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Novel and Efficient Synthetic Path to Proaporphine Alkaloids: Total Synthesis of (±)-Stepharine and (±)-Pronuciferine

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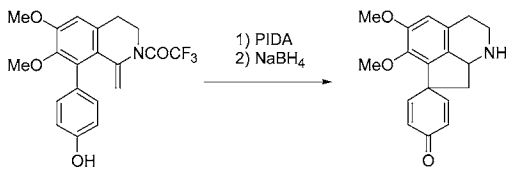
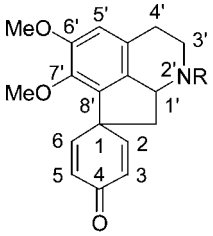
ABSTRACT



A novel synthetic path to proaporphine alkaloids was established by employing aromatic oxidation with a hypervalent iodine reagent, where an unprecedented carbon–carbon bond forming reaction between the para-position of a phenol group and an enamide-carbon took place smoothly to give the desired spiro-cyclohexadienone.

Proaporphine alkaloids, a major isoquinoline alkaloid, have been recognized as the biosynthetic precursors of aporphine alkaloids bearing a wide range of oxygenated substitution patterns with mainly a spiro-cyclohexadienone ring system.[1] It has also been known that some of these alkaloids exhibit interesting biological activities. For example, stepharine **1** has antihypertensive activity without side effects such as α- or *β*-adrenergic blockade, sedative or depressant effects, or ganglion blockade,[2] and also inhibits cholinesterase and pseudocholinesterase in vitro.[3]

The crucial step for the synthesis of these alkaloids obviously lies in the construction of a spiro-cyclohexadienone ring system. Although different routes to the proaporphine skeleton involving phenol oxidation,[4] photolysis,[5] and Pschorr cyclization[6] of 1-benzylisoquinoline derivatives have been developed, formation of the C8′−C1 bond serves as the key step in many of the previous syntheses[7] (Figure 1).



Stepharinine **1** R = H
Pronuciferine **2** R = Me

Figure 1. Sturctures of typical proaporphines.

Our own interest in proaporphine chemistry grew out of a desire to develop an entirely new, perhaps practical and general, route for the total synthesis of this class of natural alkaloids.

(1) Kametani, T. In *The Chemistry of the Isoquinoline Alkaloids*; Kinkodo Publishing Company: Sendai, Japan, 1974; Vol. 2, pp 141−150.
(2) Bhat, S. V.; Bhattacharya, B. K.; De Souza, N. J.; Dohadwalla, A. N.; Kohl, H. Ger. Offen. 1977, CODEN GWXXBX DE 2557282 19770707.
(3) Berezhinskaya, V. V.; Trutneva, E. A. *Tr. Vses. Nauchno-Issled. Inst. Lek. Rast.* **1971**, *14*, 66−69.
(4) (a) Kametani, T.; Yagi, H. *Chem. Commun.* **1967**, 366−367. (b) Kametani, T.; Yagi, H. *J. Chem. Soc., Perkin Trans. 1* **1967**, 2182−2184.
(5) (a) Horii, Z.; Nakashita, Y.; Iwata, C. *Tetrahedron Lett.* **1971**, 1167−1168. (b) Kametani, T.; Sugahara, T.; Sugi, H.; Shibuya, S.; Fukumoto, K. *Chem. Commun.* **1971**, 724. (c) Kametani, T.; Sugahara, T.; Sugi, H.; Shibuya, S.; Fukumoto, K. *Tetrahedron* **1971**, *27*, 5993−5998. (d) Kametani, T.; Fukumoto, K.; Shibuya, S.; Nemoto, H.; Nakano, T.; Sugahara, T.; Takahashi, T.; Aizawa, Y.; Toriyama, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1435−1441. (e) Horii, Z.; Iwata, C.; Nakashita, Y. *Chem. Pharm. Bull.* **1978**, *26*, 481−483.

