, the **13A** configuration can be tentatively ascribed to the product.



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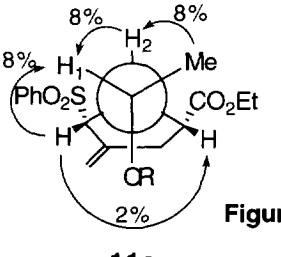
10

R = CH_2OEt

11 **a** : anti
b : syn



11a

Figure 1

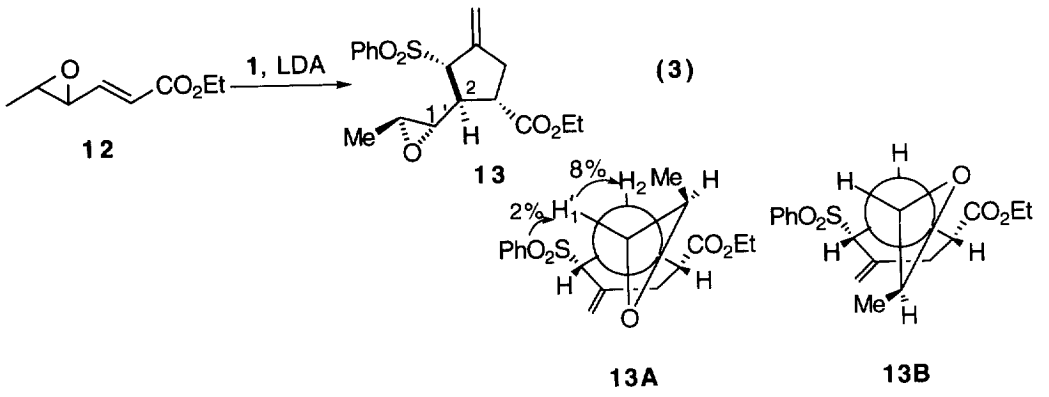


Figure 2

Asymmetric cyclopentanation

The obtained stereofacial selectivity justified the utilization of an optically active substrate, namely the commercially available (S)-acrylate derivative **14**, for asymmetric cyclopentanation. Reaction of **14** with lithiated **1** (91% yield) occurred with high enantiomeric and diastereomeric excess (95:5, Scheme 2). ^{1}H NMR and NOE data for both separated diastereomers enabled us to ascribe the *anti*-configuration to the major component **15** and *syn*- to **16** with *trans-trans* trisubstitution in the rings of both stereomers. The conformations depicted in Fig. 3 are based on a "gauche" interaction of the hydrogens at the involved stereogenic centers ($J_{2,4'}$=4.5 Hz) as well as on the determined NOE data. Ozonolysis of **15** led smoothly to the cyclopentanone **17** (90%). The relative and absolute stereochemistry of **17**, which originates from optically pure **14**, is thus secured.

Scheme 2

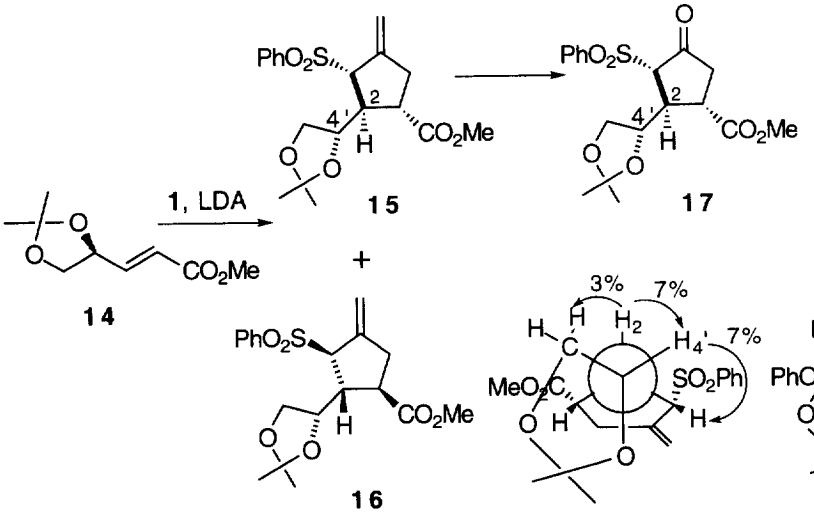
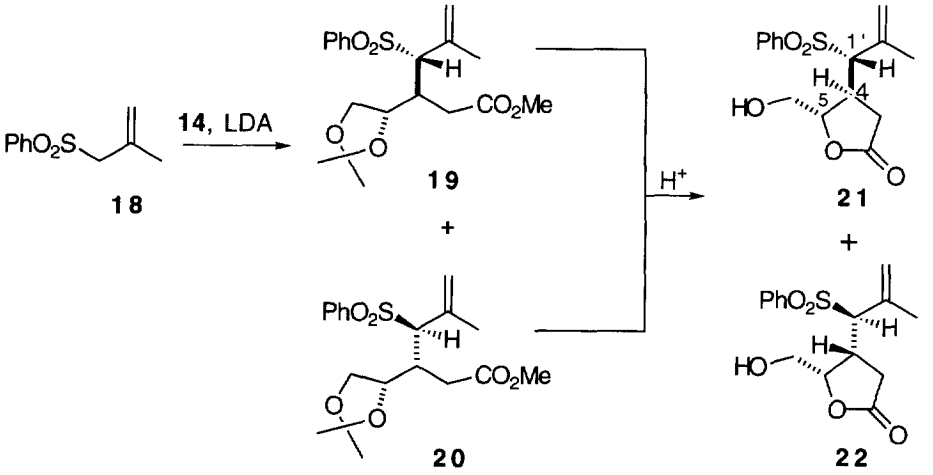


