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Asymmetric Synthesis of a D-ring synthon for Strigol Analogues and its Application to the Synthesis of all Four Stereoisomers of Germination Stimulant GR7

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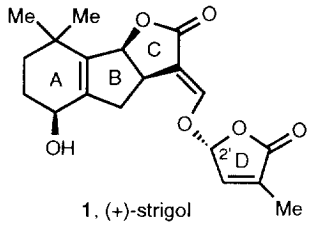
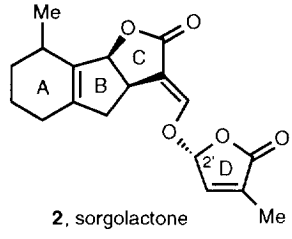
Abstract: A novel asymmetric synthesis of the strigol analogue GR7 has been developed. The olefinic double bond of the butenolide D-ring was protected as a Diels-Alder adduct with cyclopentadiene. The thus obtained tricyclic compound was resolved and transformed into a suitable D-ring synthon. The coupling reaction with the GR7-precursor, hydroxymethylenolactone proceeded with complete stereocontrol. Cycloreversion under relatively mild conditions gave GR7 in an optically pure form.

Introduction

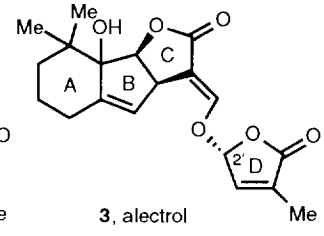
Parasitic weeds of the genera *Striga*, *Alectra*, and *Orobanche* cause severe damage to graminaceous and leguminous crops in tropical and semitropical areas of the eastern hemisphere[1,2]. Germination of the seeds of these parasitic weeds is triggered by a chemical species exuded by roots of a suitable host plant. (+)-Strigol **1** was the first isolated naturally occurring germination stimulant from the root exudate of the false host cotton (*Gossypium hirsutum* L.) and its structure was elucidated by Cook[3]. The absolute configuration was unambigously determined by Brooks several years later[4]. Only very recently strigol has also been found in the root exudates of *Striga* host plants[5].



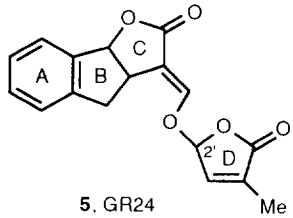
1, (+)-strigol



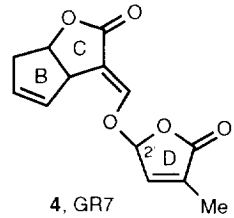
2, sorgolactone



3, alectrol



5, GR24



4, GR7

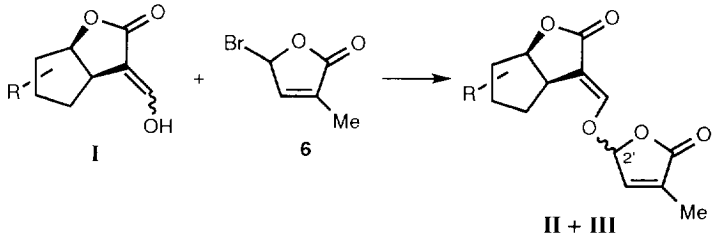
Some structures closely related to strigol (sorgolactone **2** and alectrol **3**) have been proposed to occur in the root exudates of *Sorghum bicolor* and *Vigna unguiculata*, which are hosts for *Striga* and *Alectra* species, respectively[6,7].

An attractive way for parasitic weed control is to use these germinating agents as herbicides in the absence of suitable host plants (concept of suicidal germination)[8]. However, these naturally occurring germination stimulants are not suitable for this purpose, due to their complicated structures and to their intrinsic lability in alkaline soils. Inspired by the work of Johnson[9] and Pepperman[10] we have synthesized several structurally simpler analogues of (+)-strigol with the aim to overcome these problems and to retain the biological activity[11,12,13,14]. Highly potent strigol analogues are compounds **4** and **5**, commonly known as GR7 and GR24, respectively[9].

Thus far, relatively scarce attention has been paid to the influence of the stereochemistry on the activity of strigol analogues. This is mainly due to the fact that no general method is known toward the synthesis of homochiral strigol analogues. Optically active strigol has been obtained by resolution of racemic strigol[15], resolution of the ABC-part of strigol[4,16,17], and by asymmetric synthesis (chiral pool approach)[18]. Recently, we synthesized all four stereoisomers of GR7 starting from commercially available enantiopure Corey's lactone[19], and of GR24 , which were synthesized by chromatographic resolution of the tricyclic ABC-moiety on cellulose triacetate. From appropiate bioassays we concluded that the stereochemistry at C-2' is more important, with respect to germination stimulant activity, than the configuration at the other stereogenic centers[19,20]. This finding was confirmed by Welzel in a study in which the seeds of *Orobanche crenata* were treated with all stereoisomers of strigol[21].

