A Library of Pyranocoumarin Derivatives *via* a One-Pot Three-Component Hetero Diels-Alder Reaction [1]

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A hetero Diels-Alder reaction with inverse electron demand between 4-hydroxycoumarin, aromatic aldehydes and electron-rich alkenes yielded a multitude of 2,4-disubstituted 3,4-dihydropyranocoumarins. This route opened an easy access to coumarin anticoagulants and provided a library of pyranocoumarin derivatives.

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Coumarin derivatives are widespread in Nature, especially in higher plants [2]. In particular the pyrano[3,2-*c*]coumarin system is the core of important natural products and a versatile template for the preparation of a variety of biologically active molecules. The hemorrhagic toxin ferprenine (A) [3], the antiprotozoan ethuliacoumarins (B) [4] as well as the uterotonic pterophyllins (C) [5] (Figure 1), all of them objects of previous synthetic studies of ours [6], show how wide a range of activities may be expected from this family of compounds. Its basic structure has been thoroughly exploited in order to synthesize new oral anticoagulants, and many pyranocoumarin derivatives have been tested. The most active among them was found to be warfarin (D) [7], the prototype of 4-hydroxycoumarin anticoagulants; in 1952 its water soluble sodium salt was introduced for clinical use [8].

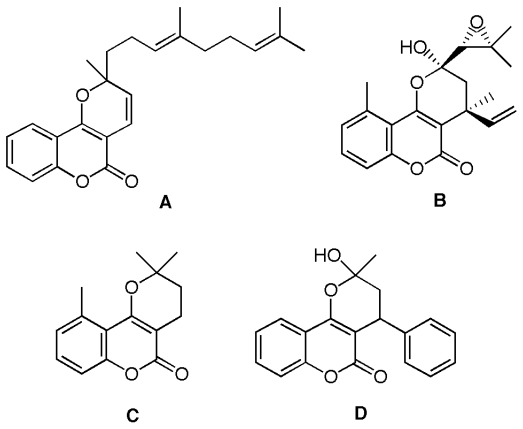
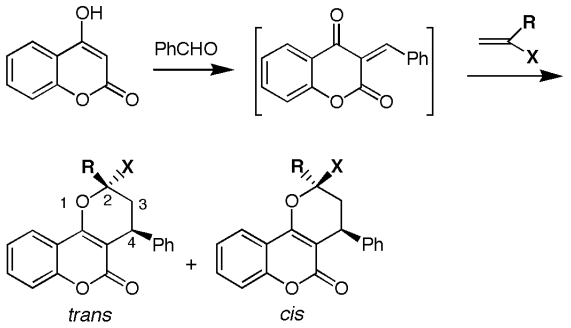


Figure 1. Biologically active pyranocoumarins: A) ferprenine; B) ethuliacoumarin A; C) pterophyllin III; D) cyclocoumarol (hemiacetalic form of warfarin).

We deemed it desirable for assay purposes to provide a library of analogues that would allow the pharmacological potential of the pyranocoumarin core to be systematically investigated.

We wish to report a distinct improvement in the synthesis of pyranocoumarin derivatives through a pericyclic approach [9]. This route offers a valid alternative to the standard industrial synthesis for warfarin and its analogues that exploits the Michael addition to 4-hydroxycoumarin of the corresponding phenyl-substituted benzalacetones. In the following one-pot reaction, 2,4-disubstituted 3,4-dihydropyranocoumarins were obtained by a hetero Diels-Alder (HDA) with inverse electron demand between 4-hydroxycoumarin, aromatic aldehydes and electron-rich alkenes.

Scheme 1 Synthesis of pyranocoumarins **1** - **14**.

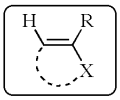


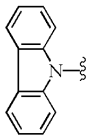
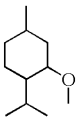
By using benzaldehyde to generate the chromanedione intermediate and by varying the R^1 and X groups of the 2π component (Scheme 1), a library of these compounds was obtained and characterized (Table 1). An analysis of the HOMO-LUMO interaction between dienophile and diene showed vinylethers and enamines to be the best 2π candidates for this type of [4π + 2π] cycloaddition. The reaction is usually a concerted nonsynchronous transformation in which the configuration of the dienophile is retained; it exhibits normally high regioselectivity [10].

In all diastereomer couples of entries **1-6** the predominant configuration was *cis*, as confirmed unequivocally by NOE and 2D NOESY nmr spectra. The *cis* and *trans* isomers (scheme 1) correspond to the *endo* and *exo* addition products regarding the X group. As shown in Figure 2, in the *cis* isomers H-2 and H-4 protons must be spatially close in the B conformer (giving rise to an appreciable NOE), whereas in the *trans* isomers a weak or non-existent NOE effect is to be expected. Moreover all 2D NOE spectra of *cis* derivatives reveal a magnetization transfer between the H-2 and H-4 hydrogens [11].

Table 1

Reaction Data for the HDA Reaction; Columns R and X Refer to Substituents on Dienophyles **1 - 8**



Entry	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
R	H	H	H	H	H	H	Me	H
X								
Reaction time (h)	5	30	48	24	5	24	4	5
Yield %	58	60	30	67	55	69	64	65
cis:trans	60:40	62:38	79:21	68:32	75:25	80:20	73:27	61:39

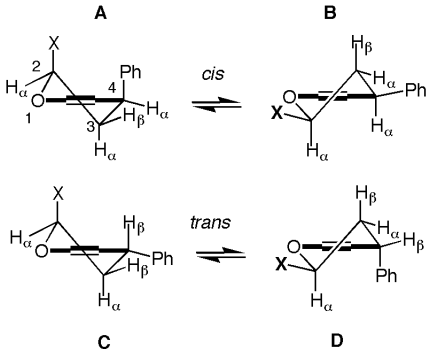


Figure 2. Conformers for *cis* and *trans* diastereomers of pyranocoumarins **1 – 8**.

