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Ruthenium Dioxide in Fluoro Acid Medium V. Application to the Non Phenolic Oxidative Coupling of Diarylbutanes.[1] Conformational Studies of cis and trans Deoxyschizandrins.

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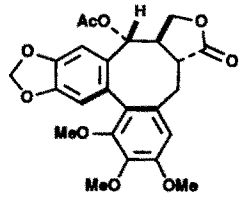
Abstract : *Ruthenium (IV) dioxide dihydrate in fluoro acidic medium was found to be a very efficient agent for the non phenolic oxidative coupling of diarylbutanes. We observed along with the expected aryl-aryl coupling, an unusual aryl-benzyl coupling, leading to a known class of lignans, the aryltetralins. Conformational studies of resultant cis and trans deoxy-schizandrins were performed using high resolution NMR and molecular models.*

We have shown in previous report that oxidative coupling of substituted dibenzylbutanolides, using $RuO_2,2H_2O$ in fluoro acidic medium led to the formation of the bisbenzocyclooctadiene (BBCOD) lactone skeleton in good yields.[1,2] Naturally occuring bisbenzocyclooctadienes as steganes (e.g. steganacin **1**), schizandrin **2a** and gomisin **2b** have attracted considerable synthetic interests, due to their wide range of biological activities[3,4] (scheme I). Thus, We reinvestigated the non phenolic coupling of diarylbutanes **4a-c**,[5] precursors of schizandrin analogs **3a-e**,[4] by using the ruthenium procedure (Scheme II).



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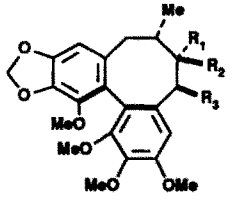
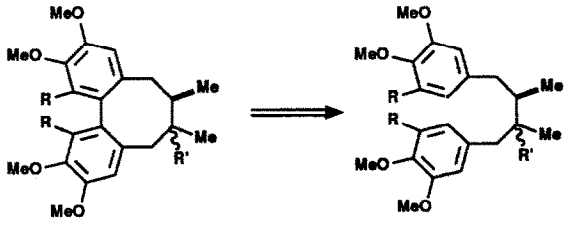


2a, R_1= Me; R_2= OH; R_3= H

2b, R_1= OH; R_2= Me; R_3= O_2CAr

Scheme I



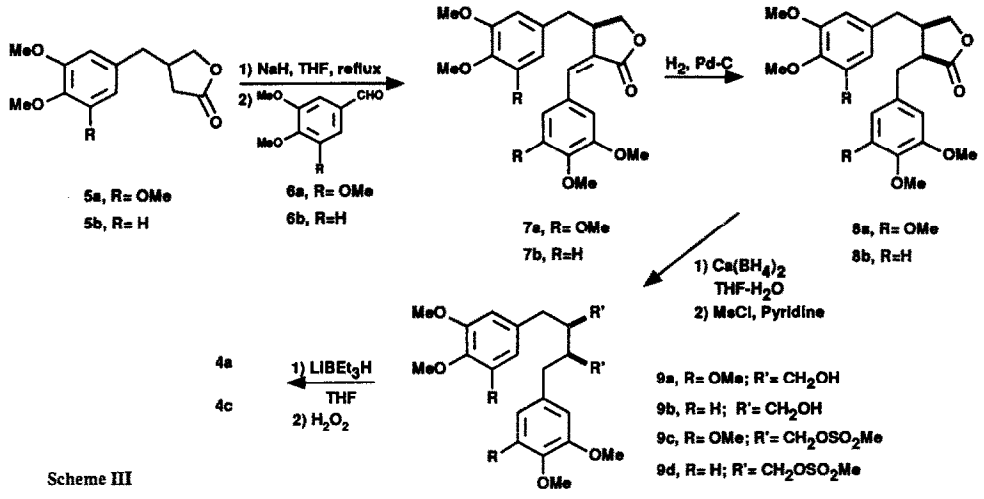
3a, R= OMe; R'= H_α
3b, R= OMe; R'= H_β
3c, R= H; R'= H_α
3d, R= H; R'= H_β

4a, R= OMe; R'= H_α
4b, R= OMe; R'= H_β
4c, R= H; R'= H_α
4d, R= H; R'= H_β

Scheme II

Synthesis of diarylbutanes precursors **4a-c**

Synthesis of precursors was based on a Stobbe condensation of lactones **5a-b** with substituted aldehydes **6a-b** to give (E)-3-benzyl-2-benzylidene-4-butanolides **7a-b** in 60-70% yield.[1b] The lactones were reduced by catalytic hydrogenation with 10% Pd-C, affording exclusively *cis*-lactones **8a-b**, which were converted in dimethyl derivatives using a three-steps sequence: reduction of **8a-b** with $Ca(BH_4)_2$ in THF-H_2O gave the diols **9a-b**. Mesylation followed by reduction with $LiBEt_3H$ and oxidation with H_2O_2[7] gave the precursors **4a** and **4c** in 73 and 53% overall yield respectively (from **7a-b**) (scheme III). *Trans* precursor **4b** has been synthetized using two different procedures, starting in both cases from cordigerine **10**.[1b,6] This latter was prepared either by a simple isomerization of *cis*-dibenzylbutanolide **8a**, followed by lactonic ring closure, or by alkylation of lactone **5a** with 3,4,5-trimethoxybenzyl bromide.[1b] Conversion of **10** into **4b** was carried out as illustrated in scheme IV, via the diol **11a** and its mesylate **11b**.



