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Ruthenium Dioxide in Fluoro Acid Medium: I. A New Agent in the Biaryl Oxidative Coupling. Application to the Synthesis of Non Phenolic Bisbenzocyclooctadiene Lignan Lactones.

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Abstract: Ruthenium (IV) dioxide dihydrate in fluoro acid medium was found to be a very efficient agent for the oxidative coupling of non phenolic lignans and their derivatives, and this method was applied to the total synthesis of (+/-)-neoisostegane **2a** and (+/-)-steganolide A **2b**. This procedure was also used to obtain the first stereospecific synthesis of a *cis*-bisbenzocyclooctadiene lactone, the (+/-)-deoxyschizandrin **17**, of which, was afforded by a short reduction sequence.

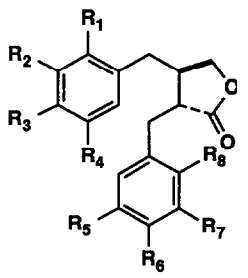
Résumé: Le dioxyde de ruthénium (IV) dihydraté, en milieu fluoracide, s'est avéré être un agent très performant de couplage oxydant de lignanes non phénoliques et dérivés, et cette méthode a été appliquée à la synthèse totale du (+/-)-néoisostégane **2a** et du (+/-)-stéganolide A **2b**. De la même façon a pu être effectuée la première synthèse stéréospécifique d'une *cis*-bisbenzocyclooctadiène lactone permettant l'accès, par une courte séquence de réduction, à la (+/-)-déoxyschizandrine **17**.

As a part of our continuing effort toward the synthesis of potential antitumor and antiviral drugs, we have been interested in the wide class of naturally occurring compounds which possess a biaryl linkage.[1] The search for new selective and versatile reagents to prepare the biaryl bond of such compounds has attracted considerable attention over the last two decades.[2] Kupchan[3] and more recently Taylor and McKillop[4] reported that vanadium (V) oxyhalides and thallium (III) trifluoroacetate (TTFA) respectively, made significant improvements to previous methods for oxidative coupling. These powerful oxidative reagents have been extensively used in the synthesis of natural bridged biaryl compounds, particularly in the area of alkaloid synthesis.[3,5,6]

During the course of our work on isolation and synthesis of Bisbenzocyclooctadienes (BBCOD) lignan lactones related to Steganacin and its congeners,[7] we found that, using precedented literature procedures, non phenolic dibenzylbutanolides **1** yielded the corresponding BBCOD **2** as previously reported by Schlessinger[8] and Cambie[9] for the derivatives **1d** and **1f** (Scheme I). The particularly good selectivity of thallium (III) trifluoroacetate prepared *in situ* by combination of Tl_2O_3 with acid and trifluoroacetic acid and anhydride suggested to us the possibility of using other metal oxides with redox potential near to that of the Tl(III)/Tl(I) potential. Although the thallium procedure[9] is very mild and efficient, the toxicity of thallium salts presents problems for its large scale use. Accordingly, we undertook a systematic study of the different redox couples with a potential

close to that of thallium (III)/thallium(I) couple (1.26V).[10] We found that ruthenium (IV) dioxide (Ru(IV)/-Ru(III): 0.86V and RuO_2/Ru: 0.79V) is an efficient alternative to thallium (III) and vanadium (V) oxidants.[11] This paper describes the general oxidative properties of RuO_2, $2H_2O$ for the oxidation of dibenzylbutanolides and derivatives to bisbenzocyclooctadiene lignans.[11a,b]

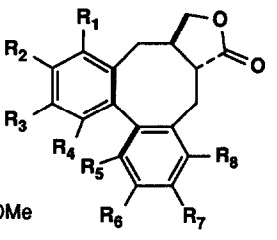
Scheme I



1a-1f

Tl(III) or Ru(IV)

1a $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = R_6 = R_7 = R_8 = OMe$
1b $R_4 = R_5 = H$; $R_1 = R_2 = R_3 = R_6 = R_7 = R_8 = OMe$
1c $R_1 = R_8 = H$; $R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = OMe$
1d $R_1 = R_4 = R_8 = H$; $R_2 = R_3 = OCH_2O$; $R_5 = R_6 = R_7 = OMe$
1e $R_1 = R_4 = R_8 = H$; $R_2 = R_3 = R_5 = R_6 = R_7 = OMe$
1f $R_1 = R_4 = R_5 = R_8 = H$; $R_2 = R_3 = R_6 = R_7 = OMe$



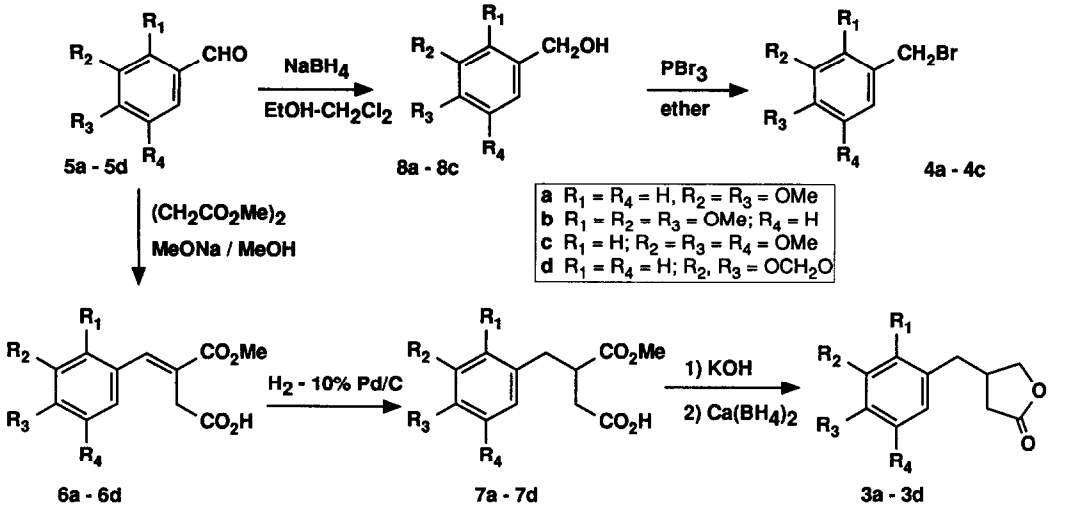
2a-2f

1. Synthesis of dibenzylbutanolides lignans and derivatives

The dibenzylbutanolides were prepared by improvements of previously reported procedures.[12] Thus the precursors **1a-1f** were obtained by alkylation of the suitably substituted lactones **3a-3d** with the desired benzylhalides **4a-4c** (Scheme II). The lactones **3a**,[13] **3c-3d**[14] and the new lactone **3b** were respectively prepared in three steps from the commercially available benzaldehydes **5a-5d**. Stobbe condensation between these benzaldehydes and dimethylsuccinate afforded the unsaturated hemiesters **6a-6d** which were subsequently hydrogenated over 10% Pd-C to give the corresponding saturated hemiesters **7a-7d** in good yields. Chemoselective reduction[14] of the potassium salts of these saturated hemiesters with $Ca(BH_4)_2$ in ethanol gave the desired lactones **3a-3d** in 65-70% overall yield (calculated from the starting benzaldehydes) (Scheme II).

The alkylating benzylbromides **4a**,[15] **4b**[16] and **4c**[17] were prepared in a two-step sequence[17] from the corresponding benzaldehydes in 90-95% overall yield. Thus, reduction of the benzaldehydes **5a-5c** with $NaBH_4$ in a mixture of CH_2Cl_2-EtOH gave the benzyl alcohols **8a-8c**, which were converted into the desired benzyl-bromides using PBr_3 in ether (Scheme II). The successful synthesis of dibenzylbutanolides **1a-1f** was accomplished by alkylation of the anion of lactones **3a-3d**, generated by reaction with either LDA (lithium diisopropylamide) or LHMDS (lithium hexamethyldisilylamide) in THF, with the bromides **4a-4c**. It is noteworthy that better yields were obtained using the lactone anions generated with LHMDS (80-85% yield). The prominent features of the aliphatic protons in the NMR spectra of compounds **1a-1f** showed clearly that alkylation was stereospecific and afforded the only *trans* lactones.

Scheme II



2. Oxidative coupling of open-chain precursors

The oxidative coupling of dibenzylbutanolides, as shown above, was initially investigated as previously reported procedures using VOF_3[8] and TTFA[9] to permit a direct comparison with RuO_2, $2H_2O$ oxidations (table I).

Table I. Reaction of RuO_2,$2H_2O$ in trifluoroacetic medium with representative dibenzylbutanolides. Comparison with known reagents as VOF_3 and TTFA.

