Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1147–1152

TETRAHEDRON: *ASYMMETRY*

Synthesis and absolute configuration of the four possible stereoisomers of prandiol

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Received 14 March 2002; accepted 22 May 2002

Abstract—Prandiol and its three stereoisomers were synthesized in five steps starting either from (*R*)-(+)-2,3-dihydro-2-(1′-methylethenyl)-6-methoxybenzofuran **1a** or from its enantiomer (*S*)-(−)-**1b**. The synthesis involved condensation of the corresponding phenol **4** with ethyl propiolate to afford furocoumarins **6**. The absolute configuration of the newly formed stereogenic center at C(1′) was established by circular dichroism spectroscopy in combination with X-ray crystallographic analysis.

1. Introduction

Derivatives of 2,3-dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one **6** are secondary metabolites widely distributed in plants of several genera.[1–7] One of the stereoisomers of **6**, prandiol, was isolated for the first time in 1974 from *Prangos alata* and *P. biebersteinii*.[1] The authors prepared the mono- and diacetylated derivatives, but did not report the absolute configuration, nor the specific rotations for the natural product or their acetyl derivatives. Seven years later, an optically active prandiol analogue was isolated from the seeds of *Apium graveolens*.[2] Based on the large difference in melting points, the authors concluded that their molecule was a diastereoisomer of prandiol. The roots of *Seseli tortuosum*[3] afforded a derivative of **6** having a seneciate attached to the tertiary hydroxyl group. Again, no specific rotation was reported for this natural product. A glycoside derivative of coumarin **6** was isolated from the water-soluble root extracts of *Angelica archangelica*.[4] By comparison with the CD-extreme of the glycoside marmesin, the authors tentatively assigned the 2*S*-configuration to their derivative, but the absolute configuration at C(1′) remained unknown. Later, a glycoside derivative of furocoumarin **6** was isolated from the aerial part of *Diplolophium buchananii*.[5] Enzymatic hydrolysis of this glycoside, afforded a furocoumarin **6** which showed UV and IR data virtually identical to those of the coumarin isolated from the *Angelica* species, although the CD spectra were nearly antipodal and the NMR spectra showed some differences. Therefore, the authors concluded that the two glycosides were diastereoisomers having opposite configuration at C(2), and they did not determine the configuration at C(1′).

The prandiol isomer, dorsteniol, isolated from *Dorstenia contrajerva*[6] as an insoluble amorphous solid, allowed us to determine the (2*S**,1′*S**)-relative configuration by X-ray diffraction analysis of its monoacetate derivative. Additionally, acetylation of the chloroform extract of *Dorstenia excentrica*[7] afforded a monoacetate derivative of prandiol, whose structure was established based on its ^{1}H NMR spectrum, while its (2*S*,1′*S*)-absolute configuration was determined by CD and NMR measurements. Recently, a seneciate derivative of coumarin **6**, having the ester residue at C(2′) was isolated from the roots of *Ferulago capillaris*.[8] The configuration of the two stereogenic centers was proposed by chemical synthesis and computational methodology.

Since we have been interested in the isolation, total synthesis and configurational analysis of this class of compounds for over a decade,[6,9] we describe herein the first total synthesis of the four possible stereoisomers of **6**.

