Biogenetically Inspired Approach to the *Strychnos* Alkaloids. Concise Syntheses of (±)-Akuammicine and (±)-Strychnine

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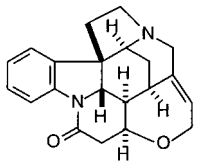
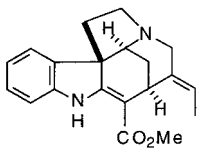
Received April 11, 2001

Abstract: A linear synthesis of the indole alkaloid (±)-akuammicine (**2**) was completed by a novel sequence of reactions requiring only 10 steps from commercially available starting materials. The approach features a tandem vinylogous Mannich addition and an intramolecular hetero Diels−Alder reaction to rapidly assemble the pentacyclic heteroyohimboid derivative **8** from the readily available hydrocarboline **6**. Oxidation of the E ring of **8** gave the lactone **9** that was converted into deformylgeissoschizine (**11**). The subsequent elaboration of **11** into **2** was effected by a biomimetically patterned transformation that involved sequential oxidation and base-induced skeletal reorganization. A variation of these tactics was then applied to the synthesis of the C(18) hydroxylated akuammicine derivative **36**. Because **36** had previously been converted into strychnine (**1**) in four steps, its preparation constitutes a concise, formal synthesis of this complex alkaloid.

Strychnine (**1**), which is found in large amounts in the Indian poison nut (*Strychnos nux vomica*) and Saint Ignatius' bean (*Strychnos ignatii*), has a long and rich history as one of the most notorious of the indole alkaloids.[1,2] The renowned toxicity of strychnine results from its interaction with the strychnine-sensitive glycine receptor in the lower brain stem and the spinal cord, thereby disrupting normal nerve cell signaling and leading to overexcitation of the motor system and intense muscular convulsions.[3] Strychnine was first isolated in pure form by Pelletier and Caventou in 1818.[4] The extensive degradative and structural studies that ensued finally culminated in 1946 when Robinson first proposed the correct structure of strychnine.[5] A year later, Woodward independently suggested the same structure and referred to strychnine as the most complex substance known for its molecular size.[6] Given that a mere 24 skeletal atoms are arrayed in seven rings with six contiguous stereogenic centers in **1**, this elite status arguably endures. The structure and absolute configuration of strychnine were unequivocally established by X-ray crystallography.[7] The related alkaloid akuammicine (**2**) was isolated from the seeds of *Picralima klaineana* more than a century after the isolation of strychnine,[8] and its structure was elucidated shortly after that of **1**.[9]



1



2

The daunting structural complexity of **1** coupled with its biological activity has served as the impetus for numerous synthetic investigations. It is only fitting that the first total synthesis of **1** was completed by Woodward in 1954, an event that perhaps signaled the genesis of the modern era of complex molecule synthesis.[10] After Woodward's pioneering achievement, there was considerable interest in the *Strychnos* alkaloids,[1] but strychnine did not succumb again to total synthesis until 1992 when Magnus reported the synthesis of **1** via the Wieland−Gumlich aldehyde.[11] Shortly thereafter, Stork,[12] Overman,[13] Kuehne,[14] Rawal,[15] and more recently Bonjoch and Bosch[16] and

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(2) Creasey, W. A. In *The Monoterpene Indole Alkaloids*; Saxton, J. E., Ed.; Interscience: New York, 1983; p 800. (b) Franz, D. N. *The Pharmacological Basis of Therapeutics;* Gilman, A. G., Goodman, L. S., Gilman, A., Eds.; Macmillan: New York, 1980. (c) Barron, S. E.; Guth, P. S. *Trends Pharm. Sci.* **1987**, *8*, 204.

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(6) Woodward, R. B.; Brehm, W. J.; Nelson, A. L. *J. Am. Chem. Soc.* **1947**, *69*, 2250. (b) Woodward, R. B.; Brehm, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 2107.

(7) Robinson, J. H.; Beevers, C. A. *Acta Crystallogr.* **1951**, *4*, 270. (b) Peerdeman, A. F. *Acta Crystallogr.* **1956**, *9*, 824.

(8) Henry, T. A.; Sharp, T. M. *J. Chem. Soc.* **1927**, 1950.

(9) Millson, P.; Robinson, R.; Thomas, A. F. *Experientia* **1953**, *9*, 89. (b) Edwards, P. N.; Smith, G. F. *J. Chem. Soc.* **1961**, 152.