Starting material	Product	Conditions	Time (h)	Yield[a] (%)
1a	2a	VOF_3[b]	3	46
1a	2a	$VOCl_3$[b]	3	50
1a	2a	A[c]	1	75
1a	2a	B[d]	18	98
1b	2b	A	1	69
1b	2b	B	24	96
1c	2c	A	1	73
1c	2c	B	24	93
1d	2d	A	1	30
1d	2d	B	24	0
1e	2e	A	1	72
1e	2e	B	24	94
1f	2f	A	1	80
1f	2f	B	24	97

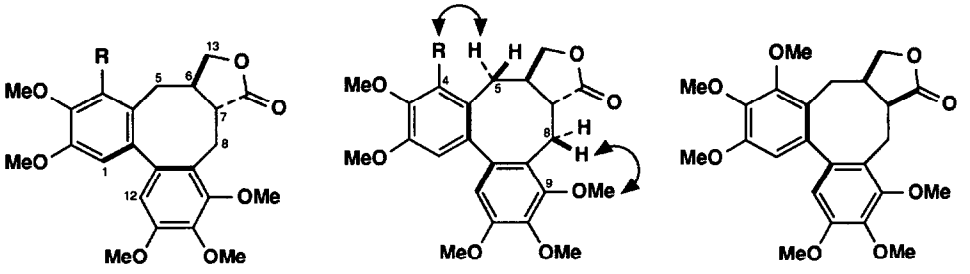
[a] Yield of isolated crystallized product [b] 2 5 eq. in CH_2Cl_2-TFA-TFAA, T= -45°C
[c] A Tl_2O_3 (0 54 eq), TFA-TFAA, BF_3-Et_2O [d] B: RuO_2, $2H_2O$ (2 eq), TFA-TFAA, BF_3-Et_2O.

The different precursors were then submitted to reactions with our reagent. In our procedure, a suspension of 2 equivalents of RuO_2, $2H_2O$ was prepared in trifluoroacetic acid and anhydride with CH_2Cl_2 as solvent. The

butanolides were added to this suspension at 0°C and the mixture was stirred at room temperature for a period of 10-24 hours (see table I). The course of the reaction was monitored by TLC (Toluene-EtOAc 7:3). Reactions conducted in CH_2Cl_2-TFA-TFAA in which $RuO_2,2H_2O$ is insoluble were complete after 24 hours stirring. Similar reactions using either CH_3CN, CCl_4 or $CHCl_3$ instead of CH_2Cl_2 were less successful.[6]

It is noteworthy that this reagent led to the thermodynamically more stable "*iso*" atropoisomer as the major product in the oxidation of **1a-1f**. Similarly, Schlessinger[8] and Cambie[9] have reported that the oxidative coupling of the dibenzylbutanolides yatein **1d** and dimethylmatairesinol **1f** afforded respectively only the "*iso*" atropoisomer (M*, 6R*).[18] However, a careful study of the NMR spectrum (500 MHz) of the crude product from oxidation of **1a** and **1b** clearly showed the presence of small amounts of what we believe to be the "*normal*" atropoisomers (P*, 6R*) respectively **9a** and **9b** (scheme III). The percentages of the ratio *"iso/normal"* were calculated from integration on the NMR spectrum and showed a 88:12 mixture for **2a:9a** and 94:6 for **2b:9b**. In order to account for the high diastereoselectivity of oxidative coupling of dimethylmatairesinol **1f**, it has been proposed[19] that unfavorable interactions between the bridgehead hydrogens of the future biaryl bond and those of the lactone favored rearomatization of a bridged dication intermediate *via* an *"iso-like"* transition state of lower energy rather than rearomatization *via* a *"normal-like"* transition state.

Scheme III



"Normal" (P*, 6R*, 7R*) — **9a**, R = H; **9b**, R = OMe

"Iso" (M*, 6R*, 7R*) — **2a**, R = H; **2b**, R = OMe

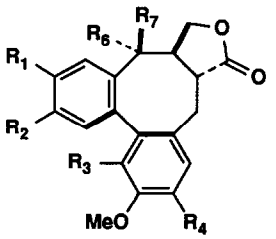
"Iso - cis" (M*, 6R*, 7S*) — **10**

The formation of a significant quantity of the *"normal"* atropoisomer in the oxidative coupling of **1a** and **1b** was probably due to an unfavorable steric interaction between aromatic methoxy in C-4 and C-9 and benzylic hydrogens (H-5 and H-8) (Scheme III). There crude products were submitted to thermal isomerisation by a procedure developed by our group.[20] After 4 hours at 200°C, attempts to separate the mixture of **2a** *"iso"* and **9a** *"normal"* were unsuccessful but the NMR spectrum indicated that the ratio of *"iso/normal"* remained unchanged upon heating. In the case of **2b**, a very surprising and unusual result was observed, the formation of *cis* bisbenzocyclooctadiene lactone **10** (M*,6R*,7S*) probably resulting from the combined action of high temperature and the basicity of the glassware used in the thermal isomerisation.

Among the bisbenzocyclooctadiene lactones recently isolated from *Steganotaenia araliacea*,[7d] the steganolides B **11a** and C **11b** possess a particular biaryl substitution pattern which cannot be obtained by direct

oxidative coupling of precursors like **1f**[9] (Scheme IV). The possible anticancer activity of these steganacin **11c** analogs[21] led us to extend our method to BBCOD precursors of **11a** and **11b**. In order to prepare the desired biaryl compound, we envisaged to protect the *"b"* position with a halogen in a suitable dibenzylbutanolide precursor. The presence of such a substituent should direct biaryl bond formation to position *"c"* and so furnish the desired oxidative coupling regiochemistry.

Scheme IV

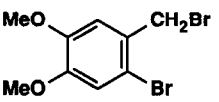


11a - c

a $R_1 = R_2 = R_3 = OMe$; $R_4 = R_6 = H$; R_7 = angelate

b $R_1 = R_2 = R_3 = OMe$, $R_4 = R_6 = H$, R_7 = tiglate

c $R_1 = R_2 = OCH_2O$, $R_7 = H$, $R_3 = R_4 = OMe$, R_6 = acetate



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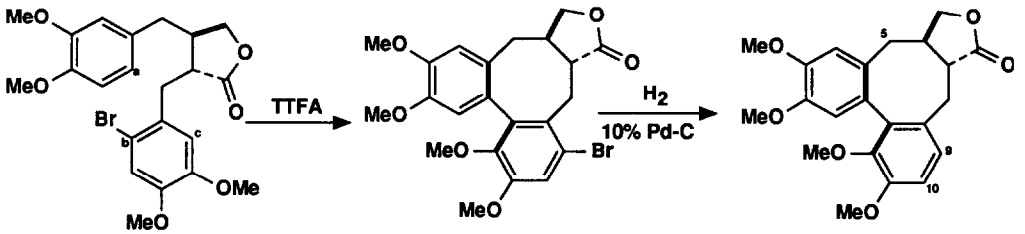
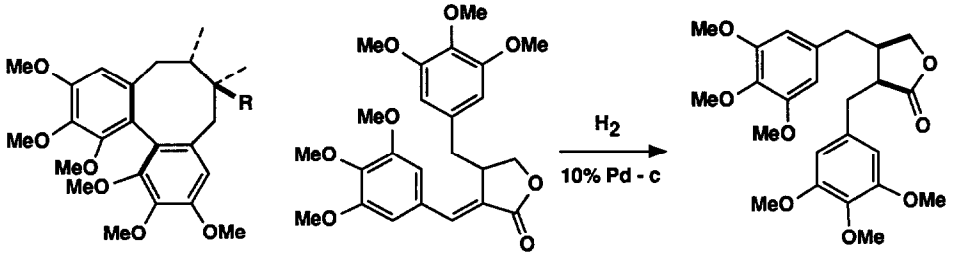


The bromodibenzylbutanolide **13** was prepared from alkylation of lactone **3a** with the suitable bromide **12** prepared in two steps by reduction of veratraldehyde **5a** to veratryl alcohol **8a**[15] and dibromination with Br_2 in chloroform[17] (85% overall yield). The oxidative coupling of **13** with 1.08 equivalents of TTFA afforded the BBCOD **14** in a poor yield of 10% (Scheme IV). By using our procedure with 2 equivalents of $RuO_2,2H_2O$ in CH_2Cl_2 and a mixture of TFA and TFAA, the precursor **13** was unfortunately consumed in unwanted side-reactions, probably by the bromine substituent prior to the oxidative coupling. Only a few traces of the desired BBCOD **14** appeared in TLC, and attempts to improve the reaction remained unsuccessful. Removal of the bromine protecting group by hydrogenolysis with palladium on charcoal 10% gave **15** which has the desired biaryl substitution of steganolides B and C, but possesses the *"iso"* BBCOD stereochemistry. The NMR spectra of **15** showed an AB system for the two protons H-9 (δ 7.05 ppm) and H-10 (δ 6.09 ppm), which have a typical "ortho" coupling constant of 8.4 Hz, and the coupling constants $J_{5\alpha\text{-}6}$ and $J_{7\text{-}8\beta}$ were both equal to 0.0 Hz, in agreement with dihedral angles of 90° observed in the *"iso"* biaryl configuration.[7a] Although this compound **15** may be regarded as a possible synthetic precursor of steganolides B and C, as atropoisomerization of **15**,[22a] functionalisation at C-5 by the Koga's method,[22b] and esterification of the corresponding alcohol would represent a formal synthesis of **11a** and **11b**.

