NEW STEREOSELECTIVE SYNTHESIS OF SPIROCYCLOHEXANBENZOPYRANS DERIVATIVES

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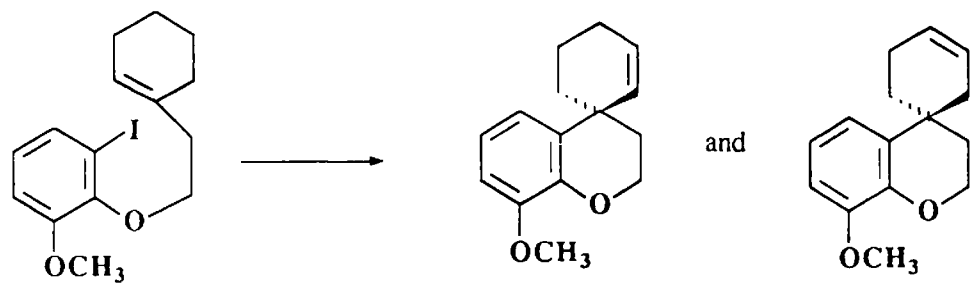
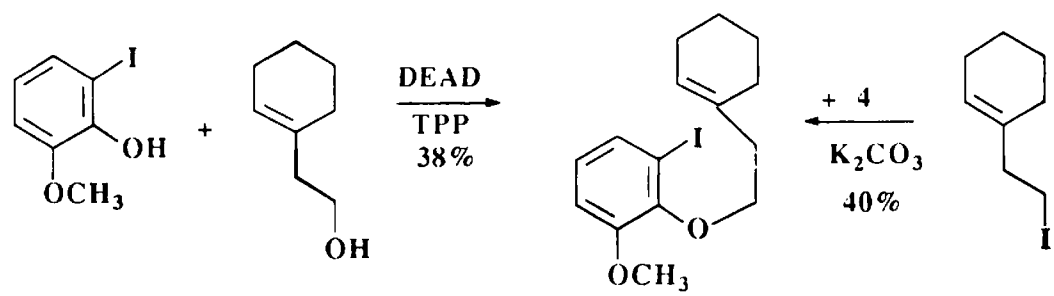
Abstract :
Synthesis of new spirocyclohexanbenzopyrans derivatives is described by using intramolecular Heck arylation and stereospecific epoxidation.

Our interest in spirocyclohexanbenzopyrans derivatives (1,2), prompted us to devise a shorter scheme involving an intramolecular Heck reaction, on the ether 1 and leading to the two isomeric heterocycles 2 and 3 :



1 2 3

The creation of a quaternary spirocenter by a Heck reaction (3) is well known and examples have recently been described by Overman (4) and Dyker (5) in the case of spirocyclohexenyltetrahydrofurans. The ether 1 is prepared by reaction (6) of orthoiodogaiacol 4 either with alcohol 5 or with the iodo derivative 6 :



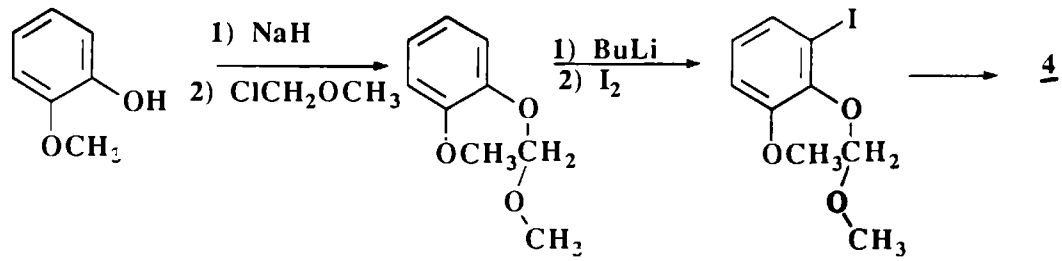
4 5 1 6

A general selective method of ortho-lithiation of phenols (7) does not exist and the ortho iododerivatives are obtained mixed with the para-derivatives or the ortho-para-derivatives. With the gaiacol, we note moreover two possibilities of ortho or parasubstitution and we tried several techniques for improving the yield of 4.