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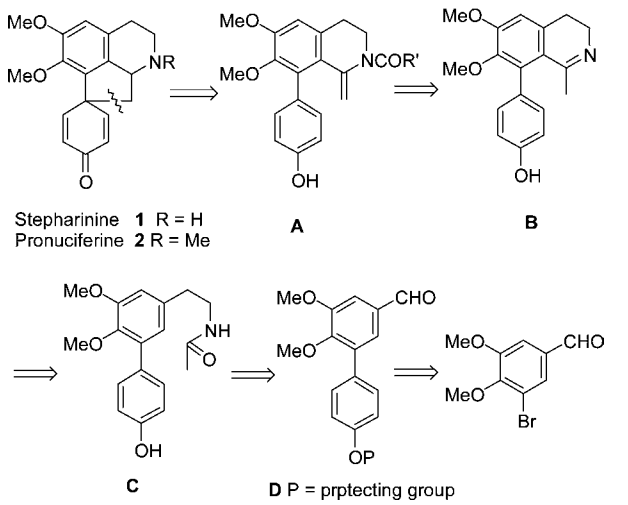
Thus, we decided to investigate a synthesis of typical proaporphine alkaloids, stepharine **1** and its *N*-methyl derivative, pronuciferine **2**, isolated from *Nelumbo nucifera*[8] and *Stephania glabra*,[9] respectively, as the target compounds. There is only one report for the synthesis of **1**,[10] although several syntheses of **2** have appeared to date.[11]

In searching the structures of **1** and **2** for retrosynthetic disconnection, we focused our attention on the direct formation of the spiro-cyclohexadienone function by intramolecular aromatic oxidation of a phenolic enamide **A** with a hypervalent iodine reagent,[12] as shown in Scheme 1,

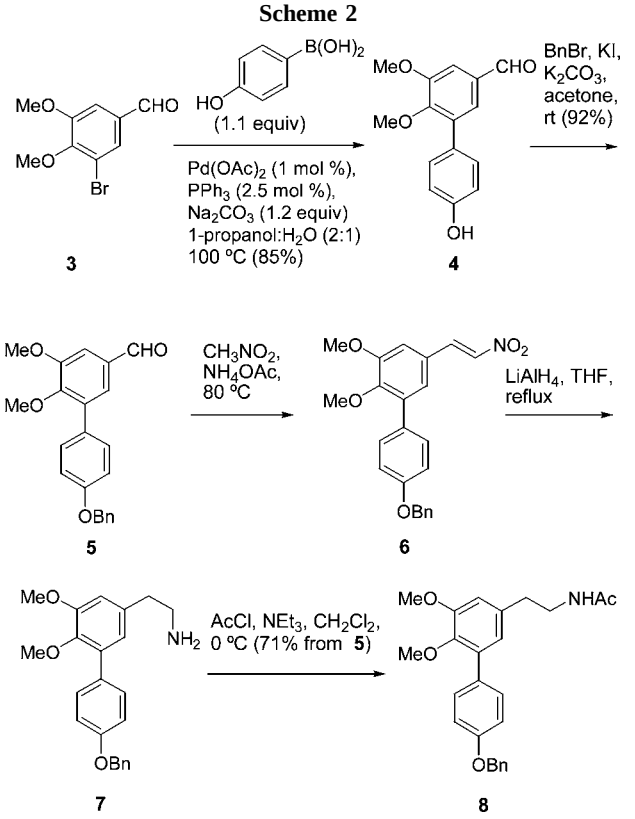
Scheme 1



where an unprecedented carbon−carbon bond formation between the para-position of a phenol group and an enamide-carbon was involved as the key reaction.

The key intermadiate, enamide **A**, would be prepared from the corresponding 3,4-dihydroisoquinoline derivative **B** by simple acylation, and **B** would be derived from amide **C** by Bischler−Napieralski cyclization. The preparation of amide **C** also would be possible from 5-bromo-3,4-dimethoxybenzaldehyde **3** by palladiun-catalyzed arylation, followed by elongation of the side chain of aldehyde **D**.

