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Synthesis of Enantiopure 3-Hydroxymethylchromanes *via* Intramolecular Nitrone Cycloaddition

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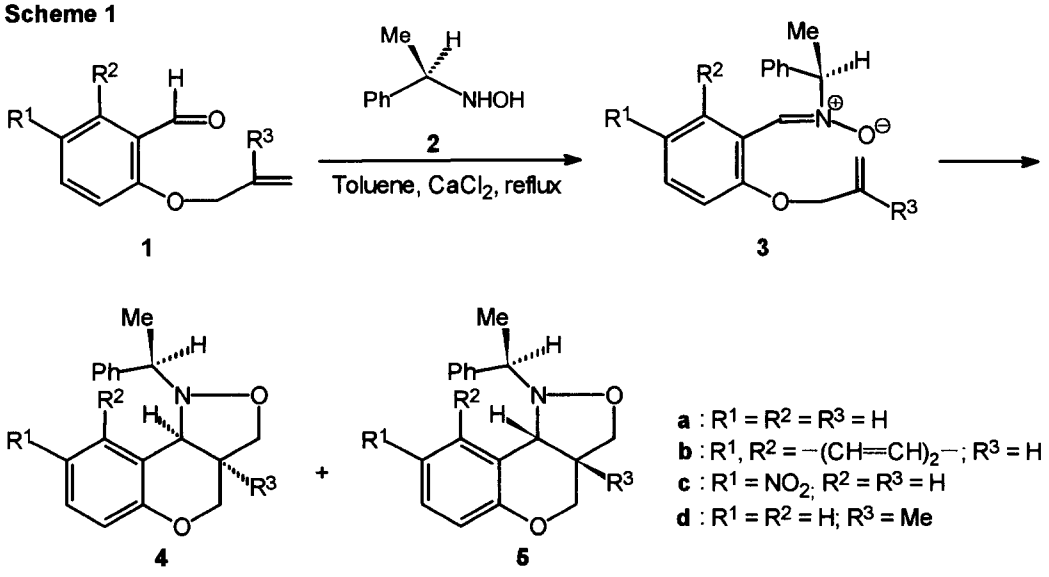
Abstract: Enantiopure (*R*) and (*S*) 3-hydroxymethylchromanes were prepared by the intramolecular nitrone cycloaddition strategy, starting from allyl-type ethers of 2-hydroxybenzaldehydes and using (*R*)-*N*-(α-phenylethyl)hydroxylamine as chiral auxiliary.

The importance of the chromane skeleton in the area of biologically active compounds is well recognised.[1-6] 3-Hydroxymethylchromanes find application as intermediates in the synthesis of α-adrenergic blocking agents[7] and nootropic drugs.[8] These compounds, however, are hitherto unreported in optically active form. The present paper just describes the preparation of enantiopure 3-hydroxymethylchromanes by means of the intramolecular nitrone cycloaddition strategy.[9]

Result and Discussion

The starting materials of our synthetic sequence were allyl-type ethers of 2-hydroxybenzaldehydes **1** (Scheme 1). These substrates were reacted with (*R*)-*N*-(α-phenylethyl)hydroxylamine **2**[10] in boiling toluene in

Scheme 1



order to generate the functionalized nitrones **3**, which we had perceived prone towards the intramolecular cycloaddition onto the ethylenic bond. In all cases, the reaction resulted in a mixture of the two isomeric products **4** and **5**, both of which were obtained in the pure state by chromatography. Reaction times, product ratios, and isolation yields are given in Table 1.

Table 1. Reaction of Aldehydes 1 with Hydroxylamine 2

Entry	Reaction time (h)	Overall yield (%)	Product ratio[a] 4 : 5	Isolation yields (%)[b] 4	5
a	12	95	65 : 35	40	28
b	20	95	60 : 40	32	33
c	20	90	65 : 35	53	27
d	36	90	60 : 40	32	15

[a] From the ^{1}H-NMR spectrum of the crude product mixture.

[b] After chromatographic separation.

For the cycloadducts **4a-c** and **5a-c**, the observed coupling constants of the isoxazolidinic hydrogens supported a *cis* relationship, thus indicating that the relative configuration of the newly created stereocentres was the same in all cases. The absolute configuration was established on submitting the major product derived from **1b** (*i.e.* **4b**) to the X-ray diffractometric analysis (see Figure 1). The same stereochemistry was reasonably ascribed to the other preferred cycloadducts **4a** and **4c**. In the case of **4d** and **5d**, the NMR spectroscopy gave no indication on the stereochemical relationship, which in fact was determined by means of the X-ray diffractometric analysis of the predominant isomer **4d** (see Figure 2).