5a, R= OMe
5b, R= H

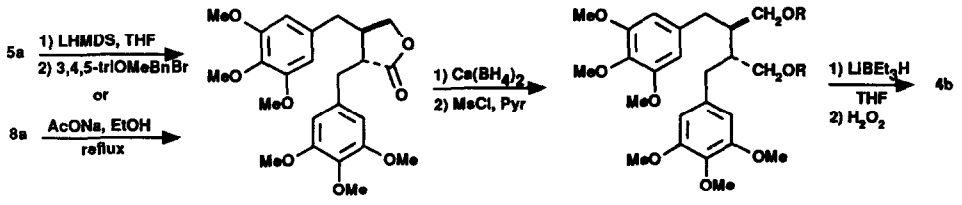
6a, R= OMe
6b, R=H

7a, R= OMe
7b, R=H

8a, R= OMe
8b, R=H

9a, R= OMe; R'= CH_2OH
9b, R= H; R'= CH_2OH
9c, R= OMe; R'= CH_2OSO_2Me
9d, R= H; R'= CH_2OSO_2Me

Scheme III



10

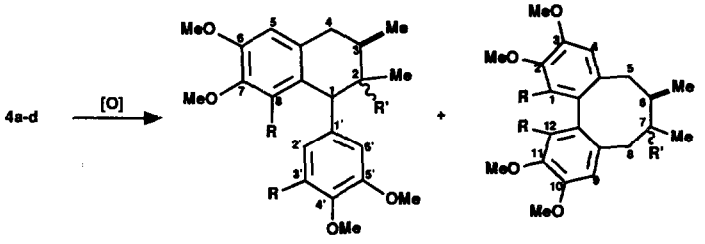
11a, R=H

11b, R=O_2SMe

Scheme IV

Oxidative coupling of diarylbutanes **4a-c**

Cis and *trans* dimethyldiarylbutanes **4a-c** were submitted to oxidative conditions summarized in table I. The reaction was complete after several hours (8-17h) at room temperature with $RuO_2,2H_2O$ and only a few minutes with TTFA. Surprisingly, TLC and NMR showed that two major products were formed, the ratio depending on the structure of precursors. A carefull study of 500 MHz ^1H NMR spectra showed that bisbenzocyclooctadiene skeletons **3a-b**[5] were produced in all cases (^1H NMR, mp, and IR identical with those reported in literature[4,5]), accompanied with aryltetralins **12a-c**, in 75-85% overall yields (scheme V).



12a, R= OMe; R'= H_α

12b, R= OMe; R'= H_β

12c, R= H; R'= H_α

12d, R= H; R'= H_β

3a, R= OMe; R'= H_α

3b, R= OMe; R'= H_β

3c, R= H; R'= H_α

3d, R= H; R'= H_β

Scheme V

The major NMR features exhibited by **12a-b**, including a high-field OMe-8 signal and 3 aromatic protons, instead of 2 for the corresponding BBCOD, proved without any ambiguities, that unknown compounds in oxidative coupling of **4a** and **4b** possess an aryltetralin skeleton such as **12a**[5a,8] and **12b**.[5a] In the same way, oxidative coupling of the *cis* derivative **4c** afforded BBCOD **3c**[5a] and aryltetralin **12c**.[9] Studies of molecular models and 500 MHz ^1H NMR, followed by comparison with the structure of aryltetralins described in the literature,[5,8,9] allowed us to report the following relative stereochemistry for **12a-c** (scheme VI).

Table I. Oxidative coupling of diarylbutanes 4a-c.

Starting material	Products	Conditions	Time h	Yield[a] %	ratio[b] BBCOD/aryltet
4a	3a + 12a	A[c]	8	83	50 : 50
4a	3a + 12a	B[d]	8	87	50 : 50
4a	3a + 12a	C[e]	0.5	80	60 : 40
4b	3b + 12b	A	8	80	55 : 45[g]
4b	3b + 12b	B[f]	8	78	45 : 55[g]
4b	3b + 12b	C	0.5	75	60 : 40
4c	3c + 12c	A	17	82	75 : 25

[a] Overall yield (BBCOD + aryltetraline).

[b] Ratio calculated from integration of ^{1}H NMR (500 MHz) of the mixture.

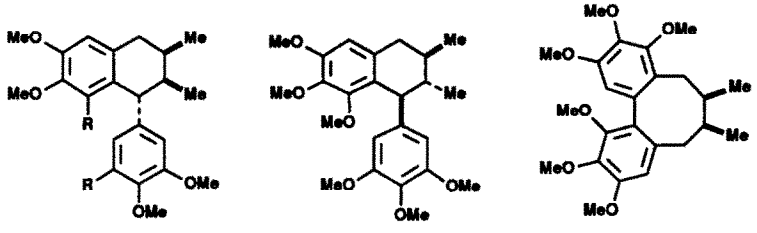
[c] A: RuO_2, $2H_2O$ (2eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T= 18-20°C.

[d] B: RuO_2, $2H_2O$ (1.4 eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, Ultra-sound, T= 18-20°C.

[e] C: Tl_2O_3 (0.54 eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T=18-20°C.

[f] Procedure B was followed using 2 eq. of RuO_2, $2H_2O$ instead of 1.4 eq.

[g] Included the two conformers.

