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ROUTES TO DERIVATIVES OF STRIGOL (THE WITCHWEED GERMINATION FACTOR) MODIFIED IN THE 5-POSITION

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Abstract - The title compounds were prepared using nucleophilic substitution in the 5-position of **5b**, **6b**, **11a**, and **11b** or electrophilic addition to the diene system in **4** as key reactions. Methods for configurational assignment at C-5 and C-2' are discussed.

Introduction

Striga asiatica (L.) Kuntze (Scrophulariaceae) is an obligate parasitic plant (witchweed), which attaches to the roots of many warm-season grasses, including millet, sorghum, rice, maize, and sugarcane. The seeds of this parasite remain dormant in the soil for many years until an exudate from the host plant induces germination. A highly potent seed germination stimulant for Striga asiatica is (+)-strigol (**10a**). Inducing Striga germination by strigol or an analogue in the absence of the host plant results in starvation of the seedling. This could form the basis of a novel method for parasitic weed control.[1] Interestingly, until now (+)-strigol was only isolated from the root exudates of cotton (Gossypium hirsutum L.)[2] which is itself not attacked by Striga, and it has been questioned whether (+)-strigol plays a role in the natural ecological host-parasite relation at all.[3] In any case, the high activity of (+)-strigol in seed germination of Striga is a fascinating problem. Basic questions such as

- how is (+)-strigol recognized by the Striga seeds
- which structural units of strigol are essential for seed germination[4]
- how does the primary chemical signal initiate the biochemical processes that are involved in germination

are virtually unanswered.

We are concerned with investigations aimed at making available strigol and compounds related to it that can be used to study some of the questions raised above. In this context, we prepared (+)-strigol (**10a**), 2'-epistrigol (**10b**), and their respective enantiomers.[5] Seed germination studies indicate that the activity is dependent both on the absolute configuration and on the configuration at C-2', at least as far as the germination

of Orobanche crenata and O.aegyptiaca is concerned (personal communication of Prof.K.Wegmann, University of Tübingen).[6]
Several routes are described in this paper that can be used to prepare strigol analogues modified in the 5-position.

(±)-5-epi-Strigol (rac-**11a**) and its 2'-isomer (rac-**11b**)

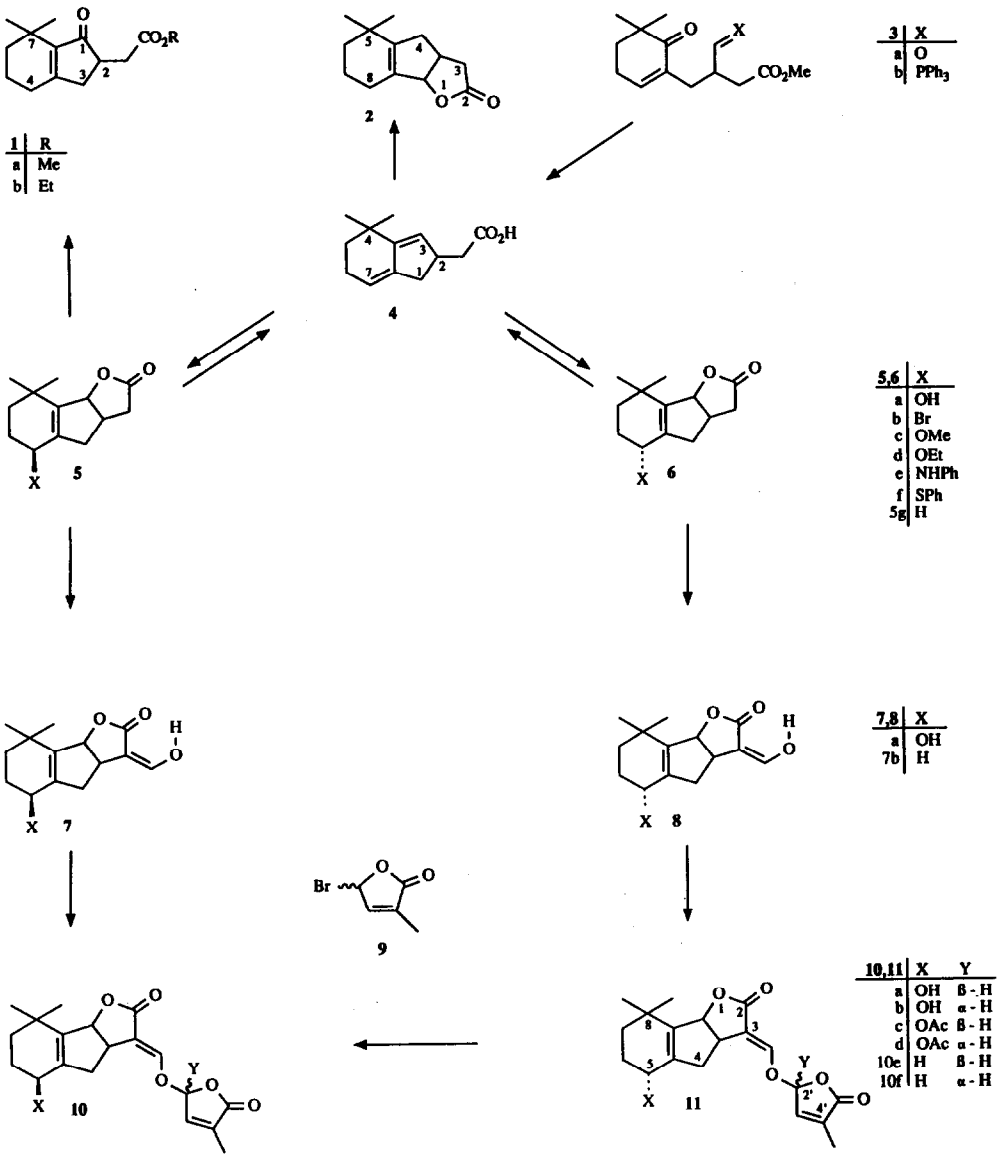
The conventional route to strigol leads via a diketone, the reduction of which gives a 1 : 1 mixture of the hydroxy lactones rac-**5a** and rac-**6a**. Ester condensation of rac-**5a** with ethyl formate (rac-**5a** —> rac-**7a**) followed by alkylation with racemic **9** provides strigol (rac-**10a**) and 2'-epi-strigol (rac-**10b**) in a 1 : 1 ratio. In the same way rac-**6a** is converted to rac-**11a** and rac-**11b** via rac-**8a**.[7,8] We have been able now to determine the hitherto unknown configuration at C-2' of the latter two compounds (vide infra): The lower melting isomer (156-158°C) is rac-**11b** and the higher melting isomer (188-190°C) is rac-**11a**. Thus, according to results mentioned in Raphael's paper, it is rac-**11b** (the lower melting isomer) that has almost the same germination stimulant activity for Striga hermonthica seeds as (±)-strigol (rac-**10a**) whereas the higher melting isomer rac-**11a** and (±)-epi-strigol (rac-**10b**) both have considerably less activity.[8]

Mitsunobu reaction of (±)-5-epi-strigol (rac-**11a**)

Treatment of rac-**11a** with diethyl azodicarboxylate - triphenylphosphine in the presence of acetic acid[9] led to the formation of rac-**10c** which was identical with a specimen obtained from rac-**10a** by acetylation.[10] In the same way rac-**11b** was converted to rac-**10d** identical with the acetyl derivative obtained from rac-**10b**. It seems likely that other substituents such as an amino function can be introduced into the 5-position as well making use of the Mitsunobu methodology.[11]

Nucleophilic substitution in the 5-position of rac-**5b** and rac-**6b**

Treatment of either rac-**5a** or rac-**6a** with carbon tetrabromide - triphenylphosphine[12] yielded a mixture of rac-**5b** and rac-**6b** which could be separated by column chromatography. However, the bromo lactones turned out to be configurationally so labile, that we were only able to obtain from rac-**6b** spectra uncontamminated with the signals of the other diastereoisomer.
When the mixture of rac-**5b** and rac-**6b** was allowed to react with methanol (2 h at 20°C) the methoxy lactones rac-**5c** and rac-**6c** were formed, which were separated by column chromatography. The methoxy lactones were not stable in methanolic solution. A reaction product was slowly formed that was shown to be rac-**1a**, previously prepared by Raphael in a different way.[8] We believe that **1a** is formed from **5c** and **6c** via methanolysis of the lactonic grouping followed by 1,4-elimination of methanol and tautomerization.
Treatment with ethanol converted rac-**5b** / rac-**6b** to rac-**5d** and rac-**6d** which on further reaction with ethanol decomposed to yield rac-**1b**.


