Synthesis and circular dichroism of steroids with 2,3-dihydro-1-benzofuran and 4*H*-benzopyran chromophores; revision of the absolute configuration of some norneolignans from *Krameria cystisoides*

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Starting from cholesterol the 2,3-dihydrobenzo[*b*]furans **12a**, **12b**, and the 4*H*-benzopyran derivative **14** with known absolute conformation were synthesized by a stereocontrolled sequence. The same helicity rule was found to be valid for both chromophores; the P/M helicity of the heteroring leads to a negative/positive CD within the α-band. On the basis of this rule the absolute configuration of norneolignans **24**–**26** isolated from *Krameria cystisoides* was also revised.

Introduction

The 2,3-dihydro-1-benzofuran and 4*H*-benzopyran chromophores are found in many naturally occurring chiral O-heterocycles possessing a wide range of remarkable biological activity.[1] In many cases chiroptical methods (ORD or CD) have been used to determine their absolute configuration.[2] These examinations were usually based on a simple comparison of their chiroptical data with those of the analogous compounds whose absolute configuration had been deduced by chemical correlation or X-ray analysis. Although this method is widely used in natural product chemistry, there is a possibility that the absolute configuration for the above-mentioned chromophore systems is incorrectly assigned. In terms of chromophore systems, chiral 2,3-dihydrobenzo[*b*]furan and 4*H*-benzopyran in fact belong to the benzene chromophores with a chiral second sphere according to Snatzke's terminology.[3] For this type of benzene chromophore a simple helicity rule was discovered by Snatzke and Ho[4] as depicted in Fig. 1.

If *pseudoaxial* substituents are not present at the benzylic carbon atoms, P-helicity of the non-aromatic ring leads to a positive Cotton effect (CE) within the $^1B_{2u}$ transition (α-band), and M-helicity leads to a negative Cotton effect. The terms P- and M-helicity, which describe the chirality, can be used even in those cases when the chiral non-aromatic ring adopts a conformation other than the regular half chair. Snatzke and co-workers[3,5] have found that the substitution pattern of the aromatic ring or the substituent at the benzylic positions cannot always be neglected. Namely, the sign of the $^1B_{2u}$ CE can be reversed by some patterns of substitution of the aromatic ring, as well as by a *pseudoaxial* substituent at the benzylic carbon atom.

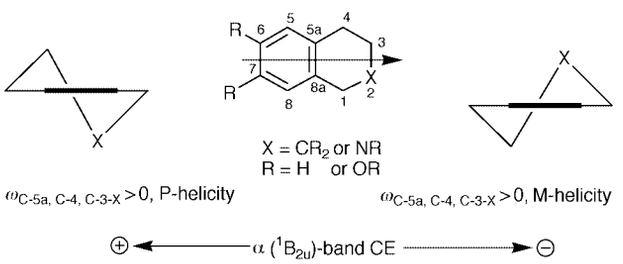


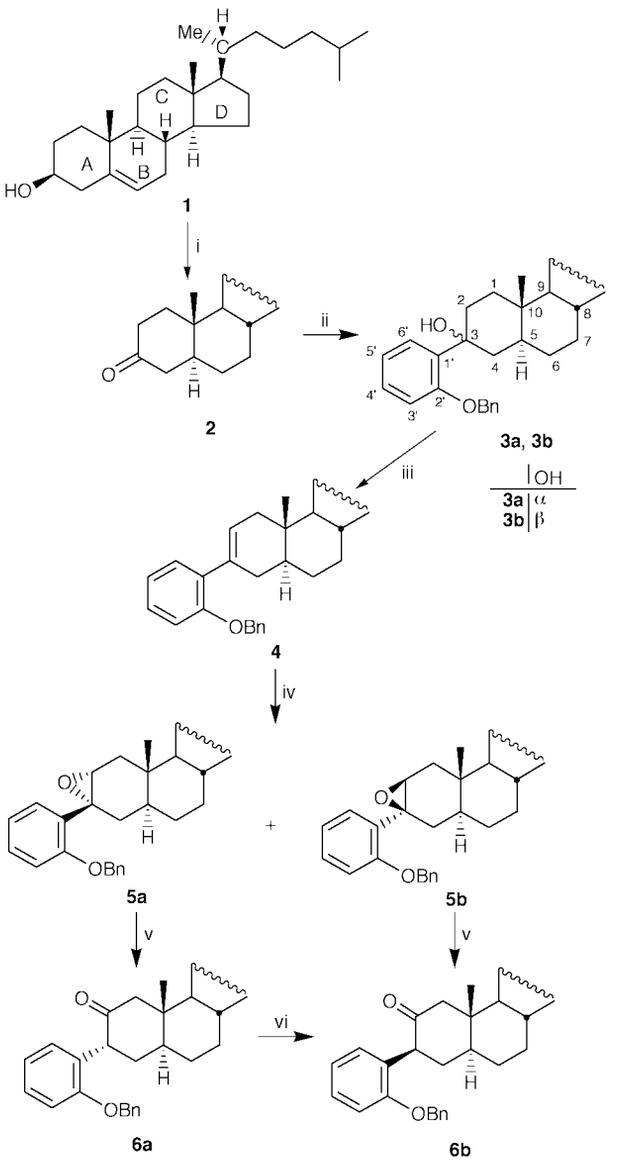
Fig. 1 Sign of the second sphere contribution of tetralin (tetrahydroisoquinoline) derivatives to the $^1B_{2u}$ band CD. The arrow indicates the direction of projection. P and M refer to the absolute conformation (helicity) of the non-aromatic ring.

Therefore, to unambiguously determine the absolute configuration of this type of compound by chiroptical methods, it is necessary to examine thoroughly which form of Snatzke's helicity rule is valid for both the studied and the reference ring-systems or compounds. To continue our program on the chiroptical properties of naturally occurring O-heterocycles,[6] we investigated a possible extension of Snatzke's helicity rule to the 2,3-dihydrobenzo[*b*]furan and 4*H*-benzopyran chromophore systems. In order to study the relationship between the stereochemistry and the chiroptical properties of these chromophore systems, using our method,[7] we synthesized a few derivatives, in which the 2,3-dihydro-1-benzofuran and the 4*H*-benzopyran rings are connected to ring A of a steroid as a chiral perturber. Below we discuss their synthesis and CD spectra.

Results and discussion

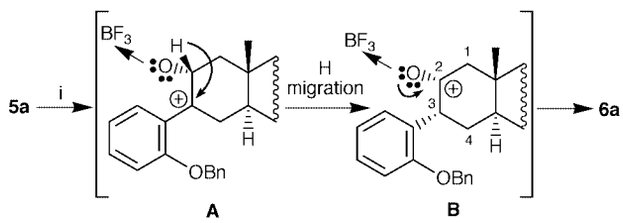
2,3-Dihydro-1-benzofurocholestanes have not yet been described in the literature. The synthesis of the desired model compounds (**12a**,**b** and **13**) containing a chiral second sphere with M- and P-helicity, respectively, started from cholesterol (**1**). Cholesterol (**1**) was converted to 5α-cholestan-3-one (**2**) in two steps as described in the literature.[8] Compound **2** was then treated with 2-benzyloxyphenylmagnesium bromide prepared from 2-benzyloxybromobenzene[9] in THF in the presence of magnesium turnings. This resulted in a 1:1 mixture of the C-3 epimeric alcohols **3a** and **3b**, which could be separated by column chromatography on silica gel. The stereochemistry of **3a** was established by NOE experiments. Crystallisation from methanol of the alcohol **3a** with the bulky 2-benzyloxy group in an *equatorial* position furnished a pure crystalline compound with mp 79–81 °C; the 3β-hydroxy isomer **3b** suffered elimin-

ation of water under similar conditions to give the cholest-Δ^2-ene derivative **4**. The olefin **4** was also prepared from **3a** in the presence of toluene-*p*-sulfonic acid in dry toluene at room temperature in 48% yield (Scheme 1). The Δ^2 position of the double



Scheme 1 *Reagents*: i, ref. 8; ii, 2-BnO-C_6H_5Br, Mg, THF; iii, toluene, PTSA, room temp.; iv, *m*-CPBA or DMD, CH_2Cl_2, room temp.; v, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; vi, NaOMe, MeOH–CH_2Cl_2.