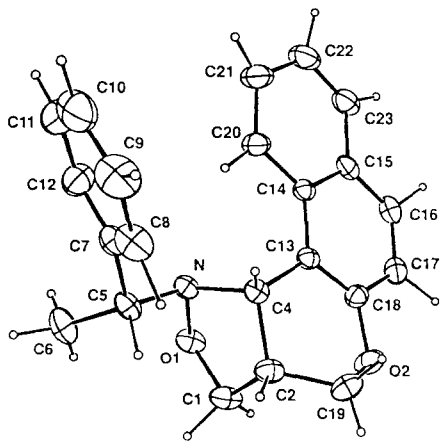


Fig. 1. Molecular structure of **4b**

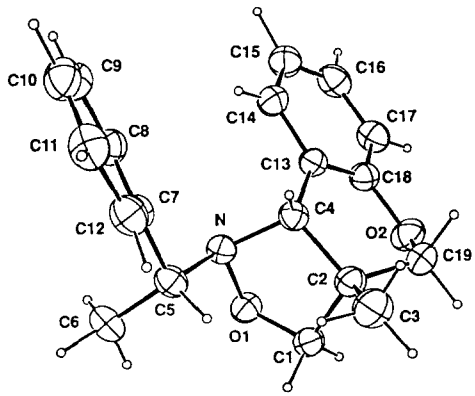
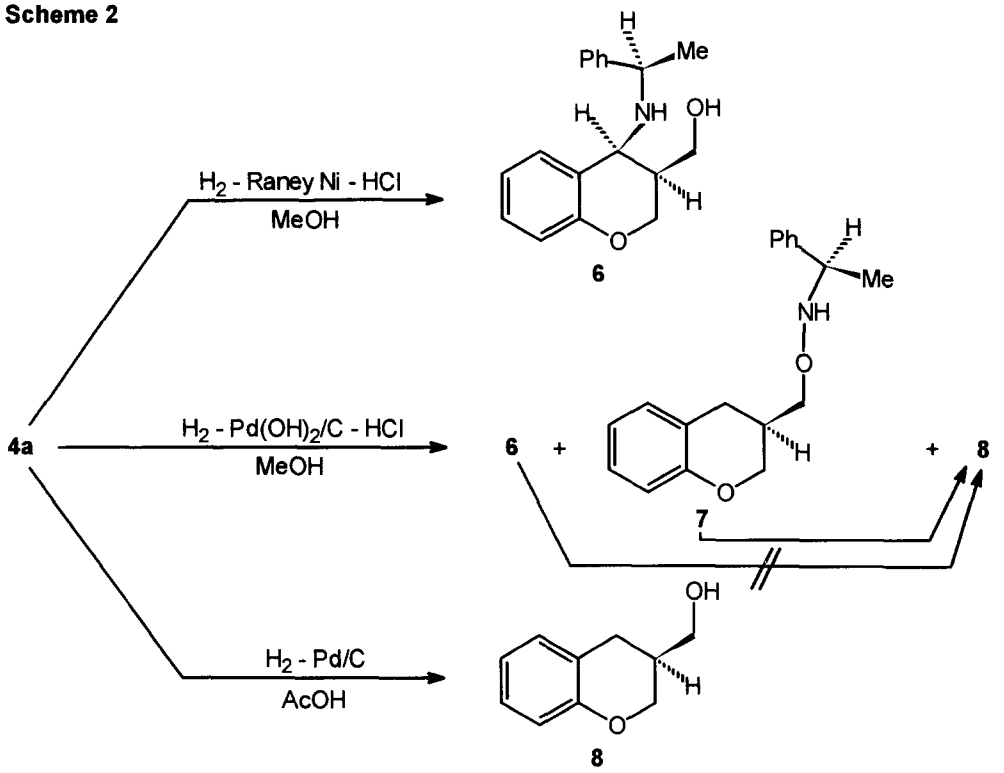


Fig. 2. Molecular structure of **4d**

At this point of our work, we undertook a systematic study on the behaviour of **4a** under hydrogenolytic conditions. First of all, compound **4a** was found to be inert in the absence of acidic species. In

methanolic solution in the presence of Raney nickel and hydrogen chloride, the hydrogenation of **4a** furnished the aminoalcohol **6** in 60% yield (Scheme 2). However, upon hydrogenation in the same solvent in the presence of $Pd(OH)_2/C$ and hydrogen chloride, compound **4a** led to a complex mixture, whose chromatographic treatment allowed isolation of **6**, **7**, and **8**. Control experiments showed that **7** changed to **8** under the conditions of its formation, while **6** was reluctant to further hydrogenolysis. Finally, in acetic acid in the presence of Pd/C, the hydrogenation of compound **4a** gave **8** as the predominant product.

