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SYNTHESIS OF DIARYLBUTANES FROM CORDIGERINES AND REINVESTIGATION OF THEIR OXIDATIVE COUPLINGS IN DEOXYSCHIZANDRINS. - AN UNUSUAL FORMATION OF PHENYLTETRALIN LIGNANS -

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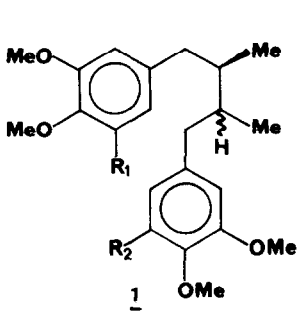
Abstract: Dibenzylbutanolide lignans including cordigerines were synthetized and transformed in the corresponding diarylbutane lignans which were submitted to non-phenolic oxidative coupling conditions by using RuO_2 or Tl_2O_3 in trifluoroacetic medium to give deoxyschizandrins. A concurrently aryl-benzyl coupling leads to the formation of the corresponding phenyltetralin of which the structure was confirmed by total synthesis.

We have recently found that ruthenium dioxide in trifluoroacetic acid is the most efficient described medium in **non-phenolic** biaryl oxidative coupling applied to the synthesis of bioactive bridged biaryls, including lignans and alkaloids.[1] The present work describes a new application of Ru(IV) to the biomimetic oxidative coupling of **2,3-dimethyl-1,4-diphenylbutanes** 1 to give **deoxyschizandrins** (DOS) 2 and, surprinsingly, the corresponding **phenyltetralins** 3.



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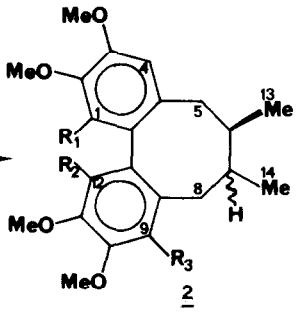

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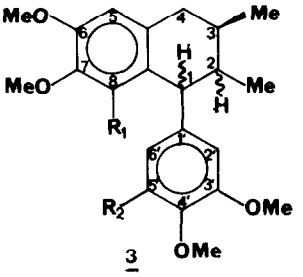


3

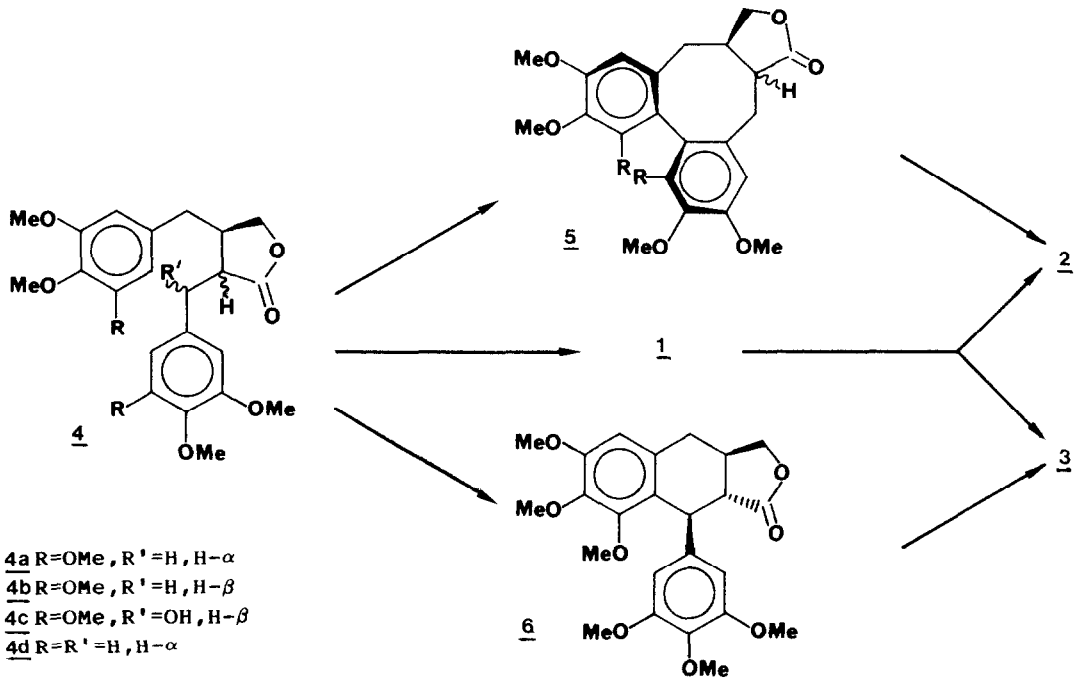
1a R_1, R_2=OMe, H-2α
1b R_1, R_2=OMe, H-2β
1c R_1, R_2=H, H-2α