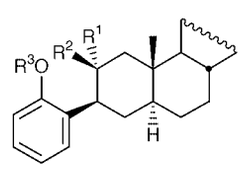
bond in **4** was established by NMR (decoupling and HETCOR) experiments. Epoxidation of **4** was performed with *m*-chloroperbenzoic acid in dichloromethane at room temperature as the next step of the synthesis of the target molecules **12a**,**b** and **13**. In agreement with our expectations, the attack of the reagent took place at the less-hindered α-side of the steroid nucleus to afford the thermodynamically more stable α-epoxide **5a** as the main product, in which the 2-benzyloxyphenyl group adopted a *quasiequatorial* position. This stereochemistry was supported by an NOE effect between the C-10 methyl group and the proton at C-2. TLC monitoring of the epoxidation of **4** clearly showed that a small amount of the β-epoxide **5b** was also formed, but it was transformed very quickly to the cholestan-2-one **6b** under the acidic conditions of the epoxidation. Although this process could be stopped by using dimethyldioxirane (DMD) as a neutral oxidizing agent,[10] isolation of **5b** failed because of its high instability. Rearrangement of the epoxide **5a** to the corresponding ketone derivative **6a** was carried out by treatment with a catalytic amount of boron trifluoride–diethyl ether in dichloromethane at 0 °C. It is reasonable to assume that by cleavage of the C-3 carbon–oxygen bond of **5a**, a stable carbocation was formed first, which could be stabilized by the migration of the hydrogen from C-2 (**A**→**B**) followed by the formation of a carbonyl group at C-2 as depicted in Scheme 2. According to



Scheme 2 *Reagents*: i, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C.

this mechanism, the 2-benzyloxyphenyl group must be attached to C-3 in the thermodynamically less favoured *axial* position in **6a**. In accordance with this stereochemistry, a substantial NOE effect could be detected in **6a** between the H-1α proton and the 3′,6′-protons of the aryl group at C-3. This stereochemistry was also supported by epimerization at C-3. Treatment of **6a** with sodium methoxide in a 1 : 1 mixture of methanol and dichloromethane resulted in **6b**, carrying the bulky 2-benzyloxyphenyl group in a *pseudoequatorial* position. This configuration of the aryl group in **6b** was unequivocally determined by NMR and CD measurements. The diagnostic NMR spectral parameters of H-3 (δ = 3.84 ppm, J = 12.8 and 6.3 Hz) are indicative of an *axially* oriented hydrogen at C-3. According to the octant rule,[11] the smaller positive n→π* band CE of the carbonyl group compared to that of the 5α-cholestan-2-one ($\Delta\varepsilon$ +2.95) proved the *equatorial* orientation of the aryl group at C-3. Reduction of **6b** with lithium aluminium hydride in THF took place with high stereoselectivity to furnish a *ca.* 12 : 1 mixture of the corresponding alcohols **7** and **8**, which were separated by flash chromatography. The configuration of the hydroxy group at C-2 in **7** was determined unambiguously by means of the coupling constants of H-2 and the absence of an NOE effect between H-2 and the C-19 methyl protons.

Starting from **7**, the main product of the reduction of **6b**, we intended to synthesize the *trans*-fused 2,3-dihydro-1-benzo[*b*]furan derivative **13** in three steps (**7**→**9**→**10**→**13**) following

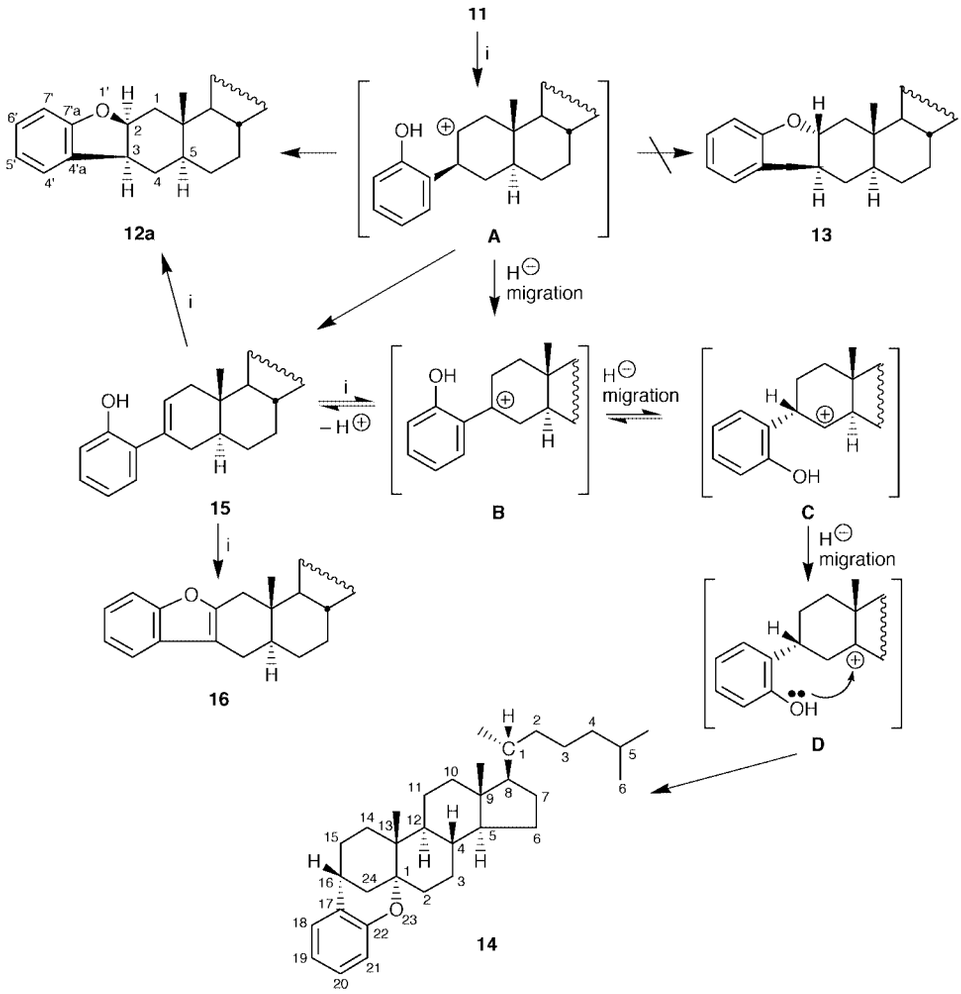


7-11

	R^1	R^2	R^3
7	H	OH	Bn
8	OH	H	Bn
9	H	OMs	Bn
10	H	OMs	H
11	H	OH	H

our earlier methodology,[12] but attempts to prepare the mesylate **9** under standard conditions were completely unsuccessful. Therefore, after removal of the benzyl protecting group (**7**→**11**) by catalytic hydrogenation over palladium on charcoal in THF, ring closure was attempted by treating **11** with boron trifluoride–diethyl ether in dry dichloromethane. As shown in Scheme 3, we supposed that the carbocation **A** could be generated from **11** by a Lewis acid which would give **13** and **12a** by the attack of the phenolic hydroxy group from the α- and β-side of the steroid nucleus, respectively.

TLC monitoring of the reaction showed that three products were formed instead of the expected two, which were isolated by means of preparative TLC. Their structures were elucidated



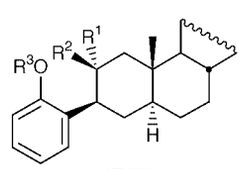
Scheme 3 *Reagents*: i, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temp.

by spectroscopic methods (MS, NMR) and chemical correlations. Although the MS and elemental analysis of the main product **14** (mp 124–125 °C) were in good agreement with the molecular formula of the expected 2,3-dihydro-1-benzofuran derivatives **12a**, **13** ($C_{35}H_{50}O$), these structures were unambiguously excluded since the ^1H and ^{13}C NMR spectra revealed that the oxygen atom is bonded to a quaternary carbon. From an HMBC experiment this carbon was identified as C-1.

This unexpected transformation of **11** to **14** can be explained by a threefold hydride shift (**A**→**B**→**C**→**D**) starting from the carbocation **A** as depicted in Scheme 3. The structure of the second major compound (mp 130–132 °C), isolated in 17% yield, was also determined by NMR and MS to be the 1-benzofuran derivative **16**, which means that the expected ring closure of **11** *via* the carbocation **A** to **12a** or **13** was apparently followed by dehydrogenation to result in **16** in moderate yield. In order to clarify the route of this transformation, the cholest-Δ^2-ene **15** was synthesized in three steps from the alcohol **17**, prepared from the ketone **6a** [**6a**→**17**, (**18**)→**19**→**15**, see the Experimental section].

According to our assumption, both carbocations **A** and **B** could lose a hydrogen to give **15**, whose reaction with boron trifluoride–diethyl ether could result in **16**. To confirm these speculations, **15** was transformed to **16**, **12a** and **14**.† It is noteworthy that the presence of the *trans*-fused 2,3-dihydro-1-benzofuran derivative **13** could not be detected in the transformation of either **11** or **15** with $BF_3{\cdot}OEt_2$, which is in good agreement with the observation of Rupprecht *et al.*[13]

† The reaction was followed by TLC using hexane as the eluent and the formerly assigned compounds as standards (for comparison).



17-19

	R^1	R^2	R^3
17	OH	H	Bn
18	H	OH	Bn
19	OH	H	H

Quantum chemical calculations and stereocontrolled synthetic studies clearly showed that the *cis*-fused 2,3-dihydro-1-benzofuran ring system is 3 kcal mol^{-1} more stable than the *trans* system. The synthesis of **16** was also achieved *via* a more simple route starting from the ketone **6b**. As shown in Scheme 4, on treating **6b** with excess boron trifluoride–diethyl ether in dichloromethane, the Lewis acid first cleaved the benzyl protecting group to afford the hydroxyketone **20**, which then spontaneously cyclized to **16** *via* the hemiketal **21**. Catalytic hydrogenation of **16** resulted in **12a** and the other *cis*-fused 2,3-dihydro-1-benzofuran **12b** in good yield (79%), which also served as a suitable model compound for our CD studies.

