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Synthesis of Non-Phenolic Bisbenzocyclooctadiene Lignan Lactones and Aporphinic Alkaloids, by Oxidative Coupling with New Agents in Fluoro Acid Medium. IV.[1]

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Abstract : *A systematic study of oxidants used in fluoro acid medium allowed us to increase notably the number of efficient reagents for the non-phenolic oxidative coupling of lignan and alkaloid precursors. If dibenzylbutanolide had no methylenedioxyle group, Re_2O_7 and $RuO_2.2H_2O$ were the most efficient. With a methylenedioxyle group, best results were obtained with Tl_2O_3, $Mn(OAc)_3.2H_2O$ and $Ce(OH)_4$. Finally, aporphines were obtained with good yields with $Ce(OH)_4$, $RuO_2.2H_2O$ and $Fe(OH)(OAc)_2$.*

Activity in our group concentrated, over the last few years, towards the development of a biomimetic approach for the synthesis of potential antitumor and antiviral drugs. We have been interested, among active alkaloids and lignans, in the wide class of naturally occuring compounds which possess a biaryl linkage.[2] These can be synthesized from open-chain precursors, using selective oxidative metallic reagents.[3,4,5] Thus, Landais and Robin discovered that ruthenium (IV) dioxide dihydrate in fluoro acid medium was a powerful and efficient reagent for the oxidative non phenolic and phenolic coupling of lignans and alkaloids.[1,6,7] Meanwhile, ruthenium (IV) dioxide dihydrate was found to be inefficient for the coupling of some precursors, especially compounds which possess a methylenedioxyle substituent on the aromatic ring. Therefore, we undertook a systematic study of the different redox couples[8] (Table I) in order to prepare new selective and versatile reagents which could overcome these problems.

1. *Experimental conditions*

Metallic trifluoroacetates were prepared *in situ* by combination of commercial metallic salts (oxides, acetates, hydroxides) with trifluoroacetic acid (pka=0.3) and its anhydride, as previously reported.[9] CH_2Cl_2 was used as the reaction solvent. Similar reactions using either CH_3CN, CCl_4 or $CHCl_3$ instead of CH_2Cl_2 were less successful.[1,10] BF_3-Et_2O was used as an electrophilic assistance agent.[9,11] Finally, ultra-sonic assistance allowed us to reduce notably reaction times and quantities of metallic salts.[1]

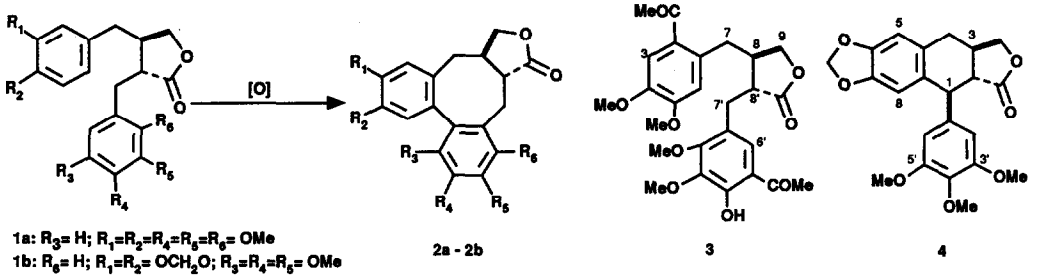
Table I

Redox couples	E° (V)
Sb_2O_3 / Sb	0.15
Ag^+ / Ag	0.79
As_2O_3 / As	0.23
Bi^{3+} / Bi	0.29
Ce^{IV} / Ce^{III}	1.74
$Cr_2O_7^{2-}$ / Cr^{3+}	1.33
Co^{III} / Co^{2+}	1.77
Cu^{2+} / Cu^+	0.17
Sn^{IV} / Sn^{II}	0.14
Fe^{3+} / Fe^{2+}	0.77
IrO_2 / Ir	0.93
Mn^{III} / Mn^{II}	1.49
MoO_2^{2+} / MoO^{3+}	0.48
Ni_2O_3 / NiO	0.42
Pr^{4+} / Pr^{3+}	2.86
ReO_4^- / ReO_3	0.77
Rh_2O_3 / Rh	0.87
TeO_2 / Te	0.59
VO_2^+ / VO^{2+}	0.99
Tl^{3+} / Tl^+	1.26
RuO_2 / Ru	0.79

