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Stereospecific Synthesis of a 2β-H-indoloquinolizidinone: Key Intermediate in Indole Alkaloids Synthesis

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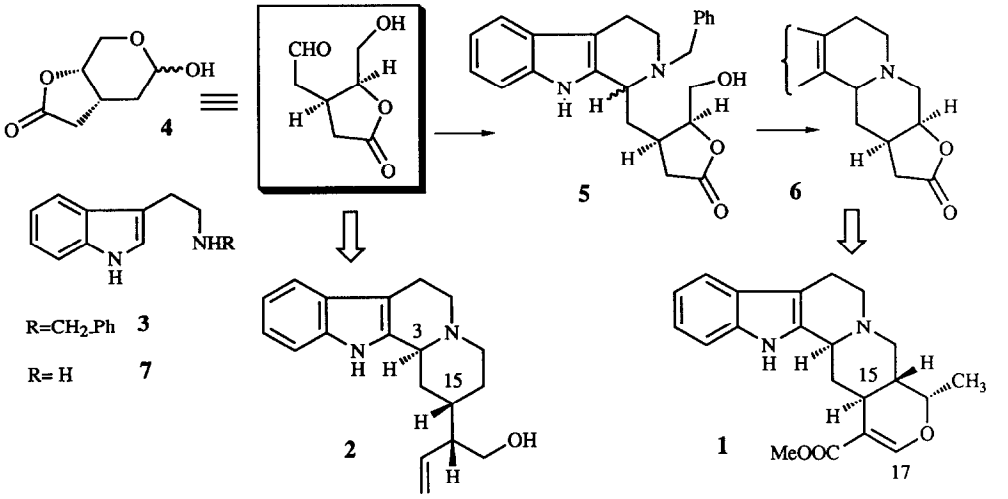
Key Words :2β-H-indoloquinolizidinone , carbohydrates , alkaloids , 2-oxa-8-aza-bicyclo [3.3.1] nonane , Pictet-Spengler.

***Abstract** : The pyranose **4** yielded the 2-oxa-8-aza-bicyclo [3.3.1] nonane **14** by condensation with tryptamine **7**; the intermediate acyliminium **18** led to the expected 2β-H-indoloquinolizidinone **15ab** through a Pictet-Spengler cyclisation.*

In the course of a total synthesis of indole alkaloids, we were interested in searching for new strategies directed to construction of indoloquinolizidine skeleton. Our approaches in this area were grounded on the use of carbohydrates as chiral starting materials.

In a previous work[1], concerned with a synthetic approach of (-)-ajmalicine **1**, the 15α-H stereocontrol was obtained by a Pictet-Spengler condensation between N_b-benzyl-tryptamine **3** and pyranose **4** [1,2],affording lactones **6** in good yield (scheme 1).

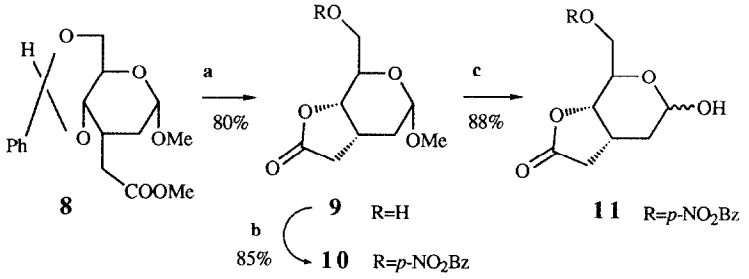


Scheme 1

In order to obtain the reverse15β-H structure present in (-)-antirhine **2** [3] we decided to use unprotected

tryptamine **7** instead of **3** in the Pictet-Spengler cyclisation (scheme 1).

The methyl glycoside **8** [2] when submitted to hydrogenation (H_2,5% Pd-C, MeOH), gave the methyl pyranoside **9** (80 %) , the primary alcohol of which was protected as a *p*-nitro-benzoate **10** . The methyl glycoside **10** furnished **11** after acid hydrolysis in 88 % yield [4] (scheme 2).