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(11) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. (b) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116.

(12) Stork, G. Reported at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992.

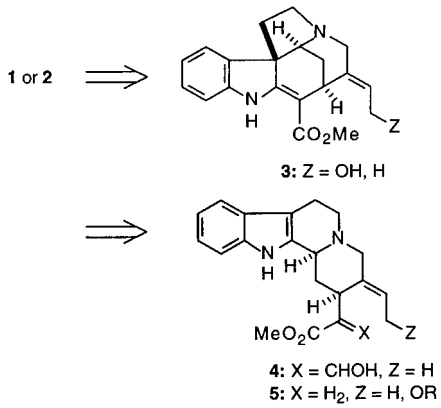
(13) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293−9294. (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776.

(14) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. (b) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427.

(15) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.

10.1021/ja010935v CCC: $20.00
Published on Web 07/31/2001

Scheme 1

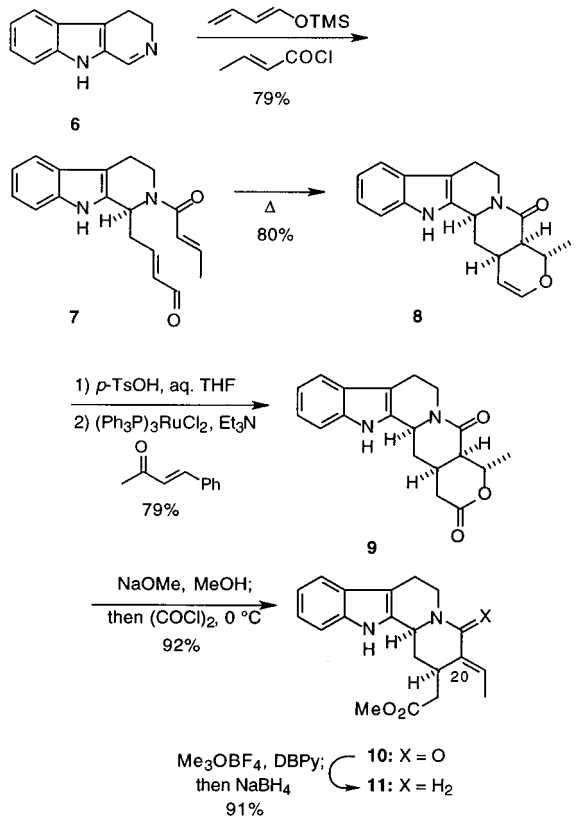


Vollhardt[17] published their separate accounts of the total synthesis of **1**. It is noteworthy that each of these approaches highlighted novel chemistry that was developed and applied to solve specific problems or challenges associated with the synthesis of this complex natural product. During the course of their investigations in the *Strychnos* area, the groups of Overman,[18] Kuehne,[19] and Bonjoch and Bosch[20] also completed the total synthesis of the related akuammicine (**2**) using strategies and tactics similar to those they had successfully applied to **1**.

In developing our own approach to alkaloids of the *Strychnos* family, we were intrigued by the possibility of implementing a novel strategy that owed its conception to a consideration of their biogenesis.[21,22] Feeding studies using the *Corynanthe* alkaloid geissoschizine (**4**) have shown that it is a biosynthetic precursor of strychnine and akuammicine.[21g−i] Several mechanistic pathways have been proposed for the series of skeletal reorganizations that interconnect the two respective alkaloid families, but the key question we sought to address was whether it would be possible to mimic one of these putative biosynthetic pathways to convert either geissoschizine itself or related corynantheoid compounds such as **5** (Z = H, OR) into the pentacyclic skeleton **3** (Scheme 1). We now report the details of our concise, biomimetic syntheses of akuammicine (**2**) and strychnine (**1**) that feature a cascade of reactions involving the oxidation and rearrangement of the *Corynanthe* skeleton.[23]