2. *Applications to the synthesis of lactonic bisbenzocyclooctadiene lignans*

The oxidative properties of the different metallic salts, listed above, in fluoro acid medium were studied in the oxidative coupling of dibenzylbutanolides **1a-b** to the corresponding bisbenzocyclooctadienes (BBCOD) lignan lactones **2a-b** (Scheme I).

Scheme I



1a: R_3= H; R_1=R_2=R_4=R_5=R_6= OMe
1b: R_6= H; R_1=R_2= OCH_2O; R_3=R_4=R_5= OMe

2a - 2b 3 4

Dibenzylbutanolides **1a-b** were prepared by known procedures.[1] The study of the different redox couples consisted firstly in carrying out reactions with the best appropriate model to oxidative biaryl coupling in order to eliminate metallic reagents which were not efficient for coupling (Table II). Precursor **1a** was choosen because of its easy synthesis[1], and also because aromatic rings are activated by methoxyles which favours the biaryl coupling (Table II). Difficulties encountered with some metallic oxides such as MoO_3, Ni_2O_3, SnO_2, Sb_2O_3, Bi_2O_3, As_2O_3, IrO_2 and $Rh_2O_3.5H_2O$ were probably attributable to a difficult attack by trifluoroacetic acid. Over five metals showed close performances with that of thallium (III) and eight metals were more efficient than TTFA. Moreover, we observed with $Cu(OAc)_2.H_2O$, the formation of an unexpected by-product **3** (Scheme I). Finally, six metallic oxides which gave no coupling reactions (MoO_3, Ni_2O_3, SnO_2, Sb_2O_3, Bi_2O_3, As_2O_3) were eliminated. These results could be explained by the poor redox potential of these reagents (Table I).

Table II: Oxidative coupling of 1a to 2a using different oxidants in fluoro acid medium. Comparison with known reagents as TTFA[5] and $RuO_2.2H_2O$[1].

		$CF_3CO_2H/(CF_3CO)_2O$			$C_2F_5CO_2H/(C_2F_5CO)_2O$		
metal	oxidant	(eq.)[d]	time	yield[a] (%)	(eq)[g]	time	yield[a] (%)
Ru (IV)	$RuO_2.2H_2O$	(2)	18h	98	-	-	-
Tl (III)	Tl_2O_3	(0.52)	30mn	73	(0.66)	2h	85
Mn (III)	$Mn(OAc)_3.2H_2O$	(1.9)	15mn	84	(2.45)	2h	90
Ce (IV)	$Ce(OH)_4$	(4.8)	3h	72	(4.8)	2h	83
V (V)	V_2O_5	(4.8)	5d	87	(4.8)	11d	85
Re (VII)	Re_2O_7	(1.9)	3h	98	(1.9)	4h	100
Fe (III)	$Fe(OH)(OAc)_2$	(3.8)	5h	62	(3.8)	42h	46[h]
Co (III)	Co_3O_4	(9.5)	3d[b]	78	(10)	5d[b]	0[j]
Ag (I)	CF_3CO_2Ag	(14)	1d	86	-	-	-
Cr (VI)	CrO_3	(3.8)	6d	71	(4.8)	7d	74
Rh (III)	$Rh_2O_3.5H_2O$	(4.8)	14d	39[e]	(4.8)	2d[b]	0[j]
Ir (IV)	IrO_2	(4.8)	16d	77	(4.8)	2d[b]	0[j]
Pr (IV)	Pr_6O_{11}	(11.6)[f]	64h	74	(11.6)[f]	5d	94
Se (IV)	SeO_2	(5)	8h	70	(5)	12h	72
Te (IV)	TeO_2	(10)	2d[b]	80	(10)	35h[b]	90
Cu (II)	$Cu(OAc)_2.H_2O$	(3.8)	1d	22[c]	(3.8)	4d	34[i]

