67. Synthesis of Spiro[cyclohexane-1,2′-[2*H*]indene] Derivatives as Inhibitors of Steroid 5α-Reductase

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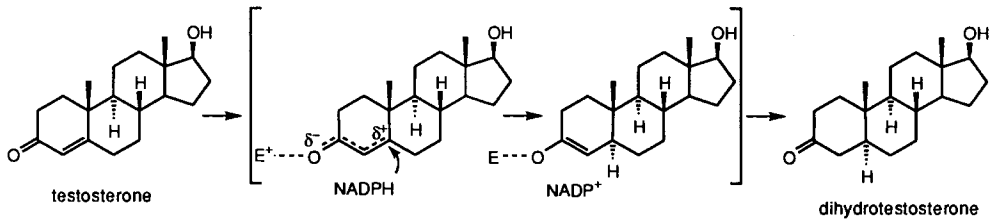
(9.II.95)

The spiro[cyclohexane-1,2′-[2*H*]indene] derivatives **15a,b** with molecular dimensions and nucleophilic functional groups similar to known steroid 5α-reductase inhibitors (*e.g.* **2**) were synthesized. The spiro[cyclohexane-1,2′-[2*H*]indene]-1′(3′*H*),4-dione (**5**) was synthesized from 5-methoxyindan-1-one (= 2,3-dihydro-5-methoxy-1*H*-inden-1-one). A *Grignard* reaction and a dehydration step led to the cyclohexene (±)-**7** which, upon a stereoselective hydrogenation catalyzed by *Raney*-Ni under mild conditions, gave **8a** as a pure epimer. Further hydrogenation and hydrogenolysis of **8a** over Pd/C at room temperature reduced the keto group to give pure **9a**. Finally, the 5′-substituted derivatives **12a**, **14a**, and **15a** were generated by deprotection and *Heck*-type reaction.

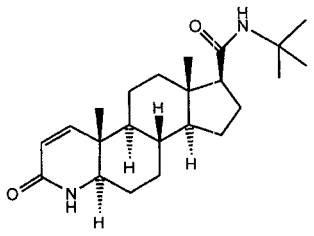
1. Introduction. – Dihydrotestosterone, a main androgen hormone, is assumed to be a causative factor in the progression of benign prostatic hyperplasia in elderly males and androgenic alopecia [1]. It is generated from testosterone under the catalysis of the enzyme steroid 5α-reductase (*cf. Scheme 1*) [2]. Finasteride (**1**), a 4-aza-3-oxo steroid, is a potent slow binding inhibitor [3] [4]. Recently, it was reported that carboxylic acids like dienecarboxylic acid **2** and its derivatives also strongly inhibit the human enzyme in a noncompetitive way by binding to the enzyme-$NADP^+$ complex [1] [2].

Scheme 1. *The Reaction Carried Out by Steroid 5α-Reductase*[a])



[a]) E represents the electrophilic residue in the active site of 5α-reductase.

The lactam group of **1** and the carboxy group of **2** probably mimic the nucleophilic oxy anion of the putative transition state of the substrate in the active site of the enzyme 5α-reductase [1] [2] [5]. Our goal was to synthesize non-steroidal 5α-reductase inhibitors with a similar molecular dimension to the lead compound **2**. The spiro[cyclohexane-1,2′-[2*H*]indene] series prepared in the following represents an attractive way to combine a carboxy group and the lipophilic *tert*-butyl group *via* a rigid spacer.



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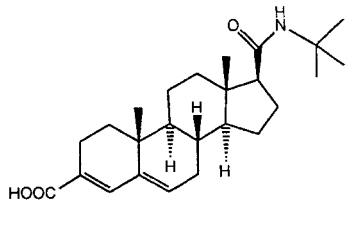
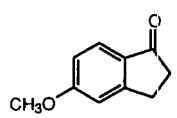
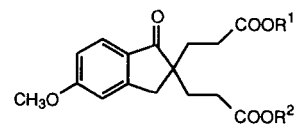


2

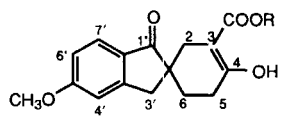
2. Results and Discussion. – The spiro[cyclohexane-1,2′-[2*H*]indene] skeleton was obtained following a modified procedure published by *Doggett et al.* [6]. Although diethyl 1-oxoindan-2,2-dipropanoate (**3a**) was easily prepared by *Michael* condensation of two ethyl acrylates with 5-methoxyindan-1-one (= 2,3-dihydro-5-methoxy-1*H*-inden-1-one), the following *Dieckmann* condensation did not lead to cyclization, but gave ethyl hydrogen 1-oxoindan-2,2-dipropanoate (**3b**) if NaOEt was used. β-Keto ester **4a** was obtained quantitatively by vigorously stirring **3a** with Na in dry toluene at refluxing temperature – a method described by *Pinkney* [7]. The β-keto ester **4a** exists exclusively in the enol form (NMR). β-Ketocarboxylic acid **4b**, also exclusively an enol tautomer (IR, NMR), was generated after saponification and then quantitatively decarboxylated either by refluxing in toluene or by pyrolysis at the melting point to give 5′-methoxyspiro[cyclohexane-1,2′-[2*H*]indene]-1′(3′*H*),4-dione (**5**).