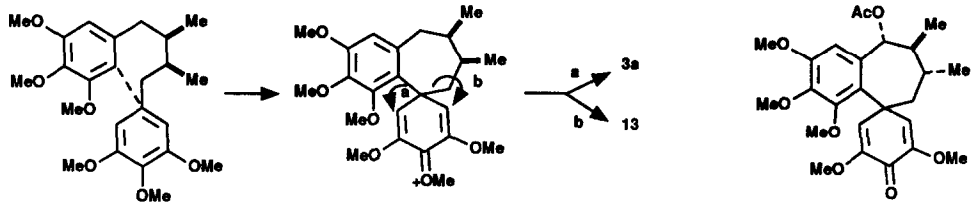


12a, R= OMe 12b 13

12c, R= H

Scheme VI

It is noteworthy that oxidative coupling of precursor **4a** gave, along with **3a** and **12a**, a minor product, with only one high-field methoxyl signal, which was assumed to be the BBCOD **13**, an isomer of deoxyschizandrin **3a**. The presence of this BBCOD can be explained by a mechanism involving an hypothetical spirodienone **14**. This hypothesis comes from the observed rearrangement of eupodienones (e.g. eupodienone **15** isolated from *Eupomatia laurina*)[10] which were presented as possible precursors of schizandrin **2a** and analogs (scheme VII).



4a 14 Scheme VII 15

In an opposite way, oxidative coupling of *trans* precursor **4b** gave, along with **3b** and **12b**, a minor product identified as a stable conformer of BBCOD **3b**. Unfortunately, we have been unable to purify this compound, but its structure has been assigned without any ambiguities from 500 MHz ^{1}H NMR spectrum of the reaction mixture. The complete structure of these different BBCOD will be presented further in this paper. No regioisomer such as **13** were isolated in the *trans* series.

The presence of aryltetralines **12a-c** as the result of the oxidative coupling of diarylbutanes gives rise to two hypothesis:

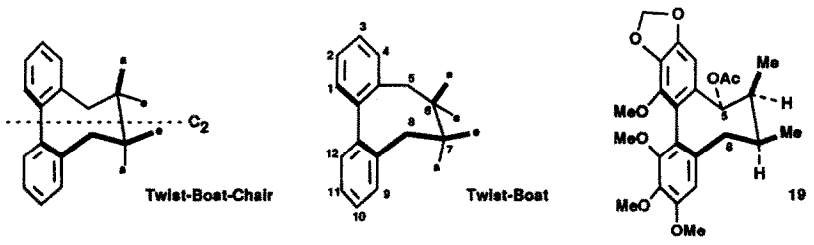
- previously, in presence of a lactone ring, aryl-benzyl coupling was prohibited because of ring strain.[1,2] In this series, aryl-benzyl coupling are more favoured.
- the two bulky methoxyls *"ortho"* to the biaryl bond are unfavourable to aryl-aryl coupling.

During oxidative coupling of phenolic and non phenolic dibenzylbutanolides, we have never detected any trace of aryltetralin lactones.[11] These observations support the first hypothesis of a particular conformation of the transition state, imposed by the lactonic ring. Influence of steric effects of methoxyles in 3' and 8 was checked by oxidative coupling of *cis* precursor **4c**, which gave a 3:1 mixture of BBCOD **3c**[5a] and isogalbuline **12c**[9] respectively, instead of the 1:1 ratio described with models **4a** and **4b**, confirming the second hypothesis.[12] The same result has been observed by Cambie and Coll[13] with *trans* isomer **4d**, using TTFA as oxidant. We also noted independently, that whatever the oxidants used, $RuO_2,2H_2O$ or TTFA, the ratio of products were identical.

The results discussed above allow us to assume that unexpected formation of aryltetralin skeleton is presumably due to the combined effects of the absence of a lactonic ring, and the presence of methoxyl groups in 3' and 8 in the precursor structures (Scheme V).

Conformational studies of Cis and Trans deoxyschizandrins.

Relatively few studies have been carried out about conformations of bisbenzocyclooctadiene skeletons.[5b,14] Among them, the pioneering work of K. Mislow et al,[14a] and more recently, the study of Ghera and co-workers[14b] have shown that BBCOD ring could exist as two stable conformers named twist-boat (TB) and twist-boat-chair (TBC) (this one possess a two-fold axis) (scheme VIII). Empirical force-field calculations[14c] showed that the most stable conformation of simple bisbenzocyclooctadiene was the TBC form with a TB form 2.8 kcal/mol higher in energy. In natural products field, a crystallographic study of kadsurine **19** and analogs also clearly demonstrated that the TBC form was the most stable, except when the structure possess a carbonyl in C-5 or C-8.[14b]



Scheme VIII

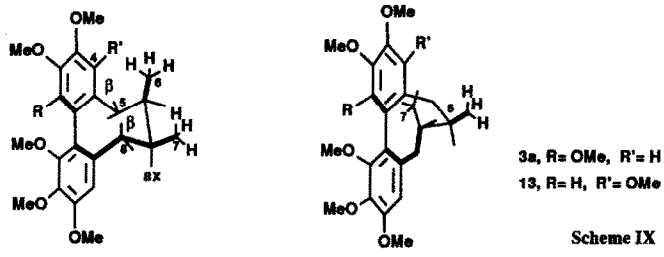
TB and TBC conformations associated with a possible *"cis-trans"* stereochemistry lead to numerous conformers and isomers. We can distinguish two cases:

- If aromatic rings are differently substituted, we can expect (in racemic series): 4 *cis* 6,7-dimethyl BBCOD conformers: (6a,7e) TB, (6e,7a) TB, (6a,7e) TBC, and (6e,7a) TBC and 4 *trans* conformers: (6a,7a) TB, (6e,7e) TB, (6a,7a) TBC, and (6e,7e) TBC.

- If two aromatic rings have the same substituents, we can expect 4 *trans* BBCOD as above, but only 2 *cis*: (6a,7e) TB and (6a,7e) TBC due to the *"meso"* configuration of the C-6 and C-7 stereogenic centres.

