Resolution and configurational assignment of 3,4,5,6-tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocine derivatives

Tibor Kurtán,[a] Eszter Baitz-Gács,[b] Zsuzsa Májer,[c] Attila Bényei[d] and Sándor Antus*[a]

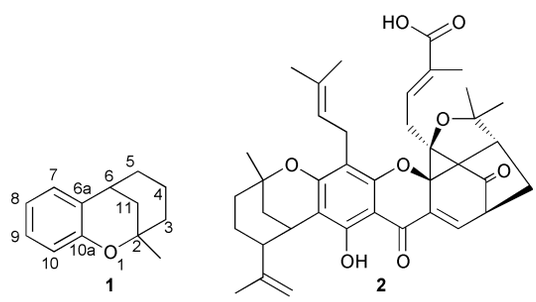
[a] *Department of Organic Chemistry, University of Debrecen, P.O.B. 20, H-4010 Debrecen, Hungary*
[b] *Institute of Chemistry, C. R. C., Hungarian Academy of Sciences, P.O.B. 32, H-1515 Budapest, Hungary*
[c] *Institute of Organic Chemistry, L. Eötvös University, H-1518 Budapest 112, P.O.B. 32, Hungary*
[d] *Department of Chemistry, Laboratory for X-Ray Diffraction, University of Debrecen, P.O.B. 7, H-4010 Debrecen, Hungary*

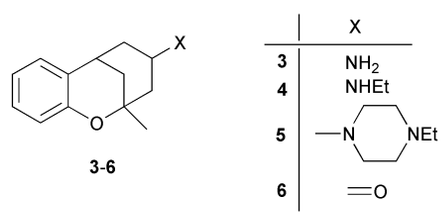
Received (in Cambridge, UK) 21st January 2002, Accepted 13th February 2002
First published as an Advance Article on the web 8th March 2002

Chemical resolutions of the rigid, tricyclic 3,4,5,6-tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4-one (**6**) of biological and chiroptical interest have been performed. The configurational assignment was made by X-ray analysis and chemical correlation of its ketal (+)-**9a** synthesized with (2*R*,3*R*)-butane-2,3-diol. Kinetic resolution of the hydroxy derivative *rac*-**10** by means of lipase from *Pseudomonas cepacia* proved the most effective procedure for resolution. The stereochemistry of the faster reacting enantiomer (+)-**10** was deduced by chemical correlation with the ketal (+)-**9**. Model compounds (+)-**1** and (−)-**1** for chiroptical study of the chromane chromophore were also prepared.

Introduction

3,4,5,6-Tetrahydro-2-methyl-2*H*-1-benzoxocine bridged by a methylene unit across the 2,6 positions (**1**) is a rigid tricyclic compound which contains a chirally perturbed chromane chromophore with axial substituents on the heterocyclic ring. This residue is a building block of gambogellic acid **2**,[1] which has been found to be cytotoxic against HeLa cells, and the racemic C-4 substituted derivatives **3**–**5** have shown central nervous system activity.[2] Moreover, it is noteworthy that the oxygen analogs, which have an oxygen bridge across the 2,6 positions, have shown remarkable monoamine oxidase inhibitor[3] and antibacterial activity.[4] Due to their rigid structure, this type of optically active chromane derivative can be also used as model compounds to study the chiroptical properties of the chromane chromophore containing an axial carbon–carbon bond at the benzylic position. We have found recently that *P*/*M* helicity of the heterocyclic ring leads to a negative/positive CD within the ^1L_b band[5,6] and this helicity rule is valid in its inverse form if an axial carbon–oxygen bond is present at the benzylic position.[7,8] In order to study the scope and limitation of our rule and elaborate a simple route for the synthesis of the enantiomerically pure chromane derivatives **3**–**5**, we set our sights on the enantioselective synthesis of **1** *via* **6**.