Figure 3

Open-chain additions of allyl and alkyl sulfone

We examined next open-chain asymmetric Michael additions of allylic α-phenylsulfonyl-substituted organolithium reagents to the enoate **14**, in an attempt to rationalize the observed stereochemical outcome. Thus, the use of methallylsulfone **18** instead of bromosulfone **1**, could eventually show the influence of the ring closure step on the stereofacial outcome of the conjugate addition. Moreover, the reagent **18**, in contrast to **1**, is stable under basic conditions in the presence of HMPA[8b] which could provide information on the influence of chelation in the transition state. The reaction of lithiated **18** with the enoate **14** gave two stereomers in a 8:1 ratio. In the presence of HMPA the stereoselectivity increased to 12:1, as determined by the integration of vinyl signals in the ^{1}H NMR spectrum of the crude mixture. The stereochemical assignments for the products **19** and **20** were based on their acid-catalyzed conversion to the chromatographically separable lactones **21** and **22** (Scheme 3, furan numbering). The conformations (Fig. 4) are based on anti-positioned H-4 and H-1′ (J=11 Hz) in both **21** and **22** and consequently, the obtained NOE data indicated an *anti*-configuration[20] for the major component **19** and *syn* for **20**. Moreover, these data agree with a fully selective *threo*-relationship between C-4 and C-1′ centers in both stereoisomers.

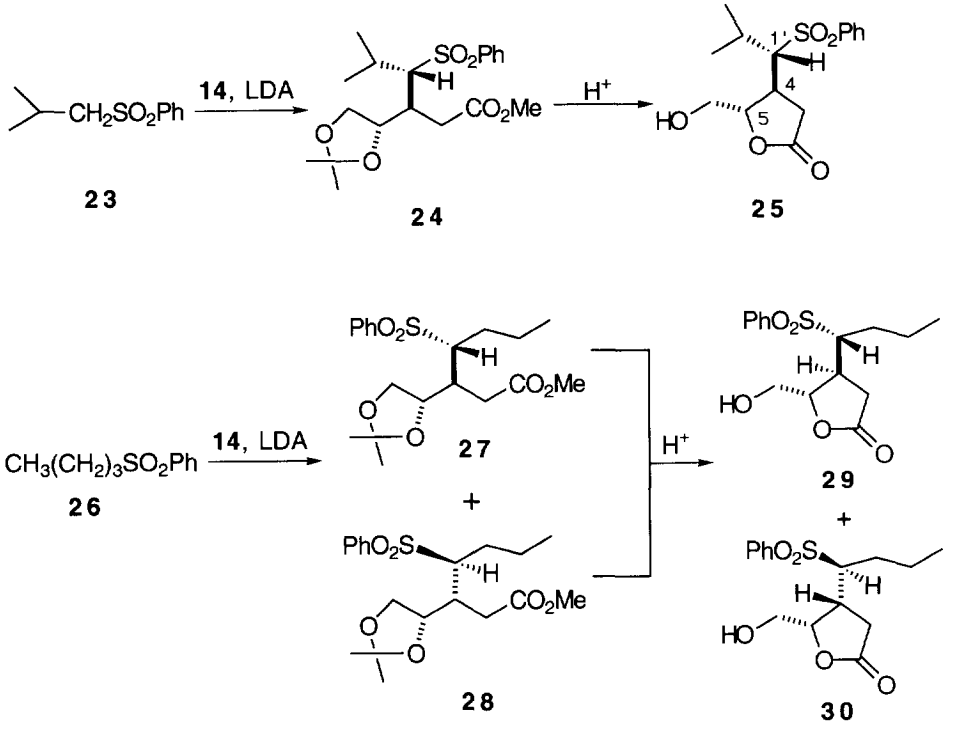
Scheme 3



In an early report, limited to γ-oxygenated α,β-unsaturated oxazolines as acceptors,[12] allyllithium reagents were shown to lead to *anti*-adducts, in contrast to alkyllithium organometallics which were repeatedly reported (as cited before) to give *syn*-products. The influence of an α-phenylsulfonyl group in allyl *vs.* alkyllithium reagents therefore needed clarification: an eventual π-π interaction in the transition state, involving the allyl group,[22] could lead to a different stereochemical outcome. Remarkably, when **14** was submitted to lithiated isobutylsulfone **23**, a single optically active adduct **24** was obtained in 82% yield (Scheme 4). Conversion to the crystalline lactone **25** (95%) provided evidence for an *anti*-configuration (C-4 and C-5) in **25** and therefore also in **24** and a reversal from *threo* (as observed for **19** and **20**) to *erythro*-selectivity, involving

the C-4 and C-1′ centers. The given lactone stereochemistry is based on the conformation shown in Fig. 4 ($J_{4,1'}$=4 Hz) and the determined NOE data. Hence, the presence of the α-phenylsulfonyl group in lithium reagents results in the formation of *anti*-adducts, in contrast to results reported for other alkyllithium reagents.

Scheme 4



However, by using the sterically less demanding n-butylsulfone **26**, a minor diastereomer **28** was also formed (4:1 ratio for **27**:**28**, Scheme 4). The configurational assignments were made after conversion to the separable lactones **29** and **30** . As shown in Fig. 4, the NMR data for **29** ($J_{4,1'}$ = 3Hz, and the corresponding NOE data) indicate an *anti*-configuration (involving the dioxolane group) for the major product **27** . The *syn*-configuration of **28** is deduced from the conformation and NMR data of **30** ($J_{4,1'}$=11Hz, NOE H-4 to H-5=10%). In both stereomers the above data agree with a *threo*-relationship between the C-4 and C-1′. The presence of HMPA did not influence the stereochemical outcome, indicating the minor role of chelation. Therefore, a non-chelated nucleophilic attack on enoate **14**, in terms of a modified Felkin-Anh transition state model,[23] as previously proposed for similar γ-oxygenated acceptors[15,16,24,25] can be postulated. The direction of the attack, (Fig. 5), favors the approach of the sterically crowded α-phenylsulfonyl nucleophile to give preferentially the *anti*-adduct, in contrast to alkyllithium reagents in which the chelation factor can explain the observed preferential *syn*-attack.[16] Concerning the C-4 and C-1′ centers, in the open-chain Michael reactions

the large phenylsulfonyl group adopts in the transition state the outside position resulting in complete *threo*-selectivity when R=allyl or n-butyl. However, in **23** the isopropyl group is probably more hindering than the sulfone group and therefore a reversal to *erythro* configuration occurs, as observed for **24**.