1 | R
a | Me
b | Et
2
3 | X
a | O
b | PPh3
4
5,6 | X
a | OH
b | Br
c | OMe
d | OEt
e | NHPh
f | SPh
5g | H
7,8 | X
a | OH
7b | H
9
10,11 | X | Y
a | OH | β-H
b | OH | α-H
c | OAc | β-H
d | OAc | α-H
10e | H | β-H
10f | H | α-H

Other nucleophiles that were used to replace the bromo substituent in rac-**5b** and rac-**6b** were aniline (to give rac-**5e** and rac-**6e**) and thiophenol (to furnish rac-**5f** and rac-**6f**).

(±)-5-Deoxy-strigol (rac-**10e**)

Reduction of bromo lactones rac-**5b** and rac-**6b** with either samarium diiodide[13] or zinc-copper couple[14] furnished the dienic acid rac-**4**. This compound was previously obtained from rac-**3a** by an intramolecular McMurry[15] and from **3b** by an intramolecular Wittig reaction.[16]

4 was reconverted to lactones of type **5** and **6** by a number of electrophiles. Thus, cyclization with N-bromosuccinimide provided a mixture of rac-**5b** / rac-**6b**, and treatment with camphorsulfonic acid led to the formation of rac-**5g**, unsubstituted in the 5-position. The acid-promoted lactonization occurred very readily, especially from the zinc salt obtained in the zinc-copper reduction of rac-**5b** / rac-**6b**. In this latter reaction a side product was obtained which was assigned structure rac-**2**. The spectra of this compound are very similar to those of its structural isomer rac-**5g**. Fully in accord with structure rac-**2** are NOE's (difference spectra) between (i) the 5-CH_3 groups and the protons at C-4 and (ii) the large ^{13}C chemical shift difference for C-4 (δ = 37.57 in **2** and δ = 42.56 ppm in rac-**5g**) which is caused by the γ-gauche effect of the two 5-methyl groups in rac-**2**.

Rac-**5g** was then converted in the usual way via rac-**7b** (in $CDCl_3$ solution according to ^1H NMR a 1 : 1 mixture of the hydroxymethylene and the formyl tautomer) to 5-deoxy-strigol (rac-**10e**) and its 2'-isomer, rac-**10f**.

Configurational assignment at C-5

In the 5-unsubstituted lactone **5g** the chemical shifts of 4_t-H and 4_c-H (cis and trans refers to the reference substituent at C-3a[17]) are δ = 2.08 - 2.16 and 2.53 - 2.62, respectively. The substituent in 5_t position causes in all compounds **5** and **10** a shift of the 4_t-H signal to higher δ values, whereas in the **6** and **11** series it is the 4_c-H signal that is downfield shifted by the substituent at C-5 (Table 1). NOE results in the hydroxy series (**5a**: 5-H <--> 4_c-H; **6a**: 5-H <--> 4_t-H) support this assignment.

In **5a** an NOE between 5-H and the higher-field 7-H signal is observed indicating a $^8H_5$ conformation of the cyclohexene ring with the 7_c-H in the axial position. The signals of the C-7 protons of **5a** have a very typical splitting pattern that is also observed for the other compounds **5** and **10** (with the exception of **5f**) indicating that these compounds adopt the same preferred conformation.

In **6a** the proton at C-7 cis to 5-H is also identified by an NOE (7_t-H <--> 5_t-H). This proton signal shows, however, the typical splitting pattern of an equatorial 7-H when compared with **5a**. We take this as evidence of a conformational equilibrium. The observed NOE would then arise from the minor conformer. With respect to chemical shift the order of axial and equatorial protons at C-7 is reversed in **6a** when compared with **5a**. This holds also for all other compounds of the **6** and **11** series and for **5f**.

Table 1. ^1H NMR signals of CH_2-4 in lactones **5** and **6** (in $CDCl_3$ solution)

5t isomers			5c isomers		
	4t-H	4c-H		4t-H	4c-H
5a[5]	2.43 - 2.51	2.54 - 2.65	**6a**[5]	2.11 - 2.19	2.93 - 3.01
5b	2.52 - 2.58		**6b**	2.10 - 2.18	2.99 - 3.14
5c	2.39 - 2.48	2.50 - 2.59	**6c**	2.08 - 2.17	2.92 - 2.99
5d	2.42 - 2.51	2.52 - 2.59	**6d**	2.06 - 2.15	2.92 - 3.00
5e	2.36 - 2.44	2.54 - 2.64	**6e**	2.12 - 2.20	2.84 - 2.95
5f	2.53 - 2.62		**6f**	2.12 - 2.21	2.99 - 3.13
10a[5]	2.62 - 2.75		**11a**	2.30 - 2.38	3.02 - 3.10
10c	2.34 - 2.39	2.64 - 2.73	-	-	-

Configurational assignment at C-2'

Until now determination of the configuration at C-2' in strigol and related compounds has only been possible by means of of X-ray analysis.[2] We now demonstrate the use of two further procedures.

Fig. 1 exhibits the CD curves of (+)-strigol (**10a**), (+)-2'-epi-strigol (**10b**) and their enantiomers.[18] The curves are, of course, sum curves that arise from the different chromophores present in **10a** and its stereoisomers. But it appears that the sign of the Cotton effect above 250 nm is correlated with the configuration at C-2'. For comparison, menthyloxy-butenolides **12** and ent-**12** were prepared as described by Feringa et al..[19] They contain only the 2-alkoxy-2,5-dihydro-furan-5-one chromophore. Fig. 2 shows that the (2'R)-compound **12** has a negative Cotton effect around 250 nm and the (2'S)-isomer ent-**12** a positive. The same relation between the configuration at C-2' and the sign of the CD at 250 nm has been found for (+)-strigol and its stereoisomers: **10a** and ent-**11a** correspond with **12** both in configuration at C-2' and sign of CD above 250 nm and the same is true for ent-**10a** and **11a** when compared with ent-**12**. We assume from these results, that CD can be used to determine the C-2' configuration in non-racemic strigol derivatives.

For racemic compounds the situation is more complicated since neither from ^1H nor from ^{13}C NMR spectra any hint concerning the relative configuration at C-2' can be extracted. In the 5_c-OH series configurational assignment was achieved by chemical correlation. Rac-**11a** and rac-**11b** were converted to rac-**10c** and rac-**10d**, respectively (with known configuration at C-2'), by Mitsunobu inversion as described above.

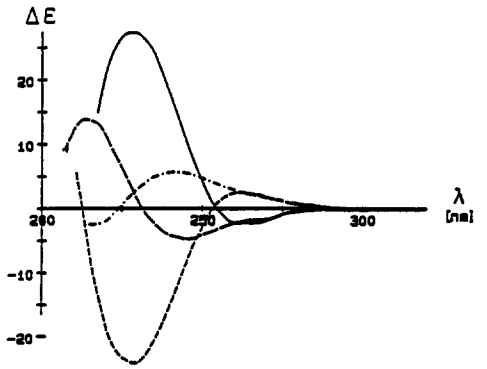


Fig.1. CD spectra of **10a** (———), ent-**10a** (- - -), **10b** (-·-·-) and ent-**10b** (— —)

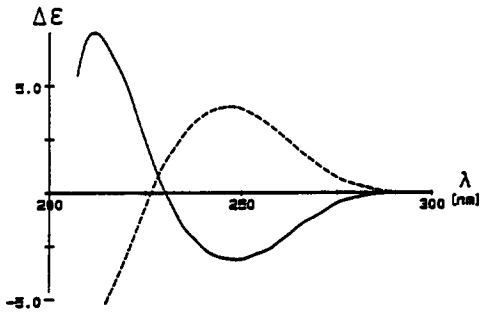


Fig.2. CD spectra of **12** (———) and ent-**12** (- - -).

