Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 7, pp. 1575-1583, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00201-4

An Improved Synthesis and Resolution of (±)-*cis,cis*-2,2'-Spirobiindane-1,1'-diol

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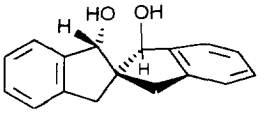
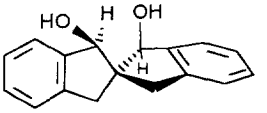
Abstract: (±)-*cis,cis*-2,2'-Spirobiindane-1,1'-diol (**1**) is synthesized stereoselectively in four steps beginning with 1-indanone in 68% overall yield. An improved resolution of diol **1** is described by preparing and separating diastereomeric mono-esters of **1** using (2*S*)-*O*-(*tert*-butyldimethylsilyl)mandeloyl chloride (**10**).

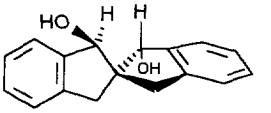
In our continuing efforts to prepare various C_2 symmetric chiral spiro diols for use as ligands in Lewis acid promoted organic reactions,[1] we required a short synthesis of (±)-*cis,cis*-2,2'-spirobiindane-1,1'-diol (**1**) for resolution into the enantiomeric forms. Although a synthesis of *cis,cis*-diol (−)-**1** has been reported by Kabuto *et al*,[2] the synthetic sequence was low yielding and provided diol (−)-**1** with an enantiomeric excess (e.e.) of only 21%.[3] Since we have reported that spiro[4.4]nonane-1,6-dione can be stereoselectively reduced (100%) to the *cis,cis*-spiro[4.4]nonane-1,6-diol by treatment with lithium *tert*-butyldiisobutylaluminium hydride,[1] we developed a new synthesis of (±)-**1** by converting the readily available 1-indanone (**4**) into 2,2'-spirobiindane-1,1'-dione (**7**) and hence into diol (±)-**1** via a similar reduction. In addition, an improved resolution of diol (±)-**1** was developed by preparing diastereomeric mono-esters of (±)-**1** using (2*S*)-2-(*tert*-butyldimethylsilyl)mandeloyl chloride (**10**) as the chiral source. This paper describes our results to date.



(*cis,cis*) **1**



2 (*cis, trans*)

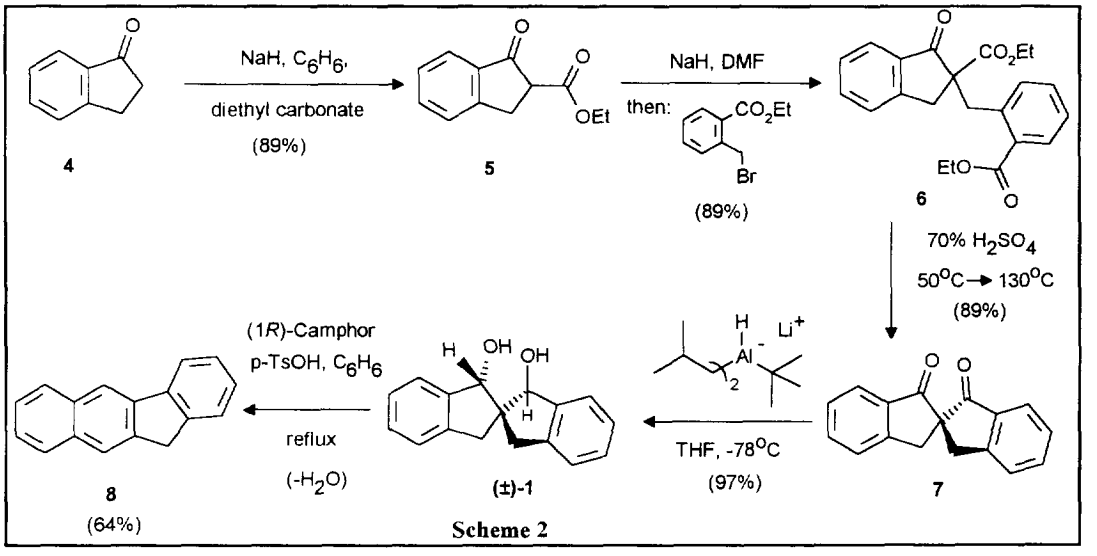


3 (*trans, trans*)

