First Asymmetric Synthesis of a Hasubanan Alkaloid. Total Synthesis of (+)-Cepharamine

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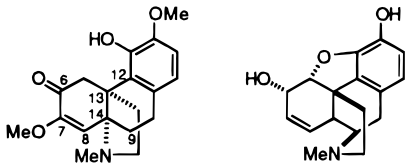
(−)-Cepharamine (**1**), isolated from *Stephania cepharantha*

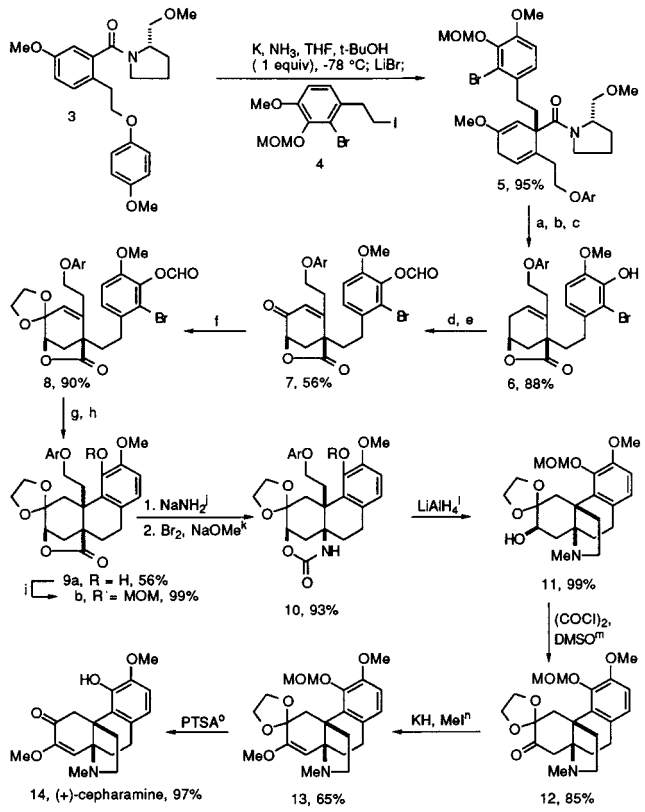


Haijata, is a member of the hasubanan family of alkaloids.[1] The hasubanan alkaloids are of pharmacological interest because of their structural resemblance to the morphine alkaloids; see morphine (**2**).[2] However, the absolute configuration at C(13) in **1** is opposite to that in morphine, resulting in an inversion of the critical spatial relationship of the nitrogen atom to the aromatic ring in **1** relative to **2**. Thus, the natural enantiomers of cepharamine and other hasubanan alkaloids are expected to be ineffective analgesic agents.[3] Although there has been substantial interest in the synthesis of hasubanan alkaloids,[4,5] an enantioselective synthesis has not been reported. Herein we describe the first asymmetric synthesis of (+)-cepharamine, the unnatural enantiomer of **1**, by a highly convergent strategy dependent upon the asymmetric Birch reduction−alkylation protocol[6] and a radical cyclization reaction to fashion the critical C(9)−C(14) and C(12)−C(13) bonds.

Birch reduction of the chiral benzamide **3**[7] with potassium in NH_3, THF, and *tert*-butyl alcohol (1 equiv) at −78 °C, followed by addition of LiBr[8] and then the alkylation reagent **4**[9] gave the 1,4-cyclohexadiene **5** in 95% yield as a single diastereomer (Scheme 1).[10,11] Enol ether hydrolysis[12] and reduction of the resulting cyclohexenone derivative with $NaBH_4$ gave a mixture of diastereomerically related alcohols (∼1:1). As expected from earlier model studies,[13] both diastereomers gave the phenolic lactone **6** on treatment with *p*-toluenesulfonic acid (PTSA) in refluxing benzene solution. It is assumed that the *syn*-hydroxyamide converts to **6** by an acid-catalyzed transesterification and the *anti*-hydroxyamide by an amide carbonyl assisted ionization of the protonated alcohol.