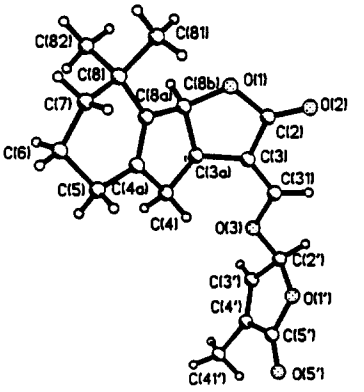


Fig.3. X-ray crystal structure of rac-**10f**.

For the deoxy derivatives rac-**10a** and rac-**10f** recourse was made to X-ray analysis. Fig. 3 shows the result for rac-**10f**.

Experimental

For instrumentation and general methods, see ref..[20] All reactions were performed under argon. All reported coupling constants result from first-order analysis.

CD data of (+)-strigol (**10a**), ent-**10a**, (+)-2'-epi-strigol (**10b**), ent-**10b**, and model compounds **12** and ent-**12**

Solvent: acetonitrile.

10a	(0.554 mmol/l) :	λ_{max} ($\Delta\varepsilon$) = 263 (-2.25), 228 (27.39)
ent-**10a**	(0.542 mmol/l) :	λ_{max} ($\Delta\varepsilon$) = 262 (2.55), 229 (-24.15)
10b	(0.727 mmol/l) :	λ_{max} ($\Delta\varepsilon$) = 241 (5.68)
ent-**10b**	(0.533 mmol/l) :	λ_{max} ($\Delta\varepsilon$) = 245 (-4.78), 207 (9.62)
12	(0.434 mmol/l) :	λ_{max} ($\Delta\varepsilon$) = 249 (-3.13), 212 (7.47)
ent-**12**	(0.720 mmol/l) :	λ_{max} ($\Delta\varepsilon$) = 247 (4.03), 213 (-5.97)

Preparation of rac-**11a** and rac-**11b**

rac-**6a** (329.1 mg, 1.48 mmol) was converted to a mixture of rac-**11a** and rac-**11b** using the experimental conditions described by Brooks[21] for the conversion of **5a** into **10a** and **10b**. MPLC (90 g SiO_2, hexanes - ethyl acetate 1 : 1) gave rac-**11a** (90.4 mg, 18 %), rac-**11b** (100.5 mg, 20 %), and a mixture of rac-**11a** and rac-**11b** (31.0 mg, 6 %).

(3aRS)-5c-Hydroxy-8,8-dimethyl-3-((RS,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**11a**)

M.p. 188 - 189°C (hexanes - ethyl acetate), lit.[8] 188 - 190°C - IR ($CHCl_3$): 3100 - 2800, 1790, 1740, 1680 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H, 8-CH_3), 1.11 (s, 3H, 8-CH_3), 1.39 - 1.46 (ddd, 1H, 7t-H), 1.51 - 1.59 (ddd, 1H, 7c-H), 1.63 - 1.74 (m, 2H, 6-H, OH), 1.90 - 2.00 (m, 1H, 6-H'), 2.00 (t, 3H, 4'-CH_3), 2.30 - 2.38 (d^{22}, 1H, 4t-H), 3.02 - 3.10 (dd^{21}, 1H, 4c-H), 3.58 - 3.64 (m, 1H, 3a-H), 4.09 - 4.15 (t, 1H, 5-H), 5.48 - 5.53 (dd, 1H, 8b-H), 6.13 - 6.16 (m, 1H, 2'-H), 6.87 - 6.90 (m, 1H, 3'-H), 7.39 - 7.41 (d, 1H, =CHO); $J_{7c,7t}$ = 13.5 Hz, $J_{7c,6t}$ = 10.0 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 8.0 and 3.5 Hz, $J_{4c,4t}$ = 17.0 Hz, $J_{4c,3a}$ = 9.0 Hz, $J_{8b,3a}$ = 8.0 Hz, $J_{2',3'}$ = 1.5 Hz, $J_{2',4'\text{-}CH3}$ = 1.5 Hz, $J_{3',4'\text{-}CH3}$ = 1.5 Hz.- ^{13}C NMR (100.6 Hz, $CDCl_3$): δ = 10.97 (4'-CH_3), 27.56 (8-CH_3-groups), 29.63 (C-7), 32.63 (C-8), 35.53 (C-3a), 36.86 (C-6), 38.53 (C-4), 66.28 (C-5), 88.36 (C-8b), 100.64 (C-2'), 114.11 (C-4'), 136.23 and 143.16 (C-8a and C-4a), 141.16 and 141.22 (C-3' and C-3), 150.37 (=CHO), 170.43 (C-5'), 171.68 (C-2). - MS ($C_{19}H_{22}O_6$, 346.14): m/z (%) = 346 (M^+, 1.1), 328 (4), 249 (9), 231 (26), 204 (13), 97 (100).- HRMS calcd for $C_{19}H_{22}O_6$: 346.1416, found: 346.1415.

(3aRS)-5c-Hydroxy-8,8-dimethyl-3-((SR,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**11b**)

M.p. 150 - 151°C (hexanes - ethyl acetate), lit.[8] 156 - 158°C.- IR ($CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100.6 MHz, $CDCl_3$), MS : these spectra are superimposable with those obtained from rac-**11a**.- HRMS calcd for $C_{19}H_{22}O_6$: 346.1416, found: 346.1418.

(3aRS)-5t-Acetoxy-8,8-dimethyl-3-((RS,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**10c**)

To a solution of acetic anhydride (5.0 µl, 5.4 mg, 0.05 mmol) and dimethylaminopyridine[23] (1.9 mg, 0.01 mmol) in pyridine (0.4 ml) was added rac-**10a** (15.4 mg, 0.05 mmol) at 0°C. The mixture was stirred at 20°C for 2 h. Partitioning between ether and 1 N HCl, followed by washing the organic layer with water, drying, solvent evaporation and LC (1.7 g SiO_2, hexanes - ethyl acetate 1 : 2) gave rac-**10c** (11.8 mg, 68%).- IR ($CHCl_3$): 1790, 1740 (broad), 1680 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H, 8-CH_3), 1.18 (s, 3H, 8-CH_3), 1.41 - 1.51 (m, 1H, 7c-H), 1.53 -1.59 (m, 1H, 7t-H), 1.68 - 1.79 (m, 1H) and 1.90 - 2.00 (m, 1H, CH_2-6), 2.00 (t, 3H, 4'-CH_3), 2.05 (s, 3H, $COCH_3$), 2.34 - 2.39 (m, 1H, 4t-H), 2.64 - 2.73 (dd, 1H, 4c-H), 3.58 - 3.65 (m, 1H, 3a-H), 5.23 - 5.28 (m, 1H, 5-H), 5.43

- 5.48 (d, 1H, 8b-H), 6.13 - 6.15 (m, 1H, 2'-H), 6.87- 6.90 (m, 1H, 3'-H), 7.40 - 7.42 (d, 1H, =CHO); $J_{7c,7t}$ = 13.5 Hz, $J_{7c,6t}$ = 11.0 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 3.0 and 7.0 Hz, $J_{4c,4t}$ = 17.0 Hz, $J_{4c,3a}$ = 9.0 Hz, $J_{8b,3a}$ = 8.0 Hz, $J_{2',3'}$ = 1.5 Hz, $J_{2',4'-CH_3}$ = 1.5 Hz, $J_{3',4'-CH_3}$ = 1.5 Hz.- MS ($C_{21}H_{24}O_7$, 388.42): m/z (%) = 388 (M^+, 0.7), 346 (6), 328 (9), 231 (26), 97 (100).

(3aRS)-5t-Acetoxy-8,8-dimethyl-3-((SR,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**10d**)
rac-**10d** was prepared from rac-**10b** as described for rac-**10c** (reaction time: 21 h). Yield: 74%.- IR ($CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100.6 MHz, $CDCl_3$), MS : these spectra are superimposible with those obtained from rac-**10a**.

