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RUTHENIUM(IV) TETRAKIS(TRIFLUOROACETATE), A NEW OXIDIZING AGENT. II. A NEW ACCESS TO SCHIZANDRINS SKELETON USING BIARYL OXIDATIVE COUPLING OF CIS-SUBSTITUTED BUTANOLIDES[1]

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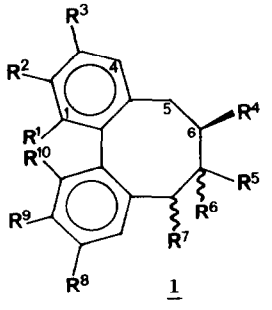
The use of the title reagent -RUTFA- was applied to the first stereospecific synthesis of bridged biaryl lactones from the corresponding cis-2,3-dibenzyl- and 3-benzyl-2-benzyliden- butanolides, respectively. A short reduction sequence afforded deoxyschizandrin and formation of gomisins K was established.

During the course of our synthetic work on bisbenzocyclooctadiene lignan lactones related to steganacin and its congeners, we found a new efficient oxidative biaryl coupling reagent based on ruthenium(IV).[1,2] This same reaction performed on many examples of trans-dibenzylbutanolides systematically gave better results (90-100% yield) than the known oxidant thallium(III) tris(trifluoroacetate) -TTFA- developped by MacKillop (60-80% yield).[3]

Schizandrins, gomisins, kadsurins, wuweizisus and schizantherins (skeleton **1** R^4 = R^5 = Me, R^6-α) belong to bisbenzocyclooctadiene lignans -a new class of biologically active[4] natural compounds- all isolated from Schizandra and Kadsura (Schizandraceae).[5]

The present communication describes the use of ruthenium(IV) tetrakis(trifluoroacetate) -RUTFA- in the total, efficient and atropospecific synthesis of the lignan deoxyschizandrin **1a**, from a cis-2,3-dibenzyl butanolide using non-phenolic intramolecular oxidative coupling, and in the synthesis of the dibenzocyclooctatriene skeleton from the corresponding (E)-3-benzyl-2-benzylidene-4-butanolide **3a** lignan closely related to savinin **3b** and its natural analogues.[6]



