Pergamon

Tetrahedron 54 (1998) 233–242

TETRAHEDRON

A valuable route to benzopyrane[4,3-*c*]isoquinolines

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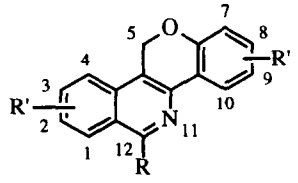
Received 7 October 1997; revised 28 October 1997; accepted 30 October 1997

Abstract: A direct synthesis of benzopyrane[4,3-*c*]isoquinolines **4** employing isoflavanone **2** as starting material is described. An alternative route for the preparation of dihydrobenzopyrane[4,3-*c*]isoquinolines **11** is also reported.

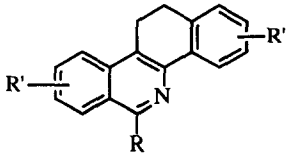
Introduction

In 1984 Shamma and cols. reported[1] the isolation of the first alkaloid with a benzopyraneisoquinoline skeleton from the Berberis *darwinii* species. Under that name, literature shows a variety of examples of this type of compounds, which in many cases exhibit a remarkable physiological activity. Thus, for example, antiinflammatory, antirheumatic, central nervous system depressor, dopaminergic, bactericide, antidepressive and parasympatholytics activities, *inter alia*, have been found.[2] Benzopyraneisoquinoline derivatives have also industrial applications and some of them have been used as dyes for polyester and polyamide tissues.[3] Besides, the synthetic strategies reported for the preparation of this kind of structures employ rather complex precursors, long synthetic pathways and, occasionally, strong reaction conditions.[4]

Considering these precedents, as well as our experience in the field of isoquinoline alkaloids, we undertook the challenge of designing a concise approach to benzopyrane[4,3-*c*]isoquinoline derivatives, isosteric compounds of the benzo[*c*]phenanthridines, a family of alkaloids which also exhibit a potent pharmacological activity.[5] We would like to report our results now that we have carried out the preparation of a series of benzopyraneisoquinolines with different substituents at C-12.



benzopyrane[4,3-*c*]isoquinoline



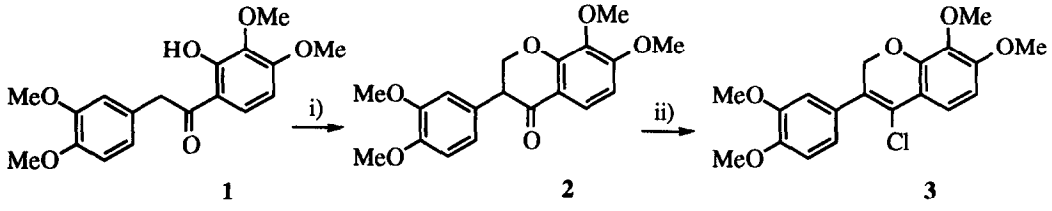
benzo[*c*]phenanthridine

0040-4020/98/$19.00
PII: S0040-4020(97)10273-3

Results and discussion

With the aim of preparing the target molecule in a high yield by a short and novel synthetic sequence, the known isoflavanone **2** was selected as the immediate precursor. The synthesis of the latter derivative **2** had been already optimized by our group (90% yield) by reaction of deoxybenzoin **1** with paraformaldehyde and dimethylamine in refluxing ethanol.[6] In order to attempt the following heterocyclization step, we studied the conditions reported by Zielinski[7] who showed that the reaction of alkyl benzyl ketones with nitriles in the presence of $POCl_3$ led to the formation of isoquinoline derivatives in variable yields. Nevertheless, when we first tested the action of $POCl_3$ on ketone **2** in refluxing acetonitrile, chlorostilbene **3** was obtained as the major product (77% yield) and only traces (<5% yield) of the desired tetracycle **4a** were detected. Similar results had been previously observed when the classical Bischler-Napieralski cyclization conditions were applied to 1,2-diarylethylamides.[8] Even higher yield (92%) for compound **3** was found when the former reaction was carried out using the $AlCl_3/P_2O_5$ system in acetonitrile as solvent. (Table 1)

Scheme 1



1 **2** **3**

i) $(HCHO)_n$, Me_2NH, EtOH, reflux
ii) $POCl_3$, MeCN, r. t.