Mitsunobu reaction of rac-**11a**
Diethyl azodicarboxylate (19.8 mg, 0.11 mmol) was added to a solution of rac-**11a** (27.5 mg, 0.08 mmol), acetic acid (5.0 µl, 5.3 mg, 0.09 mmol) and triphenylphosphine (29.8 mg, 0.11 mmol) in tetrahydrofuran (1.5 ml). The reaction mixture was stirred at 40°C for 7 d. LC (10.1 g SiO_2, hexanes - ethyl acetate 3 : 2), followed by MPLC (toluene - hexanes - ethanol 5 : 5 : 1) gave rac-**10c** (25.0 mg, 81 %), identical with the specimen described above, according to ^1H NMR (400 MHz) and TLC (hexanes - ethyl acetate 1 : 4).

Mitsunobu reaction of rac-**11b**
Diethyl azodicarboxylate (11.7 mg, 0.07 mmol) was added to a solution of rac-**11b** (16.4 mg, 0.05 mmol), acetic acid (4.8 µl, 5.0 mg, 0.08 mmol) and triphenylphosphine (17.6 mg, 0.07 mmol) in tetrahydrofuran (1.0 ml). The reaction mixture was stirred for 72 h at 20°C. LC (6.3 g SiO_2, hexanes - ethyl acetate 1 : 1), followed by MPLC (toluene - hexanes - ethanol 5 : 5 : 1) gave rac-**10d** (4.0 mg, 22%). The low yield is due to difficulties to get rac-**10d** free of diethyl hydrazodicarboxylate. rac-**10d** was identical with the specimen described above, according to ^1H NMR (400 MHz) and TLC (hexanes - ethyl acetate 1 : 4). The R_f value of rac-**10c** was slightly larger than that of rac-**10d**.

Conversion of hydroxy lactones rac-**5a** and rac-**6a** to bromo lactones rac-**5b** and rac-**6b**
Solutions of triphenylphosphine (186.8 mg, 0.71 mmol) in CH_2Cl_2 (5 ml) and of CBr_4 (362.4 mg, 1.09 mmol) in CH_2Cl_2 (5 ml) were slowly added to a well-stirred solution of rac-**5a** and rac-**6a** (86.1 mg, 0.39 mmol) in CH_2Cl_2 (2 ml). The reaction mixture was stirred for 15 min at 20°C. Solvent evaporation and LC (8.5 g SiO_2, hexanes - ethyl acetate 3 : 1) gave a roughly 1 : 1 mixture of rac-**5b** / rac-**6b** (105.8 mg, 96%). R_f values (hexanes - ethyl acetate 1 : 1) rac-**5b**: 0.66, rac-**6b**: 0.73. Pure samples of rac-**5b** and rac-**6b** could be obtained by LC (hexanes - ethyl acetate 3 : 1), but the compounds proved to be very unstable and quickly epimerized.

(±)-5t-Bromo-8,8-dimethyl-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**5b**)
The ^1H NMR sample of rac-**5b** could not be kept completly pure, and the signals listed below were obtained by substraction of the rac-**6b** signals.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 3H, 8-CH_3), 1.18 (s, 3H, 8-CH_3), 2.31 - 2.38 (dd, 1H, 3t-H), 2.52 - 2.58 (m, 2H, CH_2-4), 2.74 - 2.82 (m, 1H, 3c-H), 4.57 - 4.63 ($W_{1/2}$ = 13.0 Hz, 1H, 5-H), 5.38 - 5.43 (m, 1H, 8b-H); $J_{3c,3t}$ = 17.5 Hz, $J_{3t,3a}$ = 5.0 Hz, $J_{8b,3a}$ = 7.0 Hz. The following spectra were also obtained from a mixture.- IR ($CHCl_3$): 1765, 1610 cm^{-1}.- MS ($C_{13}H_{17}O_2Br$, 285.2): m/z (%) = 286 (0.8), 284 (0.7), 205 (100), 187 (22), 159 (44), 145 (81), 105 (61).

(±)-5c-Bromo-8,8-dimethyl-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**6b**)
^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H, 8-CH_3), 1.17 (s, 3H, 8-CH_3), 1.43 - 1.49 (ddd, 1H, 7-H), 1.80 - 1.87 (ddd, 1H, 7-H'), 2.10 - 2.18 (m, 2H, 4t-H and 6-H), 2.20 - 2.32 (m, 2H, 6-H' and 3t-H), 2.76 - 2.84 (dd, 1H, 3c-H), 2.99 - 3.14 (m, 2H, 3a-H and 4c-H), 4.69 - 4.72 ($W_{1/2}$ = 9.0 Hz, 1H, 5-H), 5.46 - 5.50 (m, 1H, 8b-H); $J_{7,7'}$ = 13.0 Hz, $J_{7',6}$ = 13.0 Hz, $J_{7',6'}$ = 3.5 Hz , $J_{7,6}$ and $J_{7,6'}$ = 7.5 Hz and 3.5 Hz, $J_{3c,3t}$ = 18.5 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{3t,3a}$ = 5.5 Hz, $J_{4c,4t}$ = 16.0 Hz, $J_{4c,3a}$ = 8.0 Hz, $J_{8b,3a}$ = 7.0 Hz.

Reaction of rac-**5b** and rac-**6b** with methanol
A solution of rac-**5b** / rac-**6b** (41.6 mg, 0.14 mmol) in MeOH (5 ml) was stirred for 2 h at 20°C. Work-up (CH_2Cl_2) was performed before the bromo lactones were completly consumed. LC (3.8 g SiO_2, hexanes - ethyl acetate 3 : 1) gave rac-**5c** and rac-**6c** (18.6 mg, 54%) as an equimolar mixture. R_f values ($CHCl_3$ - acetone 10 : 1) rac-**5c**: 0.38, rac-**6c**: 0.44. Pure samples of rac-**5c** and rac-**6c** were obtained by subsequent LC ($CHCl_3$ - acetone 50 : 1).

(±)-5*t*-Methoxy-8,8-dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**5c**)
M.p. 76 - 78°C (ether - pentane).- IR ($CHCl_3$): 1760, 1675, 1170 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 3H, 8-CH_3), 1.11 (s, 3H, 8-CH_3), 1.35 - 1.42 (ddd, 1H, 7$_c$-H), 1.52 - 1.60 (m, 1H, 7$_t$-H), 1.65 - 1.76 (m, 1H) and 1.88 - 1.97 (m, 1H, CH_2-6), 2.25 - 2.36 (dd, 1H, 3$_t$-H), 2.39 - 2.48 (m, 1H, 4$_t$-H), 2.50 - 2.59 (m, 1H, 4$_c$-H), 2.69 - 2.80 (dd, 1H, 3$_c$-H), 2.95 - 3.09 (m, 1H, 3a-H), 3.33 (s, 3H, O-CH_3), 3.63 - 3.74 ($W_{1/2}$ = 14.0 Hz, 1H, 5-H), 5.40 - 5.47 (m, 1H, 8b-H); $J_{7c,7t}$ = 14.5 Hz, $J_{7c,6t}$ = 11.5 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 3.0 Hz and 6.5 Hz, $J_{4c,4t}$ = 17.0 Hz, $J_{4c,3a}$ = 8.5 Hz, $J_{3c,3t}$ = 18.5 Hz, $J_{3c,3a}$ = 10.5 Hz, $J_{3t,3a}$ = 5.5 Hz, $J_{8b,3a}$ = 7.5 Hz.- HRMS calcd for $C_{14}H_{20}O_3$: 236.1413, found 236.1401.

(±)-5*c*-Methoxy-8,8-dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**6c**)
M.p. 59 - 61°C (ether - pentane).- IR ($CHCl_3$): 1760, 1170, 1080 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H, 8-CH_3), 1.13 (s, 3H, 8-CH_3), 1.37 - 1.44 (ddd, 1H, 7$_t$-H), 1.54 - 1.62 (m, 1H, 7$_c$-H), 1.73 - 1.91 (m, 2H, CH_2-6), 2.08 - 2.17 (m, 1H, 4$_t$-H), 2.28 - 2.37 (dd, 1H, 3$_t$-H), 2.75 - 2.84 (dd, 1H, 3$_c$-H), 2.92 - 2.99 (m, 1H, 4$_c$-H), 3.00 - 3.10 (m, 1H, 3a-H), 3.37 (s, 3H, O-CH_3), 3.67 ($W_{1/2}$ = 12.0 Hz, 1H, 5-H), 5.41 - 5.49 (m, 1H, 8b-H); $J_{7c,7t}$ = 13.5 Hz, $J_{7c,6t}$ = 10.0 Hz, $J_{7c,6c}$ = 3.5 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 3.5 Hz and 7.5 Hz, $J_{4c,4t}$ = 16.5 Hz, $J_{4c,3a}$ = 8.5 Hz, $J_{3c,3t}$ = 18.0 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{3t,3a}$ = 4.5 Hz, $J_{8b,3a}$ = 7.5 Hz.- HRMS calcd for $C_{14}H_{20}O_3$: 236.1413, found 236.1412.