Setting the Stage. We have had a longstanding interest in developing short and efficient syntheses of complex indole alkaloids, and some time ago we reported a concise and general entry to the natural bases of the heteroyohimboid and corynantheoid families. The approach featured the vinylogous Mannich reaction of **6** with 1-trimethylsilyloxybutadiene in the presence of crotonyl chloride to give **7** followed by the intramolecular hetero Diels−Alder reaction of **7** to give **8**, thereby assembling the pentacyclic heteroyohimboid skeleton in only four steps from tryptamine (Scheme 2).[24] Prior to examining the feasibility of mimicking biosynthetic pathways according to Scheme 1, it was first necessary to convert **8** into **10** and **11**. Indeed, deformylgeissoschizine (**11**) is a key intermediate in numerous syntheses of the *Corynanthe* alkaloids. Thus, hydration of the enol ether moiety of **8** followed by a ruthenium-catalyzed oxidation[25] of the intermediate lactol furnished the lactone **9** in 79% yield. Although we briefly examined several known methods for converting the dihydropyran D ring of **8** directly into the requisite lactone using pyridinium chlorochromate (PCC)[26] and palladium-catalyzed oxidations,[27] these procedures failed to give usable quantities of **9** from **8**. When **9** was exposed to sodium methoxide, facile β-elimination ensued to give an acid that was esterified in situ to deliver **10** in 92% yield. Selective reduction of the amide moiety of **10** proceeded in 91% yield to furnish synthetic **11**, the spectral data of which were identical to those reported in the literature.[28]

Scheme 2



First-Generation Approach. With the corynantheoid intermediates **10** and **11** in hand, the stage was set for our exploration

(16) Solé, D.; Bonjoch, J.; García,-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 395. (b) Solé, D.; Bonjoch, J.; García,-Rubio, S.; Peidró, E.; Bosch, J. *Eur. J. Chem* **2000**, *6*, 655.

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(20) Solé, D.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 4194. (b) Solé, D.; Bonjoch, J.; Garcia-Rubio, S.; Suriol, R.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 5213. (c) Bonjoch, J.; Sole, D.; Garcia-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230.

(21) For a review of indole alkaloid biosynthesis, see: (a) Rahman, A.-ur; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, U.K., 1983; p 45. See also: (b) Woodward, R. B. *Nature* **1948**, *162*, 155. (c) Harley-Mason, J.; Waterfield, W. R. *Tetrahedron* **1963**, *19*, 65. (d) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580. (e) Gaskelle, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053. (f) Scott, A. I.; Qureshi, A. A. *J. Am. Chem. Soc.* **1969**, *91*, 1, 5874. (g) Battersby, A. R.; Hall, E. S. *Chem. Commun.* **1969**, 793. (h) Scott, A. I.; Cherry, P. C.; Qureshi, A. A. *J. Am. Chem. Soc.* **1969**, *91*, 4932. (i) Heimberger, S. I.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1973**, 217.

(22) For a review of some examples of biomimetic alkaloid synthesis, see: Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000**, *17*, 349.

(23) For a preliminary account of portions of this work, see: Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804.

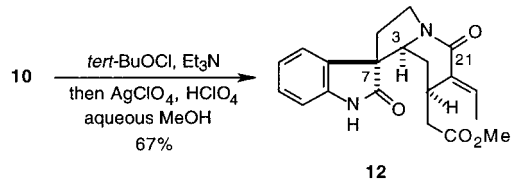
(24) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. P. *J. Am. Chem. Soc.* **1991**, *113*, 6161 and references therein.

(25) Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Tetrahedron Lett.* **1983**, *24*, 2677.

(26) Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* **1977**, *39*, 3483.

(27) Rodeheaver, G. T.; Hunt, D. F. *J. Chem. Soc., Chem. Commun.* **1971**, 818. (b) Januszkiewicz, K.; Alper, H. *Tetrahedron Lett.* **1983**, *24*, 5159. (c) Alper, H.; Januszkiewicz, K.; Smith, D. J. H. *Tetrahedron Lett.* **1985**, *26*, 2263.