Scheme 1

(±)-*cis,cis*-2,2'-Spirobiindane-1,1'-diol (**1**) was synthesized stereoselectively in four steps as illustrated in Scheme 2. The readily available 1-indanone (**4**)[4] was added slowly (over 4.5 h) to a mixture of sodium hydride and diethyl carbonate in benzene (reflux, 0.5 h) to provide β-keto ester **5** in 89% yield.[5] Alkylation of β-keto ester **5** with ethyl 2-(bromomethyl)benzoate[6] (NaH, DMF, 60°C, 87 h) provided diester **6** (89%),[7] which when treated with 70% sulfuric acid (50°C→130°C, monitor by GC)[8,9] provided 2,2'-spirobiindane-1,1'-dione (**7**) in 89% yield.[10,11] Treatment of dione **7** with either $LiAlH_4$ or diisobutylaluminium hydride provided a mixture of

diols **1-3**; however, reduction of dione **7** with lithium *tert*-butyldiisobutylaluminium hydride[1] provided only (±)-*cis,cis*-2,2'-spirobiindane-1,1'-diol (**1**) (Table 1, Scheme 1). This synthetic route therefore constitutes a new short stereoselective synthesis of (±)-diol **1** in four steps from 1-indanone (**4**) in 68% overall yield.



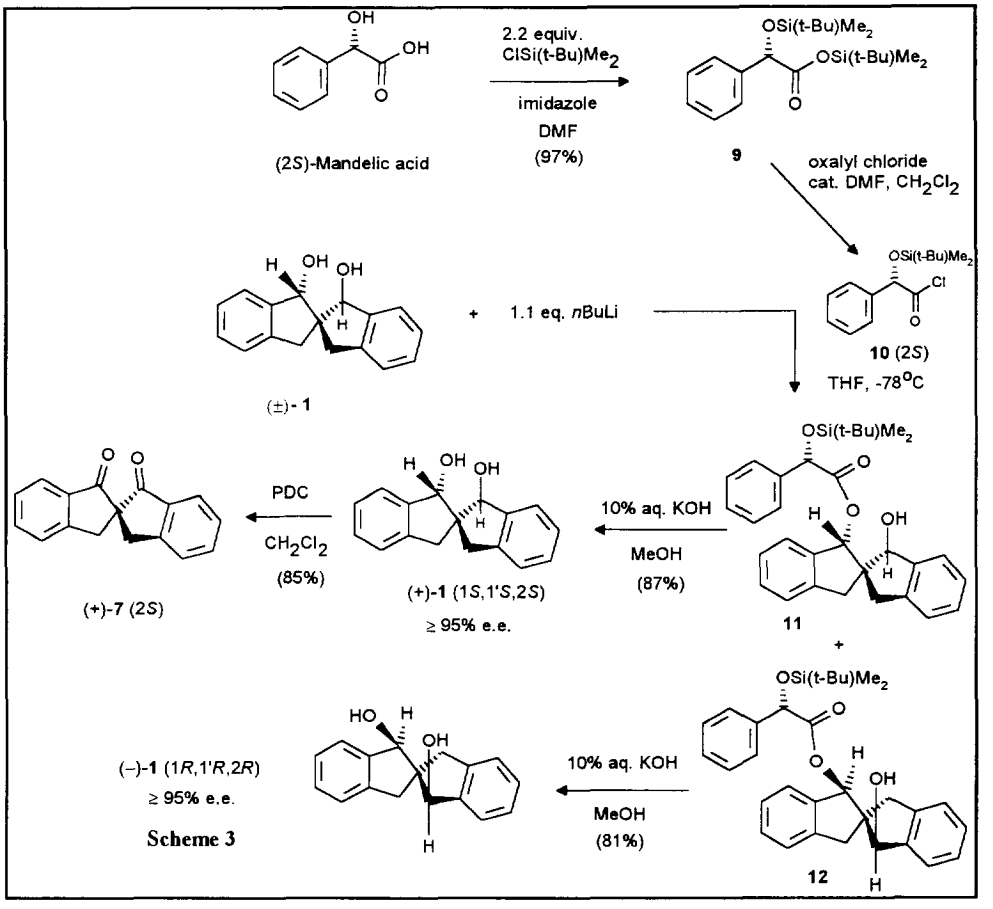
Scheme 2

We recently reported that *cis,cis*-spiro[4.4]nonane-1,6-diol could be resolved by preparing diastereomeric ketals of (1*R*)-camphor (benzene, p-TsOH, reflux).[1] Unfortunately, (±)-diol **1** rearranged to provide 11*H*-benzo[b]fluorene **8** under identical conditions.[12] Therefore, a new resolution of (±)-diol **1** was developed using (2*S*)-*O*-(*tert*-butyldimethylsilyl)mandeloyl chloride (**10**) (Scheme 3). Acid chloride **10** was prepared in two steps by the bis-silylation of (2*S*)-mandelic acid (97%) followed by the direct conversion of resulting ester **9** into **10**.[13] The crude acid chloride **10** was used immediately in the next step. Addition of (±)-diol **1** to acid chloride **10** with DMAP in pyridine resulted in partial epimerization of the stereogenic centre adjacent to the acid chloride. Similar occurrences have been observed with other asymmetric centres with hydrogen atoms α to acid

Table 1: Results From the Reduction of Spirodione 7.