According to the Dreiding model of **12a**, it seemed obvious to suppose that the ring A of the cholestane skeleton adopts the thermodynamically more stable chair conformation, to which the heteroring is fused at C-2 and C-3 in an envelope conformation with an M-helicity defined by the torsional angle of C-7′a, O, C-2, C-3. In this stereochemistry the substituted

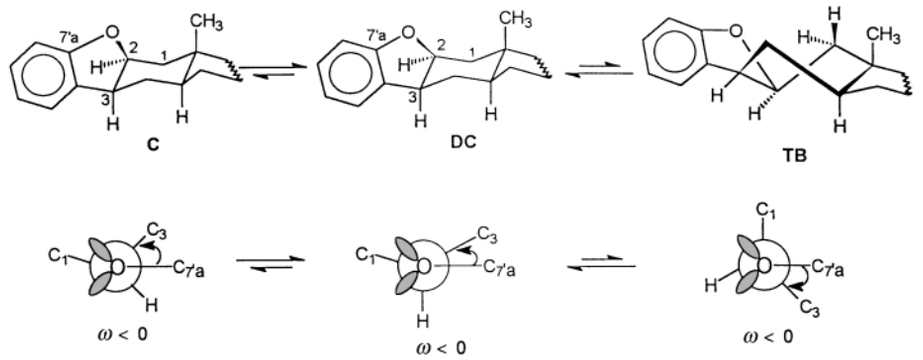
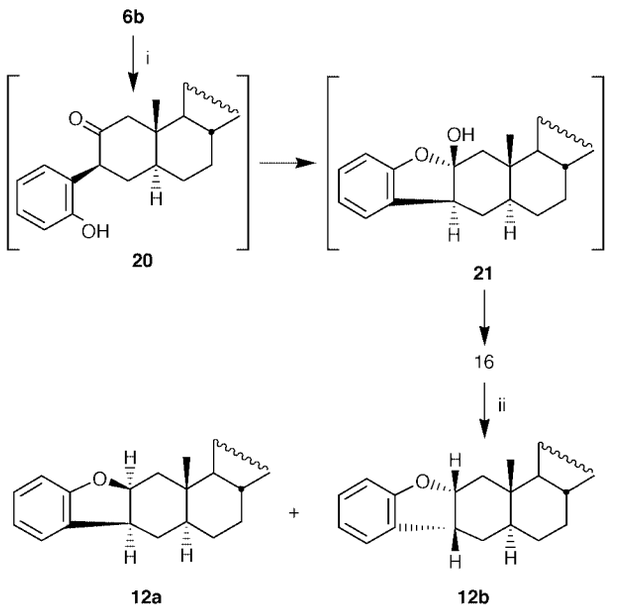


Fig. 2 Ring inversions of **12a**.



Scheme 4 *Reagents*: i, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temp.; ii, H_2, Pd(C), THF.

phenyl group at C-3 would assume *equatorial* orientation while the oxygen bridge at C-2 would be in the *axial* position. Although the ^1H NMR data of **12a** in d_{12}-cyclohexane solution were in complete agreement with this stereochemistry, the coupling constants between the proton at C-2 and the α- and β-protons at C-1 (J = 5.0 and 1.5 Hz, respectively) clearly showed that the preferred conformation of ring A of the steroid moiety differs from a real chair form. The coupling data are consistent with a distorted chair conformation of ring A, where the aryloxy group is shifted away from the *axial* orientation to relieve the steric strain between the C-2–O bond and the C-10 methyl group (Fig. 2). However, this conformational change of ring A did not invert the helicity of the heteroring. The CD spectrum of **12a** in *n*-hexane shows a positive Cotton effect (Δε 0.89 at 279 nm) within the α band, and a smaller positive one in acetonitrile (Δε 0.32 at 279 nm), whose first line wavelengths (0–0 transition) are in good agreement with the predicted values[14] (286 nm) (Fig. 3).

The decrease of the Δε value with the increasing polarity of the solvent indicated that C-1 moves upward by a greater extent which causes the heteroring to shift from the envelope conformation toward the plane of the aromatic ring. The very small Δε value of the α band CE in acetonitrile reflects the fact that the heteroring approaches a conformation which is pseudoachiral (C-7a–O and C-3–C-4a bonds are differently polarized) since the heteroring becomes almost planar while C-2 moves into the plane of the benzene ring, and the second sphere contribution becomes almost zero. The notable presence of the twist boat conformation as an extreme case of the distortion of

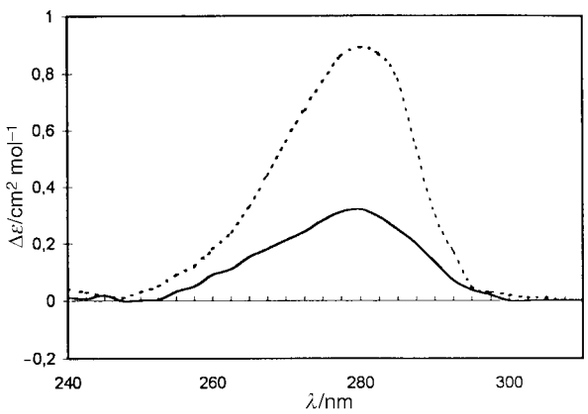


Fig. 3 $^1B_{2u}$ (α) band CE of compound **12a** in hexane (– – –) and in acetonitrile (——).

ring A accompanied by P-helicity, however, can be excluded. This conformation would lead to the *trans-diaxial* orientation of the H-1β and H-2 protons, which is in contradiction with the measured value of the $J_{1\beta,2}$ coupling (1.5 Hz). Moreover, the presence of a strong NOE connection of C-19 methyl protons with H-1β and the absence of this connection with H-1α corroborate that the participation of the boat conformer in the conformational equilibrium is also negligible.

Inspection of the Dreiding model of **12b** reveals that in the real chair conformation of the steroid ring A, the H-5 proton is in the shielding zone of the aryl ring. By contrast, both the chemical shift of this proton (1.12 ppm) and the coupling constants of H-3 with the H-4α and H-4β protons (1.0 and 7.0 Hz, respectively) indicate that the preferred conformation of ring A is a distorted chair, where the C-4′a, C-3, C-4, C-5 torsional angle is somewhat flattened. In this conformation the aryl residue is in a *pseudoequatorial* position which causes the P-helicity of the heteroring (Fig. 4). In addition to the coupling constant information the measured NOE effects also exclude the notable participation of the chair form in the conformational equilibrium. In that conformation a significant NOE is expected between the H-4β and C-19 methyl protons, which was not observable. This is in agreement with the fact that **12b** shows a strong negative Cotton effect with pronounced fine structure within the α band (Δε for 0–0 line is −3.30 at 289 nm) in *n*-hexane, which is somewhat smaller in acetonitrile (Δε −2.50 at 287 nm) (Fig. 5).

It is to be noted that the absolute values of the α band CE of **12b** both in *n*-hexane and acetonitrile are significantly larger than those of **12a** which compares favourably with the NMR data. The $J_{1\beta,2}$ and $J_{2,3}$ coupling constants of **12b** (6.9 and 7.9 Hz, respectively) reflect a more puckered heteroring than that of **12a** (the corresponding $J_{1\alpha,2}$ and $J_{2,3}$ values in **12a** are 5.0 and 6.5 Hz, respectively). The CD data can be explained by the sector rule revealed by Dornhege and Snatzke.[15] According to this rule, shown in Fig. 6, the measured positive CE for $^1B_{2u}$

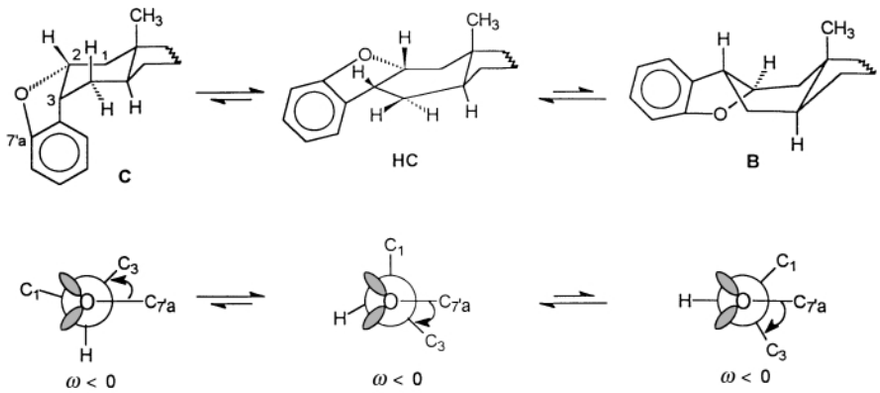


Fig. 4 Ring inversions of **12b**.

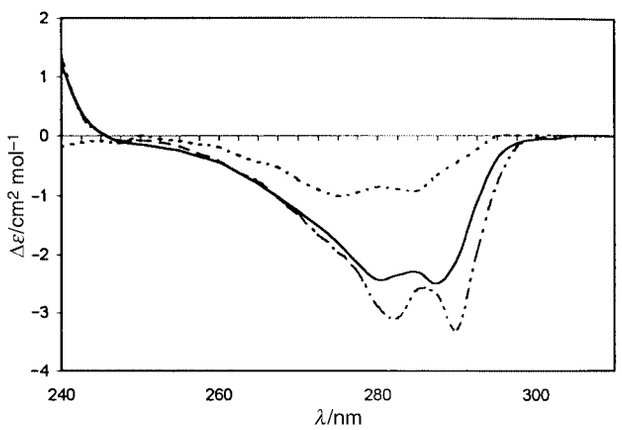


Fig. 5 $^1B_{2u}$ (α) band CE of compound **14** in acetonitrile (– – –) and **12b** in acetonitrile (——) and in hexane (– – ——– –).