Scheme 3

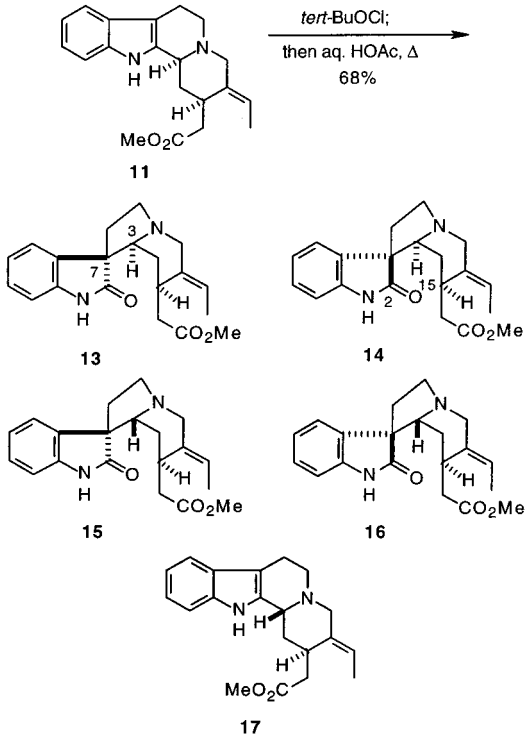


of tactics for effecting their rearrangement into the *Strychnos* skeleton. Our initial plan was to evaluate a strategy reminiscent of the biosynthetic pathway favored by Scott.[21h] We were mindful of the failure of Winterfeldt, who first attempted to induce a similar reorganization of a related corynantheoid intermediate lacking the ethylidene moiety at C(20),[29] but we were not deterred as we envisioned several possible tactics that had not yet been pursued. We also believed that an (*E*)-ethylidene group at C(20) would play a key role and enable the process by enforcing a conformation upon the D ring that would orient the ester side chain in the axial orientation required for cyclization to form a pentacyclic ring system (vide infra).

In our first experiments, the lactam **10** was first allowed to react with *tert*-butyl hypochlorite, and solvolysis of the intermediate chloroindolenine(s) in the presence of silver perchlorate gave the spirocyclic oxindole **12**, the structure of which was established unequivocally by X-ray analysis (67% overall yield) (Scheme 3).[30] Only trace amounts of the C(7) epimeric spiroindole were detected. A comparison of the structures of **1**, **2**, and **12** reveals that the stereochemistry at C(7) of **1** and **2** is *opposite* that found in **12**. This stereochemical issue did not concern us unduly because it was well known that spiroindoles related to **12** having amino, not amide, nitrogens in the D ring undergo facile equilibration and epimerization at C(7).[30,31] We thus reasoned that the amino spiroindole obtained upon selective reduction of the C(21) carbonyl group in **12** would readily isomerize to give a compound having the correct configuration at C(7).

To test this hypothesis, we selectively reduced the D ring lactam in **12** (Me_3OBF_4, 4-Å molecular sieves; $NaBH_4$, MeOH; H_3O^+, Δ), but we found that the reaction was rather inefficient. On the other hand, the oxidative rearrangement of the amine **11** proceeded in 68% yield to give a separable mixture of oxindoles we initially believed to be **13** and **14** (Scheme 4). After a series of unsuccessful attempts to cyclize the ester side chain at C(15) onto C(2) of the oxindole we had presumed was **14**, we more carefully scrutinized the basis for our original structural assignments. A series of NOE analyses of the two oxindoles derived from **11** suggested that these compounds were in fact the isomeric oxindoles **15** and **16**, and the structure of **15** was verified by X-ray analysis. A subsequent survey of the literature revealed that Wenkert had previously prepared **15** and **16** by the oxidative rearrangement of **17**, and the ^1H and ^{13}C NMR spectral characteristics of our compounds were identical with those reported.[32] Inasmuch as the ester side chain at C(15)

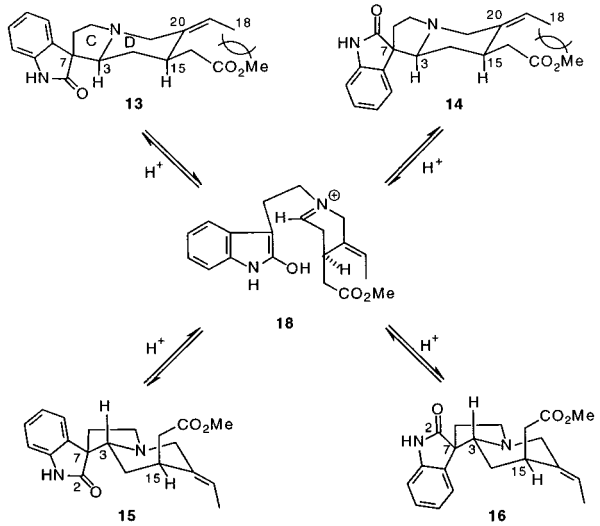
Scheme 4



in **16** and the oxindole carbonyl group are on opposite sides of the D ring, it is not surprising that we were unable to cyclize either of these compounds to generate the *Strychnos* skeleton.

