SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS LIII[1]. A SIMPLE SYNTHESIS OF (±)-3-OXOVINCADIFFORMINE AND (±)-3-OXOMINOVINE

György Kalaus[a], Chau Phan Dinh[a], Mária Kajtár-Peredy[b], János Brlik[c], Lajos Szabó[a], and Csaba Szántay[a,b,*]

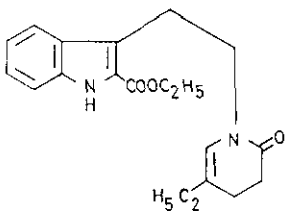
[a]Institute of Organic Chemistry, Technical University, H-1521 Budapest

[b]Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, Hungary

[c]MS Laboratory of Institute for General and Analytical Chemistry, Technical University, H-1521 Budapest, Hungary

Abstract - Starting from compound 1 syntheses of the title compounds were achieved via linear reaction sequences.

We have reported[2] that 2-(ethoxycarbonyl)tryptamine and methyl 4-formylhexanoate react to give the key intermediate (1) of a convenient syntheses of (±)-vincadifformine (2), (±)-ψ-vincadifformine (3) and (±)-minovine (4).[3]



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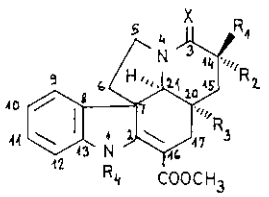


2 X=H_2, R_1=R_2=R_4=H, R_3=C_2H_5

3 X=H_2, R_2=R_3=R_4=H, R_1=C_2H_5

4 X=H_2, R_1=R_2=H, R_3=C_2H_5, R_4=CH_3

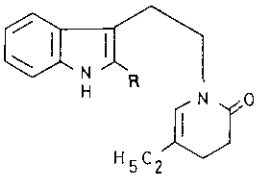
5 X=O, R_1=R_2=R_4=H, R_3=C_2H_5

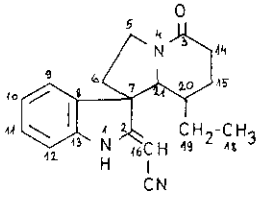
6 X=O, R_1=R_2=H, R_3=C_2H_5, R_4=CH_3

Compound 1 proved to be a useful starting material also for the syntheses of (±)-3-oxovincadifformine (5) and (±)-3-oxominovine (6).

Le Men et al.[4] reported the synthesis of 5 as an intermediate in their total synthesis of (±)vincadifformine (2). It's noteworthy that its 14,15-unsaturated derivative was isolated from *Amsonia elliptica*.[5]

The ester group in compound 1 was reduced with lithium aluminium hydride in THF (-40 °C, 3 h) to yield compound 7 in 60 % yield, mp 149-151 °C (from methanol-water). Next, the elongation of the carbon chain was effected according to Kutney's method[6] as follows. Benzoylation of 7 with benzoyl chloride in dichloromethane, in the presence of triethylamine and 4-dimethylaminopyridine catalyst, at -5 °C for 1 h, gave 8 as an oil in 87 % yield. It was made to react with potassium cyanide in dry acetonitrile (80 °C, 5 h) to give compound 9 in 87 % yield, mp 151-152 °C (from acetonitrile-ether mixture). The product was treated at room temperature for 50 min with methanol saturated with hydrogen chloride. Surprisingly instead of the expected substance 12 the product was proved to be compound 10[7] of an unusual structure, formed in 65 % yield, mp 227-229 °C.