3. Application of the ruthenium procedure to the synthesis of non lactonic bisbenzocyclooctadiene lignans

As we obtained good results for oxidative coupling of dibenzylbutanolides, we considered the oxidative coupling of different lactonic derivatives which can be presented as precursors of schizandrin **16** and its dehydroxy analog desoxyschizandrin **17**. These biologically active compounds[23] belong to the bisbenzocyclo-octadiene lignans isolated from *Schizandra chinensis*, *Kadsura japonica* and *K. coccinea*[24] (Scheme V).

Scheme V



The butanolide precursors **18a** and **18b** were synthesised using an improvement of Stobbe-like alkylidenation[11] of 3,4,5-trimethoxybenzyl-4-butanolide **3c** with 3,4,5-trimethoxybenzaldehyde **5c**. The E configuration of the double bond in **18a** was confirmed by the characteristic position of the olefinic hydrogen at 7.48 ppm (doublet, J= 1.5 Hz). Catalytic hydrogenation of **18a** gave the corresponding saturated *cis*-butanolide **18b** as an oil. Compounds **18a** and **18b** were then submitted to oxidative coupling using both the optimal RuO_2,$2H_2O$ TTFA procedures described above (Table II). Higher yields were obtained with the ruthenium procedure. Surprisingly, the study of the ^{1}H-NMR at 500 MHz showed that **19b** possesses a *"normal"* (P*, 6R*, 7S*) biaryl stereochemistry. This result is in marked contrast to the previously oxidative couplings of *trans* dibenzylbutanolide **1a-1f**.

Table II: oxidative coupling of 18a and 18b using $RuO_2.2H_2O$ and TTFA

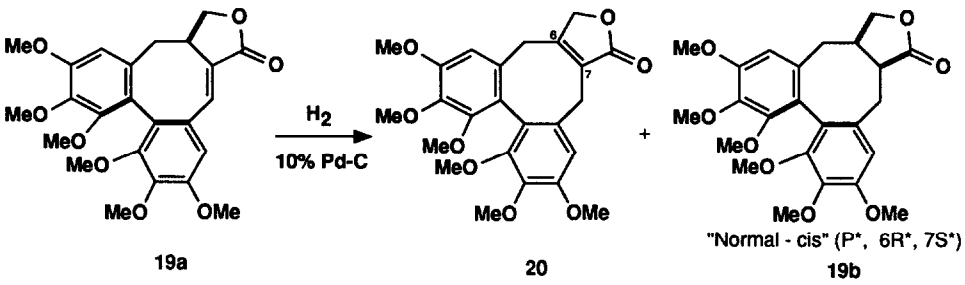
Starting material	Product	Conditions[a]	Yield[b] (%)
18a	**19a**	A	83
18a	**19a**	B	90
18b	**19b**	A	65
18b	**19b**	B	90

[a] A Tl_2O_3 (0 54 eq), TFA-TFAA, BF_3-Et_2O, B RuO_2, $2H_2O$ (2eq), TFA-TFAA, BF_3-Et_2O

[b] Isolated crystalline product

The biaryl configuration of **19a** was determined after catalytic hydrogenation in acetic acid over 10% Pd-C. This gave a mixture (7:3 respectively) of the bisbenzocyclooctadiene **19b** and butenolide **20** resulting from double bond migration (Scheme VI). When the hydrogenation of **19a** was performed using rhodium on charcoal at 20°C for 6 hours, the ratio of **19b/20** was estimated to be 3:7 by ^{1}H NMR of the mixture. The structure of **20** was readily confirmed by the disappearance of the olefinic proton H-8 (^{1}H-NMR spectrum) and the presence of two olefinic carbons C-6 and C-7 (^{13}C-NMR spectrum).

Scheme VI

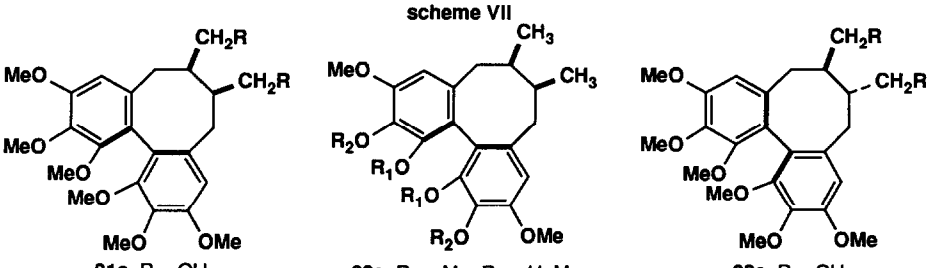


19a **20** **19b**

Assuming that the *"normal"* bisbenzocyclooctadiene **19b** does not isomerise during hydrogenation, we propose the same stereochemistry for **19b** and its precursor **19a**. Interestingly, no atropoisomerisation occurred when **19b** was heated under argon during 4 hours at 220°C. The thermal stability of **19b** is probably due to the presence of OMe groups vicinal to the biaryl bond which increases very much the barrier of rotation.

The successful synthesis of (+/-)-desoxyschizandrin **17** was accomplished by the following sequence of reactions Reduction of the saturated lactone **19b** by $Ca(BH_4)_2$ in aqueous THF afforded, in very high yield, the diol **21a** which was converted into the bismesylate **21b**. Attempted reduction of the latter with $LiBEt_3H$[25] in THF by reflux for 2 hours resulted in the formation of **17** in poor yield accompanied by its demethylation by-products[26] **22a** and **22b** whose phenolic substitutions were determined by 500 MHz ^{1}H-NMR (Scheme VII). When the same reaction was carried out at room temperature, we obtained the racemic *cis* bisbenzocyclo-octadiene **17** in high yield after 1 hour, with spectroscopic data and melting point in agreement with those reported previously.[1b,27]

scheme VII



21a, R = OH
21b, R = OSO_2Me
17, R = H

22a, R_1 = Me, R_2 = H, Me
22b, R_1 = H; R_2 = Me

23a, R = OH
23b, R = OSO_2Me
24, R = H

The same two-step sequence was applied to the bisbenzocyclooctadiene **2d**, *trans* isomer of **19b**. On the basis of the ^{1}H-NMR data (chemical shifts and coupling constants), we have been able to assign the structure **24** to this compound,[28] which is in agreement with the structure described in the literature (Scheme VII).[1b,27]

4. Improvement of the RuO_2,$2H_2O$ procedure by using fluorosulfonic medium and ultrasonic assistance.

Following the development of the method outlined in table I, we examined the possibility of reducing the reaction times and the quantity of RuO_2,$2H_2O$ necessary for the reaction. The importance of fluoroacid medium was established by carrying out the reaction of **1a** with 2 equivalents of RuO_2,$2H_2O$ in CH_2Cl_2 in the absence of TFA and TFAA. Cyclization in this case failed and the starting material was recovered unchanged even after 3 days at room temperature. Accordingly, we decided to replace the trifluoroacetic acid and its anhydride by the more acidic trifluoromethanesulfonic acid and its anhydride.[29] The study was performed on three models, **1a**, **1b** and the ethylenic derivative **18a**. The reaction was carried out as described above, the different precursors were added dropwise at 0°C to a suspension of RuO_2,$2H_2O$ in a mixture of CF_3SO_3H-$(CF_3SO_2)_2O$ (2:1) in CH_2Cl_2. We noted shorter times of reaction in this medium, the yields of conversion in bisbenzocyclooctadienes remaining similar to those obtained previously (Table III).

Table III: oxidative coupling using RuO_2, $2H_2O$, fluorosulfonic acid medium and ultra-sonic assistance

Starting material	Product	Conditions[a]	Time	Yield[b] (%)
1a	**2a**	C	3	94
1b	**2b**	C	3	92
18a	**19a**	C	4	92
1a	**2a**	D	7	93
1b	**2b**	D	7	91
18a	**19a**	D	17	90

[a] C· RuO_2, $2H_2O$ (2 eq), CH_2Cl_2, CF_3SO_3H- $(CF_3SO_2)_2$, BF_3-Et_2O, T= 20°C
D RuO_2, $2H_2O$ (1 1eq), CH_2Cl_2, TFA- TFAA, BF_3-Et_2O, Ultra-sound, T=20°C

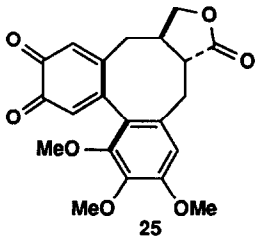
[b] yield of isolated crystalline product

Next, we investigated the effect of ultra-sonic assistance[30] for the conversion of precursors **1a**, **1b** and **18a** into the corresponding bisbenzocyclooctadienes. Ultra-sound is particularly efficient in this case as summarized in table III. The previous attempts to reduce the quantity of metal oxide needed for complete reaction had been unsuccessful. However, with ultra-sonic assistance for periods between 7 and 17 hours, we obtained BBCOD in

good yields using only 1.1 equivalents of ruthenium dioxide. The experiments were accomplished in an ultra-sonic bath equipped with a thermostatic control (T= 18°C ±2°C) and the reaction was monitored by TLC. Nevertheless, to reduce the quantity of $RuO_2,2H_2O$ we had to combine the ultra-sonic and solvent effects. Thus, the reaction was performed in a mixture of (2:1:0.5) CH_2Cl_2-TFA-TFAA. In reaction using larger quantities of acid and anhydride, we observed the formation of unwanted by-products after 1 hour.

