Natural Products Synthesis

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Polycyclic Molecules from Linear Precursors: Stereoselective Synthesis of Clavolonine and Related Complex Structures**

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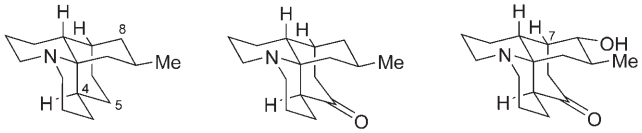
At the time of this publication, over 100 lycopodium alkaloids have been isolated.[1] The 16-carbon-atom-containing lycopodium alkaloid family features a variety of polycyclic ring sizes, stereochemistry, and oxidation patterns. The classic tetracyclic skeleton of the lycopodane family has a rich history in organic chemistry and has been a proving ground for new approaches to the synthesis of polycyclic alkaloid targets.[2] Despite the number of research groups that have contributed to the synthesis of this family of alkaloids, all have proceeded in a linear fashion from cyclic starting materials.

The structure of lycopodine provides an instructive model to explore a strategy centered on 1) a convergent synthesis of a linear precursor that contains the complete carbon backbone and 2) the incorporation of a reaction cascade sequence to construct the remaining carbon–carbon bonds. In this study, we pursued the synthesis of clavolonine (**2**), which was



lycopodane (**1**) lycopodine clavolonine (**2**)

first isolated in Jamaica in 1960[3] from the club moss *Lycopodium clavatum* and was synthesized as a racemate by Wenkert and Broka.[4a]

The disconnections required to transform the lycopodium skeleton **3** into its derived acyclic precursor may be accomplished with three principal constructions: 1) a Mannich reaction, 2) a Michael addition, and 3) a C–N alkylation (Figure 1). If the C–N alkylation is the last skeletal disconnection, then these reactions are implemented in a macrocyclic manifold (path A). Alternatively, if the C–N alkylation is the first skeletal disconnection, the same reactions are implemented in a linear environment (path B). Herein, we report the evaluation of both distinct approaches to the synthesis of the lycopodium skeleton.

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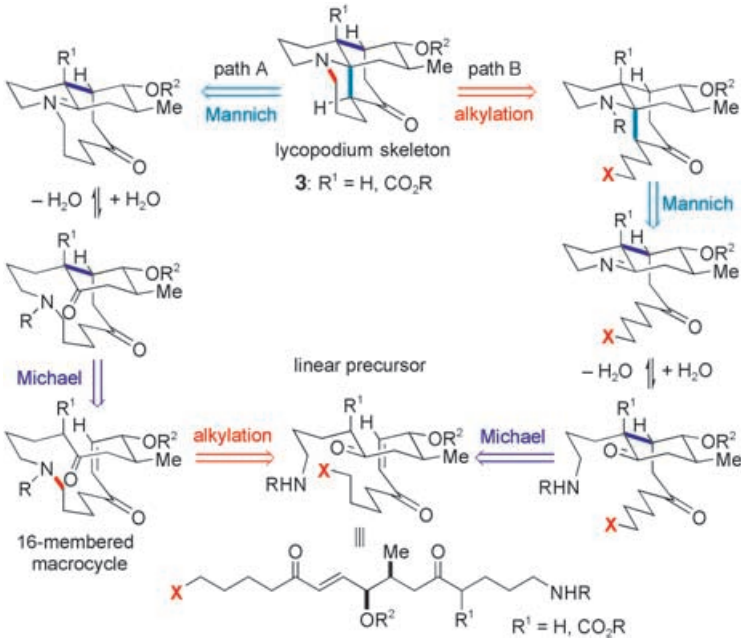
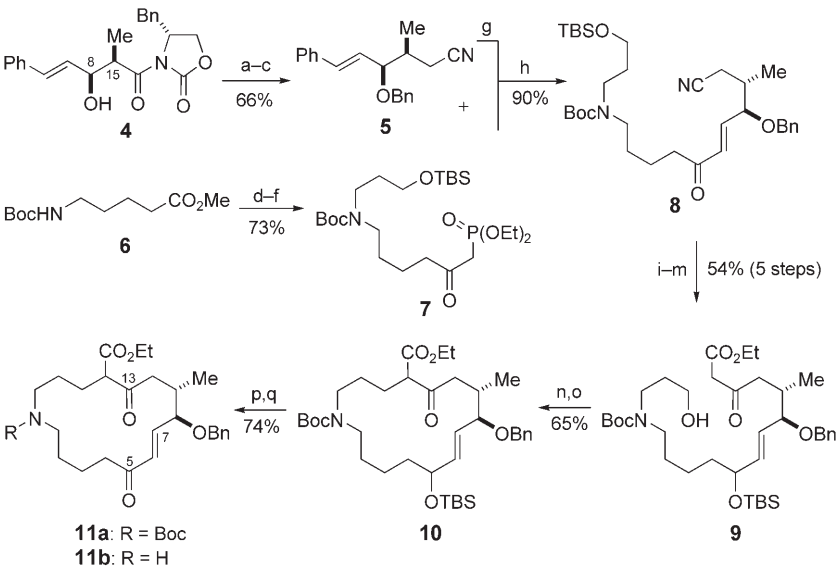


