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# STUDIES IN BIOMIMETIC ALKALOID SYNTHESES—10

## THE SYNTHESIS OF A 19-OXOSECODINE AND ITS CYCLIZATION TO MINOVINCINE

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**Abstract**—The synthesis, isolation and characterization of 19-oxo $\Delta^{20,21}$ secodine (**2**) is described. This compound is the first example of a stabilized, potentially reactive secodine intermediate in alkaloid synthesis. It cyclized to minovincine (**1**) in 77% yield in refluxing *m*-xylene.

THE structure of minovincine (**1**) is noteworthy in that this 19-oxygenated vincadifformine derivative can serve as a biogenetic turntable between the vindolinine and kopsinine classes of alkaloids.[1] Its existence as a biogenetic keystone was proposed even before its isolation.[2b] In the first postulate to replace the classical biogenetic origin of the non-tryptophan moiety of indole alkaloids, long thought to be derived from phenyl alanine,[3] a shikimic-prephenic acid pathway was suggested in which the great structural diversity of indole alkaloids could be visualized from molecular rearrangements of the non-tryptamine moiety, subsequent to its condensation with tryptophan.[2] Minovincine (**1**) and its biogenetic precursor, a **19**-oxosecodine (**2**), occupied pivotal positions in this postulate. The later proposal[4] and establishment[5] of a terpene secoiridoid origin of indole alkaloids brought forth the suggestions of dehydrosecodine and secodine (19-desoxy **2**) intermediates as precursors for the tabersonine—vincadifformine class of alkaloids,[6] with a shift in perspective, at least formally, from CO condensation reactions to intramolecular Diels-Alder type processes. It was then found that the experimental generation of $\Delta^{20-21}$ (19-desoxy **2**) or of $\Delta^{3-14}$ secodines indeed resulted in instantaneous formation of vincadifformine (19-desoxy **1**) or of the $\psi$-vincadifformines, respectively.[7,8]

One could now speculate about the stage at which the final ketone function of minovincine is introduced into the alkaloid. That is, would a 19-oxosecodine (**2**) allow the formation of the pentacyclic ring system or would the vinylogous amide function of **2**, in place of the usual, more reactive enamine function of a $\Delta^{20-21}$ secodine prevent cyclization? From the results obtained with the oxo-secodine model described in the preceding paper,[1] one was encouraged to explore the synthesis, isolation and reactivity of a 19-oxo $\Delta^{20-21}$ secodine, which would furnish the first example of stabilization of the key intermediates of aspidosperma alkaloid biosynthesis.