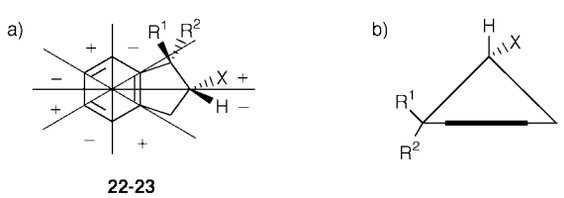
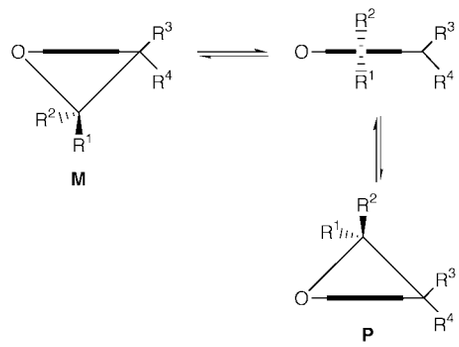


Fig. 6 Projections perpendicular to (a) and along (b) the long axis of the benzene ring. P-helicity of the envelope conformation leads to negative Cotton effects of the α band CE of **22** (X = NH_3^+, R^1 = OH, R^2 = H) and **23** (X = NH_3^+, R^1 = H, R^2 = OH).

(α band) transition of **12a** reflects the M-helicity of its heteroring.

Since the plane of the benzene ring itself is not a nodal plane, contributions have the same signs above and below this plane. Therefore, epimerization at the benzylic carbon atom (Hα or Hβ at C-3) or at both chiral centers does not change the sign of the Cotton effect, as long as the chirality of the envelope conformation does not change. If both **12a** and **12b** adopted the chair conformation of ring A of the cholestane skeleton, the helicity of both heterorings would be M and their Cotton effect would have the same sign, but **12b** turns over P-helicity as C-4 moves upward flipping ring A into a distorted chair (Scheme 5). This is in agreement with the coupling constants measured between H-4α, H-4β and H-3 in d_{12}-cyclohexane ($J_{4\alpha,3}$ 1.0 Hz, $J_{4\beta,3}$ 7.0 Hz). In addition, $J_{1\alpha,2}$ was found to be 10.5 Hz which unambiguously shows that H-2 is *axially* oriented. The difference in the value of $J_{2,3}$ of **12a** and **12b** (6.5 and 7.9 Hz, respectively) is mostly due to the different degree of distortion of ring A.

In the CD spectrum of **14** four Cotton effects were observed in acetonitrile, of which the band with negative sign at the longest wavelength could be unequivocally assigned to the $^1B_{2u}$ transition of the 4*H*-benzopyran chromophore. Since its hetero



Scheme 5 Conformations of heteroring of **12a** (R^1 = Hα, R^2 = C-1, R^3 = C-4, R^4 = Hα), **12b** (R^1 = C-1, R^2 = Hβ, R^3 = Hβ, R^4 = C-4).

ring is fixed in a half-chair conformation with P-helicity (torsion angle is defined by C-17, C-16, C-24, C-1), any conformational change of the heteroring is totally impossible because of the annulation with ring A of the steroid skeleton. The negative sign of the α band CE can be predicted according to our former rule,[7b] although a substituent at the benzylic position (C-16) is present. In this case the heteroring cannot adopt a sofa conformation unlike the 4-substituted flavanone derivatives,[5] and therefore the contribution of the chiral third sphere must be smaller than the second as usually expected, and this determines the sign of the α band CD.

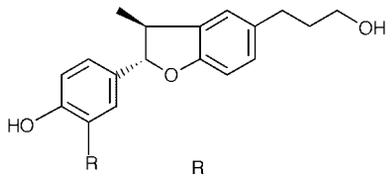
Conclusion

The synthesis and the study of the chiroptical properties of 2,3-dihydro-1-benzofuran and 4*H*-benzopyran derivatives with rigid and known conformation were performed. It was found that the same helicity rule is valid for both chromophores: the P/M helicity of the heteroring leads to a negative/positive CD within the $^1B_{2u}$ (α) band. Considering this helicity rule, the 2*R*,3*R* configuration for norneolignans **24**–**26** isolated from *Krameria cystisoides*[2d] must be revised (Chart 1).

Since the CD spectra of **24** and **25** published by Achenbach and co-workers[2d] exhibit a negative Cotton effect at 281 nm, which corresponds well with the predicted $^1B_{2u}$ (α band) transition of the dihydro-1-benzofuran chromophore, their heterorings should adopt P-helicity according to the above-mentioned helicity rule. Taking into account that the substituents attached to the heteroring at C-2 and C-3 are *equatorially* oriented in both cases ($J_{2,3}$ 8.9 and 9.3 Hz), their absolute configurations are 2*S*,3*S*. As **26** was chemically correlated with **24**, its absolute configuration must also be the opposite from that assigned previously.

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed in the



R
24 H
25 OMe

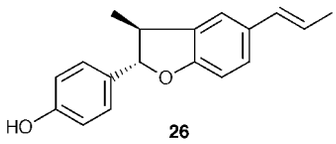


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Chart 1 The revised absolute configuration of norneolignans based on the helicity rule set up above.

Lajos Kossuth University microanalysis laboratory. Infrared spectra were recorded on a Perkin-Elmer 16PC FT-IR spectrometer. Optical rotations were measured with a Carl Zeiss (Jena) Polamat-A polarimeter, 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-NMR 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. The notation "aromatics" in the NMR assignment refers to the aryl protons or carbons of the benzyl group. Flash chromatography was carried out using Merck-Kieselgel 60 (0.040–0.063 mm). TLC was visualized with UV light (254 nm) and with phosphomolybdenic acid hydrate in methanol. Electron ionisation mass spectra were obtained on a VG 7035 spectrometer at 70 eV. For work-up the solutions were dried over $MgSO_4$, and the solvents were evaporated in vacuum. All the reagents were purchased from Sigma or Aldrich.

3β-(2-Benzyloxyphenyl)-5α-cholestan-3α-ol 3a

Mg (3.90 g, 0.16 mol) in dry THF was activated with 1,2-dibromoethane (0.2 ml). After the cessation of evolution of ethylene, 2-benzyloxybromobenzene (10.0 g, 38.00 mmol, vacuum-distilled) in dry THF was added dropwise to the solution under an argon atmosphere. It was stirred for 30 minutes and then 5α-cholestan-3-one (**2**) (10.0 g, 25.86 mmol) in THF was added. After one hour the reaction mixture was poured into a saturated NH_4Cl solution and extracted with ether. The combined organic extracts were dried, and evaporation of the solvent resulted in a yellow oil which was purified by silica gel column chromatography (1:2 hexane–toluene) to afford **3a** (4.40 g, 30%) and **3b** (4.26 g, 29%). Compound **3a** could be crystallized from methanol–acetone, 3:1. Mp 79–81 °C, $[\alpha]_D^{20}$ = +29.2 (*c* 0.13 in chloroform) (Found: C, 84.1; H, 10.2; $C_{40}H_{58}O_2$ requires C, 84.2; H, 10.2%); δ_H(400 MHz, $CDCl_3$) 0.64 (3H, s, H-18), 0.71 (3H, s H-19), 0.8–1.9 (38H, m, steroid skeleton), 1.92 (1H, dd, *J* 13.1 and 12.5, H-4β), 2.03 (1H, m, *J* 13.5, 13.0 and 4.8, H-2β), 3.60 (1H, s, OH), 5.12 (2H, s, OCH_2), 6.9–7.0 (2H, m, Ar-H), 7.1–7.2 (1H, m, Ar-H), 7.3–7.4 (6H, m, Ar-H); δ_C(100 MHz, $CDCl_3$) 11.07 and 11.84 (C-18 and C-19), 18.41 (C-21), 20.72 (C-11), 22.29 and 22.56 (C-26 and C-27), 23.56 (C-23), 23.94 (C-15), 27.75 (C-25), 27.99 (C-6), 28.33 (C-16), 31.80 (C-1), 32.25 (C-2), 33.73 (C-7), 35.28 (C-10), 35.29 (C-8), 35.54 (C-20), 35.91 (C-22), 38.78 (C-12), 39.26 (C-24), 39.82 (C-4), 40.38 (C-5), 42.35 (C-13), 53.82 (C-9), 55.95 (C-14), 56.30 (C-17), 70.28 (OCH_2), 75.30 (C-3), 112.16 (C-3′), 120.95 (C-5′), 125.56 (C-4′), 128.03 (C-6′), 127.51, 127.64, 128.53 and 136.01 (aromatics), 136.01 (C-1′), 156.07 (C-2′).