The ability of P_2O_5 to transform deoxybenzoins into isoquinolines in good yields using the appropriate nitrile as solvent in a Ritter-type reaction *via* nitrilium salts intermediates has been reported.[9] In fact, when isoflavanone **2** was made to react under the already mentioned conditions using acetonitrile, benzopyrane-isoquinoline **4a** was obtained in moderate yield. In order to examine the scope and limitations of the described procedure, a series of isoquinolines **4a-d** was prepared employing aliphatic and aromatic nitriles.

As shown in Table 1, a direct relationship between the yield and the bulkiness of the employed nitrile could be observed. Thus, the best yield was reached for **4a**, since acetonitrile is the smallest compound used as solvent. We would also like to inform that we attempted the preparation of derivative **4e** using solid 3,4-dimethoxybenzonitrile and CH_2Cl_2 as solvent, nevertheless, in this case, the experiment furnished a mixture of the desired isoquinoline **4e** (R=H, 7%) and the hydroxyisoflavanone **5** (40%) among other compounds.

Scheme 2

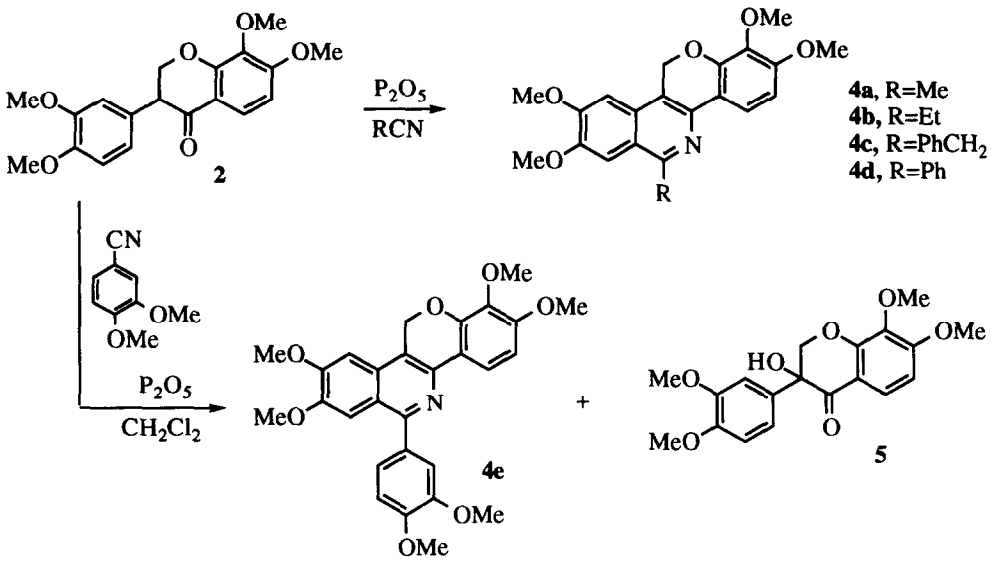


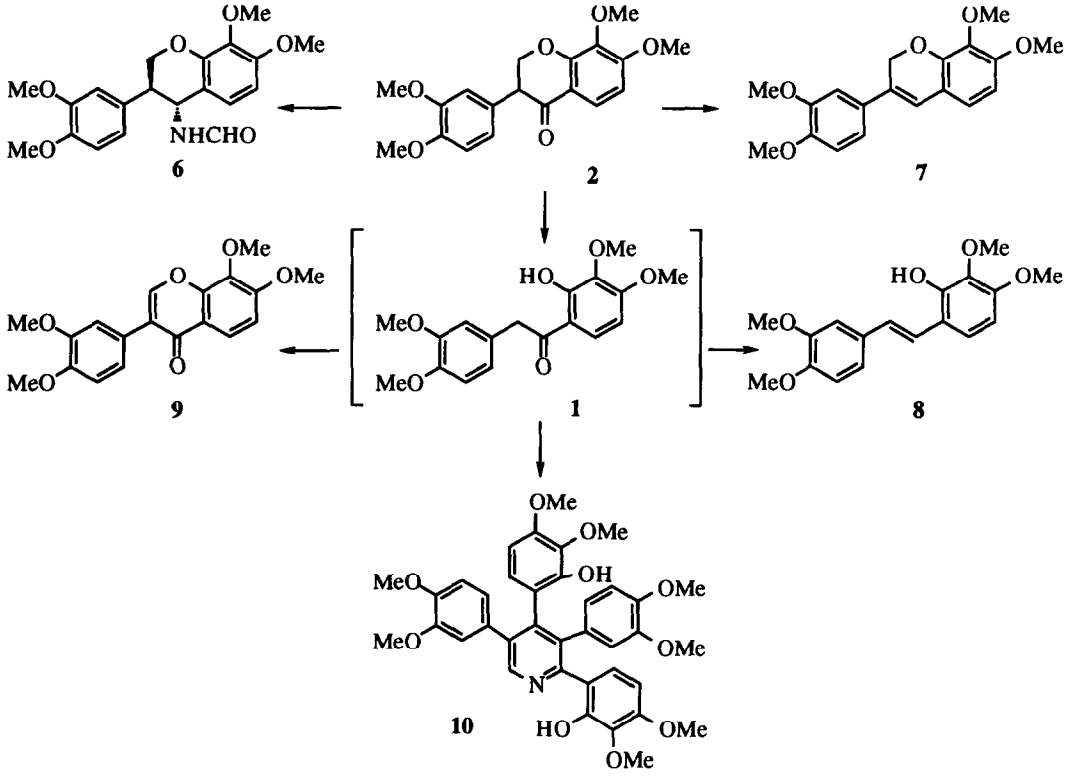
Table 1. Synthetic and physical data of compounds **3-5** prepared from isoflavanone **2**.

compound	reagent	solvent	reaction time (h)	yield (%)	m. p. (°C)
3	$POCl_3$	MeCN	7	77	155-156[a]
3	$P_2O_5/AlCl_3$	MeCN	92	92	"
4a	P_2O_5	MeCN	20	66	211-212[a]
4b	P_2O_5	EtCN	12	56	176-177[a]
4c	P_2O_5	BnCN	46	34	192-193[a]
4d	P_2O_5	PhCN	24	27	152-153[a]
4e	P_2O_5	CH_2Cl_2	72	7	138-139[a]
5	P_2O_5	CH_2Cl_2	72	40	208-209[b]

