Tetrahedron Letters, Vol.32, No.35, pp 4483-4486, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Carbohydrates In Total Synthesis of (-)-Antirhine

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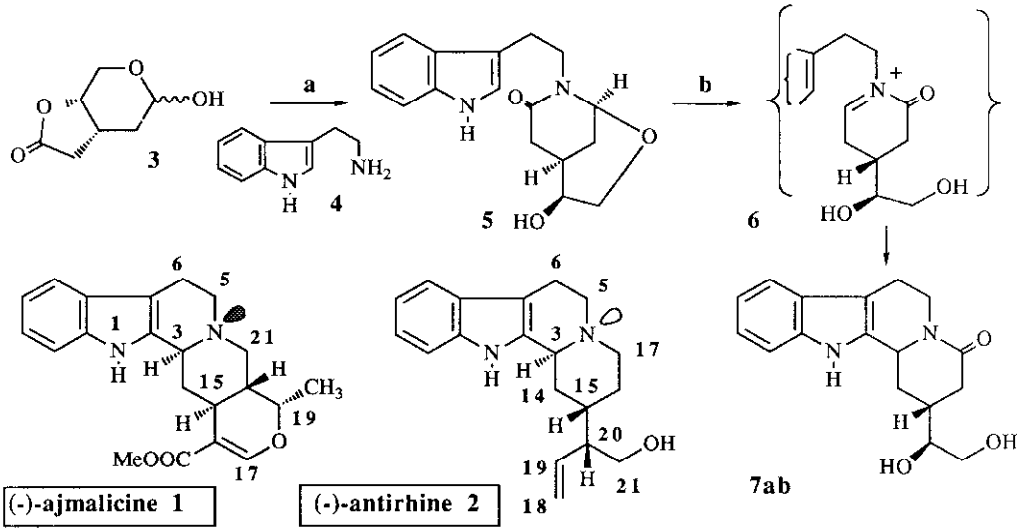
Key Words :Pictet-Spengler cyclisation , alkaloids , carbohydrates , total synthesis , (-)-antirhine

Abstract : Amide 5 was obtained by condensation between pyranose 3 and tryptamine 4 ; in few steps, the indoloquinolizidine 13a was prepared with a perfect stereocontrol of the 2β-H configuration ; total synthesis of (-)-antirhine 2 was then achieved from 13a.

Yohimbines or heteroyohimbines indole alkaloids such as (-)-ajmalicine **1** possess a *cis* 3α-H, 15α-H configuration ; however (-)-antirhine **2** [1], the major alkaloid of *Antirhea jutaminosa*, presents a *trans* 3α-H, 15βH structure with a *cis* C/D ring junction (scheme 1).

Owing to difficulties encountered in the stereocontrolled formation of the three chiral centers C-3, C-15 and C-20, few total syntheses of (-)-antirhine **2** have been reported [2].



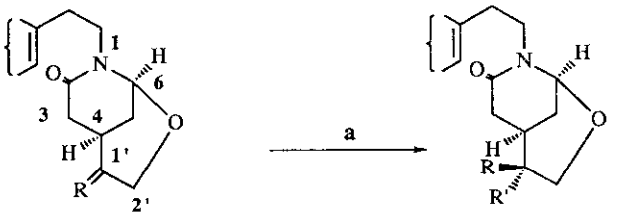
a) C_6H_6 , reflux 3h (>95%) ; b) toluene , reflux 48h (90%)

Scheme 1

In the letter [3] we described the preparation of the amide **5** by a coupling reaction between tryptamine **4** and pyranose **3** ; subsequent Pictet-Spengler cyclisation led to the indolo [2.3-a]-4-quinolizidinones **7a,b** with a 15β-H configuration *via* the acyliminium **6**.

In our approach to the total synthesis of (-)-antirhine **2**, compound **5** was oxidised by the SO_3-pyridine complex [4] into the ketone **8** (70 %) [5] ; a subsequent Wadsworth-Emmons reaction furnished the unsaturated ester **9** in quantitative yield.