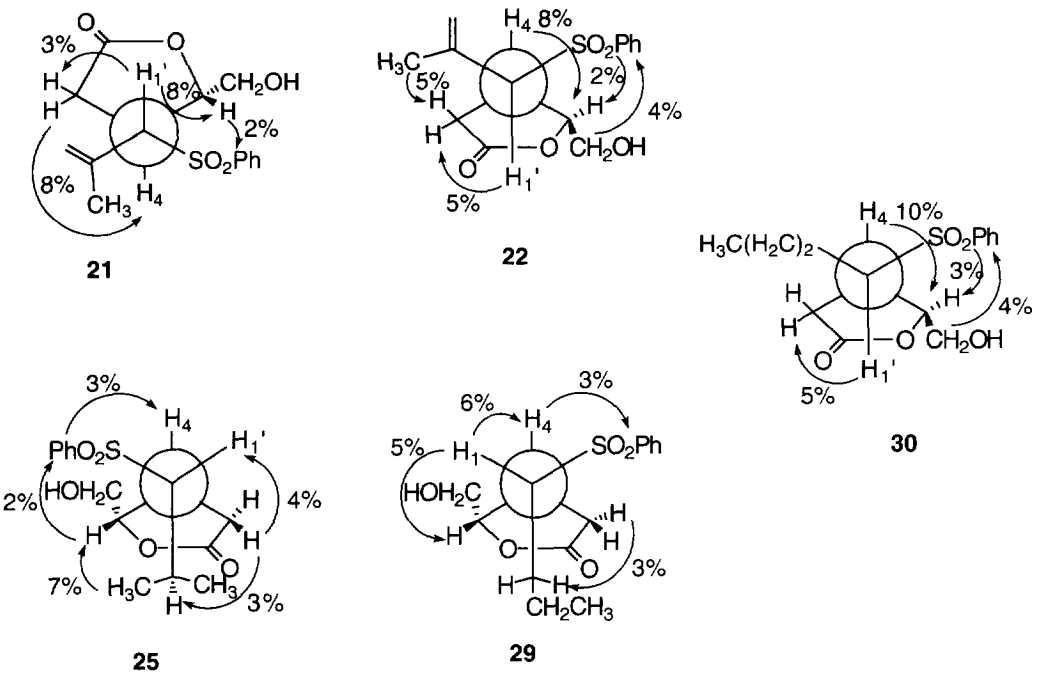


Figure 4. Stereochemical data for lactones

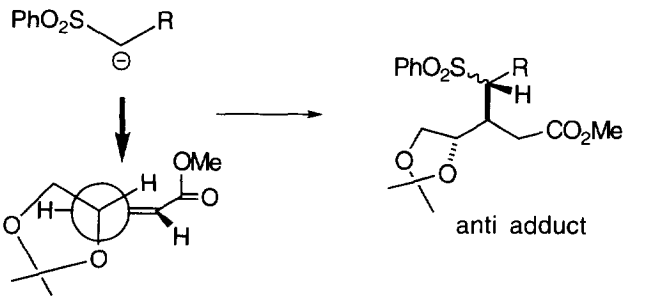


Figure 5

CONCLUSIONS

In summary, good diastereofacial *anti*-selectivity has been achieved in MIRC reactions of the conjunctive reagent **1** with γ-oxygenated enoates which afforded *trans-trans* trisubstituted methylenecyclopentanes. Additional oxygen bonding between the γ and δ-carbons of these acceptors strongly improves the *anti* selectivity with respect to the γ-oxygenated stereogenic center. The use of a nonracemic acceptor **14** led to the synthesis of the optically active cyclopentanone **17** with very good *de*. Lithiated α-

benzenesulfonyl allyl and alkyl reagents add preferentially in an *anti*-manner to the enoate **14** to afford asymmetric Michael additions. Excellent stereofacial selectivity can be achieved in such reactions when the organometallic reagent possesses a bulky alkyl group.

EXPERIMENTAL

General. All air-and moisture-sensitive reactions were carried out in flame-dried, argon-flushed, two necked flasks sealed with rubber septa, and the reagents were introduced with a syringe. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophone. Reactions with cooling at -95 °C were performed using a mixture of liquid nitrogen and MeOH. Chromatography was done on Merck silica gel 60 (230-400 mesh), and precoated Merck silica gel plates (60F-25H) were used for TLC. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-200 or on a Bruker AM-300 spectrometer. Coupling constants were determined directly from ^{1}H NMR spectra. Mass spectra (CI) were recorded at 60-70 eV. Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter with a path length of 0.1 dm.

