ORGANIC LETTERS

2003
Vol. 5, No. 15
2703−2706

First Asymmetric Total Synthesis of (−)-Antofine by Using an Enantioselective Catalytic Phase Transfer Alkylation

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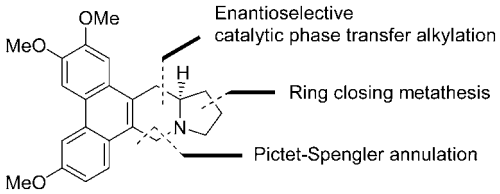
Received May 21, 2003

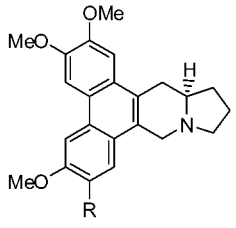
ABSTRACT



The first asymmetric total synthesis of a potential antitumor phenanthroindolizidine alkaloid, (−)-antofine, is described. An important feature of this synthesis is the creation of a stereogenic center by using enantioselective catalytic phase transfer alkylation, affording an unnatural α-amino acid derivative, together with a ring closing metathesis for pyrrolidine ring construction.

Phenanthroindolizidine alkaloids are a small group of alkaloids isolated mainly from *Cynanchum*, *Pergularia*, *tylophora*, and some genera of the Asclepiadaceae family.[1,2] These pentacyclic natural products are known for their profound cytotoxic activity through the inhibition of protein and nucleic acid syntheses.[2,3] Due to their interesting bioactivity and unusual architecture, many unique and interesting methodologies have been designed for their synthesis.[2,4]

Among these alkaloids, (−)-antofine (**1**, Figure 1) has recently attracted attention because of its extremely potent inhibition of cancer cell growth. Antofine has IC_{50} values in the low nanomolar range, comparable to that of clinically employed cytotoxic drugs.[2,3,5] It is cytotoxic to drug-sensitive and multidrug-resistant cells.[3] Recent mechanism studies by



R = H (-)-antofine (**1**)
R = OMe (-)-tylophorine (**2**)

Figure 1. Chemical structures of compounds **1** and **2**.

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(1) Gellert, E. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Academic Press: New York, 1987; pp 55−132.
(2) Suffness, M.; Cordell, G. A. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 25, pp 3−355.
(3) Stærk, D.; Lykkeberg, A. K.; Christensen, J.; Budnik, B. A.; Abe, F.; Jaroszewski, J. W. *J. Nat. Prod.* **2002**, *65*, 1299−1302 and references therein.

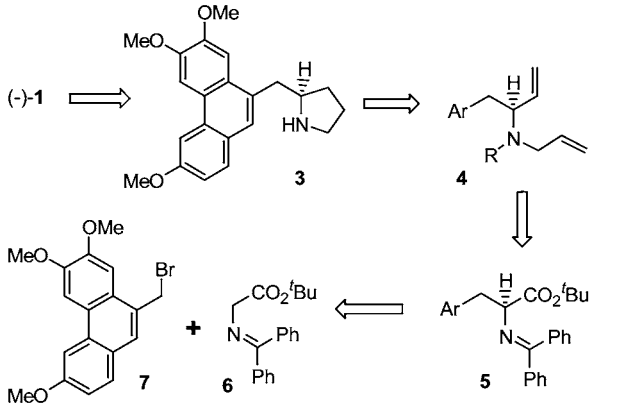
10.1021/ol0349007 CCC: $25.00
Published on Web 07/03/2003

Lee et al. indicated that antofine exhibits an inhibitory activity on cell proliferation by arresting the G2/M phase of the cell cycle.[5]

To further investigate the biochemical and pharmaceutical effects of (−)-antofine, we needed to synthesize this alkaloid in large quantities, due to its low natural abundance. A variety of syntheses of antofine and other phenanthroindolizidine alkaloids, e.g. tylophorine (**2**, Figure 1), in both racemic and optically active forms have been reported.[2,4,6,7] However, the selective asymmetric synthesis of naturally occurring (−)-antofine has not been achieved yet. Thus far, the synthesis of the optical antipode of natural antofine has only once been carried out, using an (*S*)-amino acid derivative, (*S*)-5-(toluene-4-sulfonyloxymethyl)pyrrolidin-2-one, as the chiral precursor.[7] In this context, we describe an enantioselective synthetic approach to (−)-antofine, which is unique as compared to other previous phenanthroindolizidine alkaloid syntheses. In our synthesis, the chirality was introduced by employing the enantioselective catalytic phase transfer alkylation reaction, thus affording an unnatural α-amino acid derivative.