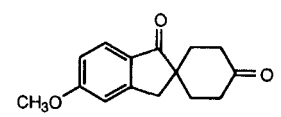
5-Methoxy-1-indanone



3a $R^1 = R^2 = Et$
b $R^1 = Et, R^2 = H$
c $R^1 = R^2 = H$



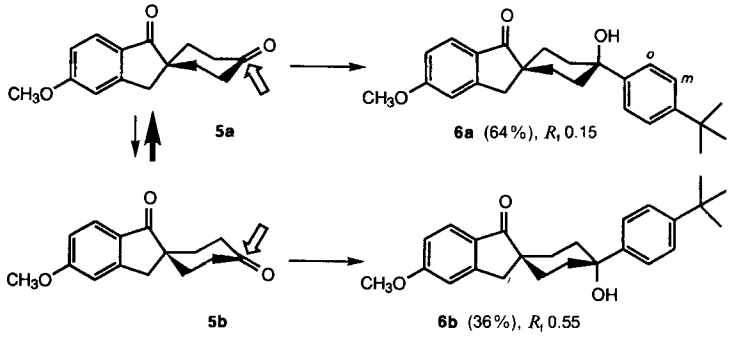
4a R = Et
b R = H



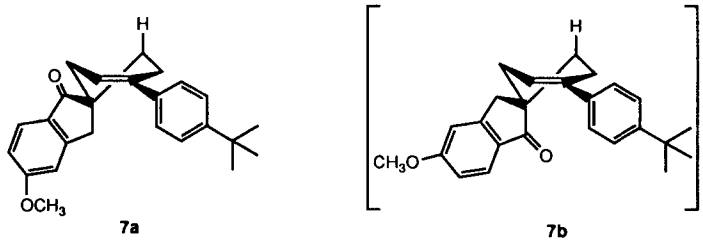
5

Diketone **5** was transformed to alcohol **6** through a *Grignard* reaction with the precursor 1-bromo-4-(*tert*-butyl)benzene. Product **6** consisted of a mixture of the two alcohols **6a** and **6b** (ratio 2:1), their structures (1D-NOE) and their possible formation being shown in *Scheme 2*. Conformer **5a** in which the keto group next to the spiro atom is in an equatorial position is more favorable (*cf.* also structure **7a**). We assume that the nucleophilic attack at the sterically less hindered side leads to the formation of a mixture with **6a** as the main component. The two isomers **6a** and **6b** were easily separated by flash chromatography.

Scheme 2



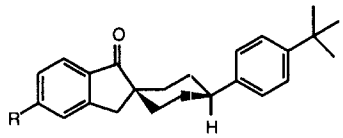
Both isomers **6a** and **6b** were dehydrated by refluxing with toluene-4-sulfonic acid for 5 min to give quantitatively the identical racemic cyclohexene (±)-**7**. The latter can exist as two different conformers. In (±)-**7a**, the keto group is in an equatorial position. Another conformer, (±)-**7b**, is not observed (1D-NOE).



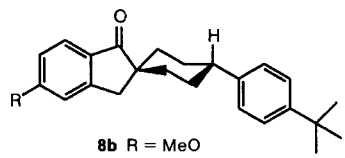
Hydrogenolysis of alcohol **6a** catalyzed by Pd/C gave a mixture of at least four components (TLC), with the hydrogenated (3 equiv. of H_2) **9a** (30%), a monohydroxy derivative **10** (20%), and a dihydroxy compound (±)-**11** (30%) being isolated and their configurations determined by 1D-NOE.

Using *Raney*-Ni as catalyst under normal H_2 pressure and at 20°, the slow hydrogenation of (±)-**7a** provided ketone **8a** as the sole epimeric product, as a result of the *cis*-addition from the lower side of the C=C bond of (±)-**7a** – the other side was presumably occupied first by adsorbing onto the metal catalyst. At 40° under otherwise the same catalytic conditions, the product was a mixture of the two epimers **8a** (78%) and **8b** (22%) which could be separated by flash chromatography.

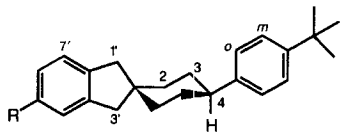
While Pd/C(10%)-catalyzed hydrogenation of the C=C bond of (±)-**7** was completed within seconds, the hydrogenation of the carbonyl group and the subsequent hydrogenolysis turned out to be a rather slow process. Due to its rapid uptake of the first mole of H_2 to hydrogenate the olefin bond, two final hydrogenated epimers **9a** (65%) and **9b** (35%) were detected from NMR. They have very similar chemical and physical properties, and their separation could not be achieved. Their derivatives, the phenols **12**, the triflates **13**, and the methyl carboxylates **14** as well as the corresponding carboxylic acids **15**, obtained by modification at the 5′-position, also could not be separated.



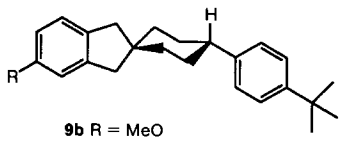
8a R = MeO



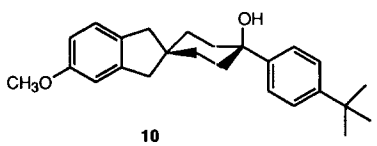
8b R = MeO



9a R = MeO
12a R = OH
13a R = CF_3SO_3
14a R = COOMe
15a R = COOH



9b R = MeO
12b R = OH
13b R = CF_3SO_3
14b R = COOMe
15b R = COOH



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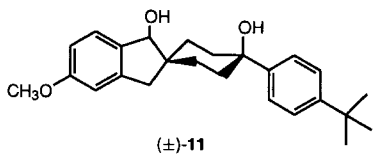
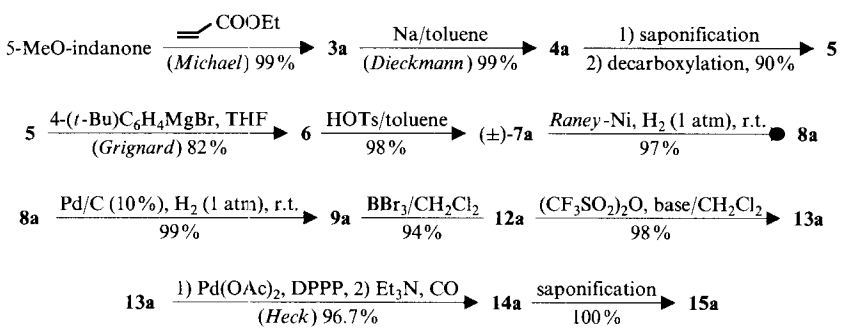


(±)-**11**

An optimized route for the synthesis of pure isomer **9a** and its derivatives **12a**, **13a**, **14a**, and **15a** was developed as shown in *Scheme 3*, where in every individual step the yield was excellent. It is noteworthy that in this strategy the 1′-keto group, which was removed only on conversion of **8a** to **9a**, served as an auxiliary functional group for the clean transformation of olefin (±)-**7a** to pure isomers **8a** and **9a** through selective catalytic hydrogenation. *Heck*-type reaction similar to the one used by *Holt et al.* [5] was carried out on **13** to prepare the carboxylic acids **15**.

Scheme 3



3. Conclusions. – We succeeded in preparing the spiro[cyclohexane-1,2′-[2*H*]indene] derivatives. Compound **15a** was shown to act as an inhibitor of steroid 5α-reductase. The detailed results of both the *in vitro* and *in vivo* biological tests will be described elsewhere.