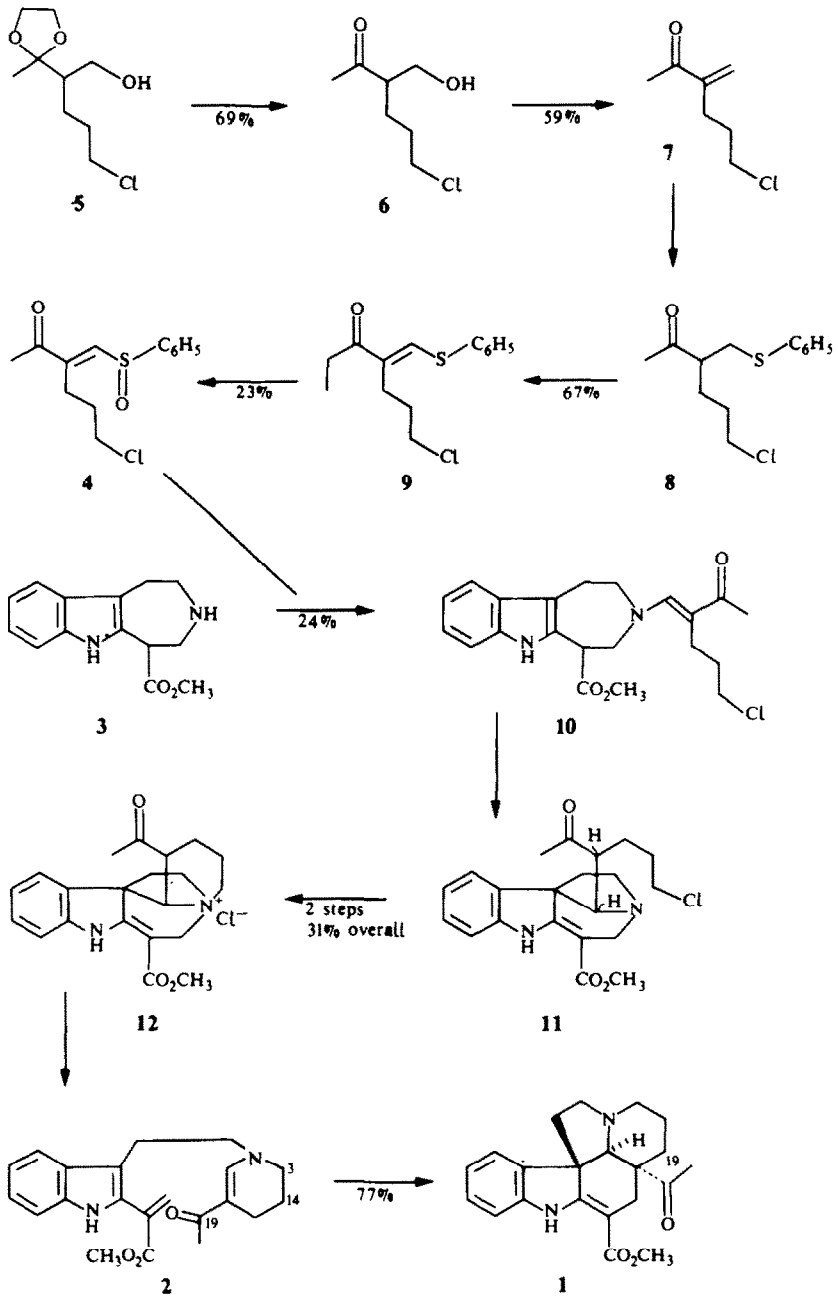
In order to reach a 19-oxosecodine (**2**) through our synthetic strategy starting from the indoloazepine ester **3**,[7] we required a formyl acetone synthon bearing a three C substituent, activated for terminal alkylation. Since intermediate stage ketal cleavage of a formyl acetone derivative had failed,[1] the vinyl sulfoxide **4** was chosen as the potential formyl acetone equivalent.

Hydrolysis of the ketal alcohol **5** and dehydration of the resulting $\beta$-hydroxy ketone **6** furnished the vinyl ketone **7**. This enone reacted with thiophenol to form a Michael addition product **8**. Subsequent chlorination and dehydrochloroination steps were followed by periodate oxidation of the resultant vinylogous thioester **9**, thus providing the desired synthetic intermediate **4**.

When the vinyl ketosulfoxide **4** was stirred with the indoloazepine **3** and potassium carbonate, an amine-sulfoxide exchange on the vinyl ketone resulted in formation of the vinylogous amide **10**. The product displayed IR CO absorption at 1730 $cm^{-1}$ and UV maxima at 227 and 299 nm, expected for the saturated indolic ester enamino ketone structure and inconsistent with a bridged indoloazepine with $\beta$-anilinoacrylate (UV $\lambda_{max}$ 325 nm) and saturated ketone (IR $\nu_{max}$ 1710 $cm^{-1}$) functions. However, cyclization with dry HCl and subsequent neutralization gave bridged indoloazepine products **11**, which underwent spontaneous intramolecular quaternization. On heating in methanol with triethylamine the quaternary salts **12** fragmented and gave the 19-oxosecodine **2**.