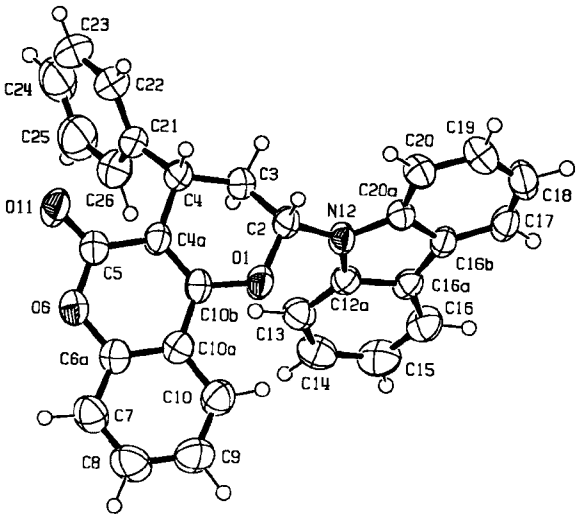
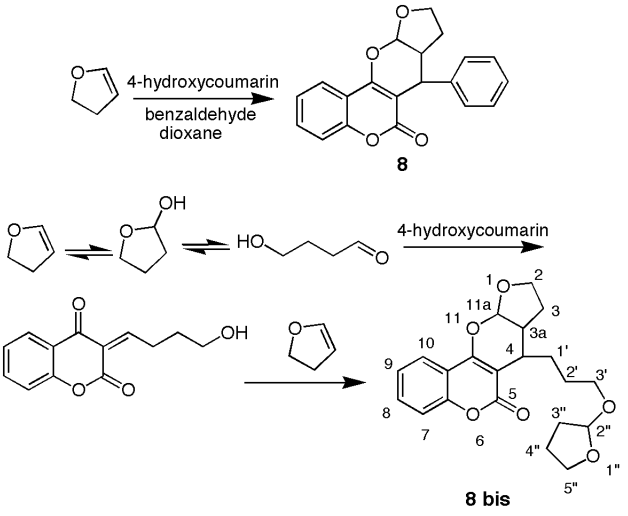


Figure 3. Plot of one independent molecule of **1** in the crystal. Thermal ellipsoids at 50% probability level. H atoms not to scale.

The cycloadducts deriving from *N*-vinylcarbazole (**1**) [12] and 2,3-dihydrofuran (**8**) gave crystals suitable for X-ray analysis, which confirmed the relative configurations of the two stereogenic centers (Figure 3).

In the reaction of 2,3-dihydrofuran, benzaldehyde and 4-hydroxycoumarin we isolated as a by-product a new heterocyclic compound (**8 bis**), arising from the tandem Knoevenagel hetero Diels-Alder reaction described in Scheme 2. After the hydratation of dihydrofuran and the lactol ring opening, a Knoevenagel condensation took place between the resulting hydroxyaldehyde and 4-hydroxycoumarin, affording the alkylidenchromanedione that underwent the final Diels-Alder cycloaddition with 2,3-dihydrofuran.

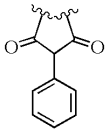
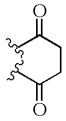
Scheme 2 Cycloadducts (**8** - **8 bis**) of 2,3-dihydrofuran.



Although several examples are reported [13] of cycloadditions with dienophiles **9 - 14** (Table 2), in our hands

Table 2

R and X Substituents on Non-reacting Dienophiles (**9** – **14**)

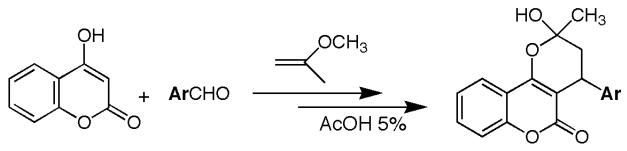
Entry	**9**	**10**	**11**	**12**	**13**	**14**
R	H	Me	H	H	H	H
X						

these compounds uniformly failed to undergo the HDA reaction with the 3-(het)arylidene-2,4-chromanedione intermediates.

The library was further extended by using 2-methoxypropene as dienophile and by varying the 4π component (Scheme 2). The results (Table 3) demonstrate an easy access to coumarin anticoagulants.

The acetal function of pyranocoumarin can easily be hydrolyzed by treatment with 5% AcOH or 3*N* HCl in the presence of SiO_2 as a promoter [14]. By reacting together 4-hydroxycoumarin, benzaldehyde and 2-methoxypropene, and by further hydrolysis of the acetal product, we obtained the anticoagulant drug cyclocumarol, that is the hemiacetalic form of warfarin.

Scheme 3 Synthesis of the coumarin anticoagulants **15 - 18**.



Spectroscopic data quantified the relation between the two anomers (74:26, *cis* being the prevalent form). At equilibrium the closed hemiacetalic form predominated (2:1) over the open-chain form, in accordance with published data concerning equilibria in warfarin solutions [15]. Resolution of the racemate was achieved by liquid chromatography using a chiral stationary phase. By this synthetic route it is possible to prepare the common coumarin anticoagulants used in therapy: coumachlor [16], acenocoumarol [17], coumafuryl [18].