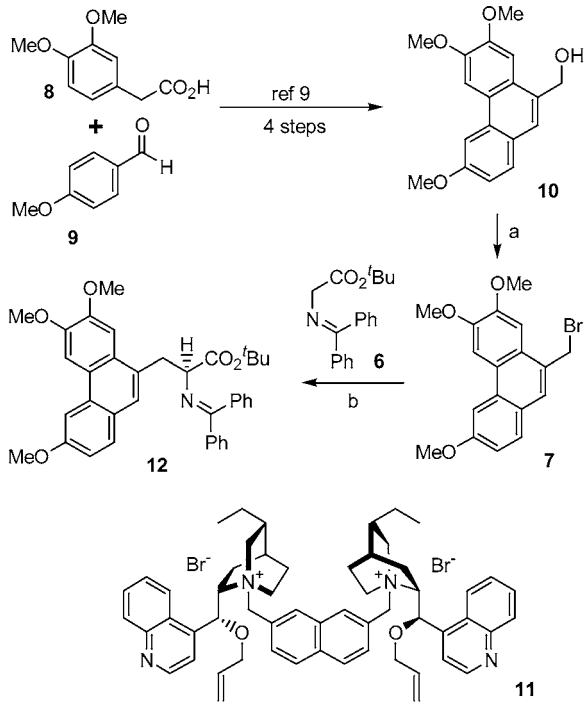
The strategy of our synthesis is presented in Scheme 1. The D ring of the phenanthroindolizidine skeleton could be constructed at the last stage of the synthesis by employing the reported Pictet−Spengler annulation of the amine **3**,[4a,7] which has been previously synthesized via a different synthetic route. We envisioned the pyrrolidine ring of the cyclization precursor **3** coming from the bis-allylated amine **4**, via sequential ring-closing metathesis[8] and hydrogenation. The requisite amine **4** could be synthesized from the chiral α-amino ester **5**, which would be accessed by the enantioselective catalytic phase transfer alkylation of the protected glycine derivative **6** with phenanthryl bromide **7**.

Scheme 1. Retrosynthetic Analysis of Antofine



The synthesis began by preparing the known phenanthryl alcohol **10** from the commercially available homoveratric acid **8** and *p*-anisaldehyde **9** via the conventional four-step sequence, according to the previously reported procedure of Weinreb and co-workers (Scheme 2).[9] Treatment of alcohol **10** with CBr_4 and PPh_3 provided bromide **7** in 98% yield.[10]

Scheme 2[a]



[a] Reagents and conditions: (a) CBr_4, PPh_3, CH_3CN, 0 °C, 1 h, 98%; (b) **6**, **11** (2 mol %), 50% aq NaOH, $PhCH_3/CHCl_3$ (7:3), 0 °C, 3 days, 97%, 96% ee.

There are a number of methodologies in the literature concerning the enantioselective synthesis of unnatural α-ami-

(4) For a good review with citations to recent work, see: (a) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1999**, *55*, 2659−2670. (b) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082−12089. (c) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **1994**, *50*, 12293−12304.

(5) Lee, S. K.; Nam, K.-A.; Heo, Y.-H. *Plant Med.* **2003**, *69*, 21−25.

(6) For a synthesis of racemic antofine, see: (a) Govindachari, T. R.; Ragade, I. S.; Viswanathan, N. *J. Chem. Soc.* **1962**, 1357−1360. (b) Chauncy, B.; Gellert, E. *Aust. J. Chem.* **1970**, *23*, 2503−2516. (c) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; De Silva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955−1962. (d) Iwao, M.; Watanabe, M.; De Silva, S. O.; Snieckus, V. *Tetrahedron Lett.* **1981**, *22*, 2349−2352. (e) Bhakuni, D. S.; Gupta, P. K. *Indian J. Chem., Sect. B* **1982**, *21B*, 393−395. See also refs 4a and 4b.

(7) For a synthesis of the antipodal isomer of antofine, see: (a) Faber, L.; Wiegrebe, W. *Helv. Chim. Acta* **1976**, *59*, 2201−2212. (b) Faber, L.; Wiegrebe, W. *Helv. Chim. Acta* **1973**, *56*, 2882−2884.

