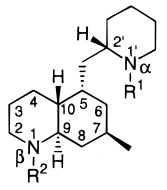
Asymmetric Synthesis of the *Lycopodium* Alkaloid, N_a-Acetyl-N_b-methylphlegmarine

Daniel L. Comins,* Adam H. Libby,
Rima S. Al-awar, and Christopher J. Foti

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

Received February 2, 1999

The plentiful and structurally interesting *Lycopodium* alkaloids provide challenging targets for total synthesis.[1] The phlegmarines are a $C_{16}N_2$ skeletal group of *Lycopodium* alkaloids discovered by Braekman and co-workers in 1978.[2] The members of this group (**1a**−**d**) differ from one another by their substituent pattern on the two nitrogen atoms. Unlike most other perhydroquinoline containing *Lycopodium* alkaloids, the phlegmarines possess a *trans*-decahydroquinoline unit in their skeleton rather than the usual cis arrangement. Racemic N_α-methyl-N_β-acetylphlegmarine (**1e**) was



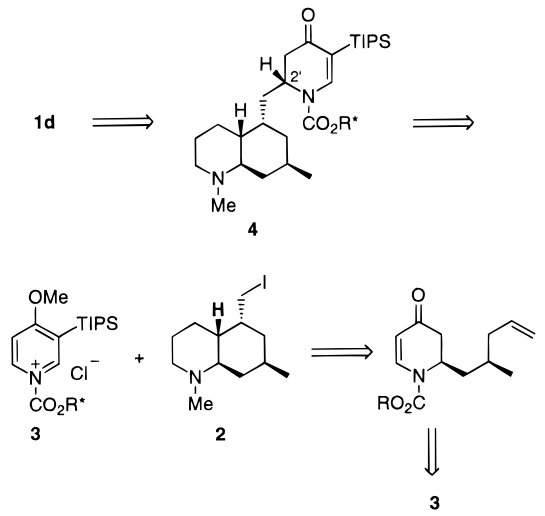
1a:	R^1= H, R^2= H	phlegmarine
b:	R^1= H, R^2= Me	N_β-methylphlegmarine
c:	R^1= Me, R^2= H	N_α-methylphlegmarine
d:	R^1= COMe, R^2= Me	N_α-acetyl-N_β–methylphlegmarine
e:	R^1= Me, R^2= COMe	N_α-methyl-N_β–acetylphlegmarine

synthesized by MacLean and co-workers, an accomplishment that defined the relative stereochemistry of the phlegmarines.[3] The absolute sense of chirality of the phlegmarine alkaloids had not been determined. We now report the first asymmetric synthesis of a naturally occurring phlegmarine alkaloid, (−)-N_α-acetyl-N_β-methylphlegmarine (**1d**).

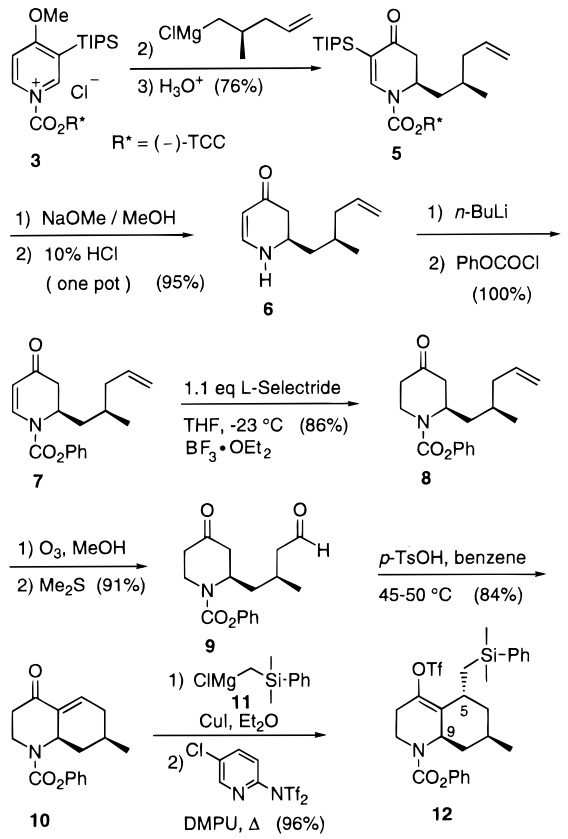
Our synthetic plan followed the retrosynthetic analysis depicted in Scheme 1. The strategy involves enantioselective preparation of key fragment **2**, which after conversion to an organometallic is added to chiral 1-acylpyridinium salt **3** to give phlegmarine precursor **4** with control of stereochemistry at C-2′. We chose the enantiomer depicted in structure **1d** as our target based on analogy to other related *Lycopodium* alkaloids, i.e., lycodine, of known absolute stereochemistry.[1b]