The equilibration of spiro oxindoles related to **13** and **14** is well known,[30,31] and the epimerization at C(7) presumably involves a reversible Mannich reaction that proceeds via the intermediate **18**, cyclization of which may produce either **13** or **14** (Scheme 5). However, it now appears that this equilibration

Scheme 5



is also accompanied by concomitant epimerization at C(3) in *normal* oxindoles such as **13** and **14**, which have an exocyclic (*E*)-ethylidene moiety at C(20), to give the corresponding *pseudo* diastereomers **15** and **16** as the preferred products. The probable driving force for forming **15** and **16** is to relieve the unfavorable $A^{1,3}$-interaction between the ester side chain at C(15) and the C(18) methyl group on the ethylidene moiety of the D rings in **13** and **14**, respectively. In this context, it is perhaps noteworthy that all known oxindole alkaloids bearing

(28) For example, see: (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (b) Wenkert, E.; Guo, M.; Pestchanker, M. J.; Shi, Y.-J.; Vankar, Y. D. *J. Org. Chem.* **1989**, *54*, 1166. (c) Lounasmaa, M.; Jokela, R.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 1497.

(29) Gaskell, A. J.; Radunz, H.-E.; Winterfeldt, E. *Tetrahedron* **1970**, *26*, 5353.

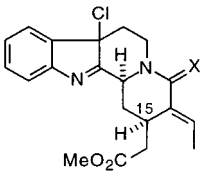
(30) Martin, S. F.; Mortimore, M. *Tetrahedron Lett.* **1990**, *31*, 4557 and references therein.

(31) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 1318. (b) Shavel, J.; Zinnes, H. *J. Am. Chem. Soc.* **1962**, *84*, 1320. (c) Awang, D. V. C.; Vincent, A.; Kindack, D. *Can. J. Chem.* **1984**, *62*, 2667. (d) Stahl, R.; Borschberg, H.-J.; Acklin, P. *Helv. Chim. Acta* **1996**, *79*, 1361.

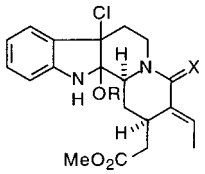
(32) Wenkert, E.; Shi, Y.-J. *Synth. Commun.* **1989**, *19*, 1071.

alkyl substituents at C(20) have either the *normal* or *allo* configurational relationships in which the hydrogens at C(3) and C(15) are *both* α; the hydrogen at C(20) in these compounds may be either α or *β*. To our knowledge, there are no natural oxindoles having an ethylidene side chain at C(20).[33]

Second-Generation Approach. The misfortunes of these attempts notwithstanding, we were still attracted to the possibility of inducing a biomimetic reorganization of the corynantheoid ring system into the *Strychnos* skeleton. The mechanism for the conversion of chloroindolenines such as **19** into

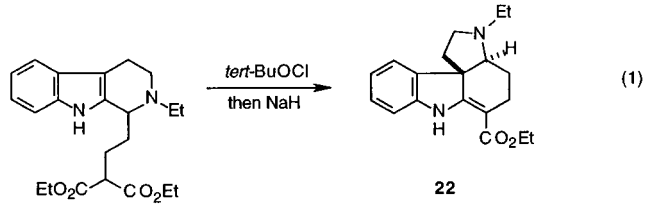


19: X = O, H_2

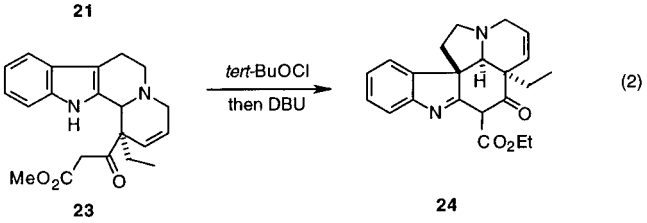


20: X = O, H_2; R = Me, H

spiroindole derivatives is believed to involve the rearrangement of the methanol or water adducts **20**.[31] An intriguing question then arose: Would it be possible to initiate the skeletal reorganization of the chloroindolenine **19** (X = H_2) with a carbon nucleophile derived from enolization of the C(15) side-chain ester moiety? Although the additions of carbon nucleophiles to the C(2) carbon of chloroindolenines are rare, such transformations had been reported by Massiot (**21** → **22**, eq 1)[34] and Rapoport (**23** → **24**, eq 2).[35] In light of these promising



21 **22** (1)

