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Enantiocontrolled Synthesis of (−)-9-*epi*-Pentazocine and (−)-Aphanorphine

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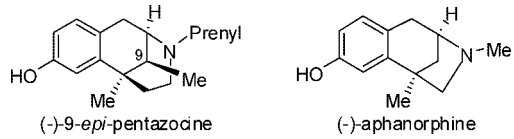
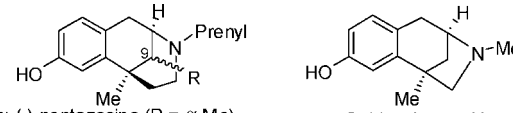
ABSTRACT



We have developed novel asymmetric routes to (−)-9-*epi*-pentazocine and (−)-aphanorphine from a D-tyrosine derivative. The tricyclic frameworks of (−)-9-*epi*-pentazocine and (−)-aphanorphine were assembled stereoselectively via intramolecular Friedel−Crafts reaction of the corresponding bicyclic precursors, generated with titanium-promoted enyne cyclization and indium-initiated atom-transfer radical cyclization, respectively.

(−)-Pentazocine (**1a**), featuring a quaternary carbon and three consecutive stereocenters, was first synthesized by Archer and co-workers as a strong nonnarcotic analgesic without significant addiction liability.[1] Remarkedly, for subcutaneously injected 2,5-dimethyl-2′-hydroxy-9-propyl-6,7-benzomorphans, the 9β-propyl levo isomer was considerably more analgesically potent than the 9α- counterpart; the latter has the same configuration at C-9 as in **1a** and was analgesically equipotent with morphine.[1d] A similar trend was observed with (−)-9-*epi*-pentazocine (**1b**, the diastereomer of **1a**) when compared to **1a** itself.[1e] (−)-Aphanorphine (**2**), a 3-benzazepine alkaloid with a quaternary benzylic stereocenter isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*,[2] bears close structural similarity to both (−)-pentazocine and some natural analgesics such as morphine and eptazocine. Both pentazocine and aphanorphine have emerged as attractive target molecules for synthetic chemists due to their prominent or potential pharmacological activities.[1e,3,4] Herein we wish to report an efficient enantiocontrolled approach to constructing (−)-9-*epi*-pentazocine (**1b**) and (−)-aphanorphine (**2**) from commercially available chiral starting materials.



The retrosynthetic analysis is outlined in Scheme 1. The frameworks of **1b** and **2** may be accessed stereoselectively

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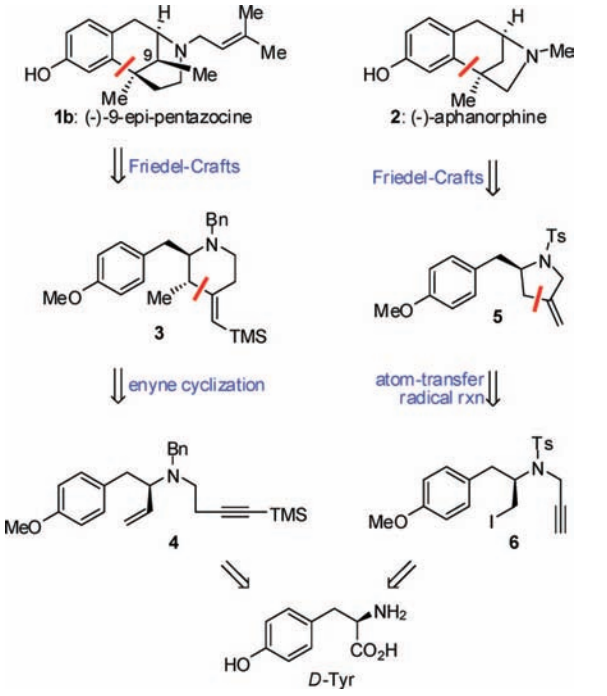
Scheme 1. Retrosynthetic Analyses of (−)-9-*epi*-Pentazocine (**1b**) and (−)-Aphanorphine (**2**)



via intramolecular Friedel−Crafts reaction of bicyclic precursors **3** and **5**, respectively. The formation of **3** and **5** may, in turn, be accomplished using titanium-promoted enyne cyclization of **4** and indium-initiated atom-transfer radical cyclization of **6**, respectively. The precursors **4** and **6** may both be generated efficiently from D-tyrosine as a chiral pool. As shown in Scheme 2, the assembly of (−)-9-*epi*-pentazocine (**1b**) commenced from *O*-Me-D-tyrosine methyl ester hydrochloride salt[5] (**7**), converted from D-tyrosine in excellent overall yield (92%) in four simple operations. Nosylation of **7** (NsCl, TEA), Mitsunobu alkylation (3-butyn-1-ol, PPh_3, DIAD) and denosylation (PhSH, K_2CO_3) followed by treatment with HCl gas in ether afforded **10** (in 88% overall yield from **7**) as the HCl salt. Selective monobenzylation (BnBr (1.05 equiv), Bu_4NI, K_2CO_3) and reduction of the ester functionality with $LiAlH_4$ led to benzylamino alcohol **12**, which was further converted to enyne **4** after a reaction sequence including Swern oxidation, Wittig olefination ($MePPh_3I$, KHMDS), and trimethylsilylation of the terminal alkyne (BuLi, TMSCl).