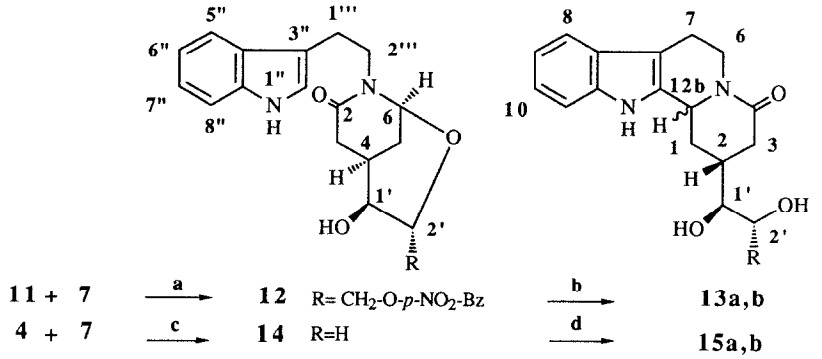


a) Pd 5%, MeOH, H_2 ; b) *p*-NO_2-Bz-Cl , Py, 20° 12h ; c) H_2O , AcOH 5%, reflux 12h

Scheme 2

The masked aldehyde **11** was condensed with tryptamine **7** in acidic medium and gave the amide **12** (85%) [5]. Under these conditions the Pictet-Spengler cyclisation did not occur .However **12** when subsequently warmed in H_2O, AcOH 30 % (reflux, 3 h), the two isomeric derivatives **13a** and **13b** with the expected 2β-H configuration (**13a** /**13b** =1/1) were obtained [6].

Similarly,when pyranose **4** was treated under neutral conditions with tryptamine **7** (C_6H_6, reflux 3h) 2-oxa-8-aza-bicyclo [3.3.1] nonane derivative **14** [7] was obtained in quantitatively yield. Subsequent treatment (toluene, AcOH 20 %, reflux 48 h) applied to **14** led to the **15a,b** indoloquinolizidinones in 90 % yield [8] (**15a** / **15b** =1 / 1) (scheme 3).

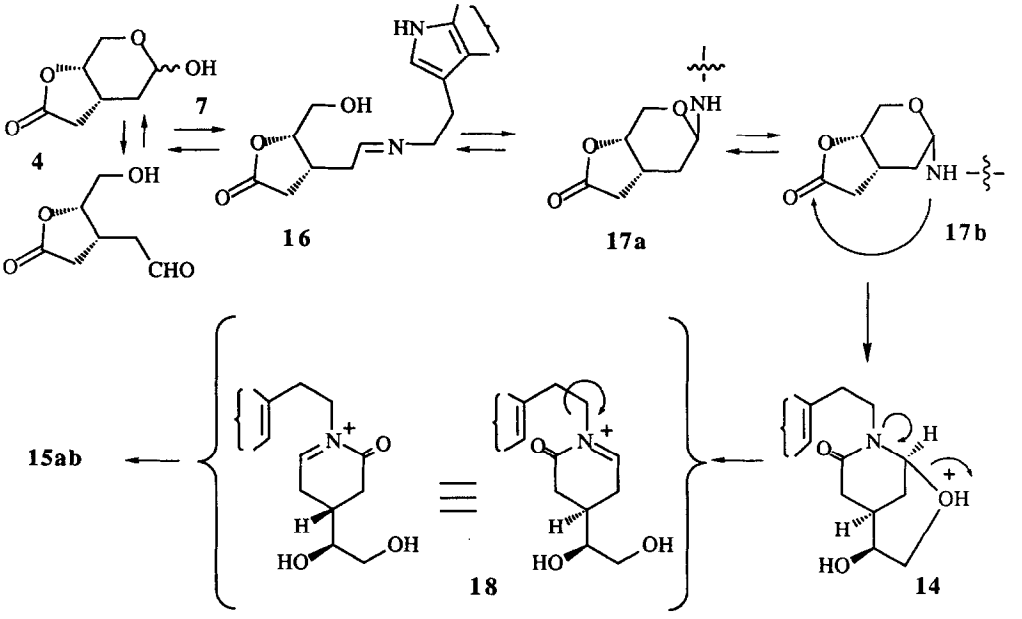


a) C_6H_6 , AcOH 5%, reflux 2h (85%) ; b) H_2O, AcOH 30%, reflux 3h (90%) ; c) C_6H_6 , reflux 3h (>95%)
d) toluene, AcOH 20%, reflux 48h (90%)

Scheme 3

These reactions led to the indoloquinolizidinones **13a,b** or **15a,b** with the expected 2β-H configuration which corresponds to the 15β-H structure of (-)-antirhine **2**, but more interesting was the obtention of the 2-oxa-8-aza-bicyclo [3.3.1] nonane derivatives **12** and **14**.

From the above results we can infer that condensation of **4** and tryptamine **7**, furnished the intermediate imine **16** which led to the two N-glycoside derivatives **17a** and **17b**.The latter could then yield the lactam **14** in an essentially irreversible process.In acid medium, the lactam **14** was converted into the acyliminium **18**[9] and thus inducing the Pictet-Spengler cyclisation into **15a,b** (scheme 4)



Scheme 4

The approach developed here to a stereospecific 2β-H indoloquinolizidinone synthesis from chiral building blocks, as sugar derivatives, represents an efficient route

More generally this work appears a new and general method for chiral synthesis of 2-oxo-8-aza-bicyclo [3.3.1] nonane derivatives and substituted piperidines as well ; investigations in this area are currently in progress.

