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Ruthenium Dioxide in Fluoro Acid Medium: II. Application to the Formation of Steganes Skeleton by Oxidative Phenolic Coupling.[1]

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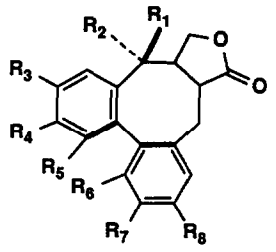
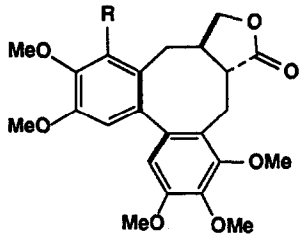
Abstract: Ruthenium (IV) dioxide dihydrate in fluoro acidic medium was found to be a very efficient agent for the oxidative coupling of the phenolic lignans (±)-presteganes A and B. Different attempts to oxidise the diphenolic dibenzylbutanolide (±)-HPMF were also carried out, but were unsuccessful. Likely explanation for these failures are given.

Résumé: Le dioxide de ruthénium (IV) dihydraté, en milieu fluoracide, s'est avéré être un agent très performant pour effectuer le couplage oxydant des lignanes phénoliques (±)-prestéganes A et B. Diverses tentatives d'oxydation du dibenzylbutanolide diphénolique (±)-HPMF ont aussi été effectuées, mais sans succès, et une explication vraisemblable de ces échecs est donnée.

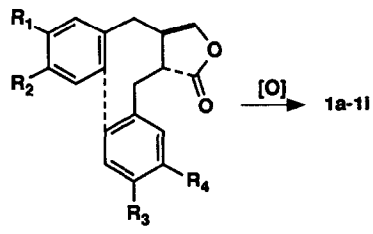
During our studies of the synthesis of bisbenzocyclooctadienes (BBCOD) lignan lactones, we have found that ruthenium dioxide dihydrate is a very powerful and efficient reagent for the oxidative coupling of non-phenolic dibenzylbutanolides.[3] The reports of Barton[4] and Battersby[5] on biogenesis of aporphines suggested that compounds which possess biaryl bonds are formed in the plant by an enzymatic intramolecular biaryl oxidative coupling of phenolic precursors. The recent investigations carried out by our group on *Steganotaenia araliacea* allowed us to isolate, in addition to the bisbenzocyclooctadiene lactones **1a-d** already discovered by Kupchan and co-workers,[6] five new BBCOD (**1e-i**)[7] and two phenolic dibenzylbutanolides (**2a-b**).[8] The latter possess one or two hydroxyl groups *"meta"* substituted to the aliphatic chain. The presence of this interesting and original feature gives rise to speculation that bisbenzocyclooctadiene lactones **1a-i** are biosynthetically derived from presteganes A **2a** and B **2b** by an oxidative phenolic coupling[4] (Scheme I). In 1973, Schlessinger and co-workers[9] investigated first the oxidative coupling, with VOF_3, of dibenzylbutanolide to form eight membered ring compounds. More recently, Cambie[10] utilised thallium (III) tristrifluoroacetate (TTFA, generated in situ) as oxidant in this reaction. A wide range of oxidants has been used in the past for oxidative coupling.[11] Among them, $K_3Fe(CN)_6$[12a] and $FeCl_3$[12b] were the more commonly used in aporphinic and homoaporphinic alkaloid chemistry. Generally these reagents gave poor yields, and often complex mixtures. The improvement of the methodology for oxidative phenolic coupling with VOF_3[13] and TTFA[14] prompted us to examine the reaction in the lignan series of *S. araliacea*. We describe here the chemistry leading to the synthesis of phenolic bisbenzocyclooctadienes by oxidative phenolic couplings of (±)-presteganes A and B with ruthenium dioxide in fluoro acidic medium.



1a, $R_1 = R_2 = O$; $R_3 = R_4 = OCH_2O$; $R_5 = H$; $R_6 = R_7 = R_8 = OMe$
1b, $R_1 = R_5 = H$; $R_2 = OH$; $R_3 = R_4 = OCH_2O$; $R_6 = R_7 = R_8 = OMe$
1c, $R_1 = R_5 = H$; $R_2 = OAc$; $R_3 = R_4 = OCH_2O$; $R_6 = R_7 = R_8 = OMe$
1d, $R_1 = H$; R_2 = angelate; $R_3 = R_4 = OCH_2O$; $R_6 = R_7 = R_8 = OMe$
1e, R_1 = angelate; $R_2 = R_3 = R_6 = H$; $R_4 = R_5 = OMe$; $R_7 = R_8 = OCH_2O$
1f, R_1 = angelate; $R_2 = R_5 = R_8 = H$; $R_3 = R_4 = R_6 = R_7 = OMe$
1g, R_1 = tiglate; $R_2 = R_5 = R_8 = H$; $R_3 = R_4 = R_6 = R_7 = OMe$



1h, R= H
1i, R= OMe



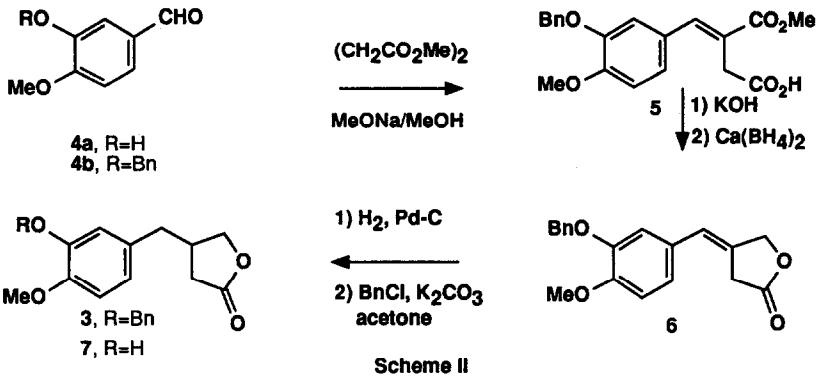
2a, $R_1 = R_2 = R_3 = OMe$; $R_4 = OH$
2b, $R_1 = R_4 = OH$; $R_2 = R_3 = OMe$
2c, $R_1 = R_4 = OH$; $R_2 = R_3 = H$

