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Strigol Synthetic Studies
The Problem of Stereocontrol at C-2'

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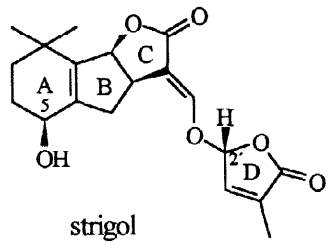
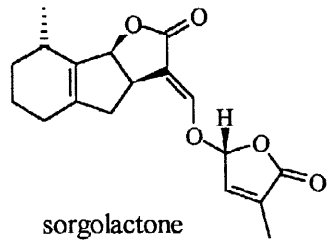
Abstract - The problem of stereocontrol at C-2′ in the synthesis of strigol-type compounds is introduced. Experiments are discussed in which mainly methods from carbohydrate chemistry (stereoselective glycoside formation) are used to control the configuration at C-2′.

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 stimulants are sorgolactone and alectrol (structure not shown) which have been isolated from the root exudates of *Sorghum vulgare* (host for *Striga*) and *Vigna unguiculata* (host for *Striga* and *Alectra*), respectively.[1,2]



strigol



sorgolactone

Scheme 1

Two compounds, which are structurally closely related to sorgolactone, namely strigol and its acetate, have first been isolated from cotton (*Gossypium hirsutum*) which is neither a host for *Striga* nor for *Orobanche*[3], recently they have also been found in the root exudates of *Striga* host plants.[4]

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.[5] For *Orobanche crenata* seeds it has been found that both the absolute configuration and the relative configuration at C-2′ are of major importance as far

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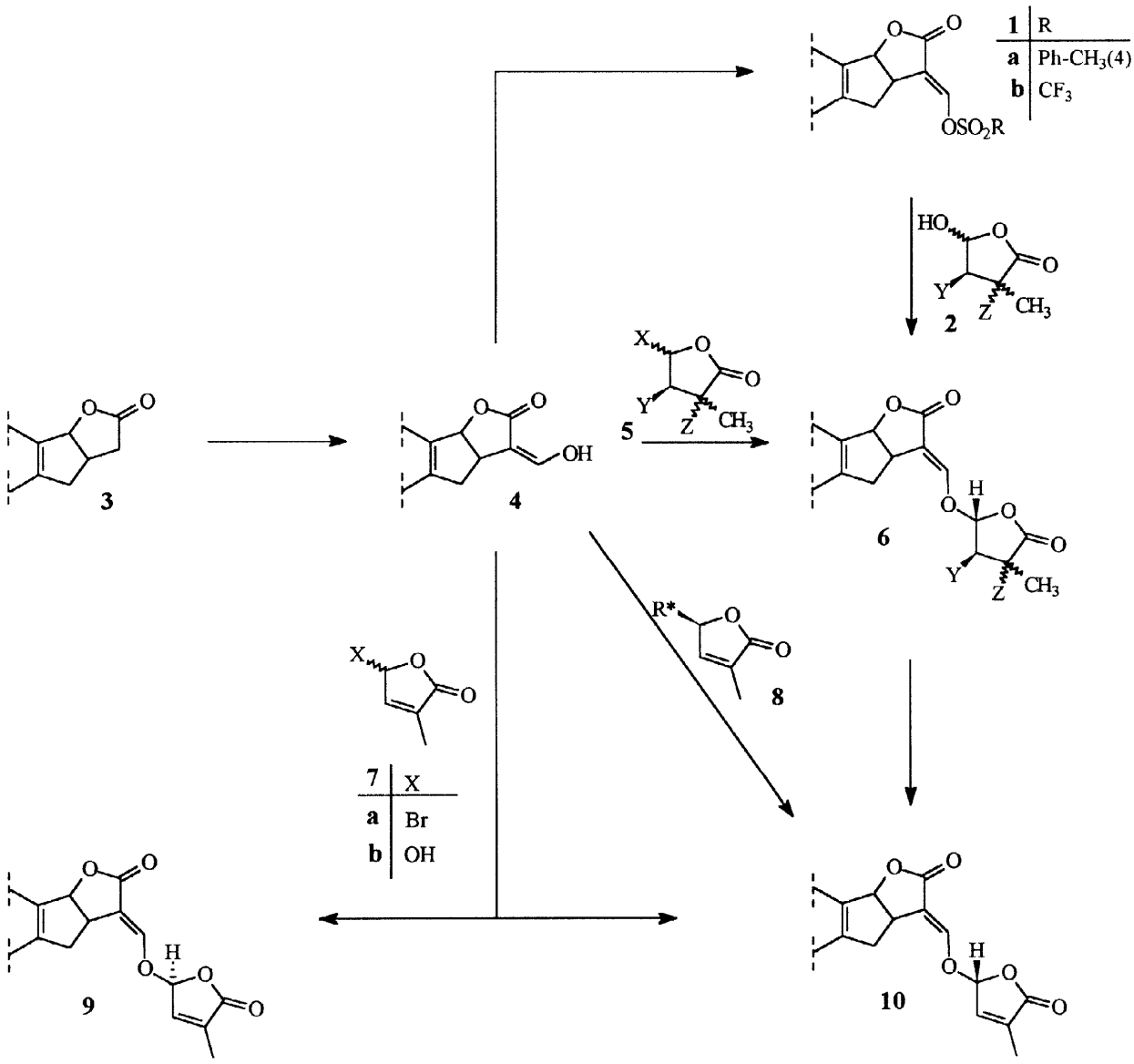


Scheme 2

as seed germination potency is concerned. In an extended set of structural analogues the stereoisomers with the strigol-like configuration at C-2′ turned out to be more active than their C-2′-epimers.[6, 7] Similar observations concerning the relation between configuration and seed germination potencies of two series of stereoisomers have been reported by Zwanenburg.[8, 9, 10] The situation may be more complicated, however. This is suggested by recent results of Mori.[11]

Non-racemic samples of strigol, its stereoisomers, and of structural analogues have been obtained both by conventional resolution[5, 12, 13, 14] and by different types of EPC synthesis including kinetic resolution.[8, 15, 16, 17] For one stereochemical problem in the synthesis of strigol-like compounds only very recently solutions have been found, i.e. control of the configuration at C-2′. The classical approach is that a synthetic intermediate of type **3** is converted into a hydroxymethylene derivative **4**. This is in turn coupled with racemic,