Reducing Agent	Conditions	Ratio of Diols (by ^{1}H NMR spectroscopy) 1:2:3	Isolated Yield (%)
$LiAlH_4$	Et_2O 0°C	9:75:16	94
DIBAL-H	THF -78°C	35:46:19	96
Li *t*-Bu(*i*-Bu)$_2$AlH	THF -78°C	100:0:0	97

chlorides.[14] Epimerization was avoided by treating (±)-diol **1** with 1.1 equivalents of *n*-BuLi in THF at -78°C, warming the solution to room temperature, followed by dropwise addition of this mixture to acid chloride **10** in THF at -78°C.[15] Normal workup provided a mixture of diastereomers **11** and **12** in 72% yield.



Scheme 3

Esters **11** and **12** were separated using a column of silica gel eluting with $CHCl_3$ (R_f of **11** = 0.14; R_f of **12** =0.24). Analysis of the separated esters **11** and **12** by ^1H NMR spectroscopy indicated that the diastereomeric excess of **11** and **12** was ≥95%. Hydrolysis of the esters **11** and **12** with 10% aqueous KOH in MeOH provided (+)-diol **1** (87%, ≥95% e.e.) and (−)-diol **1** (81%, ≥95% e.e.), respectively. The enantiomeric excess was checked by conversion of the (−)-diol **1** to the mono Mosher's ester;[2,16] only one diastereomer was observed by ^1H NMR spectroscopy. The absolute stereochemistry of the spiro-carbon atom of diols (+)-**1** and (−)-**1** was assigned by oxidation of (+)-**1** to dione **7** (PDC, CH_2Cl_2, 85%) and comparison of the observed

rotation of synthesized dione **7** ($[\alpha]_D^{22.5}$ +147.4 (c 1.25, 0.1 dm, $CHCl_3$)) with the literature value ($[\alpha]_D^{22.5}$ +151.86 (c 3.22, $CHCl_3$; 97.1% e.e.)).[17] Thus, the absolute stereochemistry of the spiro-carbon atom of (+)-dione **7** was 2*S* and hence the spiro-carbon atom of (+)-diol **1** was assigned 2*S*. By analogy, *cis,cis*-(+)-diol **1** and *cis,cis*-(−)-diol **1** were assigned to have the (1*S*,1'*S*,2*S*) and (1*R*,1'*R*,2*R*) absolute configurations, respectively (Scheme 3).

In summary, we have developed: 1) a four step stereoselective synthesis of (±)-*cis,cis*-2,2'-spirobiindane-1,1'-diol (**1**), and 2) a resolution of *cis*,cis-diol **1** using (2*S*)-2-(*tert*-butyldimethylsilyl)-mandeloyl chloride as a new chiral auxiliary.

