ORGANIC LETTERS

2001
Vol. 3, No. 20
3217−3220

Model Studies toward the Total Synthesis of the *Lycopodium* Alkaloid Spirolucidine

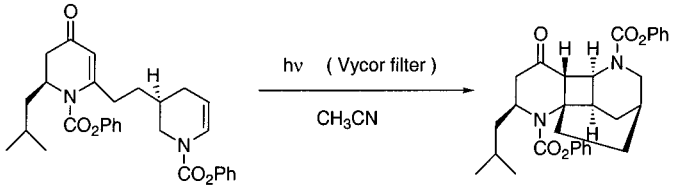
Daniel L. Comins* and Alfred L. Williams

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

daniel_comins@ncsu.edu

Received August 9, 2001

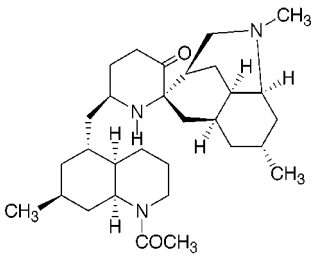
ABSTRACT



4a 17

A strategy for the synthesis of the spirocyclic core of spirolucidine was explored through a model study. The diene 4a was prepared and photolyzed to give the desired [2 + 2] photoadduct 17 containing the correct relative stereochemistry corresponding to spirolucidine.

Spirolucidine (**1**) was isolated from *Lycopodium lucidulum* by Ayer and co-workers, and the relative stereochemistry of the alkaloid was determined by chemical, spectroscopic, and X-ray studies.[1] No biological or synthetic studies have been previously reported on this complex natural product. As part of our program directed at developing *N*-acyl-2,3-dihydro-4-pyridones as chiral building blocks for alkaloid synthesis,[2,3] we have been exploring strategies for the construction of spirolucidine. Herein is reported a model study of a photochemical approach to the spirocyclic core of **1**.

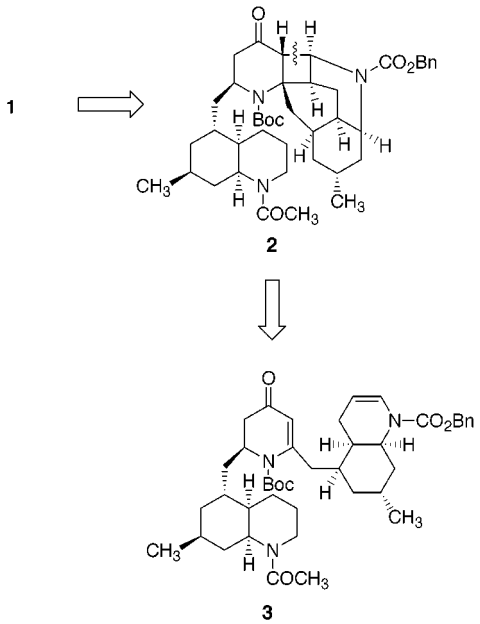


1

spirolucidine

One potential route to **1** involves the preparation and cyclobutane ring opening of intermediate **2**, which would arise from an intramolecular [2 + 2] photocyclization of dihydropyridone **3** (Scheme 1). To determine the feasibility

Scheme 1



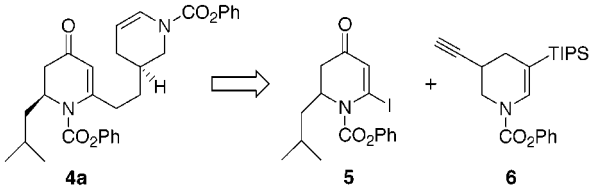
2 **3**

10.1021/ol016556o CCC: $20.00
Published on Web 09/11/2001

of the key photocyclization step, a model study was carried out.

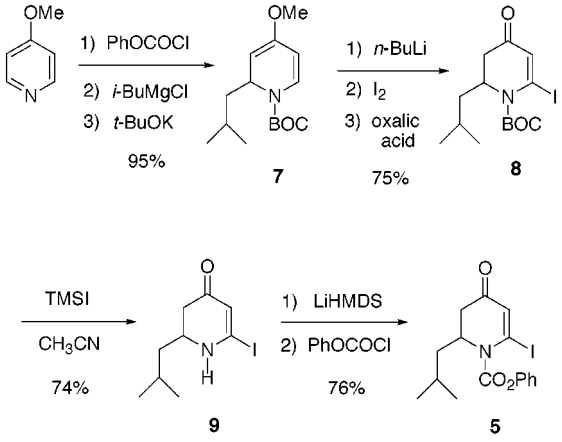
Dihydropyridone **4a** was chosen as a model photosubstrate that would mimic **3** in the photocycloaddition step. The synthesis of **4a** was accomplished by the coupling of 6-iodo-2,3-dihydro-4-pyridone **5** with alkyne **6** followed by selective reduction and desilylation (Scheme 2).