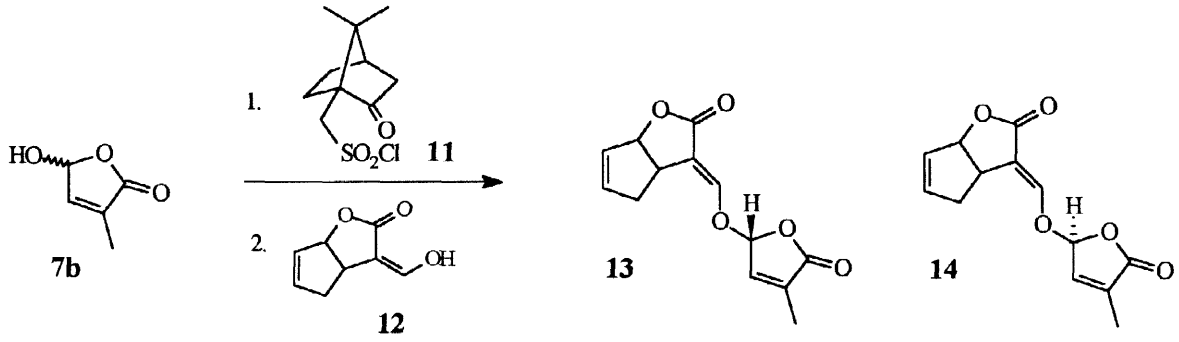
configurationally unstable bromolactone **7a** to give a 1:1-mixture of **9** and **10**.[8, 9, 11, 14, 18 - 21] It is purpose of this and the accompanying publications to discuss work that has been carried out with the aim of finding satisfactory solutions for this problem. In principle, a stereohomogeneous and configurationally stable compound of type **8** with R* as leaving group under strictly S_N2-conditions would lead to **10**. Formation of **8** with an achiral R* would require either a resolution step or an asymmetric synthesis. A simpler option would make use of a chiral auxiliary R*.[22] We shall report on a few examples of this type.

In another approach compounds of type **5** could be used as synthetic equivalents of **7a**. The reagents were anticipated to have either nucleophilic properties (**2**) and react with a compound of type **1** to give a coupling product **6** or to be electrophilic and react with **4**, also yielding **6**. In either case the substituent Y would have the duty to exert the desired stereocontrol. In a final step of the synthesis **6** would have to be converted into **10** by an elimination process.

Some time ago, in a preliminary communication we reported on a type **5** compound with X = Br, Y = SPh, and Z = H, obtained from a stereohomogenous alkoxy butenolide derived from **7b** by Michael addition.[23] A full account of this work will be given in the accompanying paper.[24] Subsequently, Zwanenburg and coworkers introduced an equivalent of **5** obtained by a sequence of cycloaddition / reduction / resolution and used this reagent to synthesize stereohomogeneous compounds of type **6**.[16, 17, 25, 26] In the final step **10** was liberated by a retro-Diels-Alder reaction. We shall comment on this work in more detail in the final paper of this series and report on a very efficient Diels-Alder/retro-Diels-Alder approach.[27]

Attempts to control the configuration at C-2′ using reagents of type 8

First it was tried to achieve the desired goal via the sulfonates obtained from **7b** and the camphor-derived sulfonyl chloride **11**. The very unstable diastereomeric sulfonates were prepared in THF solution in the presence of triethylamine.[28] They could not be isolated because of their sensitivity towards hydrolysis, but a strong downfield shift of the 2′-H NMR signal was taken as evidence for their formation. When the sulfonates were treated with hydroxymethylene lactone *rac*-**12** (used for reasons of convience in the present study) at -40 °C a 2:1-mixture of **13** and **14** (GR28 and it's 2′-epimer) resulted in an overall yield of 64 %.[29] The origin of the stereoselectivity in this reaction (either preferred formation of the precursor of **13** or higher reactivity of the precursor of **13** and *in-situ*-anomerisation[30]) is at present unknown. In any case, the diastereomeric ratio is too small to be synthetically useful. With the intention to prepare a more suitable reagent of type **8**, bromo lactone *rac*-**7a** was treated with thiol **15**[31, 32] to yield the two diastereomeric sulfides **16a** und **16b** which were easily separated by chromatography. Thioglycosides play an important role in modern glycoside synthesis.[33] For the coupling reaction the thioglycosides have to be activated, in most cases with thiophilic reagents. In our case, the soft electrophiles, which were used with the intention to activate **16a** and **16b**, also interacted with the enolized β-dicarbonyl compound *rac*-**12**. Thus, a mixture of **16a** and *rac*-**12** on treatment with methanesulfenyl bromide (CH_3SBr, MSB)[34] in the presence of silver triflate furnished a complex mixture of products from which disulfides **19a** and **19b** as well as coupling products **20a - 20d** have been isolated. The desired compounds **13** and **14** could not be detected (TLC). Quite obviously, the formation of **19a** and **19b** can be explained by activation of the "thioglycoside" unit in the desired sense, C-2′ is however then attacked by the isoborneol OH group. We assume that *rac*-**12** is not available as a nucleophile since in a separate experiment reaction of *rac*-**12** with MSB led to the formation of *rac*-**18** (identified by ^1H NMR).