Figure 1. Synthesis plan: macrocyclic path A and linear path B.

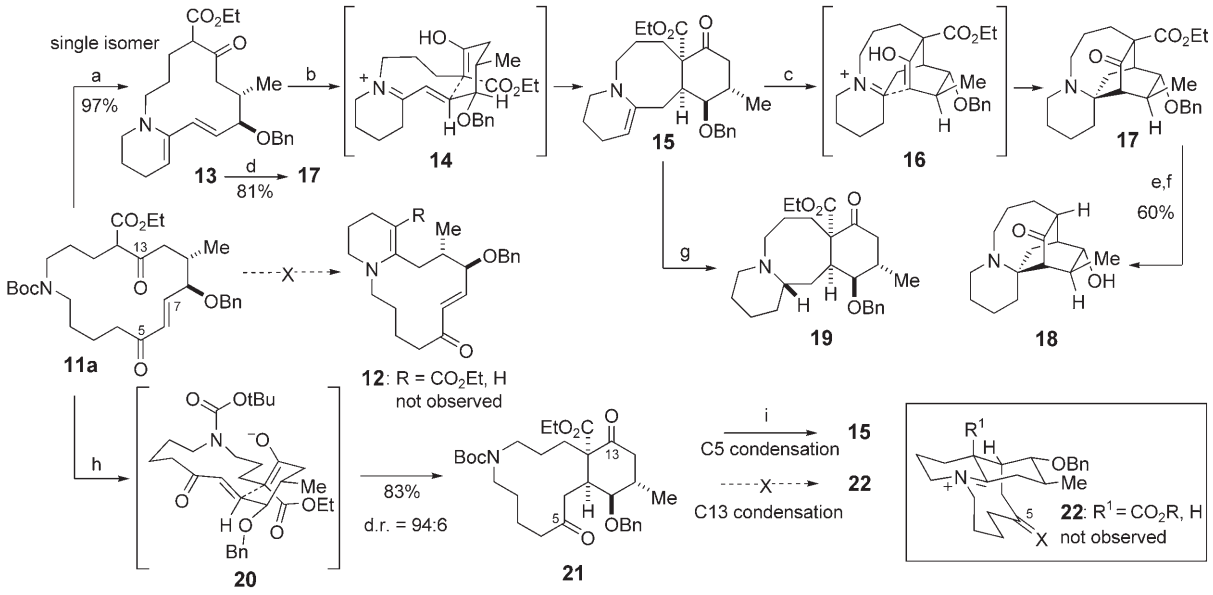
First, let us consider path A. Macrocycles often adopt well-defined conformations that exhibit a pronounced influence on the stereochemical course of reactions.[5] The investigation of this route required the synthesis of the 16-membered macrocycle **11a** (Scheme 1). The synthesis began by the boron-mediated aldol addition of (*R*)-3-propionyl-4-benzyloxazolidinone to cinnamaldehyde to provide crystalline **4** as a single diastereomer.[6] This aldol adduct was successively reduced to the diol and trapped as the derived benzylidine acetal. Subsequent reductive cleavage revealed the primary alcohol (DibalH, CH_2Cl_2, −35 °C) which was transformed into nitrile **5** via the intermediate tosylate.[7] Following ozonolysis of the styrene moiety, the aldehyde derived from **5** was condensed with β-ketophosphonate **7** to afford α,β-unsaturated ketone **8** in 90% yield.[8] After protection of the enone in **8**, the nitrile and protected hydroxyl termini were modified to the macrocyclization requisite precursor **9**.[9] Macrocyclization was accomplished by activation of the primary alcohol as its iodide derivative, which was immediately subjected to ketoester alkylation conditions (Cs_2CO_3, THF, 37 °C, 0.007 M).[10] In this manner, macrocycle **10** was reproducibly obtained in good yield. Oxidation of the allylic alcohol afforded the desired enone **11a**, which was crystallized as a single diastereomer (m.p.: 127 °C) and analyzed by X-ray diffraction.

