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Asymmetric Synthesis of a Key Synthetic Precursor for (+)-Strigol and Sorgolactone

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Abstract - *En-route* to non-racemic iodomethyl butyrolactone **23g** a number of stereoselective 1,4-additions and reductions have been studied. The only satisfactory approach involved baker's yeast reduction (**21c**→**23c**) as key step.

Introduction

Germination of seeds of root parasitic flowering plants of the genera *Striga*, *Alectra* (Scrophulariaceae), and *Orobanche* (Orobanchaceae) is stimulated by substances from their host plants. Prominent examples are sorgolactone (**29**) and alectrol (structure unpublished) which have been isolated from the root exudates of *Sorghum vulgare* (host for *Striga*) and *Vigna unguiculata* (host for *Striga* and *Alectra*), respectively.[1]

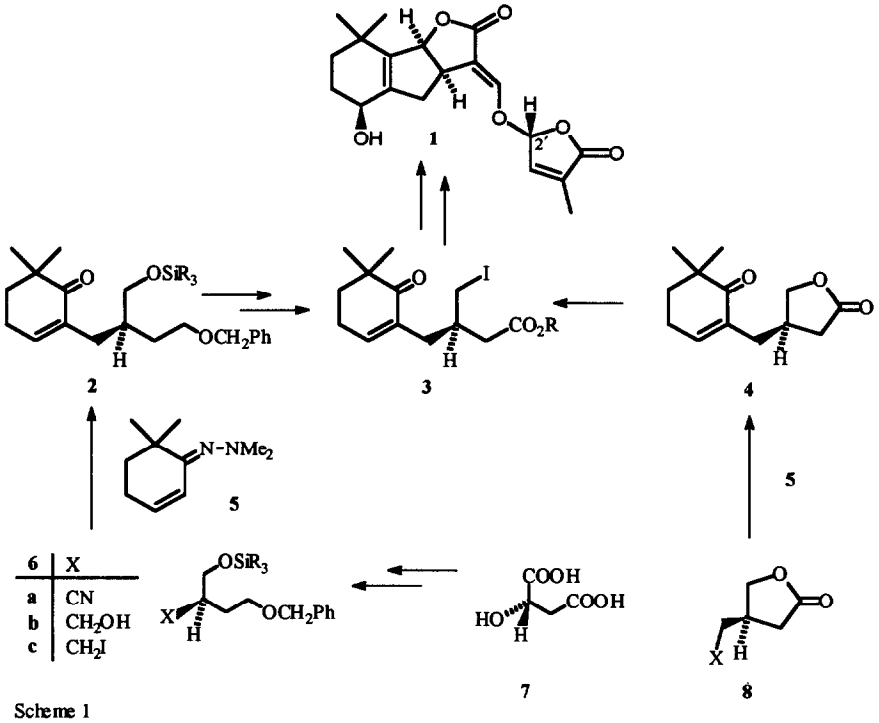
Two compounds, which are structurally closely related to sorgolactone, namely strigol (**1**) and its acetate, have first been isolated from cotton (*Gossypium hirsutum*) which is neither a host for *Striga* nor for *Orobanche*[2], but recently they have also been found in the root exudates of *Striga* host plants.[3]

There seem to exist very specific interactions between the stimulant and the binding site(s) at the seed which need careful analysis and which are, in addition, species-dependent.[4] Both the absolute and the relative configuration at C-2′ are of major importance as far as seed germination potency is concerned.[5,6,7]

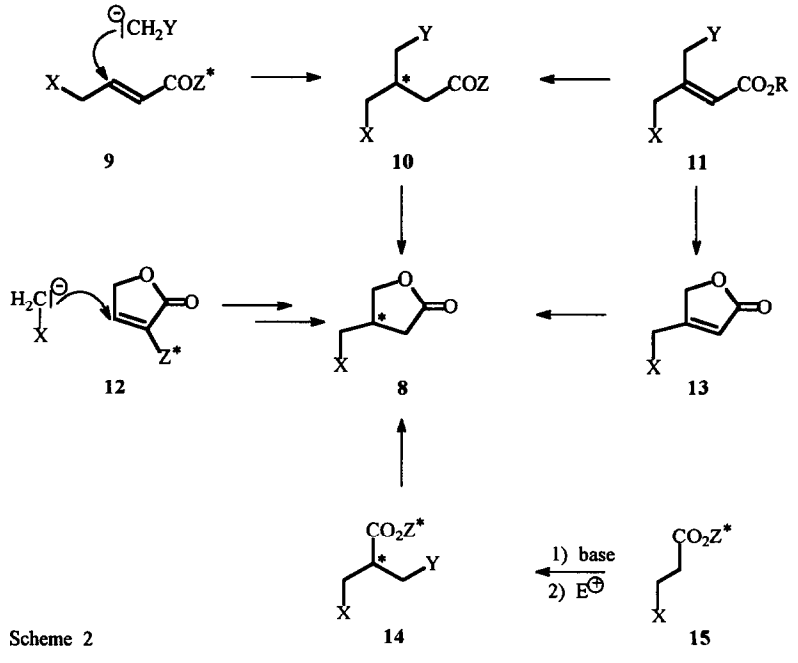
Non-racemic samples of strigol, its stereoisomers, and of structural analogues are known but were obtained in most instances by resolution.[4,8,9,10] Some time ago, we have developed an asymmetric synthesis of (+)-strigol (chiral pool approach),[11] and for one structural analogue of strigol an asymmetric synthesis has been reported by Zwanenburg.[6]

Our synthesis of (+)-strigol commenced from (S)-malic acid (**7**) which, in an not entirely satisfying way, was converted to nitrile **6a** with inversion of configuration. Transformation of **6a** into **6b** was accompanied by partial racemization. Iodide **6c** was then coupled to **5**, to give (after hydrolysis and double bond shift) compound **2**, which in turn was converted to **3** by a rather lengthy route involving mainly functional group interconversions. We felt that the synthesis could be considerably improved by coupling **8** to **5**. From **4** the strigol precursor **3** was believed to be accessible by treatment with trimethylsilyl iodide.

The synthesis of *racemic* type **8** compounds may be achieved straightforwardly. For example, Curran has described the preparation of *rac*-**8** (X = I) making use of an atomic tranfer process.[12] For the asymmetric



Scheme 1



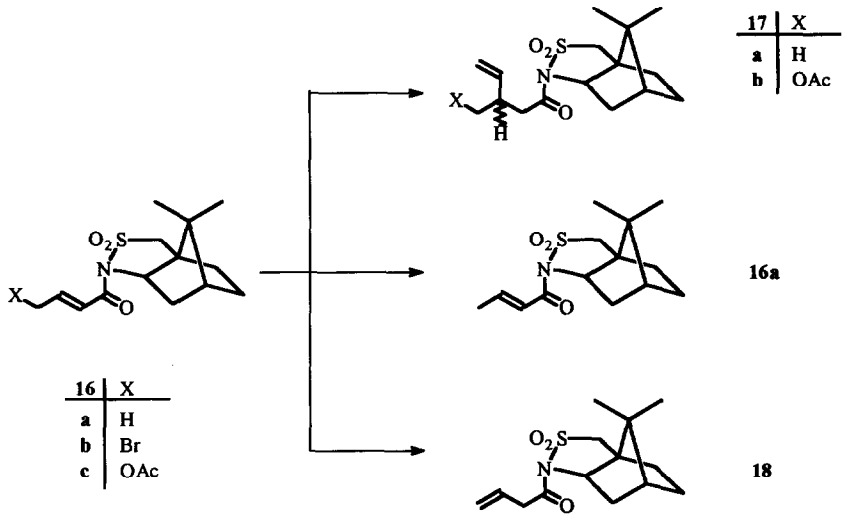
Scheme 2

synthesis of type **8** compounds many approaches can be envisaged. Some of them are schematically summarized in Scheme 2. All routes which include hydroxy lactone **8** (X = OH) are problematic as this compound is known to racemize readily.[13] In the present publication, we shall describe experiments based on the sequences **9→10→8**, **11→10→8**, and **11→13→8**. The approach **12→8** has been investigated by Posner[14] in the course of an A-factor synthesis. In this synthesis the final deprotection of **8** ($X = OCH_2OCH_2Ph$) to give **8** (X = OH) turned out to be accompanied by partial racemization. Experiments which are related to sequence **15→14→8** have been reported by Shapiro and Chengzhi.[15]

Approach 9→10→8

This route includes a Michael addition of an organometallic reagent to a 4-substituted crotonic acid derivative. Ibuka and coworkers[16] have shown in many brilliant publications that for this system organocopper chemistry is very complex. S_N2, S_N2' reactions as well as reductive cleavage of the C-X bond may compete with conjugate addition.

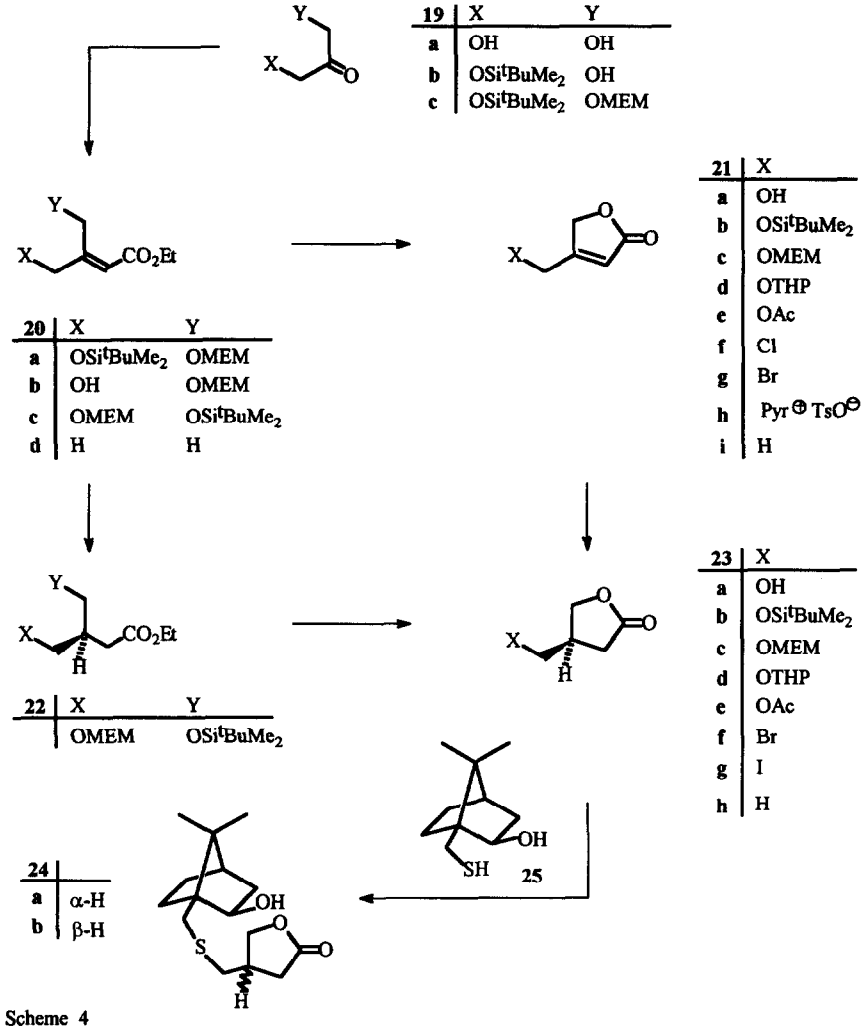
Crotonoyl sultams of type **16** show many reactions found by Ibuka for ester systems. We shall describe here only a few cases which are beyond the examples already reported.[17] Thus, acetoxy compound **16c** (prepared from **16b** by nucleophilic substitution) reacted with lithium divinylcuprate to give the diastereomeric Michael adducts **17b** in 46% yield alongside with the reduction product **18** (25%). The stereoselectivity of the Michael addition was low (d.e. = 48%, the configuration was not established). For comparison, unsubstituted **16a** was also treated with lithium divinylcuprate. In this case the yield of the Michael adduct was 77%, but again the stereoselectivity was only modest (d.e. = 64%). When the reaction of **16c** with lithium divinylcuprate was performed in the presence of trimethylsilyl chloride, two reduction products were formed. Beside the expected β,γ-unsaturated compound **18** (52%) the α,β-unsaturated isomer **16a** (29%) was obtained.



