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A BIOMIMETIC SYNTHESIS OF (±)-CORYNOLINE, (±)-11-EPICORYNOLINE, (±)-ISOCORYNOLINE, AND (±)-11-EPIISOCORYNOLINE FROM CORYSAMINE

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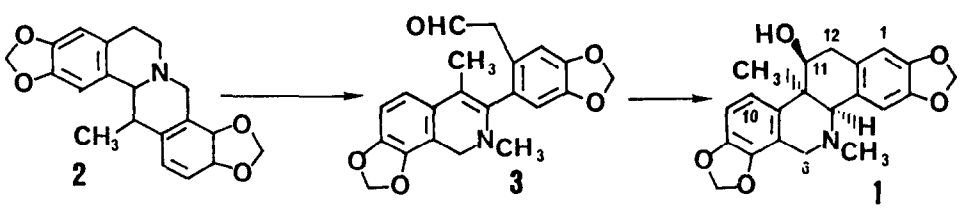
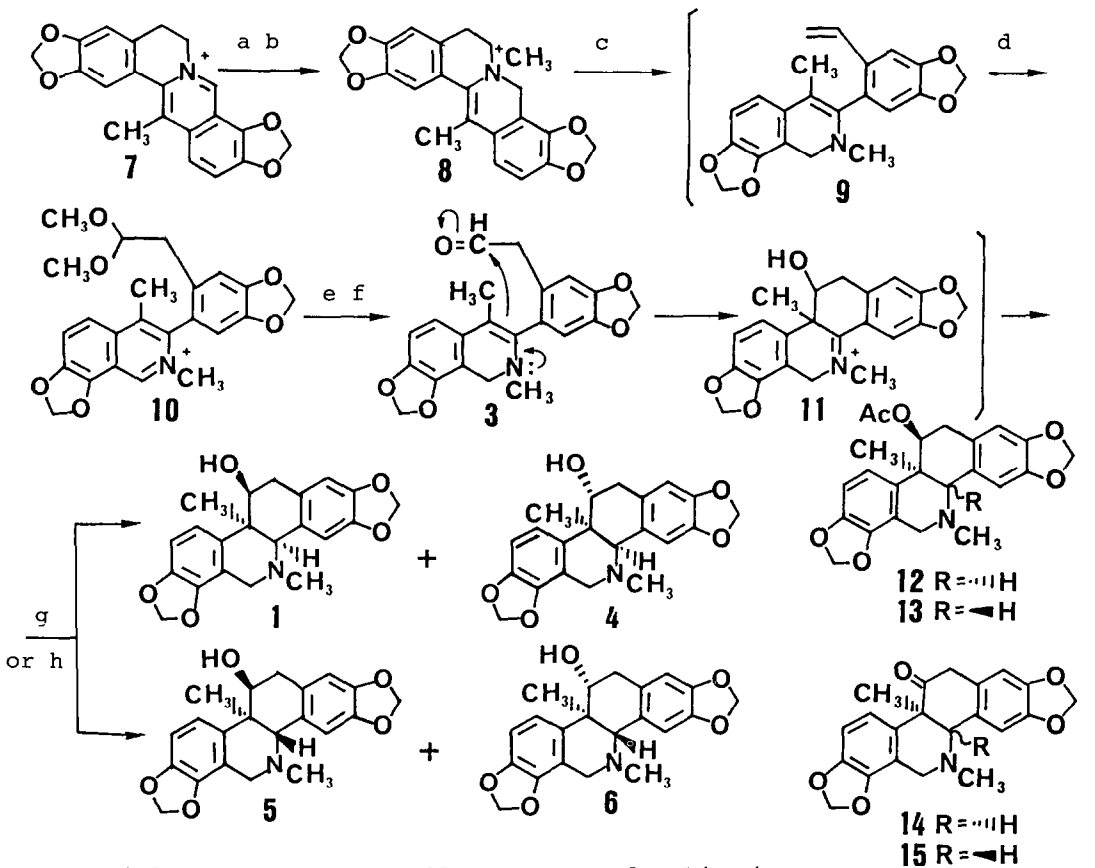
Summary: A novel and efficient synthesis of hexahydrobenzo[c]phenanthridine alkaloids, (±)-corynoline, (±)-11-epicorynoline, (±)-isocorynoline, and (±)-11-epiisocorynoline was accomplished from protoberberine alkaloid, corysamine through a biogenetic route.

Corynoline (**1**),[1] a representative 10b-methylhexahydrobenzo[c]phenanthridine alkaloid,[2] has been isolated both as a racemate and (+)-form and shown to be biosynthesized[3] from the corresponding protoberberine alkaloid, tetrahydrocorysamine (**2**) *via* a hypothetical intermediate enamine-aldehyde (**3**). Three other diastereoisomeric alkaloids, 11-epicorynoline (**4**),[4] isocorynoline (**5**),[1e,4-6] and 11-epiisocorynoline (**6**),[7,8] have also been isolated. Several total synthesis of corynoline[9-11] and its related alkaloids such as 12-hydroxycorynoline,[9] 11-epicorynoline,[9] 6-oxocorynoline,[10] isocorynoline,[10,12] and 11-epiisocorynoline[10] have been reported. However, no report has so far appeared on a synthesis of corynoline and its diastereoisomers according to the above biogenetic process. This communication deals with a first biomimetic transformation of a protoberberine alkaloid, corysamine into corynoline, 11-epicorynoline, isocorynoline, and 11-epiisocorynoline *via* a proposed biogenetic intermediate, enamine-aldehyde (**3**).