Experimental Section:

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker ACE - 200 (^1H 200 MHz, ^{13}C 50 MHz) spectrometer. Unless otherwise stated, all NMR samples were obtained in $CDCl_3$ and the chemical shifts (ppm) are relative to the $C\underline{H}Cl_3$ peak as an internal reference (7.27 ppm for ^1H and 77.00 ppm for ^{13}C). Infrared (IR) spectra were recorded on a Mattson Model 4030 FT - IR spectrometer. Mass spectra (MS) were run on either a Varian CH5 or a VG 7070 instrument. Gas Chromatography Mass Spectrometry (GC/MS) analysis were performed on a Hewlett Packard 5890 Series II. High Resolution Mass Spectometry (HRMS) were recorded on a Kratos MS80. Microanalyses were performed by Ms. D. Fox, Department of Chemistry, University of Calgary. All melting and boiling points are uncorrected. Flash column chromatography was performed using silica gel 60 having a particle size of 0.040-0.063 mm (230-400 mesh).[18]

Anhydrous THF was distilled from sodium benzophenone ketyl. Anhydrous benzene and methylene chloride were obtained by distillation from calcium hydride. All reactions were performed in oven dried glassware (120°C) under an atmosphere of nitrogen, except the saponification of diastereomers **11** and **12**.

Ethoxycarbonyl-1-indanone (5)

A 60% dispersion of sodium hydride (4.36 g, 109 mmol) was washed three times with diethyl ether (Sure/Seal™). The residual ether was removed by passing a stream of nitrogen gas over the mixture. Benzene (45 mL) and diethyl carbonate (8.80 mL, 72.6 mmol) were added and the resulting solution mechanically stirred and refluxed (the reaction mixture turned green).[5] Freshly distilled 1-indanone (4.80 g, 36.3 mmol) in benzene (15 mL) was added slowly to the refluxing solution over 4.5 hours. The addition funnel was washed with benzene (5 mL) and the reaction mixture refluxed for an additional 0.5 hours. Acetic acid and water were added until all the solid dissolved and the aqueous layer was approximately pH 5. The aqueous layer was extracted three times with benzene and the combined benzene extracts were washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo*. The crude product was purified by bulb-to-bulb distillation to give a

colorless liquid (6.61 g, 89%): bp 72 - 88°C (air bath)/ 0.045 torr. IR (neat): 1741, 1716, 1649, 1573 cm^{-1}. ^1H NMR spectrum indicated the ratio of keto:enol was 67:33. ^1H NMR δ 10.43 (br. s, 1H, enol), 7.81-7.37 (m, 4H, keto and enol), 4.33 (q, 2H, J=7.1 Hz, enol), 4.26 (q, 2H, J=7.1 Hz, keto), 3.73 (dd, 1H, J=4.1 and 8.2 Hz, keto), 3.58 (dd, 1H, J=4.1 and 17.3 Hz, keto), 3.53 (s, 1H, enol), 3.38 (dd, 1H, J=8.2 and 17.3 Hz, keto), 1.38 (t, 3H, J=7.1 Hz, enol), 1.32 (t, 3H, J=7.1 Hz, keto). ^{13}C NMR spectrum indicated both the keto and enol forms were present. ^{13}C NMR δ 199.3, 168.9, 153.4, 143.5, 135.2, 135.1, 129.1, 127.6, 126.6, 126.4, 124.5, 124.4, 120.4, 102.2, 61.5, 59.9, 53.1, 32.3, 30.1, 14.3, 14.0. GC\MS: m/z= 204 (M^+,42%), 159 (M^+-OEt, 22%), 130 (M^+-HCO_2Et, 100%). Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58%; H, 5.92%. Found: C, 70.76%; H, 6.07%.

2-Ethoxycarbonyl-2-(2-(ethoxycarbonyl)phenylmethyl)-1-indanone (6)

NOTE: This procedure results in the vigorous evolution of H_2 gas!

