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Aza-dibenzocyclooctadiene Analogue of Stegane via the CN(R, S) Method.

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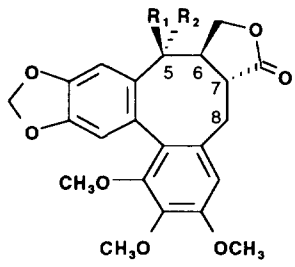
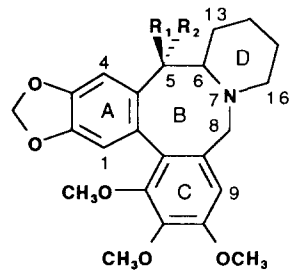
Abstract *:* The optically pure 2-benzylpiperidine **4** obtained from synthon 2-cyano-6-phenyloxazolopiperidine (-) **3** via the CN(R, S) method, gave after N-alkylation, the dibenzylpiperidine **5** which was cyclised to **2a** under non-phenolic VOF_3 coupling conditions. Treatment of hydroxylated dibenzyl piperidine **8** with RuO_2 furnished the unexpected benzoquinolizidine **9**.

In the course of our program dealing with the asymmetric synthesis of benzoquinolizidine analogues of podophyllotoxin, we successfully replaced the lactone moiety of this lignan by a piperidine structure [1]. In order to extend this methodology to other cytotoxic lignans, we decided to investigate the preparation of aza-dibenzocyclooctadiene **2a** and **2b** as analogues of natural antimitotic stegane **1a** and steganacine **1b**.[2,3] Aza-steganes have been previously synthesized and have been claimed to be potent cytotoxic agents.[4]



1 a R_1=R_2=H stegane
b R_1=H, R_2=OAc steganacin



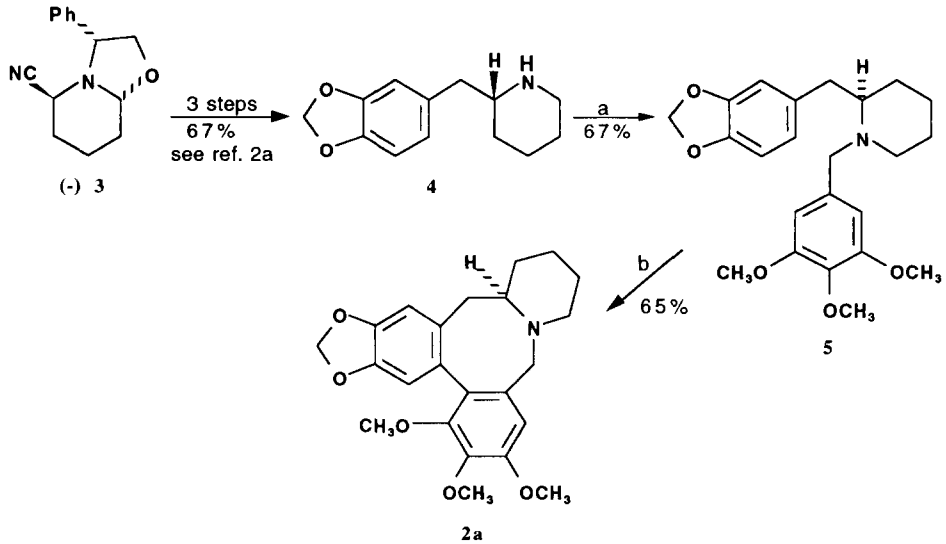
2 a R_1=R_2=H
b R_1=H, R_2=OAc

Herein we report our first results dealing with the synthesis of this new skeleton. Our strategy was based on an application of the CN(R,S) method[5] starting from synthon **3**.[6] We envisaged the preparation of the desired products **2** by a non phenolic VOF_3 coupling[2b,7] of a bis-aromatic chiral piperidine.

α-Substituted piperidine **4** has been previously prepared in an enantiomerically pure form in 67% yield from synthon **3** via diastereoselective alkylation with piperonyl bromide, reduction with $NaBH_4$, then hydrogenolysis to remove the chiral appendage.[1a] N-alkylation of **4** with 3,4,5,-trimethoxybenzylchloride furnished derivative **5** (Y=67%).

