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Synthesis of the carbonated skeleton of stephaoxocanidine

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Introduction

Stephaoxocanes (Deng *et al.*, 1993; Kashiwaba *et al.*, 1996, 1997; Deng and Zhao, 1997; da-Cunha *et al.*, 1998) are tetracyclic alkaloids with an isoquinoline nucleus, which are obtained from natural sources of Far East (China and Japan), and Brazil. Five members of this family (stephaoxocanidine, eletefine, excentricine, *N*-methylexcentricine and stephaoxocanine) (Fig. 1) were isolated during the last decade from specimens of *Stephania cepharantha* Hayata, *Stephania excentrica* H. S. Lo and *Cissampelos glaberrima*, all belonging to Menispermaceae family of use in folk medicine in the countries of origin (Pío-Corrêa, 1984; Rutter, 1990; Duke and Vasquez, 1993; Schwontkowski, 1993; Beckstrom-Sternberg and Duke, 1994).

In our laboratory a series of analogues of stephaoxocanes have been synthesized (Kaufman, 2001; Bianchi and Kaufman, 2003; Bianchi *et al.*, 2003, 2004). Some of them showed a potent inhibitory activity of the enzyme acetylcholinesterase, one of the most important therapeutic targets for the treatment of Alzheimer's disease (Bianchi *et al.*, 2005).

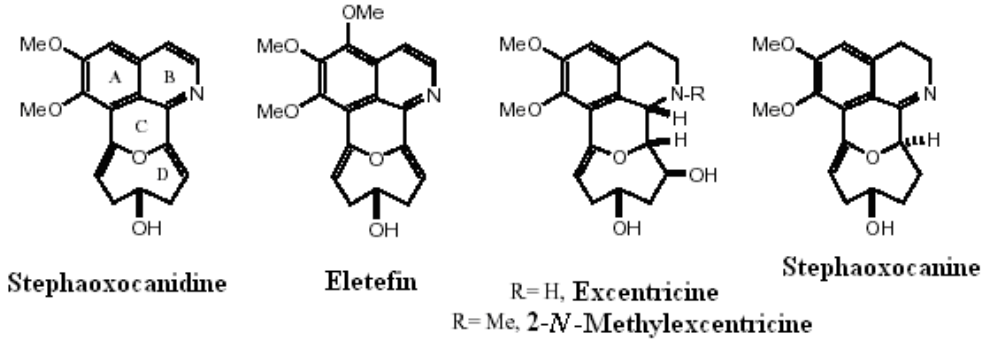

Figure 1

Owing to the low proportion of these alkaloids in natural sources, it is of great importance to carry out the synthesis of these compounds in order to perform studies on biological activity, and to allow eventual pharmacological developments. Therefore, the aim of this study was the chemical synthesis of the carbon skeleton of stephaoxocanidine as an approach to the preparation of stephaoxocane analogues.

Methodology

Chemical reactions were carried out under positive argon pressure, and monitored by thin layer chromatography. Spots were visualized under UV light (254 nm) and further sprayed with ethanolic *p*-anisaldehyde/sulfuric acid reagent and careful heating. The separation and purification of the reaction products were performed by column chromatography using solvent gradients for elution.

IR spectra were recorded on a FT-IR Shimadzu Prestige 21 model spectrophotometer, while ^{1}H- and ^{13}C-NMR spectra were acquired in a Bruker AC200-E spectrometer operating at 200.13 and 50.33 MHz, respectively.

Results

The multiple-step synthesis of compound **1** was carried out, which sets the carbon skeleton of stephaoxocanidine, a structural analogue of this natural product. This is a tricyclic compound devoid of the typical oxygen bridge of stephaoxocanes. In the preliminary retrosynthetic analysis (Scheme 1), and taking into account marked disconnections, it was planned to obtain **1** from alcohol **2**, just forming the nitrogen heterocyclic ring (Birch *et al.*, 1972) as last synthetic step. It was thought that cyclodecenol **2** could be obtained

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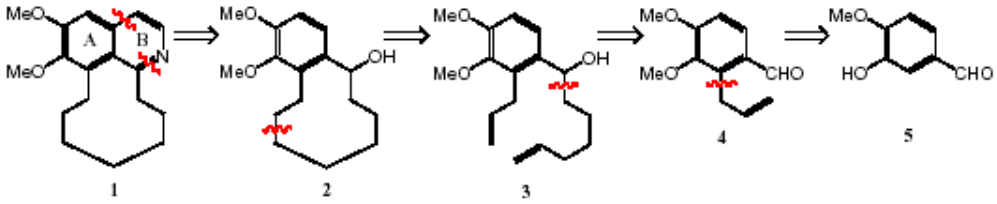
from the alcohol **3** (by a cyclization as olefin metathesis with ring closure) (Ronsheim and Zercher, 2003), which in turn was considered that would be accessible from aldehyde **4**. Finally, it was envisaged that this aldehyde could be obtained by simple chemical transformations of commercial isovanillin (**5**).



