An Efficient Synthesis of (1*R*,4*S*)-1-Methyl-8-methoxy-3-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine. A Formal Synthesis of (–)-Aphanorphine

Hanwei Hu, Hongbin Zhai*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, China
E-mail: zhaih@mail.sioc.ac.cn

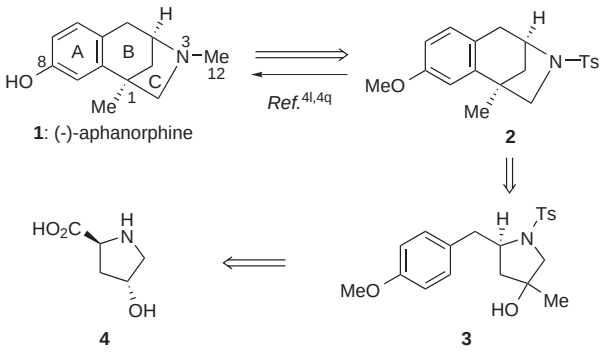
Received 23 August 2003

Abstract: We report a highly efficient synthesis of (1*R*,4*S*)-1-methyl-8-methoxy-3-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine in six steps from **5**. The present work constitutes a new formal synthesis of marine alkaloid (–)-aphanorphine.

Key words: aphanorphine, benzazepine, Friedel–Crafts alkylation, marine alkaloid, synthesis

(–)-Aphanorphine (**1**, Scheme 1) was isolated by Shimizu and Clardy in 1988 from the freshwater blue-green alga *Aphanizomenon flos-aquae*.[1] This tricyclic 3-benzazepine derivative possesses a benzylic quaternary carbon and is structurally analogous to another two naturally occurring alkaloids, morphine[2] and eptazocine.[3] The presence of a methylene bridge (C10) between stereogenic carbon centers C1 and C4 endows **1** with a rigid conformation. Due to its structural novelty and potential analgesic property, the syntheses of (–)-, (+)-, or (±)-aphanorphine, or the key intermediates have stimulated considerable interest from the synthetic community.[4] In the majority of the previous syntheses ring B was constructed prior to ring C; however, there were three exceptions. Funk[4n] proved that rings B and C could be simultaneously generated from a substituted ε-lactam by an intramolecular mesylate displacement. Ishibashi's strategy[4m] involved the final formation of ring B via an aryl radical cyclization. Recently, our laboratory[4q] disclosed a formal asymmetric synthesis of **1** featuring the formation of ring B at the final stage by Lewis acid-promoted Friedel–Crafts alkylative cyclization of 2-arylmethyl-4-methyl-4-pyrrolidinol (corresponding to **3** in Scheme 1), which was derived by a facile reaction sequence including asymmetric Roush methallylation and intramolecular endo epoxy displacement, etc.[4q]

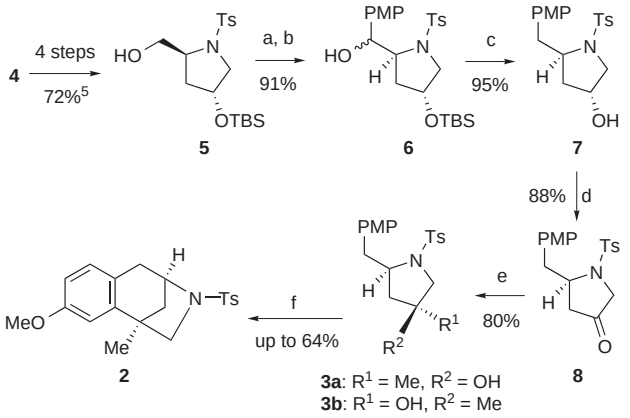
(2*S*,4*R*)-4-Hydroxyproline (**4**) was envisaged as an appropriate starting point to secure the key intermediates for aphanorphine synthesis, such as **3** and eventually **2**, as delineated in Scheme 1. If successful, the current 'chiral pool' strategy would constitute a new formal synthesis of (–)-aphanorphine. Although we were not the first to 'extract' the chiron from **4** in synthesizing **1**, the previous approach[4m] made use of an initial enolate benzylation of a derivative of **4** and decarboxylation at a later stage, which adversely affected the overall synthetic efficiency in terms of atom economy and stereoselectivity.



