A STEREOSPECIFIC TOTAL SYNTHESIS OF CHASMANINE

T.Y.R. Tsai, Connie S.J. Tsai, W.W. Sy,
M.N. Shanbhag, W.C. Liu, S.F. Lee and
Karel Wiesner*
Natural Products Research Center, The University of New Brunswick, P.O. Box 4400, Fredericton, N.B. E3B 5A3 Canada

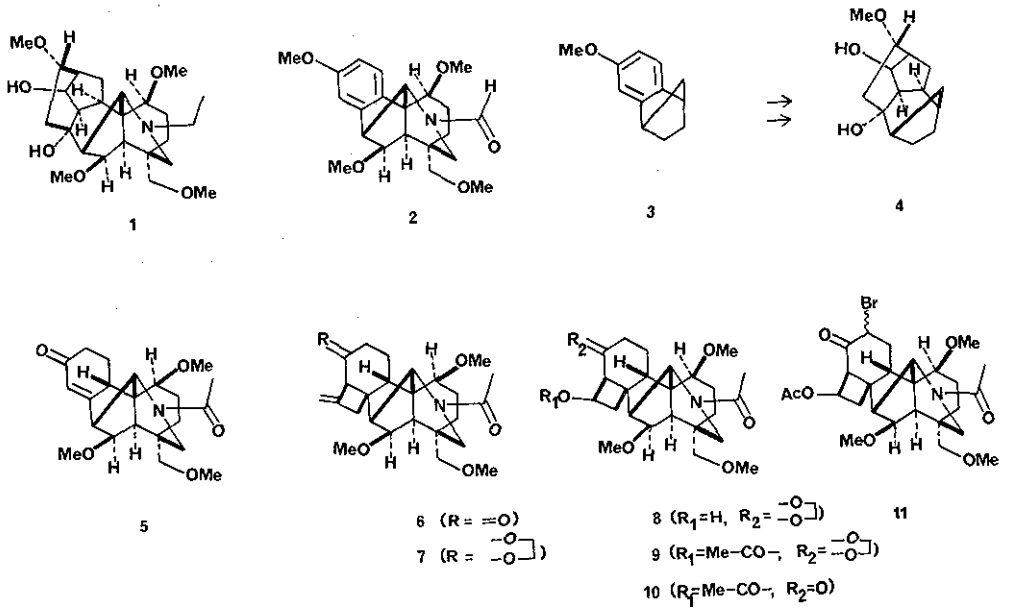
(Dedicated with best wishes to the Sixtieth Anniversary of Professor R.B. Woodward.)

The "aromatic intermediate" 2 was transformed by the photochemical route to the "nordenudatine" intermediate 21. Rearrangement of 21 to 22 and functionalization of this last product yielded racemic chasmanine 1.

1. Total Synthesis of Chasmanine

As part of our continuing effort to develop progressively more effective and simple synthetic strategies for the construction of delphinine type alkaloids, we wish to disclose a stereospecific synthesis of racemic chasmanine (1).

Our starting material was the "aromatic intermediate" 2 (2) which we have synthesized with the use of our aziridine rearrangement method. It should be pointed out that the synthesis of 2 was stereospecific and that all the substituents emerged automatically in the correct



positions simultaneously with the construction of the skeleton. It will be seen in the sequel that this principle is maintained in the remainder of the chasmanine synthesis.

Before proceeding with the conversion of compound 2 to chasmanine 1 we have performed several studies which involved the synthesis of the tetracyclic model compound 4 from the methoxybenzobicycloheptene 3 (3, 4).

It is difficult to exaggerate the importance of these studies in spite of the fact that some differences in behaviour between the model series and the synthesis proper were observed (4).

It would have been quite impossible to develop our present process without this preliminary work. As an additional bonus the NMR spectra

of the model intermediates served as a reliable and precise simulation of the corresponding NMR patterns in the synthesis proper. Thus, at no stage in the synthesis proper have there been any doubts as to whether a desired intermediate was in fact in hand.

The N-formyl compound 2 was reduced with lithium in a mixture of THF and liquid ammonia. The resulting dihydro-derivative was acetylated with pyridine and acetic anhydride and the product was heated under reflux with 0.6 N methanolic hydrochloric acid for 30 minutes. Under these conditions the exo-protonated compound 5 is formed exclusively (3). The yield of the product 5 from 2 was 72%[1].

IR: 1625, 1660 cm^{-1} (N-CO-CH_3, >C=O).

UV (EtOH: λ_{max} = 256 nm, log ε = 4.15.

NMR: τ = 4.23 (t, J=3, 1H, vinylic H), 6.67 (s, 9H, 3-OCH_3), 7.86, 7.92 (2s, 3H, N-CO-CH_3).