The Grignard of (*R*)-5-chloro-4-methylpentene[4] was added to chiral 1-acylpyridinium salt **3**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[5] and the chloroformate of (−)-*trans*-2-(α-cumyl)-cyclohexanol (TCC),[6] to give the crude *N*-acyldihydropyridone **5** in 90% yield and 88% de (Scheme 2). Purification by recrystallization from ethanol provided a 76% yield of the major diastereomer **5** as a white solid. A one-pot reaction of **5** with NaOMe/MeOH followed by aqueous 10% HCl furnished dihydropyridone **6** in 95% yield with 95% recovery of the chiral auxiliary, (−)-TCC. N-Acylation of **6** with *n*-BuLi and phenyl chloroformate gave

Scheme 1



Scheme 2



(1) (a) Ayer, W. A.; Trifonov, L. S. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: San Diego, 1994; Vol. 45, pp 233−274. (b) Blumenkopf, T. A.; Heathcock, C. H. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 185−240. (c) Schumann, D.; Naumann, A. *Liebigs Ann. Chem.* **1984**, 1519. (d) Szychowski, J.; MacLean, D. B. *Can. J. Chem.* **1979**, *57*, 1631. (e) Tori, M.; Shimoji, T.; Takaoka, S.; Nakashima, K.; Sono, M.; Ayer, W. A. *Tetrahedron Lett.* **1999**, *40*, 323.

(2) Nyembo, L.; Goffin, A.; Hootele, C.; Braekman, J.-C. *Can. J. Chem.* **1978**, *56*, 851.

(3) (a) Leniewski, A.; Szychowski, J.; MacLean, D. B. *Can. J. Chem.* **1981**, *59*, 2479. (b) Leniewski, A.; MacLean, D. B.; Saunders, J. K. *Ibid.* **1981**, *59*, 2695.

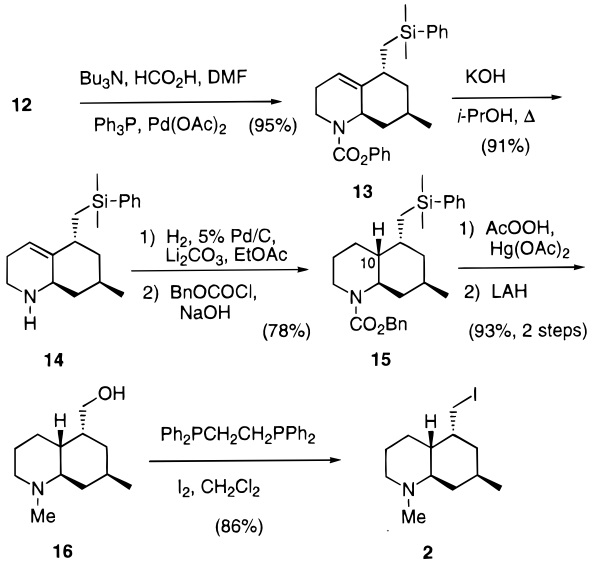
(4) The chloride was prepared (NCS, Ph_3P, CH_2Cl_2) from the known enantiopure alcohol; see: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(5) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

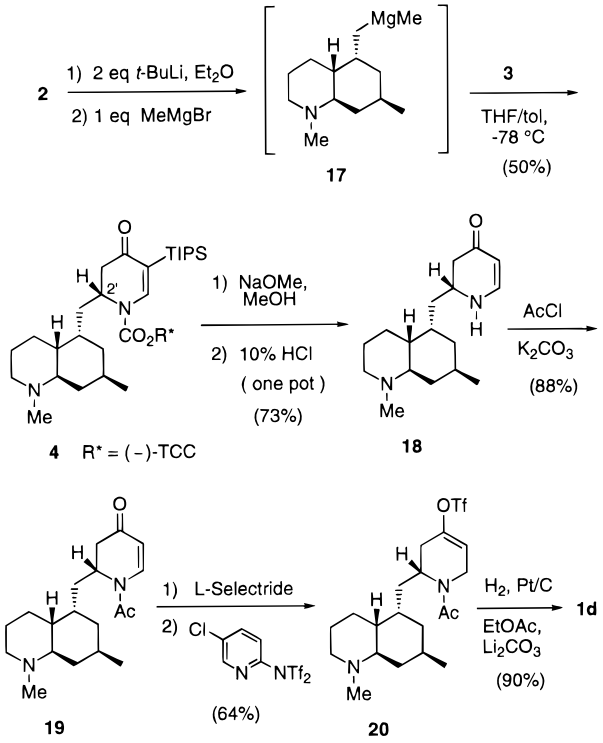
(6) (a) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. (b) The (+)- and (−)-TCC alcohols are available from Aldrich Chemical Co.