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Experimental Part

General. Reaction solvents and chemical reagents were purchased from commercial laboratory supply houses, mainly *Fluka*. Oxygen- and moisture-sensitive reactions were carried out as follows: Apparatus was dried by cooling the hot apparatus with continuous inert gas (N_2 or Ar) flushing; reactants were evaporated *in vacuo* once with the absolute solvent and added against the inert gas stream; an inert-gas balloon was applied during the reaction. Flash chromatography (FC) and TLC: silica gel *60* (230–400 mesh, *Merck*) and silica gel HF_{254} plates (*Merck*), resp., with the mobile phase of pure solvent (*Ciba* products) or mixed solvents (*v*/*v* ratio). HPLC: retention time t_R in min. Melting points (m.p.): *Thomas-Hoover* melting-point apparatus, in open capillary tubes; uncorrected. IR Spectra: *Perkin-Elmer-290* instrument, in CH_2Cl_2 (*Merck*; spectroscopically pure) at a concentration of 10 mg/0.4 ml; for those solid samples not soluble in CH_2Cl_2, KBr pellets were measured on a *Perkin-Elmer-983* spectrometer. ^{1}H- and ^{13}C-NMR Spectra: *Varian-Gemini* 300-MHz spectrometer; chemical shifts δ in ppm rel. to $SiMe_4$, *J* in Hz; 1D-NOE studies on a *Varian-Unity* 500-MHz spectrometer; $CDCl_3$ (*Fluka*) as NMR solvent. Fast-atom-bombardment (FAB) mass spectra: *ZAB* HF instrument, thioglycerin or nitrobenzyl alcohol as matrix. Elemental analyses (found values within 0.3% deviation of the calc. percentage elemental composition) were performed by Analytical Research Services, *Ciba-Geigy Ltd.*

*Diethyl 2,3-Dihydro-5-methoxy-1-oxo-1*H*-indene-2,2-dipropanoate* (**3a**). Under N_2, *Triton B* (benzyl(trimethyl)ammonium hydroxide; 40% in MeOH, 2.48 ml) was added to a soln. of 2,3-dihydro-5-methoxy-1*H*-inden-1-one (20.16 g, 0.124 mol) in toluene (120 ml) all at once and stirred at 50° for 10 min. Ethyl acrylate (31.0 ml, 0.286 mol) was added at 50°. The mixture was stirred under reflux overnight, then cooled to r.t., poured into H_2O (150 ml), and extracted with CH_2Cl_2 (4 × 100 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. The oily residue was flash chromatographed (180 g of silica gel, AcOEt): **3a** (44.73 g, 99%). Viscous brown oil. TLC (AcOEt): R_f 0.6. IR (CH_2Cl_2): 3055, 1731 (C=O, COOEt), 1697 (C=O, ArCO), 1600 (Ar), 1185. ^{1}H-NMR ($CDCl_3$): 1.21 (*t*, 2 *Me*CH_2O); 1.95 (*m*, 4 H, CH_2, 2 sets of diastereotopic H's); 2.20 (*m*, 4 H, CH_2, 2 sets of diastereotopic protons); 2.96 (*s*, 2 H–C(3)); 3.89 (*s*, MeO); 4.08 (*q*, 2 MeCH_2O); 6.87 (*s*, H–C(4)); 6.91 (*d*, *J* = 8.5, H–C(6)); 7.66 (*d*, H–C(7)).

*Ethyl Hydrogen 2,3-Dihydro-5-methoxy-1-oxo-1*H*-indene-2,2-dipropanoate* (**3b**). To a suspension of NaOEt (0.37 g, 16 mmol) in DMF (8 ml), **3a** (4.38 g, 12 mmol) in DMF (9 ml) was added and stirred at 40° under N_2 overnight. After evaporation at 45°, the residue was diluted with 2N HCl (10 ml) and H_2O (50 ml) and the mixture extracted with AcOEt (50 ml). The org. phase was washed with H_2O (2 × 50 ml), dried (Na_2SO_4), and evaporated: viscous yellow oil (3.98 g). A 1st FC (AcOEt) recovered **3a** (1.23 g, 3.4 mmol). A 2nd FC (AcOEt/hexane 1:1) gave **3b** (1.54 g, 39%). Yellow oil. TLC (AcOEt/hexane 1:1). R_f 0.07. IR (CH_2Cl_2): 3000–2500 (COOH), 1731 (C=O of COOEt), 1712, 1700 (C=O or ArCO, sh), 1600 (Ar). ^{1}H-NMR ($CDCl_3$): 1.21 (*t*, *Me*CH_2O); 1.95 (*m*, 4 H, CH_2, diastereotopic); 2.20 (*m*, 4 H, CH_2, diastereotopic); 2.96 (*s*, 2 H–C(3)); 3.89 (*s*, MeO); 4.10 (*q*, MeCH_2O); 6.87 (*s*, H–C(4)); 6.91 (*d*, *J* = 8.5, H–C(6)); 7.66 (*d*, H–C(7)).

*2,3-Dihydro-5-methoxy-1-oxo-1*H*-indene-2,2-dipropanoic Diacid* (**3c**). A soln. of **3b** (1.54 g, 4.63 mmol) in EtOH (10 ml) was stirred with 4% aq. NaOH soln. (10 ml) for 1 h under N_2. Then the EtOH was evaporated at 40° and, the remaining aq. soln. neutralized with 4N HCl (*ca.* 2.5 ml) to give a white suspension which was extracted with AcOEt (2 × 50 ml). After washing with H_2O (3 × 50 ml), the combined org. layer was dried (Na_2SO_4) and evaporated and the solid washed with Et_2O/AcOEt to give **3c** (0.654 g) as white solid. Additional **3c** (0.670 g) precipitated from the aq. soln. after standing for 30 days. Combined yield 93%. Insoluble in $CDCl_3$, CH_2Cl_2, and toluene. M.p. 150–151°. TLC (7% MeOH/AcOEt): R_f 0.20. IR (KBr): 3000–2500 (COOH), 1728 (C=O of COOH), 1689 (C=O of ArCO), 1603 (Ar), 1295, 1263 (C–O), 835. ^{1}H-NMR ((D$_6$)DMSO): 1.75 (*m*, 4 H, CH_2, diastereotopic); 1.9 (*m*, 2 H, CH_2, diastereotopic); 2.1 (*m*, 2 H, CH_2, diastereotopic); 2.96 (*s*, 2 H–C(3)); 3.87 (*s*, MeO), 6.97(*dd*, H–C(6)); 7.08 (*d*, H–C(4)); 7.56 (*d*, H–C(7)).

