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A SHORT STEREOSELECTIVE SYNTHESIS OF (±)-12-DESMETHOXY CUANZINE

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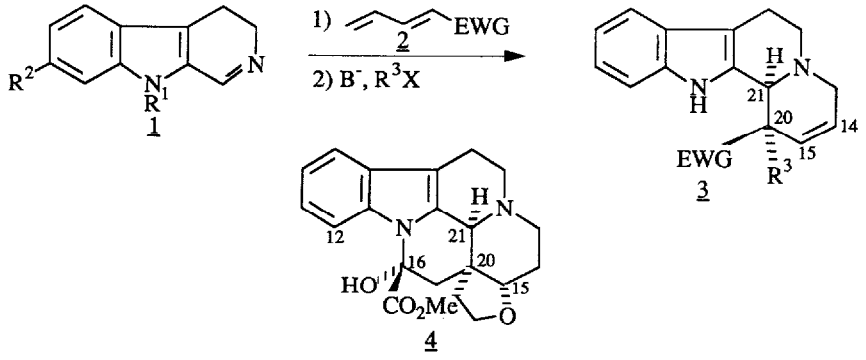
Summary : The synthesis of (±)-12-desmethoxy cuanzine **4** was achieved *via* a stereoselective alkylation of the mixture of indolo-quinolizidines **5** and **6** followed by an oxidative cyclisation and an alkylation of the aldehyde intermediate **14** by methyl isocyanoacetate.

An imino Diels-Alder reaction between a dihydro β-carboline **1** and a diene conjugated with an electron-withdrawing group **2** followed by a regio- and stereoselective alkylation gave rise to indolo-quinolizidines of general formula **3** (Scheme I).

This process which has been used in the total synthesis of indole alkaloids vindoline[1] and vincamine[2] allowed us to control in two steps not only the relative configurations at C-20 and C-21[3] but also the position of the C-14 -C-15 double bond. It is noteworthy that the introduction of this double bond during the first steps of the synthesis provides a great versatility in the elaboration of complex indole alkaloids. According to this strategy, we present in this paper the total synthesis of (±)-12-desmethoxy cuanzine **4**[4].

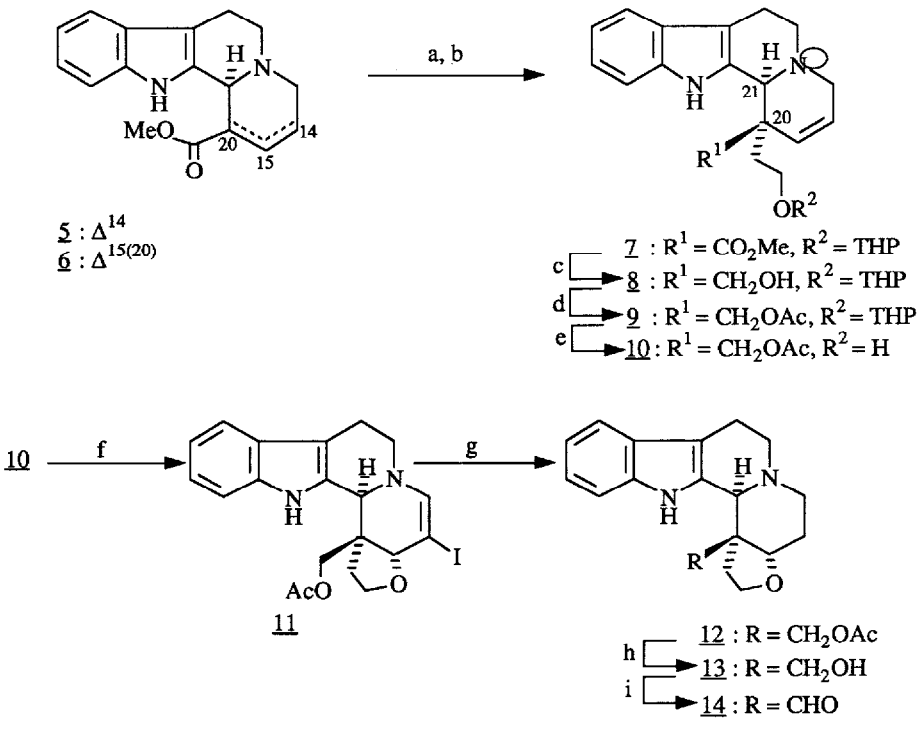


Scheme I

Thus the mixture of indoloquinolizidines **5** and **6**[2] deprotonated with LDA in the presence of HMPA in THF[5] was alkylated with 2-(2'-iodo-ethyloxy)-tetrahydropyran giving rise to the