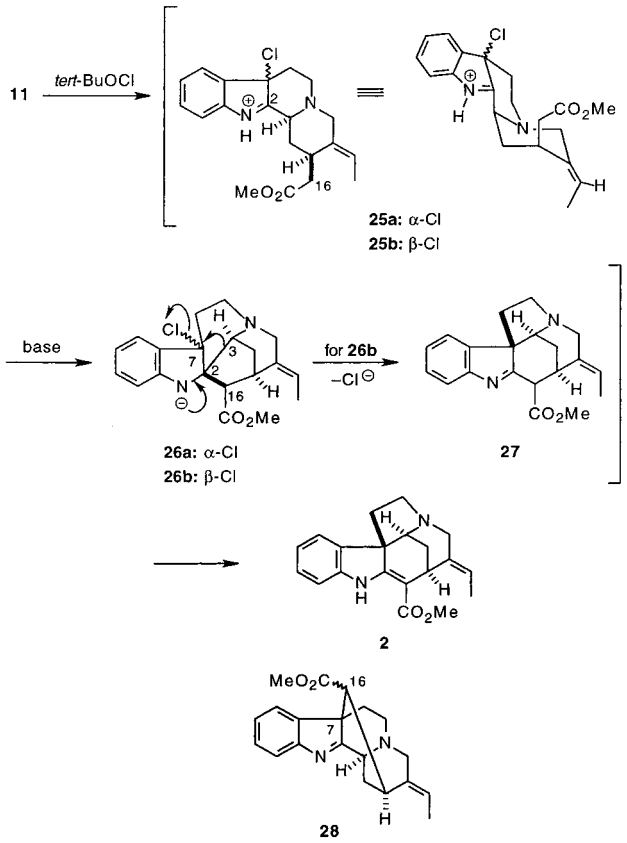


23 **24** (2)

precedents, we turned our efforts to evaluating the feasibility of converting **11** directly into **2**.

In our first experiments, **11** was chlorinated with *tert*-butyl hypochlorite and the epimeric chloroindolenines **25a,b** thus obtained were exposed to excess lithium diisopropylamide (LDA) to give a complex reaction mixture that was almost intractable. However, we were fortunate to have an authentic sample of **2** that had been generously provided by Overman, and we were able to detect a faint spot on the TLC of the reaction mixture that had an R_f corresponding to that of **2**. After some experimentation using a variety of bases to deprotonate the intermediate chloroindolenines, we were eventually able to isolate **2** in ∼10% yield. The synthetic **2** thus obtained was identical (TLC, ^{1}H and ^{13}C NMR) with an authentic sample.

Scheme 6



25a: α-Cl
25b: β-Cl
26a: α-Cl
26b: β-Cl
27
2
28

The precise mechanistic course of this novel biogenetically patterned transformation has not been established, but we believe that the basic features are summarized in Scheme 6. The initial oxidation of the indole ring of **11** with electropositive halogen to give the epimeric chloroindolenines **25a,b** is well precedented.[30,31] Deprotonation of **25a,b** at C(16) may envisioned to give an enolate that could first cyclize onto C(2) to give **26a,b**. Subsequent skeletal reorganization would lead to **27** via 1,2-migration of C(3) from C(2) to C(7), perhaps by an S_N2-like process; tautomerization of **27** would then furnish **2**. An alternative pathway entails cyclization of the enolate derived from **25a,b** onto C(7) to give **28**, one epimer of which corresponds to the alkaloid strictamine. The base-induced rearrangement of strictamine into akuammicine is known, although the reaction proceeds in poor yield under forcing conditions.[36] Because we did not have an authentic sample of strictamine nor did we isolate any material having the spectral properties of strictamine, we cannot offer any evidence supporting this latter pathway.

The excitement associated with being able to achieve the first biomimetic synthesis of **2** was tempered by the poor yield of the overall transformation. Efforts were thus directed toward improving the overall efficiency of the process. Examination of the TLCs and the ^{1}H NMR spectra of the crude reaction mixtures obtained after the chlorination step and after treatment of the intermediate chloroindolenines with base provided an important clue: Two chloroindolenines were being formed in ratios that ranged from approximately 4:1 to 10:1 depending upon the conditions. It was the more polar chloroindolenine, which was the minor product in our initial experiments, that

(33) See: (a) Trager, W. F.; Lee, C. M.; Phillipson, J. D.; Haddock, R. E.; Dwuma-Badu, D.; Beckett, A. H. *Tetrahedron* **1968**, *24*, 523. (b) Bindra, J. S. In *The Alkaloid, Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. XIV, p 83.

