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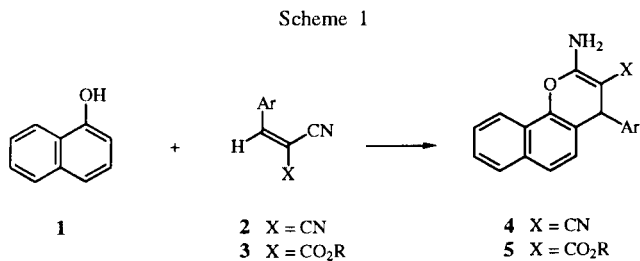
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The first asymmetric synthesis of 3-alkoxycarbonyl-2-amino-4-aryl-4*H*-naphtho[1,2-*b*]pyrans, by Michael addition of 1-naphthol to chirally modified arylidenecyanoacetates **6** and **7**, is described. Good yields and low diastereomeric excesses have been obtained in the 1,4-conjugate additions. The absolute stereochemistry at C-4 in major isomers of pyrans **8** and **9** has been assigned as *S* by X-ray analysis of major pyran **8**.

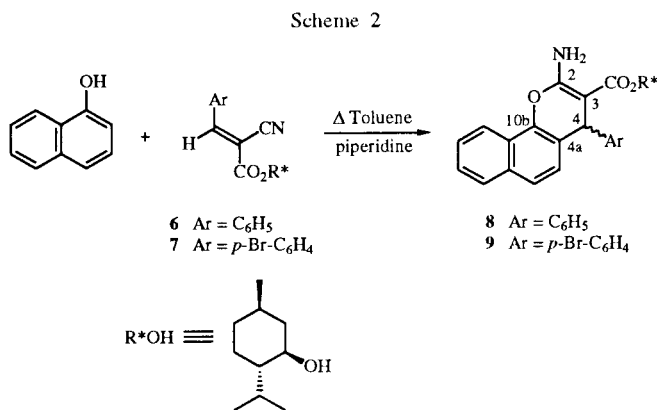
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Some recent reports [1,2] have addressed the biological and pharmacological activity of 2-amino-4-aryl-3-cyano-4*H*-naphtho[1,2-*b*]pyrans **4**. These products have been prepared by standard Michael addition of 1-naphthol (**1**) to arylidenemalononitriles **2** using piperidine as a base [2] (Scheme 1). For years we have been interested in the preparation of racemic, densely functionalized 2-amino-4*H*-pyrans [3], and recently we have described several approaches for the synthesis of those target molecules in enantiomerically pure form [4]. Continuing our work in this area we have now directed our attention to the analogous 4*H*-naphtho[1,2-*b*]pyrans of type **5** (Scheme 1), which we have identified as a potentially active prodrugs. Very recently we have described the revisited synthesis of racemic 2-amino-4-aryl-3-ethoxycarbonyl-4*H*-naphtho[1,2-*b*]pyrans [5]. In this report we describe for the first time the asymmetric synthesis of 3-alkoxycarbonyl-2-amino-4-aryl-4*H*-naphtho[1,2-*b*]pyrans **5**.



The synthesis of compounds of type **5** has been reported in the literature several times [6]. These products have been prepared by Michael addition of 1-naphthol to arylidenecyanoacetates **3** (Scheme 1). In our strategy for

asymmetric synthesis [4] we needed some modified, chiral acceptors of type **3** (Scheme 1). For this purpose we have selected (1*R*,2*S*,5*R*)-menthol, as readily available chiral auxiliary, and have synthesized compounds **6** [7] and **7** (Scheme 2). Using the conditions described by Dell



[2] slightly modified by us, the addition of 1-naphthol to Michael acceptors **6** and **7** provided the desired 2-amino-4*H*-naphtho[1,2-*b*]pyrans **8** and **9** (Scheme 2) in good yield (63-64%). The diastereomeric ratios were low (26-28%) and independent of the type of substituent in the phenyl ring in the Michael acceptor. The new 4*H*-naphtho[1,2-*b*]pyrans **8** and **9** showed good analytical and spectroscopic data (see Experimental). In the <sup>1</sup>H and <sup>13</sup>C nmr spectra, H-4 and NH<sub>2</sub> or C-4 appear always more deshielded in the major isomer than in the minor ones. Compounds **8** and **9** were isolated as a mixture of diastereomers at C-4 that we were unable to separate by

chromatography. Only the major isomer in compound **8** was finally obtained pure by recrystallization.