Thus far, homochiral strigol and some analogues have been obtained starting from an enantiopure ABC-precursor **I**, which upon coupling with bromobutenolide **6** and separation of the thus obtained diastereomers, affords the corresponding homochiral strigol analogues **II** and **III** (scheme 1).

Scheme 1



It should be more beneficial to control the stereochemistry at C-2' for the following reasons:

i The germination activity is highly sensitive to structural modifications in the D-ring[22]. This means that the D-ring is a common structural feature in strigol analogues.

ii The configuration at C-2' is essential for a high biological activity (*vide supra*).

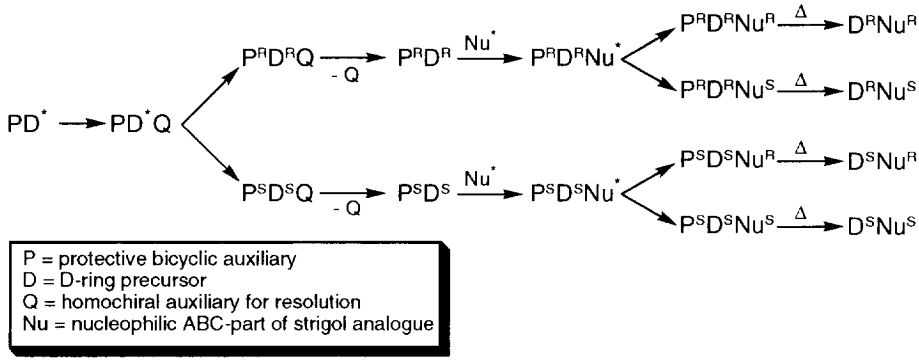
iii Control of the stereochemistry at C-2' will enable the synthesis of homochiral strigol analogues, which are achiral in the ABC-part.

In this paper we present a novel, versatile synthetic route to homochiral strigol analogues with complete stereocontrol at C-2'.

Results and discussion

In order to achieve stereocontrol at C-2' it is essential to protect the double bond in **6**. While our investigations were in progress, Welzel[23] published a strategy, involving a phenylthio group as double bond protection and to control stereoselective bond formation at C-2'. However, this method is rather laborious and needs considerable improvement. Conceptually, our approach is outlined in figure 1.

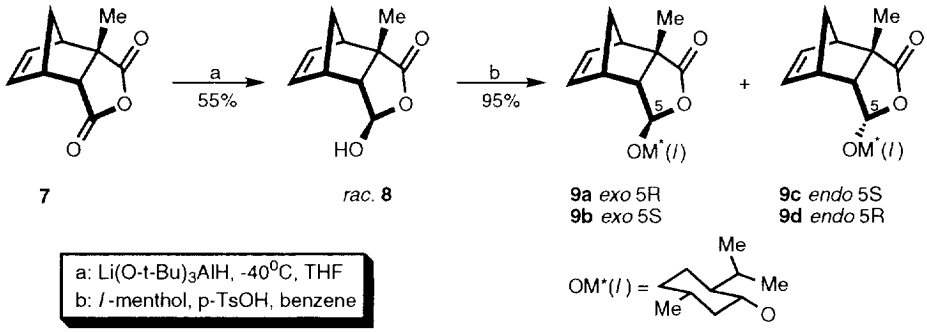
Figure 1



Protection of the double bond of the D-ring as a Diels-Alder adduct gives racemic PD*, which is subsequently resolved by an enantiopure auxiliary Q. A suitable racemic ABC-synthon of a strigol analogue is coupled to the thus obtained enantiomers of PD. Separation of the diastereomers, followed by removal of the auxiliary P affords all possible stereoisomers of the strigol analogue.

