

Synthesis and anti-inflammatory activity of *rac*-2-(2,3-dihydro-1,4-benzodioxin)propionic acid and its *R* and *S* enantiomers

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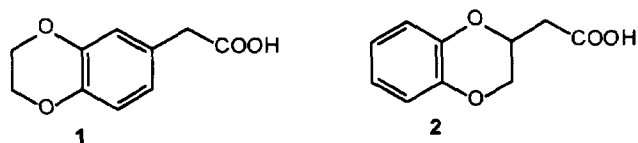
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Summary — Racemic (*R,S*)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)propionic acid (**3**) has been prepared from 2,3-dihydro-1,4-benzodioxin. *R*-(-)-Pantolactone has been used as auxiliary for the synthesis of *R*-**3** and *S*-**3**. The anti-inflammatory properties of the new carboxylic acids are described and compared with other anti-inflammatory agents. The highest activity is exhibited by compound *S*-**3**.

anti-inflammatory activity / 1,4-benzodioxan derivatives / aryl propionic acid

Introduction

In a previous paper [1] it was shown that the 2,3-dihydro-1,4-benzodioxin nucleus bearing an acidic acetic moiety conferred anti-inflammatory activity (compounds **1** and **2**) as non-steroidal acid anti-inflammatory drugs (NSAIDs).



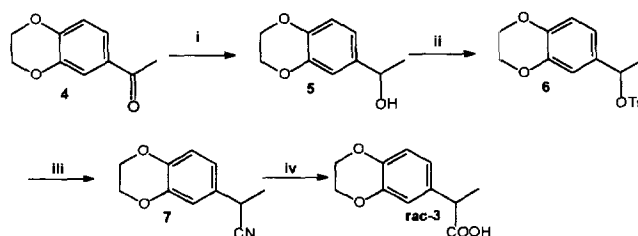
A study on the structure–activity relationships (SAR) showed that the relative position of the methyl carboxylic acid on the heterocyclic nucleus for optimization of anti-inflammatory activity was in the 6th position (compound **1**). Compound **2**, with the methyl carboxylic acid in position 2 of 2,3-dihydro-1,4-benzodioxin showed mediocre anti-inflammatory activity [1].

In this paper, as an extension of the previously mentioned work, we report the synthesis and pharmacological activity of the racemic *rac*-**3** and both enantiomers *R*-**3** and *S*-**3** of 2-(2,3-dihydro-1,4-benzo-

dioxin-6-yl)propionic acid **3**. Among the NSAIDs, arylpropionic acids constitute an important class and it is known that acids possessing an (*S*)-configuration at the asymmetric center are more active [2, 3].

Chemistry

Three approaches to the racemic 2-(2,3-dihydro-1,4-benzodioxin-6-yl)propionic acid *rac*-**3** can be envisioned. In the first approach (scheme 1), *rac*-**3** was prepared in four steps, first by reduction of (2,3-dihydro-1,4-benzodioxin-6-yl)methylketone **4**. Alcohol **5**, thereby obtained in quantitative yield, was converted into the desired propionitrile **7** via the *o*-tosyle **6**, which was obtained from alcohol **5**. Propionitrile **7** was converted into the desired acid by acidic hydrolysis in good yield.



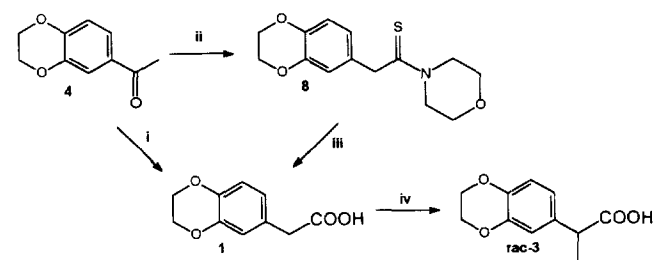
Scheme 1. Reagents and conditions: i: NaBH₄/MeOH; ii: TsCl/TEA/CH₂Cl₂; iii: NaCN/DMSO; iv: 5 N HCl.