Scheme 2



On the basis of the latter result, we submitted all cycloadducts to hydrogenation in acetic acid in the presence of Pd/C. However, different patterns of behaviour were observed for the different substrates (see Table 2 and Chart 1). While **5a** behaved as **4a** thus giving **9**, **4b** and **5b** led to the corresponding alcohols **10** and **11** provided that the reaction was stopped after the absorption of the stoicheiometric amount of hydrogen. When the reaction was prolonged until no more hydrogen was consumed, the products were **12** and **13** respectively. On the other hand, the hydrogenolysis of **4d** and **5d** resulted in the aminoalcohols **14** and **15**. Finally, in the case of **4c** and **5c**, owing to the concomitant reduction of the nitro group, the hydrogenation furnished the polifunctional products **16** and **17**. The enantiomeric purity of the final 3-hydroxymethyl-chromanes was tested in the case of **8** and **9** *via* the corresponding esters with the *R* enantiomer of Moscher's

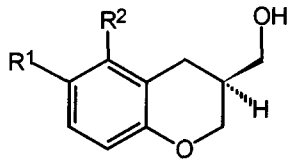
acid. It was confirmed to be total within the experimental error limits of the ^{1}H-NMR spectroscopy at 300 MHz.

Table 2. Hydrogenation of 4 and 5 in AcOH in the Presence of Pd/C

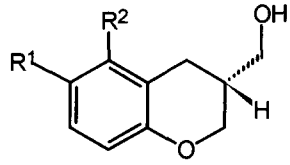
Substrate	Product	Yield (%)	$[\alpha]_D^{25}$
4a	**8**	52	-19
5a	**9**	54	+19
4b[a]	**10**	66	-8.4
	12	62	-14
5b[a]	**11**	68	+8.4
	13	66	+14
4c	**16**	53	-43
5c	**17**	51	+41
4d	**14**	88	-59
5d	**15**	89	+56

[a] See text.

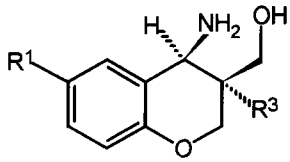
Chart 1



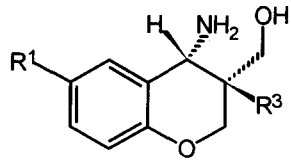
8 : $R^1 = R^2 = H$
10 : $R^1, R^2 = -(CH{=}CH)_2-$
12 : $R^1, R^2 = -(CH_2)_4-$



9 : $R^1 = R^2 = H$
11 : $R^1, R^2 = -(CH{=}CH)_2-$
13 : $R^1, R^2 = -(CH_2)_4-$



14 : $R^1 = H$; $R^3 = Me$
16 : $R^1 = NH_2$; $R^3 = H$



15 : $R^1 = H$; $R^3 = Me$
17 : $R^1 = NH_2$; $R^3 = H$

It is to be noticed that the intramolecular cycloaddition of **3** proceeds in fully diastereoselective mode as concerns the relative configuration of the two new stereocentres, while the asymmetry induced by the chiral pendant is modest. Nevertheless, the described entry to enantiopure 3-hydroxymethylchromanes seems to be of synthetic value in the light of (i) the inexpensiveness of the chiral auxiliary, (ii) the ability to obtain both diastereoisomeric cycloadducts in the pure state, and (iii) the good yields of the hydrogenolytic cleavage.

Experimental Section:

Melting points were determined using a Büchi apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin-Elmer 1725X spectrophotometer. ^{1}H-NMR spectra were obtained using a Bruker 300 MHz

apparatus; chemical shifts are given in ppm from $SiMe_4$, with coupling constants in Hz. Mass spectra were obtained with a VG-70EQ apparatus. The optical rotations were measured using a Perkin-Elmer 241 polarimeter, with a 1 dm pathlength at 25 °C.