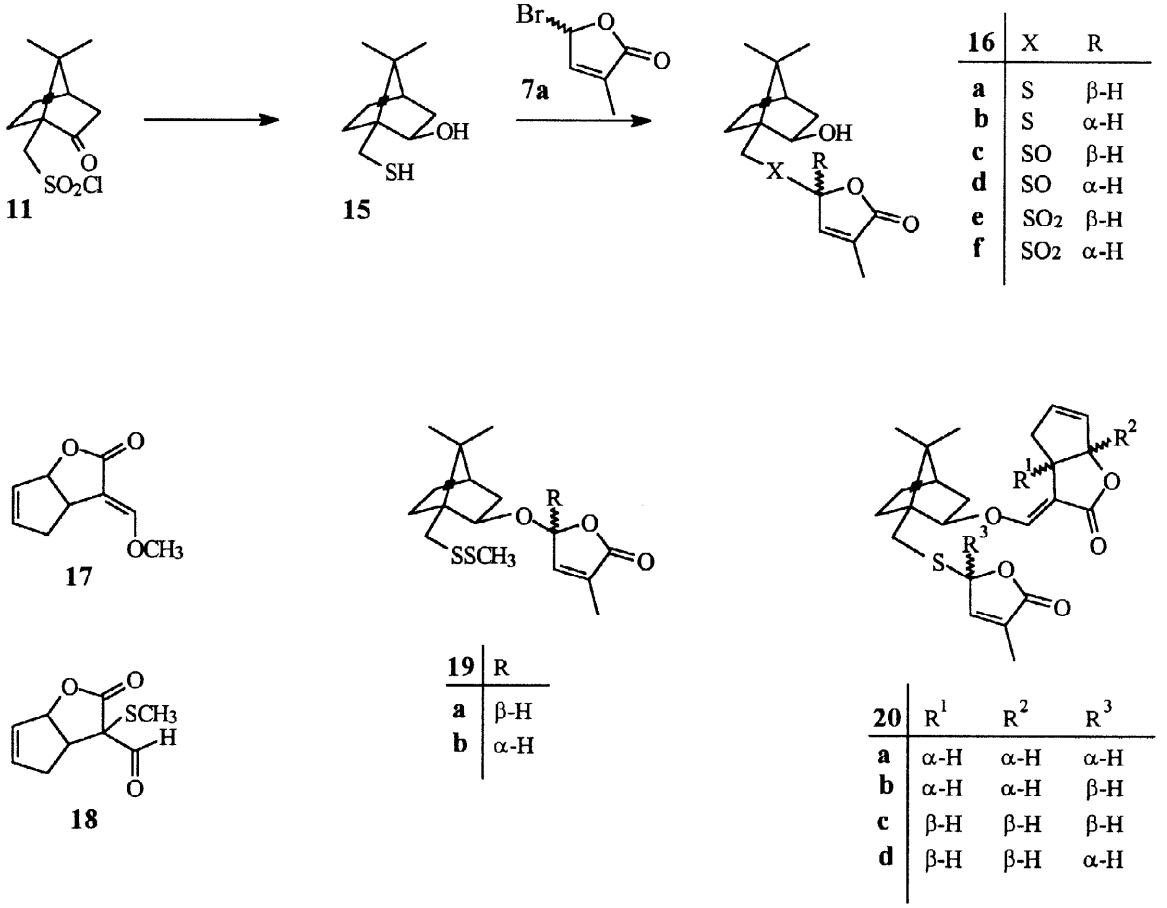
Scheme 3

Intermediate *rac*-**18** would also explain the formation of **20a** - **20d**. Aldehyde *rac*-**18** could react with the OH group of **16a,b** to yield a hemiacetal which by a reductive β-elimination would yield **20a** - **20d**. Similar results were obtained when **16a** was activated with benzeneselenyl triflate[35] and dimethyl(methylthio)sulfonium triflate (DMTST[36]). Finally, activation of **16a** with methyl iodide and methyl triflate also failed to yield the desired products. In the absense of a base no reaction occurred whereas with methyl iodide / DBU enolether *rac*-**17** was formed, and a mixture of **16a** and **16b** was recovered. The formation of C-2′-epimers in all these experiments needs some comment. Although **16a** and **16b** were isolated as pure stereoisomers they are quite prone to epimerisation. Thus, in the presence of DBU both from pure **16a** and **16b** an equilibium mixture was obtained.

Unreactive alcohols and even amides can be glycosylated when the thioglycosides are first converted into the corresponding sulfoxides and these activated with triflic anhydride.[37] For the oxidation of sulfides to sulfoxides many reagents can be used. The use of m-chloroperbenzoic acid (MCPBA)[31, 38, 39] and of potassium peroxomonosulfate (Oxone®)[40] seemed to be most promising. The oxidation of **16a** with Oxone® in methanol / water (15 min at 0 °C) yielded a mixture of stereoisomeric sulfoxides in 60 % yield whereas oxidation of **16a** and **16b**, respectively, with MCPBA in dichloromethane (30 min at -78 °C) provided the corresponding stereohomogeneous sulfoxides in quantitative yield. The high stereoselectivity in the MCPBA oxidation of related sulfoxides has been reported to be the result of a preferred conformation of the educt around the bond between C-10 and S and a hydrogen bond between the isoborneol OH group and the peracid.[31, 39, 41] Under certain conditions the sulfoxide derived from **16b** was found to be configurationally labile. After "chromatographic purification" a mixture of two stereoisomers was obtained which according to ^{1}H NMR were identical with those obtained from the Oxone® oxidation. This would mean that they differ in their configuration at sulfur and that the epimerisation occurs by a Mislow allylic sulfoxide mechanism.[42]

Treatment of sulfoxide **16c** (derived from **16a** with MCPBA) with *rac*-**12** in the presence of triflic anhydride / 2,6-lutidine and 2,6-di-^{t}butyl-4-methylpyridine, respectively, (toluene, -78 °C) did not lead to the desired coupling products **13** and **14**. Finally, sulfones **16e** and **16f** were tested as synthetic equivalents of reagent **8**. Ley has shown that 1-*O*-sulfonyl glycosides can be used as glycosyl donors after activation with $MgBr_2$-ether complex.[43] Sulfones **16e** and **16f** were obtained by oxidation of sulfides **16a** and **16b**, respectively, with Oxone®. ^{1}H NMR spectra indicated that both from **16a** and **16b** a mixture of stereoisomers **16e** and **16f** was obtained. Under the reaction condition reported by Ley,[43] **16e** and **16f** could not be coupled with *rac*-**12**.

In conclusion: The approach **4** + **7** → **10** using inter alia well-established methods of carbohydrate chemistry seems not to be very promising.



Scheme 4

EXPERIMENTAL

General: See ref.[21]

Identification of the camphorsulfonates derived from 5-hydroxy-3-methyl-2(5*H*)-furanone (*rac*-7b)
A solution of *rac*-**7b**[44] (obtained by hydrolysis of the corresponding bromobutenolide, 2 h at reflux in 1:5 water-THF,[45] 16.1 mg, 0.14 mmol) and triethylamine (78 µL, 0.56 mmol) in $CDCl_3$ (1.0 mL) was cooled to -40 - -50 °C. A solution of (+)-10-camphorsulfonyl chloride (35.4 mg, 0.14 mmol) in $CDCl_3$ (0.5 mL) was added und the mixture was stirred at -40 - -50 °C for 2 h. ^1H NMR (80 MHz, $CDCl_3$) displayed signals at δ = 6.51-6.67 (2*dq, 1H, 2*2'-H), 6.84-6.98 (dq, 1H, 3'-H) which were taken as evidence for the formation of the sulfonates.

Formation of *rac*-13 and *rac*-14 via the camphorsulfonates of *rac*-7b
Triethylamine (36.5 µL, 0.26 mmol) and (+)-(10)-camphorsulfonyl chloride (16.4 mg, 0.07 mmol), dissolved in THF (0.6 mL), were added to a -40 °C cold solution of *rac*-**7b** (7.8 mg, 0.07 mmol) in THF (0.4 mL). The

mixture was stirred at -40 - -50 °C for 0.5 h, then *rac*-**12** (10.4 mg, 0.06 mmol), dissolved in THF (1.0 mL) was added and the reaction mixture was allowed to warm to 20 °C within 2.5 h, then it was stirred at 20 °C for 96 h. Quenching with sat. aq. $NaHCO_3$ and usual work-up (CH_2Cl_2) followed by LC (petrol-ethyl acetate 1:1) yielded a mixture of *rac*-**13** and *rac*-**14** (10.1 mg, 64 %). The d.e. as determined by HPLC (250 mm * 4 mm, 5 µm Si 100, 13000 plates, *i*-octane-^{t}butyl methyl ether-2-propanol 40:15:2) was ≈ 2:1.