Table 3

Reaction Data for the Preparation of Coumarin Anticoagulants **15 - 18**

Entry	**15**	**16**	**17**	**18**
Ar	phenyl	*p*-chlorophenyl	*p*-nitrophenyl	furyl
Yield %	83	74	70	68
Product	warfarin	coumachlor	acenocoumarol	coumafuryl
cis:trans	76 : 24	66 : 34	64 : 36	59 : 41

X-Ray Crystallographic Study of **1**.

Single-crystal X-ray diffraction measurements were performed on a Bruker P4 diffractometer, with a graphite monochromator, using Mo-Kα radiation (λ = 0.71073 Å). Crystal data are as follows: $C_{30}H_{21}NO_3$, M_r = 443.48, monoclinic, space group $P2_1/n$, a = 9.4862(9), b = 27.245(3), c = 17.4803(15) Å, β = 95.067(6)°, V = 4500.2(8) Å3, Z = 8, D_c = 1.309 gcm-3, μ(Mo-Kα) = 0.084 mm-1; 9922 reflections collected (2θ < 50°), 7938 independent, R_{ave} = 0.0157; the structure was solved by *SIR-92* [19], and refined on $F2$ by *SHELX-97* [20], 782 parameters refined, $R_w(F2)$ = 0.0947, R = 0.798 for all independent reflections [0.0781 and 0.373, respectively for 4759 reflections with $I > \sigma(I)$]. The asymmetric unit contains two molecules that essentially differ for the conformation of the carbazole-bonded ring: in one molecule the ring (O1,C2,C3,C4,C4A,C10B, see Figure 1) has an envelope conformation (^{3}E according to Boyens notation) [21], with puckering ring parameters [22] φ_2 = 114.9(3)°, θ_2 = 53.2(2)°, Q_t = 0.438(2) Å; in the other molecule the same ring is a half-chair ($^3H_2$), with φ_2 = 84.1(2)°, θ_2 = 56.5(2)°, Q_t = 0.534(2) Å. The chemically equivalent hydrogen atoms bonded to C2 and C52 are quite acidic; they are actually implied in a chain of hydrogen bonds, namely, C2-H2…O11 and C52-H62…O61I (where I means *1+x,y,z*), bond lengths being 3.154(2) Å for C2…O11, 2.14(2) Å for H2…O11, 162(2) A° for C2-H2…O11, 3.284(2) Å for C52…O61', 2.45(2) Å for H52…O61' and 138.(2) A° for C52-H52…O61'. All crystallographic data (excluding structure factors) were deposited to the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-158091. Copies can be obtained free of charge on application to CCDC, 2 Union Road, Cambridge CB2 1EZ, UK (e-mail deposit@ccdc,cam.ac.uk).

EXPERIMENTAL

General Methods.

Anhydrous conditions were achieved (when indicated) by flame-drying flasks and equipment. Reactions were monitored by TLC on Alugram Sil - Macherey Nagel (F254, 0.25 mm) plates; spots were detected firstly by UV inspection, then by staining with

5% aqueous $KMnO_4$ or 5% H_2SO_4 in ethanol and heating. Merck silica gel was used for open-column- (CC) and medium-pressure liquid chromatography (MPLC) (70-230 mesh and 230-440 mesh, respectively). MPLC was carried out on a Büchi instrument B 680A, equipped with a B 685-type column. A Waters microPorasil column (0.8 x 30 cm) was employed for semi-preparative HPLC, a Waters differential refractometer 340 being used for detection. Racemate resolution was achieved by chiral HPLC with a (*R,R*)-Welk column (Merck). Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H-nmr (300 MHz) and ^{13}C-nmr (75 MHz) spectra were recorded on a Bruker AC-300 spectrometer at 25 °C. LRMS were performed on a Finnigan-MAT TSQ70, using isobutane as reactant gas for CIMS. IR spectra were recorded with a Shimadzu FT-IR 8001. Dioxane was dried by distillation from Na-benzophenone ketyl. $MgSO_4$ was used for drying organic solutions in all work-up procedures. Commercially available reagents and solvents were used without further purification unless otherwise noted.

General Synthetic Procedure for Entries **1-15** .

In a 100 mL two-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser and a nitrogen inlet, the following were placed: dry dioxane (20 mL), oven-dried powdered 5-Å molecular sieves (0.3 g), 4-hydroxycoumarin, (500 mg, 3.08 mmol) and a catalytic amount of ethylendiammonium diacetate (Tietze base). To this stirred suspension benzaldehyde (470 mL, 4.6 mmol, 1.5 mol equivalent) and the appropriate electron-rich alkene (6.8 mol equivalent) were then added. The reaction mixture was heated at 90 °C until 4-hydroxycoumarin disappeared (4-24 hours). After evaporation of the solvent under vacuum, the residue was purified either by chromatography on a column packed with silica gel or by MPLC using hexane-EtOAc mixtures as eluents. In some cases further purification was achieved by semi-preparative HPLC

General Synthetic Procedure for Entries **16-19**.

Under the same reaction conditions, 2-methoxypropene (8.0 mol equivalent) was used as 2π component; in entries **17-19** benzaldehyde was replaced by the corresponding enal.

2,3,4,5-Tetrahydro-2-(carbazol-9'-yl)-4-phenylpyrano[3,2-*c*]benzopyran-5-one (**1**).

Both diastereomers, as obtained after CC purification (petroleum ether/EtOAc 7:3), were colorless foams. R_f (hexane/EtOAc 3:7) 0.26 (*trans*), 0.23 (*cis*); ir (KBr) 1713, 1595, 1464, 1234, 1055, 980, 871 cm^{-1}; ms: m/z 443 (M^+), 263, 193, 167, 121; CI: 244 (MH^+).

