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Synthesis of (−)-Aphanorphine Using Aryl Radical Cyclization

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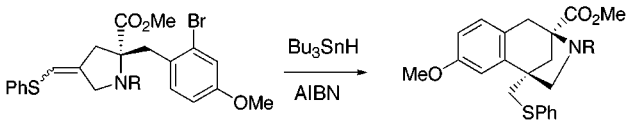
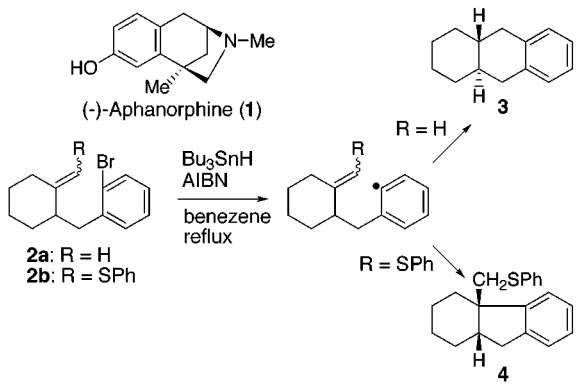
ABSTRACT



The synthesis of (−)-aphanorphine was achieved by using Bu_3SnH-mediated aryl radical cyclization of 1-benzyloxycarbonyl-2-(2-bromo-4-methoxyphenylmethyl)-2-methoxycarbonyl-4-(phenylthiomethylene)pyrrolidine, leading to exclusive formation of the 6-*exo* cyclization product.

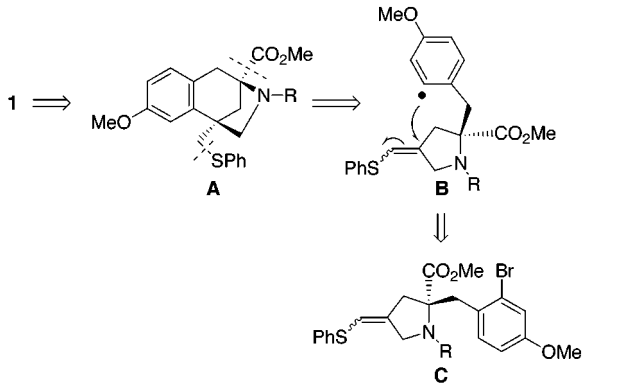
(−)-Aphanorphine (**1**) is an alkaloid isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*. One of the structural characteristics of the alkaloid is its possession of a quaternary carbon at the benzylic position.[1] We recently reported sulfur-directed *exo*-selective aryl radical cyclization onto methylenecycloalkanes, which provides an excellent method for the construction of benzylic quaternary centers.[2] For example, while treatment of **2a** with Bu_3SnH in the presence of AIBN causes aryl radical cyclization to give 6-*endo* product **3**,[3] reaction of **2b** leads to exclusive formation of 5-*exo* cyclization product **4** (Scheme 1). We describe here the total synthesis of **1** based on this methodology for construction of the quaternary carbon of **1**.

Scheme 1



The key transformation of our synthetic planning of **1** is 6-*exo* aryl radical cyclization of **B** generated from **C**, leading to tricyclic compound **A**, which possesses structural characteristics of **1** (Scheme 2).

Scheme 2



To examine this aryl radical cyclization, model radical precursor **10a** was prepared from commercially available *trans*-4-hydroxy-L-proline (**5**) (Scheme 3). Thus, acid-

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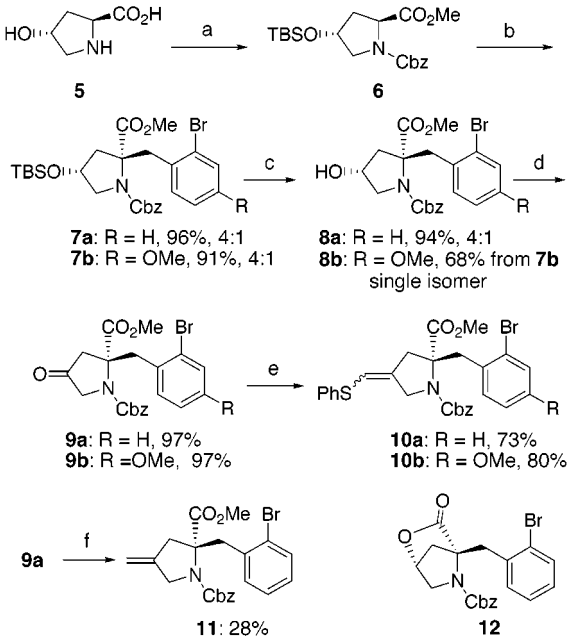
Scheme 3[a]