Although it was found that **6** underwent radical cyclization (*as the unprotected phenol*) to give the desired hydrophenanthrene ring system,[14] problems associated with the development of a regiospecific construction of the 7-methoxy enone functionality

Scheme 1[a]



[a] Reaction conditions: (a) $BF_3{\cdot}OEt_2$, $Bu_4NF{\cdot}XH_2O$, CH_2Cl_2; (b) $NaBH_4$, THF; (c) PTSA, PhH, reflux; (d) CH_3CO_2CHO, pyridine, CH_2Cl_2; (e) *t*-BuOOH, CuBr, PhH; (f) $(TMSOCH_2)_2$, TMSOTf; (g) AIBN, Bu_3SnH, PhH, reflux; (h) Na_2CO_3, MeOH, H_2O, THF; (i) NaH, THF, MOMCl, reflux; (j) NH_3, THF, −33 °C to 25 °C; (k) MeOH, THF, −78 °C to reflux; (l) THF, reflux; (m) Et_3N, CH_2Cl_2, −10 °C; (n) 18-crown-6, DMF, 25 °C; (o) acetone, H_2O, reflux.

(1) (a) Bentley, K. W. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. 13, pp 131−143. (b) Inubushi, Y.; Ibuka, T. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1977; Vol. 16, pp 393−430. (c) Matsui, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 33, pp 307−347.

(2) For the pharmacology of the hasubanan alkaloids, see ref 1c.

(3) The unnatural enantiomers of codeine, morphine, and heroin showed no antinociceptive activity on subcutaneous injection in mice; see: Iijima, I.; Minamikawa, J.; Jacobson, A. E.; Brossi, A.; Rice, K. *J. Org. Chem*. **1978**, *43*, 1462−1463.

(4) For syntheses of racemic cepharamine, see: (a) Inubushi, Y.; Ibuka, T.; Kitano, M. *Tetrahedron Lett*. **1969**, 1611−1614. (b) Inubushi, Y.; Kitano, M.; Ibuka, T. *Chem. Pharm. Bull*. **1971**, *19*, 1820−1841. (c) Kametani, T.; Nemoto, H.; Kobari, T.; Shishido, K.; Fukumoto, K. *Chem. Ind*. (London) 1972, 538−540. (d) Kametani, T.; Kobari, T.; Fukumoto, K. *J. Chem. Soc., Chem. Commun*. **1972**, 288−289. (e) Kametani, T.; Kobari, T.; Shishido, K.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1059−1064. (f) Schwartz, M.; Wallace, R. *Tetrahedron Lett*. **1979**, 3257−3260.

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(6) (a) Schultz, A. G. *Acc. Chem. Res*. **1990**, *23*, 207−213. (b) Schultz, A. G. *J. Chin. Chem. Soc. (Taiwan)* **1994**, *41*, 487−495.

(7) Benzamide **3** was prepared in 5 steps (58% overall yield) from commercially available 2-bromo-5-methoxybenzoic acid by way of a literature procedure; see: Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607−2619.

(8) LiBr is added to prevent elimination of HI from **4**.

(9) Alkylation reagent **4** was prepared in 5 steps (55% overall yield) from isovanillin by modification of a literature procedure; see: Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem*. **1988**, *53*, 4694−4708.

(10) For the related highly diastereoselective alkylation of a chiral 2-alkyl substituted benzamide, see: Schultz, A. G.; Kirincich, S. J. *J. Org. Chem*. **1996**, *61*, 5626−5630.

(11) All synthetic intermediates were characterized by ^1H and ^{13}C NMR, IR and low resolution MS analyses. Compounds **3**, **6**, **9a**, **12**, **13**, and **14** gave satisfactory combustion analyses. All other compounds gave satisfactory high-resolution MS analyses.

(12) Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett*. **1995**, *36*, 7765−7766.

(13) Wang, A. Ph.D. Thesis, Rensselaer Polytechnic Institute, 1997.

(14) For a discussion of the importance of the lactone bridge in a substrate related to **6** that undergoes radical cyclization by the 6-exo-trig pathway, see: Schultz, A. G.; Wang, A. *J. Org. Chem*. **1996**, *61*, 4857−4859.