*Ethyl 1′,3′-Dihydro-5′-methoxy-1′,4-dioxospiro[cyclohexane-1,2′-[2*H*]indene]-3-carboxylate* (**4a**). A soln. of **3a** (4.40 g, 12.1 mmol) in toluene (22 ml) was dropwise added to a flask containing Na (0.30 g, 13 mmol) and dry toluene (15 ml) refluxing at 120°. The resulting slurry was refluxed at 120° for 1.5 h, then cooled to r.t., and poured into H_2O (40 ml) containing 4N HCl (4 ml) to afford a white suspension. This was then extracted with AcOEt (4 × 100 ml), evaporated, and chromatographed (silica gel (140 g), AcOEt/CH_2Cl_2 1:9): **4a** (3.83 g, 99%). Yellow viscous oil. TLC (AcOEt/CH_2Cl_2 1:9): R_f 0.54. IR (CH_2Cl_2): 2941, 1739, 1698, 1656, 1600 (Ar). ^{1}H-NMR ($CDCl_3$): 1.26 (*t*, *Me*CH_2O); 1.58 (*m*, 1 H–C(6)); 2.04 (*m*, 1 H–C(6)); 2.17 (*d*, 1 H–C(2)); 2.48 (*m*, 2 H–C(5)); 2.57 (*d*,

1 H–C(2)); 2.95 (*q*, 2 H–C(3′)); 3.90 (*s*, MeO); 4.18 (*m*, MeCH_2O, diastereotopic); 6.87 (*s*, H–C(4′)); 6.93 (*d*, H–C(6′)); 7.72 (*d*, H–C(7′)); 12.31 (*s*, 1 H, OH–C(4); 100% enol form).

*1′,3′-Dihydro-5′-methoxy-1′,4-dioxospiro[cyclohexane-1,2′-[2*H*]indene]-3-carboxylic Acid* (**4b**). To a soln. of **4a** (2.30 g, 7.2 mmol) in EtOH (10 ml) was added 4% aq. NaOH soln. (40 ml). EtOH was removed from the mixture by evaporation at 40°. The aq. soln. was acidified with 4N HCl (4 ml) to immediately give a white suspension which was extracted with AcOEt and then precipitated with hexane. Evaporation and washing with Et_2O (2 × 5 ml) gave **4b** (0.76 g, 37%). Colorless crystals. M.p. 120° (dec.). TLC (AcOEt/hexane 1:1): R_f 0.05. IR (KBr): 3000–2500 (COOH), 2946, 1696, 1548, 1612 (Ar), 1258, 1201, 1026. ^{1}H-NMR ($CDCl_3$): 1.60 (*m*, 1 H–C(6)); 2.05 (*m*, 1 H–C(6)); 2.20 (*d*, H–C(2)); 2.50 (*m*, 2 H–C(5)); 2.60 (*d*, 1 H–C(2)); 2.95 (*q*, 2 H–C(3′)); 3.89 (*s*, MeO); 6.87 (*s*, 1 H–C(4′)); 6.92 (*d*, 1 H–C(6′)); 7.72 (*d*, 1 H–C(7′)); 12.00 (*s*, 1 H, OH–C(4); 100% enol form).

*5′-Methoxyspiro[cyclohexane-1,2′-[2*H*]indene]-1′(3′*H*),4-dione* (**5**). Compound **4b** (0.21 g, 0.7 mmol) was placed in a test tube and melted in a 150° oil bath. Immediate gas evolution upon melting gave, after recrystallization (Et_2O), a white solid **5** (0.12 g, 70%). In a separate run, **4b** (0.325 g, 1.13 mmol) in 20 ml toluene was refluxed for 2 h with a 120° oil bath. The solid residue was recrystallized from Et_2O to afford **5** (0.23 g, 80%). An up-scaled run starting directly from **4a** was carried out by dissolving **4a** (22.89 g, 72.4 mmol) in EtOH (150 ml). The resulting soln. was stirred with a soln. of NaOH (6.13 g) in H_2O (200 ml). After workup, **4b** was decarboxylated by refluxing in toluene (70 ml) for 2 h. The residue was flah chromatographed (500 g of silica gel, CH_2Cl_2/AcOEt 9:1): **5** (15.98 g, 90% based on **4a**). White solid. M.p. 114°. TLC (AcOEt/CH_2Cl_2 1:9): R_f 0.25. IR (CH_2Cl_2): 2940, 1714, 1700, 1601, 1491, 1090, 846. ^{1}H-NMR ($CDCl_3$): 1.84 (*m*, 1 H–C(2), 1 H–C(6)); 2.20 (*m*, 1 H–C(2), 1 H–C(6)); 2.45 (*m*, 1 H–C(3), 1 H–C(5)); 2.70 (*d*, 1 H–C(3), 1 H–C(5)); 3.17 (*s*, 2 H–C(3′)); 3.90 (*s*, MeO); 6.90 (*s*, H–C(4′)); 6.92 (*d*, H–C(6′)); 7.73 (*d*, H–C(7′)). Anal. calc. for $C_{15}H_{16}O_3$ (244.29): C 73.75, H 6.60; found: C 73.47, H 6.57.

*4-[4-(*tert*-Butyl)phenyl]-4-hydroxy-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]inden]-1′(3′*H*)-one* (**6a** and **6b**). Mg (0.243 g, 10 mmol) and THF (10 ml) were placed in a 100-ml 4-necked flask under N_2. A soln. of 1-bromo-4-(*tert*-butyl)benzene (1.56 ml, 9.0 mmol) in THF (20 ml) was placed in a dropping funnel. The reaction was started by releasing 1 ml of the soln. from the dropping funnel and heating with a heating gun until the mixture in the flask was grey and cloudy. The rest of the bromide soln. was added dropwise (1 drop/4 s) under intensive stirring. The mixture was refluxed at 80° (oil bath) for 1 h and then cooled to 10°. A soln. of **5** (2.00 g, 8.19 mmol) in THF (20 ml) was added gradually at 10° within 5 min under intensive stirring. The resulting mixture was allowed to warm up to r.t. and then refluxed (80° oil bath) for 1 h. It was then poured into a mixture of 1N HCl (10 ml) and ice (10 g) and extracted one with CH_2Cl_2. The CH_2Cl_2 phase was washed with a mixture of 1N HCl (5 ml) and H_2O (15 ml). Evaporation gave a white precipitate which, upon FC (silica gel (100 g), CH_2Cl_2/AcOEt 9:1), gave, besides unreacted **5** (0.18 g), the two well-separated stereoisomers **6a** and **6b** (total yield 2.32 g, 82%; based on consumed **5**).

