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Tetrahedron: *Asymmetry* 14 (2003) 3689–3696

TETRAHEDRON: *ASYMMETRY*

Kinetic resolution of 3-hydroxymethylbenzocycloalkanols by selective asymmetric hydrogen-transfer oxidation

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Received 18 July 2003; accepted 6 August 2003

Abstract—Kinetic resolution of 3-hydroxymethylbenzocycloalkanols was performed by selective asymmetric hydrogen-transfer oxidation using the Ru(II)-(*S*,*S*)-TsDPEN catalyst. Thus, several 3-hydroxymethyl-1-tetralols **7a–d** afforded (1*R*,3*R*)-3-hydroxymethyl-1-tetralols (1*R*,3*R*)-**7a–d** and (*S*)-3-hydroxymethyl-1-tetralones (*S*)-**9a–d**, and 3-hydroxymethyl-1-indanol **7e** gave (1*R*,3*S*)-3-hydroxymethyl-1-indanol (1*R*,3*S*)-**7e** and (*R*)-3-hydroxymethyl-1-indanone (*R*)-**9e**, with high enantioselectivities.

1. Introduction

The introduction of the butyrophenone haloperidol (Haldol®, Fig. 1) into the clinic in 1959 was a significant advance in the treatment of schizophrenia, due to its efficacy in countering the hallucinatory and delusional (positive) symptoms of the disease.[1] However, haloperidol is ineffective in the treatment of negative symptoms and neurocognitive deficiencies,[2] a therapeutic profile that could be rationalized by the relatively low affinity for 5-HT_{2A} receptors compared to D_2 receptors.[3] Over the last few years we have been working on modulation of the butyrophenone system with the aim of combining antagonism at the 5-HT_2 family and D_2 receptors in a single molecule.[4] We have reported the synthesis, pharmacology and molecular modelling of the aminobutyrophenones QF0104B **1** and QF0108B **2** (Fig. 1),[5–7] which showed high affinity for the 5-HT_{2A} receptor subtype with K_i values of 1.6 and 2.7 nM, respectively, compound **1** being the most selec-

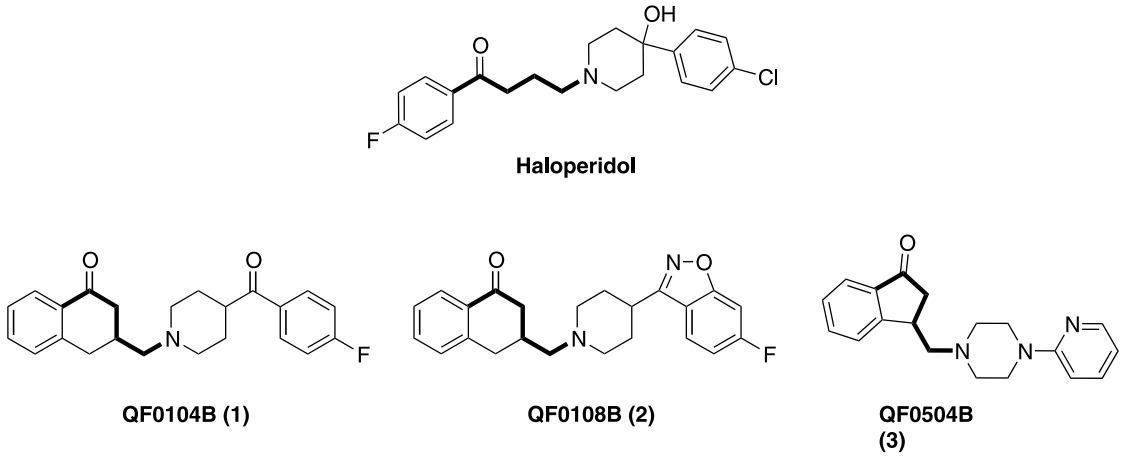

Figure 1.

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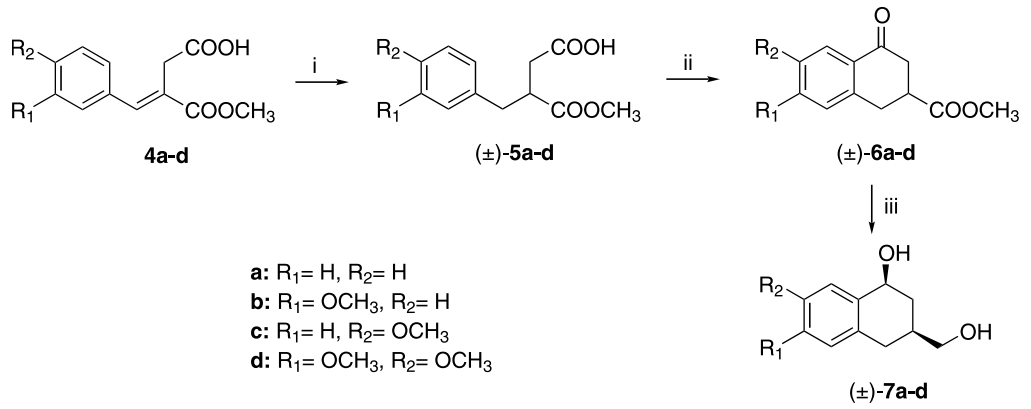
doi:10.1016/j.tetasy.2003.08.016



Scheme 1. *Reagents and conditions*: (i) Pd/C, H_2, MeOH, rt, 3 h, 92–96%; (ii) CF_3COOH, $(CF_3CO)_2O$, rt, 8 h, 50–85%; (iii) $LiAlH_4$, THF, rt, 12 h, 85–90%.

tive for the serotonin 5-HT_{2A} receptor subtype, with a 5-HT_{2A}/5-HT_{2C} K_i ratio as high as 150.[7] These compounds are also potent D_2 receptor antagonists, although they display K_i values higher than those at 5-HT_{2A} receptors.