Scheme 2



Thus, the arylation of 3-bromo-4,5-dimethoxybenzaldehyde[13] **3** with (*p*-hydroxyphenyl)boronic acid (1.1 equiv) was carried out in the presence of palladium acetate (1 mol %), triphenylphosphine (2.5 mol %), and sodium carbonate (1.2 equiv) in 1-propanol−H_2O (2:1)[14] at 100 °C to give biaryl compound **4** in 85% yield. After protection of the phenolic hydroxy group as its benzyl ether, aldehyde **5** was condensed with nitromethane in the presence of ammonium acetate at 80 °C to afford nitrostyrene **6**, which on reduction with lithium aluminum hydride gave the corresponding phenethylamine **7**. Acetylation of **7** with acetyl chloride in the presence of triethylamine provided amide **8** in 71% yield from **5**.

Since a phenolic function would be required for the aromatic oxidation, the benzyl group of **8** was removed under catalytic hydrogenation conditions to give phenolic compound **9**, before the Bischler−Napieralski cyclization.

Although two positions are possible for the Bischler−Napieralski cyclization of **9**, we assumed that the para-position of the methoxy group would be the preferred cyclization position. Indeed, the Bischler−Napieralski cy-

(6) Ishiwata, S.; Itakura, K.; Misawa, K. *Chem. Pharm. Bull.* **1970**, *18*, 1219−1223.

(7) Foe reviews, see: (a) Shamma, M. *Alkaloids* (*London*) **1975**, *6*, 170−188. (b) Stephenson, E. K.; Cava, M. P. *Heterocycles* **1994**, *39*, 891−902 and references cited therein.

(8) Cava, M. P.; Nomura, K.; Schlessinger, R. H.; Buck, K. T.; Douglas, B.; Raffauf, R. F.; Weisbach, J. A. *Chem. Ind.* **1964**, 282−283.

(9) Bernauer, K. F. *Helv. Chim. Acta* **1963**, *46*, 1783−1785.

(10) Bernauer, K. *Helv. Chim. Acta* **1968**, *51*, 1120−1123.

(11) Synthesis of racemic pronuciferine, see: (a) Bernauer, K. *Experientia* **1964**, *20*, 380−381. (b) Kametani, T.; Yagi, H. *J. Chem. Soc., Perkin Trans. 1* **1967**, 2182−2184. (c) Ishiwata, S.; Itakura, K.; Misawa, K. *Chem. Pharm. Bull.* **1970**, *18*, 1219−1223. (d) Kametani, T.; Sugahara, T.; Sugi, H.; Shibuya, S.; Fukumoto, K. *Tetrahedron* **1971**, *27*, 5993−5998. (e) Horii, Z.; Nakashita, Y.; Iwata, C. *Tetrahedron Lett.* **1971**, *17*, 1167−1168. (f) Horii, Z.; Iwata, C.; Nakashita, Y. *Chem. Pharm. Bull.* **1978**, *26*, 481−483.

(12) For reviews, see: (a) Ochiai, M. *Rev. Heteroatom Chem.* **1989**, *2*, 92−111. (b) Moriarty, R. M. *Synthesis* **1990**, 431−447. (c) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365−383. (d) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers Inc.: New York, 1992. (e) Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem.* **1992**, *3*, 113−128. (f) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123−1178. (g) Varvogolis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, CA, 1997. (h) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409−458. Recent application to natural product synthesis; see: (i) Mizutani, H.; Takayama, J.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411−2414. (j) Mizutani, H.; Takayama, J.; Honda, T. *Synlett* **2004**, 328−330.

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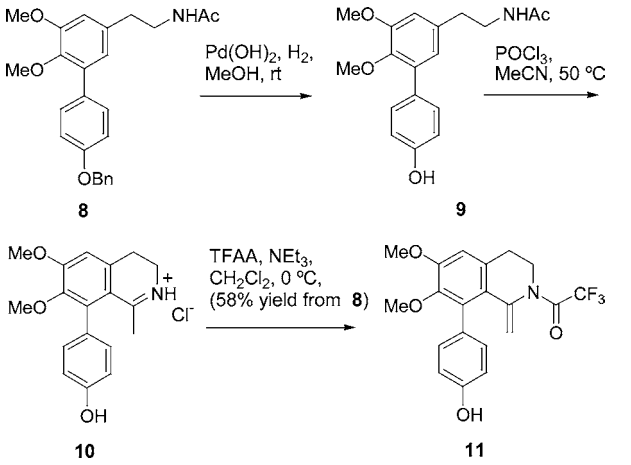
Scheme 3