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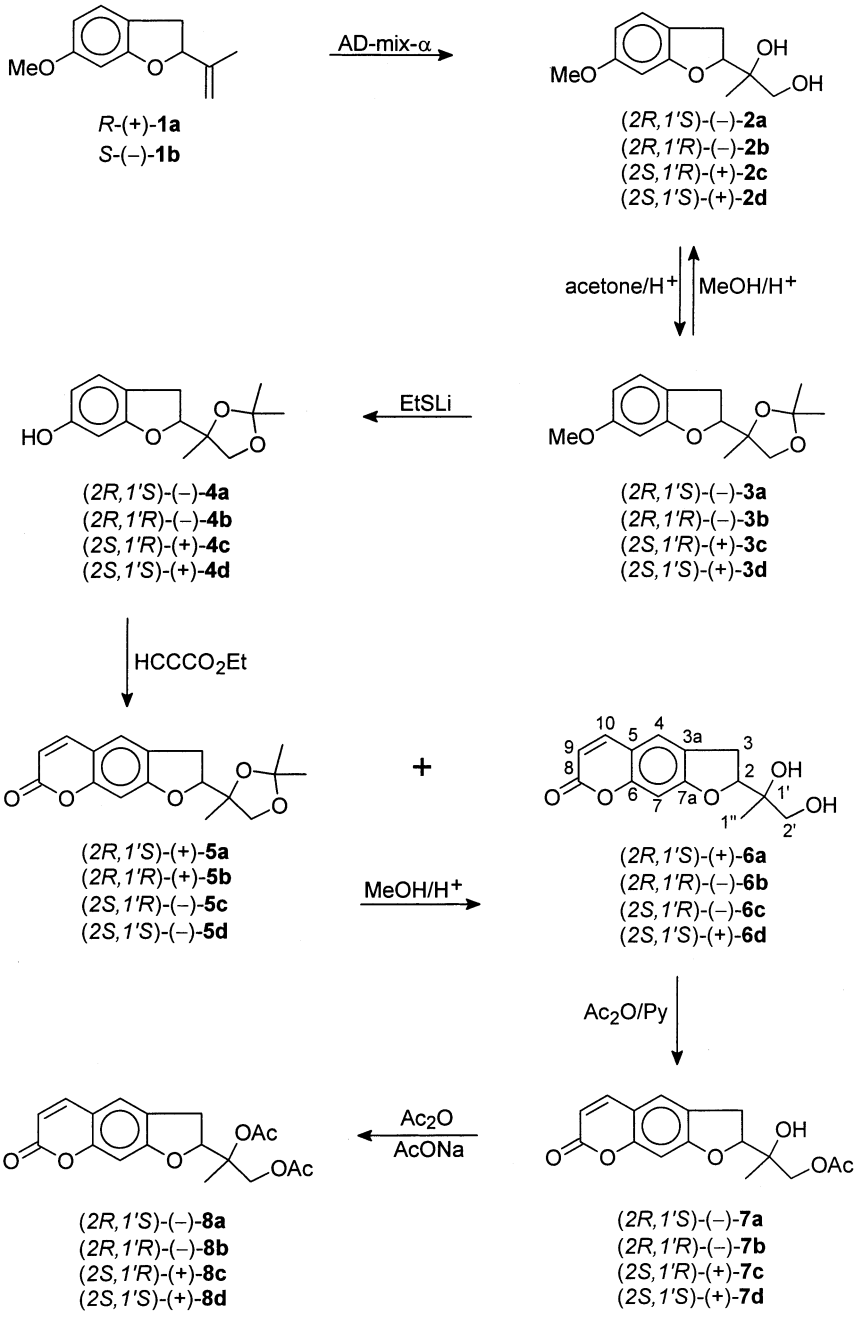
0957-4166/02/$ - see front matter
PII: S0957-4166(02)00267-7

2. Results and discussion

The synthesis of the dihydrofurocoumarins (2*R*,1′*S*)-(+)-**6a**, (2*R*,1′*R*)-(−)-**6b**, (2*S*,1′*R*)-(−)-**6c** and (2*S*,1′*S*)-(+)-**6d** is shown in Scheme 1. Thus, the first step involved Sharpless catalytic asymmetric dihydroxylation[10] of olefin (*R*)-(+)-**1a** of known configuration[11] at 0°C to afford a diastereoisomeric mixture of diols **2a** and **2b**, in 85% yield. This mixture could not be separated, and therefore, the diol mixture was treated with anhydrous acetone and *p*-toluenesulfonic acid to give the corresponding mixture of ketals **3a** and **3b** in 90% yield which was separated by column chromatography on silica gel to afford diastereoisomeric ketals (−)-**3a** and (−)-**3b** in a 3:2 ratio. Separate treatment of (−)-**3a** and (−)-**3b** with *p*-toluenesulfonic acid in methanol cleanly afforded diols (−)-**2a** and (−)-**2b**, respectively.

Each ketal, (−)-**3a** and (−)-**3b**, was then subjected to the following reaction sequence: *O*-demethylation, ethyl propiolate condensation, hydrolysis and acetylation. The *O*-demethylation of (−)-**3a**/(−)-**3b** was carried out using lithium ethanethiolate (prepared from ethanethiol and lithium hydride) in *N*,*N*-dimethylformamide[12] at 85°C to give the desired phenols (−)-**4a**/(−)-**4b** in 80% yield. Acid-catalyzed condensation of ethyl propiolate, under Kaufman and Kelly[13] conditions, with phenols (−)-**4a**/(−)-**4b** afforded the ketalfurocoumarins (+)-**5a**/(+)-**5b** and the furocoumarins (+)-**6a**/(−)-**6b**, in 35 and 5% yield, respectively. Acid hydrolysis of (+)-**5a**/(+)-**5b**,



Scheme 1.

with *p*-toluenesulfonic acid in methanol, was completed within 90 min to cleanly give the furocoumarins (+)-**6a**/(−)-**6b** in almost quantitative yields. Monoacetate derivatives were prepared using acetic anhydride and pyridine at room temperature, whereby (+)-**6a**/(−)-**6b** gave (−)-**7a**/(−)-**7b**, respectively, in 80% yield. Treatment of (−)-**7a**/(−)-**7b** with acetic anhydride and sodium acetate under reflux afforded diacetate derivatives (−)-**8a**/(−)-**8b** in 70% yield.