Scheme 1

Thus we embarked on a novel expeditious synthesis of **2**, an advanced intermediate for aphanorphine synthesis, as outlined in Scheme 2. By an established four-step process (esterification, N-tosylation, O-silylation, and reduction), (2*S*,4*R*)-4-hydroxyproline (**4**) could be efficaciously converted to fully protected alcohol **5** in 72% yield.[5] Swern oxidation[6] of **5** led to an aldehyde, which, without tedious purification, was directly alkylated with 4-methoxyphenylmagnesium bromide[7] to provide the chain extension products **6** as a pair of diastereomeric alcohols (91%, dr = 3:2). Being equally useful, the two isomers were not separated. Upon treatment of **6** with triethylsilane[8] in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane at 0 °C, PMB-substituted pyrrolidinol **7** was attainable in high yield (95%), as a result of benzylic reductive dehydroxylation with concomitant O-desilylation. Under typical Swern conditions,[6] alcohol **7** was oxidized to afford pyrrolidinone **8** in 88% yield. Nucleophilic addition[9] of methylmagnesium iodide to ketone **8** in diethyl ether produced the tertiary alcohols **3a**/**3b** (apparently equally utilizable, 80%). The diastereomeric ratio was measured by ^{1}H NMR integral analysis to be 4:1, presumably favoring **3a** (according to steric hindrance considerations). By following the same protocol[4q] developed in this laboratory previously, $AlCl_3$-promoted Friedel–Crafts alkylative cyclization of alcohols **3a**/**3b** was effected to furnish the desired intermediate **2**[10] as colorless needles (64%). The sample obtained from the abovementioned sequence was determined by HPLC analysis (Chiralpak AD column (250 × 4.6 mm), UV detector 254 nm, eluent hexanes/2-

SYNLETT 2003, No. 14, pp 2129–2130
Advanced online publication: 29.10.2003
DOI: 10.1055/s-2003-42102; Art ID: U16903ST



Scheme 2 *Reagents and conditions*: a) Swern oxidation; b) PMP–MgBr, THF, –78 °C; 0 °C; c) Et_3SiH, $BF_3{\cdot}OEt_2$, DCM, 0 °C; d) Swern oxidation; e) MeMgI, Et_2O, –78 °C; –25 °C; f) $AlCl_3$, DCM, r.t. PMP = *p*-methoxyphenyl.

propanol (4:1), flow rate 0.7 mL/min) to be in high enantiopurity (99.8% ee), indicating that essentially no epimerization ever took place. The $[\alpha]_D^{20}$ of **2** was found to be –14.2 (*c* 0.93, $CHCl_3$) {lit.[4q] $[\alpha]_D^{20}$ –13.4 (*c* 0.969, $CHCl_3$)}. Other spectroscopic data of **2** were also in agreement with those disclosed in the literature.[4q]

In summary, we have accomplished an efficient synthesis of (1*R*,4*S*)-1-methyl-8-methoxy-3-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine (**2**) in six steps from a known building block **5**. The present work can be considered as a new formal synthesis of marine alkaloid (–)-aphanorphine, since **2** could further be manipulated to give **1** in three steps (desulfurization,[4q] N-methylation,[4q] and 8-O-demethylation[4l]). The prominent features of our synthesis include (i) preserving both C2 chirality and C6 atom of **4** (*cf* Ishibashi's strategy[4m]), (ii) concomitant benzylic reductive dehydroxylation and O-desilylation in the formation of **7**, and (iii) simultaneous construction of ring B and the quaternary carbon center (C1) in **2** via an intramolecular Friedel–Crafts reaction. Finally, it is noteworthy that both epimers of **3** and of **6** were equivalently useful for their subsequent transformations, respectively.

Acknowledgment

We thank Chinese Academy of Sciences ('Hundreds of Talent' Program), STCSM ('Venus' Program), and National Natural Science Foundation of China for financial support.