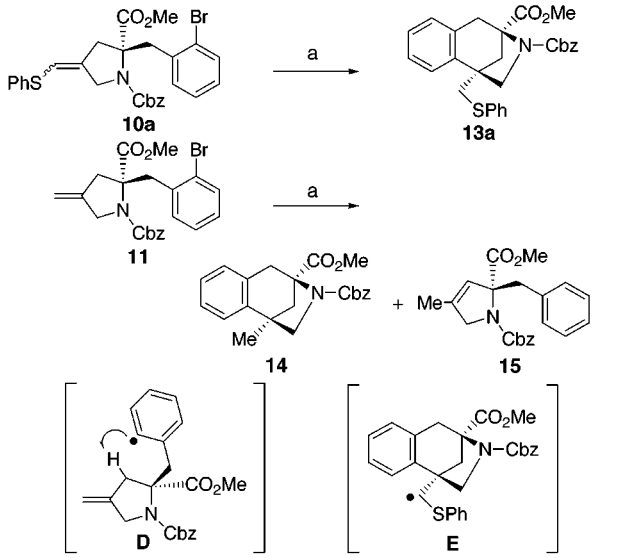


[a] Key: (a) see, ref 4; (b) LHMDS, 2-bromobenzyl bromide, THF for **7a**; LHMDS, 2-bromo-4-methoxybenzyl bromide, THF for **7b**; (c) TBAF, THF; (d) PCC, CH_2Cl_2; (e) $PhSCH_2P(O)Ph_2$, BuLi, $CeCl_3$, THF, then NaH, THF; (f) Tebbe reagent, THF.

catalyzed esterification of **5**, protection of the amino group with benzyl chloroformate, and silylation of the hydroxyl group provided fully protected amino acid **6**.[4] The lithium enolate of **6** was alkylated with 2-bromobenzyl bromide to give a 4:1 inseparable mixture of **7a** and its diastereomer in 96% yield.[5,6] Treatment of the mixture with TBAF followed by oxidation of the resulting alcohol **8a** afforded ketone **9a** in 97% yield. Horner−Wittig reaction of **9a** with the lithium salt of $PhSCH_2P(O)Ph_2$[7] in the presence of $CeCl_3$ followed by treatment of the adduct with NaH afforded radical precursor **10a** in 73% yield.[8] To investigate the effect of the phenylthio group in the radical cyclization, radical precursor **11** having no substituent at the olefin terminus was also prepared from **9a** by employing Tebbe reagent[9] even in low yield.[10]

The crucial radical cyclization was next examined (Scheme 4). On treatment of **10a** with Bu_3SnH in the presence of

Scheme 4[a]



[a] Key: (a) Bu_3SnH, AIBN, benzene, reflux. **13a**, 71%; **14**, 20%; **15**, 17%.

AIBN in boiling benzene, aryl radical cyclization proceeded smoothly, leading to exclusive formation of 6-*exo* cyclization product **13a** in 71% yield. In contrast, treatment of **11** with Bu_3SnH under similar conditions gave 6-*exo* cyclization product **14** and olefin **15** in 20% and 17% yields, respectively. Olefin **15** might result from a 1,5-hydrogen shift of intermediary radical **D**. These results clearly show that the phenylthio group of **10a** is essential for efficient 6-*exo* cyclization, probably as a result of its radical-stabilization ability in radical **E**.

With these results of model experiments in hand, we turned our attention to the total synthesis of (−)-aphanorphine (**1**). Alkylation of the lithium enolate of **6** with 2-bromo-4-methoxybenzyl bromide[11] gave a 4:1 mixture of **7b** and its diastereomer in 91% yield. After desilylation, recrystallization from *n*-hexane−Et_2O afforded alcohol **8b** in diastereomerically pure form in 68% yield. Alcohol **8b** was led to radical precursor **10b** by the same procedure as that used

(1) For isolation of **1**, see: (a) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett*. **1988**, *29*, 4381. For synthesis or synthetic studies of **1**, see: (b) Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1591. (c) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290. (d) Honda, T.; Yamamoto, A.; Cui, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 531. (e) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265. (f) Meyers, A. I.; Schmidt, W.; Santiago, B. *Heterocycles* **1995**, *40*, 525. (g) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 893. (h) Hallinan, K. O.; Honda, T. *Tetrahedron* **1995**, *51*, 12211. (i) Node, M.; Imazato, H.; Kurosaki, R.; Kawano, Y.; Inoue, T.; Nishide, K.; Fuji, K. *Heterocycles* **1996**, *42*, 811. (j) Shiotani, S.; Okada, H.; Nakamata, K.; Yamamoto, T.; Sekino, F. *Heterocycles* **1996**, *43*, 1031. (k) Fadel, A.; Arzel, P. *Tetrahedron*: *Asymmetry* **1997**, *8*, 371. (l) Shimizu, M.; Kamikubo, T.; Ogasawara, K. *Heterocycles* **1997**, *46*, 21.

(2) (a) Ishibashi, H.; Kobayashi, T.; Takamasu, D. *Synlett* **1999**, 1286. (b) Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. *J. Org. Chem.* **2000**, *65*, 9022.

(3) Pal, S.; Mukhopadhyaya, J. K.; Ghatak, U. R. *J. Org. Chem.* **1994**, *59*, 2687.

(4) Mayer, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A. J.; Joullié, M. M. *J. Org. Chem.* **1994**, *59*, 5192.

(5) Nagumo, S.; Mizukami, M.; Akutsu, N.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209.

(6) The stereochemistry of the major isomer **7a** was established by three-step transformation into **12** in 57% yield. See ref 5.