Alkylation of (1*S*)-7,7-dimethyl-1-sulfanylmethyl-bicyclo[2.2.1]heptan-2*exo*-ol (15) with *rac*-7a

To a mixture of potassium carbonate (329.3 mg, 2.38 mmol) and dry N-methylpyrrolidone (7.0 mL) solutions of **15** (202.7 mg, 1.08 mmol) in N-methylpyrrolidone (10.0 mL) and *rac*-**7a** (425.9 mg, 2.41 mmol) in N-methylpyrrolidone (3.0 mL) were added at 20 °C. The reaction mixture was stirred for 24 h at 20 °C. Excess potassium carbonate was destroyed with 5 per cent HCl. Usual work-up (ethyl acetate) and subsequent LC (petrol-ethyl acetate 4:1) furnished **15** (20.6 mg, 10 %), **16a** (149.9 mg, 49 %), **16b** (65.7 mg, 22 %) and a fraction containing **16a** and **16b** (35.8 mg, 12 %).

(*S*)-5-{(1*S*)-2*exo*-Hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethylsulfanyl}-3-methyl-5*H*-furan-2-one (16a)

R_f (petrol-ethyl acetate 1:1): 0.47.- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (s, 3H, 7-CH_3), 1.05 (s, 3H, 7-CH_3), 1.15-1.26 (ddd, 1H) and 1.43-1.53 (ddd, 1H) and 1.64-1.83 (m, 5H) (Σ = 7H, CH_2-3, 4-H, CH_2-5, CH_2-6), 1.93-1.97 (dd, 3H, 3'-CH_3), 1.94-2.15 (s (broad), 1H, OH), 2.71 and 3.08 (AB system, 2H, CH_2-10), 3.86-3.91 (dd, 1H, 2-H), 5.98-6.03 (dq, 1H, 5'-H), 6.95-6.98 (dq, 1H, 4'-H), $J_{2,3}$= 8.5 Hz, $J_{2,3*}$= 4.0 Hz, $J_{10,10*}$= 11.5 Hz, $J_{4',3'\text{-}CH3}$= $J_{5',3'\text{-}CH3}$= $J_{4',5'}$= 1.5 Hz.- IR ($CHCl_3$): 3600 - 3400, 1760 cm^{-1}.- MS: m/z (%) = 282 (M^+, 6), 264 (10), 238 (7), 130 (100), 108 (59), 98 (46), 97 (47), 41 (66).- CD (c 0.864 mmol/L, acetonitrile): λ_{max} (Δε) = 266.6 (1.40), 261.4 (1.46), 248.4 (2.42), 213.8 nm (16.65). -HRMS calcd for $C_{15}H_{22}O_3S$: 282.1290, found: 282.1291.

(*R*)-5-{(1*S*)-2*exo*-Hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethylsulfanyl}-3-methyl-5*H*-furan-2-one (16b)

R_f (petrol-ethyl acetate 1:1): 0.42.- M.p.: 74-76 °C (petrol-ethyl acetate).- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 3H, 7-CH_3), 1.05 (s, 3H, 7-CH_3), 1.14-1.23 (ddd, 1H) and 1.47-1.55 (ddd, 1H) and 1.64-1.90 (m, 6H) (Σ = 8H, CH_2-3, 4-H, CH_2-5, CH_2-6, OH), 1.96-1.99 (dd, 3H, 3'-CH_3), 2.75 and 2.93 (AB system, 2H, CH_2-10), 3.83-3.89 (dd, 1H, 2-H), 6.00-6.04 (dq, 1H, 5'-H), 6.95-6 99 (dq, 1H, 4'-H), $J_{2,3}$= 8.5 Hz, $J_{2,3*}$= 4.0 Hz, $J_{10,10*}$= 11.0 Hz, $J_{4',3'\text{-}CH3}$= $J_{5',3'\text{-}CH3}$= $J_{4',5'}$= 1.5 Hz.- IR ($CHCl_3$): 3700 - 3400, 1760 cm^{-1}.- MS: m/z (%) = 282 (M^+, 3), 264 (6), 181 (16), 130 (47), 98 (43), 97 (100), 41 (51).- CD (c 0.776 mmol/L, acetonitrile): λ_{max} (Δε) = 269.8 (-0.92), 243.8 (-1.94), 212.6 nm (-13.26).- $C_{15}H_{22}O_3S$ (282.4), calcd: C 63.80 H 7.85, found: C 63.95 H 7.88.

CH_3I / DBU-promoted reaction of 16a and *rac*-12

Iodomethane (3.2 µL, 0.05 mmol) was added at 0 °C to a solution of **16a** (13.0 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 10 min at 0 °C a solution of *rac*-**12** (7.2 mg, 0.05 mmol) and DBU (7.8 µL, 0.05 mmol), which was stirred for 20 min at 20 °C, was added to the reaction mixture. The reaction mixture was stirred 5 h at 0 °C and 4 d at 20 °C. Again iodomethane (3.2 µL, 0.05 mmol) and DBU (7.8 µL, 0.05 mmol) were added and the mixture was stirred for 7 d. Quenching with sat. aq. $NaHCO_3$, usual work-up (CH_2Cl_2), and LC (petrol-ethyl acetate 4:1) gave a mixture of **16a** and **16b** (10.8 mg, 82 %) and *rac*-**17** (3.1 mg, 43 %). When the same experiment was carried out in the absence of DBU no reaction could be observed.

(*E*)-3-Methoxymethylene-(3a*r*,6a*c*)-3,3a,4,6a-tetrahydro-cyclopenta[*b*]furan-2-one (*rac*-17)
^{1}H NMR (80 MHz, $CDCl_3$): δ = 2.45-2.81 (m, 2H, CH_2-4), 3.40-4.01 (m, 4H, containing: 3.86 (s, 3H, OCH_3), 3a-H), 5.36-5.60 (d, 1H, 6a-H), 5.74-5.90, 5.90-6.10 (2*m, 2*1H, 6-H, 5-H), 7.21-7.25 (m, 1H, CHO).- IR ($CHCl_3$): 2860, 1740, 1670 cm^{-1}.- MS: m/z (%) = 166 (M^+, 44), 137 (100), 77 (67), 39 (65).- HRMS calcd for $C_9H_{10}O_3$: 166.0630, found: 166.0634.

Methyl trifluoromethanesulfonate-promoted reaction of 16b and *rac*-12
A solution of *rac*-**12** (7.4 mg, 0.05 mmol) in diethyl ether (1.0 mL) was stirred with 4 Å molecular sieves at 20 °C for 15 min. **16b** (14.0 mg, 0.05 mmol) dissolved in diethyl ether (2.0 mL) and methyl trifluoromethanesulfonate (27.0 µL, 0.25 mmol) were added. After 29 h only **16b**, *rac*-**12** and traces of *rac*-**17** could be detected by TLC.