The deprotected macrocyclic amine **11b** may react with either the C13 or the C5 carbonyl groups. We predicted that deprotection of the amine would result in condensation at the C13 ketone to provide the vinylogous urethane **12** (Scheme 2).[11] In the event, carbamate cleavage of amine **11a** afforded none of the desired enaminone **12**; rather, exclusive formation of **13** (attack at C5) was observed (97% yield). Exposure of **13** to protic or Lewis acids promoted a stereoselective transannular Michael addition of the ketoester to the α,β-unsaturated iminium ion **14**. The derived tricyclic enamine **15** was unstable and underwent a spontaneous intramolecular Mannich cyclization to the tetracyclic ketoester **17** upon attempted purification by chromatography on silica gel or alumina. In practice, enamine **13** was transformed directly into **17** (81% yield) upon heating in ethanol with piperidinium acetate. The structural assignment of this compound was verified by X-ray diffraction analysis of derivative **18** (m.p.: 194 °C). For the purpose of complete characterization, enamine **15** was selectively reduced to amine **19** and analyzed by X-ray diffraction as its hydrochloride salt (m.p.: 225 °C). An examination of the solid-state conformation of macrocycle **11a** provides no clear rationale for the observed N–C5 condensation of amine **11b**. The protected amine is positioned at the same distance from both the ketones at C5 and C13 (5.38 and 5.41 Å, respectively). As a result of the undesired chemoselectivity of the transannular amine condensation,[12] we turned our attention to an alternative sequence of events.



Scheme 1. Reagents and conditions (see reference [7] for explanation of abbreviations): a) $LiBH_4$, Et_2O, H_2O, 0 °C; $PhCH(OMe)_2$, TsOH, 93%; b) DibalH, CH_2Cl_2, −35 °C, 76%; c) TsCl, NEt_3, DMAP; KCN, DMSO, 50 °C, 94%; d) NaH, allyl bromide, DMF, −20 to 10 °C, 55%, 90% based on recovered material; e) 9-BBN, H_2O_2; TBSCl, imid, DMF, 83%; f) *n*BuLi, $MePO(OEt)_2$, THF, −78 °C, 98%; g) O_3, −78 °C; DMS; h) NaH, THF, −78 to −20 °C, 90%; i) L-selectride, THF, −78 °C; j) TBSCl, imid, DMF, 81% (2 steps); k) DibalH, CH_2Cl_2, −50 °C, 87%; l) ethyldiazoacetate, $SnCl_2$, 82%; m) HF·py, THF, 0 °C, 72% (93% based on recovered material); n) I_2, PPh_3, imid, −5 °C; o) Cs_2CO_3, THF (0.007 M), 37 °C, 65% (2 steps); p) F·py, THF, 23 °C; q) DMP, $NaHCO_3$, 74% (2 steps).