indoloquinolizidine **7** (yield 60%). Comparison of the chemical shift of C-21-H (4.02 ppm) in the PMR spectrum of compound **7** with other indoloquinolizidines as well as the presence in the infrared of the Wenkert-Bohlmann bands[6] were in agreement with a *cis* relationship between C-21-H and the side chain at C-20 and with a *trans* quinolizidine conformation.

Reduction of the ester group in **7** and acetylation followed by the selective hydrolysis of the acetal provided compound **10** (95% overall). The cyclisation of the primary alcohol in **10** in the presence of I_2-KIO_3[7] gave rise to the tetracyclic indoloquinolizidine derivative **11** (53%). Hydrogenolysis of **11** with concomitant reduction afforded compound **12** which, on saponification, furnished quantitatively the alcohol **13**. Oxidation of **13** gave the corresponding aldehyde **14** (overall yield from **11** : 90%) (Scheme II).



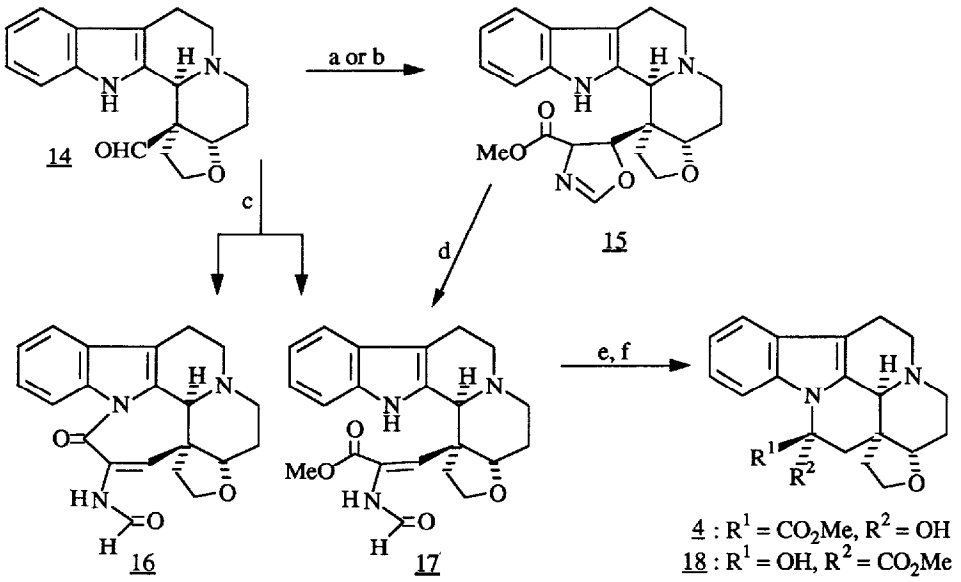
a: LDA (2.2 eq.), HMPA, THF -70°C→ -40°C, 20 min. b: $I(CH_2)_2OTHP$ (1 eq.), -40°C, 20 min. c: $LiAlH_4$ (2.6 eq.), THF, -70°C, 1h30. d: Ac_2O (3eq.), C_5H_5N, 14h, R.T. e: TsOH (1.1 eq.), MeOH, H_2O, Rfx, 15 min. f: I_2 (1.5 eq.), KIO_3 (0.8 eq.), CH_3CO_2H, dioxane, H_2O, R.T., 6h. g: PtO_2, H_2, MeOH, 1h. h: K_2CO_3, MeOH (2M), 20°C, 1h. i: DMSO, SO_3-C_5H_5N (4 eq.), Et_3N, R.T., 1h.

Scheme II

At this stage, we anticipated that the experimental conditions used in the synthesis of vincamine[2] should provide the target intermediate **17**. Thus methyl isocyanoacetate was deprotonated with *t*BuOK and condensed at low temperature with the aldehyde **14** (Scheme III). Unexpectedly, the oxazoline **15** was the only product isolated (25%) along with the recovered aldehyde **14** (35%). The yield of **15** went up to 92% when LDA was used as the base at -70°C. At this point, we suspected that the presence of an additional ring precluded the cyclisation observed during the vincamine synthesis[2]. But, when the reaction was performed at a higher temperature between -20°C and 0°C, only a mixture of polar unidentified products was obtained either with *t*BuOK or with LDA. In a similar manner, treatment of the oxazoline intermediate **15** with the same bases did not give any identifiable material.

