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AN ANTIINFLAMMATORY CUM IMMUNOMODULATORY PIPERIDINYLBENZOPYRANONE FROM *DYSOXYLUM BINECTARIFERUM* : ISOLATION, STRUCTURE AND TOTAL SYNTHESIS

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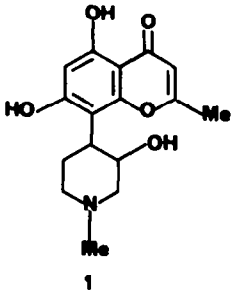
Abstract - (+)-*cis*-5,7-Dihydroxy-2-methyl-8-[4-(3-hydroxy-1-methyl) piperidinyl]-4H-1-benzopyran-4-one was identified as the antiinflammatory cum immunomodulatory principle of the stem bark of *Dysoxylum binectariferum*. The sequence devised for its total synthesis was also used to synthesise its (-)-enantiomer and the racemate.

In the treatment of rheumatic diseases, basically two types of drugs are used, non-steroidal antiinflammatory drugs (NSAIDs)[1] and disease-modifying antirheumatic drugs (DMARDs)[2]. NSAIDs mainly inhibit the cyclooxygenase pathway of the arachidonic acid cascade, preventing the formation of proinflammatory prostaglandins. DMARDs are immunomodulators claimed to regulate a distorted immune system. In continuation of our efforts to detect novel lead compounds from natural sources[3], we started a programme targetted at the detection of a compound combining both antiinflammatory and immunomodulatory properties. A compound that emerged from our programme to meet this target was found to be (+)-*cis*-5,7-dihydroxy-2-methyl-8-[4-(3-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one **1**. It displayed antiinflammatory activity in the carrageenin-induced rat paw oedema assay (ED_{50} = 9 mg/kg., p.o.) and inhibited the reverse passive Arthus reaction in rats, (50.8±5.9% inhibition at 2.5 mg/kg., p.o.). In this paper is described the isolation of **1** from *Dysoxylum binectariferum*[4] , its identification and its total synthesis. In the process, the (-)-enantiomer of **1** and the racemate were also synthesised.

Isolation

Bioassay-directed purification of the methanol extract of the stem-bark of the plant led to the isolation of **1** as the active principle (cf. experimental). The residue from the methanol extract was separated into alkaloidal and non-alkaloidal portions by acid-base treatment. The acidic alkaloidal-containing portion, on careful basification with ammonia solution and cooling, gave an amorphous powder. Purification of this material by crystallisation and by passage through a column of HP-20 gave compound **1**. The yield of compound **1** was estimated to be 0.9% of the dry weight of the plant material.



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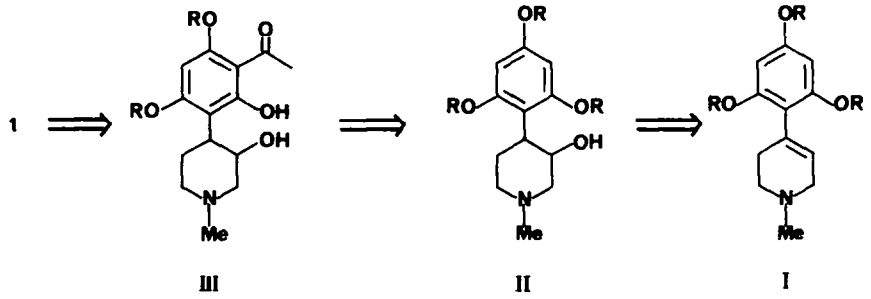
Structure Elucidation