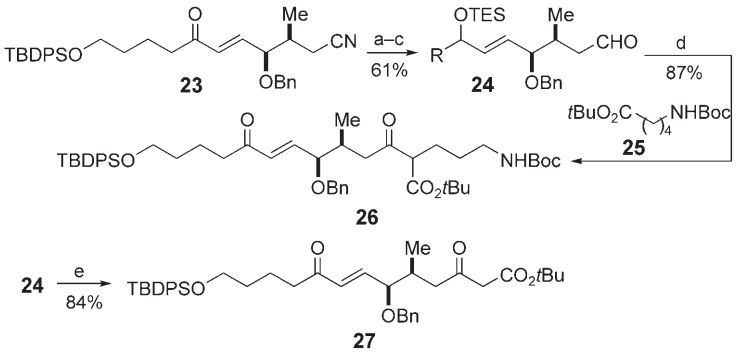
Macrocycle **11a** underwent a selective transannular Michael reaction upon exposure to base (Cs_2CO_3, EtOH, −78 °C) to



Scheme 2. Reagents and conditions: a) TFA, CH_2Cl_2, DMS, 0 °C, 97 %; b) $ZnCl_2$; c) SiO_2; d) piperidinium acetate, EtOH, 80 °C, 48 h, 81 %; e) *t*BuOK, DMSO; HCl, 40 °C, 85 %; f) H_2, $Pd(OH)_2/C$, EtOH, 70 %; g) $NaBH_3CN$, MeOH, AcOH; h) Cs_2CO_3, EtOH, −78 °C, 83 %; i) TMSOTf, CH_2Cl_2, −20 °C.

provide **21** as a mixture of diastereomers (94:6) in 83 % yield (Scheme 2, m.p.: 136 °C). The stereochemical outcome of this cyclization was established by X-ray crystallography. Both newly formed stereocenters are those desired for construction of the lycopodium core. The crystal structure of the Michael product **21** depicts a cyclohexane-ring conformer that minimizes non-bonding interactions. If we assume that the transition state resembles the solid-state conformer, then the transannular addition of the dipole minimized *E*,*E*-enolate **20** into a pseudo-axially disposed enone rationalizes the outcome and minimizes developing *syn*-pentane interactions. Removal of the carbamate protecting group in **21** results in condensation at C5 to yield the previously described tricyclic enamine **15**. It was apparent that protection of the ketone at C5, which is positioned in close proximity to the carbamate nitrogen center (4.7 Å by X-ray crystallography), would be necessary to divert the condensation to the carbonyl group at C13. A variety of protections at C5 were investigated, however, no reaction between the free amine and C13 ketone could be observed. In conclusion, it appears that the C13 condensation pathway to provide intermediate **22** is disfavored for both entropic and steric reasons. To effect reaction between the amine and C13, we reasoned that disconnection of the N–C1 bond would be necessary (Figure 1, path B).

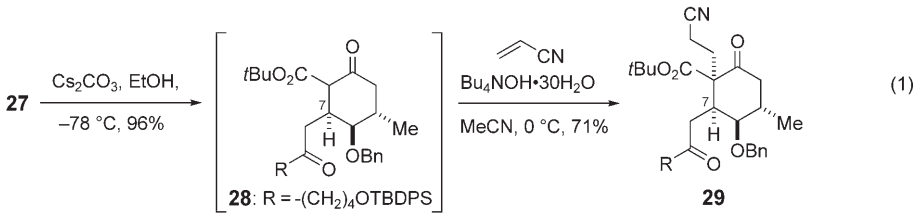
With respect to path B, the linear precursors **26** and **27** were selected as targets and assembled in a manner analogous to the preparation of **8** (see above, Scheme 1). This synthesis employed a similar Horner–Wadsworth–Emmons coupling to afford **23**. After reduction of the ketone and protection of the alcohol as its silyl ether, the nitrile terminus was converted into aldehyde **24** (DibalH, CH_2Cl_2, −50 °C). An aldol–oxidation sequence provided flexibility in the synthesis of both substituted and unsubstituted β-ketoesters **26** and **27** (Scheme 3)