Scheme 2



Intermediate **5** was prepared using 1-acylpyridinium salt chemistry.[2] Treatment of 4-methoxypyridine with phenyl chloroformate and isobutylmagnesium chloride provided a crude 1-phenoxycarbonyl-1,2-dihydropyridine that was converted to the Boc derivative **7** with *t*-BuOK in THF.[4a] The overall yield for the two-step process was 95% (Scheme 3).

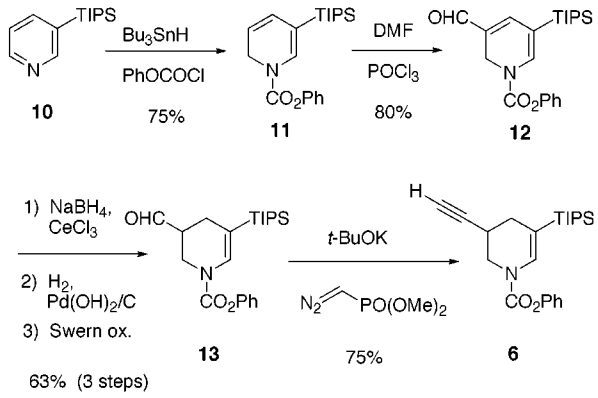
Scheme 3



Directed lithiation of dihydropyridine **7** with *n*-BuLi, addition of iodine, and workup with oxalic acid afforded the 6-iodo-2,3-dihydro-4-pyridone **8** in 75% yield. A carbamate exchange[4b] was effected in two steps by removal of the *N*-Boc group with TMSI to give **9**. Deprotonation and reacylation with phenyl chloroformate provided intermediate **5**.

The alkyne **6** was prepared as depicted in Scheme 4. The silylpyridine **10** was prepared from 2-chloropyridine in two

Scheme 4



steps as previously described.[5] Regioselective reduction of **10** with phenyl chloroformate and tributyltin hydride[6] provided a 75% yield of the 1,2-dihydropyridine **11**. The next step in the synthesis required a regioselective functionalization at C-3 of **11**. The Vilsmeier−Haack reaction afforded the desired aldehyde **12** in 80% yield. In the absence of a C-5 TIPS group, this type of 1,2-dihydropyridine formylates regioselectively at C-5.[5,7] Luche reduction of the aldehyde, regioselective catalytic hydrogenation of the 3,4-double bond, and Swern oxidation provided aldehyde **13**. The desired alkyne intermediate **6** was prepared by adding **13** to the Seyfert−Gilbert reagent[7] and *t*-BuOK in THF at −78 °C.

The two heterocycles, **5** and **6**, were joined using a Sonogashira reaction.[9] In the presence of palladium(II) iodide, triphenylphosphine, and copper(I) iodide, cross-coupling occurred to give an 87% yield of diastereomers **14** (Scheme 5). With the TIPS group still protecting its appended double bond, chemoselective reduction of the alkyne could be carried out. Catalytic hydrogenation of **14** gave dihydro-

(1) Ayer, W. A.; Ball, L. F.; Browne, L. M.; Tori, M.; Delbaere, L. T. J.;Silverberg, A. *Can. J. Chem.* **1984**, *62*, 298.

(2) (a) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press Inc.; Greenwich, CT, 1996; Vol. 2, pp 251−294. (b) Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; McKillop, A., Ed.; Pergamon Press: Oxford, England, 1996; Vol. 5, pp 37−89.