Following the report of Cambie and *al.* (8) (iodine with thallium acetate) we failed to observe the described selectivity and recovered the unchanged gaiacol. Using a technique previously described for veratrol (9), butyllithium and iodine, we obtained a mixture of ortho and ortho-para-substituted derivatives. Whilst *tert.*butyllithium with iodine and TMEDA or tertiobutanol according to Morey and *al* (10) gave a mixture of mono and disubstituted derivatives.

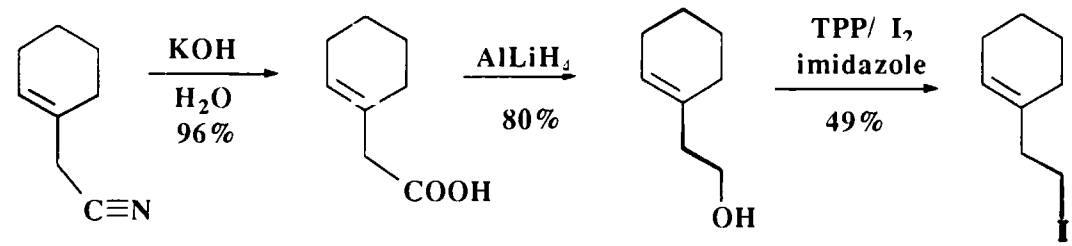
We did not try the selective paradeiodation of ortho-parasubstituted derivatives described by Horne and *al* (11), because low yields are observed in this reaction.

We finally used the methoxymethyl ether of gaiacol. This protective group is easily eliminated by acid and led to the iodo derivative 4 with a yield of 67% for the three steps :



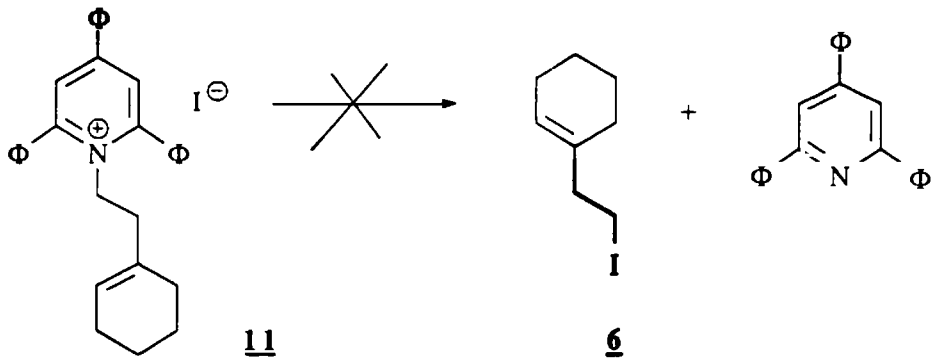
7 8

We prepared the alcohol 5, starting from the 2-(cyclohex-1-enyl)-acetonitrile 9, according to Lednicer and *al.* (12) and converted it to the iodo derivative 6 by use of TPP/I_2 (13) :