However, with LiHMDS as the base, between -70°C and -40°C, a mixture of lactam **16** and ester **17** was smoothly obtained in 23% and 63% yields respectively. Furthermore, treatment of oxazoline **15** with the same base afforded the ester **17** in 55% yield. The difference of behaviour between LDA and *t*BuOK and the less basic LiHMDS is worthy of note.

Having in hands compounds **16** and **17**, the synthesis was achieved in a one pot two-step process, by acidic and basic treatment, performed on the mixture of those two derivatives, which furnished 12-desmethoxy cuanzine **4**[8] and 16-epi-12-desmethoxy cuanzine **18**[8] in 95% yield (ratio 2:1).



a: *t*BuOK (3 eq.), $CNCH_2CO_2Me$ (2 eq.), THF, -70°C→-20°C, 1h30. b: LDA (3 eq.), $CNCH_2CO_2Me$ (2 eq.), THF, -70°C, 1 h. c: LiHMDS (3 eq.), $CNCH_2CO_2Me$ (2 eq.), THF, -70°C→-40°C, 14h. d: LiHMDS (2.2 eq.), THF, -70°C, 1h.e: MeOH, HCl (0.2 M), 4 eq. f: MeOH, Na_2CO_3 (8 eq.).

Scheme III

This work constitutes the first total synthesis in the cuanzine series[9]. It was achieved in eleven steps from the mixture of indoloquinolizidines **5** and **6**.

References

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8) ^{1}H NMR (400 MHz) (C_6D_6; TMS: 0 ppm, J=Hz): **4** : 8.02 (m, 1H) arom.; 7.62 (m, 1H) arom.; 7.30 (m, 2H) arom.; 4.08 (s, 1H) C-21-H; 3.87 (dd, 1H, $J_{14a\text{-}15}$=11, $J_{14b\text{-}15}$=6.4) C-15-H; 3.80 (m, 1H) C-18-Ha; 3.72 (m, 1H) C-18-Hb; 3.11 (s, 3H) CO_2CH_3; 2.68 (d, 1H, J_{AB}=15) C-17-Ha; 1.71 (m, 1H) C-14-Hb; 1.27 (d, 1H, J_{AB}=15) C-17-Hb; 1.08 (m, 1H) C-19-Hb. UV (λ max, nm, MeOH) 270, 220; MS: 368 (M^+), 367, 308, 266 (100%), 185, 170; IR ($CHCl_3$, cm^{-1}) 3400, 2925, 2850, 1730.
18 : 7.58 (d, 1H) arom; 7.23 (m, 3H) arom.; 4.82 (dd, 1H, $J_{14a\text{-}15}$=11, $J_{14b\text{-}15}$=6.5), C-15-H; 4.12 (s, 1H), C-21-H; 3.87 (m, 1H) C-18-Ha; 3.76 (m, 1H) C-18-Hb; 3.23 (s, 3H) CO_2CH_3; 3.02 (dd, 2H, C-5-H_2); 2.71 (m, 2H) C-6-Ha, C-19-Ha; 2.28 (m, 2H) C-6-Hb, C-3-Ha; 2.15 (m, 2H) C-3-Hb, OH; 2.10 (d, 1H, J_{AB}=14) C-17-Ha; 1.92 (d, 1H, J_{AB}=14) C-17-Hb; 1.69 (m, 1H) C-14-Ha; 1.52 (m, 1H) C-14-Hb; 1.07 (m, 1H) C-19-Hb. U.V. (λmax, nm, MeOH) 274, 222, 206; MS (m/z): 368 (M^+), 367, 308, 266, 197, 185 (100%), 170; IR ($CHCl_3$, cm^{-1}) 3380, 2925, 2850, 1730.
9) After submission of this manuscript, a synthetic approach of the structural cuanzine unit appeared in the litterature: Palmisano, G., Danieli, D., Lesma, G. and Passarella, D., *Tetrahedron* , **1989**, 45, 3583.

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