THE ENANTIOSELECTIVE SYNTHESIS OF (+)-RETRONECINE, (-)-PLATYNECINE, AND (+)-CROALBINECINE AND ITS C-1 EPIMER

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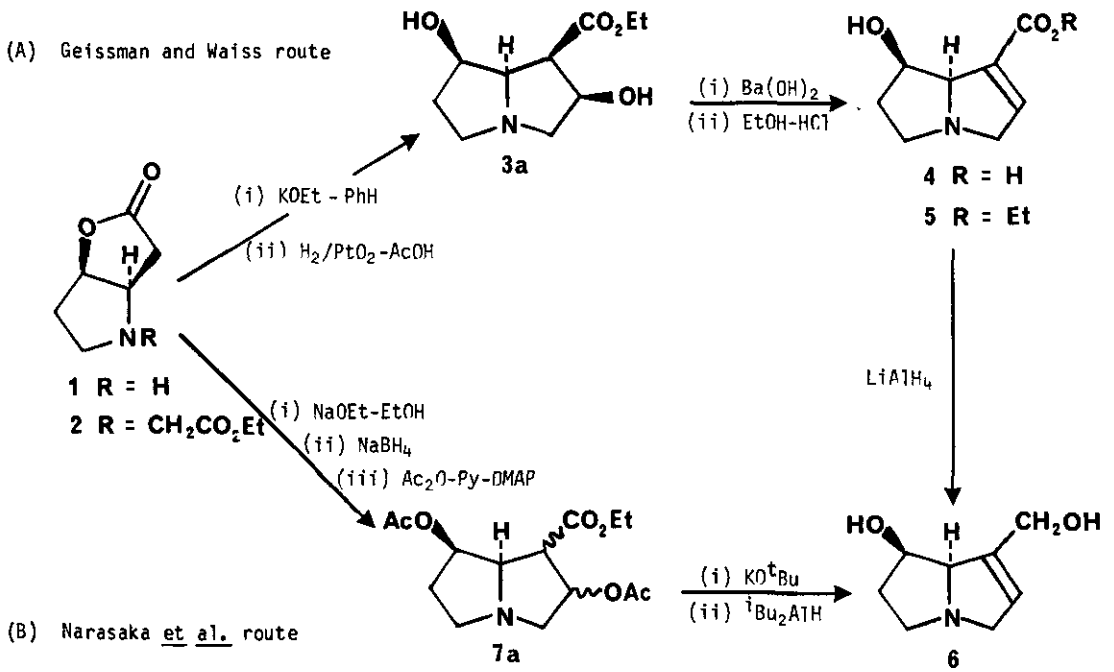
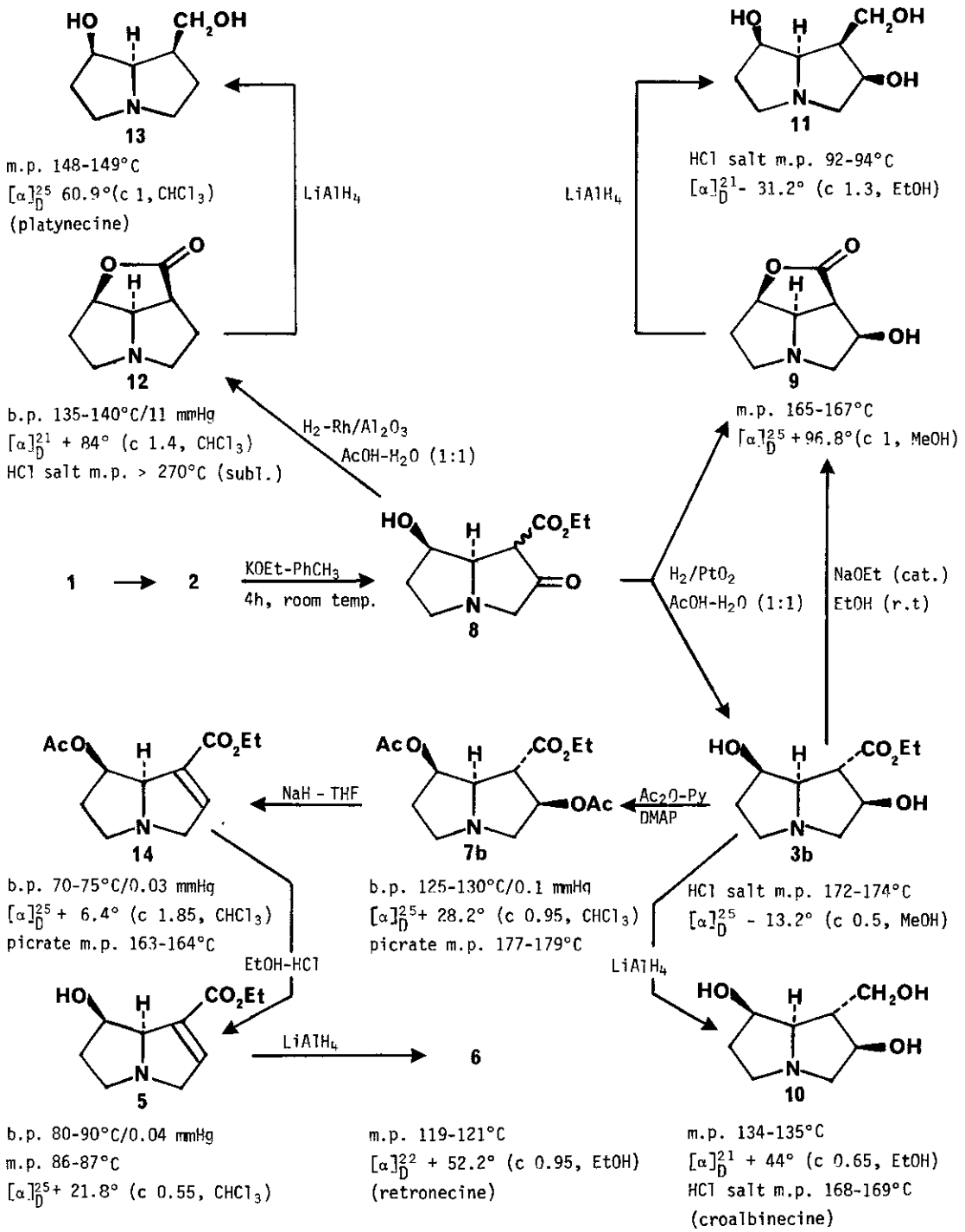
Abstract - The Geissman-Waiss lactone, (+)-6-aza-2-oxabicyclo[3,3,0]octan-2-one, obtained from (2S,4R)-4-hydroxyproline was used as a synthon for the preparation of (+)-retronecine, (-)-platynecine, and (+)-croalbinecine (helifolinecine) and its C-1 epimer.