2a R_1, R_2=OMe; R_3=H, H-2α
2b R_1, R_2=OMe; R_3=H, H-2β
2c R_1, R_2, R_3=H, H-2α
2d R_1, R_3=OMe; R_2=H, H-2α

3a R_1, R_2=OMe, H-2α, H-1β
3b R_1, R_2=OMe, H-2β, H-1α
3c R_1, R_2=H, H-2α, H-1β

Thus, meso-(2R*,3S*)-**1a**, and (2R*,3R*)-**1b** were prepared by using the following sequence: (E)-3-benzyl-2-benzylidene-4-butanolide was hydrogenated to give the corresponding cis saturated lactone **4a** as previously described.[1c] The latter was isomerized (AcONa/EtOH, reflux, 24h; HCl 10%) in the more stable trans-dibenzylbutanolide **4b** named cordigerine,[2] a lignan recently isolated from Hernandia cordigera.[3a]

Alternatively, alkylation of the anion of 3-(3,4,5-trimethoxybenzyl)-4-butanolide with 3,4,5-trimethoxybenzyl bromide ($LiN(SiMe_3)_2$/THF-HMPA, -80°C, 2h), gave also **4b** in 63% yield, mp 92-93°C (ether).[3b] Reduction of **4a** and **4b**, by using calcium borohydride in aqueous medium (30°C, 30 min) gave the corresponding crude diols (85% yield) which were subsequently reduced in diarylbutanes **1a** and **1b** in 91% and 77% yields respectively, via the corresponding bismesylates (MsCl/pyridine, 0°C, 1h; $LiBEt_3H$/THF, 20°C, 1h; H_2O_2).



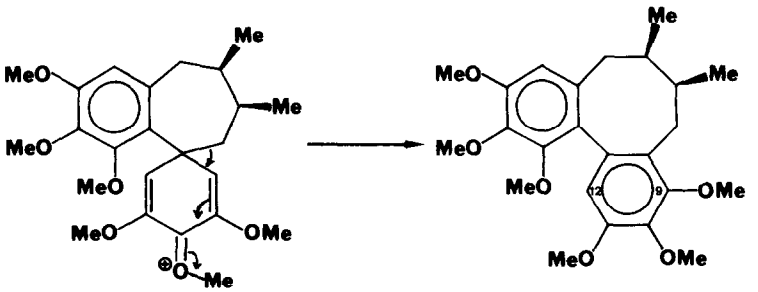
4a R=OMe, R'=H, H-α
4b R=OMe, R'=H, H-β
4c R=OMe, R'=OH, H-β
4d R=R'=H, H-α

According to our preceding approach, the above open precursors were submitted to oxidative coupling by using comparatively Ru(IV) and Tl(III);[4] table exhibits the high efficiency of RuO_2 versus the best known agents.[5]

Entry	Substrate	Product	Conditions[a]	Time	Yield %	R[b]
1	**1a**	**2a** + **3a**	A	8 h	83	50/50
2	**1a**	**2a** + **3a**	B	7.5 h	87	50/50
3	**1b**	**2b** + **3b**	A	8 h	80[c]	55/45
4	**1b**	**2b** + **3b**	B[d]	8 h	78[c]	43/57
5	**1c**	**2c** + **3c**	A	17 h	82	75/25
6	**1a**	**2a** + **3a**	C	35 min	80	60/40
7	**1b**	**2b** + **3b**	C	35 min	75[c]	60/40
8	**1a**	**2a**	D	1 h	9	-
9	**1a**	**2a**	E	2 min	32	-
10	**1b**	**2b**	D	1 h	9	-

TABLE: Comparative coupling conditions of diarylbutanes
[a](A) 1.6 Eq RuO_2, TFA/TFAA/BF_3-Et_2O, 20°C; (B) 1.1 Eq RuO_2, TFA/TFAA/BF_3-Et_2O, 20°C, ultra-sounds; (C) 0.54 Eq Tl_2O_3, TFA/TFAA/BF_3-Et_2O, 20°C; (D) VOF_3, CH_2Cl_2/TFA, -78° ⟶ 20°C;[4] (E) [$FeCl_2$ $(AC_2O)_2$] ($FeCl_4$).[4] [b]DOS/aryltetralin; [c]including both the trans-diastereoisomers; [d]1.6 Eq/RuO_2, instead 1.1 Eq.