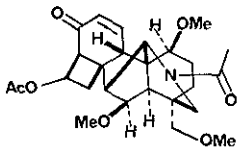
Photoaddition of allene under our standard conditions (3, 4) yielded 86% of the single adduct 6 predictable by our addition rule (5).

IR: 1622, 1665, 1700 cm^{-1} (N-CO-CH_3, double bond, >C=O).

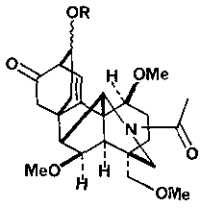
NMR: τ = 5.04 (m, 2H, vinylic H), 6.65, 6.70, 6.75 (3s, 3H each, 3-OCH_3), 7.86, 7.93 (2s, 3H, N-CO-CH_3).

---

1 All compounds gave correct molecular ions in mass spectrometry and all crystalline compounds gave in addition correct C, H and N values in microanalysis. The amorpheous compounds were isolated by preparative TLC on silica gel and their homogeneity was checked by TLC in several systems. IR spectra were recorded in $CHCl_3$ and NMR spectra in $CDCl_3$ solution.

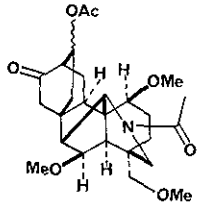


12

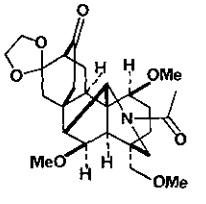


13 (R=H)

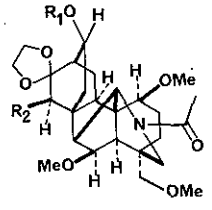
14 (R=–OAc)



15



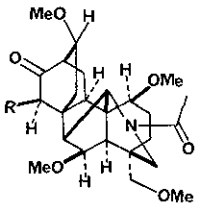
16



17 (R_1=H, R_2=H)

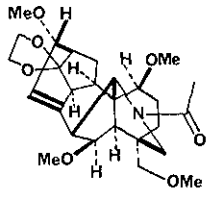
18 (R_1=–Me, R_2=H)

21 (R_1=–Me, R_2=Br)

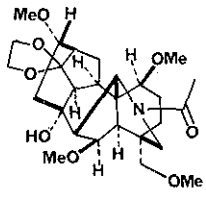


19 (R=H)

20 (R=Br)



22



23

The photoadduct 6 was converted quantitatively into the ethylene glycol acetal 7 under standard conditions in benzene with p-toluenesulfonic acid.

IR: 1622 cm^{-1} (N-CO-CH_3).

NMR: τ = 4.75, 5.12 (2d, J=3, 1H each, vinylic H), 6.02 (s, 4H, O-CH_2-CH_2-O), 6.68, 6.75 (3s, 9H, 3-OCH_3), 7.90, 7.95 (2s, 3H, N-CO-CH_3).

Compound 7 was ozonized in methanol at dry-ice acetone temperature and the ozonide was reduced in the same solution with sodium borohydride. The crude resulting alcohol 8 was acetylated with acetic anhydride in pyridine and the product 9 was stirred at room temperature for 4 h with 0.1 N aqueous methanolic hydrochloric acid. The

crystalline acetoxy ketone 10 (mp 174-6°C) was obtained in an overall yield of 72% from 7.

IR: 1622, 1700, 1738 cm^{-1} (N-CO-CH_3, >C=O, O-CO-CH_3).

NMR: τ = 4.72 (q, J=8, 1H, >C<u>H</u>-OAc), 6.63, 6.70, 6.72 (3s, 3H each, 3-OCH_3), 7.83, 7.92 (2s, 3H, N-CO-CH_3), 7.97 (s, 3H, O-CO-CH_3).

The acetoxy ketone 10 was brominated in THF with pyridine hydrobromide perbromide at room temperature for 2 h. The crystalline bromo derivative 11 (mp 221-3°C) was obtained in a yield of 80%.

IR: 1625, 1710, 1745 cm^{-1} (N-CO-CH_3, >C=O, -O-CO-CH_3).

NMR: τ = 4.73 (q, J=8, 1H, >C<u>H</u>-OAc), 5.54 (t, J=3, 1H, >C<u>H</u>Br), 6.62, 6.68, 6.69 (3s, 3H each, 3-OCH_3), 7.82, 7.92 (2s, 3H, N-CO-CH_3), 7.95 (s, 3H, -O-CO-CH_3).

Compound 11 was heated for 2.5 h in DMF with LiBr and Li_2CO_3 to 135°C. The α,β-unsaturated ketone 12 was obtained in a yield of 87%.

IR: 1623, 1659, 1736 cm^{-1} (N-CO-CH_3, >C=O, O-CO-CH_3).

UV (EtOH): λ_{max} = 212 nm, log ε = 4.17.