Preparation of cinnamate 5. To a solution of 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose[10] (**4**, 260 mg, 1mmol) and cinnamic acid (163 mg, 1.1 mmol) in dry CH_2Cl_2 (10 mL) was added DCC (227 mg, 1.1 mmol) and DMAP (12 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 4 h and the precipitated dicyclohexyl urea was filtered. Work up and chromatography (hexane-ethyl acetate 4:1) afforded the ester **5** in 72% yield (280 mg), mp 167-168 °C; ^{1}H NMR δ 7.72 (d, J=16 Hz, 1H), 7.34-7.60 (m, 5H), 6.44 (d, J=16 Hz, 1H), 5.93 (d, J=4 Hz, 1H), 5.38 (d, J=2 Hz, 1H), 4.58 (d, J=4 Hz, 1H), 4.23-4.37 (m, 2H), 4.01-4.18 (m, 2H), 1.55 (s, 3H), 1.43 (s, 3H), 1.32 (1, 3H), 1.31 (s, 3H); ^{13}C NMR δ 165.40 (s), 145.95 (d), 134.05 (s), 130.59 (d), 128.91 (d), 128.15 (d), 117.08 (d), 112.25 (s), 109.29 (s), 105.06 (d), 83.40 (d), 79.83 (d), 76.16 (d), 72.52 (d). 67.09 (t), 26.81 (q), 26.73 (q), 26.21 (q), 25.27 (q).

Preparation of cinnamate 7. 1,2:5,6-Di-o-isopropylidene-D-galactose (**6**) was reacted with cinnamic acid as shown for **4**, to give the ester **7** (59%), mp 105 °C; ^{1}H NMR δ 8.1 (d, J=16 Hz, 1H), 7.88-8.12 (m, 5H), 6.5 (d, J=16 Hz, 1H), 5.58 (d, J=5 Hz, 1H), 4.67 (dd, J=8, 3 Hz, 1H), 4.45 (dd, J=12.5 Hz, 1H), 4.38 (m, 2H), 4.10 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 1.91 (s, 3H), 1.89 (s, 3H); ^{13}C NMR δ 166.69 (s), 144.99 (d), 134.32 (s), 130.20 (d), 128.78 (d), 128.03 (d), 117.78 (d), 109.58 (s), 108.70 (s), 96.27 (d), 71.09 (d), 70.69 (d), 70.45 (d), 66.07 (d), 63.47 (t), 25.99 (q), 25.94 (q), 24.93 (q), 24.48 (q).

Cyclopentanation of 5 to 8a,b. To a stirred solution of LDA prepared from diisopropylamine (0.07 mL, 0.52 mmol) and n-BuLi (0.34 mL, 1.57M solution in hexane) in dry THF (1 mL) under argon and cooled to -95 °C, was added dropwise a solution of **1** (110 mg, 0.4 mmol) in 1 mL THF. After 10 min was added the ester **5** (170 mg, 0.43 mmol) in THF (1 mL) and the reaction mixture was stirred for 15 min at -95 °C, quenched with aqueous NH_4Cl, poured into water and extracted with CH_2Cl_2. The extract was washed successively with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography (hexane-ethyl acetate 4:1) afforded a mixture of two diastereomers (70%), homogeneous by TLC which could not be separated even by HPLC. The ratio of diastereomers **8a,b** (71:29) was determined by

integration of ^{1}H NMR signals in the mixture. **Major diastereomer**: ^{1}H NMR δ 6.90-7.28 (m, 10H), 5.80 (d, J=4 Hz, 1H), 5.36 (m, 1H), 5.16 (m, 2H), 4.35 (d, J=4 Hz, 1H), 3.78-4.20 (m, 6H), 2.70-3.08 (m, 3H), 1.49 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.20 (s, 3H); ^{13}C NMR δ 170.78 (s), 141.27 (s), 140.98 (s), 137.03 (s), 133.65 (d), 129.18 (d), 128.85 (d), 128.61 (d), 127.11 (d), 116.01 (t), 112.22 (s), 109.22 (s), 104.90 (d), 83.13 (d), 79.59 (d), 76.47 (d), 75.22 (d), 72.21 (d), 66.84 (t), 51.93 (d), 49.31 (d), 38.30 (t), 26.69 (q), 26.64 (q), 26.14 (q), 25.08 (q). **Minor diastereomer:** ^{1}H NMR δ 6.90-7.80 (m, 10H), 5.51 (d, J=4 Hz, 1H), 5.36 (m, 1H), 5.16 (m, 2H), 4.43 (d, J=4 Hz, 1H), 3.78-4.20 (m, 6H), 2.70-3.08 (m, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR δ 170.86 (s), 141.27 (s), 140.78 (s), 137.05 (s), 133.65 (d), 129.13 (d), 128.81 (d), 128.57 (d), 127.18 (2d), 115.94 (t), 104.90 (d), 83.04 (d), 79.75 (d), 76.30 (d), 74.78 (d), 72.21 9d), 67.30 (t), 51.98 (d), 49.92 (d), 38.04 (t), 26.72 (q), 26.64 (q), 26.10 (q), 25.16 (q).

Cyclopentanation of 7 to 9a,b. Ester 7 was reacted with **1** under the conditions described for **5**, to give an inseparable mixture of two diastereomers **9a,d** (71%), and the ratio 2:1 was determined as shown for **8a,b**; **Major diastereomer**: ^{1}H NMR δ 6.90-7.80 (m, 10H), 5.48 (d, J=5 Hz, 1H), 5.36 (m, 1H), 5.18 (m, 1H), 4.56 (dd, J=8, 2.5 Hz, 1H), 4.28 (dd, J=5, 2.5 Hz, 1H), 4.05-4.22 (m, 4H), 3.76-4.00 (m, 2H), 2.92-3.04 (m, 1H), 2.62-2.83 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR δ 171.92 (s), 141.49 (s), 141.05 (s), 137.07 (s), 133.52 (s), 129.14 (d), 128.73 (d), 128.50 (d), 128.38 (d), 127.23 (d), 126.82 (d), 115.64 (t), 109.44 (s), 108.58 (s), 96.06 (d), 75.04 (d), 70.81 (d), 70.50 (d), 70.27 (d), 65.83 (d), 63.75 (d), 51.95 (d), 49.23 (d), 38.60 (t), 25.83 (2q), 24.86 (q), 24.35 (q). **Minor diastereomer**: ^{1}H NMR δ 6.95-7.72 (m, 10H), 5.48 (d, J=5 Hz, 1H), 5.36 (m, 1H), 5.21 (m, 1H), 4.50 (dd, J=8, 2.5 Hz, 1H), 4.28 (dd, J=5, 2.5 Hz, 1H), 4.05-4.22 (m, 4H), 3.76-4.00 (m, 2H), 2.92-3.04 (m, 1H), 2.62-2.83 (m, 2H), 1.50 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 171.99 (s), 141.40 (s), 140.85 (s), 137.07 (s), 133.52 (d), 129.14 (d), 127.83 (d), 128.50 (d), 128.38 (d), 127.23 (d), 126.82 (d), 115.70 (t), 109.27 (s), 108.58 (s), 96.06 (d), 74.78 (d), 70.43 (d), 70.37 (d), 70.32 (d), 65.20 (d), 63.09 (d), 51.95 (d), 49.66 (d), 38.60 (t), 25.95 (q), 25.76 (q), 24.86 (q), 24.26 (q).