Scheme 3

Routes 13→8 and 11→10→8

For the enantioseletive conjugate reduction as it is required for the transformations **11→10** and **13→8** respectively, impressive examples have been reported by Noyori[18] and by Pfaltz.[19] However, reduction of type **13** lactones has been shown by Takaya[20] to proceed with low enantioselectivity when Noyori's catalyst is used. We preferred, therefore, to employ the Pfaltz catalyst in our studies. The required starting materials **20** and **21** were prepared from dihydroxyacetone (**19a**) and senecio acid (**20d**), respectivley. **19a** was converted into **19c** by reaction with (i) ^{t}butyldimethylsilyl chloride and (ii) MEM chloride. Subsequent Horner-Emmons reaction converted **19c** into a mixture of **20a** and **20c** which could be seperated chromatographically. For configurational assignment the silyl group was removed with p-toluenesulfonic acid in ethanol-water. From **20a** hydroxy derivative **20b** was obtained, whereas from **20c** cyclization product **21c** was formed. **21a** was prepared according to Gadir et al.[21] Subsequent simple derivatizations led to **21b**, **21c**, **21d**, **21h**.



Scheme 4

Bromomethyl compound **21g** was obtained from senecio acid as described by Takabe.[22] Subsequent substitution reactions led to the formation of **21e** and **21f**.

For the Pfaltz reduction, **21f**, **21g** and **21h** turned out to be unsuitable substrates, since with $NaBH_4/NiCl_2$ they yielded mixtures of **21i** and *rac*-**23h**.[23] When **21a** and **21b** were submitted to the same conditions, *rac*-**23a** and *rac*-**23b** were obtained in good yields. Therefore, for the enantioselective reductions ethers **21b**, **21c** and **21d** were chosen. The respective reduction products (**23b**, **23c**, **23d**) were obtained with yields in the range of 52-61%. The stereoselectivity was rather poor (39-45%, see Experimental). In the case of the reduction products of **21b** and **21c**, respectively, the e.e. was determined directly by chiral phase GLC (heptakis-(2,6-di-O-methyl-3-O-trifluoroacetyl)-β-cyclodextrin). We also developed a method which is based on chemical correlation in conjunction with NMR. This will be described below.

Since the unsaturated lactones turned out to be poor precursors for the enantioselective Pfaltz reduction, we applied the method to the corresponding unsaturated esters **20c** and **20a**. Interestingly, the reduction of **20c** and **20a**, respectivly, proceeded with opposite enantioselectivity. From **20a** the (S)-compound **22** was obtained whereas **20c** was reduced to provide *ent*-**22**. In these cases, too, the enantioselectivity was low (≈ 50-60% e.e.).

In 1992, Takabe et al. reported in two publications on the yeast reduction of various 4-hydroxymethyl- and 4-phenylthiomethyl-*5H*-furan-2-one derivatives.[22,24] The highest e.e. was obtained on reduction of the 4-acetoxymethyl compound (**21e**→**23e**). However, according to Mori, deprotection of **23e** to give **23a** (the precursor of **23g**) was found to be accompanied by considerable racemization.[13] Therefore the yeast reduction of the MEM ether **21c** was investigated. Both the yield (85%) and the e.e. (≈ 100%) of product **23c** were very satisfactory.

Stereoselectivity determinations and configurational assignments

At this stage of the discussion we wish to describe, how the stereoselectivities of the reactions discussed above and the configuration at the newly created stereogenic centers were determined. The method is based on the coupling of type **23** lactones to thiol **25**.[25] To this end, lactone formation from **22** and *ent*-**22** was induced by removal of the silyl protecting group (*ent*-**22**→*ent*-**23c**, **22**→**23c**). Lactones **23b**, **23c** and **23d** were treated with triphenylphosphine dibromide[26] to give **23f** which reacted with **25** in N-methylpyrrolidone in the presence of potassium carbonate to yield the diastereomeric sulfides **24a** and **24b**. The ratio of **24a/24b** was determined by ^1H NMR spectroscopy, integrating the signals of the gem. dimethyl groups after addition of 0.4 equiv. of a paramagnetic shift reagent ($Eu(FOD)_3$-d_{27}). The results have been discussed above, the exact e.e.'s and d.e.'s are found in the experimental part. For **23b** and **23c** the GLC method decribed above and the NMR integrations at the stage of **24a/24b** gave identical results, which means that the conversion of the silyl and MEM ether, repectivly, into **23f** proceeded without racemization. However, when **23b** was cleaved with trimethylsilyl iodide, a sample of **23g** was obtained which (after reaction with **25**) was found to be completely racemic.[27]

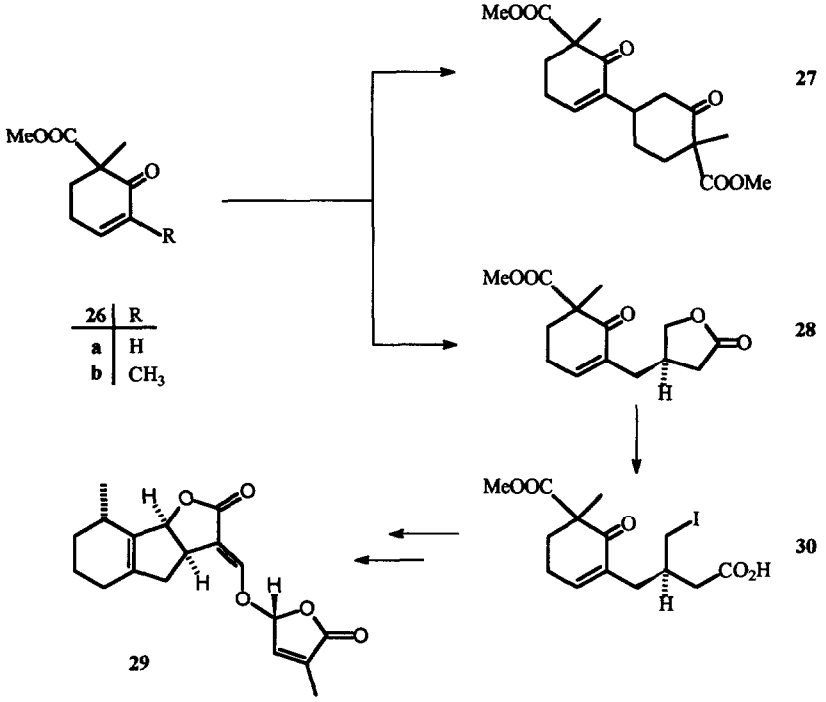
Since all compounds obtained by reduction with yeast or the under the Pfaltz conditions have been converted into the diastereoisomers **24a** and **24b** and since these isomers were readily identified by ^1H NMR as decribed above, for the assignment of the absolute configuration of the reduction products it was sufficient to determine the absolute configuration in a *single* case. This was accomplished by treatment of *ent*-**23f** (obtained from *ent*-**22**, 58% e.e.) with potassium acetate in acetonitrile solution in the presence of 18-crown-6. The resulting

acetoxy lactone *ent*-**23e** showed a negative rotation. The excess enantiomer of this specimen was thus shown, according to Takabe's results,[22] to have (R)-configuration (*ent*-**23e**).

Conversion of 23c into 23f and 23g

For preparitive purposes the conversion of **23c** into **23f** with triphenylphosphine dibromide was not sufficiently efficient. The yield was only in the range of 40%. Therefore, the MEM ether was cleaved under carefully selected conditions with titanium(IV) chloride. Quenching of the reaction mixture was performed in such a way, that a neutral solution resulted. After work-up, the crude paraconyl alcohol (**23a**) was immediately converted into **23g** by treatment with triphenylphosphine diiodide/imidazole in THF solution.[28] The overall yield was 73%. The sample of **23g** thus obtained on reaction with **25** yielded **24a** without any detectable trace of **24b**.

Preliminary experiments for the coupling of 23g to a cyclohexenone.



Scheme 5

As enone component we chose the known methoxycarbonyl substituted compound **26a**.[29,30] **26a** was deprotonated with sodium bis(trimethylsilyl) amide in THF/DMPU solution, then alkylating agent *rac*-**23g** was added. **28** was isolated in 33% yield (not optimized). In addition, Michael adduct **27** was formed. Probably the formation of **27** does not reflect incomplete deprotonation of **26a**, since trapping of the anion with methyl iodide provided the methyl derivative **26b** without any formation of **27**. We believe, therefore, that the anion obtained from **26a** acts also as a base and abstracts a proton from *rac*-**23g**.

Cleavage of **28** proceeded readily and furnished **30** which may be viewed as an advanced precursor *en-route* to sorgolactone (**29**).