[a]: crystallized from MeOH; [b]: crystallized from EtOH

In order to attempt the synthesis of the benzopyraneisoquinoline system with different oxidation patterns, an alternative sequence was applied to ketone **2**. Thus, when it was submitted to the typical Leuckart reductive amination conditions[10] the desired 4-*N*-formylamine-7,8,3',4'-tetramethoxyisoflavane **6** was isolated in moderate yield (37%) together with the known[10a,b] isoflavene **7** (16%), stilbene **8** (8%), isoflavone **9** (5%) and pyridine **10** (6%). The formation of compounds **8**, **9** and **10** can be explained by assuming a pyrane ring opening to furnish the intermediate ketone **1**, unstable compound that evolves in the reaction mixture. (Scheme 3) In fact, during previous experiments carried out in our laboratory, a similar result was observed when phenolic deoxybenzoin **1** was submitted to Leuckart reaction conditions. Moreover, the formation of isoflavene **7** may be postulated as the result of a retro-Ritter competitive process, as it could be assumed by comparison with similar systems.[8]

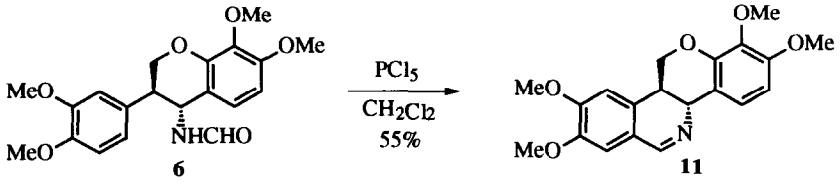
Scheme 3



Compound **6** was obtained as a single diastereoisomer in a mixture (88:12) of rotamers.[11] The identity of each rotamer was deduced on the basis of homonuclear decoupling experiments and, furthermore, NOE experiments carried out on the major rotamer *syn*-**6** (NOE between H-4/H-2a and H-3/H-2e, absence of NOE between H-3/H-4 and $J_{H3\text{-}H4}$ = 10 Hz) revealed a *trans* relationship between the substituents at C-3 and C-4.