Freshly distilled ester **5** (4.86 g, 23.8 mmol) in DMF (10 mL, Sure/Seal™) was slowly added to a 60% dispersion of sodium hydride (1.047 g, 26.2 mmol). Once the vigorous evolution of H_2 had ceased, the solution was heated to 60°C for one hour (turned dark red-purple) and ethyl 2-(bromomethyl)benzoate[6] (6.31 g, 26 mmol) was added in DMF (15 mL, Sure/Seal™).[7] The reaction mixture was heated at 60°C for 87 h (the loss of starting material was monitored by GC/MS). The reaction was cooled to room temperature and a few of drops of water were added. The mixture extracted with diethyl ether and the ether washed with saturated sodium chloride. The ether was dried (Na_2SO_4) and removed *in vacuo*. The crude product was distilled bulb-to-bulb yielding a yellow solid. Purification by silica gel chromatography (hexanes:EtOAc (5:1)) gave a white solid (7.72 g, 89%): mp 93.5-94°C, bp 178-190°C (air bath) /0.05 torr (slight dec.). IR (neat): 1737 (ester C=O), 1711 (ketone C=O) cm^{-1}. ^1H NMR δ 7.80 (d, 1H, J=7.1 Hz), 7.23 (d, 1H, J=7.6 Hz), 7.50 (t, 1H, J=7.4 Hz), 7.33-7.13 (m, 5H), 4.30 (q, 2H, J=7.1 Hz), 4.15 (q, 2H, J=7.1 Hz), 4.08 (d, 1H, J=14.1 Hz), 3.68 (d, 1H, J=14.1 Hz), 3.60 (d, 1H, J=16.7 Hz), 3.07 (d, 1H, J=16.7 Hz), 1.32 (t, 3H, J=7.1 Hz), 1.17 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 202.6, 170.8, 167.7, 153.7, 137.9, 135.1, 135.0, 131.5, 131.2, 130.4, 127.4, 126.6, 126.0, 124.4, 61.7, 61.0, 35.6, 35.5, 14.1, 13.9. GC/MS: m/z= 366 (M^+, 1%), 320 (M^+-EtOH, 46%). Anal. Calcd. $C_{22}H_{22}O_5$: C, 72.12%; H, 6.05%. Found: C, 72.10%; H, 6.17%.

2,2'-Spirobiindane-1,1'-dione (7)

A solution of diester **6** (215 mg, 0.587 mmol) in 70% sulfuric acid (35 mL)[8] was heated from 50°C to 130°C over 1 hour (the solution turned black while being monitored by GC). The mixture was cooled to room temperature and extracted with methylene chloride. The combined organic layers were dried (Na_2SO_4) and removed *in vacuo*. The product was purified by bulb-to-bulb sublimation, 162°C-180°C (air bath)/0.05 torr, to

provide a light yellow solid (129 mg, 89%). No further purification was necessary for the subsequent steps; however, silica gel column chromatography ($CHCl_3$) or recrystallization from benzene[3a] yielded a white solid, mp 172.6-175.5°C. ^{1}H NMR δ 7.76 (d, 2H, J=7.6 Hz), 7.65 (t, 2H, J=7.6 Hz), 7.55 (d, 2H, J=7.6 Hz), 7.40 (t, 2H, J=7.6 Hz), 3.72 (d, 2H, J=17.0 Hz), 3.19 (d, 2H, J=17.0 Hz). ^{13}C NMR δ 202.6, 153.8, 135.3, 135.2, 127.7, 126.3, 124.7, 65.2, 39.9. The ^{1}H NMR spectrum was consistent with that reported by Dynesen.[7]

(±)-*cis,cis*-2,2'-Spirobiindane-1,1'-diol (1)

tert-Butyllithium (8.20 mL, 1.7M in pentane) was slowly added to a solution of DIBAL-H (13.94 mL, 1M in THF) at -78°. The solution was stirred 5 minutes, warmed to room temperature, and cooled to -78°C. To this mixture, freshly distilled (±)-dione **7** (1.15 g, 4.65 mmol) in THF (30 mL) was added very slowly (10 mL more THF used to rinse the equalized dropping funnel) and the resulting mixture warmed to room temperature overnight. Saturated ammonium chloride was added dropwise until the evolution of H_2 ceased. The mixture was poured into a beaker containing $CHCl_3$ (200 mL) and saturated ammonium chloride (100 mL), followed by vigorous stirring (precipitation of the aluminum salts). The solids were filtered through Celite® and the solution extracted with methylene chloride or chloroform. The organic layer was dried (Na_2SO_4) and removed *in vacuo*. Column chromatography using silica gel[19] ($CHCl_3$:EtOH (97.5:2.5)) provided a white powder (1.14 g, 97%).[20] mp 234.5-236°C. IR (neat): 3498 (O-H), 3360 (O-H) cm^{-1}. NMR δ 7.51-7.47 (m, 2H), 7.32-7.21 (m, 6H), 5.21 (s, 2H), 3.19 (d, 2H, J=15.5 Hz), 2.95 (br. s, 2H), 2.56 (d, 2H, J=15.5 Hz). ^{13}C NMR (DMSO-d_6 , reference peak= 39.5) δ 144.7, 142.7, 128.0, 126.4, 125.0, 80.0, 58.3, 41.7. The ^{1}H spectrum was consistent with that reported by Kabuto *et. al.*[2] GC/MS: m/z = 234 (M^+-H_2O), 216 (M^+-(2 x H_2O)).