EXPERIMENTAL

(R)- and (S)-1-{(1S)-10,10-Dimethyl-3,3-dioxo-3-thia-4*exo*-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl}-3-methyl-pent-4-en-1-one (17a)

A solution of vinyllithium (0.85 mmol) in 2-methyltetrahydrofuran (0.85 ml) - pentane (1.20 ml) was prepared as described by Seebach.[31] At -50°C a solution of copper(I) iodide-tri-n-butylphosphine[32] (167.1 mg, 0.425 mmol) in 2-methyltetrahydrofuran (1.5 ml) was added and the reaction flask was left at -50°C for 45 min. At -120°C a solution of **16a**[33] (80.4 mg, 0.284 mmol) in 2-methyltetrahydrofuran (2 ml) was added. The mixture was then stirred at -78°C for 18 h. Quenching with saturated aqu. NH_4Cl (10 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 5:1) provided **17a** (68.0 mg, 77%). D.e.: 64% (determined by ^{1}H NMR), the configuration was not established.- M.p. 122-123°C (petrol).- ^{1}H NMR (400 MHz, $CDCl_3$) of the major isomer: *auxiliary unit*: δ = 0.95 (s, 3H, 10-CH_3), 1.14 (s, 3H, 10-CH_3'), 1.32-1.42 (m, 2H, CH_2-8), 1.83-1.93 (m, 3H, CH_2-9, 7-H), 2.04-2.08 (m, 2H, CH_2-6), 3.40 and 3.47 (AB system, 2H, CH_2-2, J_{AB} = 14.0 Hz), 3.85 (t, 1H, 5-H), *acid moiety*: δ = 1.04 (d, 3H, 3'-CH_3), 2.54-2.87 (m, 3H, CH_2-2', 3'-H), 4.93 (ddd, 1H, 5'-$H_{(cis)}$), 5.00 (dt, 1H, 5'-$H_{(trans)}$), 5.77 (ddd, 1H, 4'-H), $J_{5',5'}$ = 2.0 Hz, $J_{3',6'}$ = 6.5 Hz, $J_{3',4'}$ = 7.0 Hz, $J_{4',5'(trans)}$ = 17.5 Hz, $J_{4',5'(cis)}$ = 10.5 Hz, $J_{3',5'} \approx$ 1 Hz.- IR ($CDCl_3$): 1697, 1335 cm^{-1}. MS: m/z (%) = 311 (16), 218 (11), 152 (10), 135 (30), 97 (66), 69 (100).- $C_{16}H_{25}NO_3S$ (311.4) calcd C 61.71, H 8.09, found C 61.72, H 8.00.

4-Bromo-1-{(1S)-10,10-dimethyl-3,3-dioxo-3-thia-4*exo*-aza-tricyclo-[5.2.1.0^{1,5}]dec-4-yl}-but-2-en-1-one (16b)

To a suspension of sodium hydride (55 per cent dispersion in oil, 138.9 mg, 3.183 mmol) in toluene (1 ml) slowly a solution of Oppolzer's bornane-10,2-sultam (453.3 mg, 2.104 mmol) in toluene (6 ml) was added and the mixture was stirred at 20°C for 30 min. After addition of a solution of (E)-4-bromo-but-2-enoyl chloride (497.9 mg, 2.715 mmol) in toluene (1 ml) the reaction mixture was stirred at 20°C for 3.5 h. Usual work-up (ethyl acetate) and LC (petrol - ethyl acetate 4:1) provided **16b** (488.1 mg, 64%).- M.p. 115-116°C (petrol).- ^{1}H NMR (400 MHz, $CDCl_3$), *auxiliary unit*: δ = 0.96 (s, 3H, 10-CH_3), 1.04 (s, 3H, 10-CH_3'), 1.32-1.44 (m, 2H, CH_2-8), 1.87-1.96 (m, 3H, CH_2-9, 7-H), 2.05-2.15 (m, 2H, CH_2-6), 3.44 and 3.52 (AB system, 2H, CH_2-2, J_{AB} = 14.0 Hz), 3.92 (dd, 1H, 5-H), *acid moiety*: δ = 4.03 (dt, 2H, CH_2-4'), 6.73 (dm, 1H, 2'-H), 7.07 (dt, 1H, 3'-H), $J_{2',3'}$ = 15.0 Hz, $J_{3',4'}$ = 7.5 Hz, $J_{2',4'} \approx$ 1 Hz.- IR ($CDCl_3$): 1680, 1637, 1330 cm^{-1}.- MS: m/z (%) = 363 (4.0), 361 (3.6), 282 (29), 218 (80), 149 (76), 147 (86), 135 (47), 134 (42), 68 (100).- $C_{14}H_{20}BrNO_3S$ (362.3) calcd C 46.41, H 5.56, found C 46.35, H 5.49.

4-{(1S)-10,10-Dimethyl-3,3-dioxo-3-thia-4*exo*-aza-tricyclo-[5.2.1.0^{1,5}]dec-4-yl}-4-oxo-but-2-enyl acetate (16c)

To a mixture containing KOAc (42.4 mg, 0.432 mmol), 18-crown-6 (11.5 mg, 0.044 mmol), and acetonitrile (5 ml) a solution of **16b** (29.8 mg, 0.082 mmol) in acetonitrile (2 ml) was added at 0°C. The mixture was stirred at 20°C for 8 h. Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 5:1) yielded **16c** (23.0 mg, 82%).- M.p. 84-85°C (petrol).- ^{1}H NMR (80 MHz, $CDCl_3$), *auxiliary unit*: δ = 0.96 (s, 3H, 10-CH_3), 1.16 (s, 3H, 10-CH_3'), 1.33-1.43 (m, 2H, CH_2-8), 1.86-1.95 (m, 3H, CH_2-9, 7-H), 2.05-2.15 (m, 2H, CH_2-6), 3.47 (s, 2H, CH_2-2), 3.92 (t, 1H, 5-H), *acid moiety*: δ = 2.10 (s, 3H, CH_3CO), 4.75 (dd, 2H, CH_2-4'), 6.72 (dt, 1H, 2'-H), 7.04 (dt, 1H, 3'-H), $J_{2',3'}$ = 14.5 Hz, $J_{3',4'}$ = 4.0 Hz, $J_{2',4'} \approx$ 1 Hz.- IR ($CDCl_3$): 1750, 1690, 1655, 1380 cm^{-1}.- MS: m/z (%) = 341 (0.4), 282 (18), 193 (7), 151 (8), 150 (9), 135 (15), 134 (18), 85 (77), 43 (100).- $C_{16}H_{23}NO_5S$ (341.4) calcd C 56.29, H 6.79, found C 56.16, H 6.83.

Reaction of 4-{(1S)-10,10-dimethyl-3,3-dioxo-3-thia-4*exo*-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl}-4-oxo-but-2-enyl acetate (16c) with lithium divinylcuprate

a) without added trimethylsilyl chloride: A solution of lithium divinylcuprate (0.22 mmol) in 2-methyltetrahydrofuran - pentane was prepared as described above. At -110°C **16c** (49.9 mg, 0.146 mmol), dissolved in 2-methyltetrahydrofuran (2 ml) was added and the mixture was stirred at -110°C for 2 h. Quenching with sat. aqu. NH_4Cl (2 ml), followed by work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 10:1) provided pure samples of **18** (10.5 mg, 25%) and the diastereomeric Michael adducts (**17b**), isomer A (18.4 mg, 34%) and isomer B (6.5 mg, 12%) . The d.e. was thus calculated to be 48%. The configuration was not determined.

b) in the presence of trimethylsilyl chloride: A solution of lithium divinylcuprate (0.22 mmol) in 2-methyltetrahydrofuran - pentane was prepared as described above. Trimethylsilyl chloride (0.10 ml, 0.79 mmol) was added at -78°C. At -110°C **16c** (50.1 mg, 0.147 mmol), dissolved in 2-methyltetrahydrofuran (2 ml), was added and the mixture was stirred at -110°C for 1.5 h. Quenching and work-up as described in a), followed by LC (petrol - ethyl acetate 10:1) furnished **18** (21.6 mg, 52%) and **16a** (12.1 mg, 29%).

(R)- and (S)-2-[2-{(1S)-10,10-Dimethyl-3,3-dioxo-3-thia-4*exo*-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl}-2-oxo-ethyl]-3-but-3-enyl acetate (17b)

Isomer A: ^{1}H NMR (400 MHz, $CDCl_3$), *auxiliary unit*: δ = 0.96 (s, 3H, 10-CH_3), 1.13 (s, 3H, 10-CH_3'), 1.30-1.42 (m, 2H, CH_2-8), 1.83-1.90 (m, 3H, CH_2-9, 7-H), 2.05-2.07 (m, 2H, CH_2-6), 3.42 and 3.48 (AB system, 2H, CH_2-2, J_{AB} = 14.0 Hz), 3.85 (t, 1H, 5-H), *acid moiety*: δ = 2.03 (s, 3H, CH_3CO), 2.79 (dd, 1H, 6'-H), 2.87 (dd, 1H, 6'-H'), 3.04 (m, 1H, 3'-H), 3.97 (dd, 1H, 2'-H), 4.12 (dd, 1H, 2'-H'), 5.07 (dt, 1H, 5'-$H_{(cis)}$), 5.14 (dt, 1H, 5'-$H_{(trans)}$), 5.73 (ddd, 1H, 4'-H), $J_{2',2'}$ = 11.0 Hz, $J_{6',6'}$ = 11.0 Hz, $J_{5',5'} \approx$ 1 Hz, $J_{2a',3'}$ = 6.0 Hz, $J_{2b',3'}$ = 8.0 Hz, $J_{3',6a'}$ = 7.0 Hz, $J_{3',6b'}$ = 6.0 Hz, $J_{3',4'}$ = 8.0 Hz, $J_{4',5'(trans)}$ = 17.5 Hz, $J_{4',5'(cis)}$ = 10.0 Hz, $J_{3',5'} \approx$ 1 Hz.- IR ($CDCl_3$): 1740, 1700, 1340 cm^{-1}.- MS: m/z (%) = 369 (1.4), 309 (11), 297 (4), 193 (12), 151 (10), 150 (9), 135 (26), 113 (35), 43 (100).- $C_{18}H_{27}NO_5S$ (369.5) calcd C 58.51, H 7.37, found C 58.43, H 7.27.

Isomer B: ^{1}H NMR (400 MHz, $CDCl_3$), *auxiliary unit*: δ = 0.96 (s, 3H, 10-CH_3), 1.14 (s, 3H, 10-CH_3'), 1.30-1.42 (m, 2H, CH_2-8), 1.84-1.91 (m, 3H, CH_2-9, 7-H), 2.05-2.09 (m, 2H, CH_2-6), 3.41 and 3.48 (AB system, 2H, CH_2-2, J_{AB} = 14.0Hz), 3.85 (dd, 1H, 5-H), *acid moiety*: δ = 2.03 (s, 3H, CH_3CO), 2.75 (dd, 1H, 6'-H), 2.94 (dd,1H, 6'-H'), 3.04 (m, 1H, 3'-H), 3.95 (dd, 1H, 2'-H), 4.17 (dd, 1H, 2'-H'), 5.10 (dt, 1H,

5'-$H_{(cis)}$), 5.14 (dt, 1H, 5'-$H_{(trans)}$), 5.73 (ddd, 1H, 4'-H), $J_{2',2'}$ = 11.0 Hz, $J_{6',6'}$ = 11.0 Hz, $J_{5',5'} \approx 1$ Hz, $J_{2a',3'}$ = 7.5 Hz, $J_{2b',3'}$ = 6.0 Hz, $J_{3',6a'}$ = 6.0 Hz, $J_{3',6b'}$ = 5.5 Hz, $J_{3',4'}$ = 7.5 Hz, $J_{4',5'(trans)}$ = 17.5 Hz, $J_{4',5'(cis)}$ = 10.0 Hz, $J_{3',5'} \approx 1$ Hz.- IR ($CDCl_3$): 1740, 1700, 1340 cm^{-1}.- MS: m/z (%) = 369 (1.8), 309 (16), 297 (5), 257 (3), 193 (17), 151 (12), 150 (13), 135 (39), 113 (51), 43 (100).- $C_{18}H_{27}NO_5S$ (369.5) calcd C 58.51, H 7.37, found C 58.49, H 7.42.

