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New Agents of Biaryl Oxidative Coupling in Fluoro Acid Medium. VI. Application to the Synthesis of Phenolic Bisbenzocyclooctadiene Lignans.[1]

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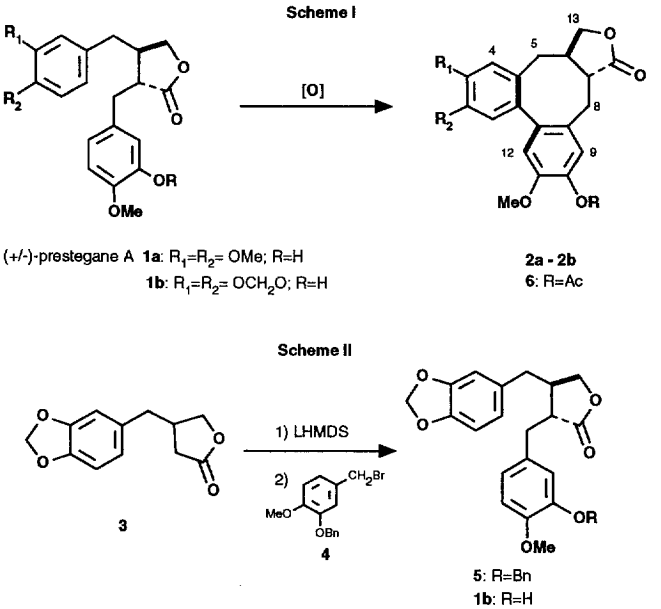
Abstract : *A systematic study of redox couples in fluoro acid medium has been carried out for the oxidative coupling of bisbenzocyclooctadiene lignan precursors. Tl_2O_3 and Re_2O_7 were found to be the more efficient reagents with precursors possessing methylenedioxy substituents for the former and only methoxy groups for the latter. Finally, oxidative coupling of a phenolic dibenzylbutane led to a mixture of two BBCOD's, resulting from para and ortho coupling to the phenolic group.*

During the course of our studies directed towards the use of redox couples (in fluoro acid medium), we found that Re_2O_7, $Mn(OAc)_3.2H_2O$ and $Ce(OH)_4$ are efficient reagents in the non-phenolic biaryl oxidative coupling.[1] The pionering studies of Barton[2] and Battersby[3] demonstrated that natural compounds possessing a biaryl moiety (i.e. aporphines and analogs) are formed by oxidation of open phenolic precursors. Moreover, a recent report by Landais and Robin[4] also suggested that a similar relationship may exist between bisbenzocyclooctadiene lignans and phenolic dibenzylbutanolides (Scheme I). Encouraged by the promising results obtained with $RuO_2.2H_2O$ in fluoro acid medium, we embarked upon a systematic study of the oxidation of phenolic dibenzylbutanolides using cheap commercially available metal oxides in fluoro acid medium. We report herein a detailed study of the oxidation of the representative phenolic precursors **1a**[5]**-b**, and a comparison between several metal oxides and acetates.

1. *Synthesis of the phenolic dibenzylbutanolides*

The precursors **1a-b** were prepared according to procedures previously reported by our group.[6,7] Alkylation of the anion of lactone **3**[8] (generated by deprotonation of **3** with Lithium Hexamethyldisilazane (LHMDS) in THF) with the bromide **4**[4] gave the dibenzylbutanolide **5** in 97% yield (Scheme II). Hydrogenolysis of **5** on palladium on charcoal in an AcOH-EtOAc solvent mixture, gave the expected (+/-)-dibenzylbutanolide **1b** in 82% yield.



2. *Oxidative coupling of dibenzylbutanolide precursors*

A systematic investigation of the oxidative coupling of (+/-)-prestegane A **1a** was then undertaken under the conditions as previously described[1](Table I). We observed that trifluoroacetic and pentafluoropropionic acid medium gave similar results. Good results were obtained when V_2O_5, $Cu(OAc)_2.H_2O$ and $RuO_2.2H_2O$ were used as oxidant, however by for the best result was into Re_2O_7. Interestingly, we noticed the formation of an acetylated bisbenzocyclooctadiene (BBCOD) **6** on reaction of **1a** with $Fe(OH)(OAc)_2$ (Scheme I).

Table I: Oxidative coupling of 1a to 2a in fluoro acid medium.

	trifluoroacetic medium[a]		pentafluoropropionic medium[b]	
oxidant (eq.)	time	yield[c] (%)	time	yield[c] (%)
Tl_2O_3 (0.6)	2h	56	30mn	68
$Mn(OAc)_3.2H_2O$ (2.5)	1h	34	30mn	25
Re_2O_7 (2.5)	1h	98	2h	96
V_2O_5 (10)	5d[d]	75	16h[d]	84
Pr_6O_{11} (10)[e]	1d[d]	58	30h[d]	52
$RuO_2.2H_2O$ (4)	15h	76	15h	80
TeO_2 (10)	40h[d]	70	40h[d]	60
$Cu(OAc)_2.H_2O$ (5)	30mn	90	10mn (0°C)	80
CrO_3 (5)	22h[d]	44	24h[d]	36
$Fe(OH)(OAc)_2$ (10)	24h	0[f]	36h	0[f]
Co_3O_4 (10)	15h[d]	72		

[a] CH_2Cl_2/TFA/TFAA/BF_3-OEt_2, T=20°C. [b] $CH_2Cl_2/C_2F_5CO_2H/(C_2F_5CO)_2O/BF_3$-$OEt_2$, T=20°C.
[c] yield of isolated product. [d] ultra-sound. [e] 10 eq. of PrO_2. [f] formation of **6** (72% in TFA, 68% in $C_2F_5CO_2H$)

The dibenzylbutanolide **1b**, possessing a methylenedioxyle group, was then also reacted under the

different oxidative conditions (Table II). Tl_2O_3 proved to be the best oxidant (60-65% yield) but the yields of resulting phenolic couplings were generally lower than those of **1a**, presumably due to the degradation of the benzodioxole ring.[9] A careful examination of aliphatic vicinal coupling constants in ^1H NMR clearly showed that **2b** possess an "*iso*" biaryl junction.[10] Moreover, the ^1H NMR spectrum revealed that the phenolic oxidative coupling of **1b** led exclusively to the "*para-para*" biaryl coupling.