9 10 5 6

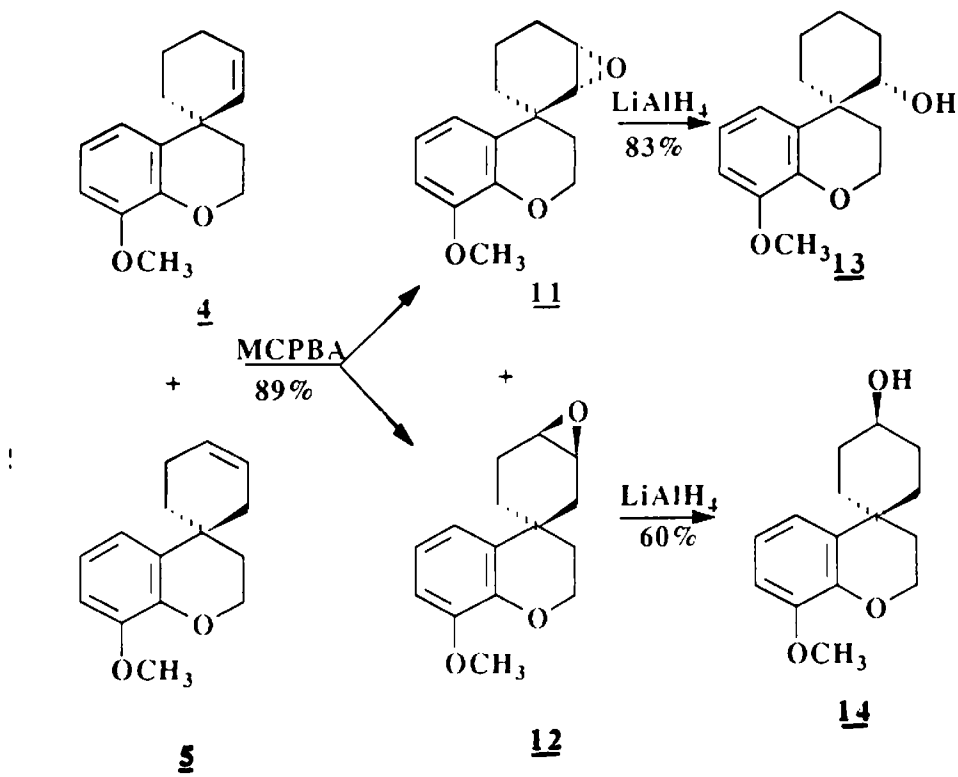
We were unable to prepare the iodide 6 by decomposition, according to Katritzky (14), of the iodide of 1-[2-(cyclohex-1-enyl)-ethyl]-2,4,6-triphenylpyridinium 11, which is easily prepared by reaction of the 2-(cyclohex-1-enyl)-ethylamine, a cheap commercial product, with the 2,4,6-triphenylpyrilium iodide :



11 6

The use of iodide 6 does not improve significantly the yield of ether 1.

The ether 1 leads to spirans 2 and 3 by intramolecular arylation according to Heck (15). Addition of silver nitrate and triethylamine according to Abelman and *al.* (4) does not prevent isomerisation of the double bond and hydrolysis of reaction mixture by sodium hydroxide leads to mixture of 2 (#90%) and 3 (#10%). Addition of metachloro-perbenzoic acid to the mixture of the two isomers 2 and 3 leads to the epoxides 12 and 13, which were separated by chromatography.



Compound 12 is identical to the compound previously obtained (1) by a different reaction scheme. Some typical spectral data (1H NMR, NOESY) are given in figure 1.