Scheme 1. Retrosynthetic analysis of the tricyclic target **1**.

Therefore, isovanillin (**5**) was used as starting material for this synthesis (Scheme 2). It was subjected to a Williamson etherification using allyl bromide, K_2CO_3 and EtOH to generate compound **6** in 92% yield. The latter was subjected to a Claisen rearrangement in 1,2-dichlorobenzene under reflux to give compound **7** in 97% yield.

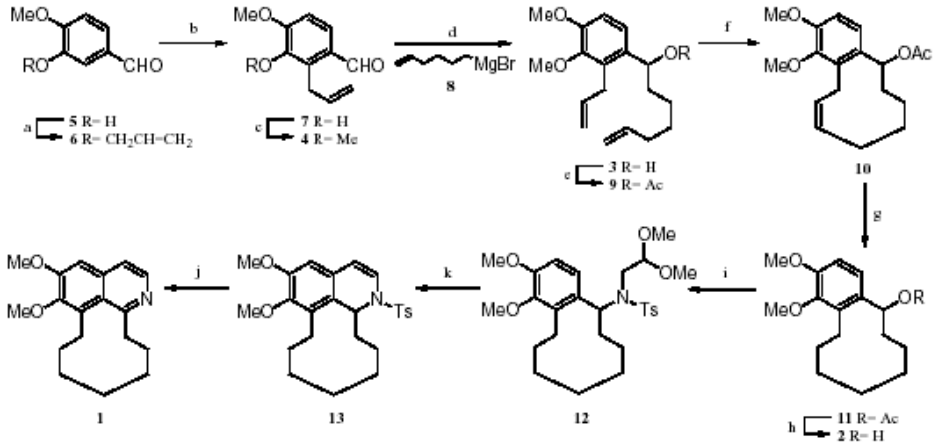
Subsequently, a Williamson etherification was carried out by treatment of phenol **7** with MeI, K_2CO_3 and EtOH to generate the intermediate **4** in a 90% yield. This aldehyde suffered addition of the Grignard reagent **8**, providing a 60% of the benzylic alcohol **3**.

When **3** was subjected to the reaction of olefin metathesis with ring closure using Grubbs catalyst of 1st generation, the cycled compound was obtained in a low yield (35%). Therefore, it was decided to acetylate the alcohol in order to avoid interactions, in which this group participates, thus being possible causes of reaction yield decrease.

In this way, the acetylated compound **9** was subjected to the reaction of olefin metathesis with ring closure, thus obtaining the cycled product **10** in a 77% yield. ^{1}H-NMR spectrum of **10** showed that this product accounts for the *Z* isomer. Then, **10** was quantitatively hydrogenated in the presence of PtO_2 and EtOH, and compound **11** was obtained, which was further hydrolyzed (NaOH, THF, MeOH) to give the benzylic alcohol **2** in a 91% yield.

This alcohol was subjected to a Mitsunobu reaction with *N*-tosylaminoacetal to give 68% of sulfonamidoacetal **12**, required precursor for Jackson cyclization.

This cyclization was performed in the presence of 6 N HCl and EtOH in dioxane in order to produce a 50% of the dihydroisoquinoline **13**. Finally, **13** underwent an oxidative desulfonylation, the expected isoquinoline **1** being obtained in a 70% yield.



Scheme 2. *Reagents and conditions:* a) BrCH2CH=CH2, K2CO3, EtOH, reflux, 3 h (92%); b) 1,2- Cl2C6H4, reflux, 10 h (97%); c) MeI, K2CO3, EtOH, reflux, 8 h (90%); d) **8**, THF, rt, 3 h (60%); e) Ac2O, C5H5N, DMAP (cat.), CH2Cl2, rt, 4 h (90%); f) Grubbs catalyst (1st generation), CH2Cl2, rt, 10 h (77%); g) H2 (1 atm), PtO2 (cat.), EtOH, rt, 5 h (100%); h) 2.75N NaOH, MeOH, THF, 0ºC→50ºC, 8 h (91%); i) TsNHCH2CH(OMe)2, PPh3, DIAD, THF, 60ºC, 4 h (68%); j) 6N HCl, EtOH,dioxane, reflux, 20 min (50%); k) K*t*BuO, 2,6-C5H3N, reflux, 3 h (70%).

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Conclusions

Isoquinoline derivative **1** was obtained as a structural analogue of stephaoxocanidine, which possesses the carbon skeleton of the natural product. The synthesis was achieved in 11 steps and with an overall yield of 7%.

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