Oxidative intramolecular coupling was realised with VOF_3 in methylene chloride in the presence of the dehydrating mixture TFA/TFAA at -78°C.[8] A mixture of two isomeric compounds was obtained in 65% yield.

The major product was isolated by means of preparative HPLC. The structure was confirmed as the expected aza-dibenzocyclooctadiene **2a** by the study of the aromatic part of ^{1}H and ^{13}C NMR; the disappearance of an ortho aromatic system in ^{1}H NMR and of two aromatic CH signals in ^{13}C NMR were observed. Unfortunately, it has been impossible to isolate the minor isomer as it immediately regenerated the same mixture, suggesting these two compounds are atropoisomers.



Reagents and conditions *: (a) 3,4,5-trimethoxybenzylchloride, K_2CO_3, acetone, reflux. (b) VOF_3, CH_2Cl_2, TFA/TFAA, -78°C, 4h.*

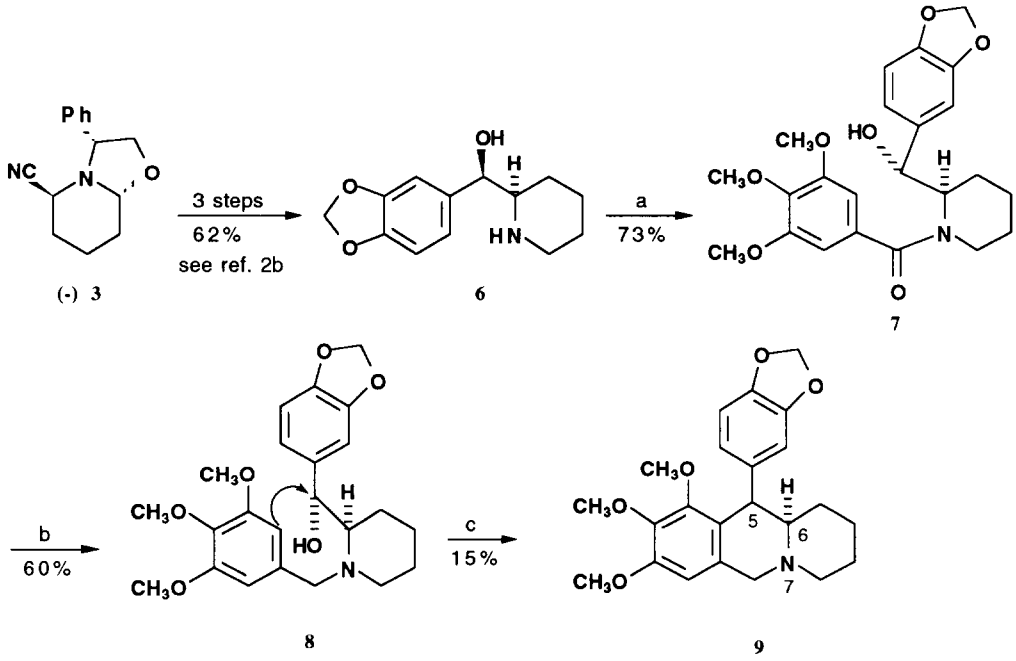
The introduction of an hydroxyl group at C-5 was particularly interesting in order to provide access to the steganacin functionalization. The most straightforward way to synthesize such products was the direct oxidation of compound **2a**. Unfortunately, as observed in the aza-podophyllotoxin series, all attempts to oxidize selectively the C-5 position failed. We then decided to study the preparation of C-5 functionnalized products starting from hydroxylated piperidine **6** previously obtained from synthon **3** by reaction of the corresponding carbanion with piperonal.[1b]

Treatment of compound **6** in Schotten-Baumann conditions with 3,4,5-trimethoxybenzoylchloride provided benzamide **7** in 73% yield. This amide was easily reduced in THF with LAH in 60% yield leading to key intermediate **8**.

