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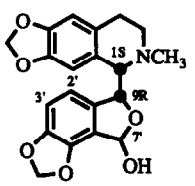
SYNTHESIS OF (–)-EGENINE (DECUMBENSINE) BY ASYMMETRIC CARBONYL ADDITION

Kathleen S. Rein and Robert E. Gawley*

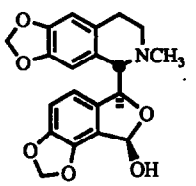
Department of Chemistry, University of Miami, Coral Gables, Florida 33124, USA

Abstract: *The first synthesis of the phthalideisoquinoline hemiacetal egenine is reported, along with spectral data suggesting that egenine and decumbensine are one and the same. These synthetic studies are part of a larger investigation into the face-selectivity of additions of chiral dipole-stabilized organometallics to aldehydes. The synthesis of egenine and the correlation to bicuculline diol establish the absolute configuration of the major stereoisomer formed as being opposite to that expected based on earlier work.*

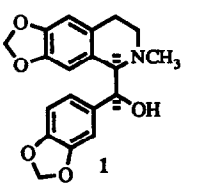
In 1983, Shamma isolated the first phthalideisoquinoline hemiacetal, (+)-egenine, from *Fumaria vailantii* Loisel, and suggested its possible implication in the biosynthesis of the phthalideisoquinoline lactone bicuculline.[1] In 1988, Wu, et al., isolated a second phthalideisoquinoline hemiacetal, (+)-corytensine, from *Corydalis ochotensis* Turcz., whose structure was proven by single crystal x-ray analysis.[2] Corytensine is epimeric to egenine at the C-9 position. Also in 1988, Zhang, Xu, and Quirion isolated two alkaloids from *Corydalis decumbens*, which they named decumbensine and epi-α-decumbensine, and postulated as structures **1** and **2**, respectively.[3]



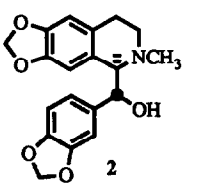
(+)-egenine



(+)-corytensine



1

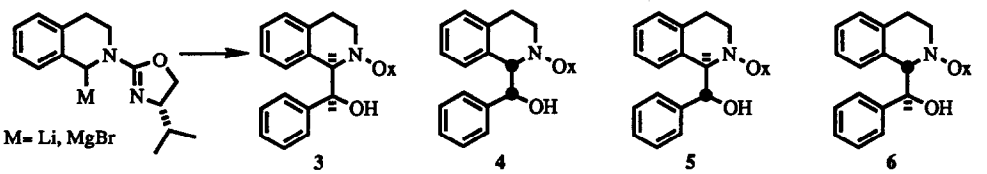


2

As part of a program on the chemistry of chiral dipole-stabilized organometallics,[4] we have been investigating face-selectivity in the addition of chiral, metallated tetrahydroisoquinoline derivatives to aldehydes. In so doing, four diastereomers may be formed (Scheme 1). In a related (achiral) system, Seebach has shown that addition of a lithiated tetrahydroisoquinoline pivalamide gives a mixture of both *erythro* and *threo* diastereomers, whereas transmetallation with magnesium bromide prior to addition affords only the *erythro* isomer.[5] We find the same trend: the lithiated isoquinolyloxazoline affords a mixture of both *erythro* (**3** and **4**) and *threo* (**5** and **6**) diastereomers, whereas the Grignard species gives a 2:1 mixture of the two *erythro* isomers. The analysis of stereoisomers was done by chiral stationary phase HPLC, using a Pirkle column, and the N-naphthamides corresponding to **3** - **6** are all separable using gradient elution. And although comparison with authentic samples[5]

showed which pair of peaks belong to the *erythro* isomers, we did not know the absolute configuration of the major one obtained in the asymmetric addition.[6] Thus, a correlation with one of the natural products shown above seemed to be in order. Herein we report the synthetic correlation of a major *erythro* isomer to egenine and bicuculline diol, along with spectral data suggesting the probable identity of egenine and decumbensine.