[a] yield of isolated product. [b] ultra-sound. [c] presence of compound 3 (29%). [d] eq. in suspension in CH_2Cl_2/TFA/TFAA/BF_3-Et_2O/T=20°C. [e] presence of recovered starting material, corrected yield: 50%. [f] 11.6 eq. of PrO_2. [g] eq. in suspension in $CH_2Cl_2/C_2F_5CO_2H/(C_2F_5CO)_2O/BF_3$-$ET_2O$/T=20°C. [h] presence of 3 (16%). [i] presence of 3 (32%). [j] recovered starting material.

Next, we decided to improve the biaryl coupling of compounds which possess a methylenedioxyle group. We previously reported the failure of $RuO_2.2H_2O$ in the oxidation of yatein **1b** to isostegane **2b**. Degradation due to the opening of benzodioxole ring was generally observed.[1] Likewise, Cambie and co-workers[12] obtained the formation of an orthoquinone by oxidation of **2b** with TTFA, showing clearly that overoxidation of isostegane **2b** in the medium was responsible for the low yield in the oxidation of **1b**. We solved these problems by using the procedure of Cambie and co-workers[12] who successfully carried out the oxidative coupling of **1b** to **2b**, using TTFA in neat TFA (Table III). In most cases (Re_2O_7, V_2O_5, Co_3O_4, CF_3CO_2Ag, CrO_3, $Rh_2O_3.5H_2O$, IrO_2, Pr_6O_{11}, SeO_2, TeO_2, $Cu(OAc)_2.H_2O$), degradation was observed. However, we obtained good yields with $Ce(OH)_4$ (68%) and $Mn(OAc)_3.2H_2O$ (78%). An improved yield (85% vs 65%[12]) was obtained with TTFA, using a shorter reaction time (10s vs 15mn[12]).

Table III: Oxidative coupling of 1b to 2b using different oxidants in fluoro acid medium

		CF_3CO_2H			$C_2F_5CO_2H$		
metal	oxidant	(eq.)[b]	time[c]	yield[a] (%)	(eq.)[d]	time[c]	yield[a](%)
Tl (III)	Tl_2O_3	(0.55)	5-10s (0°C)	85	(0.6)	1mn(0°C)	75
Mn (III)	$Mn(OAc)_3.2H_2O$	(2.5)	5-10s (0°C)	78	(3)	5mn(0°C)	68
Ce (IV)	$Ce(OH)_4$	(5)	30mn (0°C)	68	(5)	3h	62
Fe (III)	$Fe(OH)(OAc)_2$	(10)	3h30	18	-	-	-

[a] yield of isolated product. [b] eq. in TFA/BF_3-Et_2O. [c] reactions at room temperature unless otherwise indicated. [d] eq. in $C_2F_5CO_2H/BF_3$-Et_2O.

3. *Utilization of pentafluoropropionic medium*

In order to test the mildest oxidative coupling conditions, we replaced trifluoroacetic acid and its anhydride by the less acidic pentafluoropropionic acid ($C_2F_5CO_2H$) and its anhydride ($(C_2F_5CO)_2O$).

Pentafluoropropionic acid has never been used in this type of reaction. First, the study was carried out on the model **1a** used previously (Table II). We generally noted better yields in pentafluoropropionic medium with longer reaction times than those obtained in trifluoroacetic medium. Meanwhile, we recovered unchanged starting material with Co_3O_4, Rh_2O_3 and IrO_2. These results were certainly due to a more difficult attack of these oxides by pentafluoropropionic acid than by trifluoroacetic acid. Secondly, we tested the pentafluoropropionic medium on model **1b** which possesses a methylenedioxyle group. We observed lower yields in pentafluoropropionic medium (Table III).