Table II: Oxidative coupling of 1b to 2b in fluoro acid medium.

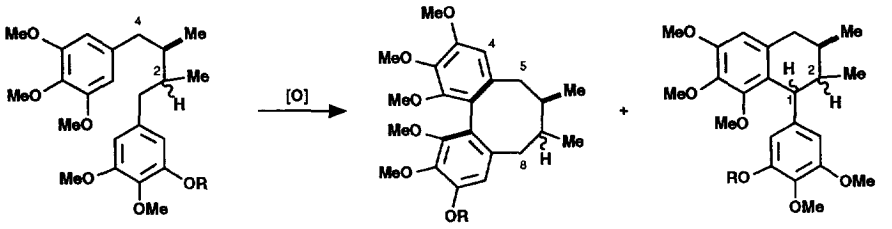
	trifluoroacetic medium[a]		pentafluoropropionic medium[b]	
oxidant (eq.)	time[d]	yield[c] (%)	time[d]	yield[c] (%)
Tl_2O_3 (0.55)	2mn (0°C)	64	5mn (0°C)	60
$Mn(OAc)_3.2H_2O$ (2.5)	2mn (0°C)	30	5mn (0°C)	24
$RuO_2.2H_2O$ (1.5)	2h	18	4h[e]	10
$Fe(OH)(OAc)_2$ (10)	6h30	20	5h30	26
SeO_2 (10)	1h30[e]	18	-	0[f]
CF_3CO_2Ag (10)	5h	30		

[a] TFA/BF_3-Et_2O. [b] $C_2F_5CO_2H/BF_3$-Et_2O. [c] yield of isolated product. [d] reactions at room temperature unless otherwise indicated. [e] ultra-sound. [f] degradation of starting material.

3. *Extension to the oxidative coupling of phenolic dibenzylbutanes*

The above results prompted us to extend our procedure to the synthesis of non-lactonic phenolic BBCOD. Several years ago,[11] we described a biomimetic oxidative coupling of diarylbutanes **7a-b**, which gave, along with the expected deoxyshizandrins **8a-b**, the corresponding phenyltetralins **9a-b** (Scheme III). As an attempt to resolve the problems of regioselectivity during this oxidative coupling, we decided to study the oxidation of some precursors possessing a phenolic group (i.e. **7c**) likely to orientate selectively the biaryl coupling towards the formation of BBCOD (i.e. **8a-b**)

Scheme III



7a: R= Me, H-2 α
7b: R= Me, H-2 β
7c: R= H, H-2 α

8a: R= Me, H-7 α
8b: R= Me, H-7 β

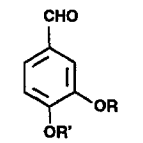
9a: R= Me, H-1 β, H-2 α
9b: R= Me, H-1 α, H-2 β

4. *Synthesis of phenolic dibenzylbutane*

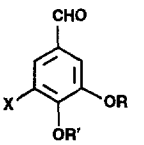
Reprotected benzaldehyde **16** was synthesized via two different routes, starting from the commercially available vanillin **10** and isovanillin **11** respectively. In the first sequence, iodination[12] of **10** afforded iodovanillin **14** which was treated with NaOH in the presence of $CuSO_4$[13] to give the diphenol **17**. Selective methylation[14] of this diphenolic compound gave aldehyde **18** which was further benzylated with benzyl chloride in EtOH. The four-step sequence gave **16** in 28% overall yield (from vanillin **10**) (Scheme IV). In the second route, isovanillin **11** was protected with benzyl chloride in acetone[15] to give **12**, which was demethylated using sodium p-thiocresolate in toluene and HMPA to afford the phenol **13**. This was then brominated using Br_2 in AcOH, giving the aldehyde **15** which was then treated with NaOMe in the presence

of $CuCl_2$ in DMF, to afford **19** which was further methylated using Me_2SO_4 in acetone. The five-step sequence gave the expected benzaldehyde **16** in 22% overall yield (from isovanillin **11**) (Scheme IV).

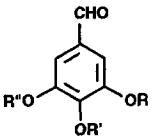
Scheme IV



10: R= Me; R'= H
11: R= H; R'= Me
12: R= Bn; R'= Me
13: R= Bn; R'= H



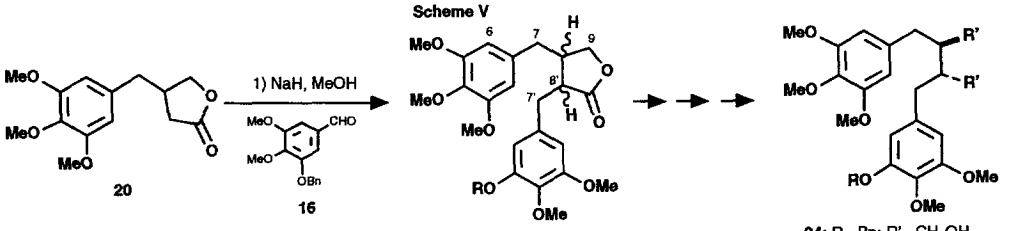
14: R= Me; R'= H; X= I
15: R= Bn; R'= H; X= Br