* *Conformational studies of cis BBCOD (3a and 13)*

Referring to what was summarized before, oxidative coupling of diarylbutanes **4a** should have produced 2 *cis* BBCOD. In fact, we observed only formation of deoxyshizandrin **3a** which had identical NMR data with those described in the literature.[4,5] A prominent feature in ^{1}H NMR 500 MHz of **3a** is the shielding effect of aromatic ring on methyl 6 (δ= 0.74 ppm), which is only possible if Me-6 is axial (and therefore Me-7 equatorial). This leads to H-8β undergoing steric compression from Me-6, and hence to a deshielding effect on this proton (δ= 2.28 ppm). This allow us to assign a (6a,7e) TBC for **3a**, as reported before in the literature.[5b] Using this assignment, we were able to state that **13** is also a (6a,7e), since there is only one high shielded methoxyl (OMe-4) instead of two, and an observed deshielding effect on proton H-5β (table II), the remaining chemical shifts being very close of those of **3a**. TB conformer was turned down, due to important interactions between Me-7 (axial) and the aromatic ring (scheme IX).



Scheme IX

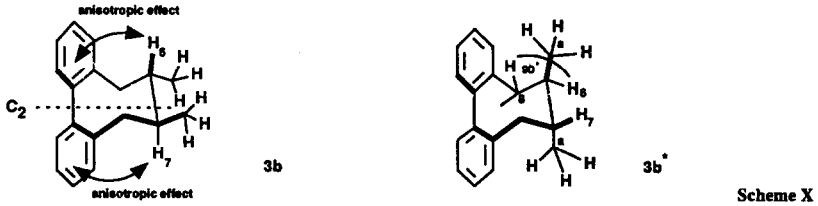
* *Conformational studies of trans BBCOD (3b and 3b*)*

Theoretically, 4 *trans* BBCOD could be formed during oxidation of precursor **4b**, but only two were detected. The major BBCOD **3b** presents only half of a ^{1}H NMR spectrum of one phenyl propane moiety, due to a two-fold axis, observable only in *trans* series (scheme X). Methyls Me-6 and Me-7 give rise to a single doublet at 1.05 ppm, typical of equatorial methyls. Moreover, protons H-6 and H-7 are strongly shielded (1.26 ppm) compared to H-6 and H-7 in **3a**, (table II), due to anisotropic effect of aromatic rings.

Table II. 500MHz ^{1}H NMR spectral data of bisbenzocyclooctadiene dimethyl lignans.

	H-5α	H-5β	H-8α	H-8β	H-6	H-7	Me-6	Me-7	OMe-1	OMe-12
3a	2.50	2.59	2.06	2.28	1.81	1.91	0.74(a)	1.00(e)	3.59	3.60
13	2.10	3.09	2.05	2.33	1.92	1.79	0.78(a)	0.99(e)	/	3.47
3b	2.34	2.17	2.17	2.34	1.26	1.26	1.05(e)	1.05(e)	3.64	3.64
3b*	2.53		2.53				0.86(a)	0.86(a)	3.57	3.57
	(a): axial (e): equatorial									

These observations are in favour of a (e,e) TBC structure,[5b] TB conformers being excluded due to their instability ((a,a) TB have two methyls too close to aromatic rings) (scheme X).



Scheme X

Oxidative coupling of **4b** afforded together with BBCOD **3b**, a minor BBCOD **3b*** which structure was assigned from the reaction mixture ^{1}H NMR (mixture of **3b** and **3b*** only). We noted a coupling constant J= 0 at 2.53 ppm. This observation allowed us to eliminate (e,e) TB conformation which does not possess such a feature. Thermodynamical reasons also exclude diaxial (a,a) TB for the reason given before. As summarized in table II, methyls 6 and 7 have a chemical shift located at 0.86 ppm, between expected axial and equatorial chemical shifts. Molecular models show that, by twisting around the C-6-C-7 bond until there is a 90° dihedral angle between H-6-C-C-H-8β, methyls become equivalent and fit perfectly with ^{1}H NMR datas. This small torsion probably appears when the molecule takes an average conformation in solution, explaining the differences noted between NMR spectrum and molecular models, allowing us to propose a (a,a) TBC structure for **3b*** (scheme X).

We found again what was observed in lactonic bisbenzocyclooctadiene series.[15] Oxidative biaryl coupling lead preferentially to rigid molecules such as *"iso"* compounds in lactonic series (e.g. neoisostegane)[2a] and to *"twist-boat-chair"* compounds in non lactonic series (e.g. deoxyschizandrin **3a**). Our results confirm those obtained by Cambie et al,[13] who performed an X-ray analysis on BBCOD **3d**, assuming an *"isostegane-like"* (TBC) conformation for **3d**, instead of a *"stegane-like"* (TB) reported by Tobinaga et al[5b] for similar analog **3b**.

Similar results have been published recently by Cameron and co-workers,[14d] who studied the configuration of *trans* dibenzodibromocyclooctadiene by ^{1}H NMR and X-ray analysis. They have shown that the (e,e) TBC was the predominant one, in opposition with MMP2-(85)[16] force-field predictions which proposed a (a,a) TBC form as stable conformation.

Conclusion

The results summarized in table I illustrate the efficiency and the applicability of the ruthenium procedure. However, none of the reagents used have been able to produce exclusively the expected BBCOD. Use of suitable phenolic precursors (OH in *"meta"* position) should overcome this problem of regioselectivity.[17]

Experimental

Most of the organic compounds used in this study were commercial products of very high purity. $RuO_2,2H_2O$, Tl_2O_3, Trifluoroacetic acid and anhydride were used without purifications. 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. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 90 or on a Brucker 500 spectrospin spectrometer using as internal standard tetramethylsilane (Me_4Si), and $CDCl_3$ as solvent unless indicated otherwise. Mass spectra were obtained on a Varian Mat 311 spectrometer. Elemental analysis were performed by analysis centre of CNRS in Lyon-Vernaison. The compounds **5a**, **7a** and **8a** have been prepared using reported procedures.[1b] Since the reactions performed are all similar in many respects, typical reactions will be described as specific examples.