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7 R = CH_2OH

8 R = $CH_2-O-\overset{O}{\overset{\|}{C}}-C_6H_5$

9 R = CH_2CN

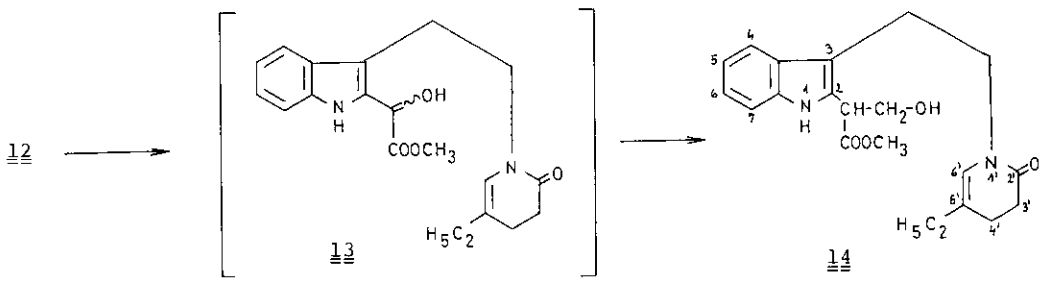
11 R = CH_2COOH

12 R = CH_2COOCH_3

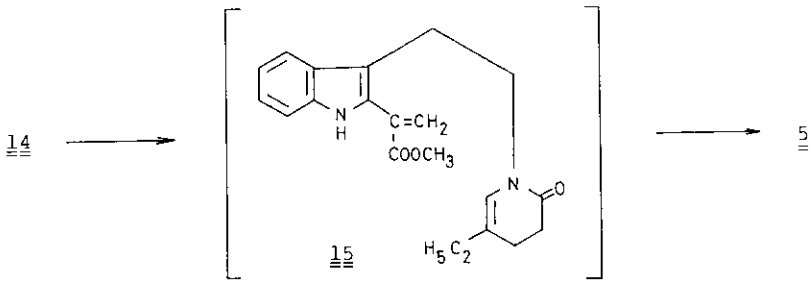
When compound 9 was refluxed in 2M sodium hydroxide solution for 5 h, acidification of the mixture gave 11 in 80 % yield, mp 214-216 °C (from methanol-water). Treatment of this product with diazomethane furnished 12 in 93 % yield, mp 88-90 °C.

As a continuation of the synthesis, the ester 12 was dissolved in benzene and formylated with methyl formate in the presence of sodium hydride[9] at 35 °C for 2 h. The resulting enol 13 was immediately reduced with sodium borohydride in THF at -40 °C to give the racemate 14[10] in 49 % yield.

As an alternative synthesis, compound 14 was also prepared by treatment of 12 with gaseous formaldehyde[11,12] in THF in the presence of lithium diisopropylamide for 1 h, the yield being 23 %. Elimination of the elements of water from 14 (heating with toluene and acetic anhydride for 50 h) gave - through the secodine-type

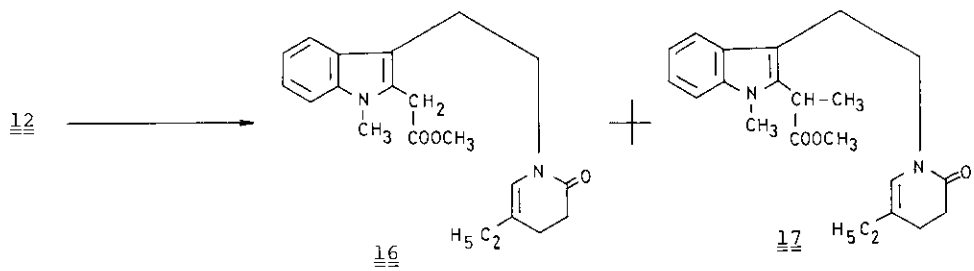


intermediate 15 - the required product, i.e. racemic 3-oxovincadifformine[13] (5), yield: 48 %, mp 202-204 °C (from methanol) [lit.[14] mp 206-207 °C].



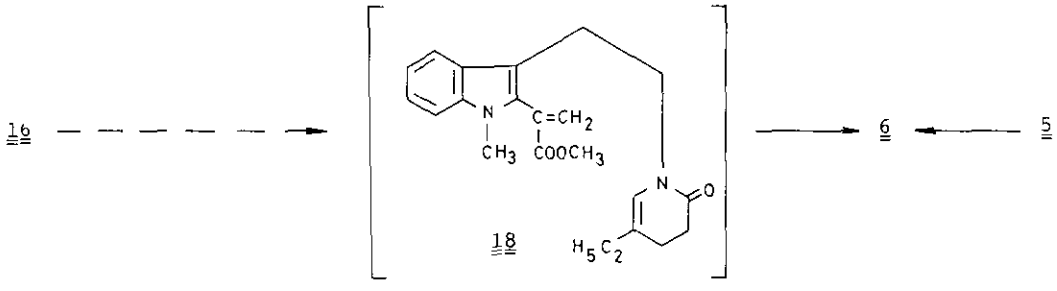
The reaction sequence 12 ⟶ 15 ⟶ 5 was also realized by the use of Eschenmoser's salt [a.) THF/n-BuLi, -75 °C, $CH_2 = N^{(+)}(CH_3)_2\ I^{(-)}$, 2 h. b.) CH_3I/CH_3OH, room temperature, 12 h. c.) $NaHCO_3/H_2O$, room temperature, 2 h. d.) heating in toluene for 60 h, yield 13.6 %].