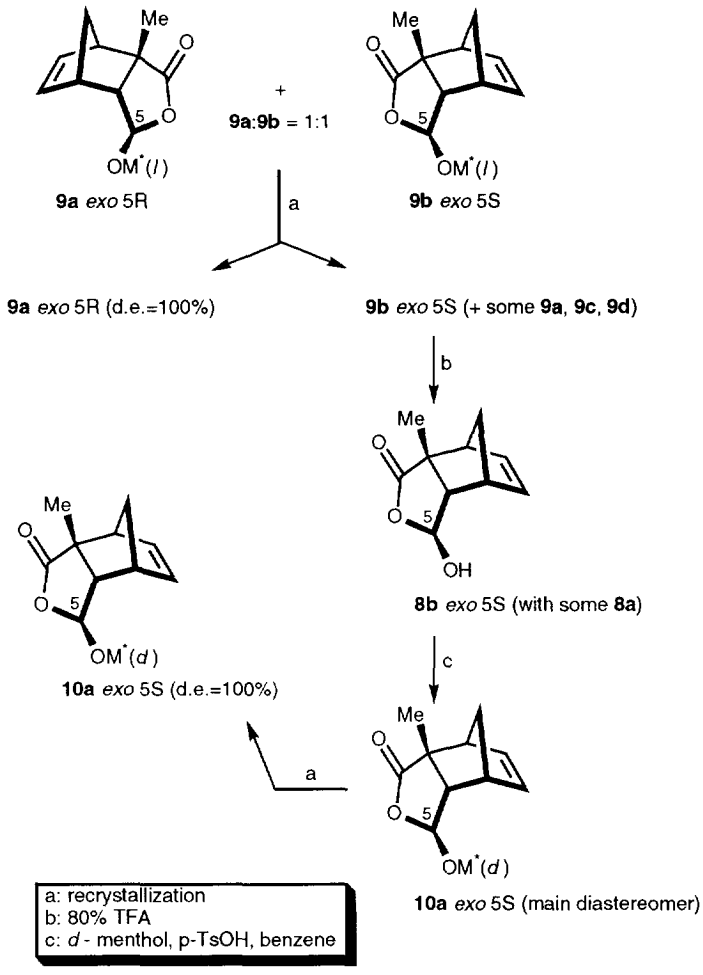
As is depicted in scheme 2 we started with the Diels-Alder adduct of citraconic anhydride and cyclopentadiene **7**, which we used already in the synthesis of the racemic butenolide **6**.[24]

Scheme 2



Partial reduction employing $Li(O\text{-}t\text{-}Bu)_3AlH$ gave hydroxy lactone *rac.* **8**.[25] At this stage it is appropiate to perform the resolution. Treatment of *rac.* **8** with *l*-menthol in the presence of a catalytic amount of *p*-TsOH under azeotropic conditions for 18 h gave a mixture of *exo* 5R-, *exo* 5S-, *endo* 5R-, and *endo* 5S-*l*-menthyloxy lactones in a ratio of 44:44:6:6. If the reaction was stopped after 4 h the product distribution of **9(a+b)**:**9(c+d)**:**8** amounted to 52:24:22, suggesting that the initially formed isomers **9(c+d)** (kinetic products) epimerize under the reaction conditions to the thermodynamically isomers **9(a+b)**. The product distribution could unambigously be determined by an ^{1}H-NMR analysis. The *exo*/*endo* assignments were made on the basis of chemical shifts and coupling constants, The acetal proton H_5 of the *endo* isomers **9(c+d)** exhibited a doublet (^3J = 6.7 Hz) at ca. 0.7 ppm lower field as compared to the corresponding *exo* isomers **9(a+b)** (^3J = 1.2 Hz). The coupling constants were verified by MM-2 calculations and are in complete agreement with those reported for similar systems[26]. Diastereoisomer **9a** has already been synthesized by Feringa[27] via a different route, although no analytical data were reported. Without any further purification diastereomer **9a** could be crystallized selectively from the crude reaction mixture (from *n*-hexane, 100% d.e., 28% yield). It was not possible to obtain more of this diastereoisomer in a pure form by repeated crystallization of the

Scheme 3



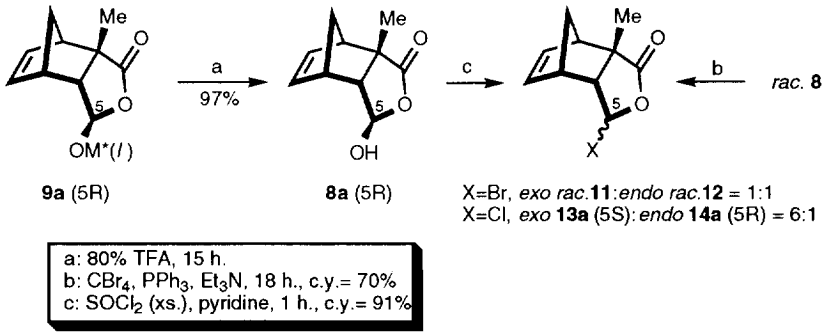
residue. Therefore, the starting hydroxy lactone **8** (enantiomerically enriched) was recovered and treated as is outlined in scheme 3.

The residue, containing mainly **9b** and smaller amounts of **9a**,**9c**, and **9d** was hydrolyzed in 80% TFA to give **8b** (enantiopurity Y 69%), which could readily be purified by a quick filtration on silica. Subsequent treatment with *d*-menthol under azeotropic conditions gave **10a** as the main stereoisomer, which is the enantiomer of **9a** and could thus again readily be crystallized from the crude mixture (24% yield, 100% d.e.). This procedure is easy to perform and can be accomplished without significant loss of material.