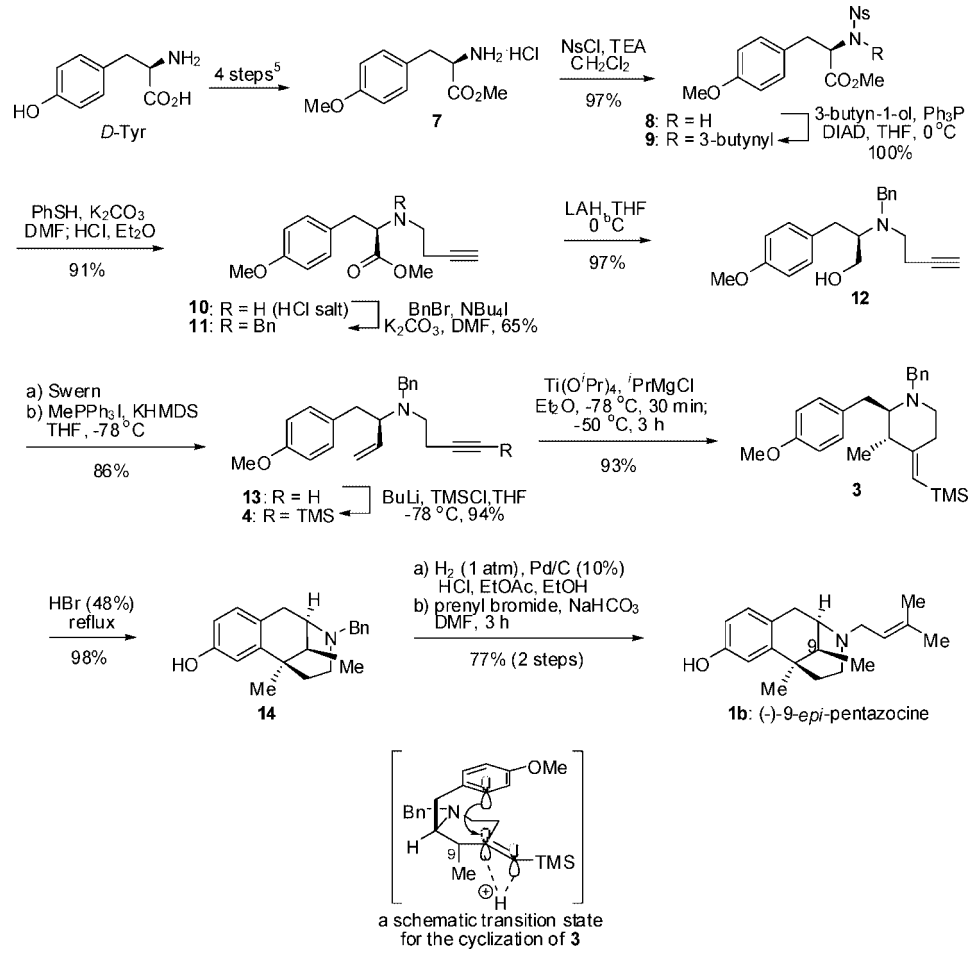
With the key intermediate **4** in hand, the organozirconium and organotitanium-mediated reductive enyne cyclizations were extensively investigated.[6] Upon treatment[6b] with 2 equiv of $Cp_2Zr(^nBu)_2$, enyne **4** remained essentially unreacted. When the amount of $Cp_2Zr(^nBu)_2$ was increased to 5 equiv, only a small amount of the desired product was isolated at the expense of complete consumption of the starting material. However, the reaction presented a striking contrast when an organotitanium species, $^iPr_2Ti(O^iPr)_2$,[6e] was employed as a promoter. Approximately half of the substrate underwent the expected cyclization in the presence of 2 equiv of $^iPr_2Ti(O^iPr)_2$. The conversion rate was greatly improved when 3 equiv or more of the titanium species was included in the reaction mixture. To our delight, alkene **3** was stereoselectively obtained as a reductive cyclization product in 93% yield by subjecting enyne **4** to 4.4 equiv of $^iPr_2Ti(O^iPr)_2$ in ether at −78 °C for 10 min and then at −50 °C for 3 h. In addition, our experiments also confirmed that protecting the terminal alkyne with a silyl group was necessary[6c] because the relatively acidic *sp*-CH would otherwise interfere with the cyclization. It is worthy of note that the presence of sulfonamide functionalities in the substrates was incompatible with the reductive cyclization. An analogue of enyne **4**, in which the benzyl on the nitrogen was replaced with a tosyl, failed the cyclization. Essentially no cyclization took place when the Ts-substituted enyne was exposed to Cp_2ZrCl_2/BuLi[6a,b] or $Cp_2ZrCl_2/HgCl_2$/Mg,[6d] although alkynyl desilylation was observed in some cases. Even though in one case this tosyl analogue cyclized when treated with $Ti(O^iPr)_4/^iPrMgCl$,[6e] the diastereoselectivity was too low to be useful. Intramolecular Friedel−Crafts reactions have been applied successfully to the construction of alkaloids such as aphanorphine.[4n,q,v,w] Reaction of silylalkene **3** with $AlCl_3$ (2.5−10 equiv) in CH_2Cl_2 at rt for a period from 10 min to 12 h resulted in a desilylated terminal alkene and the unreacted starting material; reaction with $MeSO_3H$ in CH_2Cl_2 at rt for 12 h only led to complete desilylation.

