ORGANIC LETTERS

2012
Vol. 14, No. 14
3712–3715

Total Synthesis of (±)-Decinine via an Oxidative Biaryl Coupling with Defined Axial Chirality

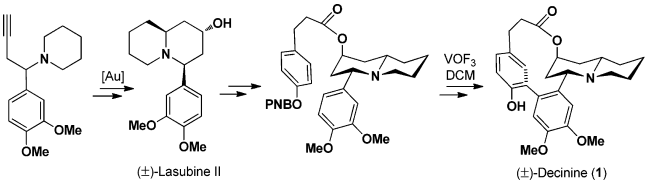
Zhen-Hua Shan,[†] Ji Liu,[†] Ling-Min Xu,[†] Ye-Feng Tang,[*,‡] Jia-Hua Chen,[*,†] and Zhen Yang[*,†]

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Beijing National Laboratory for Molecular Science (BNLMS), and Peking-Tsinghua Center for Life Sciences at College of Chemistry of Peking University, Chengfu Road, 202, Beijing, China, 100871, and The Comprehensive AIDS Research Center, School of Life Science and School of Medicine, Tsinghua University, Beijing 100084, China

yefengtang@tsinghua.edu; jhchen@pku.edu.cn; zyang@pku.edu.cn

Received June 6, 2012

ABSTRACT



The total synthesis of (±)-decinine has been achieved. The key steps in the synthesis involved the formation of lasubine II via a gold catalyzed annulation of 1-(but-3-yn-1-yl)piperidine and the formation of the 12-membered ring of decinine (1) with complementary atropselectivity via a VOF_3-mediated oxidative biaryl coupling reaction.

Decinine (**1**) was first isolated in 1962 by Ferris from *Decodon verticillatus (L.) Ell*[1] and classified as a member of the Lythraceae alkaloid family,[2] whose other family members include lythrine (**2**)[1a,3] and lyfoline (**3**) (Figure 1).[4]

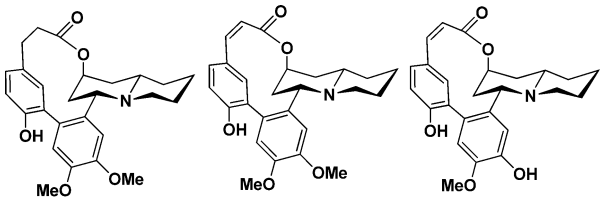


Figure 1. Naturally occurring Lythraceae alkaloids.

This family of quinolizidine alkaloids possesses a wide profile of interesting biological activities, including anti-inflammatory, antispasmodic, and diuretic properties.[5]

The structure of decinine (**1**) was determined by X-ray crystallographic analysis of its derivative,[6] which contained a macrocyclic ring and consisted of a quinolizidine ring and a biphenyl moiety. The strained 12-membered

[†] Beijing National Laboratory for Molecular Science (BNLMS) and Peking-Tsinghua Center for Life Sciences at College of Chemistry of Peking University.

[‡] Tsinghua University.

(1) (a) Ferris, J. P. *J. Org. Chem.* **1962**, *27*, 2985. (b) Ferris, J. P. *J. Org. Chem.* **1963**, *28*, 817. (c) Ferris, J. P.; Boyce, C. B.; Briner, R. C. *J. Am. Chem. Soc.* **1971**, *93*, 2942. (d) Ferris, J. P.; Briner, R. C.; Boyce, C. B. *J. Am. Chem. Soc.* **1971**, *93*, 2958. (e) Ferris, J. P.; Boyce, C. B.; Briner, R. C.; Weiss, U.; Qureshi, I. H.; Sharpless, N. E. *J. Am. Chem. Soc.* **1971**, *93*, 2963.

(2) Wright, H.; Clardy, J.; Ferris, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 6467.

(3) (a) Douglas, B.; Kirkpatrick, J. L.; Weisbach, J. A.; Riberio, O.; Raffauf, R. F. *Lloydia* **1964**, *27*, 25. (b) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515.