Attempts to reduce **9** by catalytic hydrogenation (H_2 10 % Pd-C, MeOH) or by NaHTe [6] led to the compound **11** instead of the suitable epimer **10** (scheme 2).



8 R= O

9 R=CH-CO_2Me

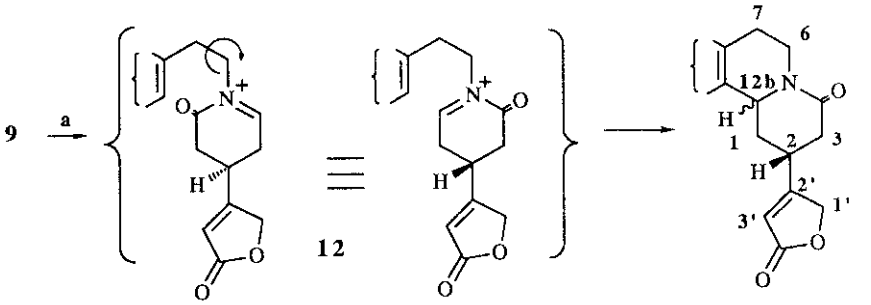
10 R=H , R'=CH_2-CO_2Me

11 R=CH_2-CO_2Me , R'=H

a) 10% Pd-C , MeOH , H_2 (90%) or NaHTe, EtOH (75%)

Scheme 2

Indoloquinolizidinones **13a** and **13b** were conveniently obtained by acidic treatment of **9** (toluene-AcOH 20 %, Dean-Stark, 48 h) . Acid catalysed opening of the oxygenated ring led to the formation of the intermediate acyliminium **12** (scheme 3).



13a H $_{12b}$ - α

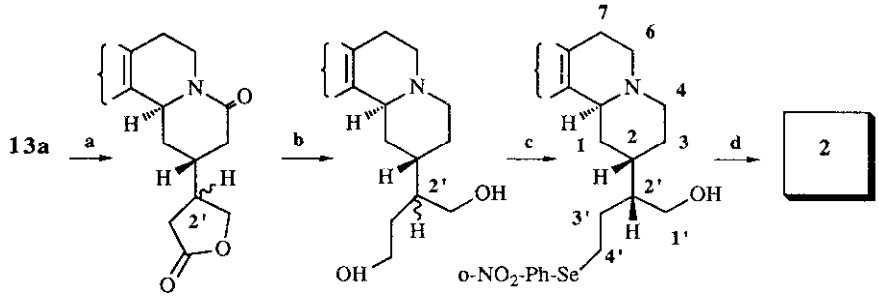
13b H $_{12b}$ -β

a) toluene, AcOH 20% reflux 48h (90%) , **13a** /**13b** =70 /30

Scheme 3

Purified major 12b H-α isomer **13a**[7] was reduced into the two saturated lactones **14a** and **14b** by catalytic hydrogenation (H_2- 10 % Pd -C, MeOH, 90 %, **14a** / **14b** ≈ 50/50) [8].

The two lactones **14a** and **14b** were isolated by HPLC and readily reduced into the corresponding indoloquinolizidines **15a** and **15b** ($LiAlH_4$-THF, reflux, 4h, 80 %) (scheme 4).



14a (2'R) ▬H **15a** **16**

14b (2'S) ┈H **15b**

a) 10% Pd-C, MeOH, H_2 (90%) ; b) $LiAlH_4$,THF, reflux 4h (80%) ; c) o-NO_2-Ph-SeCN, Bu_3P,THF reflux 4h (80%) ;d) MCPBA , CH_2Cl_2, (45%)

Scheme 4

Structural elucidation of the 3α-H, 15β-H, 2'(R) isomer **15a** [9] was ascertained in an unusual way ; the ester **11** with undesirable configuration was successively treated in acidic medium (toluene-AcOH, 20 %, Dean-Stark, 12 h) and with $LiAlH_4$-THF (reflux 4 h) to furnish after purification the 3α-H, 15β-H, 2'(S) alcohol **15b**.