Oxygenation of the enamine (**9**),[13] the Hofmann degradation product of **8** derived from corysamine (**7**), with thallium (III) nitrate[14] in methanol at



a: $LiAlH_4$ b: Me_2SO_4 c: 25% KOH-MeOH d: $Tl(NO_3)_3$
e: $NaBH_4$ f: 15% HCl g: $NaBH_3CN$ h: Zn-AcOH

room temperature for 30 min afforded the acetal (**10**). Successive treatments of the crude product (**10**) with sodium borohydride at 0°C for a few min, 15% hydrochloric acid in methanol at room temperature overnight, and then sodium cyanoborohydride at 0°C for 1 hr effected reduction of a C-N double bond in **10**, deacetalization, cyclization, and further reduction of a C-N double bond in **11** to provide (±)-corynoline (**1**) [45% form **8**; mp 219-220°C (lit.[9] 218-220°C); m/z 367 (M^+); 6.92, 6.81 (1H each, AB-q, J=8.3 Hz), 6.66 (2H, s), 3.98 (1H, s), 3.38 (1H, d, J=1.2 Hz), 2.26 (3H, s), 1.15 (3H, s)] along with (±)-11-epicorynoline (**4**) [13% from **8**; mp 191-192°C (lit.[4] 195.5-196.5°C); m/z 367 (M^+); 4.56 (1H, dd, J=9.5; 7.1 Hz), 3.22 (1H, s), 2.19 (3H, s), 1.11 (3H, s)] via the enamine-aldehyde (**3**)[3] and the iminium (**11**)[3]. Synthetic (±)-corynoline and (±)-11-epicorynoline were identical with natural (+)-corynoline and the authentic (±)-11-epicorynoline, respectively. Acetylation of **1** with acetic anhydride in pyridine afforded (±)-acetylcorynoline (**12**) [mp 157-158°C

(lit.[5a] 158-159°C), m/z 409 (M^+), 5.18 (1H, dd, J=8.1, 6.7 Hz), 1.86 (3H, s)].

Reduction of **11** with zinc-acetic acid instead of sodium cyanoborohydride in the last step of the above reaction gave (±)-isocorynoline (**5**) [28% from **8**; mp 204-205°C (lit.[10] 174-176°C); m/z 367 (M^+); 4.51 (1H, s), 4.33 (1H, d, J=4.9), 3.22 (1H, dd, J=17.8, 4.9), 2.84 (1H, d, J=17.8) 2.49 (3H, s), 1.11 (3H, s)] accompanied with (±)-11-epiisocorynoline (**6**) [7% from **8**; mp 185-186°C (lit.[10,15] 238-240°C); m/z 367 (M^+); 3.97 (1H, s), 3.10 (1H, dd, J=17.1, 7.1), 2.81 (1H, dd, J=17.1, 10.0), 2.43 (3H, s), 1.19 (3H, s)] as well as **1** (4%) and **4** (7%). Acetylation of **5** gave (±)-acetylisocorynoline (**13**) [mp 178-180°C, m/z 409 (M^+), 5.52 (1H, dd, J=5.1, 1.7 Hz), 1.77 (3H, s)]. Synthetic (±)-isocorynoline was identical with natural (+)-isocorynoline. ^{1}H-NMR spectral data of synthetic (±)-11-epicorynoline were in good agreement with those reported for natural alkaloid.[7]

The Swern oxidation of **1** or **4** with trifluoroacetic anhydride in dimethyl sulfoxide afforded the ketone (**14**)[4,5b] in 77% or 72% yield, respectively. The product was reduced either with lithium aluminum hydride[16] in tetrahydrofuran or with sodium cyanoborohydride in t-butanol in the presence of 15% hydrochloric acid to furnish stereoselectively (±)-corynoline (**1**) in 94% or 91% yield, respectively.[17] On the other hand, similar reduction of the diastereoisomeric ketone (**15**), derived from **5** (84%) or **6** (75%), with lithium aluminum hydride afforded (±)-isocorynoline (**5**) (81%) along with (±)-11-epiisocorynoline (**6**) (10%), whereas that with sodium cyanoborohydride provided **5** (19%) and **6** (54%).

Thus, we developed a novel and biomimetic synthesis of corynoline, 11-epicorynoline, isocorynoline, and 11-epiisocorynoline. As the starting protoberberine alkaloid is readily accessible and the reaction procedure is very simple, the present synthesis provides a general method for a synthesis of hexahydrobenzo[c]phenanthridine alkaloids.

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