Methanesulfenyl trifluoromethanesulfonate-promoted reaction of 16a with *rac*-12
A solution of bromine (160.6 mg, 1.01 mmol) in CH_2Cl_2 (2.0 mL) and dimethyl disulfide (90 µL, 1.00 mmol) was stirred at 20 °C for 20 h. This solution of methanesulfenyl bromide (MSB, c. 1 mol/L) was used for the reaction described below.- To a mixture of **16a** (82.8 mg, 0.29 mmol), 4 Å molecular sieves (c. 400 mg), and CH_2Cl_2 (4.0 mL), a solution of *rac*-**12** (45.6 mg, 0.30 mmol) in CH_2Cl_2 (4.0 mL) was added at 20 °C. After stirring at 20 °C for 30 min, silver triflate (105.5 mg, 0.41 mmol), CH_2Cl_2 (4.0 mL), and (very slowly) the MSB solution (350 µL, c. 0.35 mmol) were added. The reaction mixture was stirred at 20 °C for 2 h. Quenching with triethylamine, filtration, washing the organic phase with sat. aq. $NaHCO_3$ and water, drying, solvent evaporation, and LC (petrol-ethyl acetate 15:1), followed by MPLC ($CHCl_3$-acetone 200:3), then MPLC (petrol-acetone 6:1) yielded **19a** (6.5 mg, 7 %) and **19b** (11.8 mg, 12 %), as well as **20a** (7.3 mg, 6 %), **20b** (7.5 mg, 6 %), **20c** (5.0 mg, 4 %) and **20d** (6.5 mg, 5 %).

(*R*)-5-{7,7-Dimethyl-(1*S*)-methyldisulfanylmethyl-bicyclo[2.2.1]hept-2*exo*-yloxy}-3-methyl-5*H*-furan-2-one (19a)
R_f (petrol-ethyl acetate 3:1): 0.41.- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3H, 7-CH_3), 1.00 (s, 3H, 7-CH_3), 0.97-1.10 (m, 1H) and 1.20-1.33 (m, 2H) and 1.62-1.80 (m, 3H) and 1.86-1.97 (m, 1H) (Σ = 7H, CH_2-3, 4-H, CH_2-5, CH_2-6), 1.93-1.97 (dd, 3H, 3'-CH_3), 2.38 (s, 3H, $SSCH_3$), 2.71 and 3.16 (AB system, 2H, CH_2-10), 3.88-3.94 (dd, 1H, 2-H), 5.87-5.92 (dq, 1H, 5'-H), 6.80-6.84 (dq, 1H, 4'-H), $J_{2,3}$= 3.5 Hz, $J_{2,3*}$= 7.5 Hz, $J_{10,10*}$= 12.0 Hz, $J_{4',3'\text{-}CH3}$= $J_{5',3'\text{-}CH3}$= $J_{4',5'}$= 1.5 Hz.- IR ($CHCl_3$): 1760 cm^{-1}.- MS: m/z (%) = 328 (M^+, 5), 215 (6), 135 (10), 97 (100), 41 (20).- CD (c 0.872 mmol/L, acetonitrile): λ_{max} (Δε) = 246.4 (-2.39), 205.4 nm (8.21).- HRMS calcd for $C_{16}H_{24}O_3S_2$: 328.1167, found: 328.1167.

(*S*)-5-{7,7-Dimethyl-(1*S*)-methyldisulfanylmethyl-bicyclo[2.2.1]hept-2*exo*-yloxy}-3-methyl-5*H*-furan-2-one (19b)
R_f (petrol-ethyl acetate 3:1): 0.49.- M.p.: 106-108 °C (petrol).- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (s, 3H, 7-CH_3), 0.94 (s, 3H, 7-CH_3), 1.03-1.14 (m, 1H) and 1.27-1.37 (m, 1H) and 1.58-1.77 (m, 3H) and 1.77-1.86 (dd, 1H) and 1.96-2.05 (m, 1H) (Σ = 7H, CH_2-3, 4-H, CH_2-5, CH_2-6), 1.90-1.96 (dd, 3H, 3'-CH_3), 2.44 (s, 3H, $SSCH_3$), 2.76 and 3.13 (AB system, 2H, CH_2-10), 3.83-3.91 (dd, 1H, 2-H), 5.80-5.86 (dq, 1H, 5'-H), 6.75-6.80 (dq, 1H, 4'-H), $J_{2,3}$= 3.5 Hz, $J_{2,3*}$= 8.0 Hz, $J_{10,10*}$= 12.0 Hz, $J_{4',3'\text{-}CH3}$= $J_{5',3'\text{-}CH3}$= $J_{4',5'}$= 1.5 Hz.- IR ($CHCl_3$): 1760 cm^{-1}.- MS: m/z (%) = 328 (M^+, 6), 135 (10), 97 (100), 40 (24).- CD (c 0.229 mmol/L, acetonitrile): λ_{max} (Δε) = 247 (7.0), 209 nm (-29.6).- $C_{16}H_{24}O_3S_2$ (328.5), calcd: C 58.50 H 7.36, found: C 58.57 H 7.24.

(3aΞ,*E*)-3-{(1*S*)-7,7-Dimethyl-1-((2Ξ)-4-methyl-5-oxo-2,5-dihydro-furan-2-ylsulfanylmethyl)-bicyclo[2.2.1]hept-2-yloxymethylene}-(3a*r*,6a*c*)-3,3a,4,6a-tetrahydro-cyclopenta[*b*]furan-2-one (20a)
R_f ($CHCl_3$-acetone 200:3 (3*developed)): 0.27.- ^1H NMR (400 MHz, $CDCl_3$, NOE): δ = 0.89 (s, 3H, 7-CH_3^B), 1.04 (s, 3H, 7-CH_3^B), 1.05-1.15 (m, 1H) and 1.20-1.34 (m, 2H) and 1.56-1.66 (m, 1H) and 1.70-1.80 (m, 1H) and 1.80-1.90 (m, 2H) (Σ = 7H, CH_2-3^B, 4-H^B, CH_2-5^B, CH_2-6^B), 1.90-1.97 (dd, 3H, 4-CH_3^A), 2.44-2.53 (m, 1H, 4-H^C), 2.76 and 2.94 (AB system, 2H, CH_2-10^B), 2.76-2.87 (m, 1H, 4-H^{*C}), 3.60-3.68 (m, 1H, 3a-H^C), 4.11-4.18 (dd, 1H, 2-H^B), 5.47-5.53 (m, 1H, 6a-H^C), 5.72-5.76 (dq, 1H, 2-H^A), 5.82-5.88 (m, 1H, 5-H^C), 6.02-6.08 (m, 1H, 6-H^C), 6.98-7.02 (dq, 1H, 3-H^A), 7.50-7.55 (d, 1H, CHO^C), A: $J_{2,3}$= $J_{2,4\text{-}CH3}$= $J_{3,4\text{-}CH3}$= 1.5 Hz, B: $J_{2,3}$= 3.0 Hz, $J_{2,3*}$= 8.0 Hz, $J_{10,10*}$= 11.5 Hz, C: $J_{3a,4}$= 2.5 Hz, $J_{3a,4*}$= 9.0 Hz, $J_{3a,6a}$= 8.0 Hz, $J_{4,4*}$= 17.5 Hz, $J_{3a,CHO}$= 2.5 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 10.86 (4-CH_3^A), 20.19 (7-CH_3^B), 20.60 (7-CH_3^B), 27.01, 30.50, 31.44, 39.25, (C-3^B, C-4^B, C-6^B, C-8^B), 37.72 (C-3a^C), 38.75 (C-4^C), 45.38 (C-4^B), 48.58, 53.07 (C-1^B, C-7^B), 85.66 (C-2^B), 87.63 (C-6a^C), 90.12 (C-2^A), 108.24 (C-4^A), 129.23 (C-5^C), 132.11 (C-3^C), 137.17 (C-3^A), 145.44 (C-6^C), 156.43 (CHO^C), 172.80 (C=O), 173.16 (C=O).- IR ($CHCl_3$): 1760, 1730, 1660 cm^{-1}.- MS: m/z (%) = 416 (M^+, 0.7), 319 (8), 265 (60), 167 (42), 135 (26), 84 (36), 49 (43), 41 (42).- CD (c 0.459 mmol/L, acetonitrile): λ_{max} (Δε) = 243.4 (10.70), 210.4 nm (-25.56).- HRMS calcd for $C_{23}H_{28}O_5S$: 416.1657, found: 416.1656.