Scheme I

1. Synthesis of the phenolic dibenzylbutanolides

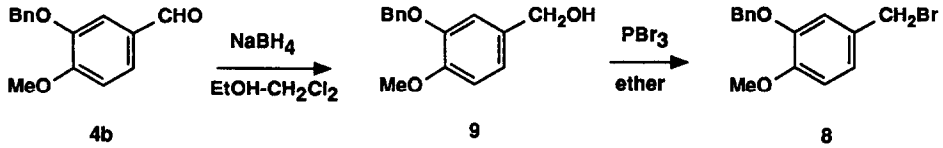
The synthesis of open phenolic precursor **2b** required some modifications in the previously described strategy[3] due to the presence of a phenol moiety in the molecule. The (±)-prestegane A **2a** was prepared according to the method formerly designed in our group.[8a] We also synthetised (±)-enterolactone **2c** (HPMF) which has been recently isolated from mammalian fluid.[15] This natural product is the only other known example of dibenzylbutanolide lignan bearing a phenol group in the *"meta"* position.

The O-benzylated lactone **3** was synthetised in five steps from the commercially available isovanillin **4a**. The Stobbe condensation between the benzylated benzaldehyde **4b**[16] (prepared from isovanillin: BnCl, KOH, EtOH, reflux, 94%) and dimethylsuccinate in presence of NaOMe afforded the unsaturated hemiester **5** in 78% yield. The ethylenic lactone **6** was obtained by reaction of the previous hemiester with calcium borohydride in ethanol, a procedure that gave the lactone **6** in high yield (84%). Catalytic hydrogenation of **6** with palladium on charcoal yielded the corresponding deprotected saturated lactone **7**, which was rebenzylated with benzyl chloride in acetone. The two-step sequence gave the expected lactone **3** in 81% yield (50% yield from isovanillin) (SchemeII).



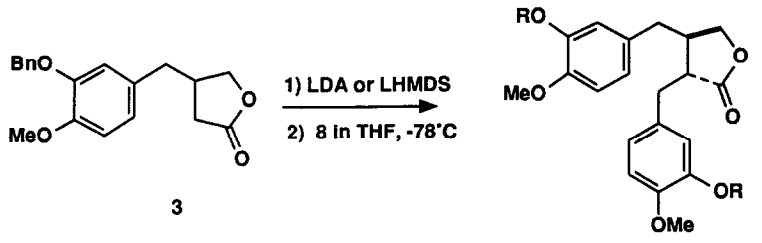
Scheme II

The compound **3** was readily alkylated by the benzyl bromide **8**[16] prepared, in two steps (81% overall yield), by reduction of benzylated isovanillin **4b** with $NaBH_4$ in a mixture of CH_2Cl_2-EtOH and bromination of the corresponding alcohol **9** (Scheme III).



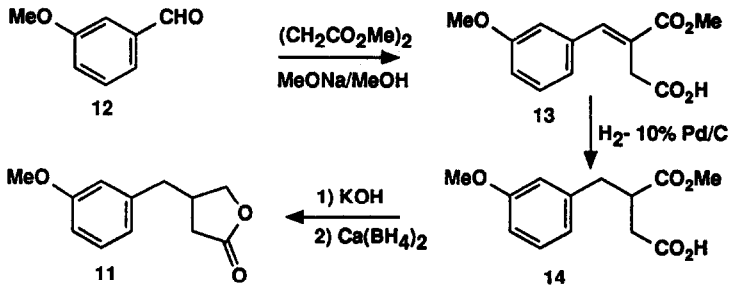
Scheme III

Two conditions were considered in the alkylation of the lactone **3** by the bromide **8**. The lithium hexamethyldisilylamide (LHMDS) procedure was proved to be better than the lithium diisopropylamide (LDA) procedure. The expected dibenzyl prestegane B **10** was isolated in 87% yield using LHMDS and only in 65% yield using LDA (Scheme IV). Hydrogenolysis of **10** with palladium on charcoal in a mixture of AcOH and EtOAc gave the expected (±)-prestegane B **2b**, which exhibited satisfactory analytical data and was identical (^1H NMR, ^{13}C NMR, IR and MS) with a natural sample.[8b]



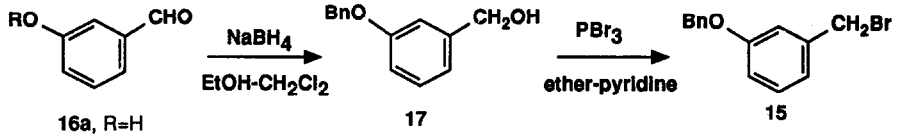
Scheme IV

(±)-HPMF **2c** was prepared in a similar manner. The lactone **11** was obtained from a three-step sequence in 57% overall yield, starting from 3-methoxy benzaldehyde **12** (Scheme V).



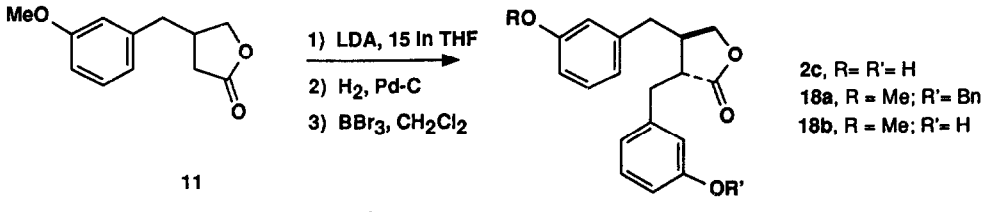
Scheme V

The bromide **15**[17] was synthesised using the above procedure. The reduction of the protected benzaldehyde **16b** (prepared from **16a** with BnCl, EtOH, 88% yield) afforded the alcohol **17** which was converted to the required halide **15** (67% overall yield from **16a**) with PBr_3 in a mixture of ether and pyridine[18] (Scheme VI).