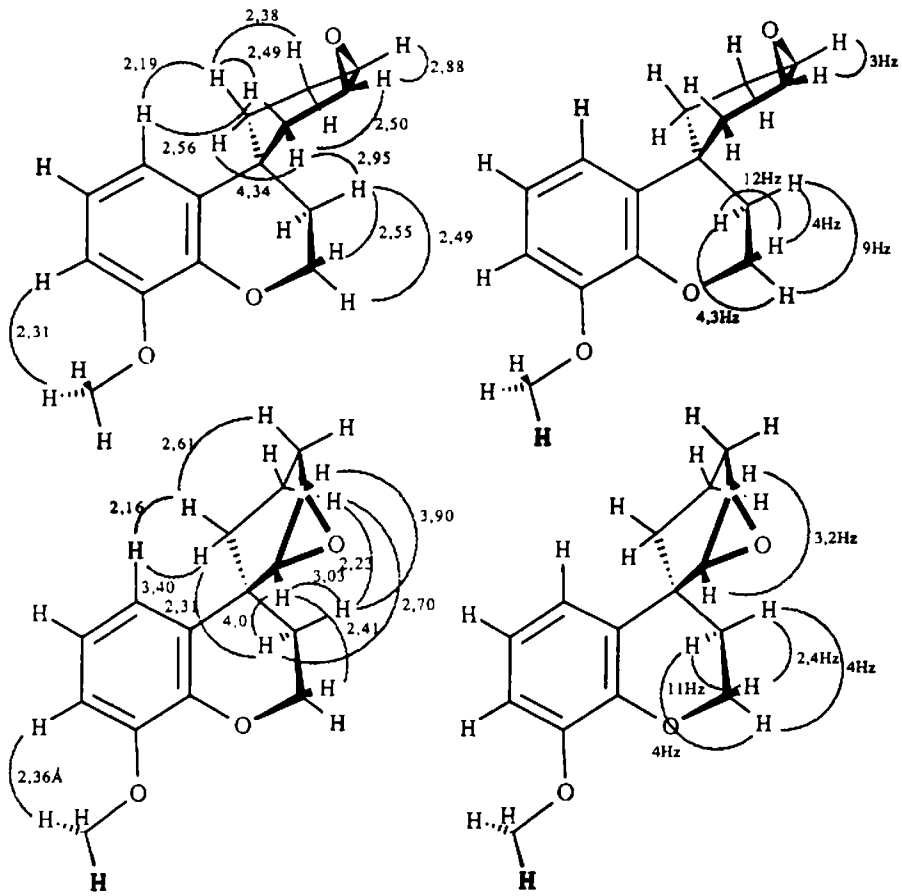


Figure 1

Distances (Å) are those given by computation of the lowest energy conformers according to distance strains given by NOESY CARD.

The stereochemistry of compound **13** results from examination of its spectral data (NMR, NOESY) and was confirmed by NMR studies on the alcohol derivative **14** obtained after reduction of **13** by lithium aluminum hydride.

The alcohol **14** has such a conformation that the hydroxyl in equatorial position has a 1,3 diaxial interaction with one of the hydrogens on the carbon 3, leading to a shielding of this hydrogen (1). The alcohol **15** has a hydroxyl in axial position, proved by the coupling constants of the proton H4' : J_1 = 3 Hz, J_2 = 3Hz. This conformation is explained by the less crowding of the molecule in relation to the others conformational possibilities.

In conclusion, stereospecific epoxidations of isolated double bonds are scarce and not well understood. In the case of the compounds studied, an explanation based upon conformational analysis and theoretical data is under investigation.

Experimental Section.

Thin layer chromatography was performed on Kieselgel 60 F Merck or Riedel-DeHaen . Flash chromatography was done with Merck 9385 40-63 mm or Riedel-DeHaen 31607 silica . Mass spectrum were performed on a V.G 70-70 apparatus and elementary analysis on a Perkin Elmer 240 apparatus. ^{1}H NMR pectra were recorded on a Bruker AC 200 P (200 MHz or 400 MHz for compounds **12** and **13**) in deuterated chloroform and tetramethylsilane (TMS) used as internal reference. Chemical shifts were expressed in ppm et coupling constants in Hz.

3-Iodo-2-methoxymethoxyanisole 8

A solution of 10 mmol (1.68 g) of 2-methoxymethoxyanisole 7 prepared according to Kluge and *al* [16] in 15 ml of anhydrous THF was chilled to - 10 °C. 11 mmol (7 ml of a 1.6 M solution of butyllithium) was added dropwise; the mixture was stirred 2 hours at room temperature and then chilled to - 40 °C. A solution of 11 mmol (2.7 g) of iodine in 20 ml of anhydrous THF was added dropwise under agitation and the mixture was kept overnight at room temperature. After addition of 100 ml of diethyl ether, the organic layer was washed with a solution of $NaHSO_3$ until decoloration, then neutralised with a solution of $NaHCO_3$ and washed with water.The organic layer was dried over sodium sulfate and evaporated. The oily residue was chromatographied on silica gel (hexane / CH_2Cl_2 : 70/30) to give 2.35 g (yield = 80%) of 8

Anal. $C_9H_{11}O_3I$ (294); Calc. C : 36.77; H : 3.77. found C : 36.94; H : 3.91.