Methyl (7,7-dimethyl-1-oxo-2,3,4,5,6,7-hexahydro-1H-inden-2-yl)-acetate (rac-**1a**)
A solution of rac-**5b** / rac-**6b** (19.1 mg, 0.07 mmol) in MeOH (3 ml) was stirred for 28 h at 20°C. Solvent evaporation followed by LC (2.2 g SiO_2, hexanes - ethyl acetate 5 : 1) gave pure rac-**1a** (15.5 mg, 98%).- IR (CCl_4): 1745, 1675, 1630 cm^{-1}.- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.12 (s, 6H, 7-CH_3-groups), 1.45 - 1.70 (2H, CH_2-6), 1.72 - 1.98 (2H, CH_2-5), 2.20 - 2.97 (7H, CH_2-4, CH_2-3, 2-H, 2-CH_2-CO_2Me), 3.65 (s, 3H, O-CH_3).- ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.52, 26.41, 32.81, 33.75, 35.22, 35.85, 38.33, 39.63, 40.33, 51.84 (O-CH_3), 134.78 and 171.04 (C-3a and C-7a), 173.31 ($\underline{C}O_2Me$), 197.57 (C-1).- MS ($C_{14}H_{20}O_3$, 236.3): m/z (%) = 236 (M^+, 17), 205 (6.5), 163 (100), 147 (12), 119 (27).

Reaction of (rac)-**5b** and (rac)-**6b** with ethanol
A solution of rac-**5b** / rac-**6b** (33.7 mg, 0.12 mmol) in EtOH (2 ml) was stirred for 20 h at 20°C. Work-up (CH_2Cl_2) was performed before the bromo lactones were completly consumed. LC (3.5 g SiO_2, hexanes - ethyl acetate 5 : 1) gave rac-**5d** and rac-**6d** (25.0 mg, 84%) as an equimolar mixture. R_f values ($CHCl_3$ - acetone 10 : 1) rac-**5d**: 0.47, rac-**6d**: 0.51. Pure samples of rac-**5d** and rac-**6d** were obtained by subsequent LC ($CHCl_3$ - acetone 50 : 1).

(±)-5*t*-Ethoxy-8,8-dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**5d**)
IR ($CHCl_3$): 1760, 1670 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 3H, 8-CH_3), 1.12 (s, 3H, 8-CH_3), 1.18 (t, 3H, O-CH_2-$\underline{C}H_3$), 1.32 - 1.43 (ddd, 1H, 7$_c$-H), 1.51 - 1.60 (m, 1H, 7$_t$-H), 1.67 - 1.78 (m, 1H) and 1.89 - 1.96 (m, 1H, CH_2-6), 2.28 - 2.37 (dd, 1H, 3$_t$-H), 2.42 - 2.51 (m, 1H, 4$_t$-H), 2.52 - 2.59 (m, 1H, 4$_c$-H), 2.70 - 2.80 (dd, 1H, 3$_c$-H), 2.99 - 3.10 (m, 1H, 3a-H), 3.39 - 3.48 (dq, 1H) and 3.58 - 3.65 (dq, 1H, O-$\underline{C}H_2$-CH_3), 3.71 - 3.80 ($W_{1/2}$ = 14.0 Hz, 1H, 5-H), 5.40 - 5.46 (m, 1H, 8b-H); $J_{vic,ethyl}$ = 6.5 Hz, $J_{gem,ethyl}$ = 9.0 Hz, $J_{7c,7t}$ = 14.0 Hz, $J_{7c,6t}$ = 11.0 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6c}$ and $J_{7t,6t}$ = 3.0 Hz and 6.5 Hz, $J_{4c,4t}$ = 17.0 Hz, $J_{4c,3a}$ = 8.0 Hz, $J_{3c,3t}$ = 18.0 Hz, $J_{3t,3a}$ = 5.5 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{8b,3a}$ = 7.0 Hz.- HRMS calcd for $C_{15}H_{22}O_3$: 250.1569, found 250.1576.

(±)-5c-Ethoxy-8,8-dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**6d**)

IR ($CHCl_3$): 1760 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 3H, 8-CH_3), 1.12 (s, 3H, 8-CH_3), 1.19 (t, 3H, O-CH_2-CH_3), 1.36 - 1.45 (ddd, 1H, 7t-H), 1.54 - 1.65 (m, 1H, 7c-H), 1.71 - 1.79 (m, 1H) and 1.81 - 1.90 (m, 1H, CH_2-6), 2.06 - 2.15 (m, 1H, 4t-H), 2.29 - 2.38 (dd, 1H, 3t-H), 2.76 - 2.83 (dd, 1H, 3c-H), 2.92 - 3.00 (dd, 1H, 4c-H), 3.01 - 3.10 (m, 1H, 3a-H), 3.38 - 3.46 (dq, 1H) and 3.59 - 3.68 (dq, 1H, O-CH_2-CH_3), 3.76 ($W_{1/2}$ = 11.0 Hz, 1H, 5-H), 5.43 - 5.47 (m, 1H, 8b-H); $J_{vic,ethyl}$ = 7.0 Hz, $J_{gem,ethyl}$ = 9.0 Hz, $J_{7c,7t}$ = 13.0 Hz, $J_{7c,6t}$ = 10.0 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6c}$ and $J_{7t,6t}$ = 3.0 Hz and 7.5 Hz, $J_{4c,4t}$ = 16.5 Hz, $J_{4c,3a}$ = 8.5 Hz, $J_{3c,3t}$ = 18.5 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{3t,3a}$ = 4.5 Hz, $J_{8b,3a}$ = 7.5 Hz.- ^{13}C NMR (DEPT, 100.6 MHz, $CDCl_3$): δ = 15.61 (CH_3-CH_2-O), 25.13 (CH_2-6), 27.12 (8-CH_3), 27.28 (8-CH_3), 32.24 (C_q-8), 34.54 (CH-3a), 35.37 (CH_2-3), 36.04 (CH_2-7), 39.47 (CH_2-4), 64.68 (CH_3-CH_2-O), 73.15 (CH-5), 89.92 (CH-8b), 141.15 and 143.46 (C_q-4a and C_q-8a), 177.41 (C_q-2).- HRMS calcd for $C_{15}H_{22}O_3$: 250.1569, found 250.1569.

Ethyl (7,7-dimethyl-1-oxo-2,3,4,5,6,7-hexahydro-1H-inden-2-yl)-acetate (rac-**1b**)

A solution of rac-**5b** / rac-**6b** (19.1 mg, 0.07 mmol) in EtOH (3 ml) was stirred for 50 h at 20°C. Solvent evaporation followed by LC (3.0 g SiO_2, hexanes - ethyl acetate 5 : 1) gave rac-**1b** (9.7 mg, 55%).- IR ($CHCl_3$): 1730, 1660, 1625 cm^{-1}.- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.12 (s, 6H, 7-CH_3-groups), 1.25 (t, 3H, O-CH_2-CH_3), 1.40 - 1.65 (2H, CH_2-6), 1.70 - 2.00 (2H, CH_2-5), 2.12 - 2.95 (7H, CH_2-4, CH_2-3, 2-H, 2-CH_2-CO_2Et), 4.12 (q, 2H, O-CH_2-CH_3); $J_{vic,ethyl}$ = 7.0 Hz.- MS ($C_{15}H_{22}O_3$, 250.3): m/z (%) = 250 (M^+, 14), 205 (8), 163 (100), 119 (19).- HRMS calcd for $C_{15}H_{22}O_3$: 250.1569, found 250.1569.