The absolute configuration at the new stereocenter (C-4) formed in the Michael addition in the major isomer **8** has been established as (*S*) by X-ray analysis of a suitable crystal (Figure 1). In Figure 1 we show the molecular structure with the crystallographic numbering.

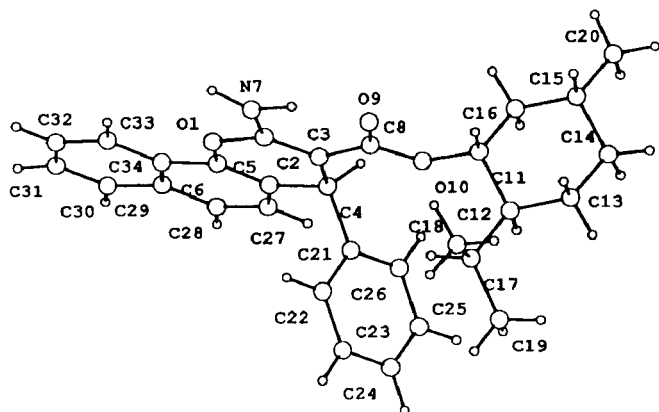


Figure 1. A view of the molecular structure of compound **8** showing the atomic numbering.

From this analysis it is clear that the pyran and the hexane rings are in a 1,4-boat and a chair conformation, respectively. The general conformation of the molecule could be described in terms of the interplanar angles

Table 1

Geometrical Characteristics in the Compound Studied (Å,°)

Atomic item	Distance (e.s.d)	Atomic item	Distance (e.s.d)
O1-C2	1.366 (3)	C14-C15	1.52 (1)
O1-C6	1.379 (4)	C15-C20	1.52 (1)
C2-N7	1.35 (1)	C15-C16	1.52 (1)
C2-C3	1.35 (1)	C17-C19	1.52 (1)
C3-C8	1.451 (4)	C17-C18	1.52 (1)
C3-C4	1.51 (1)	C21-C26	1.38 (1)
C4-C5	1.522 (4)	C21-C22	1.39 (1)
C4-C21	1.528 (4)	C22-C23	1.39 (1)
C5-C6	1.36 (1)	C23-C24	1.37 (1)
C5-C27	1.40 (1)	C24-C25	1.36 (1)
C6-C34	1.429 (4)	C25-C26	1.40 (1)
C8-O9	1.22 (1)	C27-C28	1.37 (1)
C8-O10	1.39 (1)	C28-C29	1.40 (1)
O10-C11	1.457 (3)	C29-C34	1.42 (1)
C11-C16	1.52 (1)	C29-C30	1.42 (1)
C11-C12	1.52 (1)	C30-C31	1.36 (1)
C12-C13	1.53 (1)	C31-C32	1.40 (1)
C12-C17	1.53 (1)	C32-C33	1.36 (1)
C13-C14	1.51 (1)	C33-C34	1.42 (1)
Atomic item	Angle (e.s.d)	Atomic item	Angle (e.s.d)
C2-O1-C6	118.6 (2)	C14-C15-C20	113.2 (5)
N7-C2-C3	127.2 (3)	C14-C15-C16	110.0 (4)
N7-C2-O1	109.4 (3)	C20-C15-C16	110.3 (5)
C3-C2-O1	123.3 (3)	C11-C16-C15	110.9 (4)

Table 1 (continued)