16: R= R'= Me; R"= Bn
17: R= Me; R'= R"= H
18: R= R'= Me; R"= H
19: R= Bn; R'= H; R"= Me

The phenolic dibenzylbutane **7c** was prepared following reported procedures[16] (Scheme V). Lactone **20** was synthesized using a known three-step sequence.[1] Alkylidenation of lactone **20** with aldehyde **16** in the presence of NaH in methanol afforded the compound **21** which was hydrogenolysed on palladium on charcoal to give the deprotected *cis* phenolic **22**. Protection of **22** with benzyl chloride in ethanol and K_2CO_3 gave the *trans* dibenzylbutanolide **23** instead of the expected *cis* dibenzylbutanolide. In the light of our previous results in the field,[1] we decided to carry out our studies in the *trans* series, considering that the stereochemistry at C-3 and C-4 (in the dibenzylbutane) should not have any effect on the regioselectivity of the biaryl oxidative coupling. The *trans* diol **24**, obtained by reduction of **23** with calcium borohydride in ethanol, was treated with methanesulfonyl chloride in pyridine to afford the *trans* bismesylate **25** which was further reduced with $LiBEt_3H$ to give the *trans* dibenzylbutane **26**. Finally, catalytic hydrogenation of **26** with palladium on charcoal afforded the expected phenolic *trans* dibenzylbutane **27** in 24% overall yield (from lactone **20**)(Scheme V).

Scheme V

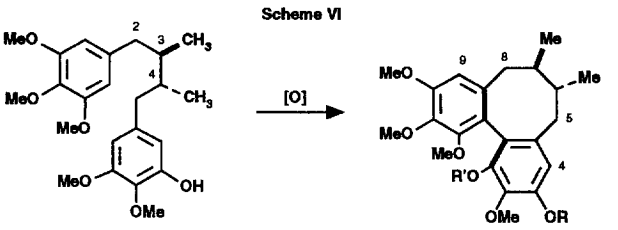


20
16
22: R= H; H-8' α
23: R= Bn; H-8' β
24: R= Bn; R'= CH_2OH
25: R= Bn; R'= CH_2OMs
26: R= Bn; R'= CH_3
27: R= H; R'= CH_3
30: R= $COCH_3$; R'= CH_3

5. *Oxidative coupling of dibenzylbutane precursor*

The phenolic dibenzylbutane **27** was submitted to the above oxidative conditions, with different metallic salts in CH_2Cl_2-TFA-TFAA mixture (Table III). We observed the formation of the expected BBCOD **28** resulting from coupling *para* to the phenolic group and surprisingly, the formation of BBCOD **29**, resulting from coupling *ortho* to the phenolic group (Scheme VI). In contrast to the non-phenolic coupling of **7a-b**,[11] we did not observed the presence of phenyltetralin in the crude ^1H NMR spectrum, demonstrating the selective directing effect of the OH group towards the unique formation of the eight-membered ring structure. Unfortunately, the reagents studied afforded low yields of BBCOD, probably due to the steric overcrowding of meta-methoxy groups. $Cu(OAc)_2.H_2O$ was found to be ineffective for the biaryl coupling giving the acetate **30** as sole product (76% yield).

Scheme VI



27

28: R= H; R'= Me
29: R= Me; R'= H

Table III: Oxidative coupling of 27 in trifluoroacetic medium.[a]

oxidant (eq.)	time	product and yield[b] (%)	
		28	29
Tl_2O_3 (0.6)	2h	24	0
$RuO_2.2H_2O$ (2.5)	4h	30	9
V_2O_5 (5)	3h[c]	32	15

[a] CH_2Cl_2/TFA/TFAA/BF_3-Et_2O, T=20°C. [b] yield of isolated product. [c] ultra-sound.

Conclusion

We report that several, cheap commercially available metallic oxides and salts were found to be particularly efficient oxidants in the biaryl oxidative coupling of dibenzylbutanolides. The nature of the substituents on the aromatic rings has an important effect on the outcome of the reaction. When a methylenedioxy was present in one aromatic ring, Tl_2O_3 was found to be the most efficient, the other reagents giving large amount of tarry products. On the contrary, when only methoxy groups were present, Re_2O_7 and to a lesser extent V_2O_5 and $Cu(OAc)_2.H_2O$ were found the most effective. Finally, the oxidative coupling of a phenolic dibenzylbutane (i.e. **27**) afforded uniquely the BBCOD skeleton demonstrating the powerful directing effect of the OH group.

Experimental section

1a was prepared following reported procedure.[7] Most of the organic compounds and metallic salts used in this study were commercially available in very high purity. Dichloromethane was dried through a column of alumina and stored over 4-Å molecular sieves. All glassware was dried thoroughly in a drying oven and cooled in a desiccator containing P_2O_5 and silicagel. Melting points determined on a Reichert microscope are reported in °C (uncorrected). Infrared spectra (IR) were recorded on a FT Nicolet 5DX spectrophotometer or on a Beckman (acculab 2) spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 90, on a Brucker 300 or on a Brucker 500 spectrospin spectrometer using tetramethylsilane (Me_4Si) as internal standard, and $CDCl_3$ as solvent unless indicated otherwise. Mass spectra were obtained on a Varian Mat 311 spectrometer. Elemental analysis were performed by the analysis centre of CNRS in Lyon-Vernaison. Since the coupling reactions performed are all similar in many respects, typical reactions will be described as general method. The numbering used to describe NMR spectra of BBCOD **2a-b**, **28-29** has been indicated in Scheme I and Scheme VI respectively.