^{1}H nmr (δ, ppm) : 7.25 (dd, 1 H), 6.75 (dd, 1H), 6.5 (t, 1H), 6.1 (s, 2H), 3.8 (2s, 6H).

2-Methoxy-6-iodophenol 4

8 mmol (2,35 g) of compound **8** was refluxed for one hour in methanol with 0.5 ml of 10N hydrochloric acid. The solvant was evaporated and the oily residue was chromatographied on silicagel (cyclohexane / CH_2Cl_2 : 95/5) to give 2 g (yield = 98%) of 4

Anal. $C_7H_7O_2I$ (250); Calc. C : 33.63; H : 2.82. found C : 33.59; H : 3.10.

^{1}H NMR (δ, ppm) : 7.30 (d, 1 H), 6.85 (d, 1H), 6.6 (t,1H), 6,1 (s, D_2O exchanged, 1H), 3.85 (s, 3H).

2-(Cyclohex-1-enyl)-1-iodoethane 6

A solution of 7.9 mmol (1 g) of **5** (12), 10 mmol (2.62 g) of triphenylphosphine, 10 mmol (0.66 g) of imidazole and 10 mmol (2.53 g) of iodine in 100 ml of anhydrous toluene was warmed under nitrogen for 4 hours between 90 and 100 °C. The mixture was cooled and a solution of sodium bisulphite was added. Ethyl acetate was added and the organic layer was washed with a saturated solution of $NaHCO_3$ and dried over sodium sulfate and evaporated. The oily residue was chromatographied on silica gel (cyclohexane) to give 0.98 g (yield = 49%) of 6.

Anal. $C_8H_{13}I$ (236); Calc. C : 40.71; H : 5.55. found C : 40.61; H : 5.46.

^{1}H NMR (δ, ppm) : 5.45 (m, 1H), 3.2 (t, 2H1), 2.5 (t, 2H2), 2.05-1.85 (m, 4H), 1.7-1.45 (m, 4H).

^{13}C NMR : 136.3 (C3), 123.7 (C4), 42.2 (C2), 29.6 (C1), 27.5 (C8), 25.11 (C5), 22.7 (C7), 22.2 (C6).

3-Iodo-1-[2-cyclohex-2-enylethoxy]anisole 1

- starting from cyclohexenylethanol 5

To a solution of 5 mmol (0.63 g) of **5** (12), 5 mmol (1.25 g) of **4** and 5 mmol (1.31 g) of triphenylphosphine in 30 ml of anhydrous CH_2Cl_2 under nitrogen was added dropwise 5 mmol (0.87 g) of diethylazodicarboxylate and the solution was stirred over-night at room temperature. The solvent was evaporated and the oily residue was chromatographied on silica gel (cyclohexane / $CHCl_3$ 70:30) to give 0.5 g (yield = 38%) of 1.

- starting from cyclohexenyliodoethane 6

A suspension of 4 mmol (1g) of iodogaiagol, 4 mmol (0.94 g) of **6**, 4 mmol (0.56 g) of potassium carbonate in 30 ml of acetone was retluxed for 24 h. The solvent was evaporated, the residue washed with water and extracted with ether.The organic layer was dried over sodium sulfate and evaporated. The oily residue was chromatographied on silica gel (cyclohexane / $CHCl_3$: 70/30) to give 0.57 g (yield = 40%) of 1.

Anal. $C_{15}H_{19}O_2I$ (358.2); Calc. C : 50.32; H : 5.35. found C : 50.49; H : 5.48.

^1H NMR (δ, ppm) : 7.35 (dd, 1 H), 6.85 (dd, 1H), 6.75 (t, 1H), 5.55 (m, 1H), 4.05 (t, 2H), 3.85 (s, 3H), 2.5 (t, 2H), 2.10-1.90 (m, 4H), 1.80-1.5 (m, 4H).

^{13}C NMR : 152.9 (C1'), 148.4(C2'), 134.2 (C3), 130.6 (C5'), 125.6 (C4'), 123.0 (C4), 112.8 (C3'), 93.05 (C6'), 71.7 (C1), 55.9 (CH_3), 38.6 (C2), 28.6 (C8), 25.3 (C5), 22.9 (C7), 22.4 (C6).