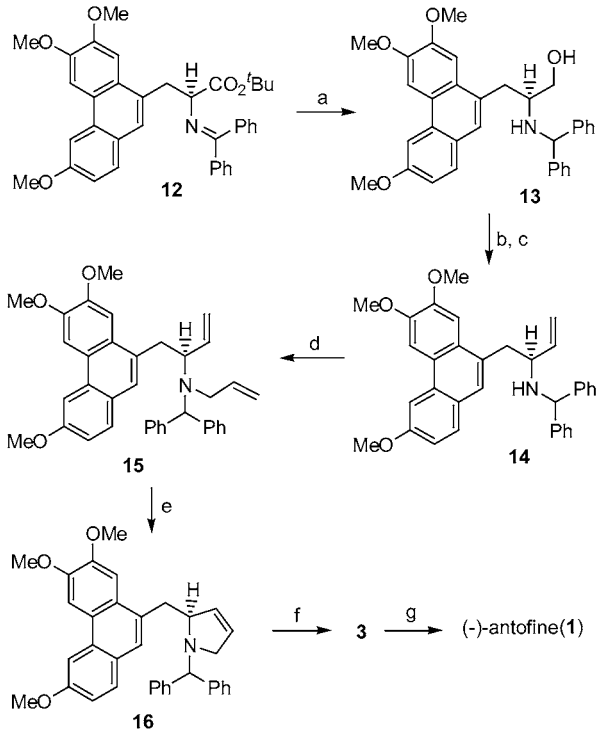
(8) For the application of the ring-closing metathesis reaction to the synthesis of 2,5-dihydropyrroles from dienes, see: (a) Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2376−2378. (b) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem Commun.* **1998**, 1315−1316. (c) Cerezo, S.; Cortes, J.; Moreno-Manas, M.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998**, *54*, 14869−14884. (d) Fürstner, A.; Ackermann, L. *Chem. Commun*. **1999**, 95−96. (e) Bujard, M.; Briot, A.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 8795−8788. (f) Fürstner, A.; Liebl, M.; Hill, A. F.; Wilton-Ely, J. D. E. T. *Chem. Commun*. **1999**, 601−602. (g) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Hermann, W. A. *Tetrahedron Lett*. **1999**, *40*, 4787−4790. (h) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett*. **1999**, *40*, 8657−8662. (i) Evans, P. A.; Robinson, J. E. *Org. Lett*. **1999**, *1*, 1929−1931. (j) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771−1772. (k) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774−7780.

(9) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661−3666.

no acids by the alkylation of an alkyl or aryl halide.[11,12] Among those, we adapted the catalytic phase transfer alkylation reaction[13] for its practical operation and efficiency. The carbon−carbon bond formation between the aryl bromide **7** and the *tert*-butyl glycinate-benzophenone Schiff base **6** was investigated by using the phase transfer catalyst **11** that was recently developed by one of us.[13a] To our delight, the enantioselective catalytic phase transfer alkylation reaction to the synthesis of α-amino ester **12**, bearing a bulky substituent on the α-carbon, by using a catalyst **11** was successfully achieved under the slightly modified reaction conditions.[14] Treatment of aryl bromide **7** with a slight excess of **6** (1.2 equiv) in the presence of 50% aqueous NaOH and **11** (2 mol %) in $PhCH_3/CHCl_3$ (7:3) at 0 °C led to the formation of the desired α-amino ester **12** with excellent enantioselectivity (96% ee) and yield (97%).[15] We believe that such successful synthetic application would broaden the utility of this catalytic phase transfer alkylation in natural product synthesis.

With multigram quantities of **12** in hand, we began the second stage of our synthesis of antofine by converting the α-amino ester functional group to a pyrrolidine ring (Scheme 3). Treatment of **12** with LAH effected the reduction of

Scheme 3[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 1 h, 81%; (b) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, −78 °C to rt, 30 min; (c) $CH_3PPh_3^+I^-$, *n*-BuLi, THF, 0 °C, 30 min, 68% from **13**; (d) allyl bromide, K_2CO_3, DMF, 60 °C, 2 days, 86%; (e) Grubbs's catalyst (2 mol %), CH_2Cl_2, rt, 1 day, 92%; (f) H_2, 10% Pd/C, EtOH, 16 h, 82%; (g) HCHO, HCl, EtOH, reflux, 21 h, 64%, in the dark.