(3) For recent and leading references, see: (a) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248. (b) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435. (c) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182. (d) Comins, D. L.; Green, G. M. *Tetrahedron Lett.* **1999**, *40*, 217. (e) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184. (f) Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229. (g) Comins, D. L.; Zhang, Y.; Joseph, S. P. *Org. Lett.* **1999**, *1*, 657. (h) Comins, D. L.; Fulp, A. B. *Org. Lett.* **1999**, *1*, 1941. (i) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855. (j) Huang, S.; Comins, D. L. *J. Chem. Soc., Chem. Commun.* **2000**, *7*, 569. (k) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001**, *3*, 469. (l) Comins, D. L.; Sandelier, M. J.; Abad Grillo, T. *J. Org. Chem.* In press.

(4) (a) Comins, D. L.; Weglarz, M. A.; O'Connor, S. *Tetrahedron Lett.* **1988**, *29*, 1751. (b) The *N*-Boc group was necessary to effect the directed lithiation of **7**; however, subsequent carbamate exchange, **8** → **5**, was needed to provide easily purified intermediates and crystalline photocycloaddition products.

(5) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292.

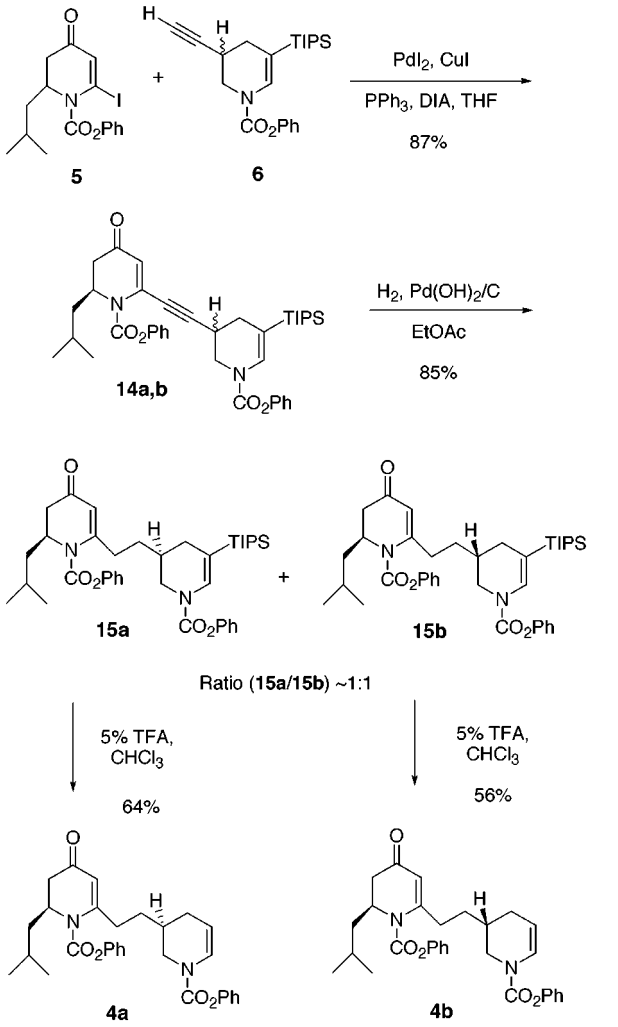
(6) Tributyltin hydride has been used to reduce *N*-acylisoquinolinium salts to dihydroisoquinolines, see: Yamaguchi, R.; Hamasaki, T.; Utimoto, K. *Chem. Lett.* **1988**, 913.

(7) (a) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732. (b) Comins, D. L.; Herrick, J. J. *Heterocycles* **1987**, *26*, 2159.

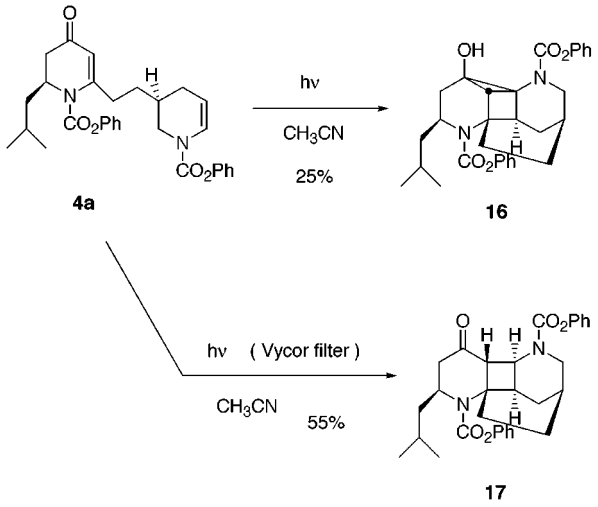
(8) (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *48*, 4155. (b) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.