5. Limitations

Although we have shown that oxidative coupling with $RuO_2,2H_2O$ in a fluoro acid medium is more efficient than procedures employing other oxidative coupling reagents, we noted the failure of the $RuO_2,2H_2O$ reagent in the oxidation of yatein **1d** to isostegane **2d**. Indeed, when the reaction was carried out with TTFA, we obtained **2d** in only 30% yield, the conversion of **1d** using the ruthenium procedure did not afford **2d** but degradation by-products probably due to the opening of benzodioxole ring. However the oxidation of **1e**, pentamethoxylated analog of **1d**, gave us the corresponding BBCOD **2e** with 94% yield. The results described by Cambie and co-workers[31] are in agreement with those presented here obtained as the former authors the orthoquinone **25** by oxidation of **2d** with TTFA , showing clearly that overoxidation of isostegane in the medium was responsible of the low yield in the oxidation of **1d**. Simultaneously, we observed the degradation in oxidation of **2d** with $RuO_2,2H_2O$ in TFA-TFAA but we could not isolate the quinone **25** (Scheme VIII).



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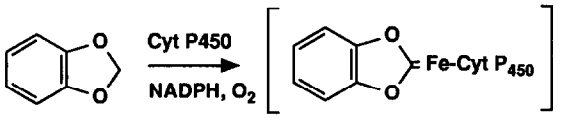
Scheme VIII



26 27

It is interesting to note that the fragility of the benzodioxole moiety can have some applications in pharmacology. Indeed, recent studies[32] have demonstrated that benzodioxole **26** and derivatives combine with cytochrome P450 by formation of metallo-carbene intermediates such as **27** (Scheme VIII) . Moreover, the particular reactivity of the benzodioxole ring may be an explanation of the good antitumor activity of lignans of the steganacin group.[1b,21] Indeed, some studies of structure-activity relationship carried out in our group showed the inactivity of methoxylated compounds compared with the corresponding methylenedioxy derivatives.[c3]

In contrast to reactions using TTFA, the mechanism of the Ru(IV) oxidations remains unknown. All attempts to isolate ruthenium trifluoroacetate or reductive species, as Ru(III), Ru(II) or Ru(0) failed. Similarly, M.A. Schwartz[34] has noted that, during the oxidative biaryl coupling using 2 equivalents of AgO in trifluoroacetic medium, no Ag(0) was detected and that a two electron concerted mechanism was improbable.

Conclusion

We have demonstrated the successful oxidative coupling of a number of dibenzyl butanolides and related compounds using ruthenium dioxide in fluoro acid medium. The reagent is a very mild oxidative agent. With the exception of benzodioxole and halogeno precursors, most functional groups studied, lactones, double bonds, methoxyls were inert toward these reagents. In comparison with TTFA, our studies clearly reveal that $RuO_2,2H_2O$ in a fluoro acid medium is a reagent of choice in the transformation of dibenzyl open precursors into the corresponding biaryl compounds. Indeed the latter method has several advantages over TTFA, particulary the milder conditions (due to heterogeneous medium) and improved yields. We are currently utilizing the reaction to prepare other natural compounds and analogs containing a biaryl bond.

Experimental Section

Most of the organic compounds used in this study were commercial products with very high purity. $RuO_2,2H_2O$ and Tl_2O_3 were obtained from Janssen and were used without purification. Tetrahydrofuran was distilled over sodium and benzophenone under nitrogen. Dichloromethane was dried through an alumina column and stored over 4Å molecular sieves. All glassware was dried thoroughly in a drying oven and cooled in a desiccator containing P_2O_5 and silicagel. Sonication experiments were performed with a Bransonic B 220 apparatus (120 W; 50 Khz). Melting points were taken on a Reichert microscope and are uncorrected. Infrared spectra were recorded on a FT Nicolet 5DX spectrophotometer. NMR spectral data were obtained on a Varian EM 90 or on a Brucker 500 spectrospin spectrometer in $CDCl_3$ unless otherwise indicated, using as internal standard tetramethylsilane (Me_4Si) for proton (δ expressed in ppm). Mass spectra were recorded on a Varian Mat 311 spectrometer. Elemental analysis were performed by 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. The uniform numbering used to describe NMR spectra of BBCOD is explicited on scheme III.

4-(2,3,4-trimethoxyphenyl)-3-methoxycarbonyl-3-butenoic acid (6b). To a stirred suspension of 2.8 g (0.12 mol) of sodium were added, under argon at room temperature, 40 ml of freshly distilled MeOH. After the mixture was refluxed for 15 mn, a solution of 15 g (0.076 mol) of **5b** and 14.3 ml (0.106 mol) of dimethyl-succinate were added under argon atmosphere. The flask was kept under reflux condition for 5 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 brine, water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated in ether and recrystallization from the same solvent gave **6b** (18.7 g, 79%) as white crystals: mp 104-105°C; IR (nujol) 1710 (C=O), 1637 (C=C) cm^{-1}; ^1H NMR δ 3.60 (s, 2H, CH_2), 3.88 (s, 3H, CO_2CH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 6H, 2 OCH_3), 6.80 (d, 1H, J= 9Hz, aromatic proton), 7.10 (d, 1H, J= 9Hz, aromatic proton), 8.10 (s, 1H, ethylenic proton), 10.86 (s, 1H, CO_2H). Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.86; O, 36.09. Found: C, 58.29; H, 5.83; O, 35.38.

4-(2,3,4-trimethoxyphenyl)-3-methoxycarbonyl butanoic acid (7b). 10 g (0.032 mol) of **6b** in a solution of ethyl acetate (100 ml) were introduced in an hydrogenation flask and 1.2 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 under vacuo. The residue refused to crystallize giving 9.5 g (94%) of pure oily **7b**. An analytical sample was obtained by molecular distillation (0.04 mm Hg): IR (nujol) 1735 (C=O), 1712 (C=O), 1602 (C=C) cm^{-1}; ^1H NMR δ 2.45-3.35 (m, 5H, aliphatic protons), 3.68 (s, 3H, CO_2CH_3), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.64 (d, 1H, J= 9Hz, aromatic proton),

6.85 (d, 1H, J= 9Hz, aromatic proton), 10.15 (s, 1H, CO_2H). Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.69; H, 6.45; O, 35.86. Found: C, 57.82; H, 6.62; O, 35.98.

4-(2,3,4-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (3b). To a stirred solution of 8.7 g (0.028 mol) of **7b** in 350 ml of absolute ethanol, was added at room temperature 1.6 g (0.028 mol) of KOH and after complete dissolution, 7.6 g (0.068 mol) of powdered $CaCl_2$. The white suspension was cooled to 0°C and a solution of 4.2 g (0.108 mol) of $NaBH_4$ in 50 ml of 1M aqueous KOH was introduced dropwise. The mixture was stirred at room temperature for 5 hours, then cooled to 0°C and acidified with 6N 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, H_2O and dried ($MgSO_4$). The solvent was removed in vacuo yielding 6.9 g (92%) of compound **3b** as a white crystalline solid, TLC homogeneous (7:3 Toluene/EtOAc): mp 59-60°C (Ether); IR (nujol) 1772 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR δ 2.05-3.0 (m, 5H, aliphatic protons), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.0-4.5 (m, 2H, CH_2OCO), 6.68 (d, 1H, J= 9Hz, aromatic proton), 6.90 (d, 1H, J= 9Hz, aromatic proton).Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81; O, 30.04. Found: C, 63.22; H, 6.76; O, 30.38.

General procedure for the preparation of dibenzylbutanolides (1). (3R*,4R*) 3-(2,3,4-trimethoxybenzyl)-4-(2,3,4-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone(1b). To a stirred solution of 1.6 ml of n-BuLi (1.6 M in hexane) in dry THF (3 ml), was added at -78°C, 0.62 ml (2.94 mmol) of hexamethyldisilazane. The resultant colorless solution was allowed to warm at -20°C for 10 mn and 0.56 g (2.10 mmol) of **3b** in dry THF (3 ml) was added dropwise at -78°C. The yellow solution of anion was stirred for 1 h at -78°C and 20 mn at -30°C. Then, 0.55 g (2.10 mmol) of the bromide **8b** in dry THF (2.5 ml) and 0.4 ml (2.3 mmol) of HMPA were added at -78°C. The mixture was then warmed 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 water, saturated brine and dried over $MgSO_4$. The solvents were evaporated to give an oil which gave after trituration in ether 0.80 g (85%) of **1b**. One recrystallization from ether gave pure **1b** as white crystals: mp 87-88°C; IR (nujol) 1772 (C=O), 1601 (C=C) cm^{-1}; ^1H NMR (C_6D_6) δ 2.15-3.40 (m, 6H, aliphatic protons), 3.45 (s, 6H, 2 OCH_3), 3.65 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3) 3.85-4,30 (m, 2H, CH_2OCO), 6.38 (d, 1H, J= 8.5 Hz, aromatic proton), 6.44 (d, 1H, J= 8.5 Hz, aromatic proton), 6.62 (d, 1H, J= 8.5 Hz, aromatic proton), 6.98 (d, 1H, J= 8.5 Hz, aromatic proton). Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77; O, 28.67. Found: C, 64.79; H, 6.51; O, 28.43.