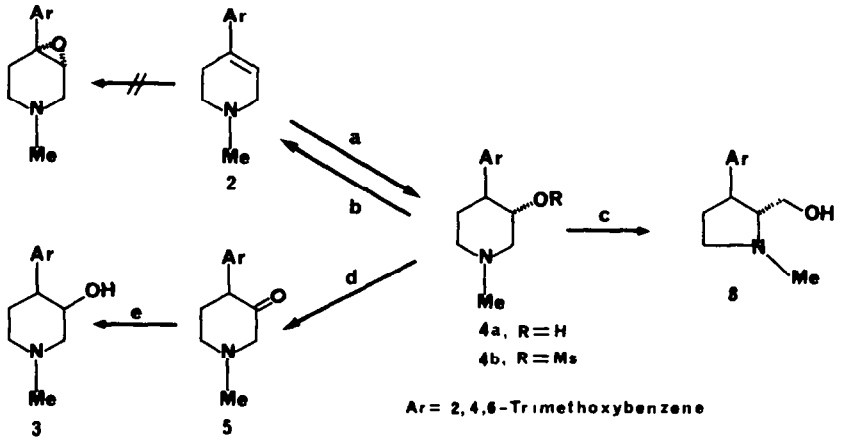
Mass spectrum and elemental analysis established the molecular formula as $C_{16}H_{19}NO_5$. The IR spectrum of the compound revealed the presence of hydroxyl groups (3400 cm^{-1}, broad), and conjugated carbonyl (1660 cm^{-1}). The peaks at 1610 and 1555 cm^{-1} suggested a γ-pyrone moiety. N-H absorptions were absent. The compound gave a positive ferric chloride test. In the 90 MHz ^1H NMR spectrum three peaks were present at δ, 6.06, 6.68 and 7.24 ppm each accounting for one proton. On D_2O exchange the last peak disappeared. The low proton count in the aromatic/alkene region suggested a highly substituted aromatic ring. A broad singlet integrating for one proton was present at δ, 4.36 and could be ascribed to a methine proton attached to a hydroxyl group. In the upfield region of the spectrum two singlets each accounting for three protons were present at δ, 2 17 and 2.24 ppm and were attributed to a N-methyl and a methyl attached to a sp^2 carbon. Four clusters of multiplets were seen at δ, 3.55, 3.0, 2.0 and 1.55 ppm. With this cumulative data it was possible to identify the compound as a dihydroxy chromone bearing a N-methyl-piperidinol group. A literature search at this stage revealed that compound 1 is constitutionally the same as the alkaloid rohitukine isolated from *Amoora rohituka*[5]. X-ray analysis[6] carried out on the crystal obtained from aqueous acetone confirmed the identity of 1 with rohitukine, leaving unresolved the enantiomeric identity of the two compounds as no optical rotation value was reported for rohitukine

Synthesis

Our retrosynthetic analysis (scheme 1) of 1 showed that the success of a synthetic route depended on two critical steps : regio- and stereo-controlled introduction of a hydroxyl group in the aryltetrahydropyridine (I) to give the *cis*-3-arylpiperidinol (II), and conversion of (II) to the *o*-hydroxyacetophenone intermediate (III)



Scheme 1

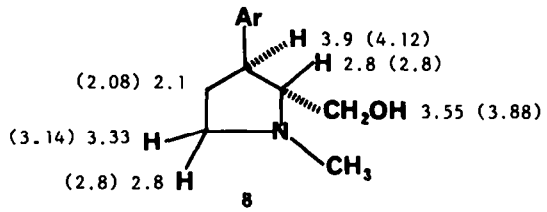


a) 1. B_2H_6 2 H_2O_2, OH^- b) DEAD, ϕ_3P, ϕCO_2H c) 1 MsCl 2. CsOAc or KO_2 or KNO_2 3 OH^- d) DMSO, $(COCl)_2$, Et_3N e) $NaBH_4$

Scheme 2

The trimethoxyphenyltetrahydropyridine **2** was readily obtained in 90% yield by heating N-methyl-4-piperidinone with 1,3,5-trimethoxybenzene in a glacial acetic acid/hydrochloric acid mixture[7]. Our initial strategy to convert **2** to the *cis*-arylpiperidinol **3** was through epoxidation of **2** and subsequent reduction of the epoxide (scheme 2). Different attempts at epoxidation of the double bond using peracids were unsuccessful. On the assumption that oxidation of the nitrogen atom was an interfering competitive reaction, epoxidation was carried out on various salts of **2** such as the hydrochloride and fluoroborate salts. The products were, however, only intractable mixtures.