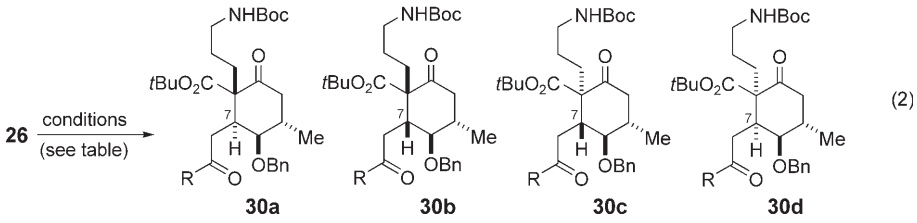


Scheme 3. Reagents and conditions: a) L-selectride, −78 °C; b) TESCl, imid., DMF, 73 %; c) DibalH, CH_2Cl_2, −50 °C, 83 %; d) LDA, **25**; PPTS, EtOH; DMP, $NaHCO_3$, 87 % (3 steps); e) LDA, *t*BuOAc; PPTS, EtOH; DMP, $NaHCO_3$, 84 % (3 steps).

A survey of conditions to effect a selective intramolecular Michael reaction was undertaken (Scheme 4). The unstable β-ketoester precursor **27** was immediately subjected to cyclization conditions (Cs_2CO_3, EtOH, −78 °C) to provide **28** as a mixture (> 10:1) of diasteromers (Scheme 4, equation (1)).[13] The additional three carbon atoms and amino terminus were appended through an acrylonitrile Michael addition ($Bu_4NOH{\cdot}30H_2O$, MeCN, 0 °C, 71 %) to provide **29** as a single diastereomer.

In general, Michael additions with the substituted β-ketoester **26** were less selective than with its unsubstituted counterpart **27** (Scheme 4, equation (2)). Products **30a** and





E,E-enolate (extended):	30a	30b	30c	30d
Cs_2CO_3, EtOH, –78 °C	5	2	0	0
$BnMe_3NOMe$, 0 °C, CH_2Cl_2	5	2	0	0
Z,Z-enolate (chelate):				
LiOMe, $LiClO_4$, Et_2O, 0 °C	1	1	6	0
NaH, toluene, 0 °C	1	0	3	0

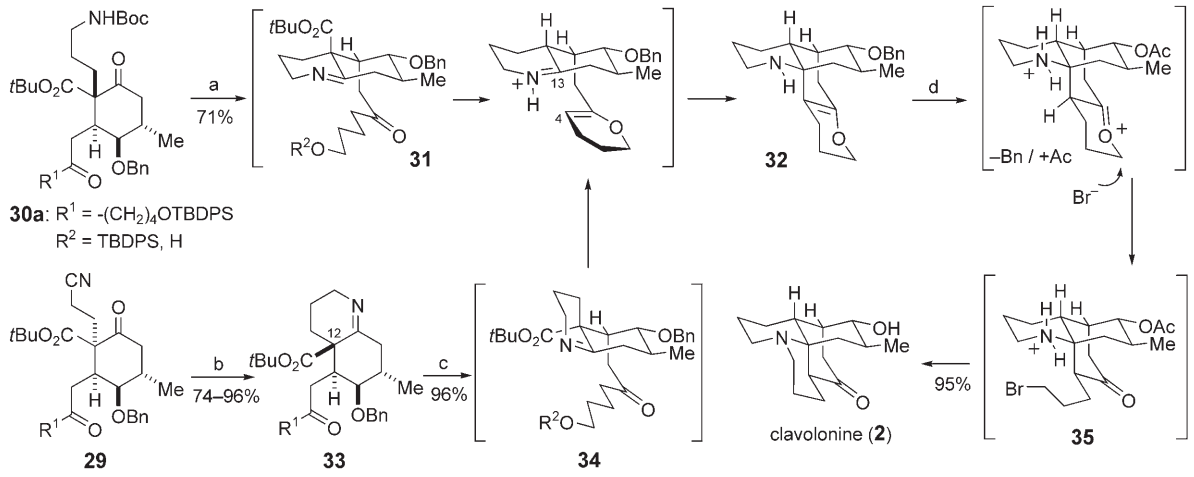
Scheme 4. Survey of conditions for selective intramolecular Michael reaction; the table shows the conditions for equation (2), and the relative proportions of product obtained.

