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# RECENT STUDIES ON VERATRUM ALKALOIDS: A NEW REACTION OF SODIUM TRIACETOXYBOROHYDRIDE [$NaBH(OAc)_3$]

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Abstract: In the presence of a hydroxyl group juxtaposed for participation, $NaBH(OAc)_3$ reduced even ketones in a stereo and regiospecific manner and in excellent yields.

The veratrum alkaloids of ceveratrum group have several exceedingly desirable characteristics as anti-hypertensive agents.[1] However, the narrow therapeutic ratio between hypotensive and undesired emetic activity preclude their use in modern medicine. In an effort to separate the two activities, classical work on these alkaloids centered mainly on the systematic variation of ester groups at positions 3,6,7 and 15 but had little success. Towards the same endeavor, we sought to bring about some more deep seated changes on these complex alkaloids. We present here some of our results pertaining to selective epimerisation of hydroxyl groups (e.g. at positions 7 and 16) in the alkamine germine.

Due to the axial (and hindered) nature of all the secondary hydroxyl groups in germine, selective derivatization and possibility of elimination, did not allow for efficient $S_N2$ type inversions. Also, the abnormally high susceptibility of certain germine esters to solvolysis plus the base lability of the 4,9-hemiketal system[2] limited our scope even further. We therefore decided to explore the oxidation-reduction approach, although past experience suggested that $NaBH_4$ reduction of both 7 and 16-keto groups would sterically favor the retention products, 7α and 16β-alcohols.[2]

$NaBH(OAc)_3$ selectively reduces aldehydes in the presence of ketones.[3a] Its weak reactivity may be due to the electron withdrawing effect of the acetoxy groups as well as to steric shielding of the B-H bond.[3b] With an alcohol (ROH) sodium triacetoxyborohydride may exchange either to give a species such as $NaBOR(OAc)_3$ or $NaBH(OR)(OAc)_2$. The extremely slow rate of exchange of the lone $H^{\theta}$ in $NaBH(OAc)_3$ with acetic acid[4] suggested that the species $NaBH(OR)(OAc)_2$ may preponderate. It seemed possible that this relatively electron rich species might act as an improved $H^{\theta}$ donor compared to $NaBH(OAc)_3$ at least in an intramolecular sense.

When the 7-keto 3,15,16-triester 1 was treated with $NaBH(OAc)_3$ in neat acetic acid, the exclusive product obtained was the 7β-alcohol 2 (yield 92%).[5] $NaBH_4$ reduction of the same ketone in t-BuOH or EtOH gave as expected, the 7α-alcohol 3 as the major product in ~50% yield.[6] The other 7-keto triesters 4 and 6 when treated in the same manner with $NaBH(OAc)_3$ gave the 7β-alcohols 5 and 7 in excellent yields. We rationalise this stereospecific formation of 7-epi-germine triesters in terms of exchange of one of the acetoxy groups in $NaBH(OAc)_3$ with the 14α-hydroxyl group (see 8) followed by intramolecular delivery of $H^{\ominus}$ to the hindered α-face of the ketone.

In a different context we had prepared a new rearrangement product 10 (yield 95%)[7] by solvolysis of germine 3-tosylate 14,15-acetonide 9 (arrows). Reduction of this bicyclic 4-ketone 10 with $NaBH_4$ in ethanol took place from the exo-face to give the endo-alcohol 11 (X=H, Y=OH)[8] in virtually quantitative yield. In contrast treatment of 10 with $NaBH(OAc)_3$ as above gave the 4-exo-alcohol 12 (X=OH, Y=H)[9] exclusively (yield 85%) -- a result which may be attributed to complexation of the sort as depicted in 8, this time with the 7α-hydroxyl group.

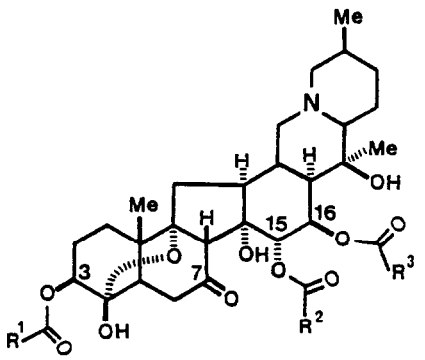
The above examples indicated to us that for $NaBH(OAc)_3$ to become an effective $H^{\ominus}$ donor to a ketone, its complexation with a suitably placed hydroxyl group was an obligatory factor. This was clearly borne out by the fact that reduction of the 4,16-diketo iso-germine 13 (R=cyclopropyl) with this reagent (aided by the 20β-hydroxyl group), gave only the 16α-alcohol 14 (yield 96%).[10] No 16β-epimer could be detected and no reduction was observed at the 4-keto position. Molecular models showed that complexation of $NaBH(OAc)_3$ with the 9α-hydroxyl group would be of no consequence since the 4-keto group lies too far from it for an intramolecular reduction.