1-{(1S)-10,10-Dimethyl-3,3-dioxo-3-thia-4*exo*-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl}-but-3-en-1-one[34] (18b)
M.p. 65-66°C (petrol).- ^1H NMR (80 MHz, $CDCl_3$), *auxiliary unit*: δ = 0.96 (s, 3H, 10-CH_3), 1.14 (s, 3H, 10-CH_3'), 1.24-1.43 (m, 2H, CH_2-8), 1.85-1.93 (m, 3H, CH_2-9, 7-H), 2.04-2.13 (m, 2H, CH_2-6), 3.47 (s, 3H, CH_2-2, covering the 2'-H signal of the *acid moiety*), 3.87 (t, 1H, 5-H), *acid moiety*: δ = 3.54 (s, 1H, 2'-H'), 5.10 (m, 1H, 4'-H), 5.27 (m, 1H, 4'-H') 5.70-6.21 (m, 1H, H-3'), $J_{2',3'}$ = 7.0 Hz.- IR ($CDCl_3$): 1700, 1337 cm^{-1}.- MS: m/z (%) = 283 (7), 242 (8), 135 (35), 69 (30), 41 (100).- $C_{14}H_{21}NO_3S$ (283.4) calcd C 59.34, H 7.47, found C 59.36, H 7.44.

1-{(1S)-10,10-Dimethyl-3,3-dioxo-3-thia-4*exo*-aza-tricyclo[5.2.1.$0^{1,5}$]dec-4-yl}-but-2-en-1-one (16a)
M.p. 186-187°C (petrol).- For spectral data, see ref.[33]

4-Chloromethyl-*5H*-furan-2-one (21f)
To a mixture containing finely powdered potassium chloride (4.008g, 53.767 mmol), 18-crown-6 (0.712 g, 2.693 mmol), and acetonitrile (20 ml) a solution of **21g** (0.468 g, 2.645 mmol) in acetonitrile (3 ml) was added at 20°C. The reaction was stirred at 40°C for 4 d. Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 5:1) provided **21f** (0.301 g, 86%). For spectral data, see ref.[35]

4-(Pyridinium-methyl)-*5H*-furan-2-one tosylate (21h)
At 0°C a solution of p-toluenesulfonic acid anhydride (249.4 mg, 0.764 mmol) in pyridine (2 ml) was added to **21a** (57.2 mg, 0.501 mmol) dissolved in pyridine (1 ml). The reaction mixture was stirred at 0°C for 2.5 h and then quenched with water (1 ml). Usual work-up (CH_2Cl_2), followed by solvent evaporation furnished crystalline **21h** (120.0 mg, 69%), which could be further purified by recrystallization (toluene - acetonitrile).- M.p. 134-135°C (toluene/acetonitrile).- ^1H NMR (80 MHz, CD_3CN), *tosylate unit*: δ = 2.33 (s, 3H, CH_3), 7.13 (dm, 2H), 7.60 (dt, 2H), *pyridinium unit*: 8.07 (br.t, 2H), 8.58 (dt, 1H), 8.93 (dd, 2H), *lactone unit*: 4.92 (dt, 2H, CH_2-6), 5.72 (br.s, 2H, CH_2-5), 5.78 (m, 1H, 3-H), $J_{3,5}$ = 2.0 Hz, $J_{3,6}$ = 2.0 Hz, $J_{5,6} \approx 1$ Hz.- IR (CD_3CN): 1795, 1765 cm^{-1}.- Mass spectra were not characteristic, the partial spectra of pyridine and the tosyloxy lactone were observed.- $C_{17}H_{17}NO_5S$ (347.4) calcd C 58.78, H 4.93, found C 58.60, H 4.86.

4-[(^{t}Butyl)dimethylsilyloxy-methyl]-*5H*-furan-2-one[36] (21b)
To a mixture of imidazole (0.7809 g, 11.470 mmol), ^{t}butyldimethylsilyl chloride (1.7166 g, 11.389 mmol), and DMF (40 ml) a solution of **21a** (1.0000 g, 8.764 mmol) in DMF (10 ml) was added. The reaction mixture was stirred at 20°C for 5 h. Quenching with saturated aqu. NaCl (60 ml), followed by usual work-up (ether), and LC (petrol - ethyl acetate 5:1) provided **21b** (1.8572 g, 93%).- M.p. 31-32°C (petrol at -18°C).- ^1H NMR (80 MHz, $CDCl_3$), δ = 0.07 (s, 6H, Si^{t}Bu(CH_3)$_2$), 0.89 (s, 9H, Si^{t}Bu(CH_3)$_2$), 4.55 (dt, 2H, CH_2-6), 4.80 (dt, 2H, CH_2-5), 5.95 (quint, 1H, 3-H), $J_{3,5}$ = 2.0 Hz, $J_{3,6}$ = 2.0 Hz, $J_{5,6} \approx 1$ Hz.- IR ($CDCl_3$): 1785, 1755 cm^{-1}.- MS:

m/z (%) = 228 (2), 213 (2), 171 (39), 143 (20), 113 (30), 75 (57), 55 (100).- $C_{11}H_{20}SiO_3$ (228.4) calcd C 57.86, H 8.83, found C 57.84, H 8.93.

4-(Tetrahydro-pyran-2-yloxy-methyl)-*5H*-furan-2-one (21d)

Dihydropyran (250 µl, 230 mg, 2.754 mmol) was added to a solution of **21a** (100.2 mg, 0.878 mmol) and p-toluenesulfonic acid monohydrate (0.2 mg, 0.001 mmol) in CH_2Cl_2 (3 ml) at 0°C. The reaction mixture was then stirred at 20°C for 3h. Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate - triethylamine 5:1:0.05) provided **21d** (164.1 mg, 94%).- M.p. 40-41°C (petrol - ether).- ^{1}H NMR (80 MHz, $CDCl_3$), δ = 1.50-1.82 (m, 6H, CH_2-2, CH_2-3, CH_2-4), 3.38-3.95 (m, 2H, CH_2-5), 4.32 (dquint, 1H, 6'-H), 4.64 (br.s, 1H, 1-H), 4.64 (dquint, 1H, 6'-H'), 4.83 (dt, 2H, CH_2-5'), 6.00 (quint, 1H, 3'-H), $J_{6',6'}$ = 15.5 Hz, $J_{3',5'}$ = 2.0 Hz, $J_{3',6'}$ = 2.0 Hz, $J_{5',6'} \approx$ 1 Hz.- IR ($CDCl_3$): 1780, 1750 cm^{-1}.- MS: m/z (%) = 198 (1), 197 (3), 143 (15), 97 (55), 96 (15), 85 (100).- $C_{10}H_{14}O_4$ (198.2) calcd C 60.60, H 7.12, found C 60.68, H 7.12.

4-(2-Methoxy-ethoxymethoxy-methyl)-*5H*-furan-2-one (21c)

To **21a** (4.00 g, 35.06 mmol), dissolved in CH_2Cl_2 (250 ml), at 20°C diisopropylethylamine (12.0 ml, 9.1 g, 70.6 mmol) and MEMCl (7.0 ml, 7.7 g, 61.8 mmol) were added. The reaction mixture was refluxed for 18 h. Quenching with diluted aqu. NaOH (20 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - acetone 3:1) furnished **21c** (6.39 g, 90%).- ^{1}H NMR (80 MHz, $CDCl_3$), δ = 3.37 (s, 3H, CH_2-O-CH_2-CH_2-O-C$\underline{H}_3$), 3.46-3.58 (m, 2H, CH_2-O-CH_2-C$\underline{H}_2$-O-CH_3), 3.65-3.77 (m, 2H, CH_2-O-C$\underline{H}_2$-CH_2-O-CH_3), 4.47 (m, 2H, CH_2-6), 4.76 (s, 2H, C$\underline{H}_2$-O-CH_2-CH_2-O-CH_3), 4.82 (dt, 2H, CH_2-5), 6.00 (quint., 1H, 3-H), $J_{3,5}$ = 2.0 Hz, $J_{3,6}$ = 2.0 Hz, $J_{5,6} \approx$ 1 Hz.- IR ($CDCl_3$): 1780, 1750 cm^{-1}.- MS: m/z (%) = 127 (14), 112 (5), 98 (30), 97 (20), 96 (16), 89 (28), 73 (7), 67 (43), 59 (61), 45 (100).- $C_9H_{14}O_5$ (202.2) calcd C 53.46, H 6.98, found C 53.46, H 7.03.

1-(^{t}Butyl)dimethylsilyloxy-3-hydroxy-propan-2-one (19b)

To a mixture of **19a** (9.407 g, 104.43 mmol), imidazole (2.956 g, 43.42 mmol), and DMF (100 ml) ^{t}butyldimethylsilyl chloride (5.048 g, 33.49 mmol), dissolved in DMF (20 ml), was added. The reaction mixture was stirred at 20°C for 17 h. Quenching with water (100 ml), followed by usual work-up (ether), and LC (petrol - ethyl acetate 5:1) provided **19b** (4.040 g, 59% based on ^{t}BuMe$_2$SiCl).- ^{1}H NMR (80 MHz, $CDCl_3$), δ = 0.08 (s, 6H, Si^{t}Bu(C$\underline{H}_3$)$_2$), 0.90 (s, 9H, Si$^t\underline{Bu}$(CH$_3$)$_2$), 2.95 (br.t, 1H, OH), 4.30 (s, 2H, CH_2-1), 4.47 (d, 2H, CH_2-3), further signals at 3.58-3.98.- IR ($CHCl_3$): 3600-3440, 1725 cm^{-1}.- MS: m/z (%) = 159 (4), 147 (25), 117 (100), 101 (6), 89 (12), 75 (42), 73 (26).- $C_9H_{20}O_3Si$ (204.3) calcd C 52.90, H 9.87, found C 53.03, H 9.92.