3-(2-Benzyloxyphenyl)cholest-Δ^2-ene 4

Compound **3a** (11.9 g, 20.84 mmol) and toluene-*p*-sulfonic acid monohydrate (5.2 g, 27.33 mmol) were stirred in dry toluene for 24 h at room temperature and then poured into water. After extraction with toluene and evaporation of the solvent, the crude product was crystallized from acetone to give white crystals of **4** (5.6 g, 48%). Mp 110–112 °C, $[\alpha]_D^{20}$ = +56.4 (*c* 0.12 in chloroform) (Found: C, 86.8; H, 10.1; $C_{40}H_{56}O$ requires C, 86.9; H, 10.2%); ν_{max} (KBr)/cm^{-1} 3026, 2930, 2866, 2850, 1598, 1578, 1498; δ_H(400 MHz, $CDCl_3$) 0.65 (3H, s, H-18), 0.70 (1H, m, H-9), 0.82 (3H, s, H-19), 0.86 (6H, d, *J* 6.8, H-26 and H-27), 0.88 (1H, m, H-7), 0.92 (3-H, d, *J* 6.3, H-21), 0.98 (1H, m, H-17), 0.98 (1H, m, H-22), 1.00 (1H, m, H-15), 1.05 (1H, m, H-14), 1.10 (1H, m, H-12), 1.10 (1H, m, H-23), 1.08–1.12 (2H, m, H-24), 1.18 (1H, m, H-16), 1.20 (1H, m, H-6), 1.30 (1H, m, H-20), 1.30 (1H, m, H-22), 1.30 (1H, m, H-23), 1.32 (1H, m, H-11), 1.32 (1H, m, H-8), 1.40 (1H, m, H-6), 1.44 (1H, m, H-5), 1.44 (1H, m, H-11), 1.47 (1H, m, H-25), 1.57 (1H, m, H-15), 1.65 (1H, m, H-7), 1.78 (1H, m, H-16), 1.87 (1H, m, *J* 17, 2.5 and 2.5, 2.0, H-1), 1.99 (1H, m, *J* 12.5, 3.0 and 3.0, H-12), 2.10 (1H, m, *J* 17.0 and 5.5, H-1), 2.18 (2H, m, H-4), 5.10 (2H, s, OCH_2), 5.68 (1H, m, *J* 5.5 and 2.5, H-2), 6.90 (1H, m, *J* 7.8 and 1.1, H-3′), 6.91 (1H, m, *J* 7.2, 7.0 and 1.0, H-5′), 7.13 (1H, m, *J* 7.2 and 1.9, H-6′), 7.17 (1H, m, *J* 7.8, 7.0 and 1.9, H-4′), 7.27–7.43 (5H, m, aromatics); δ_C(100 MHz, $CDCl_3$) 11.92 (C-18), 12.06 (C-19), 18.75 (C-21), 21.13 (C-11), 22.61 (C-26), 22.87 (C-27), 23.88 (C-23), 24.28 (C-15), 28.06 (C-25), 28.29 (C-16), 28.75 (C-6), 31.91 (C-7), 33.84 (C-4), 34.27 (C-10), 35.71 (C-8), 35.85 (C-20), 36.23 (C-22), 39.56 (H-24), 40.10 (C-12), 40.52 (C-1), 41.91 (C-5), 42.56 (C-13), 54.03 (C-9), 56.32 (C-14), 56.57 (C-17), 70.36 (OCH_2), 112.62 (C-3′), 121.00 (C-5′), 125.19 (C-2), 127.15 (C-6′), 127.63 (C-4′), 127.66, 128.38 and 129.63 (aromatics), 134.10 (C-3), 135.87 (aromatics), 137.45 (C-1′), 155.93 (C-2′); *m*/*z* (EI) 461 (46%), 173 (16), 91 (100).

3β-(2-Benzyloxyphenyl)-2,3-epoxy-5α-cholestane 5a

To a solution of **4** (2.56 g, 4.63 mmol) in dichloromethane (50 ml, distilled from $KMnO_4$) was added *m*-chloroperbenzoic acid (1.60 g, 9.27 mmol) at room temperature. The precipitation of *m*-chlorobenzoic acid showed the progress of the reaction. After two hours stirring, the reaction mixture was washed with $NaHCO_3$ solution, and evaporation of the solvent gave a yellow oil which crystallized slowly. Recrystallization from 2:1 acetone–methanol furnished **5a** as white crystals (1.28 g, 48%). Mp 156–157 °C, $[\alpha]_D^{20}$ = +49.5 (*c* 0.12 in chloroform) (Found: C, 84.4, H, 9.9; $C_{40}H_{56}O_2$ requires C, 84.4; H; 9.9%); δ_H(400 MHz, $CDCl_3$) 0.61 (3H, s, H-18), 0.92 (3H, s, H-19), 0.8–2.0 (38H, m, steroid skeleton), 3.11 (1H, d, *J* 5.4, H-2), 5.06 and 5.12 (2H, 2 × d, *J* 11.8, OCH_2), 6.86 (1H, dd, *J* 7.7, 1.2, H-3′), 6.92 (1H, m, *J* 7.6, 7.0, 1.2, H-5′), 7.18 (1H, m, *J* 7.7, 7.0, 1.3, H-4′), 7.6 (1H, overlapped multiplet, H-6′), 7.6–7.8 (5H, m, aromatics); δ_C(100 MHz, $CDCl_3$) 11.97 and 12.52 (C-18 and C-19), 18.67 (C-21), 20.93 (C-11), 22.57 and 22.83 (C-26 and C-27), 23.81 (C-23), 24.19 (C-15), 28.02, 28.18, 28.20 (C-25, C-16, C-6), 31.71 (C-7), 33.52 and 33.64 (C-10 and C-4), 35.61 (C-20), 35.80 (C-8), 36.15 (C-22), 37.62 (C-5), 39.03 (C-1), 39.52 (C-24), 39.92 (C-12), 42.42 (C-13), 53.96 (C-9), 56.18 (C-14), 56.33 (C-17), 58.85 (C-2), 60.28 (C-3), 70.21 (OCH_2), 111.39 (C-3′), 120.74 (C-5′), 128.01 and 128.42 (C-4′ and C-6′), 128.05–128.52 (aromatics), 136.67 (C-1′), 155.62 (C-2′).

3α-(2-Benzyloxyphenyl)-5α-cholestan-2-one 6a

BF_3·OEt_2 (0.4 ml) was added at 0 °C to **5a** (5.17 g, 9.08 mmol) dissolved in dichloromethane (50 ml) and stirred for 50 minutes. The mixture was poured into water and washed with $NaHCO_3$ solution. The organic layer was dried and evaporated to afford 5.07 g crude product whose purification by flash chromatography (toluene) gave **6a** as a yellow syrup (4.44 g, 86%); δ_H(400 MHz, $CDCl_3$) 0.65 (3H, s, H-18), 0.86 (3H, s, H-19), 0.86–2.00 (36H, m, steroid skeleton), 2.07 (1H, d, *J* 15.3, H-1β), 2.42 (1H,

d, *J* 15.3, H-1α), 3.88 (1H, dd, *J* 2.0 and 8.0, H-3), 5.02 (2H, s, OCH_2), 6.8–6.9 (2H, m, H-3′ and H-5′), 7.3–7.45 (7H, m, H-4′, H-6′ and aromatics); δ_C(100 MHz, $CDCl_3$) 11.96 and 13.18 (C-18 and C-19), 18.64 (C-21), 21.02 (C-11), 22.56 and 22.83 (C-26 and C-27), 23.86 (C-23), 24.19 (C-15), 28.00, 28.13, 28.22 (C-25, C-16, C-6), 31.52 (C-7), 34.27 (C-10), 34.85 and 35.79 (C-8 and C-20), 36.15 (C-22), 39.24–39.76 (C-4, C-12 and C-24), 41.16 (C-5), 42.46 (C-13), 49.17 (C-3), 53.65 (C-1), 53.82 (C-9), 56.25 (C-14), 56.27 (C-17), 70.23 (OCH_2), 112.09 (C-3′), 120.73 (C-5′), 127.9 and 128.0 (C-4′ and C-6′), 127.81–128.6 (aromatics), 136.68 (C-1′), 155.62 (C-2′), 213.21 (C-2).

3β-(2-Benzyloxyphenyl)-5α-cholestan-2-one 6b

Compound **6a** (4.44 g, 7.80 mmol) was dissolved in MeOH–CH_2Cl_2 (1:1, 100 ml), the pH was adjusted to 9–10 with a methanolic NaOMe solution, and the mixture was refluxed for 8 hours. The reaction mixture was acidified with 5% hydrochloric acid solution and extracted with dichloromethane. The organic layer was washed with aqueous $NaHCO_3$ and dried. Evaporation of the solvent yielded 4.3 g of a white crystalline solid whose recrystallization from 2:1 acetone–methanol gave **6b** (3.24 g, 73%). Mp 143–144 °C, $[\alpha]_D^{20} = +20.0$ (*c* 0.20 in chloroform) (Found: C, 84.5; H, 9.9; $C_{40}H_{56}O_2$ requires C, 84.4; H, 9.9%); λ_{max} (CH_3CN)/nm 221.8sh ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 0.63), 271.6 (0.17), 279.6 (0.12); CD in CH_3CN nm ($\Delta\varepsilon$) 203.60 (+1.89), 210.80 (+1.66), 225.20 (+2.64), 272.00 (+0.71), 278.20 (+0.66), 301.20 (+0.71); ν_{max} (KBr)/cm^{-1} 2932, 2866, 1714, 1600, 1586, 1540; δ_H(400 MHz, $CDCl_3$) 0.58 (3H, s, H-18), 0.64 (3H, s, H-19), 0.70–2.00 (36H, m, steroid skeleton), 2.02 and 2.43 [(1H, d, *J* 3.5) and (1H, d, *J* 13.5) H-1α and H-1β], 3.84 (1H, dd, *J* 12.8 and 6.3, H-3), 4.94 (2H, s, OCH_2), 6.8–6.9 (2H, m, H-3′, H-5′), 7.0–7.6 (7H, m, H-4′, H-6′ and aromatics); δ_C(100 MHz, $CDCl_3$) 12.00 and 12.49 (C-18 and C-19), 18.64 (C-21), 21.05 (C-11), 22.55 and 22.81 (C-26 and C-27), 23.81 (C-23), 24.19 (C-15), 27.74, 28.21 and 27.99 (C-25, C-16 and C-6), 31.70 (C-7), 34.79 (C-8), 35.71 (C-10), 35.76 (C-20), 36.13 (C-22), 39.48, 39.77 and 41.10 (C-4, C-12 and C-24), 42.48 (C-13), 45.86 (C-5), 51.88 (C-3), 54.12 (C-1), 53.88 (C-9), 56.19 (C-14), 56.32 (C-17), 70.34 (OCH_2), 112.03 (C-3′), 120.83 (C-5′), 127.79 and 127.99 (C-4′ and C-6′), 127.6–129.28 (aromatics), 137.10 (C-1′), 156.34 (C-2′), 209.55 (C-2); *m/z* (EI) 568 (M, 11%), 553 (12), 550 (6), 477 (100), 460 (52).