6a (64% of the total yield): Colorless crystals. M.p. 183–184°. TLC (CH_2Cl_2/AcOEt 8:1): R_f 0.15. IR (CH_2Cl_2): 3590 (OH), 2966, 1693 (C=O), 1660 (Ar). ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.27 (*s*, *t*-Bu); 1.32 (br. *d*, J = 14, H_{eq}–C(2), H_{eq}–C(6)); 1.51 (*s*, OH); 1.87 (br. *d*, J = 14, H_{eq}–C(3), H_{eq}–C(5)); 1.94 (*td*, J = 13.5, 3.6, H_{ax}–C(3), H_{ax}–C(5)); 2.26 (*td*, J = 13.5, 4.1, H_{ax}–C(2), H_{ax}–C(6)); 3.01 (*s*, 2 H–C(3′)); 3.83 (*s*, MeO); 6.84 (*d*, J = 2, H–C(4′)); 6.86 (*dd*, J = 8.5, 2, H–C(6′)); 7.33 (*d*, J = 8.5, 2 H_m); 7.42 (*d*, J = 8.5, 2 H_o); 7.67 (*d*, J = 8.5, H–C(7′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 29.0 (CH_2); 31.2 (*Me*$_3$C); 34.3 (Me$_3$*C*); 35.2 (CH_2); 37.9 (CH_2); 49.6 (C(2)); 55.5 (MeO); 71.4 (C(4)); 109.7 (C(4′)); 115.3 (C(6′)); 124.0 (C$_m$); 125.0 (C$_o$); 126.0 (C(7′)); 128.9 (quat. C); 145.8 (quat. C); 149.7 (quat. C); 155.2 (quat. C); 165.3 (C(5′)); 208.8 (C(1′)). Anal. calc. for $C_{25}H_{30}O_3$ (378.51): C 79.33, H 7.99; found: C 79.39, H 8.23.

6b (36% of the total yield): Colorless crystals. M.p. 165–166°. TLC (CH_2Cl_2/AcOEt 8:1): R_f 0.55. IR (CH_2Cl_2): 3590 (OH), 2966, 1693 (C=O), 1601 (Ar). ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.34 (*s*, *t*-Bu); 1.57 (*s*, OH); *ca.* 1.76 (*m*, H_{eq}–C(3), H_{eq}–C(5)); *ca.* 1.76 (*m*, H_{eq}–C(2), H_{eq}–C(6)); 1.94 (*m*, H_{ax}–C(3), H_{ax}–C(5)); 2.72 (*m*, H_{ax}–C(2), H_{ax}–C(6)); 3.0.1 (*s*, 2 H–C(3′)); 3.88 (*s*, MeO); 6.86 (*d*, J = 2, H–C(4′)); 6.90 (*dd*, J = 8.5, 2, H–C(6′)); 7.40 (*d*, J = 8.5, 2 H_m); 7.54 (*d*, J = 8.5, 2 H_o); 7.66 (*d*, J = 8.5, H–C(7′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 30.5 (CH_2); 31.0 (*Me*$_3$C); 34.1 (Me$_3$*C*); 34.5 (CH_2); 42.2 (CH_2); 47.7 (C(2)); 55.3 (MeO); 72.3 (C(4)); 109.2 (C(4′)); 115.0 (C(6′)); 124.4 (C$_m$); 125.0 (C$_o$); 125.5 (C(7′)); 128.8 (quat. C); 144.3 (quat. C); 149.5 (quat. C); 154.7 (quat. C); 165.0 (C(5′)); 208.5 (C(1′)). Anal. calc. for $C_{25}H_{30}O_3$ (378.51): C 79.33, H 7.99; found: C 79.50, H 8.22.

*4-[4-(*tert*-Butyl)phenyl]-5′-methoxyspiro[cyclohex-3-ene-1,2′-[2*H*]inden]-1′(3′*H*)-one* ((±)-**7a**). To **6a** or **6b** (50 mg, 138 μmol each), a soln. (5 ml) of toluene-4-sulfonic acid in toluene (31.5 μmol in 11.4 ml, dissolved only after stirring at 120°) was added and the clear soln. stirred at 130° for 10 min. Both **6a** and **6b** gave the same compound (±)-**7a**, as indicated by TLC (CH_2Cl_2/AcOEt 8:1, R_f 0.70). The respective reaction mixtures were combined, treated with ice/H_2O, and extracted with AcOEt: (±)-**7a** (98 mg, 98%). White powder. M.p. 192–193°. IR (CH_2Cl_2): 2966, 1695 (C=O), 1600 (Ar), 1089. ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.33 (*s*, *t*-Bu); 1.68

(*ddt*, J = 13.1, 6.0, 2.0, H_{eq}–C(6)); 2.01 (*ddm*, J = 18, *ca.* 6, H–C(2)); 2.07 (*ddd*, J = 13.2, 11.9, 6 H_{ax}–C(6)); 2.58 (*dm*, *J ca.* 18, H_{ax}–C(5)); 2.67 (br. *d*, J = 18, H_{eq}–C(5)); 2.67 (br. *d*, J = 18, H–C(2)); 2.90 (*d*, J = 17.0, 1 H–C(3′)); 3.06 (*d*, J = 17.0, 1 H–C(3′)); 3.89 (*s*, MeO); 6.21 (br. *d*, J = 4.3, H–C(3)); 6.87 (*d*, J = 2.2, H–C(4′)); 6.93 (*dd*, J = 8.6, 2.2, H–C(6′)); 7.37 (*d*, J = 8.7, 2 H_m); 7.40 (*d*, J = 8.7, 2 H_o); 7.73 (*d*, J = 8.5, H–C(7′)). Anal. calc. for $C_{25}H_{28}O_2$ (360.50): C 83.29, H 7.83; found: C 83.12, H 7.68.

Hydrogenation of **6a** *to* **9a**, **10**, *and (±)-*11. Alcohol **6a** (100 mg, 264 µmol) in MeOH (5 ml) was hydrogenated at 21° over 5% Pd/C (20 mg) by shaking with H_2 (1 atm) for 5 h. Consumption: 3 equiv. of H_2. FC (twice; silica gel (10 g), CH_2Cl_2; silica gel (30 g) toluene) gave three white solids; **9a** (30 mg, 30%; TLC (CH_2Cl_2): R_f 0.98), **10** (22 mg, 22%; TLC (CH_2Cl_2): R_f 0.30), and (±)-**11** (30 mg, 30%; TLC (toluene): R_f 0.02).

*4-[4-(*tert*-Butyl)phenyl]-1′,3′-dihydro-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]indene]* (**9a**). IR (CH_2Cl_2): 2926, 1610 (Ar), 1491, 1248, 833. ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.32 (*s*, *t*-Bu); 1.54 (*m*, H_{ax}–C(3), H_{ax}–C(5)); 1.64 (*dq*, J = 12.9, 2.0, H_{ax}–C(2), H_{ax}–C(6)); 1.81 (br. *d*, H_{eq}–C(2), H_{eq}–C(3), H_{eq}–C(5), H_{eq}–C(6)); 2.51 (*tt*, J = 12.0, 3.5, H_{ax}–C(4)); 2.75 (*s*, 2 H–C(3′)); 2.83 (*s*, 2 H–C(1′)); 3.78 (*s*, MeO); 6.69 (*dd*, J = 8, 2, H–C(6′)); 6.84 (*d*, J = 2, H–C(4′)); 7.07 (*d*, J = 8, H–C(7′)); 7.18 (*d*, J = 8.5, 2 H_o); 7.33 (*d*, J = 8.5, 2 H_m).