(4) Kim, H. J.; Lee, I. S.; Youn, U. J.; Chen, Q. C.; Ngoc, T. M.; Ha, D. T.; Liu, H.; Min, B. S.; Lee, J. Y.; Seong, R. S.; Bae, K. H. *J. Nat. Prod.* **2009**, *72*, 749.

(5) (a) Malone, M. H.; Rother, A. *J. Ethnopharmacol.* **1994**, *42*, 135. (b) Blomster, R. N.; Bobbitt, J. M.; Schawarting, A. E. *Lloydia* **1964**, *27*, 15. (c) Kaplan, H. R.; Malone, M. H. *Lloydia* **1966**, *29*, 348. (d) Lema, W. J.; Blankenship, J. W.; Malone, M. H. *J. Ethnopharmacol* **1986**, *15*, 161. (e) Rother, A.; Edwards, J. M. *Phytochemistry* **1994**, *36*, 911. (f) Malone, M. H.; Rother, A. *J. Ethnopharmacol.* **1994**, *42*, 135.

(6) Zacharias, D. E.; Jeffrey, G. A.; Douglas, B.; Weisbach, J. A.; Kirkpatrick, J. L.; Ferris, J. P.; Boyee, C. B.; Briner, R. C. *Experientia* **1965**, *21*, 247.

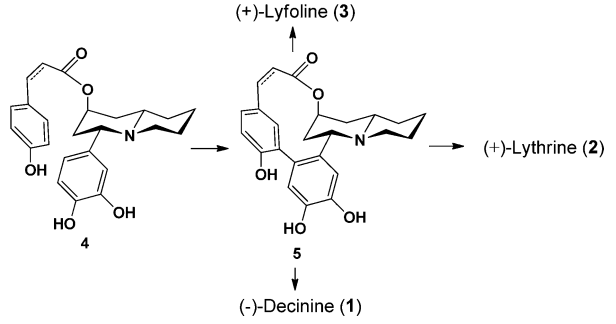
10.1021/ol3015573
Published on Web 06/29/2012

macrolactone structure incorporates three stereogenic centers, two of which are part of the macrocycle, and an induced chiral biaryl axis, representing a significant synthetic challenge.

The construction of biaryl compounds, particularly unsymmetrical and axially chiral biaryls, continues to represent a challenging goal in organic synthesis.[7]

Although Lythraceae alkaloids can be synthesized using both acid-catalyzed lactonization and ring closing metathesis (RCM) reactions as the key steps in the formation of their macrocyclic rings,[8] earlier efforts to affect the same transformation using the oxidative biaryl coupling for the formation of alkaloids failed to afford any annulated product.[9]

Scheme 1. Biosynthetic Analysis of Quinolizidine Alkaloids



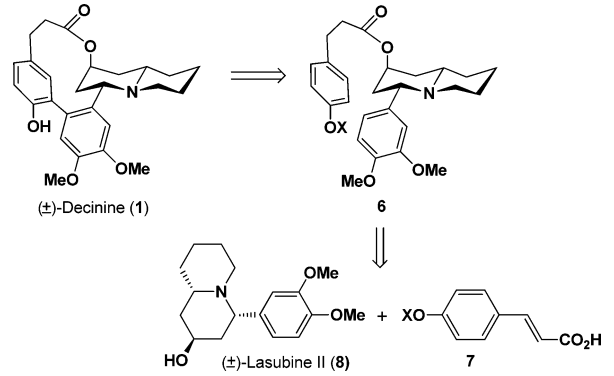
Biosynthetically, compounds **1**–**3** can be traced back to phenol **4** (Scheme 1), which presumably undergoes an oxidative biaryl coupling reaction, followed by a series of functionalizations to afford quinolizidine alkaloids, such as **1**–**3**.[10] It is therefore conceivable, for example, that decinine (**1**) could be derived from ester **4** via an initial intramolecular oxidative biaryl coupling to afford the annulated product **5**, followed by a 1,4-reduction and regioselective dimethylation.[10d]

We became fascinated with the idea of testing this biomimetic synthesis to explore the possibility of emulating this oxidative pathway in the laboratory. Herein, we report the synthesis of decinine (**1**) using a VOF_3-mediated nonphenolic oxidative biaryl coupling reaction[11] for the formation of the 12-membered ring. The reaction proceeded in the presence of an excess of TFA[12] and enabled the unprecedented coupling of a biaryl substrate containing a quinolizidine subunit.