General coupling procedure for the preparation of (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 2a (method A). To a stir-

red suspension of Re_2O_7 (0.163 g; 0.33 mmol) in CH_2Cl_2 (5 ml), TFA (0.8 ml) [or $C_2F_5CO_2H$ (0.6 ml)] and TFAA (0.1 ml) [or $(C_2F_5CO)_2O$ (0.1 ml)], a solution of **1a** (0.05 g; 0.13 mmol) in CH_2Cl_2 (2 ml) was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.032 ml; 0.26 mmol). The mixture was stirred at room temperature (1h for TFA, 2h for $C_2F_5CO_2H$) and was treated by saturated $NaHCO_3$. The organic layer was decanted and the aqueous layer was extracted several times with CH_2Cl_2. The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under vacuum gave an oil which was chromatographed on silica gel (C_6H_{12}-EtOAc 8:2). Crystallization from CH_2Cl_2-Et_2O gave **2a** (TFA: 0.049 g; 98%. $C_2F_5CO_2H$: 0.048 g; 96%) as a white solid. The compound was found to be identical (mp, IR, ^1H NMR) with material described in literature: mp 204-205°C [lit.[1] mp 203-205°C]; IR ($CHCl_3$) 3530 (OH), 1770 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR δ 2.1-3.25 (m, 6H, aliphatic protons), 3.75 (m, 2H, H-13), 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4,34 (broad s, 1H, OH), 6.72 (s, 3H, aromatic protons), 6.87 (s, 1H, H-9).

Reaction of 1a with $Fe(OH)(OAc)_2$/TFA/TFAA/BF_3-Et_2O. To a stirred suspension of 0.513 g (2.7 mmol) of $Fe(OH)(OAc)_2$ in CH_2Cl_2 (10 ml), TFA (4 ml), TFAA (0.6 ml), a solution of 0.1 g (0.27 mmol) of **1a** in CH_2Cl_2 (2 ml) was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.07 ml; 0.54 mmol). The mixture was stirred at room temperature for 24h, then treated as above to give 0.08 g (72%) of **6** as a colorless oil: IR ($CHCl_3$) 1720 (C=O), 1590 (C=C) cm^{-1}; ^1H NMR δ 2.03-3.25 (m, 6H, aliphatic protons), 2.3 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.31 (m, 2H, H-13), 6.69 (s, 2H, aromatic protons), 6.76 (s, 1H, aromatic proton), 6.96 (s, 1H, H-9); MS m/e 412.15 (M^+); Anal. calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.86. Found: C, 66.85; H, 6.14.

(3R*,4R*)-3-(3-benzoxy-4-methoxybenzyl)-4-(3,4-methylenedioxybenzyl)-4,5-dihydro-2(3H)-furanone 5. To a stirred solution of 5.06 ml of n-BuLi (1.6 M in hexane) in dry THF (9 ml), 1.98 ml (9.38 mmol) of hexamethyldisilazane was added at -78°C. The resultant colorless solution was allowed to warm at -20°C for 15 mn and 1.474 g (6.7 mmol) of the lactone **3** in dry THF (9 ml) was added dropwise at -78°C. The colorless mixture was stirred for 1 h at -78°C and 10 mn at -30°C. Then, 2.06 g (6.7 mmol) of the bromide **4** in dry THF (8 ml) and 1.28 ml (7.34 mmol) of HMPA were slowly added at -78°C. The mixture was then allowed to warm to RT over 1 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 chromatographed on silica gel (CH_2Cl_2), affording 2.9 g (97%) as an oil **5**: IR ($CHCl_3$) 1760 (C=O), 1590 (C=C) cm^{-1}; ^1H NMR δ 2.40 (m, 4H, aliphatic protons), 2.70 (m, 2H, aliphatic protons), 3.86 (s, 3H, OCH_3), 3.90 (m, 2H, CH_2OCO), 5.13 (s, 2H, $ArC\underline{H}_2O$), 5.92 (s, 2H, OCH_2O), 6.41 (m, 2H, aromatic protons), 6.62 (m, 4H, aromatic protons), 7.40 (m, 5H, aromatic protons).

(3R*,4R*)-3-(3-hydroxy-4-methoxybenzyl)-4-(3,4-methylenedioxybenzyl)-4,5-dihydro-2(3H)-furanone 1b. 2.76 g (6.19 mmol) of **5** in a 100 ml solution of a 1:1 EtOAc:AcOH mixture were introduced in an hydrogenation flask and 0.55 g of 10% palladium on charcoal were added. The flask was placed in a Parr apparatus and flushed 10 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 an oil which was chromatographed on silica gel (C_6H_{12}-EtOAc 8:2) affording 1.8 g (82%) as an oil **1b**: IR ($CHCl_3$) 3510 (OH), 1750 (C=O), 1575 (C=C) cm^{-1}; ^1H NMR δ 2.47 (m, 4H, aliphatic protons), 2.89 (m, 2H, aliphatic protons), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, CH_2OCO), 5.69 (broad s, 1H, OH), 5.89 (s, 2H, OCH_2O), 6.41 (m, 2H, aromatic protons), 6.69 (m, 4H, aromatic protons).