The **15a** isomer so distinguished was then regioselectively selenated (Takano's method [2a]) into **16** (O-NO_2Ph-SeCN-Bu_3P-THF, 30 % yield) ; oxidation of **16** (MCPBA-CH_2Cl_2, 45 % yield) gave finally the expected (-)-antirhine **2.**

^{1}H NMR (250 MHz), IR and mass spectra are in full agreement with those of the natural compound [10]; As so optical purity , **2** has an $[\alpha]_D$ = - 2 (c = 0.1, $CHCl_3$) identical with that reported in litterature : (Litt. [1] $[\alpha]_D$ = - 2, c = 0.23, $CHCl_3$) [11].

References and Notes

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5 . **8** : ^{1}H NMR (400 MHz) : 1.87 (ddd, J = 13.5, 2.5, 2.5 Hz, 1H, H-5a) ; 2.24 (ddd, J = 13.5, 3, 2.5 Hz, 1H, H-5b) ; 2.57 (dd, J = 18, 2 Hz, 1H, H-3a) ; 2.77 (dd, J = 18, 6.5 Hz, 1H, H-3b) ; 2.87 (dddd, J = 6.5, 3, 2.5, 2 Hz, 1H, H-4) ; 3.98 (d, J = 17.5 Hz, 1H, H-2'a) ; 4.11 (d, J = 17.5 Hz, 1H, H-2'b) ; 4.86 (dd, J = 2.5, 2.5 Hz, 1H, H-6).

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7 . **13a** : (12b H-α) ^{1}H NMR (400 MHz) : 2;46 (ddd, J = 10.4, 3.5 Hz, 1H, H-1a) ; 2.47 (ddd, J = 10, 6, 1 Hz, H-1b) ; 2.55 (dd, J = 17, 8 Hz, 1H, H-3a) ; 2.72 (dd, J = 17, 5 Hz, 1H, H-3b) ; 2.76 (ddd, J = 12, 2.5, 1 Hz, 1H, H-7a) ; 2.95 (m, 1H, H-2) ; 2.95 (ddd, J = 12, 12, 2.5 Hz, 1H, H-6a) ; 2.97 (ddd, J = 12, 12, 4.5 Hz, 1H, H-7b) ; 4.8 (dd, J = 17.5, 1.5 Hz, 1H, H-1'a) ; 4.91 (dd, J = 17.5, 1.5 Hz, 1H, H-1'b) ; 4.91 (ddd, J = 6, 3.5, 2.5 Hz, 1H, H-12b) ; 5.08 (dddd, J = 12, 4.5, 2, 1 Hz, 1H, H-6b) ; 6.0 (dd, J = 15, 1.5 Hz, 1H, H-3').

13b : (12b H-β) ^{1}H NMR (400 MHz, Pyridine) : 1.79 (ddd, J = 12, 12, 12Hz, 1H, H-1a) ; 2.56 (dd, J = 17, 11.5 Hz, 1H, H-3a) ; 2.86 (ddd, J = 12, 2.5, 2 Hz, 1H, H-1b) ; 2.94 (m, 1H, H-2) ; 2.97 (dd, J = 17, 2.5 Hz, 1H, H-3b) ; 4.83 (dd, J = 17.5, 2 Hz, 1H, H-1'a) ; 4.91 (dd, J = 17.5, 2 Hz, 1H, H-1'b) ; 4.97 (ddd, J = 12, 2.5, 2 Hz, 1H, H-12b) ; 6.05 (dd, J = 2.2 Hz, 1H, H-3').