NMR: τ = 3.12, 3.73 (2d, J=11, 1H each, vinylic H), 4.59 (m, 1H, >C<u>H</u>-OAc), 6.61, 6.71, 6.78 (3s, 3H each, 3-OCH_3), 7.87, 7.93 (2s, 3H, N-CO-CH_3), 7.99 (s, 3H, -O-CO-CH_3).

The conjugated ketone 12 was stirred for 30 minutes at room temperature with 0.3 N aqueous methanolic NaOH under nitrogen. The mixture of epimeric aldols 13 was obtained in a yield of 90%. Acetylation of 13 with acetic anhydride and pyridine yielded quantitatively the corresponding acetates 14.

IR: 1625, 1730 (N-CO-CH_3, O-CO-CH_3, >C=O).

NMR: τ = 4.38 (d, J=6, 1H, vinylic H), 4.99 (m, 1H, >C<u>H</u>-OAc), 6.67, 6.70 (3s, 9H, 3-OCH_3), 7.85, 7.96 (2s, 3H, N-CO-CH_3).

The ketoacetates 14 were hydrogenated in methanol with 5% rhodium on alumina at room temperature and 85 psi for 18 h. The hydrogenation products were oxidized in CH_2Cl_2 with CrO_3-pyridine at room temperature and the epimeric acetates 15 were obtained after purification by preparative TLC in an overall yield of 86%.

The hydrogenation which in the model series was only stereoselective (4) had a stereospecific outcome with compound 14. We have in fact anticipated this result; it is clearly due to the shielding influence of the ring A methoxy group.

IR: 1622, 1726 cm^{-1} (N-CO-CH_3, O-CO-CH_3, $\geq$C=O).

NMR: τ = 4.76 (m, 1H, C<u>H</u>-OAc), 6.67, 6.71, 6.73 (3s, 9H, 3-OCH_3), 7.82, 7.92 (2s, 3H, N-CO-CH_3), 7.99, 8.01 (2s, 3H, O-CO-CH_3).

The following three operations converted the epimeric acetates 15 to the single homogeneous and crystalline (mp 249-251°C) ketoacetal 16 in an overall yield of 80%. (a) Formation of an ethylene glycol acetal in benzene with p-toluenesulfonic acid under standard conditions. (b) Saponification with 0.2 N aqueous methanolic KOH at room temperature. (c) Oxidation with CrO_3-pyridine in CH_2Cl_2. The product 16 was purified by crystallization from chloroform-ether.

IR: 1620, 1725 cm^{-1} (N-CO-CH_3, $\geq$C=O).

NMR: τ = 6.06 (s, 4H, -O-CH_2-CH_2-O-), 6.67, 6.73, 6.75 (3s, 3H each, 3-OCH_3), 7.88, 7.94 (2s, 3H, N-CO-CH_3).

Stereospecific reduction of compound 16 with $NaBH_4$ in methanol gave quantitatively the oily alcohol 17 and this product was methylated in dry dioxane with sodium hydride and methyl iodide under reflux for 2 h (3, 4). The pure oily methoxyacetal 18 was

isolated by preparative TLC in a yield of 82%.

IR: 1618 cm^{-1} (N-CO-CH_3).

NMR: τ = 6.1 (s, 4H, -O-CH_2-CH_2-O-), 6.63, 6.65, 6.71, 6.73 (4s, 3H each, 4-OCH_3), 7.85, 7.94 (s, 3H, N-CO-CH_3).

At this point we had to deviate from our published model series (3) since we were unable to brominate the methoxyacetal 18 directly. The following process was first worked out on the model system and then applied to the intermediate 18. Compound 18 was heated for 3 h to 85°C in 80% acetic acid and the liberated ketone 19 was immediately used for the subsequent step. The bromination of 19 was performed in ether at room temperature with an excess of liquid bromine. The bromoketone 20 (mp 245-247°C) was recrystallized from ether-chloroform and was obtained in a yield of 82%. As in the corresponding model system (3) the configuration of the bromine follows from the success of the subsequent rearrangement step rather than from an analysis of spectral data.

IR: 1622, 1730 cm^{-1} (N-CO-CH_3, $\geq$C=O).

NMR: τ = 5.68 (broad s, 1H, $\geq$C<u>H</u>Br), 6.67, 6.70, 6.73 (3s, 12H, 4-OCH_3), 7.80, 7.91 (2s, 3H, N-CO-CH_3).

The bromoketone 20 was converted quantitatively into the acetal 21 by Barton's method with diethylene orthocarbonate and p-toluenesulfonic acid in chloroform (6). Compound 21 was recrystallized from ether to a mp of 217-8°C.

IR: 1620 cm^{-1} (N-CO-CH_3).