Hydroboration[8] of **2** readily provided the *trans*-arylpiperidinol **4a**. Attempts to invert the stereochemistry of the hydroxyl group in **4a** under Mitsunobu reaction conditions[9] resulted only in elimination and reversion to olefin **2**. S_N2 displacements of the *trans*-mesylate group in **4b** with oxygen nucleophiles (cesium acetate[10], potassium dioxide[11], potassium nitrite[12]) provided in each case only the pyrrole derivative **8**. Similar ring-contracted products have been previously reported[13]. The 90 MHz ^{1}H-NMR spectra of **8** in $CDCl_3$ and C_5D_5N, and decoupling studies conclusively established its structure. The assignments of the proton shifts of **8** in the two solvents (C_5D_5N values in parenthesis) are shown in the figure below. The values for the aromatic protons, the methoxy protons and the N-methyl protons were similar to those of the corresponding protons in the *trans*-piperidinol **4a**. A double doublet integrating for two protons was present at δ, 3.55 ppm, which was assigned to the $-CH_2OH$ protons. In C_5D_5N this double doublet showed up as an apparent triplet δ, 3.88 ppm. In the upfield region of the spectrum three multiplets were seen at δ, 3.33 (3.14), 2.8 (2.8) and 2.1 (2.08) ppm integrating for 1,2 and 2 protons respectively. The first multiplet was assigned to one of the C_5 methylene protons. The second multiplet (δ, 2.9) was assigned to the other of the C_5 methylene protons and to the C_2-methine proton, on the basis of the following decoupling experiments. Irradiation ($CDCl_3$) of the multiplet at δ, 2.8 ppm resulted in simplification of the multiplet at δ, 3.33 ppm and collapse of the double doublet at δ, 3.55 ppm into two broad singlets. Furthermore, irradiation of the multiplet at δ, 3.33 ppm had no effect on the double doublet at δ, 3.55 ppm.



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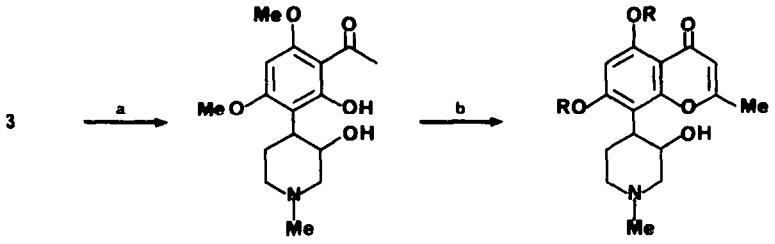
Irradiation (C_5D_5N) of the multiplet at δ, 2.08 ppm resulted in the collapse of the multiplets at δ, 3.14 and δ, 4.12 ppm into doublets (J = 9 and 10 Hz resp.), establishing the assignment of peak at δ, 4.12 ppm to the benzylic proton. The coupling constant of 10 Hz between the benzylic and the C_2 methine proton supports their *trans*-orientation to each other as required by the reaction mechanism.

The *cis* compound **3** was finally obtained by Swern oxidation of **4a** to the keto intermediate **5**, followed by reduction of **5** with sodium borohydride. The reduction product was a mixture of *cis*/*trans* alcohols **3** and **4a**, present in a 7:3 ratio as determined by GC analysis (3% OV-1 on chromosorb Q). Separation of the *cis* alcohol from the *trans* alcohol was efficiently achieved by crystallisation of the hydrochloride of the mixture from acetone. The most prominent ^{1}H-NMR spectral difference between compounds **3** and **4a** was the chemical shift value for the proton attached to the secondary alcohol group, which in the case of the *cis* alcohol **3** (δ, 3.8 ppm, overlapped by methoxy groups) was more shielded compared to the *trans* isomer (δ, 4.2 ppm, m).

Resolution of **3** was accomplished by one of two ways, either by fractional crystallisation of its diastereomeric salts with (-)-dibenzoyl-D-tartaric acid, or by separation (silica gel flash chromatography) of its diastereomeric ester mixture with (-)-menthyloxyacetic acid. The two enantiomers and the racemate were separately treated as described below.



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7a, R=Me
7b, R=H

a) 1 BF_3: Et_2O, Ac_2O 2. OH^- b) 1 EtOAc, Na 2. H^+ 3 $PyHCl$

Scheme 3

The optimal conditions for converting the *cis* arylpiperidinols **3** to the targetted *o*-hydroxyacetophenone intermediate **6** were determined through studies of acylation of **3** using different conventional acetylating agents. The use of acetic anhydride with **3** in the presence of boron trifluoride etherate (5 equiv.), followed by saponification to cleave the *in situ* formed acetate of the hydroxy group in the piperidine moiety, provided **6** in the best yield of 73%. Initially it was unclear from ^{1}H-NMR spectral data which of the two methoxy groups ortho to the acetyl substituent was demethylated. Based on literature precedents[14] that the most hindered methoxy group is preferentially demethylated, structure **6** was assigned to the demethylated product. Later this assignment was proved correct by direct comparison of the natural product with the one obtained through total synthesis. Compound **6** was subjected to reaction with ethyl acetate and sodium, whereby the chromone ring was formed. The product was demethylated by heating with pyridine hydrochloride and a small amount of quinoline. The product **7b** obtained from the sequence in scheme 3 using the (-)-enantiomer of **3** was identical in all respects with the natural product **1**. The (-)-enantiomer of **1** and the racemate were also synthesised using the appropriate *cis*-arylpiperidinols **3**. The racemate of **1** was obtained in an overall yield of 14.3%

