A Novel Route to Chiral, Nonracemic 1-Alkyl- and 1-Aryl-Substituted Tetrahydroisoquinolines. Synthesis of (−)-Salsolidine and (+)-Cryptostyline II

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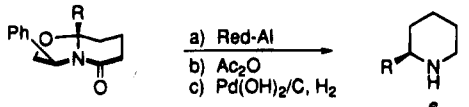
Received August 23, 1995

Several important asymmetric routes have recently appeared for the stereoselective synthesis of tetrahydroisoquinoline alkaloids.[1] Although 1-alkyl substituents are readily introduced in an asymmetric manner, it is less common to introduce 1-aryl substituents present in a number of tetrahydroisioquinoline natural products *(vide infra)*. We now describe a novel asymmetric approach to the synthesis of tetrahydroisoquinolines derived from chiral bicyclic lactams which allows both 1-alkyl and 1-aryl substituents to be introduced. The pivotal system utilized is based upon lactam **1a** which had earlier been employed to reach chiral, nonracemic naphthalenones **4**. By a minor, but significant modification in the structure and chemistry of **1**, we are now able to transform the latter into the titled tetrahydroisoquinolines.

In an earlier report, we had dialkylated lactam **1a** and subsequently reduced it to the corresponding aminal **2** (Scheme 1).[2] Hydrolysis of the latter furnished the intermediate keto aldehyde **3** which spontaneously cyclized to yield the chiral, quaternary carbon naphthalenones **4**. Furthermore, we recently succeeded in reducing chiral lactam **5** to the corresponding 2-substituted piperidine **6** in high enantiomeric purity.[3] In possession of the knowledge of both these findings, we addressed the reduction of lactams analogous to **1**, namely **1b**, with the expectation of preparing enantiomerically pure tetrahydroisoquinolines.

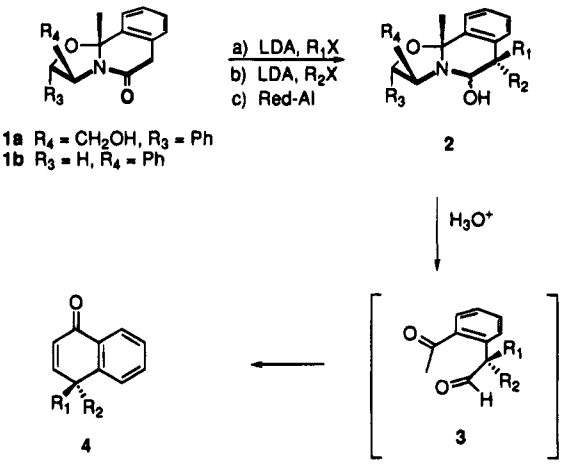


5 **6**

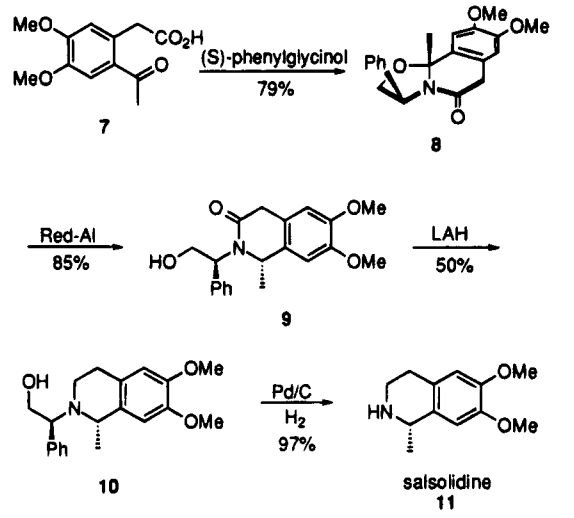
Initial efforts were directed toward the synthesis of the simple isoquinoline alkaloid, (−)-salsolidine **11**,[4] which required the preparation of bicyclic lactam **8**, possessing methoxy substituents at the 3- and 4-positions of the aromatic ring (Scheme 2). By condensing the known acid **7**[5] with (*S*)-phenylglycinol, **8** was obtained in 79% yield as a single diastereomer. Treatment of the latter with Red-Al furnished lactam **9** as a separable 94:6 mixture of diastereomers. In contrast to the lactam **5** in which the lactam carbonyl is readily reduced prior to cleavage of the ring C–O bond,[3] the carbonyl in **8** was found to be inert to Red-Al reduction. We felt this behavior may be a consequence of a conformational change affecting the alignment of the nitrogen lone pair with the carbonyl π system and/or the C–O bond, thus altering the steric and electronic behavior of the amide moiety. The acquisition of **9**, itself an intriguing intermediate for further elaboration, was smoothly reduced to **10** ($LiAlH_4$). Reductive removal of the *N*-benzyl group gave (−)-salsolidine (**11**) $[\alpha]_D$ −61.5 (lit.[1b] −59.9), which was identical in all respects to the natural alkaloid.[1b]

To further demonstrate this facile and novel route to isoquinoline alkaloids, we directed our attention to the more challenging 1-aryl-substituted cryptostylines (**12**–**14**). Cryptostylines I–III have been isolated from the plant *Cryptostylis fulva*[6] and are of considerable biological significance since numerous analogs of the cryptostylines have been studied as pharmacological probes for the D_1 dopamine receptor.[7] Additionally, benzhydrin-containing compounds have been shown to be an effective antagonist of substance P, a peptide neurotransmitter that binds to neurokinin-1 and is involved in pain transmission and

Scheme 1



Scheme 2



(1) (a) Carbonnelle, A. C.; Gott, V.; Roussi, G. *Heterocycles* **1993**, *36*, 1763. (b) Yamoto, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909. (c) Cho, B. T.; Han, C. K. *Bull. Korean Chem. Soc.* **1990**, *11*, 81. (d) Polniaszek, R. P.; Dillard, L. W. *Tetrahedron Lett.* **1990**, *31*, 797. (e) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095. (f) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M. Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117.