The known chiral discriminatory properties of drug-receptor interactions have prompted us to investigate further whether the receptor affinities of these compounds are associated with chirality, specifically, the effect of the stereochemistry at C-3 of the tetralone on the in vitro affinities and selectivities of **1** and **2** at 5-HT_2 and D_2 receptors.

Recently, we have reported the preparation of (+)- and (−)-3-hydroxymethyl-1-tetralone tosylates as single enantiomers by resolution of synthetic precursors,[8] in order to obtain enantiomerically pure aminobutyrophenones **1** and **2**. Herein we report a new methodology for the kinetic resolution of 3-hydroxymethyl-1-tetralol **7a**, an intermediate in the synthesis of the aminobutyrophenones **1** and **2**, by selective asymmetric hydrogen-transfer oxidation using Noyori's catalyst [Ru(II)(*p*-cymene)-TsDPEN], (TsDPEN = *N*-tosyl-1,2-diphenylethylenediamine). We have extended our study to mono- and dimethoxy-substituted 3-hydroxymethyl-1-tetralols **7c**–**d**, precursors of new series of butyrophenones under development, and to the 3-hydroxymethyl-1-indanol **7e**, in turn, the precursor of pyridylpiperazine derivative QF0504B **3**, which is a 5-HT_{2C} selective ligand, with a 5-HT_{2A}/5-HT_{2C} K_i ratio of 0.027.[7]

2. Results and discussion

A large number of kinetic resolution strategies that rely on the use of chiral catalysts for the enantioselective oxidation of one enantiomer of a racemic secondary alcohol to its corresponding ketone have been reported to date.[9] Since Noyori's report on reversible catalytic asymmetric transfer hydrogenation complexes for asymmetric catalysis, the use of chiral diamine Ru(II) complexes to transfer hydride from a racemic alcohol substrate to acetone has been widely used as a method for the kinetic resolution of secondary alcohols.[10]

In particular, Ru(II) complexes of chiral mono-*N*-tosyl-1,2-diphenylethylenediamines catalyze the hydrogen transfer reaction of racemic allylic and benzylic secondary alcohols to ketones enantioselectively by converting one enantiomer, leaving the other enantiomer intact. We wished to examine the use of this asymmetric hydrogen-transfer oxidation to the 3-hydroxymethyl-1-tetralol system. To this end, a range of 3-hydroxymethyl-1-tetralols (±)-**7a**–**d** were prepared from dimethylsuccinate and the corresponding benzaldehydes via Stobbe condensation, hydrogenation of the benzylidenhemisuccinates **4** obtained, cyclization with trifluoroacetic anhydride in trifluoroacetic acid, and subsequent lithium aluminum hydride reduction (Scheme 1). Diols (±)-**7a**–**d** were obtained in 50–70% overall yield as white crystalline solids.

The *cis*-relative stereochemistry between the C1 hydroxyl and the C3 hydroxymethyl groups in diols (±)-**7a**–**d** was evident from the proton NMR spectrum. In the spectrum of the previously reported tetralol *cis*-(±)-**7a**,[8] the signal of the H1 proton appears as a double doublet ($J = 10.5$, 5.8 Hz). The magnitude of the largest vicinal coupling constant ($J = 10.5$ Hz) indicates a *trans*-diaxial relationship between H2ax and H1 in a preferred half-chair conformation that places the hydroxy group at C1 (and consequently the hydroxymethyl group at C3) in an equatorial position (Fig. 2).

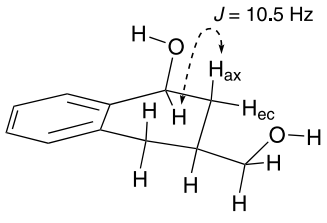
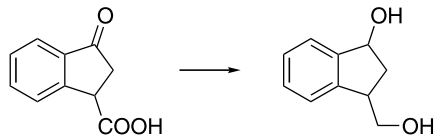


Figure 2.

In the NMR spectra (CD_3OD) of tetralols **7b**–**d**, the signal of the H1 protons appears as a double doublet

($J_{H1-H2ax} = 10.1–10.6$). As in the above mentioned compound **7a** and other previously reported tetralols,[11] consideration of the Karplus relationship suggest that the H1 protons of the hydroxymethyltetralols exist in a quasi-axial conformation on a half-chair ring. Assuming that the conformation of hydroxymethyl groups is equatorial in these compounds, these results indicate a *cis* relation between the 3-hydroxymethyl group and the 1-hydroxy group.

The study of the resolution of the 3-hydroxymethyl-1-tetralols was extended to an 1-indanol derivative. Thus, 3-hydroxymethyl-1-indanol (±)-**7e** was prepared by esterification and subsequent lithium aluminum hydride reduction of the known 3-oxo-1-indancarboxylic acid **8**[12] (Scheme 2). Lithium aluminum hydride reduction of 3-substituted-1-indanones has been described to give *cis*-products.[13] In our case, almost pure *cis*-3-hydroxymethyl-1-indanol was obtained. Stereochemical assignment was further supported by the study of the ^{1}H NMR spectrum, where the signals of the protons at C2 appear at different chemical shifts (two signals at 1.87 and 2.61 ppm) due to the shielding of C1 and C3 substituents over H2 *cis*.[14]

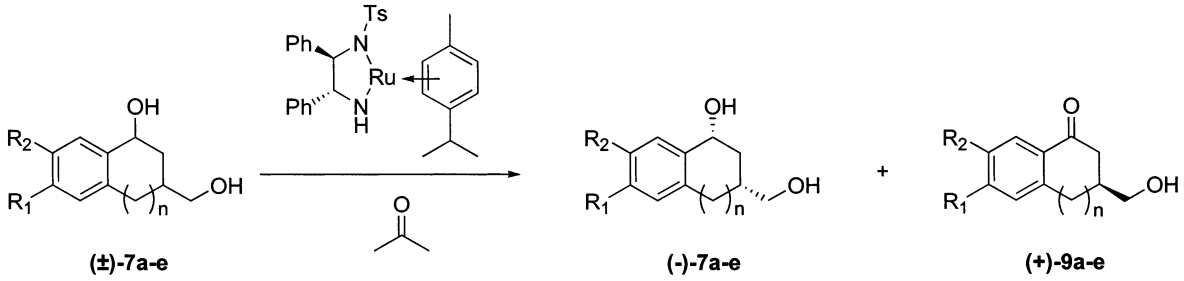


8 (±)-**7e**

Scheme 2. *Reagents and conditions*: (i) MeOH, *p*-TsOH, reflux, 5 h, 90%; (ii) $LiAlH_4$, THF, rt, 12 h, 70%.