Similarly, treatment of (*S*)-(−)-**1b** under the same reaction conditions gave the dihydrofurocoumarins (−)-**6c**/(+)-**6d**. Comparison of spectroscopic data of optically active compounds prepared in this work with those reported for the natural products[1,2,6,7] and racemic form[6] revealed that they are identical.

Recrystallization of (+)-**5a** from ethyl acetate and very slow crystallization of (+)-**5b** from ethyl acetate–hexane provided suitable crystals for X-ray diffraction studies. The absolute stereochemistry of ketalcoumarins (+)-**5a** and (+)-**5b** was confirmed unambiguously by combined use of X-ray analysis and CD spectra. The X-ray computer generated arrangements for (+)-**5a** (top) and (+)-**5b** (bottom) are shown in Fig. 1, whereas the CD spectra of (+)-**5a** and its enantiomer (−)-**5c** are depicted in Fig. 2. The most important aspects of their geometry are that in (+)-**5a** the methyl group at C(1′) and H(2) are *anti*-oriented, the torsion angle H(2)–C(2)–C(1′)–C(1″) being close to 180° (175.6°) and therefore the (2*R*,1′*S*)-absolute configuration is observed for these stereogenic centers. The furocoumarin ring system and the dioxolane ring in (+)-**5a** provide a torsion angle O(1)–C(2)–C(1′)–O(4) of −176.4°. We rationalize this fact as the result of electronic repulsion between the oxygen atoms O(1) and O(4). In contrast, for diastereoisomer (+)-**5b** the stereoelectronic effects favored the *gauche*-rotamer, in which torsion angles H(2)–C(2)–C(1′)–C(1″) and O(1)–C(2)–C(1′)–O(4) are close to 60° (−64.1 and 60.7°, respectively) and therefore the (2*R*,1′*R*)-configuration is evident. The furocoumarin system in both structures, (+)-**5a** and (+)-**5b**, is essentially planar with a maximum deviation

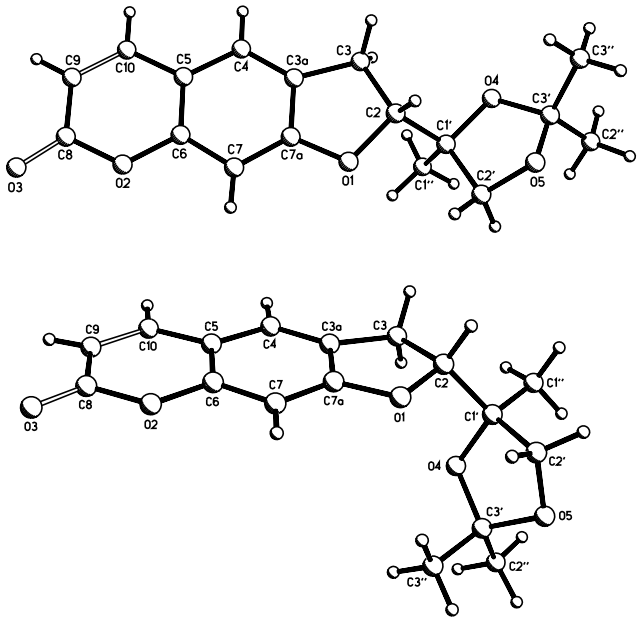


Figure 1. X-Ray structures of (+)-**5a** (top) and (+)-**5b** (bottom).

from the least-squares plane of 0.13 and 0.08 Å, respectively.

3. Conclusion

The four stereoisomers of furocoumarin **6** have been prepared starting from previously synthesized olefins (*R*)-(+)-**1a** and (*S*)-(−)-**1b**, and their absolute configuration[11] has been established by chemical correlation. The absolute configuration of the newly generated stereogenic center is assigned by X-ray and CD analyses of ketalcoumarins (+)-**5a** and (+)-**5b** and therefore determines the absolute configuration of the compounds obtained in this work. Based on the reported[2,6,7] data, it is now possible to establish that the dihydrofurocoumarin isolated from *A. graveolens*[2] has the (2*R*,1′*R*)-configuration, while that isolated from *Dorstenia*[6,7] species has the (2*S*,1′*S*)-configuration.