The *trans*-isomer has mp 164 °C; ^{1}H nmr ($CDCl_3$): δ 7.87 (d, 1H, J = 7.65 Hz, H-10), 7.45-6.90 (m, 16H, H-9, H-8, H-7, Ph, 8H carbazole), 6.13 (br d, 1H, J = 11.0 Hz, H-2), 4.289 (m, 1H, H-4), 2.46 (m, 1H, H-3a), 2.39 (m, 1H, H-3b); ^{13}C nmr ($CDCl_3$): δ 170.5 (C-4'b), 170 (C-4'a), 169.4 (C-8'a), 168.6 (C-9'a), 161.6 (C-5), 161.2 (C-10b), 153.0 (C-6a), 142.1 (C-1'), 142.0 (C-1"), 132.0 (C-8), 129.0 (C-2"), 128.9 (C-2'), 128.7 (C-6'), 128.0 (C-8'), 127.6 (C-3' and C-7'), 127.5 (C-3"), 127.2 (C-4'), 127.0 (C-4"), 126.4 (C-5'), 123.4 (C-9), 122.7 (C-10), 116.5 (C-7), 115.2 (C-10a), 104.4 (C-4a), 79.7 (C-2), 38.0 (C-4), 36.9 (C-3).

Anal. Calcd for $C_{30}H_{21}O_3N$: C, 81.25; H, 4.77. Found: C, 81.07; H, 4.70.

The*cis*-isomer has mp 130 °C; ^{1}H nmr ($CDCl_3$): δ 7.84 (d, 1H, J = 7.65 Hz, H-10), 7.49-6.90 (m, 16H, H-9, H-8, H-7, Ph, 8H carbazole), 6.59 (dd, 1H, J = 11.60, 2.23 Hz, H-2), 4.19 (dd, 1H, J = 11.26, 7.05 Hz, H-4), 2.86 (dt, 1H, J = 14.1, 11.45 Hz, H-3a), 2.39 (ddd, 1H, J = 14.18, 7.10, 2.23 Hz, H-3b); ^{13}C nmr ($CDCl_3$): δ 171.1 (C-4'b), 170.2 (C-4'a), 170.0 (C-8'a), 169.5 (C-9'a), 161.6 (C-5), 160.6 (C-10b), 152.6 (C-6a), 142.7 (C-1'), 125.0 (C-1"), 131.9 (C-8), 128.9 (C-2'), 128.6 (C-2"), 128.4 (C-6'), 129.0 (C-8'), 128.0 (C-7'), 126.6 (C-3'), 127.0 (C-3"), 126.8 (C-4'), 126.9 (C-4"), 126.3 (C-5'), 123.6 (C-9), 122.7 (C-10), 116.7 (C-7), 115.5 (C-10a), 104.8 (C-4a), 76.3 (C-2), 36.3 (C-4), 32.4 (C-3).

Anal. Calcd for $C_{30}H_{21}O_3N$: C, 81.25; H, 4.77. Found: C, 81.15; H, 4.88.

2,3,4,5-Tetrahydro-2-[1'-(2'-oxopyrrolidinyl)]-4-phenylpyrano-[3,2-*c*]benzopyran-5-one (**2**).

Both diastereomers, after CC purification (petroleum ether/EtOAc 1:1), were pale yellow powders. R_f (hexane/EtOAc 3:7) = 0.26 (*trans*), 0.24 (*cis*); ir (KBr) 1717, 1624, 1388, 1282, 997, 760 cm^{-1}; ms: m/z 361 (M^+), 299, 281, 214, 121; CI : 362 (MH^+).

The*trans*-isomer has mp 164 °C; ^{1}H nmr ($CDCl_3$): δ 7.83 (br d, 1H, J = 8.2 Hz, H-10), 7.55 (br t, 1H, J = 7.8 Hz, H-8), 7.33 (m, 2H, H-7, H-9), 7.30 (m, 5H, Ph), 6.0 (dd, 1H, J = 2.4, 12.0 Hz, H-2), 4.4 (dd, 1H, J = 1.6, 5.7 Hz, H-4), 3.55 (m, 1H, H-5'), 2.47 (m, 1H, H-3'), 2.46 (m, 1H, H-3a), 2.13 (m, 2H, H-3b, H-4'); ^{13}C nmr ($CDCl_3$): δ 175.8 (C-2'), 160.6 (C-5), 160.0 (C-10b), 153.0 (C-6a), 142.1 (C-1"), 132.0 (C-8), 128.9 (C-2"), 127.6 (C-3"), 127.2 (C-4"), 123.8 (C-9), 122.9 (C-10), 116.7 (C-7), 115.5 (C-10a), 105.0 (C-4a), 76.6 (C-2), 42.4 (C-5'), 36.1 (C-4), 32.0 (C-3), 31.2 (C-3'), 18.1 (C-4').

Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30. Found: C, 72.89; H, 5.44.