(E) 3-(3,4-dimethoxy-benzylidene)-4-(3,4-dimethoxybenzyl)-4,5-dihydro-(3H)-furanone (7b). To a stirred suspension of 1.52 g (63.5 mmol) of NaH in anhydrous toluene (25 ml) was introduced, under nitrogen at 0°C, a solution of 10 g (42 mmol) of lactone **5b** and 7 g (42 mmol) of **6b** in toluene (70 ml), then were added 0.17 ml (0.42 mmol) 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 saturated brine, water, and dried ($MgSO_4$). The solvent was evaporated *in vacuo* yielding an orange oil which crystallize slowly from ether to give 6.3 g (40%) of **7b**: mp 129-131°C (Ether); IR (nujol) 1735 (C=O), 1635, 1580 (C=C), and 1445 cm^{-1}; ^1H NMR δ 2.66 (dd, 1H, J= 15 Hz, and J= 10.5 Hz, benzylic proton), 3.10 (dd, 1H, J= 15 Hz, and J= 3.8 Hz, benzylic proton), 3.85 (m, 1H, aliphatic proton), 3.85 (s, 6H, OCH_3), 3.90 (s, 6H, OCH_3), 4.31 (m, 2H, CH_2OCO), 6.38 (m, 3H, aromatic protons), 6.83 (m, 3H, aromatic protons), 7.48 (d, 1H, J= 1.5 Hz, vinylic proton). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.75; H, 6.25; O, 25.00. Found: C, 68.67; H, 6.13.

(3S*,4R*)-3-(3,4-dimethoxybenzyl)-4-(3,4-dimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (8b). 15.7 g (40.9 mmol) of **7b** in a solution of acetic acid (150 ml) were introduced in an hydrogenation flask and 1.9 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 evaporated *in vacuo*. The residue was crystallized from ether to give 11.6 g (73%) of lactone **8b** as white crystals: mp 99-101°C (Ether); IR ($CHCl_3$) 1750 (C=O), 1580 (C=C), 1500 and 1440 cm^{-1}; ^1H NMR δ 2.0-3.5 (m, 6H, aliphatic protons), 3.80 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 3.86 (s, 6H, OCH_3), 4.03 (d, 2H, J= 3Hz, CH_2OCO), 6.52-6.81 (m, 6H, aromatic protons). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.39; H, 6.74; O, 24.87. Found: C, 68.46; H, 6.64.

General procedure for the preparation of diols from lactones. (2R*,3S*)-2,3-dihydroxymethyl-1,4-bis-(3,4,5-trimethoxyphenyl)butane (9a). To a stirred solution of 5 g (11.2 mmol) of lactone **8a** in ethanol (150 ml) was added, at room temperature, 1.6 g (14.4 mmol) of powdered $CaCl_2$, then

portionwise 0.91 g (24 mmol) of $NaBH_4$. The mixture was stirred at room temperature for 15 minutes, the temperature being maintained at 30°C. The suspension was cooled to 0°C and HCl 6N (40 ml) was added dropwise. Ethanol was then evaporated *in vacuo* and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with saturated brine, dried over $MgSO_4$, then evaporated to give a colorless oil which crystallize on standing in ether, affording 4.2 g (83%) of diol **9a** as white crystals: mp 124-127°C (Ether); IR (nujol) 1580 (C=C), 1330, 1230, 1115, and 1035 cm^{-1}; ^1H NMR δ 1.88-2.27 (m, 2H, aliphatic protons), 2.47-2.80 (m, 4H, benzylic protons), 3.48-3.68 (m, 4H, CH_2OH), 3.78 (s, 20H, OCH_3 and OH), 6.38 (s, 4H, aromatic protons). Anal. Calcd for $C_{24}H_{34}O_8$: C, 64.00; H, 7.56; O, 28.44. Found: C, 63.64; H, 7.59.

(2R*,3S*)-2,3-dihydroxymethyl-1,4-bis-(3,4-dimethoxyphenyl)butane (9b). As described above, 7,5 g (82%) of the diol **9b** were obtained as colorless crystals: mp 88-92°C (Ether); ^1H NMR δ 1.82-2.21 (m, 2H, aliphatic protons), 2.48-2.81 (m, 4H, benzylic protons), 3.54 (m, 4H, CH_2OH), 3.70 (s, 6H, OCH_3), 3.73 (s, 6H, OCH_3), 6.61-6.94 (m, 6H, aromatic protons).

General procedure for the preparation of mesylates from diols. (2R*,3S*)-2,3-(methylsulfonyloxymethyl)-1,4-bis-(3,4,5-trimethoxyphenyl)butane (9c). To a solution of 3.5 g (7.8 mmol) of diol **9a** in dry pyridine (30 ml) was added dropwise at 0°C, 4.9 ml (46.7 mmol) of methanesulfonyl chloride. The mixture was stirred for 20 minutes at 0°C, then poured into crushed ice and extracted with CH_2Cl_2. The combined extracts were washed with 1N HCl, saturated brine, dried over $MgSO_4$ and evaporated *in vacuo* to give 4.3 g (91%) of the bis-mesylate **9c** as a white solid: mp 184-185°C (Ether); IR ($CHCl_3$) 1580 (C=C), 1420, 1330, 1200, and 1120 cm^{-1}; ^1H NMR δ 2.11-2.58 (m, 2H, aliphatic protons), 2.58-2.91 (m, 4H, benzylic protons), 3.01 (s, 6H, CH_3SO_2), 3.83 (s, 18H, OCH_3), 4.29 (m, 4H, CH_2O), 6.39 (s, 4H, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_{12}S_2$: C, 51.48; H, 6.27; O, 31.68; S, 10.56. Found: C, 51.64; H, 6.21; O, 31.50.