This total synthesis offers the flexibility to prepare a variety of structural analogues for SAR studies. The results of the structure activity studies will be published elsewhere.

EXPERIMENTAL

Melting points are determined on a Bristoline hot stage apparatus and are uncorrected. Infrared spectra are recorded on Perkin Elmer model 157 and 782 spectrophotometers. Optical rotations are determined using Perkin Elmer model 141 polarimeter in methanol using cell of 10 cm path length. ^{1}H-NMR spectra are recorded on Varian T-60, Jeol FX 90 Q spectrometers. G.C. analyses are carried out on a Perkin Elmer 900 machine. Analytical thin layer chromatography (tlc) is performed on Merck precoated silica gel F_{254} plates. Solvents are purified by standard techniques. Hydrochlorides are prepared by adding dry ethereal HCl to compounds in dry methanol and evaporated to dryness after 5 minutes. The crude hydrochlorides are crystallised from methanol-diisopropyl ether

Isolation of Compound 1. The stembark (31 kg) of *Dysoxylum binectariferum* is extracted successively with methanol (40 lx4), 4% sodium hydroxide solution in MeOH:H_2O (9:1) (40 l x 2) and 1% acetic acid in MeOH:H_2O (9:1) (40 l x 2) The combined extracts are evaporated to remove methanol. The aqueous extract is cooled in ice, acidified to pH 2 with 2N HCl and extracted with chloroform (2 5 l x 4).

The aqueous extract is cooled to 10°C and basified to pH 9 with liquor ammonia The precipitate thus obtained is filtered. Acetone is added to the filtrate (aqueous) in a ratio of one part of acetone to three parts of water and the solution is cooled to 10°C overnight The precipitate is filtered and combined with the previous crop. The combined precipitate is crystallised twice from aqueous acetone, 310 g. A small portion (1.0 g) of the crystallised sample is purified further by passing through a column of HP20 and eluting with water, and water-methanol mixture with increasing concentration of methanol. The compound is eluted out with water:methanol (4:1). m.p. 227-232°C, $[\alpha]_D^{20}$ = +44.3° (MeOH); IR (KBr) ν_{max} : 3400, 1660, 1610, 1555 cm^{-1}; ^{1}H-NMR (90 MHz, C_5D_5N) : δ, 7.24 (s, 1H, acidic), 6 68 (s, 1H), 6.06 (s, 1H), 4.36 (bs, 1H), 3.55 (m, 1H), 3 0 (m, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 2.0 (m, 2H), 1.55 (m, 1H). Analysis : Found. C, 59.43; H, 6.71; N, 4 25%, calcd. for $C_{16}H_{19}NO_5.H_2O$, C, 59.43; H, 6.5; N, 4.33%. Hydrochloride, m.p. 242-243°C, $[\alpha]_D$ = -27.2° (MeOH).

1-Methyl-4-(2,4,6-trimethoxyphenyl)-1,2,3,6-tetrahydropyridine 2. 1-Methyl-4-piperidone (316.4 g, 2.8 mol) is added with stirring to a solution of 1,3,5-trimethoxybenzene (400 g, 2.38 mol) in glacial acetic acid (750 ml) while maintaining the temperature at 25°C. After the addition is over hydrogen chloride is bubbled through the reaction mixture for *ca.* one hour, and later the reaction mixture is heated at 95°-100°C for 3 hours. Acetic acid is removed by distillation, and water (750 ml) is added to the residue. The aqueous solution is extracted with ether (250 ml x 4), and the aqueous portion is basified by addition of 40% sodium hydroxide solution. The precipitate obtained is filtered, washed with water and dried. Recrystallisation from petroleum ether (60°-80°C) afforded the pure olefin, m.p. 118°-121°C, 550 g (80%). IR ν_{max} : 1600, 1580, 1430, 950 and 810 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ, 6.1 (s, 2H), 5.6 (m, 1H), 3.7-3.9 (3s, 9H), and 2.4 (s,3H). Analysis :Found, C, 68.54; H, 7.84; N, 4.91%, calcd. for $C_{15}H_{21}NO_3$, C, 68.44; H, 7.98; N, 5.32%.