Reaction of rac-**5b** and rac-**6b** with aniline

25 µl aniline were added at 20°C to a solution of rac-**5b** / rac-**6b** (35.1 mg, 0.12 mmol) in CH_3CN (2 ml). The reaction mixture was stirred for 24 h at 20°C. Work-up (CH_2Cl_2) followed by LC (6.0 g SiO_2, hexanes - ethyl acetate 6 : 1) gave rac-**5e** and rac-**6e** (31.5 mg, 86%) as an equimolar mixture. R_f values (hexanes - ethyl acetate 3 : 1) rac-**5e**: 0.18, rac-**6e**: 0.12. Pure samples of rac-**5e** and rac-**6e** were obtained by subsequent LC (hexanes - ethyl acetate 6 : 1).

(±)-5t-Anilino-8,8-dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**5e**)

M.p. 175 - 177°C (ether - pentane).- IR ($CHCl_3$): 1760, 1605, 1500 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H, 8-CH_3), 1.14 (s, 3H, 8-CH_3), 1.42 - 1.51 (ddd, 1H, 7c-H), 1.52 - 1.63 (ddd, 1H, 7t-H), 1.67 - 1.78 (m, 1H) and 1.89 - 1.99 (m, 1H, CH_2-6), 2.27 - 2.35 (dd, 1H, 3t-H), 2.36 - 2.44 (m, 1H, 4t-H), 2.54 - 2.64 (m, 1H, 4c-H), 2.72 - 2.81 (dd, 1H, 3c-H), 2.98 - 3.09 (m, 1H, 3a-H), 3.57 (broad s, 1H, N-H), 3.91 - 3.99 ($W_{1/2}$ = 15.0 Hz, 1H, 5-H), 5.43 - 5.47 (m, 1H, 8b-H), 6.57 - 6.62 (m, 2H), 6.65 - 6.73 (m, 1H) and 7.12 - 7.20 (m, 2H, arom. H's); $J_{7c,7t}$ = 13.0 Hz, $J_{7c,6t}$ = 9.0 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 3.0 Hz and 8.0 Hz, $J_{4c,4t}$ = 17.0 Hz, $J_{4c,3a}$ = 8.5 Hz, $J_{3c,3t}$ = 17.5 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{3t,3a}$ = 5.0 Hz, $J_{8b,3a}$ = 7.0 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.45 (C-6), 27.38 (8-CH_3), 27.89 (8-CH_3), 32.28 (C-8), 34.57 (C-3a), 35.89 (C-3), 36.88 (C-7), 39.81 (C-4), 49.72 (C-5), 89.58 (C-8b), 113.13, 117.48 and 129.35 (arom. C's), 142.37 and 143.25 (C-4a and C-8a), 147.28 (arom. C), 177.22 (C-2).- HRMS calcd for $C_{19}H_{23}O_2N$: 297.1729, found 297.1729.

(±)-5c-Anilino-8,8-dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**6e**)

M.p. 172 - 174°C (ether - pentane).- IR ($CHCl_3$): 1760, 1600, 1500, 1170 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3H, 8-CH_3), 1.14 (s, 3H, 8-CH_3), 1.42 - 1.60 (m, 2H, CH_2-7), 1.73 - 1.81 (m, 1H) and 1.86 - 1.97 (m, 1H, CH_2-6), 2.12 - 2.20 (m, 1H, 4t-H), 2.27 - 2.36 (dd, 1H, 3t-H), 2.72 - 2.81 (dd, 1H, 3c-H), 2.84 - 2.95 (dd, 1H, 4c-H), 2.96 - 3.06 (m, 1H, 3a-H), 3.54 (broad s, 1H, N-H), 4.00 ($W_{1/2}$ = 10.0 Hz, 1H, 5-H), 5.43 - 5.51 (m, 1H, 8b-H), 6.57 - 6.62 (m, 2H), 6.65 - 6.73 (m, 1H) and 7.12 - 7.20 (m, 2H, arom. H's); $J_{4c,4t}$ = 17.0 Hz, $J_{4c,3a}$ = 8.5 Hz, $J_{3c,3t}$ = 18.0 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{3t,3a}$ = 4.5 Hz, $J_{8b,3a}$ = 7.5 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.83 (C-6), 27.29 (8-CH_3), 27.62 (8-CH_3), 32.29 (C-8), 34.58 (C-3a), 35.69 (C-3), 35.95 (C-7), 39.98 (C-4), 48.87 (C-5),

89.59 (C-8b), 113.11, 117.52 and 129.39 (arom. C's), 141.74 and 143.58 (C-4a and C-8a), 147.16 (arom. C's), 177.11 (C-2).- HRMS calcd for $C_{19}H_{23}O_2N$: 297.1729, found 297.1727.

Reaction of rac-**5b** and rac-**6b** with thiophenol

DBU (50 µl, 0.33 mmol) was slowly added at 20°C to a solution of thiophenol (30 µl, 0.29 mmol) in CH_3CN (1 ml). The mixture was stirred for 15 min, then a solution of rac-**5b** / rac-**6b** (40.9 mg, 0.14 mmol) in CH_3CN (3 ml) was added. The reaction mixture was stirred for 4 h at 20°. Work-up (CH_2Cl_2) followed by LC (9.0 g SiO_2, hexanes - ethyl acetate 6 : 1) gave pure rac-**5f** (25.7 mg, 58%), rac-**6f** (8.8 mg, 20%) and a mixture of rac-**5f** and rac-**6f** (7.7 mg, 17%). R_f values (hexanes - ethyl acetate 3 : 1) rac-**5f**: 0.23, rac-**6f**: 0.28.

(±)-8,8-Dimethyl-5*t*-phenylsulfanyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**5f**)

M.p. 118 - 120°C (ether - pentane).- IR ($CHCl_3$): 1760, 1585 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 3H, 8-CH_3), 1.09 (s, 3H, 8-CH_3), 1.33 - 1.47 (ddd, 1H, 7$_t$-H), 1.67 - 1.76 (ddd, 1H, 7$_c$-H), 1.81 - 1.92 (m, 1H) and 1.93 - 2.04 (m, 1H, CH_2-6), 2.28 - 2.37 (dd, 1H, 3$_t$-H), 2.53 - 2.62 (m, 2H, CH_2-4), 2.71 - 2.81 (dd, 1H, 3$_c$-H), 2.97 - 3.09 (m, 1H, 3a-H), 3.62 - 3.70 ($W_{1/2}$ = 14.5 Hz, 1H, 5-H), 5.41 - 5.50 (m, 1H, 8b-H), 7.18 - 7.30 (m, 3H) and 7.33 - 7.40 (m, 2H, arom. H's); $J_{7c,7t}$ = 13.0 Hz, $J_{7c,6t}$ = 9.0 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 3.0 Hz and 8.0 Hz, $J_{3c,3t}$ = 18.0 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{3t,3a}$ = 5.5 Hz, $J_{8b,3a}$ = 7.0 Hz.- ^{13}C NMR (100.6 MHz, H,C-Cosy, $CDCl_3$): δ= 27.30, 27.46 and 28.26 (8-CH_3-groups and C-6), 32.52 (C-8), 34.61 (C-3a), 36.03 (C-3), 36.58 (C-7), 40.76 (C-4), 45.74 (C-5), 89.75 (C-8b), 127.33, 129.20 and 131.96 (arom. C's), 135.48 and 140.22 (C-4a and C-8a), 144.09 (arom. C), 177.33 (C-2).- HRMS calcd for $C_{19}H_{22}O_2S$: 314.1341, found 314.1334.

(±)-8,8-Dimethyl-5*c*-phenylsulfanyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**6f**)

M.p. 105 - 107°C (ether).- IR ($CHCl_3$): 1760 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 3H, 8-CH_3), 1.11 (s, 3H, 8-CH_3), 1.36 - 1.42 (ddd, 1H, 7$_t$-H), 1.69 - 1.78 (m, 1H, 7$_c$-H), 1.81 - 1.90 (m, 1H) and 1.99 - 2.09 (m, 1H, CH_2-6), 2.12 - 2.21 (m, 1H, 4$_t$-H), 2.29 - 2.34 (dd, 1H, 3$_t$-H), 2.74 - 2.85 (dd, 1H, 3$_c$-H), 2.99 - 3.13 (m, 2H, 3a-H, 4$_c$-H), 3.74 ($W_{1/2}$ = 10.0 Hz, 1H, 5-H), 5.45 - 5.50 (m, 1H, 8b-H), 7.16 - 7.41 (m, 5H, arom. H's); $J_{7c,7t}$ = 13.0 Hz, $J_{7c,6t}$ = 13.0 Hz, $J_{7c,6c}$ = 3.0 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 3.0 Hz and 5.5 Hz, $J_{3c,3t}$ = 18.0 Hz, $J_{3c,3a}$ = 10.0 Hz, $J_{3t,3a}$ = 5.0 Hz.- HRMS calcd for $C_{19}H_{22}O_2S$: 314.1341, found 314.1328.