(3R*,4R*)-3-(2,3,4-trimethoxybenzyl)-4-(3,4-dimethoxybenzyl)-4,5 -dihydro-2(3H)-furanone (1a). The general procedure was followed and 0.79 g (90%) of **1a** were obtained after chromatography on silica gel (Toluene-EtOAc 7:3) and crystallization from CH_2Cl_2-ether: mp 113-114°C; IR (nujol) 1770 (C=O), 1601 (C=C) cm^{-1}; ^1H NMR δ 2.15-3.40 (m, 6H, aliphatic protons), 3.80 (s, 6H, 2 OCH_3), 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.00-4,45 (m, 2H, CH_2OCO), 6.55-7.25 (m, 5H, aromatic protons). Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; O, 26.89. Found: C, 66.31; H, 6.66; O, 26.49.

(3R*,4R*)-3-(3,4,5-trimethoxybenzyl)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (1c). According to the general procedure, 1 g (63%) of **1c**[35] was obtained after chromatography on silica gel (C_6H_{12}/EtOAc 7:3) and crystallization from ether: mp 87-90°C; IR ($CHCl_3$) 1760 (C=O), 1420, 1320 et 1200 cm^{-1}; ^1H NMR δ 2.57 (m, 4H, aliphatic protons), 2.93 (d, 2H, J= 6 Hz, aliphatic protons), 3.82 (s, 18H, OCH_3), 4.01-4.37 (m, 2H, CH_2OCO), 6.21 (s, 2H, aromatic protons), 6.38 (s, 2H, aromatic protons); Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.57; H, 6.73; O, 28.70. found: C, 64.58; H, 6.99.

(3R*,4R*)-3-(3,4,5-trimethoxybenzyl)-4-(3,4-methylenedioxybenzyl)-4,5-dihydro-2(3H)-furanone (1d). As above, 1.2 g (72%) of **1d** were obtained after chromatography on silica gel (Toluene-EtOAc 96:4) and crystallization from ether: mp 71-73°C [lit.[36] described as an oil]; IR (nujol) 1771 (C=O), 1591 (C=C) cm^{-1}; ^1H NMR δ 2.50 (m, 4H, aliphatic protons), 2.75-2.80 (m, 2H, aliphatic protons), 3.79 (s, 9H, 3 OCH_3), 4.05-4,35 (m, 2H, CH_2OCO), 5.86 (s, 2H, OCH_2O), 6.30-6.75 (m, 5H, aromatic protons). MS m/e 400 (M^+).

(3R*,4R*)-3-(3,4-dimethoxybenzyl)-4-(3,4-dimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (1e). The general procedure was followed and 2.95 g (76%) of **1e** were obtained after chromatography on silica gel (C_6H_{12}/EtOAc 7:3) and crystallization from ether: mp 92-94°C [lit.[12b] mp 99-102 °C (ether)]; IR (Nujol) 1750 (C=O), 1500, 1370, 1250 et 1135 cm^{-1}; ^1H NMR δ 2,54 (m, 4H, aliphatic protons), 2,94 (m, 2H, aliphatic protons), 3,83 (s, 12H, OCH_3), 3,3-4,4 (m, 2H, CH_2OCO), 6,3-7,0 (m, 6H, aromatic protons).

(3R*,4R*)-3-(3,4-dimethoxybenzyl)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (1f). Following the general procedure 2 g (68%) of white crystalline **1f** were afforded after chromatography on silica gel (C_6H_{12}/EtOAc 7:3) and crystallization from ether: mp 78-80°C; IR (Nujol) 1760 (C=O), 1585, 1335, and 1115 cm^{-1}; ^1H NMR δ 2.2-2.7 (m, 4H, aliphatic protons), 2.8-3.3 (m, 2H, aliphatic protons), 3.75 (s, 15H, OCH_3), 3.6-4.4 (m, 2H, CH_2OCO), 6.32 (s, 2H, aromatic protons), 6.4-6.8 (m, 3H, H aromatic protons). Anal. Calcd for $C_{23}H_{27}O_7$:C, 66.35; H, 6.73; O, 26.92. found: C, 66.51; H, 6.74.

(+/-)-Neoisostegane (2a). To a stirred solution of 0.149 g (1.2 mmol) of VOF_3 in CH_2Cl_2 (6 ml), trifluoroacetic acid (TFA) (3 ml) and trifluoroacetic anhydride (TFAA) (0.2 ml), were added at -45°C a solution of 0.2 g (0.48 mmol) of dibenzylbutanolide **1a** in CH_2Cl_2 (4 ml). The mixture was stirred at -45°C for 3 h and the solvents were removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and the layer was washed with saturated $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the solvent gave a red oil which was chromatographied on silica gel (Toluene-EtOAc 95:5). Crystallization from CH_2Cl_2-ether gave 0.091 g (46%) of **2a** as a white solid: mp 183-185°C; IR (nujol) 1776 (C=O), 1604 (C=C) cm^{-1}; ^1H NMR δ 1.91 (dd, 1H, J= 9.3 Hz, 13.3 Hz, H-8α), 2.02 (dd, 1H, J= 13.2 Hz, 9.0 Hz, H-7), 2.23 (m, 1H, H-6), 2.41 (dd, 1H, J= 10.0 Hz, 13.3 Hz, H-5β), 2.66 (d, 1H, J= 13.3 Hz, H-5α), 3.67 (d, 1H, J= 13.2 Hz, H-8β), 3.77 (dd, 1H, J= 11.5 Hz, 8.4 Hz, H-13β), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.38 (dd, 1H, J= 6.9 Hz, 8.4 Hz, H-13α), 6.50 (s, 1H, H-1), 6.68 (s, 1H, H-4), 6.71 (s, 1H, H-12). MS m/e 414 (M^+). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.55; H, 6.32; O, 27.02. Found: C, 66.37; H, 6.49; O, 27.08.

Oxidation of 1a by $VOCl_3$. To a stirred solution of 275 µl (2.92 mmol) of $VOCl_3$ in CH_2Cl_2 (150 ml), TFA (28 ml) and TFAA (2 ml), were added at -80°C a solution of 0.5 g (1.2 mmol) of **1a** in CH_2Cl_2 (150 ml). The mixture was stirred at -80°C for 3 h and the solvents were evaporated *in vacuo*. The residue was treated as above to give 0.25 g (50%) of **2a** as an oil which crystallised from CH_2Cl_2-ether. Compound **2a** was found to be identical (mp, IR, ^1H NMR) with the material prepared above.

Oxidation of 1a by TTFA (method A). To a stirred suspension of 0.118 g (0.26 mmol) of Tl_2O_3 in CH_2Cl_2 (10 ml), TFA (1 ml) and TFAA (0.5 ml), were added at -10°C a solution of 0.2 g (1.2 mmol) of **1a** in CH_2Cl_2 (10 ml), then immediately BF_3-Et_2O (0.1 ml). The mixture was stirred at room temperature for 1 h and the solvents were evaporated *in vacuo*. The work-up was the same as before and pure **2a** (0.15 g, 75%) was obtained from crystallization (CH_2Cl_2-ether). **2a** was found to be identical (mp, IR, ^1H NMR) with the material prepared above.

The bisbenzocyclooctadienes **2b-2f** were prepared by using the method A and the results are listed in table I.

(+/-)-Steganolide A (2b): mp 173-175°C (CH_2Cl_2-ether); IR ($CHCl_3$) 1776 (C=O), 1604 (C=C) cm^{-1}; ^1H NMR δ 1.91 (dd, 1H, J= 9.0 Hz, 13.2 Hz, H-8α), 1.97 (dd, 1H, J= 9.5 Hz, 12.8 Hz, H-5β), 2.01 (dd, 1H, J= 13.3 Hz, 9.0 Hz, H-7), 2.09 (m, 1H, H-6), 3.14 (d, 1H, J= 12.8 Hz, H-5α), 3.66 (d, 1H, J= 13.2 Hz, H-8β), 3.79 (dd, 1H, J= 11.2 Hz, 8.4 Hz, H-13β), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3) 4.38 (dd, 1H, J= 6.7 Hz, 8.3 Hz, H-13α), 6.52 (s, 2H, aromatic protons). MS m/e 444 (M^+). Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35; O, 28.80. Found: C, 64.88; H, 6.53; O, 28.72.