trans-1-Methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinol **4a**. Boron trifluoride etherate (500 ml, 4.06 mol) is added with stirring to an ice cooled mixture of the olefin (500 g, 1.9 mol), sodium borohydride (125 g, 3.26 mol) and dry tetrahydrofuran (4 l) under nitrogen atmosphere. After the addition, the reaction mixture is heated at 50°C for 1 h. The organoborane reaction mixture is cooled to 0°C and water (250 ml) is carefully added followed by conc. hydrochloric acid (1.25 l). The mixture is stirred for 2 h. at 50°C. Oxidation is carried out by successive addition of 40% sodium hydroxide solution (1.5 l) and 30% hydrogen peroxide (1 l). The organic layer is separated and the aqueous layer is extracted with ethyl acetate (500 ml x 2). The combined organic portion is concentrated and the residue treated with 2N hydrochloric acid until acidic and extracted with ethyl acetate (200 ml x 2). The aqueous layer is basified with 10% sodium hydroxide solution and extracted with ethyl acetate (250 ml x 4), washed with brine, dried and concentrated. The residue crystallised from hot water, m.p. 88°-89°C, 374 g (70%). IR ν_{max} : 3500 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) : δ, 6.15 (s, 2H), 4.2 (m, 1H), 3.75 (s, 3x 3H), 3.0 (m, 3H), 2.3 (s, 3H), 1.9 (m, 3H) and 1.55 (m, 2H). Analysis : Found, C 64.32; H, 8.13; N, 4.56%, calcd. for $C_{15}H_{23}NO_4$, C, 64.05; H, 8.18; N, 4.98%.

1-Methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinone **5**. Dimethyl sulfoxide (35 ml, 0.493 mol) in dry dichloromethane (100 ml) is added to freshly distilled oxalyl chloride (20 ml, 0.225 mol) in dry dichloromethane (500 ml) at -60°C with stirring under nitrogen atmosphere. After the addition the reaction mixture is stirred for 15 min and the *trans*-hydroxy compound **4a** (62.26 g, 0.220 mol) in dry dichloromethane (300 ml) is added in a continuous stream through a dropping funnel while the temperature is maintained at -60°C. After stirring for 15 min triethylamine (155 ml) is added and the reaction mixture is allowed to warm to -30°C. Water (200 ml) is added to the reaction mixture and basified with sodium bicarbonate. The organic layer is separated and the aqueous portion is extracted with ethyl acetate. The combined organic portion is washed with brine,dried and concentrated. The residue is crystallised from isopropanol, m.p. 110°-112°C, 47 g (76%). IR ν_{max} : 1725, 1620 and 1425 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ, 6.1 (s, 2H), 3.7-3.9 (3s, 9H) and 2.4 (s, 3H). Analysis : Found, C, 64.75; H, 7.48; N, 4.72%, calcd. for $C_{15}H_{21}NO_4$, C, 64.51; H, 7.52; N, 5.01%.

cis-1-Methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinol **3**. Sodium borohydride (10 g, 0.263 mol) is added to a refluxing solution of the ketone **5** (36 g, 0.129 mol) in absolute alcohol under stirring and the stirring is continued for one hour. Cooled, and water (100 ml) is added and alcohol is removed under reduced pressure. The residue is dissolved in water and extracted with chloroform, and the extract dried and concentrated. The residue is taken in methanol and excess of ethereal hydrogen chloride is added. The precipitated salt is filtered and crystallised from acetone. The free base is regenerated by addition of aqueous sodium carbonate solution, m.p. 124-125°C, 24 g (66%). IR ν_{max} : 3500, 1600, 1460, 1340, 1240 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) : δ, 6.1 (s, 2H), 3.8 (bs, 9H+1H), 3.3 (m, 1H), 3.0 (m, 3H), 2.25 (s, 3H), 2.1 (m, 3H) and 1.4 (m, 1H), Analysis : Found, C, 64.33; H, 8.28; N, 4.76%, calcd. for $C_{15}H_{23}NO_4$, C, 64.05; H, 8.18; N, 4.98%.

Resolution of (+)-*cis*-1-Methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinol **3**.