4,4-Dimethyl-2,4,5,6-tetrahydro-1H-indan-2-yl-acetic acid (rac-**4**)

a) Reduction of bromo lactones rac-**5b** and rac-**6b** with samarium diiodide.

SmI_2 (0.1 M solution in THF (Aldrich), 2.2 ml, 0.22 mmol) was slowly added at 20°C to a solution of rac-**5b** / rac-**6b** (31.7 mg, 0.11 mmol) in THF (3 ml). The reaction mixture was stirred for 2 h at 20°C. Then water was added and CO_2 bubbled through the solution to liberate the free acid. Extraction with ether, drying and evaporation gave rac-**4** (23.3 mg, quantitative yield).

b) Reduction of rac-**5b** / rac-**6b** with Zn-Cu.

A solution of rac-**5b** / rac-**6b** (113.9 mg, 0.40 mmol) in THF (8 ml) was added at 20°C to zinc - copper couple (216.6 mg, 3.38 mmol). After addition of 10 µl acetic acid, the reaction mixture was stirred for 15 min at 20°C, then hydrolysed. The excess of Zn - Cu was filtered off and work-up (CH_2Cl_2) gave rac-**4** (67.7 mg, 83%), that was used without further purification.

M.p. 72 - 74°C (hexanes).- IR (CCl_4): 3300 - 2800, 1705 cm^{-1}.- ^1H NMR (400 MHz, C_6D_6): δ = 1.00 (s, 3H, 4-CH_3), 1.01 (s, 3H, 4-CH_3), 1.30 (t, 2H, CH_2-5, $J_{5,6}$ = 6.0 Hz), 1.97 - 2.31 (m, 5H, CH_2-6, CH_2-1, 2-CH_2-CO_2H), 2.64 - 2.79 (m, 1H, 2-CH_2-CO_2H), 3.12 (broad s, 1H, 2-H), 5.35 (s, 1H, 7-H), 5.54 (s, 1H, 3-H).- ^{13}C NMR (100.6 MHz, C_6D_6): δ = 23.23 (C-5), 27.80 (4-CH_3), 27.86 (4-CH_3), 31.90 (C-4), 35.59 (C-6), 37.04 (C-1), 39.66 (C-2), 41.16 (2-CH_2-CO_2H), 115.35 (C-7), 128.45 (C-3), 143.22 and 151.52 (C-3a and C-7a), 179.70 (C-9).- MS ($C_{13}H_{18}O_2$, 206.1): m/z (%) = 206 (M^+, 23), 191 (10), 173 (8), 147 (100), 131 (31), 119 (34), 105 (52), 91 (37).- HRMS calcd for $C_{13}H_{18}O_2$: 206.1307, found 206.1296.

Reaction of rac-**4** with N-bromosuccinimide
A solution of NBS (14.5 mg, 0.07 mmol) in THF (1.5 ml) was slowly added at 0°C to a solution of rac-**4** (13.0 mg, 0.06 mmol) in THF (0.5 ml). The reaction mixture was stirred for 15 min at 20°C. Solvent evaporation and LC (2.5 g SiO_2, hexanes - ethyl acetate 3 : 1) gave bromo lactones rac-**5b** and rac-**6b** (13.6 mg, 76%) as a roughly 1 : 1 mixture identical with a sample prepared as described above.

(±)-8,8-Dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**5g**)
A solution of (±)-10-camphorsulfonic acid (11.5 mg, 0.05 mmol) in CH_2Cl_2 (2 ml) was added at -70°C to a solution of rac-**4** (21.4 mg, 0.11 mmol) in CH_2Cl_2 (1 ml). The reaction mixture was stirred for 4 h (-70°C --> 20°C). Work-up (CH_2Cl_2) followed by LC (2.5 g SiO_2, hexanes - ethyl acetate 3 : 1) gave pure rac-**5g** (14.0 mg, 66%).- M.p. 43 - 45°C (hexanes).- IR ($CHCl_3$): 1760, 1170 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$, $^1H,^1H$ COSY, $^1H,^{13}C$ COSY, NOE): δ = 1.06 (s, 3H, 8-CH_3), 1.08 (s, 3H, 8-CH_3), 1.31 - 1.39 (ddd, 1H, 7$_c$-H), 1.43 - 1.49 (ddd, 1H, 7$_t$-H), 1.58 - 1.74 (m, 2H, CH_2-6), 1.85 - 2.03 (m^{24}, 2H, CH_2-5), 2.08 - 2.16 (d^{23}, 1H, 4$_t$-H), 2.27 - 2.35 (dd, 1H, 3$_t$-H), 2.53 - 2.62 (dd, 1H, 4$_c$-H), 2.72 - 2.82 (dd, 1H, 3$_c$-H), 2.94 - 3.04 (m, 1H, 3a-H), 5.42 - 5.47 (d^{23}, 1H, 8b-H); $J_{7c,7t}$ = 13.0 Hz, $J_{7c,6t}$ = 9.5 Hz, $J_{7c,6c}$ = 4.0 Hz, $J_{7t,6t}$ and $J_{7t,6c}$ = 4.0 and 6.5 Hz, $J_{4c,4t}$ = 16.5 Hz, $J_{4c,3a}$ = 8.5 Hz, $J_{4t,3a}$ = ca. 3.5 Hz, $J_{3c,3t}$ = 18.0 Hz, $J_{3c,3a}$ = 10.5 Hz, $J_{3t,3a}$ = 5.0 Hz, $J_{8b,3a}$ = 7.5 Hz, $J_{8b,4t}$ = ca. 1.5 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 19.54 (CH_2-6), 26.68 (CH_2-5), 28.03 (CH_3), 28.35 (CH_3), 32.16 (C_q-8), 34.75 (CH-3a), 36.49 (CH_2-3), 39.21 (CH_2-7), 42.56 (CH_2-4), 90.46 (CH-8b), 140.21 (C_q), 141.76 (C_q), 177.90 (C_q-2).- MS ($C_{13}H_{18}O_2$, 206.28): m/z (%) = 206 (M^+, 15), 191 (100), 131 (68).- HRMS calcd for $C_{13}H_{18}O_2$: 206.1307, found 206.1308.

Reaction of the bromo lactones rac-**5b** and rac-**6b** with Zn - Cu to give rac-**5g** and rac-**2**
A solution of bromo lactones rac-**5b** and rac-**6b** (276.0 mg, 0.97 mmol) in THF (14 ml) was added to zinc - copper (640.0 mg, 9.93 mmol). 96% acetic acid (50µl) were added and the reaction mixture was stirred for 1 h at 20°C. The excess of Zn - Cu was filtered off and the solvent was evaporated. The residue was redissolved in $CHCl_3$ (30 ml) and the solution stirred at 20°C for 2 d. LC (30 g SiO_2, hexanes - ethyl acetate 5 : 1) gave a fraction containing rac-**5g** and rac-**2** (114.8 mg, 58%). Such a mixture (257.1 mg, 1.25 mmol) was separated by MPLC (90 g SiO_2, n-heptane - tert-butyl methyl ether 3.5 : 1) to provide rac-**2** (2.1 mg, 1%), rac-**5g** (136.5 mg, 53%, identical with a sample prepared as described above), and a mixture of rac-**5g** and rac-**2** (87.2 mg, 34%).