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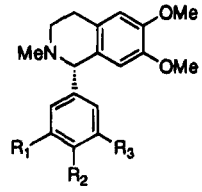
neurogenic inflammation.[8] It was anticipated that if the appropriate bicyclic lactams possessing various aryl substituents at the angular position could be prepared, they would readily provide access to the enantiopure cryptostylines.[9]

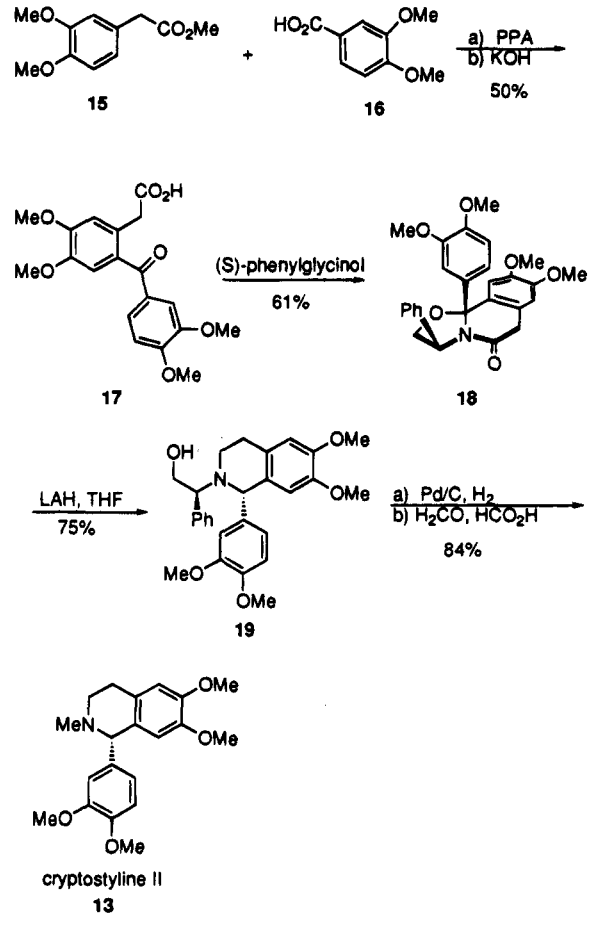


12 Cryptostyline I: R_1 = H, R_2,R_3 = O-CH_2-O
13 Cryptostyline II: R_1 = H, R_2,R_3 = OCH_3
14 Cryptostyline III: R_1,R_2,R_3 = OCH_3

Scheme 3 outlines the route employed from commercial starting materials to the alkaloid cryptostylene II in five steps. Synthesis of the requisite keto acid **17** was accomplished by heating ester **15** with 3,4-dimethoxybenzoic acid in polyphosphoric acid. Following hydrolysis of the ester, **17** was isolated in 50% yield. Condensation with (*S*)-phenylglycinol (toluene, reflux, 16 h) furnished diastereomerically pure bicyclic lactam **18** in 61% yield. Attempted reduction of **18** with Red-Al surprisingly gave a complex mixture of products,[3] however, lithium aluminum hydride (THF, −78 → 25°C, 18 h) afforded the desired isoquinoline **19** as a 14:1 mixture of diastereomers (^{1}H NMR). The mixture was readily purified to a single product by filtration through silica gel (EtOAc–hex 1:1). Debenzylation of **19** was effected by hydrogenation (Pd/C 95% yield),[10] followed by Eschweiler-Clarke methylation to furnish (+)-cryptostyline II $[\alpha]_D$ +65.5 (lit.[1b] +58.0) in 88% yield, identical in all respects to the natural alkaloid.

In summary, a general route to natural 1-alkyl- and 1-aryltetrahydroisoquinolines has been developed from the chiral bicyclic lactams. It is noteworthy that (*S*)-phenylglycinol leads to the natural enantiomer of the alkaloids whereas (*R*)-phenylglycinol is expected to provide the unnatural enantiomers. Studies are currently in progress to extend this route to more highly substituted tetrahydroisoquinolines and related polycyclic alkaloids.

Scheme 3



Acknowledgment. The authors are grateful to the National Institutes of Health for financial support. A NIH-NSRA Postdoctoral Fellowship (M.J.M.) is also warmly acknowledged.

Supporting Information Available: Experimental details, physical data, ^{1}H- and ^{13}C-NMR spectra (18 pages).

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(9) For previous asymmetric synthesis of cryptostyline II see refs 1b and 1c.

(10) HPLC analysis of the 1-naphthoyl amide (Chiral OD column, 60:40 hex:*i*-PrOH) showed the material to be greater than 98% ee.