For the kinetic resolution of the intermediates in the synthesis of our previously mentioned aminobutyrophenones by asymmetric hydrogen-transfer oxidation, we first examined the hydrogen transfer reaction of the diol (±)-**7a** in acetone at 28°C in the presence of the Ru(II)-(1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine [Ru(II)-(*S*,*S*)-TsDPEN] catalyst prepared from [$RuCl_2(\eta^6$-*p*-cymene]. [10] The reaction was found to occur chemoselectively at the secondary centre to give the chiral ketone (+)-**9a** leaving the chiral diol (−)-**7a** without affecting the hydroxy functionalities (Table 1, entries 1–4). The enantioselective oxidation occurred to the (1*S*)-stereoisomer, affording the (*S*)-3-hydroxymethyltetralone (+)-**9a**[8] with 99.9% e.e., and the

Table 1. Kinetic resolution of diols **7a**–**e** by chiral Ru(II) complex



(±)-**7a-e** (-)-**7a-e** (+)-**9a-e**

Entry	Substrate				Concentr. (M)	Solvent system[a]	S/C[b]	Time (h)	Ketone		Unreact. substr.	
		n	R_1	R_2					Yield[c]	E.e.	Yield[c]	E.e.[d]
1	(±)-**7a**	1	H	H	0.50	A	500	48	3	45[d]	90	—
2	(±)-**7a**	1	H	H	0.50	A	200	48	16	99.9[d]	70	23[e]
3	(±)-**7a**	1	H	H	0.50	A	100	28	48	99.9[d]	43	95[e]
4	(±)-**7a**	1	H	H	0.50	A	50	36	42	95[d]	40	99.9[e]
5	(±)-**7b**	1	OCH_3	H	0.75	B	100	21	45	93.5[d]	40	96[e]
6	(±)-**7b**	1	OCH_3	H	0.75	B	50	24	48.5	95[d]	40	97[e]
7	(±)-**7b**	1	OCH_3	H	0.75	B	50	36	47	99.9[d]	40	99.9[e]
8	(±)-**7c**	1	H	OCH_3	0.50	C	100	36	30	99.9[d]	50	46[e]
9	(±)-**7c**	1	H	OCH_3	0.50	C	100	72	40	99.9[d]	45	80[e]
10	(±)-**7c**	1	H	OCH_3	0.50	C	50	96	42	95[d]	44	86[e]
11	(±)-**7d**	1	OCH_3	OCH_3	0.20	A	100	48	—	—		
12	(±)-**7d**	1	OCH_3	OCH_3	0.60	C	50	24	34	96[d]	48	51[e]
13	(±)-**7d**	1	OCH_3	OCH_3	0.60	C	50	38	44	99.9[d]	42	99.9[e]
14	(±)-**7e**	0	H	H	1.20	A	100	24	38	62	47	78[d]
15	(±)-**7e**	0	H	H	1.20	A	50	18	30	90	57	60[d]
16	(±)-**7e**	0	H	H	1.20	A	50	40	44	80	38	84[d]

[a] Solvent system: A: acetone; B: acetone/MeOH (4:1); C: acetone/MeOH (3:2).
[b] Substrate to catalyst ratio.
[c] Yields after purification.
[d] Determined by HPLC analysis using a Daicel Chiralcel OD-H column.
[e] Determined by HPLC analysis using a Daicel Chiralcel OD-H column, after oxidation with MnO_2.

(1*R*,3*R*)-diol (−)-**7a** with 95% e.e., using a substrate to catalyst (S/C) ratio of 100 (entry 3). The enantiopurity of the unreacted diol could be increased to 99.9% e.e. when the S/C ratio was decreased from 100 to 50, the enantiomeric excess of the oxidated compound being 95% (entry 4).

Excellent enantioselectivities (>99% e.e.) with high chemical yields were obtained when the 6-methoxy- and the 6,7-dimethoxy- derivatives (±)-**7b** and (±)-**7d**, respectively, were treated with 2% (S/C = 50) Ru(II)-(*S*,*S*)-TsDPEN at 28°C for 36–38 h (entries 8 and 14). Decreasing the catalyst concentration (entries 6 and 12) or the reaction time (entries 7 and 13) resulted in lower enantioselectivity.

For the 7-methoxytetralol derivative (±)-**7c**, the best result was obtained using a S/C ratio of 100 for 72 h (entry 9). Under these conditions ketone (+)-**9c** and diol (−)-**7c** were isolated in 40% yield (99.9% e.e.) and 45% yield (80% e.e.), respectively. By increasing the amount of Ru(II)-(*S*,*S*)-TsDPEN to 2% (S/C = 50) and the reaction time to 96 h (entry 10), we only could raise the diol enantiopurity to 85% e.e.

The kinetic resolution of the indanol (±)-**7e** proceeded with slightly lower enantioselectivity, affording, in the best case, the indanone (+)-**9e** with 90% e.e. (30% yield) after 18 h by using S/C of 50 (entry 15). When the reaction time was increased to 40 h, both the ketone yield and the enantiopurity of the unreacted indanol were improved to 44% and 84% e.e., respectively (entry 16); on the contrary, the enantiomeric purity of the hydroxymethylindanone (+)-**9e** decreased to 80% e.e.

