Communications to the Editor

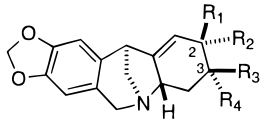
Enantioselective Total Syntheses of the 5,11-Methanomorphanthridine *Amaryllidaceae* Alkaloids (−)-Pancracine and (−)-Coccinine

Jian Jin and Steven M. Weinreb*

Department of Chemistry
The Pennsylvania State University
University Park, Pennsylvania 16802

Received November 12, 1996

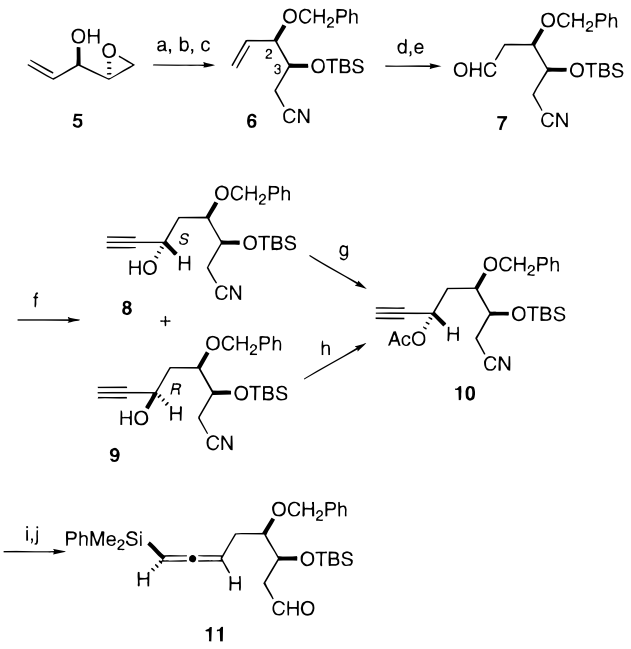
The 5,11-methanomorphanthridine alkaloids are a small subclass of compounds of the *Amaryllidaceae* type first isolated by Wildman and co-workers over four decades ago.[1] These natural products, produced by plants of various *Pancratium*, *Narcissus*, and *Brunsvigia* species, have a unique pentacyclic structural framework exemplified by the alkaloids (−)-montanine (**1**), (−)-coccinine (**2**), (−)-pancracine (**3**), and (−)-brunsvigine (**4**). In general, the alkaloids of this group are identical except for the oxygen substitution (*i.e.*, methoxyl *vs* hydroxyl) and stereochemistry at C-2 and C-3.[2,3] Despite extensive synthetic effort in the area of *Amaryllidaceae* alkaloids,[3] the construction of the 5,11-methanomorphanthridines has received little attention. Overman and Shim have described an elegant approach to both racemic and (−)-pancracine (**3**).[4] In a nice series of papers, Hoshino and co-workers reported total syntheses of alkaloids **1**−**4** in racemic form.[5] In this communication, we describe the application of our recently discovered stereospecific intramolecular allenylsilane imino ene chemistry[6] as the pivotal step in enantioselective total syntheses of (−)-coccinine (**2**) and (−)-pancracine (**3**).



1 (-)-montanine R_1=H, R_2=OMe, R_3=OH, R_4=H
2 (-)-coccinine R_1=OMe, R_2=H, R_3=OH, R_4=H
3 (-)-pancracine R_1=H, R_2=OH, R_3=OH, R_4=H
4 (-)-brunsvigine R_1=H, R_2=OH, R_3=H, R_4=OH

Our synthesis commenced with enantiomerically pure hydroxy epoxide **5**, readily available by Sharpless asymmetric epoxidation of divinylcarbinol.[7] This compound was first *O*-benzylated, the epoxide was regioselectively opened with cyanide, and the resulting secondary alcohol was *O*-silylated to yield nitrile **6** having differentially functionalized C-2,3 oxygen atoms (methanomorphanthridine numbering) (Scheme 1). The vinyl group of **6** was then hydroborated and the intermediate primary alcohol oxidized to afford aldehyde **7**. Addition of ethynylmagnesium bromide to **7** produced a 2:1 mixture of (*S*)- and (*R*)-propargyl alcohols **8** and **9**, respectively. Each of these chromatographically separable epimers could be efficiently processed to the desired *S*-acetate **10**. Thus, alcohol **8** was directly acetylated, whereas **9** could be transformed cleanly to **10** via a Mitsunobu inversion.[8] Subjection of propargyl acetate **10** to the silyl cuprate conditions of Fleming and Terrett[9] stereospecifically afforded the desired (*R*)-allenylsilane nitrile, which was reduced to aldehyde **11**.

Scheme 1[a]



[a] (a) $PhCH_2Br$, NaH, TBAI, THF, −20 °C to room temperature (rt), 96%; (b) KCN, MeOH, Δ, 93%; (c) TBSCl, imidazole, DMF, 0 °C−rt, 94%; (d) disiamylborane, THF, 0 °C−rt/NaOH, H_2O_2, 88%; (e) Swern ox, 96%; (f) HCCMgBr, CH_2Cl_2, −78 to 0 °C, 89%; (g) Ac_2O, TEA, DMAP, CH_2Cl_2, 98%; (h) DEAD, Ph_3P, HOAc, pyr, THF, −45 °C−rt, 86%; (i) $(Me_2PhSi)_2CuCNLi_2$, THF, −96 °C, 84%; (j) DIBALH, PhMe, −78 to 0 °C, 78%.