References and Notes

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4. **9** $[\alpha]_D$ = + 118 (c = 1.06, $CHCl_3$) ; **10** mp = 135°C $[\alpha]_D$ = + 8 (c = 1.12, $CHCl_3$) ; **11** $[\alpha]_D$ = + 47 (12h,c=0.62,MeOH).

5 . **12** ^{1}H NMR (400 MHz) : 2.48 (m, 1H, H-3a) ; 2.56 (m, 1H, H-3b) ; 2.42 (m, 1H, H-4) ; 1.82 (ddd, J = 13.0, 4.0, 2.0 Hz, 1H, H-5a) ; 1.92 (ddd, J = 13.0, 3.0, 3.0 Hz, 1H, H-5b) ; 4.87 (m, 1H, H-6) ; 3.44 (m, 1H, H-1) ; 3.8 (m, 1H, H-2') ; 3.64 (m, 1H, H-3'a) ; 3.76 (m, 1H, H-3'b) ; 3.64 - 3.76 (m, 2H, H-2"'a + H-2"'b) ; 3.1 (m, 2H, H-1"'a + H-1"'b) ; 6.95 (d, J = 3 Hz, 1H, H-2") ; 7.54 (d, J = 7.5 Hz, 1H, H-5") ; 7.03 (t, J = 7.5 Hz, 1H, H-6") ; 7.14 (t, J = 7.5 Hz, 1H, H-7") ; 7.33 (d, J = 7.5 Hz, 1H, H-8") ; 8.7 (br s, 1H, N-H).

6 . **13a** and **13b** were acetylated (Ac_2O/Py) and the corresponding acetates **13c** and **13d** were purified by chromatography on silica gel.

13c (12b H-α) ; ^{1}H NMR (400 MHz) : 2.08 (ddd, J = 13,0, 11,0 , 4.0 Hz, 1H, H-1a) ; 2.71 (ddd, J = 11.0, 4.0, 2.0 Hz, 1H, H-1b) ; 2.27 (m, 1H, H-2) ; 2.47 (dd, J = 15.0, 1.0 Hz, 1H, H-3b) ; 2.99 (m, 1H, H-6a) ; 5.05 (m, 1H, H-6b) ; 2.99 (m, 2H, H-7a + H-7b) ; 7.56 (d, J = 7.5 Hz, 1H, H-8) ; 7.25 (t, J = 7.5 Hz, 1H, H-9) ; 7.17 (t, J = 7.5 Hz, 1H, H-10) ; 7.40 (d, J = 7.5 Hz, 1H, H-11) ; 7.9 (s, 1H, NH) ; 4.77 (dd, J = 11.0, 4.0 Hz, 1H, H-12b) ; 5.27 (dd, J = 7.0, 4.0 Hz, 1H, H-1') ; 5.51 (ddd, J = 7,0, 6.5, 2.0 Hz, 1H, H-2') ; 4.43 (dd, J = 12.5, 6.5 Hz, 1H, H-3'a) ; 4.72 (dd, J = 12.5, 2.0 Hz, 1H, H-3'b) ; 1.87 (s, 3H, $COCH_3$) ; 2.18 (s, 3H, $COCH_3$).

13d (12b H-β) ; 1.55 (ddd, J = 13.0, 11.0, 12.5 Hz, 1H, H-1a) ; 2.56 (ddd, J = 13.0, 4.0, 2..0 Hz, 1H, H-1b) ; 2.32 (m, 1H, H-2) ; 2.27 (dd, J = 13.0, 8.0 Hz, 1H, H-3a) ; 2.68 (dd, J = 13.0, 2.0 Hz, 1H, H-3b) ; 2.86 (m, 1H, H-6a) ; 5.17 (m, 1H, H-6b) ; 2.86 (m, 2H, H-7a + H-7b) ; 4.77 (dd, J = 11.0, 4.0 Hz, 1H, H-12b) ; 5.27 (dd, J = 7.0, 4.0 Hz, 1H, H-1') ; 5.51 (ddd, J = 7.0, 6.5, 2.0 Hz, 1H, H-2') ; 4.43 (dd, J = 12.5, 6.5 Hz, 1H, H-3'a) ; 4.72 (dd, J = 12.5, 2.0 Hz, 1H, H-3'b) ; 2.15 (s, 3H, $COCH_3$) ; 2.16,(s, 3H, $COCH_3$).