The*cis*-isomer has mp 130 °C; ^{1}H nmr ($CDCl_3$): δ 7.78 (br d, 1H, J = 7.8 Hz, H-10), 7.53 (m, 1H, H-8), 7.33 (m, 7H, H-7, H-9, Ph), 7.30 (m, 3H, H-2", H-3", H-4"), 6.13 (dd, 1H, J = 2.0, 12.0 Hz, H-2), 4.22 (dd, 1H, J = 7.0 Hz, H-4), 3.67 (m, 1H, H-5'), 2.53 (m, 1H, H-3'), 2.42 (m, 1H, H-3a), 2.23 (m, 1H, H-3b), 2.13 (m, 1H, H-4'); ^{13}C nmr ($CDCl_3$): δ 175.8 (C-2'), 161.0 (C-5), 160.6 (C-10b), 152.8 (C-6a), 142.7 (C-1"), 131.9 (C-8), 128.9 (C-2"), 126.6 (C-3"), 126.8 (C-4"), 123.7 (C-9), 122.9 (C-10), 116.5 (C-7), 115.2 (C-10a), 104.4 (C-4a), 79.7 (C-2), 42.3 (C-5'), 39.0 (C-4), 37.0 (C-3), 31.1 (C-3'), 18.1 (C-4').

Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30. Found: C, 72.94; H, 5.40.

2,3,4,5-Tetrahydro-2,4-diphenylpyrano[3,2-*c*]benzopyran-5-one (**3**).

Both diastereomers, as obtained after CC purification (petroleum ether/EtOAc 7:3), were gums. R_f (hexane/EtOAc 3:7) = 0.47 (*trans*), 0.25 (*cis*); ir (KBr) 1726, 1622, 1493, 1454, 1111, 981 cm^{-1}; ms: m/z 354, 339, 263, 249, 221, 121; CI 355 (MH^+).

The *trans*-isomer has ^{1}H nmr ($CDCl_3$): δ 7.83 (d, 1H, J = 8.2 Hz, H-10), 7.53 (t, 1H, J = 7.8 Hz, H-8), 7.43-7.26 (m, 12H, 2Ph, H-7, H-9), 5.13 (dd, 1H, J = 2.6, 7.0 Hz, H-2), 4.35 (dd, 1H, J = 6.2 Hz, H-4), 2.38 (m, 2H, H-3a, 3b); ^{13}C nmr ($CDCl_3$): δ 161.85 (C-5), 161.2 (C-10b), 152.9 (C-6a), 143.25 (C-1"), 139.0 (C-1'), 131.5 (C-8), 128.8 (C-3', C-2"), 128.7 (C-2'), 126.8 (C-3", C-4'), 126.0 (C-4"), 123.9 (C-9), 122.7 (C-10), 117.0 (C-7), 115.7 (C-10a), 104.9 (C-4a), 79.3 (C-2), 41.5 (C-4), 39.1 (C-3).

Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.07; H, 5.20.

The *cis*-isomer has ^{1}H nmr ($CDCl_3$) δ 7.88 (d, 1H, J = 8.0 Hz, H-10), 7.53 (t, 1H, J = 7.5 Hz, H-8), 7.43-7.23 (m, 12H, 2Ph, H-7,

H-9), 5.30 (dd, 1H, J = 2.6, 6.0 Hz, H-2), 4.23 (m, 1H, H-4), 2.67 (m, 1H, H-3a), 2.30 (m, 1H, H-3b); ^{13}C nmr ($CDCl_3$): δ 161.85 (C-5), 161.2 (C-10b), 152.9 (C-6a), 143.25 (C-1"), 139.0 (C-1'), 131.7 (C-8), 128.8 (C-3', C-2"), 128.7 (C-2'), 126.8 (C-3"), 126.6 (C-4'), 126.0 (C-4"), 123.75 (C-9), 122.9 (C-10), 116.6 (C-7), 115.7 (C-10a), 104.9 (C-4a), 79.65 (C-2), 41.5 (C-4), 39.1 (C-3).

Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.30; H, 5.10.

2,3,4,5-Tetrahydro-2-*tert*-butyloxy-4-phenylpyrano[3,2-*c*]benzopyran-5-one (**4**).

The two diastereomers, after CC purification (petroleum ether/EtOAc 19:1), were colorless solids. R_f (hexane/EtOAc 8:2) = 0.54 (*cis*), 0.46 (*trans*); ir (KBr) 1713, 1626, 1493, 1088, 941, 758 cm^{-1}; ms: m/z 350(M^+), 294, 265, 251, 175, 121; CI: 351 (MH^+).

The *trans*-isomer has mp 162 °C; ^{1}H nmr ($CDCl_3$): δ 7.81 (d, 1H, J = 8.1 Hz, H-10), 7.53 (t, 1H, J = 7.7 Hz, H-8), 7.33 (m, 1H, H-7), 7.29 (m, 1H, H-9), 7.27-7.24 (m, 5H, Ph), 5.51 (dd, 1H, J = 2.5, 8.0 Hz, H-2), 4.25 (dd, 1H, J = 5.8, 4.7 Hz, H-4), 2.33 (m, 1H, H-3b), 2.12 (m, 1H, H-3a), 1.29 (s, 9H, *t*-But); ^{13}C nmr ($CDCl_3$): δ 161.5 (C-5), 159.4 (C-10b), 152.9 (C-6a), 140.15 (C-1'), 131.6 (C-8), 128.7 (C-2'), 127.3 (C-3'), 126.7 (C-4'), 123.7 (C-9), 122.8 (C-10), 116.6 (C-7), 115.8 (C-10a), 102.3 (C-4a), 94.0 (C-2), 76.2 (C-*t*-But), 37.0 (C-3), 35.5 (C-4), 28.6 (*t*-But).

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.63; H, 6.44.