This compound showed characteristic acrylate protons in its NMR spectra at $\delta$ 6.53 and 6.03 (d, J = 1.1) and the expected UV absorption at 225 and 312 nm. The 19-oxosecodine **2** proved to be somewhat more resistant to thermal cyclization than the vinylogous N-benzyl amide acrylate studied before.[1] However, on refluxing in *m*-xylene for 24 hr, minovincine (**1**) was obtained as only isolable product in relatively good yield (77%), considering that some decomposition of the product can be expected at such high temperature.

The notable stability found for the 19-oxosecodine **2** encourages one to search for its natural occurrance.[9] At the same time it seems less likely that this compound, rather than a corresponding 19-ol, with




expected high cyclization reactivity, is the direct precursor of natural minovincine (**1**), although for a natural cyçlization of the achiral 19-oxosecodine **2** an enzymatic assistance would have to be considered in view of the natural formation of only one enantiomer of minovincine.

## EXPERIMENTAL

*Phenyl 2-acetyl-5-chloro-1-pentenyl sulfoxide* (**4**). A soln of 3.68 g (18.6 mmol) of (**5**) in 20 ml ether and 6 ml MeOH was stirred for 4 hr with 6 ml 20% HCl aq. Extraction with three 60 ml portions ether and concentration of the extracts and chromatography over 100 g $SiO_2$, eluting with ether, gave 2.01 g (69%) of **6**.[10] TLC ($SiO_2$, ether, DNP) $R_f$ 0.6; 100 MHz NMR ($CDCl_3$) $\delta$ 3.74 (d, J = 5, 2H), 3.60–3.40 (m, 2 H), 2.95 (s, 1 H), 2.80–2.56 (m, 1 H), 2.22 (s, 3 H), 1.89–1.60 (m, 4 H); IR (neat) $\nu_{max}$ 3420, 2940, 2880, 1703, 1445, 1420, 1353, 1170, 1025 $cm^{-1}$.

Dehydration of 1.8 g (11 mmol) of **6** was accomplished by heating the compound and a crystal of *p*-toluenesulfonic acid in 50 ml benzene with a Dean–Stark water separator for 2 hr. The mixture was then diluted with 150 ml ether and washed with 10 ml conc $NaHCO_3$ aq. Concentration and distillation at 95° (20 mm) gave 950 mg (59%) of **7**.[10a] TLC ($SiO_2$, $CH_2Cl_2$, DNP or UV) $R_f$ 0.5; 100 MHz NMR ($CDCl_3$) $\delta$ 6.0 (s, 1 H), 5.78 (s, 1 H), 3.86 (t, J = 6 Hz, 2 H), 2.28–2.46 (m, 2 H), 2.28 (s, 3 H), 1.86 (q, J = 6 Hz, 2 H); IR (neat) $\nu_{max}$ 3030, 1675 $cm^{-1}$.

At 0° 0.76 g (0.71 ml, 6.9 mmol) thiophenol was added to 0.96 g (6.6 mmol) of **7** in 6 ml $CHCl_3$. After addition of three drops $Et_3N$ the mixture was stirred at 20° for 2 hr. Partitioning of the mixture between 10 ml 10% NaOH and two 30 ml portions $CH_2Cl_2$, concentration of the organic extracts and distillation of the residue at 140° (0.25 mm) gave 1.65 g (98%) of **8**.[10b] TLC ($SiO_2$, $CH_2Cl_2$, DNP) $R_f$ 0.6; 100 MHz NMR ($CDCl_3$) $\delta$ 6.96–7.32 (m, 5 H), 3.00–3.22 (m, 2 H), 2.80–3.00 (m, 2 H), 2.40–2.72 (m, 1 H), 2.00 (s, 3 H),