The absolute configuration of the hydroxymethyltetralones (+)-**9a** and (+)-**9b** was confirmed by X-ray crystallographic analysis of their tosylates (+)-**10a**[8] (+)-**10b**, respectively, in turn obtained by treatment of the hydroxyketone with tosyl chloride in pyridine. Figure 3 shows the crystal structure of (+)-**10b** is (*S*).

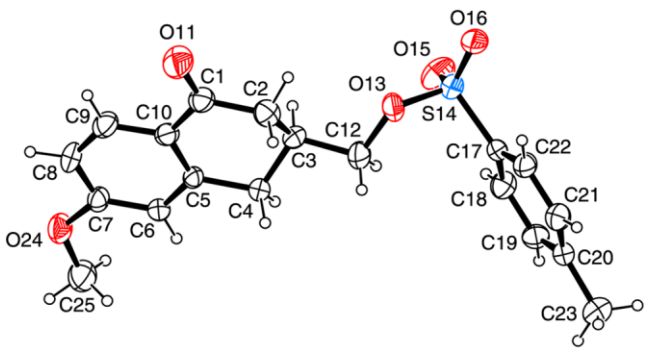


Figure 3. ORTEP drawing of (+)-**10b**.

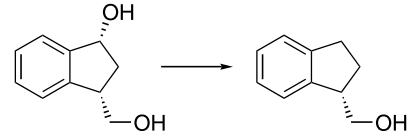
Although the absolute configuration of hydroxyketones (+)-**9c** and (+)-**9d** could not be determined by X-ray crystallography, we assumed that these enantiomers have the (*S*)-configuration according to the above established stereochemical course of kinetic resolution of (±)-**7a** and (±)-**7b**, and the previously reported resolution of (±)-1-tetralol using Ru(II)-(*S*,*S*)-TsDPEN catalyst, where the (*S*)-enantiomer was converted to the corresponding ketone, leaving the unreacted (*R*)-enantiomer.[10b] In addition, comparison of both chiroptical properties and chiral HPLC elution orders of the tetralones **9c–d** with those of **9a–b** [(*S*)-enantiomers are eluted faster, and good resolutions were obtained] supports our assignment (Table 2).

Table 2. Optical and chiral HPLC properties of hydroxyketones **9a–d**[a]

Compound	$[\alpha]_D^{20}$	t_R (min)	R_S[b]
(*S*)-(+)-**9a**[c]	+28.5	44	2.6
(*R*)-(−)-**9a**	−28.3	49	
(*S*)-(+)-**9b**[c]	+37.0	59	1.1
(*R*)-(−)-**9b**	−36.3	64	
(*S*)-(+)-**9c**[d]	+35.3	64	1.2
(*R*)-(−)-**9c**	−28.2[e]	70	
(*S*)-(+)-**9d**[d]	+53.1	98	1.1
(*R*)-(−)-**9d**	−53.0	104	

[a] Analytical HPLC was performed on Daicel Chiralcel® OD-H, 5 μ, 250×4.6 mm column.
[b] Resolution between HPLC peaks: $R_S = (t_{R2} - t_{R1})/0.5(w_1 - w_2)$.
[c] Absolute configuration established by X-ray crystallography of their tosylates [for tosylate (*S*)-(+)-**10a** see Ref. 8].
[d] Proposed absolute configuration.
[e] 80% e.e.

The absolute configuration of the C3 in the indane derivatives was established by chemical correlation of the (−)-3-hydroxymethyl-1-indanol (−)-**7e** with the known (*S*)-1-indanylmethanol,[15] as shown in Scheme 3. To this end, (−)-**7e** was dehydroxylated by hydrogenation on palladium/carbon to afford (*S*)-1-indanylmethanol. The same absolute configuration, which turned out to be (*S*), could be attributed to C3 in the parent indanol, and hence, the absolute configuration of *cis*-(−)-**7e** is (1*R*,3*S*), and that of hydroxyindanone (+)-**9e** is (3*R*).



Scheme 3. *Reagents and conditions*: H_2, Pd–C, $HClO_4$, AcOH, rt, 2 h, 55%.

In summary, we have accomplished the resolution of racemic 3-hydroxymethylbenzocycloalkanols by a Ru(II)-chiral amine complex-mediated selective asymmetric hydrogen-transfer oxidation to give precursors of potent CNS chiral agents in high enantiomeric excess. Receptor binding assays and behavioural studies of these CNS agents as single enantiomers are now in progress and will be reported in due course.

3. Experimental

3.1. General

Melting points were determined with a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer 1600 FTIR spectrophotometer; the main bands are given in cm^{-1}. ^1H NMR spectra were recorded with a Bruker WM AMX (300 MHz); chemical shifts are recorded in parts per million (δ) downfield from tetramethylsilane (TMS). Mass spectra were performed on a Hewlett-Packard HP5988A mass spectrometer by electron impact (EI), or on a Finnigan Trace-MS mass spectrometer by chemical ionization (CI). Optical rotations at the sodium D-line were determined using a Perkin Elmer 241 polarimeter. HPLC analyses were performed with an instrument that consisted of a Waters 1525 binary pump, a Waters 2487 dual λ absorbance detector, a Waters 2414 refractive index detector, and Breeze® data processor. Flash column chromatography was performed using Kieselgel 60 (60–200 mesh, E. Merck AG, Darmstadt, Germany). Reactions were monitored by thin-layer chromatography (TLC) on Merck 60 GF_{254} chromatogram sheets using iodine vapour and/or UV light for detection.

3.2. General procedure for the preparation of the benzyl hemiesters 5a–d

A mixture of the hemisuccinate **4a–d** (14.5 mmol) and 10% palladium on activated carbon (0.3 g) in anhydrous methanol (50 mL) was stirred at room temperature under H_2 for 3 h. The reaction mixture was filtered through Celite® and the solvent was evaporated under reduced pressure to give pure benzylsuccinic-hemiesters.

3.2.1. 2-Benzylsuccinic acid 1-methyl ester, 5a.[16] Obtained from hemisuccinate **4a**[16] as yellowish-brown oil (92% yield).