Method A :

The racemic **3** (90 g, 320 mmol) is dissolved in methanol (300 ml). A solution of (-)-dibenzoyl-D-tartaric acid (126.4 g, 335.8 mmol) in methanol (200 ml) is added and the solution is heated to boiling. Diisopropyl ether (*ca.* 500 ml) is slowly added and the clear solution is allowed to cool. The tartarate salt crystallises out slowly. Filtered and recrystallised five times from methanol and diisopropyl ether, 44 g, $[\alpha]_D^{20}$ = -48.3° (MeOH). The tartarate salt (43 g) is suspended in water (200 ml) and hydrochloric acid (2N, 100 ml) is added and stirred. The reaction mixture is extracted with ethyl acetate and the aqueous layer is basified by addition of sodium carbonate solution and extracted with chloroform. The organic extract is washed with water, dried and concentrated to afford (+)-**3**, 17.7 g, m.p. 109-111°C, $[\alpha]_D^{20}$ = +53.81° (methanol).

The filtrate from the tartarate crystallisations are combined and the free base (60 g) is recovered as described above. The free base (20 g) is dissolved in methanol (110 ml), (+)-dibenzoyl-L-tartaric acid (29 g) is added and the solution is heated to boiling. Diisopropyl ether (*ca.* 110 ml) is added slowly. On standing at room temperature the tartarate salt crystallises out. The salt is filtered and recrystallised five times from the same solvent system, 20.2 g, $[\alpha]_D^{20}$=+49° (MeOH). The free base is isolated as described above, 8.2 g, m.p. 109-111°C, $[\alpha]_D^{20}$= -54.13° (MeOH).

Method B :

The racemic **3** is esterified with (-)-menthyloxyacetic acid as follows. A mixture of **3** (2 g, 7.16 mmol), (-)-menthyloxyacetic acid (1.827 g, 8.5 mmol), N,N'-dicyclohexylcarbodiimide (2.9 g, 14 mmol) and 4-pyrrolidinopyridine (0.1 g) in dry dichloromethane (10 ml) for 5 hours.The reaction mixture is filtered and the precipitate washed with dichloromethane. The combined filtrate is concentrated, stirred with dilute hydrochloric acid and filtered through filter aid. The filtrate is extracted with ethyl acetate and the aqueous layer basified by addition of sodium carbonate solution. The product is extracted with dichloromethane, and the extract dried and concentrated to give a gummy material. tlc examination on silica gel (10% pet. ether + 1% NH_4OH in chloroform) showed two distinct spots with R_f *ca.* 0.45 along with other minor spots. The two diastereomers

were separated by flash chromatography on silica gel using 1% methanol + 1% NH_4OH in chloroform, and showed the following optical rotations : isomer of higher R_f, $[\alpha]_D^{20} = -11.6°$ and isomer of lower R_f, $[\alpha]_D^{20} = -62.98°$ (methanol). The two isomers were separately stirred with 5% potassium hydroxide in methanol for 3 hours, and the free bases are isolated in the usual way. They displayed the following optical rotations, + 45.25° and -52.3° respectively. They were not purified further.

(-)-*cis*-4-(3-Acetyl-4,6-dimethoxy-2-hydroxy)phenyl-1-methyl-3-piperidinol **6**. The (-)-3 (35 g, 124.5 mmol) in dry dichloromethane (500 ml) is cooled in an ice bath. Boron trifluoride etherate (107.6 ml) is added at a steady rate followed by dropwise addition of acetic anhydride (76.2 ml, 808.3 mmol). After the addition, the reaction mixture is stirred at room temperature overnight. The reaction mixture is basified by addition of sodium carbonate solution. The organic phase is separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is washed and concentrated. The residue is stirred with potassium hydroxide solution (25 g in 500 ml water + 200 ml methanol) for 24 hours under nitrogen atmosphere. The reaction mixture is partially concentrated, the pH adjusted to about 8, and extracted with chloroform. The chloroform extract is washed, dried, concentrated and the residue crystallised from methanol-water (1:1), 28 g (73%), m.p. 181-182°C, $[\alpha]_D^{20} = -45.19°$ (MeOH). IR ν_{max} . 3500, 1670, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : 6 0 (s, 1H), 3.8 (s, 6H), 2.6 (s, 3H) and 2.3 (s, 3H). Analysis : Found, C, 55.57; H, 6.94; N, 4.05; Cl, 10 27%, calcd. for $C_{16}H_{23}NO_5.HCl$, C, 55.24; H, 7.04; N, 3.88; Cl, 10.40%.