***tert*-Butyldimethylsilyl (2*S*)-(*O*-*tert*-butyldimethylsilyl)mandelate (9)**

Mandelic acid (10.0 g, 65.7 mmol), imidazole (18.8 g, 276 mmol) and *tert*-butyldimethylsilyl chloride (29.7 g, 197 mmol) were dissolved in DMF (110 mL, Sure/Seal™) at 0°C. The mixture was stirred at room temperature for 84 hours, extracted with diethyl ether and the ether was washed three times with saturated sodium chloride. The organic layer was dried (Na_2SO_4) and removed *in vacuo* to give a colourless oil. Bulb-to-bulb distillation yielded a colorless oil (24.3 g, 97%). bp 90°C-110°C (air bath)/0.045 torr. IR (neat): 1741, 1717 cm^{-1}. ^{1}H NMR δ 7.49-7.42 (m, 2H), 7.42-7.28 (m, 3H), 5.15 (s, 1H), 0.92 (s, 9H), 0.83 (s, 9H), 0.20 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H), 0.02 (s, 3H). ^{13}C NMR δ 172.1, 139.6, 128.1, 127.9, 126.5, 75.3,

25.6, 25.3, 18.2, 17.6, -5.0, -5.1, -5.2. HRMS m/z= 365.1955 (M^+-CH_3), 323.1470 (M^+-*t*Bu). $[\alpha]_D^{22}$ +46.17 (c 1.62, 0.1 dm, chloroform).

(1*S*,1'*S*,2*S*)- & (1*R*,1'*R*,2*R*)-2,2'-Spirobiidan-1-((2*S*)-(*O*-*tert*-butyldimethylsilyl)mandeloxy)-1'-ol (11 & 12)

To a solution of compound **9** (205 mg, 0.54 mmol)[21] in methylene chloride (10 mL) at 0°C were added DMF (3 drops, Sure/Seal™) and oxalyl chloride (61.3 μL, 0.702 mmol).[13a] The solution was stirred for 0.5 hours, warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* and the flask back purged with dry N_2 to provide compound **10**. THF (10 mL) was added and the mixture cooled to -78°C.

In a separate round bottom flask, racemic diol **1** (54.5 mg, 0.216 mmol) was placed under a vacuum (approximately 0.1 torr) for 1 hour. After back purging with N_2, THF (5 mL) was added and the suspension cooled to -78°C whereupon *n*-butyllithium (97.2 μL, 1M in THF) was added. After stirring 5 minutes, the solution was warmed to room temperature and transferred to an equalized dropping funnel. This solution was added slowly to the acid chloride (**10**) solution (at -78°C). The resulting solution was slowly warmed to room temperature overnight. Saturated sodium bicarbonate was added and the aqueous layer extracted numerous times with diethyl ether. The combined ether layers were dried (Na_2SO_4) and removed *in vacuo*. The diastereomers were separated from other impurities by column chromatography (hexanes:EtOAc (9:1)). This procedure provided an oil (78 mg, 72%) which solidified on standing. The mixture of diastereomers was separated using a column of silica gel ($CHCl_3$) (R_f of **11** = 0.14; R_f of **12** = 0.24).

Diastereomer **11**: oil: IR (neat): 3567 (O-H), 1750 (C=O) cm^{-1}. ^1H NMR δ 7.63 (dd, 1H, J= 7.0 and 1.6 Hz), 7.51-7.15 (m, 11H), 6.12 (s, 1H), 5.14 (s, 1H), 4.77 (d, 1H, J=4.5 Hz), 3.12 (d, 1H, J=15.3 Hz), 3.09 (d, 1H, J=15.3 Hz), 2.41 (d, 1H, J=15.3 Hz), 2.37 (d, 1H, J=15.3 Hz), 1.55 (d, 1H, J=4.5 Hz), 0.90 (s, 9H), 0.09 (s, 3H), -0.04 (s, 3H). HRMS: m/z = 483.2348 (M^+-OH), 443.1625 (M^+-*t*Bu). $[\alpha]_D^{22.5}$ +102.34 (c 7.0, 0.1 dm, chloroform).

