The Aza-Cope–Mannich Approach to *Strychnos* Alkaloids. Short Stereocontrolled Total Syntheses of (±)-Dehydrotubifoline and (±)-Akuammicine[1]

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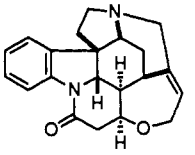
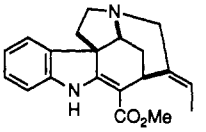
Abstract: A direct approach for the total synthesis of *Strychnos* alkaloids has been developed. The key strategic element is the aza-Cope–Mannich rearrangement (Scheme II) of formaldiminium ions derived from azabicyclo[3.2.1]octanols **5** (Scheme I). This reorganization occurs with perfect stereochemical fidelity in high yield to form the intricate skeleton of this complex alkaloid group. Critical to the success of this synthesis endeavor was the evolution of an efficient sequence for assembling the azabicyclo[3.2.1]octanol rearrangement substrates (Scheme V). Using a pivaloyl group to protect the nitrogen of the aromatic ring, we prepared the akuammicine degradation product (±)-dehydrotubifoline in 12 chemical operations and ~6% overall yield from 2-cyclopentenone (Schemes VI–VIII). A related sequence that employed a *tert*-butoxycarbonyl group to protect the aromatic nitrogen led to the synthesis of the tetracyclic enecarbamate **63** (Scheme IX). Additional refinements of the aza-Cope–Mannich strategy allowed the total synthesis of (±)-akuammicine to be accomplished by way of 10 isolated intermediates and in nearly 8% overall yield from 2-cyclopentenone (Scheme X). Notable features of this final sequence are (a) the convergent carbonylative coupling of vinylstannane **64** and aryl iodide **65** to afford enone **66**, (b) the use of the 1,3-dimethylhexahydro-2-oxo-1,3,5-triazine group to protect the primary aniline nitrogen, and (c) the strategic use of an intramolecular epoxide aminolysis to assemble the azabicyclooctanol **71**. Incorporation of oxidation at the terminal carbon of the ethylidene appendage should allow this total synthesis approach to be extended to more complex *Strychnos* alkaloids such as strychnine.

The cationic aza-Cope rearrangement–Mannich cyclization reaction has been shown to be a powerful method for preparing a wide variety of nitrogen heterocycles.[2] Previous reports from our laboratories have described efficient syntheses of *Amaryllidaceae*, *Melodinus*, and *Aspidosperma* alkaloids that employ the aza-Cope–Mannich reaction as the key strategic element.[3] In this paper we detail the application of this important strategem to the arena of *Strychnos* alkaloid total synthesis.[4]

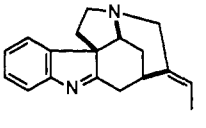
The synthesis of *Strychnos* alkaloids has been an area of intense research ever since the remarkable structural elucidation of strychnine (**1**) by Robinson et al. in 1946.[5] This work is highlighted by Woodward's classic preparation of strychnine[6] and more recently by syntheses of **1** by the Magnus and Stork groups.[7] Remarkably, in spite of the large effort directed at this area, few methods for assembling the core pentacyclic curan or strychnan skeletons (exemplified in **2** and **3**) have been developed.[6-9]



strychnine (**1**)



akuammicine (**2**)



dehydrotubifoline (**3**)

Our initial synthetic target in this area was the widely occurring pentacyclic *Strychnos* alkaloid akuammicine (**2**) Akuammicine was first isolated in 1927 from the seeds of *Picralima klaineana* and has subsequently been found in various genera of *Apocynaceae*.[8,10] It is found in several plant species in both optically active (levorotatory) and racemic forms.[10] The structure of **2**,

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(1) Publication 24 in the series: Synthesis Applications of Cationic Aza-Cope Rearrangements. For 23, see: Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.

(2) For brief reviews, see: (a) Overman, L. E.; Ricca, D. J. *Comp. Org. Synth.* **1991**, *2*, 1007. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.

(3) (a) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (b) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. (c) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598. (d) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685. (e) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.

(4) A portion of this work was described in preliminary form: Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085.

(5) Robinson, R. *Experientia* **1946**, *2*, 28.

(6) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.

(7) (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. (b) Stork, G. Presented at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992.

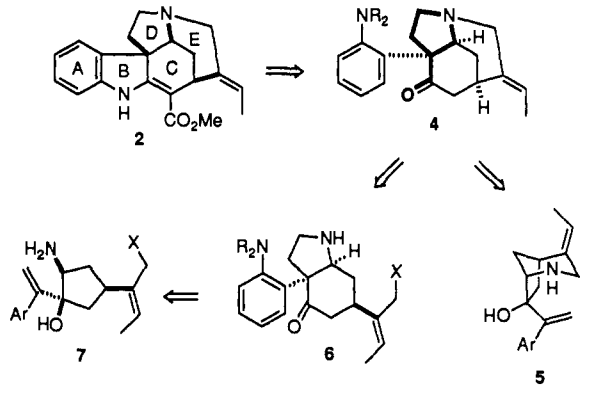
(8) For the most recent comprehensive review, see: Husson, H. P. In *Indoles: Monoterpene Indole Alkaloids*; Saxon, J. E., Ed.; Wiley: New York, 1983; Chapter 7.

(9) For recent syntheses of pentacyclic *Strychnos* alkaloids or new approaches to the strychnan skeleton, see: (a) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299 and references therein. (b) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653. (c) Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem.* **1990**, *55*, 1624. (d) Kraus, G. A.; Bougie, D. *Synlett* **1992**, 279. (e) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696. (f) Rawal, V. H.; Michoud, C.; Monestel, R. *J. Am. Chem. Soc.*, submitted for publication.

(10) (a) Henry, T. A.; Sharp, T. M. *J. Chem. Soc.* **1927**, 1950. (b) Edwards, P. N.; Smith, G. F. *Proc. Chem. Soc., London* **1960**, 215.

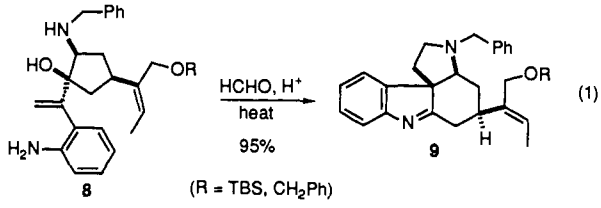
0002-7863/93/1515-3966$04.00/0

Scheme I

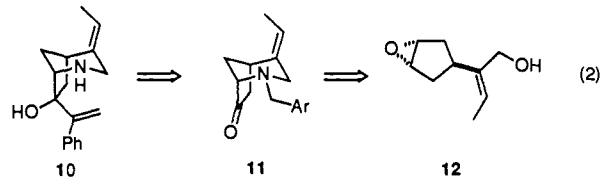


first proposed by Robinson[11] and later confirmed by Smith,[12] was established by correlation with strychnine (**1**). Herein we detail the first total syntheses of akuammicine (**2**) and the akuammicine degradation product 1,2-dehydrotubifoline (**3**).

Synthesis Plan. Our approach to the curane skeleton is shown in antithetic format in Scheme I. Disconnection of the dihydroindole ring (ring B) provides tetracycle **4**, whose 3-acylpyrrolidine core is shown in boldface type. The 3-acylpyrrolidine unit is the basic structure constructed by the aza-Cope–Mannich reaction.[2] One approach to **4** envisages having the E ring installed prior to aza-Cope–Mannich rearrangement of an azabicyclo[3.2.1]octane precursor (**5** → **4**). Alternatively, aza-Cope–Mannich rearrangement of a cyclopentanoid precursor (**7** → **6**) could precede construction of the E ring. As previously recorded, this latter approach can give rise to tetracyclic hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles such as **9** (eq 1).[13] However, initial attempts to close the E ring from this tetracyclic platform were not successful.[13]

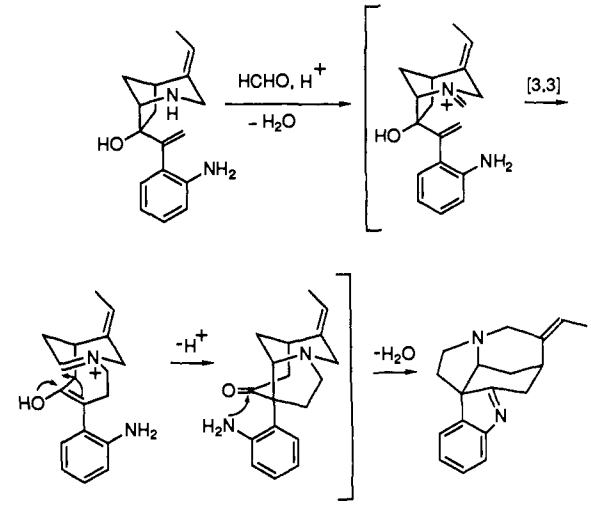


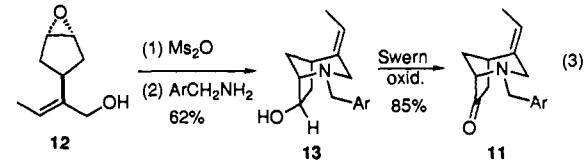
A stereochemical analysis of the aza-Cope–Mannich rearrangement in the azabicyclo[3.2.1]octane series is shown in Scheme II. It is apparent from this exercise that the endo orientation of the styrene functionality on the 2-azabicyclo[3.2.1]-octane skeleton would be required to bring the alkene and iminium ion termini within bonding distance. The amino alcohol **10** (eq 2), containing a simple styrene unit, was originally targeted in order to test the feasibility of this azabicyclooctane approach to the pentacyclic skeleton of the *Strychnos* alkaloids.



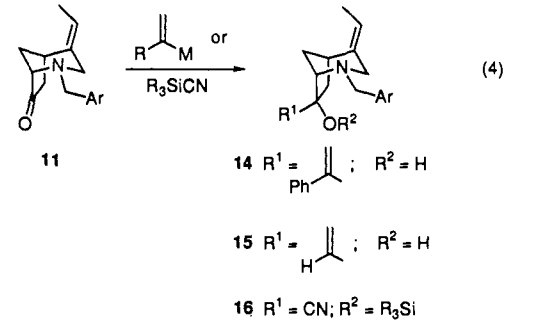
Construction of Azabicyclooctanol 10. We initially pursued the preparation of the azabicyclic alcohol **10** from the bicyclic ketone precursor **11** (Ar = *p*-methoxyphenyl), an intermediate that should be readily accessible from the known epoxide **12** (eq 2).[13] In the event, activation of epoxy alcohol **12** with methanesulfonic anhydride followed by reaction with *p*-methoxybenzylamine ($ArCH_2NH_2$) effected mesylate displacement and subsequent intramolecular opening of the oxirane to provide azabicyclooctanol **13** in 62% yield (eq 3). Oxidation of **13** under standard Swern conditions[14] gave the desired azabicyclo[3.2.1]-octanone **11** in 85% yield.

Scheme II





It was our original hope that the basic nitrogen of the α-amino ketone **11** might direct the addition of vinyl nucleophiles from the endo face and thus provide direct access to allylic alcohol **10**.[15] However, the reaction of α-styrenyllithium, α-styrenylmagnesium bromide, or vinylmagnesium bromide with ketone **11** took place exclusively from the face of the smaller one-carbon bridge to provide alcohols **14** or **15** having an exo-oriented alkene moiety (eq 4). Even trimethylsilyl cyanide and *tert*-butyldimethylsilyl



cyanide reacted with **11** to provide exclusively the silyl cyanohydrins **16**. The secondary amine **17** containing an exo-oriented styrene residue was prepared from **14** by chloroformate debenzylation.[16] In accord with our expectations, this amino alcohol stereoisomer did not suffer aza-Cope–Mannich reorganization

(11) (a) Millson, P.; Robinson, R.; Thomas, A. F. *Experientia* **1953**, *9*, 89. (b) Robinson, R.; Thomas, A. F. *J. Chem. Soc.* **1955**, 2049. (c) Robinson, R.; Aghoramurthy, K. *Tetrahedron* **1957**, *1*, 172.

(12) Edwards, P. N.; Smith, G. F. *J. Chem. Soc.* **1961**, 152.

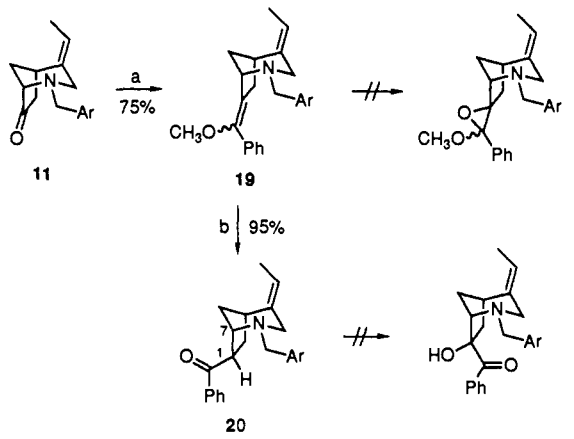
(13) Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021.