The *cis*-isomer has mp 162 °C; ^{1}H nmr ($CDCl_3$): δ 7.81 (d, 1H, J = 8.2 Hz, H-10), 7.53 (t, 1H, J = 7.8 Hz, H-8), 7.33 (m, 1H, H-7), 7.29 (m, 1H, H-9), 7.27-7.24 (m, 5H, Ph), 5.67 (dd, 1H, J = 2.5, 5.5 Hz, H-2), 4.16 (m, 1H, H-4), 2.4 (m, 1H, H-3b), 2.27 (m, 1H, H-3a), 1.22 (s, 9H, *t*-But); ^{13}C nmr ($CDCl_3$): δ 161.5 (C-5), 159.35 (C-10b), 152.9 (C-6a), 140.1 (C-1'), 131.6 (C-8), 128.0 (C-2'), 126.2 (C-3'), 126.1 (C-4'), 123.7 (C-9), 122.8 (C-10), 116.6 (C-7), 115.9 (C-10a), 103.6 (C-4a), 95.1 (C-2), 76.2 (C-*t*-But), 37.3 (C-3), 35.5 (C-4), 28.3 (*t*-But).

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.33; H, 6.34.

2,3,4,5-Tetrahydro-2-ethoxy-4-phenylpyrano[3,2-*c*]benzopyran-5-one (**5**).

The two diastereomers, after CC purification (petroleum ether/EtOAc 19:1), were colorless solids. R_f (hexane/EtOAc 8:2) = 0.45 (*cis*), 0.36 (*trans*); ir (KBr) 1713, 1626, 1493, 1084, 849, 758 cm^{-1}; ms: m/z 322(M^+), 293, 265, 249, 121; CI 323 (MH^+).

The *trans*-isomer has mp 142 °C; ^{1}H nmr ($CDCl_3$): δ 7.87 (br d, 1H, J = 7.2 Hz, H-10), 7.53 (t, 1H, J = 7.8 Hz, H-8), 7.33 (m, 7H, H-7, Ph, H-9), 5.27 (dd, 1H, J = 3.0, 7.7 Hz, H-2), 4.25 (dd, 1H, J = 6.0 Hz, H-4), 4.08 (m, 1H, OCH_2a), 3.69 (m, 1H, OCH_2b), 2.30-2.28 (m, 2H, H-3a, H-3b), 1.28 (t, 3H, J = 6.6 Hz, CH_3); ^{13}C nmr ($CDCl_3$): δ 161.5 (C-5), 158.9 (C-10b), 152.9 (C-6a), 142.95 (C-1'), 131.7 (C-8), 128.7 (C-2'), 127.45 (C-3'), 126.2 (C-4'), 123.8 (C-9), 122.7 (C-10), 116.6 (C-7), 115.7 (C-10a), 105.0 (C-4a), 99.3 (C-2), 65.6 (OCH_2), 35.8 (C-3), 35.4 (C-4), 15.2 (CH_3).

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.63; H, 6.44.

The *cis* -Isomer has mp 144 °C; ^{1}H nmr ($CDCl_3$): δ 7.87 (br d, 1H, J = 7.1 Hz H-10), 7.53 (t, 1H, J = 7.8 Hz, H-8), 7.32-7.23 (m, 7H, H-7, Ph, H-9), 5.44 (dd, 1H, J = 2.5, 4.6 Hz, H-2), 4.15 (dd, 1H, J = 6.0 Hz, H-4), 3.95 (m, 1H, OCH_2a), 3.62 (m, 1H, OCH_2b), 2.46 (m, 1H, H-3a), 2.31 (m, 1H, H-3b), 1.12 (t, 3H, J = 6.6 Hz, CH_3); ^{13}C nmr ($CDCl_3$): δ 161.5 (C-5), 158.9 (C-10b), 152.9 (C-6a), 142.95 (C-1'), 131.7 (C-8), 128.1 (C-2'), 127.45 (C-3'), 126.2 (C-4'), 123.8 (C-9), 122.7 (C-10), 116.6 (C-7), 115.7 (C-10a), 103.8 (C-4a), 100.1 (C-2), 65.1 (OCH_2), 35.8 (C-3), 35.1 (C-4), 15.0 (CH_3).

Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.56; H, 6.49.

2,3,4,5-Tetrahydro-2-[3'-(±)-menthyloxy]-4-phenylpyrano[3.2-*c*]-benzopyran-5-one (**6**).

The two diastereomers, after MPLC purification (petroleum ether/EtOAc 19:1), were colorless oils. R_f (hexane-EtOAc 8:2) = 0.32 (*cis*), 0.29 (*trans*); ir (liquid film) 1815, 1690, 1410, 1299, 870, 750 cm^{-1}; ms: m/z 432 (M^+), 294, 265, 251, 121; CI: 433 (MH^+).

The *trans*-isomer has ^{1}H nmr ($CDCl_3$): δ 7.85 (d, 1H, J = 7.0 Hz, H-10), 7.53 (t, 1H, J = 7.7 Hz, H-8), 7.33-7.27 (m, 2H, H-7, H-9), 7.21-7.18 (m, 5H, Ph), 5.56 (dd, 1H, J = 3.0, 7.7 Hz, H-2), 4.18, (dd, 1H, J = 6.4 Hz, H-4), 3.63 (m, 1H, H-3'), 2.46 (m, 1H, H-3a), 2.33 (m, 1H, H-3b), 2.27 (m, 1H, H-2'a), 1.62-1.60, (m, 4H, H-5'a, H-6'a,b, H-8'), 1.40 (m, 1H, H-1'), 1.33 (m, 1H, H-4') 0.93 (m, 1H, H-5'b), 0.89 (m, 3H, H-7'), 0.80 (m, 4H, H-2'b, H-9'), 0.69 (br d, 3H, H-10'); ^{13}C nmr ($CDCl_3$): δ 161.7 (C-5), 159.3 (C-10b), 152.8 (C-6a), 142.8 (C-1"), 131.7 (C-8), 128.0 (C-3"), 127.3 (C-2"), 126.0 (C-4"), 123.87(C-9), 122.8 (C-10), 116.6 (C-7), 115.8 (C-10a), 103.5 (C-4a), 97.6 (C-2), 77.8 (C-3'), 47.3 (C-4'), 40.2 (C-2'), 36.8 (C-4), 35.4 (C-6'), 34.0 (C-3), 31.4 (C-1'), 25.0 (C-8'), 23.0 (C-5'), 22.2 (C-7'), 20.9 (C-9'), 15.9 (C-10').