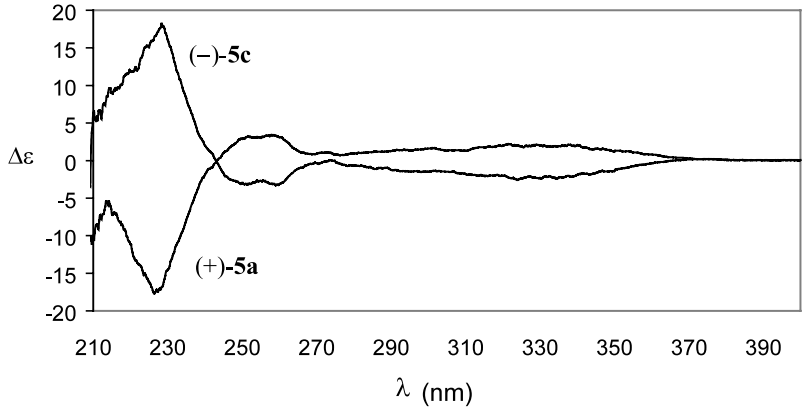


Figure 2. CD spectra of (+)-**5a** and (−)-**5c**.

4. Experimental

4.1. General methods and materials

Columns for chromatographic separations were packed with Si gel 60 (230–400 mesh ASTM). The purification of the coumarin derivatives was performed on a preparative radial thin-layer chromatograph (Chromatotron) using rotors with 2 and 4 mm thickness. Melting points were measured on a Fisher–Johns apparatus and are uncorrected. UV spectra were determined on a Perkin–Elmer UV–vis Lambda 12 spectrophotometer. IR spectra were recorded on a Perkin–Elmer 16F PC FT-IR spectrophotometer. ^{1}H and ^{13}C NMR measurements were performed on Varian XL-300GS and Mercury 300 spectrometers operating at 300 MHz (proton) or 75 MHz (carbon) from $CDCl_3$ solutions containing TMS as internal standard. MS were obtained on a Hewlett–Packard 5989A spectrometer at 20 eV or a Varian Saturn 2000 at 70 eV. HRMS and FABHRMS were measured on a JEOL JMS–SX 102A spectrometer or a VG 7070 high resolution mass spectrometer at the UCR Mass Spectrometry Facility, University of California, Riverside. Specific rotations were measured at the sodium-D line using a Perkin–Elmer 241 polarimeter at 25°C. The concentration, *c*, given after specific rotation is indicated in g/100 mL. CD spectra were recorded on a Jasco J-720 spectropolarimeter in methanol.

4.2. Preparation of ketals 3a–3d

Treatment of olefin (*R*)-(+)-**1a** (3 g, 15.8 mmol) with ADmix-α in *tert*-butyl alcohol–water,[10] using the procedure described[6] for the racemic mixture, afforded a mixture of diols **2a** and **2b** (3 g, 85%) which could not be separated. The mixture was treated with acetone and *p*-toluenesulfonic acid under reflux, as described,[6] yielding the ketal mixture **3a** and **3b** (3.19 g, 90%). This mixture, which was separated by flash column chromatography eluting with hexane–AcOEt (99:1), gave **3a** (1.76 g, 50%) and **3b** (1.18 g, 33%). Under the same procedure was treated (*S*)-(−)-**1b** (3 g, 15.8 mmol), which gave **3c** (1.74 g, 51%) and **3d** (1.15 g, 34%). The ^{1}H and ^{13}C NMR, UV, IR, MS and HRMS data are identical to those reported[6] for the racemic mixtures.

4.2.1. (2*R*,1′*S*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-methoxybenzofuran 3a. $[\alpha]_D^{25}$ −45.1 (*c* 7.71, $CHCl_3$).

4.2.2. (2*R*,1′*R*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-methoxybenzofuran 3b. $[\alpha]_D^{25}$ −31.2 (*c* 6.94, $CHCl_3$).

4.2.3. (2*S*,1′*R*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-methoxybenzofuran 3c. $[\alpha]_D^{25}$ +45.1 (*c* 10.41, $CHCl_3$).

4.2.4. (2*S*,1′*S*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-methoxybenzofuran 3d. $[\alpha]_D^{25}$ +31.1 (*c* 5.28, $CHCl_3$).