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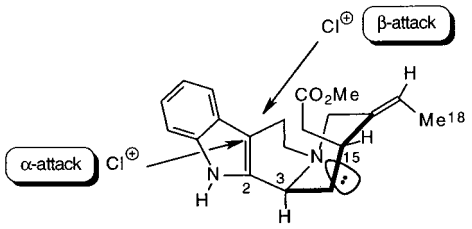


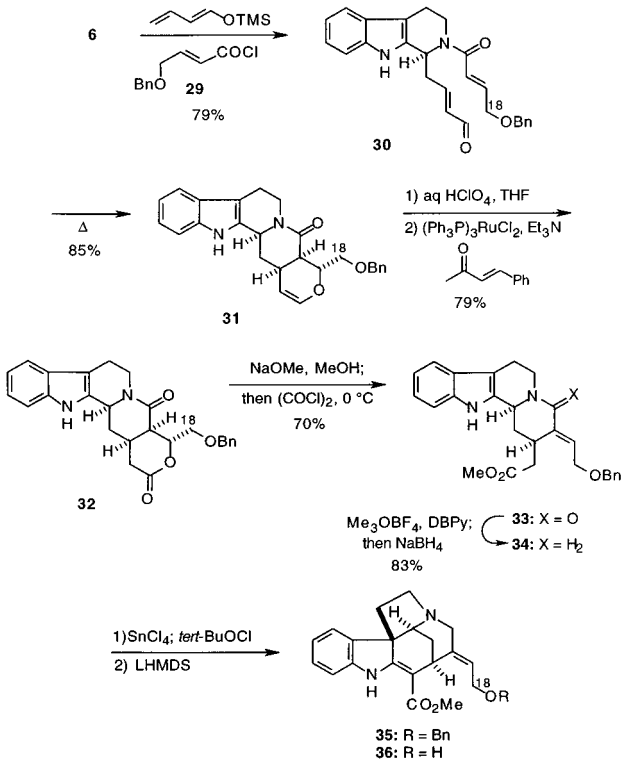
Figure 1. Preferred conformation of **11** showing α-attack of electropositive chlorine from the convex α-face and from the more hindered *β*-concave face.[28b,37,38]

was converted into akuammicine by the action of strong base; the less polar, major spot remained primarily unchanged. In this context, it is perhaps noteworthy that only one of the epimeric chloroindolenines generated in the reaction depicted in eq 1 rearranged to give **22**.[34] In a number of other studies with closely related compounds, the less polar chloroindolenine has been shown to be the α-isomer, whereas the more polar one was the *β*-isomer.[31] These observations clearly suggested that the major product formed upon reaction of **11** with *tert*-butyl hypochlorite was the α-chloroindolenine **25a**, and the more polar, minor product was the requisite *β*-isomer **25b**.

In light of the above analysis, we reasoned that if the stereochemical course of the initial chlorination step could be reversed to give **25b** as the major product, the overall efficiency of this biomimetic sequence to akuammacine might be significantly improved. A possible basis for the stereoselectivity of this chlorination step emerged upon consideration of the preferred conformation of the starting 16-deformylgeissoschizine (**11**), which has been proposed by Wenkert, Lounasmaa, and Winterfeldt to correspond to that shown in Figure 1.,[28b,37,38] In this conformation, the D ring is forced into a chair conformation in which the ester side chain at C(15) is positioned in an axial orientation to relieve $A^{1,3}$-strain between this side chain and the C(18) methyl group in a manner reminiscent of the conformational factors that helped drive the isomerizations of the spirocyclic indoles **13** and **14** to give **15** and **16**, respectively (Scheme 5). The concave *β*-face is somewhat more hindered than the convex α-face in this conformation, so chlorination would be expected to occur preferentially from the α-face to give **25a**. Because the lone pair on the basic nitrogen atom is projected on the α-face, we were intrigued by the possibility that a Lewis acid might complex with this lone pair, thereby reducing access to the α-face and leading to increased *β*-attack.