clization of **9** with phosphoryl chloride in acetonitrile provided the desired 3,4-dihydroisoquinoline **10**, regioselectively. The structure of **10** could be confirmed by observation of NOEs between 5-H and 6-methoxy group, respectively. Acylation of **10** with trifluoroacetic anhydride yielded the key intermediate, enamide **11**, in 58% yield from **8**.

With the requisite enamide available, a study was made for the best conditions for the aromatic oxidation.

On screening a variety of reaction conditions, such as the species of iodine reagents, temperature, and solvents, for an aromatic oxidation of **11**, we found proper reaction conditions for obtaining the desired cyclization product in reasonable yield, as follows. The aromatic oxidation of **11** with PIDA (iodobenzene diacetate) (1.1 equiv) in trifluoroethanol at 0 °C, followed by sodium borohydride reduction of the resulting mixture, proceeded smoothly to give the desired spiro-dienone **1** in 90% yield as the sole product. The labile *N*-protecting trifluoroacetyl group was removed during this conversion, simultaneously. The spectroscopic data of the synthesized compound were identical with those reported in the literature.[15]

Thus, we succeeded in the facile synthesis of proaporphine alkaloid, stepharine, in very short steps with remarkably high yield, in which an unprecedented carbon−carbon bond-forming reaction was involved as the key step.

Stepharine **1** was further converted into pronuciferine **2** by *N*-methylation with formalin under the reductive reaction

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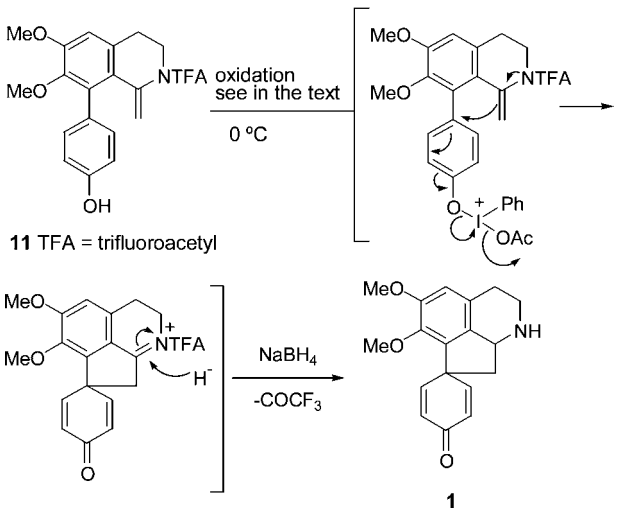
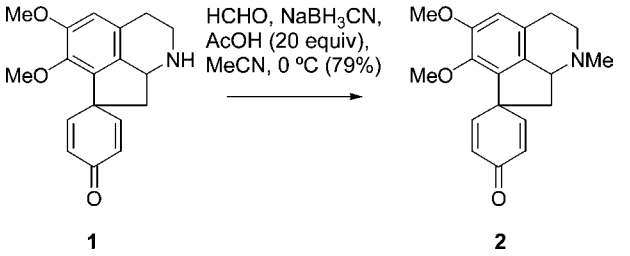
(16) Kametani, T.; Yagi, H. *J. Chem. Soc., C* **1967**, 2182−2184.

Scheme 4



conditions in 79% yield. Again, the spectroscopic data of the synthesized compound were identical with those reported.[16]

Scheme 5



In summary, we were able to develop a novel and efficient synthesis of proaporphine alkaloids, and the synthetic strategy developed was successfully applied to the total synthesis of stepharine and pronuciferine. Further utilization of this procedure in the synthesis of other types of isoquinoline and indole alkaloids is in progress in our laboratory.

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Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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