4.3. Preparation of diols 2a–2d

To a solution of the corresponding ketal **3a**–**3d** (150 mg, 0.57 mmol) in MeOH (10 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was heated under reflux for 90 min, concentrated to a small volume under vacuum, diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried and evaporated to give a yellow oil, which was purified by flash column chromatography eluting with hexane–AcOEt (2:3) to give **2a** (114.6 mg, 90%), **2b** (117 mg, 92%), **2c** (113 mg, 89%), and **2d** (116 mg, 91%). The ^{1}H and ^{13}C NMR, UV, IR, MS and HRMS data are identical to those reported[6] for the racemic mixtures.

4.3.1. (2*R*,1′*S*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-6-methoxybenzofuran 2a. $[\alpha]_D^{25}$ −27.6 (*c* 2.88, $CHCl_3$).

4.3.2. (2*R*,1′*R*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-6-methoxybenzofuran 2b. $[\alpha]_D^{25}$ −21.2 (*c* 9.53, $CHCl_3$).

4.3.3. (2*S*,1′*R*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-6-methoxybenzofuran 2c. $[\alpha]_D^{25}$ +27.9 (*c* 2.11, $CHCl_3$).

4.3.4. (2*S*,1′*S*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-6-methoxybenzofuran 2d. $[\alpha]_D^{25}$ +20.3 (*c* 8.44, $CHCl_3$).

4.4. Preparation of phenols 4a–4d

In a dry 25 mL round bottom flask equipped with a magnetic stirring bar was added LiH (944 mg, 118.7 mmol) under a nitrogen atmosphere and cooled to −78°C. Then EtSH (8.81 mL, 119.0 mmol) was added dropwise. The reaction mixture was stirred 30 min, then warmed to room temperature and the excess EtSH was evaporated under vacuum. The formed EtSLi was added to a room temperature solution of the corresponding ketal **3a**–**3d** (950 mg, 3.6 mmol) in anhydrous DMF (15 mL). Each reaction was stirred for 24 h at 85°C, acidified with 5% HCl and extracted with Et_2O. The organic layer was washed with water, dried, and evaporated to give a solid residue, which was purified by column chromatography eluting with hexane–AcOEt (4:1) to give **4a** (720 mg, 80%), **4b** (723 mg, 80%), **4c** (727 mg, 81%), and **4d** (725 mg, 81%). The ^{1}H and ^{13}C NMR, UV, IR, MS and HRMS data are identical to those described[6] for the racemic mixtures.

4.4.1. (2*R*,1′*S*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-hydroxybenzofuran 4a. $[\alpha]_D^{25}$ −42.1 (*c* 1.52, $CHCl_3$).

4.4.2. (2*R*,1′*R*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-hydroxybenzofuran 4b. $[\alpha]_D^{25}$ −57.6 (*c* 1.91, $CHCl_3$).

4.4.3. (2*S*,1′*R*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-hydroxybenzofuran 4c. $[\alpha]_D^{25}$ +42.6 (*c* 1.43, $CHCl_3$).

4.4.4. (2*S*,1′*S*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-6-hydroxybenzofuran 4d. $[\alpha]_D^{25}$ +56.1 (*c* 2.28, $CHCl_3$).

4.5. Preparation of ketals 5a–5d

Condensation of the corresponding phenol **4a**–**4d** (300 mg, 1.2 mmol) with ethyl propiolate, using the procedure[6] described for the racemic mixture, afforded **5a** (127 mg, 35%) and **6a** (15.7 mg, 5%), **5b** (130 mg, 36%) and **6b** (16.1 mg, 5%), **5c** (130 mg, 36%) and **6c** (15 mg, 5%), and **5d** (125 mg, 35%) and **6d** (14 mg, 5%). The ^1H and ^{13}C NMR, UV, IR, MS and HRMS data for **5a** and **5c** are identical to those described[6] for the racemic mixture.

4.5.1. (2*R*,1′*S*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5a. $[\alpha]_D^{25}$ +4.1° (*c* 1.72, $CHCl_3$). CD $\Delta\varepsilon_{328}$ +2.03, $\Delta\varepsilon_{274}$ +0.94, $\Delta\varepsilon_{255}$ +3.04, $\Delta\varepsilon_{226}$ −17.34 (*c* 6.89×10^{-5} M, MeOH).