(+)-*cis*-5,7-Dihydroxy-2-methyl-8-[4-(3-hydroxy-1-methyl) piperidinyl]-4H-1-benzopyran-4-one **7b**. (-)-6 (8.0 g, 25.88 mmol) in ethyl acetate (400 ml) is refluxed with sodium (7 g) for 3 hours A saturated solution of sodium bicarbonate is added and the organic layer is separated. The aqueous layer is extracted with ethyl acetate and the organic extracts are combined and concentrated to about 100 ml. Conc hydrochloric acid (10 ml) is added and the reaction mixture is stirred for 0 5 hour. Water (100 ml) is added to the reaction mixture and extracted with chloroform. The combined extracts is dried and concentrated. The residue (8 g) is heated with pyridinium hydrochloride (80 g) and quinoline (5 ml) at 180°C for 2 hours. The reaction mixture is cooled and a saturated solution of sodium bicarbonate is added The pasty mass is thoroughly extracted with chloroform:methanol (4:1) several times. The organic extracts are combined and the residue, obtained after evaporation of the solvents, is chromatographed on silica gel (20% MeOH in $CHCl_3$ + 1% ammonia solution) to obtain (+)-*cis*-5,7-dihydroxy-2-methyl-8-[4-(3-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one, m.p. 227-228°C, $[\alpha]_D^{20} = +42.5°$ (MeOH). IR ν_{max} : 3400, 1655, 1610, 1555 cm^{-1}; ^{1}H-NMR (90 MHz, pyridine-d^5) : δ, 7 24 (s, 1H, acidic), 6 68 (s, 1H), 6.06 (s, 1H), 4 36 (bs, 1H), 3.55 (m, 1H), 3.0 (m,3H), 2.24 (s, 3H), 2.17 (s, 3H), 2.0 (m, 2H), 1 55 (m, 2H). Analysis : Found : C, 59.56; H, 6.78; N, 4.3%, calcd. for $C_{16}H_{19}NO_5.H_2O$, C, 59.44; H, 6.5; N, 4.33% Hydrochloride, m.p. 242-45°, $[\alpha]_D^{20} = -25.37°$ (MeOH). Analysis : Found, C, 53.88; H, 6 19, N, 3.82; Cl, 10 4%, calcd. for $C_{16}H_{19}NO_5.HCl.H_2O$, C, 53.4; H, 6 11; N, 3.89 and Cl, 9.87%

trans-2-Hydroxymethyl-1-methyl-3-(2,4,6-trimethoxy)phenylpyrrolidine **8**. Methanesulfonyl chloride (6.63 g, 58 mmol) in dry dichloromethane (20 ml) is added dropwise to a cooled (0°C) solution of the alcohol **4a** (15.5 g, 55 mmol), triethylamine (16 ml) and dry dichloromethane (170 ml) After three hours stirring a saturated solution of sodium carbonate is added and the reaction mixture is extracted with chloroform. The combined organic extract is dried, and concentrated. The residue (13 g) is used without further purification.

The mesylate (1.2 g) is heated with cesium acetate (0.5 g) in an appropriate solvent for 3 hours. The reaction mixture is cooled to room temperature and stirred with 10% potassium hydroxide solution overnight. The reaction mixture is extracted with ethyl acetate, dried and concentrated. The residue is purified further by flash chromatography on silica gel (10% methanol in chloroform) to give 0.83 g of **8**, m.p 84-85°C, IR, ν_{max} : 3450 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) · δ, 6.1 (s, 2H), 3 9 (m, 1H), 3.8 (s, 3x 3H), 3.55 (dd, 2H), 3.33 (m, 1H), 2.8 (m, 1H+1H), 2.5 (s, 3H), 2.1 (m,2H); in C_5D_5N : δ, 6.3 (s, 2H), 4.12 (m, 1H), 3.88 (t, 2H), 3.72 (s, 3H), 3.68 (s, 2x3H), 3.14 (m,1H), 2.8 (m,2H), 2.56 (s, 3H), 2.08 (m, 2H). Analysis : Found, C, 62.16; H, 8.33; N, 4.30%, calcd. for $C_{15}H_{23}NO_4.0\ 5H_2O$, C, 62.07; H, 8.28; N, 4 83%.

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