References

(1) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 4381.
(2) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1.
(3) Shiotani, S.; Kometani, T.; Mitsuhashi, K.; Nozawa, T.; Kurobe, A.; Fitsukaichi, O. *J. Med. Chem.* **1976**, *19*, 803.
(4) (a) Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1591. (b) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290. (c) Honda, T.; Yamamoto, A.; Cui, Y. S.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 531. (d) Hume, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265. (e) Meyers, A. I.; Schmidt, W.; Santiago, B. *Heterocycles* **1995**, *40*, 525. (f) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 893. (g) Hallinan, K. O.; Honda, T. *Tetrahedron* **1995**, *51*, 12211. (h) Node, M.; Imazato, H.; Kurosaki, R.; Kawano, Y.; Inoue, T.; Nishide, K. *Heterocycles* **1996**, *42*, 811. (i) Shiotani, S.; Okada, H.; Nakamata, K.; Yamamoto, T.; Sekino, F. *Heterocycles* **1996**, *43*, 1031. (j) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 283. (k) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 371. (l) Shimizu, M.; Kamikubo, T.; Ogasawara, K. *Heterocycles* **1997**, *46*, 21. (m) Tamura, O.; Yangimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett.* **2001**, *3*, 2427. (n) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923. (o) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049. (p) El Azab, A. S.; Taniguchi, T.; Ogasawara, K. *Heterocycles* **2002**, *56*, 39. (q) Zhai, H.; Luo, S.; Ye, C.; Ma, Y. *J. Org. Chem.* **2003**, *68*, ASAP; MS No. JO0348726.
(5) For the preparation of compound **5**, see: (a) Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293. (b) Westwood, N. B.; Walker, R. T. *Tetrahedron* **1998**, *54*, 13391.
(6) For Swern oxidation, see: Anthory, J. M.; Debra, S. B.; Daniel, S. *J. Org. Chem.* **1979**, *44*, 4148.
(7) Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 588.
(8) For reduction with triethylsilane, see: (a) Orfanopoulos, M.; Smonou, I. *Synth. Commun.* **1988**, *18*, 833. (b) Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* **1988**, *29*, 5793.
(9) For methylation of similar pyrrolidinones, see: (a) Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1998**, *63*, 3411. (b) Moulines, J.; Bats, J.-P.; Hautefaye, P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* **1993**, *34*, 2315.
(10) Compound **2**, a colorless solid: mp 137–138 °C; 99.8% ee; $[\alpha]_D^{20}$ –13.4 (*c* 0.969, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 1.46 (ddd, *J* = 11.1, 6.3, 1.5 Hz, 1 H, 0.5CH_2), 1.79 (d, *J* = 11.1 Hz, 1 H, 0.5CH_2), 2.43 (s, 3 H, benzylic CH_3), 2.93 (dd, *J* = 16.6, 2.8 Hz, 1 H, 0.5 CH_2), 3.02 (d, *J* = 8.7 Hz, 1 H, 0.5 CH_2), 3.12 (d, *J* = 16.8 Hz, 1 H, 0.5 CH_2), 3.40 (dd, *J* = 8.6, 1.4 Hz, 1 H, 0.5 CH_2), 3.79 (s, 3 H, OCH_3), 4.39–4.45 (m, 1 H. NCH), 6.72 (dd, *J* = 8.6, 2.8 Hz, 1 H, CH), 6.78 (d, *J* = 2.1 Hz, 1 H, CH), 6.98 (d, *J* = 8.1 Hz, 1 H, CH), 7.28 (d, *J* = 8.1 Hz, 2 H, 2 CH), 7.69 (d, *J* = 8.4 Hz, 2 H, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 21.5, 38.2, 41.7, 42.3, 55.3, 57.8, 62.9, 110.0, 111.7, 125.2, 127.1, 129.6, 130.4, 135.6, 143.1, 144.9, 157.9. MS (EI): 357 (18) [M^+], 202 (15), 173 (100). Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.18; H, 6.55; N, 3.80.