4.5.2. (2*R*,1′*R*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5b. $[\alpha]_D^{25}$ +36.4 (*c* 1.62, $CHCl_3$). White prism: mp 155–157°C, UV (EtOH) λ_{max} (log ε) 203 (4.76), 225 (4.25), 335 (4.40). IR (KBr) ν_{max} 1705, 1629, 1567, 1126 cm^{-1}. CD $\Delta\varepsilon_{328}$ +0.81, $\Delta\varepsilon_{267}$ +0.56, $\Delta\varepsilon_{257}$ +1.56, $\Delta\varepsilon_{227}$ −3.21 (*c* 6.49×10^{-5} M, MeOH). ^1H NMR ($CDCl_3$): δ 7.59 (1H, d, $J=9.6$ Hz, H-10), 7.21 (1H, s, H-4), 6.75 (1H, s, H-7), 6.21 (1H, d, $J=9.6$ Hz, H-9), 4.83 (1H, t, $J=8.6$ Hz, H-2), 4.15 (1H, d, $J=8.8$ Hz, H-2′a), 3.82 (1H, d, $J=8.8$ Hz, H-2′b), 3.26 (2H, d, $J=8.6$ Hz, H-3), 1.41 (3H, s, CH_3-*gem*), 1.38 (3H, s, CH_3-1″), 1.34 (3H, s, CH_3-*gem*). ^{13}C NMR ($CDCl_3$): δ 163.39 (C-7a), 161.36 (C-8), 155.76 (C-6), 143.62 (C-10), 124.56 (C-3a), 123.29 (C-4), 112.69 (C-5), 112.27 (C-9), 110.40 (C-O_2), 97.92 (C-7), 87.61 (C-2), 81.97 (C-1′), 70.97 (C-2′), 30.07 (C-3), 26.79 (CH_3-*gem*), 26.48 (CH_3-*gem*), 22.62 (CH_3-1″). EIMS *m*/*z* 302 $[M]^+$ (7), 187 (7), 115 (100), 43 (10). HREIMS *m*/*z* 302.114709 (calcd for $C_{17}H_{18}O_5$ $[M]^+$ 302.115424).

4.5.3. (2*S*,1′*R*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5c. $[\alpha]_D^{25}$ −3.6 (*c* 1.40, $CHCl_3$). CD $\Delta\varepsilon_{328}$ −2.26, $\Delta\varepsilon_{272}$ −0.09, $\Delta\varepsilon_{251}$ −3.12, $\Delta\varepsilon_{228}$ +17.61 (*c* 7.15×10^{-5} M, MeOH).

4.5.4. (2*S*,1′*S*)-2,3-Dihydro-2-(2′,2′,4′-trimethyl-1′,3′-dioxolan-4′-yl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5d. $[\alpha]_D^{25}$ −35.1 (*c* 1.65, $CHCl_3$). CD $\Delta\varepsilon_{330}$ −1.79, $\Delta\varepsilon_{270}$ +0.04, $\Delta\varepsilon_{249}$ −2.98, $\Delta\varepsilon_{227}$ +10.77 (*c* 6.09×10^{-5} M, MeOH). The remaining the ^1H and ^{13}C NMR, UV, IR, MS and HRMS data for **5d** are identical to those described above for **5b**.

4.6. Preparation of coumarins 6a–6d

A solution of the corresponding ketalcoumarin **5a**–**5d** (200 mg) and *p*-toluenesulfonic acid (20 mg) in MeOH (20 mL) was heated under reflux for 90 min. The solution was concentrated to a small volume and water (20 mL) was added. The precipitate formed was collected by filtration and washed with water to give **6a** as a white cotton-like material (168 mg, 97%), **6b** (165 mg, 95%), **6c** (170 mg, 98%), and **6d** (160 mg, 92%). The ^1H and ^{13}C NMR, UV, IR, MS and HRMS data are identical to those described[6] for the racemic mixtures.

4.6.1. (2*R*,1′*S*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5a. $[\alpha]_D^{25}$ +17.2 (*c* 0.99, MeOH). CD $\Delta\varepsilon_{329}$ +0.88, $\Delta\varepsilon_{277}$ +0.16, $\Delta\varepsilon_{255}$ +1.62, $\Delta\varepsilon_{227}$ −8.64 (*c* 7.48×10^{-5} M, MeOH).

4.6.2. (2*R*,1′*R*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5b. $[\alpha]_D^{25}$ −16.7 (*c* 0.30, MeOH). CD $\Delta\varepsilon_{333}$ +1.57, $\Delta\varepsilon_{280}$ −0.43, $\Delta\varepsilon_{250}$ +1.88, $\Delta\varepsilon_{230}$ −4.26 (*c* 6.87×10^{-5} M, MeOH).