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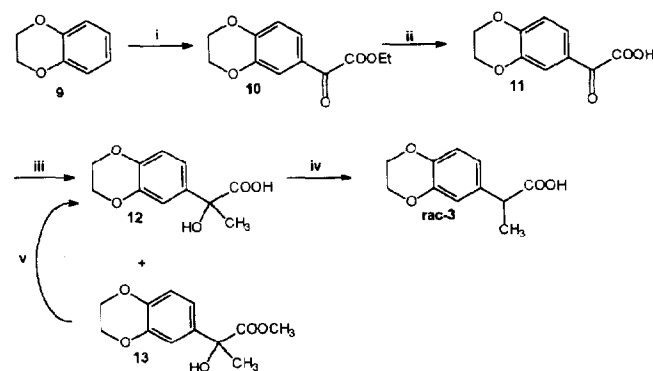
A second approach (scheme 2) utilizes the same ketone **4** as starting material. Ketone **4** was derived to acetic acid **1** from a Willgerdt reaction using S_8 and morpholine [1], or a viable alternative was with $AgNO_3$ [4]. The last attempt to synthesize **1** gave the desired compound in 55% yield. Addition of LDA to a $-78^\circ C$ THF solution of acid **1**, followed by addition of methyl iodide and later a workup with a NH_4Cl solution, gave the 2-(2,3-dihydro-1,4-benzodioxin-6-yl)propionic acid **rac-3** in 72% yield.

An alternative method to the arylpropionic acid **3** synthesis is described in scheme 3.

2,3-Dihydro-1,4-benzodioxin **9** was converted in satisfactory yield to the α -ketoester **10**. Next, compound **10** was hydrolyzed to the desired ketoacid **11** in good yield (75%). After examining a variety of reaction conditions, we finally obtained a 75% yield of **12** by reaction of the acid **11** with methyl lithium. Under these conditions, ester **13** is also obtained, but it can be converted to the acid **12** by alkaline hydrolysis in quantitative yield. The α -hydroxy acid **12** was finally reduced by means of $SnCl_2$ [5], obtaining **rac-3** in 75% yield.



Scheme 2. Reagents and conditions: i: $AgNO_3/MeOH$; trimethylorthoformate; ii: S_8 /morpholine; iii: $NaOH$ 8%; iv: LDA/MeI .



Scheme 3. Reagents and conditions: i: $AlCl_3/CICOCOOEt/CS_2$; ii: $KOH/EtOH/water$; iii: $MeLi/THF$; iv: $SnCl_2/HCl/CH_3COOH$; v: $NaOH$ 8%.

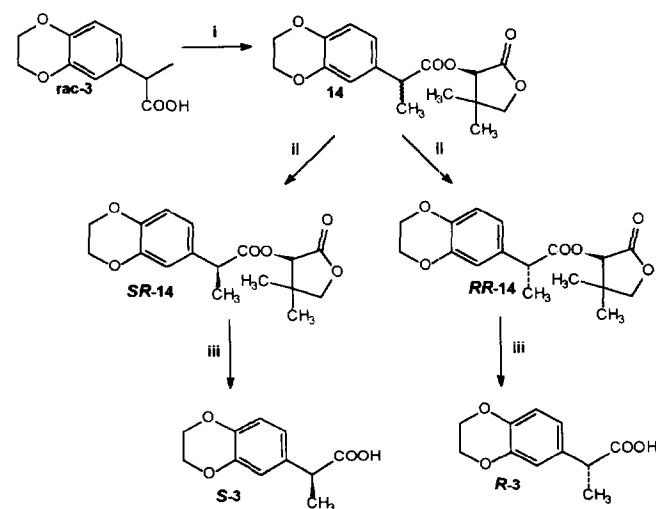
Separation of the diastereomers

We decided to perform the resolution of 2-(2,3-dihydro-1,4-benzodioxin-6-yl)propionic acid via the *R*-(-)-pantolactone derivatives as shown in scheme 4. The procedure consists of the formation of a mixture of the diastereomeric esters by addition of the chiral alcohol to the racemic acid **3**. The esterification reaction was performed at $0^\circ C$. Thus, diastereomeric esters were obtained in 90% yield and were separated by column chromatography. The diastereoselectivity was assayed by 1H - and ^{13}C -NMR and was determined to be around 99%. The configuration of the *S,R*-**14** derivative was established by X-ray diffraction analysis (fig 1). Finally, controlled basic hydrolysis afforded the corresponding *R* or (*S*)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)propionic acid. The purity of each enantiomer was assayed by HPLC analysis and was determined to be around 91%.

Pharmacology

Anti-inflammatory activity

All acids were subjected to in vivo tests in order to evaluate their activity. Compounds **rac-3**, **S-3** and **R-3** were evaluated for anti-inflammatory activity by using the carrageenan-induced paw edema assay in rats [1]. The results obtained are shown in table I.



Scheme 4. Diastereomeric separation: reagents and conditions: i: *R*-(-)-Pantolactone/ $DCC/DMAP$; ii: separation by silica gel chromatography; iii: $NaOH$ 8%.