4. *Modification of regioselectivity in absence of BF_3-Et_2O*

Cambie and co-workers[12] observed that oxidative coupling of **1b** by TTFA without BF_3-Et_2O gave predominantly the aryltetraline **4** [13] (Scheme I). Rationalization of these results could be made by the influence of BF_3-Et_2O on the methoxyle C-3' and C-5'. Lewis acids activate the para-position of the methoxyle group by association and favours oxidative coupling of **1b** to BBCOD. In the absence of BF_3-Et_2O, the benzylic radical is more stabilized by uncomplexed methoxyles and led preferentially to the aryltetraline **4**. So, we investigated this reaction by using the oxidants studied above (Table IV). We observed lower yields in pentafluoropropionic medium as shown above. Again, we found that Tl_2O_3, $Mn(OAc)_3.2H_2O$ or $Ce(OH)_4$ were the most efficient reagents even in the absence of BF_3-Et_2O (yield=0% for $Cu(OAc)_2.H_2O$, $Fe(OH)(OAc)_2$, V_2O_5, $Rh_2O_3.5H_2O$, IrO_2, Pr_6O_{11} and CrO_3).

Table IV: Oxidative coupling of 1b in fluoro acid medium in absence of BF_3-Et_2O

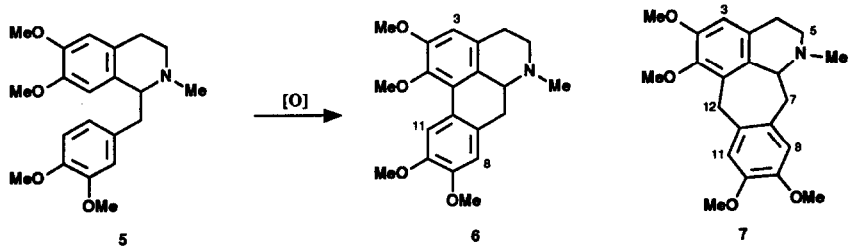
oxidant (eq.)	solvent	time[a]	product and yield[b] (%) 4	2b
Tl_2O_3 (0.55)	TFA	20mn (0°C)	52	9
Tl_2O_3 (1)	$C_2F_5CO_2H$	1h30 (0°C)	48	6
$Mn(OAc)_3.2H_2O$ (3)	TFA	20mn (0°C)	50	4
$Mn(OAc)_3.2H_2O$ (4)	$C_2F_5CO_2H$	30mn	20	8
$Ce(OH)_4$ (5)	TFA	45mn	18	10
$Ce(OH)_4$ (5)	$C_2F_5CO_2H$	4h30	37	10

[a] reactions at room temperature unless otherwise indicated. [b] yield of isolated product.

5. *Application to the synthesis of aporphines*

The good results obtained with non-phenolic dibenzylbutanolides prompted us to extend our procedures to the synthesis of alkaloids which possess a biaryl linkage.[2] Within this large family, we limited our study to the synthesis of aporphins. The study was performed on a commercial product, the laudanosine **5**, which was reported to give the glaucine **6**[14] by oxidative coupling (Scheme II).

Scheme II



5 6 7

By comparison with trifluoroacetic medium, pentafluoropropionic medium gave systematically lower yields (Table V). Three metallic salts gave good results ($Ce(OH)_4$, $RuO_2.2H_2O$ and $Fe(OH)(OAc)_2$) and seven metals gave middling performances. It is worth mentionning the remarkable reaction using IrO_2 which gave predominantly the benzocycloheptisoquinoline **7** probably formed by a Friedel and Crafts reaction between laudanosine and CH_2Cl_2 in oxidative medium (Scheme II).