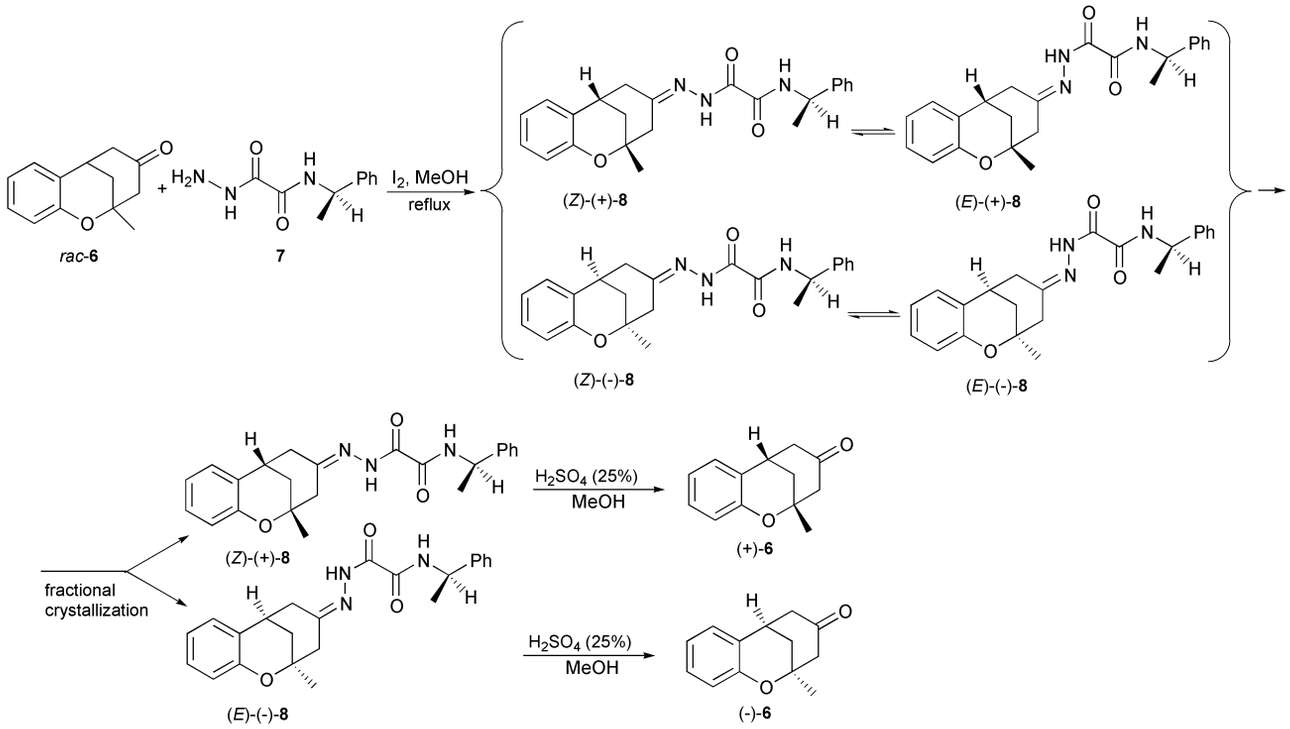




Results and discussion

The racemic 2,6-methanobenzoxocinone derivative **6** was prepared from salicylideneacetone and ethyl acetoacetate by using the procedure of Kuhn and Weiser.[9] Its chemical resolution was carried out with (+)-(1-phenylethyloxamoyl)hydrazine **7**, a carbonyl derivatizing agent[10–13] (Scheme 1). In contrast to previous findings,[10–13] where the resolution of chiral ketone derivatives with **7** resulted in the two corresponding diastereomers, which could be separated by fractional crystallization, the condensation of *rac*-**6** with this reagent, monitored by TLC, showed the formation of four products of comparable ratio instead of two. The ^{1}H NMR spectrum of the crude product clearly indicated that the *syn Z*- and *anti E*-isomers of both diastereomers [(*Z*)-(+)-**8**/(*E*)-(+)-**8**, (*Z*)-(−)-**8**/(*E*)-(−)-**8**] were present in this mixture (Scheme 1). It was shown previously that similarly to oximes, the barrier of the *syn–anti* inversion in hydrazones can be high enough to allow the isolation of a pure non-inverting isomer[14,15] whose inversion can be also achieved by UV light irradiation.[16] Although these isomers had quite different retentions on TLC, they could not be separated either by column chromatography or by preparative TLC due to their rapid conversion on silica gel. Crystallization of the crude product from methanol resulted in a mixture of (*Z*)-(+)-**8** and (*E*)-(−)-**8** with (*Z*)-(+)-**8** as the main component whose repeated crystallization afforded the pure dextrorotatory *syn*-isomer [(*Z*)-(+)-**8**] while the levorotatory

 DOI: 10.1039/b200751g



Scheme 1 Resolution of 3,4,5,6-tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4-one (*rac*-**6**) with (+)-(1-phenylethyloxamoyl)hydrazine **7**.

anti-isomer [(*E*)-(−)-**8**] was obtained from the mother liquor of the first crystallization. The *syn* or *anti* arrangement of these compounds was deduced from NOE experiments; the significant effect between the hydrazone proton and H-5α in (*E*)-(−)-**8** unambiguously proved its *anti* arrangement about the C=N double bond. It is interesting to note that when MeOD was added to the $CDCl_3$ solution of (*E*)-(−)-**8**, a new set of signals appeared, which was assigned to the *syn*-isomer (*Z*)-(−)-**8** on the basis of its NOE between the hydrazone proton and H-3α. After three weeks the ratio of the *syn* and *anti* isomers was approximately 2 to 3 in the solution. The *syn–anti* isomerism of (*E*)-(−)-**8** was also followed by CD spectroscopy which showed a characteristic change in the CD transitions of (*E*)-(−)-**8** in acetonitrile when acid was added to the solution, indicating the formation of the *Z*-isomer, as shown in Fig. 1(a). The CD spectra of the isolated isomers (*Z*)-(+)-**8** and (*E*)-(−)-**8** were found to be almost mirror image. [Fig. 1(b)] Since their chiroptical properties are dominated by the chirality of the tricyclic skeleton, they must contain heterocyclic rings with opposite configuration. Due to the lack of similar examples in the literature, the signs of the CD transitions could not be used to assign safely their absolute configurations and our efforts to obtain a suitable single crystal for X-ray analysis were also unsuccessful.

Acidic hydrolysis of (*Z*)-(+)-**8** and (*E*)-(−)-**8** provided the optically active ketones (+)-**6** and (−)-**6**, respectively, whose CD spectra proved that their precursors (*Z*)-(+)-**8** and (*E*)-(−)-**8** indeed had enantiomeric annulation points. It might be assumed that their absolute configuration could be deduced from the sign of the Cotton effect belonging to the n⟶π* transition of the carbonyl chromophore on the basis of the well-known octant rule[17] and by comparison with 3-substituted cyclohexanone derivatives.[18,19] However, the following detailed analysis of the contribution from the different parts of the molecule to the n⟶π* Cotton effect of the 3-methylcyclohexanone moiety of (2*S*,6*R*)-**6** has shown that our assumption was too optimistic. The cyclohexanone residue of (2*S*,6*R*)-**6** adopts the thermodynamically more stable chair conformation and the C-2 equatorial methyl group is situated in the rear upper left or lower right octant (Fig. 2), which has a positive contribution to the n⟶π* Cotton effects according to the

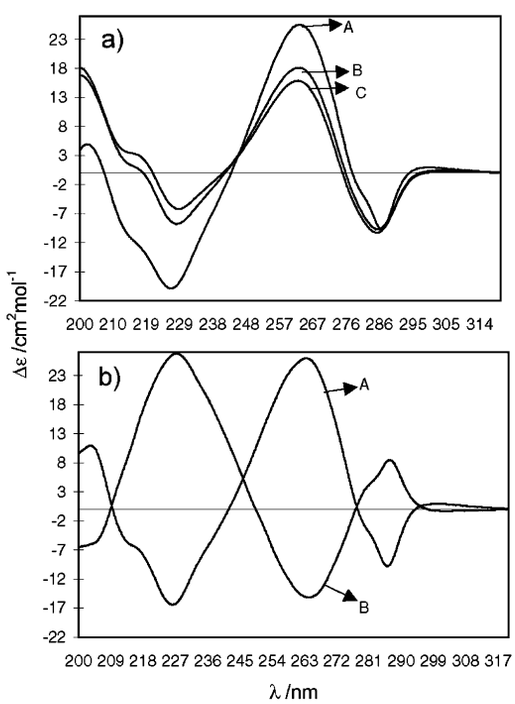
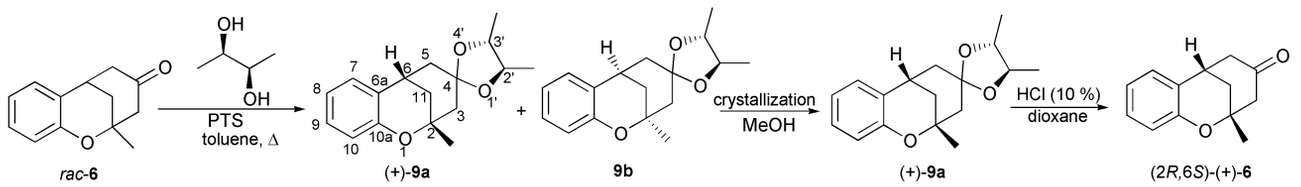


Fig. 1 (a) *syn–anti* isomerism of (*E*)-(−)-**8** followed by CD spectroscopy in MeCN: A, CD spectrum of (*E*)-(−)-**8**; B, CD spectrum measured immediately after the addition of acid to (*E*)-(−)-**8**, *i.e* a mixture of (*E*)-(−)-**8** and (*Z*)-(−)-**8**; C, CD spectrum measured 24 h after the addition of acid to (*E*)-(−)-**8**. (b) CD spectra of (*E*)-(−)-**8** and (*Z*)-(+)-**8** in MeCN indicating the enantiomeric annulation points of the tricyclic skeleton.

octant rule. However, β-axial substituents at C-2 and C-6 are also present and they show antioctant behavior with weak contributions according to the literature.[18,20] Since the axial oxygen and the phenyl residue at C-6 are located in sectors of opposite sign, they can compensate each other to some extent. Further difficulties arise from the fact the condensed phenyl group points in the direction of the carbonyl group and hence toward the front sectors, which means a part of the phenyl group is



Scheme 2 Resolution of *rac*-**6** with (2*R*,3*R*)-butane-2,3-diol and transformation of the isolated diastereomer (+)-**9a**.