(M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro-6,7,8,9,10,11-hexamethoxy-dibenzo [4,5:6,7] cycloocta [1,2-c] furan-1(3H)- one (2c): mp 169-170°C (CH_2Cl_2- ether); IR ($CHCl_3$) 1779 (C=O), 1595, 1578 (C=C) cm^{-1}; ^1H NMR δ 1.95-2.50 (m, 4H, aliphatic protons), 2.62 (d, 1H, J= 12.6 Hz, H-5α), 3.12 (d, 1H, J= 12.6 Hz, H-8β), 3.55 and 3.58 (2s, 6H, OCH_3-1 and OCH_3-12), 3.70-3.90 (m, 1H, H-13β), 3.84 (s, 6H, 2 OCH_3), 3.87 (2s, 6H, 2 OCH_3), 4.20-4.45 (m, 1H, H-13α), 6.49 (s, 1H, H-4), 6.61 (s, 1H, H-9). Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35; O, 28.80. Found: C, 64.96; H, 6.40; O, 28.74.

(+/-)-Isostegane (2d): mp 169-170°C (CH_2Cl_2-cyclohexane) [lit.[20] mp 174-175°C (EtOH)]; IR ($CHCl_3$) 1775 (C=O), 1596 (C=C) cm^{-1}; ^1H NMR δ 2.0-3.40 (m, 6H, aliphatic protons), 3.55 (s, 3H, OCH_3-12), 3.70 (m, 1H, H-13β), 3.88 (2s, 6H, 2 OCH_3), 4.32 (m, 1H, H-13α), 5.98 (s, 2H, OCH_2O), 6.61 (s, 2H, aromatic protons), 6.68 (s, 1H, aromatic proton). MS m/e (M^+) 398.

(M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro-6,7,9,10,11-pentamethoxy-dibenzo [4,5:6,7] cycloocta [1,2-c] furan-1(3H)- one (2e): mp 213-215°C (CH_2Cl_2- ether); IR (nujol) 1776 (C=O), 1596 (C=C) cm^{-1}; ^1H NMR δ 2.10-2.55 (m, 4H, aliphatic protons), 2.69 (d, 1H, J= 12.3 Hz, H-5α), 3.12 (d, 1H, J= 12.6 Hz, H-8β), 3.53 (s, 3H, OCH_3-12), 3.70-3.90 (m, 1H, H-13β), 3.84 (s, 3H, OCH_3), 3.89 (s, 6H, 2 OCH_3), 3.92 (s, 3H, OCH_3), 4.39 (m, 1H, H-13α), 6.63 (s, 1H, H-4), 6.64 (s, 1H, H-4), 6.69 (s, 1H, H-9). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32; O, 27.02. Found: C, 66.71; H, 6.52; O, 27.08.

(M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro-6,7,10,11-tetramethoxy-dibenzo [4,5:6,7] cycloocta [1,2-c] furan-1(3H)- one (2f): mp 212-213°C (CH_2Cl_2- ether); 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, aromatic protons), 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.

Oxidation of 1a by $RuO_2,2H_2O$ (method B)(Table I). To a stirred solution of 64 mg (0.48 mmol) of $RuO_2,2H_2O$ in CH_2Cl_2 (10 ml), TFA (0.5 ml) and TFAA (0.25 ml), were added at -10°C a solution of 0.1 g (0.24 mmol) of **1a** in CH_2Cl_2 (5 ml), then immediately BF_3-Et_2O (0.1 ml). The mixture was stirred vigorously at room temperature for 18 h and the mixture was treated by 5% $NaHCO_3$. The organic layer was decanted and the aqueous layer extracted with CH_2Cl_2. The combined extracts were washed with saturated brine, dried over $MgSO_4$ and evaporation of the solvent after filtration gave **2a** as a white solid recrystallized from CH_2Cl_2-ether (98 mg, 98%). Compound **2a** was found to be identical (mp, IR, ^1H NMR) with the material prepared above.

The BBCOD **2b-2f** were prepared by using the above procedure and the results are listed in table I. These compounds were found to be identical with those prepared with the TTFA procedure.

Isomerisation of steganolide A (2b). In a pyrex test-tube fitted with an inlet of argon was placed 0.1 g (0.22 mmol) of powdered **2b**. The air was removed with argon and the tube heated in a metallic bath at 200°C (± 10°C) for 4 h. After cooling, the residue was filtered on a short silica gel column (Toluene-EtOAc 9:1) affording a pale yellow amorphous solid (86 mg), TLC homogeneous (Toluene-EtOAc 7:3). 500 MHz ^1H-NMR showed that this sample was in fact a mixture of starting material **2b** and its atropoisomer **9b**, accompanied with **(M*,3aR*,13aS*)-3a,4,31,13a-tetrahydro-6,7,8,9,10,11-hexamethoxy-dibenzo [4,5;6,7] cycloocta [1,2-c] furan-1(3H)-one (10)** (65%). All attempts to isolate pure **10** failed, so its structure was determined by difference on the spectrum of the mixture: ^1H NMR δ 2.23 (dd, 1H, J= 13.4 Hz, 13.4 Hz, H-5β), 2.36 (dd, 1H, J= 3.1 Hz, 15.5 Hz, H-8α), 2.68 (m, 1H, H-6), 2.93 (dd, 1H, J= 4.9 Hz, 15.5 Hz, H-8β), 2.94 (m, 1H, H-7), 3.02 (dd, 1H, J= 13 Hz,3.0 Hz, H-5α), 3.66 (d, 1H, J= 13.2 Hz, H-8β), 3.80-4.0 (m, 1H, H-13β), 3.89 (s, 6H, 2 OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.59 (dd, 1H, J= 8 Hz, 9 Hz, H-13α), 6.56 (s, 1H, aromatic proton), 6.62 (s, 1H, aromatic proton).

1-bromo-2-bromomethyl-4,5-dimethoxybenzene (12). As described by Liebeskind,[17a] 1 g (5.95 mmol) of **8a**[15] in dry $CHCl_3$ (10 ml) were treated at O°C by 0.33 ml (6.37 ml) of bromine in $CHCl_3$ (10 ml). The mixture was stirred at room temperature for 1 h, then treated with saturated $NaHSO_3$. The organic layer was decanted, washed with saturated brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give 1.7 g (92%) of **12** as a white solid recrystallized from ether: mp 82-84°C; IR (nujol) 1599 (C=C) cm^{-1}; ^1H NMR δ 4.00 (s, 6H, 2 OCH_3), 4,75 (s, 2H, CH_2Br), 7.01 (s, 1H, aromatic proton), 7.10 (s, 1H, aromatic proton). MS m/e 307.9 (M^+). Anal. Calcd for $C_9H_{10}O_2Br_2$: C, 34.87; H, 3.25; O, 10.32; Br, 51.55. Found: C, 34.89; H, 2.93; O, 10.67; Br, 52.06.

(3R*,4R*)-3-(2-bromo-4,5-dimethoxybenzyl)-4-(3,4-dimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (13). This compound was prepared by using the procedure described for the synthesis of **1a-1f**. Crystallization of the pale yellow oil from ether gave 0.87 g (88%) of **13** as white needles: mp 97-99°C; IR ($CHCl_3$) 1769 (C=O), 1603 (C=C) cm^{-1}; ^1H NMR δ 2.30-2.90 (m, 4H, aliphatic protons), 2.95-3.60 (m, 2H, aliphatic protons), 3.80 (s, 9H, 3 OCH_3), 3.81 (s, 3H, OCH_3), 4.00-4,30 (m, 2H, CH_2OCO), 6.40-6.60 (m, 2H, aromatic protons), 6.68 (d, 1H, J= 9 Hz, aromatic proton), 6.76 (s, 1H, aromatic proton), 6.96 (s, 1H, aromatic proton). MS m/e 464 (M^+). Anal. Calcd for $C_{22}H_{25}O_6Br$: C, 56.78; H, 5.41; O, 20.62; Br, 17.17. Found: C, 56.90; H, 5.13; O, 20.35; Br, 16.59.

(M*,3aR*,13aR*)-12-bromo-3a,4,13,13a-tetrahydro-6,7,9,10-tetramethoxy-dibenzo [4,5:6,7] cycloocta [1,2-c] furan-1(3H)-one (14). This compound was prepared by using the TTFA procedure described for the synthesis of **2a-2f**. Crystallization from CH_2Cl_2-ether gave 10 mg (10%) of **14** as white crystals: mp 248-250°C; IR (KBr) 1786 (C=O), 1584, 1560 (C=C) cm^{-1}; ^1H NMR δ 2.80-2.90 (m, 6H, aliphatic protons), 3.40-3.60 (m, 1H, H-13β), 3.41 (s, 3H, OCH_3-12), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.20-4.50 (m, 1H, H-13α), 6.66 (s, 1H, aromatic proton), 6.69 (s, 1H, aromatic proton). MS m/e 464 (M^+).