(7) Grayson, J. I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263.

(8) Without $CeCl_3$, the reaction gave only a trace amount of **10a**, probably as a result of facile enolization of ketone **9a**.

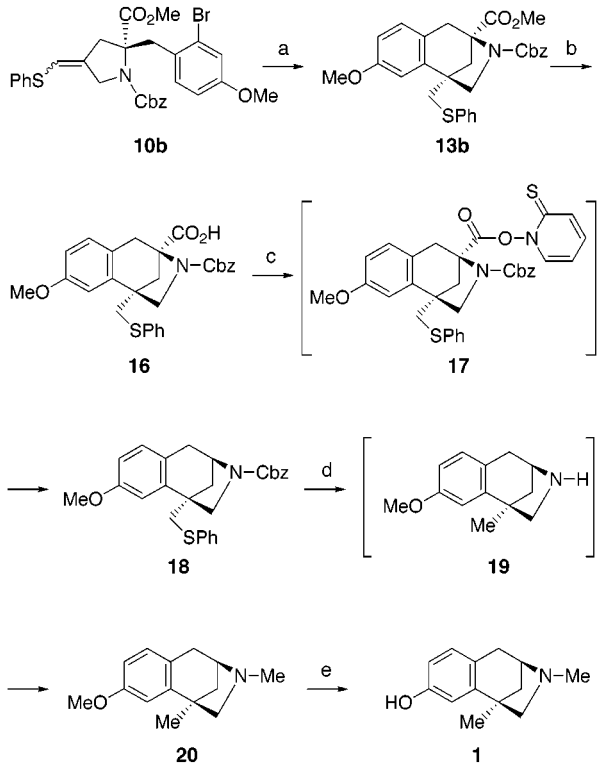
(9) For a review, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 743.

(10) Neither Wittig reaction with $Ph_3P{=}CH_2$ nor Peterson reaction with $TMSCH_2Li$ took place.

(11) Ghosh, A. K.; Mukhopadhyaya, J. K.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2747.

for **10a** (Scheme 3). Treatment of **10b** with Bu_3SnH and AIBN in boiling benzene also caused clean 6-*exo* radical cyclization to afford the desired tricyclic compound **13b** in 76% yield (Scheme 5). Alkaline hydrolysis of the ester group of **13b** gave carboxylic acid **16** in quantitative yield. Condensation of **16** with 2-mercaptopyridine *N*-oxide followed by treatment of the resulting thiohydroxamate ester **17** with Bu_3SnH in the presence of AIBN induced Barton decarboxylation,[12] affording **18** in 52% yield. Heating **18** with Raney nickel in methanol caused simultaneously desulfurization, deprotection of the benzyloxycarbonyl group, and reductive methylation[13] of the resulting secondary amine **19** to furnish known *O*-methyl aphanorphine (**20**) in 65% yield, $[\alpha]^{20}_D$ +9.4 (*c* 0.30, $CHCl_3$) {lit.[1c] $[\alpha]^{29}_D$ +8.46 (*c* 0.35, $CHCl_3$), lit.[1j] $[\alpha]^{21}_D$ +10.4 (*c* 1.24, $CHCl_3$)}. Finally, synthesis of (−)-aphanorphine (**1**) was accomplished by demethylation using BBr_3,[1c,j] mp 200−210 °C (lit.[1c] mp 215−222 °C, lit.[1j] mp 223−228 °C), $[\alpha]^{20}_D$ −23.6 (*c* 0.20, MeOH) {lit.[1j] $[\alpha]^{23}_D$ −24.0 (*c* 0.33, MeOH)}.

Scheme 5[a]



[a] Key: (a) Bu_3SnH, AIBN, benzene, reflux, 76%; (b) 5 N NaOH, MeOH, reflux, quant.; (c) 2-mercaptopyridine *N*-oxide, EDC, DMAP, benzene, rt, then Bu_3SnH, AIBN, reflux, 52%; (d) Raney Ni (W-2), MeOH, reflux, 65%; (e) ref 1c,j.

In conclusion, we have successfully applied sulfur-directed aryl radical cyclization to the total synthesis of (−)-aphanorphine (**1**). This synthesis clearly demonstrates the value of this cyclization for the construction of a benzylic quaternary center in a considerably complex molecule. Further applications of this cyclization are currently under investigation.

Acknowledgment. We are grateful to Prof. K. Ogasawara (Tohoku University) for providing ^1H and ^{13}C spectra of (−)-aphanorphine. We also thank Dr. S. Nagumo (Hokkaido College of Pharmacy) for kind discussion on the alkylation of *trans*-4-hydroxy-L-proline derivatives.

Supporting Information Available: Experimental procedures for compounds **7b**, **8b**, **9b**, **10b**, **13b**, **18**, **20**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For reductive methylation of a secondary amine with Raney nickel in methanol, see: François, D.; Lallemand, M.-C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H.-P. *Angew. Chem., Int. Ed.* **1998**, *37*, 104. See also: He, X.-S.; Brossi, A. *J. Heterocycl. Chem.* **1991**, *28*, 1741.