With both enantiopure menthyloxy lactones **9a** and **10a** in hand, these were transformed into suitable synthons for coupling reactions with strigol precursors of type I (scheme 1). The chiral auxiliary *l*-menthol was readily removed by hydrolysis in 80% TFA leading to enantiopure hydroxy lactone **8a** (scheme 4). In order to transform the hydroxyl function into a halogen atom, some test experiments were performed starting from rac. **8**. Bromination under S_N2 conditions (CBr_4, PPh_3, Et_3N) of racemic **8** gave after 18h a mixture of two isomeric products (*exo*-**11** and *endo*-**12**) in a ratio 1:1. Careful TLC analysis revealed that initially *endo*-**12** was formed as the kinetic product, which slowly epimerized to *exo*-**11**. Unfortunately, *exo*-**11** and *endo*-**12** are unstable and, in addition, they did not give satisfactory results in the coupling reactions. Therefore, the

synthesis of the corresponding chloro lactone **13a** was undertaken. Treatment of enantiopure **8a** with excess $SOCl_2$ in the presence of 1 equivalent of pyridine smoothly gave both epimers *exo*-**13a** and *endo*-**14a** in a ratio of 6:1 in almost quantitative yield. Again, *endo*/*exo* assignments were made on the basis of coupling constant (1.0 vs. 7.0 Hz) and the difference in chemical shift. By column chromatography enantiopure *exo*-**13a** was obtained.

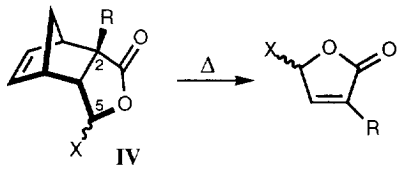
Scheme 4



The coupling reaction of *exo*-**13a** with the GR7 precursor, rac. hydroxymethylenolactone **15**[19], gave two diastereomeric adducts **16a** and **16b** in the expected ratio of 1:1 with complete *exo* selectivity (scheme 5). It should be noted that the R/S-assignment in **13a** and **16** has changed, due to the priority rules. Starting from *exo*-**13b**, the corresponding enantiomers **16c** and **16d** could be synthesized in the same manner.

Finally, the cycloreversion step was investigated. In the literature only three reports are known in which a system of type IV, having an alkyl substituent at C-2, is subjected to a retro Diels-Alder reaction (scheme 6):