(M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro-6,7,9,10-tetramethoxy-dibenzo[4,5;6,7] cycloocta [1,2-c] fu-

ran-1(3H)-one (15). 54 mg (1.17 mmol) of **14** in a 1:1 mixture of EtOAc-AcOH (10 ml) were introduced in an hydrogenation flask and 20 mg 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 from ether gave 38 mg (85%) of **15** as a white solid: mp 153-155°C; IR ($CHCl_3$) 1781 (C=O), 1603 (C=C) cm^{-1}; ^1H NMR δ 2.08 (dd, 1H, J= 9.3 Hz, 13.2 Hz, H-7), 2.23 (m, 1H, H-6), 2.25 (dd, 1H, J= 9.5 Hz, 13.6 Hz, H-8α), 2.43 (dd, 1H, J= 13.2 Hz, 10.0 Hz, H-5β), 2.69 (d, 1H, J= 13.0 Hz, H-5α), 3.19 (d, 1H, J= 13.6 Hz, H-8β), 3.46 (s, 3H, OCH_3-12), 3.77(dd, 1H, J= 11.4 Hz, 8.5 Hz, H-13β), 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.39 (dd, 1H, J= 6.9 Hz, 8.4 Hz, H-13α), 6.69 (s, 1H, H-1), 6.71 (s, 1H, H-4), 6.93 (d, 1H, J= 8.4 Hz, H-10), 7.05 (d, 1H, J= 8.4 Hz, H-9). MS m/e 384 (M^+).

(E) 3-(3,4,5-trimethoxy-benzylidene)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (18a). To a stirred suspension of 1.4 g (0.058 mol) of sodium hydride in anhydrous toluene (50 ml) was introduced under nitrogen at 0°C a solution of 10 g (0.038 mol) of lactone **3c** and 7.4 g (0.038 mol) of **5c** in toluene (50 ml), then were added dropwise 0.15 ml (0.004 mol) of methanol. The mixture was stirred vigorously at 0°C until no hydrogen emission was observed, and was stirred one hour more at room temperature. The resultant mixture was acidified with 25 ml of chilled 6N HCl. The aqueous layer was extracted with toluene and the resulting extracts were washed with satured brine, water, and dried ($MgSO_4$). The solvent was removed *in vacuo* yielding a thick orange oil. Recrystallization from ether gave 10.5 g (62%) of **18a**: mp 106-107°C (ether); IR ($CHCl_3$) 1735 (C=O), 1635, 1585 (C=C) cm^{-1}; ^1H NMR δ 3.10 (dd, 1H, J_1= 15 Hz J_2= 3,8 Hz, H_a benzylic proton), 3.85 (m, 1H, aliphatic proton), 3.90 and 3.85 (2s, 18H, OCH_3), 4.31 (m, 2H, CH_2OCO), 6.38 (s, 2H, aromatic protons), 6.83 (s, 2H, benzylidene aromatic protons), 7.48 (d, 1H, J= 1,5 Hz, (E) vinylic proton). Anal. Calcd for C_{24} H_{28} O_8: C, 64.86; H, 6.31; O, 28.82. found: C, 64.72; H, 6.20; O, 29.08.

(3S*,4R*)- 3-(3,4,5-trimethoxybenzyl)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (18b). 12 g (0.027 mol) of **18a** in a solution of acetic acid (150 ml) were introduced in an hydrogenation flask and 1.3 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 4 hours under H_2 pressure (50 psi) at room temperature. Then the catalyst was removed by filtration and the solvent was evapored *in vacuo*. The residue was submitted to high *vacuo* in order to remove the last trace of acetic acid. The residue obtained refused to crystallize giving 12 g (99%) pure oily **18b**: IR ($CHCl_3$) 1760 (C=O), 1580 (C=C), 1450 and 1420 cm^{-1}; ^1H NMR δ 2.1-3.3 (m, 6H, aliphatic protons), 3.83 (s, 6H, OCH_3), 3.77 (s, 12H, OCH_3), 4.06 (d, 2H, J= 3 Hz, CH_2OCO), 6.22 (s, 2H, aromatic protons), 6.48 (s, 2H, aromatic protons). Anal. Calcd for C_{24} H_{30} O_8: C, 64.57; H, 6.73; O, 28.70. found: C, 64.38; H, 7.01.

(P*,3aR*)-13,13a-dihydro-6,7,8,9,10,11-hexamethoxy-dibenzo [4,5:6,7] cycloocta [1,2-c] furan-1 (3H)-one (19a). This compound was prepared by using the thallium and ruthenium procedures described for the synthesis of **2a-2f** (Table II). Crystallization from ether-petrolum ether gave **19a** as white crystals: mp 159-160°C; IR ($CHCl_3$) 1752 (C=O) cm^{-1}; ^1H NMR δ 2.45 (dd, 1H, J= 1 Hz, 14 Hz, H-5β), 3.15 (dd, 1H, J= 6 Hz, 14 Hz, H-5α), 3.55 and 3.65 (2s, 6H, OCH_3-1 and OCH_3-12), 3.80 (s, 12H, 4 OCH_3), 4.15 and 4.40 (2dd, 2H, J= 9 Hz, H-13α and H-13β), 6.35 and 6.55 (2s, 2H, aromatic protons), 7.45 (d, 1H, J= 3.5 Hz, ethylenic proton). Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92; O, 28.93. Found: C, 64.81; H, 5.98; O, 28.92.

(P*,3aR*,13aS*)-3a,4,13,13a-tetrahydro-6,7,8,9,10,11-hexamethoxy-dibenzo [4,5:6,7] cycloocta [1,2-c] furan-1 (3H)- one (19b). This compound was prepared by using the thallium and ruthenium procedure described for the synthesis of **2a-2f** (Table II). Crystallization from ether gave **19b** as white needles: mp 157-159°C; IR ($CHCl_3$) 1767 (C=O) cm^{-1}; ^1H NMR (C_6D_6) δ 1.95 (dd, 1H, J= 5.8 Hz, 14.5 Hz, H-5β), 2.10 (m, 1H, H-6), 2.34 (dd, 1H, J= 2.3 Hz, 14.5 Hz, H-5α), 2.40 (m, 2H, H-7 and H-8β), 2.75 (m, 1H, J~ 0 Hz and J= 10.3 Hz, H-8α), 3.32 and 3.39 (2s, 6H, OCH_3-1 and OCH_3-12), 3.54 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.70 (m, 2H, H-13α and H-13β), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.91 (s, 1H, H-4), 6.46 (s, 1H, H-9). Anal. Calcd for $C_{24}H_{28}O_8$: *C, 64.85; H, 6.35; O, 28.80.* Found: C, 65.09; H, 6.32; O, 28.73.

4,13-dihydro-6,7,8,9,10,11-hexamethoxy-dibenzo [4,5:6,7] cycloocta [1,2-c] furan-1 (3H)- one (20). 1 g (2.3 mmol) of **19a** in a solution of THF (40 ml) were introduced in an hydrogenation flask and 0.18 g of 5%

rhodium on charcoal were added. The flask was placed in a Parr apparatus and flushed 3 times with hydrogen and the suspension was stirred 6 hours under H_2 pressure (50 psi) at room temperature. Then the catalyst was removed by careful filtration and the solvent was evapored under vacuo. The obtained residue showed 2 spots on TLC (C_6H_{12}/t-butyl methyl ether) and was submitted to chromatography on silica gel (C_6H_{12}/t-butyl methyl ether 1:1). 0.25 g (25%) of cristalline **19b** was obtained was found to be identical (mp, IR, ^1H NMR) with this prepared by using the thallium and ruthenium procedure, and 0.57 g (57%) of **20** was collected as major product: mp 190-191°C (ether); IR ($CHCl_3$) 1735 (C=O), 1580 (C=C), 1320 cm^{-1};^1H NMR δ 3.0-3.5 (m, 4H, geminal AB system), 3.62 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.85 (s, 12H, OCH_3), 4.65 (m, 2H, CH_2OCO), 6.45 (s, 1H, aromatic proton), 6.55 (s, 1H, aromatic proton). Anal. Calcd for C_{24} H_{26} O_8: C, 65.16; H, 5.88; O, 28.96. found: C, 65.77; H, 6.00.

(P*,6R*,7S*)-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-bis(hydroxy methyl)-dibenzo [a,c] cyclooctene (21a). To a stirred solution of 0.5 g (1.1 mmol) of **19b** in 20 ml of absolute ethanol, was added at room temperature 0.18 g (1.65 mmol) of powdered $CaCl_2$ and 0.125 g (3.3 mmol) of $NaBH_4$ was introduced portionwise. The mixture was stirred at room temperature for 15 mn, then cooled to 0°C and acidified with 6N HCl. Distillated water was added (10 ml) and EtOH was removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 and the resulting extracts were washed with H_2O and dried ($MgSO_4$). The solvent was removed in vacuo yielding 0.47 g (93%) of compound **21a** as a white solid from crystallization with ether: mp 122-126°C; IR ($CHCl_3$) 3550-3180 (broad OH), 1580 (C=C), 1400, 1320, 1200 cm^{-1}; ^1H NMR δ 1.8-3.1 (m, 6H, aliphatic protons), 3.4-3.9 (m, 4H, CH_2O), 3.58 (s, 6H, OCH_3-1 and OCH_3-12), 3.88 (s, 12H, OCH_3), 6.55 (s, 1H, H-9), 6.65 (s, 1H, H-4).