Scheme VI

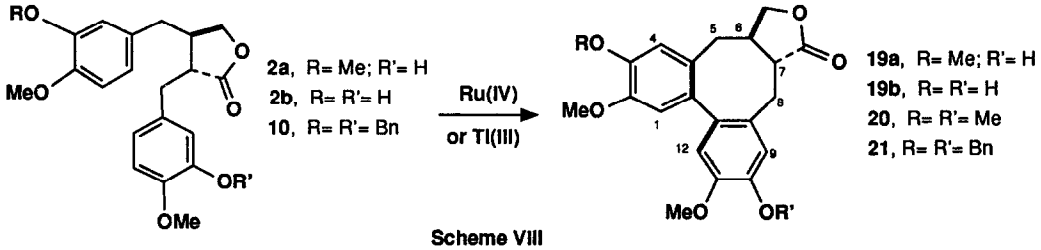
The alkylation of the lactone **11** by the bromide **15** with LDA in THF provided access to the desired dibenzylbutanolide **18a** in 48% yield (Scheme VII). The decrease in yield was probably due to the lack of an activating group *"para"* to the benzyl group in **11**. Also, ^1H NMR and TLC showed clearly that the lactone **11** behaved as an equilibrium mixture of lactone and the corresponding hydroxy-acid. The dibenzylbutanolide **18a** was converted to the monophenol **18b** by hydrogenolysis with palladium on charcoal (94% yield). The crude product was then treated by BBr_3 (2.5 eq.)[19] in CH_2Cl_2 affording, after chromatography and crystallization, the (±)-HPMF **2c**[15] (with analytical data according to the literature).



Scheme VII

2. Oxidative couplings of open-chain precursors

The (±)-presteganes A and B were submitted to the oxidative conditions as described previously[1,3] with 2 equivalents of $RuO_2,2H_2O$ in a mixture of CH_2Cl_2-TFA-TFAA and a trace of BF_3-Et_2O (Table I). Extensive work has been reported in this area,[11,12,20] but the yields of the resulting phenolic oxidative couplings are generally poor. Surprisingly, ruthenium (IV) oxidation of the two compounds studied **2a** and **2b** gave the corresponding bisbenzocyclooctadienes **19a** and **19b** respectively in 80-85% yield. Simple removal of metallic salts followed by a filtration on silica gel afforded the crystalline products **19a** and **19b** without any trace of other products. Comparatively, the oxidation of **2a** and **2b** with TTFA[12,14c,20] (0.75 eq. of Tl_2O_3 in TFA-TFAA) gave us the expected bisbenzocyclooctadiene, but in only 45-50% yield (Scheme VIII).



Scheme VIII

A careful examination, in the ^1H NMR (250 MHz) spectrum, of aliphatic vicinal coupling constants showed clearly that **19a** and **19b** possess an *"iso"* biaryl junction ($J_{5\alpha\text{-}6}$= $J_{7\text{-}8\beta}$= 0 Hz).[21] Moreover, the study of aromatic protons proved that phenolic oxidative coupling of **2a** and **2b** led exclusively to the *"para-para"* biaryl coupling. This good regioselectivity was particularly noteworthy, if we compared our results to those reported in the literature.[11,20] In order to confirm the assignment of the structure of **19a** and **19b**, we methylated their phenolic functions with diazomethane, the expected compound **20** being already known.[3b,10] The bisbenzocycloctadiene **20** was obtained from **19a** and **19b** in 78% and 83% yield respectively and was identical in all respects with the one reported before.[3b,10] These results showed that the two phenolic BBCOD possess an *"iso"* biaryl bond with the expected aromatic substitution.

As previously reported for the non phenolic series,[1,2] we tried to improve our procedure by using ultrasonic assistance and by substitution of the couple trifluoroacetic acid and anhydride by the pair triflic acid and anhydride (CF_3SO_3H-$(CF_3SO_2)_2O$). As before, use of these conditions reduced the reaction times. The products were not affected by the drastic reaction conditions (triflic acid is a powerful acid already used as solvent in anodic oxidation[22]). The results are summarised in Table I.

Only very few examples of cyclisation of O-protected open-chain precursors are described in the literature,[14c] so we tried to oxidise the di O-benzylated prestegane B **10** with the different reagents developed above. The precursor **10** was thus oxidised with TTFA (1.08 eq. in CH_2Cl_2-TFA-TFAA) in only 15 minutes producing the di O-benzylated BBCOD **21** in 69% yield (Scheme VIII). Hydrogenolysis with 10% palladium on charcoal in a 4:1 mixture of EtOAc-HOAc gave **19b** in 85% yield. The compound obtained by this way

was found to be indistinguishable from the compound obtained by the direct oxidative coupling of (±)-prestegane B. Thus, we can assigned an *"iso"* biaryl structure for **21**, this being confirmed in the ^1H NMR spectrum by the perfectly superimposable aliphatic pattern of **21** and its O-methylated analog **20**.

Table I. Oxidative coupling of presteganes A and B by using $RuO_2,2H_2O$ procedures. Comparison with TTFA.