Scheme 6



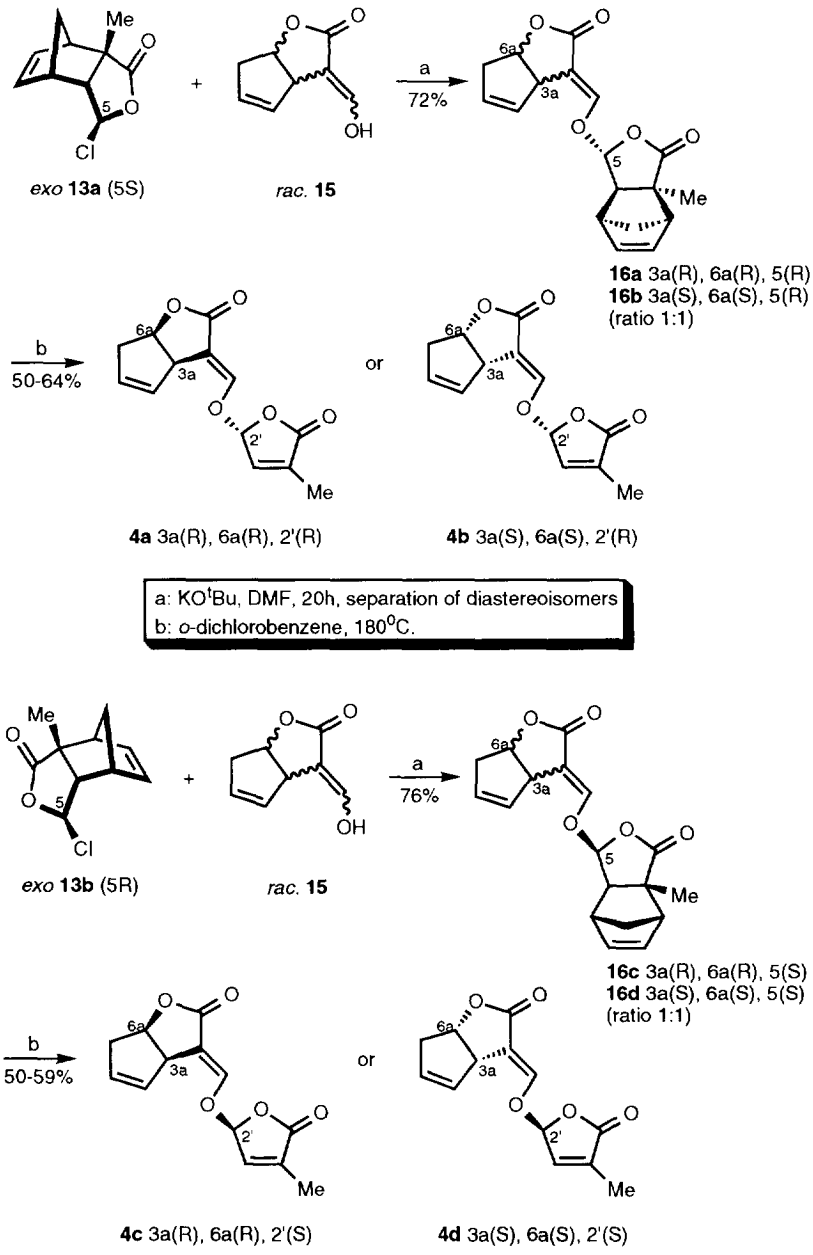
IV

The reaction conditions are either heating at 240^{0}C-285^{0}C for several days in a sealed tube[28] or thermolysis under flash vacuum conditions (short contact time) at 300^{0}C-330^{0}C[29] or at 500^{0}C (X = H)[24].

In order to prevent epimerization at C-2' in **4** during the thermolysis, the reaction should be carried out under mild conditions. This could be accomplished by heating the Diels-Alder adducts **16a**, **16b** and **16c**, **16d** in *o*-dichlorobenzene at 180^{0}C for 15h (scheme 5). Under these conditions the cycloreversion occurred without significant epimerization in yields of 50-64%. In this manner the 4 diastereomers of GR7, *viz* **4a**, **4b**, **4c** & **4d** were obtained in enantiopure form. The physical data are in complete agreement with those previously reported[19]. It is noteworthy that heating of the *l*-menthyloxy lactone **9a** under the same conditions led to the corresponding butenolide, which was completely epimerized at C-5.

In conclusion, a highly efficient route with excellent stereocontrol is developed for the synthesis of all stereoisomers of the synthetic strigol analogue GR7. This method can easily be extended to the asymmetric synthesis of other strigol analogues. This topic, along with the optimalization of the cycloreversion step is under active investigation in our laboratory.

Scheme 5


Me
O
O
5
O
Cl
exo 13a (5S)
+
O
O
OH
rac. 15
a
72%
6a
3a
O
O
O
5
Me
16a 3a(R), 6a(R), 5(R)
16b 3a(S), 6a(S), 5(R)
(ratio 1:1)
b
50-64%
or
2'
Me
4a 3a(R), 6a(R), 2'(R)
4b 3a(S), 6a(S), 2'(R)
a: KO^{t}Bu, DMF, 20h, separation of diastereoisomers
b: o-dichlorobenzene, 180^{0}C.
exo 13b (5R)
76%
16c 3a(R), 6a(R), 5(S)
16d 3a(S), 6a(S), 5(S)
(ratio 1:1)
50-59%
4c 3a(R), 6a(R), 2'(S)
4d 3a(S), 6a(S), 2'(S)

Experimental section

General remarks

100 MHz ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer (Me_4Si as internal standard) and 400 MHz ^{1}H-NMR spectra were recorded on a Bruker AM-400 spectrometer (Me_4Si as internal standard). All coupling constants are given as ^3J in Hz, unless indicated otherwise. For mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS spectra were run on a Varian Saturn 2 GC-MS ion-trap system. Separation was carried out on a fused-silica capillary column (DB-5, 30m x 0.25 mm). Helium was used as carrier gas, and electron impact (EI) was used as ionization mode.

GLC was conducted with a Hewlet-Packard HP 5890 gas chromatograph, using a capillary column (25m) of HP-1, and nitrogen (2 ml/min, 0.5 atm) as the carrier gas. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed at the Department of Micro-analysis of this laboratory.

Solvents were dried using the following methods: Dimethylformamide (DMF) P.A. was dried on 4-A molecular sieves. Dichloromethane was distilled from P_2O_5. Diethyl ether was distilled from NaH. Hexane was distilled from CaH_2. Ethyl acetate was distilled from K_2CO_3. Trifluoroacetic acid (TFA) was used as an 80% (v/v) aqueous solution. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F254 plates (0.25 mm) using the eluents indicated. Spots were visualized with UV or using a molybdate spray. "Flash" chromatography was carried out at a pressure of *ca.* 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was carried out, using Merck Kieselgel 60.