(P*,6R*,7S*)-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-bis(methanesulfonylmethyl)-dibenzo [a,c] cyclooctene (21b). To a stirred solution of 0.57 g (1.3 mmol) of **21a** in 10 ml of dry pyridine at 0°C was added dropwise 0.59 ml (7.6 mmol) of methanesulfonyl chloride. The solution was allowed to stand 20 min more stirring at 0°C and small pieces of ice were introduced into the solution. The resultant mixture was diluted with 50 ml of water and extracted with CH_2Cl_2 (60 ml). The organic layer was washed with 1N HCl, brine, water and was dried ($MgSO_4$). Concentration in vacuo gave white flakes as the crude product. Recrystallization from ether/CH_2Cl_2 yielded 0.57 g (74%) of **21b**: mp 165.5-167°C; IR ($CHCl_3$) 1595, 1490, 1455, 1170, 1120, 1100 cm^{-1}; ^1H NMR δ 2.05-2.95 (m, 6H, aliphatic protons), 3.02 and 3.08 (6H, 2s, CH_3SO_3), 3.60 (s, 6H, OCH_3), 3.90 (s, 12H, OCH_3), 4.25 (m, 4H, CH_2O-), 6.60 and 6.71 (2s, 2H, aromatic protons).

(+/-)-Deoxyschizandrin (17). To a stirred suspension of 0.55 g (0.91 mmol) of **21b** in THF (7 ml) at 0°C were added dropwise 5 ml (5.5 mmol) of lithium triethylborohydride 1M solution in THF. The solution was allowed to stand at room temperature and was stirred for 1h. Then 4 ml of water were added, the mixture was cooled to 0°C, 8 ml NaOH 3M and 8 ml H_2O_2 33% solution were respectively introduced, and the mixture stirred for 15 min more. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine, water, and dried ($MgSO_4$). Concentration in vacuo gave yellowish oily residue who was submitted to careful chromatography on silica gel (C_6H_{12}/AcOEt 8:2). Recrystallization from MeOH gave 0.39 g (71%) of (+/-)-desoxyschizandrin **17**: mp 113-115°C [lit.[27] 112-113°C (CH_3OH)]; IR ($CHCl_3$) 1580, 1400, 1200 cm^{-1}; ^1H NMR δ 0.75 (d, 3H, J=7.5 Hz, CH_3-6), 1.0 (d, 3H, J=7.5 Hz, CH_3-7), 1.6-2.05 (m, 2H, H-6 and H-7), 2.05-2.65 (m, 4H, aliphatic protons), 3.57 (s, 6H, OCH_3-1 and OCH_3-12), 3.86 (s, 12H, OCH_3), 6.52 (s, 2H, H-4 and H-9). Anal. Calcd for $C_{24}H_{32}0_6$: C, 69.23; H, 7.69. found: C, 69.34; H, 7.70.

Formation of demethylation by-products 22a and 22b. The reduction of 0.8 g (1.4 mmol) of bimesylate **21b** was carried out by using the preceding procedure, but the stirring at room temperature was replaced by heating at reflux of THF for 2 h. The residue showed an extensive degradation; however, by chromatography on silica gel (C_6H_{12}/AcOEt 7:3), 10 mg (2%) of deoxyschizandrin **17**, 35 mg (6%) of an isomeric mixture of monophenols **22a** and 50 mg (9%) of diphenol **22b** were isolated.

(P*,6R*,7S*)-5,6,7,8-tetrahydro-6,7-dimethyl-2-(or 11)-hydroxy-1,3,10,11 (or 2),12-pentamethoxy-dibenzo [a,c] cyclooctene (22a): ^1H NMR δ 6.55 (s, 2H, H-4), 5.57 (2s, 1H, phenolic protons), 3.92 - 3.88 (5s, 9H, OCH_3), 3.54 (s, 3H, OCH_3-1 (or 12)), 3.41 and 3.40 (2s, 3H, OCH_3-12 (or 1)), 2 57 and 2.50 (2m, 2H, CH_2-5), 2.29 and 2.04 (2m, 2H, CH_2-8), 1.91 (s, 1H, H-6), 1.81 (s, 1H, H-7), 1.00 (2d, 3H, J=7.1 Hz, CH_3-7), 0.73 (2d, 3H, J=7.2 Hz, CH_3-6).

(P*,6R*,7S*)-5,6,7,8-tetrahydro-1,12-dihydroxy-6,7-dimethyl-2,3,10,11-tetramethoxy-dibenzo [a,c] cyclooctene (22b): mp 172.5-175°C (Ether-CH_2Cl_2); ^1H NMR δ 6.41 (s, 2H, H-4 and H-9), 5.82 (s, 2H, phenolic protons), 3.88, 3.87 and 3.85 (3s, 12H, OCH_3), 2.7-1.6 (m, 6H, aliphatic protons), 1.0 (d, 3H, J=7 Hz, CH_3-7), 0.76 (d, 3H, J=7 Hz, CH_3-6).

(M*,6R*,7R*)-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-bis (hydroxymethyl)-dibenzo [a,c] cyclooctene (23a). Prepared by using the procedure already described for the compound **21a**. from 1.5 g (3.4 mmol) of **2c** was obtained 1.3 g (86%) of crystalline **23a**: mp 137-138°C (ether); IR ($CHCl_3$) 3400 (OH), 1580, 1200 cm^{-1}; ^1H NMR δ 1.3-1.85 (m, 2H, H-6 and H-7), 1.85-2.8 (m, 4H, aliphatic protons), 3.5-3.8 (m, 4H, CH_2O), 3.62 (s, 6H, OCH_3-1 and OCH_3-12), 3.88 (s, 12H, OCH_3), 6.61 (s, 2H, H-4 and H-9).

(M*,6R*,7R*)-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-bis (methanesulfonylmethyl)-dibenzo [a,c] cyclooctene (23b). Prepared by using the procedure already described for the compound **21b**. From 1g (2.2 mmol) of **23a** was obtained 1.05 g (78%) of crystalline **23b**: mp 161.5-162°C (ether); IR ($CHCl_3$) 1575, 1400, 1330, 1170 cm^{-1}; ^1H NMR δ 1.5-2.9 (m, 6H, aliphatic protons), 3.04 (s, 6H, CH_3-SO_3), 3.67 (s, 6H, OCH_3-1 and OCH_3-12), 3.90 (s, 12H, OCH_3), 4.0-4.5 (m, 4H, CH_2O), 6.61 (s, 2H, H-4 and H-9).

(M*,6R*,7R*)-5,6,7,8-tetrahydro-6,7-dimethyl-1,2,3,10,11,12-hexamethoxy-dibenzo [a,c] cyclooctene (24). Following the procedure described for the compound **17**, 1 g (1.7 mmole) of **23b** afforded 0.5 g (73%) of crystalline **24**: mp 129-131°C (MeOH) [lit.[1b] mp 129-131°C (MeOH)]; IR ($CHCl_3$) 1575, 1390, 1320, 990 cm^{-1}; ^1H NMR δ 1.05 (d, 6H, J=6 Hz, CH_3), 1.1-1.4 (m, 2H, H-6 and H-7), 2.1-2.6 (m, 4H, aliphatic protons), 3.64 (s, 6H, OCH_3-1 and OCH_3-12), 3.91 (s, 12H, OCH_3), 6.58 (s, 2H, H-4 and H-9). Anal. Calcd for $C_{24}H_{32}O_6$: C, 29.23; H, 7.69 found C, 29.04; H, 7.73.

General procedure for oxidation of dibenzylbutanolide and derivatives using method C (Table III). To a stirred solution of 64 mg (0.48 mmol) of $RuO_2,2H_2O$ in CH_2Cl_2 (5 ml), trifluoromethanesulfonic acid (0.6 ml) and trifluoromethanesulfonic anhydride (0.3 ml), were added at -10°C a solution of 0.1 g (0.24 mmol) of **1a** in CH_2Cl_2 (5 ml), then immediately BF_3-Et_2O (0.1 ml). The mixture was stirred vigorously at room temperature for 3 h and the mixture was treated by 5% $NaHCO_3$. After dilution, the organic layer was decanted and the aqueous layer extracted with CH_2Cl_2. The combined extracts were treated as before in method A and B. Crystallization of the pale yellow oil from ether gave 94 mg (94%) of **2a** as a white solid recrystallized from CH_2Cl_2-ether.

The BBCOD **2b** and **19a** were prepared according the same procedure (listed in table III). These compounds were found to be identical (mp, IR, ^1H NMR) with those prepared with method A and B.

General procedure for oxidation of dibenzylbutanolide and derivatives using method D (Table III). In a 50 ml two necked round bottom flask equipped with a septum and an inlet for argon, was placed 45 mg (0.26 mmol) of $RuO_2,2H_2O$ in dry CH_2Cl_2 (2.5 ml), TFA (5 ml) and TFAA (2.5 ml). Then, 0.1 g (0.24 mmol) of **1a** in CH_2Cl_2 (2.5 ml) were added dropwise at 0°C and immediately BF_3-Et_2O (0.3 ml). The flask was immerged 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 5% $NaHCO_3$ and the product was isolated as above. Crystallization from CH_2Cl_2-ether gave 93 mg (93%) of **2a** as white crystals.

The BBCOD **2b** and **19a** were prepared according the same procedure (listed in table III). These compounds were found to be identical (mp, IR, ^1H NMR) with those prepared with method A, B and C.

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