3β-(2-Benzyloxyphenyl)-5α-cholestan-2β-ol 7

LAH (248 mg, 6.53 mmol) was added to a well-stirred solution of **6b** (805 mg, 1.41 mmol) in dry THF (30 ml). After 1.5 hours, ethyl acetate was added to decompose the excess of LAH. The mixture was then extracted with dichloromethane, the organic layer was dried, and the solvent evaporated. The resulting brownish oil was purified by flash chromatography (12:1 hexane–ethyl acetate) to furnish **7** (576 mg, 71%) and **8** (47 mg, 5%).

7: mp 124–125 °C, $[\alpha]_D^{20} = +70.3$ (*c* 0.10 in chloroform) (Found: C, 84.08; H, 10.1; $C_{40}H_{58}O_2$ requires C, 84.1; H, 10.2%); δ_H(400 MHz, $CDCl_3$) 0.59 (3H, s, H-18), 0.96 (3H, s, H-19), 0.80–1.93 (37H, m, steroid skeleton and OH), 1.31 (1H, dd, *J* 14.8 and 3.0, H-1α), 2.00 (1H, dd, *J* 14.8 and 2.5, H-1β), 3.33 (1H, m, *J* 13.0, 3.0 and 3.0, H-3), 4.22 (1H, m, *J* 3.0, 3.0 and 2.5, H-2), 4.98 and 5.03 (2H, 2 × d, *J* 11.7, OCH_2), 6.82 (1H, dd, *J* 7.8 and 1.2, H-3′), 6.88 (1H, m, *J* 7.6, 7.0 and 1.2, H-5′), 7.20 (1H, m, *J* 7.8, 7.0 and 1.3, H-4′), 7.39 (1H, dd, *J* 7.6 and 1.3, H-6′), 7.62 (5H, m, aromatics); δ_C(100 MHz, $CDCl_3$) 12.13 and 14.65 (C-18 and C-19), 18.67 (C-21), 21.13 (C-11), 22.57 and 22.83 (C-26 and C-27), 23.85 (C-23), 24.20 (C-15), 27.95 (C-4), 28.02 (C-25), 28.26 (C-16), 28.67 (C-6), 32.13 (C-7), 34.96 (C-8), 35.81 (C-20), 36.19 (C-22), 35.81 (C-10), 39.52 (C-24), 40.13 (C-12), 42.47 (C-3), 42.67 (C-13), 44.48 (C-1), 47.91 (C-5), 55.40 (C-9), 56.31 (C-14), 56.61 (C-17), 69.41 (C-2), 69.81 (OCH_2), 111.68 (C-3′), 120.84 (C-5′), 127.47 (C-4′), 127.80 (C-6′), 131.48 (C-1′), 156.12 (C-2′), 126.98, 128.54, 128.59 and 137.20 (aromatics).

3β-(2-Hydroxyphenyl)-5α-cholestan-2β-ol 11

Compound **7** (991 mg, 1.73 mmol) in dry THF was hydrogenated over 10% Pd/C (690 mg) at room temperature. After 24 hours, the reaction mixture was diluted with dichloromethane and the catalyst was filtered off. The solvent was evaporated and the crude product was crystallized from acetone to give **11** as white crystals (281 mg, 81%). Mp 217–218 °C, $[\alpha]_D^{20} = +55.4$ (*c* 0.14 in chloroform) (Found: C, 82.5; H, 10.9; $C_{33}H_{52}O_2$ requires C, 82.4; H, 10.9%); δ_H(400 MHz, $CDCl_3$) 0.63 (3H, s, H-18), 0.88 (3H, s, H-19), 0.90–1.90 (36H, m, steroid skeleton and OH), 1.37 (1H, dd, *J* 15.0 and 3.0, H-1α), 2.01 (1H, dd, *J* 15.0 and 2.5, H-1β), 2.34 (1H, m, *J* 13.0, 13.5 and 11.0, H-4β), 2.82 (1H, m, *J* 13.0, 3.0 and 3.0, H-3), 4.38 (1H, m, *J* 3.0, 3.0 and 2.5, H-2), 6.83 (1H, m, *J* 7.8, 7.0 and 1.2, H-5′), 6.86 (1H, dd, *J* 7.8 and 1.2, H-3′), 7.05 (1H, dd, *J* 7.7 and 1.3, H-6′), 7.13 (1H, m, *J* 7.8, 7.0 and 1.3, H-4′), 8.3 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) 12.14 and 15.21 (C-18 and C-19), 18.67 (C-21), 21.15 (C-11), 22.57 and 22.82 (C-26 and C-27), 23.83 (C-32), 24.16 (C-15), 28.02 (C-25), 28.10 (C-16), 28.23 (C-4), 28.38 (C-6), 31.99 (C-7), 34.89 (C-8), 35.17 (C-22), 35.64 (C-10), 35.79 (C-20), 39.51 (C-24), 40.08 (C-12), 42.66 (C-13), 46.09 (C-1), 48.35 (C-5), 49.60 (C-3), 55.33 (C-9), 56.28 (C-14), 56.47 (C-17), 73.05 (C-2), 117.85 (C-3′), 120.36 (C-5′), 128.21 (C-4′), 130.06 (C-1′), 131.06 (C-6′), 155.23 (C-2′).

8-[(1*R*)-1,5-Dimethylhexyl]-9,13-dimethyl-(1*R*,4*S*,5*S*,8*R*,9*R*,12*S*,13*R*,16*R*)-23-oxahexacyclo[14.7.1.0^{1,13}.0^{4,12}.0^{5,9}.0^{17,22}]-tetracosa-17(22),18,20-triene 14

$BF_3{\cdot}OEt_2$ (2 ml) was added to a dichloromethane solution of **11** (104 mg, 0.21 mmol) and the mixture was stirred for two days. After usual work-up, the crude product was purified by preparative TLC with hexane to yield **14** (28 mg, 28%), **16** (17 mg, 17%) and **12a** (8 mg, 8%).

14: mp 124–125 °C, $[\alpha]_D^{20} = +62.0$ (*c* 0.22 in chloroform) (Found: C, 85.6; H, 10.8; $C_{33}H_{50}O$ requires C, 85.6; H, 10.9%); λ_{max} (CH_3CN)/nm 200.80 ($\varepsilon \times 10^{-4}/M^{-1}$ cm^{-1} 3.04), 227.00 (0.52), 278.00 (1.17), 283.80 (0.16); CD in CH_3CN nm ($\Delta\varepsilon$) 204.20 (+8.58), 227.40 (−4.69), 277.20 (−1.01), 284.00 (−0.93); δ_H(400 MHz, $CDCl_3$) 0.67 (3H, s, C(9) Me), 0.86 (3H, d, *J* 6.8, H-6 acyclic), 0.87 (3H, d, *J* 6.8, C(5) Me), 0.91 (3H, d, *J* 6.3, C(1) Me), 0.98 (1H, m, H-2 acyclic), 0.99 (3H, s, C(13) Me), 1.03 (1H, m, H-8), 1.06 (1H, m, H-6), 1.08 (1H, m, H-5), 1.08 (1H, m, H-7), 1.09 (1H, m, *J* 15.5, 14.0 and 5.3, H-14α) 1.05–1.12 (2H, m, H-4 acyclic), 1.13 (1H, m, H-3 acyclic), 1.14 (1H, m, H-10), 1.24 (1H, m, H-11), 1.25 (1H, m, H-3), 1.32 (1H, m, H-3 acyclic), 1.34 (1H, m, H-2 acyclic), 1.36 (1H, m, H-1 acyclic), 1.40 (1H, m, H-15), 1.41 (1H, m, H-24), 1.42 (1H, m, H-4), 1.42 (1H, m, H-2), 1.43 (1H, m, H-14β), 1.43 (1H, m, H-12), 1.46 (1H, m, H-11), 1.50 (1H, m, H-5 acyclic), 1.55 (1H, m, H-6), 1.61 (1H, m, H-7), 1.78 (1H, m, *J* 13.3, 3.2 and 3.0, H-15), 1.82 (1H, m, H-3), 2.01 (1H, m, *J* 12.3, 3.1 and 3.0, H-10), 2.06 (1H, m, *J* 13.3, 13.1 and 5.6, H-2), 2.53 (1H, m, *J* 13.6 and 3.2, H-24), 2.97 (1H, m, *J* 3.4, 3.2, 3.0 and 3.0, H-16), 6.78 (1H, m, *J* 7.2, 6.9 and 1.3, H-19), 6.79 (1H, m, *J* 8.1 and 1.3, H-21), 6.95 (1H, m, *J* 7.2 and 1.6, H-18), 7.07 (1H, m, *J* 8.1, 6.9 and 1.6, H-20); δ_C(400 MHz, $CDCl_3$), 12.11 [C(9) Me], 17.65 [C(13) Me], 18.65 [C(1) Me], 21.35 (C-11), 22.58 (C-6 acyclic), 22.84 [C(5) Me], 23.83 (C-3 acyclic), 24.20 (C-6), 27.71 (C-14), 28.03 (C-5 acyclic), 28.23 (C-7), 28.32 (C-3), 28.88 (C-15), 30.47 (C-24), 32.61 (C-16), 34.58 (C-2), 34.93 (C-4), 35.78 (C-1 acyclic), 36.16 (C-2 acyclic), 39.52 (C-4 acyclic), 40.15 (C-10), 42.67 (C-9), 42.68 (C-13), 43.66 (C-12), 56.22 (C-5), 56.66 (C-8), 79.53 (C-1), 114.95 (C-21), 118.93 (C-19), 126.82 (C-17), 127.30 (C-20), 127.97 (C-18), 156.67 (C-22); *m/z* (EI) 462 (M, 8%), 256 (10), 43 (100).