Reaction of aldehyde 1a with hydroxylamine 2. Hydroxylamine **2** (1.2 g, 8.8 mmol) and $CaCl_2$ (1.0 g, 8.8 mmol) were added to a solution of aldehyde **1a**[11] (1.2 g, 7.3 mmol) in toluene (140 ml). The mixture was refluxed for 12 h. After filtration of the suspension and evaporation of the solvent, the residue was chromatographed on silica gel column with light petroleum/ethyl acetate 5:1 as eluent. The first fractions gave (+)-(α*R*,3a*S*,9b*R*)-1-(α-phenylethyl)-1,3a,4,9b-tetrahydro-3*H*-benzopyrano[4,3-*c*]isoxazole (**5a**) (0.57 g, 28%). M.p. 120-121 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 1.56 (3H, d, *J*=6.7), 2.92-3.03 (1H, m), 3.78 (1H, dd, *J*=5.2, 8.1), 4.03-4.20 (4H, overlapping), 4.31 (1H, d, *J*=8.5), 6.84 (1H, d, *J*=8.2), 6.98 (1H, dd, *J*=7.3, 7.3), 7.16 (1H, ddd, *J*=1.5, 7.8, 7.8), 7.26-7.48 (6H, m); $[\alpha]_D^{25}$ = +29 (c = 0.30 $CHCl_3$); MS: *m/z* = 281 (M^+); Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.83; H, 6.81; N, 4.98. Found: C, 76.86; H, 6.76; N, 5.01. The last fractions gave (+)-(α*R*,3a*R*,9b*S*)-1-(α-phenylethyl)-1,3a,4,9b-tetrahydro-3*H*-benzopyrano[4,3-*c*]isoxazole (**4a**) (0.82 g, 40%). M.p. 138-139 °C (hexane/benzene); ^{1}H-NMR ($CDCl_3$) δ 1.50 (3H, d, *J*=6.5), 3.17-3.26 (1H, m), 3.92 (1H, q, *J*=6.5), 4.03-4.22 (4H, overlapping), 4.35 (1H, dd, *J*=8.1, 9.5), 6.74 (1H, d, *J*=8.2), 6.86 (1H, dd, *J*=7.0, 7.0), 7.05 (1H, d, *J*=7.6), 7.28-7.40 (6H, m); $[\alpha]_D^{25}$ = +70 (c = 0.30 $CHCl_3$); MS: *m/z* = 281 (M^+); Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.83; H, 6.81; N, 4.98. Found: C, 76.78; H, 6.71; N, 5.03. The above cycloadducts counted for 95% of the crude reaction mixture (NMR analysis).

Reaction of aldehyde 1b with hydroxylamine 2. Hydroxylamine **2** (2.5 g, 18.0 mmol) and $CaCl_2$ (2.0 g, 18.0 mmol) were added to a solution of aldehyde **1b**[12] (3.2 g, 15.0 mmol) in toluene (300 ml). The mixture was refluxed for 20 h. After filtration of the suspension and evaporation of the solvent, the residue was chromatographed on silica gel column with light petroleum/ethyl acetate 4:1 as eluent. The first fractions gave (+)-(α*R*,3a*R*,11c*S*)-1-(α-phenylethyl)-1,3a,4,11c-tetrahydro-3*H*-naphtho[1',2':5,6]pyrano[4,3-*c*]isoxazole (**4b**) (1.58 g, 32%). M.p. 198-200 °C (hexane/benzene); ^{1}H-NMR ($CDCl_3$) δ 1.53 (3H, d, *J*=6.7), 3.53-3.60 (1H, m), 4.00-4.06 (2H, overlapping), 4.24-4.45 (3H, overlapping), 4.90 (1H, d, *J*=8.0), 6.74 (1H, d, *J*=8.5), 6.96-7.05 (2H, m), 7.21 (1H, dd, *J*=7.5, 7.5), 7.45-7.64 (7H, m); $[\alpha]_D^{25}$ = +240 (c = 0.22 $CHCl_3$); MS: *m/z* = 331 (M^+); Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.80; H, 6.45; N, 4.19. The last fractions gave (-)-(α*R*,3a*S*,11c*R*)-1-(α-phenylethyl)-1,3a,4,11c-tetrahydro-3*H*-naphtho[1',2':5,6]pyrano[4,3-*c*]isoxazole (**5b**) (1.64 g, 33%). M.p. 254-256 °C (hexane/benzene); ^{1}H-NMR ($CDCl_3$) δ 1.72 (3H, d, *J*=6.7), 3.08-3.16 (1H, m), 4.00 (1H, dd, *J*=7.2, 7.2), 4.10 (1H, dd, *J*=2.1, 11.4), 4.17-4.27 (3H, overlapping), 5.20 (1H, d, *J*=8.0), 6.99 (1H, d, *J*=8.9), 7.22-7.42 (6H, m), 7.51 (1H, ddd, *J*=1.2, 7.9, 8.5), 7.64 (1H, d, *J*=8.9), 7.74 (1H, d, *J*=7.9), 8.18 (1H, d, *J*=8.5); $[\alpha]_D^{25}$ = -239 (c = 0.27 $CHCl_3$); MS: *m/z* = 331 (M^+); Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.81; H, 6.31; N, 4.17. The above cycloadducts counted for 95% of the crude reaction mixture (NMR analysis).

