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LEWIS ACID COMPLEXED HETEROATOM CARBANIONS; A CONVENIENT ROUTE TO α-HYDROXYBENZYLTETRAHYDROISOQUINOLINE ALKALOIDS

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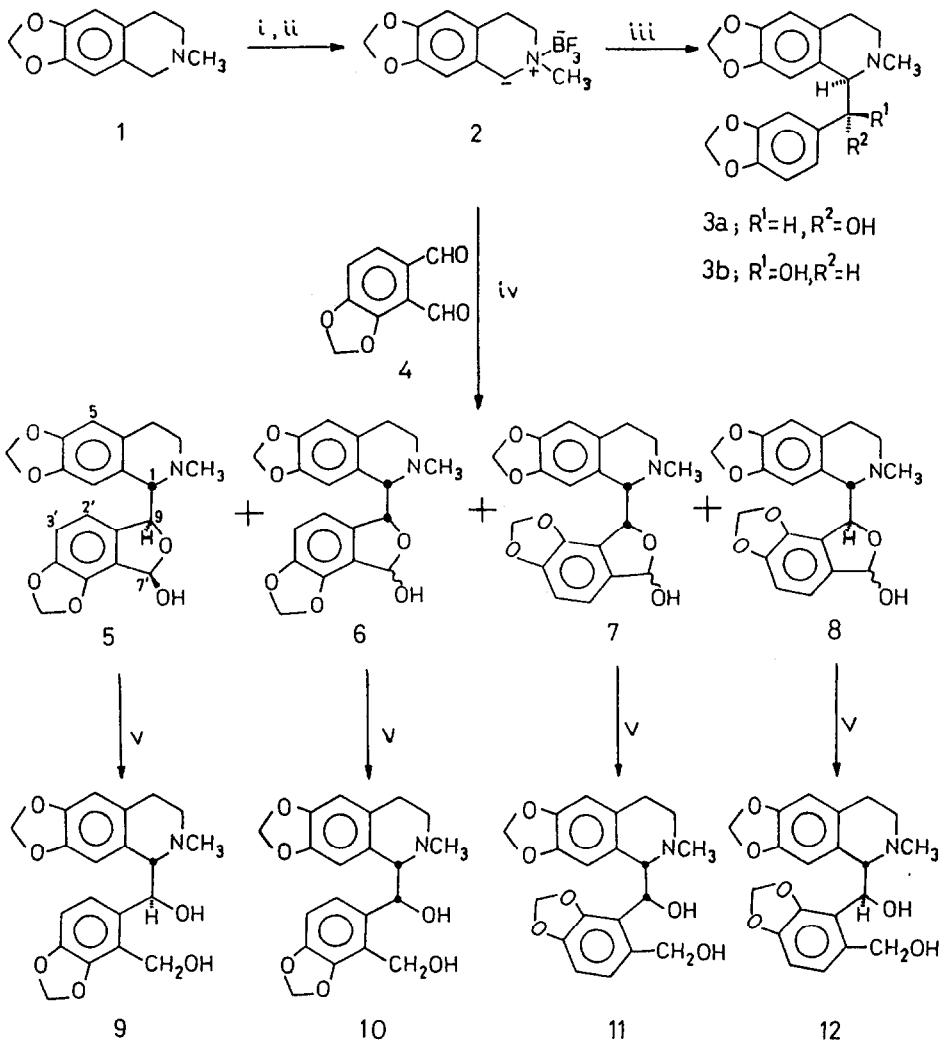
Abstract: Treatment of the BF_3 complex of 6,7-methylenedioxy-2-methyltetrahydroisoquinoline (**2**) with sec-butyllithium followed by addition of piperonal gave α -hydroxybenzyltetrahydroisoquinolines **3a** and **3b**, while addition of 3,4-methylenedioxyphthaldehyde (**4**) afforded alkaloids (±)corytensine (**5**) and (±) egenine (**6**) along with isomeric hemiacetals **7** and **8**.

The alkaloids decumbensine and epi- α -decumbensine were isolated from Corydalis decumbens[1] and postulated to have structures **3a** and **3b**. However, authentic **3a** and **3b** synthesised by Rozwadowska et al.[2] turned out to be different from these alkaloids. It was, therefore, suggested that epi- α-decumbensine is identical with the earlier known alkaloid corytensine having the hemiacetal structure **5** as shown by X-ray analysis.[3] About the same time, Gawley[4] reached the conclusion that decumbensine is identical with another alkaloid egenine[5] which had been presumed[3] to be isomeric with corytensine at C-7′. However, detailed ^1H NMR spectral studies indicated that the two alkaloids are isomeric at C-9. Thus, egenine was assigned structure **6** with undefined stereochemistry at C-7′.[4] It may be noted that in these compounds, in addition to stereoisomerism at C-9 and C-7′, regioisomerism due to methylenedioxy group location is also possible. Therefore, it would be useful to obtain compounds corresponding to structures **7** and **8**, along with **3a**, **3b**, **5** and **6**.