The procedure for carrying out $NaBH(OAc)_3$ reduction in the present examples is very simple: a solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (0.65g; 1.7mmol)[11] to glacial acetic acid (25 ml) while keeping the temperature[4] below 20° (ice bath). After the $H_2$ evolution had ceased (5 min. approx.) the ketone 1 (0.5g; 0.69mmol) was added in one portion and the reaction stirred for 3-4 hours at room temperature. Evaporation of acetic acid in vacuo (temp. 40-50°) followed by extractive isolation with methylene chloride provided the alcohol 2, virtually pure by t.l.c. and p.m.r.

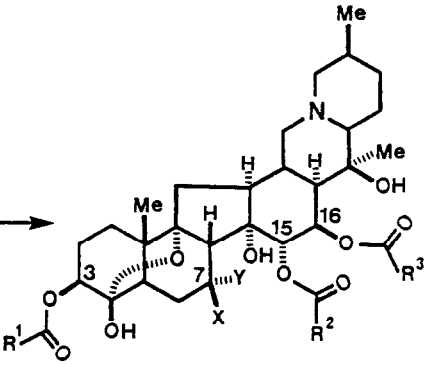
Complexation of hydroxy or amino substituents with $NaBH_4$ followed by intramolecular $H^{\ominus}$ delivery has been invoked to explain the stereochemical outcome of certain ketone reductions.[12a-c] However, due to competing inter vs intramolecular $H^{\ominus}$ transfers, mixtures of epimeric alcohols were usually formed.[13] $NaBH(OAc)_3$ does not suffer from this drawback since it becomes a reducing species towards a ketone only when complexed with a suitably placed hydroxyl group. Such a requirement leaves the other sensitive groups intact.

We hope to extend this unique feature of $NaBH(OAc)_3$ to reduction of some acyclic ketones having chiral participating groups.[14]

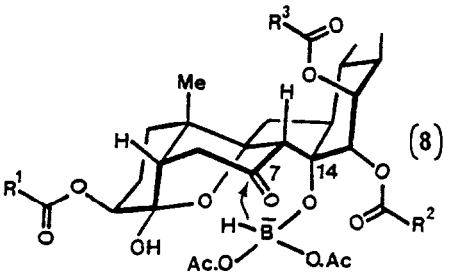
Acknowledgements: We cordially thank Drs. M.J. Green and A.K. Ganguly for many stimulating discussions. We should also like to thank Dr. M. Puar, Mr. R. Novotny and Mr. P. Bartner for providing PMR and mass spectra.



**1** $R^1$, $R^2$, $R^3$ = $^i$Bu
**4** $R^1$, $R^2$ = $^i$Bu; $R^3$ = Me
**6** $R^1$ = cyclo-Pr; $R^2$ = $^i$Bu; $R^3$ = Me



**2** $R^1$, $R^2$, $R^3$ = $^i$Bu; X = OH; Y=H
**3** $R^1$, $R^2$, $R^3$ = $^i$Bu; X = H; Y = OH
**5** $R^1$, $R^2$ = $^i$Bu; $R^3$ = Me; X = OH; Y = H
**7** $R^1$ = cyclo-Pr; $R^2$ = $^i$Bu; $R^3$ = Me X = OH; Y = H



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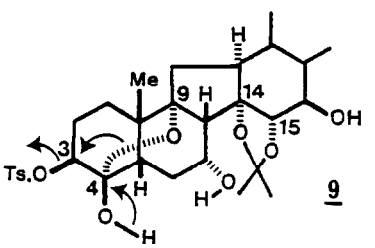
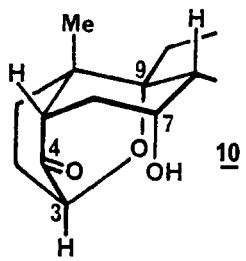
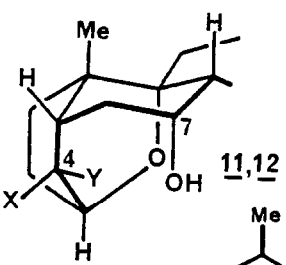