Lasubine II (**8**) is an essential fragment in many bioactive alkaloids, and studies aimed at developing concise and convergent synthetic approaches to the compound are an ongoing, with many unique methods having already been developed in this area.[14]

Retrosynthetically, it was anticipated that the macrocyclic ring of decinine (**1**) could be constructed via the oxidative biaryl coupling of ester **6**, which could itself be obtained via the condensation reaction of acrylic acid **7** and lasubine II (**8**) (Scheme 2). It was also envisaged that the chirality already present in lasubine II (**8**) would determine the steric course of the coupling reaction, providing the desired axial chirality in decinine (**1**) through a chirality transfer[13] process.

Scheme 2. Retrosynthetic Analysis



The transition-metal-catalyzed cyclization of alkynes is one of the most powerful methods for the construction of

(7) For reviews on biaryl synthesis, see: (a) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405. (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Bolm, C.; Hildebrand, J. P.; Muz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.

(8) (a) Blank, B.; Vaiday, P. D. *J. Chem. Eng. Data* **1971**, *16*, 254. (b) Montaudo, G.; Finocchiaro, P.; Caccamese, S.; Bottino, F. *J. Chem. Eng. Data* **1971**, *16*, 249. (c) Wrobel, J. T.; Golebiewski, W. M. *Tetrahedron Lett.* **1973**, *14*, 4293. (d) Hanaoka, M.; Ogawa, N.; Arata, Y. *Tetrahedron Lett.* **1973**, *14*, 2355. (e) Loev, B.; Van Hoeven, H. *Tetrahedron Lett.* **1974**, *15*, 1101. (f) Loev, B.; Lantos, I. *Tetrahedron Lett.* **1975**, *16*, 201. (g) Lantos, I.; Razgaitis, C.; Van Hoeven, H.; Loev, B. *J. Org. Chem.* **1977**, *42*, 228. (h) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1556. (i) Chausset-Boissarie, L.; Arvai, R.; Cumming, G. R.; Besnard, C.; Kundig, E. P. *Chem. Commun.* **2010**, *46*, 6264.

(9) (a) Rosazza, J. P.; Bobbitt, J. M.; Schwarting, A. E. *J. Org. Chem.* **1970**, *35*, 2564. (b) Quick, J.; Ramachandra, R. *Tetrahedron* **1980**, *36*, 1301.

(10) (a) Hedges, S. H.; Herbert, R. B.; Wormald, P. C. *J. Chem. Soc., Chem. Commun.* **1983**, 145. (b) Herbert, R. B.; Jackson, F. B.; Nicolson, I. *J. Chem. Soc., Chem. Commun.* **1984**, 825. (c) Rother, A. *J. Nat. Prod.* **1985**, *48*, 33. (d) Hedges, S. H.; Herbert, R. B.; Wormald, P. C. *J. Nat. Prod.* **1993**, *56*, 1259.

(11) (a) Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3772. (b) Feldman, K. S.; Ensel, S. M.; Minard, R. D. *J. Am. Chem. Soc.* **1995**, *116*, 1742. (c) Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426. (d) Evans, D. A.; Dinsmore, C. J.; Ratz, A. M.; Evrard, D. A.; Barrow, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 3417.

(12) Lewis acids and the salts of HCl or $HClO_4$ were utilized to protect tertiary amines during the oxidation. Schwartz, M.; Rose, B.; Vishnurajjala, B. *J. Am. Chem. Soc.* **1973**, *95*, 612.

(13) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (c) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (d) Narasaka, K. *Synthesis* **1991**, 1. (e) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (f) Lemieux, R. P. *Acc. Chem. Res.* **2001**, *34*, 845.