Table V: Oxidative coupling of 5 to 6 in fluoro acid medium.

	trifluoroacetic medium[a]		pentafluoropropionic medium[b]	
oxidant (eq.)	time[c]	yield[d] (%)	time[c]	yield[d] (%)
Tl_2O_3 (0.8)	10mn (0°C)	66	30mn	36
$Mn(OAc)_3.2H_2O$ (3.5)	1h	40	-	0[g]
Re_2O_7 (2.8)	8h30	60	2d	40
$Fe(OH)(OAc)_2$ (10)	3d	72	3d	10
SeO_2 (5)	60h	46	3d	44
$Ce(OH)_4$ (5)	6h	80		
V_2O_5 (10)	5d[e]	60		
Pr_6O_{11} (12)[f]	5d[e]	50		
TeO_2 (10)	5d[e]	44		
$RuO_2.2H_2O$ (4)	1d	76		
CF_3CO_2Ag (20)	3d	0[h]		
CrO_3 (10)	-	0[g]		
$Rh_2O_3.5H_2O$ (5)	2d[e]	0[h]		
Co_3O_4 (10)	2d[e]	0[h]		
IrO_2 (10)	2d[e] (30°C)	0[i]		

[a] CH_2Cl_2/TFA/TFAA/BF_3-Et_2O. [b] $CH_2Cl_2/C_2F_5CO_2H/(C_2F_5CO)_2O/BF_3$-$Et_2O$. [c] reactions at room temperature unless otherwise indicated. [d] yield of isolated product. [e] ultra-sound. [f] 12 eq. of PrO_2. [g] degradation of starting material. [h] recovered starting material. [i] formation of **8** (72%).

Conclusion

We found new efficient reagents for the non phenolic oxidative coupling of bisbenzocyclooctadiene lignan and aporphinic alkaloid precursors. It is possible to establish a classification for each representative precursor. First, if dibenzylbutanolide has no fragile substituant (benzodioxole ring), the reaction is possible with 13 oxidants. Best results were obtained with Re_2O_7 and $RuO_2.2H_2O$. Oxidative couplings with Pr_6O_{11}, TeO_2, CF_3CO_2Ag and particularly Re_2O_7 have not been reported before. If dibenzylbutanolide possesses a methylenedioxyle group, only Tl_2O_3, $Mn(OAc)_3.2H_2O$ and $Ce(OH)_4$ are efficient. Finally, non phenolic aporphines were obtained using eight different metals; best results were obtained with $Ce(OH)_4$, $RuO_2.2H_2O$ and $Fe(OH)(OAc)_2$. We are currently using these different procedures to prepare natural phenolic compounds and analogs containing a biaryl bond.

Experimental section

Organic compounds **1a-b** were prepared from known procedures.[1] Laudanosine **6** 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 dessiccator containing P_2O_5 and silicagel. Ultra-sound experiments were accomplished

in an ultra-sonic bath equipped with a thermostatic control (T=20°C +/- 2°C) and the reaction was monitored by TLC. 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 an internal standard, and $CDCl_3$ as the solvent unless indicated otherwise. Mass spectra were obtained on a Varian Mat 311 spectrometer. Since the coupling reactions performed are all similar in many respects, typical reactions will be described as a general method. For more details about equivalents of used oxidants, see theoretical part. Numbering systems used to describe NMR spectra of BBCOD **2a-b**, aryltetralin **4**, glaucine **6** and isoquinoline **7** are explained in Scheme I and Scheme II.

General coupling procedure for the preparation of (+/-)-Neoisostegane 2a (method A). To a stirred suspension of Re_2O_7 (0.178 g; 0.37 mmol) in CH_2Cl_2 (10 ml), TFA (1 ml) [or $C_2F_5CO_2H$ (0.7 ml)] and TFAA (0.7 ml) [or $(C_2F_5CO)_2O$) (0.4 ml)], a solution of **1a** (0.08 g; 0.19 mmol) in CH_2Cl_2 (4 ml) was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.05 ml; 0.38 mmol). The mixture was stirred at room temperature (3h in TFA; 4h in $C_2F_5CO_2H$) and was treated with 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 ether gave **2a** (TFA: 78 mg; 98%. $C_2F_5CO_2H$: 80 mg; 100%) as a white solid. Compound was found to be identical (mp, IR, ^1H NMR) to the material reported in the literature: mp 183-184°C [lit.[1] mp 183-185°C (CH_2Cl_2-Et_2O)]; IR ($CHCl_3$) 1770 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR δ 1.7-3.25 (m, 6H, aliphatic protons), 3.75 (m, 1H, H-13), 3.8-4.04 (5s, 15H, 5 OCH_3), 4.38 (m, 1H, H-13), 6.50 (s, 1H, H-1), 6.70 (s, 1H, H-4), 6.72 (s, 1H, H-12).