Atomic item	Angle (e.s.d)	Atomic item	Angle (e.s.d)
C2-C3-C8	117.6 (3)	C19-C17-C18	109.9 (5)
C2-C3-C4	122.5 (3)	C19-C17-C12	111.3 (5)
C8-C3-C4	119.7 (3)	C18-C17-C12	114.1 (4)
C3-C4-C5	110.6 (3)	C26-C21-C22	119.0 (3)
C3-C4-C21	114.0 (3)	C26-C21-C4	120.4 (3)
C5-C4-C21	109.9 (2)	C22-C21-C4	120.6 (3)
C6-C5-C27	118.1 (3)	C21-C22-C23	120.2 (4)
C6-C5-C4	121.4 (3)	C24-C23-C22	120.0 (4)
C27-C5-C4	120.5 (3)	C25-C24-C23	120.0 (4)
C5-C6-O1	123.2 (3)	C24-C25-C26	120.7 (4)
C5-C6-C34	122.6 (4)	C21-C26-C25	120.0 (4)
O1-C6-C34	114.1 (3)	C28-C27-C5	121.7 (4)
O9-C8-O10	122.4 (3)	C27-C28-C29	120.7 (4)
O9-C8-C3	126.0 (3)	C28-C29-C34	119.3 (3)
O10-C8-C3	111.5 (3)	C28-C29-C30	122.4 (4)
C8-O10-C11	119.2 (3)	C34-C29-C30	118.3 (4)
O10-C11-C16	106.4 (3)	C31-C30-C29	120.6 (5)
O10-C11-C12	109.0 (3)	C30-C31-C32	120.7 (3)
C16-C11-C12	112.5 (4)	C33-C32-C31	120.8 (5)
C11-C12-C13	106.8 (3)	C32-C33-C34	119.7 (4)
C11-C12-C17	114.2 (4)	C33-C34-C29	119.9 (3)
C13-C12-C17	115.3 (4)	C33-C34-C6	122.6 (4)
C14-C13-C12	112.5 (4)	C29-C34-C6	117.5 (3)
C13-C14-C15	113.4 (5)		
Atomic item	Angle (e.s.d)	Atomic item	Angle (e.s.d)
C16-C11-C12-C13	59 (1)	C11-C12-C17-C18	-67 (1)
C11-C12-C13-C14	-56 (1)	C3-C4-C21-C22	51.1 (4)
C12-C13-C14-C15	55 (1)	C2-C3-C8-O10	-172.7 (3)
C13-C14-C15-C16	-52 (1)	C3-C8-O10-C11	179.2 (3)
C14-C15-C16-C11	53 (1)	C8-O10-C11-C12	120.4 (4)
C12-C11-C16-C15	-60 (1)		

between that plane defined by the pyran ring (O-1 to C-6) and those planes defined by the C-3, C-8, O-9 and O-10 atoms [172.5(1)], the hexane ring [C-11 to C-16, 90.0(1)], the phenyl ring [C-21 to C-26, 86.4(1)] and the naphthalene system [C-5, C-6 and C-27 to C-34, 178.7(1)]. All bond distances and angles are within the range of those analogues found in the literature [8]. The crystal packing (Figure 2) presents a system of aromatic interactions involving both naphthalene and phenyl rings. An intramolecular hydrogen bond has been found involving N-7, H-71 and O-9 [distances N-7...O-9 2.650(4) Å and H-71...O-9 1.77 Å, angle N-7,H-71...O-9 138.9] (Figure 2).

Due to the similar chemical shifts in the  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra between major isomers in compounds **8** and **9** (see Experimental), we can conclude that the major isomer in all cases has the same absolute stereochemistry in C-4.

In summary, in spite of the low degree of asymmetric induction obtained in the Michael addition, it is important to point out that this is the first asymmetric synthesis of densely functionalized 4*H*-naphtho[1,2-*b*]pyrans described. Work is now in progress to extend this methodology to other related heterocyclic rings.