3.2.2. 2-(3-Methoxybenzyl)succinic acid 1-methyl ester, 5b. Obtained from hemisuccinate **4b**[17] as yellow solid (95% yield); mp 76–79°C. Lit.[17] mp 77–78°C.

3.2.3. 2-(4-Methoxybenzyl)succinic acid 1-methyl ester, 5c. Prepared from hemisuccinate **4c**[18] as yellow solid (96% yield); mp 77–79°C (CH_2Cl_2/hexane). IR: 2953, 1732, 1613, 1514 cm^{-1}; ^1H NMR (CD_3OD): δ 2.43 (dd, 1H, $J=16.9$, 4.9 Hz, H3), 2.58–2.67 (m, 1H, H3), 2.77 (dd, 1H, $J=13.5$, 7.6 Hz, Ph-*H*CH-), 2.91 (dd, 1H, $J=13.6$, 6.8 Hz, Ph-HC*H*-), 3.01–3.09 (m, 1H, H2), 3.63 (s, 3H, $COOCH_3$), 3.77 (s, 3H, Ph-OCH_3), 6.85 (d, 2H, $J=8.6$ Hz, H3 and H5 Ph), 7.09 (d, 2H, $J=8.6$ Hz, H2 and H6 Ph); MS (EI, m/z): 252 (M^+). Anal. calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.61; H, 6.17%.

3.2.4. 2-(3,4-Dimethoxybenzyl)succinic acid 1-methyl ester, 5d. Prepared from hemisuccinate **4d**[19] as yellowish solid (94% yield); mp 108–110°C (hexane). Lit.[19] mp 108–109°C.

3.3. General procedure for the cyclization of the benzyl hemiesters 5a–d. Preparation of the tetralones 6a–d

To a solution of the hemiester (9.0 mmol) in CF_3COOH (41.5 mL) was added at 0°C $(CF_3CO)_2O$ (4.0 mL). After 8 h of stirring at room temperature, the mixture was poured into ice water, basified with $NaHCO_3$ and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated under vacuum to afford a residue, which was purified by column chromatography.

3.3.1. Methyl (4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)carboxylate, 6a.[20] Yellow oil (70% yield).

3.3.2. Methyl (7-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)carboxylate, 6b. Yellow solid (85% yield); mp 107–108°C (EtOAc/hexane). IR: 1733, 1684, 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.75–2.93 (m, 2H, H1), 3.00–3.20 (m, 3H, H2, H3), 3.72 (s, 3H, CO_2CH_3), 3.85 (s, 3H, OCH_3), 6.72 (d, 1H, $J=2.3$ Hz, H8), 6.84 (dd, 1H, $J=8.7$, 2.5 Hz, H6), 8.00 (d, 1H, $J=8.75$ Hz, H5); MS (EI, m/z): 234 (M^+). Anal. calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.30, H, 6.09%.

3.3.3. Methyl (6-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)carboxylate, 6c.[21] White solid (50% yield); mp 77–79°C. Lit.[21] mp 76–78°C.

3.3.4. Methyl (6,7-dimetoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)carboxylate, 6d. Yellowish solid (85% yield); mp 147–148°C. IR: 1730, 1718, 1667 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.75–2.98 (m, 2H, H1), 3.14–3.20 (m, 3H, H2, H3), 3.72 (s, 3H, CO_2CH_3), 3.91, 3.94 (s, 3H, 2×OCH_3), 6.68 (s, 1H, H8), 7.50 (s, 1H, H5); MS (EI, m/z): 264 (M^+). Anal. calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.61; H, 6.17%.

3.4. Synthesis of the diols 7a–e

Ketoester **6** (5 mmol) was dissolved in anhydrous THF (50 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (1.90 g, 50 mmol) in anhydrous THF (80 mL) under Ar. After stirring for 12 h at room temperature, water (2.0 mL), 5% NaOH (3.0 mL) and water (12.0 mL) were added dropwise. The precipitate was removed by filtration and washed with EtOAc. The filtrate was concentrated in vacuo to give a residue, which was dissolved in CH_2Cl_2, dried (Na_2SO_4) and concentrated at reduced pressure to afford the *cis*-diol.

3.4.1. 3-Hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-ol, 7a. White solid (85% yield); mp 104–105°C. Lit.[8] mp 103–105°C.

3.4.2. 3-Hydroxymethyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol, 7b. White solid (85% yield); mp 130–131°C. IR: 3268, 2956, 1616, 1499 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47–1.58 (m, 1H, H4), 2.04–2.28 (m, 2H, H3, H4), 2.61 (dd, 1H, $J=16.5$, 9.3 Hz, 1H2), 2.80 (dd, 1H, $J=16.1$, 5.2 Hz, 1H2), 3.63 (d, 2H, $J=6.1$ Hz, CH_2OH), 3.78 (s, 3H, OCH_3), 4.75–4.84 (m, 1H, H1), 6.62 (d, 1H, $J=2.4$ Hz, H5), 6.78 (dd, 1H, $J=8.5$, 2.4

Hz, H7), 7.41 (d, 1H, $J=8.5$ Hz, H8); MS (EI, m/z): 208 (M^+). Anal. calcd for $C_{12}H_{16}O_3 \cdot 1/6H_2O$: C, 68.22; H, 7.79. Found: C, 68.13; H, 7.60%.

3.4.3. 3-Hydroxymethyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol, 7c. White solid (90% yield); mp 118–119°C. IR: 3398, 3342, 2934, 1611, 1499 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48–1.63 (m, 1H, H4), 2.09–2.17 (m, 1H, H3), 2.26–2.34 (m, 1H, H4), 2.53 (dd, 1H, $J=16.2$, 9.9 Hz, H2), 2.83 (dd, 1H, $J=16.2$, 5.3 Hz, H2), 3.66 (d, 2H, $J=6.2$ Hz, -CH_2-OH), 3.81 (s, 3H, CH_3O-), 4.79–4.84 (m, 1H, H1), 6,78 (dd, 1H, $J=8.4$, 2.7 Hz, H6), 7.03 (d, 1H, $J=8.4$ Hz, H5), 7.09 (d, 1H, $J=2.6$ Hz, H8); MS (EI, m/z): 208 (M^+). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.42; H, 7.99%.