(14) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(15) For a summary of the stereochemical outcome of reductions of α-aminoketones, see: Tramontini, M. *Synthesis* **1982**, 605.

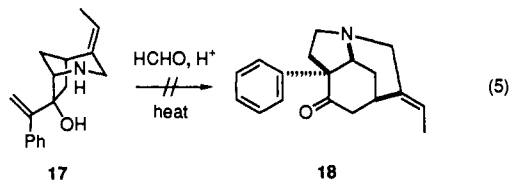
(16) Angle, S. R. Ph.D. Dissertation, University of California, Irvine, CA, 1985.

Scheme III[a]



[a] Ar = *p*-methoxyphenyl. Conditions: (a) $PhCH(TMS)OCH_3$, *n*-BuLi, THF, 0 °C, then **11**; (b) 1 N HCl, 23 °C.

to **18** when treated with formaldehyde and acid in refluxing acetonitrile under standard aza-Cope–Mannich conditions (eq 5).[16-18]

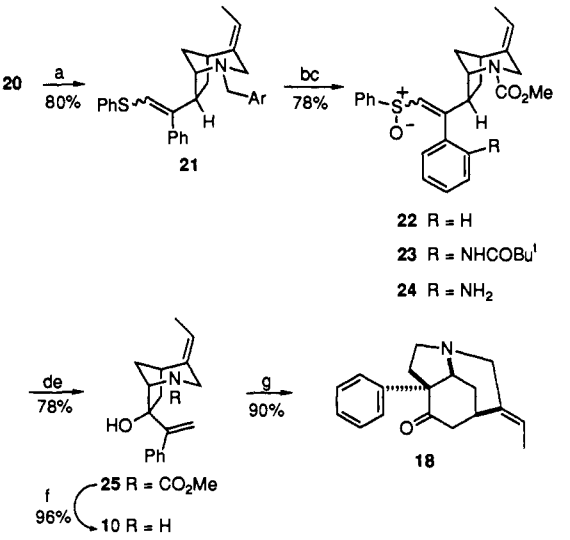


(5)

The high preference for reagents to add to ketone **11** from the exo face suggested that the desired amino alcohol **10** might be best accessed from **11** by a sequence that forms the exo carbon–oxygen bond last (eq 2). Our initial investigations of this strategy are summarized in Scheme III. Peterson olefination of **11** with the lithium salt of $PhCH(SiMe_3)OCH_3$[19] provided the tetrasubstituted enol ether **19** in 75% yield. However, numerous attempts to epoxidize **19** failed.[20] On the other hand, acidic hydrolysis of this enol ether occurred cleanly to afford a single phenyl ketone (**20**). The exo stereochemistry assigned to this intermediate is consistent with the lack of vicinal coupling observed in the ^1H NMR spectrum between the methine hydrogens at C(1) and C(7).[20] Attempts to α-hydroxylate ketone **20** under a variety of standard conditions [e.g., *t*-BuOK, O_2; LDA, MoOPh; KHMDS, $PhSO_2N(O)CHPh$], however, were once again unsuccessful.[20,21]

The sigmatropic rearrangement of allylic sulfinate esters has been employed to form bridged bicyclic allylic alcohols in which the alkene moiety resides on the more congested endo face of the bicyclo[2.2.1]heptane ring system.[22,23] The ultimately successful preparation of azabicyclooctanol **10** using this key transformation is summarized in Scheme IV. Treatment of ketone **20** with the

Scheme IV[a]



[a] Ar = *p*-methoxyphenyl. Conditions: (a) $PhSCH_2TMS$, *n*-BuLi, THF, 0 °C, then **11**; (b) MeOCOCl, $NaHCO_3$, $CHCl_3$, reflux; (c) *m*-CPBA, CH_2Cl_2, −78 °C; (d) 10% KOH, MeOH–H_2O, reflux; (e) $(MeO)_3P$, EtOH, reflux; (f) CH_3SLi, DMF, 0 °C; (g) $(CH_2O)_n$, camphorsulfonic acid, Na_2SO_4, CH_3CN, reflux.

lithium salt of $PhSCH_2SiMe_3$ provided the vinyl sulfides **21** in 80% yield as a 1:1 mixture of stereoisomers. Debenzylation of **21** with methyl chloroformate followed by oxidation of the resulting carbamate with *m*-chloroperoxybenzoic acid afforded the vinyl sulfoxides **22** in 78% overall yield. Treatment of this mixture of vinyl sulfoxides with KOH in refluxing MeOH–H_2O occasioned conversion to the corresponding allylic sulfoxides. Finally, when these intermediates were heated in ethanol in the presence of $(MeO)_3P$, allylic alcohol **25** was obtained in 78% overall yield from **22**.[23] Cleavage of the carbamate group of **25** with lithiomethyl mercaptide proceeded in 96% yield to provide the desired rearrangement substrate, azabicyclooctanol **10**.[24-26]

To our delight, the reaction of **10** under standard aza-Cope–Mannich conditions[2,3] occurred cleanly to finish (*E*)-2-ethylidene-7-phenyl-4-azatricyclo[5.2.2.$0^{4,8}$]undecan-11-one (**18**) in 90% yield. The structural assignment for **18** was supported by a full analysis of its ^1H NMR spectrum with the aid of ^1H–^1H COSY experiments.[20] Moreover, the ring carbons of **18** were in reasonable agreement with the ^{13}C NMR spectrum reported for the parent 4-azatricyclo[5.2.2.$0^{4,8}$]undecan-11-one ring system.[27]

With an approach in hand for accessing azabicyclooctanols having an endo-oriented styryl residue and the feasibility of the key aza-Cope–Mannich rearrangement established, our attention turned to the preparation of analogs of **18** that carried appropriate functionality in the aromatic ring to allow development of the dihydroindole B ring of the *Strychnos* alkaloids. The conversion of ketone **11** to vinyl sulfoxides **23** and **24** having nitrogen functionality at the ortho position was accomplished in a fashion analogous to the preparation of **22** (Scheme IV).[20] However, the subsequent transformation of these intermediates to aryl analogs of the allylic alcohol **25** could not be realized.[28] We speculate that the pivotal sigmatropic reorganization of the allylic sulfoxide

(17) If bond cleavage preceded bond formation in the aza-Cope rearrangement, the formaldiminium ion derived from **17** could conceivably have rearranged to **18**. Such a mechanistic scenario has been suggested to occur in the aza-Cope–Mannich rearrangement of iminium ions derived from (*E*)-2-amino-1-vinylcyclobutanols.[18]

(18) Overman, L. E.; Okazaki, M. E.; Jacobsen, E. J. *J. Org. Chem.* **1985**, *5*, 2403.

(19) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103.

(20) Marquis, R. W., Jr. Ph.D. Dissertation, University of California, Irvine, CA, 1988.

(21) (a) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578. (b) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 999. (c) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (d) Dvais, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

(22) Brown, W. L.; Fallis, A. G. *Can. J. Chem.* **1985**, *8*, 1828.

(23) (a) Hoffman, R. W.; Goldman, S.; Maak, N.; Gerlach, R.; Frickel, F.; Steinbach, G.; Geueke, K.-J. *Chem. Ber.* **1980**, *113*, 819, 831, 845. (b) Goldman, S. *Synthesis* **1980**, 640.

(24) Protecting groups on the nitrogen of 2-azabicyclo[3.2.1]octanes that have large endo substituents at C(1), the styrene moiety in the case of **25**, are remarkably resistant to cleavage. Other nitrogen protecting groups, e.g., ethoxycarbonyl and *p*-methoxybenzyl, could not be removed from analogs of **25**.[20]

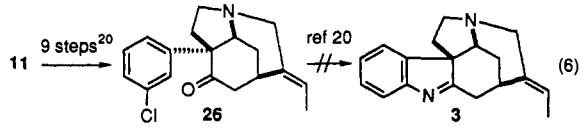
(25) The application of LiSMe to cleave methyl carbamates in this series was initially developed by Dr. Susan Vice of these laboratories.

(26) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, 1051.

(27) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodríguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267.

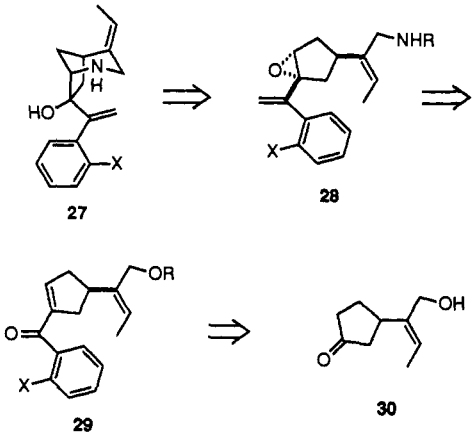
(28) (a) This conversion also failed when the ortho substituent was OH. (b) These experiments are described in detail in ref 20.

intermediates was undermined by the presence of an ortho substituent on the aromatic ring. Consistent with this speculation, we were able to access, by the general sequence outlined in Schemes III and IV, the tetracyclic ketone **26** containing a meta chloride substituent.[28b] However, all attempts to close the final azacyclic ring through the intermediary of benzyne intermediates failed (eq 6).[28b,29]

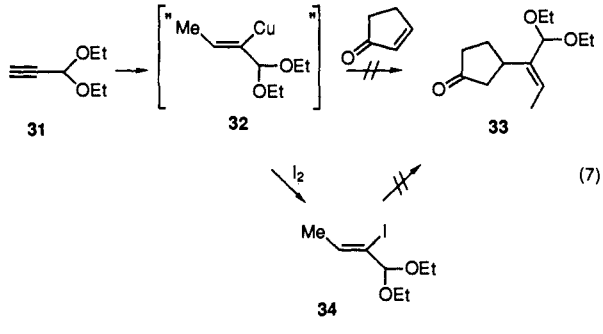


A More Direct Route to Azabicyclooctanol Rearrangement Substrates. An Efficient Total Synthesis of (±)-Dehydrotubifoline. The difficulty encountered in introducing an ortho substituent to allow elaboration of the dihydroindole nucleus prompted the development of an alternative strategy for assembling the aza-Cope–Mannich rearrangement substrates. As outlined in Scheme V, intramolecular opening of epoxide **28** at the less-substituted carbon would provide the required azabicyclooctanol **27**. Careful consideration of molecular models suggested that an ortho substituent on the aromatic ring should not undermine the desired sense of epoxide ring-opening. The enone **29** is an attractive progenitor of **28**, since epoxidation of **29** from the less hindered α-face would set the stereochemistry required for intramolecular epoxide aminolysis. Cyclopentanone **30** was envisaged as a plausible precursor of **29**.

Scheme V

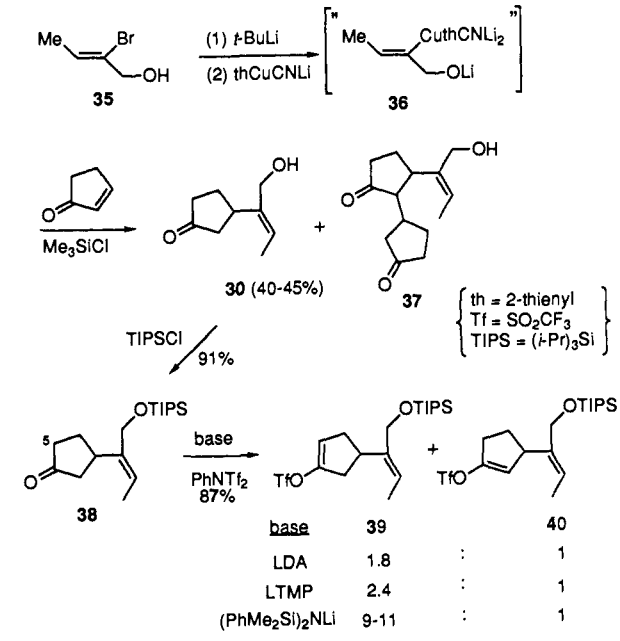


Our introductory efforts were directed toward preparing ketone **33** from 2-cyclopentenone. Carbocupration of the acetylenic acetal **31**, as described by Alexakis and Normant,[30] was initially investigated to access the required vinylcuprate intermediate (eq 7). Reaction of **31** was either lithium dimethylcuprate or lithium



(29) Huisgen, R.; Konig, H.; Bleeker, N. *Chem. Ber.* **1959**, *92*, 424.
(30) Alexakis, A.; Commercon, A.; Coulentianos, C.; Normant, J. F. *Tetrahedron* **1984**, *40*, 715.