General conditions for further cyclopentanations. Conditions described above (for **5** and **6**) were modified for all further cyclopentations as follows: to freshly prepared LDA (1.25 mmol in 5.5 mL THF) was added dropwise a solution of **1** (385 mg, 1.4 mmol) in 4.5 mL THF at -95 °C. After 10 min was added dropwise the ester (1mmol) in 2.5 ml THF and the reaction mixture was stirred at the above temperature for 20 min, then quenched (20% aqueous AcOH) and worked up as before. The diastereomeric ratio was established by integration of the vinylic protons in the crude mixture.

Preparation of the ethoxymethyl ether of ethyl 4-hydroxy-2-pentenoate 10. To a solution of the alcohol[19] (110 mg, 0.78 mmol) and diisopropyl ethyl amine (0.4 mL, 2.35 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise chloromethyl ethyl ether (0.135 mL, 2 mmol) at room temperature. The reaction mixture was stirred for 3h, diluted with CH_2Cl_2, and washed successively with saturated NH_4Cl solution and water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatographic purification

(EtOAc:petroleum ether 1:3) gave **10** (109 mg, 69%); ^{1}H NMR δ 6.86 (dd, J=16, 6 Hz, 1H), 6.00 (dd, J=16, 2 Hz, 1H), 4.72 (d, J=7 Hz, 1H), 4.68 (d, J=7 Hz, 1H), 4.38 (dtd, J=12, 6, 2 Hz, 1H), 4.21 (q, J=7 Hz, 2H), 3.78-3.47 (m, 2H), 1.33 (d, J=7 Hz, 3H), 1.29 (t, J=7 Hz, 3H), 1.22 (t, J=7 Hz, 3H).

Ethyl(1R*,2R*,3R*,1′S*)-2-[(1′-ethoxymethoxy)ethan-1′-yl]-4-methylene-3-(phenylsulfonyl)-cyclopentanecarboxylate 11a. The ethoxymethyl ether **10** was reacted with **1** as shown above and the residue was chromatographed (EtOAc:petroleum ether, 1:3) to give, in order of elution **11a** (157 mg), and then a mixture of **11a** and **11b** (181 mg, 86% total yield). **11a**: ^{1}H NMR δ 7.95-7.87 (m, 2H), 7.70-7.62 (m, 1H), 7.59-7.51 (m, 2H), 5.16 (dt, J=3, 1.5 Hz, 1H), 4.95 (dt, J=3, 1.5 Hz, 1H), 4.64 (d, J=7 Hz, 1H), 4.57 (d. J=7 Hz, 1H), 4.13 (qd, J=7, 1.5 Hz, 2H), 4.00 (dq, J=6, 1.5 Hz, 1H), 3.76 (qd, J=6, 3 Hz, 1H), 3.63-3.45 (m, 2H), 3.15 (ddd, J=9, 6, 3 Hz, 1H), 2.88 (ddd, J=12, 9, 7 Hz, 1H), 2.54 (dd, J=15, 7 Hz, 1H), 2.31 (ddt, J=15, 12, 3 Hz, 1H), 1.24 (t, J=7 Hz, 3H), 1.20 (t, J=7 Hz, 3H), 1.09 (d, J=6.5 Hz, 3H); ^{13}C NMR δ 174.07 (s), 142.73 (s), 137.25 (s), 133.78 (d), 129.84 (d, 2 x CH), 128.91 (d, 2 x CH), 114.68 (t), 93.84 (t), 74.33 (d), 71.42 (d), 63.70 (t), 60.82 (t), 49.22 (d), 43.28 (d), 38.96 (t), 18.36 (q), 15.06 (q), 14.15 (q); Ms (CI/NH_3) 414 (MNH_4^+, 80), 397 (MH^+, 100).

Preparation of 4,5-epoxy-2-hexenoate 12. To a solution of ethyl 2,4-hexadienoate (330 mg, 2.36 mmol) in CH_2Cl_2 (20 mL) was added portionwise at room temperature m-CPBA (496 mg, 80%) during 24 h. After completing the reaction (TLC) the mixture was diluted (CH_2Cl_2), washed with saturated $NaHCO_3$ solution and water and the organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. Chromatographic purification (EtOAc/petroleum ether 1:5) gave **12** (212 mg, 58%); ^{1}H NMR δ 6.67 (dd, J=16, 7 Hz, 1H), 6.12 (dd, J=16, 1 Hz, 1H), 4.21 (q, J=7 Hz, 2H), 3.18 (dd, J=7, 2 Hz, 1H), 2.98 (qd, J=5, 2 Hz, 1H), 1.39 (d, J=5 Hz, 3H), 1.29 (t, J=7 Hz, 3H).