3.4.4. 6,7-Dimethoxy-3-hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-ol, 7d. White solid (85% yield); mp 115–116°C. IR: 1609, 1515, 1459, 1257, 1218 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47–1.58 (m, 1H, H4), 2.16 (m, 1H, H3), 2.24–2.32 (m, 1H, H4), 2.53 (dd, 1H, $J=16.1$, 9.6 Hz, 1H2), 2.80 (dd, 1H, $J=16.1$, 5.2 Hz, 1H2), (d, 2H, $J=6.1$ Hz, CH_2OH), 3.84, 3.87 (s, 3H, 2×OCH_3), 4.77–4.81 (m, 1H, H1), 6.57 (s, 1H, H5), 7.05 (s, 1H, H8); MS (EI, m/z): 238 (M^+). Anal. calcd for $C_{13}H_{18}O_2 \cdot 1/2$ H_2O: C, 64.31; H, 7.68. Found: C, 64.03; H, 7.45%.

3.4.5. 3-Hydroxymethylindan-1-ol, 7e. A solution of 3-oxo-1-indancarboxylic acid[12] **8** (2.5 g, 0.014 mol) and *p*-TsOH (catalytic) in methanol (15 mL) was refluxed with stirring for 5 h. After cooling, the solvent was distilled off under reduced pressure. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed with 10% $NaHCO_3$ and water and then dried (Na_2SO_4). After removal of the solvent in vacuo the resulting orange oil was ball-to-ball distilled (130–133°C/0.4 mmHg) to give methyl 3-oxo-1-indancarboxylate (2.4 g, 90%) as a colourless oil. The ketoester (5 mmol) was dissolved in anhydrous THF (125 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (4.90 g, 0.129 mol) in anhydrous THF (200 mL) under Ar. After stirring for 12 h at room temperature, water (5 mL), 5% NaOH (8 mL) and water (30 mL) were added dropwise. The precipitate was removed by filtration and washed with EtOAc. The filtrate was concentrated in vacuo to give a residue, which was dissolved in CH_2Cl_2, dried (Na_2SO_4), concentrated at reduced pressure. The resulting yellow oil was purified by column chromatography (silica gel, EtOAc:hexane, 2:1) to afford *cis*-(±)-**7e** (0.57 g, 70%) as a white solid, mp 86–87°C; IR: 3316, 2957, 1461 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.87 (dt, 1H, $J=14.2$, 2.5 Hz, 1H2), 2.61 (ddd, 1H, $J=14.2$, 8.7, 6.9 Hz, 1H2), 2.28–3.34 (m, 1H, H3), 3.81–3.93 (m, 2H, CH_2OH), 5.05 (dd, 1H, $J=6.8$, 1.8 Hz, H1), 7.24–7.34 (m, 3H, H4, H5, H6), 7.41 (dd, 1H, $J=7.6$, 1.4 Hz, H7); MS (EI, m/z): 164 (M^+). Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.29; H, 7.10%.

3.5. General procedure for resolution of diols 7a–e

A mixture of diol **7a–e** (1 mmol) and Ru(II)-(*S*,*S*)-TsDPEN[10b] was stirred at 28°C in the solvent and conditions indicated in Table 1. Then, the mixture was filtered and the solvent was evaporated under reduced pressure to give a residue which was purified by chromatography (silica gel, CH_2Cl_2:MeOH or hexane:EtOAc) to give the diols (−)-**7a–e** and the ketones (+)-**9a–e**.

3.5.1. (1*R*,3*R*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-ol, (−)-7a.[8] $[\alpha]_D^{20}=-104$ (*c* 1.0, EtOAc), 99.9% e.e. Lit.[8] $[\alpha]_D^{20}=-103$ (*c* 1.0, EtOAc).

3.5.2. (*S*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-one, (+)-9a. $[\alpha]_D^{20}=+28.5$ (*c* 0.5, AcOEt), 99.9% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 94:6, flow 0.5 mL/min, λ 254 nm. $t_R=44$ min.

3.5.3. (1*R*,3*R*)-3-Hydroxymethyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol, (−)-7b. $[\alpha]_D^{20}=-97.3$ (*c* 0.5, EtOAc), 99.9% e.e.

3.5.4. (*S*)-3-Hydroxymethyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-one, (+)-9b. Yellow solid, mp 70–72°C; $[\alpha]_D^{20}=+37.0$ (*c* 0.5, EtOAc), 99.9% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 90:10, flow 0.3 mL/min, λ 254 nm. $t_R=59$ min. IR: 3258, 2925, 1670, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35–2.46 (m, 2H, H4), 2.66–2.87 (m, 2H, 1H2, H3), 3.03 (dd, 1H, $J=16.4$, 1.9 Hz, 1H2), 3.68–3.78 (m, 2H, CH_2OH), 3.85 (s, 3H, OCH_3), 6.72 (d, 1H, $J=2.2$ Hz, H5), 6.83 (dd, 1H, $J=8.7$, 2.4 Hz, H7), 8.00 (d, 1H, $J=8.7$ Hz, H8); MS (EI, m/z): 206 (M^+).

3.5.5. (1*R*,3*R*)-3-Hydroxymethyl-7-methoxy-1,2,3,4-tetrahydronaphtalen-1-ol, (−)-7c. $[\alpha]_D^{20}=-94.0$ (*c* 0.5, EtOAc), 80% e.e.