Starting material	Product	Conditions[a]	Time (h)	Yield[b] (%)
2a	**19a**	A	16	80
2b	**19b**	A	14	82
2a	**19a**	B	7	82
2b	**19b**	B	7	80
2a	**19a**	C	3	80
2b	**19b**	C	3	84
2a	**19a**	D	2	45
2b	**19b**	D	2	50

a A: RuO_2, $2H_2O$ (2eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T= 18-20°C.
B: RuO_2, $2H_2O$ (2eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, Ultra-sound, T= 18-20°C
C: RuO_2, $2H_2O$ (2eq.), CH_2Cl_2-CF_3SO_3H-$(CF_3SO_2)_2O$- BF_3-Et_2O, T= 18-20°C.
D: Tl_2O_3 (0.54 eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T=18-20°C.

b Yield of isolated crystalline product (after filtration on silica gel and recrystallisation).

3. Scope and limitations

After the encouraging results obtained for oxidations of (±)-presteganes A and B, we tried an oxidative phenolic coupling on diphenolic dibenzylbutanolide (±)-HPMF **2c**, using the above procedure. Unfortunately, the different attempts to obtain the corresponding bisbenzocyclooctadiene(s) failed in all the conditions used. We suggest two hypotheses to explain the failure of this oxidative coupling. A careful examination of the ^1H NMR spectrum of (±)-HPMF **2c** in different solvents ($CDCl_3$, CD_3COCD_3, D_2O) indicated that this product exists in differents forms: in the free or chelated hydroxy-acid form or in the lactone form. The free carboxylic acid function could trap the radical cation formed during the oxidation preventing the required cyclisation. The second explanation is the lack of methoxy substituents on the aromatic ring which normally activate the aromatic nucleus. Indeed, Ronlan and co-workers[23] showed that the lower the number of methoxy substituents on the aromatic ring, the higher the oxidative potential needed to carry out the oxidative biaryl coupling.

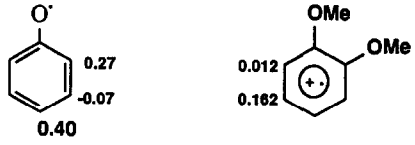
Additionally, the attempted cyclisation of the monophenolic dibenzylbutanolide **18b** with TTFA or with the ruthenium procedures failed, the starting material being recovered unchanged. This result confirmed the latter hypothesis. It is possible in this particular case that the oxidants we used were too weak to generate the cation-radical, key-intermediate in the biaryl formation.

Independently, when the cyclisation of **10** was carried out with 2 eq. of $RuO_2,2H_2O$ in CH_2Cl_2-TFA-

TFAA, we noted, by TLC, the appearance of polar compounds, which could not be isolated. Trifluoroacetic acid is known to be a good cleavage agent of benzyl ethers,[24] so these by-products are probably phenolic compounds resulting from debenzylation of **10** or **21**. Attempts to oxidise **10** using $RuO_2,2H_2O$- CH_2Cl_2-TFA-TFAA-ultra-sound or $RuO_2,2H_2O$-CF_3SO_3H-$(CF_3SO_2)_2O$ also failed.

4. Mechanism

The very good regioselectivity observed in our case is particularly noteworthy. There are two possible effects that would influence the *"para-para"* regioselectivity. Firstly, the greater electronic population is localised in the neighbourhood of the carbon *"para"* to the electron-donating group. Calculations on simple models support this evidence, whether for a phenoxy-radical as **22**[25] or for a radical-cation as **23**.[11b] Steric effects, especially *"ortho"* to the hydroxy group, could also influence the regioselectivity of radical attack.



22 **23**

Scheme IX

These considerations and the abundant literature about the lignans biogenesis[11c,26] lead us to suggest that the oxidative coupling of prestegane A and B occurred via a phenoxy radical as **22**.

Conclusion

The present data clearly indicate that ruthenium dioxide in fluoro acidic medium is a very efficient oxidative reagent for oxidative phenolic coupling. The present procedure is highly advantageous since it requires only the filtration of metal salts to obtain pure crystalline BBCOD. Moreover, this study is of biogenetic interest because we have demonstrated without any ambiguity the relationship between phenolic dibenzylbutanolides and bisbenzocyclooctadienes lignans in *Steganotaenia araliacea*. Unfortunately, (±)-HPMF **2c** cannot be readily oxidised by our procedure, this failure being probably due to the particularly unusual structure of **2c** and its O-methylated analog **18b**.

Experimental Section

Most of the organic compounds used in this study were commercially available in very high purity. $RuO_2,2H_2O$, Tl_2O_3, trifluoroacetic acid and anhydride were used without purification. Dichloromethane was dried through an alumina column and stored over 4-Å molecular sieves. Tetrahydrofuran was distilled over

sodium and benzophenone under nitrogen. All glassware, syringes and needles were dried thoroughly in a drying oven and cooled in a dessiccator containing P_2O_5 and silicagel. Melting points were determined on a Reichert microscope and are uncorrected. Infrared spectra (IR) were recorded on a FT Nicolet 5DX spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a VARIAN EM 90 or on a CAMECA 350 spectrometer using tetramethylsilane (Me_4Si) as internal standard, chemical shifts are expressed in δ (ppm) and $CDCl_3$ as solvent unless indicated otherwise. Mass spectra were obtained on a Varian Mat 311 spectrometer. Elemental analyses were performed by the analysis centre of CNRS in Lyon-Vernaison.

Since the reactions performed are all similar in many respects, typical reactions will be described as specific examples. Numbering used to describe NMR spectra of BBCOD is explicited in scheme VIII.