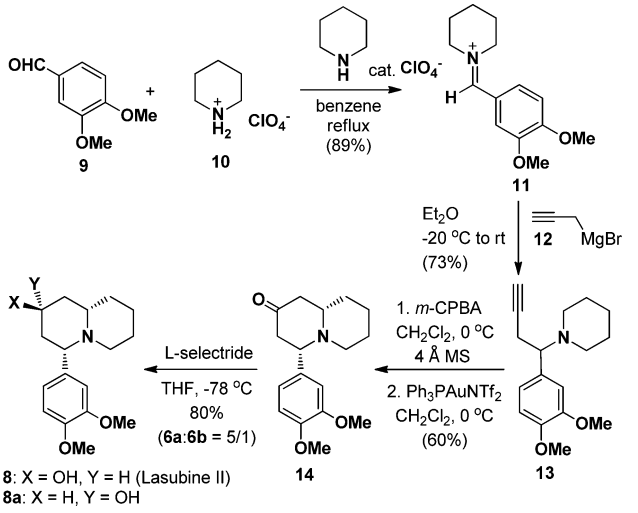
(14) (a) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1842. (b) Rawal, V. H.; Florjancic, A. S.; Singh, S. P. *Tetrahedron Lett.* **1994**, *35*, 8985. (c) Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 649. (d) Lin, G.-Q.; Zhong, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1369. (e) Vorogushin, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Am. Chem. Soc.* **2002**, *124*, 6512. (f) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773.

highly functionalized carbocyclic molecules,[15] and gold-(I/III) catalysts have been widely used in this regard because of their unique π-acidity and alkynophilicity.[16] Zhang and co-workers recently reported the application of a Au-catalyzed tandem cyclization to the synthesis of piperidine-4-ones from substituted 3-butynyl amines via a two-step formal [4 + 2] approach.[17] We were intrigued by the efficiency and mild reaction conditions of Zhang's protocol and decided to synthesize Lasubine II (**8**) according to the same methodology.

Thus, aldehyde **9** was reacted with piperidine perchlorate **10** in the presence of a catalytic amount of piperidine in refluxing benzene under Dean−Stark conditions to give the iminium salt **11** in 89% yield.[18] Compound **11** was then reacted with the Grignard reagent **12**[19] to afford butynyl piperidine **13** in 73% yield.

Lasubine II (**8**) was constructed from substrate **13** using a formal [4 + 2] approach involving the sequential treatment of **13** with *m*-CPBA and $Ph_3PAuNTf_2$[17] to give the desired product quinolizinone **14** in 60% yield. Compound **14** was then reduced with L-selectride to afford lasubine II (**8**) in 66% yield,[20] together with its diastereoisomer **8a** in 14% yield (Scheme 3).

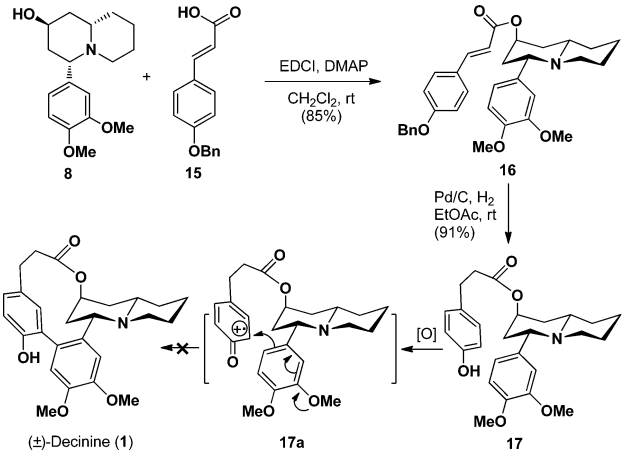
Scheme 3. Synthesis of Lasubine II (**8**)



With lasubine II **8** in hand, we proceeded to explore the oxidative biaryl annulation for the synthesis of the target molecule decinine (**1**). Phenol **17** was the preferred choice of substrate because its oxidative annulation through **17a**[21] was able to afford decinine (**1**) directly.