Reaction of 1a with $Cu(OAc)_2.H_2O$/TFA/TFAA/BF_3-Et_2O. To a stirred suspension of 0.183 g (0.92 mmol) of $Cu(OAc)_2.H_2O$ in CH_2Cl_2 (7 ml), TFA (1.8 ml), TFAA (0.3 ml), a solution of 0.1g (0.24 mmol) of **1a** in CH_2Cl_2 (2 ml) was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.06 ml; 0.48 mmol). The mixture was stirred at room temperature for 24 h. The work-up was carried out as before to give 22mg (22%) of **2a** and 34mg (29%) of **3** as white needles which was recrystallized from ether: mp 146-148°C; IR ($CHCl_3$) 1763 (C=O), 1670 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR δ 2.47 (s, 3H, CH_3CO), 2.56 (s,3H, CH_3CO), 2.64 (m, 1H, H-8') (by irradiation of 7'a), 2.67 (m, 1H, H-8) (by irradiation of 9a), 2.79 (dd, 1H, J= 8.0 Hz, 13.8 Hz, H-7'b), 2.93 (m, 2H, H-7), 3.06 (dd, 1H, J= 5.0 Hz, 13.7 Hz, H-7'a), 3.88 (s, 3H, OCH_3), 3.91 (s, 6H, 2 OCH_3), 4.00 (dd, 1H, J= 7.0 Hz, 8.8 Hz, H-9b), 4.01 (s, 3H, OCH_3), 4.18 (dd, 1H, J= 7.1 Hz, 9.1 Hz, H-9a), 6.57 (s, 1H, H-6), 7.16 (s, 1H, H-3), 7.33 (s, 1H, H-6'), 12.63 (s, 1H, chelated OH); MS m/e 486.1889 (M^+).

General coupling procedure for the preparation of (+/-)-Isostegane 2b (method B). To a stirred suspension of $Mn(OAc)_3.2H_2O$ (0.168 g; 0.62 mmol) in TFA (1.5 ml) [or $C_2F_5CO_2H$ (1.5 ml)] and BF_3-Et_2O (0.06 ml; 0.5 mmol), a solution of **1b** (0.1 g; 0.25 mmol) in TFA (1 ml) [or $C_2F_5CO_2H$ (1 ml)] was added quickly at 0°C under nitrogen. The mixture was stirred at 0°C (5-10s in TFA, 5mn in $C_2F_5CO_2H$) and was then treated as described above in method A to give **2b** (TFA: 78 mg; 78%. $C_2F_5CO_2H$: 68 mg; 68%) as a white solid which was recrystallized from ether: mp 168-170°C [lit.[1] mp 169-170°C (CH_2Cl_2-cyclohexane)]; IR ($CHCl_3$) 1720 (C=O), 1590 (C=C) cm^{-1}; ^1H NMR δ 2.1-3.33 (m, 6H, aliphatic protons), 3.57 (s, 3H, OCH_3), 3.75 (m, 1H, H-13), 3.93 (s, 6H, 2 OCH_3), 4.29 (m, 1H, H-13), 6.03 (s, 2H, OCH_2O), 6.65 (s, 2H, H-4, H-1), 6.77 (s, 1H, H-9).