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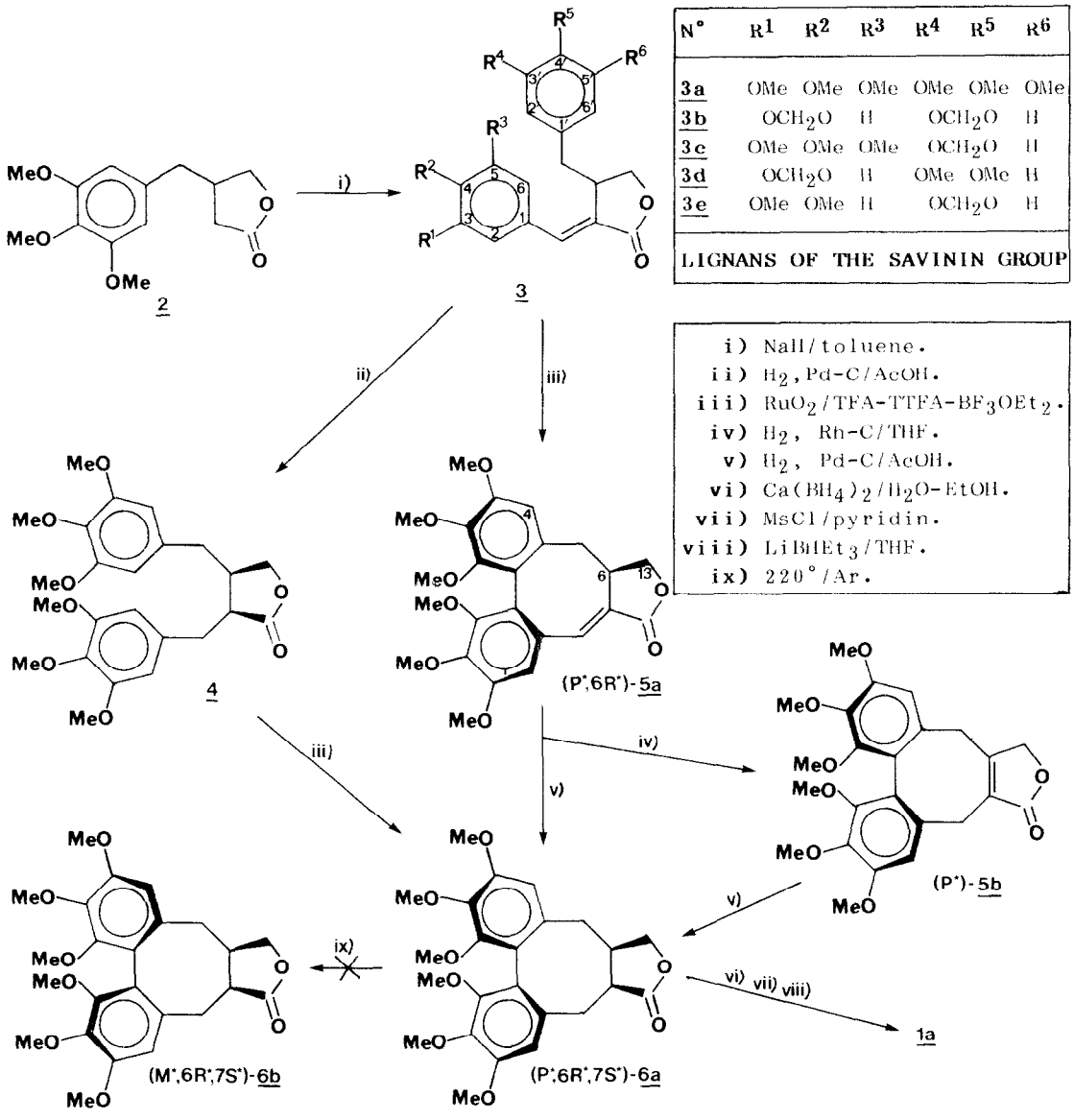
N°	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}
1a	OMe	OMe	OMe	Me	Me	Hα	H	OMe	OMe	OMe
1b	OMe	OMe	OMe	Me	Me	OH	H	OMe	OMe	OMe
1c	OMe	OMe	OMe	Me	Me	OH	OH	OMe	OMe	OMe
1d	OMe	OMe	OMe	CH_2OH	CH_2OH	Hα	H	OMe	OMe	OMe
1e	OMe	OMe	OMe	CH_2OMs	CH_2OMs	Hα	H	OMe	OMe	OMe
1f	OMe	OMe	OMe	$-CH_2O-CO-$		Hα	OH	OMe	OMe	OMe
1g	OMe	OMe	OMe	$-CH_2O-CO-$		Hα	OMs	OMe	OMe	OMe
1h	OH	OMe	OMe	Me	Me	Hα	H	OMe	OMe	OH
1i	OMe	OMe	OH	Me	Me	Hα	H	OMe	OMe	OMe
1j	OH	OMe	OMe	Me	Me	Hα	H	OMe	OMe	OMe

3a was one-step synthesized using an improvement of Stobbe-like alkylidenation[9] of 3,4,5-trimethoxybenzyl-4-butanolide **2**[10] (NaH/toluene-0.1 Eq. MeOH, 20°C, 30 min.) in 63% yield, **mp** 106-107°C (ether), **IR** ($CHCl_3$) 1735 cm^{-1}, C=O lactone, **^{1}H NMR** ($CDCl_3$) 7.48

(1H, d, J = 1.5 Hz) olefinic H (typical of **E** configuration). Catalytic hydrogenation of the latter (H_2, Pd-C/AcOH, 4h) gave the corresponding saturated cis-butanolide **4**[11] as an oil, in 96% yield.