General procedure for the preparation of unsaturated hemiesters according to scheme II. 4-(3-benzoxy--4-methoxyphenyl)-3-methoxycarbonyl-3-butenoic acid (5). To a stirred suspension of 1.4 g (0.061 mol) of sodium was added, under argon at room temperature, 50 ml of freshly distilled MeOH. After the mixture was refluxed for 15 mn, a mixture of 10 g (0.04 mol) of **4b** and 7.5 ml (0.057 mol) of dimethylsuccinate were added rapidly under argon atmosphere. The flask was kept under reflux for 2 h. Then, the major part of MeOH was evaporated at room temperature *in vacuo* and the resulting mixture was diluted with CH_2Cl_2 and acidified with 10% HCl at 0°C. The organic layer was decanted and the aqueous layer extracted with CH_2Cl_2. The combined extracts were washed with saturated NaCl, water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated in ether and recrystallization from the same solvent gave **5** (11.1 g, 78%) as white crystals: mp 125-126°C; IR (nujol) 1717 (C=O), 1695, 1623, 1590 cm^{-1}; ^1H NMR δ 3.55 (s, 2H, CH_2), 3.84 (s, 3H, CO_2CH_3), 3.94 (s, 3H, OCH_3), 5.25 (s, 2H, $ArCH_2O$), 7.11 (m, 3H, aromatic protons), 7.50 (m, 5H, aromatic protons), 7.90 (s, 1H, ethylenic proton). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66; O, 26.94. Found: C, 67.18; H, 5.68; O, 26.74.

4-(3-benzoxy-4-methoxybenzylidene)-4,5-dihydro-2(3H)-furanone (6). To a stirred solution of 15 g (0.042 mol) of **5** in 400 ml of absolute ethanol was added, at room temperature, 2.4 g (0.043 mol) of KOH and, after complete dissolution, 12 g (0.108 mol) of powdered $CaCl_2$. A solution of 4.2 g (0.108 mol) of $NaBH_4$ in 50 ml of 1M KOH was then introduced dropwise at 20°C. The white suspension was stirred at room temperature for 3 hours, then cooled to 0°C and acidified with 10% HCl. Distillated water was added until the solution become clear and EtOH was removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 and the resulting extracts were washed with saturated brine and dried ($MgSO_4$). The solvent was removed *in vacuo* affording 11 g (84%) of compound **6** as white crystals: mp 126-127°C (Ether); IR (nujol) 1779 (C=O), 1602 (C=C) cm^{-1}; ^1H NMR δ 3.15-3.30 (m, 2H, aliphatic protons), 3.95 (s, 3H, OCH_3), 5.0 (m, 2H, CH_2OCO), 5.23 (s, 2H, $ArCH_2O$), 6.38 (m, 1H, ethylenic proton), 6.84 (s, 1H, aromatic proton), 7.05 (m, 2H, aromatic protons), 7.50 (m, 5H, aromatic protons). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85; O, 20.62. Found: C, 73.56; H, 5.88; O, 20.66.

4-(3-hydroxy-4-methoxybenzyl)-4,5-dihydro-2(3H)-furanone (7). A solution of 2 g (6.4 mmol) of the lactone **6** in 40 ml of a 7:3 mixture of ethyl acetate and acetic acid was introduced in an hydrogenation flask and 0.3 g of 10% palladium on charcoal were added. The flask was placed in a Parr apparatus and flushed 3 times with hydrogen and the suspension was stirred overnight under H_2 pressure (50 psi) at room temperature. Then, the black catalyst was removed by careful filtration and the solvent was evaporated *in vacuo*. Crystallization of the colorless oil gave 1.2 g (84%) of the pure lactone **7** which was recrystallized from ether: mp 67-68°C; IR (nujol) 3411 (OH), 1764 (C=O), 1513 (C=C) cm^{-1}; ^1H NMR δ 2.10-3.0 (m, 5H, aliphatic protons), 3.88 (s, 3H, OCH_3), 4.0-4.5 (m, 2H, CH_2OCO), 5.85 (s, 1H, OH), 6.60-7.0 (m, 3H, aromatic protons). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; O, 28.80. Found: C, 64.75; H, 6.34; O, 28.99.

4-(3-benzoxy-4-methoxybenzyl)-4,5-dihydro-2(3H)-furanone (3). To a solution of 2 g (9 mmol) of the lactone **7** in 30 ml of anhydrous acetone were added 2.8 g (0.02 mol) of potassium carbonate and 0.06 g (0.4 mmol) of sodium iodide. Then, 2.4 ml (0.02 mol) of freshly distilled benzyl chloride were added dropwise and the resultant suspension was stirred under reflux for 10 h. After filtration of mineral salts and evaporation of the solvent *in vacuo*, the oily residue was crystallized from ether, affording the lactone **3** as white crystals (2.7 g, 96%): mp 56-57°C; IR (nujol) 1759 (C=O), 1607 (C=C), 1142 cm^{-1}; ^1H NMR δ 2.10-2.80 (m, 5H, aliphatic protons), 3.89 (s, 3H, OCH_3), 3.95-4.35 (m, 2H, CH_2OCO), 5.20 (s, 2H, $ArCH_2O$), 6.70-6.95 (m, 3H, aromatic protons), 7.50 (m, 5H, aromatic protons). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; O,

20.49. Found: C, 72.88; H, 6.52; O, 20.23.

General procedure for the preparation of dibenzylbutanolides according to scheme IV. (3R*,4R*)-3-(3-benzoxy-4-methoxybenzyl)-4-(3-Benzoxy-4-methoxybenzyl)-4,5-dihydro-2(3H)-furanone (10). To a stirred solution of 0.75 ml of n-BuLi (1.6 M in hexane) in dry THF (1.5 ml) was added, at -78°C, 0.29 ml (1.4 mmol) of hexamethyldisilazane. The resultant colorless solution was allowed to warm at -20°C for 10 mn and 0.31 g (0.994 mmol) of the lactone **3** in dry THF (2.5 ml) was added dropwise at -78°C. The yellow anion was stirred for 1 h at -78°C and 20 mn at -30°C. Then, 0.306 g (0.997 mmol) of the bromide **8** in dry THF (1.5 ml) and 0.2 ml (1 mmol) of hexamethylphosphoramide were added at -78°C. The mixture was then allowed to warm to room temperature over 2 h and treated with 3N HCl. The organic layer was decanted and the residue extracted with EtOAc. The combined extracts were washed successively with H_2O, saturated brine and dried over $MgSO_4$. The solvents were evaporated to give an oil which was chromatographied on silica gel (Toluene-EtOAC 97:3), affording 0.47 g (87%) of **10**. Recrystallization from ether gave pure **10** as white crystals: mp 62-63°C; IR (nujol) 1769 (C=O), 1605 (C=C), 1140 cm^{-1}; ^1H NMR δ 2.35 (m, 4H, aliphatic protons), 2.85 (m, 2H, aliphatic protons), 3.40-3.90 (m, 2H, CH_2OCO), 3.85 (s, 6H, 2 OCH_3), 5.13 (s, 4H, 2 $ArCH_2O$), 6.50-6.65 (m, 2H, aromatic protons), 6.65-6.95 (m, 4H, aromatic protons), 7.25-7.60 (m, 10H, aromatic protons).