Scheme I



The synthesis of (–)-egenine is detailed in Scheme 2. The *N*-oxazolyl substituted isoquinoline **7** was lithiated with *t*-butyllithium and transmetallated with magnesium bromide etherate. The subsequent addition of piperonal yielded *N*-oxazolyl-α-hydroxybenzyltetrahydroisoquinoline **8** (plus its 1*S*, 9*R* diastereomer) in 55% combined yield. Lithium aluminum hydride reduction afforded **9** in 90% yield. The enantiomeric excess of **9** was determined, by Pirkle analysis of the *N*-napthamide, to be 30%.[6] This, however, was enriched to 100% ee by a single recrystallization of the (+)-tartrate salt. Cyclization with phosgene provided the oxazolidinone **10** (98%) which was reduced with lithium aluminum hydride to the N-methyl-α-hydroxybenzyltetrahydroisoquinoline **1** in 95% yield. In comparing the spectral data of synthetic **1** with that reported for decumbensine, we found that they did not match.[7] Shortly after this phase of our work was completed, Rozwadowska reported syntheses of both **1** and **2**, and established that they were not the correct structures for decumbensine and epi-α-decumbensine.[8] She also suggested that corytensine and epi-α-decumbensine might be the same, however the comparison was made with the misdrawn representation of corytensine.[2]

Metallation of the 6' position followed by the addition of dimethylformamide yielded (–)-egenine in 31% yield.[9] Reduction with $NaBH_4$ afforded a 73% yield of (+)-bicuculline diol.[10] 400MHz homonuclear COSY and difference nOe experiments established the assignments for all of the protons of synthetic egenine, which are shown in Table 1. These signals correspond with those reported for egenine and for decumbensine, although the published assignments for egenine are apparently scrambled. Specifically, the signals corresponding to 6.58, 6.53, 6.34, and 5.65 are assigned to positions 3', 2', 5, and 7', respectively.[1,11]

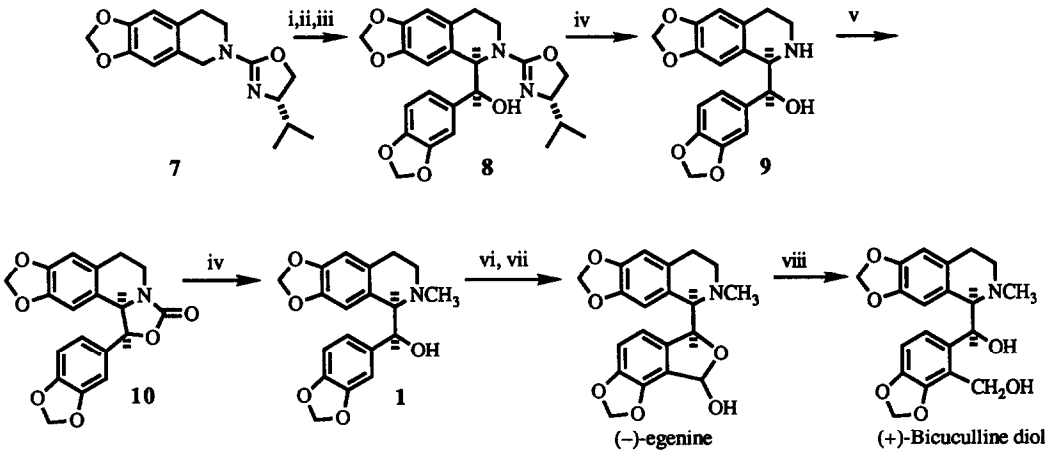
A ^{13}C NMR spectrum was not reported for (+)-egenine, however, our ^{13}C data[12] (Table 1) are quite similar to that of corytensine and correspond exactly to that of decumbensine, with the following exception. At 100MHz, two signals appear very close together at 123.99 and 124.11 ppm. The ^{13}C spectrum of decumbensine at 22.63MHz showed only a single peak at 124.1 ppm.[3] The lower spectral dispersion at 22MHz probably accounts for the observation of only 19 carbons for decumbensine.