1.40–1.64 (m, 4 H); IR(neat) $\nu_{max}$ 3060, 1710, 1580, 1480, 1438, 1358, 1025 $cm^{-1}$. Chlorination of 5.4 g (21 mmol) of **8** in 30 ml $CCl_4$ was carried out by addition of 3.1 g (23 mmol) N-chlorosuccinimide at 0°. After stirring the cold soln for 2 hr, the mixture was filtered, concentrated and the residue dissolved in 20 ml $CHCl_3$. Then, addition of 3.0 g (23 mmol) $Et_3N$ was followed by 1.5 hr at reflux. The subsequently cooled mixture was stirred for 12 hr at 20° and then concentrated under vacuum. Addition of 30 ml ether, filtration, concentration and chromatography on 150 g $SiO_2$, eluting with $CH_2Cl_2$ gave 3.6 g (67%) of **9**.[10b] TLC ($SiO_2$, $CH_2Cl_2$, DNP) $R_f$ 0.38; 100 MHz NMR ($CDCl_3$) $\delta$ 7.2–7.7 (m, 6 H), 3.4–3.7 (m, 2 H), 2.28–2.68 (m, 2 H), 2.32 and 2.28 (2s, 3 H), 1.68–2.12 (m, 2 H); IR(neat) 3040, 1655, 1565, 1530, 1480, 1445, 1375, 1030 $cm^{-1}$.

Oxidation of 5.2 g (20 mmol) of **9** with 4.81 g (22 mmol) sodium periodate in 75 ml MeOH and 10 ml water gave 1.26 g (23%) of **4**.[10] TLC ($SiO_2$, ether, DNP) $R_f$ 0.35 (compared to $R_f$ 0.66 for **9** under these conditions.); 100 MHz NMR ($CDCl_3$) $\delta$ 7.52–7.92 (m, 5 H), 7.10 (s, 1 H), 3.64 (t, J = 6 Hz, 2 H), 2.72–3.04 (m, 2 H), 2.38 (s, 3 H), 1.80–2.20 (m, 2 H); IR (neat) 3040, 1680, 1442, 1365, 1315, 1203, 1040, 748, 690 $cm^{-1}$; direct insertion probe mass spectrum (70 eV) *m/z* (relat. intensity) 274 (4.5), 273 (30), 272 (18), 271 (100), 270 (24), 255 (12), 254 (16), 253 (26), 237 (13), 235 (10), 119 (9), 217 (11), 177 (20), 175 (13), 157 (10), 147 (17), 145 (33), 141 (21), 127 (12), 126 (20), 115 (17), 111 (10), 109 (24), 105 (15), 101 (19), 97 (27), 87 (12), 78 (13), 77 (30).

19-*Oxosecodine* **2**. A mixture of 0.80 g (3.3 mmol) of **3**, 0.54 g (3.9 mmol) $K_2CO_3$, 1.06 g (3.9 mmol **4** and 10 ml THF was stirred at 20° for 4 days. Concentration and partitioning of the residue between 5 ml brine and three 25 ml portions of $CH_2Cl_2$ was followed by chromatography of the concentrated organic extracts on 25 g of $SiO_2$, eluting with EtOAc 0.31 g (24%) of **10** as a yellow amorphous solid. TLC on $SiO_2$ (4:1 EtOAc:EtOH) $R_f$ 0.58, (EtOAc) $R_f$ 0.27, green with CAS; IR (film from evaporation of $CHCl_3$ soln) $\nu_{max}$ 3385, 3231, 3004, 2952, 1731, 1622, 1574, 1461, 1404, 1358, 1331, 1264, 1194, 1164, 751 $cm^{-1}$; UV (EtOH) $\nu_{max}$ 227, 299 nm; direct exposure probe mass spectrum (70 eV) *m/z* (relat. intensity) 390 (3), 389 (5), 388 (7), 352 (54), 214 (100), 154 (52), 138 (56), 126 (43), 110 (57), 84 (71); 250 MHz NMR ($CDCl_3$) $\delta$ 8.65 (s, 1 H), 7.48–7.53 (m, 1 H), 7.31–7.33 (m, 2 H), 7.09–7.21 (m, 2 H), 4.12–4.16 (m, 1 H), 3.93–4.07 (m, 2 H), 3.73 (s, 3 H), 3.54–3.69 (m, 4 H), 3.10–3.16 (m, 2 H), 2.45–2.69 (m, 2 H), 2.23 (s, 3 H), 1.81–2.07 (m, 2 H).