Scheme VI



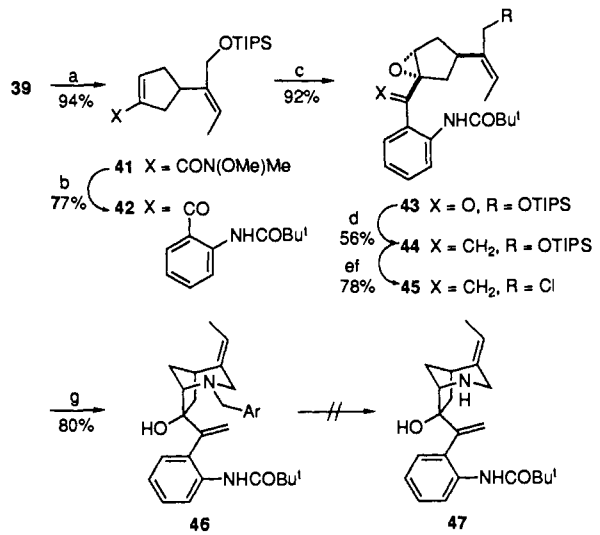
methyl(thiophenyl)cuprate followed by addition of 2-cyclopentenone, however, failed to give any of the desired 1,4-adduct **33**. The presumed intermediate in this sequence, **32**, could be trapped with I_2 to give the trisubstituted vinyl iodide **34** (45% yield), a result that demonstrated that the initial carbocupration step was indeed taking place. An examination of more reactive vinylcuprates potentially available from **34** was precluded by the instability of the vinyllithium reagent derived from iodide **34**. This intermediate rapidly suffered β-elimination to form allene products even at −78 °C.[31]

The desired conjugate addition reaction was finally successfully accomplished with a higher-order cuprate reagent derived from (*Z*)-2-bromo-2-buten-1-ol (**35**) (Scheme VI). Treatment of **35** at −78 °C with 3 equiv of *t*-BuLi and 1 equiv of lithium thienylcyanocuprate[32] to form an intermediate of stoichiometry **36** followed by addition of 2-cyclopentenone afforded the desired 1,4-adduct **30** in 30–35% yield. However, **30** was contaminated with ca. 10–15% of the diketone **37** resulting from the reaction of the intermediate enolate with a second molecule of 2-cyclopentenone. Fortunately, this unwanted side reaction could be suppressed by adding Me_3SiCl.[33] With this modification, ketone **30** could be prepared in one step on a multigram scale in 40–45% yield from 2-cyclopentenone, with no detectable amount of **37** being present in the reaction mixture.[34] The modest yield of this reaction is partially offset by the directness of this entry to **30**. Protection of the alcohol group of **30** as a triisopropylsilyl (TIPS) ether furnished ketone **38** in 91% yield.[35]

To elaborate ketone **38** to an enone intermediate we needed to regioselectively enolize **38** at C(5) and subsequently functionalize the C–O bond of the derived enolate. Kinetic enolization of **38** with lithium diisopropylamide (LDA) followed by trapping with

(31) The instability of this lithium reagent must derive from steric interactions with the *cis*-β-methyl group, since the corresponding lithium reagent derived from 3,3-diethoxy-2-iodo-1-propene is considerably more stable: (a) Marino, J. P.; Farina, J. S. *Tetrahedron Lett.* **1975**, 3901. (b) Grieco, P. A.; Wang, C.-L. J.; Majetich, G. *J. Org. Chem.* **1976**, *41*, 726. (c) Boeckman, R. K., Jr.; Ramaiah, M. *J. Org. Chem.* **1977**, *42*, 1581.
(32) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.
(33) (a) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.
(34) At this time it is not clear what makes up the remainder of the mass, although it is conceivable that enolization or other pathways may produce a volatile, water-soluble alcohol that is not isolated.
(35) A longer synthesis of this intermediate is described in ref 16.

Scheme VII[a]



[a] Conditions: (a) 5% $Pd(PPh_3)_4$, CO (1 atm) MeONHMe, DMF, 55 °C; (b) 2-(trimethylacetamido)bromobenzene, MeLi, then *t*-BuLi, THF, −78 °C, then **41**; (c) *t*-BuOOH, Triton B, THF, 0 °C; (d) $Ph_3P{=}CH_2$, THF, −78 → 23 °C; (e) TBAF, THF, 0 °C; (f) MsCl, *i*-Pr_2NEt, CH_2Cl_2, −23 °C, LiCl, DMF, 23 °C; (g) *p*-$MeOC_6H_4CH_2NH_2$ ($ArCH_2NH_2$), benzene, reflux.

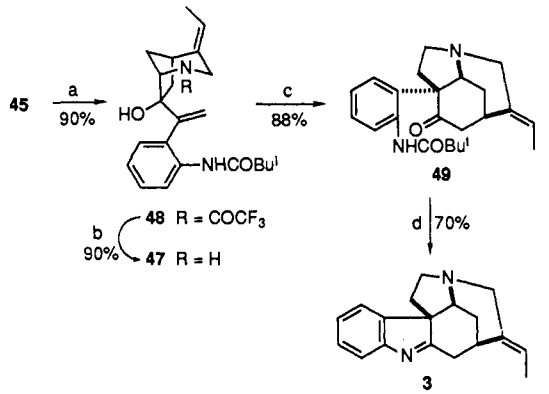
N-phenyltriflamide[36] afforded the enol triflates **39** and **40** in a ratio of 1.8:1 (Scheme VI). The use of lithium tetramethylpiperidide (LTMP) provided little improvement. However, the bulky silylamide $(PhMe_2Si)_2NLi$ introduced by Masamune afforded the required enol triflate **39** in 87% yield with acceptable regioselectivity.[37] To achieve high regioselection in this conversion it was essential that ketone **38** be free of protic impurities.

Our efforts were next directed toward the introduction of an appropriately substituted aromatic ring. Palladium-catalyzed carbonylation of **39** in the presence of *N,O*-dimethylhydroxylamine gave the α,β-unsaturated amide **41** in high yield (Scheme VII).[38] Acylation[39] of **41** with the lithium dianion[40] prepared from 2-(trimethylacetamido)bromobenzene afforded enone **42** in 63% overall yield from cyclopentanone **38**.

Nucleophilic epoxidation of enone **42** proceeded with satisfactory facial selectivity (10–13:1) under standard conditions to provide epoxide **43** in good yield. Subsequent treatment of **43** with (methylene)triphenylphosphorane provided the ortho acylamino-substituted styrene **44** in 52% overall yield from **42**. Desilylation of **44** with $(n\text{-Bu})_4NF$ followed by chlorine substitution of the liberated alcohol gave the allylic chloride **45** in 78% yield.

In our initial attempt to prepare the bicyclic amino alcohol **47** directly from the allylic chloride **45**, this latter intermediate was allowed to react at room temperature in a pressure bottle with excess ammonia. However, this treatment afforded a mixture of several products. In contrast, aminolysis of **45** and subsequent intramolecular epoxide ring opening occurred readily at 80 °C with *p*-methoxybenzylamine. Disappointingly, attempts to remove the *p*-methoxybenzyl protecting group from **46** under a variety of standard conditions were uniformly unsuccessful.[24,41] The desired aminolysis and epoxide ring opening were eventually accomplished by treating **45** with 2 equiv of the sodium salt of trifluoroacetamide to give the bicyclic amide **48** in 90% yield

Scheme VIII[a]



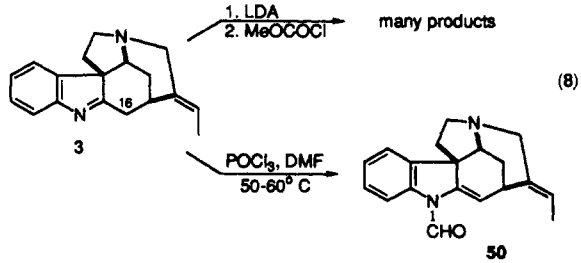
[a] Conditions: (a) H_2NCOCF_3, NaH, DMF, 23 °C, then **45**, 50 °C; (b) KOH, EtOH–H_2O, 80 °C; (c) $(CH_2O)_n$, camphorsulfonic acid, Na_2SO_4, CH_3CN, reflux; (d) KOH, EtOH–H_2O, 80 °C.

(Scheme VIII).[42] Cleavage of the trifluoroacetamide with KOH in refluxing EtOH–H_2O furnished the amino alcohol **47** in 90% yield (35% overall yield from enone **42**). The necessity of using these notably harsh conditions to remove the trifluoroacetamide group illustrates the steric hindrance about the ring nitrogen in substituted 2-azabicyclo[3.2.1]octanes of this type.[24]

The pivotal rearrangement of **47** was occasioned under standard mild conditions [paraformaldehyde, camphorsulfonic acid, Na_2SO_4, CH_3CN at reflux] to provide a single crystalline product **49** in 88% yield. Hydrolysis of this intermediate with a large excess of KOH in EtOH–H_2O at reflux provided, in 70% yield, (±)-dehydrotubifoline (**3**) as a colorless powder. This synthetic product was identical to an authentic sample prepared by acid treatment of natural akuammicine.[12]

The sequence finally developed for accessing (±)-dehydrotubifoline (**3**) is notably direct, requiring only 12 chemical operations, and affords **3** in ~6% overall yield from 2-cyclopentenone. Of major significance, this preparation demonstrates the viability of the aza-Cope–Mannich reaction for assembling the pentacyclic core of the *Strychnos* alkaloids.

Initial Attempts to Prepare Akuammicine. A Detour Caused by Problems with Nitrogen Protecting Groups. With a concise route to dehydrotubifoline (**3**) in hand, we initially sought to prepare akuammicine by direct C-acylation of **3**. We had earlier demonstrated a related acylation in the *Aspidosperma* alkaloid series.[3d] However, the reaction of **3** with an excess of LDA followed by trapping with methyl chloroformate did not provide **2** (eq 8).[43,44] Attempts to C-formylate **3** under a variety of

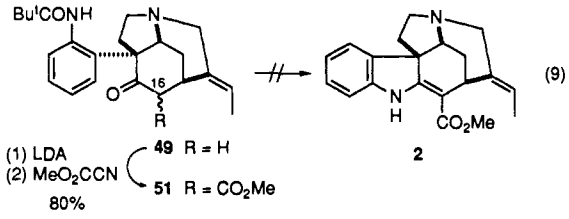


Vilsmeier–Haack conditions[45] were also unrewarding and provided only the *N*-formyl derivative **50**. This marked difference with related transformations of pentacycles with the *Aspidosperma*

(36) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(37) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.
(38) For the preparation of simple α,β-unsaturated amides in this way, see: Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(39) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(40) Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767.
(41) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.
(42) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820.
(43) The enecarbamate resulting from *N*-carbomethoxylation was isolated in low yield.[9a] This intermediate could, in principle, be converted to akuammicine by photoisomerization. This approach was not pursued, since typically the yield of the photoisomerization to form related indoloacrylates is low.[44,9a]
(44) Lenz, G. R. *Synthesis* **1978**, 489. Wenkert, E.; Orito, K.; Simmons, D. P.; Dunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719.

alkaloid skeleton[3d,45] undoubtedly reflects the additional congestion at C(16) occasioned by the adjacent bridged E ring of the *Strychnos* alkaloids.

We next examined the possibility of introducing the carbomethoxy group prior to ring closure to form the pentacyclic skeleton. Acylation of ketone **49** following the general procedure of Mander[46] gave β-keto ester **51** in 80% yield (eq 9). However, all attempts to remove the pivaloyl group from **51**, including treatment with strong acid or base, either returned **51** or led to the formation of dehydrotubifoline (**3**).



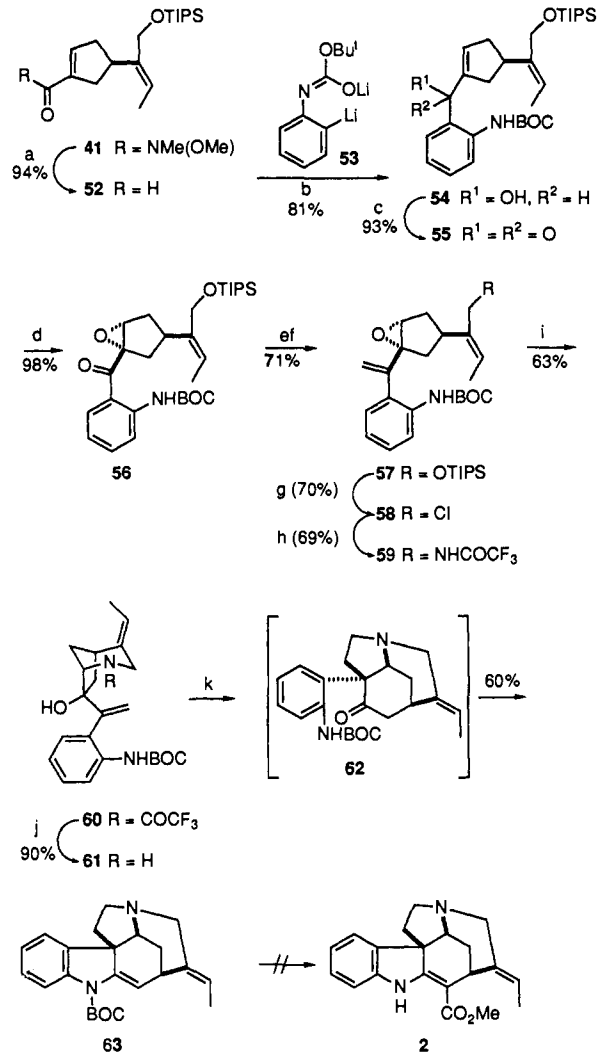
Our inability to convert **51** to akuammicine (**2**) certainly arose from the robustness of the pivaloyl group. The chemistry we had developed in the pivalamide series (Schemes VI–VIII) to access tetracycles **49** and **51** appeared on the surface to be compatible with other *N*-acyl nitrogen protecting groups. A *tert*-butoxycarbonyl (BOC) protecting group was an obvious choice, since conversion of the BOC analog of **51** to akuammicine could likely be occasioned by mild acid treatment.