In conclusion, we have confirmed by synthesis the structural assignment of egenine and also determined that decumbensine and egenine are identical. This study also reveals that the major isomer obtained in the asymmetric addition, at C-1 of the α-hydroxybenzylisoquinoline, is opposite to that obtained by alkylation,[4a] but that the order of elution of the two enantiomers of α-hydroxybenzylisoquinoline **9** (on a Pirkle column) is the same as that expected based on the order of elution of the same compound minus the hydroxyl.[6] A detailed study of the asymmetric addition of metallated tetrahydroisoquinolines to aldehydes will be reported shortly.

Table 1. 400 MHz Proton and 100MHz Carbon Chemical Shifts for (–)-Egenine

Position	NCH_3	1	5	8	9	2'	3'	7'
^1H Shift	2.51	3.89 (d,J=3.6)	6.58	6.80	5.40 (d,J=3.6)	5.65 (d,J=7.6)	6.53 (d,J=7.6)	6.34
^{13}C Shift	43.97	64.91	108.65	107.58	86.94	114.60	108.31	97.88

Scheme II



i. *t*-BuLi, THF, –78°C, 5 min. *ii.* $MgBr_2 \cdot OEt_2$, 0°, 20 min. *iii.* piperonal, –78°C, 15h. *iv.* $LiAlH_4$, THF, Δ *v.* $COCl_2$. *vi.* *n*-BuLi, THF, –45°, 2h. *vii.* DMF. *viii.* $NaBH_4$

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Notes and References

1. B. Gözler, T. Gözler, M. Shamma, *Tetrahedron* **1983**, *39*, 577-580.
2. T. S. Wu, S. C. Huang, S. T. Lu, Y. C. Wu, D. R. McPhail, A. T. McPhail, K. H. Lee, *Heterocycles* **1988**, *27*, 1565-1568. These authors incorrectly transcribed the x-ray picture to the line drawing in this reference. The correct structure is shown above, and a corrigendum has been submitted (A. T. McPhail, private communication.)
3. J.-S. Zhang, R.-S. Xu, J. C. Quirion *J. Nat. Prod.* **1988**, *51*, 1241-1242.
4. (a) R. E. Gawley, G. A. Smith *Tetrahedron Lett.* **1988**, *29*, 301-2; (b) L. J. Bartolotti, R. E. Gawley *J. Org. Chem.* **1989**, *54*, 2980-2982; (c) R. E. Gawley, K. Rein, S. Chemburkar *ibid*, **1989**, *54*, 3002-3004.
5. D. Seebach, J. Hansen, P. Seiler, J. M. Gromek *J. Organomet. Chem.* **1985**, *285*, 1-13.
6. For simple alkylated tetrahydroisoquinoline naphthamides, the order of retention is established, but for α-hydroxybenzylisoquinolines, the effect of the second stereocenter on the relative binding of the enantiomers was not known. In the present case, the retained enantiomer has the C-1 hydrogen α, as is the case with the simple alkylated isoquinolines, although the *R, S* designation is reversed. W. H. Pirkle, C. J. Welch, G. S. Mahler, A. I. Meyers, L. M. Fuentes, M. Boes *J. Org. Chem.*, **1984**, *49*, 2504-6.
7. Professor Quirion has informed us by letter that the published structures are incorrect and that a corrigendum will be forthcoming.
8. M. D. Rozwadowska, D. Mateka, D. Brózda *Tetrahedron Lett.* **1989**, *30*, 6215-6218.
9. $[\alpha]_D$ –214° (c 0.55, $CHCl_3$), –94° (c 0.55, MeOH). Lit. for the 1-*S*, 9-*R* enantiomer:[1] +214° (c 0.55, $CHCl_3$), +99° (c 0.12, MeOH). DCI/MS (CH_4) showed a MH^+ ion at *m/e* 370, and fragments at 190, 179, and 163.
10. $[\alpha]_D$ +16.3° (c 0.44, $CHCl_3$). Lit. for the 1-*S*, 9-*R* enantiomer:[1] –17° (c 0.15, $CHCl_3$)
11. Additionally, the 6.58 proton was reported to be a doublet, where we find only a singlet (there were 5 doublets reported altogether).[1] Unfortunately, neither an authentic sample nor a spectrum are available (M. Shamma, private communication).
12. Assignments were established by $^1H/^{13}C$ HETCOR experiments. The only carbons that remain specifically unassigned are the unprotonated aromatic carbons.

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