(±)-Prestegane B (2b). As described for the preparation of the lactone **7**, 0.377 g (0.7 mmol) of dibenzylbutanolide **10** in solution in 20 ml of a 1:1 mixture of ethyl acetate and acetic acid were introduced in an hydrogenation flask and 0.08 g of 10% palladium on charcoal were added. The flask was placed in a Parr apparatus and flushed 3 times with hydrogen and the suspension was stirred overnight under H_2 pressure (50 psi) at room temperature. Then, the black catalyst was removed by careful filtration and the solvent was evaporated *in vacuo* to give 0.12 g (83%) of pure oily prestegane B **2b** identical with an authentic sample;[8b] IR (nujol) 3542 (OH), 1765 (C=O), 1595 (C=C), 1130 cm^{-1}; ^1H NMR δ 2.50 (m, 4H, aliphatic protons), 2.95 (m, 2H, aliphatic protons), 3.85 (m, 1H, CH_2OCO), 3.88 (s, 6H, 2 OCH_3), 4.09 (m, 1H, CH_2OCO), 5.25 (s, 2H, 2 OH), 6.50-6.80 (m, 6H, aromatic protons).

4-(3-methoxyphenyl)-3-methoxycarbonyl-3-butenoic acid (13). Using the above procedure, the unsaturated hemiester **13** has been isolated as a crystalline product (155 g; 78%): mp 81-82°C (Ether) [lit[27] oily]; IR (nujol) 1716 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR δ 3.63 (s, 2H, CH_2), 3.81 (s, 3H, CO_2CH_3), 3.87 (s, 3H, OCH_3), 6.85-7.15 (m, 3H, aromatic protons), 7.30-7.55 (m, 1H, aromatic protons), 8.0 (s, 1H, ethylenic proton). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64; O, 31.97. Found: C, 62.17; H, 5.81; O, 31.98.

4-(3-methoxyphenyl)-3-methoxycarbonyl butanoic acid (14). 20 g (0.08 mol) of the hemiester **13** were hydrogenated following the procedure described for the preparation of **5**. Evaporation of the solvents afforded 20 g (99%) of the acid **14** as a solid recrystallized from a mixture of ether and petroleum ether: mp 77-78°C [lit[27] mp 77-78°C]; IR ($CHCl_3$) 1736 (C=O), 1712 (C=O) cm^{-1}; ^1H NMR δ 2.20-3.30 (m, 5H, aliphatic protons), 3.67 (s, 3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 6.75-6.95 (m, 3H, aromatic protons), 7.15-7.45 (m, 1H, aromatic proton). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39; O, 31.71. Found: C, 61.71; H, 6.27; O, 31.17.

4-(3-methoxybenzyl)-4,5-dihydro-2(3H)-furanone (11). The procedure was identical to the one used with the lactone **6**, except that addition of the $NaBH_4$ solution in ethanolic KOH has been carried out at 0°C. The lactone **11** has been isolated as a pale yellow oil[28] (6.4 g, 74%) which was used without further purification; IR (nujol) 1778 (C=O), 1601 (C=C) cm^{-1}; ^1H NMR δ 2.05-3.05 (m, 5H, aliphatic protons), 3.81 (s, 3H, OCH_3), 3.85-4.50 (m, 2H, CH_2OCO), 6.75-7.10 (m, 3H, aromatic protons), 7.20-7.50 (m, 1H, aromatic proton).

(3R*,4R*)-3-(3-benzoxybenzyl)-4-(3-methoxybenzyl)-4,5-dihydro-2(3H)-furanone (18a). The procedure was identical with the one used for the preparation of **10**, except that 1.4 equivalents of diisopropylamine were used instead of 1.4 equivalents of hexamethyldisilazane. The alkylation product of the lactone **11** with the bromide **15** was isolated by chromatography on silica gel (Cyclohexane-EtOAc 95:5→8:2), affording 3.9 g (48%) of a pale yellow oil; IR (nujol) 1771 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR δ 2.30-2.75 (m, 4H, aliphatic protons), 2.85-3.10 (m, 2H, aliphatic protons), 3.75 (s, 3H, OCH_3), 3.80-4.20 (m, 2H, CH_2OCO), 5.07 (s, 2H, $ArCH_2O$), 6.55-7.65 (m, 13H, aromatic protons). Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51; O, 15.90. Found: C, 77.38; H, 6.48; O, 15.75.

(3R*,4R*)-3-(3-hydroxybenzyl)-4-(3-methoxybenzyl)-4,5-dihydro-2(3H)-furanone (18b). The reaction was carried out as described above for the preparation of **2b**, using ethyl acetate as unique solvent. The monophenol **18b** was obtained as a colorless oil (0.14 g, 94%), TLC homogeneous; IR (nujol) 3330 (OH), 1740 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR δ 2.20-3.10 (m, 6H, aliphatic protons), 3.78 (s, 3H, OCH_3), 3.80-4.30 (m, 2H, CH_2OCO), 6.50-7.0 (m, 6H, aromatic protons), 7.10-7.40 (m, 2H, aromatic protons).