The coupling of the meso-diarylbutane 1a gave a diastereoisomeric mixture which after careful chromatography afforded several compounds of which spectroscopic data were consistent with DOS. First, is together identical to the natural DOS 2a[6] and to our compound obtained by a stereospecific way.[1c] Second, is a highly crystalline compound of which the presence of two aromatic hydrogens H-2' and H-6' in PMR indicated the absence of biaryl bond, only one of its six methoxyls bearing a high-field shift. Carefully examination of aliphatic part leads to confirm the structure of cis-aryltetralin 3a.[7] Third 2d is a minor by-product closely related to 2a, which exhibits surprising features in high-field PMR (500 MHz): identical aliphatic coupling constants but one of the H-8 protons very low-field shifted (0.5 ppm) and only one of its six methoxyls high-field shifted in the place of two in 2a. Like neoisostegane and steganolide A, this compound bears a methoxyl in C-9 in the place of C-12,[1a] the methyl of the former being in contact with H-8β. Particular rearrangement of the spirodienone 7 intermediate resulting from radical ion formation was presumed.[8] Concurrently, coupling of the trans-butane 1b gave a diastereoisomeric mixture of DOS 2b accompagned with the corresponding all trans-phenyltetralin 3b[7,9] as in the cis-series. After chromatography the mixture gave several compounds; first was one of the two possible trans-A and trans-B stereoisomers as formely established by K. Mislow,[10] second was a minor diastereoisomer and was studied as a mixture in high-resolution PMR. These closely related trans-isomers bear in PMR a half-spectrum of only one phenyl propane moiety, indicating their symetrical substitution and a two-fold axis.[11] On the other hand, a sample of raccordigerine[3] was directly coupled into the corresponding bisbenzocyclooctadiene lactone (M*,6R*,7R*)-5 by using the same above conditions (RuO_2, TFA/TFAA) in 93 % yield. Reduction of 5 into diol, followed by mesylation and reduction gave a unic isomer of trans-DOS, identical to the major trans-stereoisomer resulting from the preceding coupling of 1b.[4]



7 2d

In order to confirm unambiguously the structure of the phenyltetralin 3b, a short synthetic sequence was performed. Hydroxyalkylation of 3-(3,4,5-trimethoxybenzyl)-4-butanolide by 3,4,5-trimethoxybenzaldehyde ($LiN(Si(CH_3)_3)_2/C_6H_5CH_3$, -10°C, 20 min) gave 4c as an epimeric mixture. Cyclisation ($HClO_4/CH_2Cl_2$, 20°C, 20 min)[12a] led to the isodeoxypodophyllotoxin analogue 6[12b] of which the lactone was reduced to the corresponding dimethyl ($Ca(BH_4)_2/H_2O$-EtOH, 30°C, 20 min; MsCl/pyridine; $LiBEt_3H$/THF, 20°C, 1h) in 40% overall yield, identical to the above phenyltetralin 3b.

So, the present result indicates good performances for Ru(IV) versus others known oxidative coupling agents. However none of these catalysts were able to induce regioselective coupling of diarylbutanes.[13] Whereas no such aryl-benzyl couplings were pointed out in all the dibenzylbutanolides we have coupled in the same conditions. Steric hindrance of the methoxyls in the ortho-position of the biaryl bond and the absence of locking of the position of the benzyl substituents by the lactone ring were proposed to explain the poor regiospecificity of the butane coupling. Moreover, in order to

verify the importance of the steric hindrance, the tetramethoxybutane **1c** was readily synthetized by above similar reduction of cis-di-O-methylmatairesinol. Finally, oxidative coupling of the latter[7] (see table) gave **2c** and only 25% of the corresponding phenyltetralin **3c**[14] confirming the influence of the bulkiness of the methoxyls.[15,16]

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15. Since, no phenyltetralin had been yet found together with schizandrins in higher plants, the present mechanism is not really biogenetic. Regio and stereospecific couplings of suitably substituted phenolic diarylbutanes are in progress in our laboratory.
16. Similar conclusions were drawn in an independent work performed on a related series. Dr. P. Craw (Edmonton, Canada), personal communication.

Acknowledgments

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