Reaction of aldehyde 1c with hydroxylamine 2. Hydroxylamine **2** (3.5 g, 25.4 mmol) and $CaCl_2$ (2.8 g, 25.4 mmol) were added to a solution of aldehyde (**1c**)[13] (4.4 g, 21.2 mmol) in toluene (400 ml). The mixture was refluxed for 20 h. After filtration of the suspension and evaporation of the solvent, the residue was chromatographed on silica gel column with light petroleum/ethyl acetate 3:1 as eluent. The first fractions gave (-)-(α*R*,3a*S*,9b*R*)-8-nitro-1-(α-phenylethyl)-1,3a,4,9b-tetrahydro-3*H*-benzopyrano[4,3-*c*]isoxazole (**5c**) (1.86 g, 27%) (oil); ^{1}H-NMR ($CDCl_3$) δ 1.57 (3H, d, *J*=6.6), 2.98-3.08 (1H, m), 3.77 (1H, dd, *J*=6.0, 8.4), 4.05-4.32 (4H, overlapping), 4.43 (1H, d, *J*=7.8), 6.89 (1H, d, *J*=9.0), 7.24-7.48 (5H, m), 8.02 (1H, dd, *J*=2.7, 9.0), 8.33 (1H, d, *J*=2.7); $[\alpha]_D^{25}$ = -87 (c = 0.54 $CHCl_3$); MS: *m/z* = 326 (M^+); Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.34; H, 5.45; N, 8.70. The last fractions gave (+)-(α*R*,3a*R*,9b*S*)-8-nitro-1-(α-phenylethyl)-1,3a,4,9b-tetrahydro-3*H*-benzopyrano[4,3-*c*]isoxazole (**4c**) (3.66 g, 53%). M.p. 151-152 °C (hexane/benzene); ^{1}H-NMR ($CDCl_3$) δ 1.52 (3H, d, *J*=6.3), 3.26-3.31 (1H, m), 3.93 (1H, q, *J*=6.3), 4.04 (1H, dd, *J*=5.9, 8.2), 4.16 (1H, dd, *J*=2.8, 11.8), 4.23 (1H, d, *J*=7.8), 4.31 (1H, dd, *J*=2.8, 11.8), 4.40 (1H, dd, *J*=8.2, 8.2), 6.83 (1H, d, *J*=8.9), 7.33-7.38 (1H, m), 7.43-7.50 (4H, m), 7.93-7.99 (2H, m); $[\alpha]_D^{25}$ = +64 (c = 1.0 $CHCl_3$); MS: *m/z* = 326 (M^+); Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.31; H, 5.48; N, 8.49. The above cycloadducts counted for 90% of the crude reaction mixture (NMR analysis).

Reaction of aldehyde 1d with hydroxylamine 2. Hydroxylamine **2** (1.7 g, 12.7 mmol) and $CaCl_2$ (1.4 g, 12.7 mmol) were added to a solution of aldehyde (**1d**)[14] (1.9 g, 10.6 mmol) in toluene (200 ml). The mixture was refluxed for 36 h. After filtration of the suspension and evaporation of the solvent, the residue was chromatographed on silica gel column with light petroleum/ethyl acetate 5:1 as eluent. The first fractions gave (+)-(α*R*,3a*S*,9b*R*)-3a-methyl-1-(α-phenylethyl)-1,3a,4,9b-tetrahydro-3*H*-benzopyrano[4,3-*c*]isoxazole (**5d**) (0.47 g, 15%) (oil). ^{1}H-NMR ($CDCl_3$) δ 1.00 (3H,s), 1.61 (3H, d, *J*=6.9), 3.51 (1H, s), 3.55, 3.67 (2H, AB, *J*=8.1), 3.83, 4.19 (2H, AB, *J*=10.6), 4.20 (1H, q, *J*=6.9), 6.90-7.01 (2H, m), 7.20-7.43 (5H, m), 7.52-7.58 (2H, m); $[\alpha]_D^{25}$ = +165 (c = 0.26 $CHCl_3$); MS: *m/z* = 295 (M^+); Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.15; H, 7.23; N, 4.81. The last fractions was richromatographed on silica gel column with light petroleum/ethyl acetate 20:1 as eluent to give (+)-(α*R*,3a*R*,9b*S*)-3a-methyl-1-(α-phenylethyl)-1,3a,4,9b-tetrahydro-3*H*-benzopyrano[4,3-*c*]isoxazole (**4d**) (1.00 g, 32%). M.p. 102-103 °C (hexane/benzene); ^{1}H-NMR ($CDCl_3$) δ 1.31 (3H, s), 1.58 (3H, d, *J*=6.5), 3.73 (1H, s), 3.83, 4.04 (2H, AB, *J*=10.7), 3.84, 3.98 (2H, AB, *J*=8.6), 4.29 (1H, q, *J*=6.5), 6.55 (1H, dd, *J*=1.1, 7.7), 6.74 (1H, dd, *J*=7.7, 7.7), 6.82 (1H, d, *J*=8.0), 7.09 (1H, ddd, *J*=1.5, 8.0, 8.0), 7.25-7.44 (5H, m); $[\alpha]_D^{25}$ = +9 (c = 0.33 $CHCl_3$); MS: *m/z* = 295 (M^+); Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.29; H, 7.26; N, 4.63. The above cycloadducts counted for 90% of the crude reaction mixture (NMR analysis).