NMR: τ = 5.71 (broad s, 1H, $\geq$CHBr), 6.08 (m, 4H, -O-CH_2-CH_2-O-) 6.63, 6.71 (2s, 12H, 4-OCH_3), 7.85, 7.93 (2s, 3H, N-CO-CH_3).

The rearrangement of the bromoacetal 21 to the oily oxo-pyrochasmanine

derivative 22 proceeded as expected cleanly and in a yield of 85%. It was carried out under reflux in a mixture of xylene and DMSO (1:1) in the presence of a thirty molar excess of 1,5-diazabicyclo(3,4,0)-nonene and it was complete in 4 h.

The totally synthetic racemate 22 was found to be identical by IR, NMR and mass spectrometry with the corresponding optically active derivative prepared from natural chasmanine[2].

IR: 1618 cm^{-1} (N-CO-CH_3).

NMR: τ = 4.33 (d, J=6, 1H, vinylic H), 6.08 (s, 4H, -O-CH_2-CH_2-O-), 6.60, 6.67, 6.71, 6.82 (4s, 3H each, 4-OCH_3), 7.86, 7.95 (2s, 3H, N-CO-CH_3).

The oxymercuration of the racemate 22 was performed like in the model series (3) but aqueous THF had to be substituted for acetone as solvent. It was not possible to optimize the process due to shortage of material and thus the yield of the product 23 was only 65%. The totally synthetic racemate 23 crystallized from ether and melted at 210-2°C. It was found to be identical by IR, NMR, mass spectrometry and TLC in several solvent systems with the corresponding oily optically active derivative prepared from natural chasmanine.

IR: 3645, 3440, 1618 cm^{-1} (OH, N-CO-CH_3).

NMR: τ = 6.03 (broad s, 4H, -O-CH_2-CH_2-O-), 6.69, 6.71, 6.82 (4s, 12 H, 4-OCH_3), 7.86, 7.96 (2s, 3H, N-CO-CH_3).

---

2 The various optically active derivatives of chasmanine were prepared by I. H. Sanchez and will be reported separately.

The oxymercuration product 23 was heated in 80% acetic acid to 85°C for 3 h. The racemic 14-dehydro-α-oxochasmanine was obtained as a colorless glass and it was identical with the corresponding optically active derivative prepared from chasmanine by TLC in several systems, IR and mass spectroscopy.

IR: 1622, 1750 cm^{-1} (N-CO-CH_3, $\rangle$C=O).

Reduction of optically active 14-dehydro-α-oxochasmanine with $LiAlH_4$ in dioxane gave chasmanine 1 which was identified with the natural alkaloid by IR, TLC, mass and NMR spectroscopy and by mixed melting point (83-84°C). All the remaining totally synthetic racemic 14-dehydro-α-oxochasmanine was then reduced in the same manner and the product was carefully purified by preparative TLC. The pure totally synthetic racemate 1 was indistinguishable from the optically active natural material by TLC in several systems, IR, NMR and mass spectrometry. It was crystalline, but could not be recrystallized possibly since only 2 mg were available.

The present synthesis demonstrates clearly the superiority of the "nordenudatine" route to delphinine type alkaloids over the "noratisine" route which we have previously used in the preparation of talatisamine (7). Further considerable improvements of this route are in progress and will be reported in the hopefully near future.

ACKNOWLEDGEMENTS We wish to thank the National Research Council of Canada (Ottawa) and the Hoffmann La Roche Company, Vaudreuil, for the support of these studies over many years. We also thank Merck, Sharp and Dohme Company, Montreal, for a grant. Finally, we thank Dr. O. E. Edwards, NRC, Ottawa, for donating to us his entire supply of chasmanine which enabled us to perform the correlations.

REFERENCES

1. S. W. Pelletier, Z. Djarmati and S. Lajšić, J. Amer. Chem. Soc., 1974, 96, 7817.

2. S. F. Lee, G. M. Sathe, W. W. Sy, P. T. Ho and K. Wiesner, Can. J. Chem., 1976, 54, 1039.

3. K. Wiesner, P. T. Ho, W. C. Liu and M. N. Shanbhag, Can. J. Chem., 1975, 53, 2140.

4. K. Wiesner, I. H. Sanchez, K. S. Atwal and S. F. Lee, Can. J. Chem., 1977, 55, 1091.

5. K. Wiesner, Tetrahedron, 1975, 31, 1655.

6. D. H. R. Barton, C. C. Dawes and P. D. Magnus, Chem. Comm., 1975, 432.

7. K. Wiesner, T. Y. R. Tsai, K. Huber, S. E. Bolton, and R. Vlahov, J. Amer. Chem. Soc., 1974, 96, 4990; K. Wiesner, Pure and Applied Chem., 1975, 41, 93. Compare also reference 3.

Received, 24th June, 1977