(3aΞ,*E*)-3-{(1*S*)-7,7-Dimethyl-1-((2Ξ)-4-methyl-5-oxo-2,5-dihydro-furan-2-ylsulfanylmethyl)-bicyclo[2.2.1]hept-2-yloxymethylene}-(3a*r*,6a*c*)-3,3a,4,6a-tetrahydro-cyclopenta[*b*]furan-2-one (20b)
R_f (petrol-THF 2:1 (2*developed)): 0.50.- ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 3H, 7-CH_3^B), 1.03 (s, 3H, 7-CH_3^B), 1.06-1.14 (m, 1H) and 1.21-1.33 (m, 2H) and 1.56-1.66 (m, 1H) and 1.69-1.80 (m, 1H) and 1.80-1.90 (m, 2H) (Σ = 7H, CH_2-3^B, 4-H^B, CH_2-5^B, CH_2-6^B), 1.90-1.98 (dd, 3H, 4-CH_3^A), 2.41-2.50 (m, 1H, 4-H^C), 2.74-2.81 (m, 1H, 4-H^{*C}), 2.81 and 2.86 (AB system, 2H, CH_2-10^B), 3.64-3.71 (dddd, 1H, 3a-H^C), 4.11-4.17 (dd, 1H, 2-H^B), 5.49-5.55 (m, 1H, 6a-H^C), 5.79-5.82 (dq, 1H, 2-H^A), 5.82-5.88 (m, 1H, 5-H^C), 5.99-6.04 (m, 1H, 6-H^C), 6.97-7.01 (dq, 1H, 3-H^A), 7.42-7.47 (d, 1H, CHO^C), A: $J_{2,3}$= $J_{2,4\text{-}CH3}$= $J_{3,4\text{-}CH3}$= 1.5 Hz, B: $J_{2,3}$= 3.5 Hz, $J_{2,3*}$= 8.0 Hz, $J_{10,10*}$= 12.0 Hz, C: $J_{3a,4}$= 2.5 Hz, $J_{3a,4*}$= 8.5 Hz, $J_{4,4*}$= 17.5 Hz, $J_{3a,6a}$= 8.5 Hz, $J_{3a,CHO}$= 2.5 Hz.- IR ($CHCl_3$): 1760, 1730, 1660, 1070 cm^{-1}.- MS: m/z (%) = 446 (<1, soiling), 416 (M^+, <1), 319 (4), 265 (47), 135 (31), 97 (100), 40 (44).- CD (c 0.443 mmol/L, acetonitrile): λ_{max} (Δε) = 243.4 (-5.59), 213.2 nm (-20.06).- HRMS calcd for $C_{23}H_{28}O_5S$: 416.1657, found: 416.1646.

(3aΞ,*E*)-3-{(1*S*)-7,7-Dimethyl-1-((2Ξ)-4-methyl-5-oxo-2,5-dihydro-furan-2-ylsulfanylmethyl)-bicyclo[2.2.1]hept-2-yloxymethylene}-(3a*r*,6a*c*)-3,3a,4,6a-tetrahydro-cyclopenta[*b*]furan-2-one (20c)
R_f (petrol-THF 2:1 (2*developed)): 0.46.- M.p.: 128-131 °C (petrol-ethyl acetate).- ^1H NMR (400 MHz, $CDCl_3$, NOE): δ = 0.90 (s, 3H, 7-CH_3^B), 1.02 (s, 3H, 7-CH_3^B), 1.06-1.15 (m, 1H) and 1.21-1.33 (m, 2H) and 1.60-1.70 (m, 1H) and 1.70-1.87 (m, 3H) (Σ = 7H, CH_2-3^B, 4-H^B, CH_2-5^B, CH_2-6^B), 1.87-1.92 (dd, 3H, CH_3-4^A), 2.40-2.48 (m, 1H, 4-H^C), 2.59 and 2.85 (AB system, 2H, CH_2-10^B), 2.76-2.87 (m, 1H, 4-H^{*C}), 3.57-3.66 (m, 1H, 3a-H^C), 4.05-4.12 (dd, 1H, 2-H^B), 5.46-5.52 (m, 1H, 6a-H^C), 5.83-5.88 (m, 1H, 5-H^C), 5.90-5.96 (dq, 1H, 2-H^A), 6.05-6.10 (m, 1H, 6-H^C), 6.93-6.97 (dq, 1H, 3-H^A), 7.36-7.40 (d, 1H, CHO^C), A: $J_{2,3}$= $J_{2,4\text{-}CH3}$= $J_{3,4\text{-}CH3}$= 1.5 Hz, B: $J_{2,3}$= 3.0 Hz, $J_{2,3*}$= 7.5 Hz, $J_{10,10*}$= 11.5 Hz, C: $J_{3a,4}$= 2.5 Hz, $J_{3a,4*}$= 9.0 Hz, $J_{3a,6a}$= 8.0 Hz, $J_{3a,CHO}$= 2.5 Hz, $J_{4,4*}$= 17.5 Hz.- IR ($CHCl_3$): 1760, 1730, 1660, 1070 cm^{-1}.- MS: m/z (%) = 416 (M^+, 0.8), 319 (6), 265 (20), 135 (30), 97 (100), 40 (43).- CD (c 0.443 mmol/L, acetonitrile): λ_{max} (Δε) = 245.4 (7.01), 198.6 nm (-4.30).- HRMS calcd for $C_{23}H_{28}O_5S$: 416.1657, found: 416.1658.