General coupling procedure for the preparation of (M*,3aR*,13aR*)-3a,4,13,13a-tetrahydro-11-hydroxy-10-methoxy-6,7-methylenedioxydibenzo-[4,5:6,7]cycloocta[1,2-c] furan-1(3H)-one 2b (method B). To a stirred suspension of Tl_2O_3 (0.07 g; 0.15 mmol) in TFA (1 ml) [or $C_2F_5CO_2H$ (1 ml)] and BF_3-Et_2O (0.07 ml; 0.56 mmol), a solution of **1b** (0.1 g; 0.28 mmol) in TFA (0.7 ml) [or $C_2F_5CO_2H$ (0.7 ml)] was added quickly at 0°C under nitrogen. The mixture was stirred at 0°C (2mn for TFA, 5mn for $C_2F_5CO_2H$) and was treated as described above in method A to give **2b** (TFA: 0.064 g; 64%. $C_2F_5CO_2H$: 0.06g; 60%) as white needles recrystallized from ether: mp 142-144°C; IR ($CHCl_3$) 3515 (OH), 1770

(C=O), 1580 (C=C) cm^{-1}; ^1H NMR δ 2.11 (dd, 1H, J= 9.2 Hz, 13.2 Hz, H-7), 2.19 (m, 1H, H-6), 2.27 (dd, 1H, J= 9.4 Hz, 13.5 Hz, H-8α), 2.37 (dd, 1H, J= 9.4 Hz, 13.2 Hz, H-5β), 2.61 (d, 1H, J= 13.2 Hz, H-5α), 3.12 (d, 1H, J= 13.5 Hz, H-8β), 3.76 (dd, 1H, J= 8.5 Hz, 10.9 Hz, H-13β), 3.86 (s, 3H, OCH_3), 4.36 (dd, 1H, J= 6.5 Hz, 8.5 Hz, H-13α), 5.61 (s, 1H, OH), 5.98 (d, 1H, J= 1.4 Hz, OCH_2O), 6.00 (d, 1H, J= 1.4 Hz, OCH_2O), 6.64 (s, 1h, aromatic proton), 6.66 (s, 1H, aromatic proton), 6.67 (s, 1H, aromatic proton), 6.86 (s, 1H, H-9); ^{13}C NMR δ 31.77 (t, C-8), 34.25 (t, C-5), 47.00 (d, C-6), 50.01 (d, C-7), 56.08 (q, OCH_3), 69.98 (t, C-13), 101.26 (t, OCH_2O), 108.87 (d, C-4), 111.13 (d, C-1), 113.32 (d, C-12), 113.98 (d, C-9), 131.94 (s, C-12a), 132.31 (s, C-4a), 132.82 (s, C-8a), 133.60 (s, C-12b), 145.02 (s), 145.63 (s), 146.16 (s), 147.51 (s), 176.35 (s, C-15); MS m/e 354.1130 (M^+); Anal. calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.76; H, 5.25.

3-benzoxy-4-hydroxy-benzaldehyde 13. To a stirred solution of 1.652 g (0.04 mol) of 60% sodium hydride in anhydrous toluene (30 ml), a solution of 5.13 g (0.04 mol) of para-thiocresol in toluene (30 ml) was added under nitrogen. The mixture was stirred at room temperature for 30 mn, then a solution of 7.2 ml (0.04 mol) of HMPA in toluene (20 ml) was added very slowly. The suspension was stirred at room temperature for 20 mn, then a solution of 5 g (0.02 mol) of **12** in toluene (20 ml) was added dropwise. The mixture was heated under reflux for 5 h. After cooling, the resulting suspension was diluted with CH_2Cl_2, then the organic layer was extracted several times with 5% NaOH. The combined extracts were acidified with 6N HCl at 0°C, then extracted with CH_2Cl_2. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (C_6H_{12}-CH_2Cl_2 1:1) to give a white solid which was recrystallized from Et_2O-CH_2Cl_2 affording 2.44 g (52%) of pure **13**: mp 113-114°C [lit.[17] mp 112-113°C]; IR ($CHCl_3$) 3510 (OH), 1675 (C=O) cm^{-1}; ^1H NMR δ 5.05 (s, 2H, Ar$\underline{CH_2}$O), 6.39 (broad s, 1H, OH), 6.88 (d, 1H, H-5), 7.25 (m, 7H, aromatic protons), 9.58 (s, 1H, CHO).

3-benzoxy-5-bromo-4-hydroxybenzaldehyde 15. To a stirred solution of **13** (10 g; 0.044 mol) in acetic acid (60 ml), bromine (2.5 ml; 0.048 mol) was added dropwise at room temperature. The mixture was stirred for 1h then, was poured in ice-cold water (200 ml). The precipitated solid was filtered, washed with water and recrystallized from ethanol to give **15** (11.4 g; 85%) as white crystals: mp 159-160°C; IR ($CHCl_3$) 3000, 1684 (C=O) cm^{-1}; ^1H NMR (DMSO) δ 5.25 (s, 2H, Ar$\underline{CH_2}$O), 7.42 (m, 6H, aromatic protons), 7.68 (d, 1H, H-6), 9.74 (s, 1H, CHO); Anal. calcd for $C_{14}H_{11}O_3Br$: C, 54.71; H, 3.58; Br, 26.08. Found: C, 54.60; H, 3.69; Br, 25.77.