Diastereomer **12**: oil: IR (neat): 3582 (O-H), 1730 (C=O) cm^{-1}. ^1H NMR δ 7.54-7.17 (m, 13H), 6.12 (s, 1H), 5.21 (s, 1H), 5.07 (d, 1H, J=4.8 Hz), 3.16 (d, 1H, J=15.4 Hz), 3.14 (d, 1H, J=15.4 Hz), 2.51 (d, 1H, J=15.4 Hz), 2.47 (d, 1H, J=15.4 Hz), 2.03 (d, 1H, J=4.8 Hz), 0.84 (s, 9H), -0.04 (s, 3H), -0.11 (s, 3H). HRMS: m/z = 483.2347 (M^+-OH). $[\alpha]_D^{22.5}$ -79.99 (c 11.25, 0.1 dm, chloroform).

(-)- and (+)-2,2'-Spirobiindane-1,1'-diol (1)

To a solution of compound **10** or **11** (159 mg, 0.317 mmol) in methanol (20 mL) was added potassium hydroxide (10 mL of 10%) at room temperature. A white precipitate formed slowly. When tlc indicated there was no starting material remaining the aqueous layer was extracted with methylene chloride. The organic layer

was dried (Na_2SO_4) and removed *in vacuo*. Column chromatography ($CHCl_3$:EtOH (97.5:2.5)) provided a white solid (69.5 mg, 87%). All the spectroscopic data for (+)-**1** and (–)-**1** were identical with the data obtained from (±)-diol **1**. (+)-**1** (from diastereomer **11**): mp 236- 237°C (dec.). $[\alpha]_D^{22}$ +38.6 (c 0.102, 1 dm, Sure/Seal™ acetone).[2] (–)-**1** (from diastereomer **12**): mp 243-244°C (dec.). $[\alpha]_D^{21}$ –41.4 (c 0.084, 1 dm, Sure/Seal™ acetone).[2]

(+)-(2*S*)-2,2'-Spirobiindane-1,1'-dione ((+)-7)

To diol (+)-**1** (21.3 mg, 0.0844 mmol) was added PDC (381 mg, 1.013 mmol) and methylene chloride (12 mL). After 2 hours at room temperature (tlc showed no starting material) diethyl ether was added. The mixture was stirred for 15 minutes, filtered through Celite® and the solvent removed *in vacuo*. Column chromatography ($CHCl_3$) provided a white solid (17.7 mg, 85%) whose spectroscopic data were the same as (±)-dione **7**. $[\alpha]_D^{22.5}$ +147.4 (c 1.25, 0.1 dm, $CHCl_3$).[3a]

Acknowledgments: We thank the Natural Sciences and Engineering Research Council of Canada, The Merck Frosst Centre for Therapeutic Research (Pointe-Claire, Quebec, Canada), and the University of Calgary Research Board for financial support.

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(4) 1-Indanone (**4**) was purchased from the Aldrich Chemical Co. and distilled prior to use.

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(9) β-Keto ester **5** could be directly converted into spiro dione **7** (81%) by treating the crude reaction mixture containing ester **6** from step 2 (Scheme 2) directly with 70% sulfuric acid.

(10) For previous achiral syntheses of spiro dione **7**, see: (a) Leuchs, H.; Radulescu, D. *Chem. Ber.* **1912**, *45*, 189. (b) Ingold, C.K.; Wilson, C.L. *J. Chem. Soc.* **1934**, 776. (c) ref. 7. (d) Petersen, K.B.; Danielsen, J. *Acta Cryst.* **1974**, *B 30*, 338. (e) Iversen, B.B.; Møller, E.R.; Krogh, L.; Holm, M.F.; Dynesen, E.; Larsen, F.K.; Hazell, R.G. *Acta Cryst.* **1993**, *C 49*, 1104.

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(19) Trituration with diethyl ether was simplier but resulted in lower yields.

(20) Compound **1** was only slightly soluble in most organic solvents, but soluble in DMSO.

(21) If compound **9** is left to stand for any considerable length of time, it is very important to pass it through a short column of silica gel (hexanes:EtOAc (20:1)) and to remove the solvent *in vacuo*. This procedure removes byproducts which slowly form over time.

(*Received in USA* 6 *April* 1995)