(2R*,3S*)-2,3-(methanesulfonyloxymethyl)-1,4-bis-(3,4-dimethoxyphenyl)butane (9d). As described above, 10.3 g (98%) of the bis-mesylate **9d** were obtained as a white solid: mp 140-145°C (Ether); IR ($CHCl_3$) 1500 (C=C), 1410, 1335, and 1200 cm^{-1}; ^1H NMR δ 2.10-3.0 (m, 6H, benzylic and aliphatic protons), 2.95 (s, 6H, CH_3SO_2), 3.84 (s, 12H, OCH_3), 4.56 (d, 4H, J= 3Hz, CH_2O), 6.63-6.89 (s, 6H, aromatic protons).

(3R*,4R*)-3-(3,4,5-trimethoxybenzyl)-4-(3,4,5-trimethoxybenzyl)-4,5-dihydro-2(3H)-furanone (10). 12 g (27 mmol) of the lactone **8a** in a mixture of EtOH and H_2O (3/4) (200 ml) were treated with powdered sodium acetate (12 g) and the mixture was refluxed for 2 days. The resulting solution was poured into water (300 ml) and acidified with 1N HCl (pH 3). The aqueous layer was then extracted with CH_2Cl_2 (3 x 100 ml). The combined extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil which crystallized on standing in ether to afford 11.64 g (97%) of (+/-)-cordigerine **10** identical in many respect with the one prepared before.[1b]

(2R*,3R*)-2,3-dihydroxymethyl-1,4-bis-(3,4,5-trimethoxyphenyl)butane (11a). Following the general procedure, 3.5 g (87%) of the diol **11a** were obtained as colorless crystals: mp 145-147°C (Ether); IR (nujol) 1580 (C=C), 1330, 1175, 1120 and 1030 cm^{-1}; ^1H NMR δ 1.69-2.22 (m, 2H, aliphatic protons), 2.49-2.89 (m, 4H, benzylic protons), 3.08-3.72 (m, 4H, CH_2OH), 3.78 (s, 18H, OCH_3), 6.34 (s, 4H, aromatic protons). Anal. Calcd for $C_{24}H_{34}O_8$: C, 64.00; H, 7.56; O, 28.44. Found: C, 63.84; H, 7.52.

(2R*,3R*)-2,3-(methanesulfonyloxymethyl)-1,4-bis-(3,4,5-trimethoxyphenyl)butane (11b). Following the general procedure, 2.4 g (89%) of the bis-mesylate **11b** were obtained as white crystals: mp 195-197°C (Ether); IR ($CHCl_3$) 1580 (C=C), 1420, 1335, and 1120 cm^{-1}; ^1H NMR δ 2.11-2.51 (m, 2H, aliphatic protons), 2.51-2.91 (m, 4H, benzylic protons), 2.97 (s, 6H, CH_3SO_2), 3.83 (s, 18H, OCH_3), 4.30 (m, 4H, CH_2O), 6.39 (s, 4H, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_{12}S_2$: C, 51.48; H, 6.27; O, 31.68; S, 10.56.

Found: C, 51.31; H, 6.07; O, 31.86.

General procedure for the preparation of diarylbutanes from bis-mesylates. (2R*,3S*)-2,3-dimethyl-1,4-bis-(3,4,5-trimethoxyphenyl)butane (4a). To a solution of 3.5 g (5.78 mmol) of bis-mesylate **9c** in anhydrous THF (10 ml) was added dropwise at 0°C, 34.6 ml (34.6 mmol) of a 1 M solution of $LiBEt_3$ in THF. The mixture was then allowed to warm to room temperature and was stirred for 1 hour. Water (20 ml) was then added slowly and the mixture was stirred for 10 minutes. A 3M NaOH solution (40 ml) and 33% H_2O_2 (40 ml) were added successively at 0°C and the mixture was stirred for 15 minutes. The organic layer was decanted and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated to give 2.4 g (98%) of the diarylbutane **4a**: mp 115-117°C (Ether)[lit.[5a] mp 87-89°C (MeOH)] ; IR ($CHCl_3$) 1580 (C=C), 1410, 1320, 1200, and 1120 cm^{-1}; ^1H NMR δ 0.89 (d, 6H, J= 6Hz, CH_3), 1.55-2.07 (m, 2H, aliphatic protons), 2.07-2.29 (m, 4H, benzylic protons), 3.82 (s, 18H, OCH_3), 6.35 (s, 4H, aromatic protons). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.90; H, 8.13; O, 22.97. Found: C, 68.91; H, 8.13.

(2R*,3R*)-2,3-dimethyl-1,4-bis-(3,4,5-trimethoxyphenyl)butane (4b). As described above, 0.9 g (87%) of the diarylbutane **4b** were obtained as white crystals: mp 127-129°C (Ether); IR ($CHCl_3$) 1580 (C=C), 1490, 1420, and 1115 cm^{-1}; ^1H NMR δ 0.86 (d, 6H, J= 6Hz, CH_3), 1.52-2.08 (m, 2H, aliphatic protons), 2.08-2.74 (m, 4H, benzylic protons), 3.80 (s, 18H, OCH_3), 6.28 (s, 4H, aromatic protons). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.90; H, 8.13; O, 22.97. Found: C, 69.02; H, 8.21.