30d contain the requisite stereochemistry at C7 for elaboration to the lycopodium skeleton. Generation of chelate-organized *Z,Z*-enolate complexes (NaH or LiOMe/$LiClO_4$) afforded predominately diastereomer **30c**.[14] Conditions that favor extended or dipole-minimized *E,E*-ketoester enolates ($Me_3NBnOMe$ or Cs_2CO_3) afforded a turnover in selectivity, providing a modest bias for the desired diastereomeric Michael reaction product **30a**.[15,14c–f] Both $Me_3NBnOMe$ or Cs_2CO_3 reaction conditions were equally convenient to execute and high yielding (55–60% **30a**, 22–24% **30b**). Product **30d** was not detected under any conditions.[16]

With the configuration at C7 established through a selective Michael reaction, the next objective toward the lycopodium skeleton was the Mannich addition between the C4 enol and C13-derived imminium ion. This objective was realized on both Michael adducts **30a** and **29** which were independently carried forward to the common tetracyclic dihydropyran **32** (Scheme 5). Carbamate deprotection (TFA, CH_2Cl_2) of **30a** initiated condensation, leading to intermediate imine **31**. On exposure to methanolic HCl,[17] a series of reactions ensued, including decarboxylation, formation of a dihydropyran, and Mannich cyclization to provide **32** in 71% yield. To effect a similar sequence from **29**, it was necessary to reduce the nitrile (Raney Ni, H_2) to give imine **33**. The adjacent quaternary center sufficiently retards reduction of the imine moiety to prevent over-reduction.[18] Methanolic HCl converted imine **33** into the aforementioned dihydropyran **32**. Inspection of intermediates **31** and **34** indicates an epimeric configuration at C12. Owing to the stereoelectronic imperatives of the Mannich reaction, the latter will not undergo cyclization without prior decarboxylation and formal inversion.[19]

Treatment of dihydropyran **32** with HBr/HOAc cleaved both the benzyl ether and the dihydropyran functions to provide intermediate ammonium bromide salt **35**. On exposure to methanolic base, intramolecular *N*-alkylation and saponification of the acetate was realized, leading to clavolonine (**2**) in 95% yield. The structure of clavolonine (**2**) was verified by single-crystal X-ray crystallography (m.p.: 227 °C).[20]

In conclusion, the synthesis of clavolonine (**2**) has been an exercise in the conversion of functionalized linear carbon chains into polycyclic architectures. The end products include



Scheme 5. Reagents and conditions: a) TFA, DMS, CH_2Cl_2, 23 °C; HCl, MeOH, 70 °C, 24 h (71%); b) Raney Ni, H_2, EtOH, 74–96%; c) HCl, MeOH, 70 °C, 42 h, 96%; d) HBr, HOAc, CH_2Cl_2; MeOH, NaOH, 95%.

not only the target structure but also a diverse array of complex nitrogen-containing polycyclic structures that are accessible from simple Michael–Mannich reaction cascades. The illustrated strategy of cyclization-based multistep bond constructions is currently being applied to other complex natural products.