(3R*,4R*)-3-(3-hydroxybenzyl)-4-(3-hydroxybenzyl)-4,5-dihydro-2(3H)-furanone [(±)-HPMF] (2c). To a stirred solution of 0.8 g (2.56 mmol) of **18b** in 60 ml of dry CH_2Cl_2, was slowly added at -40°C, 6.4 ml (6.4 mmol) of 1M BBr_3 in hexane. The white suspension was stirred for 2 h at room temperature, then poured into

crushed ice and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford a crude brown oil, which was purified by flash chromatography (silica gel, cyclohexane-EtOAc 7:3). 0.49 g (64%) of (±)-HPMF **2c** was obtained as a white solid recrystallized from EtOH: mp 144-145°C [lit.[15] mp 141-143°C (EtOH)]; IR (nujol) 1715 (C=O), 1616 (C=C) cm^{-1}; ^1H NMR (CD_3COCD_3-D_2O) δ 2.40-2.80 (m, 4H, aliphatic protons), 2.85-3.10 (m, 2H, aliphatic protons), 3.85-4.35 (m, 2H, CH_2OCO), 6.80-6.90 (m, 6H, aromatic protons), 7.10-7.40 (m, 2H, aromatic protons). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08; O, 21.45. Found: C, 72.34; H, 5.81; O, 21.40.

General coupling procedure according to Method A (table I). (M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro--11-hydroxy-6,7,10-trimethoxydibenzo-[4,5:6,7]cycloocta[1,2-c] furan-1(3H)-one (19a). To a stirred solution of 72 mg (0.538 mmol) of RuO_2,$2H_2O$ in CH_2Cl_2 (4 ml), TFA (1.2 ml) and TFAA (0.6 ml), were added at -10°C a solution of 0.1 g (0.27 mmol) of **2a** in CH_2Cl_2 (4 ml), then immediately BF_3-Et_2O (0.3 ml). The mixture was stirred vigorously at room temperature for 16 h and the mixture was treated by a cold solution of saturated $NaHCO_3$. The organic layer was decanted and the aqueous layer extracted with EtOAc. The combined extracts were washed with saturated brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford a crude yellow oil. Filtration on silica gel (Toluene-EtOAc 9:1) gave **19a** as a white solid recrystallized from CH_2Cl_2-ether (80 mg, 80%): mp 203-205°C; IR ($CHCl_3$) 1781 (C=O), 1773 (C=O), 1603, 1593 (C=C) cm^{-1}; ^1H NMR (350 MHz) δ 2.12 (dd, 1H, J= 13 Hz, 9.0 Hz, H-7), 2.21 (m, 1H, H-6), 2.27 (dd, 1H, J= 9.0 Hz, 13.5 Hz, H-8α), 2.41 (dd, 1H, J= 13.3 Hz, 9.5 Hz, H-5β), 2.65 (d, 1H, J= 13.3 Hz, H-5α), 3.14 (d, 1H, J= 13.5 Hz, H-8β), 3.79 (dd, 1H, J= 11.5 Hz, 8.5 Hz, H-13β), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.38 (dd, 1H, J= 6.5 Hz, 8.5 Hz, H-13α), 5.60 (broad s, 1H, OH), 6.68 (s, 2H, H-1 and H-12), 6.70 (s, 1H, H-4), 6.88 (s, 1H, H-9). MS m/e 370.1420 (M^+).

(M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro-6,11-dihydroxy-7,10-dimethoxydibenzo-[4,5:6,7]cyclo-octa[1,2-c] furan-1(3H)-one (19b)(Method A, table I). The reaction was carried out as described above for **19a**. Chromatography on silica gel (Toluene-EtOAc 9:1) afforded the bisbenzocyclooctadiene **19b** (82 mg, 82%) as a white solid recrystallized from CH_2Cl_2-ether: mp 228-230°C; IR ($CHCl_3$) 1781 (C=O), 1594 (C=C) cm^{-1}; ^1H NMR (350 MHz) δ 2.11 (dd, 1H, J= 12.9 Hz, 9.0 Hz, H-7), 2.20 (m, 1H, H-6), 2.27 (dd, 1H, J= 9.0 Hz, 13.3 Hz, H-8α), 2.35 (dd, 1H, J= 13.3 Hz, 9.5 Hz, H-5β), 2.61 (d, 1H, J= 13.3 Hz, H-5α), 3.13 (d, 1H, J= 13.3 Hz, H-8β), 3.76 (dd, 1H, J= 11.2 Hz, 8.6 Hz, H-13β), 3.88 (s, 6H, 2 OCH_3), 4.36 (dd, 1H, J= 6.45 Hz, 8.2 Hz, H-13α), 5.60 (broad s, 2H, 2 OH), 6.67 (s, 2H, H-1 and H-12), 6.77 (s, 1H, H-4), 6.87 (s, 1H, H-9). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66; O, 26.94. Found: C, 67.53; H, 5.84; O, 26.65.

Bisbenzocyclooctadiene (19a)(Method B, table I). To a stirred suspension of 107 mg (0.80 mmol) of RuO_2,$2H_2O$ in CH_2Cl_2 (7 ml), TFA (2 ml) and TFAA (1 ml), were added at -10°C, a solution of 0.15 g (0.40 mmol) of **2a** in CH_2Cl_2 (7 ml), then immediately BF_3-Et_2O (0.3 ml). The flask was immersed in an ultra-sound bath (water) thermostated at 18°C (± 2°C) and the mixture was stirred for 7 h. The suspension was treated at 0°C with a 5% $NaHCO_3$ solution and the product was isolated as above. Crystallization from CH_2Cl_2-ether gave **19a** (0.123 g, 82%) as white crystals, identical (mp, IR, ^1H NMR) with the material prepared precedently.