Hydrogenation of 4a with Raney nickel. Raney nickel (720 mg) and HCl 37% (0.15 ml) were added to a solution of **4a** (280 mg, 1.0 mmol) in MeOH (25 ml). The mixture was stirred under H_2 for 4 h and then neutralised with NaOH 0.5N. After filtration through celite, the solvent was evaporated under reduced pressure to give (-)-(α*R*,3*S*,4*S*)-[2*H*-3,4-dihydro-4-(α-phenylethylamino)benzopyran]-3-methanol (**6**) (170 mg, 60%)

(oil). ^{1}H-NMR ($CDCl_3$) δ 1.55 (3H, d, *J*=6.6), 2.16-2.26 (1H, m), 3.40 (1H, s br), 3.92-4.00 (2H, overlapping), 4.08-4.37 (4H, overlapping), 6.73-6.85 (2H, m), 6.94 (1H, d, *J*=7.6), 7.08-7.17 (1H, ddd, *J*=1.4, 7.6, 7.6), 7.22-7.38 (5H, m); $[\alpha]_D^{25}$ = -51 (c = 0.25 $CHCl_3$); IR (neat): 3350 cm^{-1}; MS: *m/z* = 283 (M^+); Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.20; H, 7.36; N, 4.87.

Hydrogenation of 4a with $Pd(OH)_2/C$. 20% $Pd(OH)_2/C$ (150 mg) and HCl 37% (0.3 ml) were added to a solution of **4a** (520 mg, 1.85 mmol) in MeOH (50 ml). The mixture was stirred under H_2 for 4 h and then neutralised with NaOH 0.5N. After filtration through celite, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum/ethyl acetate 1:1 as eluent. The first fractions gave (α*R*,3*R*)-*O*-[(2*H*-3,4-dihydro-benzopyran-3-yl)-methyl]-*N*-(α-phenylethyl)hydroxyl-amine (**7**) (110 mg, 21%). M.p. 32 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 1.38 (3H, d, *J*=6.8), 2.22-2.33 (1H, m), 2.40-2.48 (1H, m), 2.72 (1H, dd, *J*=5.1, 16.0), 3.55-3.60 (2H, overlapping), 3.70-3.83 (1H, dd, *J*=9.4, 10.3), 4.09-4.21 (2H, overlapping), 5.60 (1H, s br), 6.75-6.85 (2H, m), 6.98-7.11 (2H, m), 7.24-7.37 (5H, m); IR (nujol): 3260 cm^{-1}; MS: *m/z* = 283 (M^+); Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.42; H, 7.63; N, 5.07. The next fractions contained **6** (84 mg, 16%). The last fractions gave (-)-(3*S*)-(2*H*-3,4-dihydro-benzopyran)-3-methanol (**8**) (70 mg, 23%). M.p. 63-64 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 1.48 (1H, s br), 2.23-2.34 (1H, m), 2.59 (1H, dd, *J*=7.8, 16.4), 2.87 (1H, dd, *J*=5.7, 16.4), 3.62-3.74 (2H, overlapping), 3.99 (1H, dd, *J*=7.6, 10.9), 4.29 (1H, ddd, *J*=1.1, 3.0, 10.9), 6.77-6.87 (2H, m), 7.03.7.11 (2H, m); $[\alpha]_D^{25}$ = -19 (c = 0.30 $CHCl_3$); IR (nujol): 3300 cm^{-1}; MS: *m/z* = 164 (M^+); Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.34.

Hydrogenation of 4a with Pd/C in AcOH. 10% Pd/C (150 mg) was added to a solution of **4a** (250 mg, 0.90 mmol) in AcOH (12 ml). The mixture was stirred under H_2 for 6 h. After filtration through celite, the solvent was evaporated under reduced pressure to give pratically pure **8** (77 mg, 52%).

Hydrogenation of 5a with Pd/C in AcOH. According to the procedure described for **4a**, compound **5a** (250 mg, 0.90 mmol) gave (+)-(3*R*)-(2*H*-3,4-dihydro-benzopyran)-3-methanol (**9**) (80 mg, 54%). Physical and spectroscopic data were the same as for **8**. $[\alpha]_D^{25}$ = +19 (c = 0.30 $CHCl_3$); Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.23; H, 7.48.