Ethyl(1R*,2R*,3R*,1′S*,2′S*)-2[(1′,2′-epoxy)propan-1′-yl]-4-methylene-3-(phenylsulfonyl)-cyclopentanecarboxylate 13. The reaction of **12** with **1**, as described above, was followed by chromatographic purification (EtOAc:petroleum ether, 1:3) to give **13** in 80% yield, mp 52-43 °C; ^{1}H NMR δ 7.95-7.89 (m, 2H), 7.72-7.63 (m, 1H), 7.57-7.52 (m, 2H), 5.21 (ddd, J=2.5, 2, 1 Hz, 1H), 4.98 (ddd, J=3, 2, 1 Hz, 1H), 4.13 (q, J=7 Hz, 2H), 3.96 (dq, J=7, 2 Hz, 1H), 3.15 (ddd, J=9.5, 7, 4.5 Hz, 1H), 2.80 (dd, J=4.5, 2 Hz, 1H), 2.77 (qd, J=5, 2 Hz, 1H), 2.62-2.48 (m, 2H), 2.38-2.19 (m, 1H), 1.25 (t, J=7 Hz, 3H), 1.24 (d, J=5 Hz, 3H); ^{13}C NMR δ 172.70 (s), 141.31 (s), 136.60 (s), 133.93 (d), 129.72 (d, 2 x CH), 128.96 (d, 2 x CH), 115.61 (t), 70.81 (d), 60.98 (t), 60.10 (d), 54.01 (d), 44.55 (d), 44.20 (d), 38.10 (t), 17.26 (q), 14.09 (q). Ms (CI/NH_3) m/z 368 (MNH_4^+, 70), 351 (MH^+, 100), 322 (30).

Methyl(1R,2R,3R,4′S)-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4-methylene-3-(phenylsulfonyl)-cyclopentanecarboxylate 15 and the **(1S,2S,3S,4′S)** isomer **16**. The reaction of **1** with (E)-methyl-(S)-3- (2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenoate **14** as described for **11** gave a residue which by integration of the ^{1}H NMR vinyl protons (δ 5.11 for **16** and δ 5.16 for **15**) indicated a ratio 95:5 for **15**:**16**. Chromatography (EtOAc-petroleum ether 1:3) gave, in order of elution **16** (4%) and then **15** (87%); **16**: ^{1}H NMR δ 7.95-7.83

(m, 2H), 7.70-7.62 (m, 1H), 7.60-7.51 (m, 2H), 5.11 (dt, J=2.5, 1.5 Hz, 1H), 4.63 (dt, J=2.5, 1.5 Hz, 1H), 4.34 (dt, J=6, 4 Hz, 1H), 4.07 (dd, J=9, 6.5 Hz, 1H), 4.01 (dd, J=9, 6.5 Hz, 1H), 3.94 (dq, J=4.5, 1.5 Hz, 1H), 3.72 (s, 3H), 3.27 (dt, J=8, 4 Hz, 1H), 2.91 (dt, J=11, 8.5 Hz, 1H), 2.69-2.49 (m, 2H), 1.30 (s, 6H); ^{13}C NMR δ 173.42 (s), 142.74 (s), 136.74 (s), 133.79 (d), 129.68 (d, 2 x CH), 128.88 (d, 2 x CH), 115.12 (t), 109.02 (s), 76.10 (d), 70.29 (d), 66.71 (t), 52.10 (q), 45.35 (d), 45.19 (d), 36.62 (t), 25.99 (q), 24.52 (q); Ms (CI/Isobutane m/z 381 (MH^+, 88), 365 (17), 323 (100). **15**: mp 120-122 °C; $[\alpha]_D^{25}$+ 80 (C=1, $CHCl_3$). ^{1}H NMR δ 7.94-7.87 (m, 2H), 7.70-7.63 (m, 1H), 7.58-7.52 (m, 2H), 5.16 (t, J=1.5 Hz, 1H), 4.87 (t, J=1.5 Hz, 1H), 4.21 (td, J=6.5, 4.5 Hz, 1H), 3.98 (dd, J=8.5, 6.5 Hz, 1H), 3.87 (dq, J=6, 1 Hz, 1H), 3.69 (s, 3H), 3.66 (dd, J=8.5, 6.5 Hz, 1H), 3.32 (dt, J=8, 5 Hz, 1H), 2.88 (dt, J=12, 8 Hz), 2.57 (dd, J=15, 8 Hz, 1H), 2.36 (ddq, J=15, 12, 2.5 Hz, 1H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR δ 174.05 (s), 142.08 (s), 136.69 (s), 133.96 (d), 129.89 (d, 2 x CH), 128.95 (d, 2 x CH), 115.47 (t), 109.19 (s), 77.20 (d), 71.76 (d), 66.93 (t), 52.16 (q), 45.15 (d) 43.75 (d), 38.15 (t), 26.22 (q), 25.13 (q); Ms (CI/Isobutane) m/z 381 (MH^+, 65), 365 (15), 349 (8), 323 (100). Anal. Calcd. for $C_{19}H_{24}O_6S$: C, 59.98; H, 6.36. Found: C, 59.91; H, 6.40.