In the first place, intramolecular biaryl coupling of ethylenic lactone **3a** using **RUTFA** (RuO_2-TFA-TFAA-BF_3OEt_2/CH_2Cl_2, 20°C, 24 h) gave the bisbenzocyclooctatrienolide **5a** (90-95% range yield),[10] **mp** 159-160°C (ether), **IR** ($CHCl_3$) 1752 cm^{-1}, **^{1}H NMR** ($CDCl_3$) 7.45 (1H, d, J = 3.5 Hz, vinyl H), 6.55 and 6.35 (2H, 2s, aromatic H) 4.40 and 4.15 (2H, 2 dd, $J_{13\alpha-6} = J_{13\beta-6} = 9$Hz, H-13$\alpha$ and H-13β), 3.80 (12H, s, OMe x 4) 3.65 and 3.55 (6H, s, OMe x 2, OMe-1 and OMe-12), 3.15 (1H, dd, $J_{5\alpha-6} = 6$ Hz, $J_{5\alpha-5\beta} = 14$ Hz, H-5α), and 2.45 (1H, dd, $J_{5\beta-6} = 1$ Hz, $J_{5\beta-5\alpha} = 14$ Hz, H-5β).

The above prepared cis-2,3-bis(3,4,5-trimethoxybenzyl)-4-butanolide **4** was subsequently submited to oxidative coupling by **RUTFA** under the same conditions, to give the bisbenzocyclooctadiene lactone **6a** **mp** 157-158.5°C (ether), in 90-95% yield (65% by using TTFA), **IR** ($CHCl_3$) 1767 cm^{-1}, **^{1}H NMR** ($CDCl_3$) 6.65 (1H, s), 6.40 (1H, s), 4.40 (1H, dd),



4.15 (1H, dd), 3.85 (12H, s), 3.65 (6H, s), and 2.70-2.50 (6H, m), which has the same "normal" (P*,6R*) biaryl stereochemistry as picrostegane **1** (R^1 = H; R^2, R^3 = OCH_2O; R^4, R^5 = $-CH_2OCO-$; R^6 = H ; R^7 = H; R^8 = R^9 = R^{10} = OMe).[11] The present result is clearly different from the previously described trans dibenzylbutanolide oxidative couplings since, in the latter cases, "iso" (M*,6R*) configurations were systematically obtained.[1]

Thus, the biaryl configuration of the bisbenzocyclooctatrienolide **5a**, was demonstrated by performing its catalytic hydrogenation (H_2, Pd-C/AcOH, 20°C, 12h), which gave two closely related compounds; chromatography of the mixture (SiO_2, cyclohexane/methyl tert-butyl ether, 4/6) gave the expected satured cis-lactone in 61% yield, identical to above **6a**; tail fraction (24% yield), gave butenolide **5b** resulting from double bond migration,[12] **mp** 190-191°C (ether), **IR** ($CHCl_3$) 1735 cm^{-1}, **^{1}H NMR** ($CDCl_3$) 6.55 and 6.45 (2H, 2s, aromatic H), 4.65 (2H, m, H lactone), 3.85 (12H, s, OMe x 4), 3.65 and 3.62 (6H, 2s, OMe x 2) and 3.5-3.0 (two overlapping geminal AB systems). An alternate reduction procedure (H_2, Rh-C/THF, 20°C, 6h) lead to reversal of the **6a**/**5b** ratio, (estimated at 3/7 by **^{1}H NMR** of the mixture). Since **5a** was not presumed to be termally isomerized during reduction[13] and since it has an unequivocaly "normal" (P*,6R*) configuration, it was reasonably assumed that the initial ethylenic bridged biaryl **5a** also has the same stereochemistry. Satured lactone **6a** was reduced in an aqueous medium [$Ca(BH_4)_2$/H_2O-EtOH, 30°C, 20 min.] to give one single diol (**1d**), **mp** 122-126°C (ether), in nearly quantitative yield, which was tranformed to the bismesylate **1e** **mp** 165.5-167 °C (ether-Cl_2CH_2) (MsCl/C_6H_5N, 0°C, 15 min.),[14] identical to the compound obtained by one of us (JPR), using an alternate pathway.[8,15] An attempt to reduce **1e** using lithium triethylborohydride ($LiBHEt_3$/THF, 0°C, 1h, reflux 2h),[16] led to a surprising lack of aromatic methyl ethers giving deoxyschizandrin **1a** in poor yield, accompanied by its demethylation by-products.[17] Thus, careful chromatography was performed on the preceding mixture to give two phenols **1h** and **1i** closely related to deoxyschizandrin (similar PMR spectra) except for the absence of two high-field methoxyls for the former (**1h**), **mp** 172.5-175°C (ether), and except for the absence of one down-field methoxyl for the latter (**1i**) (amorphous), related to gomisins K_1, K_2 (= **1i**), and K_3(= **1j**). Finally, on using lithium triethylborohydride at room temperature (60 min.) rac-deoxyschizandrin **1a** was obtained in high yield (**92 %**),[18] as prisms **mp** 113-115°C (MeOH) litt.[19] 112-113°C (MeOH).