(4) For synthesis of (−)-aphanorphine, see: (a) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290. (b) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265. (c) Hallinan, K. O.; Honda, T. *Tetrahedron* **1995**, *51*, 12211. (d) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 893. (e) Meyers, A. I.; Schmidt, W.; Santiago, B. *Heterocycles* **1995**, *40*, 525. (f) Node, M.; Imazato, H.; Kurosaki, R.; Kawano, Y.; Inoue, T.; Nishide, K.; Fuji, K. *Heterocycles* **1996**, *42*, 811. (g) Shiotani, S.; Okada, H.; Nakamata, K.; Yamamoto, T.; Sekino, F. *Heterocycles* **1996**, *43*, 1031. (h) Shimizu, M.; Kamikubo, T.; Ogasawara, K. *Heterocycles* **1997**, *46*, 21. (i) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 371. (j) Tamura, O.; Yanagimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett.* **2001**, *3*, 2427. (k) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049. (l) ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Heterocycles* **2002**, *56*, 39. (m) Tamura, O.; Yanagimachi, T.; Ishibashi, H. *Tetrahedron: Asymmetry* **2003**, *14*, 3033. (n) Zhai, H.; Luo, S.; Ye, C.; Ma, Y. *J. Org. Chem.* **2003**, *68*, 8268. (o) Taylor, S. K.; Ivanovic, M.; Simons, L. J.; Davis, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 743. (p) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917. (q) Hu, H.; Zhai, H. *Synlett* **2003**, 2129. (r) Bower, J. F.; Szeto, P.; Gallagher, T. *Chem. Commun.* **2005**, 5793. (s) Katoh, M.; Inoue, H.; Suzuki, A.; Honda, T. *Synlett* **2005**, 2820. (t) Li, M.; Zhou, P.; Roth, H. F. *Synthesis* **2007**, 55. (u) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2007**, *5*, 143. (v) Ma, Z.; Zhai, H. *Synlett* **2007**, 161. (w) Ma, Z.; Hu, H.; Xiong, W.; Zhai, H. *Tetrahedron* **2007**, *63*, 7523. (x) Grainger, R. S.; Welsh, E. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377. For synthesis of (±)-apanorphine, see: (y) Honda, T.; Yamamoto, A.; Cui, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 531. (z) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923. For synthesis of (+)-apanorphine, see: (aa) Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1591.

(5) For synthesis of *O*-Me-D-tyrosine methyl ester hydrochloride salt (**7**), see: Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2002**, *4*, 265.

(6) (a) Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synthesis* **1998**, 557. (b) Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421. (c) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. (d) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568. (e) Urabe, H.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7329. (f) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014. (g) *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH Verlag: Weinheim, Germany, 2002.

Scheme 2. Asymmetric Total Synthesis of (−)-9-*epi*-Pentazocine (**1b**)



Nevertheless, heating **3** in hydrobromic acid (48%) at reflux for 10 h provided **14** in excellent yield (98%). This transformation involved a series of reactions including alkenyl desilylation, Friedel−Crafts alkylative cyclization onto the phenyl ring with excellent stereocontrol, and cleavage of the ether linkage. Finally, catalytic hydrogenolysis of **14** under 1 atm of H_2 in HCl (2.5 M)-EtOAc-EtOH (1:5:5) in the presence of 10% Pd/C followed by prenylation afforded (−)-9-*epi*-pentazocine[7] (**1b**) in 77% overall yield.

