Carbocyclic Ring Construction via an Intramolecular Diels-Alder Reaction of an *in Situ*-Generated, Heteroatom-Stabilized Allyl Cation: Total Synthesis of (±)-Lycopodine

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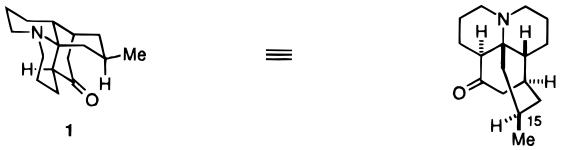
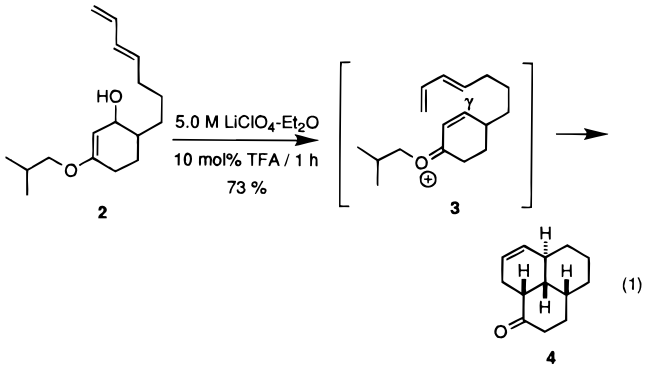
Since the first total synthesis of (±)-lycopodine (**1**) in 1968,[1] **1** has served as an extremely useful target in the development of new regio- and stereochemically controlled synthetic processes.[2] Our particular interest in **1** stems, in part, from our recently described protocol for the construction of carbocyclic systems



via intramolecular ionic Diels−Alder reactions of in situ-generated heteroatom-stabilized allyl cations (cf. **3**) in polar media (eq 1).[3]

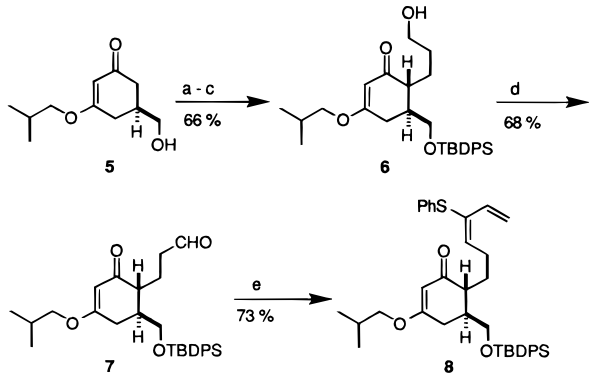


(1)

The usefulness of such a cycloaddition reaction in the elaboration of highly structured carbocyclic systems raised the question whether this particular methodology could be extended to generate quaternary carbon atoms by incorporating substituents at the γ carbon atom of an allyl cation (cf. **3**). We detail below a total synthesis of (±)-lycopodine which features the following: (1) a [4 + 2] cycloaddition of a heteroatom-stabilized allyl cation leading to the formation of a tricyclic ketone possessing not only the quaternary carbon atom of **1** but all the necessary carbon atoms needed for elaboration of **1**, (2) radical cyclization leading to the exclusive formation of the correct stereocenter at C(15), and (3) a Stieglitz rearrangement to establish the bridgehead nitrogen.

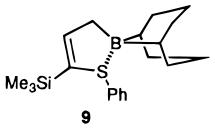
The required vinylogous ester **8**, needed for the preparation of **10** and its subsequent conversion into tricyclic ketone **12**, was synthesized as outlined in Scheme 1 commencing with the known vinylogous ester **5**.[4] Protection of the hydroxymethyl group in **5** followed by alkylation and cleavage of the trimethylsilyl ether

Scheme 1



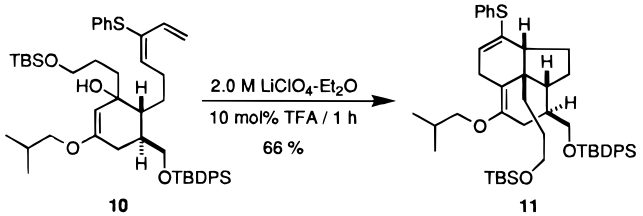
[a] (a) 1.0 equiv of TBDPSCl, 2.0 equiv of imidazole, CH_2Cl_2, 0 °C → room temperature (13 h); (b) 1.2 equiv of LDA, THF, −78 °C; 1.0 equiv of $ICH_2CH_2CH_2OTMS$, HMPA, −78 °C → −20 °C (12 h); (c) 5.0 mol % K_2CO_3, MeOH, 0 °C, 1 h; (d) 1.2 equiv of *t*-BuOMgBr, THF, 20 min; 1.2 equiv of ADDP, THF, −78 °C → room temperature (6 h); (e) 1.1 equiv of **9**, THF, 0 °C → room temperature (5.5 h); 4.0 N aqueous NaOH, 4 h.

led directly to alcohol **6,** which upon oxidation[5] provided aldehyde **7**. Condensation of **7** with Pearson's allylborane **9** (generated in



situ from 1-phenylthio-1-trimethylsilyl allene and 9-borabicyclo-[3.3.1]nonane)[6] gave rise to the corresponding β-boron oxysilane, which upon exposure to 4.0 N sodium hydroxide provided the *E*-diene **8**.