1-(^{t}Butyl)dimethylsilyloxy-3-(2-methoxy-ethoxymethoxy)-propan-2-one (19c)

To a solution of **19b** (5.074 g, 24.83 mmol) in CH_2Cl_2 (200 ml) diisopropylethylamine (8.4 ml, 6.4 g, 49.5 mmol) and MEMCl (4.2 ml, 4.6 g, 37.1 mmol) were added. The mixture was refluxed for 20 h. Further portions of diisopropylethylamine (4.2 ml, 3.2 g, 24.8 mmol) and MEMCl (2.8 ml, 3.1 g, 24.7 mmol) were added and refluxing was continued for 40 h. Quenching with water (20 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 5:1 + 1% NEt_3) provided **19c** (5.605 g, 77%).- ^{1}H NMR (80 MHz, $CDCl_3$), δ = 0.08 (s, 6H, Si^{t}Bu(C$\underline{H}_3$)$_2$), 0.91 (s, 9H, Si$^t\underline{Bu}$(CH$_3$)$_2$), 3.36 (s, 3H, CH_2-O-CH_2-CH_2-O-C$\underline{H}_3$),

3.45-3.58 (m, 2H, CH_2-O-CH_2-C$\underline{H}_2$-O-CH_3), 3.67-3.79 (m, 2H, CH_2-O-C$\underline{H}_2$-CH_2-O-CH_3), 4.28 (s, 2H, CH_2-1), 4.44 (s, 2H, CH_2-3), 4.77 (s, 2H, C$\underline{H}_2$-O-CH_2-CH_2-O-CH_3).- IR ($CDCl_3$): 1735 cm^{-1}.- MS: m/z (%) = 217 (3), 171 (3), 159 (8), 129 (69), 115 (6), 101 (4), 89 (57), 75 (9), 73 (25), 59 (100).- $C_{13}H_{28}O_5Si$ (292.4) calcd C 53.39, H 9.65, found C 53.46, H 9.82.

Reaction of 19c with diethyl ethoxycarbonylmethanephosphonate

To a THF washed NaH suspension (0.2508 g, 5.748 mmol) in THF (20 ml) freshly distilled diethyl ethoxycarbonylmethanephosphonate (1.05 ml, 1.18 g, 5.24 mmol) was slowly added. The mixture was stirred at 20°C for 45 min, then **19c** (1.1695 g, 3.999 mmol), dissolved in THF (10 ml), was added at -70°C. The mixture was refluxed for 1 h. Quenching with water (20 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 10:1, 5:1, 3:1) furnished **20c** (0.3635 g, 25%) and **20a** (0.8119 g, 56%). 0.1459 g (13%) of **19c** were recovered.

Ethyl (Z)-4-(^{t}butyl)dimethylsilyloxy-3-(2-methoxy-ethoxymethoxy-methyl)-but-2-enoate (20c)

^{1}H NMR (80 MHz, $CDCl_3$), δ = 0.05 (s, 6H, Si^{t}Bu(C$\underline{H}_3$)$_2$), 0.88 (s, 9H, Si^{t}B$\underline{u}$(CH_3)$_2$), 1.25 (t, 3H, CH_2-C$\underline{H}_3$), 3.38 (s, 3H, CH_2-O-CH_2-CH_2-O-C$\underline{H}_3$), 3.47-3.60 (m, 2H, CH_2-O-CH_2-C$\underline{H}_2$-O-CH_3), 3.65-3.78 (m, 2H, CH_2-O-C$\underline{H}_2$-CH_2-O-CH_3), 4.14 (q, 2H, C$\underline{H}_2$-CH_3), 4.33 (m, 2H, CH_2-5), 4.75 (s, 2H, C$\underline{H}_2$-O-CH_2-CH_2-O-CH_3), 4.84 (m, 2H, CH_2-4), 5.94 (quint., 1H, 2-H), $J_{2,4}$ = 2.0 Hz, $J_{2,5}$ = 2.0 Hz, $J_{4,5} \approx 1$ Hz, $J_{ethyl\ group}$ = 7 Hz.- IR ($CDCl_3$): 1705, 1655 cm^{-1}.- MS: m/z (%) = 305 (19), 256 (8), 199 (17), 133 (21), 89 (78), 75 (32), 73 (31), 59 (100).- $C_{17}H_{34}O_6Si$ (362.5) calcd C 56.32, H 9.45, found C 56.56, H 9.46.

Ethyl (E)-4-(^{t}butyl)dimethylsilyloxy-3-(2-methoxy-ethoxymethoxy-methyl)-but-2-enoate (20a)

^{1}H NMR (80 MHz, $CDCl_3$), δ = 0.05 (s, 6H, Si^{t}Bu(C$\underline{H}_3$)$_2$), 0.91 (s, 9H, Si^{t}B$\underline{u}$(CH_3)$_2$), 1.26 (t, 3H, CH_2-C$\underline{H}_3$), 3.37 (s, 3H, CH_2-O-CH_2-CH_2-O-C$\underline{H}_3$), 3.45-3.58 (m, 2H, CH_2-O-CH_2-C$\underline{H}_2$-O-CH_3), 3.63-3.75 (m, 2H, CH_2-O-C$\underline{H}_2$-CH_2-O-CH_3), 4.15 (q, 2H, C$\underline{H}_2$-CH_3), 4.34 (m, 2H, CH_2-4), 4.68 (s, 4H, CH_2-5, C$\underline{H}_2$-O-CH_2-CH_2-O-CH_3), 6.04 (m, 1H, 2-H), $J_{ethyl\ group}$ = 7 Hz.- IR ($CDCl_3$): 1705, 1660 cm^{-1}.- MS: m/z (%) = 305 (0.5), 287 (1), 257 (2), 133 (9), 89 (100).- $C_{17}H_{34}O_6Si$ (362.5) calcd C 56.32, H 9.45, found C 56.69, H 9.41.

Configurational assignment of 20a and 20c

a) **20c**: A mixture containing **20c** (22.6 mg, 0.062 mmol), EtOH (1 ml), p-toluenesulfonic acid (3.0 mg, 0.016 mmol), and water (1 ml) was stirred at 20°C for 18 h. Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 1:1) provided **21c** (12.3 mg, 98%), identical with the specimen described above.

b) **20a**: To p-toluenesulfonic acid (2.4 mg, 0.013 mmol), dissolved in water (1 ml), the solution of **20a** (21.6 mg, 0.060 mmol) in EtOH (1 ml) was added. The mixture was stirred at 20°C for 18 h. Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 1:1) provided **20b** (14.9 mg, 100%).

Ethyl (Z)-4-hydroxy-3-(2-methoxy-ethoxymethoxy-methyl)-but-2-enoate (20b):

^{1}H NMR (80 MHz, $CDCl_3$), δ = 1.25 (t, 3H, CH_2-C$\underline{H}_3$), 2.54 (br.s, 1H, OH), 3.37 (s, 3H, CH_2-O-CH_2-CH_2-O-C$\underline{H}_3$), 3.47-3.59 (m, 2H, CH_2-O-CH_2-C$\underline{H}_2$-O-CH_3), 3.64-3.77 (m, 2H, CH_2-O-C$\underline{H}_2$-CH_2-O-CH_3), 4.15 (q, 2H, C$\underline{H}_2$-CH_3), 4.30 (m, 2H, CH_2 -4), 4.72 (s, 2H, C$\underline{H}_2$-O-CH_2-CH_2-O-CH_3), 4.77 (m, 2H, CH_2-5), 5.95

(quint., 1H, 2-H), $J_{2,4}$ = 2.0 Hz, $J_{2,5}$ = 2.0 Hz, $J_{4,5} \approx 1$ Hz, $J_{ethyl\ group}$ = 7 Hz.- IR ($CDCl_3$): 3700-3300, 1710, 1660 cm^{-1}.- MS: m/z (%) = 230 (1), 173 (6), 143 (11), 142 (10), 115 (18), 113 (12), 89 (57), 85 (9), 69 (9), 59 (100).- $C_{11}H_{20}O_6$ (248.3) calcd C 53.22, H 8.12, found C 53.18, H 8.20.

Reduction of 4-Bromomethyl-*5H*-furan-2-one (21g) with $NaBH_4/NiCl_2$

To a solution of $NiCl_2 \times 6H_2O$ (12.1 mg, 0.051 mmol) and **21g** (51.1 mg, 0.288 mmol) in MeOH (2 ml) solid $NaBH_4$ (32.7 mg, 0.864 mmol) was added carefully at 0°C. The reaction mixture was stirred at 0°C for 30 min. Acetone (5 ml) was added to destroy excess reducing agent. The solvents were evaporated and the residue was taken up in CH_2Cl_2 (1 ml). The resulting suspension was filtered through silica gel (elution with CH_2Cl_2). The clear eluate was evaporated and the reaction products (22.5 mg) then analyzed by ^1H NMR without further purification. According to the spectrum the mixture consisted of **21i**[37] (≈ 6 mg, ≈ 20%) and *rac*-**23h**[24] (≈ 17 mg, ≈ 60%).

Reduction of 4-Chloromethyl-*5H*-furan-2-one (21f) with $NaBH_4/NiCl_2$

Reaction and work-up were performed as described for **21g**. According to ^1H NMR (80 MHz) the crude product contained **21i**[37] (yield ≈ 15%) and *rac*-**23h**[24] (yield ≈ 60%).

Reduction of 4-Pyridinium-methyl-*5H*-furan-2-one tosylate (21h) with $NaBH_4/NiCl_2$

Reaction and work-up were performed as described for **21g**. LC (petrol - ethyl acetate 3:1) furnished **21i**[37] (10%) and *rac*-**23h**[24] (31%).

(R/S)-4-[(^{t}Butyl)dimethylsilyloxy-methyl]-dihydrofuran-2-one (*rac*-23b)

To a solution of $NiCl_2 \times 6H_2O$ (8.0 mg, 0.034 mmol) and **21b** (50.8 mg, 0.222 mmol) in MeOH (2 ml) solid $NaBH_4$ (27.3 mg, 0.722 mmol) was carefully added at -10°C. The reaction mixture was stirred at -10°C for 1 h and was then allowed to warm to 20°C. Usual work-up (CH_2Cl_2), followed by LC (petrol - ethyl acetate 8:1) furnished *rac*-**23b** (43.5 mg, 85%). For spectral data, see ref.[38]

(R/S)-4-Hydroxymethyl-dihydrofuran-2-one (*rac*-23a)

21a (300.3 mg, 2.632 mmol) and $NiCl_2 \times 6H_2O$ (97.3 mg, 0.409 mmol) were dissolved in MeOH (20 ml). To this solution solid $NaBH_4$ (300.6 mg, 7.946 mmol) was added carefully. The reaction mixture was allowed to warm to 20°C within 1.5 h and was then diluted with acetone (10 ml). Silica gel (1.5 g) was added and the solvents were evaporated. LC (petrol - ethyl acetate 1:2) provided *rac*-**23a** (249.1 mg, 82%). For spectral data, see ref.[13]

(R)-4-[(^{t}Butyl)dimethylsilyloxy-methyl]-dihydrofuran-2-one (23b)

$NaBH_4$ (52.7 mg, 1.393 mmol), dissolved in degassed DMF (0.5 ml), was added to a solution of **21b** (150.1 mg, 0.673 mmol), semicorrin[19] (5.9 mg, 0.013 mmol), and $CoCl_2 \times 6H_2O$ (1.9 mg, 0.011 mmol) in degassed ethanol (1 ml). The reaction mixture was stirred for 5.5 h at 20°C. Usual work-up (ethyl acetate) and LC (petrol - ethyl acetate 10:1) provided **23b** (79.0 mg, 52%). For spectra, see ref.[38] The e.e. was determined by capillary GLC (0.25 mm × 36 m heptakis-(2,6-di-O-methyl-3-O-trifluoracetyl)-β-cyclodextrin in OV-1701, temperatures: 150°C (column), 190°C (injector and detector), carrier gas: H_2, retention times: 65 min (**23b**),

67 min (*ent*-**23b**). In four different experiments the following e.e.'s [%] were determined: 39, 41, 42, 45. The products of the 42% e.e. experiment were converted into the corresponding bromo derivatives as described below, and these were converted into **24a/24b**. A NMR analysis then yielded a d.e. of 46%, in good agreement with the GLC value.