4.6.3. (2*S*,1′*R*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5c. $[\alpha]_D^{25}$ −16.3 (*c* 0.55, MeOH). CD $\Delta\varepsilon_{328}$ −1.45, $\Delta\varepsilon_{270}$ +0.55, $\Delta\varepsilon_{255}$ −1.47, $\Delta\varepsilon_{229}$ +7.45 (*c* 6.72×10^{-5} M, MeOH).

4.6.4. (2*S*,1′*S*)-2,3-Dihydro-2-(1′,2′-dihydroxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 5d. $[\alpha]_D^{25}$ +17.6 (*c* 0.74, MeOH). CD $\Delta\varepsilon_{331}$ −0.92, $\Delta\varepsilon_{271}$ +0.96, $\Delta\varepsilon_{249}$ −1.14, $\Delta\varepsilon_{230}$ +3.20 (*c* 6.87×10^{-5} M, MeOH).

4.7. Preparation of monoacetates 7a–7d

A solution of the corresponding dihydrofurocoumarin **6a**–**6d** (150 mg, 0.57 mmol) in Ac_2O (2 mL) and pyridine (1.5 mL) was stirred at room temperature for 12 h, poured over ice, and extracted with CH_2Cl_2. After standard extractive workup, the residue was purified by circular chromatography using a 2 mm rotor and hexane–acetone 4:1, to afford **7a** (138 mg, 79%), **7b** (140 mg, 80%), **7c** (137 mg, 79%), and **7d** (141 mg, 81%). The ^1H and ^{13}C NMR, UV, IR, MS and HRMS data for **7a** to **7d** are identical to those described[6] for the racemic mixtures.

4.7.1. (2*R*,1′*S*)-2,3-Dihydro-2-(1′-hydroxy-2′-acetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 7a. $[\alpha]_D^{25}$ −20.8 (*c* 0.77, $CHCl_3$). CD $\Delta\varepsilon_{329}$ +1.26, $\Delta\varepsilon_{274}$ +0.53, $\Delta\varepsilon_{250}$ +2.06, $\Delta\varepsilon_{226}$ −5.12 (*c* 6.32×10^{-5} M, MeOH).

4.7.2. (2*R*,1′*R*)-2,3-Dihydro-2-(1′-hydroxy-2′-acetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzo pyran-7-one 7b. $[\alpha]_D^{25}$ −39.5 (*c* 0.81, $CHCl_3$). CD $\Delta\varepsilon_{332}$ +0.89, $\Delta\varepsilon_{279}$ −0.22, $\Delta\varepsilon_{254}$ +1.25, $\Delta\varepsilon_{228}$ −6.81 (*c* 6.58×10^{-5} M, MeOH).

4.7.3. (2*S*,1′*R*)-2,3-Dihydro-2-(1′-hydroxy-2′-acetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzo pyran-7-one 7c. $[\alpha]_D^{25}$ +22.0 (*c* 1.00, $CHCl_3$). CD $\Delta\varepsilon_{327}$ −1.31, $\Delta\varepsilon_{270}$ +0.57, $\Delta\varepsilon_{253}$ −1.15, $\Delta\varepsilon_{226}$ +6.43 (*c* 6.58×10^{-5} M, MeOH).

4.7.4. (2*S*,1′*S*)-2,3-Dihydro-2-(1′-hydroxy-2′-acetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 7d. $[\alpha]_D^{25}$ +41.8 (*c* 0.55, $CHCl_3$). CD $\Delta\varepsilon_{327}$ −0.55, $\Delta\varepsilon_{273}$ +0.88, $\Delta\varepsilon_{252}$ −0.61, $\Delta\varepsilon_{229}$ +2.25 (*c* 6.32×10^{-5} M, MeOH).

Table 1. X-Ray data collection and processing for (+)-**5a** and (+)-**5b**

Compound	(2*R*,1′*S*)-(+)-**5a**	(2*R*,1′*R*)-(+)-**5b**
Empirical formula	$C_{17}H_{18}O_5$	$C_{17}H_{18}O_5$
Formula weight	302.31	302.31
Size (mm)	$0.45\times0.37\times0.32$	$0.55\times0.47\times0.34$
Crystal system	Orthorhombic	Triclinic
Space group	$P2_12_12_1$	$P1$ bar
a (Å)	8.6472(4)	6.672(1)
b (Å)	11.5032(5)	7.310(1)
c (Å)	14.9594(7)	16.942(2)
α (°)	90.000	89.755(3)
β (°)	90.000	79.840(3)
γ (°)	90.000	67.598(3)
V (Å^3)	1488.02	750.05
D_{calcd} (g cm^{-3})	1.349	1.339
Z value	4	2
F (000)	640	320
μ (mm^{-1})	0.099 (MoKα)	0.098 (MoKα)
T (K)	293(2)	293(2)
$2\theta_{range}$ (°)	2.23–23.24	1.22–26.06
Total reflections	7706	4983
Unique reflections	2129	2951
R_{int} (%)	2.3	2.1
$I\geq3\sigma(I)$	1987	1815
Parameters	225	235
Goodness-of-fit (F^2)	0.906	0.952
R (%), R_W (%)	3.2, 7.4	4.8, 11.3
Largest diff. peak (e Å^{-3})	0.17	0.24