Bisbenzocyclooctadiene (19b)(Method B, table I). The reaction was carried out as described above. Filtration (Toluene-EtOAc 9:1) afforded the BBCOD **19b** (0.12 g, 80%) as a crystalline product identical to the one obtained by the procedure A (mp, IR, ^1H NMR).

Bisbenzocyclooctadiene (19a)(Method C, table I). To a stirred solution of 72 mg (0.54 mmol) of RuO_2,$2H_2O$ in CH_2Cl_2 (4 ml), Trifluoromethanesulfonic acid (0.7 ml) and trifluoromethanesulfonic anhydride (0.35 ml), were added at -10°C, a solution of 0.1 g (0.24 mmol) of **2a** in CH_2Cl_2 (4 ml), then immediately BF_3-Et_2O (0.3 ml). The mixture was stirred vigorously at room temperature for 3 h, then cooled at 0°C and poured into a cold solution of saturated $NaHCO_3$. The organic layer was treated as above and the resultant crude oil was filtrated on silica gel (Toluene-EtOAc 9:1) affording **19a** (80 mg, 80%) as a crystalline product identical in all respects (mp, IR, ^1H NMR) with the one obtained by the above procedures.

The BBCOD **19b** was prepared according the same procedure (listed in table I). This compound was found to be identical (mp, IR, ^1H NMR) with the one prepared with method A.

Bisbenzocyclooctadiene (19a)(Method D, table I). To a stirred suspension of 0.187 g (0.409 mmol) of Tl_2O_3 in CH_2Cl_2 (13 ml), TFA (2 ml) and TFAA (1 ml), were added at -10°C, a solution of 0.203 g (0.546 mmol) of **2a** in CH_2Cl_2 (10 ml), then immediately BF_3-Et_2O (0.3 ml). The green mixture was stirred at room temperature for 2 h, then cooled at 0°C and poured into a cold solution of saturated $NaHCO_3$. The work-up was the same as before and pure **19a** (91 mg, 45%) was obtained after filtration of the crude red oil on silica gel (Toluene-EtOAc 9:1) and crystallization from CH_2Cl_2-ether. **19a** was found to be identical (mp, IR, ^1H NMR) with the material prepared above.

The bisbenzocyclooctadiene **19b** was prepared by using the same method (listed in table I).

Methylation of bisbenzocyclooctadiene (19a). In a diazomethane distillation apparatus was introduced at

room temperature, 1 ml of 95% EtOH, 0.1 g of potassium hydroxyde and 1 ml of distillated water. After complete dissolution of the KOH, 0.29 g (1.3 mmol) of N-methyl-N-nitroso-p-toluenesulfonamide (DIAZALD) in 10 ml of ether were added dropwise at 65°C. The resultant yellow ethereal solution of diazomethane was collected in a cooled (c.a 0°C) flask containing 48 mg (0.13 mmol) of phenol **19a** in 20 ml of MeOH. The yellow solution was then isolated and stirred for 20 h at room temperature. Excess of diazomethane was destroyed with AcOH and the solvents were evaporated carefully *in vacuo*. The residue was crystallized in ether affording the BBCOD **20**[3b,10] (39 mg, 78%) as a white solid recrystallized from a mixture of CH_2Cl_2 and ether: mp 210-212°C; IR (nujol) 1773 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR δ 2.20-3.45 (m, 6H, aliphatic protons), 3.75 (m, 1H, H-13β), 3.85 (s, 6H, 2 OCH_3), 3.90 (s, 6H, 2 OCH_3), 4.36 (m, 1H, H-13α), 6.68 (s, 3H, H-1, H-4 and H-12), 6.79 (s, 1H, H-9). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29; O, 24.97. Found: C, 68.87; H, 6.49; O, 24.47.

Following the same procedure, the BBCOD **19b** was methylated to give **20** as white crystals (45 mg, 83%) recrystallized from CH_2Cl_2-ether. The compound was identical in all respects (mp, IR, ^1H NMR) with those obtained above and in the literature.[3b,10]

(M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro-6,11-dibenzoxy-7,10-dimethoxydibenzo-[4,5:6,7]cyclo-octa[1,2-c] furan-1(3H)-one (21). To a stirred suspension of 0.115 g (0.25 mmol) of Tl_2O_3 in CH_2Cl_2 (20 ml), TFA (2 ml) and TFAA (1 ml), were added at -10°C, a solution of 0.25 g (0.465 mmol) of **10** in CH_2Cl_2 (8 ml), then immediately BF_3-Et_2O (0.05 ml). The deep green mixture was stirred at room temperature for 15 minutes, then cooled at 0°C and poured into a cold solution of saturated $NaHCO_3$. The organic layer was then treated as above for the BBCOD **19a** and **19b**. Flash chromatography of the residue (Toluene-EtOAc 97:3) afforded the BBCOD **21** (0.172 g, 69%) as a white solid recrystallized from CH_2Cl_2-ether: mp 168-169°C; IR (nujol) 1773 (C=O), 1603 (C=C) cm^{-1}; ^1H NMR δ 1.90-3.35 (m, 6H, aliphatic protons), 3.70 (m, 1H, H-13β), 3.85 (s, 6H, 2 OCH_3), 4.32 (m, 1H, H-13α), 5.16 (s, 4H, 2 $ArCH_2O$), 6.86 (s, 1H, H-9), 7.15-7.65 (m, 10H, aromatic protons). Anal. Calcd for $C_{34}H_{32}O_6$: C, 76.10; H, 6.10; O, 17.89. Found: C, 76.02; H, 6.30; O, 17.95.

Hydrogenolysis of (21). The reaction was carried out as described above for the preparation of **10**, using a 4:1 mixture of EtOAc and AcOH as solvent. The diphenol **19b** was obtained as a crystalline product (68 mg, 85%) identical in all respects with those obtained by oxidative phenolic coupling of prestegane **2b**.

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