2β,3β-Dihydro-1-benzofuro[2′,3′:2,3]-5α-cholest-2-ene 12b, and 2α,3α-dihydro-1-benzofuro[2′,3′:2,3]-5α-cholest-2-ene 12a

Compound **16** (55 mg, 0.12 mmol) in dry THF was hydrogenated over 10% Pd/C (220 mg) at 16 bar pressure and room temperature. Usual work-up gave **12b** (44 mg, 79%) and **12a** (6 mg, 11%).

12b: mp 115–116 °C, $[\alpha]_D^{20} = +85.44$ (*c* 0.20, in chloroform) (Found: C, 85.7; H, 10.8; $C_{33}H_{50}O$ requires C, 85.6; H, 10.9%); λ_{max} (*n*-hexane)/nm 282.2 ($\varepsilon \times 10^{-3}/M^{-1}$ cm^{-1} 3.18), 288.8 (3.08); CD in *n*-hexane nm ($\Delta\varepsilon$) 282 (−3.1), 289 (−3.3), in CH_3CN 281 (−2.4), 287 (−2.5); δ_H(400 MHz, $CDCl_3$) 0.63 (3H, s, H-18), 0.81 (3H, s, H-19), 0.85–2.0 (33H, m, steroid skeleton), 1.12 (1H, m, H-5), 1.78 (1H, m, H-4β), 1.84 (1-H, m, H-1α), 1.98 (1H, m, *J* 14.5, 3.8 and 1.0, H-4α), 2.06 (1H, dd, *J* 13.0 and 6.5, H-1β), 3.56 (1H, m, *J* 8.0, 7.5 and 1.0, H-3), 4.92 (1H, m, *J* 10.5, 8.0 and 6.5, H-2), 6.78 (1H, dd, *J* 6.8 and 1.2, H-7′), 6.90 (1H, m, *J* 6.8, 7.0 and 1.3, H-5′), 7.12 (1H, dd, *J* 7.0 and 1.3, H-4′), 7.13 (1H, m, *J* 7.0, 7.0 and 1.2, H-6′); δ_C(100 MHz, $CDCl_3$) 11.61 and 11.97 (C-18 and C-19), 18.62 (C-21), 20.77 (C-11), 22.54 and 22.81 (C-26 and C-27), 23.80 (C-23), 24.18 (C-15), 27.99 (C-25), 28.20 (C-16), 28.29 (C-6), 28.45 (C-4), 31.56 (C-7), 34.86 (C-8), 35.55 (C-10), 35.77 (C-20), 36.11 (C-22), 39.49 (C-24), 39.84 (C-12), 39.99 (C-1), 40.12 (C-5), 40.29 (C-3), 40.39 (C-13), 53.29 (C-9), 56.12 (C-14), 56.36 (C-17), 81.83 (C-2), 110.28 (C-7′), 120.32 (C-5′), 123.05 (C-6′), 127.77 (C-4′), 130.61 (C-4′a), 159.02 (C-7′a).

Relevant ^{1}H data in d_{12}-cyclohexane: 0.62 (3H, s, H-18), 0.78 (3H, s, H-19), 3.39 (1H, m, *J* 7.9, 7.0 and1.0, H-3), 4.70 (1H, m, *J* 10.5, 7.9 and 6.9, H-2); *m*/*z* (EI) 462 (M, 32%), 460 (43), 144 (95), 43 (100).

12a: mp 144–145 °C, $[\alpha]_D^{20} = -7.88$ (*c* 0.16 in chloroform) (Found: C, 85.7; H, 10.9; $C_{33}H_{50}O$ requires C, 85.6; H, 10.9%); λ_{max} (*n*-hexane)/nm 279.4 ($\varepsilon \times 10^{-3}/M^{-1}$ cm^{-1} 2.36), 285.8 (2.13); CD in CH_3CN nm ($\Delta\varepsilon$) 199.60 (−10.13), 214.20 (+1.09), 226.80 (+2.42), 279.60 (+0.32) in *n*-hexane 279.5 (+0.89); δ_H(400 MHz, $CDCl_3$) 0.66 (3H, s, H-18), 0.91 (3H, s, H-19), 1.0–2.04 (36H, m, steroid skeleton), 1.36 (1H, m, H-1α), 2.43 (1H, dd, *J* 15.2 and 1.5, H-1β), 3.04 (1H, m, *J* 10.7, 7.0 and 6.5, H-3), 4.65 (1H, m, *J* 6.5, 5.5 and 1.5, H-2), 6.78–6.85 (2H, m, H-7′ and H-5′), 7.05–7.20 (2H, m, H-6′ and H-4′); δ_C(100 MHz, $CDCl_3$) 12.03 and 12.92 (C-18 and C-19), 18.67 (C-21), 20.86 (C-11), 22.57 and 22.82 (C-26 and C-27), 23.82 (C-23), 24.21 (C-15), 28.02, 28.20 and 28.61 (C-25, C-16 and C-6), 31.94 (C-7), 34.01 (C-4), 34.95 (C-10), 35.00 (C-8), 35.80 (C-20), 36.18 (C-22), 39.52, 40.01 and 40.03 (C-1, C-12 and C-24), 40.77 (C-3), 42.50 (C-13), 43.39 (C-5), 54.93 (C-9), 56.27 (C-14), 56.54 (C-17), 83.39 (C-2), 109.89 (C-7′), 120.37 (C-5′), 123.75 and 127.67 (C-6′ and C-4′), 134.96 (C-4′a), 158.78 (C-7′a).

Relevant ^{1}H data in d_{12}-cyclohexane: 0.62 (3H, s, H-18), 0.81 (3H, s, H-19), 2.36 (1H, dd, *J* 15.1 and 1.4, H-1β), 2.82 (1H, m, *J* 10.7, 7.0 and 6.5, H-3), 4.44 (1H, m, *J* 6.5, 5.0 and 1.5, H-2).

3-(2-Hydroxyphenyl)cholest-Δ^2-ene 15

$BF_3{\cdot}OEt_2$ (2 ml) was added to a dry dichloromethane solution of **19** (101 mg, 0.21 mmol) and stirred for 24 h. After usual work-up, the crude product was purified by preparative TLC in hexane to yield **14** (19 mg, 19%), **15** (18 mg, 18%), **12a** (11 mg, 11%) and **16** (10 mg, 10%). **15**: (Found: C, 85.6; H, 10.7; $C_{33}H_{50}O$ requires C, 85.6; H, 10.9%); δ_H(200 MHz, $CDCl_3$) 0.7 (3H, s, H-18), 0.8 (3H, s, H-19), 0.9–2.3 (21H, m, steroid skeleton), 5.6 (1H, s, OH), 5.7 (1H, m, H-2), 6.8–7.0 (2H, m, Ar-H), 7.0–7.1 (2H, m, Ar-H).