To complete the targeted synthesis, formamide **6** was treated with the PCl_5/CH_2Cl_2 system to furnish, *via* Bischler-Napieralski cyclization,[12] the *trans*-2,3,7,8-tetramethoxy-10b,4b-dihydro-5H-(1)-benzopyrane-[4,3-*c*]isoquinoline **11** as an unique diastereoisomer. Again, the absence of NOE between the protons at C-10b and C-4b was used as diagnosis for the stereochemical assignation. It should be mentioned that the benzopyraneisoquinoline **11** was purified by flash column chromatography and crystallized from MeOH producing a stable solid which underwent aereal oxidation in chloroform or acetone solutions to yield the benzopyraneisoquinoline **4f** (R=H).

Scheme 4



6 **11**

In summary, one pot synthesis of new tetracyclic compounds with a benzopyrane[4,3-*c*]-isoquinoline frame has been achieved by employing isoflavanone **2** as the starting material *via* a cyclization process which uses P_2O_5 and different nitriles as solvent. An alternative route, which includes a reductive amination reaction - Bischler-Napieralski heterocyclization process, led to the diastereoselective preparation of the dihydro-benzopyrane[4,3-*c*]isoquinolines **11** in good yield.

Experimental

General Procedures: Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were measured in a Perkin-Elmer 1430 spectrophotometer as KBr plates or as neat liquid and peaks are reported in cm^{-1}. ^1H NMR spectra were recorded in a Bruker ACE-250 apparatus at 250 MHz with $CHCl_3$ (7.26 ppm) as an internal reference in $CDCl_3$ solutions. ^{13}C NMR spectra were recorded in the same spectrometer at 62.8 MHz with $CHCl_3$ (77.0 ppm) as an internal reference in $CDCl_3$ solutions. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), dd (doublet of doublets) or dt (doublet of triplets). Coupling constants, J, are reported in hertz. All solvents used were technical grade and purified according to standard procedures.[13] Thin layer chromatography was performed on silica gel 60 F_{254} plates and visualized by UV light or Dragendorf's reagent.[14] Flash column chromatography[15] was performed on Merck kieselgel 60 (70-230 mesh ASTM). All tranfers of liquid solution and solvents were performed by syringe techniques or *via* canula.[16] Combustion analyses were performed with a Perkin-Elmer 2400 CHN apparatus.

4-Chloro-7,8,3',4'-tetramethoxyisoflav-3-ene 3: To a cold (0 °C) solution of isoflavanone **2** (200 mg, 0.08 mmol) and P_2O_5 (114 mg, 0.80 mmol) in 20 mL of MeCN, $AlCl_3$ (77 mg, 0.58 mmol) was added and the mixture was stirred for 30 h. Then, water was added and extracted twice with 20 mL of CH_2Cl_2. The combined extracts were washed with brine and dried with Na_2SO_4. The solvent was evaporated and the resulting oil was crystallized from MeOH to afford **3** as a pale yellow solid. **^{1}H NMR**: δ 3.89-3.91 (s, 12H, 4xOCH_3), 5.05 (s, 2H, H-2), 6.57 (d, J=8.7, 1H, H-6), 6.91 (d, J=8.1, 1H, H-5'), 6.97-7.01 (m, 2H, H-2', H-6'), 7.29 (d, J=8.7, 1H, H-5); **^{13}C NMR**: δ 55.8, 55.9, 61.1 (OCH_3), 70.7 (C-2), 104.6, 110.8, 111.8 (tCarom), 117.0 (qCarom), 120.0, 121.0 (tCarom), 122.9, 126.9, 128.4, 136.6, 147.5, 148.6, 148.8, 154.0 (qCarom); **IR** (KBr) υ 1600. **EI-MS** ***m/z*** 364 (37), 363 (31), 362 (M^+, 100), 361 (30), 327 (45), 295 (17), 210 (72), 209 (19), 181 (16). **Anal. Calcd for $C_{19}H_{19}ClO_5$:** C, 62.97; H, 5.29. **Found:** C, 62.77; H, 5.33.

Cyclization reaction. Typical procedure for the synthesis of benzopyrane[4,3-*c*]-isoquinolines 4a-d: To a stirred solution of isoflavanone **2** dissolved in the corresponding nitrile, small amounts of P_2O_5 were added until total consumption of the starting material (tlc, CH_2Cl_2/EtOAc, 95/5). Then, the solution was made alkaline with 20% NaOH (aq) and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, the solvent was evaporated and, in all cases, the residues were purified by chromatography followed by crystallization from MeOH.