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[1] a) D. B. McLean, *The Alkaloids: Chemistry and Physiology, Vol. 14* (Ed.: R. H. F. Manske), Academic Press, New York, **1973**, p. 347; b) D. B. McLean, *The Alkaloids: Chemistry and Physiology, Vol. 10* (Ed.: R. H. F. Manske), Academic Press, New York, **1968**, p. 305; c) J. C. Braekman, L. Nyembo, P. Bourdoux, N. Kahindo, C. Hootele, *Phytochemistry* **1974**, *13*, 2519; d) W. A. Ayer, G. C. Kasitu, *Can. J. Chem.* **1989**, *67*, 1077; e) M. Castillo, L. A. Loyola, G. Morales, I. Singh, C. Calvo, H. L. Holland, D. B. MacLean, *Can. J. Chem.* **1976**, *54*, 2893.

[2] a) C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1982**, *104*, 1054; b) G. Stork, R. A. Kretchmer, R. H. Schlessinger, *J. Am. Chem. Soc.* **1968**, *90*, 1647; c) W. A. Ayer, W. R. Bowman, T. C. Joseph, P. Smith, *J. Am. Chem. Soc.* **1968**, *90*, 1648; d) G. A. Kraus, Y. S. Hon, *J. Am. Chem. Soc.* **1985**, *107*, 4341; e) A. Padwa, M. A. Brodney, J. P. Marino, S. M. Sheehan, *J. Org. Chem.* **1997**, *62*, 78; f) P. A. Grieco, Y. J. Dai, *J. Am. Chem. Soc.* **1998**, *120*, 5128; g) M. Mori, K. Hori, M. Akashi, M. Hori, Y. Sato, M. Nishida, *Angew. Chem.* **1998**, *110*, 659; *Angew. Chem. Int. Ed.* **1998**, *37*, 636. For reviews of lycopodium alkaloid chemistry, see also references [1a,b].

[3] a) R. H. Burnell, D. R. Taylor, *Chem. Ind.* **1960**, 1239; b) R. H. Burnell, B. S. Mootoo, *Can. J. Chem.* **1961**, *39*, 1090.

[4] a) E. Wenkert, C. A. Broka, *J. Chem. Soc. Chem. Commun.* **1984**, 714; b) E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, H. P. Schenk, *J. Am. Chem. Soc.* **1973**, *95*, 8427.

[5] W. C. Still, I. Galynker, *Tetrahedron* **1981**, *37*, 3981.

[6] D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.* **1988**, *110*, 2506.

[7] Abbreviations: 9-BBN = 9-borabicyclo[3.3.1]nonane; Bn = benzyl; Boc = *tert*-butyloxycarbonyl; DibalH = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; DMP = Dess–Martin periodinane; DMF = *N*,*N*-dimethylformamide; DMS = dimethyl sulfide; DMSO = dimethyl sulfoxide; imid = imidazole; LDA = lithium diisopropylamide; PPTS = pyridinium *p*-toluenesulfonate; py = pyridine; TBDPS = *tert*-butyldiphenylsilyl; TBSCl = *tert*-butyldimethylsilyl chloride; TESCl = triethylsilyl chloride; TFA = trifluoroacetic acid; TMSOTf = trimethylsilyl trifluoromethanesulfonate; TsOH = *p*-toluenesulfonic acid.

[8] β-Ketophosphonate **7** was prepared in four steps from the previously synthesized protected δ-amino valeric acid **6**: D. L. Flynn, R. E. Zelle, P. A. Grieco, *J. Org. Chem.* **1983**, *48*, 2425.

[9] C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258.