*4-[4-(*tert*-Butyl)phenyl]-1′,3′-dihydro-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]inden]-4-ol* (**10**). ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.35 (*s*, *t*-Bu); 1.63 (br. *d*, J = 13, H_{eq}–C(2), H_{eq}–C(6)); 1.80 (br. *d*, J = 13, H_{eq}–C(3), H_{eq}–C(5)); 1.95 (*td*, J = 13, 3, H_{ax}–C(2), H_{ax}–C(6)); 2.16 (*td*, J = 13, 3, H_{ax}–C(3), H_{ax}–C(5)); 2.78 (*s*, 2 H–C(1′)); 2.87 (*s*, 2 H–C(3′)); 3.79 (*s*, MeO); 6.71 (*d*, J = 8, H–C(6′)); 6.76 (*s*, H–C(4′)); 7.10 (*d*, J = 8, H–C(7′)); 7.40 (*d*, J = 8.5, 2 H_m); 7.48 (*d*, J = 8.5, 2 H_o).

*4-[4-(*tert*-Butyl)phenyl]-1′,3′-dihydro-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]indene]-1′,4′-diol* ((±)-**11**). M.p. 102–106°. IR (CH_2Cl_2): 3591 (OH), 2963, 1610 (Ar), 1492, 831. ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.32 (*s*, *t*-Bu); 1.54–2.05 (*m*, 4 CH_2); 2.71 (*d*, J = 15.9, 1 H–C(3′)); 2.89 (*d*, J = 15.9, 1 H–C(3′)); 3.81 (*s*, MeO); 4.70 (br. *s*, H–C(1′)); 6.78 (*s*, H–C(4′)); 6.79 (*d*, J = 8, H–C(6′)); 7.33 (*d*, J = 8, H–C(7′)); 7.40 (*d*, J = 8.5, 2 H_m); 7.48 (*d*, J = 8.5, 2 H_o). FAB-MS (pos. mode): 381 ($[M + H]^+$). FAB-MS (neg. mode): 379 ($[M - H]^-$).

cis-*4-[4-(*tert*-Butyl)phenyl]-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]inden]-1′(3′*H*)-one* (**8a**). A soln. of (±)-**7a** (0.4935 g, 1.37 mmol) in THF (50 ml) was subjected to slow hydrogenation with *Raney*-Ni (0.1 g) and H_2 (1 atm, 1 equiv.) at 22° for 40 h. The solid residue was chromatographed (silica gel (25 g), first toluene, then 10% acetone/toluene): (±)-**7a** (0.1366 g, 0.38 mmol) and **8a** (0.3132 g, 97% based on consumed (±)-**7a**). M.p. 115–116°. TLC (toluene): R_f 0.20. IR (CH_2Cl_2): 2966, 1693 (C=O), 1601 (Ar). ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.37 (*s*, *t*-Bu); 1.70 (*td*, J = 13.2, 3.9, H_{ax}–C(2), H_{ax}–C(6)); 1.75 (*dq*, J = 13.5, 3.9, H_{eq}–C(3), H_{eq}–C(5)); 2.00 (br. *d*, J = 13.7, H_{eq}–C(2), H_{eq}–C(6)); 2.42 (*qd*, J = 12.6, 3.6, H_{ax}–C(3), H_{ax}–C(5)); 2.61 (*tt*, J = 11.4, 3.6, H_{ax}–C(4)); 2.96 (*s*, 2 H–C(3′)); 3.89 (*s*, MeO); 6.86 (*d*, J = 2, H–C(4′)); 6.91 (*dd*, J = 8.5, 2, H–C(6′)); 7.32 (*d*, J = 8.1, 2 H_o); 7.38 (*d*, J = 8.1, 2 H_m); 7.70 (*d*, J = 8.5, H–C(7′)). Anal. calc. for $C_{25}H_{30}O_2$ (362.51): C 82.83, H 8.34; found: C 82.68, H 8.21.

trans-*4-[4-(*tert*-Butyl)phenyl]-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]inden]-1′(3′*H*)-one* (**8b**). *Raney*-Ni (4.5 g) catalyzed hydrogenation of (±)-**7a** (5.46 g, 15.2 mmol) in THF (400 ml) was carried out at 40° for 40 h. The solid residue was chromatographed (silica gel (150 g), toluene) to give **8a** (4.1234 g, 75%; spectroscopic data as described above) and **8b** (1.14 g, 21%). Total yield 96%. **8b**: M.p. 166–167°. TLC (toluene): R_f 0.05. IR (CH_2Cl_2): 2966, 1695 (C=O), 1600 (Ar), 1091. ^{1}H-NMR ($CDCl_3$): 1.33 (*s*, *t*-Bu); 1.50–1.70 (*m*, 2 CH_2); 1.90–2.00 (*m*, 2 CH_2); 2.65 (*tt*, J = 11.4, 3.6, H_{ax}–C(4)); 3.18 (*s*, 2 H–C(3′)); 3.90 (*s*, MeO); 6.91 (*s*, H–C(4′)); 6.92 (*d*, J = 8, H–C(6′)); 7.20, 7.38 (2*d*, J = 8.5, 2 H_o, 2 H_m); 7.72 (*d*, J = 8, H–C(7′)). Anal. calc. for $C_{25}H_{30}O_2$ (362.51): C 82.83, H 8.34; found: C 82.76, H 8.21.

trans-*4-[4-(*tert*-Butyl)phenyl]-1′,3′-dihydro-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]indene]* (**9a**). Hydrogenation (1 equiv. of H_2) and hydrogenolysis (1 equiv. of H_2) of **8a** (4.00 g, 11.03 mmol) in THF (200 ml) were achieved in one step over 10% Pd/C (2 g) with H_2 (1 atm) at 23° for 16 h. Filtration and precipitation with CH_2Cl_2/MeOH gave **9a**. White solid. M.p. 84–85°. TLC (toluene): R_f 0.62. ^{1}H-NMR and IR: as described above for an authentic sample prepared from **6a**. Anal. calc. for $C_{25}H_{32}O$ (348.53): C 86.16, H 9.25; found: C 85.92, H 9.20.

cis-*4-[4-(*tert*-Butyl)phenyl]-1′,3′-dihydro-5′-methoxyspiro[cyclohexane-1,2′-[2*H*]indene]* (**9b**). As described for **9a**, with **8b** (0.109 g, 0.30 mmol), THF (10 ml), 10% Pd/C (0.1 g), and H_2 (1 atm; 15 h). FC and precipitation from CH_2Cl_2/MeOH gave **9b** (86.4 mg, 83%). White solid. M.p. 80–81°. TLC (toluene): R_f 0.62. IR (CH_2Cl_2): same as for **9a**. ^{1}H-NMR ($CDCl_3$): 2.70, 2.88 (2*s*, 2 H–C(1′), 2 H–C(3′)); remaining signals as described for **9a**. Anal. calc. for $C_{25}H_{32}O$ (348.53): C 86.16, H 9.25; found: C 86.24, H 9.35.