The preparation of the BOC-protected 2-azabicyclo[3.2.1]-octanol **61** is summarized in Scheme IX. Although the general route is similar to that developed in the *N*-pivaloyl series, this seemingly small change in the nitrogen protecting group necessitated a number of critical modifications in the experimental sequence. Immediately at the outset, the significance of this protecting group change was signaled when the dianion **53** (prepared from the corresponding bromide)[40] reacted with the Weinreb amide **41** in only ~20% yield to provide enone **55**. The desired coupling could be accomplished with the enal **52**, an intermediate readily prepared from **41** by reduction with (*i*-Bu)$_2$AlH.[47] Oxidation of the resulting allylic alcohol **54** with activated MnO_2 then provided the required enone **55**.

Epoxidation of **55** under the conditions employed in the pivalamide series yielded not the expected epoxide **56** but rather one major product that lacked an NH hydrogen. Although this compound eluded rigorous characterization, spectroscopic data were most consistent with a tricyclic compound resulting from intramolecular opening of the oxirane of **56** by the aniline nitrogen. This side reaction could be prevented by carrying out the nucleophilic epoxidation at –45 °C, reaction conditions that provided **56** in nearly quantitative yield. The unexpected base sensitivity of the BOC-protected epoxide intermediate **56** was again apparent when attempted Wittig olefination of **56** led to several products, none of which was the expected styrene **57**. This problem was circumvented by the use of a two-step olefination procedure in which **56** was treated with MeLi and the resulting tertiary alcohol dehydrated with methanesulfonic anhydride to give styrene **57** in 71% yield. Desilylation of **57** at –23 °C followed by chlorination of the liberated alcohol afforded the allylic chloride **58** in good yield.

Aminolysis of **58** with sodium trifluoroacetamide at 50–60 °C did not afford the desired azabicyclooctane ring system, but a product that we could not fully characterize that lacked the NH hydrogen of the protected aniline. Once again we surmise that the conjugate base of the BOC-protected aniline, which would

Scheme IX[a]



[a] Conditions: (a) (*i*-Bu)$_2$AlH, THF, –78 °C; (b) THF, –78 °C; (c) MnO_2, CH_2Cl_2, 23 °C; (d) *t*-BuOOH, Triton B, THF, –45 °C; (e) MeLi, THF, –78 °C, 99%; (f) Ms_2O, Et_3N, DMAP, benzene, reflux, 71%; (g) TBAF, THF, –23 °C, 85%; MsCl, *i*-Pr_2NEt, CH_2Cl_2, –23 °C, LiCl, DMF, 23 °C, 82%; (h) H_2NCOCF_3, K_2CO_3, TBAB, DMF, 23 °C, 69%; (i) K_2CO_3, $(Bu)_4NBr$, DMF, 50 °C, 63%; (j) KOH, EtOH–H_2O, 80 °C, 90%; (k) $(CH_2O)_n$, Na_2SO_4, CH_3CN, reflux.

be more basic than the related intermediate in the pivaloyl series, was triggering an undesired reorganization. The use of milder phase-transfer conditions (CF_3CONH_2, K_2CO_3, and Bu_4NBr) allowed allylic displacement to be accomplished at room temperature to give the secondary trifluoroacetamide **59** in 69% yield. Subsequent cyclization of this intermediate in DMF at 50 °C in the presence of the K_2CO_3 and Bu_4NBr finally provided the 2-azabicyclooctanol **60** in 63% yield. Deacylation of this intermediate with KOH in refluxing EtOH–H_2O provided the desired BOC-protected rearrangement substrate **61** in high yield.

Our final surprise in this series came when the aza-Cope–Mannich reorganization of **61** was examined. Reaction of **61** under standard aza-Cope–Mannich conditions led not to the expected ketone **62** but rather gave the tetracyclic enecarbamate **63**. All attempts to isolate the intermediate ketone **62**, for example by conducting the aza-Cope–Mannich rearrangement at room temperature, led only to the formation of **63**. This result provides final testament to the striking difference in reactivity of BOC- and pivaloyl-protected anilines in this series. Presumably the ready dehydration of **62** arises from the greater nucleophilicity of the nitrogen atom of a carbamate than an amide and underscores

(45) (a) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242. (b) Yoshida, K.; Nomura, S.; Ban, Y. *Tetrahedron* **1985**, *41*, 5495.
(46) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(47) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

the profound effects on reaction outcome that can arise from small changes in electron density.

Although the lengthy experimental endeavor summarized in Scheme IX did not realize our original objectives, the experience gained during this study did point the way to an eventual, highly successful, solution. In brief, it was apparent at this point that both hydrogens of the aniline nitrogen should be protected, both during the assembly of the azabicyclooctanol rearrangement substrate and the aza-Cope–Mannich reorganization.

An Efficient Total Synthesis of (±)-Akuammacine. Although a wide variety of groups are available for protecting one hydrogen of a primary amine, only a small handful shield both hydrogens. For our application we required a protecting group with considerable base stability yet one that would be readily removed at the end of the synthesis, preferably under conditions that would not cleave a methyl ester. A group that appeared to comply with these criteria was the 1,3-dimethylhexahydro-2-oxo-1,3,5-triazine ("triazone") protecting group, recently introduced by Knapp.[48]

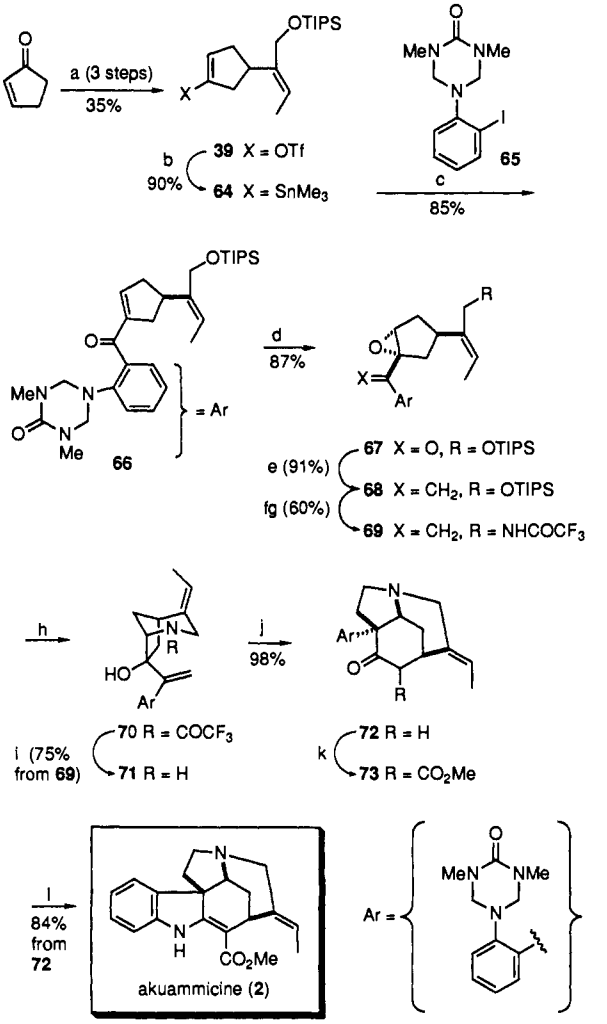
With the triazone protecting group, the total synthesis of (±)-akuammicine was readily accomplished, as summarized in Scheme X. The enol triflate **39** was initially converted to the vinylstannane **64** in 90% yield by palladium-catalyzed coupling with hexamethylditin.[49] Carbonylative cross coupling of this intermediate[50] with the triazone-protected 2-iodoaniline **65**[48] could be accomplished in good yield by using carbonylation conditions we had recently optimized for this application.[51] Critical to obtaining high yields of **66** in this carbonylative cross coupling was the use of Ph_3As, a ligand recently introduced by Farina for Stille-type alkylations of vinylstannanes.[52]

According to a sequence nearly identical to that originally developed in the pivaloyl series, enone **66** was epoxidized at −15 °C with *t*-BuOOH and Triton B to afford the anti epoxide **67** in 87% yield after separation of a minor amount of the syn stereoisomer on silica gel. Wittig methylenation of **67** provided the styrene **68**, which was readily converted to the allylic trifluoroacetamide **69** (55% overall from **67**) by displacement of the crude allylic chloride intermediate with sodium trifluoroacetamide at room temperature. Cyclization of the sodium salt of **69** occurred cleanly at 100 °C to provide the bicyclic amide **70**, which upon deacylation provided the desired rearrangement substrate **71** in 75% yield. This short sequence delivers the 2-azabicyclooctanol **71** in 11 total steps (nine purified intermediates) from 2-cyclopentenone.

Attempted aza-Cope–Mannich rearrangement of **71** by treatment with excess paraformaldehyde and 1.0 equiv of camphorsulfonic acid in refluxing acetonitrile led, not surprisingly, to destruction of the triazone protecting group. Cleavage of the triazone was easily avoided, however, by allowing the key aza-Cope–Mannich rearrangement of **71** to occur in the absence of added acid. This procedure afforded the desired azatricycloundecane **72** in essentially quantitative yield. The trace of formic acid present in paraformaldehyde is apparently sufficient to catalyze the iminium ion reorganization. The ability to orchestrate this key conversion under essentially neutral conditions is a particularly attractive feature of the aza-Cope–Mannich conversion.

Acylation of **72** with methyl cyanoformate[46] provided the β-keto ester **73**, which was not purified but directly converted to (±)-akuammicine (**2**) upon treatment at room temperature with 1 N HCl. This two-step sequence provided **2** in 84% overall yield from the azatricycloundecanone **72**. Synthetic (±)-akuammicine, mp 184 °C dec, was indistinguishable from a natural sample of (−)-akuammicine by 500-MHz ^1H NMR, 125-MHz ^{13}C NMR, and TLC comparisons. The synthesis (±)-akuammicine summarized in Scheme X is the first total synthesis of this widely-occurring *Strychnos* alkaloid. This synthesis was achieved by way of 10 isolated intermediates and was accomplished in ~8% overall yield from 2-cyclopentenone.

Scheme X[a]



[a] Conditions: (a) see Scheme VI; (b) 5% $Pd(PPh_3)_4$, $(Me_3Sn)_2$, LiCl, THF, reflux; (c) 2.5% $Pd_2(dba)_3$, 22% $AsPh_3$, CO (50 psi), **64**, LiCl, THF, 70 °C; (d) *t*-BuO_2H, Triton B, THF, −15 °C; (e) Ph_3PCH_3Br, KHMDS, THF, 0 °C, then **67**, 23 °C, 91%; (f) TBAF, THF, −15 °C, 97%; (g) MsCl, LiCl, DMF, −23 → 23 °C; H_2NCOCF_3, NaH, DMF, 23 °C, 62% two steps; (h) NaH, benzene, 100 °C; (i) KOH, EtOH–H_2O, 80 °C, 75% two steps; (j) $(CH_2O)_n$, Na_2SO_4, CH_3CN, reflux; (k) LDA, $NCCO_2Me$, THF, −78 °C; (l) 1 N HCl, 23 °C.

Conclusion

A direct approach for the total synthesis of *Strychnos* alkaloids has been developed. The key strategic element is the aza-Cope–Mannich rearrangement (Scheme II) of formaldiminium ions derived from azabicyclo[3.2.1]octanols **5** (Scheme I). This reorganization occurs with perfect stereochemical fidelity in high yield to form the intricate skeleton of this complex alkaloid group. The most refined realization of this strategy to date is found in the total synthesis of the natural *Strychnos* alkaloid (±)-akuammicine (**2**). The concise sequence leading to **2** is summarized in Scheme X; this total synthesis proceeds by way of 10 isolated intermediates and affords **2** in nearly 8% overall yield from 2-cyclopentenone.

(48) Knapp, S.; Hale, J. J.; Bastos, M.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109.
(49) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.
(50) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(51) Overman, L. E.; Pairaudeau, G., to be submitted for publication.
(52) (a) Farina, V.; Baker, S. R.; Begigni, D. A.; Hauck, S. I.; Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833. (b) Farina, V.; Krishman, B. J. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (c) Farina, V.; Baker, S. R.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 6043. (d) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243.

Critical to the success of this synthesis endeavor was the evolution, through extensive experimentation, of an efficient procedure for assembling the azabicyclo[3.2.1]octanol rearrangement substrates. Notable features of the final sequence are (a) the convergent carbonylative coupling of vinylstannane **64** and aryl iodide **65** to afford enone **66**, (b) the use of the 1,3-dimethylhexahydro-2-oxo-1,3,5-triazine group to protect the primary aniline nitrogen,[48] and (c) the strategic use of an intramolecular epoxide aminolysis to assemble the azabicyclooctanol **71**.

