Tetrahedron Letters,Vol.26,No.24,pp 2857-2860,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

THE SYNTHESIS OF HELIOTRIDINE AND RELATED ALKALOIDS

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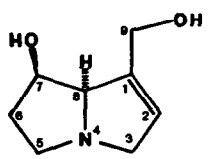
Abstract: An efficient synthesis of heliotridine from readily available retronecine was accomplished by nucleophilic displacement of the 7-mesylate, in the 7-mesyl-9-benzoate of retronecine with various cesium carboxylates in DMF, followed by hydrolysis. The synthetic procedure also permits the ready synthesis of a number of naturally occurring pyrrolizidine alkaloids possessing dissimilar acyl groups at C-7 and C-9.

It has been estimated that 3% of the world's flowering plants contain pyrrolizidine alkaloids.[2] These alkaloids, as a class, show extensive biological activity and have resulted in heavy loss of livestock in many countries of the world[3] and are also a human health hazard.[4] One of the alkaloids, indicine N-oxide, has progressed to clinical evaluation as an anti-tumor agent[5] and efforts are underway to exploit the subtle structure-activity relationships which distinguish between toxicity and anti-tumor activity[5,6,7].

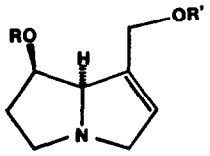
Most of the biologically active pyrrolizidine alkaloids are either 9-monoesters of retronecine (**1**) or heliotridine (**2**), unsymmetrical 7,9-diesters of retronecine or heliotridine or 7,9-macrocyclic diesters of retronecine[8]. For the preparation of pyrrolizidine alkaloid analogs for anti-tumor screening, we required rather large amounts of heliotridine. Recently, Chamberlin and Chung[9] reported an elegant synthesis of heliotridine from S-malic acid. However, this procedure did not lend itself to a practical solution to our problem.

Since we had in hand relatively large quantities of retronecine, readily available to us from natural sources[7], we sought an efficient means of converting it into heliotridine. Three methods have frequently been used for the inversion of secondary alcohols[10,11,12]. Of these three methods, practicality and preliminary experimental work suggested that the method of Kellogg et al. would be best suited for our purposes. Initial attempts to utilize 7,9-dimesylretronecine revealed that this compound was too unstable to be useful. Therefore, 9-benzoylretronecine (**3**) was prepared by site-specific coupling of retronecine with benzoic acid using 1,1'-carbodiimidazole (CDI)[7]. This, in turn, was converted, in high yield, into the key intermediate **4**[13]. The inversion of the 7-mesylate in **4** was examined with the cesium salts of acetic, propionic, tiglic, angelic and benzoic acids under the conditions and with the results indicated in the diagram. Thus, in a typical procedure using cesium propionate as the



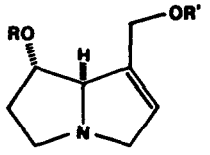
RETRONECINE, 1

i, ii

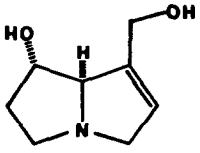


3: R = H, R' = PhCO.
4: R = $MeSO_2$, R' = PhCO.

iii



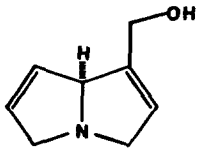
iv



HELIOTRIDINE, 2

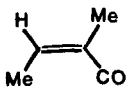
5a: R = CH_3CO, R' = PhCO (12h, 76°C, 75%).
5b: R = CH_3CH_2CO, R' = PhCO (17h, 76°C, 80%).
5c: R = angelyl, R' = PhCO (18h, 76°C, 72%).
5d: R = tiglyl, R' = PhCO (18h, 76°C, 72%).
5e: R = R' = PhCO (40h, 85°C, 30%).

7: R = CH_3CO, R' = 1-viridifloryl.
8: R = angelyl, R' = 1-viridifloryl.
9: R = angelyl, R' = H.

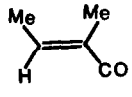


6

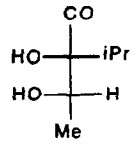
i: PhCOOH(1 eq.),CDI(1.1 eq.),THF, r.t.,16 h,95%; ii: $MeSO_2Cl$(1.3 eq.), Et_3N(1.5 eq.),CH_2Cl_2,-2°C,1.5 h, 93%; iii: RCOOCs(4 eq.),DMF; iv: $Ba(OH)_2$aq.,r.t.,87% from pure **5b**.



angelyl



tiglyl



1-viridifloryl

nucleophile, approximately 75% of the inverted product **5b** is obtained, accompanied by unsaturated products. Pure **5b**[14] could be isolated by chromatography on alumina; however, as a general method for the preparation of heliotridine, the crude product was used directly for the next step. Yields in the diagram represent isolated yields and are not optimized. It is worthwhile noting that substitution by cesium angelate led to the isolation of the 7α-angelate (**5c**) uncontaminated with the isomeric 7α-tiglate (**5d**), whereas attempted esterification of retronecine with angelic acid, using CDI led to a mixture of angelate and tiglate esters; a similar mixture of products has been obtained by the use of dicyclohexylcarbodiimide[15].