Bibliography and notes

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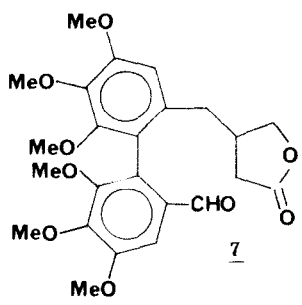
9. Cis isomer of a recently isolated lignan from Hernandia cordigera; P. Richome, J. Bruneton, P. Cabalion and M. M. Debray, J. Nat. Prod., **47**, 879 (1984).
10. 80-85% range on using thallium(III) tris(trifluoroacetate).
11. They exhibit in their PMR spectra superimposable aliphatic pattern (in both $CDCl_3$ and C_6D_6).
12. Supported by lack of olefinic H (contrary to **5a**), presence of quasi-equivalent downfield lactonic protons in PMR, and two quaternary ethylenic carbones (C-6 and C-7) in CMR. On reduction (Pd-C/AcOH) **5b** gave only 10% of **6a** after 48h.
13. On the other hand, on keeping **6a** in the melt (220°C/Ar, 4h), no atropoisomerisation occurred.
14. Cis-fused lactones may occur as two pairs of diastereoisomers, rac-(P*,6R*,7S*)-**6a** and rac-(M*,6R*,7S*)-**6b**, which become symmetrically substituted upon reduction. Thus, due to the symmetry of the substitution of each phenyl propane moitie, deoxyschizandrin itself occurs as only one pair of enantiomers. See L.V. Dvorken, R.B. Smith, and K. Mislow, J. Am. Chem. Soc., 80, 486 (1958).
15. Intramolecular hydroxyalkylation of the described aldehyde lactone **7**[8] {$LiN(SiMe_3)_2/C_6H_6$, 20°C, 15 min.},[8] gave **1f** as an atropoisomeric mixture in 83% yield; careful mesylation of the latter (MsCl/pyridin, 0°C, 3h) afforded the mesylates **1g**, (H-8β) **mp** 166-168°C (ether), **IR** ($CHCl_3$) 1772 cm^{-1}, **^{1}H NMR** ($CDCl_3$) 7.0 (1H, s), 6.37 (1H,s), 5.51 (1H, d, J = 10 Hz) 4.15 and 4.36 (2H, m), 3.95 (3H, s), 3.90 (6H, 2s), 3.88 (3H ,s), 3.71 (6H, 2s), and 2.88 (3H, s); and **1g** (H-8α) **mp** 121-123°C , **IR** ($CHCl_3$) 1770 cm^{-1}, **^{1}H NMR** ($CDCl_3$) 7.42 (1H, s), 6.61 (1H, s), 5.61 (1H, d, J = 3 Hz), 4.35 and 4.1 (2H, 2m), 3.97 (3H,s), 3.91 (9H, 3s), 3.75 (3H, s), 3.67 (3H, s), 3.50 (1H, dd), 3.30 (1H, dd), 2.83 (3H, s), and 2.5 (2H, m). The preceding mesylates were directly reduced in the diol **1d** ($LiAlH_4$/THF, 20°C, 2h) and subsequently mesylated to give the same above bismesylate **1e** (MsCl/pyridin, 0°C, 2h).



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17. Formation of lithium methylsulfide was assumed to result from reduction of methanesulfonate by superhydride as cleaving agent.
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