(±)-5,5-Dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**2**)
IR ($CHCl_3$): 1760, 1170 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$, $^1H,^1H$ COSY, $^1H,^{13}C$ COSY, NOE): δ = 0.96 (s, 3H, 5$_c$-CH_3), 0.99 (s, 3H, 5$_t$-CH_3), 1.34 - 1.43 (ddd, 1H, 6$_c$-H), 1.43 - 1.50 (ddd, 1H, 6$_t$-H), 1.58 - 1.73 (m, 2H, CH_2-7), 1.88 - 1.94 (m, 1H, 8-H), 2.06 - 2.21 (m, 2H, 8-H', 4$_t$-H), 2.17 - 2.24 (dd, 1H, 3$_t$-H), 2.60 - 2.69 (m, 1H, 4$_c$-H), 2.76 - 2.84 (dd, 1H, 3$_c$-H), 2.98 - 3.08 (m, 1H, 3a-H), 5.24 - 5.29 (d, 1H, 8b-H); $J_{6c,6t}$ = 13.0 Hz, $J_{6c,7}$ = 7.0 Hz, $J_{6c,7'}$ = 5.5 Hz, $J_{6t,7'}$ = 7.0 Hz, $J_{6t,7}$ = 4.0 Hz, $J_{3c,3t}$ = 18.5 Hz, $J_{3c,3a}$ = 10.5 Hz, $J_{3t,3a}$ = 6.0 Hz, $J_{8b,3a}$ = 7.5 Hz. The 8b-H signal shows two further coupling constants (1.5 and 3.5 Hz).- ^1H NMR (400 MHz, C_6D_6, $^1H,^1H$ COSY, NOE): δ = 0.29 (s, 3H, 5-CH_3), 0.74 (s, 3H, 5-CH_3), 1.11 - 1.44 (m, 4H, CH_2-6, CH_2-7), 1.55 - 1.64 (m, 1H, 4-H), 1.64 - 1.73 (m, 1H, 8-H), 1.73 - 1.80 (dd, 1H, 3$_t$-H), 1.96 -2.18 (m, 3H, 4-H', 8-H', 3a-H), 2.17 - 2.23 (dd, 1H, 3$_c$-H), 4.68 - 4.72 (d, 1H, 8b-H).- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): δ = 19.61 (CH_2-7), 23.95 (CH_2-8), 27.24 (5-CH_3), 27.91 (5-CH_3), 32.47 (C_q-5), 34.30 (CH-3a), 36.72 (CH_2-3), 37.57 (CH_2-4), 38.49 (CH_2-6), 92.75 (CH-8b), 132.16 (C_q-8a), 148.28 (C_q-4a), 178.12 (C_q-2).- MS ($C_{13}H_{18}O_2$, 206.28): m/z (%) = 206 (M^+, 30), 191 (100), 147 (53), 145 (66), 91 (76), 41 (53). - HRMS calcd for $C_{13}H_{18}O_2$: 206.1307, found 206.1308.

(±)-2-Hydroxymethylen-8,8-dimethyl-(3a*r*,8b*c*)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**7b**)
Prepared as described by Brooks[21] for **7a**. Yield after LC (14.5 g SiO_2, hexanes - ethyl acetate 1 : 1): 91%.- IR ($CHCl_3$): 3600 - 3400, 1760, 1670, 1180 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 - 1.17 (2s, 6H, 8-CH_3-groups), 1.39 -1.41 (m, 1H, 7-H), 1.41 - 1.51 (m, 1H, 7-H'), 1.57 - 1.74 (m, 2.5H, CH_2-6, OH (enol)), 1.83 -2.07 (m, 2H, CH_2-5), 2.15 + 2.19 (2d, 1H, 4$_t$-H), 2.69 + 2.72 (2 dd, 1H, 4$_c$-H, aldehyde and enol), 3.37 - 3.66 (m,

1.5H, 3a-H and 3-H from the aldehyde), 5.47 (d, 0.55H, 8b-H enol), 5.59 (d, 0.45H, 8b-H aldehyde), 7.04 (broad s, 0.55H, C=CH enol), 9.81 (s, 0.45H, CHO); $J_{4c,4t}$= 16.5 Hz, $J_{4c,3a}$ = 8.0 Hz, $J_{8b,3a}$ = 8.0 Hz.- MS ($C_{14}H_{18}O_3$, 234.29): m/z (%) = 234 (M^+, 28), 219 (100), 201 (65), 173 (54), 133 (100), 131 (100), 105 (56), 91 (100), 77 (50), 55 (66), 41 (84).

Alkylation of rac-**7b** with bromo butenolide rac-**9**
Reaction and work-up were performed as described by Brooks[2] for the alkylation of **7a**. LC (14 g SiO_2, hexanes - ethyl acetate 5 : 1) gave rac-**10f** (34%, based on rac-**5g**) and rac-**10e** (43%, based on rac-**5g**).

(3aRS)-8,8-Dimethyl-3-((RS,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**10e**)
M.p. 139°C (hexanes - CH_2Cl_2).- IR ($CHCl_3$): 1790, 1740, 1680, 1340, 1180, 1100, 1010, 950 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H, 8-CH_3), 1.10 (s, 3H, 8-CH_3), 1.28 - 1.39 (ddd, 1H, 7t-H), 1.42 - 1.50 (ddd, 1H, 7c-H), 1.59 -1.72 (m, 2H, CH_2-6), 1.80 - 2.02 (m, 2H, CH_2-5), 2.01 (t, 3H, 4'-CH_3), 2.28 - 2.35 (d, 1H, 4t-H), 2.64 - 2.73 (dd, 1H, 4c-H), 3.52 - 3.60 (m, 1H, 3a-H), 5.46 - 5.52 (d, 1H, 8b-H), 6.09 - 6.12 (m, 1H, 2'-H), 6.90 - 6.93 (m, 1H, 3'-H), 7.39 - 7.42 (d, 1H, =CHO, J = 2.5 Hz); $J_{7c,7t}$ = 13.5 Hz, $J_{7t,6t}$ = 10.0 Hz, $J_{7t,6c}$ = 4.0 Hz, $J_{7c,6t}$ and $J_{7c,6c}$ = 6.0 and 4.0 Hz, $J_{2',3'}$= 1.5 Hz, $J_{2',4'\text{-}CH3}$ = 1.5 Hz, $J_{3',4'\text{-}CH3}$ = 1.5 Hz, $J_{4c,4t}$ = 17.0 Hz, $J_{4c,3a}$ = 9.0 Hz, $J_{8b,3a}$ = 8.0 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 10.97 (CH_3-4'), 19.46 (C-6), 26.62 (C-5), 28.04 (CH_3-8), 28.41 (CH_3-8), 32.18 (C-8), 36.84 (C-3a), 39.31 (C-7), 41.60 (C-4), 88.66 (C-8b), 100.79 (C-4'), 114.79 (C=C), 136.10 (C=C), 139.84 (CH=), 141.20 (C=C), 141.97 (C=C), 150.19 (=CHOR), 170.45 (C=O), 171.87 (C=O).- MS ($C_{19}H_{22}O_5$, 330.38): m/z (%) = 330 (M^+, 5), 233 (26), 215 (42), 187 (30), 97 (100).- Anal calcd for $C_{19}H_{22}O_5$: C 69.08, H 6.71, found C 68.99, H 6.52.

(3aRS)-8,8-Dimethyl-3-((SR,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-**10f**)
IR ($CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100.6 MHz, $CDCl_3$), MS : these spectra are superimposable with those obtained from rac-**10e**.- HRMS calcd for $C_{19}H_{22}O_5$: 330.1467, found 330.1461.

X-ray structure analysis of **10f**
10f, $C_{19}H_{22}O_5$, crystallises in the monoclinic space group $P2_1/n$ (No. 14) with a = 14.843(3), b = 5.806(1), c = 20.136(4) Å, β = 92.38(3)°, V = 1733.8(6) $Å^3$, Z = 4, D_c = 1.27 $Mg.m^{-3}$. The structure was refined to R = 0.069, wR = 0.069 for 1315 observed reflections with $F_o > 3\sigma(F_o)$ (CuK_α radiation, $2\theta_{max}$ = 115°, 2348 independent reflections measured, crystal size 0.12 x 0.25 x 0.4 mm, empirical absorption correction). Anisotropic temperature factors were introduced for the nonhydrogen atoms; hydrogen atoms were included at geometrically calculated positions. Further details of the crystal structure investigation may be obtained from Fachinformationszentrum Energie, Physik, Mathematik GmbH, W-7514 Eggenstein-Leopoldshafen 2 (Germany), on quoting the deposition number CSD 55684. Any request should be accompanied by the full literature citation of this paper.

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