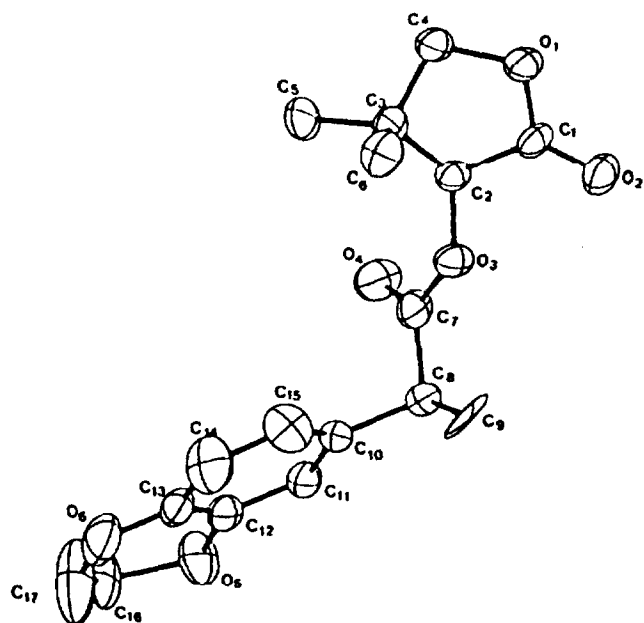


Fig 1. Perspective drawing (ORTEP) of (*S,R*)-14. The numbering is the same as that used for the X-ray analysis.

Results and discussion

An examination of the results in table I shows that the *S*-enantiomer can be considered more potent than the corresponding *R*-enantiomer. Moreover, compound *S*-3 exhibited a long duration of action, and after 5 h oral administration (4 h post-carrageenan) was 3.23 times more active than its enantiomer, *R*-3, which is in agreement with data in the literature, where it is indicated that the eutomers of the anti-inflammatory α -arylpropanoic acids are the *S*-enantiomers. The racemic 3 is 1.8 and 2.0 times less potent than *S*-3 at 3 and 4 h post-carrageenan administration, respectively. Based on the screening data, the decrease in anti-inflammatory activity of 1 (70 mg) in 1 h (from 33% inhibition in 3 h to 25% inhibition in 4 h) is evident, and the activity of ibuprofen (70 mg) is also rapidly reduced with the passage of time.

Both ibuprofen and compound *S*-3 show similar anti-inflammatory activity 3 h after carrageenan administration. However, the anti-inflammatory activity of compound *S*-3 after 4 h is 1.76 times greater compared to that of ibuprofen. This behaviour may be attributed to the metabolism of this compound when administered orally.

Table I. Antiinflammatory activity. Carrageenan-induced paw edema assay was conducted by the method of Winter et al [6]. Male Sprague-Dawley rats weighing ~ 200 g were used. Test compounds suspended in 0.5% Tween-80 solution were administered orally 1 h before a subplantar injection of 1% carrageenan in 0.1 mL physiological saline solution into the hind paw. The paw volumes were measured by a plethysmometer immediately, 3 and 4 h after carrageenan was injected.

Compound	Dose (mg/kg po)	Carrageenan-induced paw edema (CPE)			
		3 h Post-carrageenan		4 h Post-carrageenan	
		Swelling (%) ^{a,b}	Inhib (%)	Swelling (%) ^{a,b}	Inhib (%)
1	50	31.3 ± 3.8 ^{c,***}	25.5	30.0 ± 3.3 ^{d,**}	16.3
1	70	25.6 ± 3.7 ^{e,**}	33.0	37.2 ± 7.4 ^{f,**}	25.5
2	70	35.8 ± 8.4 ^{g,**}	10.8	34.4 ± 10.2 ^{h,*}	0.5
3	70	21.6 ± 2.4 ^{i,*}	20.7	21.6 ± 3.3 ^{j,#}	20.7
(<i>S</i>)-3	70	30.3 ± 5.6 ^{k,***}	37.4	31.7 ± 7.8 ^{i,***}	42.0
(<i>R</i>)-3	70	31.6 ± 8.8 ^{m,*}	23.7	33.5 ± 9.7 ^{n,#}	13.0
Ibuprofen	50	33.3 ± 3.1 ^{c,***}	21.0	30.4 ± 3.8 ^{d,**}	15.1
Ibuprofen	70	27.1 ± 3.6 ^{o,***}	30.3	34.3 ± 6.9 ^{p,**}	23.9