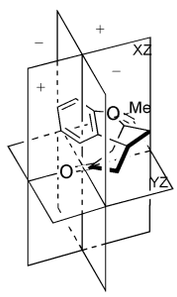


Fig. 2 Octant rule diagram for the ketone carbonyl n⟶π* transition of (2*S*,6*R*)-(−)-**6**; for clarity, the third nodal surface is represented as a nodal plane. The signs depict the contribution of the octants.

most likely located in the front upper right or lower left sector while the rest is in the rear upper right or lower left, which makes the prediction even more ambiguous. Therefore, the measured positive n⟶π* CD transition ($\Delta\varepsilon$ = 0.23 at 316 nm) could not be used to deduce unequivocally the absolute configuration of (−)-**6**.

Since the resolution with (+)-(1-phenylethyloxamoyl)-hydrazine provided very low yields due to the *syn–anti* isomerism and the stereochemistry of the resolved compounds were not determined, another resolving agent, the (2*R*,3*R*)-(−)-butane-2,3-diol,[21] was tried. The reaction of *rac*-**6** with (2*R*,3*R*)-(−)-butane-2,3-diol in toluene with a catalytic amount of toluene-*p*-sulfonic acid (PTS) afforded a 1 : 1 mixture of the two corresponding diastereomers (+)-**9a** and **9b** (Scheme 2), as shown by the ^{1}H NMR spectrum of the crude product. Although these compounds [(+)-**9a**, **9b**] could not be separated by TLC, their crystallization from concentrated methanolic solution yielded colourless needles whose ^{1}H NMR and optical rotation proved that they consisted of a pure dextrarotatory diastereomer. NOE experiments and the magnetic anisotropy effect of the phenyl ring on the methyl groups of the ketal moiety turned out to be insufficient to determine the absolute configuration. However, a single crystal grown in methanol was found suitable for X-ray measurement, from which the structure of (2*R*,6*S*)-(+)-**9a** was deduced (Fig. 3), relying on the known absolute configuration of the ketal moiety. The crystal data also clearly showed that the cyclohexane moiety of the molecule adopted a chair conformation while the O-heterocyclic ring was fixed in a rigid envelope conformation, *i.e.* C-6, C-7a, C-10a, O-1 and C-2 were located approximately in the same plane, and C-11 was out of the plane. The O-heterocyclic ring has *P*-helicity, which is defined by the positive C(10a)–O(1)–C(2)–C(11) torsional angle (+31.3°). Acidic hydrolysis of (2*R*,6*S*)-(+)-**9a** was carried out with dilute hydrochloric acid in dioxane in order to correlate the resultant ketone with the previously synthesized optically active ketones (+)-**6** and (−)-**6**. The 2*R*,6*S* ketone obtained was dextrorotatory which allowed the configurational assignment of the oxamoylhydrazone precursors (+)-(*Z*)-**8** and (*E*)-(−)-**8**, as shown earlier in Scheme 1.

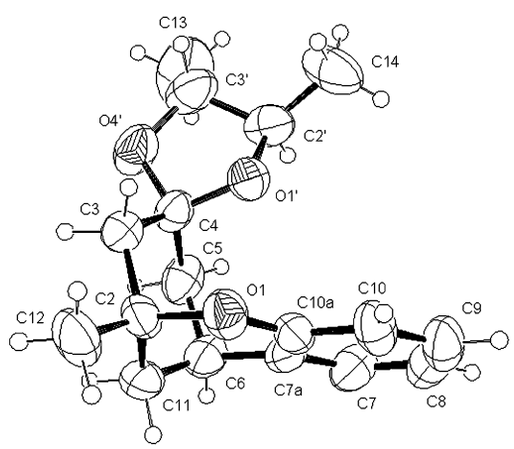
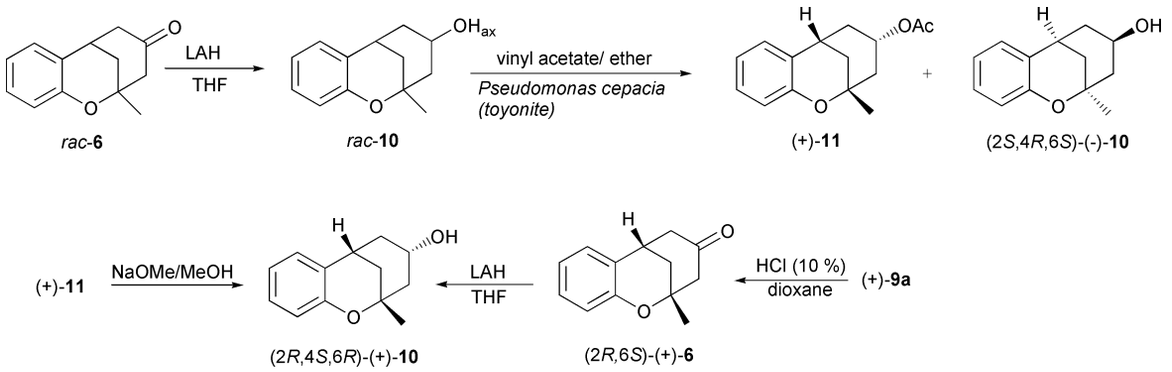


Fig. 3 ORTEP view and numbering scheme of (+)-**9a** at the 50% probability level. Selected torsional angles (°): C(10a)–O(1)–C(2)–C(11), +31.3; O(1)–C(2)–C(11)–C(6), −60.3; C(2)–C(11)–C(6)–C(7a), +58.8; C(11)–C(6)–C(7a)–C(10a), −29.6; C(6)–C(7a)–C(10a)–O(1), +0.6; C(7a)–C(10a)–O(1)–C(2), −1.0.