3-benzoxy-4-hydroxy-5-methoxybenzaldehyde 19. To 7.5 g (0.326 mol) of sodium were added under nitrogen at room temperature 80 ml of freshly distilled methanol. After complete disparition of the sodium, methanol was evaporated under reduced pressure. Then, a solution of 10 g (0.032 mol) of **15** in dimethylformamide (40 ml) and 1.72 g (0.013 mol) of $CuCl_2$ were added under nitrogen. The flask was kept under reflux for 2h. After cooling, the mixture was diluted with water (200 ml) and acidified with 6N HCl at 0°C. After filtration of mineral salts, the solution was extracted several times with CH_2Cl_2. The combined extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated to give an oil which was chromatographed on silica gel (CH_2Cl_2-C_6H_{12} 8:2). Crystallization from ether gave 5.8 g (69%) of pure **19** as white crystals: mp 113-114°C; IR ($CHCl_3$) 3000, 1680 (C=O) cm^{-1}; ^1H NMR δ 3.91 (s, 3H, OCH_3), 5.15 (s, 2H, Ar$\underline{CH_2}$O), 6.36 (broad s, 1H, OH), 7.10 (d, 1H, aromatic proton), 7.14 (d, 1H, aromatic proton), 7.37 (m, 5H, aromatic protons), 9.71 (s, 1H, CHO); Anal. calcd for $C_{15}H_{14}O_4$: C, 69.78; H, 5.43. Found: C, 69.70; H, 5.49.

3-benzoxy-4,5-dimethoxybenzaldehyde 16. First method: to a stirred solution of 10 g (0.039 mol) of **19** in acetone (55 ml), 5.13 g (0.048 mol) of Na_2CO_3 and 4.03 ml (0.043 mol) of Me_2SO_4 were added. The mixture was heated under reflux for 3h. After evaporation of the solvent, the residue was poured into a 2M NaOH solution. The aqueous layer was extracted several times with CH_2Cl_2. The combined extracts were washed successively with saturated brine, water and dried over $MgSO_4$. The solvent was evaporated to give a brown oil which was chromatographed on silica gel (CH_2Cl_2), affording 8.5 g (81%) of **16**. Recrystallization from ether gave **16** as pale yellow crystals: mp 50-51°C; IR ($CHCl_3$) 3000, 1686 (C=O)

cm^{-1}; ^1H NMR δ 3.80 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.07 (s, 2H, $ArC\underline{H}_2O$), 7.04 (d, 1H, H-6), 7.10 (d, 1H, H-2), 7.33 (m, 5H, aromatic protons), 9.73 (s, 1H, CHO); ^{13}C NMR δ 56.10 (q, OCH_3(5)), 60.83 (q, OCH_3(4)), 71.11 (t, C-7'), 106.63 (d, C-6), 109.00 (d, C-2), 127.41 (d, C-2', C-6'), 128.07 (d, C-4'), 128.59 (d, C-3', C-5'), 131.74 (s, C-1), 136.54 (s, C-1'), 144.26 (s, C-4), 152.70 (s, C-3), 153.85 (s, C-5), 190.78 (d, CHO); Anal. calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.37; H, 6.01.

Second method: to a stirred solution of 1.66 g (0.009 mol) of **18** in absolute ethanol (10 ml) were added 1.385 g (0.01 mol) of potassium carbonate and 0.06 g (0.36 mmol) of potassium iodide. Then, 1.23 ml (0.01 mol) of freshly distilled benzyl chloride were added dropwise and the resulting suspension was stirred under reflux for 2h. The mixture was then allowed to warm to RT and water (50 ml) was added. After evaporation of ethanol in vacuo, the solution was poured into a 2M NaOH solution (30 ml). The aqueous layer was extracted several times with CH_2Cl_2. The combined extracts were treated as described above to give 2.3 g (93%) of pure **16**.

(E)-3-(3-benzoxy-4,5-dimethoxy-benzylidene)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone 21. To a stirred suspension of 1.86 g (0.046 mol) of 60% sodium hydride in anhydrous toluene (50 ml), a solution of 8.245 g (0.031 mol) of lactone **20** and 9.28 g (0.034 mol) of benzaldehyde **16** in toluene (50 ml) was added at 0°C under nitrogen, then 0.2 ml (4.93 mmol) of methanol were added dropwise. The mixture was stirred vigorously at 0°C until no evolution of H_2 was observed, and was stirred for 4 hours at RT. The resulting mixture was acidified with 6N HCl. The aqueous layer was extracted with CH_2Cl_2 and the resulting extracts were washed with saturated brine, water and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil which was chromatographed on silica gel (C_6H_{12}-EtOAc 8:2), affording 8.7 g (54%) of pure **21** as an oil: IR ($CHCl_3$) 3000, 1650, 1425, 1135 cm^{-1}; ^1H NMR δ 2.44-3.13 (m, 3H, aliphatic protons), 3.77 (s, 6H, 2 OCH_3), 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.23 (m, 2H, H-9), 5.13 (s, 2H, $ArC\underline{H}_2O$), 6.51 (s, 2H, H-2, H-6), 6.83 (d, 2H, H-2', H-6'), 7.35 (m, 6H, aromatic protons, vinylic proton); Anal. calcd for $C_{30}H_{32}O_8$: C, 69.22; H, 6.19; O, 24.59. Found: C, 69.63; H, 6.07; O, 24.30.