[10] a) P. Deslongchamps, *Pure Appl. Chem.* **1996**, *68*, 1831; b) D. A. Evans, J. T. Starr, *Angew. Chem.* **2002**, *114*, 1865; *Angew. Chem. Int. Ed.* **2002**, *41*, 1787; c) D. A. Evans, J. T. Starr, *J. Am. Chem. Soc.* **2003**, *125*, 13531.

[11] If carbinolamine dehydration is rate-limiting, formation of the stabilized vinylogous urethane **12** is predicted to occur favorably. If carbinolamine formation is rate-determining, condensation at the more electrophilic (C13) ketone should be observed. These predictions are reinforcing for C13 condensation. Saturated ketones are more electrophilic than unsaturated ketones. This can be observed spectroscopically (e.g. IR shift approximately $\Delta\tilde{\nu} = 40\ cm^{-1}$) and experimentally, for example, by competitive reductive amination. A saturated carbonyl group is preferentially reduced in the presence of $NaB(OAc)_3H$, as noted in the following reference: A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849. Macrocycle **11a** demonstrates no enol content by ^1H NMR or IR spectroscopy. For this reason, the ketone at C13 should be regarded as a saturated ketone.

[12] Macrocycle **11a** was decarboxylated under Krapcho conditions. This material also exclusively favors condensation at C5.

[13] Ketoester **28** exists as a mixture of keto and enol tautomers. For this reason, an accurate diastereomeric ratio of the preceding Michael addition could not be determined. A small amount of **28** was decarboxylated under Krapcho conditions. The derived ketone was isomerically pure (d.r. ≥ 10:1), and the stereochemistry at C7 was proven by 2D ^1H NMR spectral analysis (NOESY).

[14] a) G. Stork, J. D. Winkler, N. A. Saccomano, *Tetrahedron Lett.* **1983**, *24*, 465; b) G. Stork, C. S. Shiner, J. D. Winkler, *J. Am. Chem. Soc.* **1982**, *104*, 310; c) E. M. Arnett, S. G. Maroldo, S. L. Schilling, J. A. Harrelson, *J. Am. Chem. Soc.* **1984**, *106*, 6759; d) M. Raban, D. P. Haritos, *J. Am. Chem. Soc.* **1979**, *101*, 5178; e) M. Raban, E. A. Noe, G. Yamamoto, *J. Am. Chem. Soc.* **1977**, *99*, 6527; f) L. M. Jackman, B. C. Lange, *Tetrahedron* **1977**, *33*, 2737.

[15] L. N. Mander, S. G. Pyne, *J. Am. Chem. Soc.* **1979**, *101*, 3373.

[16] Product **30d** was prepared independently by alkylation of **28** with 1-iodo-3-amino-*tert*-butylcarbamate and *t*BuOK provided **30d** as a single isomer in less than 30% yield.

[17] The use of methanolic HCl to effect a Mannich addition finds precedent in the Heathcock synthesis of lycopodine; see reference [2a].

[18] C. H. Heathcock, M. H. Norman, D. A. Dickman, *J. Org. Chem.* **1990**, *55*, 798.

[19] a) R. V. Stevens, A. W. M. Lee, *J. Am. Chem. Soc.* **1979**, *101*, 7032; b) R. V. Stevens, *Acc. Chem. Res.* **1984**, *17*, 289.

[20] CCDC 280174–280177 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif. **19** (280174) $C_{26}H_{38}ClNO_4$: $a = 33.325(6)$, $b = 7.0106(12)$, $c = 10.5283(17)$, space group $P21212$; **18** (280175) $C_{16}H_{25}NO_2$: $a = 7.0625(6)$, $b = 9.9378(9)$, $c = 20.3461(18)$, space group $P212121$; **11a** (280176) $C_{31}H_{45}NO_7$: $a = 9.3342(17)$, $b = 10.0515(17)$, $c = 16.339(3)$, $\beta = 93.755(4)$, space group $P21$; **2** (280177) $C_{16}H_{25}NO_2$: $a = 13.5174(12)$, $c = 7.7656(10)$, space group $P41$.