^aPaw edema was calculated as [(volume at t_x) - (volume at T_0)]/(latter volume) × 100. Each value represents the mean ± SEM in the groups of eight rats; ^bvalues were statistically different from controls, as indicated: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; and # non significant data, according to an unpaired one-tailed Student's *t*-test. Control value of swelling was: ^c42.1 ± 3.4; ^d35.8 ± 5.9; ^e38.2 ± 6.6; ^f49.9 ± 5.3; ^g40.2 ± 4.7; ^h34.6 ± 2.3; ⁱ27.2 ± 3.6; ^j27.2 ± 6.8; ^k48.4 ± 2.3; ^l54.5 ± 3.0; ^m41.4 ± 2.5; ⁿ38.5 ± 3.7; ^o38.9 ± 6.0; ^p45.1 ± 5.0. Statistically significant differences were found between references and experimental values.

The number of compounds tested is too small to allow definitive conclusions to be made in this series, but the preliminary results obtained show that the anti-inflammatory activity of compound **S-3** is greater than that of the corresponding arylacetic analogue **1**.

Experimental protocols

Melting points were determined on a Gallenkamp apparatus (MFB.595.010M) using open tubes and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer FTIR (model 1600) spectrometer in solid phase (KBr) or solution (CHCl_3), and were consistent with the assigned structures. $^1\text{H-NMR}$ were recorded on either a Varian Gemini spectrometer at 200 MHz or a Varian Gemini spectrometer at 300 MHz; chemical shifts are reported in parts per million (ppm) downfield from TMS, unless otherwise noted. The following abbreviations are used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Coupling constants are expressed in Hertz. $^{13}\text{C-NMR}$ were recorded on a Varian Gemini spectrometer at 50.4 or 75.4 MHz. Chemical shifts are reported in ppm internally referenced to the solvent peak (77.0 ppm) unless otherwise noted. Elemental analyses were performed and results are within 0.4% of theoretical values. Where anhydrous conditions were required, an argon atmosphere was employed and solvents were freshly distilled. Column chromatography was carried out using silica gel, SDS 60A CC (70–230 mesh) and mixtures of hexane/ethyl acetate as eluent unless otherwise noted. Unless stated otherwise, reagents were obtained from commercial sources and used directly. Compound **4** is commercially available, but it was synthesized as described in the experimental part. The spectroscopic and analytical data of the compound synthesized correspond to those described in the bibliography.

Method 1

(2,3-Dihydro-1,4-benzodioxin-6-yl)methylketone **4**

To a cooled solution (0 °C) of 2,3-dihydro-1,4-benzodioxin (5 g, 36.7 mmol) in CS_2 (100 mL), acetylchloride (13.2 mL, 168 mmol) and AlCl_3 (10 g, 73.49 mmol) were successively added and the reddish suspension obtained was stirred at room temperature for 10 h. The resulting mixture was poured onto ice (20 mL), allowed to stand for 15 min and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with saturated NaHCO_3 (2 x 50 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a brown solid, which was purified by silica gel chromatography using hexane/ethyl acetate (9:1) as eluent. The ketone **4** (6 g, 33.5 mmol) was obtained as a white solid (91% yield).

1-(2,3-Dihydro-1,4-benzodioxin-6-yl)ethanol **5**

To a cooled solution (0 °C) of the ketone **4** (0.45 g, 2.52 mmol) in methanol (7 mL), NaBH_4 (120 mg, 3.17 mmol) was slowly added, and the resulting mixture was stirred for 1 h at room temperature (18–20 °C). Then the mixture was poured onto ice (10 mL), the methanol was evaporated under reduced pressure and the resulting mixture was extracted with CH_2Cl_2 (5 x 20 mL). The extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the alcohol **5** (437 mg, 2.42 mmol) as a clear oil (96% yield).

$\text{C}_{10}\text{H}_{12}\text{O}_3$. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz), δ (ppm): 1.36 (d, $J = 6.6$ Hz, 3H, $\text{C}_2\text{-H}_3$); 3.30 (bs, 1H, OH); 4.12 (s, 4H, $\text{C}_{2(3)}\text{-H}_2$); 4.65 (q, $J_1 = 12.9$ Hz, $J_2 = 6.4$ Hz, 1H, $\text{C}_1\text{-H}$); 6.77 (m, 3H, $\text{C}_{5(7,8)}\text{-H}$). $^{13}\text{C-NMR}$ (CDCl_3 , 75.4 MHz), δ (ppm): 24.6 (CH_3), (C_2); 63.9 (CH_2), (C_7 and C_3); 69.1 (CH), (C_1); 114.0 (CH), 116.7 (CH) and 118.2 (CH), (C_5 , C_7 and C_8); 139.2 (C), (C_6); 142.2 (C) and 142.8 (C), (C_{4a} and C_{8a}). IR (CHCl_3) ν (cm^{-1}): 1150 (C–O, st); 3604 (O–H, st).