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in cepharamine (*vide infra*) required an earlier introduction of the C(6) carbonyl group. Protection of the phenolic hydroxyl group as the formate ester and allylic oxidation with *tert*-butyl hydroperoxide and CuBr[15] gave enone **7**. Ketalization of **7** under aprotic conditions[16] provided **8**, and radical cyclization of **8**, followed by basic hydrolysis of the formate ester gave **9a**.

The phenol **9a** was converted to a base-stable MOM derivative **9b**, from which a very efficient Hofmann-type rearrangement gave the cyclic carbamate **10**. Formation of the cis-fused *N*-methylpyrrolidine ring was then effected in one experimental operation by treatment of **10** with $LiAlH_4$ in refluxing THF. This remarkably efficient transformation of **10** to **11** evolved from a careful study[17] of the less efficient stepwise process involving (1) cleavage of the aryl ether with CAN, (2) conversion of the resulting alcohol to the mesylate, (3) intramolecular carbamate N-alkylation, and (4) reduction of the cyclic carbamate with $LiAlH_4$.

Swern oxidation of **11** gave ketone **12**, and alkylation of the enolate of **12** under conditions that favor O-alkylation with MeI afforded enol ether **13**.[18] It should be noted that this solution to the challenge of construction of the C(6)−C(8) keto enol ether in cepharamine is a considerable improvement with respect to methodology involving oxidation to a 6,7-diketone derivative followed by acid-catalyzed enol ether formation.[19] Finally, acid-catalyzed ketal and MOM ether hydrolysis proceeded without disruption of the enol ether to give (+)-cepharamine (**14**) in 97% yield: mp 184−185 °C (colorless prisms from ether); $[\alpha]^{26}_D$ +246 (*c* 2.8, $CHCl_3$); lit. mp for (−)-cepharamine (**1**) 187−188 °C; $[\alpha]^{22}_D$ −243 (*c* 0.88, $CHCl_3$).[20]

In summary, the first asymmetric synthesis of a hasubanan alkaloid, (+)-cepharamine (**14**), has been carried out with complete regio- and stereocontrol. The synthesis of **14** required 16 steps from the chiral benzamide **3** and was carried out with an overall yield of 12%. Important features of the synthesis are the convergency of the asymmetric Birch reduction−alkylation step 3 + 4 → **5**, the efficient release of the chiral auxiliary by the acid-catalyzed lactonization to give **6**, the radical cyclization that generates a quaternary center at C(13) by way of the 6-exo-trig pathway, the efficient carboxyl to amino conversion **9b** → **10** which very effectively extends the utility of the asymmetric Birch reduction−alkylation protocol,[21] and the development of a potentially general solution to the introduction of C-ring functionality in the hasubanan alkaloids. The opioid receptor pharmacology of **14** and congeners is under investigation and will be reported elsewhere when completed.

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Supporting Information Available: Experimental details and characterization of isolated intermediates (14 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(16) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357−1358.

(17) Details of this study will be provided in the full account of this work.

(18) For an analogous O-alkylation of a ketone enolate flanked by two quaternary centers, see: Schultz, A. G.; Kashdan, D. S. *J. Org. Chem.* **1973**, *38*, 3814−3815.

(19) For perspective, see the conversion of the keto lactam **65** to **68** (~10% yield) in ref 4b. In contrast to the reactivity of the lactam described in ref 4b, the 6,7-diketone derived from **12** gave the regioisomeric keto enol ether. For a related α-diketone O-alkylation developed in the context of cephalotaxine construction, see: Burkholder, T. P.; Fuchs, P. L. *J. Org. Chem.* **1988**, *110*, 2341−2342.

(20) For a recent listing of physical and spectroscopic properties of (−)-cepharamine, see: Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M.; Toda, J.; Suzuki, H.; Sano, T. *J. Nat. Prod.* **1996**, *59*, 476−480. IR, ^1H and ^{13}C NMR spectra of (+)-cepharamine compared favorably to spectra of the natural product. We thank Dr. Noriaki Kashiwaba and Professors Osamu Hoshino and Toshiro Ibuka for the provision of key spectra of (−)-cepharamine.

(21) For a discussion of the strategic evolution of the asymmetric Birch reduction−alkylation, see: Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210−6219.