10.1021/jo990192k CCC: $18.00
Published on Web 03/06/1999

Scheme 3



Scheme 4



a quantitative yield of enantiopure carbamate **7**. Conjugate reduction of the endocyclic double bond with L-Selectride in the presence of $BF_3{\cdot}OEt_2$ afforded ketone **8** in 86% yield. In the absence of $BF_3{\cdot}OEt_2$, a significant amount of 1,2-reduction was observed.[7] Ozonolysis of the teminal alkene of **8** provided a 91% yield of aldehyde **9**, which underwent an acid-mediated cyclization to the bicyclic enone **10** (84%).

The copper-mediated reaction of Grignard **11** with enone **10** and enolate trapping with *N*-5-(chloro-2-pyridyl)triflimide[8] gave a high yield (96%) of **12** with complete stereoselectivity. The selectivity was anticipated on the basis of model studies that indicated stereoelectronically controlled axial attack at C-5 would occur.[9] The vinyl triflate was smoothly reduced to alkene **13** in 95% yield using Cacchi's procedure[10] (Scheme 3). Hydrolysis of the carbamate group in **13** was effected with KOH in refluxing 2-propanol to provide amine **14** in 91% yield. Hydrogenation of **14** gave a mixture of crude amines that were isolated as carbamate derivative **15** and the corresponding cis C-10 epimer. HPLC analysis of this mixture showed a ratio of 89/11 favoring the trans diastereomer **15**. The trans selectivity is due to significant shielding of the bottom face of the alkene in **14** by the axial (phenyldimethylsilyl)methyl group. Purification by chromatography provided a 78% yield of pure **15**. Oxidation of the phenyldimethylsilyl group using Fleming's procedure[11] and subsequent reduction with lithium aluminum hydride gave amino alcohol **16** (93%), which was converted to the iodide **2** (86%) on treatment with 1,2-bis(triphenylphospino)ethane tetraiodide.[12] Organometallics prepared from **2** (R−MgX, R−Li, R−CuX) were added to 1-acylpyridinium salt **3** with little or no success (0−13% yield).[13] After several attempts, the mixed Grignard reagent **17** and 2 equiv of **3** afforded the desired dihydropyridone **4** in moderate yield (50%, Scheme 4) along with the corresponding methyl addition product (50%).[14] A single-crystal X-ray structure of **4** confirmed that all five stereogenic centers were correctly installed with respect to the target alkaloid. One-pot removal of the TIPS group and TCC auxiliary provided a 73% yield of dihydropyridone **18**, which was acylated to give **19** (88%). The synthesis was completed by formation of vinyl triflate **20**[8a] and subsequent catalytic reduction (90%) to provide N_α-acetyl-N_β-methylphlegmarine (**1d**), which exhibited spectral data in agreement with reported data for authentic material.[2,3] The optical rotation [$[\alpha]_D$ −18.5 (*c* 0.33, $CHCl_3$)] is also in agreement with the literature value [$[\alpha]_D$ −11 (*c* 0.7, $CHCl_3$)].[2]

In summary, the first asymmetric synthesis of a phlegmarine alkaloid, (−)-N_α-acetyl-N_β-methylphlegmarine (**1d**), has been accomplished in 18 steps with a high degree of stereocontrol.[15] Our asymmetric synthesis of **1d** has established the absolute stereochemistry of this alkaloid as 2′*S*,5*S*,7*R*,9*R*,10*R*. The stereochemical relationship (5*S*,7*R*,-10*R*) corresponds to several other *Lycopodium* alkaloids. This determination strengthens the postulate that phlegmarine may serve as an intermediate for the biosynthesis of a variety of related *Lycopodium* compounds.[2]

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research. R.A. also thanks the Burroughs Wellcome Fund for a graduate fellowship. We are grateful to Dr. J.-C. Braekman for copies of a mass spectrum and an ^{1}H NMR spectrum of natural N_α-acetyl-N_β-methylphlegmarine. NMR and mass spectra and X-ray analysis of **4** were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grant CHE-9121380, CHE-9509532).

Supporting Information Available: Experimental procedures and spectroscopic data for **1d**, **2, 4, 5**−**10**, **12**−**16**, and **18**−**20**, ^{1}H and/or ^{13}NMR spectra of **1d, 2, 4, 6**, **9**, **14**−**16**, and **18**−**20**, and X-ray data of compound **4**.

JO990192K

(7) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053.
(8) (a) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299. (b) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1996**, *74*, 77.
(9) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1995**, *60*, 711.
(10) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821.
(11) Fleming, I.; Sanderson, P. E. *Tetrahedron Lett.* **1987**, *28*, 4229.
(12) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *28*, 767.
(13) Comins, D. L.; Foti, C. J.; Libby, A. H. *Heterocycles* **1998**, *48*, 1313.
(14) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990,** *55*, 2574.
(15) The structure assigned to each new compound is in accord with its IR, ^{1}H and ^{13}C NMR spectra, and elemental analysis or high-resolution mass spectra.