Thus, phenyl acrylic acid **15** was coupled with lasubine II (**8**) in the presence of EDCI and DMAP to give ester **16** in 85% yield, which was then catalytically hydrogenated with palladium on carbon to afford **17** in 91% yield (Scheme 4). Unfortunately, although several oxidative agents were investigated under various conditions to promote the oxidative biaryl coupling, none of the desired product was formed, with substrate **17** simply decomposing in the majority of cases.

Scheme 4. First Generation of Oxidative Biaryl Coupling



The oxidative coupling was then investigated using phenol **4**, which was regarded to be a potential substrate in the biomimetic syntheses of Lythraceae alkaloids.[10]

Phenol **4** was prepared from ketone **14** via a five-step linear sequence (Scheme 5). Ketone **14** was demethylated with BBr_3 in CH_2Cl_2 at −40 °C, and the resulting diphenol intermediate was protected as the corresponding benzyl ether by treatment with BnBr in the presence of K_2CO_3 and a catalytic amount of KI (50 Mol%) in an acetone solvent to give **18** in 44% yield over the two steps. Compound **18** was then reduced stereoselectively with L-selectride[20] in THF to afford alcohol **19** in 64% yield.

Following the condensation of alcohol **19** with phenyl acrylic acid **15**, the resulting ester **20** was subjected to catalytic hydrogenation to afford phenol **4**. Unfortunately, although several oxidative agents were again investigated under various conditions to promote the oxidative biaryl coupling, none of the desired product was formed, with substrate **4** suffering a similar fate as substrate **17** and simply decomposing in the majority of cases.

(15) For selected reviews on gold catalysis, see: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (e) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Pathil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.

(16) (a) Hashimi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem* **2004**, *8*, 795. (c) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (d) Zhang, L.; Sun, J.; Kozmin, S. *Adv. Synth. Catal.* **2006**, *348*, 2271. (e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

(17) Zhang, L.; Cui, L.; Peng, Y. *J. Am. Chem. Soc.* **2009**, *131*, 8394.

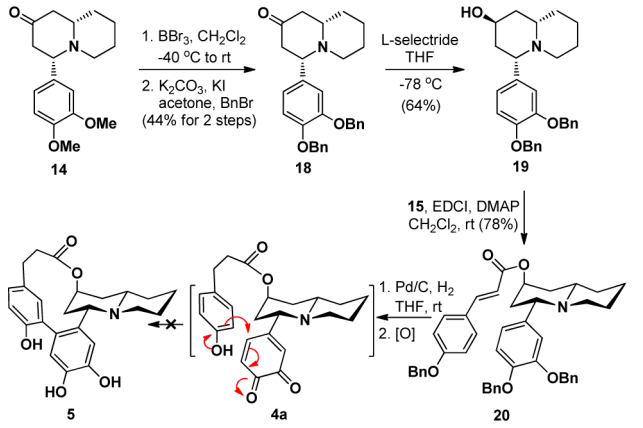
(18) (a) Paukstelis, J. V.; Leonard, N. J. *J. Org. Chem.* **1963**, *28*, 3021. (b) Gupton, J. T.; Coury, J.; Moebus, M.; Fitzwater, S. *Synth. Commun.* **1986**, *16*, 1575.

(19) Acharya, H. P.; Miyoshi, K.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3535.

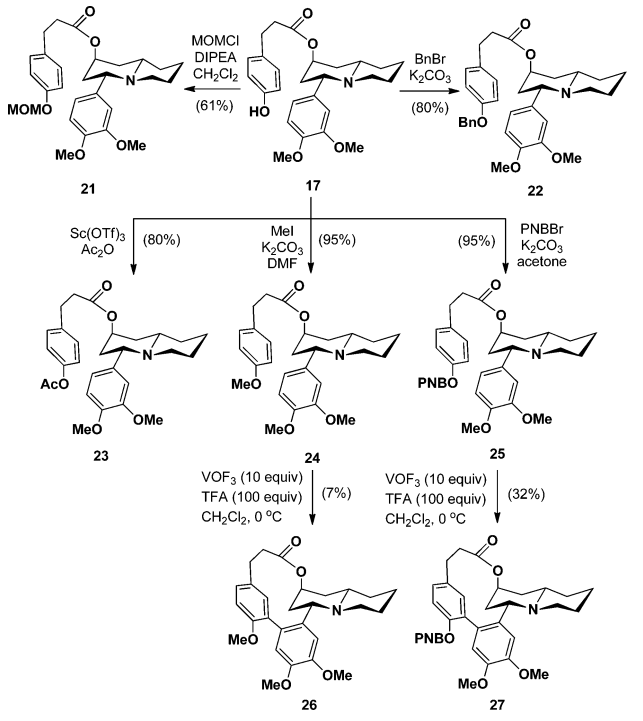
(20) (a) Rother, A.; Schwarting, A. E. *Lloydia* **1975**, *38*, 477. (b) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807. (c) Mancheno, O. G.; Arrayas, R. G.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 10294.