2-(2,3-Dihydro-1,4-benzodioxin-6-yl)propionitrile **7**

To a solution of the alcohol **5** (217 mg, 1.024 mmol) in dry CH_2Cl_2 (2 mL), a mixture of triethylamine (152 mg, 1.503 mmol) and dry CH_2Cl_2 (0.5 mL) was added. The mixture was stirred for 5 min at 0 °C and then a solution of tosyl chloride (270 mg, 1.4 mmol) in dry CH_2Cl_2 (1 mL) was added. The resulting suspension was stirred for 10 min at 0 °C and then allowed to stand for 40 h at –20 °C. The mixture was filtered, and the filtrate was successively washed with 10% tartaric acid solution (4 x 10 mL) and 0.5 N potassium chloride solution (5 x 10 mL). The resulting organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the product **6** as a brown oil, which was dissolved in anhydrous DMSO (10 mL), under an argon atmosphere. To the solution NaCN (58 mg, 1.19 mmol) was added. The resulting brown solution was heated at 90 °C for 17 h, then poured onto ice (10 mL) and extracted with ether (4 x 20 mL). The extracts were washed with 20% potassium chloride solution (5 x 10 mL), dried (MgSO_4), filtered and evaporated under reduced pressure to give product **7** (87 mg, 0.46 mmol) as a brown solid (50% yield, crude).

2(R,S)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-propanoic acid **rac-3**

A solution of product **7** (85 mg, 0.44 mmol) in 5 N hydrochloric acid (15 mL) was heated for 14 h at 80 °C. The resulting mixture was extracted with ether (4 x 20 mL), and the extracts dried (MgSO_4), filtered and evaporated under reduced pressure to give a brown solid which was recrystallized from hexane/ethyl acetate, 70:30. The acid **rac-3** (69 mg, 0.33 mmol) was obtained as a white solid (75% yield).

$\text{C}_{11}\text{H}_{12}\text{O}_4$. $^1\text{H-NMR}$ (CDCl_3 , 200 MHz), δ (ppm): 1.45 (d, $J = 7.1$ Hz, 3H, $\text{C}_3\text{-H}_3$); 3.62 (q, $J_1 = 14.3$ Hz, $J_2 = 7.1$ Hz, 1H, $\text{C}_2\text{-H}$); 4.23 (s, 4H, $\text{C}_{2(3)}\text{-H}_2$); 6.80 (m, 3H, $\text{C}_{5(7,8)}\text{-H}$); 9.00 (bs, 1H, $\text{C}_1\text{-OOH}$). $^{13}\text{C-NMR}$ (CDCl_3 , 50.4 MHz), δ (ppm): 17.9 (CH_3), (C_3); 44.5 (CH), (C_2); 64.2 (CH_2), (C_7 and C_3); 116.3 (CH) and 117.2 (CH), (C_5 and C_8); 120.5 (CH), (C_7); 132.9 (C), (C_6); 142.7 (C) and 143.3 (C), (C_{4a} and C_{8a}); 180.9 (C), ($\text{C}_1\text{-O}$). IR (CCl_4) ν (cm^{-1}): 1702 (CO, st); 2979 (COO–H, st); hexane/ethyl acetate, mp = 77–78 °C.

Method 2

2-(2,3-Dihydro-1,4-benzodioxin-6-yl)acetic acid **1**

To a solution of ketone **4** (292 mg, 1.64 mmol) in a (3:1) mixture of trimethylorthoformate/methanol (10 mL), silver nitrate (602 mg, 3.54 mmol) and iodine (228 mg, 1.8 mmol) were successively added. The mixture was refluxed for 24 h, filtered and evaporated under reduced pressure. The residue was extracted with ether (3 x 20 mL), and the extracts dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a brown solid (300 mg) which was dissolved in a mixture (4:1) of ethanol/water (25 mL). To the solution, potassium hydroxide (1.4 mg, 24 mmol) was added, and the resulting mixture was refluxed for 12 h. Ethanol was evaporated under reduced pressure and the residue was acidified with 5 N hydrochloric acid, extracted with ether (4 x 20 mL) and the extracts

dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a yellow oil which was recrystallized from hexane/ethyl acetate (7:3). The arylacetic acid **1** (175 mg, 0.9 mmol) was obtained as a white solid (55% yield). Spectroscopic and analytical data are reported in [1].