(2R*,3S*)-2,3-dimethyl-1,4-bis-(3,4-dimethoxyphenyl)butane (4c). As described above, 0.77 g (90%) of the diarylbutane **4c** were obtained as white crystals: mp 101-102°C (Ether); IR ($CHCl_3$) 1590 (C=C), 1480, 1410, and 1120 cm^{-1}; ^1H NMR δ 0.88 (d, 6H, J= 6Hz, CH_3), 1.50-2.0 (m, 2H, aliphatic protons), 2.10-3.0 (m, 4H, benzylic protons), 3.83 (s, 12H, OCH_3), 6.61-6.87 (m, 6H, aromatic protons).

General procedure for the oxidative coupling of the diarylbutanes 4a-c following method A (table I). Oxidative coupling of 4a. To a stirred suspension of 0.127 g (0.96 mmol) of $RuO_2,2H_2O$ in anhydrous CH_2Cl_2 (20 ml), TFA (1 ml), and TFAA (0.5 ml), were added at -10°C, a solution of 0.2 g (0.48 mmol) of **4a** in CH_2Cl_2 (15 ml), then immmediately BF_3-Et_2O (0.2 ml). The mixture was stirred vigorously at room temperature for 8 h and the mixture was treated with a 5% $NaHCO_3$ solution. The organic layer was decanted and the aqueous layer extracted with CH_2Cl_2. The combined extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated *in vacuo*, to give after filtration through silica gel (Toluene-EtOAc 9:1) a colorless oil (0.166 g, 83%) which was chromatographied on preparative TLC (Cyclohexane-EtOAc 95:5 → 7:3) affording respectively deoxyschizandrin **3a** (50 mg, 25%): mp 114-115°C (Ether-petroleum ether)[lit.[5a] mp 114-115°C (MeOH)]; IR ($CHCl_3$) 1599 (C=C),and 1581 cm^{-1}; ^1H NMR δ 0.74 (d, 3H, J= 7.1 Hz, CH_3-6_{ax}), 1.00 (d, 3H, J= 7.2 Hz, CH_3-7_{eq}), 1.81 (m, 1H, H-7), 1.91 (m, 1H, H-6), 2.06 (d, 1H, J= 13.1 Hz, H-8α), 2.28 (dd, 1H, J= 9.6 Hz, 13.2 Hz, H-8β), 2.50 (dd, 1H, J= 1.8 Hz, 13.6 Hz, H-5α), 2.59 (dd, 1H, J= 7.4 Hz, 13.6 Hz, H-5β), 3.59 and 3.60 (2s, 6H, OCH_3-1 and OCH_3-12), 3.88 (s, 3H, OCH_3), 3.89 (s, 6H, 2 x OCH_3), 3.90 (s, 3H, OCH_3), 6.54 (s, 1H, aromatic proton), 6.55 (s, 1H, aromatic proton), BBCOD **13** (5 mg, 2.5%): mp 146-148°C (MeOH-ether); IR ($CHCl_3$) 1597 (C=C), and 1577 cm^{-1}; ^1H NMR δ 0.78 (d, 3H, J= 7.1 Hz, CH_3-6_{ax}), 0.99 (d, 3H, J= 7.1 Hz, CH_3-7_{eq}), 1.79 (m, 1H, H-7), 1.92 (m, 1H, H-6), 2.05 (dd, 1H, J= 1.2 Hz, 13.2 Hz, H-8α), 2.10 (dd, 1H, J= 1.4 Hz, 13.8 Hz, H-5α), 2.33 (dd, 1H, J= 9.6 Hz, 13.2 Hz, H-8β), 3.09 (dd, 1H, J= 8.2 Hz, 13.8 Hz, H-5β), 3.47 (s, 3H, OCH_3-12), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.54 (s, 1H, aromatic proton), 6.55 (s, 1H, aromatic proton) and aryltetraline **12a** (70 mg, 35%): mp 103-105°C (Hexane)[lit.[5a] mp 105-107°C (Hexane)]; IR ($CHCl_3$) 1599 (C=C), 1591, and 1346 cm^{-1}; ^1H NMR δ 0.92 (d, 3H, J= 6 Hz, CH_3-3), 0.98 (d, 3H, J= 7 Hz, CH_3-2), 1.65-2.15 (m, 2H, H-2 and H-3), 2.30-2.95 (m, 2H, H-4α and H-4β), 3.38 (s, 3H, OCH_3-8), 3.76 (s, 6H, 2 x OCH_3), 3.82 (s, 6H, 2 x OCH_3), 3.88 (s, 3H, OCH_3), 4.00 (d, 1H, J= 3 Hz, H-1), 6.22 (s, 2H, H-2' and H-6'), 6.48 (s, 1H, H-5).