1-Benzofuro[2′,3′:2,3]-5α-cholest-2-ene 16

$BF_3{\cdot}OEt_2$ (2.5 ml) was added to a dichloromethane solution of **6b** (807 mg, 1.42 mmol) at room temperature and was stirred for 8 hours. Usual work-up gave a brown oil, which was purified by flash chromatography (hexane) to yield white crystalline **16** (128 mg, 19.5%). Mp 130–132 °C, $[\alpha]_D^{20} = +60.08$ (*c* 0.24 in chloroform) (Found: C, 86.0; H 10.4; $C_{33}H_{48}O$ requires C, 86.0; H, 10.5%); ν_{max} (KBr)/cm^{-1} 2928, 2868, 1644, 1452; δ_H(400 MHz, $CDCl_3$) 0.68 and 0.83 [(3H, s and 3H, s) H-18 and H-19], 0.86 (3H, d, *J* 6.8, H-26), 0.87 (3H, d, *J* 6.8, H-27), 0.91 (3H, d, *J* 6.3, H-21), 0.92 (1H, m, H-9), 0.95 (1H, m, H-7), 1.00 (1H, m, H-22), 1.02 (1H, m, H-15), 1.03 (1H, m, H-17), 1.05–1.15 (2H, m, H-24), 1.08 (1H, m, H-14), 1.08 (1H, m, H-23), 1.18 (1H, m, H-12), 1.20 (1H, m, H-11), 1.20 (1H, m, H-16), 1.30 (1H, m, H-23), 1.35 (1H, m, H-22), 1.35 (1H, m, H-8), 1.40 (1H, m, H-20), 1.40 (1H, m, H-6), 1.50 (1H, m, H-25), 1.50 (1H, m, H-11), 1.52 (1H, m, H-5), 1.58 (1H, m, H-15), 1.6 (1H, m, H-6), 1.75 (1H, m, H-7), 1.80 (1H, m, H-16), 1.99 (1H, m, *J* 12.4, 3.0 and 3.0, H-12), 2.23 (1H, m, *J* 16.0, 10.0, 2.5 and 2.5, H-4β), 2.39 (1H, m, *J* 16.5, 2.5 and 1.5, H-1α), 2.56 (1H, m, *J* 16.0, 5.0 and 1.5, H-4α), 2.69 (1H, m, *J* 16.5 and 1.5, H-1β), 7.16 (1H, m, H-6′), 7.16 (1H, m, H-4′), 7.36 (1H, m, H-7′), 7.36 (1H, m, H-5′); δ_C(100 MHz, $CDCl_3$) 12.02 and 12.16 (C-18 and C-19), 18.72 (C-21), 21.25 (C-11), 22.61 (C-26), 22.86 (C-27), 23.88 (C-23), 24.30 (C-15), 25.46 (C-4), 28.05 (C-25), 28.28 (C-16), 28.90 (C-6), 31.79 (C-7), 35.55 (C-8), 35.84 (C-20), 36.20 (C-22), 37.26 (C-10), 37.76 (C-1), 39.55 (C-24), 39.95 (C-12), 42.32 (C-5), 42.52 (C-13), 53.94 (C-9), 56.29 (C-14), 56.37 (C-17), 110.79 (C-7′), 111.20 (C-3), 118.40 (C-5′), 122.09 (C-6′), 122.73 (C-4′), 128.62 (C-4a′), 154.08 (C-2), 154.60 (C-7a′); *m*/*z* (EI) 460 (M, 70%), 144 (100).

3α-(2-Benzyloxyphenyl)-5α-cholestan-2α-ol 17

LAH (500 mg, 13.17 mmol) was added to **6a** (3.47 g, 6.09 mmol) in dry THF. After 20 minutes, ethyl acetate was added to the mixture to decompose the excess of LAH. The mixture was then extracted with dichloromethane, the extract was dried and evaporated to dryness. Chromatography on silica gel with 1:2 hexane–toluene gave a white crystalline product which was recrystallized from methanol to give pure **17** (1.52 g, 52%). Mp 147–149 °C (Found: C, 84.0; H, 10.2; $C_{40}H_{58}O_2$ requires C, 84.1; H, 10.2%); δ_H(400 MHz, $CDCl_3$) 0.65 (3H, s, H-18), 0.81 (3H, s, H-19), 0.7–2.0 (34H, m, steroid skeleton), 2.22 (1H, d, *J* 4.2, OH), 3.90 (1H, m, *J* 6.3, 6.0 and 1.4, H-3), 4.24 (1H, m, *J* 12.0, 6.3, 5.0 and 4.2, H-2), 5.09 and 5.13 (2H, 2 × d, *J* 11.6, OCH_2), 6.90 (2H, m, H-3′ and H-5′), 7.20 (1H, m, H-4′), 7.30–7.50 (5H, m, aromatics), 7.62 (1H, m, H-6′).

3α-(2-Hydroxyphenyl)-5α-cholestan-2α-ol 19

Compound **17** (360 mg, 0.63 mmol) was hydrogenated in dry THF over 10% Pd/C (300 mg) at room temperature. After stirring for 24 h the mixture was filtered. The solvent was evaporated and the crude product was purified by silica gel chromatography with 8:1 hexane–ethyl acetate to yield **19** (296 mg, 97%). Mp 88–89 °C, $[\alpha]_D^{20} = -12.76$ (*c* 0.10 in chloroform) (Found: C, 82.4; H, 10.8; $C_{33}H_{52}O_2$ requires C, 82.4; H, 10.9%); δ_H(400 MHz, $CDCl_3$) 0.66 (3H, s, H-18), 0.90 (3H, s, H-19), 0.85–1.95 (38H, m, steroid skeleton), 2.08 (1H, br s, OH), 3.56 (1H, m, *J* 5.5, 4.0 and 3.5, H-3), 4.37 (1H, m, *J* 11.9, 6.3 and 4.0, H-2), 6.92 (2H, m, H-3′ and H-5′), 7.16 (1H, m, H-4′), 7.41 (1H, m, H-6′), 8.3 (1H, s, OH); δ_C(100 MHz, $CDCl_3$) 12.16 and 13.32 (C-18 and C-19), 18.69 (C-21), 21.00 (C-11), 22.60 and 22.86 (C-26 and C-27), 23.90 (C-23), 24.18 (C-15), 27.96 (C-6), 28.05 (C-25), 28.28 (C-16), 31.70 (C-4), 31.91 (C-7), 34.87 (C-8), 35.84 (C-20), 36.17 (C-22), 37.50 (C-10), 38.58 (C-3), 39.53 (C-24), 39.91 (C-12), 42.68 (C-13), 42.87 (C-5), 43.39 (C-1), 54.69 (C-9), 56.29 (C-14), 56.37 (C-17), 72.03 (C-2), 117.98 (C-3′), 120.56 (C-5′), 127.92 (C-4′), 128.49 (C-1′), 129.27 (C-6′), 156.19 (C-2′).

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References

1 (*a*) L. J. Porter, in *Flavanoids: Advances and research since 1986*, ed. J. B. Harborne, Chapman and Hall, London, 1994, p. 23; (*b*) P. M. Dewick, in *Flavanoids: Advances and research since 1986*, ed. J. B. Harborne, Chapman and Hall, London, 1994, p. 117; (*c*) E. Middleton Jr. and C. Kandaswami, in *Flavanoids: Advances and research since 1986*, ed. J. B. Harborne, Chapman and Hall, London, 1994, p. 619.

2 (*a*) G. Cardillo, L. Merlini, G. Narini and P. Salvadori, *J. Chem. Soc.*, *Perkin Trans. 1*, 1971, 3967; (*b*) A. Zanarotti, *Heterocycles*, 1982, **19**, 1585; (*c*) F. Abe and T. Yamauchi, *Chem. Pharm. Bull.*, 1986, **34**, 4340; (*d*) H. Achenbach, J. Groß, X. A. Dominguez, G. Cano, J. V. Star, G. Brussolo, G. Munoz, F. Salgado and L. Lopez, *Phytochemistry*, 1987, **26**, 1159; (*e*) N. Kaneda, J. M. Pezzuto, D. D. Soljarto, A. D. Kinghorn and N. R. Farnsworth, *J. Nat. Prod.*, 1991, **54**, 196; (*f*) K. Yoshikawa, H. Kinoshita, Y. Kan and S. Arihara, *Chem. Pharm. Bull.*, 1995, **43**, 578; (*g*) N. Matsudo, H. Sato, Y. Yaoita and M. Kikuchi, *Chem. Pharm. Bull.*, 1996, **44**, 1122; (*h*) Y. Fukuyama, M. Nakahara, H. Minami and M. Kodama, *Chem. Pharm. Bull.*, 1996, **44**, 1418.

3 G. Snatzke, M. Kajtár and F. Snatzke, in *Fundamental Aspects and Recent Developments in ORD and CD*, ed. F. Ciardelli and P. Salvadori, Heyden, London, 1973, p. 148.

4 G. Snatzke and P. C. Ho, *Tetrahedron*, 1971, **27**, 3645.

5 G. Snatzke, F. Snatzke, A. L. Tökés, M. Rákosi and R. Bognár, *Tetrahedron*, 1973, **29**, 909.

6 S. Antus, G. Snatzke and I. Steinke, *Liebigs Ann. Chem.*, 1983, 2247.

7 (*a*) S. Antus, E. Baitz-Gács and G. Snatzke, *Liebigs Ann. Chem.*, 1991, 633; (*b*) S. Antus, E. Baitz-Gács, J. Kajtár, G. Snatzke and A. Tökés, *Liebigs Ann. Chem.*, 1994, 497.

8 (*a*) C. W. Shoppee, *J. Chem. Soc.*, 1948, 1032; (*b*) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, 1956, **12**, 1547.

9 K. N. Dalby, A. J. Kirby and F. Hollfelder, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, **7**, 1269.

10 W. Adam, R. Curci and J. O. Edwards, *Acc. Chem. Res.*, 1989, **22**, 205.

11 W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, 1961, **83**, 4013.

12 S. Antus, E. Baitz-Gács, G. Snatzke and T. S. Tóth, *Chem. Ber.*, 1989, **122**, 1017.

13 K. M. Rupprecht, J. Boger, K. Hoogsten, R. B. Nachbar and J. P. Springer, *J. Org. Chem.*, 1991, **56**, 6180.

14 J. Petruska, *J. Chem. Phys.*, 1961, **34**, 1111.

15 E. Dornhege and G. Snatzke, *Tetrahedron*, 1970, **26**, 3059.

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