Hydrogenation of 4b with Pd/C in AcOH. *A)* 10% Pd/C (100 mg) was added to a solution of **4b** (270 mg, 0.81 mmol) in AcOH (100 ml). The mixture was stirred under H_2 for 3 h. After filtration through celite, the solvent was evaporated under reduced pressure to give (-)-(2*S*)-2,3-dihydro-2-hydroxymethyl-1*H*-naphtho[2,1-*b*]pyran (**10**) (114 mg, 66%). M.p. 74-75 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 2.36-2.50 (1H, m), 2.82 (1H, dd, *J*=7.4, 16.6), 3.18 (1H, dd, *J*=6.2, 16.6), 3.71-3.85 (2H, overlapping), 4.09 (1H, dd, *J*=7.5, 10.6), 4.37 (1H, dd, *J*=3.0, 10.6), 7.05 (1H, d, *J*=8.9), 7.34 (1H, dd, *J*=7.6, 8.0), 7.48 (1H, ddd, *J*=1.0, 7.6, 8.4), 7.61 (1H, d, *J*=8.9), 7.76 (1H, d, *J*=8.0), 7.80 (1H, d, *J*=8.4); $[\alpha]_D^{25}$ = -8.4 (c = 0.25 $CHCl_3$); IR (nujol): 3365 cm^{-1}; MS: *m/z* = 214 (M^+); Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.53; H, 6.70. *B)* 10% Pd/C (60 mg) was added to a solution of **4b** (170 mg, 0.51 mmol) in AcOH (50 ml). The mixture was stirred under H_2 for 24

h. After filtration through celite, the solvent was evaporated under reduced pressure to give (-)-(2*S*)-2,3,7,8,9,10-hexahydro-2-hydroxymethyl-1*H*-naphtho[2,1-*b*]pyran (**12**) (69 mg, 62%). M.p. 106-107 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 1.68-1.85 (4H, overlapping), 2.23-2.38 (2H, overlapping), 2.51-2.56 (2H, overlapping), 2.64-2.71 (3H, overlapping), 3.67-3.72 (2H, overlapping), 3.92 (1H, dd, *J*=7.8, 10.6), 4.22 (1H, dd, *J*=2.8, 10.6), 6.63 (1H, d, *J*=8.3), 6.84 (1H, d, *J*=8.3); $[\alpha]_D^{25}$ = -14 (c = 0.30 $CHCl_3$); IR (nujol): 3400 cm^{-1}; MS: *m/z* = 218 (M^+); Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.16; H, 8.48.

Hydrogenation of 5b with Pd/C in AcOH. *A)* According to the procedure described for **4b**, compound **5b** (300 mg, 0.90 mmol) gave (+)-(2*R*)-2,3-dihydro-2-hydroxymethyl-1*H*-naphtho[2,1-*b*]pyran (**11**) (130 mg, 68%). Physical and spectroscopic data were the same as for **10**. $[\alpha]_D^{25}$ = +8.4 (c = 0.25 $CHCl_3$); Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.39; H, 6.67. *B)* According to the procedure described for **4b**, compound **5b** (270 mg, 0.81 mmol) gave (+)-(2*R*)-2,3,7,8,9,10-hexahydro-2-hydroxymethyl-1*H*-naphtho[2,1-*b*]pyran (**13**) (116 mg, 66%). Physical and spectroscopic data were the same as for **12**. $[\alpha]_D^{25}$ = +14 (c = 0.50 $CHCl_3$); Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.90; H, 8.14.

Hydrogenation of 4c with Pd/C in AcOH. 10% Pd/C (110 mg) was added to a solution of **4c** (300 mg, 0.92 mmol) in AcOH (30 ml). The mixture was stirred under H_2 for 7 h. After filtration through celite, the solvent was evaporated under reduced pressure. The residue was treated with NaOH 0.5N and extracted with CH_2Cl_2. The organic phase was separated, dried on Na_2SO_4 and evaporated to give (-)-(3*S*,4*S*)-(2*H*-4,6-diamino-3,4-dihydro-3-methyl-benzopyran)-3-methanol (**16**) (95 mg, 53%). M.p. 138-139 °C (hexane/benzene); ^{1}H-NMR (D_2O) δ 2.22-2.31 (1H, m), 3.63, 3.76 (2H, AB part of ABM, J_{AB}=11.3, J_{AM}=8.1, J_{BM}=6.6), 4.04-4.10 (2H, overlapping), 4.16 (1H, dd, *J*=3.4, 11.1), 6.72 (2H, s), 6.80 (1H, s); $[\alpha]_D^{25}$ = -43 (c = 0.11 EtOH); IR (nujol): 3360, 3280, 3200 cm^{-1}; MS: *m/z* = 194 (M^+); Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.67; H, 7.15; N, 14.29.

Hydrogenation of 5c with Pd/C in AcOH. According to the procedure described for **4c**, compound **5c** (125 mg, 0.38 mmol) gave (+)-(3*R*,4*R*)-(2*H*-4,6-diamino-3,4-dihydro-3-methyl-benzopyran)-3-methanol (**17**) (38 mg, 51%). Physical and spectroscopic data were the same as for **16**. $[\alpha]_D^{25}$ = +41 (c = 0.14 EtOH); Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.96; H, 7.39; N, 14.57.