*5(R)-[2(S)-Isopropyl-5(R)-methyl-(R)-cyclohexyloxy]-2(S)-methyl-4-oxa-*endo *tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (9a) and its enantiomer (10a)*

Rac. *exo*-hydroxy tricyclic lactone **8**[25] (7.60 g, 42.2.mmol) and *l*-menthol (7.90 g, 50.7 mmol) were dissolved in benzene (125 mL) containing 0.05 eq. *p*-TsOH (401 mg, 2.11 mmol). The mixture was heated under reflux for 18h, using a Dean-Stark trap. After evaporation of the solvent, the residue was dissolved in a mixture of saturated $NaHCO_3$ and ethyl acetate. Extraction with ethyl acetate (2x), washing the combined organic layers with brine, and drying ($MgSO_4$) provided crude product in quantitative yield. Based on ^{1}H-NMR analysis the product consisted of a mixture of 4 diastereomers **9a-d** in a ratio 44:44:6:6. The crude mixture was crystallized from *n*-hexane to give pure **9a** (3.72 g, 28%) as colorless needles. Mp 131.5-132.5 ^{0}C; $[\alpha]_D$ -147^0 (c 0.40, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$. 100 MHz): δ 0.72-1.02 (m, 12H), 1.20 (m, 3H), 1.52 (s, 3H), 1.64 (m, 3H), 2.01-2.18 (m, 2H), 2.45 (dd, J = 0.9, 4.1 Hz, 1H), 2.82 (m, 1H), 3.10 (m, 1H), 3.48 (dt, J = 4.2, 10.5 Hz, 1H), 5.02 (d, J = 0.9 Hz, 1H), 6.21 (m, 2H); GC-MS (EI, m/z, rel. int. (%)): 319 (M^++1, 1.6), 253 (1.8), 181 (100), 163 (17.4), 115 (20.3), 91 (10.3), 66 (41.3); Analysis calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.55; H, 9.11).

The mother liquor (9.73 g) was dissolved in 80% TFA (30 mL) and stirred for 18 h at room temperature. After evaporation of the solvent under reduced pressure the crude product, containing hydroxy tricyclo lactone **8** (enantiopurity Y 69%) was purified by chromatography (SiO_2, hexane / ethyl acetate 9:1) to remove the apolar by-products *l*-menthol and *l*-menthyl trifluoroacetate. The product was then quickly eluted from the column (hexane / ethyl acetate 1:1) to give **8** as a solid (4.00 g, 73%). Without further purification **8** was treated with *d*-menthol under the same conditions as described for the preparation of **9a**. Yield of **10a** (d.e.> 98%) after crystallization from *n*-hexane 3.29 g, 24% (calculated from starting rac. alcohol **8**). Mp 131-132.5 ^{0}C; $[\alpha]_D$ +148^0 (c 0.38, CH_2Cl_2); Analysis calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.35; H, 9.67. ^{1}H-NMR and mass data were the same as for compound **9a**.

*5(R)-Hydroxy-2(S)-methyl-4-oxa-*endo *tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (8a)*

Enantiopure *l*-menthyloxy lactone **9a** (3.65 g, 11.5 mmol) was dissolved in 80% (v/v) TFA (50 mL) and stirred for 18h at room temperature. After evaporation of the solvent under reduced pressure the crude product was purified by chromatography (SiO_2, hexane / ethyl acetate 9:1) to remove the apolar by-products *l*-menthol and *l*-menthyl trifluoroacetate. The product was then quickly eluted from the column (hexane / ethyl acetate 1:1) to give **8a** as a solid (1.99 g, 97%), which was sufficiently pure for further reactions. An analytical sample was obtained by recrystallization from hexane/ethyl acetate. Mp 180-182^{0}C; $[\alpha]_D$ +21.7^0 (c 0.42, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$. 100 MHz): δ 1.55 (s, 3H), 1.66 (m, 2H), 2.52 (dd, J = 1.2, 4.1 Hz, 1H),

2.82 (m, 1H), 3.14 (m, 1H), 4.94 (br s, 1H), 5.22 (d, J = 1.2 Hz, 1H), 6.22 (m, 2H); GC-MS (EI, m/z, rel. int. (%)): 181 (M^++1, 2.6), 163 (1.3), 115 (7.8), 91 (40.7), 66 (100); Analysis calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.39; H, 6.48).

5(S)-Hydroxy-2(R)-methyl-4-oxa*-endo *tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (8b)

This compound was prepared from *d*-menthyloxy lactone **10a** (3.12 g, 9.80 mmol) in the same way as described for its enantiomer **8a**. Yield 1.71 g, 97%. Mp 173-175^{0}C; $[\alpha]_D$ -21.8^0 (c 0.40, CH_2Cl_2); Analysis calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.41; H, 6.57. ^{1}H-NMR, and mass data were the same as for compound **8a**.