The former VOF_3 coupling conditions applied to this substrate led only to degradation products. Protection of the alcohol function (Ac_2O, $PhCH_2Br$) prior to coupling did not allow the isolation of the desired product. We then decided to effect the coupling reaction with ruthenium dioxyde in the presence of $BF_3.OEt_2$.[9] However, in these conditions only benzoquinolizidine derivative **9**[10] was obtained albeit in poor yield (15%). This compound resulted from the electrophilic displacement of the labile benzylic hydroxyl by the electron enriched trimethoxyphenyl moiety. Such a reaction has already been described during the synthesis of lignans.[11] Scarcity of material precluded the study of the stereochemistry of the newly created center at C-5.

Compound **2a** did not exhibit any cytotoxic activity against KB cells. Furthermore, no action on

polymerization or depolymerization of tubuline was detected. These results indicate that the presence of a functionnalized D ring is essential for the activity of aza-analogues of this family of lignans.



Reagents and conditions: *(a) 3,4,5-trimethoxybenzoylchloride, CH_2Cl_2, NaOH, rt. (b) $LiAlH_4$, THF, -78°C. (c) RuO_2, CH_2Cl_2, -10°C.*

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8 To a stirred solution of compound **5** (90 mg, 0.23 10^{-3} mol) in 12 mL of the mixture CH_2Cl_2/(TFA/TFAA(20/1)) (5/1) at -78°C, was added a solution of VOF_3 (112mg, 0.90 10^{-3} mol) in 2 mL of the mixture of AcOEt/(TFA/TFAA (20/1)) (1/1). The solution was stirred at -78°C for 3 h. An aqueous solution of citric acid (10%) was then added, the mixture was neutralised with NaOH (10%) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and distilled. Flash chromatography on silica gel (CH_2Cl_2/MeOH (95/5)) furnished 58 mg (65%) of a mixture of two compounds.
HPLC (RP-Select-B C-8, MeOH/H_2O/TEA (80/19.9/0.1)) furnished one of the cyclised products as an amorphous product (48 mg, 54 %).
2a : $[\alpha]_D$ = -25 ($CHCl_3$, c = 0.3), MS (EI), m/z: 397 ($C_{23}H_{27}NO_5^+$, 68), 315 (73), 314 (97), 300 (30), 284 (30), 263 (36), 181 (100). HR-MS : 397.1865 ($C_{23}H_{27}NO_5^+$, calc. 397.1889).^{1}H RMN ($CDCl_3$, 250 MHz) δ (ppm) : 1.20-1.80 (m, 7H), 2.18 (m, H-16), 2.32-2.57 (m, 2H-5), 2.99 (m, H-6), 3.07 (d, J = 13.5 Hz, H-8), 3.40 (d, J = 13.5 Hz, H-8), 3.54 (s, OMe), 3.84 (s, 2 OMe), 5.95 (m, OCH_2O), 6.70-6.80 (m, H-1, H-4 and H-9).^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) : 24.6, 26.6 and 29.8 (C-13, C-14 and C-15), 35.6 and 41.1 (C-5 and C-16), 58.9 (C-6), 60.7 , 60.9 and 61.1 (3 OMe), 66.3 (C-8), 101.0 (OCH_2O), 109.0 , 110.0 and 110,3 (C-1, C-4 and C-9), 126.3 (s), 128.1 (s), 134.9 (s), 135.3 (s), 141.5 (s), 145.3 (s), 147.4 (s), 150.6 (s), 152.6 (s).

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10 **9** : $[\alpha]_D$ = +24 ($CHCl_3$, c = 1.0), MS (EI), m/z : 397 (73), 314 (100), 284 (40), 283 (61), 253 (10), 181 (15). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) : 1.20-1.65 (m, 6H), 2.02-2.21 (m, 4H), 3.05 (m, H-6), 3.18 (s, OMe), 3.70 and 3.85 (2s, 2 OMe), 3.80 (m, H-5 and 2 H-8), 5.95 (m, 2H, OCH_2O), 6.60-6.70 (m, 4H ar).

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