Table 2

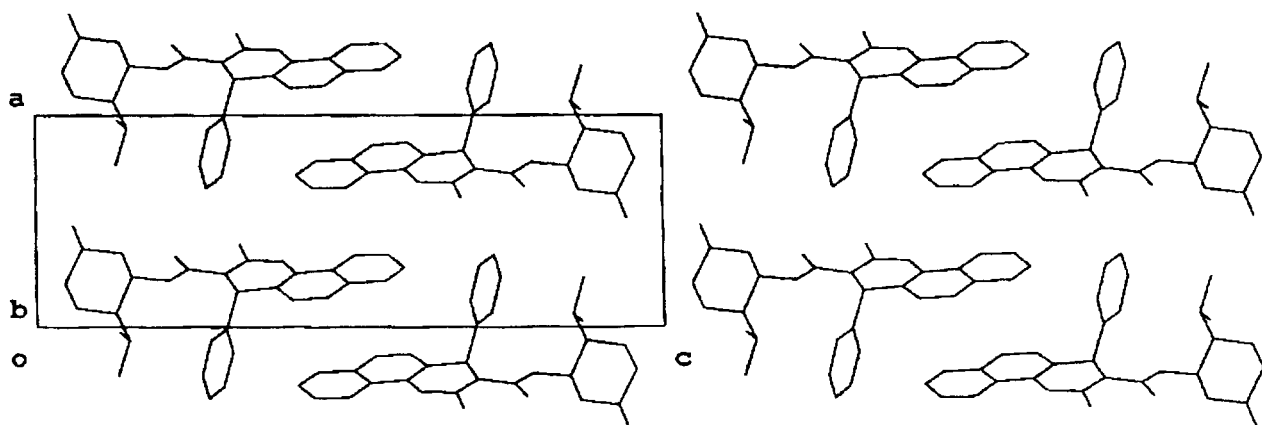
Table 2 (continued)

## Non-Hydrogen Positional and Isotropic Displacement Parameters

	x/a	y/b	z/c	U
O (1)	0.3120 (3)	0.71414	0.39150 (8)	* 0.0507 (8)
C (2)	0.3149 (3)	0.6899 (7)	0.3358 (1)	* 0.041 (1)
C (3)	0.2504 (3)	0.8322 (7)	0.3001 (1)	* 0.0392 (9)
C (4)	0.1698 (3)	1.0324 (6)	0.3188 (1)	* 0.0395 (9)
C (5)	0.1857 (3)	1.0555 (7)	0.3809 (1)	* 0.0412 (9)
C (6)	0.2535 (4)	0.9005 (7)	0.4127 (1)	* 0.042 (1)
N (7)	0.3900 (3)	0.5077 (6)	0.3234 (1)	* 0.0512 (9)
C (8)	0.2727 (4)	0.7946 (7)	0.2418 (1)	* 0.043 (1)
O (9)	0.3345 (4)	0.6384 (6)	0.2214 (1)	* 0.0667 (9)
O (10)	0.2207 (3)	0.9578 (6)	0.21152 (8)	* 0.0505 (7)
C (11)	0.2355 (4)	0.9490 (8)	0.1520 (1)	* 0.055 (1)
C (12)	0.0650 (5)	0.9700 (9)	0.1257 (1)	* 0.064 (1)
C (13)	0.0890 (7)	0.972 (1)	0.0634 (2)	* 0.089 (2)
C (14)	0.2043 (8)	1.144 (1)	0.0454 (2)	* 0.097 (2)
C (15)	0.3715 (7)	1.136 (1)	0.0741 (2)	* 0.090 (2)
C (16)	0.3497 (5)	1.1276 (9)	0.1362 (1)	* 0.067 (1)
C (17)	-0.0614 (5)	0.811 (1)	0.1466 (2)	* 0.081 (2)
C (18)	-0.0248 (8)	0.584 (1)	0.1307 (3)	* 0.103 (2)
C (19)	-0.2352 (6)	0.869 (1)	0.1283 (3)	* 0.108 (2)
C (20)	0.483 (1)	1.318 (2)	0.0588 (3)	* 0.136 (3)
C (21)	-0.0110 (3)	1.0536 (6)	0.3009 (1)	* 0.0397 (9)
C (22)	-0.1223 (4)	0.8926 (7)	0.3108 (1)	* 0.051 (1)
C (23)	-0.2878 (4)	0.9155 (9)	0.2959 (2)	* 0.066 (1)
C (24)	-0.3419 (4)	1.0987 (9)	0.2718 (2)	* 0.067 (1)
C (25)	-0.2334 (5)	1.2562 (9)	0.2617 (2)	* 0.068 (1)
C (26)	-0.0669 (4)	1.2353 (7)	0.2761 (1)	* 0.053 (1)
C (27)	0.1284 (4)	1.2372 (7)	0.4071 (1)	* 0.049 (1)
C (28)	0.1390 (4)	1.2606 (8)	0.4629 (1)	* 0.056 (1)
C (29)	0.2084 (4)	1.1023 (8)	0.4961 (1)	* 0.052 (1)
C (30)	0.2167 (4)	1.1180 (9)	0.5542 (1)	* 0.065 (1)
C (31)	0.2804 (5)	0.958 (1)	0.5851 (1)	* 0.072 (2)
C (32)	0.3420 (5)	0.776 (1)	0.5600 (2)	* 0.072 (2)
C (33)	0.3373 (4)	0.7547 (8)	0.5042 (1)	* 0.058 (1)
C (34)	0.2681 (4)	0.9165 (7)	0.4711 (1)	* 0.048 (1)