2(R,S)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-propionic acid rac-3

To a cooled solution (-78°C) of the arylacetic acid **1** (204 mg, 1.05 mmol) in anhydrous THF (3 mL) under an argon atmosphere, a 2 M solution of LDA in hexane (1.6 mL, 3.2 mmol) and TMEDA (0.3 mL, 1.9 mmol) were added dropwise with stirring over a 15-min period. The mixture was slowly stirred at -78°C for 3 h, and then methyl iodide (0.17 mL, 2.7 mmol) was slowly added with stirring. The solution was allowed to warm to room temperature (20°C) overnight, and was then neutralized with saturated aqueous ammonium chloride solution (10 mL). The resulting mixture was stirred at room temperature over a 1-h period. The THF layer was separated and the aqueous alkaline phase was acidified with 5 N hydrochloric acid, and the product extracted into ether (3 x 20 mL). The extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil, which was purified by silica gel chromatography using hexane/ethyl acetate (7:3) as eluent, followed by recrystallization from hexane/ethyl acetate (8:2). The product **rac-3** (160 mg, 0.76 mmol) was obtained as a white crystalline powder (72% yield).

Method 3

2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-oxoacetic acid ethyl ester 10

To a cooled solution (0°C) of the product **9** (4 g, 29.38 mmol) in CS_2 (100 mL), ethyloxalylchloride (15 mL, 131.8 mmol) and AlCl_3 (2 g, 59.9 mmol) were successively added, and the reddish suspension obtained was stirred at room temperature for 14 h. The resulting mixture was poured onto ice (20 mL) and extracted with CH_2Cl_2 (4 x 30 mL). The combined extracts were washed with saturated NaHCO_3 (2 x 30 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a brown solid which was purified by silica gel chromatography using hexane/ethyl acetate (7:3) as eluent. The α -ketoester **10** (5.07 g, 21.47 mmol) was obtained as a white solid (73% yield).

$\text{C}_{15}\text{H}_{12}\text{O}_5$. $^1\text{H-NMR}$ (CDCl_3 , 200 MHz), δ (ppm): 1.43 (t, $J = 6.2$ Hz, 3H, $\text{O-CH}_2\text{-CH}_3$); 4.30 (m, 4H, $\text{C}_{2(3)}\text{-H}_2$); 4.40 (q, $J_1 = 6.2$ Hz, $J_2 = 13.8$ Hz, $\text{O-CH}_2\text{-CH}_3$); 6.90 (m, 1H, $\text{C}_8\text{-H}$); 7.50 (m, 2H, $\text{C}_{5(7)}\text{-H}$). $^{13}\text{C-NMR}$ (CDCl_3 , 50.4 MHz), δ (ppm): 13.9 (CH_3) ($\text{CH}_3\text{-CH}_2$); 62.0 (CH_2) ($\text{CH}_3\text{-CH}_2$); 63.8 (CH_2) and 64.6 (CH_2), (C_2 and C_3); 117.51 (CH) and 119.0 (CH), (C_5 and C_8); 124.3 (CH), (C_7); 125.8 (C), (C_6); 143.4 (C), (C_{4a}); 149.7 (C), (C_{8a}); 163.9 (C), (COOEt); 184.7 (C), (CO). IR (CCl_4), ν (cm^{-1}): 1736 (CO-OEt, st); 1685 (CO, st); hexane/ethyl acetate, mp = $66\text{--}68^\circ\text{C}$.

2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-oxo-acetic acid 11

To a solution of the α -ketoester **10** (960 mg, 4.06 mmol) in 7:3 ethanol/water (100 mL), potassium hydroxide (440 mg, 7.8 mmol) was added, and the resulting mixture was stirred at room temperature for 12 h. Ethanol was evaporated under reduced pressure and the resulting mixture was extracted with ether (2 x 20 mL). The alkaline aqueous phase was acidified with 5 N hydrochloric acid and extracted with CH_2Cl_2 (4 x 30 mL). The extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a yellow solid which was recrystallized from hexane/ethyl acetate (6:4). The product **11** (624 mg, 3.0 mmol) was obtained as a yellow solid (75% yield).