Since the resolution of the racemic ketone **6** by both (+)-(1-phenylethyl)oxamoylhydrazine (**7**) and (2*R*,3*R*)-(−)-butane-2,3-diol required crystallization of the diastereomeric mixture, which occurred in relatively low yields, the racemic ketone **6** was reduced to the racemic alcohol **10** which was also expected to be suitable for resolution (Scheme 3). According to our expectation, the reduction of *rac*-**6** with lithium aluminium hydride proceeded diastereoselectively because the addition of the hydride to the carbonyl carbon was sterically hindered from the direction of the chromane residue of the molecule. Thus, the addition of the hydride was favored from the opposite face and afforded almost exclusively the axial alcohol *rac*-**10**. The axial orientation of the hydroxy group in *rac*-**10** was verified by the coupling constants of the equatorial 4-H with the vicinal protons (*J* 5.2, 4.0, 2.2 and 2.6 Hz), but the axial hydroxy group could not be derivatized with chiral acids such as (*S*)-(+)-*O*-acetylmandelic acid and (−)-camphanic acid even in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DDC), which was most likely due to its hindered position.

The *Pseudomonas* lipases have been found to be very effective enzymes in the kinetic transesterification of numerous racemic secondary alcohols with remarkable enantiopreference and tolerance for a great variety of substrates, including hindered ones.[22] This prompted us to use the lipase from *Pseudomonas cepacia* (PCL) for the kinetic resolution of *rac*-**10** which was succesfully performed in ether with vinyl acetate as an irreversible acyl donor (Scheme 3). The kinetic resolution was found to be sensitive to both the carrier of PCL and the type of solvent used. It proceeded smoothly with PCL immobilized on Toyonite in ether and it was somewhat slower in dioxane but there was no detectable conversion in acetonitrile and PCL on Diatomite did not catalyze the esterification in ether at all. It took 16 days to reach a conversion of 52% for the reaction of *rac*-**10** with PCL on Toyonite in ether which indicated the hindered position of the axial hydroxy group. Besides the coupling constant, the unusual upfield chemical shift of the acetyl methyl protons (δ_H = 1.28, $CDCl_3$) in the acetate (+)-**11** also confirmed the axial orientation of the acetoxy group because it was due to the magnetic anisotropy effect on the acetoxy group situated above the benzene moiety, *i.e.* in an axial position.

Although the active site of PCL has been modelled[23,24] extensively and an empirical rule[25–27] [Fig 4(a)] has been introduced to predict the absolute configuration of the faster reacting enantiomer of secondary alcohols, the prediction of the faster reacting enantiomer of *rac*-**10** was not straightforward. In the empirical rule, the prediction is based on the difference in the size of substituents flanking the stereogenic center of the



Scheme 3 Kinetic resolution of the 4-hydroxy derivative *rac*-**10** with lipase from *Pseudomonas cepacia* and configurational assignment of the resolved enantiomers by chemical correlation.

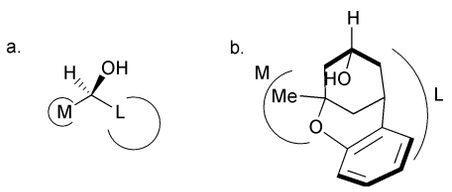
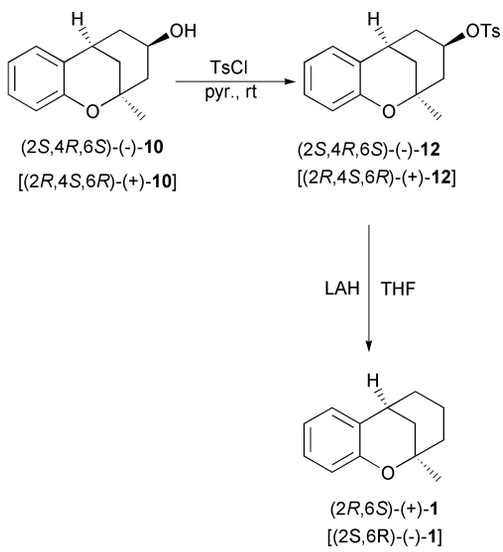


Fig. 4 (a) Simple model to predict the faster reacting enantiomer in the kinetic resolution of secondary alcohols with lipase from *Pseudomonas cepacia* (PCL); M and L depict the medium and large substituents flanking the stereogenic center based on differentiation by the enzyme. (b) The faster reacting enantiomer [(2*R*,4*S*,6*R*)-(+)-**10**] in the kinetic resolution of *rac*-**10** oriented in the same manner as in Fig. 4(a); M, L assignment of the two sides flanking the C-4 stereogenic center.

hydroxy group. In our case, the α-substituents are the same, namely, methylene groups, and the effect of the C-2 methyl group at the β position should be compared with the more remote but bulkier phenyl ring that contributes to the other side. In order to clarify this question and unequivocally deduce the absolute configuration of the resolved molecules, the well established 2*R*,6*S* absolute configuration of the acetal (+)-**9a** was chemically correlated with the products of the kinetic resolution. The hydrolysis of (+)-**9a** resulted in the dextrorotatory ketone of 2*R*,6*S* absolute configuration [(+)-**6**] whose reduction with LAH in THF provided the dextrorotatory alcohol (+)-**10** with known absolute configuration (Scheme 3). Since the remaining alcohol in the transesterification of *rac*-**10** [(−)-**10**] was levorotatory, it must be the enantiomer of the alcohol obtained from the reduction of (2*R*,6*S*)-(+)-**6**. The saponification of the acetate (+)-**11** indeed afforded the dextrorotatory alcohol (+)-**10** (Scheme 3). Thus, the absolute configuration of the faster reacting alcohol (+)-**10** is 2*R*,4*S*,6*R* because the Cahn–Ingold–Prelog priority of the groups flanking the C-6 stereogenic center is exchanged after the reduction of the carbonyl group. Moreover, the addition of hydride took place in a stereoselective manner yielding the axial alcohol as the major product which defined the *S* absolute configuration at C-4.

This means the alcohol (+)-**10** with 4*S* absolute configuration was acylated faster than its enantiomer in the presence of PCL, which rendered the C-5 side with the C-6 phenyl group the large side (L) and the C-3 side with the C-2 methyl group the medium side (M) according to the empirical rule[25–27] [Fig 4(b)]. This could be interpreted that the large pocket of PCL, lined with hydrophobic side-chains, attracts the phenyl group, while the C-2 methyl group and the oxygen are oriented toward the medium-sized pocket that contains both polar and hydrophobic side chains. Since the optical purity of the crystallized ketal (+)-**9** was found to be over 99%, and it was chemically correlated with the products of the enzymatic resolution through its hydrolysis to the ketone (+)-**6**, the comparison of the optical rotations gave the ee of the remaining alcohol (−)-**10** as 91% with a conversion of 52%. In order to produce the tricyclic skeletons (+)-**1** and (−)-**1** with no substituents at C-4, the optically active alcohols (−)-**10** and (+)-**10** were tosylated and reduced with LAH, respectively (Scheme 4). While the optical



Scheme 4 Removal of the hydroxy group from the optically active 4-hydroxy derivatives (−)-**10** and (+)-**10**; the structures depict the transformation of (−)-**10**.

rotations changed signs when the C-4 stereogenic center was removed, *i.e.* (−)-**10** was converted into (+)-**1** or (+)-**10** to (−)-**1**, the sign of the ^1L_b band CD at 275–285 nm did not change. Since the CD spectra of (−)-**1** and (+)-**1** are determined by the chirality of the heterocyclic ring and there are no more remote stereogenic centers to interfere, they are suitable model compounds to study the effect of axial benzylic substituents on the chromane chromophore. They can also be used for comparison with compounds that contain stereogenic centers in the cyclohexane ring to evaluate the contribution of remote spheres to the ^1L_b band CD. Further chiroptical studies of these and related compounds, as well as their theoretical CD calculations, are in progress.