## Hydrogen Positional and Isotropic Displacement Parameters

	x/a	y/b	z/c	U
H (4)	0.2288	1.1559	0.3001	0.039
H (71)	0.3899	0.4914	0.2806	0.048
H (72)	0.4494	0.4128	0.3500	0.048
H (11)	0.2886	0.8156	0.1375	0.056
H (12)	0.0117	1.1113	0.1382	0.060
H (131)	-0.0188	0.9683	0.0420	0.086
H (132)	0.1326	0.8274	0.0508	0.086
H (141)	0.1455	1.2829	0.0523	0.096
H (142)	0.2073	1.1496	0.0044	0.096
H (15)	0.4327	1.0068	0.0593	0.090
H (161)	0.4571	1.1239	0.1575	0.065
H (162)	0.3056	1.2663	0.1509	0.065
H (17)	-0.0458	0.8153	0.1881	0.077
H (181)	0.0881	0.5357	0.1459	0.093
H (182)	-0.0226	0.5651	0.0898	0.093
H (183)	-0.1037	0.4666	0.1443	0.093
H (191)	-0.2456	0.8814	0.0877	0.110
H (192)	-0.2670	1.0151	0.1445	0.110
H (193)	-0.3193	0.7676	0.1422	0.110
H (201)	0.4267	1.4571	0.0708	0.129
H (202)	0.4962	1.3309	0.0175	0.129
H (203)	0.5954	1.3203	0.0759	0.129
H (22)	-0.0789	0.7565	0.3290	0.053
H (23)	-0.3700	0.7965	0.3027	0.068
H (24)	-0.4636	1.1157	0.2623	0.091
H (25)	-0.2750	1.3923	0.2424	0.073
H (26)	0.0165	1.3559	0.2686	0.051
H (27)	0.0762	1.3564	0.3837	0.049
H (28)	0.0928	1.3953	0.4812	0.056
H (30)	0.1740	1.2468	0.5744	0.065
H (31)	0.2805	0.9697	0.6264	0.072
H (32)	0.3916	0.6624	0.5848	0.071
H (33)	0.3845	0.6227	0.4859	0.059

Figure 2. Crystal packing of compound **8** along the a axis.

## EXPERIMENTAL

All the reactions were monitored by tlc using precoated silica gel aluminum plates containing a fluorescent indicator (Merck, 5539). Flash column chromatography [9] was performed using

Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as the eluent. Melting points were determined in capillary tubes and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 681 spectrometer. The  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra were recorded on a Varian XL-300 spectrometer. Elemental analyses were performed at the IQOG (CSIC).

3-Alkoxy-carbonyl-2-amino-4-aryl-4*H*-naphtho[1,2-*b*]pyrans (**5**). General Procedure.

To a stirred mixture of 1-naphthol (1.0 equivalent) and the corresponding arylideneacyanoacetate **6** or **7** (1.0 equivalent) in toluene, piperidine (0.2 equivalent) was added. The mixture was refluxed for 2 hours. The yellow-orange solution was cooled to room temperature and the solvent evaporated. The crude was submitted to flash chromatography (hexane/ethyl acetate, 9:1) yielding compounds **8** and **9**.