The aza-Cope–Mannich approach to *Strychnos* alkaloids recorded herein is easily extended to construct these targets in enantioselective fashion.[53] Moreover, incorporation of oxidation at the terminal carbon of the ethylidene appendage should allow ready access to more complex *Strychnos* alkaloids such as strychnine.

Experimental Section[54]

(*E*)-3-[1-(Hydroxymethyl)-1-propenyl]cyclopentanone (30). To a cooled (−78 °C) solution of vinyl bromide **35** (866 mg, 5.74 mmol) in ether (15 mL) was added *t*-BuLi (1.7 M in pentane, 10.1 mL, 17.2 mmol) dropwise over 15 min. The solution was allowed to warm to 0 °C and was maintained at 0 °C for 2 h.

To a cooled (0 °C) solution of thiophene (0.51 mL, 6.3 mmol) in THF (4 mL) was added *n*-BuLi (2.57 M in hexanes, 2.23 mL, 5.74 mmol). The resulting pale yellow solution was maintained for 30 min, at which time it was added via cannula to a cooled (−78 °C) suspension of CuCN (514 mg, 5.74 mmol) in THF (10 mL). The resulting suspension was allowed to warm to −40 °C and was stirred for 30 min at −40 °C, at which time it was a homogeneous brown-tan solution. This solution was then cooled to −78 °C. The dianion derived from the vinyl bromide, at this point a bright yellow solution, was cooled to −40 °C and added via cannula to the cuprate solution over 15 min. The resulting mixture was allowed to warm to −40 °C and was stirred at −40 °C for 30 min, at which time it was cloudy and brown. The mixture was then cooled to −78 °C, and chlorotrimethylsilane (1.46 mL, 11.5 mmol) was added. After 5 min, a solution of 2-cyclopentenone (0.48 mL, 5.7 mmol) in THF (4 mL) was added. The resulting mixture was stirred at −78 °C for 2 h, at which time the reaction was quenched (1:1 aqueous NH_4Cl–3% aqueous NH_4OH, 25 mL), allowed to warm to room temperature, and stirred at room temperature for several hours. The layers were then separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were concentrated, and the residue was taken up in 1:1 THF–Et_2O (15 mL) and 10% aqueous HCl (15 mL) and stirred at room temperature for 12 h. The layers were then separated, and the aqueous layer was extracted with Et_2O, dried (K_2CO_3), and concentrated. The residue was purified by flash chromatograph (1:1 hexanes–EtOAc) to afford 366 mg (41%) of alcohol **30** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (q, J = 6.9 Hz, 1 H, =C*H*CH$_3$), 4.07 (br s, 2 H, –C*H*$_2$OH), 3.18–3.26 (m, 1 H, =CRC*H*R$_2$), 2.26–2.36 (m, 3 H), 2.04–2.18 (m, 3 H), 1.87–1.96 (m, 1 H), 1.65 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 138.8, 124.7, 65.3, 43.0, 38.6, 36.5, 27.8, 13.0; IR (film) 3600–3300, 2964, 2917, 2898, 1729, 1403, 1171, 1136, 997 cm^{-1}; MS (EI) m/z 154 (M, 12%), 136 (7%), 83 (78%), 79 (91%), 55 (100%); HRMS (EI) m/z 154.0996 (M, 154.0994 calcd for $C_9H_{14}O_2$). Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 70.26; H, 9.45.

(*E*)-3-[1-(((Triisopropylsilyl)oxy)methyl)-1-propenyl]cyclopentanone (38). To a solution of alcohol **30** (298 mg, 1.93 mmol) in CH_2Cl_2 (8 mL) at room temperature was added 4-(dimethylamino)pyridine (472 mg, 3.86 mmol) followed by chlorotriisopropylsilane (0.46 mL, 2.1 mmol). The resulting solution was maintained at room temperature for 12 h and then diluted with H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with 1 N NaOH (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (20:1 hexanes–EtOAc) to afford 545 mg (91%) silyl ether **38** as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (q, J = 6.7 Hz, 1 H, =C*H*CH$_3$), 4.19 (AB q, J_{AB} = 12.8 Hz, $\Delta\nu_{AB}$ = 8.4 Hz, 2 H, =CRC*H*$_2$OR), 3.23 (m, 1 H, =CRC*H*R$_2$), 2.27–2.42 (m, 3 H), 2.20–1.97 (m, 3 H), 1.66 (d, J = 6.8 Hz, 3 H, =CHC*H*$_3$), 0.90–1.15 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 138.2, 122.5, 66.1, 42.8, 38.6, 36.7, 27.7, 18.0 (6C), 12.9, 11.9 (3C); IR (film) 2958, 2894, 2867, 1746, 1463, 1095, 1054, 882 cm^{-1}; MS (CI) m/z 311 (MH), 293, 267, 175, 137; HRMS (CI) m/z 311.2389 (MH, 311.2406 calcd for $C_{18}H_{35}O_2Si$).

(*E*)-1-(Trifluoromethanesulfonyl)oxy-4-[1-(((triisopropylsilyl)oxy)-methyl)-1-propenyl]cyclopentene (39). To a cooled (0 °C) solution of 1,1,3,3-tetramethyl-1,3-diphenyldisilazane[37] (7.4 mL, 26 mmol) in THF (30 mL) was added *n*-BuLi (2.7 M in hexanes, 8.0 mL, 21 mmol). The resulting solution was maintained at 0 °C for 30 min and then cooled to −78 °C, whereupon a solution of ketone **38** (2.2 g, 7.1 mmol) in THF (3 mL) was added. The resulting solution was maintained at −78 °C for 2.5 h, at which time a solution of *N*-phenyltrifluoromethanesulfonamide (5.1 g, 14 mmol) in THF (3 mL) was added. This solution was allowed to warm to 0 °C, stirred at 0 °C for an additional 2 h, and concentrated. The residue was purified by flash chromatography (2 × hexanes) to afford 2.7 g (87%) of enol triflate **39**, which was contaminated with <10% of regioisomer **40** (by ^{1}H NMR analysis). Data for **39**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (m, 1 H, TfOC=C*H*R), 5.58 (q, J = 6.9 Hz, 1 H, =C*H*CH$_3$), 4.20 (br s, 2 H, RC*H*$_2$OR), 3.51 (app quintet, J = 9.1 Hz, 1 H, =CRC*H*R$_2$), 2.48–2.75 (m, 4 H), 1.65 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$), 1.03–1.15 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 139.6, 121.6, 117.3, 65.8, 35.5, 34.7, 33.3, 18.0 (6 C), 13.0, 11.9 (3 C), F_3C- appeared as a low intensity quartet centered at 118.3; IR (film) 2945, 2895, 2868, 1662, 1425, 1247, 1212, 1144, 1114, 1057, 884, 836 cm^{-1}; MS (CI) m/z 443.1860 (MH, 443.1897 calcd for $C_{19}H_{34}F_3O_4SSi$), 399, 269, 175, 119.

(*E*)-4-[1-(((Triisopropylsilyl)oxy)methyl)-1-propenyl]-1-[(*N*-methoxy-*N*-methylamino)carbonyl]cyclopentene (41). To a solution of enol triflate **39** (1.9 g, 4.3 mmol) in DMF (35 mL) was added *N*,*O*-dimethylhydroxylamine (7.0 mL, ~64 mmol). This solution was flushed with CO for 10 min, whereupon $Pd(PPh_3)_4$ (330 mg, 0.30 mmol) was added. The resulting mixture was stirred at room temperature under 1 atm of CO (maintained with a balloon) for 30 min. The mixture was then diluted with H_2O and extracted with Et_2O. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (9:1 hexanes–EtOAc) to afford 1.5 g (94%) of the amide **41** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (br s, 1 H, R*H*C=CRCONR$_2$), 5.59 (q, J = 6.9 Hz, 1 H, =CC*H*CH$_3$), 4.18 (br s, 2 H, =CRC*H*$_2$OR), 3.63 (s, 3 H, -NOC*H*$_3$), 3.37 (app quintet, J = 9.1 Hz, 1 H, =CRC*H*R$_2$), 3.22 (s, 3 H, C*H*$_3$N-), 2.50–2.78 (m, 4 H), 1.63 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$), 0.96–1.15 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 139.9, 138.8, 136.9, 120.0, 65.1, 61.0, 38.0, 37.9, 37.0, 33.1, 18.0 (6 C), 12.9, 11.9 (3 C); IR (film) 2945, 2893, 2866, 1644, 1610, 1464, 1381, 1103, 1057, 883 cm^{-1}; MS (CI) m/z 382 (MH), 352, 338, 208, 175; HRMS (CI) m/z 382.2790 (382.2777 calcd for $C_{21}H_{40}O_3NSi$).

(*E*)-4-[1-(((Triisopropylsilyl)oxy)methyl)-1-propenyl]-1-[1-(2-trimethylacetamido)benzoyl)]cyclopentene (42). To a cooled (−78 °C) solution of 2-(trimethylacetamido)bromobenzene (430 mg, 1.7 mmol) in THF (15 mL) was added MeLi (1.5 M in ether, 1.2 mL, 1.7 mmol). The resulting solution was maintained at −78 °C for 10 min, whereupon *t*-BuLi (2.0 mL of a 1.7 M solution in pentane, 3.4 mmol) was added. The resulting solution was maintained for 1 h at −78 °C and then 5 min at 0 °C and was then recooled to −78 °C, whereupon a solution of amide **41** (320 mg, 0.84 mmol) in THF (5 mL) was added. After 30 min, the reaction was quenched with 10% aqueous HCl (5 mL). The mixture was stirred for 5 min while warming to room temperature and neutralized with saturated aqueous $NaHCO_3$. This mixture was diluted with H_2O, the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (20:1 → 10:1 hexanes–EtOAc) to afford 330 mg (77%) of enone **42** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 1 H, N*H*CO*t*-Bu), 8.60 (d, J = 8.4 Hz, 1 H, Ar H), 7.73 (dd, J = 7.8, 1.5 Hz, 1 H, Ar H), 7.51 (td, J = 7.8, 1.5 Hz, 1 H, Ar H), 7.07 (td, J = 7.6, 0.9 Hz, 1 H, Ar H), 6.45 (br s, 1 H, ArCO(R)C=C*H*R), 5.62 (q, J = 7.0 Hz, 1 H, =C*H*CH$_3$), 4.26 (AB q, J_{AB} = 12.7 Hz, $\Delta\nu_{AB}$ = 15.8 Hz, 2 H, =CRC*H*$_2$-OR), 3.52 (app quintet, J = 9.0 Hz, 1 H, =CRC*H*R$_2$), 2.73–2.86 (m, 4 H), 1.69 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$), 1.32 (s, 9 H, NCO*t*-*Bu*), 1.00–1.10 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 177.9, 146.6, 144.3, 139.8, 139.7, 133.6, 132.0, 124.4, 121.8, 121.3, 120.9, 65.8, 40.1, 39.0, 36.74, 36.70, 27.6 (3 C), 18.1 (6 C), 13.0, 12.0 (3 C); IR (film) 3325, 2944, 2866, 1691, 1624, 1603, 1562, 1521, 1447, 1294, 1242, 1159, 1100, 1056, 883 cm^{-1}; MS (CI) m/z 498.3415 (MH, 498.3401 calcd for $C_{30}H_{48}NO_3Si$), 454, 362, 324, 175.

(53) Unpublished results of S. D. Knight and G. Pairaudeau of these laboratories.

(54) General experimental details have been described.[55] All reactions were conducted under an atmosphere of N_2 or argon.

(55) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

(±)-(1R*,2S*,4S*)-4-[(1-((Triisopropylsilyl)oxy)methyl)-1-(E)-propenyl]-1-[1-(2-(trimethylacetamido)benzoyl)]-6-oxabicyclo[3.1.0]hexane (43). To a cooled (−23 °C) solution of enone **42** (131 mg, 0.26 mmol) in 2 mL of THF was added *t*-BuOOH (90%, 58 μL, 0.52 mmol) followed by Triton-B (40% in MeOH, 60 μL, 0.13 mmol). The resulting solution was maintained at −23 °C for 2 h, diluted with H_2O, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (15:1 hexanes–EtOAc) to afford 125 mg (92%) of epoxide **43** (contaminated with ~7–10% of what is believed to be the β-epoxide) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, J = 8.5 Hz, 1 H, Ar H), 8.13 (d, J = 8.0 Hz, 1 H, Ar H), 7.56 (app t, J = 8.2 Hz, 1 H, Ar H), 7.10 (app t, J = 8.3 Hz, 1 H, Ar H), 5.59 (q, J = 6.9 Hz, 1 H, =C*H*CH$_3$), 4.19 (AB q, J_{AB} = 12.3 Hz, $\Delta\nu_{AB}$ = 11.9 Hz, 2 H, =CRC*H*$_2$OR), 3.77 (s, 1 H, epoxide H), 3.09 (m, 1 H, =CRC*H*R$_2$), 2.26 and 2.41 (AB portion of ABX, J_{AB} = 13.9 Hz, J_{AX} = 10.5 Hz, J_{BX} = 7.7 Hz, 2 H), 2.11 and 2.21 (AB portion of ABX, J_{AB} = 14.3 Hz, J_{AX} = 7.6 Hz, J_{BX} = 10.7 Hz, 2 H), 1.65 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$), 1.34 (s, 9 H, NCO*t*-Bu), 1.10–1.04 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 178.3, 141.8, 136.7, 135.5, 132.1, 123.1, 122.1, 121.0, 120.5, 69.7, 66.5, 63.2, 40.4, 33.8, 32.5, 31.9, 27.6 (3 C), 18.1 (6 C), 13.1, 12.0 (3 C); IR (film) 3288, 2960, 2944, 2866, 1695, 1643, 1607, 1582, 1523, 1450, 1297, 1243, 1157, 1112, 1054, 883 cm^{-1}; MS (CI) m/z 514 (MH), 496, 470, 340, 204, 175, 102; HRMS (CI) m/z 514.3339 (514.3352 calcd for $C_{30}H_{48}NO_4Si$).