(9) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 2.4.

Scheme 5



Scheme 6



pyridones **15a** and **15b** which were separated by radial PLC (silica gel, EtOAc/hexanes). The TIPS group was now removed with TFA/$CHCl_3$ to afford the corresponding intermediates **4a** and **4b** in 64% and 56% yields, respectively. The stereochemical assignments for diastereomers **15** and **4** were tentative initially, but they were confirmed through the results obtained from the subsequent photochemical studies.[10]

Irradiation of photosubstrate **4a** in acetonitrile (450-W Hanovia Hg lamp, 8 h)[11] gave a 25% yield of a white solid, mp 125−6 °C (Scheme 6). Single-crystal X-ray analysis showed that the photocycloaddition did not proceed to give the desired product but instead provided the pentacyclic cyclopropanol **16**. Examination of the literature indicated that the cyclopropane ring formation probably resulted from a secondary photoinitiated reaction on the primary adduct.[12]

In an attempt to prevent the secondary cyclization, the photocycloaddition was repeated using a Vycor filter (>210 nm). After 2 h, the starting material was gone, and only one product was observed by TLC. Chromatographic purification afforded a 55% yield of the photoadduct as a white solid, mp 152−3 °C. Single-crystal X-ray analysis confirmed that the reaction proceeded in the desired manner with complete control of stereochemistry to provide tetracyclic ketone **17**. The observed facial selectivity was anticipated on the basis of our earlier photochemical studies of 2,3-dihydro-4-pyridones.[13] Due to $A^{(1,3)}$ strain, the isobutyl group of **4a** occupies an axial orientation, and cyclization takes place on the more accessible alkene face opposite the large C-2 substituent.

This successful model study lends credence to our proposed plan for the total synthesis of spirolucidine (**1**). Although the cyclobutane cleavage of **17** was not investigated, the required regioselective ring opening of similar ring systems has been carried out in our laboratories.[13] Further synthetic studies toward **1** are underway and will be reported in due course.[14]

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research. A.W. also thanks the NIH for a

(10) Under the conditions used for the photocyclization of **4a**, irradiation of **4b** gave only recovered starting material.

(11) For recent reviews of [2 + 2] photocycloaddition, see: (a) Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3−22. (b) De Keukeleire, D.; He, S.-L. *Chem. Rev.* **1993**, *93*, 359−380. (c) Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297−588. (d) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003−2020.

(12) Related photochemical cyclopropanol syntheses have been reported, see: (a) Henning, H. G.; Haber, H.; Buchholz, H. *Pharm.* **1981**, *36*, 160. (b) Henning, H. G.; Berlinghoff, R.; Hahlow, A.; Koeppl, H. *J. Prakt. Chem.* **1981**, *323*, 914. (c) Wyss, C.; Batra, R.; Lehmann, C.; Sauer, S.; Giese, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2529. (d) Sauer, S.; Schumacher, A.; Barbosa, F.; Giese, B. *Tetrahedron Lett.* **1998**, *39*, 3685. (e) Boyle, P. H.; Nelson, P. H.; Sunder-Plassmann, P.; Crabbe, P.; Edwards, J. A.; Green, D.; Iriarte, J.; Murphy, J. W.; Zderic, J.; Fried, J. H. *Proc. Int. Symp. Drug Res.* **1967**, 206−16.

(13) (a) Comins, D. L.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1994**, 2681. (b) Comins, D. L.; Lee, Y. S.; Boyle, P. D. *Tetrahedron Lett.* **1998**, *39*, 187. (c) Comins, D. L.; Zhang, Y.-M.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1998**, 2509.

(14) The structure assigned to each new compound is in accordance with its IR, ^1H NMR, and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra.

Minority Graduate Research Assistantship. The authors thank Dr. Paul Boyle for X-ray crystallographic analyses of **16** and **17**. NMR and mass spectra and X-ray data were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grants CHE-9509532, CHE-0078253, CHE-9509532).

Supporting Information Available: Characterization data for compounds **4**−**6**, **8**−**9**, and **11**−**17**, ^{1}H and ^{13}C NMR spectra of **4**−**6**, **13**, **16**, and **17**, and ORTEP plots and X-ray crystal data (cif format) for **16** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016556O