Methyl(1R,2R,3R,4′S)-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4-oxo-3-(phenylsulfonyl)cyclopentane-carboxylate 17. Ozone was bubbled through a solution of **15** (150 mg, 0.39 mmol) in CH_2Cl_2 (20 mL) at -78 °C until the blue color persisted for 20 min. After argon purging and addition of dimethyl sulfide (0.5 mL), the reaction mixture was allowed to warm slowly to room temperature during 2h, and stirring was continued for an additional 1h at ambient temperature. Evaporation of the solvent under reduced pressure and chromatography (EtOAc:petroleum ether 2:3) gave **17** (137 mg 90% yield); mp 86 °C, $[\alpha]_D^{25}$+ 44 (C=0.45, CH_3OH); ^{1}H NMR δ 7.89-7.84 (m, 2H), 7.74-7.67 (m, 1H), 7.62-7.54 (m, 7H), 4.41 (td, J=6.5, 3 Hz, 1H), 4.12 (dd, J=9, 7 Hz, 1H), 3.85 (dd, J=9, 6 Hz, 1H), 3.79 (bd, J=5.5 Hz, 1H), 3.78 (s, 3H), 3.61 (td, J=5.5, 3 Hz, 1H), 3.17 (td, J=9, 6 Hz, 1H), 2.86 (dd, J=14, 9 Hz, 1H), 2.64 (ddd, J=14, 9, 1.5 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C NMR δ 203.23 (s), 173.32 (s), 137.18 (s), 134.39 (d), 129.23 (d, 2 x CH), 129.16 (d, 2 x CH), 109.51 (s), 76.35 (d), 72.99 (d), 66.61 (t), 52.69 (q), 42.24 (d), 41.89 (t), 38.18 (d), 26.00 (q), 24.46 (q); Ms (CI/Isobutane) m/z 383 (MH^+, 15), 365 (10), 325 (100). HRMS Calcd. for $C_{18}H_{22}O_7S$ 383.1164, found: 383.1240.

(4S,5S,1′S)-5-Hydroxymethyl-4-[1′-(phenylsulfonyl)-2′-methylenepropan-1′-yl]-(3H)-4,5-dihydrofuran-2-one 21 and the (4R, 5S,1′S)- isomer 22. To a stirred solution of LDA, prepared from 0.23 mL (1.68 mmol) of diisopropylamine, 0.99 mL of n-BuLi (1.54 mmol, 1.55 M in hexane) in 7 mL THF was added dropwise at -95 °C a solution of methallyl sulfone **18** (345 mg, 1.76 mmol) in 5.5 mL THF. After stirring the mixture for 10 min at the above temperature, the unsaturated ester **14** (234 mg, 1.26 mmol) in 3 mL THF was added dropwise. After 15 min the reaction mixture was quenched with aqueous AcOH (20%), poured into water, and extracted with CH_2Cl_2. The extracts were washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated under reduced pressure. The ratio of stereomers in the residue (8:1) was established by ^{1}H NMR integration of the vinylic protons (δ 4.96 for **19** and δ 5.13 for **20**); To the crude mixture (560 mg)

dissolved in MeOH (20 mL) was added p-TSOH (0.1 eq) and the reaction mixture was stirred at room temperature for 4 h. Evaporation of the solvent and chromatographic purification (EtOAc:petroleum ether 2:1) gave, in order of elution, unreacted **18**, then **22** (36 mg) and **21** (292 mg); **22**: mp 184-186 °C; ^{1}H NMR δ 7.87-7.81 (m, 2H), 7.71-7.68 (m, 1H), 7.60-7.51 (m, 2H), 5.03 (ddd, J=7.5, 2, 1.5 Hz, 1H), 5.01-4.93 (bs, 1H), 4.78-4.65 (bs, 1H), 4.46 (dd, J=13.5, 1.5 Hz, 1H), 4.16 (dd, J=13.5, 2 Hz, 1H), 4.14 (bd, J=12 Hz, 1H), 3.57 (dddd, J=12.5, 12, 9, 7.5 Hz, 2H), 2.66 (dd, J=17, 2.5 Hz, 1H), 2.40 (dd, J=14, 9 Hz, 1H), 1.76-1.67 (bs, 3H): ^{13}C NMR δ 175.77 (s), 136.64 9s), 134.04 (d), 128.97 (d, 2 x CH), 128.91 (d, 2 x CH), 128.91 (s), 121.93 (bt), 81.66 (d), 71.56 (bd), 62.40 (t), 36.06 (bd), 33.45 (t), 20.02 (bq); Ms (CI/NH_3) m/z 382 (MNH_4^+, 100), 311 (MH^+, 85). HRMS Calcd. for $C_{15}H_{18}O_5S$ 311.0953, found: 311.0940. **21:** mp 152-154 °C; $[\alpha]_D^{25}$+ 6.4 (C=2.8, CH_2Cl_2). ^{1}H NMR δ 7.85-7.80 (m, 2H), 7.68-7.60 (m, 1H), 7.58-7.50 (m, 2H), 5.19 (dt, J=4, 3 Hz, 1H), 4.97 (td, J=1, 1.5 Hz, 1H), 4.69 (bs, 1H), 4.11 (bd, J=14 Hz, 1H), 4.01 (bd, J=14 Hz, 1H), 3.82 (d, J=11 Hz, 1H), 3.46 (dddd, J=11, 10.5, 5, 4 Hz, 1H), 2.96 (dd, J=18.5, 10 Hz, 1H), 2.62 (bt, J=5 Hz, 1H), 2.36 (dd, J=18.5, 5 Hz, 1H), 1.67 (dd, J=1.5, 1 Hz, 3H); ^{13}C NMR δ 175.65 (s), 137.46 (s), 136.45 (s), 134.11 (d), 128.95 (d, 4 x CH), 123.20 (t), 83.78 (d), 74.76 (d), 63.73 (t), 34.21 (d), 33.20 (dd), 19.95 (q); Ms (CI/NH_3) m/z 328 (MNH_4^+, 100), 311 (MH^+, 63), 151 (30). HRMS Calcd. for $C_{15}H_{18}O_5S$ 311.0953, found 311.0915.

The above reaction was repeated under identical conditions with HMPA (0.8 mL in 0.5 mL THF) added to the reaction mixture (10 min after the addition of **18** and 5 min prior to **14**). After extraction with Et_2O a 12:1 ratio of **19/20** was established as above.