When compound 12 was methylated with methyl iodide in dimethyl sulfoxide in the presence of sodium hydride, two products were obtained: 16 in 44 % yield and 17 in 5.5 % yield.



The carbanion from 16 was generated with lithium diisopropylamide in THF, and it was allowed to react with Eschenmoser's salt at -75 °C for 2 h. The resulting basic material was treated with methyl iodide in methanol at room temperature for 12 h, the mixture was then made alkaline ($NaHCO_3/H_2O$) and the product was refluxed in toluene for 60 h. The final product, formed via the secodine-type intermediate 18, was racemic 3-oxominovine (6),[15] obtained as an oil in 16.3 % yield.

The latter compound was also prepared by the direct methylation of 3-oxovincadifformine (5) ($DMSO/NaH/CH_3I$, room temperature, 2 h, 68 % yield).



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7. Compound 10: ^{1}H-nmr ($CDCl_3$): δ 0.68 (3H, t, J=6.5Hz, C18-H_3), 0.9-2.7 (9H, m), 3.46 (1H, d, J=8.2Hz, C21-H), 3.6-4.1 (2H, m, C5-H_2), 4.18 (1H, s, C16-H), 6.7-7.4 (4H, m, aromatic H), 8.20 (1H, br s, N1-H) ppm. ^{13}C-Nmr ($CDCl_3$): 10.51 (C18), 23.46 (C19), 25.38 (C15), 31.31 (C14), 38.29 (C20), 39.21 (C6), 43.63 (C5), 58.91 (C16), 59.00 (C7), 71.82 (C21), 109.88 (C12), 119.00 (CN), 121.75^{x} (C9), 123.78^{x} (C10), 129.00 (C11), 130.82 (C8), 143.16 (C13), 167.82 (C2), 170.05 (C3) ppm.[8] Ms: m/z (%) 307 (23), 183 (15), 182 (100) 169 (8), 155 (5), 154 (5), 138 (29), 126 (20), 110 (14), 84 (19), 55 (8).

8. ^{1}H- and ^{13}C-nmr spectra were recorded on Varian XL-100-15 nmr spectrometer at 100.1 and 25.16 MHz respectively. Chemical shifts were measured relative to internal TMS, the values signed with x may be interchanged. Mass spectra were taken on a JEOL-JMS-01 SG-2 (70eV, ion source temperature, 150 °C, direct insertion) mass spectrometer. Mps. are uncorrected.

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10. Compound 14: ^{1}H-nmr ($CDCl_3$): δ 0.95 (3H, t, J=7.5Hz, C5'-CH_2-CH_3), 1.99 (2H, q, J=7.5Hz, C5'-CH_2-CH_3), 2-0-2.5 (4H, m, C3'-H_2+C4'-H_2), 3.00 (2H, t, J=7.2Hz, C3-CH_2 , 3.5-3.8 (2H, m, N1'-CH_2), 3.72 (3H, s, $COOCH_3$), 4.0-4.3 (3H, m, C2-CH-CH_2-OH), 5.71 (1H, m, C6'-H), 6.95-7.65 (4H, m, aromatic H), 9.0 (1H, br s, N1-H)ppm. ^{13}C-Nmr ($CDCl_3$): δ 12.26 (C5'-CH_2-CH_3), 23.11 (C3-CH_2), 23.94 (C4'), 26.67 (C5'-CH_2-CH_3), 30.95 (C3'), 45.54 (C2-CH), 47.73 (N1'-CH_2), 52.37 ($COOCH_3$), 63.95 (CH_2-OH), 110.61 (C3), 111.11 (C7), 118.26 (C4), 119.23 (C6), 121.78^{x} (C5'), 121.89^{x} (C5), 123.60 (C6'), 128.00 (C3a), 129.64 (C2), 135.77 (C7a), 169.17 (C2'), 172.86 ($COOCH_3$) ppm.[8] Ms: m/z (%) 370 (18), 352 (32), 246 (20), 245 (100), 232 (52), 227 (66), 215 (87), 214 (37), 202 (31), 170 (65), 154 (19), 144 (19), 138 (20), 110 (21), 84 (4).