$\text{C}_{10}\text{H}_8\text{O}_5$. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz), δ (ppm): 4.30 (m, 4H, $\text{C}_{2(3)}\text{-H}_2$); 6.96 (d, 1H, $\text{C}_8\text{-H}$); 7.45 (bs, $\text{C}_1\text{-OOH}$); 7.90 (m, 2H, $\text{C}_{5(7)}\text{-H}$). $^{13}\text{C-NMR}$ ($\text{CDCl}_3\text{-acetone}$, 50.4 MHz), δ (ppm): 63.8 (CH_2) and 64.7 (CH_2), (C_2 and C_3); 117.5 (CH) and 119.7 (CH), (C_5 and C_8); 125.1 (CH), (C_7); 125.7 (C), (C_6); 143.4 (C), (C_{4a}); 149.8 (C), (C_{8a}); 163.4 ($\text{C}_2\text{-O}$); 208.1 (C), ($\text{C}_1\text{-O}$). IR (CCl_4), ν (cm^{-1}): 1686 (CO, st); 1780 (CO, st) and 2929 (OH, st); hexane/ethyl acetate, mp = $113\text{--}116^\circ\text{C}$.

2-(R,S)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-hydroxypropionic acid 12

To a cooled (-50°C) solution of the ketoacid **11** (301 mg, 1.44 mmol) in anhydrous THF (4 mL), a 1.6 M solution of methylolithium in diethyl ether (3.2 mL, 5.12 mmol) was added under an argon atmosphere and the mixture allowed to warm to room temperature with gentle stirring for 14 h. When the temperature of the mixture reached 20°C , a saturated NH_4Cl solution (4 mL) was added, and the resulting mixture was extracted with ether (3 x 20 mL). The alkaline aqueous phase was acidified with 2 N hydrochloric acid and extracted with ether (3 x 30 mL). The acid extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a white solid which was recrystallized from hexane/ethyl acetate (6:4). The acid **12** (243 mg, 1.083 mmol) was obtained as a white solid (75% yield).

$\text{C}_{11}\text{H}_{12}\text{O}_5$. $^1\text{H-NMR}$ (CDCl_3 , 200 MHz), δ (ppm): 1.78 (s, 3H, $\text{C}_3\text{-H}_3$); 4.24 (s, 4H, $\text{C}_{2(3)}\text{-H}_2$); 5.20 (bs, $\text{C}_1\text{-OOH}$); 6.90 (m, 3H, $\text{C}_{5(7,8)}\text{-H}$). $^{13}\text{C-NMR}$ (CDCl_3 , 50.4 MHz), δ (ppm): 27.2 (CH_3) (C_3); 65.5 (CH_2), (C_2 and C_3); 77.9 (C), (C_2); 115.5 (CH), 117.6 (CH) and 119.3 (CH), (C_5 , C_7 and C_8); 139.9 (C), (C_{8a}); 143.5 (C), (C_6 and C_{4a}); 179.9 (C), (C_1). IR (CHCl_3), ν (cm^{-1}): 1682 (CO, st); 2950 (CO-OH, st).

2(R,S)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-propionic acid rac-3

To a solution of the acid **12** (50 mg, 0.223 mmol) in acetic acid (3 mL), $\text{SnCl}_4 \cdot 2\text{H}_2\text{O}$ (175 mg, 0.775 mmol) and concentrated hydrochloric acid (1.5 mL) were added. The mixture was stirred for 24 h at room temperature (25°C) and evaporated under reduced pressure. Water (10 mL) was added, and the resulting mixture was extracted with ether (2 x 10 mL). The extracts were washed with 5 N NaOH solution. The alkaline aqueous phase was acidified with 2 N hydrochloric acid, and extracted with ether (3 x 15 mL). The acid extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a brown solid which was recrystallized from hexane/ethyl acetate (8:2). The product **rac-3** (35 mg, 0.168 mmol) was obtained as a white powder (75% yield).

Separation of diastereomers

2(S)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)propionic acid (R)-pantolactone ester S,R-14 and 2(R)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)propionic acid (R)-pantolactone ester R,R-14

To a dried (1 mg of 4 Å molecular sieves/mmol) solution of the α -arylpropionic acid **rac-3** (431 mg, 2.07 mmol) in dry CH_2Cl_2 (40 mL), under an argon atmosphere, DMAP (178.3 mg, 1.46 mmol) and *R*(-)-pantolactone (398 mg, 3.06 mmol) were successively added. The solution obtained was cooled to 0°C (ice-water bath), DCC (384 mg, 1.8 mmol) was added, and the resulting mixture was magnetically stirred for 3 h at 0°C and then for 10 h at room temperature. The mixture was filtered, washed with 0.5 N NaHCO_3 (3 x 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give a white solid which was purified by silica gel chromatography (70–230 mesh silica/230–400 mesh silica; 50:50) using hexane/ethyl acetate (80:20) as eluent. The following products were successively

obtained: diastereomer **S,R-14** (208 mg, 0.648 mmol), as a white solid (31% yield); a mixture (45:55) of the two diastereomers **S,R-14** and **R,R-14** (192 mg, 0.6 mmol), (29% yield), and finally diastereomer **R,R-14** (190 mg, 0.593 mmol) which was obtained as a white solid (29% yield).