2-Amino-3-[(1*R*,2*S*,5*R*)-menthylloxycarbonyl]-4-phenyl-4*H*-naphtho[1,2-*b*]pyran (**8**).

Following the General Procedure, using (1*R*,2*S*,5*R*)-menthyl arylideneacyanoacetate **6** (0.5 g, 1.61 mmoles), after 2 hours, compound **8** (0.461 g, yield 63%) was obtained. After recrystallization, major isomer was obtained pure. The major diastereomer [C-4(*S*)] mp 213-216; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +130 (c 0.65, chloroform); ir (potassium bromide): 3480, 3280, 2960, 2860, 1680, 1620, 1520, 1500, 1460, 1380, 1310, 1270, 1110 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  8.20 (d, 1H, aromatic), 7.73 (d, 1H, aromatic), 7.55-7.43 (m, 3H, aromatics), 7.30-7.17 (m, 5H, aromatics), 7.08 (m, 1H, aromatics), 6.52 (br s, 2H, NH<sub>2</sub>), 5.03 (s, 1H, H-4), 4.67 (dt, 1H, J<sub>ax,ax</sub> = 10.8 Hz, J<sub>ax,eq</sub> = 4.2 Hz, H-1'), 2.05-0.72 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.90, 0.52, 0.42 (d, J = 6.9 Hz, 3 CH<sub>3</sub>); <sup>13</sup>C nmr (deuteriochloroform):  $\delta$  169.1 (CO<sub>2</sub>), 160.1 (C-2), 147.6 (C<sub>ipso</sub>), 142.7 (C-10b), 132.8 (C-6a), 128.1, 127.5, 126.4, 126.0, 123.8, 120.7 (aromatics), 123.3 (C-10a), 120.6 (C-4a), 78.7 (C-3), 72.6 (C-1'), 47.0 (C-2'), 41.6 (C-6'), 40.9 (C-4), 34.2 (C-4'), 31.4 (C-5'), 24.4 (C-7'), 22.5 (C-3'), 22.0 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>), 15.2 (CH<sub>3</sub>).

Anal. Calcd. for C<sub>30</sub>H<sub>33</sub>NO<sub>3</sub> (455.60): C, 79.09; H, 7.30; N, 3.07. Found: C, 79.38; H, 7.16; N, 3.09.

In the mother liquors, the mixture **8** [C-4(*S*) and C-4(*R*)] was observed. The spectroscopic analysis of this mixture allowed us to assign the following spectroscopic data for the minor diastereomer [C-4(*R*)]: <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  8.21 (d, 1H, aromatic), 7.75 (d, 1H, aromatic), 7.57-7.45 (m, 3H, aromatics), 7.27-7.08 (m, 6H, aromatics), 6.48 (br s, 2H, NH<sub>2</sub>), 5.02 (s, 1H, H-4), 4.63 (dt, 1H, J<sub>ax,ax</sub> = 10.8 Hz, J<sub>ax,eq</sub> = 4.2 Hz, H-1'), 2.05-0.80 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.95, 0.80, 0.76 (d, J = 6.9 Hz, 3 CH<sub>3</sub>); <sup>13</sup>C nmr (deuteriochloroform):  $\delta$  169.0 (CO<sub>2</sub>), 159.6 (C-2), 147.6 (C<sub>ipso</sub>), 142.8 (C-10b), 132.7 (C-6a), 127.9, 127.8, 127.4, 126.6, 126.1, 126.0, 125.9, 123.7, 120.7 (aromatics), 123.1 (C-10a), 120.3 (C-4a), 78.9 (C-3), 72.9 (C-1'), 47.1 (C-2'), 40.8 (C-6'), 40.3 (C-4), 34.1 (C-4'), 31.0 (C-5'), 26.3 (C-7'), 24.8 (C-3'), 23.4 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 16.5 (CH<sub>3</sub>).