12-Methyl-2,3,7,8-tetramethoxy-5H-(1)-benzopyrane[4,3-*c*]isoquinoline 4a: ^{1}H NMR: δ 2.96 (s, 3H, CH_3), 3.93 (s, 6H, 2xOCH_3), 4.06 (s, 6H, 2xOCH_3), 5.65 (s, 2H, CH_2O), 6.69 (d, J=8.6, 1H, H-10), 6.92 (s, 1H, H-4), 7.32 (s, 1H, H-1), 8.05 (d, J=8.6, 1H, H-9); **^{13}C NMR**: δ 22.7 (CH_3), 55.9, 56.0, 56.1, 61.1 (OCH_3), 65.4 (CH_2O), 100.2, 104.9, 105.4 (tCarom), 114.6, 118.2 (qCarom), 119.2 (tCarom), 122.1, 128.4, 137.1, 139.5, 148.7, 149.0, 152.8, 154.0, 154.7; **IR** (KBr) υ 1610, 1570. **EI-MS** ***m/z*** 367 (M^+, 100), 366 (43), 352 (9), 281 (14). **Anal. Calcd for $C_{21}H_{21}NO_5$:** C, 68.64; H, 5.76; N, 3.81. **Found:** C, 68.44; H, 5.91; N, 3.70.

12-Ethyl-2,3,7,8-tetramethoxy-5H-(1)-benzopyrane[4,3-*c*]isoquinoline 4b: ^{1}H NMR: δ 1.48 (t, J=7.4, 3H, $CH_2C\underline{H}_3$), 3.25 (q, J=7.4, 2H, $C\underline{H}_2CH_3$), 3.92 (s, 6H, 2xOCH_3), 4.02 (s, 6H, 2xOCH_3), 5.63 (s, 2H, CH_2O), 6.68 (d, J=8.7, 1H, H-10), 6.88 (s, 1H, H-4), 7.35 (s, 1H, H-1), 8.05 (d, J=8.7, 1H, H-9); **^{13}C NMR**: δ 12.9 ($\underline{C}H_3CH_2$), 28.5 ($CH_3\underline{C}H_2$), 55.9, 56.1, 61.1 (OCH_3), 65.5 (CH_2O), 100.3, 104.6, 105.4 (tCarom), 114.2, 118.2 (qCarom), 119.3 (tCarom), 121.4, 128.6, 137.1, 139.6, 148.0, 148.7, 152.6, 153.9, 159.9 (qCarom); **IR** (KBr) υ 1610, 1570. **EI-MS** ***m/z*** 381 (M^+, 100), 380 (37), 365 (13). **Anal. Calcd for $C_{22}H_{23}NO_5$:** C, 69.27; H, 6.08; N, 3.67. **Found:** C, 69.33; H, 6.12; N, 3.31.

12-Benzyl-2,3,7,8-tetramethoxy-5H-(1)-benzopyrane[4,3-*c*]isoquinoline 4c: ^{1}H NMR: δ 3.79 (s, 3H, OCH_3), 3.86 (s, 6H, 2xOCH_3), 3.94 (s, 3H, OCH_3), 4.56 (s, 2H, $C\underline{H}_2Ph$), 5.59 (s, 2H, CH_2O), 6.63 (d, J=8.7, 1H, H-10), 6.81 (s, 1H, H-4), 7.09-7.24 (m, 5H, Ph), 7.26 (s, 1H, H-1), 7.99 (d, J=8.7, 1H, H-9); **^{13}C NMR**: δ 42.9 ($Ph\underline{C}H_2$), 55.8, 56.0, 56.1, 61.1 (OCH_3), 65.5 (CH_2O), 100.2, 105.4

(tCarom), 115.0, 118.4 (qCarom), 119.4, 121.8, 126.2, 128.5, 128.6 (tCarom), 129.2, 137.1, 139.7, 139.8, 148.7, 148.9, 152.7, 154.1, 157.4 (qCarom); **IR** (KBr) υ 1610, 1570. **EI-MS** ***m/z*** 443 (M^+, 100), 442 (25), 428 (15). **Anal. Calcd for $C_{27}H_{25}NO_5$:** C, 73.11; H, 5.68; N, 3.16. **Found:** C, 73.33; H, 5.92; N, 3.36.