5(S)-Chloro-2(S)-methyl-4-oxa*-endo *tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (13a) and its 5(R) epimer (14a)

Enantiopure 5(R)-hydroxy lactone **8a** (1.90 g, 10.6 mmol) was dissolved in $SOCl_2$ (10 mL) in the presence of pyridine (0.92 g, 11.6 mmol) at 0^{0}C. The solution was allowed to warm up to room temperature and stirred for 1 h. Excess $SOCl_2$ was removed by evaporation under reduced pressure. The pyridinium.HCl salt was removed by filtration and the filtrate was concentrated to dryness. Purification by flash chromatography (hexane / ethyl acetate 9:1) gave *exo*-5(S)-chloro lactone **13a** (1.59 g, 78%) as a solid and *endo*-5(R)-chloro lactone **14a** (272 mg, 13%), which solified on standing. Analytical samples of **13a** and **14a** were obtained by recrystallization from *n*-hexane.

13a Mp 97-99^{0}C; $[\alpha]_D$ -6.7^0 (c 0.64, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 1.64 (s, 3H), 1.69 (m, 2H), 2.90 (m, 1H), 3.00 (dd, J = 1.0, 4.2 Hz, 1H), 3.24 (m, 1H), 5.70 (d, J = 1.0 Hz, 1H), 6.23 (m, 2H); GC-MS (EI, m/z, rel. int. (%)): 201/199 (M^++1, 2.3), 163 (7.5), 97 (6.0), 91 (15.2), 66 (100); Analysis calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58. Found: C, 60.48; H, 5.57.

14a Mp 67-68^{0}C; $[\alpha]_D$ -15.9^0 (c 0.4, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 1.54 (s, 3H), 1.71 (m, 2H), 2.86 (m, 1H), 2.97 (dd, J = 3.9, 7.0 Hz, 1H), 3.20 (m, 1H), 6.23 (d, J = 7.0 Hz, 1H), 6.24 (m, 1H), 6.44 (m, 1H); Analysis calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58. Found: C, 60.40; H, 5.64.

5(R)-Chloro-2(R)-methyl-4-oxa*-endo *tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (13b) and its 5(S) epimer (14b)

These compounds were prepared from enantiopure 5(S)-hydroxy lactone **8b** (1.60 g, 8.89 mmol) in the same way as described for the synthesis of **13a** and **14a**. Yield 1.14 g, 66% of *exo*-**13b** as colorless needles and 125 mg, 11% of *endo*-**14b** as a colourless oil, which crystallized on standing.

13b Mp 99^{0}C; $[\alpha]_D$ +8.0^0 (c 0.4, CH_2Cl_2); Analysis calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58. Found: C, 60.64; H, 5.50. ^{1}H-NMR, and mass data were the same as for compound **13a**.

14b Mp 67-68^{0}C; $[\alpha]_D$ +14.2^0 (c 0.47, CH_2Cl_2); Analysis calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58. Found: C, 60.55; H, 5.66. ^{1}H-NMR, and mass data were the same as for compound **14a**.

2(S)-Methyl-5(R)-(2-oxo-3a(R),6a(R)-dihydro-6H-cyclopenta[b]furan-3-ylidenemeth-oxy)-4-oxa*-endo *tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (16a) and its 3a(S),6a(S) diastereomer (16b)

Potassium *tert*-butoxide (139 mg, 1.24 mmol) was added to a solution of racemic hydroxymethylenolactone **15**[19] (180 mg, 1.18 mmol) in dry DMF (6 mL) with stirring at room temperature under nitrogen. To this solution was gradually added *exo*-5(S)-chloro lactone **13a** (213 mg, 1.07 mmol) in dry DMF (4 mL) at room temperature. After 22 h of stirring the reaction mixture was quenched with acetic acid (0.5 mL). DMF was removed *in vacuo* and the residue was dissolved in a mixture of water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, and water, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified using flash chromatography (SiO_2, hexane / ethyl acetate 3:1) to afford two diastereomeric products. The fast moving diastereomer **16a** (114 mg, 34%) was obtained as a white solid, and crystallization from hexane/ ethyl acetate afforded analytically pure **16a**. The slow moving diastereomer **16b** (128 mg, 38%) was obtained as a white solid, which gave an analytically pure sample after crystallization from hexane/ ethyl acetate.

16a Mp 180-181.5^{0}C; $[\alpha]_D$ +175^0 (c 0.12, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.58 (s, 3H), 1.73 (m, 2H), 2.69 (dm, ^{2}J = 18.6 Hz, 1H), 2.72 (d, J = 4.2 Hz, 1H), 2.80 (dm, ^{2}J = 18.6 Hz, 1H), 2.90 (m, 1H), 3.23 (m, 1H), 4.07 (m, 1H), 5.11 (dt, J = 2.5, 6.4 Hz, 1H), 5.21 (br s, 1H), 5.64 (m, 1H), 5.75 (m, 1H), 6.21 (dd, J = 2.9, 5.7 Hz, 1H), 6.30 (dd, J = 3.0, 5.7 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H); MS (EI, m/z, rel. int. (%)): 315 (M^++1, 0.06), 249 (0.13), 163 (66.0), 153 (5.3), 97 (100), 91 (4.5), 66 (8.4); Analysis calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.67; H, 5.57.