(±)-(1R*,2R*,4R*)-4-[1-((Triisopropylsilyl)oxy)methyl-1-(E)-propenyl]-1-[(1-(2-(trimethylacetamido)phenyl)ethenyl]-6-oxabicyclo[3.1.0]hexane (44). To a cooled (−78 °C) suspension of triphenylphosphonium bromide (240 mg, 0.67 mmol) in THF (1.5 mL) was added *n*-BuLi (2.5 M in hexanes, 0.24 mL, 0.61 mmol). The resulting mixture was allowed to warm to room temperature, stirred for 30 min at room temperature, and then recooled to −78 °C, whereupon a solution of keto epoxide **43** (104 mg, 0.20 mmol) in THF (1 mL) was added. The reaction was then allowed to warm to room temperature and stirred at room temperature for 3 h, at which time it was filtered through a small pad of silica gel and concentrated. The residue was purified by flash chromatography (15:1 hexanes–EtOAc) to afford 58 mg (56%) of **44** as a light oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (br s, 1 H, N*H*CO*t*-Bu), 8.02 (d, J = 8.2 Hz, 1 H, Ar H), 7.28 (td, J = 7.6, 2.0 Hz, 1 H, Ar H), 7.00–7.06 (m, 2 H, Ar H), 5.71 (d, J = 1.2 Hz, 1 H, R$_2$C=C*H*H), 5.53 (q, J = 6.9 Hz, 1 H, =C*H*CH$_3$), 5.29 (d, J = 1.2 Hz, 1 H, R$_2$C=CH*H*), 4.15 (br s, 2 H, RC*H*$_2$OR), 3.30 (s, 1 H, epoxide proton), 3.01 (app tt, J = 10.1, 7.9 Hz, 1 H, =CRC*H*R$_2$), 2.15 and 2.21 (AB portion of ABX, J_{AB} = 13.6 Hz, J_{AX} = 10.3 Hz, J_{BX} = 7.9 Hz, 2 H), 1.90 and 2.03 (AB portion of ABX, J_{AB} = 13.9 Hz, J_{AX} = 7.6 Hz, J_{BX} = 11.3 Hz, 2 H), 1.62 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$), 1.28 (s, 9 H, NHCO*t*-Bu), 1.02–1.10 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 144.4, 137.6, 135.9, 131.0, 129.5, 128.3, 123.7, 122.5, 122.4, 120.5, 68.6, 66.9, 64.3, 39.7, 32.5, 32.4, 31.6, 27.6 (3 C), 18.1 (6 C), 13.0, 11.9 (3 C); IR (film) 3431, 3350, 2960, 2944, 2856, 1687, 1583, 1521, 1448, 1303, 1100, 1056, 882 cm^{-1}; MS (CI) m/z 512 (MH), 494, 468, 338, 320, 236; HRMS (CI) m/z 512.3548 (512.3560 calcd for $C_{31}H_{50}NO_3Si$).

(±)-(1R*,2R*,4R*)-4-[1-(Chloromethyl)-1-(E)-propenyl]-1-[(1-(2-(trimethylacetamido)phenyl)ethenyl]-6-oxabicyclo[3.1.0]hexane (45). To a cooled (0 °C) solution of the silyl ether **44** (119 mg, 0.23 mmol) in THF (3 mL) was added *n*-Bu$_4$NF (1.1 M in THF, 0.85 mL, 0.93 mmol). The resulting solution was maintained for 1 h, at which time it was poured into saturated aqueous NaCl (20 mL) and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (3:2 hexanes–EtOAc) to afford 80 mg (97%) of the allylic alcohol as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (br s, 1 H, N*H*CO*t*-Bu), 8.02 (d, J = 8.2 Hz, 1 H, Ar H), 7.28 (ddd, J = 8.1, 5.7, 3.5 Hz, 1 H, Ar H), 7.04–7.07 (m, 2 H, Ar H), 5.73 (d, J = 1.2 Hz, 1 H, R$_2$C=C*H*H), 5.59 (q, J = 6.9 Hz, 1 H, =C*H*CH$_3$), 5.30 (d, J = 1.2 Hz, 1 H, R$_2$C=CH*H*), 4.03 (br s, 2 H, RC*H*$_2$OH), 3.31 (s, 1 H, epoxide H), 3.03 (app tt, J = 10.4, 7.7 Hz, 1 H, =CRC*H*R$_2$), 2.03 and 2.16 (AB portion of ABX, J_{AB} = 13.7 Hz, J_{AX} = 7.7 Hz, J_{BX} = 10.6 Hz, 2 H), 2.06 (dd, J = 14.3, 7.4 Hz, 1 H), 1.81 (ddd, J = 14.0, 10.6, 1.1 Hz, 1 H), 1.63 (d, J = 6.8 Hz, 3 H, =CHC*H*$_3$), 1.27 (s, 9 H, CO*t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 144.1, 138.3, 135.7, 130.8, 129.5, 128.4, 125.0, 123.8, 122.3 120.4, 68.2, 65.9, 64.1, 39.7, 32.7, 32.5, 31.9, 27.6 (3 C), 13.1; IR (film) 3550–3300, 2984, 2930, 2872, 1669, 1582, 1521, 1448, 1304 cm^{-1}; MS (CI) m/z 356 (MH), 338, 312, 254.

To a cooled (−23 °C) solution of a comparable sample of this alcohol (172 mg, 0.48 mmol) in CH_2Cl_2 (4 mL) was added diisopropylethylamine (0.33 mL, 1.92 mmol) followed by methanesulfonyl chloride (75 μL, 0.97 mmol). The resulting solution was maintained for 45 min, at which time it was poured into saturated aqueous NaCl (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in DMF (3 mL), and LiCl (61 mg, 1.4 mmol) was added. The resulting mixture was stirred at room temperature for 2 h and then diluted with Et_2O, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (5:1 hexanes–EtOAc) to afford 146 mg (82%) of the allylic chloride **45** as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (br s, 1 H N*H*CO*t*-Bu), 8.07 (d, J = 8.1 Hz, 1 H, Ar H), 7.29 (ddd, J = 8.2, 6.7, 2.4 Hz, 1 H, Ar H), 7.03–7.10 (m, 2 H, Ar H), 5.76 (d, J = 1.2 Hz, 1 H, R$_2$C=C*H*H), 5.74 (q, J = 6.9 Hz, 1 H, =C*H*CH$_3$), 5.33 (d, J = 1.1 Hz, 1 H, R$_2$C=CH*H*), 4.04 (br s, 2 H, RC*H*$_2$Cl), 3.33 (s, 1 H, epoxide H), 3.03 (app tt, J = 10.5, 7.7 Hz, 1 H, =CRC*H*R$_2$), 2.10 and 2.24 (AB portion of ABX, J_{AB} = 13.7 Hz, J_{AX} = 7.7 Hz, J_{BX} = 10.5 Hz, 2 H), 2.13 (app dd, J = 13.9, 7.6 Hz, 1 H), 1.88 (ddd, J = 14.0, 10.7, 1.1 Hz, 1 H), 1.67 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$), 1.28 (s, 9 H, CO*t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 144.0, 135.8, 135.1, 130.4, 129.5, 129.4, 128.5, 123.7, 122.1, 120.5, 68.0, 63.8, 48.8, 39.8, 32.9, 32.7, 31.9, 27.6 (3C), 13.7; IR (film) 3431, 3363, 2964, 2931, 2870, 1685, 1582, 1521, 1448, 1303, 1163, 923, 763 cm^{-1}; MS (EI) m/z 373 (M, 1), 337 (3), 288 (4), 169 (17), 57 (100).

(±)-(1R*,5S*,7S*)-4-(E)-Ethylidene-7-hydroxy-7-[1-(2-(trimethylacetamido)phenyl)ethenyl]-2-azabicyclo[3.2.1]octane (47). To a suspension of sodium hydride (60% dispersion in mineral oil, 14.5 mg, 0.36 mmol, washed with hexane) in DMF (3 mL) was added trifluoroacetamide (41 mg, 0.36 mmol). The resulting mixture was stirred at room temperature for 30 min, producing a clear colorless solution, to which a solution of chloride **45** (68 mg, 0.18 mmol) in DMF (3 mL) was added. The resulting solution was heated at 50–60 °C for 3 h and then poured into brine (10 mL), extracted with EtOAc, and washed with H_2O (15 mL). The combined organic extracts were dried (K_2CO_3) and concentrated. The residue was purified by flash chromatography (4:1 hexanes–EtOAc) to afford 74 mg (90%) of bicyclic amide **48** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$, peaks broadened and doubled due to the presence of conformational isomers) δ 9.0 and 8.6 (br s, 1 H, N*H*CO*t*-Bu), 8.20–8.40 (m, 1 H, Ar H), 7.30–6.95 (m, 3 H, Ar H), 5.15–5.75 (m, 3 H, vinylic H), 3.6–4.4 (m, 2 H), 3.35 (br s, 1 H), 2.50 (m, 1 H), 2.07 (m, 1 H), 1.50–1.70 (m, 3 H), 1.55 (br s, 3 H, =CHC*H*$_3$), 1.3 (m, 9 H, CO*t*-Bu); MS (CI) m/z 451 (MH), 433, 349.

To a solution of the bicyclic trifluoroacetamide **48** (74 mg, 0.16 mmol) in 2:1 EtOH–H_2O (6 mL) was added KOH (0.92 g, 16 mmol). The resulting solution was heated at reflux for 3 h, cooled, and diluted with H_2O. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were dried (K_2CO_3) and concentrated. The residue was purified by flash chromatography (8:1 $CHCl_3$–MeOH containing 2% Et_3N) to afford 52 mg (90%) of bicyclic amino alcohol **47** as an oil, which was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40–9.80 (br s, 1 H, N*H*CO*t*-Bu), 8.08 (d, J = 8.3 Hz, 1 H, Ar H), 7.27 (app t, J = 7.4 Hz, 1 H, Ar H), 7.21 (dd, J = 7.5, 1.2 Hz, 1 H, Ar H), 7.04 (app t, J = 7.4 Hz, 1 H, Ar H), 5.66 (s, 1 H, R$_2$C=C*H*H), 5.24 (s, 1 H, R$_2$C=CH*H*), 5.04 (q, J = 6.6 Hz, 1 H, =C*H*CH$_3$), 3.41 (app d, J = 13.9 Hz, 1 H), 3.27 (app t, J = 5.8 Hz, 1 H), 3.09 (br s, 1 H), 3.06 (br s, 1 H), 2.29–2.36 (m, 2 H), 2.00–2.11 (m, 2 H), 1.56 (d, J = 6.5 Hz, 3 H, =CHC*H*$_3$), 1.24 (s, 9 H, CO*t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$ some peaks doubled and/or broadened due to amide conformational isomers) 177.3, 177.2, 148.5, 136.4, 132.2, 128.3, 128.2, 127.9, 123.5, 123.4, 123.3, 123.2, 118.4, 113.6, 86.0 (br), 63.6 (br), 46.7 (br), 39.7, 35.3, 29.6, 27.6, 27.5, 12.0; MS (CI) m/z 355 (MH), 337, 108; HRMS (CI) m/z 355.2373 (355.2385 calcd for $C_{22}H_{31}N_2O_2$).