2(S)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)propanoic acid (R)-pantolactone ester S,R-14. $C_{17}H_{20}O_6$. 1H -NMR ($CDCl_3$, 300 MHz), δ (ppm): 1.06 (3H, s, C_6 -H₃); 1.18 (3H, s, C_7 -H₃); 1.57 (3H, d, $J = 7.2$ Hz, C_3 -H₃); 3.80 (1H, q, $J_1 = 14.4$ Hz, $J_2 = 7.2$ Hz, C_2 -H); 4.03 (2H, s, C_5 -H₂); 4.26 (s, 4H, $C_{2(3)}$ -H₂); 5.33 (1H, s, C_3 -H); 6.86 (3H, m, $C_{5(7,8)}$ -H). ^{13}C -NMR ($CDCl_3$, 75.4 MHz), δ (ppm): 18.2 (CH_3) and 19.6 (CH_3), (C_6 - and C_7 -); 22.8 (CH_3), (C_3); 39.8 (C), (C_4); 44.4 (CH), (C_2); 64.1 (CH_2), (C_2 and C_3); 74.9 (CH), (C_3 -H); 75.9 (CH_2), (C_5 -); 116.2 (CH) and 117.0 (CH), (C_5 - and C_8); 120.4 (CH), (C_7); 132.3 (C), (C_6); 142.6 (C) and 143.3 (C), (C_{4a} and C_{8a}); 171.9 (C), (C_1O); 173.2 (C), (C_2O). IR ($CDCl_3$) ν (cm^{-1}): 1690 (CO, st); 1770 (CO, st); hexane/ethyl acetate, mp = 82–84 °C.

2(R)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)propionic acid (R)-pantolactone ester R,R-14. $C_{17}H_{20}O_6$. 1H -NMR ($CDCl_3$, 300 MHz), δ (ppm): 0.84 (3H, s, C_6 -H₃); 1.05 (3H, C_7 -H₃); 1.51 (3H, d, $J = 7.2$ Hz, C_3 -H₃); 3.80 (1H, q, $J_1 = 14.3$ Hz, $J_2 = 7.2$ Hz, C_2 -H); 3.98 (2H, s, C_5 -H₂); 4.25 (s, 4H, $C_{2(3)}$ -H₂); 5.36 (1H, s, C_3 -H); 6.83 (3H, m, $C_{5(7,8)}$ -H). ^{13}C -NMR ($CDCl_3$, 75.4 MHz), δ (ppm): 17.9 (CH_3) and 19.3 (CH_3), (C_6 - and C_7 -); 22.7 (CH_3), (C_3); 40.2 (C), (C_4); 44.2 (CH), (C_2); 64.1 (CH_2), (C_2 and C_3); 74.7 (CH), (C_3 -H); 75.9 (CH_2), (C_5 -); 116.1 (CH) and 117.2 (CH), (C_5 - and C_8); 120.2 (CH), (C_7); 133.1 (C), (C_6); 142.6 (C) and 143.4 (C), (C_{4a} and C_{8a}); 172.3 (C), (C_1O); 173.4 (C), (C_2O). IR ($CDCl_3$) ν (cm^{-1}): 1694 (CO, st); 1770 (CO, st); hexane/ethyl acetate, mp = 85–87 °C.

General procedure for the hydrolysis of the esters **14**

A mixture of the ester **S,R-14** or **R,R-14** and 8% NaOH (50 mL/mmol) was stirred at room temperature for 24 h. Then

the mixture was acidified with 5 N hydrochloric acid and extracted with CH_2Cl_2 (3 x 30 mL). The extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a white solid, which was recrystallized from hexane/ethyl acetate (8:2).

2(S)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-propionic acid S-3
Following the general procedure from **S,R-14** (121 mg, 0.379 mmol) and 8% NaOH (20 mL), **S-3** (71 mg, 0.34 mmol) was obtained as a white solid (91% yield, 90% ee).

2(R)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-propionic acid R-3
Following the general procedure from **R,R-14** (125 mg, 0.39 mmol) and 8% NaOH (20 mL), **R-3** (73 mg, 0.35 mmol) was obtained as a white solid (90% yield, 91% ee).

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