We have previously reported the synthesis of (+)-6-aza-2-oxabicyclo[3,3,0]octan-2-one (1) from N-*benzyloxycarbonyl-(2S,4R)-4-hydroxyproline (1). We now describe the use of this compound as a* synthon for the enantioselective preparation of some necines.

Some twenty years ago, Geissman and Waiss converted (±)-1 into retronecine (6) as shown in Scheme I (2).



Scheme I. The Geissman-Waiss and Narasaka routes to retronecine.



Scheme II. Enantioselective synthesis of (+)-retronecine, (-)-platynecine, (+)-croalbinecine, and its C-1 epimer from (±)-1.

Alkylation of 1 with ethyl bromoacetate gave 2, which was then subjected to Dieckmann condensation followed by catalytic hydrogenation to yield a dihydroxy ester thought to have the relative stereochemistry shown in 3a. Base-induced elimination (with accompanying saponification), followed by reesterification, and lithium aluminum hydride reduction then gave retronecine, in about 5% overall yield from 1.

Much more recently, a considerable improvement in this yield (to about 15% from 1) has been announced by Narasaka et al. (3), whose modifications of the synthesis are also shown in Scheme I. Our work is outlined in Scheme II.

Potassium ethoxide in toluene, at room temperature, proved to be superior to all other methods (4) which we investigated for the Dieckmann condensation reaction, and gave a rapid and excellent conversion of 2 to 8. Like previous workers, we found it best to reduce this product without purification. When this was done as by Geissman and Waiss, and the hydrogenation products isolated without delay, we obtained the dihydroxy ester 3b as a crystalline hydrochloride (72% from 2), accompanied by minor amounts of the hydroxylactone 9. When a solution of 3b in ethanol was kept in ethanol containing a catalytic amount of sodium ethoxide, at room temperature, it was slowly converted to 9 (78% after 30 days). Attempts to accelerate this process by heating, or the use of an equivalent of alkoxide gave inferior conversions. Lithium aluminum hydride reduction of 3b and 9, gave different triols: (10) and (11) respectively.