It seemed that the Lewis acid complexation methodology, recently introduced by us[6] to facilitate generation of otherwise elusive α-carbanions from tertiary amines,[7,8] can provide direct access to the above mentioned structures . In the event, treatment of readily available 6,7-methylenedioxy-2-methyltetrahydroisoquinoline (**1**) with BF_3 followed by addition of sec-butyllithium gave a reddish solution, presumably of the carbanion **2**.[9] Quenching with piperonal afforded, after workup and chromatographic separation, **3a** and **3b** in 20% and 42% yield respectively.[12] This one pot procedure is considerably simpler than the earlier approaches to α-hydroxybenzyltetrahydroisoquinolines.[2,13]

For the synthesis of hemiacetals, the required dialdehyde (4)[14] was secured from 2-ethoxycarbonyl-3,4-methylenedioxybenzaldehyde[15] by lithium aluminium hydride reduction followed by Swern's oxidation[16] (84%



Reagents: i. $BF_3.Et_2O$ (2.2 equiv.), THF, -30°C, 15 min.
ii. s-BuLi. (2.5 equiv.), THF, -78°C, 1h.
iii. piperonal, -78°C, 15 min. iv. -78°C, 45 min.
v. $NaBH_4$.

overall yield). Its reaction with carbanion **2**, obtained in the above described manner, gave a mixture from which four pure compounds were isolated by repeated chromatography and crystallization. The compounds melting at 209-210° and 207-208° were identified as (±)corytensine (**5**) and (±)egenine (**6**) respectively, on the basis of ^{1}H, ^{13}C NMR and mass spectral comparison with literature values.[3,4,17] The ^{1}H NMR spectrum of the third compound[18], m.p.150-151°, showed a coupling constant of 3.8 Hz between C-1 and C-9 protons indicating an erythro configuration.[4] It could be diastereomeric with **6** due to different orientation of the hydroxyl function or it may be a regioisomer arising out of carbanion addition to the more hindered aldehydic group of **4**. The fourth product[19], m.p.177-178°, was assigned a threo configuration due to absence of coupling between C-1 and C-9 protons.[3] Again, it could be a stereo or regioisomer of **5**. This issue could not be unambigously settled by spectral data, hence evidence in favour of structures **7** and **8** was adduced by reducing all the four compounds to diols in which the stereocentre at C-7′ got eliminated. Since four new diols[20] (differing from each other in t.l.c., ^{1}H NMR and MS) were obtained, it was clear that none of the precursor hemiacetals were isomeric at C-7′ alone, and that the location of the methylenedioxy groups in **7** and **8** was different from the one in **5** and **6**.

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14. M.p.143-144°; ^{1}H NMR ($CDCl_3$): δ 6.3(s, 2H, OCH_2O), 7.1,7.65(ABq, 2H, aromatic protons, J=8.0 Hz), 10.47,10.85(s, 2H, 2xCHO); MS m/z (rel.intensity): 178(M^+, 65), 150(49), 149(M^+-CHO, 100).
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17. (-)Egenine has been synthesised earlier, see reference 4; The present work constitutes the first synthesis of (±) corytensine.
18. ^{1}H NMR ($CDCl_3$): δ 1.92-3.10 (m, 4H, CH_2-CH_2), 2.50 (s, 3H, N-CH_3), 3.90 (d, 1H, H-C_1, J=3.8 Hz), 5.51 (d, 1H, H-C_9, J=3.8 Hz), 5.49, 5.67 (d, 2H, OCH_2O, J=1.2 Hz), 5.94 (q, 2H, OCH_2O), 6.17 (s, 1H, H-$C_{7'}$), 6.55, 6.75 (s, 2H, H-C_5 and H- C_8), 6.8 (ABq, 2H, H-$C_{2'}$ and H-$C_{3'}$): MS m/z (rel.intensity): 351 (M^+ -18, 0.18), 190 (100); HRMS: calcd. for $C_{20}H_{19}NO_6$ 351.1106, found 351.1143.
19. ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, N-CH_3), 2.26-3.15 (m, 4H, CH_2-CH_2), 3.83 (s, 1H, H-C_1), 5.36 (s, 1H, H-C_9), 5.92, 6.03 (m, 4H, 2xOCH_2O), 6.05 (s, 1H, H-$C_{7'}$), 6.61, 6.74, 6.87, 6.89 (s, 4H, H-C_5, H-C_8, H-$C_{2'}$ & H-$C_{3'}$); MS m/z (rel. intensity): 352 (M^+ -17, 0.11), 351 (M^+ -18, 0.40), 190 (100); HRMS: calcd. for $C_{20}H_{19}NO_6$ 351.1106, found 351.1133.
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