(5S,4S,1′R)-5-Hydroxymethyl-4-[1′-(phenylsulfonyl)-2′-methylpropan-1′-yl]-(3H)-4,5-dihydrofuran-2-one 25. The reaction of isobutyl phenyl sulfone **23** with **14** followed the procedure described above for **18** with stirring at -70 °C for 30 min. Work up as before gave a sole product (TLC, ^{1}H NMR, 1% limit of detection). Lactonization of the crude product as described before and chromatographic purification (EtOAc/petroleum either 2:1) gave **25** (77% overall yield), mp 133-135 °C; $[\alpha]_D^{25}$ + 37 (C=2, CH_3OH). ^{1}H NMR δ 7.95-7.88 (m, 2H), 7.73-7.65 (m, 1H), 7.63-7.54 (m, 2H), 4.96 (dt, J=5, 2.5 Hz, 1H), 3.89 (ddd, J=1H, 5.5, 2.5 Hz, 1H), 3.71 (ddd, J=14, 6, 3 Hz, 1H), 3.14 (t, J=2 Hz, 1H), 3.11 (dddd, J=9, 6, 5, 2 Hz, 1H), 2.98 (dd, J=17.5, 9 Hz, 1H), 2.81 (t, J=5, 5 Hz, 1H), 2.76 (dd, J=17.5, 6 Hz, 1H), 2.16 (hept d, J=7, 2 Hz, 1H), 1.15 (d, J=7 Hz, 3H), 1.07 (d, J=7 Hz, 3H); ^{13}C NMR δ 176.07 (s), 139.14 (s), 134.02 (d), 129.47 (d, 2 x CH), 128.33 (d, 2 x CH), 82.47 (d), 70.62 (d), 62.96 (t), 34.25 (t), 34.23 (d), 27.92 (d), 21.47 (q), 19.63 (q); Ms (CI/NH_3) m/z 330 (MNH_4^+, 100), 313 (MH^+, 70). HRMS calcd. for $C_{15}H_{20}O_5S$ (MH^+) 313.1109, found: 313.1106.

(4S,5S,1′S)-5-Hydroxymethyl-4-[1′-(phenylsulfonyl)-butan-1′-yl]-(3H)-4,5-dihydrofuran-2-one 29 and the (4R,5S,1′S) isomer 30. n-Butylsulfone **26** was reacted with **14** following the procedure and amounts given for **23**. The ratio (**27/28**, 4:1) was determined by proton integration (-C<u>H</u>CO_2Me) in the NMR spectrum of the crude mixture (δ 2.51 for **27** and δ 2.19 for **28**). Lactonization of the mixture as described before and chromatography (EtOAc-petroleum ether, 2:1) gave, in order of elution, unreacted **26**, then **30** (15%) and **29**

(60%). Reaction in the presence of HMPA was performed under conditions given for **18**; The reaction mixture was allowed to warm during 30 min before quenching. An unchanged ratio of stereomers (4:1) was determined as shown above. **29**: mp 88-90 °C; ^{1}H NMR δ (CD_3CN) δ 7.95-7.87 (m, 2H), 7.82-7.65 (m, 3H), 4.41 (ddd, J=7, 4, 3 Hz, 1H), 3.68 (dd, J=12, 3 Hz, 1H), 3.52 (dd, J=12, 4 Hz, 1H), 3.30 (ddd, J=6.5, 4.5, 3 Hz, 1H), 3.24 (t, J=6 Hz, 1H), 3.03 (tdd, J=9, 6, 3 Hz, 1H), 2.67 (dd, J=18, 9 Hz, 1H), 2.53 (dd, J=18, 9 Hz, 1H), 1.83 (ddt, J=16, 10, 6 Hz, 1H), 1.60 (dddd, J=16, 11, 6, 4 Hz 1H), 1.44-1.17 (m, 2H), 0.79 (t, J=7 Hz, 3H); ^{13}C NMR (CD_3CN) δ 177.42 (s), 138.88 (s), 135.24 (d), 130.52 (d, 2 x CH), 129.48 (d, 2 x CH), 83.38 (d), 64.79 (d), 62.96 (t), 35.99 (d), 31.44 (t), 27.67 (t), 22.01 (t), 14.03 (q); Ms (CI/NH_3) m/z 330 (MNH_4^+, 100), 313 (MH^+, 40). HRMS Calcd. for $C_{15}H_{21}O_5S$ (MH^+) 313.1109, found: 311. 1094; $[\alpha]_D^{25}$ + 58 (C=3, CH_3OH). **30**: ^{1}H NMR δ 7.95-7.80 (m, 2H), 7.77-7.50 (m, 3H), 4.97 (dt, J=7.5, 2 Hz, 1H), 4.35 (dd, J=13, 2 Hz, 1H), 4.10 (dd, J=13, 2 Hz, 1H), 3.60 (dt, J=11, 4 Hz, 1H), 3.26 (dddd, J=12, 11, 9, 7.5 Hz, 1H), 2.88 (dd, J=17, 12 Hz, 1H), 2.44 (dd, J=17, 9 Hz, 1H), 1.77-1.10 (m, 4H), 0.73 (t, J=7 Hz, 3H); ^{13}C NMR 176.02 (s), 137.17 (s), 134.18 (d), 129.41 (d, 2 x CH), 128.71 (d, 2 x CH), 82.24 (d), 63.51 (d), 61.95 (t), 37.36 (d), 32.86 (t), 31.04 (t), 19.93 (t), 13.80 (q); Ms (CI/NH_3) m/z 330 (MNH_4^+, 100), 313 (MH^+, 50). HRMS Calcd. for $C_{15}H_{21}O_5S$ (MH^+) 313.1009, found 313.1210.

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