(21) (a) Moreno, I.; Tellitu, I.; Herrero, M. T.; SanMartin, R.; Dominguez, E. *Curr. Org. Chem.* **2002**, *6*, 1433. (b) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; ujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (c) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (d) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961.

Scheme 5. Second Generation Biaryl Coupling Approach



Scheme 6. Syntheses of Biaryl Esters **21**–**25** and Their Oxidative Biaryl Couplings



In light of the challenges encountered with the phenolic oxidative biaryl coupling, we proceeded to test the VOF_3-mediated nonphenolic oxidative biaryl coupling[11] for the formation of the macrocyclic ring. Thus, five additional biaryl esters **21**–**25** were prepared according to the chemistry depicted in Scheme 6 (details of their syntheses are provided in the Supporting Information).

(22) Tanaka, M.; Wakamatsu, T.; Ikeya, Y.; Mitsuhashi, H.; Maruno, M. *Tetrahedron* **1995**, *51*, 11703.

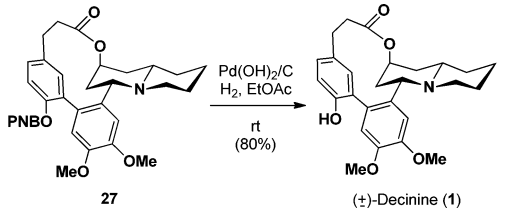
(23) Hughes, D. W.; Spenser, I. D.; Wrobel, J. T. *Magn. Reson. Chem.* **2000**, *38*, 707.

During the course of performing experiments on the oxidative biaryl coupling of esters **21**–**25** using VOF_3 as an oxidant at the optimized reaction conditions (see the Supporting Information for details of the optimization process), the anticipated annulated products **26** and **27** were isolated from their corresponding starting materials **24** and **25** in yields of 7% and 32%, respectively. In contrast, substrates **21**–**23** did not afford the desired products under the different reaction conditions tested.

It is worthy of note that a large excess of TFA played a decisive role in reducing the oxidative tendency of the tertiary amine in the substrate via the formation of its corresponding amine salt. This effectively mitigated any oxidation of the amine in the presence of a required excess of the VOF_3 oxidative agent. On the other hand, the electron-deficient PNB group may also contribute to the annulation of substrate **25** due to its stability toward TFA during the nonphenolic oxidative biaryl coupling.[11c]

We then proceeded to explore the total synthesis of decinine (**1**). Thus, lactone **27** was subjected to Pd-catalyzed hydrogenation[22] in ethyl acetate to give (±)-decinine **1** in 80% yield (Scheme 7). The NMR data for the synthesized decinine (**1**) were identical to the data reported for material isolated from natural sources.[23]

Scheme 7. Synthesis of Decinine



In summary, we have achieved for the first time the total synthesis of racemic decinine (**1**) over a nine-step linear sequence in an overall yield of 4.7%. The key steps in the sequence were the VOF_3-mediated oxidative biaryl coupling and the gold-catalyzed annulation. It is envisaged that the developed chemistry may be applied to the total syntheses of other biologically important and naturally occurring macrocyclic quinolizidine alkaloids, as well as their analogs.

Acknowledgment. This work was supported by the National Science Foundation of China (Grant Nos. 20832003, 21072006, and 21072111).

Supporting Information Available. Experimental procedure, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.