(3S*,4R*)-3-(3,4-dimethoxy-5-hydroxybenzyl)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone 22. 7.2 g (13.8 mmol) of **21** in a solution of 7:3 EtOAc-AcOH (50 ml) were introduced in an hydrogenation flask and 1.1 g of 10% palladium on charcoal were added. The flask was placed in a Parr apparatus and flushed 10 times with hydrogen. The suspension was stirred overnight under H_2 pressure (50 psi) at room temperature. Then, the catalyst was removed by careful filtration and the solvent was evaporated in vacuo. The residue was chromatographed on silica (C_6H_{12}-EtOAc 8:2) to give 5.5 g (92%) of **22**: IR ($CHCl_3$) 3000, 1640, 1130 cm^{-1}; ^1H NMR δ 2.26-3.52 (m, 6H, aliphatic protons), 3.90 (m, 15H, 5 OCH_3), 4.15 (s, 2H, H-9), 6.37 (s, 2H, H-2, H-6), 6.50 (s, 1H, aromatic proton), 6.67 (s, 1H, aromatic proton); Anal. calcd for $C_{23}H_{28}O_3$: C, 63.88; H, 6.52. Found: C, 63.44; H, 6:53.

(3R*,4R*)-3-(3-benzoxy-4,5-dimethoxybenzyl)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone 23. To a stirred solution of 3.63 g (8.4 mmol) of **22** in absolute ethanol (50 ml), 1.28 g (9.24 mmol) of potassium carbonate and 0.06 g (0.33 mmol) of potassium iodide were added. Then, 1.2 ml (10.08 mmol) of freshly distilled benzyl chloride were added dropwise and the resulting suspension was stirred under reflux for 1h. The mixture was then allowed to warm to room temperature and water (50 ml) was added. After concentration in vacuo, the mixture was kept by 2N NaOH (50 ml). The aqueous layer was extracted several times with CH_2Cl_2. The combined extracts were washed with saturated brine, water and dried ($MgSO_4$). The solvent was removed in vacuo yielding an oil which was chromatographed on silica (CH_2Cl_2-C_6H_{12} 8:2) to give 3.6 g (82%) of pure **23**: IR ($CHCl_3$) 3000, 1635, 1130 cm^{-1}; ^1H NMR δ 2.47 (m, 4H, H-7, H-7'), 2.89 (m, 2H, H-8, H-8'), 3.81 (m, 15H, 5 OCH_3), 4.11 (m, 2H, H-9), 5.10 (s, 2H, $ArC\underline{H}_2O$), 6.25 (s, 2H, H-2, H-6), 6.45 (m, 2H, H-2', H-6'), 7.37 (m, 5H, aromatic protons). Anal. calcd for $C_{30}H_{34}O_8$: C, 68.95; H, 6.56. Found: C, 69.00; H, 6:63.

(2R*,3R*)-2,3-dihydroxymethyl-1-(3-benzoxy-4,5-dimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-butane 24. To a stirred solution of 2.64 g (5 mmol) of **23** in ethanol (70 ml), a mixture of 0.73 g (6.5 mmol)

calcium chloride and 0.4 g (10.75 mmol) of sodium borohydride were added in small portions. The mixture was stirred at room temperature for 1h then acidified with 6N HCl (30 ml) at 0°C. After evaporation of ethanol under vacuum, the aqueous mixture was extracted several times with CH_2Cl_2. The combined extracts were washed with saturated brine, water and dried over $MgSO_4$. Concentration under vacuum gave a brown oil which was chromatographed on silica (CH_2Cl_2-C_6H_{12} 8:2), affording 2 g (75%) of pure **24**: IR ($CHCl_3$) 3020, 1539, 1218, 1061 cm^{-1}; ^1H NMR δ 1.97 (m, 2H, tertiary protons), 2.68 (m, 4H, 2 ArC$\underline{H}_2$), 3.52 (m, 2H, C$\underline{H}_2$O), 3.82 (m, 15H, 5 OCH_3), 4.05 (m, 2H, CH_2O), 5.14 (s, 2H, ArC$\underline{H}_2$O), 6.43 (s, 4H, aromatic protons), 7.43 (m, 5H, aromatic protons); Anal. calcd for $C_{30}H_{38}O_8$: C, 68.42; H, 7.26. Found: C, 68.40; H, 7.16.

(2R*,3R*)-2,3-bis(methanesulfonylmethyl)-1-(3-benzoxy-4,5-dimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-butane 25. To a stirred solution of 1.54 g (2.93 mmol) of **24** in 80 ml of dry pyridine at 0°C, 1.36 ml (17.6 mmol) of methanesulfonyl chloride was added dropwise under nitrogen. The solution was stirred for 4 hours at 0°C then ice was introduced into the solution. The resulting mixture was carefully acidified with 6N HCl then extracted 3 times with CH_2Cl_2. The combined extracts were washed with saturated brine, water and dried over $MgSO_4$. Concentration in vacuo gave an oil which was chromatographed on silica (CH_2Cl_2). Crystallization from ether gave 1.9 g (95%) of **25** as white crystals: mp 141-142°C; IR ($CHCl_3$) 3010, 1590 (C=C), 1510, 1180 cm^{-1}; ^1H NMR δ 2.15-2.79 (m, 6H, aliphatic protons), 2.94 (s, 3H, CH_3SO_3), 2.98 (s, 3H, CH_3SO_3), 3.81 (m, 15H, 5 OCH_3), 4.21 (m, 4H, CH_2O), 5.10 (s, 2H, ArC$\underline{H}_2$O), 6.35 (m, 4H, aromatic protons), 7.37 (m, 5H, aromatic protons); Anal. calcd for $C_{32}H_{42}O_{12}S_2$: C, 56.29; H, 6.19; S, 9.39. Found: C, 56.36; H, 6.04; S, 9.12.