12-Phenyl-2,3,7,8-tetramethoxy-5H-(1)-benzopyrane[4,3-*c*]isoquinoline 4d: ^{1}H NMR: δ 3.86 (s, 3H, OCH_3), 3.93 (s, 6H, 2xOCH_3), 4.07 (s, 3H, OCH_3), 5.73 (s, 2H, CH_2O), 6.66 (d, J=8.7, 1H, H-10), 6.96 (s, 1H, H-4), 7.42 (s, 1H, H-1), 7.50-7.58 (m, 3H, Ph), 7.76-7.99 (m, 2H, Ph), 8.07 (d, J=8.7, 1H, H-9); **^{13}C NMR**: δ 55.8, 56.1, 61.2 (OCH_3), 65.5 (CH_2O), 99.9, 105.4, 106.9 (tCarom), 115.2, 118.2 (qCarom), 119.7 (tCarom), 121.6, 128.1 (qCarom), 128.3, 128.5 (tCarom), 129.6 (qCarom), 129.9 (tCarom), 140.1, 140.2, 148.8, 149.2, 152.9, 154.2, 157.9 (qCarom); **IR** (KBr) υ 1610, 1570. **EI-MS** ***m/z*** 429 (M^+, 100), 428 (29). **Anal. Calcd for $C_{26}H_{23}NO_5$:** C, 72.70; H, 5.40; N, 3.26. **Found:** C, 72.53; H, 5.72; N, 3.39.

Cyclization reaction using 3,4-dimethoxybenzonitrile. Synthesis of 4e: To a stirred solution of isoflavanone **2** (200 mg, 0.58 mmol) and 3,4-dimethoxybenzonitrile (284 mg, 1.75 mmol) dissolved in 50 mL of CH_2Cl_2, small amounts of P_2O_5 were added until total consumption of the starting material (tlc, CH_2Cl_2/EtOAc, 95/5). Then, the solution was made alkaline with 20% NaOH (aq), decanted, extracted with more CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography to afford isoquinoline **4e** (7%) and the hydroxy-isoflavanone **5** (40%).

12-(3,4-Dimethoxyphenyl)-2,3,7,8-tetramethoxy-5H-(1)-benzopyrane[4,3-*c*]isoquinoline 4e: ^{1}H NMR: δ 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 5.73 (s, 2H, CH_2O), 6.68 (d, J=8.6, 1H, H-10), 6.96 (s, 1H, H-4), 7.05 (d, J=8.6, H-5'), 7.33-7.35 (m, 2H, H-2', H-6'), 7.50 (s, 1H, H-1), 8.09 (d, J=8.6, 1H, H-9); **^{13}C NMR**: δ 55.9, 56.0, 56.1, 61.4 (OCH_3), 65.5 (CH_2O), 99.5, 105.4, 107.0, 110.9 (tCarom), 113.2, 118.3 (qCarom), 119.7 (tCarom), 121.6, 122.5, 129.6, 133.0, 137.1, 140.2 (qCarom), 148.9 (tCarom), 149.1, 149.4, 152.9, 154.2, 157.7 (qCarom); **IR** (KBr) υ 1610, 1570. **EI-MS** ***m/z*** 489 (M^+, 100), 488 (37), 244 (11). **Anal. Calcd for $C_{28}H_{27}NO_7$:** C, 68.69; H, 5.56; N, 2.86. **Found:** C, 68.63; H, 5.52; N, 2.99.