Aldehyde **11** was then condensed with iminophosphorane **12** to afford the corresponding imine **13** (Scheme 2).[10,11] Upon heating this imine/allenylsilane in mesitylene at 162 °C, a stereospecific cyclization occurred to afford, after alkyne desilylation, a single amino acetylene **14**. No other stereoisomer was detected in this reaction. We believe that this transformation occurs via a concerted thermal imino ene reaction.[6] This pericyclic process can, in principle, proceed through two imine conformations **13a** and/or **13b**. Inspection of models indicates that the two conformers are capable of undergoing a concerted

(1) Wildman, W. C.; Kaufman, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 1249. Inubushi, Y.; Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Org. Chem.* **1960**, *25*, 2153. Wildman, W. C.; Brown, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 6439.

(2) For an apparent exception, see: Viladomat, F.; Bastida, J.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307.

(3) For reviews, see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: The Amaryllidaceae Alkaloids. San Diego, CA, 1987, 30, 252. (b) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291. (c) Southon, I. W.; Buckingham, J. *Dictionary of the Alkaloids*; Chapman Hall: New York, 1989; pp 229, 735, 817.

(4) (a) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005. (b) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662.

(5) (a) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *J. Org. Chem.* **1992**, *57*, 7285. (b) Ishizaki, M.; Kurihara, K.; Tanazawa, E.; Hoshino O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101 and references cited therein.

(6) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905. Jin, J.; Smith, D. T.; Weinreb, S. M. *J. Org. Chem.* **1995**, *60*, 5366. See also: Weinreb, S. M. *J. Heterocycl. Chem.* **1996**, *33*, 1429.

(7) Schreiber, S. L.; Schreiber, T. L.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. Babine, R. E. *Tetrahedron Lett.* **1986**, *27*, 5791.

(8) Wovkulich, P. M.; Shankaran, K.; Kiegel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832.

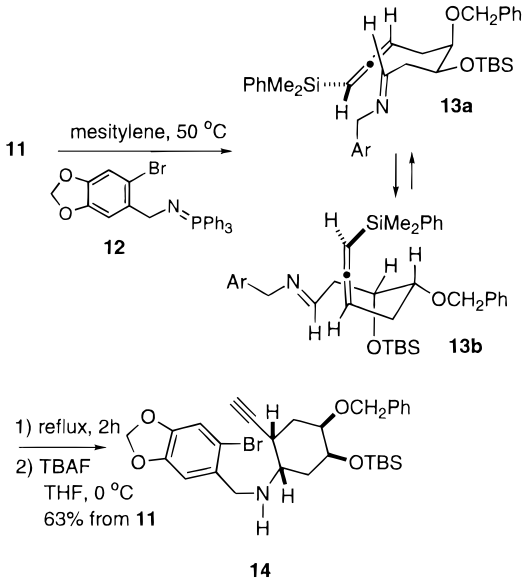
(9) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99. This reaction has been shown to proceed via an S_N2'-*anti* process.

(10) Prepared from the corresponding azide and triphenylphosphine. *Cf.:* Lambert, P. H.; Vaultier, M.; Carrie, R. *J. Chem. Soc., Chem. Commun.* **1982**, 1224 and references cited therein.

(11) Direct reaction of aldehyde **11** with *o*-bromopiperonylamine to produce the imine failed. Under forcing conditions, only the α,β-unsaturated aldehyde from β-elimination of the siloxy group was formed.

S0002-7863(96)03900-5 CCC: $14.00

Scheme 2

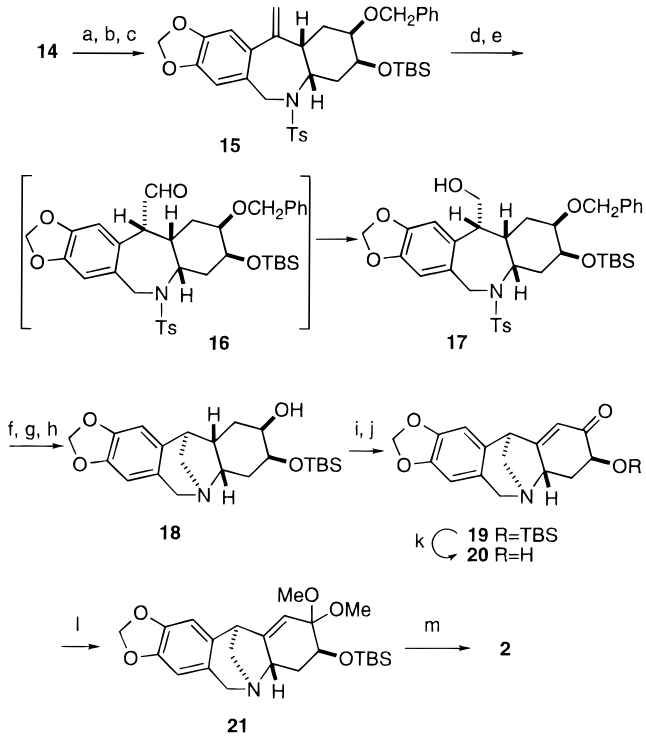


ene reaction, but this has no consequence for the synthesis since both lead to the same stereoisomeric cyclization product **14**.