Mixture **9a**/**9b** *65:35*. Compound (±)-**7a** (6.00 g, 16.64 mmol) in THF (400 ml) was treated over 10% Pd/C (2.0 g) with H_2 (1 atm) at 23° for 45 h (uptake of 3 equiv. of H_2). Filtration, evaporation, and recrystallization from

CH_2Cl_2/MeOH gave **9a**/**9b** 65:35 (by ^{1}H-NMR; 4.87 g, 84%). White solid. ^{1}H-NMR ($CDCl_3$): '*AB*' at 2.79 (2.70, 2.74, 2.82, 2.87; 4 lines, 2 H–C(1'), 2 H–C(3')).

trans-*4-[4-(*tert-*Butyl)phenyl]-1',3'-dihydrospiro[cyclohexane-1,2'-[2*H*]inden]-5-ol* (**12a**). A soln. of **9a** (3.597 g, 10.32 mmol) in CH_2Cl_2 (125 ml) was stirred with BBr_3 (1.53 ml, 15.48 mmol) at 0° for 15 min and r.t. for 40 min. H_2O (500 ml) was added to this mixture at 0° (inner temp. controlled: < 5°). The mixture was poured into H_2O (500 ml) and extracted with CH_2Cl_2. After evaporation of the combined org. layers, the solid residue was chromatographed (silica gel (140 g), toluene) and recrystallized from toluene: **12a** (3.23 g, 94%). M.p. 156°. TLC (toluene): R_f 0.25. IR (CH_2Cl_2): 3585 (OH), 2926, 1614 (Ar), 1491, 1296, 832. ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.32 (*s*, *t*-Bu); 1.54 (*m*, H_{ax}–C(3), H_{ax}–C(5)); 1.64 (*qd*, *J* = 12,9, 2.0, H_{ax}–C(2), H_{ax}–C(6)); 1.81 (br. *d*, H_{eq}–C(2), H_{eq}–C(3), H_{eq}–C(5), H_{eq}–C(6)); 2.51 (*t*, *J* = 12.0, H_{ax}–C(4)); 2.73 (*s*, 2 H–C(3')); 2.82 (*s*, 2 H–C(1')); 4.50 (*s*, OH); 6.60 (*d*, *J* = 8, H–C(6')); 6.68 (*s*, H–C(4')); 7.03 (*d*, *J* = 8, H–C(7')); 7.19 (*d*, *J* = 8.5, 2 H_o); 7.33 (*d*, *J* = 8.5, 2 H_m). Anal. calc. for $C_{24}H_{30}O$ (334.50): C 86.18, H 9.04; found: C 86.30, H 9.14.

trans-*4-[4-(*tert-*Butyl)phenyl]-1',3'-dihydrospiro[cyclohexane-1,2'-[2*H*]inden]-5-yl Trifluoromethanesulfonate* (**13a**). To **12a** (2.98 g, 8.91 mmol) in CH_2Cl_2 (60 ml), 2,6-di(*tert*-butyl)-4-methylpyridine (2.44 g, 11.88 mmol) was added against a N_2 stream and dissolved by stirring. Then Tf_2O (trifluoromethanesulfonic anhydride; 2.60 ml, 15.85 mmol) was added all at once with a syringe. CH_2Cl_2 (20 ml) was added, the mixture stirred for 2 h, then shaken with ice (200 g), and H_2O (300 ml), and extracted with CH_2Cl_2 (500 ml). The blue org. phase was washed twice with H_2O (2 × 500 ml). Evaporation and chromatography (silica gel (1 kg), hexane/CH_2Cl_2 5:1) gave **13a** (4.059 g, 98%). White solid. M.p. (after recrystallization from CH_2Cl_2/MeOH) 85–86°. TLC (hexane/CH_2Cl_2 5:1): R_f 0.26. IR (CH_2Cl_2): 2927, 1611 (Ar), 1479, 1411 (S–O), 1216 (S–O), 1140, 934, 867, 833. ^{1}H-NMR ($CDCl_3$): 1.33 (*s*, *t*-Bu); 1.50–1.70 (*m*, 4 H); 1.75–1.85 (*m*, 4 H); 2.51 (*t*, *J* = 12.0, H_{ax}–C(4)); 2.80 (*s*, 2 H–C(3')); 2.91 (*s*, 2 H–C(1')); 7.01 (*d*, *J* = 8, H–C(6')); 7.06 (*s*, H–C(4')); 7.19 (*d*, *J* = 8.5, 2 H_o); 7.22 (*d*, *J* = 8, H–C(7')); 7.33 (*d*, *J* = 8.5, 2 H_m). ^{19}F-NMR (282 MHz, $CDCl_3$): 1 *s*. Anal. calc. for $C_{25}H_{29}F_3O_3S$ (466.56): C 64.36, H 6.26; found: C 64.38, H 6.49.

Methyl trans-*4-[4-(*tert-*butyl)phenyl]-1',3'-dihydrospiro[cyclohexane-1,2'-[2*H*]indene]-5'-carboxylate* (**14a**). A soln. of palladium(II) acetate (0.1791 g, 0.7977 mmol) and 1,3-bis(diphenylphosphino)propane (DPPP; 0.3290 g, 0.7977 mmol) in DMSO (25 ml) and MeOH (16 ml) was mixed with a soln. of **13a** (3.7215 g, 7.98 mmol) in 1,2-dichloroethane (9 ml) and stirred at 70°. Et_3N (2.21 ml, 15.95 mmol) was then added and stirring at 70° continued with CO bubbling for 2 h. The cooled mixture was diluted with CH_2Cl_2 (150 ml), washed with H_2O (2 × 200 ml), filtered through a cotton plug, and evaporated. Flash chromatography (hexane/CH_2Cl_2 2:1) gave recovered **13a** (93.5 mg, 0.2 mmol) and, after precipitation from CH_2Cl_2/MeOH, **14a** (2.8498 g, 96.7% based on converted **13a**). White solid. M.p. (after recrystallization from CH_2Cl_2/MeOH) 118°. TLC (hexane/CH_2Cl_2 1:1): R_f 0.4. IR (CH_2Cl_2): 2926, 1713 (C=O), 1614 (Ar), 1435, 1296, 833. ^{1}H-NMR ($CDCl_3$): 1.32 (*s*, *t*-Bu); 1.50–1.70 (*m*, 4 H); 1.75–1.85 (*m*, 4 H); 2.52 (*t*, *J* = 12, 1 H); 2.81 (*s*, 2 H–C(3')); 2.94 (*s*, 2 H–C(1')); 3.90 (*s*, MeO); 7.19 (*d*, *J* = 8.5, 2 H_o); 7.23 (*d*, *J* = 8, H–C(7')); 7.33 (*d*, *J* = 8.5, 2 H_m); 7.83 (*d*, *J* = 8, H–C(6')); 7.85 (*s*, H–C(4')). MS: 376 (M^+), 361 ([M – Me]$^+$). Anal. calc. for $C_{26}H_{32}O_2$ (376.54): C 82.94, H 8.57; found: C 83.00, H 8.82.