3-Hydroxy-7,8,3',4'-tetramethoxyisoflavanone 5: ^{1}H NMR: δ 3.83 (s, 3H, OCH_3), 3.84 (s, 6H, 2xOCH_3), 3.93 (s, 3H, OCH_3), 4.19 (s, 1H, OH), 4.46 (d, J=11.5, 1H, H-2e), 4.94 (d, J=11.5, 1H, H-2a), 6.68 (d, J=8.9, 1H, H-6), 6.76 (d, J=8.3, 1H, H-5'), 7.05 (d, J=2.1, 1H, H-2'), 7.01 (dd, J=8.3, 2.1, 1H, H-6'), 7.71 (d, J=8.9, 1H, H-5); **^{13}C NMR**: δ 55.8, 55.9, 56.3, 61.1 (OCH_3), 72.8 (C-3), 73.9 (C-2), 106.5, 109.3, 110.9 (tCarom), 114.1 (qCarom), 118.5, 123.5 (tCarom), 130.9, 136.7, 149.2, 149.4, 155.2, 159.4 (qCarom), 193.2 (C=O); **IR** (KBr) υ 3600-3200, 1660. **EI-MS** ***m/z*** 360 (M^+, 8), 342 (2), 181 (100), 180 (51), 165 (15), 152 (16). **Anal. Calcd for $C_{19}H_{20}O_7$:** C, 63.31; H, 5.60. **Found:** C, 68.33; H, 5.50.

Synthesis of formamide 6 by reductive amination reaction: A mixture of isoflavanone **2** (2.85 g, 8.3 mmol), $HCONH_2$ (0.83 ml, 21 mmol), $HCOONH_4$ (5.26 g, 83 mmol) and HCOOH (0.83 ml, 22 mmol) was heated for 3 h at 190 °C using a modified glass equipment to allow the distillation of water. After cooling, the mixture was poured onto ice/water and the resulting precipitate was crystallized from MeOH to afford formamide **6** (37%). The mother liquors were flash column chromatographed (CH_2Cl_2/EtOAc, 95/5) to afford isoflavene **7** (16%), isoflavone **9** (5%), stilbene **8** (8%) and pyridine **10** (6%).

***syn*-4-*N*-formylamine-7,8,3',4'-tetramethoxyisoflavane 6: ^{1}H NMR:** δ 3.04 (dt J=8.8, 3.5, 1H, H-3), 3.85 (s, 12H, 4xOCH_3), 4.26 (dd, J=11.2, 8.8, 1H, H-2a), 4.41 (dd, J=11.2, 3.5, 1H, H-2e), 5.56 (t, J=8.8, 1H, H-4), 5.80 (d, J=8.8, 1H, NH), 6.53 (d, J=8.7, 1H, H-6), 6.88-6.83 (m, 3H, H-2', H-5', H-6'), 6.91 (d, J=8.7, 1H, H-5), 8.20 (s, 1H, CHO); **^{13}C NMR:** δ 44.4 (C-3), 47.4 (C-4), 55.8, 55.9, 56.0, 60.9 (OCH_3), 69.9 (CH_2O), 105.0, 1110.9, 111.4 (tCarom), 115.9 (qCarom), 120.0, 122.9 (tCarom), 130.1, 136.8, 148.3, 148.5, 149.1, 152.9 (qCarom), 160.9 (CHO).

***trans*-4-*N*-formylamine-7,8,3',4'-tetramethoxyisoflavane 6: ^{1}H NMR:** δ 3.04 (dt J=10.1, 3.5, 1H, H-3), 3.85 (s, 12H, 4xOCH_3), 4.15-4.60 (m, 2H, H-2), 4.73 (t, J=10.1, 1H, H-4), 5.56 (sa, 1H, NH), 6.56 (d, J=8.7, 1H, H-6), 6.60 (d, J=8.1, 1H, H-5'), 6.67 (d, J=2.1, 1H, H-2'), 6.73 (dd, J=8.1, 2.1, 1H, H-6'), 7.00 (d, J=8.7, 1H, H-5), 7.76 (d, J=11.7, 1H, CHO).
(*syn* + *trans*)-6: IR (KBr) υ 3600-3200, 1660. **EI-MS *m/z*** 373 (M^+, 3), 368 (2), 329 (12), 328 (54), 209 (52), 195 (13), 181 (26), 180 (24), 166 (33), 164 (100), 152 (14), 149 (16). **Anal. Calcd for $C_{20}H_{23}NO_6$:** C, 64.32; H, 6.21; N, 3.75. **Found:** C, 64.45; H, 6.00; N, 3.99.