(S)-4-(Tetrahydro-pyran-2-yloxy-methyl)-dihydrofuran-2-one[39] (23d)

To a solution of **21d** (101.8 mg, 0.508 mmol), $CoCl_2 \times 6H_2O$ (1.1 mg, 0.007 mmol), and semicorrin[19] (2.8 mg, 0.006 mmol) in degassed ethanol (1 ml) $NaBH_4$ (39.3 mg, 1.039 mmol), dissolved in degassed DMF (0.5 ml), was added at 0°C. The reaction was left for 18 h at 4°C. Usual work-up (CH_2Cl_2) and LC (petrol ether - ethyl acetate - triethylamine 5:1:0.05) furnished **23d** (55.4 mg, 54%).- ^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.42-1.58 and 1.58-1.78 (2m, 6H, CH_2-2, CH_2-3, CH_2-4), 2.31-2.38 (m, 1H, 3'-H), 2.54-2.61 (m, 1H, 3'-H'), 2.75-2.85 (m, 1H, 4'-H), 3.33-3.39 (m, 1H, 6'-H), 3.44-3.51 (m, 1H, 6'-H'), 3.70-3.81 (m, 2H, CH_2-5), 4.13-4.17 (m, 1H, 5'-H), 4.34-4.39 (m, 1H, 5'-H'), 4.52-4.56 (m, 1H, 1-H).- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT), δ = 19.49, 19.54, 25.51 and 30.60 (CH_2-2, CH_2-3 and CH_2-4), 31.37 and 31.43 (CH_2-2'), 35.53 (CH-4'), 62.53 and 62.61 (CH_2-5), 67.94 and 68.05 (CH_2-5'), 71.02 and 71.05 (CH_2-6'), 99.11 and 99.36 (CH-1), 177.14 (CO-2').- IR ($CDCl_3$): 1780, 1730 (weak) cm^{-1}.- MS: m/z (%) = 182 (4), 145 (36), 117 (39), 101 (17), 99 (12), 85 (100).- $C_{10}H_{14}O_4$ (200.2) calcd C 59.99, H 8.05, found C 60.08, H 7.95. After removal of the protecting group as described below, the resulting bromo derivatives were converted into **24a/24b** and these were analyzed by NMR (vide infra). According to this analysis the d.e. in the above reaction was 43%.

(S)-4-(2-Methoxy-ethoxymethoxy-methyl)-dihydrofuran-2-one (23c)

$NaBH_4$ (27.6 mg, 0.730 mmol), dissolved in degassed DMF (0.5 ml), was added to a solution of **21c** (72.3 mg, 0.358 mmol), semicorrin[19] (2.1 mg, 0.005 mmol), and $CoCl_2 \times 6H_2O$ (0.6 mg, 0.004 mmol) in degassed ethanol (1 ml). The reaction mixture was stirred at 20°C for 4 h and then diluted with water (10 ml). Usual work-up (ethyl acetate) and LC (petrol - ethyl acetate 1:1) provided **23c** (44.3 mg, 61%).- ^{1}H NMR (400 MHz, $CDCl_3$), δ = 2.36 (dd, 1H, 3-H), 2.51 (dd, 1H, 3-H'), 2.83 (m, 1H, 4-H), 3.37 (s, 3H, CH_2-O-CH_2-CH_2-O-CH_3), 3.53 (m, 2H, CH_2-O-CH_2-CH_2-O-CH_3), 3.55-3.60 (m, 2H, CH_2-6), 3.66 (m, 2H, CH_2-O-CH_2-CH_2-O-CH_3), 4.16 (dd, 1H, 5-H), 4.40 (dd, 1H, 5-H'), 4.70 (s, 2H, CH_2-O-CH_2-CH_2-O-CH_3), $J_{3,3}$ = 17.5 Hz, $J_{5,5}$ = 9.5 Hz, $J_{3a,4}$ = 6.0 Hz, $J_{3b,4}$ = 9.0 Hz, $J_{4,5a}$ = 5.5 Hz, $J_{4,5b}$ = 4.5 Hz.- IR ($CDCl_3$): 1780, 1735 cm^{-1}.- MS: m/z (%) = 145 (11), 129 (22), 89 (42), 59 (83), 58 (43), 55 (29), 45 (100).- $C_9H_{16}O_5$ (204.2) calcd C 52.93, H 7.90, found C 52 95, H 7.98. The e.e. (37%) was determined by capillary GLC, for conditions, see above. Retention times: 145 min (**23c**), 147 min (*ent*-**23c**). In addition, the mixture of **23c** and *ent*-**23c** was converted into **24a/24b** via the bromo derivatives (for the procedure see below). By an NMR analysis of the **24a/24b** mixture a 40% d.e.was determined.

Ethyl (R)-4-(^{t}butyl)dimethylsilyloxy-3-(2-methoxy-ethoxymethoxy-methyl)-butanoate (*ent*-22)

$NaBH_4$ (42.3 mg, 1.118 mmol), dissolved in degassed DMF (1.5 ml), was added to a solution of $CoCl_2 \times 6H_2O$ (1.1 mg, 0.007 mmol), semicorrin[19] (3.0 mg, 0.007 mmol), and **20c** (200.2 mg, 0.552 mmol) in degassed ethanol (4 ml). The reaction mixture was stirred at 40°C for 18 h. Then, further portions of semicorrin (3.3 mg, 0.007 mmol) and $CoCl_2 \times 6H_2O$ (0.9 mg, 0.005 mmol), dissolved in ethanol (0.5 ml), and $NaBH_4$ (21.5 mg, 0.567 mmol), dissolved in DMF (0.5 ml), were added, and the mixture was stirred for another 24 h at

20°C. After dilution with water (7 ml), usual work-up (ethyl acetate), and LC (petrol - ethyl acetate 10:1) provided *ent*-**22** (32.0 mg, 66%).- ^{1}H NMR (80 MHz, $CDCl_3$), δ = 0.01 (s, 6H, $Si^tBu(C\underline{H}_3)_2$), 0.86 (s, 9H, $Si^t\underline{Bu}(CH_3)_2$), 1.23 (t, 3H, $CH_2C\underline{H}_3$), 2.12-2.42 (m, 3H, CH_2-2, 3-H), 3.37 (s, 3H, CH_2-O-CH_2-CH_2-O-$C\underline{H}_3$), 3.45-3.73 (m, 8H , CH_2-O-$C\underline{H}_2$-$C\underline{H}_2$-O-CH_3, CH_2-4, CH_2-5), 4.10 (q, 2H, $C\underline{H}_2$-CH_3), 4.67 (s, 2H, $C\underline{H}_2$-O-CH_2-CH_2-O-CH_3), $J_{ethyl\ group}$ = 7 Hz.- IR ($CDCl_3$): 1730 cm^{-1}.- MS: m/z (%) = 349 (1), 307 (6), 289 (3), 259 (4), 173 (14), 133 (18), 89 (100), 75 (20), 73 (19), 59 (100).- $C_{17}H_{36}O_6Si$ (364.5) calcd C 56.01, H 9.95, found C 56.10, H 9.94. After cyclization of *ent*-**22** to *ent*-**23c** and removal of the protecting group as described below, the resulting bromo derivatives were converted into **24a/24b** and these were analyzed by NMR (vide infra). According to this analysis the e.e. in the above reaction was 58%.

Ethyl (S)-4-(^{t}butyl)dimethylsilyloxy-3-(2-methoxy-ethoxymethoxy-methyl)-butanoate (22)

$NaBH_4$ (43.0 mg, 1.137 mmol), dissolved in degassed DMF (1.5 ml) was added to a solution of $CoCl_2 \times 6H_2O$ (1.0 mg, 0.006 mmol), semicorrin[19] (3.6 mg, 0.008 mmol), and **20a** (200.7 mg, 0.554 mmol) in degassed ethanol (4 ml). The reaction mixture was stirred at 40°C for 18 h. Then, further portions of semicorrin (3.3 mg, 0.007 mmol) and $CoCl_2 \times 6H_2O$ (0.9 mg, 0.005 mmol), dissolved in ethanol (0.5 ml), and $NaBH_4$ (21.5 mg, 0.567 mmol), dissolved in DMF (0.5 ml), were added. Stirring at 40°C was continued for 48 h. Although **20a** was still detectable by TLC after this time the reaction was quenched with water (7 ml), because by-products were formed in an increasing amount. Usual work-up (ethyl acetate) and LC (petrol - ethyl acetate 10:1) furnished 106.4 mg of a 2:1 mixture (determined by ^{1}H NMR) of **22** and educt **20a** which could not be separated. According to these figures, the yield of **22** was ≈ 40%. After cyclization of **22** to **23c** and removal of the protecting group as described below, the resulting bromo derivatives were converted into **24a/24b** and these were analyzed by NMR (vide infra). According to this analysis the e.e. in the above reaction was 52%.

(S)-4-(2-Methoxy-ethoxymethoxy-methyl)-dihydrofuran-2-one (23c) via microbial reduction

A mixture of commercially available baker's yeast (20 g), saccharose (10 g), and water (200 ml) was adjusted to pH 7 with aqu. NaOH (1 mol/l solution in water). The mixture was left at 20°C for 15 min. Then a solution of **21c** (2.0147 g, 9.963 mmol) in water (5 ml) was added. The flask was closed with a perforated aluminium cap and shaken intensely for 2 d at 35°C. Then, in 2 d intervals yeast (4 g) and saccharose (10 g) were added and the solution adjusted to pH 7 with aqu. NaOH (1 mol/l solution in water). After a total of 10 d TLC indicated the complete consumption of **21c**. The yeast was removed by centrifugation and washed twice with water. The resulting solutions were combined and freeze dried. The solid residue was taken up in methanol and filtered. Silica gel (15 g) was added to the filtrate and the solvent was evaporated. After filtration through silica gel (15 g, elution with ethyl acetate), LC (petrol - acetone 3:1) provided **23c** (1.7233 g, 85%). For spectra, see above.- $[\alpha]_D$ = 28.0 (c 4.08 in $CHCl_3$). After removal of the protecting group as described below, the resulting bromo derivatives were converted into **24a/24b** and these were analyzed by NMR (vide infra). According to this analysis the e.e. in the above reaction was ≈ 100%.