16b Mp 205-207^{0}C; $[\alpha]_D$ -255^0 (c 0.13, $CHCl_3$); ^{1}H-NMR ($CDCl_3$. 400 MHz): δ 1.59 (s, 3H), 1.73 (m, 2H), 2.67 (dm, ^2J = 18.5 Hz, 1H), 2.73 (d, J = 4.2 Hz, 1H), 2.80 (dm, ^2J = 18.5 Hz, 1H), 2.90 (m, 1H), 3.22 (m, 1H), 4.08 (m, 1H), 5.11 (dt, J = 2.2, 6.6 Hz, 1H), 5.20 (br s, 1H), 5.60 (m, 1H), 5.73 (m, 1H), 6.21 (dd, J = 2.9, 5.7 Hz, 1H), 6.31 (dd, J = 3.0, 5.7 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H); MS (EI, m/z, rel. int. (%)): 315 (M^++1, 0.76), 249 (0.29), 163 (78.0), 153 (6.4), 97 (100), 91 (4.9), 66 (8.7); Analysis calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.62; H, 5.68.

2(R)-Methyl-5(S)-(2-oxo-3a(R),6a(R)-dihydro-6H-cyclopenta[b]furan-3-ylidenemeth-oxy)-4-oxa*-endo *tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (16c) and its 3a(S),6a(S) diastereomer (16d)

These compounds were prepared in the same way as described for **16a** and **16b**, starting from *exo*-5(R)-chloro lactone **13b** (260 mg, 1.31 mmol) and racemic hydroxymethylenolactone **15**[19] (200 mg, 1.31 mmol). Yield 155 mg, 38% of slow moving diastereomer **16c** as a white solid and 146 mg, 35% of fast moving diastereomer **16d** as a white solid. Both compounds were recrystallized from hexane/ ethyl acetate to obtain analytically pure samples.

16c Mp 211.5^{0}C; $[\alpha]_D$ +262^0 (c 0.18, $CHCl_3$); Analysis calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.81; H, 5.80. ^{1}H-NMR and mass data were the same as for compound **16b**.

16d Mp 181.5-182^{0}C; $[\alpha]_D$ -173^0 (c 0.18, $CHCl_3$); Analysis calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.71; H, 5.60. ^{1}H-NMR and mass data were the same as for compound **16a**.

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(R)-yloxymethylene)-3,3a(R),6,6a(R)-tetrahydro-cyclopenta[b]furan-2-one (4a)

Fast moving cycloadduct **16a** (66 mg, 0.21 mmol) was dissolved in *o*-dichlorobenzene (25 mL) and heated at 180^{0}C for 15 h. The solvent was removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexane / ethyl acetate 2:1) to give the diastereomer **4a** (34 mg, 64%) as a white solid. All analytical data (Mp, $[\alpha]_D$, ^{1}H-NMR, and mass data) were in complete agreement with those reported previously[19].

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(R)-yloxymethylene)-3,3a(S),6,6a(S)-tetrahydro-cyclopenta[b]furan-2-one (4b)

Prepared starting from the slow moving cycloadduct **16b** (30 mg, 0.095 mmol) in the same way as described for the synthesis of **4a**. Yield 14 mg, 59% of **4b** as a slightly yellow oil. All analytical data ($[\alpha]_D$, ^{1}H-NMR, and mass data) were in complete agreement with those reported.previously[19].

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(S)-yloxymethylene)-3,3a(R),6,6a(R)-tetrahydro-cyclopenta[b]furan-2-one (4c)

Prepared starting from the slow moving cycloadduct **16c** (65 mg, 0.21 mmol) in the same way as described for the synthesis of **4a**. Yield 34 mg, 66% of **4c** as a slightly yellow oil. All analytical data ($[\alpha]_D$, ^{1}H-NMR, and mass data) were in complete agreement with those reported previously[19].

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(S)-yloxymethylene)-3,3a(S),6,6a(S)-tetrahydro-cyclopenta[b]furan-2-one (4d)

Prepared starting from the fast moving cycloadduct **16d** (60 mg, 0.19 mmol) in the same way as described for the synthesis of **4a**. Yield 24 mg, 51% of **4d** as a white solid. All analytical data (Mp, $[\alpha]_D$, ^{1}H-NMR, and mass data) were in complete agreement with those reported previously[19].

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