7,8,3',4'-Tetramethoxyisoflav-3-ene 7: ^{1}H NMR: δ 3.88 (s, 3H, OCH_3), 3.92 (s, 6H, 2xOCH_3), 3.94 (s, 3H, OCH_3), 5.17 (s, 2H, H-2), 6.50 (d, J=8.4, 1H, H-5), 6.69 (s, 1H, H-4), 6.81 (d, J=8.4, 1H, H-6), 6.87 (d, J=8.3, 1H, H-5'), 6.96 (dd, J=8.3, 1.7, 1H, H-6'), 6.99 (d, J=1.7, 1H, H-2'); **^{13}C NMR:** δ 55.9, 56.0, 61.0 (OCH_3), 67.3 (C-2), 104.6, 110.8, 111.8 (tCarom), 117.0 (qCarom), 120.0, 121.0, 122.9 (tCarom), 126.9, 128.4, 136.6, 147.5, 148.6, 148.8, 154.0 (qCarom); **IR** (KBr) υ 1600. **EI-MS *m/z*** 328 (M^+, 100), 313 (15), 299 (14), 297 (12), 170 (18), 165 (61), 164 (58), 79 (29). **Anal. Calcd for $C_{19}H_{20}O_5$:** C, 69.50; H, 6.14. **Found:** C, 69.71; H, 6.21.

***trans*-2,3,7,8-Tetramethoxy-10b,4b-dihydro-5H-(1)-benzopyrane[4,3-c]isoquinoline 11:** To a stirred solution of formamide **6** (350 mg, 0.93 mmol) in 50 mL of CH_2Cl_2, small amounts of PCl_5 were added at 0 °C and the mixture was allowed to reach room temperature after each addition. After total consumption of the starting material (tlc, CH_2Cl_2/EtOAc, 95/5) the solution was made alkaline with 20% NaOH (aq), decanted and extracted with more CH_2Cl_2. The combined extracts were dried over Na_2SO_4, the solvent was evaporated and the residue was crystallized from EtOH to afford isoquinoline **11. m.p.** 109-110 °C. **^{1}H NMR:** δ 3.12 (td, J=15.4, 4.1, 1H, H-4b), 3.88 (s, 6H, 2xOCH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.24-4.34 (m, 2H, H-5a, H-10b), 5.09 (dd, J=10.5, 4.1, 1H, H-5e), 6.65 (d, J=8.7, 1H, H-9), 6.70 (s, 1H, H-4), 6.99 (s, 1H, H-1), 7.62 (d, J=8.7, 1H, H-10), 8.43 (d, J=3.1, 1H, H-12); **^{13}C NMR:** δ

33.9 (C-4b), 56.0, 56.1, 56.2, 60.9 (OCH_3), 57.3 (C-10b), 67.6 (C-5), 104.7, 105.9, 111.2 (tCarom), 118.4 (qCarom), 121.5 (tCarom), 122.1, 129.5, 136.8, 147.7, 148.3, 151.9, 152.5 (qCarom), 160.2 (C-12); **EI-MS** ***m/z*** 355 (M^+, 96), 354 (41), 340 (100). **Anal. Calcd for $C_{20}H_{21}NO_5$:** C, 67.58; H, 5.96; N, 3.94. **Found:** C, 67.69; H, 5.62; N, 3.88.

Acetone or chloroform solutions of **11** underwent aerial oxidation to afford **2,3,7,8-tetramethoxy-5H-(1)-benzopyrane[4,3-*c*]isoquinoline 4f:** ^{1}**H NMR**: δ 3.95-4.08 (s, 12H, 4xOCH_3), 5.64 (s, 2H, CH_2O), 6.68 (d, J=8.8, 1H, H-10), 6.91 (s, 1H, H-4), 7.22 (s, 1H, H-1), 8.05 (d, J=8.8, H-9), 9.01 (s, 1H, H-12); ^{13}**C NMR**: δ 56.1, 56.2, 61.1 (OCH_3), 65.2 (CH_2O), 99.9, 105.2, 108.9 (tCarom), 116.6 (qCarom), 119.4 (tCarom), 123.6, 128.8, 148.9, 149.9, 154.0, 154.2 (qCarom), 154.5 (C-12); **IR** (KBr) υ 1610, 1570. **EI-MS** ***m/z*** 353 (M^+, 100), 352 (34), 338 (15).

Acknowledgements: The authors gratefully acknowledge PETRONOR, S.A. (Muskiz, Vizcaya) for the generous gift of hexane during the last years. Financial support of the University of Basque Country (Project UPV 170.310-EA 154/96) and Basque Government (PI 96/53) is gratefully acknowledged.

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