With vinylogous ester **8** in hand, the lithio reagent[7] (3.5 equiv), prepared from 3-bromo-1-*tert*-butyldimethylsilyloxypropane, was added to a solution of **8** in tetrahydrofuran cooled to −78 °C giving rise to an 80% yield of **10.** Exposure (1 h) of **10** to 10 mol % trifluoroacetic acid in 2.0 M $LiClO_4$−Et_2O provided tricyclic enol ether **11** in 66% yield. Cleavage (1.0 N HCl, THF, 9 h) of the enol ether followed by equilibration (K_2CO_3, MeOH, 16 h) gave rise to **12**, as the sole product, in 87% yield.[8] Note that in the cycloaddition process the formation of **11** from the *E*-diene **10** proceeds exclusively via an exo transition state.[9]



(1) (a) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647. (b) Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. *J. Am. Chem. Soc*. **1968**, *90*, 1648.

(2) (a) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, *126*, 1054. (b) Schumann, D.; Muller, H.-J.; Naumann, A. *Liebigs Ann. Chem*. **1982**, 1700. (c) Wenkert, E.; Broka, C. A. *J. Chem. Soc., Chem. Commun*. **1984**, 714. (d) Kraus, G. A.; Hon, Y.-S. *J. Am. Chem. Soc*. **1985**, *107*, 4341.

(3) (a) Grieco, P. A.; Kaufman, M. D.; Daeuble, J. F.; Saito, N. *J. Am. Chem. Soc*. **1996**, *118*, 2095. (b) For the cycloaddition of allyl cations to 1,3-dienes, see: Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc*. **1984**, *106*, 6085.

(4) Nishikawa, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 5621.

(5) Narasaki, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 2773.

(6) Pearson, W. H.; Lin, K.-C.; Poon, Y.-F. *J. Org. Chem*. **1989**, *54*, 5814.

(7) Prepared by treatment of 3-bromo-1-*tert*-butyldimethylsilyloxypropane [Kuo, D. L.; Money, T. *Can. J. Chem.* **1988**, *66*, 1794] with 3.0 equiv of lithium *p*, *p*′-di-*tert*-butylbiphenylide [Cohen, T.; Doubleday, M. D. *J. Org. Chem*. **1990**, *55*, 4784] in tetrahydrofuran at −78 °C.

(8) Exclusive formation of **12** after equilibration is not surprising since MMX calculations indicate **12** is more stable than the corresponding C(4) epimeric compound by 2.0 kcal. When allyl was employed in place of the alkoxypropyl group, complex mixtures were obtained during the cycloaddition process.

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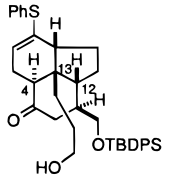
With the stereochemistry at C(4), C(12), and C(13) secure (cf. **12**), efforts were directed at elaboration of the remaining stereocenter at C(15). Toward this end, **12** was transformed [*o*-O_2N-C_6H_4SeCN, Bu_3P, THF, 13 h; 30% H_2O_2, THF, room temperature],[10] in straightforward fashion, into olefin **13** in 60%



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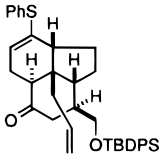

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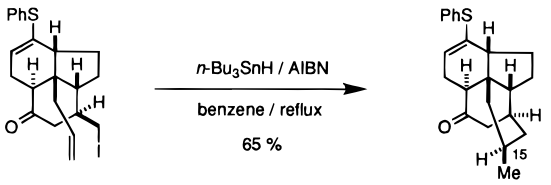
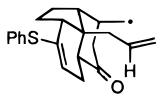
overall yield. Deprotection (TBAF, THF) of the *tert*-butyldiphenylsilyl ether provided the corresponding alcohol, which was transformed (MsCl, Et_3N, CH_2Cl_2, 0 °C; NaI, acetone, reflux) in 80% yield into iodide **14**, mp 106−107 °C. Subjection of iodide **14** to radical cyclization conditions (2.3 equiv of *n*-Bu_3SnH, AIBN, benzene, reflux)[11] gave rise (65%) to **15** as the major product. The C(15) epimeric compound could not be detected.[12] The exclusive formation of the correct stereoisomer at C(15) undoubtedly arises from the lowest energy transition state **16**.[13]

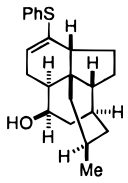


14 **15**



16

With the availability of tetracyclic ketone **15**, it remained only to introduce a nitrogen atom into the all carbon backbone of **15**. Reduction (5.0 equiv of of Li(*t*-BuO)$_3$AlH, THF, 12 h, 0 °C → room temperature) of **15** provided (90%) alcohol **17**, which upon acetylation (Ac_2O, DMAP, CH_2Cl_2, 19 h) and subsequent hydrolysis of the thioenol ether (3.0 equiv of NaI, 2.0 equiv of $HgCl_2$, 3.0 equiv of TMSCl, 3.0 equiv of H_2O, CH_3CN, 2 h) gave rise (70% overall) to crystalline tetracyclic ketone **18**,[14] mp 139−140 °C.