8 . **14a** : (12b H-α, 2'(R)), ^{1}H NMR (400 MHz) : 1.97 (m, 1H, H-2) ; 2.19 (m, 2H, H-1a + H-1b) ; 2.29 (m, 1H, H-3'a) ; 2.34 (dd, J = 17, 9 Hz, 1H, H-3a) ; 2.58 (dd, J = 17, 4.5 Hz, 1H, H-3b) ; 2.66 (m, 1H, H-2') ; 2.76 (m, 1H, H-3'b) ; 2.99 (m, 1H, H-6a) ; 3.16 (m, 2H, H-7a + H-7b)) ; 4.13 (dd, J = 8.7 Hz, 1H, H-1'a) ; 4.60 (dd, J = 8.7 Hz, 1H, H-1'b) ;5.02 (dd, J = 7.4 Hz, 1H, H-12b) ; 5.10 (m, 1H, H-6b) ; 7.18 (t, J = 7.5 Hz, 1H, H-10) ; 7.26 (t, J = 7.5 Hz, 1H, H-9) ; 7.42 (d, J = 7.5 Hz, 1H, H-11) ; 7.55 (d, J = 7.5 Hz, 1H, H-8) ; 7.9 (s, 1H, NH).

14b : (12b H-β, 2'(S)), ^{1}H NMR (400 MHz) : 1.95 (m, 1H, H-2) ; 2.20 (m, 2H, H-1a + H-1b) ; 2.30 (m, 1H, H-3'a) ; 2.35 (dd, J = 17, 9 Hz, 1H, H-3a) ; 2.60 (dd, J = 17, 5 Hz, 1H, H-3b) ; 2.70 (m, 1H, H-2') ; 2.80 (m, 1H, H-3'b) ; 3.10 (m, 1H, H-6a) ; 3.2 (m, 2H, H-7a + H-7b) ; 4.15 (dd, J = 8, 8 Hz, 1H, H-1'a) ; 4.60 (dd, J = 8, 8 Hz, 1H, H-1'b) ; 5.10 (dd, J = 6.5, 4.5 Hz, 1H, H-12b) ; 5.10 (m, 1H, H-6b) ; 7.2 (t, J = 7.5 Hz, 1H, H-10) ; 7.28 (t, J = 7.5 Hz, 1H, H-9) ; 7.45 (d, J = 7.5 Hz, 1H, H-11) ; 7.51 (d, J = 7.5Hz, 1H, H-8) ; 8.1 (s, 1H, NH).

9 . **15a** : (2'R) mp = 208 - 215° C (Litt.[2a] ; mp = 215 - 218°C) .

10 . **2** : mp = 104 - 107°C $[\alpha]_D$ = - 2 (c = 0.1, $CHCl_3$) ; (Litt. [1] : mp = 112 - 114°C), $[\alpha]_D$ = - 2 (c = 0.23, $CHCl_3$) .

^{1}H NMR (250 MHz) : 1.4 - 2.2 (m, 6H) ; 2.6 - 3.3 (m, 6H) ; 3.62 (dd, J = 10, 6 Hz, 1H, H-21a) ; 3.69 (dd, J = 10, 4 Hz, 1H, H-21b) ; 4.32 (m, 1H, H-3) ; 5.09 (dd, J = 18, 2 Hz, 1H, H-18a) ; 5.15 (dd, J = 10.5, 1 Hz, 1H, H-18b) ; 5.55 (ddd, J = 18, 10.5, 8 Hz, 1H, H-19) ; 7.07 (t, J = 7.5 Hz, 1H, H-10) ; 7.13 (t, J = 7.5 Hz, 1H, H-11) ; 7.39 (d, J = 7.5 Hz, 1H, H-9) ; 7.43 (d, J = 7.5 Hz, 1H, H-12).

11 . We are indebted to Professor P. POTIER (I.C.S.N., C.N.R.S. Gif/Yvette, France) for generously providing a sample of natural antirhine.

(Received in France 24 April 1991)