As indicated in Scheme II, we therefore viewed the process of the 3b→9 conversion as involving epimerisation at C-1, as well as lactonisation. Geissman and Waiss (2) reasoned that hydrogenation of 8 should proceed from the least hindered face to give 3a. However, we have observed (5) that a similar hydrogenation of an analogue of 8, lacking the endo, 7β-hydroxyl function, gave a mixture of C-1 epimeric hydroxy esters i.e. formation of the 1α-epimer 3b is precedented. Ready lactonisation of the 1β-epimer 3a is also to be anticipated (6,7), so we think that the dihydroxy ester isolated by Geissman and Waiss was probably (±)-3b.

The triol 10 corresponds to croalbinecine (8) [= helifolinecine (9)] and indeed the physical properties of our material are in excellent accord with those reported for the natural product. The other triol (11) does not seem to have been described before, but its physical properties (in particular its ^{1}H-NMR spectrum) (10) are in agreement with expectation.

Hydrogenation of 8 using rhodium on alumina catalyst gave mainly the lactone 12, the racemic form of which had previously been synthesised by Aasen and Culvenor (6), Viscontini and Buzek (7), and most recently by Yamada's group (11) by different routes. Lithium aluminum hydride reduction (7) of 12 gave (-)-platynecine. Since a conversion of (±)-12 into (±)-retronecine has now been described (11), our (+)-12 could also be a synthon for (+)-6.

Conversion of the dihydroxy ester 3b to retronecine was accomplished by much the same procedure as

Narasaka et al., although we found best to induce the 7b→14 elimination with sodium hydride; and to reduce the hydroxy ester 5 with lithium aluminum hydride, rather than the acetate (14) with di-isobutylaluminum hydride. By these means we prepared (+)-retronecine in 49% yield from 1, and as with the other necines in a high state of optical purity (12).

We thus report the first synthesis of (+)-croalbinecine and its C-1 epimer, and the first enantio-selective synthesis of (+)-retronecine and (-)-platynecine.

ACKNOWLEDGEMENTS

Financial support of this work was provided by the Alberta Heritage Foundation for Medical Research (Scholarship to HR), and the Natural Sciences & Engineering Research Council of Canada (Grant-in-aid to MHB). We should also like to express our thanks to Dr. C.C.J. Culvenor for an authentic reference specimen of (-)-platynecine, and Dr. Jürg Lüthy for a similar gift of (+)-retronecine.

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10. The 200 MHz ^{1}H-NMR spectrum of 11, in D_2O, shows, $J_{1,2}$ = 4.0 Hz, $J_{1,8}$ = 9.2 Hz, $J_{2,3}$ = 4.0 and 0 Hz; cf. petasinecine in D_2O (5). $J_{1\alpha,2\alpha}$ = 4.5 Hz, $J_{1\alpha,8\alpha}$ = 8 Hz, $J_{2\alpha,3\alpha}$ = 4.0 Hz, and $J_{2\alpha,3\beta}$ = 1.5 Hz.
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12. As judged by comparison of the $[\alpha]_D$ values of our crystalline products with those reported for the natural compounds: 6, m.p. 121-122°C, $[\alpha]_D$ + 50.2° (c 1.83, EtOH) (G. Barger, T.R. Seshadri, H.E. Watt, and T. Yabuta, J. Chem. Soc., 1935, 11); 10, $[\alpha]^{25}$ + 44.7° (c 0.0024, EtOH), HCl salt, m.p. 165-166°C (9); 13, m.p. 147-148°C, $[\alpha]^{20}$ - 60.3° (c 1.46, $CHCl_3$) (A.V. Danilova, L.M. Utkin, G.V. Kozyreva, and Yu. I. Syrneva, J. Gen. Chem. USSR, 1959, 29, 2396). The i.r. spectra of our synthetic (+)-retronecine and (-)-platynecine (in KBr) were identical to those of authentic samples of these alkaloids.

Received, 7th March, 1983