(±)-(1R*,7R*,8S*)-2-(E)-Ethylidene-7-[2-(trimethylacetamido)-phenyl]-4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one (49). To a solution of amino alcohol **47** (52 mg, 0.15 mmol) in CH_3CN (3 mL) was added sequentially Na_2SO_4 (42 mg, 0.29 mmol), paraformaldehyde (6.6 mg, 0.22 mmol) and camphorsulfonic acid (34 mg, 0.15 mmol). This mixture was heated at reflux for 1 h, at which time it was cooled to room temperature, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (K_2CO_3), and concentrated. The residue was purified by flash chromatography (15:1 $CHCl_3$–MeOH) to afford 47 mg (88%) of ketone **49** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (br s, 1 H, N*H*CO*t*-Bu), 7.94 (dd, J = 8.2, 1.3 Hz, 1 H, Ar H), 7.40 (d, J = 7.7 Hz, 1 H, Ar H), 7.27 (td, J = 7.7, 1.2 Hz, 1 H, Ar H), 7.10 (td, J = 7.4, 1.4 Hz, 1 H, Ar H), 5.42 (q, J = 6.8 Hz, 1 H, =C*H*CH$_3$), 3.78 (br s, 1 H, R$_2$NC*H*R$_2$), 3.38 (dt, J = 13.5, 8.5 Hz, 1 H), 3.32 (br s, 1 H), 3.28 (d, J = 14.6 Hz, 1 H), 2.85–2.92 (m,

2 H), 2.79 (ddd, J = 12.1, 8.6, 2.9 Hz, 1 H), 2.69 (app dt, J = 13.3, 2.8 Hz, 1 H), 2.64 (dd, J = 16.3, 5.2 Hz, 1 H), 2.43 (app dd, J = 16.3, 2.1 Hz, 2 H), 2.05 (ddd, J = 13.5, 9.0, 2.9 Hz, 1 H), 1.63 (dd, J = 6.8, 1.8 Hz, 3 H, =CHCH_3), 1.41 (s, 9 H, COt-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.7, 177.2, 138.3, 135.4, 129.9, 128.0, 126.5, 126.3, 124.4, 120.1, 64.8, 60.7, 54.1, 52.8, 45.4, 39.8, 36.1, 31.3, 29.5, 27.6 (3 C), 12.5; MS (EI) m/z 366 (M, 1), 351 (1), 309 (1), 281 (2), 121 (19), 57 (100); MS (CI) m/z 367 (MH); HRMS (EI) m/z 366.2294 (366.2317 calcd for $C_{23}H_{30}N_2O_2$).

Preparation of (±)-Dehydrotubifoline (3). To a solution of pivaloylamide **49** (8.0 mg, 0.022 mmol) in 2:1 EtOH–H_2O (3 mL) was added a large excess of KOH. The mixture was degassed and heated at reflux for 2.5 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc, washed with H_2O (2 × 15 mL), dried (K_2CO_3), and concentrated. The residue was purified by flash chromatography (10:1 $CHCl_3$–MeOH containing 2% Et_3N) to afford 4 mg (70%) of dehydrotubifoline (**3**) as a colorless powder, mp 80 °C dec. This sample was indistinguishable from a sample of **3** prepared from natural akuammicine[12] by ^{1}H NMR, ^{13}C NMR, MS, and TLC comparisons: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.7 Hz, 1 H, Ar H), 7.36 (d, J = 7.2 Hz, 1 H, Ar H), 7.32 (td, J = 7.6, 1.1 Hz, 1 H, Ar H), 7.20 (td, J = 7.4, 0.6 Hz, 1 H, Ar H), 5.42 (q, J = 6.9 Hz, 1 H, =CHCH$_3$), 4.05 (br s, 1 H, R_2NCHR$_2$), 3.79 (d, J = 15.5 Hz, 1 H, =CRCHHNR$_2$), 3.31–3.45 (m, 3 H), 3.21–3.24 (m, 1 H), 3.19 (d, J = 15.5 Hz, 1 H), 2.72 (d, J = 15.5 Hz, 1 H, =CRCHHNR$_2$), 2.20 (symmetrical m, 2 H), 1.73–1.88 (m, 2 H), 1.68 (d, J = 6.9 Hz, 3 H, =CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 154.5, 144.2, 142.0, 127.9, 125.4, 121.4, 120.0, 119.8, 66.8, 65.5, 55.6, 53.8, 36.1, 35.2, 30.3, 25.5, 13.0; MS (EI) m/z 264 (M, 22), 249 (4), 233 (16), 180 (29), 158 (75), 121 (86), 93 (100).

1,3-Dimethyl-5-(2-iodophenyl)-hexahydro-2-oxo-1,3,5-triazine (65): 1,3-Dimethylurea (26 g, 29 mmol) was dissolved in 37% aqueous formaldehyde solution (160 mL, 2.2 mol) and heated at 120 °C for 1 h, at which time freshly distilled 2-iodoaniline (14 g, 64 mmol) was added. The resulting solution was maintained at 120 °C for 48 h, at which time the reaction mixture was allowed to cool to room temperature and extracted with Et_2O (2 × 300 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$), and concentrated. Recrystallization of the residue from EtOAc gave 15 g (72%) of iodide **65** as a white solid. Spectral data were identical to those reported for **65**.[48]

(*E*)-1-(Trimethylstannyl)-4-[1-(((tripropylsilyl)oxy)methyl)-1-propenyl]cyclopentene (64). According to the general procedure of Wulff,[49] triflate **39** (5.0 g, 11 mmol) was dissolved in THF (50 mL) and charged with a solution of hexamethylditin (3.7 g, 11 mmol) in THF (50 mL), followed by LiCl (2.9 g, 68 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.65 g, 0.57 mmol). The resulting solution was heated at reflux for 3 h, allowed to cool to 23 °C, and concentrated. Purification of the residue by flash chromatography (3% Et_3N–hexanes) gave 4.6 g (90%) of stannane **64** as a colorless oil: ^{1}H (500 MHz, $CDCl_3$) δ 5.86 (m, SnC=CHR), 5.57 (q, J = 6.9 Hz, C=CHMe), 4.13 (s, 2 H, CH_2-OTIPS), 3.31 (quintet, J = 8.9 Hz, 1 H, C=CCHR$_2$), 2.50–2.62 (m, 2 H), 2.34–2.41 (m, 2 H), 1.65 (d, J = 6.9 Hz, 3 H, C=CCH$_3$), 1.05–1.11 (m, 21 H, OTIPS), 0.12 (t, J = 27 Hz, 9 H, Snt-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 141.5, 140.0, 118.0, 64.4, 43.6, 39.1, 37.1, 18.0, 12.8, 11.9, –10.3; IR (film) 2958, 2943, 2922, 2894, 2866, 1454, 1101, 1059, 883, 768, 882 cm^{-1}; HRMS (CI) m/z 453.1918 (MH, 453.1944 calcd for $C_{21}H_{42}OSi^{116}Sn$).

(*E*)-4-[1-(((Triisopropylsilyl)oxy)methyl)-1-propenyl]-1-[1-(2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]benzoyl)]cyclopentene (66): To a solution of tris(dibenzylideneacetone)dipalladium(0) (200 mg, 0.2 mmol) and $AsPh_3$ (580 mg, 2.0 mmol) in *N*-methyl-2-pyrrolidinone (NMP) (50 mL) was added a solution of LiCl (1.4 g, 33 mmol) in NMP (50 mL) via cannula. The resulting yellow solution was stirred for 5 min at room temperature in a Fisher-Porter pressure bottle, at which time a solution of stannane **64** (4.0 g, 8.8 mmol), iodide **65** (2.9 g, 8.8 mmol),[48] and NMP (100 mL) was added via cannula. The reaction vessel was then evacuated and refilled with CO (3 × 50 psig), and the resulting mixture was heated at 70 °C for 16 h, at which time it was diluted with EtOAc (400 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 200 mL), and the combined aqueous layers were extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (49:49:2 EtOAc–hex–Et_3N → 4:1 EtOAc–hex) gave 3.9 g (85%) of enone **66** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (td, J = 7.6, 1.2 Hz, 1 H, Ar H), 7.15–7.24 (m, 3 H, Ar H), 6.33 (app d, J = 2.0 Hz, 1 H, O=CC=CH), 5.58 (q, J = 6.8 Hz, 1 H, C=CHMe), 4.46 (s, 4 H, NCH$_2$N), 4.21 (app d, J = 8.0 Hz, 2 H, CH_2OTIPS), 3.46 (quintet, J = 9.0 Hz, 1 H, C=CCHR$_2$), 2.84 (s, 6 H, NCH$_3$), 2.67–2.83 (m, 4 H), 1.65 (d, J = 6.8 Hz, 3 H, C=CCH$_3$), 0.98–1.15 (m, 21 H, OTIPS); IR (film) 2944, 2866, 1680, 1648, 1515, 1304, 755 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 156.1, 147.9, 146.6, 145.6, 139.7, 136.0, 130.6, 128.3, 124.2, 122.6, 120.8, 68.6, 65.8, 38.7, 37.0, 35.2, 32.0, 18.0, 12.9, 11.8; MS (CI) m/z 526.3420 (MH, 526.3462 calcd for $C_{30}H_{48}N_3O_3Si$), 482, 382, 352, 252, 117.

(±)-(1*R,2*S**,4*S**)-4-[1-(((Triisopropylsilyl)oxy)methyl)-1-(*E*)-propenyl]-1-[1-(2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]benzoyl)]-6-oxabicyclo[3.1.0]hexane (67):** To a cooled (–15 °C) solution of enone **66** (1.8 g, 3.4 mmol) in THF (35 mL) was added *tert*-butylhydroperoxide (90%, 1.9 mL, 17 mmol) followed by Triton-B (40% in MeOH, 1.6 mL, 3.4 mmol). The resulting solution was maintained at –15 °C for 2 h, which time it was allowed to warm to 0 °C and was diluted with Et_2O (100 mL), washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (1:1 EtOAc–hexanes → 4:1 EtOAc–hexanes) gave 1.6 g (87%) of epoxide **67** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.39 (m, 1 H, Ar H), 7.20–7.25 (m, 3 H, Ar H), 5.56 (q, J = 6.8 Hz, 1 H, C=CHMe), 4.53 (AB, J = 11.9 Hz, 2 H, NCH$_2$N), 4.38 (AB, J = 11.9 Hz, 2 H, NCH$_2$N), 4.15 (app d, J = 8.9 Hz, 2 H, CH_2OTIPS), 3.51 (s, 1 H, epoxide H), 2.91–2.98 (m, 1 H, C=CCHR$_2$), 2.84 (s, 6 H, NCH$_3$), 2.45–2.50 (m, 1 H), 2.03–2.10 (m, 2 H), 1.90–1.95 (m, 1 H), 1.61 (d, J = 6.9 Hz, 3 H, C=CCH$_3$), 0.97–1.14 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 156.0, 147.3, 137.0, 135.1, 131.1, 126.8, 125.2, 123.2, 122.3, 69.2, 68.8, 66.3, 63.4, 32.3, 31.9, 31.7, 30.6, 17.9, 12.8, 11.9; IR (film) 2959, 2946, 2925, 1689, 1648, 1516, 1303, 765 cm^{-1}; MS (CI) m/z 542.3394 (MH, 542.3411 calcd for $C_{30}H_{47}N_3O_4Si$) 311 (8), 234 (18), 206 (12), 175 (100), 128 (72). Anal. Calcd for $C_{30}H_{47}N_3O_4Si$: C, 66.51; H, 8.74; N, 7.76. Found: C, 66.59; H, 8.77; N, 7.72.

(±)-(1*R,2*R**,4*R**)-4-[1-(((Triisopropylsilyl)oxy)methyl)-1-(*E*)-propenyl]-1-[1-(2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]phenyl)-ethenyl]-6-oxabicyclo[3.1.0]hexane (68):** To a cooled (0 °C) suspension of triphenylphosphonium bromide (5.6 g, 16 mmol) in THF (15 mL) was added KHMDS (0.5 M in toluene, 29 mL, 14 mmol). The bright yellow mixture was allowed to warm to room temperature and stirred at room temperature for 0.5 h, at which time it was cooled back to 0 °C, and a solution of epoxide **67** (1.7 g, 2.9 mmol) in THF (20 mL) was added via cannula. The resulting mixture was allowed to warm to room temperature and was stirred at room temperature for 4 h, whereupon the reaction was quenched with H_2O (25 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (1:1 EtOAc–hexane → 4:1 EtOAc–hexane) gave 1.5 g (91%) of styrene **68** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (m, 1 H, Ar H), 7.15 (m, 1 H, Ar H), 7.09 (m, 2 H, Ar H), 5.57 (d, J = 1.3 Hz, 1 H, C=CH$_2$), 5.54 (q, J = 6.9 Hz, 1 H, C=CHMe), 5.24 (d, J = 1.3 Hz, 1 H, C=CH$_2$), 4.48 (m, 4 H, NCH$_2$N), 4.00–4.07 (m, 2 H, CH_2OTIPS), 3.36 (s, 1 H, epoxide H), 2.91–3.01 (m, 1 H, C=CCHR$_2$), 2.84 (s, 6 H, NCH$_3$), 2.01–2.06 (m, 1 H), 1.90–1.94 (m, 1 H), 1.70–1.76 (m, 2 H), 1.58 (d, J = 6.9 Hz, 3 H, C=CCH$_3$), 0.98–1.14 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 146.3, 146.2, 137.1, 134.8, 131.1, 129.0, 124.7, 121.6, 121.4, 116.3, 67.8, 67.0, 65.5, 65.2, 32.9, 32.3, 31.9, 31.6, 18.0, 12.8, 11.8; IR (film) 2958, 2942, 2926, 2866, 1648, 1515, 1302, 759 cm^{-1}; MS (CI) m/z 540.3628 (MH, 540.3618 calcd for $C_{31}H_{49}N_3O_3Si$) 528 (19), 510 (27), 354 (97), 175 (43). Anal. Calcd for $C_{31}H_{49}N_3O_3Si$: C, 68.97; H, 9.15; N, 7.78. Found: C, 68.71; H, 9.13; N, 7.67.