Cyclization of *ent*-22 to *ent*-23c

A solution of p-toluenesulfonic acid (4.1 mg, 0.022 mmol) in a 1:1 mixture of water and ethanol (2 ml) was added to *ent*-**22** (47.4 mg, 0.130 mmol). The reaction mixture was stirred at 20°C for 24h. Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 1:1) furnished *ent*-**23c** (24.2 mg, 91%). For spectra, see above.

Cyclization of 22 to 23c

A solution of a 2:1 mixture (106.4 mg) of **22** (≈ 70 mg, ≈ 0.2 mmol) and **20a** (≈ 35 mg, ≈ 0.1 mmol) (these compounds could not be separated; see above) was dissolved in ethanol (1 ml). After addition of a solution of p-toluenesulfonic acid (6.2 mg, 0.326 mmol) in water (1 ml) the reaction mixture was stirred at 20°C for 24 h. Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 1:1) furnished **20b** (22.5 mg, ≈ 90%) and **23c** (43.7 mg, ≈ 100%). The spectra of these compounds were identical with the spectra described above.

(R/S)-, (R)-, and (S)-4-Bromomethyl-dihydrofuran-2-one (*rac*-23f, 23f, and *ent*-23f)

a) From (R/S)-4-[(^{t}butyl)dimethylsilyloxy-methyl]-dihydrofuran-2-one (*rac*-**23b**): To a solution of triphenylphosphine dibromide (135.4 mg, 0.321 mmol) in CH_2Cl_2 (1 ml) *rac*-**23b** (52.5 mg, 0.228 mmol), dissolved in CH_2Cl_2 (1 ml), was added. The reaction mixture was stirred at 20° C for 6 h. Quenching with water (7 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 5:1) provided *rac*-**23f** (35.9 mg, 88%).- ^{1}H NMR (80 MHz, $CDCl_3$), δ = 2.22-2.65 (m, 2H, CH_2-3), 2.80-3.24 (m, 1H, 4-H), 3.36-3.50 (m, 2H, CH_2-6), 4.10 (dd, 1H, 5-H), 4.45 (dd, 1H, 5-H'), $J_{5,5}$ = 9.5 Hz, $J_{4,5a}$ = 6.0 Hz, $J_{4,5b}$ = 7.0 Hz.- IR ($CDCl_3$): 1775 cm^{-1}.- MS: m/z (%) = 24 (2), 178 (2), 69 (11), 55 (100), 41 (55).- $C_5H_7BrO_2$ (179.0) calcd C 33.55, H 3.94, found C 33.67, H 3.99.

b) From (R)-4-[(^{t}butyl)dimethylsilyloxy-methyl]-dihydrofuran-2-one (**23b**, prepared from **21b** using the Pfaltz method). The reaction was performed as described in a).

c) From (S)-4-(tetrahydro-pyran-2-yloxy-methyl)-dihydrofuran-2-one (**23d**)

Triphenylphosphine dibromide (169.1 mg, 0.401 mmol), dissolved in CH_2Cl_2 (1.5 ml) was added to a solution of **23d** (49.7 mg, 0.248 mmol) in CH_2Cl_2 (1.5 ml). The reaction mixture was stirred at 20°C for 30 min. Quenching with water (5 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 5:1) provided **23f** (33.3 mg, 75%). For spectra, see above.

d) From (R)-4-(2-methoxy-ethoxymethoxy-methyl)-dihydrofuran-2-one (*ent*-**23c**, obtained by the sequence **20c**→*ent*-**22** (Pfaltz method)→*ent*-**23c**): A solution of *ent*-**23c** (74.9 mg, 0.367 mmol) in CH_2Cl_2 (2 ml) was dropped to triphenylphosphine dibromide (240.2 mg, 0.569 mmol), dissolved in CH_2Cl_2 (2 ml). After stirring at 20°C for 5h the reaction was quenched with water (5 ml). Usual work-up (CH_2Cl_2) and LC (petrol - ethyl acetate 6:1) furnished *ent*-**23f** (74.9 mg, 45%). For spectra, see above.

e) From (S)-4-(2-methoxy-ethoxymethoxy-methyl)-dihydrofuran-2-one (**23c**): **23f** was prepared from **23c** as described above. All samples of **23c** which were obtained by different methods (via the Pfaltz reduction of **20a** and **21c** as well as by yeast reduction of **21c**) were individually converted to **23f**.- $[\alpha]_D$ = 43.1 (c 6.40 in $CHCl_3$) for optically pure **23f**.

(R/S)- and (R)-4-Iodomethyl-dihydrofuran-2-one (*rac*-23g and 23g)

a) From (R/S)-4-hydroxymethyl-dihydrofuran-2-one (*rac*-**23a**): A solution of iodine (504.4 mg, 1.987 mmol) in THF (5 ml) was added to a stirred mixture of *rac*-**23a** (229.1 mg, 1.973 mmol), triphenylphosphine (518.9 mg, 1.978 mmol), imidazole (274.6 mg, 4.034 mmol), and THF (10 ml) at 0°C. The ice bath was removed and stirring was continued for 6 h at 20°C. Quenching with dilute aqu. $Na_2S_2O_7$ (15 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 5:1) provided *rac*-**23g** (363.2 mg, 81%). For spectra, see ref.[12]

b) From (R/S)-4-[(^{t}butyl)dimethylsilyloxy-methyl]-dihydrofuran-2-one (*rac*-**23b**): To a solution of NaI (18.2 mg, 0.121 mmol), and *rac*-**23b** (25.0 mg, 0.109 mmol) in acetonitrile (1 ml) trimethylsilyl chloride (15 µl, 13

mg, 0.122 mmol) was added. The reaction mixture was stirred at 80°C for 5 h. Quenching with dilute aqu. $Na_2S_2O_7$ (4 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate - acetic acid 10:1:0.04) furnished *rac*-**23g** (12.9 mg, 53%) and 4-iodo-3-iodomethyl-butanoic acid (2.4 mg, 6%).

c) From (R)-4-[(t-butyl)dimethylsilyloxy-methyl]-dihydrofuran-2-one (**23b**): The experiment was performed as described in b). Although optically active **23b** was used in this experiment *rac*-**23g** was obtained.

d) From (R)-4-bromomethyl-dihydrofuran-2-one (**23f**): A mixture of KI (116.2 mg, 0.700 mmol), 18-crown-6 (9.2 mg, 0.035 mmol), optically pure **23f** (12.7 mg, 0.071 mmol), and acetonitrile (2 ml) was stirred at 40°C for 48 h. Quenching with water (5 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 6:1) provided optically pure **23g** (15.7 mg, 98%).- $[\alpha]_D$ = 34.0 (c 3.85 in $CHCl_3$).

e) From (S)-4-(2-methoxy-ethoxymethoxy-methyl)-dihydrofuran-2-one (**23c**): Titanium(IV) chloride (80 µl, 140 mg, 0.73 mmol), dissolved in CH_2Cl_2 (1 ml), was added dropwise to a solution of optically pure **23c** (51.5 mg, 0.252 mmol) in CH_2Cl_2 (1 ml) at 0°C, and the mixture was stirred at 0° for 50 min. Then, the reaction mixture was rapidly added to a stirred solution of NaOH (129.6 mg, 2.946 mmol) in a NaH_2PO_4/Na_2HPO_4-buffer (3 ml, this buffer was prepared by titration of a NaH_2PO_4 solution (1 mol/l solution in water) with a Na_2HPO_4 solution (1 mol/l solution in water) until pH 7 was reached). Subsequent freeze drying provided a solid residue, which was extracted with ethanol. From the combined solutions solvents were evaporated and the crude **23a** was immediately taken up in THF (1 ml) and treated with a solution of triphenylphosphine (77.2 mg, 0.294 mmol), imidazole (38.6 mg, 0.567 mmol), and iodine (74.6 mg, 0.294 mmol) in THF (3 ml). After stirring for 1 h at 20°C the reaction was quenched with diluted aqu. $Na_2S_2O_7$ (5 ml). Usual work-up (CH_2Cl_2) and LC (petrol-ethyl - acetate 5:1) provided optically pure **23g** (41.5 mg, 73%).

4-Iodo-3-iodomethyl-butanoic acid

M.p. 51-52°C (petrol).- ^{1}H NMR (80 MHz, $CDCl_3$), δ = 1.98 (sept., 1H, 3-H), 2.57 (d, 2H, CH_2-2), 3.26 and 3.44 (8 lines, 4H, CH_2-4 and CH_2-5), $J_{4,4} = J_{5,5}$= 10.0 Hz, $J_{3,4} = J_{3,5}$ = 5.5 Hz, $J_{2,3}$ = 6.5 Hz.- IR ($CHCl_3$): 3500-2500, 1720 cm^{-1}.- MS: m/z (%) = 337 (0.4), 227 (100), 185 (12), 167 (4), 141 (6), 128 (7), 127 (7), 99 (25), 81 (9), 71 (19).- $C_5H_8I_2O_2$ (353.9) calcd C 16.97, H 2.29, found C 17.09, H 2.38.

(R)-4-{(1S)-2*exo*-Hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethyl-sulfanyl-methyl}-dihydrofuran-2-one (24a) from 25 and 23f

A mixture of K_2CO_3 (45.5 mg, 0.329 mmol), **25**[25] (19.6 mg, 0.115 mmol), optically pure **23f** (14.0 mg, 0.078 mmol), and N-methylpyrrolidone (2 ml) was stirred at 20°C for 16 h. Quenching with water, followed by usual work-up (ethyl acetate), and LC (petrol - ethyl acetate 3:1) furnished pure **24a** (6.3 mg, 28%).- ^{1}H NMR (400 MHz, $CDCl_3$), *camphor unit*: δ = 0.83 (s, 3H, 7-CH_3), 1.04 (s, 3H, 7-CH_3'), partly hidden: 1.00-1.07 (m, 1H, camphor-H), 1.16-1.25 (m, 1H, camphor-H), 1.44-1.52 (m, 1H, camphor-H), 1.65-1.80 (m, 4H, 2*CH_2-camphor), 2.14 (br.d, 1H, 2-OH), 2.53 (d, 1H, 8-H), 2.82 (d, 1H, 8-H'), 3.85 (br.dd, 1H, 2-H), $J_{8,8}$ = 11.0 Hz, *lactone unit*: δ = 2.37 (dd, 1H, 3'-H), 2.62-2.75 (m, 3H, CH_2-6', 3'-H'), 2.77-2.87 (m, 1H, 4'-H), 4.11 (dd, 1H, 5'-H), 4.45 (dd, 1H, 5'-H'), $J_{3',3'}$ = 18.0 Hz, $J_{5',5'}$ = 9.5 Hz, $J_{3a',4'} = J_{3b',4'}$ = 6.5 Hz, $J_{4',5a'}$ = 6.0 Hz, $J_{4',5b'}$ = 7.0 Hz.- IR ($CDCl_3$): 3640-3500, 1780 cm^{-1}.- MS: m/z (%) = 284 (1), 282 (1), 266 (1), 251 (2), 240 (2), 223 (1), 153 (65), 135 (17), 132 (40), 109 (56), 108 (48), 95 (35), 93 (35), 85 (100).- $[\alpha]_D$ = -24.2 (c 0.26 in $CHCl_3$).- A NMR analysis as described below proved this sample of **24a** to be stereohomogeneous.