4.8. Preparation of diacetates 8a–8d

A mixture of the corresponding monoacetate **7a**–**7d** (100 mg, 0.33 mmol), AcONa (50 mg) in Ac_2O (5 mL) was refluxed for 3 h, poured over ice, and extracted with CH_2Cl_2. After usual workup the residue was purified by circular chromatography using a 2 mm rotor and hexane–AcOEt 4:1, to give **8a** (80 mg, 70%), **8b** (82 mg, 72%), **8c** (79 mg, 69%), and **8d** (81 mg, 71%). The ^{1}H and ^{13}C NMR, UV, IR, MS and HRMS data for **8a** to **8d** are identical to those described[6] for the racemic mixtures.

4.8.1. (2*R*,1′*S*)-2,3-Dihydro-2-(1′,2′-diacetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 8a. $[\alpha]_D^{25}$ −3.8 (*c* 1.30, $CHCl_3$). CD $\Delta\varepsilon_{327}$ +1.31, $\Delta\varepsilon_{270}$ −0.57, $\Delta\varepsilon_{257}$ +1.15, $\Delta\varepsilon_{223}$ −6.43 (*c* 5.32×10^{-5} M, MeOH).

4.8.2. (2*R*,1′*R*)-2,3-Dihydro-2-(1′,2′-diacetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 8b. $[\alpha]_D^{25}$ −15.0 (*c* 1.00, $CHCl_3$). CD $\Delta\varepsilon_{323}$ +1.79, $\Delta\varepsilon_{267}$ +0.72, $\Delta\varepsilon_{254}$ +2.80, $\Delta\varepsilon_{223}$ −5.52 (*c* 5.90×10^{-5} M, MeOH).

4.8.3. (2*S*,1′*R*)-2,3-Dihydro-2-(1′,2′-diacetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 8c. $[\alpha]_D^{25}$ +5.1 (*c* 2.15, $CHCl_3$). CD $\Delta\varepsilon_{327}$ −1.47, $\Delta\varepsilon_{270}$ +0.44, $\Delta\varepsilon_{257}$ −1.33, $\Delta\varepsilon_{223}$ +7.47 (*c* 6.01×10^{-5} M, MeOH).

4.8.4. (2*S*,1′*S*)-2,3-Dihydro-2-(1′,2′-diacetyloxy-1′-methylethyl)-7*H*-furo[3,2-g][1]benzopyran-7-one 8d. $[\alpha]_D^{25}$ +15.9 (*c* 1.13, $CHCl_3$). CD $\Delta\varepsilon_{324}$ −1.23, $\Delta\varepsilon_{272}$ +0.34, $\Delta\varepsilon_{255}$ −1.10, $\Delta\varepsilon_{224}$ +5.42 (*c* 5.55×10^{-5} M, MeOH).

4.9. X-Ray structure determination of (+)-5a and (+)-5b

X-Ray data for (+)-**5a** and (+)-**5b** were collected on a Bruker Smart 6000 CCD diffractometer. Single crystals of (+)-**5a** were grown from AcOEt while those of (+)-**5b** were grown from hexane–AcOEt. A total of 1321 frames were collected at a scan width of 0.3° and exposure time of 10 s/frame. The frames were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm, and the structures were solved and refined using SHELX-97.[14] Pertinent crystal data, collection and refinement parameters are given in Table 1.

Acknowledgements

This research was partially supported by CONACyT (México). The authors thank I.Q. Luis Velasco Ibarra (Instituto de Química, UNAM) for performing the HRMS, Dr. Arturo Rojo Domínguez (UAM-Iztapalapa) for recording CD spectra and Dr. Oscar Suárez (Universidad Autónoma del Estado de Hidalgo) for providing raw X-ray data for (+)-**5a** and (+)-**5b**.

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14. Crystallographic data for (+)-**5a** (CCDC 185842) and (−)-**5b** (CCDC 185841) have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, UK.