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A SHORT SYNTHESIS OF THE 21-EPIMER OF THE (±)-ASPIDOSPERMA SKELETON

Reinald H. Huizenga[1], Jim van Wiltenburg and Upendra K. Pandit*

Organic Chemistry Laboratory, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam. The Netherlands.

Abstract : The title aspidosperma skeleton has been constructed in three simple steps via a readily available folate model.

In a strategy utilizing functionalized group transfer reactions via suitable folate models, we have reported the synthesis of a number of heterocyclic systems related to β-carboline and isoquinoline alkaloids[2]. In this communication we present a simple three-step preparation of an epimer of the aspidosperma skeleton from folate model **1**[3] (Scheme).

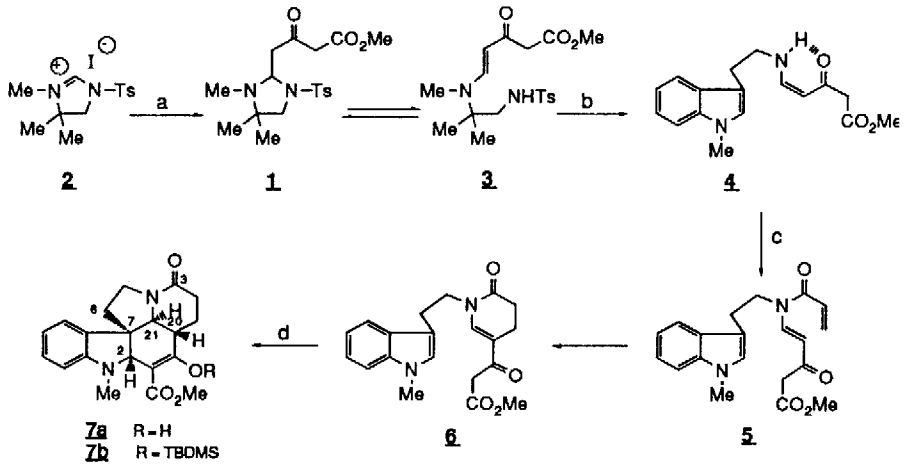
The preparation of model **1** was achieved by adding imidazolinium salt **2**[4] - now available as an Aldrich reagent (nr. 31,757-8) - to a solution of the dilithium salt of methyl acetoacetate, in THF.[5] As reported earlier[6], the imidazolidine systems of type **1** are in equilibrium with the corresponding ring-opened enaminoketo esters (e.g. **3**). If desired, compound **3** can be isolated as the only product.

When ester **3** was allowed to react with N(1)-methyltryptamine (HAc/MeCN, 3h, 80°), the tryptamine derivative **4**, corresponding to the transfer of a functionalized five-carbon fragment from the folate model, was produced in good yield[7]. The **Z**-stereochemistry of **4** is attested by the coupling (J = 7.2 Hz) between the olefinic protons and arises due to the hydrogen bonding between the N-H and the carbonyl oxygen.

Treatment of **4** with acryloyl chloride (pyridine/MeCN, DMAP-cat., room temp.) resulted initially in an insoluble substance, which slowly dissolved upon warming (90°, overnight). The product isolated from the final reaction mixture corresponded to compound **6**[8]. The first compound formed in this reaction is the product of N-acylation (**5**), which undergoes an intramolecular alkylation of the enamine function by the acrylamide moiety. The presence of this intermediate product could be established spectroscopically, the presence of $=CH_2$ protons [δ 6.40 dd, J=1.5, J=16.7, HC=CH (cis); δ 6.63 dd, J=10.4, J=16.7, HC=CH (trans)] being diagnostic for the acylated species.

The cyclization of **6** to the pentacyclic skeleton of the 21-epimer of the aspidospermine alkaloids[9] was carried out under influence of titanium tetrachloride. In connection with this reaction, a systematic study of electrophilic catalysis of the cyclization of model systems bearing analogous functionalities has been conducted[10]. When a solution of **6** in 1,2-dichloroethane was treated with titanium tetrachloride (2 eq.) at 80 °C, a mixture of **7a** and the corresponding keto compound was obtained in 63% yield. The mixture was treated with $F_3CSO_2OSi(Me)_2t$-Bu to convert it into a single product, viz. the silyl enol ether **7b**. The structure and stereochemistry of **7b** was established by 2D and NOE-difference NMR analysis[11]. In a NOE-experiment irradiation of the C_2-proton led to an enhancement of the signals of the C_{21}-H and of one of the C_6-protons.

The observed stereospecific course of the cyclization reaction leading to the 21-epimer of the alkaloid skeleton will be discussed in a forthcoming paper.



(a) $(Li^+)CH_2^-COCH^-(Li^+)CO_2Me$ / THF; (b) N(1)-methyltryptamine/HAc, MeCN; (c) CH_2=CHCOCl, pyr., DMAP / MeCN; (d) $TiCl_4$ / $ClCH_2CH_2Cl$, 80 °C.

References

* To whom correspondence should be addressed.

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7. Yield 65 %. In addition, 7 % of **3** was recovered. These and other yields reported in this communication have not been optimized.
8. **6** : ^{1}H-NMR ($CDCl_3$, 200 MHz): 2.50 (m, 2H, CH_2CH_2CON), 2.97 (s, 2H, $COCH_2CO$), 3.08 (t, J = 6.7 Hz, 2H, indole-CH_2), 3.68 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 3.76 (m, 2H, CH_2CH_2CON), 3.90 (t, J = 6.7 Hz, 2H, CH_2CH_2NCO), 6.62 (s, 1H, NCH=), 6.83 (s, 1H, indole C_2H), 7.10-7.33 (m, 3H, indole C_5H, C_6H, C_7H), 7.60 (d, J = 7.5 Hz, 1H, indole C_4H).
9. Numbering according to J.Le Men and W.I.Taylor, Experientia, 1965, 21, 508.
10. These will be presented elsewhere.
11. **7b** : ^{1}H-NMR (C_6D_6, 250 MHz): -0.18 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.85 (s, 9H, t-Bu), 1.62-1.70 (m, 1H, C_6H), 2.04-2.12 (m, 1H, $C_{14}H$), 2.30-2.50 (m, 2H, $C_{14}H$, $C_{20}H$), 2.64 (s, 3H, NCH_3), 2.77 (d, J = 10.5 Hz, $C_{21}H$), 3.38 (s, 3H, OCH_3), 3.43-3.52 (m, 1H, C_5H), 3.65-3.77 (m, 1H, C_5H), 4.59 (s, 1H, C_2H), 6.30 (d, J = 7.8 Hz, $C_{12}H$), 6.58 (t, J = 7.4 Hz, 1H, $C_{10}H$), 6.80 (d, J = 7.2 Hz, 1H, C_9H), 7.03 (dt, J = 1.0 and 7.6 Hz, 1H, $C_{11}H$). Details of the spectrum will be presented in a full paper.

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