(3aΞ,*E*)-3-{(1*S*)-7,7-Dimethyl-1-((2Ξ)-4-methyl-5-oxo-2,5-dihydro-furan-2-ylsulfanylmethyl)-bicyclo[2.2.1]hept-2-yloxymethylene}-(3a*r*,6a*c*)-3,3a,4,6a-tetrahydro-cyclopenta[*b*]furan-2-one (20d)
R_f ($CHCl_3$-acetone 200:3 (3•developed)) = 0.18.- ^1H NMR (400 MHz, $CDCl_3$, NOE): δ = 0.89 (s, 3H, 7-CH_3^B), 1.03 (s, 3H, 7-CH_3^B), 1.05-1.15 (m, 1H) and 1.21-1.35 (m, 2H) and 1.60-1.70 (m, 1H) and 1.70-1.90 (m, 3H) (Σ = 7H, CH_2-3^B, 4-H^B, CH_2-5^B, CH_2-6^B), 1.92-1.96 (dd, 3H, 4-CH_3^A), 2.38-2.46 (m, 1H, 4-H^C), 2.65 and 2.99 (AB system, 2H, CH_2-10^B), 2.75-2.87 (m, 1H, 4-H*^{C}), 3.65-3.78 (m, 1H, 3a-H^C), 4.04-4.11 (dd, 1H, 2-H^B), 5.52-5.60 (m, 1H, 6a-H^C), 5.82-5.87 (m, 1H, 5-H^C), 5.90-5.95 (dq, 1H, 2-H^A), 5.98-6.04 (m, 1H, 6-H^C), 6.90-6.95 (dq, 1H, 3-H^A), 7.28-7.35 (d, 1H, CHO^C), A: $J_{2,3}$= $J_{2,4\text{-}CH3}$= $J_{3,4\text{-}CH3}$= 1.5 Hz, B: $J_{2,3}$= 3.5 Hz, $J_{2,3*}$= 7.5 Hz, $J_{10,10*}$= 11.5 Hz, C: $J_{3a,4}$= 2.5 Hz, $J_{3a,4*}$= 9.0 Hz, $J_{3a,6a}$= 8.0 Hz, $J_{3a,CHO}$= 2.5 Hz, $J_{4,4'}$= 17.5 Hz.- IR ($CHCl_3$): 1760, 1730, 1660, 1185, 1065 cm^{-1}.- MS: m/z (%) = 416 (M^+, 0.6), 319 (4), 265 (44), 135 (32), 97 (100), 41 (43).- CD (c 0.416 mmol/L, acetonitrile): λ_{max} (Δε) = 271.6 (0.74), 242.2 (-2.71), 197.4 nm (11.21).- HRMS calcd for $C_{23}H_{28}O_5S$: 416.1657, found: 416.1667.

Reaction of 16a and 16b with MSB and silver triflate
16b (31.7 mg, 0.11 mmol) and 4 Å molecular sieves (c. 100 mg) were stirred in CH_2Cl_2 (3.0 mL) for 1 h at 20 °C. Silver triflate (40.2 mg, 0.16 mmol) and (slowly) MSB (c. 2 mol/L solution in CH_2Cl_2) (67 µL, 0.13 mmol) were added. Quenching with triethylamine after 30 min, filtration, solvent evaporation, and LC (petrol-ethyl acetate 20:1) gave **19a** (1.4 mg, 4 %) and **19b** (5.1 mg, 14 %).
In a similar reaction **16a** (86.5 mg, 0.31 mmol) was converted into **19a** (6.9 mg, 7 %) and **19b** (16.6 mg, 17 %).

3-Methylsulfanyl-2-oxo-(3a*r*,6a*c*)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-3-carbaldehyde (*rac*-18)
Rac-**12** (60.6 mg, 0.40 mmol) and 4 Å molecular sieves (c. 100 mg) were stirred in $CDCl_3$ (2.8 mL) for 1 h at 20 °C. Silver triflate (143.3 mg, 0.56 mmol) and (slowly) MSB (c. 1 mol/L solution in $CDCl_3$) (480 µL, 0.48 mmol) were added. After 30 min ^1H NMR and IR spectra were taken.- ^1H NMR (80 MHz, $CDCl_3$): δ = 2.06-3.11 (m, 5H, CH_2-4, overlapping 2.42, s, 3H, SCH_3), 3.20-4.02 (m, 1H, 3a-H), 5.39-5.61 (m, 1H, 6a-H), 5.77-6.33 (m, 2H, 5-H, 6-H), 11.27-11.59 (s (broad), 1H, CHO). In addition, the following educt signals were observed: 7.04-7.11 (d, 0.1H, =CHOH (*rac*-**12**, *Z*-isomer)), 7.74-7.81 (d, 0.3H, =CHOH (*rac*-**12**, *E*-isomer).- IR ($CDCl_3$): 1770, 1730, 1705, 1670, 1615, 1605, 1255, 1170 cm^{-1}.

Benzeneselenyl triflate-promoted reaction of 16a with *rac*-12
Silver triflate (26.6 mg, 0.10 mmol) in CH_2Cl_2 (1.5 mL) was added to a mixture of phenylselenyl chloride (19.8 mg, 0.10 mmol) and 4 Å molecular sieves in CH_2Cl_2 (1.0 mL) at 0 °C. After 10 min **16a** (19.5 mg, 0.07 mmol) and *rac*-**12** (10.6 mg, 0.07 mmol) in CH_2Cl_2 (2.0 mL) were added and the reaction mixture was stirred for 4 h. TLC showed the formation of products **20a - 20d**.

DMTST-promoted reaction of 16b with *rac*-12
A solution of methyl triflate (220 µL, 2.00 mmol) and dimethyl disulfide (180 µL, 2.00 mmol) in CH_2Cl_2 (8.0 mL) was stirred for 48 h at 20 °C.- DMTST solution (c. 0.25 mol/L, 1.0 mL, c. 0.25 mmol DMTST) was added to a mixture of *rac*-**12** (8.1 mg, 0.05 mmol), **16b** (14.7 mg, 0.05 mmol), and 4 Å molecular sieves in CH_2Cl_2 (3.0 mL). After stirring for 4.5 h **20a - 20d** could be detected by TLC.

MCPBA oxidation of 16a and 16b to 16c and 16d

A solution of **16a** (50.3 mg, 0.18 mmol) and MCPBA (55 per cent, 56.1 mg, 0.17 mmol) in CH_2Cl_2 (1.6 mL) was stirred at -78 °C for 30 min. Quenching with sat. aq. $NaHCO_3$ and usual work-up (CH_2Cl_2) provided **16c** (51.9 mg, 98%). ^1H NMR (400 MHz, $CDCl_3$) indicated that **16c** was nearly pure.

In a similar reaction **16b** (29.0 mg, 0.10 mmol) was converted into **16d** (29.9 mg, 97 %) using MCPBA (55 per cent, 32.4 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL).