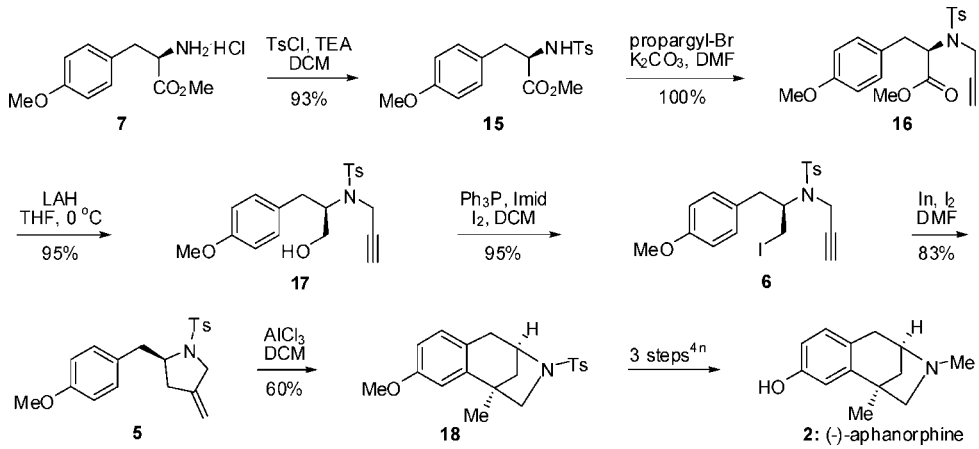
The formal synthesis of (−)-aphanorphine is described in Scheme 3. Tosylation and propargylation of **7** provided tertiary sulfonamide **16** in 93% yield over the two steps. Reduction of the ester group with $LiAlH_4$ led to the formation of primary alcohol **17**, which, after treatment with I_2, PPh_3, and imidazole, was converted to **6**, a compound suitable for indium-initiated 5-exo atom-transfer radical cyclization.[8] Indeed, reaction of **6** with In (2 equiv) and I_2 (1 equiv) in DMF for 3 days resulted exclusively in product **5** in 83% yield. Both deiodinated alkene **5** and the corresponding iodoalkenes (*Z*- and *E*-)[8] were isolated if the reaction time was shorter or if methanol was used as the solvent. Analogous to the case of (−)-9-*epi*-pentazocine, the formation of ring B was achieved by a Friedel−Crafts alkylative cyclization onto the phenyl ring. Under the reaction conditions such as $RuCl_3$/AgOTf/$ClCH_2CH_2Cl$/rt, $MeSO_3H$/CH_2Cl_2/rt, $MeSO_3H$/$ClCH_2CH_2Cl$/80 °C, and polyphosphoric acid (PPA)/80−90 °C, alkene **5** cyclized to provide tricycle **18**[4n] in 0−41% yields. Finally, exposure of **5** to $AlCl_3$ in CH_2Cl_2 at rt effected the anticipated intramolecular Friedel−Crafts reaction and led to tricycle **18**[9] in 60% yield. The ^1H and ^{13}C NMR spectroscopic data of **18** were in agreement with those reported in the literature.[4n] Because it has been known that **18** can be converted into **2** in three steps,[4n] this work constitutes a new formal asymmetric synthesis of (−)-aphanorphine (**2**).

(7) **1b**: mp 59−60 °C; $[\alpha]^{24}_D$ −120.3 (*c* 0.85, $CHCl_3$); ee = 98.5% [Chiralpak OD column (250 × 4.6 mm), UV detector 220 nm, eluent hexanes/2-propanol/diethylamine (95:5:0.2), flow rate 0.7 mL/min].

(8) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417.

(9) **18**: mp 136−138 °C; lit.[4n] mp 137−138 °C; $[\alpha]^{25}_D$ −16.9 (*c* 0.89, $CHCl_3$); lit.[4n] $[\alpha]^{20}_D$ −13.4 (*c* 0.97, $CHCl_3$); lit.[4q] $[\alpha]_D{}^{20}$ −14.3 (*c* 0.93, $CHCl_3$).

Scheme 3. Asymmetric Formal Synthesis of (−)-Aphanorphine (**2**)



In summary, we have developed efficient asymmetric routes to the synthesis of (−)-9-*epi*-pentazocine and (−)-aphanorphine starting from *O*-Me-D-tyrosine methyl ester hydrochloride salt, a known derivative of D-tyrosine. The tricyclic frameworks of (−)-9-*epi*-pentazocine and (−)-aphanorphine were assembled stereoselectively via intramolecular Friedel−Crafts reaction of the corresponding bicyclic precursors, generated with titanium-promoted enyne cyclization and indium-initiated atom-transfer radical cyclization, respectively.

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Supporting Information Available: Experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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