(2R*,3R*)-2,3-dimethyl-1-(3-benzoxy-4,5-dimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-butane 26. To a stirred suspension of 1.52 g (2.23 mmol) of **25** in tetrahydrofuran (20 ml) at 0°C, 13.4 ml (13.4 mmol) of lithium triethylborohydride (1M solution in THF) was added dropwise under nitrogen. The solution was stirred at room temperature overnight. Then, 10 ml of water were carefully added at 0°C and the solution was stirred for 15 minutes at 0°C. 20 ml of a 3M NaOH solution and 20 ml of a 33% H_2O_2 solution were successively introduced and the mixture was stirred for 20 minutes. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with saturated brine, water and dried ($MgSO_4$). The solvent was removed in vacuo affording 1 g (91 %) of **26** as a colorless oil: IR ($CHCl_3$) 3010, 1590 (C=C), 1510, 1420, 1130 cm^{-1}; ^1H NMR δ 0.85 (m, 6H, 2 CH_3), 1.64 (m, 2H, tertiary protons), 2.37 (m, 4H, 2 ArC$\underline{H}_2$), 3.78 (m, 15H, 5 OCH_3), 5,00 (s, 2H, ArC$\underline{H}_2$O), 6.11 (s, 3H, aromatic protons), 6.26 (s, 1H, aromatic proton), 7.43 (m, 5H, aromatic protons).

(2R*,3R*)-2,3-dimethyl-1-(3,4-dimethoxy-5-hydroxyphenyl)-4-(3,4,5-trimethoxyphenyl)-butane 27. 0.66 g (1.33 mmol) of **26** in acetic acid (30 ml) was introduced in an hydrogenation flask and 0.12 g of 10% palladium on charcoal was added. The flask was placed in a Parr apparatus and flushed 10 times with hydrogen. The suspension was stirred overnight under H_2 pressure (50 psi) at room temperature. Then, the catalyst was removed by careful filtration and the solvent was evaporated in vacuo. The residue was chromatographed on silica (CH_2Cl_2-C_6H_{12} 8:2) to give 0.49 g (91%) of colorless oily **27**: IR ($CHCl_3$) 2940, 1590 (C=C), 1460, 1130 cm^{-1}; ^1H NMR δ 0.80 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.77 (m, 2H, tertiary protons), 2.43 (m, 4H, 2 ArC$\underline{H}_2$), 3.81 (m, 15H, 5 OCH_3), 5.97 (broad s, 1H, OH), 6.15 (d, 1H, J= 2.0 Hz, aromatic proton), 6.28 (s, 2H, aromatic protons), 6.35 (d, 1H, J= 2.0 Hz, aromatic proton); Anal. calcd for $C_{23}H_{32}O_6$: C, 68.30; H, 7.97. Found: C, 68.22; H, 8.34.

General coupling procedure for oxidation of 27. The oxidation of **27** was carried out by using the procedure already described for the compound **1a** (method A). To a stirred suspension of V_2O_5 (0.285 g; 1.55 mmol) in CH_2Cl_2 (10 ml), TFA (2.3 ml) and TFAA (0.5 ml), a solution of **27** (0.125 g; 0.31 mmol) in CH_2Cl_2 (5 ml) was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.08 ml; 0.62 mmol). The mixture was stirred at room temperature with ultra-sonic assistance for 3 days and was treated as described above in method A to give **28** (0.04 g; 32%) and **29** (0.019 g; 15%) as colorless oils. **28**: IR ($CHCl_3$) 2930, 1585 (C=C), 1460, 1230 cm^{-1}; ^1H NMR δ 1.00 (d, 3H, J= 6 Hz, CH_3), 1.02 (d, 3H, J= 6 Hz,

CH_3), 1.23 (m, 2H, H-6, H-7), 2.05 and 2.15 (2d, 2H, J= 10.2 Hz, axial H-5, axial H-8), 2.28 and 2.32 (2d, 2H, J= 13.0 Hz, equatorial H-5, equatorial H-8), 3.58 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.88 (s, 6H, 2 OCH_3), 3.91 (s, 3H, OCH_3), 5.71 (s, 1H, OH), 6.55 (s, 1H, H-9), 6.63 (s, 1H, H-4). **29**: IR ($CHCl_3$) 2940, 1580 (C=C), 1460, 1215 cm^{-1}; ^1H NMR δ 1.04 (d, 6H, J= 6.2 Hz, 2 CH_3), 2.14 (m, 2H, H-6, H-7), 2.32 and 2.33 (2d, 2H, J= 13.2 Hz, equatorial H-5, equatorial H-8), 3.67 (s, 3H, OCH_3(12)), 3.88 (s, 6H, 2 OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.90 (s, 1H, OH), 6.39 (s, 1H, axial H-5), 6.59 (s, 1H, H-9).

Reaction of 27 with $Cu(OAc)_2.H_2O$ / TFA / TFAA / BF_3-Et_2O. To a stirred suspension of 0.308 g (1.55 mmol) of $Cu(OAc)_2.H_2O$ in CH_2Cl_2 (10 ml), TFA (2.3 ml), TFAA (0.5 ml), a solution of 0.125 g (0.31 mmol) of **27** in CH_2Cl_2 (2 ml) was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.08 ml; 0.62 mmol). The mixture was stirred at room temperature for 45 mn. The work-up was carried out as before in method A to give 0.105 g (76%) of **30** as a colorless oil: IR ($CHCl_3$) 2940, 1760 (C=O), 1680, 1460 cm^{-1}; ^1H NMR δ 0.80 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.54 (m, 1H, tertiary proton), 1.94 (m, 1H, tertiary proton), 2.30 (s, 3H, $COCH_3$), 2.23-2.63 (m, 4H, 2 $ArCH_2$), 3.81 (m, 15H, 5 OCH_3), 6.25-6.56 (m, 4H, aromatic protons).

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