benzophenonimine and the concomitant reduction of the *tert*-butyl ester to afford the desired amino alcohol **13** in 81% yield. Swern oxidation of alcohol **13**, followed by Wittig reaction of the resulting unstable aldehyde with methylidene triphenylphosphorane, provided the corresponding olefin **14** in 68% overall yield with no racemization problems.[16] The electrophilic allylation of the secondary amine **14** with allyl bromide and K_2CO_3 at 60 °C in DMF led to the formation of the bis-allylamine **15** in high yield (86%).[17] The crucial ring-closing metathesis of **15** was successfully performed with Grubbs's phosphorylidine catalyst[18] $[RuCl_2(=CHPh)(PCy_3)_2]$ in CH_2Cl_2 at room temperature, to produce the desired 2,5-dihydropyrrole derivative **16** in 92% yield. Simultaneous reduction of the double bond and deprotection of the diphenylmethyl protecting group by catalytic hydrogenation afforded the previously known pyrrolidine **3**[4a] in 82% yield. Finally, the Pictet−Spengler cyclomethylenation of amine **3**, using the previously reported reaction conditions[4a,19] (formaldehyde, HCl, EtOH, reflux), afforded (−)-antofine (**1**) in 64% yield. The spectroscopic data (^1H and ^{13}C NMR) for **1** were identical with those of the natural antofine. The optical rotation measured for the synthetic **1** $\{[\alpha]^{22}_D$ −108.2 (*c* 0.71, $CHCl_3)\}$ is between the values reported for the natural antofine.[20]

In conclusion, we have accomplished the first asymmetric total synthesis of (−)-antofine. An important feature of this synthesis is the creation of a stereogenic center by using the enantioselective catalytic phase transfer alkylation together

(10) This compound appeared to be sensitive to silica gel chromatography. It was very important to minimize the residency time of this compound on the chromatography column to obtain this product in high yield.

(11) Williams, R. M. Synthesis of Optically Active α-Amino Acids. Vol. 7 of *Organic Chemistry Series*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, UK, 1989.

(12) (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650. (b) Chakraborty, T. K.; Ghosh, A. *Tetrahedron Lett.* **2002**, *43*, 9691−9693 and references therein.

(13) For a good review with citations, see: (a) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036−3038. (b) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403−2409. (c) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3−15. (d) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 10.

(14) For the previous asymmetric phase transfer alkylation involving bulky electrophiles, see ref 13a and: Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson J. A. *Tetrahedron Lett.* **2002**, *43*, 8015−8018.

(15) The absolute configuration of **12** was reconfirmed by transformation to the authentic natural compound (−)-**1**. The enantiomeric excess of **12** was determined by chiral stationary phase HPLC analysis (CHIRALCEL OD-H, hexane/2-propanol (9:1, v/v), flow rate 0.5 mL/min, retention time 25.52 min (*S*)-isomer and 30.33 min (*R*)-isomer, detected at 254 nm).

(16) Albeck, A.; Persky, R. *J. Org. Chem.* **1994**, *59*, 653−657.

(17) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 566−574.

(18) (a) Schwab, P.; Grubbs, R. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (b) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887−3897.

(19) Nordlander, J. E.; Njoroge, F. G. *J. Org. Chem.* **1987**, *52*, 1627−1630.

(20) The optical rotation values of natural antofine range from −32° to −165°. see: (a) Cavé, A.; Leboeuf, M.; Moskowitz, H.; Ranaivo, A.; Bick, I. R. C.; Sinchai, W.; Nieto, M.; Sevenet, T.; Cabalion, P. *Aust. J. Chem.* **1989**, *42*, 2243−2263. (b) Baumgartner, B.; Erdelmeier, C. A. J.; Wright, A. D.; Rali, T.; Sticher, O. *Phytochemistry* **1990**, *29*, 3327−3330. (c) Li, X.; Peng, J.; Onda, M. *Heterocycles* **1989**, *29*, 1797−1808. (d) Herbert, R. B.; Moody, C. J. *Phytochemistry* **1972**, *11*, 1184−1184. (e) Capo, M.; Saa, J. M. *J. Nat. Prod.* **1989**, *52*, 389−390. (f) Wiegrebe, W.; Faber, L.; Brockmann, H., Jr.; Budzikiewicz, H.; Krueger, U. *Liebigs Ann. Chem.* **1969**, *721*, 154−162. See also refs 3 and 7.

with a ring-closing metathesis for pyrrolidine ring construction. We believe that this synthesis is efficient enough to allow the asymmetric preparation of other naturally occurring phenanthroindolizidine and phenanthroquinolizidine alkaloids, as well as other modified analogues.

Acknowledgment. This study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (01-PJ2-PG6-01NA01-0002).

Note Added after ASAP Posting. There were errors in compound **11** of Scheme 2 in the version posted on July 3, 2003; the corrected version was posted on July 8, 2003. In ref 15, the retention times for the (*R*)- and (*S*)-isomers were transposed. These errors were also present in the Supporting Information. The corrected version and new Supporting Information were posted on July 9, 2003.

Supporting Information Available: Full experimental procedures and analytical data of compounds; copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **3**, **12**, and **15**; HPLC data of compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0349007