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed on a Carlo-Erba analyser Tpy 1106. Optical rotations were measured with a Carl Zeiss (Jena) Polamat-A polarimeter, and the CD and UV spectra with a slightly modified Jobin-Yvon-Isa Dichrograph-6. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C spectra were recorded with a Varian Unity-Inova spectrometer with TMS as the internal standard ($\delta = 0$) for solutions in $CDCl_3$. Integrals were always in agreement with the assigned number of protons. The coupling constants *J* are quoted in Hz.

Flash chromatography was carried out using Merck Kieselgel 60 (0.040–0.063 mm).

Isomeric (+)-2-(1-phenylethyloxamoyl)hydrazones of 5,6-dihydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-one [(*E*)-(−)-8, (*Z*)-(+)-8 and (*Z*)-(−)-8]

rac-**6** (436 mg, 2.15 mmol) and **7** (522 mg, 2.52 mmol) were dissolved in methanol (30 ml) and refluxed for 2 h after the addition of an iodine crystal. TLC monitoring of the reaction showed the formation of four new compounds [(*Z*)-(+)-**8**/(*E*)-(+)-**8**, (*Z*)-(−)-**8**/(*E*)-(−)-**8**]. After 2 h, the reaction mixture was cooled and stored for overnight crystallization at rt, which resulted in a mixture of (*Z*)-(+)-**8** and (*E*)-(−)-**8** (216 mg). Repeated crystallization of this mixture from methanol yielded the pure (*Z*)-(+)-**8** (64 mg, 15%). (*E*)-(−)-**8** (57 mg, 14%) was obtained from the mother liquor of the first crystallization which was concentrated and recrystallized. Hexane and toluene were also tested as solvents for crystallization but they were found less effective in the separation.

(*Z*)-(+)-**8**: mp 209–211 °C, $[a]_D^{20}$ = +224.09 (*c* 0.08, chloroform) (Found: C, 70.56; H, 6.42; $C_{23}H_{25}N_3O_3$ requires C, 70.57, H 6.44%); λ_{max}(CH_3CN)/nm 199.6 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 3.11), 228.2 (0.97), 251.4 (0.61), 263.6 (0.64), 277.4 (0.50), 285.0 (0.40); CD in CH_3CN nm ($\Delta\varepsilon$) 227.4 (26.79), 264.2 (−15.17), 281.0sh (4.17), 286.8 (8.44); δ_H (200 MHz, $CDCl_3$) 1.51 (3H, s, 2-Me), 1.55 (3H, d, *J* 6.9, 6′-Me), 2.10 (2H, m, 11-H), 2.15 (1H, d, *J* 16.0, 3-H_{ax}), 2.67 (1H, m, 5-H_{eq}), 2.80 (1H, m, 3-H_{eq}), 2.91 (1H, m, 6-H), 5.00 (1H, m, 6′-H), 6.68–6.78 (2H, m, 10-H and 8-H), 6.94–7.09 (2H, m, 7-H and 9-H), 7.26–7.38 (5H, m, Ph), 7.68 (1H, d, *J* 8.0, NH), 10.03 (1H, s, =N–NH).

(*E*)-(−)-**8**: mp 215–216 °C, $[a]_D^{20}$ = −7.79 (*c* 0.08, chloroform) (Found: C, 70.57; H, 6.42; $C_{23}H_{25}N_3O_3$ requires C, 70.57, H 6.44%); λ_{max}(CH_3CN)/nm 215.2 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 1.5), 227.2 (1.23), 251.6 (0.76), 263.8 (0.79), 276.8 (0.77), 284.4 (0.53); CD in CH_3CN nm ($\Delta\varepsilon$) 214.8sh (−6.20), 226.2 (−16.44), 263.6 (25.96), 280.8sh (−3.83), 286.2 (−9.82), 300.2 (0.91); δ_H (400 MHz, $CDCl_3$) 1.50 (3H, s, 2-Me), 1.51 (3H, d, *J* 6.9, 6′-Me), 2.10 (2H, m, 11-H), 2.33 (1H, m, *J* 4.0, 5-H_{ax}), 2.49 (1H, d, 3-H_{ax}), 2.90 (1H, m, *J* 2.5 and 2.0, 5-H_{eq}), 3.00 (1H, m, *J* 2.0 and 1.5, 3-H_{eq}), 3.30 (1H, m, 6-H), 5.01 (1H, m, 6′-H), 6.71 (1H, m, 10-H), 6.74 (1H, m, 8-H), 6.96 (1H, m, 7-H), 7.04 (1H, m, 9-H), 7.09–7.70 (5H, m, Ph), 7.68 (1H, d, *J* 8.0, NH), 9.88 (1H, s, =N–NH); δ_c(100 MHz, $CDCl_3$) 21.60 (6′-Me), 28.79 (C-6 Me), 32.50 (C-6), 34.89 (C-5), 35.10 (C-11), 47.47 (C-3), 49.60 (C-6′), 75.35 (C-2), 116.53 (C-10), 120.22 (C-8), 123.26 (C-7a), 126.09, 128.52, 128.77 and 140.63 (Ph), 127.95 (C-7), 128.52 (C-9), 153.48 (C-10a), 155.14 and 158.59 (C-3′ and C-4′), 160.11 (C-4).

(*Z*)-(−)-**8**: δ_H(400 MHz, $CDCl_3$) 1.52 (3H, s, 2-Me), 1.54 (3H, d, *J* 6.9, 6′-Me), 2.10 (2H, m, 11-H), 2.15 (1H, d, 3-H_{ax}), 2.68 (1H, m, 5-H_{ax}), 2.86 (m, 1H, H-5$_{eq}$), 3.02 (1H, m, *J* 2.0 and 1.6, 3-H_{eq}), 3.29 (1H, m, 6-H), 5.00 (1H, m, 6′-H), 6.69 (1H, m, 10-H), 6.80 (1H, m, 8-H), 6.99 (1H, m, 7-H), 7.06 (1H, m, 9-H), 7.09–7.70 (5H, m, Ph), 7.96 (1H, d, *J* 8.0, NH), 10.07 (1H, s, =N–NH); δ_c(100 MHz, $CDCl_3$) 21.47 (6′-Me), 29.04 (2-Me), 32.69 (C-6), 35.34 (C-11), 39.45 (C-3), 42.45 (C-5), 49.67 (C-6′), 74.75 (C-2), 115.97 (C-10), 120.46 (C-8), 123.84 (C-7a), 126.06, 128.20, 128.61 and 141.65 (Ph), 127.73 (C-7), 128.76 (C-9), 152.88 (C-10a), 155.20 and 158.48 (C-3′ and C-4′), 160.44 (C-4).