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13. Compound 5: ^{1}H-nmr ($CDCl_3$): δ 0.72 (3H, t, J=6.8 Hz, C18-H_3), 1.00 (2H, q, J=6.8 Hz, C19-H_2), 1.2-2.5 (6H, m, C6-H_2+C14-H_2+C15-H_2), 1.97 (1H, d, J_{gem}=15.5 Hz, C17-H_A), 2.65 (1H, dd, $J_{long\ range}$ = 1.5 Hz, C17-H_B), 3.37 (1H, dd, J_{gem} = 11.8Hz, J_{vic}=6.3Hz, C5-H_A). 3.50 (1H, d, J=1.6Hz, C21-H), 3.78 (3H, s, $COOCH_3$), 4.17 (1H, ddd, J_{gem}=11.8Hz, J_{vic}=7.1 and 1.0Hz, C5-H_B), 6.7-7.35 (4H, m, aromatic H), 9.0 (1H, br s, N1-H)ppm. ^{13}C-Nmr ($CDCl_3$): δ 7.50 (C18), 27.98 (C19), 28.76 (C17), 30.07 (C15), 31.14 (C14), 39.45 (C20), 39.98 (C6), 43.08

(C5), 51.06 ($COO\underline{C}H_3$), 56.70 (C7), 68.17 (C21), 91.05 (C16), 109.73 (C12), 121.10[x] (C9), 121.62[x] (C10), 128.63 (C11), 135.82 (C8), 143.09 (C13), 163.90 (C2), 168.27 ($\underline{C}OOCH_3$), 171.51 (C3)$_{ppm.}$[8] Ms: m/z (%) 352 (50), 227 (100), 214 (31), 195 (32), 168 (11), 154 (13), 138 (6).

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15. Compound 6: ^{1}H-nmr ($CDCl_3$): δ 0.65-1.15 (5H, m, $CH_2\underline{CH}_3$), 1.2-2.5 (6H, m, C6-H_2+C14-H_2+C15-H_2), 2.11 (1H, d, J_{gem}=16.0Hz, C17-H_A), 2.78 (1H, dd, J_{gem}=16.0Hz, $J_{long\ range}$=2.2Hz, C17-H_B), 3.35 (3H, s, N1-CH_3), 3.38 (1H, dd, J_{gem}=11.5Hz, J_{vic}=6.6Hz, C5-H_A), 3.51 (1H, d, J=2Hz, C21-H), 3.76 (3H, s, $COOCH_3$), 4.18 (1H, ddd, J_{gem}=11.5Hz, J_{vic} = 7.5 and 1Hz, C5-H_B), 6.8-7.4 (4H, m, aromatic H) ppm. ^{13}C-Nmr ($CDCl_3$): δ 7.38 (C18), 27.88 (C19), 29.91 (C15), 31.04 (C14), 32.58 (C17), 36.10 (N1-CH_3), 38.86 (C20), 41.15 (C6), 43.40 (C5), 51.05 ($COO\underline{C}H_3$), 57.33 (C7), 70.24 (C21), 92.52 (C16), 108.80 (C12), 121.06[x] (C9), 121.46[x] (C10), 128.55 (C11), 136.51 (C8), 146.82 (C13), 163.12 (C2), 167.01 ($\underline{C}OOCH_3$), 171.38 (C3) ppm.[8] Ms: m/z (%) 366 (35), 335 (5), 241 (100), 228 (39), 182 (14), 168 (12).

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