(*S*)-5-{(1*S*)-2*exo*-Hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethyl-(Ξ)-sulfinyl}-3-methyl-5*H*-furan-2-one (16c)

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 3H, 7-CH_3), 1.10 (s, 3H, 7-CH_3), 1.41-1.61 (m, 2H) and 1.66-1.86 (m, 5H) (Σ = 7H, CH_2-3, 4-H, CH_2-5, CH_2-6), 2.03-2.07 (dd, 3H, 3'-CH_3), 2.40 and 3.57 (AB system, 2H, CH_2-10), 3.11-3.30 (s (broad), 1H, OH), 3.91-3.99 (dd, 1H, 2-H), 5.63-5.68 (dq, 1H, 5'-H), 7.08-7.14 (dq, 1H, 4'-H), $J_{2,3}$= 8.0 Hz, $J_{2,3*}$= 4.0 Hz, $J_{10,10*}$= 8.0 Hz, $J_{4',3'\text{-}CH3}$= $J_{5',3'\text{-}CH3}$= $J_{4',5'}$= 1.5 Hz.- IR ($CHCl_3$): 3600 - 3300, 1775, 1075, 1050, 1030 cm^{-1}.- MS: m/z (%) = 181 (17), 135 (5), 109 (6), 97 (100), 69 (25), 41 (53), 39 (30).

(*R*)-5-{(1*S*)-2*exo*-Hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethyl-(Ξ)-sulfinyl}-3-methyl-5*H*-furan-2-one (16d)

M.p.: 113-115 °C (petrol-ethyl acetate).- ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 3H, 7-CH_3), 1.12 (s, 3H, 7-CH_3), 1.41-1.49 (m, 1H) and 1.53-1.64 (m, 1H) and 1.70-1.88 (m, 6H) (Σ = 8H, CH_2-3, 4-H, CH_2-5, CH_2-6, OH), 2.01-2.07 (dd, 3H, 3'-CH_3), 2.85 and 3.42 (AB system, 2H, CH_2-10), 3.95-4.00 (dd, 1H, 2-H), 5.45-5.50 (dq, 1H, 5'-H), 7.40-7.46 (dq, 1H, 4'-H), $J_{2,3}$= 8.0 Hz, $J_{2,3*}$= 4.0 Hz, $J_{10,10*}$= 13.0 Hz, $J_{4',3'\text{-}CH3}$= $J_{5',3'\text{-}CH3}$= $J_{4',5'}$= 1.5 Hz.- IR ($CHCl_3$): 3600 - 3300, 1780, 1080 cm^{-1}.- MS: m/z (%) = 299 (M^+, 0.2), 184 (30), 135 (53), 109 (46), 98 (75), 97 (100), 41 (83).- $C_{15}H_{22}O_4S$ (298.4), (mixture of **16c** and **16d**) calcd: C 60.38 H 7.43, found: C 60.39 H 7.52.

Potassium peroxomonosulfate oxidation of 16a

A solution of Oxone® (Aldrich, 28.5 mg, 0.05 mmol, about 0.09 mmol $KHSO_5$) in water (0.3 mL) was slowly added at 0 °C to a solution of **16a** (20.1 mg, 0.07 mmol) in methanol (0.3 mL) . After stirring for 2 min the reaction was quenched with conc. $NaHSO_3$ (1.0 mL). Usual work-up (CH_2Cl_2) and LC (petrol-ethyl acetate 1:1) gave a mixture of stereoisomeric sulfoxides (see text, 12.8 mg, 60 %).- ^1H NMR (80 MHz, $CDCl_3$) (crude product): δ = 0.78-1.97 (m, 13H, CH_2-3, 4-H, CH_2-5, CH_2-6, 2*7-H), 1.97-2.10 (2*dd, 1H, 2*3'-CH_3), 2.39 and 3.53 / 2.64 and 3.57 (2*AB system, 2H, CH_2-10), 3.82-4.10 (m, 1H, 2-H), 5.56-5.70 (2*dq, 1H, 2*5'-H), 7.03-7.17 and 7.30-7.40 (2*dq, 1H, 2*4'-H).

Reaction of 16c and *rac*-12 with trifluoromethanesulfonic anhydride and 2,6-lutidine

16c (31.4 mg, 0.11 mmol) dissolved in toluene (0.5 mL), 2,6-lutidine (9.2 µL, 0.08 mmol) and *rac*-**12** (7.9 mg, 0.05 mmol) dissolved in toluene (1.0 mL) were added to a -78 °C cold solution of trifluoromethanesulfonic anhydride (17.5 µL, 0.11 mmol) in toluene (0.7 mL). TLC showed slow formation of the triflate of *rac*-**12** (see formula **15c** in ref.[24]) and of polar products.

(*S*)- and (*R*)-5-{(1*S*)-2*exo*-Hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethylsulfonyl}-3-methyl-5*H*-furan-2-one (16e and 16f)

A solution of Oxone® (Aldrich, 170.1 mg, 0.28 mmol, 0.55 mmol $KHSO_5$) in water (0.7 mL) was added to a 0 °C cold solution of **16b** (52.0 mg, 0.18 mmol) in methanol (0.7 mL). The reaction mixture was stirred at 0 °C

for 1 h and at 20 °C for 6 h. Usual work-up (CH_2Cl_2) and LC (petrol-ethyl acetate 3:1) gave a c. 1:1-mixture of **16e** and **16f** (47.6 mg, 82 %).- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3H, 7-CH_3), 1.17 (s, 3H, 7-CH_3), 1.10-1.19 (m, 1H) and 1.50-1.57 (m, 1H) and 1.72-1.90 (m, 6H) (Σ = 8H, CH_2-3, 4-H, CH_2-5, CH_2-6, OH), 2.02-2.09 (dd, 3H, 3'-CH_3), 2.97 and 3.66 (AB system, 1H, CH_2-10 (a)), 3.14 and 3.48 (AB system, 1H, CH_2-10 (b)), 4.05-4.11 and 4.12-4.17 (2*dd, 1H, 2-H), 5.70-5.77 (2*dq, 1H, 5'-H), 7.13-7.20 (2*dq, 1H, 4'-H), $J_{2,3}$= 8.0 Hz, $J_{2,3*}$= 4.0 Hz, $J_{10,10*}$= 13.5 Hz (a), $J_{10,10*}$= 13.0 Hz (b), $J_{4',3'\text{-}CH3}$= $J_{5',3'\text{-}CH3}$= $J_{4',5'}$= 1.5 Hz.- IR ($CHCl_3$): 3600 - 3500, 1785, 1325, 1140 cm^{-1}.- MS: m/z (%) = 153 (27), 135 (34), 109 (62), 98 (100), 97 (65), 93 (30), 69 (28), 40 (62).- $C_{15}H_{22}O_5S$ (314.4), (mixture of **16e** and **16f**) calcd: C 57.30 H 7.05, found: C 57.32 H 7.14.

Reaction of 16e / 16f and *rac*-12 with $MgBr_2$*Et_2O and $NaHCO_3$

A mixture of **16e** and **16f** (26.2 mg, 0.08 mmol), *rac*-**12** (25.6 mg, 0.17 mmol), $MgBr_2$*Et_2O (44.0 mg, 0.17 mmol) and $NaHCO_3$ (7.3 mg, 0.09 mmol) in THF (2.0 mL) was stirred for 6.5 h at 20 °C. Then the reaction mixture was stirred for 17.5 h with sonification and then for 6 d at 50 °C. During the whole reaction time only starting materials could be detected by TLC.

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