Cyclisation into spirocyclohexanbenzopyrans 2 and 3 :

To a solution of 1 mmol (0.35 g) of 1 in 30 ml of anhydrous acetonitrile were added 1 equivalent (0.262 g) of $P\Phi_3$, 1 equivalent (0.224 g) of $(AcO)_2Pd$, 1 equivalent (0.169 g) of $AgNO_3$ (0.169 g) and 3 equivalents (0.303 g) of triethylamine. The mixture was refluxed for 30 h. After filtration, the precipitate was washed with acetonitrile and the organic combined extracts were evaporated. The oily residue was chromathographied on silica gel (cyclohexane / $CHCl_3$: 50/50) to give 0.097 g (yield = 84%) of a mixture of two isomers 2 (major product) and 3 .

Anal. $C_{15}H_{18}O_2$ (230.3); Calc. C : 78.23; H : 7.83. found C : 78.08; H : 7.90.

^1H NMR (δ, ppm) : 6.9-6.65 (m, 3H), 5.95-5.6 (m, 2H, H2' et H3'), 4.5-4.1 (m, 2H2), 3.85 (s, CH_3), 2.2-1.5 (m, 10H).

2

^{13}C NMR : 147.8 (C8), 143.0 (C8a), 134.5 (C2'), 130.3 (C4a), 127.2 (C3'), 120.7 (C6), 119.1 (C5), 108.6 (C7), 62.4 (C2), 55.6 (CH_3), 36.6 and 33.8 (C3 and C6'), 35.1 (C4), 24.6 (C4'), 18.2 (C4).

3

^{13}C NMR : 148.1 (C8), 143.3 (C8a), 132.2 (C4a), 126.2 (C3'), 125.5 (C4'), 119.7 (C6), 118.9 (C5), 108.6 (C7), 63.1 (C2), 55.8 (CH_3), 38.3, 34.2 and 31.1 (C3, C2' and C6'), 32.1 (C4), 22.7 (C5').

Epoxidation of the mixture of spirocyclohexanbenzopyrans 2 and 3:

To a solution of 3 mmol (0.7 g) of the mixture of **2** and **3** in 100 ml of anhydrous CH_2Cl_2 was added dropwise a solution of 7.5 mmol (1.3 g) of metachloroperbenzoic acid in 20 ml of CH_2Cl_2. The mixture was stirred for four hours at room temperature and after standing one night, the excess of peracid was destroyed by addition of a 10% of sodium sulphite solution; the metachloroperbenzoic acid was extracted with a 5% of sodium hydrogen carbonate solution and the organic layer washed with water. The organic layer was dried over sodium sulfate and evaporated. The oily residue was chromatographied on silica gel (cyclohexane / ethylacetate : 90/10) to give 0.383 g (yield = 52%) of 12 and (cyclohexane / ethylacetate : 70/30) to give 0.273 g (yield = 37%) of 13.

12

Anal. $C_{15}H_{18}O_3$ (246.3): Calc. C : 73.14; H : 7.36. found C : 73.24; H : 7.55.

^1H NMR (δ, ppm) : 6.8-6.7 (m, 3H, Ar, H5 centered at 7.75), 4.35 (dt, 1H, H2, J = 11;4), 4.15 (dt, 1H, H2, J = 11; 2; 4), 3.80 (s, CH_3), 3.35 (m, 1H, H3'), 2.95 (d, 1H, H2', J = 3;2), 2.2-2.1 (ddd, 1H, H3ax, J = 4.1; 11.8; 14.3), 2.1-2.05 (m, 1H, H4'eq), 1.9-1.8 (m, 2H, H4'ax, H3eq), 1.65-1.55 (m, 1H, H6'ax), 1.5-1.25 (m, 3H, H6'eq, H5'ax, H5'eq).