A mixture of 0.30 g (0.77 mmol) of **10** and 12 drops THF saturated with HCl gas, in 15 ml THF, was stirred for 5 min at 20° and then poured into iced 10% NaOH aq. Extraction with three 25 ml portions of $CH_2Cl_2$ and concentration of the extracts gave the crude bridged **11**. TLC ($SiO_2$, 4:1 EtOAc: EtOH, CAS) $R_f$ 0.55; (9:1 benzene:$Et_3N$) $R_f$ 0.44, blue changing to green; UV (EtOH) $\lambda_{max}$ 229, 296, 335 nm; 100 MHz NMR ($CDCl_3$) $\delta$ 8.95 (s, 1 H), 3.82 (s, 3 H), 1.89 (s, 3 H); direct exposure probe mass spectrum (70 eV) *m/z* (relat. intensity) 353 (11), 352 (48), 309 (12), 244 (19), 218 (14), 215 (10), 214 (31), 202 (11), 155 (10), 154 (69), 138 (54), 110 (23), 109 (100), 77 (10), 67 (12), 65 (13).

The bridged **11** were stirred in 15 ml THF for 48 hr. The ppt was collected and washed with 3 × 5 ml THF and filtered to provide 95 mg (31%) of **12**. TLC ($SiO_2$, 4:1 EtOAc:EtOH, CAS) $R_f$ 0, blue; UV (MeOH) $\lambda_{max}$ 229, 294, 325 nm.

A soln of 90 mg (0.23 mmol) of **12** and 3 drops $Et_3N$ in 5 ml MeOH was stirred at 67° for 45 min. The mixture was concentrated under vacuum and the residue purified by centrifugal chromatography on $SiO_2$, eluting with 6:1 EtOAc:EtOH, to provide 55 mg (68%) of **2** after crystallization from EtOAc; m.p. 155–156°. TLC (Merck # 5539 Silica Gel 60, F-254, $R_f$ 0.107 (9:1 benzene:$Et_3N$), $R_f$ 0.56 (3:1 EtOAc:EtOH), 0.178 (EtOAc), 0.57 (4:4:1 BuOH:AcOH:$H_2O$), purple with CAS; UV (EtOH) $\lambda_{max}$ 225, 312 nm; IR (film) $\nu_{max}$ 3183, 2944, 2852, 1718, 1617, 1565, 1438, 1404, 1358, 1187, 728 $cm^{-1}$; direct exposure probe mass spectrum *m/z* (relative intensity) 354 (15), 353 (83), 352 (100), 309 (26), 255 (28), 254 (26), 217 (18), 214 (20), 149 (40), 147 (23), 139 (24), 138 (52); 250 MHz NMR ($CDCl_3$) $\delta$ 9.08 (s, 1 H), 7.56 (dd, J = 7.8, 0.7, 1 H), 7.39 (dt, J = 8.0, 0.8, 2 H), 7.25–7.12 (m, 1 H), 6.85 (brd s, 1 H), 6.53 (d, J = 1.1, 1 H), 6.03 (d, J = 1.1, 1 H), 3.85 (s, 3 H), 3.47 (t, J = 6.8, 2 H), 3.07–3.14 (m, 2 H), 2.21 (t, J = 5.3, 2 H), 1.90 (s, 3 H), 1.68–0.78 (m, 2 H). (Found: C, 71.30; H, 7.00; N, 7.98. Calc. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95%.)

*Minovincine* **1**. A soln of 156 mg (0.44 mmol) of **2** in 5 ml *m*-xylene was heated at reflux for 24 hr. The solvent was removed under vacuum and the residue purified by centrifugal chromatography on $SiO_2$, eluting 120 mg (77%) of **1** with ether. Comparisons with samples of *dl*-minovincine, obtained by our two previous syntheses, (see preceeding paper)[1] showed complete matches in 250 MHz NMR, IR, UV and mass spectra.

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