7 . **14** mp = 135° (acetone) ; $[\alpha]_D$ = - 33 (c = 1.06, MeOH) ; ^{1}H NMR (400 MHz) : 2.47 (dd, J = 18.5, 7.0 Hz, 1H, H-3a) ; 2.89 (ddd, J = 18.5, 1.5, 1.5 Hz, 1H, H-3b) ; 2.32 (m, 1H, H-4) ; 1.7 (ddd, J = 13.5, 4.0, 1.5 Hz, 1H, H-5a) ; 1.82 (ddd, J = 13.5, 3.5, 1.5, 1H, H-5b) ; 4;67 (m, 1H, H-6) ; 8.12 (s, 1H, NH) ; 7.02 (d, J = 2.0 Hz, 1H, H-2") ; 3.9 (m, 1H, H-1') ; 3.22 (dd, J = 12.5, 10.5 Hz, 1H, H-2'a) ; 3.72 (dd, J = 12.5, 6.0 Hz, 1H, H-2'b) ; 3.5 (ddd, J = 12.0, 8.5, 8.0 Hz, 1H, H-2"'a) ; 3.87 (ddd, J = 12.0, 8.5, 4.5 Hz, 1H, H-2"'b) ; 3.04 (ddd, J = 15.0, 8.5, 4.0 Hz, 1H, H-1"'a) ; 3.12 (ddd, J = 15.0, 8.5,8Hz,1H,H-1"'b)

^{13}C NMR : 171.4 (C-2) ; 30.7 (C-3) ; 31.3 (C-4) ; 30.3 (C-5) ; 81.2 (C-6) ; 66.6 (C-1') ; 61.3 (C-2') ; 122.1 (C-2") ; 112.8 (C-3") ; 127.4 (C-4") ; 118.7 (C-5") ; 121.4 (C-6") ; 119.3 (C-7") ; 111.3 (C-8") ; 136.4 (C-9") ; 23.8(C- 1"' ; 47.6 (C-2"').

8 . **15a** and **15b** were acetylated and the corresponding acetates **15c** and **15d** purified by chomatography on silica gel

15c (12b H-α) ^{1}H NMR (400 MHz) : 2.18 (m, 1H, H-1a) ; 2.72 (ddd, J = 12.0, 4.0, 2.0 Hz, 1H, H-1b) ; 2.18 (m, 1H, H-2); 2.33 (dd, J = 17.0, 10.0 Hz, 1H, H-3a) ; 2.49 (dd, J = 17.0, 5.0 Hz, 1H, H -3b) ; 2.98 (m, 1H, H-6a) ; 4.99 (m, 1H, H-6b) ; 2.98 (m, H-7a +H-7b) ; 7.51 (d, J = 7.5 Hz, 1H, H-8) ; 7.22 (t, J = 7.5 Hz, 1H, H-9) ; 7.15 (t, J = 7.5, 1H, H-10) ; 7.38 (d, J = 7.5 Hz, 1H, H-11) ; 8.18 (s, 1H, NH) ; 5.02 (dd, J = 13.0, 4.0 Hz, 1H, H-12b) ; 5.07 (ddd, J = 5.5, 5.5, 5.5 Hz, 1H, H-1') ; 4.02 (dd, J = 12.0, 5.5Hz, 1H, H-2'a) ; 4.55 (dd, J = 12.0, 5.5 Hz, 1H, H-2'b) ; 1.99 (s, 3H, $COCH_3$) ; 2.13 (s, 2H, $COCH_3$).

15d (12b H-β) ^{1}H NMR (400 MHz) : 1.58 (ddd, J = 12.5, 12.5, 12.5 Hz, 1H, H-1a) ; 2.54 (ddd, J = 12.5, 4.0, 1.0 Hz, 1H, H-1b) ; 2.37 (m, 1H, H-2) ; 2.24 (dd, J = 17.0, 13.0 Hz, 1H, H-3a) ; 2.63 (ddd, J = 17.0, 4.0, 2.0 Hz, 1H, H-3b) ; 2.87 (m, 1H, H-6a) ; 5.17 (m, 1H, H-6b) ; 2.84 (m, 2H, H-7a + H-7b) ; 4.8 (dd, J = 12.5, 4.0 Hz, 1H, H-12b) ; 4.99 (m, 1H, H-1') ; 4.09 (dd, J = 12.5, 6.0 Hz, 1H, H-2'a) ; 4.42 (dd, J = 12.5, 4.0 Hz, 1H, H-2'b).

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