Oxidative coupling of 4b (Method A, table I). As described above, the oxidation of **4b** gave a colorless oil (0.16 g, 80%) chromatographied on preparative TLC (Cyclohexane-EtOAc 95:5 → 7:3) affording respectively BBCOD **3b** (70 mg, 35%): mp 123-126°C (Ether-petroleum ether)[lit.[5b] mp 129-131°C (MeOH)]; IR ($CHCl_3$) 1595 (C=C), and 1580 cm^{-1}; ^1H NMR δ 1.05 (d, 6H, J= 6.3 Hz, CH_3-6_{eq} and CH_3-7_{eq}), 1.26 (m, 2H, H-6 and H-7), 2.17 (dd, 2H, J= 10.2 Hz, 13.3 Hz, H-5β and H-8α), 2.34 (d, 2H, J= 13.1 Hz, H-5α and H-8β), 3.64 (s, 6H, OCH_3-1 and OCH_3-12), 3.89 (s, 6H, 2 x OCH_3), 3.90 (s, 6H, 2 x OCH_3), 6.57 (s, 2H, H-4 and H-9)(Found: $\underline{M}^+$, 416.2199. $C_{24}H_{32}O_6$ requires $\underline{M}$, 416.21987), aryltetraline **12b** (60 mg, 30%): mp 134-136°C (Ether)[lit.[5a] mp 136-137°C (MeOH)]; IR ($CHCl_3$) 1591 (C=C), and 1059 cm^{-1}; ^1H NMR δ 1.02 (d, 3H, J= 5.5 Hz, CH_3-2), 1.03 (d, 3H, J= 5.5 Hz, CH_3-3), 1.38 (m, 1H, H-2), 1.45 (m, 1H, H-3), 2.59 (dd, 1H, J= 11.5 Hz, 15 Hz, H-4β), 2.64 (dd, 1H, J= 4 Hz, 15 Hz, H-4α), 3.08 (s, 3H, OCH_3-8), 3.56 (d, 1H, J= 9 Hz, H-1), 3.72 (s, 3H, OCH_3), 3.78 (s, 6H, 2 x OCH_3), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.32 (s, 2H, H-2' and H-6'), 6.41 (s, 1H, H-5)(Found: $\underline{M}^+$, 416.2199. $C_{24}H_{32}O_6$ requires $\underline{M}$, 416.21987), and BBCOD **3b*** which NMR datas have been obtained from the reaction mixture: ^1H NMR δ 0.86 (d, 6H, J= 7.2 Hz, CH_3-6_{ax} and CH_3-7_{ax}), 2.53 (d, 2H, J= 13.5 Hz, H-5α and H-8β), 3.57 (s, 6H, OCH_3-1 and OCH_3-12), 3.88 (s, 6H, 2 x OCH_3), 3.89 (s, 6H, 2 x OCH_3), 6.53 (s, 2H, H-4 and H-9).

Oxidative coupling of 4c (Method A, table I). As described for **4a**, the oxidation of **4c** gave after chromatography on preparative TLC (Cyclohexane-EtOAc 95:5 → 8:2) respectively BBCOD **3c**[5a] (91 mg, 61%) as an oil: IR ($CHCl_3$) 1590 (C=C) cm^{-1}; ^1H NMR δ 0.81 (d, 3H, J= 6.7 Hz, CH_{3ax}), 1.05 (d, 3H, J= 6.7 Hz, CH_{3eq}), 1.70-2.0 (m, 2H, H-6 and H-7), 2.10-2.70 (m, 4H, H-5α, H-5β, H-8α and H-8β), 3.87 (s, 6H, 2 x OCH_3), 3.92 (s, 6H, 2 x OCH_3), 6.72 (s, 4H, aromatic protons), and isogalbuline **12c**[9] as an oil (31 mg, 21%): IR ($CHCl_3$) 1593 (C=C) cm^{-1}; ^1H NMR δ 0.91 (d, 6H, J= 6.7 Hz, 2 x CH_3), 1.80-2.90 (m, 4H, H-2, H-3, H-4α and H-4β), 3.67 (s, 3H, OCH_3), 3.80 (s, 3H, 2 x OCH_3), 3.87 (s, 6H, 2 x OCH_3), 4.08 (d, 1H, J~ 4 Hz, H-1), 6.35-6.90 (m, 5H, aromatic protons).

General procedure for the oxidative coupling of the diarylbutanes 4a-b following method B (table I). Oxidative coupling of 4a. In a 50 ml two necked round bottom flask equipped with a septum and an inlet for argon, was placed 45 mg (0.34 mmol) of RuO_2,$2H_2O$ in anhydrous CH_2Cl_2 (2.5 ml), TFA (5 ml), and TFAA (2.5 ml). Then, 0.1 g (0.24 mmol) of **4a** in CH_2Cl_2 (2.5 ml) were added dropwise at -10°C, followed immmediately by BF_3-Et_2O (0.2 ml). The flask was immerged in an ultra sound bath (water), thermostated at 18°C (±2°C) and the mixture was stirred for 8 h. The suspension was treated at 0°C with a 5% $NaHCO_3$ solution and the products were isolated as above, affording respectively deoxyschizandrin **3a** (30 mg, 30%) and aryltetraline **12a** (35 mg, 35%). We have not been able to isolate, in this case, the BBCOD **13**, although it was present in the mixture (^1H NMR). Compounds **3a** and **12c** were found to be identical (mp, IR, ^1H NMR) with those prepared with method A.

BBCOD **3b** and aryltetraline **12b** were prepared from **4b** according to the same procedure (listed in table I). These compounds were found to be identical (mp, IR, ^1H NMR) with those prepared with method A.

General procedure for the oxidative coupling of the diarylbutanes 4a-b following method C (table I). Oxidative coupling of 4a. In a 50 ml two necked round bottom flask equipped with a septum and an inlet for argon, was placed 60 mg (0.13 mmol) of Tl_2O_3 in anhydrous CH_2Cl_2 (4 ml), TFA (0.5 ml), and TFAA (0.25 ml). Then, 0.1 g (0.24 mmol) of **4a** in CH_2Cl_2 (3 ml) were added dropwise at -10°C, followed immmediately by BF_3-Et_2O (0.1 ml). Then, the mixture was stirred for 30 minutes. The suspension was treated at 0°C with a 5% $NaHCO_3$ solution and the products were isolated as above, affording respectively deoxyschizandrin **3a** (51 mg, 51%) and aryltetraline **12a** (34 mg, 34%). Compounds **3a** and **12a** were found to be identical (mp, IR, ^1H NMR) with those prepared with method A.

BBCOD **3b** and aryltetraline **12b** were prepared from **4b** according to the same procedure (listed in table I). These compounds were found to be identical (mp, IR, ^1H NMR) with those prepared with method A.

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