X-Ray Crystal Analysis Structure of Major **8** [10] Isomer:

Crystal data: C<sub>30</sub>H<sub>33</sub>NO<sub>3</sub>, Mw = 455.596, monoclinic, P2<sub>1</sub>, a = 8.105(1) Å, b = 6.363(1) Å, c = 24.328(2) Å,  $\beta$  = 90.85(1), V = 1254.5(4) Å<sup>3</sup>, Z = 2, D<sub>c</sub> = 1.21 gr/cm<sup>3</sup>, F(000) = 488.0,  $\mu$  = 5.725 cm<sup>-1</sup>. Refined cell parameters were obtained from the setting angles of 62 reflections. Prismatic colorless crystal (0.40 x 0.30 x 0.20 mm) was used for the analysis.

Data collection: Automatic four circle diffractometer Seifert XRD300-S, running with the CRYSDOM program system with graphite oriented monochromated Cu-K radiation. The intensity data were collected using the  $\kappa/2\theta$  scan mode between 2 <  $\theta$  < 65; two standard reflections were measured every 100 reflections with no intensity variation. A total of 2270 reflections were measured and 1701 were considered as observed [I > 2 $\sigma$ (I) cri-

terium]. The data were corrected for Lorentz and Polarization effects.

Structure solution and refinement: The structure was solved by direct methods using SIR92 [11]. H atoms belonging to NH<sub>2</sub> group were located from a Fourier difference synthesis and the rest were calculated geometrically. Coordinates and isotropic thermal parameters of H atoms were considered as fixed contributors in a final mixed refinement. A convenient weighting scheme was applied to obtain no dependence in <w<sup>2</sup>F> vs. <F<sub>0</sub>> and <sin  $\theta/\lambda$ > [12]. Final R (Rw) value were 3.8 (4.6). Atomic scattering factors for the compound were taken from International Tables for X-Ray Crystallography [13] and calculations were performed using XTAL [14], HSEARCH [15] and PARST [16].

2-Amino-4-(*p*-bromo)phenyl-3-[(1*R*,2*S*,5*R*)-menthylloxycarbonyl]-4*H*-naphtho[1,2-*b*]pyran (**9**).

Following the General Procedure, using (1*R*,2*S*,5*R*)-menthyl arylideneacyanoacetate **7** (0.4 g, 1.02 mmoles), after 2 hours, compound **9** (oil, 0.348 g, yield 64%) was obtained as a mixture of isomers at C-4, that we were unable to separate; ir (potassium bromide): 3450, 3300, 2970, 1670, 1610, 1520, 1500, 1450 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): major diastereomer (C-4 *S*):  $\delta$  8.19 (d, 1H, aromatic), 7.75 (d, 1H, aromatic), 7.58-7.44 (m, 3H, aromatics), 7.36-7.09 (m, 5H, aromatics), 6.52 (br s, 2H, NH<sub>2</sub>), 5.00 (s, 1H, H-4), 4.69 (dt, 1H, J<sub>ax,ax</sub> = 10.8 Hz, J<sub>ax,eq</sub> = 4.2 Hz, H-1'), 2.05-0.80 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.95, 0.80, 0.79 (d, J = 6.9 Hz, 3 CH<sub>3</sub>); minor diastereomer (C-4 *R*):  $\delta$  8.21 (d, 1H, aromatic), 7.76 (d, 1H, aromatic), 7.58-7.44 (m, 3H, aromatics), 7.36-7.09 (m, 5H, aromatics), 6.48 (br s, 2H, NH<sub>2</sub>), 4.99 (s, 1H, H-4), 4.65 (dt, 1H, J<sub>ax,ax</sub> = 10.8 Hz, J<sub>ax,eq</sub> = 4.2 Hz, H-1'), 2.05-0.80 (m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.95, 0.80, 0.79 (d, J = 6.9 Hz, 3 CH<sub>3</sub>).

Anal. Calcd. for C<sub>30</sub>H<sub>32</sub>BrNO<sub>3</sub> (534.49): C, 67.41; H, 6.03; Br, 14.95; N, 2.79. Found: C, 67.81; H, 6.15; Br, 14.66; N, 2.38.

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