^{13}C NMR : 148.4 (C8), 143.5 (C8a), 129.2 (C4a), 120.2 (C6), 119.9 (C5), 109.4 (C7), 62.8 (C2), 60.0 (C2'), 56.0 (CH_3), 53.9 (C3'), 35.1 (C3 or C6'), 33.5 (C4), 30.8 (C3 or C6'), 24.8 (C4'), 15.1 (C5').

13

Anal. $C_{15}H_{18}O_3$, 1/2 H_2O (255.3); Calc. C : 70.63; H : 7.51. found C :70.43; H : 7.52

^1H NMR (δ, ppm) : 6.85-6.7 (d, H5, H7; t, H6), 4.4-4.3 (dt, 1H, H2eq, J = 12;4), 4.15-4.05 (ddd, 1H, H2ax, J = 12; 9; 4.3), 3.85 (s, 3H, CH_3), 3.25 (m, 1H, H4', J = 3), 3.15 (t, 1H, H3', J = 4.8), 2.3-1.8 (m, 6H), 1.2 (m, 2H, H6').

^{13}C NMR : 148.2 (C8), 143.6 (C8a), 131.3 (C4a), 120.0 (C6), 119.0 (C5), 108.6 (C7), 62.7 (C2), 55.7 (CH_3), 51.2 (C3'), 50.0 (C4'), 36.9 (C2'), 32.1 (C3), 30.6 (C4), 30.3 (C6'), 21.0 (C5').

Reduction of the epoxides 12 and 13 :

To a solution of 60 mmol (2.28 g) of $LiAlH_4$ in 100 ml of anhydrous THF at 0 °C were portionwise added 20 mmol (2.66 g) of $AlCl_3$; the mixture was stirred for 10 mn and a solution of 10 mmol (2.4 g) of epoxide 12 or 13 in 30ml of anhydrous THF was added. The mixture was stirred 4 h at room temperature and hydrolysed. After filtration of the precipitate, the solvent was dried and evaporated. The oily residue was chromatographied on silica gel (cyclohexane / ethylacetate : 70/30) to give 2 g (yield = 83%) of 14 and 1.45 g (yield = 60%) of 15.

14

Anal. $C_{15}H_{20}O_3$ (248.32); Calc. C : 72.55; H : 8.12. found C : 72.27; H : 8.49.

^1H NMR (δ, ppm) : 6.9 (m, 2H), 6.7 (d, 1H), 4.45 (dt, 1H, H2), 4.2-4.0 (m, 2H, H2 and H2'), 3.85 (s, CH_3), 2.35 (m, 1H, H3), 1.9-1.75 (m, 3H), 1.7-1.4 (m, 7H).

^{13}C NMR : 148.6 (C8), 146.0 (C8a), 128.6 (C4a), 120.3 (C6), 117.6 (C5), 109.0 (C7), 75.7 (C2'), 63.6 (C2), 55.7 (CH_3), 40.2 (C4), 38.0 (C3'), 28.6 (C6'), 24.7 (C4'), 23.7 (C3), 20.5 (C5').

15

Anal. $C_{15}H_{20}O_3$ (248.32); Calc. C : 72.55; H : 8.12. found C : 72.40; H : 8.63.

^1H NMR (δ, ppm) : 7.05 (dd, 1H, H5), 6.85 (t, 1H, H6), 6.7 (dd, 1H, H7), 4.2 (dd, 2H, 2H2), 4.1 (t, 1H, H4', J = 3 Hz), 3.85 (s, CH_3), 2.35-2.1 (dt, 2H, H2' and H6'), 2.1-1.85 (m, 2H, H3), 1.8-1.6 (m, 5H, 2H3', 2H5' and OH), 1.5-1.3 (m, 2H, H2' and H6').

^{13}C NMR : 148.1 (C8), 143.6 (C8a), 132.6 (C4a), 119.6 (C6), 118.9 (C5), 108.5 (C7), 64.9 (C4'), 63.0 (C2), 55.7 (CH_3), 33.5 (C4), 31.4 (C2' and C6'), 29.8 (C3), 28.3 (C3' and C5').

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