The ketal of 5,6-dihydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-one with (2*R*,3*R*)-(−)-butane-2,3-diol [(+)-9a]

rac-**6** (472 mg, 2.33 mmol) was dissolved in toluene, 230 mg (2.55 mmol) (2*R*,3*R*)-(−)-butane-2,3-diol and 10 mg PTS were added and the mixture was refluxed for 12 h. Afterwards it was diluted with dichloromethane and extracted with water and saturated $NaHCO_3$ solution. The crude product was purified by flash chromatography to give 507 mg (79%) of a light-yellow oil, a mixture of the two diastereomers. A concentrated methanolic solution of the mixture was prepared from which 89 mg (14%) (+)-**9a** crystallized overnight as colorless needles. A few crystals were recrystallized from methanol which afforded single crystals suitable for X-ray analysis.

X-ray parameters:† colorless prism crystals (0.42 × 0.3 × 0.22 mm) of $C_{17}H_{22}O_3$, *M* = 274.35, orthorhombic, *a* = 6.062(1) Å, *b* = 15.112(1) Å, *c* = 16.992(1) Å, *V* = 1556 Å^3, *Z* = 4, space group: $P2_12_12_1$, ρ_{calc} = 1.171 g cm^{-3}. Data were collected at 293(1) K, Enraf–Nonius MACH3 diffractometer, Mo-Kα radiation λ = 0.71073 Å, ω-2θ motion, θ_{max} = 27°, 2047 unique reflections were measured, of which 1041 were with $I > 2\sigma(I)$, decay: 4%. The structure was solved using the SIR-92 software[28] and refined on F^2 using the SHELX-97[29] program. Publication material was prepared with the WINGX-97 suite,[30] $R(F)$ = 0.0501 and $wR(F^2)$ = 0.1335 for 2047 reflections, 182 parameters.

Mp 74–76 °C, $[a]_D^{20}$ = +44.34 (*c* 0.20, chloroform) (Found: C, 74.35; H, 8.07; $C_{17}H_{22}O_3$ requires C, 74.42, H 8.08%); λ_{max}(CH_3CN)/nm 200.0 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 3.53), 213.6 (4.61), 220.0 (0.50), 246.2 (0.02), 277.2 (0.16); CD in CH_3CN nm ($\Delta\varepsilon$) 204.6 (−7.52), 226.0 (5.96), 277.2 (3.92), 283.8 (3.64); δ_H(400 MHz, C_6D_6) 0.65 (3H, d, *J* 8.5, C-3′ CH_3), 0.85 (3H, d, *J* 8.5, C-2′ Me), 1.21 (3H, s, 2-Me), 1.34 (1H, dd, *J* 12.8 and 2.9, 11-H_{ax}), 1.54 (1H, m, 11-H_{eq}), 1.67 (1H, d, *J* 14.0, 3-H_{ax}), 1.71 (1H, dd, *J* 13.7 and 4.1, 5-H_{ax}), 1.88 (1H, m, 5-H_{eq}), 2.17 (1H, m, 3-H_{eq}), 2.70 (1H, m, 6-H), 2.99 (1H, dd, *J* 8.50 and 6.8, 3′-H), 3.20 (1H, dd, 2′-H), 6.68 (1H, td, *J* 8.1, 7.1 and 1.4, 9-H), 6.80 (1H, dd, *J* 8.1 and 1.3, 10-H), 6.84 (1H, dd, *J* 7.3 and 1.4, 7-H), 6.97 (1H, m, 8-H); δ_c(100 MHz, $CDCl_3$) 16.25 (C-3′ Me), 17.19 (C-2′ Me), 29.39 (2-Me), 32.44 (C-6), 35.52 (C-5), 42.12 (C-11), 49.20 (C-3), 74.99 (C-2), 76.70 (C-2′), 78.07 (C-3′), 107.01 (C-4), 115.12 (C-10), 118.79 (C-8), 126.23 (C-7a), 127.31 and 127.32 (C-7 and C-9), 155.30 (C-10a).

Enantiomeric 5,6-dihydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4(3*H*)-ones [(−)-6 and (+)-6] from oxamoylhydrazones

To a solution of (*E*)-(−)-**8** (20 mg, 0.051 mmol) in methanol, a few drops of sulfuric acid (25%) were added and the reaction mixture was stirred for 5 hours. It was neutralized with $NaHCO_3$ and then extracted with dichloromethane. The organic layer was collected and concentrated, and its purification by preparative TLC gave 7.6 mg (74%) of a white crystalline product (−)-**6**. (+)-**6** was prepared in 65% yield in the same manner starting from (*Z*)-(+)-**8**.

(−)-**6**: mp 121–122 °C, $[a]_D^{20}$ = −15.6 (*c* 0.15, chloroform) (Found: C, 70.15; H, 6.96; $C_{13}H_{14}O_2$ requires C, 77.20, H 6.98%); λ_{max}(hexane)/nm 276.8 ($\varepsilon \times 10^{-3}/M^{-1}$ cm^{-1} 1.96), 283.8 (1.91); CD in hexane nm ($\Delta\varepsilon$) 277.0 (−2.91), 285.6 (−2.27), 308.4 (0.25), 316.0 (0.23); NMR data are the same as given in reference 2.

(+)-**6**: Mp 123–125 °C, $[a]_D^{20}$ = +19.7 (*c* 0.11, chloroform); λ_{max}(hexane)/nm 276.8 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 1.96), 283.8 (1.91); CD in hexane nm ($\Delta\varepsilon$) 205.0 (20.47), 224.8 (3.16), 246.0 (−0.23), 277.2 (2.84), 284.6 (2.66) 308.8 (−0.27), 315.2 (−0.26); CD in CH_3CN nm ($\Delta\varepsilon$) 205.8 (22.35), 227.2 (2.65), 246.8 (−0.32), 278.2 (2.56), 285.0 (2.89), 313.8 (−0.22).

(+)-6 from the ketal (+)-9

(+)-**9** (64 mg, 0.23 mmol) was refluxed in dioxane with 5 ml dilute hydrochloric acid (10%). The mixture was neutralized with $NaHCO_3$ solution and extracted with dichloromethane. The crude product was purified by preparative TLC in 8 : 1 toluene–ethyl acetate to give 32 mg (68%) of a crystalline substance, mp 124–126 °C, $[a]_D^{20}$ = +26.1 (*c* 0.10, chloroform).