Hydrogenation of 4d with Pd/C in AcOH. 10% Pd/C (50 mg) was added to a solution of **4d** (130 mg, 0.44 mmol) in AcOH (8 ml). The mixture was stirred under H_2 for 6 h. After filtration through celite, the solvent was evaporated under reduced pressure. The residue was treated with NaOH 0.5N and extracted with CH_2Cl_2. The organic phase was separated, dried on Na_2SO_4 and evaporated to give (-)-(3*S*,4*S*)-(2*H*-4-amino-3,4-dihydro-3-methyl-benzopyran)-3-methanol (**14**) (75 mg, 88%). M.p. 95-96 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 0.86 (3H, s), 2.48 (3H, s), 3.63 (1H, d, *J*=11.5), 3.67 (1H, s), 3.83 (1H, d, *J*=11.5), 3.88 (1H, dd, *J*=1.2, 11.4), 4.27 (1H, d, *J*=11.4), 6.83 (1H, d, *J*=8.1), 6.91 (1H, dd, *J*=7.2), 7.14-7.20 (2H, m); $[\alpha]_D^{25}$ = -59 (c = 0.28 EtOH); IR (nujol): 3425, 3240 cm^{-1}; MS: *m/z* = 193 (M^+); Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.29; H, 7.75; N, 7.17.

Hydrogenation of 5d with Pd/C in AcOH. According to the procedure described for **4d**, compound **5d** (200 mg, 0.68 mmol) gave (+)-(3*R*,4*R*)-(2*H*-4-amino-3,4-dihydro-3-methyl-benzopyran)-3-methanol (**15**) (117 mg, 89%). Physical and spectroscopic data were the same as for **14**. $[\alpha]_D^{25}$ = +56 (c = 0.14 EtOH); Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.39; H, 7.77; N, 7.21.

X-Ray diffraction analysis of 4b and 4d.[15] Unit cells parameters and intensity data were obtained on Enraf-Nonius CAD-4 diffractometer. Calculations were performed with the SDP software[16] on a MicroVax-3100 computer. The cell dimensions were determined by least-squares fitting of 25 centered reflections monitored in the range $30<\theta<35°$ for **4b** and $35<\theta<40°$ for **4d**. Correction for Lp and empirical absorption[17] were applied. Both the structures were solved by direct-methods (SIR88).[18] The non-hydrogen atoms were refined anisotropically by full-matrix least-squares. All the hydrogen atoms were found in the difference Fourier map, in structure **4d** inserted with an overall isotropic atomic displacement parameter equal to 5.0 Å^2 and not refined, while in structure **4b** their atomic displacement parameters were kept proportional (× 1.3) to those of their neighbouring non-H atoms. Secondary extinctions[19] were applied. Atomic scattering factors were taken from in ref. 20. Pertinent experimental details are given in Table 3. Diagrams of the molecular structure were performed by ORTEP program[21] showing 30% probability displacement ellipsoids.

Table 3. Crystal Structure Analysis: Experimental Details

	4b	**4d**
Formula	$C_{22}H_{21}NO_2$	$C_{19}H_{21}NO_2$
MW	331.42	295.38
Crystal Size mm	0.9×0.4×0.4	0.6×0.3×0.4
Crystal Colour	colourless	colourless
System	orthorhombic	monoclinic
Space Group	$P2_12_12_1$	$P2_1$
a Å	9.478(1)	10.150(1)
b Å	10.463(1)	8.206(1)
c Å	17.618(1)	10.472(1)
α °	90	90
β °	90	112.96(1)
γ °	90	90
V Å^3	1747.1(3)	803.1(1)
Z	4	2
Dcalc. Mg × m^{-3}	1.260	1.221
Radiation	Cu K_α (λ = 1.54184 Å) graphite monochromated	
μ mm^{-1}	0.599	0.589
T K°	295(2)	295(2)
θ range °	2 - 70	2 - 76
Scan Mode	ω - 2θ	ω - 2θ
Refls. Measured	$0 < h < 11$	$-12 < h < 12$
	$-12 < k < 12$	$-5 < k < 10$
	$0 < l < 21$	$0 < l < 13$
Tot. Refls. Meas.	3526	3052
Unique Reflections	1897	1798
Obs. Refls. [$I > \sigma(I)$]	1874	1787
R*	0.051	0.035
R**	0.051	0.031
Refined Parameters	227	200

* $R = \Sigma||Fo|-|Fc|| / \Sigma|Fo|$; ** $Rw = [\Sigma w(|Fo|-|Fc|)^2 / \Sigma w(Fo)^2]^{1/2}$

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