General procedure for oxidation of yatein 1b in absence of BF_3-Et_2O (method C). To a stirred suspension of $Mn(OAc)_3.2H_2O$ (0.201 g; 0.75 mmol) in TFA (1.5 ml) [or $C_2F_5CO_2H$ (1.5 ml)], a solution of

1b (0.1 g; 0.25 mmol) in TFA (1 ml) [or $C_2F_5CO_2H$ (1 ml)] was added quickly at 0°C under nitrogen. The mixture was stirred (20mn (0°C) in TFA, 30mn (20°C) in $C_2F_5CO_2H$) and was treated as described above in method A, to give **2b** (TFA: 4 mg; 4%. $C_2F_5CO_2H$: 8 mg; 8%) and isodesoxypodophyllotoxine **4** (TFA: 50 mg; 50%. $C_2F_5CO_2H$: 20 mg; 20%) as a white solid which was crystallized from CH_2Cl_2-Et_2O: mp 255-257°C [lit.[13] mp 256-258°C]; IR ($CHCl_3$) 1775 (C=O), 1455 (OCH_2O) cm^{-1}; ^1H NMR δ 2.36-3.08 (m, 5H, aliphatic protons), 3.66 (s, 9H, 3 OCH_3), 4.25-4.62 (m, 2H, H-11), 5.87 (s, 2H, OCH_2O), 6.31 (s, 1H, H-8), 6.40 (s, 2H, H-2', H-6'), 6.58 (s, 1H, H-5).

General coupling procedure for the preparation of glaucine 6 (method A). Glaucine **6** was obtained from laudanosine **5** by using the procedure reported for preparation of neoisostegane **2a** (method A). To a stirred suspension of $Ce(OH)_4$ (0.146 g; 0.7 mmol) in CH_2Cl_2 (5 ml), TFA (1.6 ml) and TFAA (0.2 ml), a solution of **6** (0.05 g; 0.14 mmol) in CH_2Cl_2 (1 ml) was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.07 ml; 0.28 mmol). The mixture was stirred at room temperature for 6h and was treated with saturated $NaHCO_3$. The work-up was carried out as in method A. After chromatography on silica gel (CH_2Cl_2-MeOH 99:1) and crystallization from CH_2Cl_2-Et_2O, glaucine **6** (40 mg; 80%) was obtained as white needles: mp 135-137°C [lit.[14] mp 137-139°C (MeOH-Et_2O)]; IR ($CHCl_3$) 1235 (NCH_3), 1600 (C=C)cm^{-1}; ^1H NMR δ 2.60 (s, 3H, NCH_3), 2.5-3.44 (m, 10H, aliphatic protons), 3.67 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.58 (s, 1H, H-8), 6.78 (s, 1H, H-3), 8.09 (s, 1H, H-11).

Reaction of laudanosine 5 with IrO_2/TFA/TFAA/BF_3-Et_2O. To a stirred suspension of 0.314 g (1.4 mmol) of IrO_2 in CH_2Cl_2 (5 ml), TFA (5 ml), TFAA (0.5 ml), a solution of 0.05g (0.14 mmol) of laudanosine **5** in CH_2Cl_2 (1 ml)was added at 0°C under nitrogen, followed immediately by BF_3-Et_2O (0.035 ml; 0.28 mmol). The mixture was stirred at 30°C with ultra-sound for 2 days. The work-up was carried out as before to give 37 mg (72%) of quinoline **7** as an oil. Compound **7** was found to be identical (IR, ^1H NMR) with material prepared in the literature[15]: IR ($CHCl_3$) 1600 (C=C), 1235 (NCH_3) cm^{-1}; ^1H NMR δ 2.63 (s, 3H, NCH_3), 2.71 (dd, 1H, J= 4.5 Hz, 15.0 Hz, aliphatic proton), 2.75-3.00 (m, 2H, aliphatic protons), 2.98 (dd, 1H, J= 12.1 Hz, 16.3 Hz, aliphatic proton), 3.16 (m, 1H, aliphatic proton), 3.39 (dd, 1H, J= 3.7 Hz, 16.2 Hz, aliphatic proton), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.00 (d, 1H, J=15.1 Hz, H-12), 4.10 (d, 1H, J= 15.1 Hz, H-12), 4.30 (dd, 1H, J= 4.0 Hz, 12.3 Hz, aliphatic proton), 6.53 (s, 1H, H-3), 6.56 (s, 1H, H-11), 6.73 (s, 1H, H-8); MS m/e 369.1932 (M^+).

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