3.5.6. (*S*)-3-Hydroxymethyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-one, (+)-9c. Colourless oil; $[\alpha]_D^{20}=+35.3$ (*c* 0.5, EtOAc), 99.9% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 90:10, flow 0.3 mL/min, λ 254 nm. $t_R=64$ min. IR: 3422, 2930, 1668, 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40–2.48 (m, 2H, H4), 2.75–2.83 (m, 2H, H2, H3), 2.99–3.05 (m, 1H, H2), 3.63–3.74 (m, 2H, -CH_2-OH), 3.83 (s, 3H, CH_3O-), 7.07 (dd, 1H, $J=8.4$, 2.8 Hz, H6), 7.19 (d, 1H, $J=8.4$ Hz, H5), 7.50 (d, 1H, $J=2.8$ Hz, H8); MS (CI, m/z): 207 (MH^+).

3.5.7. (1*R*,3*R*)-6,7-Dimethoxy-3-hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-ol, (−)-7d. $[\alpha]_D^{20}=-98.0$ (*c* 0.5, EtOAc), 99.9% e.e.

3.5.8. (*S*)-6,7-Dimethoxy-3-hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-one, (+)-9d. White solid, mp 122–123°C; $[\alpha]_D^{20}=+53.1$ (*c* 0.5, EtOAc), 99.9% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 90:10, flow 0.3 mL/min, λ 254 nm. $t_R=98$ min. IR: 1654, 1598, 1508 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35–2.43 (m, 2H, H4), 2.62–2.65 (m, 2H, 1H2, H3), 3.00 (dd, 1H, $J=16.0$, 4.0 Hz, 1H2), 3.71–3.77 (m, 2H, CH_2OH), 3.91, 3.94 (s,

3H, 2×OCH_3), 6.70 (s, 1H, H5), 7.50 (s, 1H, H8); MS (EI, m/z): 236 (M^+). Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.01; H, 6.87%.

3.5.9. (1*R*,3*S*)-3-Hydroxymethylindan-1-ol, (−)-7e. $[\alpha]_D^{20}=-13.6$ (c 0.5, EtOAc), 85% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 95:5, flow 0.5 mL/min, λ 254 nm. $t_R=40$ min.

3.5.10. (*R*)-3-Hydroxymethyl-1-indanone, (+)-9e. Colourless oil. $[\alpha]_D^{20}=+14.0$ (c 0.5, EtOAc), 90% e.e. IR: 3394, 1701, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.57 (dd, 1H, $J=19.1$, 3.1 Hz, 1H2), 2.85 (dd, 1H, $J=19.1$, 7.7 Hz, 1H2), 3.55–3.63 (m, 1H, H3), 3.90 (d, 2H, $J=5.7$ Hz, CH_2OH), 7.39–7.44 (m, 1H, H6), 7.59–7.65 (m, 2H, H4, H5), 7.76 (d, 1H, $J=7.7$ Hz, H7); MS (EI, m/z): 162 (M^+).

3.6. General procedure for oxidation of diols (−)-7a–e: preparation of hydroxyketones (−)-9a–e

Diol (−)-**7a**–**e** (1.0 mmol) was dissolved in $CHCl_3$ (15 mL) and MnO_2 (2.17 g, 25 mmol) was added. The mixture was stirred at room temperature for 4 h, and then filtered through silica gel, eluted with EtOAc and the combined filtrates were concentrated in vacuo to give an oil which was purified by column chromatography (silica gel, EtOAc/hexane, 1:1) to give the hydroxyketone (−)-**9a**–**e**.

3.6.1. (*R*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-one, (−)-9a. 75% Yield. $[\alpha]_D^{20}=-28.3$ (c 1.0, AcOEt), 99.9% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 94:6, flow 0.5 mL/min, λ 254 nm. $t_R=49$ min.

3.6.2. (*R*)-3-Hydroxymethyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-one, (−)-9b. 85% Yield. $[\alpha]_D^{20}=-36.3$ (c 0.5, EtOAc), 99.9% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 90:10, flow 0.3 mL/min, λ 254 nm. $t_R=64$ min.

3.6.3. (*R*)-3-Hydroxymethyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-one, (−)-9c. 86% Yield. $[\alpha]_D^{20}=-28.2$ (c 0.5, EtOAc), 80% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 90:10, flow 0.3 mL/min, λ 254 nm. $t_R=70$ min.

3.6.4. (*R*)-6,7-Dimethoxy-3-hydroxymethyl 1,2,3,4-tetrahydronaphthalen-1-one, (−)-9d. 90% Yield. $[\alpha]_D^{20}=-53.0$ (c 0.5, EtOAc), 99.9% e.e. Chiralcel® OD-H, hexane:propan-2-ol, 90:10, flow 0.3 mL/min, λ 254 nm. $t_R=104$ min.

3.6.5. (*S*)-3-Hydroxymethyl-1-indanone, (−)-9e. 80% Yield. $[\alpha]_D^{20}=-13.5$ (c 0.5, EtOAc), 85% e.e.

3.7. Determination of the absolute configuration of hydroxyketone (+)-9b

3.7.1. Preparation of (*S*)-(6-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl 4-methylbenzenesulfonate, (+)-10b. p-Toluenesulfonyl chloride (0.12 g, 0.60 mmol) was added to a cooled solution of the hydroxyketone (+)-**9b** (0.1 g, 0.48 mmol) in dry pyridine (5 ml) and the mixture stirred at 0°C for 48 h. Ice water (40 mL) was then added to the reaction, and the resultant mixture was extracted with CH_2Cl_2 (3×50 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated at reduced pressure to give an oil, which was purified by column chromatography (silica gel, EtOAc/hexane, 1:4) to afford the tosylate (+)-**10b** (0.13 g, 75%) as a white solid, mp 108–109°C (cyclohexane); $[\alpha]_D^{20}=+9.2$ (c 1.0, EtOAc); IR: 1676, 1601, 1358 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.27–2.36 (m, 1H, H4), 2.45 (s, 3H, CH_3-Ph), 2.50–2.64 (m, 2H, H3, H4), 2.75–2.83 (m, 1H, 1H2), 2.98 (dd, 1H, $J=17.7$, 2.0 Hz, 1H2), 3.84 (s, 3H, OCH_3), 4.01–4.07 (m, 1H, CH_2O-), 6.66 (d, 1H, $J=2.2$ Hz, H5), 6.81 (dd, 1H, $J=8.7$, 2.4 Hz, H7), 7.35 (d, 2H, $J=8.0$ Hz, H3, H5 Ph), 7.78 (d, 2H, $J=8.2$ Hz, H2, H6 Ph), (d, 1H, $J=8.7$ Hz, H8); MS (EI, m/z): 360 (M^+). Anal. calcd for $C_{19}H_{20}O_5S$: C, 63.32; H, 5.59; S, 8.90. Found: C, 63.26; H, 5.63; S, 8.65%.