(S)-4-{(1S)-2*exo*-Hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethyl-sulfanyl-methyl}-dihydrofuran-2-one (24b) from 25 and *ent*-23f

A sample of *ent*-**23f** was used which was obtained by the sequence **20c**→*ent*-**22** (Pfaltz method)→*ent*-**23c**→ *ent*-**23f**. It was converted into **24a/24b** as described above. The main isomer in the chromatographically unseparable mixture was **24b**. From the NMR spectrum of the mixture the signals of **24b** were extracted. ^{1}H NMR (400 MHz, $CDCl_3$), *camphor unit*: δ = 0.82 (s, 3H, 7-CH_3), 1.03 (s, 3H, 7-CH_3'), partly hidden: 0.99-1.08 (m, 1H, camphor-H), 1.15-1.23 (m, 1H, camphor-H), 1.44-1.52 (m, 1H, camphor-H), 1.64-1.79 (m, 4H, 2*CH_2-camphor), 2.10 (br.s, 1H, 2-OH), 2.50 (d, 1H, 8-H), 2.83 (d, 1H, 8-H'), 3.84 (br.d, 1H, 2-H), $J_{8,8}$ = 11 Hz, *lactone unit*: δ = 2.36 (dd, 1H, 3'-H), 2.61-2.74 (m, 3H, CH_2-6', 3'-H'), 2.76-2.85 (m, 1H, 4'-H), 4.09 (dd, 1H, 5'-H), 4.43 (dd, 1H, 5'-H'), $J_{3',3'}$ = 17.5 Hz, $J_{5',5'}$ = 9.5 Hz, $J_{3',4'}$ = 6.5 Hz, $J_{4',5a'}$ = 6.0 Hz, $J_{4',5b'}$ = 7.0 Hz.- IR ($CDCl_3$): 3640-3500, 1775 cm^{-1}.- MS: m/z (%) = 284 (1), 266 (1), 251 (2), 240 (2), 223 (1), 153 (58), 132 (40), 109 (52), 108 (48), 95 (33), 93 (32), 85 (100).- The d.e. of this mixture was determined by the method described below to be 58%.

Deterimantion of the optical purity of iodolactones 23g by conversion to (R)- and (S)-4-{(1S)-2*exo*-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl-methyl-sulfanylmethyl}-dihydrofuran-2-one (24a/24b)

a) *rac*-**23g**: A mixture of K_2CO_3 (45.5 mg, 0.329 mmol), **25**[25] (21.8 mg, 0.128 mmol), *rac*-**23g** (35.0 mg, 0.155 mmol), and N-methylpyrrolidone (3 ml) was stirred at 20°C for 5 h. Usual work-up (ethyl acetate) and LC (petrol - ethyl acetate 4:1) furnished a mixture of **24a/24b** (25.0 mg, 69%). The ratio **24a/24b** which were chromatographically unseparable was determined by ^{1}H NMR (400 MHz, $CDCl_3$), integrating the signals of the gem. dimethyl groups, after addition of $Eu(FOD)_3$-d_{27} (0.4 eq.) to a sample of the diastereomers. $C_{15}H_{24}O_3S$ (284.4) calcd C 63.35, H 8.51, found C 63.46, H 8.50. For spectra vide supra.

b) **23g**: The experiment was performed as described above with optically pure **23g** (obtained via the yeast reduction experiment). The NMR analysis (see above) did not give any indication of the presence of **24b**.

(R)-4-Acetoxy-methyl-dihydrofuran-2-one (*ent*-23e)

To a mixture of finely powdered KOAc (128.0 mg, 1.304 mmol), 18-crown-6 (20.8 mg, 0.079 mmol), and acetonitrile (1 ml) a solution of *ent*-**23f** (30.3 mg, 0.169 mmol) in acetonitrile (2 ml) was added. The reaction mixture was stirred at 40°C for 22h. Quenching with water (7 ml), usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 3:1) provided *ent*-**23e** (17.0 mg, 64%).- $[\alpha]_D$ = -16.7 (c 5.01 in $CHCl_3$). For optically pure **23e** $[\alpha]_D$ = 34.5 (c 4.11 in $CHCl_3$) has been reported.[22] For other analytical data, see ref.[13]

(S)-4-Acetoxy-methyl-dihydrofuran-2-one (23e)

The experiment was performed with optical pure **23f** as described above. For spectra see above.- $[\alpha]_D$ = 34.4 (c 2.83 in $CHCl_3$), lit.[22] 34.5.

Methyl 1,3-dimethyl-2-oxo-cyclohex-3-ene-carboxylate (26b)

To **26a** (54.1 mg, 0.322 mmol), dissolved in THF (1 ml), at -78°C a LDA solution[40] (0.5 mol/l solution in THF/hexane, 0.77 ml, 0.39 mmol) was added and the mixture was stirred at 0°C for 40 min. Methyl iodide (32 µl, 49 mg, 0.347 mmol) was added at -78°C. The reaction mixture was allowed to warm to 20°C and was then stirred at this temperature for 5 h. Quenching with water (5 ml), followed by usual work-up (CH_2Cl_2), and LC

(petrol - ethyl acetate 8:1) furnished **26b** (18.2 mg, 31%) and starting material **26a** (4.9 mg, 9%).- For spectral data see ref.[41]

Reaction of 26a with *rac*-23g

A solution of **26a** (321.6 mg, 1.912 mmol) in a 1:1 mixture of THF and DMPU (6 ml) was treated with a solution of sodium bis(trimethylsilyl) amide (1 mol/l solution in THF, 2.2 ml, 2.2 mmol) at -78°C. After stirring for 10 min at -78°C *rac*-**23g** (502.0 mg, 2.221 mmol), dissolved in DMPU (4 ml), was added. The reaction mixture was allowed to warm to 20°C within 2.5 h. Quenching with water (15 ml), followed by usual work-up (ethyl acetate), and LC (petrol - ethyl acetate 3:1) furnished **28** (167.5 mg, 33%) and the Michael adducts **27** (73.0 mg, 23%).

Methyl 1-methyl-2-oxo-3-(5-oxo-tetrahydrofuran-3-ylmethyl)-cyclo-hex-3-ene-carboxylate (28), mixture of stereoisomers

^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.35 (s, 3H, 1-CH_3), 1.81-2.55 (overlapping signals: m's, 6H, for CH_2-5, CH_2-6 and CH_2-6', and at 2.48 (dd, 1H, 4'-H) and 2.55 (dd, 1H, 4'-H')), 2.73 (m, 1H, 3'-H), 3.65 (s, 3H, 1-$COOCH_3$), 3.89 and 3.92 (dd, 2'-H of both stereoisomers), 4.25 and 4.31 (dd, 2'-H' of both stereoisomers), 6.64 (m, 1H, 4-H), $J_{2',2'}$ = 9.0 Hz, $J_{4',4'}$ = 8.5 Hz, $J_{2',3a'}$ = 6.0 Hz, $J_{2',3b'}$ = 7.0 Hz, $J_{3',4'}$ = 17.5 Hz.- IR ($CDCl_3$): 1775, 1735, 1680 cm^{-1}.- MS: m/z (%) = 266 (24), 251 (5), 238 (5), 219 (36), 207 (18), 206 (25), 189 (100), 178 (13), 161 (27), 138 (40), 137 (18).- $C_{14}H_{18}O_5$ (226.3) calcd C 63.15, H 6.81, found C 63.05, H 6.91.

Dimethyl 3,4'-dimethyl-2,3'-dioxo-bicyclohexyl-6-ene-3,4'-dicarboxylate (27), mixture of stereoisomers

^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.28 and 1.34 (2s, 6H, 3-CH_3 and 4'-CH_3), 1.45-2.54 (m's, 10H, CH_2-2', CH_2-5', CH_2-6', CH_2-4 and CH_2-5), 2.92 (m, 1H, 1'-H), 3.65 and 3.72 (s, 6H, 3-$COOCH_3$ and 4'-$COOCH_3$), 6.49 and 5.54 (m, 6-H of the stereoisomers).- IR ($CHCl_3$): 1730, 1715, 1680 cm^{-1}.- MS: m/z (%) = 336 (39), 308 (12), 277 (34), 276 (59), 249 (18), 248 (15), 217 (72), 189 (50), 41 (100).- $C_{18}H_{24}O_6$ (336.4) calcd C 64.27, H 7.19, found C 64.24, H 7.16.

Methyl 3-(3-carboxy-2-iodomethyl-propyl)-1-methyl-2-oxo-cyclohex-3-ene-carboxylate (30)

Trimethylsilyl chloride (36 µl, 31 mg, 0.284 mmol) was added to a solution of NaI (42.1 mg, 0.281 mmol) and **28** (30.0 mg, 0.113 mmol) in degassed acetonitrile (2 ml). The reaction mixture was stirred at 75°C for 22 h. Quenching with dilute aqu. $Na_2S_2O_7$ (5 ml), followed by usual work-up (CH_2Cl_2), and LC (petrol - ethyl acetate 5:1 + 1% acetic acid) provided unstable **30** (10.9 mg, 25%) and educt **28** (7.5 mg, 22%).- ^{1}H NMR (400 MHz, $CDCl_3$), δ = 1.36 (s, 3H, 1-CH_3), 1.83-2.47 (m's, 9H, CH_2-5, CH_2-6, CH_2-1', CH_2-3', 2'-H), 3.19 and 3.20 (6 signals, $J_{4',4'}$ = 10 Hz, 4'-H of both stereoisomers), 3.41 (d) and 3.41 (dd, $J_{4',4'}$ = 10 Hz, $J_{3',4'}$ = 7 Hz, 4'-H' of both stereoisomers), 6.76 and 6.80 (m, 4-H of both stereoisomers).- IR ($CDCl_3$): 3300-2840, 1740, 1715, 1685 cm^{-1}.- MS: m/z (%) = 394 (7), 381 (6), 317 (18), 267 (40), 249 (9), 219 (17), 217 (17), 207 (22), 189 (77), 161 (37), 41 (100).- $C_{14}H_{19}IO_5$ (394.2).- HR-MS: calcd 394.0277, found 394.0270.

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