Anal. Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.70; H, 7.96.

The *cis*-isomer has ^{1}H nmr ($CDCl_3$): δ 7.83 (d, 1H, J = 7.1 Hz, H-10), 7.53 (t, 1H, J = 7.5 Hz, H-8), 7.33 (m, 1H, H-7), 7.27 (m, 1H, H-9), 7.21-7.18 (m, 5H, Ph), 5.47 (dd, 1H, J = 2.5, 4.6 Hz, H-2), 4.08, (dd, 1H, J = 6.0 Hz, H-4), 3.38 (m, 1H, H-3'), 2.46 (m, 1H, H-3a), 2.33 (m, 1H, H-3b), 2.27 (m, 1H, H-2'a), 1.62-1.60, (m, 4H, H-5'a, H-6'a,b, H-8'), 1.40 (m, 1H, H-1'), 1.33 (m, 1H, H-4') 0.93 (m, 1H, H-5'b), 0.89 (m, 3H, H-7'), 0.80 (m, 1H, H-2'b), 0.68 (br d, 3H, H-9'), 0.62 (br d, 3H, H-10'); ^{13}C nmr ($CDCl_3$): δ 161.7 (C-5), 159.2 (C-10b), 152.8 (C-6a), 143.0 (C-1"), 131.7 (C-8), 128.0 (C-3"), 127.3 (C-2"), 126.0 (C-4"), 123.8(C-9), 122.7 (C-10), 116.7 (C-7), 115.8 (C-10a), 103.5 (C-4a), 101.5 (C-2), 82.4 (C-3'), 48.0 (C-4'), 43.2 (C-2'), 36.0 (C-4), 35.0 (C-6'), 34.0 (C-3), 31.6 (C-1'), 25.2 (C-8'), 23.0 (C-5'), 22.3 (C-7'), 20.9 (C-9'), 15.9 (C-10').

Anal. Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.60.

2,3,4,5-Tetrahydro-2-methyl-2-methoxy-4-phenylpyrano[3,2-*c*]-benzopyran-5-one (**7**).

The two diastereomers, after CC purification (petroleum ether/EtOAc 19:1), were white powders. R_f (hexane / EtOAc 8:2) = 0.43 (*cis*), 0.34 (*trans*); ir (KBr) 1709, 1626, 1493, 1068, 978, 752 cm^{-1}; ms: m/z 322(M^+), 275, 265, 249, 148, 121; CI: 323 (MH^+).

The *trans* -isomer has mp 170 °C; ^{1}H nmr ($CDCl_3$): δ 7.90 (d, 1H, J = 7.6 Hz, H-10), 7.57 (br t, 1H, J = 7.2 Hz, H-8), 7.33-7,23 (m, 7H, H-9, Ph, H-7), 4.13 (dd, 1H, J = 7.0, 4.0 Hz, H-4), 4.08 (s, 3H, OCH_3), 2.48 (m, 1H, H-3a), 2.33 (m, 1H, H-3b), 1.63 (s, 3H, CH_3); ^{13}C nmr ($CDCl_3$): δ 161.5 (C-5), 158.9 (C-10b), 152.8

(C-6a), 142.9 (C-1'), 131.7 (C-8), 128.5 (C-2'), 127.45 (C-3'), 126.2 (C-4'), 123.6 (C-9), 122.8 (C-10), 116.6 (C-7), 115.2 (C-10a), 104.6 (C-4a), 98.7 (C-2), 65.5 (CH_3), 63.5 (OCH_3), 35.6 (C-3), 35.3 (C-4).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.63; H, 5.60.

The *cis*-isomer has mp 135 °C; ^{1}H nmr ($CDCl_3$): δ 7.86 (d, 1H, J = 7.8 Hz, H-10), 7.50 (br t, J = 7.0 Hz, 1H, H-8), 7.33 (m, 1H, H-9), 7.27-7.23 (m, 6H, H-7, Ph), 4.11 (dd, 1H, J = 12.0, 7.0 Hz, H-4), 3.95 (s, 3H, OCH_3), 2.47 (dd, 1H, J = 12.0, 2.3 Hz, H-3a), 2.0 (dd, 1H, J = 7.0, 2.28 Hz, H-3b), 1.67 (s, 3H, CH_3); ^{13}C nmr ($CDCl_3$): δ 161.5 (C-5), 158.9 (C-10b), 152.8 (C-6a), 142.9 (C-1'), 131.7 (C-8), 128.1 (C-2'), 127.45 (C-3'), 126.2 (C-4'), 123.6 (C-9), 122.8 (C-10), 116.6 (C-7), 115.5 (C-10a), 103.8 (C-4a), 100.1 (C-2), 65.1 (CH_3), 63.0 (OCH_3), 35.6 (C-3), 35.3 (C-4).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.53; H, 5.54.