3.7.2. Crystallographic analysis of (+)-10b. Suitable crystals of (+)-**10b** ($C_{19}H_{20}O_5S$) were obtained from Et_2O at room temperature by slow evaporation of the solvent, $C_{19}H_{20}O_5S$, $M=360.41$, $a=6.4662(8)$, $b=32.467(4)$, $c=8.4901(11)$ Å, space group $P21$, $V=1764.0(4)$ Å^3, $T=293(2)$ K, $Z=4$, $D_{calcd}=1.357$ Mg/m^3, $F(000)=760$. Final goodness-of-fit = 1.023, $R=0.0459$, $wR=0.1001$. Absolute structure determination was completed using the Flack parameter.[22] Crystallographic data (excluding structure factors) for (*S*)-(+)-**10b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 211912. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.8. Determination of the absolute configuration of *cis*-hydroxymethylindanol (−)-7e

A mixture of *cis*-hydroxymethylindanol (−)-**7e** ($[\alpha]_D^{20}=-13.6$, 85% ee) (80 mg, 0.49 mmol) and 10% palladium on carbon (10 mg) in glacial acetic acid (10 mL) containing 70% aqueous perchloric acid (one drop) was stirred under hydrogen for 2 h. Filtration through Celite® and concentration gave the crude product, which was purified by chromatography (silica gel, CH_2Cl_2) to give (*S*)-1-indanylmethanol (40 mg, 55% yield) as a colourless oil. $[\alpha]_D^{20}=-14.3$ (c 1.0, benzene); lit.[15] $[\alpha]_D^{20}=-11.6$ (benzene), 68% e.e.

Acknowledgements

This work was supported by Spanish *Comisión Interministerial de Ciencia y Tecnología* (CICYT) under Grants SAF98-0148-C04-04 and SAF2002-04195-C03-01, and by *Xunta de Galicia* under Grant PGIDT01-PXI20309PR.

References

1. Holstein, A. P.; Chen, C. H. *Am. J. Psychiatry* **1965**, *122*, 462–463.
2. King, D. J. *Eur. Neuropsychopharmacol.* **1998**, *8*, 33–42.
3. Capuano, B.; Crosby, I. T.; Lloyd, E. J. *Curr. Med. Chem.* **2002**, *9*, 521–548.
4. Raviña, E.; Masaguer, C. F. *Curr. Med. Chem.: Central Nervous System Agents* **2001**, *1*, 43–62.
5. Cortizo, L.; Santana, L.; Ravina, E.; Orallo, F.; Fontenla, J. A.; Castro, E.; Calleja, J. M.; De Ceballos, M. L. *J. Med. Chem.* **1991**, *34*, 2242–2247.
6. Loza, M.; Verde, I.; Castro, M. E.; Orallo, F.; Fontenla, J. A.; Calleja, J. M.; Ravina, E.; Cortizo, L.; De Ceballos, M. L. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 717–720.
7. Brea, J.; Rodrigo, J.; Carrieri, A.; Sanz, F.; Cadavid, M. I.; Enguix, M. J.; Villazón, M.; Mengod, G.; Caro, Y.; Masaguer, C. F.; Raviña, E.; Centeno, N. B.; Carotti, A.; Loza, M. I. *J. Med. Chem.* **2002**, *45*, 54–71.
8. Caro, Y.; Masaguer, C. F.; Ravina, E. *Tetrahedron: Asymmetry* **2003**, *14*, 381–387.
9. (a) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446; (b) Arterburn, J. B. *Tetrahedron* **2001**, *57*, 9765–9788.
10. (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288; (b) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288–290.
11. Eirin, A. M.; Raviña, E.; Montañés, J. M.; Calleja, J. M. *Eur. J. Med. Chem.* **1976**, *11*, 29–32.
12. Hashimoto, I.; Takatsuka, R. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2495–2496.
13. Miura, M.; Yoshida, M.; Nojima, M.; Kusabayashi, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 79–83.
14. Alesso, E. N.; Moltrasio Iglesias, G. Y.; Aguirre, J. M. *An. Quim.* **1993**, *89*, 242–245.
15. (*S*)-1-Indanylmethanol: $[\alpha]_D = -11.6$ (*c* 0.71, benzene), 68% e.e. Lorentzen, R. J.; Brewster, J. H.; Smith, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 2181–2187. (*R*)-1-Indanylmethanol: $[\alpha]_D = +17$ (*c* 0.4, benzene). Battail-Robert, M. D.; Gagnaire, D. *B. Soc. Chim. Fr.* **1966**, 208–210.
16. Cohen, S. G.; Milovanovic, A. *J. Am. Chem. Soc.* **1968**, *90*, 3495–3502.
17. Barnier, J. P.; Blanco, L.; Guibe-Jampel, E.; Rousseau, G. *Tetrahedron* **1989**, *45*, 5051–5058.
18. Guirguis, N. R.; Awad, B. M.; Saad, H. A. *Liebigs Ann.* **1986**, 1003–1011.
19. Ganeshpure, P. A.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1681–1684.
20. Horning, E. C.; Walker, G. N. *J. Am. Chem. Soc.* **1952**, *74*, 5147–5151.
21. Kometani, T.; Shiotani, S. *J. Med. Chem.* **1978**, *21*, 1105–1110.
22. (a) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881; (b) Bernardinelli, G.; Flack, H. D. *Acta Crystallogr., Sect. A* **1985**, *41*, 500–511.