† CCDC reference number 178166. See http://www.rsc.org/suppdata/p1/b2/b200751g/ for crystallographic files in cif. or other electronic format.

(2*R*,4*S*,6*R*)-(+)-3,4,5,6-Tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4-ol [(+)-10] from the reduction of the ketone (+)-6

(+)-**6** (14 mg, 0.07 mmol) was reduced with 10 mg LAH in dry THF. After 30 minutes, a few drops of water were added to decompose the excess LAH. After the addition of brine the extraction was carried out with methylene chloride. Concentration of the organic layer and the subsequent purification by preparative TLC with 4 : 1 toluene–ethyl acetate gave 11.8 mg (84%) of a slowly crystallizing oil (+)-**10**.

Mp 81–83 °C, $[\alpha]_D^{20}$ = +32.12 (*c* 0.22, chloroform) (Found: C, 76.38; H, 7.91; $C_{13}H_{16}O_2$ requires C, 76.44, H 7.90%); λ_{max}(CH_3CN)/nm 198.8 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 4.14), 219.8 (0.63), 276.6 (0.29), 283.2 (0.28); CD in CH_3CN nm ($\Delta\varepsilon$) 195.6 (4.40), 204.4 (−5.35), 214.0sh (0.82), 226.8 (6.00), 270.8 (1.16), 281.0 (1.06), 284.8 (0.92); δ_H(400 MHz, $CDCl_3$) 1.42 (3H, s, 2-Me), 1.62 (1H, br s, OH), 1.75 (1H, dd, *J* 13.3 and 3.0, 11-H_{ax}), 1.81 (1H, dd, *J* 15.2 and 5.2, 3-H_{ax}), 1.88 (1H, m, 11-H_{eq}), 1.95 (1H, m, 5-H_{ax}), 2.14 (1H, m, 5-H_{eq}), 2.22 (1H, m, 3-H_{eq}), 3.06 (1H, m, 6-H), 4.04 (1H, m, 4-H), 6.78 (1H, m, 8-H), 6.78 (1H, overlapped m, 10-H), 7.02 (1H, overlapped m, 7-H). 7.04 (1H, m, 9-H).

(2*R*,4*S*,6*R*)-(+)-4-Acetoxy-3,4,5,6-tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocine [(+)-11]: kinetic resolution of *rac*-10

rac-**10** (190 mg, 0.93 mmol) was stirred in dry ether with 1 ml vinyl acetate and 81 mg lipase from *Pseudomonas cepacia* (on Toyonite). The reaction was followed by TLC and stopped after 16 days. The enzyme was filtered off and the solvent was evaporated. Column chromatography of the residue with 6 : 1 hexane–ethyl acetate gave 93 mg acetate (+)-**11** and 71 mg alcohol (−)-**10** (52% conversion).

(−)-**10**: mp 75–76 °C, $[\alpha]_D^{20}$ = −38.88 (*c* 0.10, chloroform) λ_{max}(CH_3CN)/nm 198.8 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 4.14), 219.8 (0.63), 276.6 (0.29), 283.2 (0.28); CD in CH_3CN nm ($\Delta\varepsilon$) 195.0 (−6.41), 204.6 (5.25), 217.2sh (−2.39), 227.2 (−6.39), 276.8 (−1.93), 282.8 (−1.80).

(+)-**11**: mp 101–102 °C, $[\alpha]_D^{20}$ = +95.13 (*c* 0.10, chloroform) (Found: C, 73.12; H, 7.35; $C_{15}H_{18}O_3$ requires C, 73.15, H 7.37%); δ_H(400 MHz, $CDCl_3$) 1.28 (3H, s, $COCH_3$), 1.39 (3H, s, 2-Me) 1.72 (1H, dd, *J* 13.3 and 3.2, 11-H_{ax}), 1.74 (1H, dd, *J* 15.2 and 5.0, 3-H_{ax}), 1.84 (1H, m, 5-H_{ax}), 1.87 (1H, m, 11-H_{eq}), 2.13 (1H, m, 5-H_{eq}), 2.14 (1H, m, 3-H_{eq}), 3.01 (1H, m, 6-H), 4.95 (1H, m, 4-H_{eq}), 6.66 (1H, m, 8-H), 6.67 (1H, m, 10-H), 6.96 (1H, m, 7-H), 7.02 (1H, m, 9-H); δ_c(100 MHz, $CDCl_3$) 20.53 (COMe), 29.62 (2-Me), 30.56 (C-6), 35, 57 (C-11), 36.54 (C-5), 41.88 (C-3), 68.16 (C-4), 72.90 (C-2), 115.41 (C-10), 119.03 (C-8), 126.79 (C-7a), 127.47 (C-7), 127.71 (C-9), 155.43 (C-10a), 170.58 (C=O).

(2*R*,4*S*,6*R*)-(+)-3,4,5,6-Tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocin-4-ol [(+)-10] from the hydrolysis of (+)-11

70 mg (0.28 mmol) (+)-**11** was reacted with 5 ml 1 M NaOMe in methanol at room temperature for 24 h. The mixture was then concentrated under vacuum, and the residue was dissolved in dichloromethane and washed with water. Separation by preparative TLC in 4 : 1 toluene–ethyl acetate gave 50 mg (86%) of (+)-**10**, mp 81–83 °C, $[\alpha]_D^{20}$ = +38.27 (*c* 0.11, chloroform).

Enantiomeric 3,4,5,6-tetrahydro-2-methyl-2,6-methano-4-tosyloxy-2*H*-1-benzoxocines (2*R*,4*S*,6*R*)-(+)-12 and (2*S*,4*R*,6*S*)-(−)-12

Toluene-*p*-sulfonyl chloride (300 mg, 1.57 mmol) was added to a stirred solution of (−)-**10** (70 mg, 0.34 mmol) in dry pyridine. After 48 hours, the reaction mixture was diluted with dichloromethane and washed with hydrochloric acid solution (10%). The crude product was purified by preparative TLC in 8 : 1 toluene–ethyl acetate to yield (−)-**12** (78 mg, 64%).

(2*S*,6*S*,4*R*)-(−)-**12**: mp 132–133 °C, $[\alpha]_D^{20}$ = −19.15 (*c* 0.09, chloroform); (Found: C, 66.95; H, 6.15; $C_{15}H_{18}O_3$ requires C, 67.01, H 6.19%); δ_H(200 MHz, $CDCl_3$) 1.39 (3H, s, 2-Me), 1.74–1.98 (4H, overlapping m, 11-H, 3-H_{ax} and 5-H_{ax}), 2.20–2.37 (2H, m, 3-H_{eq} and 5-H_{eq}), 2.40 (3H, s, tosyl Me), 3.03 (1H, m, 6-H), 5.07 (1H, m, 4-H), 6.60 (1H, m, 7-H).