trans-*4-[4-(*tert-*Butyl)phenyl]-1',3'-dihydrospiro[cyclohexane-1,2'-[2*H*]inden]-5'-carboxylic Acid* (**15a**). To a soln. of **14a** (1.468 g, 3.90 mmol) in THF (20 ml) and EtOH (50 ml) was added 2N aq. NaOH (10 ml). The mixture was stirred at 70° for 1 h and then poured into H_2O (500 ml) and 1N HCl (21 ml). This was extracted with AcOEt (300 ml) and evaporated to give a white solid. Recrystallization from CH_2Cl_2/MeOH yielded **15a** (1.417 g, 100%). White solid. M.p. 237°. TLC (hexane/AcOEt 1:1): R_f 0.24. IR (CH_2Cl_2): 3000–2500 (COOH), 2926, 1727 (C=O), 1614 (Ar), 1426, 1299, 833. ^{1}H-NMR ($CDCl_3$; assigned by 1D-NOE): 1.32 (*s*, *t*-Bu); 1.54–1.69 (*m*, H_{ax}–C(2), H_{ax}–C(3), H_{ax}–C(5), H_{ax}–C(6)); 1.77–1.87 (*m*, H_{eq}–C(2), H_{eq}–C(3), H_{eq}–C(5), H_{eq}–C(6)); 2.53 (*tt*, *J* = 11.8, 3.4, H_{ax}–C(4)); 2.83 (*s*, 2 H–C(3')); 2.96 (*s*, 2 H–C(1')); 7.18 (*d*, *J* = 8.4, 2 H_o); 7.27 (*d*, *J* = 8.6, H–C(7')); 7.33 (*d*, *J* = 8.4, 2 H_m); 7.90 (*dd*, *J* = 8, 1.4, H–C(6')); 7.91 (*d*, *J* = 1.4, H–C(4')). MS: 362 (M^+), 347 ([M – Me]$^+$). Anal. calc. for $C_{25}H_{30}O_2$ (362.51): C 82.83, H 8.34; found: C 82.79, H 8.45.

Mixture **12a**/**12b** *65:35*. As described for **12a**, from **9a**/**9b** 65:35 (5.00 g, 14.34 mmol): **12a**/**12b** 65:35 (4.52 g, 94%). M.p. 130–132°. TLC (toluene): R_f 0.25. HPLC (*Synchropack RP4*, 100 bar, (H_2O + 0.1% CF_3COOH)/(MeCN + 0.1% CF_3COOH) 45:55): t_R (integral) 17.34 (64.3%), 18.75 (35.2%). ^{1}H-NMR: '*AB*' at 2.79 (2.70, 2.73, 2.82, 2.85; 4 lines, 2 H–C(1'), 2 H–C(3')); remaining signals very similar to those of **12a**. Anal. calc. for $C_{24}H_{30}O$ (334.50): C 86.18, H 9.04; found: C 86.10, H 9.09.

Mixture **13a**/**13b** *65:35*. As described for **13a**, with **12a**/**12b** 65:35 (4.41 g, 13.2 mmol): **13a**/**13b** 65:35 (6.05 g, 98.2%). Oil. TLC (hexane/CH_2Cl_2 5:1): R_f 0.26. IR (CH_2Cl_2): 2927, 1611 (Ar), 1479, 1411 (S–O), 1216 (S–O), 1141, 934, 867, 833. ^{1}H-NMR ($CDCl_3$): '*AB*' at 2.85 (2.79, 2.81. 2.91, 2.93; 4 lines, 2 H–C(1'), 2 H–C(3')); remaining signals very similar to those of **13a**. ^{19}F-NMR (282 MHz, $CDCl_3$): 1 *s*. Anal. calc. for $C_{25}H_{29}F_3O_3S$ (466.56): C 64.36, H 6.26; found: C 64.35, H 6.24.

Mixture **14a**/**14b** *65:35. Heck*-type reaction of **13a**/**13b** 65:35 (6.03 g, 12.93 mmol) yielded, besides recovered educt (0.5654 g), **14a**/**14b** 65:35 (3.87 g, 88% based on the neat consumption of educt). M.p. (after recrystallization from CH_2Cl_2/MeOH) 110–118°. TLC (hexane/CH_2Cl_2 1:1): R_f 0.4. ^{1}H-NMR and IR: virtually identical to those of **14a**. MS: 376 (M^+), 361 ([M – Me]$^+$). Anal. calc. for $C_{26}H_{32}O_2$ (376.54): C 82.94, H 8.57; found: C 82.95, H 8.57.

Mixture **15a**/**15b** *65:35.* Saponification of **14a**/**14b** 65:35 (1.02 g, 2.81 mmol) yielded **15a**/**15b** 65:35 (1.015 g, 99.5%). M.p. 232–233°. TLC (hexane/AcOEt 1:1): R_f 0.24. ^{1}H-NMR and IR: same as for **15a**. Anal. calc. for $C_{25}H_{30}O_2$ (362.51): C 82.83, H 8.34; found: C 83.05, H 8.53.

cis-*Isomer Derivatives.* They were also synthesized in excellent yields by similar procedures starting from **9b** and gave satisfactory and excpected TLC, ^{1}H-NMR, and IR.

12b: M.p. 146.5–147.5°. Anal. calc. for $C_{24}H_{30}O$ (334.50): C 86.18, H 9.04; found: C 86.06, H 9.28.

13b: M.p. 73–75°. MS: 465 (M^+).

14b: M.p. 113°. MS: 377 (M^+).

15b: M.p. 226–230°. FAB-MS (pos. mode): 363 ([M + H]$^+$).

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