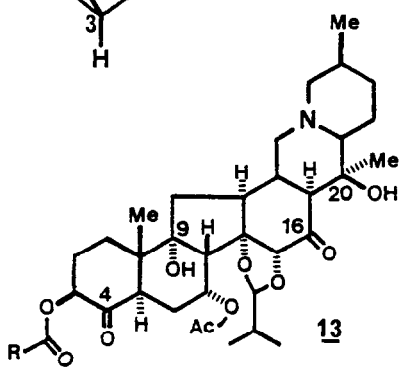
**9**



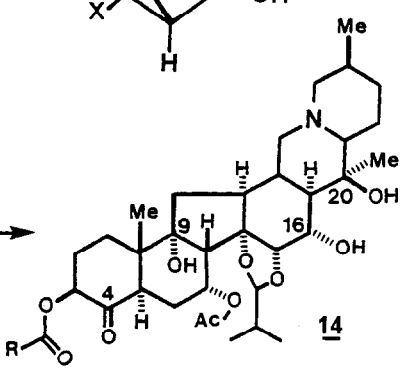
**10**



**11,12**



**13**



**14**

References and Notes:


1. For a recent review, see: O. Krayer and E. Meilman, Handbook of Experimental Pharmacology, Hefter-Heubner New Series, XXXIX, Springar-Verlag, 1977.
2. S.M. Kupchan and A.W. By, Alkaloids, Vol. 10, R.H.F. Manske (Ed.), p. 193-285, Academic Press, 1968.
3. (a) G.W. Gribble and D.C. Ferguson, Chem. Comm., 535 (1975); (b) Review: G.W. Gribble, Eastman Organic Chemical Bulletin, 51, No. 1 (1979)
4. P. Marchini, G. Liso, A. Reho, F. Libertore and F.M. Moracci, J.O.C., 40, 3433 (1975).
5. PMR ($CDCl_3$): 4.5 (dd, $J_{ae}$ = 4Hz, $J_{aa}$ = 10Hz, $H_7$), 4.85 (broad, $\frac{1}{2}W$ = 8Hz, $H_{16}$), 5.6 (d, $J_{ae}$ = 4Hz, $H_{15}$).
6. A number of unidentified products were also formed in such reductions with $NaBH_4$. In contrast, all reactions with $NaBH(OAc)_4$ were virtually free from side products as judged by t.l.c.
7. Synthetic schemes and rationale for preparing all these new compounds (1→14) will be presented in forthcoming publications from our group.
8. PMR ($CDCl_3$): 0.9 (s, Me-19), 3.78 (m, $\frac{1}{2}W$ = 6Hz, $H_3$), 3.85 (dd, $J_{4,5}$ = 9Hz; $J_{4,OH}$ = 12Hz, $H_4$). Reduction of 10 with $B_2H_6$ in THF also gave 11 as the major product (>70%).
9. PMR ($CDCl_3$): 0.85 (s, Me-19), 3.9 (m, $\frac{1}{2}W$ = 10Hz, $H_3$).
10. PMR ($CDCl_3$): 1.4 (s, Me-19), 1.96 (s, $CO.CH_3$), 3.4 (dd, $J_{ae}$ = 4Hz; $J_{aa}$ = 12Hz, $H_5$), 3.95 (dd, $J_{ae}$ = 4Hz, $J_{aa}$ = 12Hz, $H_{16}$), 4.4 (d, $J_{ae}$ = 4Hz, $H_{15}$).
11. In the presence of other free hydroxyl groups, an excess reagent was necessary to ensure its complete exchange with participating hydroxyl groups.
12. (a) P.T. Lansbury, J.F. Bieron and M. Klein, J.A.C.S., 88, 1477 (1966); (b) M. Akhtar and S. Marsh, J.C.S., C, 937 (1966); (c) S. Yamada and K. Koga, Tetrahedron Letters, 1711 (1967); (d) H.O. House, Modern Synthetic Reactions, p. 59, W.A. Benjamin (1972).
13. Contrary to precedents,[12a-c] and our present observations, it has been stated[12d] that, "such an intramolecular process would be expected to be more important for reductions with $LiAlH_4$ in aprotic solvents than for reductions with $NaBH_4$ in protic solvents." In the cited example[12b], however, the product ratios have been inadvertently reversed. We thank Prof. H.O. House for his prompt reply acknowledging this erroneous statement.
14. All new compounds gave consistent spectroscopic data. Elemental analysis were obtained for crystalline compounds only. Yields refer to isolated products.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