(2*R*,6*R*,4*S*)-(+)-**12** was prepared from (+)-**10** as described above for (−)-**12**, mp 133–135 °C, $[\alpha]_D^{20}$ = +19.80 (*c* 0.12, chloroform).

Enantiomeric 3,4,5,6-tetrahydro-2-methyl-2,6-methano-2*H*-1-benzoxocines (2*R*,6*S*)-(+)-1 and (2*S*,6*R*)-(−)-1

(2*S*,6*S*,4*R*)-(−)-**12** (28 mg, 0.08 mmol) was reduced with LAH (20 mg, 0.52 mmol) in dry 1 : 1 THF-ether under argon. After 5 hours, NH_4Cl solution was added to the reaction mixture, which was then extracted with dichloromethane. The crude product was purified with 1 : 1 hexane–toluene by preparative TLC to give (2*R*,6*S*)-(+)-**1** (6 mg, 41%) as an oil with characteristic spicy odor.

(2*R*,6*S*)-(+)-**1**: $[\alpha]_D^{20}$ = +17.41 (*c* 0.12, chloroform) (Found: C, 82.84; H, 8.51; $C_{13}H_{16}$ Orequires C, 82.94, H 8.57%); λ_{max}(CH_3CN)/nm 199.0 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 2.41), 276.6 (0.13), 283.0 (0.12); CD in CH_3CN nm ($\Delta\varepsilon$) 203.8 (5.79), 227.8 (−3.05), 276.2 (−0.67), 283.0 (−0.57); δ_H(200 MHz, $CDCl_3$) 1.43 (3H, s, 2-Me), 1.5–2.0 (8H, overlapping m, 3-H, 4-H, 5-H, 11-H), 3.03 (1H, m, 6-H), 6.74–7.22 (4H, m, ArH); δ_c(50 MHz, $CDCl_3$) 18.19 (C-4), 29.35 (2-Me), 32.58 (C-5), 32.95 (C-6), 35.86 (C-3), 39.35 (C-11), 74.63 (C-2), 114.96 (C-10), 119.01 (C-8), 125.94 (C-7a), 127.28 (C-9), 128.99 (C-7), 156.35 (C-10a).

(2*S*,6*R*)-(−)-**1**: $[\alpha]_D^{20}$ = −15.21 (*c* 0.2, chloroform); λ_{max}(CH_3CN)/nm 199.0 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 3.00), 276.6 (0.15), 283.4 (0.15); CD in CH_3CN nm ($\Delta\varepsilon$) 203.0 (−5.75), 227.8 (4.21), 276.4 (0.83), 282.4 (0.79).

Acknowledgements

The authors thank the National Science Foundation (OTKA, Grant No. T034250) for financial support. Attila Bényei is indebted to the Hungarian Academy of Sciences for a Bolyai Postdoctoral Fellowship. This paper is dedicated to Professor Nina Berova and Professor Koji Nakanishi.

References

1 J. Asano, K. Chiba, M. Tada and T. Yoshii, *Phytochemistry*, 1996, **41**, 815.
2 F. Eiden and P. Gmeiner, *Arch. Pharm. (Weinheim)*, 1987, **320**, 213.
3 M. Yamazaki, Y. Satoh, Y. Maebayashi and Y. Horie, *Chem. Pharm. Bull.*, 1988, **36**, 670.
4 K. Kojiri, S. Nakajima, A. Fuse, H. Suzuki and H. Suda, *J. Antibiot.*, 1995, **48**, 1506.
5 S. Antus, E. Baitz-Gács, J. Kajtár, G. Snatzke and A. L. Tökés, *Liebigs Ann. Chem.*, 1994, 497.
6 T. Kurtán, E. Baitz-Gács, Z. Májer and S. Antus, *J. Chem. Soc., Perkin Trans. 1*, 2000, 453.
7 G. Snatzke, F. Snatzke, A. L. Tökés, M. Rákosi and R. Bognár, *Tetrahedron*, 1973, **29**, 909.
8 S. Antus, T. Kurtán, L. Juhász, L. Kiss, M. Hollósi and Z. Májer, *Chirality*, 2001, **13**, 493.
9 R. Kuhn and D. Weiser, *Chem. Ber.*, 1955, **88**, 1601.
10 A. L. Tökés and L. Szilágyi, *Synth. Commun.*, 1987, **17**, 1235.
11 G. Nadler, I. Delimoge, P. Lahouratate, I. Leger, M. Morvan and R. G. Zimmermann, *Eur. J. Med. Chem.*, 1996, **31**, 805.
12 Y. Xia, Z. Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S. C. Kuo, E. Hamel, T. Hackl and K. H. Lee, *J. Med. Chem.*, 1998, **41**, 1155.
13 A. L. Tökés, *Liebigs Ann. Chem.*, 1987, 1007.
14 A. Srivastava, V. Srivastava, S. M. Verma and E. Subramanian, *J. Org. Chem.*, 1994, **59**, 3560.
15 G. Giorgi, F. Ponticelli, L. Savini, L. Chiasserini and C. Pellerano, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2259.

16 T. Nakazawa, Y. Mizuta, A. Kawahara, E. Miyamoto and N. Muto, *Chem. Lett.*, 1992, 1125.
17 N. Berova and K. Nakanishi, in *Circular Dichroism, Principles and Applications*, eds. N. Berova, K. Nakanishi and R. W. Woody, Wiley-VCH, New York, 2000.
18 N. L. Allinger and C. K. Riew, *J. Org. Chem.*, 1975, **40**, 1316.
19 D. A. Lightner, T. D. Bouman, A. E. Hansen and W. M. D. Wijekoon, *J. Am. Chem. Soc.*, 1986, **108**, 4484.
20 G. Snatzke, B. Ehrig and H. Klein, *Tetrahedron*, 1969, **25**, 5601.
21 W. D. Fessner and H. Prinzbach, *Tetrahedron*, 1986, **42**, 1797.
22 U. T. Bornscheuer and R. J. Kazlauskas, *Hydrolases in Organic Synthesis*, Wiley-VCH, Weinheim, 1999.
23 X. Grabuleda, C. Jaime and A. Guerrero, *Tetrahedron: Asymmetry*, 1997, **8**, 3675.
24 K. Lemke, M. Lemke and F. Theil, *J. Org. Chem.*, 1997, **62**, 6268.
25 R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport and L. A. Cuccia, *J. Org. Chem.*, 1991, **56**, 2656.
26 K. Nakamura, M. Kawasaki and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1079.
27 K. Burgess and L. D. Jennings, *J. Am. Chem. Soc.*, 1991, **113**, 6129.
28 A. Altomare, G. Cascarano, C. Giacovazzo and A. Guagliardi, *J. Appl. Crystallogr.*, 1993, **26**, 343.
29 G. M. Sheldrick, SHELXL-97, Universität Göttingen, Germany, 1997.
30 L. J. Farrugia, WINGX-97, University of Glasgow, UK, 1996.