To continue the synthesis, alkyne **14** was partially hydrogenated using Lindlar catalyst to generate the terminal olefin. We were pleased to find that this bromo alkene cyclizes under Heck conditions[12] to form the desired exocyclic seven-membered ring alkene, subsequently *N*-protected as the sulfonamide **15** (Scheme 3). A number of attempts were made to hydroborate **15** to produce the corresponding α-hydroxymethyl compound, but in general, these reactions produced mixtures of the α- and *β*-stereoisomers. An alternative strategy for stereoselectively functionalizing the exocyclic methylene group was explored using a sequence applied by Danishefsky and McClure in the FR 900482 system.[13] Therefore, oxidation of **15** was effected with dimethyldioxirane[14] to yield a 2:1 mixture of stereoisomeric epoxides. Exposure of this epoxide mixture to anhydrous ferric chloride at low temperature led to aldehyde **16**, which was immediately reduced[15] with DIBALH to afford α-hydroxymethyl compound **17** as a single stereoisomer. It seems probable that this transformation occurs via initial epoxide opening to a benzylic carbonium ion which subsequently undergoes a highly stereoselective 1,2-hydride migration from the less congested convex face of the molecule.

The *O*-benzyl group of **17** was removed by hydrogenolysis, followed by *N*-tosyl group cleavage to give an amino diol which could be efficiently cyclized in a single step by treatment with triphenylphosphine/iodine[16] to yield the desired pentacyclic alcohol **18**. This compound was then oxidized to the ketone, converted to a TMS enol ether under kinetically controlled conditions,[17] and dehydrogenated by the Saegusa methodology[18]

Scheme 3[a]



[a] (a) Lindlar catalyst, H_2, quinoline, MeOH, 93%; (b) $Pd(PPh_3)_4$, TEA, MeCN, Me_3BuNCl, 120 °C, 74%; (c) TsCl, pyr, DMAP, 100 °C, 92%; (d) Me_2CO_2; Me_2CO, −20 °C, 89%; (e) $FeCl_3$, CH_2Cl_2, −78 °C/DIBALH, 88%; (f) H_2, 10% Pd−C, MeOH; (g) Na, naphthalene, DME, −78 °C; (h) PPh_3, I_2, imidazole, Et_2O, MeCN, 0 °C, 82% from **18**; (i) TPAP, NMO, CH_2Cl_2, 96%; (j) LDA, TMSCl, THF, −78 °C/$Pd(OAc)_2$, MeCN, rt, 81%; (k) TBAF, THF, 0 °C−rt, 98%; (l) $(MeO)_3CH$, MeOH, *p*-TsOH, rt, 91%; (m) DIBALH, PhMe, rt, 81%.

to afford enone **19**. Removal of the TBS group of **19** led to hydroxy enone **20**, having ^1H and ^{13}C NMR spectra identical with those of material prepared by Overman and Shim,[4,19] which they found could be reduced to (−)-pancracine (**3**) with sodium triacetoxyborohydride. In addition, it was possible to convert enone **19** to the dimethyl ketal **21**, which upon treatment with DIBALH[5] underwent reduction and cleavage of the TBS group to afford (−)-coccinine (**2**) having a ^1H NMR spectrum identical with that of authentic alkaloid.[20−22]

Acknowledgment. We thank the National Institutes of Health (CA-34303) for generous support of this research and Dr. Stephen P. Fearnley and Professor R. L. Funk for helpful discussions.

Supporting Information Available: Spectral data and experimental procedures for synthesis of all new compounds (20 pages). See any current masthead page for ordering and Internet access instructions.

JA963900H

(12) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) *Cf.*: Cornec, O.; Joseph, B.; Merour, J. *Tetrahedron Lett.* **1995**, *36*, 8587.
(13) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094.
(14) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
(15) Aldehyde **16** epimerizes readily to the more stable *β*-stereoisomer upon attempted chromatographic purification.
(16) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.
(17) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
(18) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(19) We thank Professor Larry Overman for ^1H and ^{13}C NMR spectra of intermediate **20** and a sample of (−)-pancracine.
(20) We are grateful to Professor O. Hoshino for the ^1H NMR spectra of racemic montanine, coccinine and some synthetic intermediates.
(21) A small amount (<10%) of montanine (**1**) is also produced in this reaction, possibly due to silyl group cleavage prior to hydride reduction of the ketal. DIBALH reduction of the hydroxy ketal corresponding to **21** affords about a 1:1 mixture of coccinine (**2**) and montanine (**1**).
(22) Presented at the 212th National Meeting of the American Chemical Society, Orlando, FL, August 25, 1996; ORGN 47.