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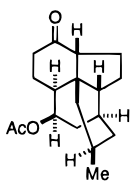
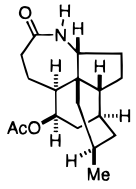


18

The availability of **18** set the stage for sequential oxime formation followed by Beckmann rearrangement. Exposure of **18** to 2.0 equiv of hydroxylamine hydrochloride in ethanol containing 5.0 equiv of sodium acetate provided a quantitative yield of a 1.6:1 mixture of oximes which could be readily separated on silica gel.[15] Upon treatment of the major *anti*-oxime, mp 157−158 °C, with thionyl chloride in dioxane (10 °C, 40 min) lactam **19,** mp 215−216 °C, was isolated in 65% yield. Reduction [12.0 equiv of Red-Al, benzene, room temperature (30 min) → reflux (3.5 h)] of **19** provided (80%) the secondary amine



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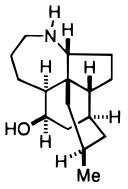

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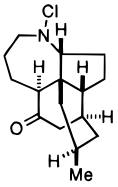

21

20, mp 207−208 °C, which, in a one-pot operation, was chlorinated and oxidized [1.1 equiv of NCS, CH_2Cl_2, 0 °C (30 min) → room temperature (30 min); 1.5 equiv of TPAP,[16] 30 min], giving rise to **21**, 80.5−81.5 °C, in 50% overall yield. Subjection of the *N*-chloro amine **21** to a Stieglitz rearrangement[17] ($AgBF_4$, benzene, 3.5 h) and subsequent reduction ($NaCNBH_3$, MeOH) provided (±)-lycopodine [**1**, mp 130−131 °C (lit.[1a] mp 130−131 °C)] in 46% yield. Synthetic racemic lycopodine was identical (IR, ^{1}H NMR, ^{13}C NMR, and MS) in all respects with a sample of synthetic lycopodine kindly supplied by Professor Heathcock.

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Supporting Information Available: Spectral data (IR, ^{1}H NMR, ^{13}C NMR, MS) for compounds **6**−**8**, **12**−**14**, and **17**−**21** (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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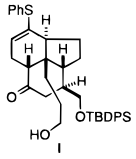
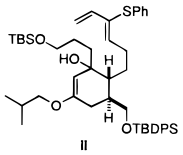
(9) During the course of the cycloaddition reaction, ca. 20% of tricyclic ketone **i** was obtained after cleavage of the corresponding enol ether and equilibration. The formation of **i** from **10** arises via isomerization of the *E*-diene to the *Z*-diene **ii** followed by cycloaddition via an exo transition state. Note that **i** possesses the undesired stereochemistry adjacent to the carbonyl.



i

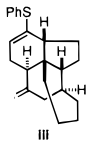


ii

(10) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(11) For a review on radical cyclizations see: Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, pp 715−772.

(12) In addition to the major product **15**, the seven-membered compound **iii** was isolated in 13% yield along with the reduced compounds **iv** (3%) and **v** (3%).



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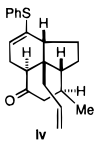

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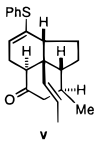

v

(13) Note that placing the terminal olefin in a equatorial-like orientation leads to the observed product. In contrast, adopting an axial-like arrangement leads to very serious steric interactions. Of the two possible boatlike transition states, the one of lowest energy would lead to the undesired stereochemistry at C(15). See: Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.

(14) The structure of **18** was confirmed by single-crystal X-ray analysis. Ketone **18** crystallized in a monoclinic space group *C*2/*c* with cell dimensions (at −165 °C) of a = 12.936(4) Å, b = 16.432(4) Å, c = 15.674(4) Å, and β = 113.63(1) Å. Calculated density ρ = 1.264 g/cm^{-3} (for Z = 8). Data were collected with use of a standard moving crystal-moving detector technique with fixed backgrounds at each extreme of the scan. Data were corrected for Lorentz and polarization effects and equivalent reflections were then averaged. The structure was readily solved with direct methods (MULTAN78) and Fourier techniques. For more information, contact Dr. John C. Huffman, Indiana University, Department of Chemistry, Molecular Structre Center, Bloomington, IN 47405, Report No. 97032.

(15) Upon standing in chloroform, the minor unwanted *syn*-oxime [R_f 0.3 (hexanes−ethyl acetate, 2:1), mp 163−164 °C] equilibrated to the desired *anti*-oxime, R_f 0.4.

(16) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(17) (a) Stieglitz, J.; Vosburgh, I. *J. Am. Chem. Soc.* **1916**, *38*, 2081. (b) Gassman, P. G.; Fox, B. L. *J. Am. Chem. Soc.*, **1967**, *89*, 338. (c) Schell, F. M.; Ganguly, R. N. *J. Org. Chem.* **1980**, *45*, 4069.