7,7a,8,9-Tetrahydro-7-phenyl-6*H*,10a*H*-furo[2',3':2,3]pyrano-[5,6-*c*][1]benzopyran-6-one (**8**).

Both CC and MPLC purification (petroleum ether/EtOAc 19:1), only yielded an enriched fraction for each diastereomer. On standing overnight, the solution that had been enriched with isomer *trans* (the minor product) crystallized. R_f (hexane/EtOAc 8:2) = 0.26 (*trans*), 0.25 (*cis*); ir (KBr) 1713, 1680, 1493, 1402, 1068, 902 cm^{-1}; ms: m/z 320 (M^+), 291, 249, 121, 70; CI 321 (MH^+).

The *trans*-isomer has mp 213 °C; ^{1}H nmr ($CDCl_3$) δ 7.93 (d, 1H, J = 8.2 Hz, H-10), 7.56 (t, 1H, J = 7.8 Hz, H-8), 7.32-7.21 (m, 7H, H-7, H-9, Ph), 5.44 (br s, 1H, H-11_a), 4.21-4.06 (m, 3H, H-4, H-2a, H-2b), 2.73 (m, 1H, H-3_a), 2.31 (m, 1H, H-3a), 1.84 (m, 1H, H-3b). ^{13}C nmr ($CDCl_3$): δ 158.0 (C-5), 156.0 (C-10b), 153.0 (C-6a), 142.8 (C-1'), 131.95 (C-8), 129.0 (C-2'), 127.0 (C-4'), 127.1 (C-3'), 123.9 (C-9), 123.1 (C-10), 116.7 (C-11), 116.2 (C-10a), 105.5 (C-4a), 92.5 (C-11a), 68.7 (C-2), 45.5 (C-4), 38.1 (C-3a), 27.2 (C-3a).

Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.09; H, 5.13.

7,7a,8,9-Tetrahydro-7-[3''-(tetrahydro-2-furyloxy)propyl]-6*H*,10a*H*-furo[2',3':2,3]pyrano[5,6-*c*][1]-benzopyran-6-one (**8bis**).

The MPLC purification as described for **8** yielded enriched fractions of another couple of diastereomers (**8bis**), as by-product. R_f (hexane / EtOAc 7:3) = 0.38 (*trans*), 0.40 (*cis*); ir (KBr) 1715, 1680, 1498, 1470, 1400, 1068, 902 cm^{-1}; ms: m/z 372 (M^+), 302, 243, 231, 121, 71; CI: 373 (MH^+); nmr data were obtained from spectra of the enriched fractions.

The *trans* -isomer has ^{1}H nmr ($CDCl_3$): δ 7.77 (d, 1H, J = 7.9 Hz, H-10), 7.45 (t, 1H, J = 7.1 Hz, H-8), 7.20 (m, 2H, H-7, H-9), 5.52 (br s, 1H, H-11_a), 5.06 (m, 1H, H-2''), 4.03 (m, 2H, H-2a,b), 3.80 (m, 2H, H-5''a,b), 3.67 (m, 1H, H-3'a), 3.33 (m, 1H, H-3'b), 3.10 (m, 1H, H-4), 2.73 (m, 1H, H-3a), 1.83 (m, 4H, H-3''a,b, H-4''a,b), 1.73 (m, 1H, H-3a), 1.60 (m, 2H, H-2'a,b), 1.43 (m, 1H, H-3b), 1.17 (m, 2H, H-1'a,b). ^{13}C nmr ($CDCl_3$): δ 161.7 (C-5), 157.8 (C-10b), 152.6 (C-6a), 131.5 (C-8), 123.6 (C-9), 123.0 (C-10), 116.1 (C-7), 115.4 (C-10a), 103.8 (C-2''), 102.25 (C-11a), 101.4 (C-4a), 68.5 (C-2), 66.8 (C-3'), 66.8 (C-5''), 41.7 (C-3a), 31.8 (C-3''), 31.4 (C-4), 27.25 (C-2'), 26.0 (C-1'), 23.5 (C-3, C-4'').

The *cis*-isomer has ^{1}H nmr ($CDCl_3$): δ 7.77 (d, 1H, J = 7.7 Hz, H-10), 7.46 (t, 1H, J = 7.0 Hz, H-8), 7.20 (m, 2H, H-7, H-9), 5.70 (br s, 1H, H-11_a), 5.03 (m, 1H, H-2''), 4.4 (m, 1H, H-2b), 4.2 (m, 1H, H-2a), 3.80 (m, 2H, H-5''a,b), 3.67 (m, 1H, H-3'a), 3.33 (m, 1H, H-3'b), 2.93 (m, 1H, H-4), 2.6 (m, 1H, H-3_a), 2.07 (m, 1H, H-3a), 1.83 (m, 4H, H-3''a,b, H-4''a,b), 1.73 (m, 1H, H-3b), 1.60 (m, 2H, H-2'a,b), 1.5 (m, 2H, H-1'a,b). ^{13}C nmr ($CDCl_3$): δ 162.5 (C-5), 157.45 (C-10b), 152.7 (C-6a), 131.5 (C-8), 123.7 (C-9), 122.9 (C-10), 116.4 (C-7), 115.3 (C-10a), 103.95 (C-2''), 100.5 (C-11a), 101.4 (C-4a), 68.4 (C-2), 67.2 (C-3'), 66.9 (C-5''), 41.4 (C-3a), 32.3 (C-3''), 31.3 (C-4), 27.4 (C-2'), 27.7 (C-3), 26.1 (C-1'), 23.5 (C-4'').

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