(±)-(1*R,2*R**,4*R**)-4-[1-((Trifluoroacetamido)methyl)-1-(*E*)-propenyl]-1-[1-(2-[5-(1,3-dimethylhexahydro-2-oxa-1,3,5-triazinyl)]-phenyl)ethenyl]-6-oxabicyclo[3.1.0]hexane (69).** To a cooled (–15 °C) solution of silyl ether **68** (1.3 g, 2.4 mmol) in THF (10 mL) was added *n*-Bu$_4$NF (1.0 M in THF, 7.2 mL, 7.2 mmol). The reaction was maintained at –15 °C for 1 h, at which time it was poured into saturated aqueous NaCl (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (3:2 hexanes–EtOAc) afforded 890 mg (97%) of the allylic alcohol: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09–7.19 (m, 2 H, Ar H), 6.95–7.04 (m, 2 H, Ar H), 5.51 (d, J = 1.5 Hz, 1 H, C=CH$_2$), 5.43 (q, J = 6.8 Hz, C=CHMe), 5.18 (d, J = 1.5 Hz, 1 H, C=CH$_2$), 4.40 (s, 4 H, NCH$_2$N), 3.85 (s, 2 H, CH_2OH), 3.27 (s, epoxide H), 2.85–2.92 (m, C=CCHR$_2$), 2.73 (s, 6 H, NCH$_3$), 2.14 (br s, OH), 1.96 (dd, J = 13.8, 7.5 Hz, 1 H, CH$_2$R$_2$), 1.83 (dd, J = 13.6, 7.7 Hz, 1 H, CH$_2$R$_2$), 1.55–1.75 (m, 2 H, CH$_2$R$_2$), 1.49 (d, J = 6.8 Hz, C=CCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 146.2,

146.0, 138.3, 134.6, 131.1, 128.9, 124.6, 124.1, 121.0, 116.1, 67.6, 66.8, 66.0, 65.5, 33.2, 32.3, 31.9, 31.7, 12.8; IR (film) 3356, 3015, 2931, 2866, 1635, 1521, 1308, 754 cm^{-1}; MS (CI) m/z 384.2292 (MH, 384.2275 calcd for $C_{22}H_{29}N_3O_3$) 340 (5), 284 (40), 266 (5), 230 (4), 139 (15).

The allylic alcohol was then converted to the allylic chloride according to the same procedure used to prepare chloride **45**. To a suspension of sodium hydride (60% dispersion in mineral oil, 160 mg, 4.0 mmol, washed with hexanes) in DMF (10 mL) was added 2,2,2-trifluoroacetamide (580 mg, 5.1 mmol). The resulting mixture was stirred at room temperature for 30 min, producing a clear colorless solution to which a solution of the crude allylic chloride (820 mg, 2.0 mmol) in DMF (10 mL) was added via cannula. The resulting solution was maintained for 12 h, at which time it was poured into 20% brine solution (30 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (2:1 EtOAc–hexane → 4:1 EtOAc–hexane) gave 690 mg (60% from **68**) of amide **69** as a white solid: mp 127–128.5 °C (EtOAc–hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.28 (m, 1 H, Ar H), 7.16–7.18 (m, 1 H, Ar H), 7.08–7.12 (m, 2 H, Ar H), 6.24 (br s, NH), 5.57 (d, J = 0.7 Hz, 1 H, C=CH_2), 5.50 (q, J = 6.7 Hz, C=C*H*Me), 5.25 (d, J = 0.7 Hz, 1 H, C=CH_2), 4.48–4.54 (m, 4 H, NCH_2N), 3.68 and 3.77 (ABX, J_{AB} = 14.5 Hz, J_{AX} = 5.6 Hz, J_{BX} = 4.5 Hz, 2 H, $CH_2NHCOCF_3$), 3.37 (s, epoxide H), 2.98–3.02 (m, C=$CCHR_2$), 2.84 (s, 6 H, NCH_3), 2.03 (dd, J = 13.7, 7.2 Hz, 1 H), 1.86 (dd, J = 13.6, 7.5 Hz, 1 H), 1.62 (d, J = 6.7 Hz, 3 H, C=CCH_3), 1.43–1.54 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5 (q, J = 6.7 Hz, *C*OCF_3), 155.9, 146.0, 145.9, 134.3, 133.3, 131.2, 129.1, 126.0, 124.7, 121.1, 116.1, 115.6 (q, J = 288.0 Hz, CF_3), 67.6, 66.5, 65.7, 42.1, 32.8, 32.6, 31.9, 31.4, 13.0; IR (film) 3250, 2931, 2877, 1716, 1636, 1522, 1308, 1199, 754 cm^{-1}; MS (CI) m/z 479.2270 (MH, 479.2270 calcd for $C_{24}H_{30}F_3N_4O_3$) 422 (57), 379 (69), 115 (56), 101 (38). Anal. Calcd for $C_{24}H_{29}F_3N_4O_3$: C, 60.22; H, 6.11; N, 11.71. Found: C, 60.39; H, 6.19; N, 11.60.

(±)-(1*R,5*S**,7*S**)-4-(*E*)-Ethylidene-7-hydroxy-7-[1-(2-[5-(1,3-dimethylhexahydro-2-oxa-1,3,5-triazinyl)]phenyl)ethenyl]-2-azabicyclo-[3.2.1]octane (71).** To a solution of amide **69** (300 mg, 0.6 mmol) in benzene (15 mL) was added sodium hydride (60% dispersion in mineral oil, 80 mg, 2.0 mmol). After H_2 evolution had ceased, the reaction mixture was heated to 100 °C and maintained for 48 h, at which time the solvent was removed in vacuo to furnish crude tertiary amide **70**. This sample was dissolved in 5:1 EtOH–H_2O (10 mL), and KOH (1.7 g, 30 mmol) was added. The resulting solution was heated to 70 °C and maintained at 70 °C for 3 h, at which time it was diluted with H_2O (20 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (9:1 $CHCl_3$–MeOH) gave 180 mg (75%) of bicyclic amine **71** as a white solid: mp 87–88 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16–7.33 (m, 4 H, Ar H), 5.72 (s, 1 H, C=CH_2), 5.39 (s, 1 H, C=CH_2), 5.03 (q, J = 6.6 Hz, C=C*H*Me), 4.48 (br s, 4 H, NCH_2N), 3.24–3.38 (br m, 1 H), 3.18–3.22 (m, 1 H), 3.04 (app d, J = 13.0 Hz, 1 H), 2.83 (s, 6 H, NCH_3), 2.21–2.28 (m, 1 H), 1.82–2.21 (m, 4 H), 1.51 (m, C=CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 152.7, 144.9, 138.6, 131.1, 129.1, 128.1, 126.5, 122.7, 120.3, 113.9, 84.4, 67.9, 63.4, 47.2, 43.6, 36.7, 35.5, 32.3, 12.0; IR (film) 3390, 2946, 2925, 2866, 1644, 1520, 1307, 753 cm^{-1}; MS (CI) m/z 383.2413 (MH, 383.2445 calcd for $C_{22}H_{31}N_4O_2$) 295 (34), 265 (35), 113 (39), 108 (81).

(±)-(1*R,7*R**,8*S**)-2-(*E*)-Ethylidene-7-[2-[5-(1,3-dimethylhexahydro-2-oxa-1,3,5-triazine)]phenyl]-4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one (72).** To a solution of bicyclic amine **71** (170 mg, 0.44 mmol) in CH_3CN (5 mL) was added sodium sulfate (630 mg, 4.4 mmol) and paraformaldehyde (67 mg, 2.2 mmol). The resulting mixture was heated to reflux for 10 min, at which time it was concentrated. Purification of the residue by flash chromatography (19:1 $CHCl_3$–MeOH) gave 172 mg (98%) of ketone **72** as a white solid: mp 135–136 °C (EtOAc–hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.9 Hz, 1 H, Ar H), 7.30 (dd, J = 7.9, 7.3 Hz, 1 H, Ar H), 7.27 (d, J = 7.6 Hz, 1 H, Ar H), 7.22 (dd, J = 7.6, 7.3 Hz, 1 H, Ar H), 5.43 (q, J = 6.7 Hz, 1 H, C=C*H*Me), 4.12 and 4.53 (AB, J_{AB} = 11.5 Hz, 2 H, NCH_2N), 3.99 (app d, J = 11.4 Hz, 2 H, NCH_2N), 3.57 (app d, J = 14.9 Hz, 1 H, NCH_2R), 3.48 (app d, J = 12.1 Hz, 1 H, NCH_2R), 3.34 (m, 1 H, C=C*H*R_2), 3.22 (s, 1 H), 2.99 (app d, J = 14.2 Hz, 1 H), 2.98 (m, 1 H), 2.93 (s, 3 H, NCH_3), 2.76 (s, 3 H, NCH_3), 2.71 and 2.73 (AB, J_{AB} = 5.4 Hz, 2 H, CCH_2C), 2.57 (app d, J = 14.3 Hz, 1 H), 2.05–2.12 (m, 2 H), 1.90 (app d, J = 14.2 Hz, 1 H), 1.62 (d, J = 6.7 Hz, C=CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 155.8, 146.8, 139.6, 134.8, 128.3, 128.2, 127.7, 126.1, 121.7, 69.6, 69.0, 68.7, 61.7, 53.8, 53.7, 46.1, 38.8, 32.7, 31.8, 31.7, 25.9, 12.7; IR (film) 2925, 2875, 1650, 1606, 1488, 1460, 1362, 1294, 754 cm^{-1}; MS (CI) m/z 395.2443 (MH, 395.2345 calcd for $C_{23}H_{31}N_4O_2$) 206 (3), 130 (28). Anal. Calcd for $C_{23}H_{30}N_4O_2$: C, 70.02; H, 7.66; N, 14.20. Found: C, 69.90; H, 7.64; N, 14.09.

Preparation of (±)-Akuammicine (2). To a cooled (0 °C) solution of diisopropylamine (0.21 mL, 1.5 mmol) in THF (2 mL) was added *n*-BuLi (2.3 M in hexanes, 0.53 mL, 1.2 mmol). The resulting solution was maintained at 0 °C for 0.5 h, at which time it was cooled to −78 °C, and ketone **72** (160 mg, 0.40 mmol) in THF (2 mL) was added via cannula. The reaction mixture was then allowed to warm to 0 °C, where it was maintained for 0.5 h, at which time it was cooled to −78 °C and methyl cyanoformate (0.10 mL, 1.2 mmol) was added. The resulting mixture was maintained at −78 °C for 2 h, whereupon the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The mixture was allowed to warm to room temperature and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to afford the crude β-ketoester **73**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.3 Hz, Ar H), 7.20–7.25 (m, 3 H, Ar H), 5.41 (q, J = 6.7 Hz, C=C*H*CH_3), 4.60 (d, J = 11.6 Hz, 1 H, NCH_2N), 4.55 (d, J = 11.2 Hz, 1 H, NCH_2N), 4.01 (dd, J = 11.2, 2.1 Hz, 1 H, NCH_2N), 3.97 (dd, J = 11.6, 2.1 Hz, 1 H, NCH_2N), 3.83 (t, J = 3.1 Hz, 1 H, NC*H*R_2), 3.78 (s, OCH_3), 3.20–3.27 (m, 4 H), 3.02 (dd, J = 11.9, 7.5 Hz, 1 H), 2.89 (s, NCH_3), 2.87 (s, NCH_3), 2.82–2.87 (m, 1 H), 2.61 (dd, J = 14.4, 6.9 Hz, 1 H), 1.77–1.84 (m, 2 H), 1.71 (d, J = 6.7 Hz, C=$CHCH_3$), 1.57–1.63 (m, 1 H); ^{13}C NMR (125 MHz) δ 177.0, 172.4, 156.0, 147.6, 141.2, 135.2, 130.2, 128.4, 128.2, 127.4, 118.4, 100.0, 69.3, 69.2, 68.6, 55.5, 55.4, 54.0, 51.7, 38.7, 32.2, 32.1, 27.8, 25.6, 12.3; MS (CI) m/z 453.2466 (MH, 453.2500 calcd for $C_{25}H_{33}N_4O_4$) 395, 353, 294, 162.

This residue was dissolved in 1 N HCl (10 mL) and maintained at room temperature for 3 h, at which time it was basified with 20% NaOH and extracted with ether (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (19:1 $CHCl_3$–MeOH) gave 110 mg (84%) of (±)-akuammicine (**2**): mp 184 °C (decomposes to red-brown froth, from EtOH–H_2O); lit.[10b] mp 187.5 °C dec. Spectral and TLC data for this material were indistinguishable from those of natural akuammicine.

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Supplementary Material Available: Experimental procedures and characterization data for the preparation of compounds **10**, **13–15**, **17–22**, **25**, **52**, **54–61** and **63** (19 pages). Ordering information is given on any current masthead page.