Finally, heliotridine could be obtained from the diesters either by hydrolysis with barium hydroxide or by reductive cleavage using lithium aluminum hydride; comparable yields were obtained by both methods. Crystalline heliotridine was obtained from the reaction mixture, identical in physical properties and chromatographically with that previously reported[9] and with an authentic sample prepared by hydrolysis of europine[6]. When crude diesters **5a-5e** were used directly for the preparation of heliotridine, two minor products were isolated by chromatography. One of these has been identified as the previously unreported Δ^6-supinidine

(**6**)[16] while the second has not been characterized but is a dimeric product of MW 274.

With the ready availability of retronecine from natural sources, the procedure outlined here provides an efficient means of obtaining not only heliotridine but, in principle, all of the alkaloids containing the heliotridine nucleus. As an example, we report here, for the first time, the syntheses of the three alkaloids 7-acetylechinatine (**7**)[17], 7-angelyl-9-l-viridiflorylheliotridine (**8**)[18] and 7-angelylheliotridine (**9**)[18]. Esterification of retronecine with the acetonide of l-viridifloric acid using CDI gave site specifically the C-9 ester (**10**) which on mesylation gave the desired 7-mesyl-9-l-viridiflorylretronecine acetonide (**11**). Reaction, as above, with cesium acetate or cesium angelate, followed by deprotection and chromatography gave **7**[19] and **8**[20], respectively. Oxidative cleavage of **8** or its acetonide by periodic acid directly gave **9**. All the three natural alkaloids: **7**, **8** and **9** were chromatographically homogeneous. Their physical properties were consistent with those published[17,18] and their 300 MHz ^{1}H NMR and mass spectra were consistent with the assigned structures.

Acknowledgement: We thank Dr. P.G. McDougal for helpful discussions and are grateful to the National Institutes of Health (CA31490) for financial support.

References and Notes

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13. MS: m/e (rel. intensity): 77(69), 80(28), 93(33), 94(60), 105(59), 120(37), 151(12), 215(5), 241(3), 258(1). CI: 338(M+1, 100%). ^{1}H NMR ($CDCl_3$/TMS): 8.02 (d, 2H), 7.55 (t,

1H), 7.42 (t, 2H), 5.84 (s, 1H), 5.22 (m, 1H), 5.00 and 4.93 (AB, C9-H_2), 4.38 (bs, 1H), 3.91 (d, 1H), 3.37 (br d, 1H), 3.32 (m, 1H), 3.03 (s, Me), 2.74 (m, 1H), 2.41 (dd, 1H), 2.13 (ddd, 1H).

14. MS: 77(49), 93(100), 94(46), 105(59), 119(80), 136(46), 154(18), 194(18), 210(21), 241(11), 315(4). CI: 123(100), 316(M+1, 21%). NMR ($CDCl_3$/TMS): 8.07 (d, 2H), 7.56 (t, 1H), 7.44 (t, 2H), 5.78 (d, 1H), 5.13 (pent, 1H), 5.04 and 5.02 (AB, C9-H_2), 4.12 (br s, 1H), 3.95 (d, 1H), 3.37 (m, 1H), 3.19 (m, 1H), 2.79 (m, 1H), 2.28 (q., $CH_3\underline{CH_2}$), 1.95 (m, 1H), 1.87 (m, 1H), 1.03 (t, $\underline{CH_3}CH_2$).
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16. MS: 79(24), 80(22), 106(100), 118(20), 136(16), 137(13). CI: 138 (M+1, 100%). Calc. for $C_8H_{11}NO$: 137.0841, found 137.0906. ^{13}C NMR ($CDCl_3$): 142.91 (C1), 128.30 (C7), 127.11 (C6), 121.58 (C2), 78.72 (C8), 63.47 (C5), 63.25 (C3), 59.74 (C9). ^1H NMR ($CDCl_3$): 5.93 (m, H7), 5.79 (m, H6), 5.53 (d, J=1.5 Hz, H2), 4.85 (s, H8), 4.26 and 4.20 (AB, J_{gem}=13.8 Hz, C9-H_2), 3.97 (dm, J_{gem}=15.5 Hz, H3α), 3.89 (dm, J_{gem}=15.5 Hz, H5α), 3.41 (dm, H5β). Assignments made with the help of a ^1H-^{13}C two-dimensional spectrum.
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(Received in USA 18 February 1985)