The correctness of this hypothesis notwithstanding, we were delighted to discover that addition of Lewis acids gave increased quantities of the desired *β*-chloroindolenine **25b.** A number of Lewis acids (e.g., $ZnCl_2$, $MgCl_2$, $BF_3{\cdot}OEt_2$, $AgBF_4$, and $TiCl_4$) were examined, but $SnCl_4$ was found to give the best results. Hence, when the complex formed upon reaction of **11** with $SnCl_4$ was oxidized with *tert*-butyl hypochlorite, the desired *β*-chloroindolenine was formed as the predominant product as evidenced by TLC and ^{1}H NMR of the reaction mixture; generally only traces of the less polar α-isomer could be detected. We surveyed a number of solvents (benzene, toluene, THF, ether) and bases (NaH, KH, LHMDS, KHMDS, NaH-

Scheme 7



MDS, BuLi, *tert*-BuOK) to effect the skeletal reorganization and found that LHMDS in THF was superior to other combinations. In the optimized sequence, **11** was first treated with $SnCl_4$ in toluene and the resulting complex allowed to react with *tert*-butyl hypochlorite at −15 °C. Deprotonation of the crude **25b** thus obtained with LHMDS in THF at −15 °C delivered **2** in 52% overall yield from **11**.

In view of the results of these experimental studies, it is now possible to refine our initial view of the details associated with transforming **11** into **2** (Scheme 6). The ester enolate of the *β*-chloroindolenine **25b** appears to cyclize first to give **26b**, and because of the anti relationship between the chlorine at C(7) and C(3), facile 1,2-migration of C(3) to C(7) ensues to furnish **27**. Although the analogous cyclization of the enolate derived from **25a** to form **26a** seems plausible, the syn orientation between the chlorine at C(7) and C(3) in **26a** apparently precludes its rearrangement to produce **27**. Another pathway for converting **25a** into **2** would involve cyclization of the ester enolate derived from **25a** to generate **28**, which would then undergo base-induced rearrangement to provide **2** as discussed previously. While it is therefore possible that any **25a** formed by the chlorination of **11** might be converted into **2**, such a process does not appear to be an efficient one.

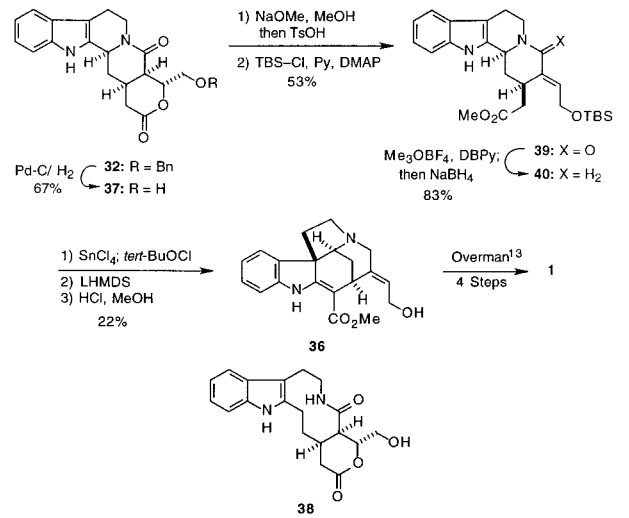
Formal Synthesis of Strychnine (1). Having demonstrated that the tetracyclic corynantheoid skeleton could be readily rearranged to the pentacyclic *Strychnos* skeleton in the laboratory, we sought to apply this novel strategy to the formal synthesis of strychnine from a hydroxylated derivative of **11** according to the plan outlined in Scheme 7. Hence, the immediate objective was to prepare 18-hydroxyakuammicine (**36**) as this compound had been previously converted into strychnine.[13]

The issue that lay before us was the selection of a suitable protecting group for the C(18) hydroxyl group. On the basis of earlier work with related compounds,[39] we anticipated that it would be possible to remove an *O*-benzyl group from the C(18)

(37) Jokela, R.; Halonen, M.; Lounasmaa, M. *Tetrahedron* **1993**, *49*, 2567. (b) Lounasmaa, M.; Jokela, R.; Hanhinen, P.; Laine, C.; Anttila, U. *Heterocycles* **1996**, *43*, 1699. (c) Lounasmaa, M.; Hanhinen, P. *Heterocycles* **1999**, *51*, 649.

(38) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winterfeldt, E. *Liebigs Ann. Chem.* **1985**, 1752. (b) Winterfledt, E.; Freund, R. *Liebigs Ann. Chem.* **1986**, 1262. (c) Ninomiya, I.; Naito, T.; Miyata, O.; Shinada, T.; Winterfeldt, E.; Freund, R.; Ishida, T. *Heterocycles* **1990**, *30*, 1031.

Scheme 8



hydroxy group of an advanced intermediate by catalytic hydrogenolysis, even in the presence of a trisubstituted ethylidene moiety. Toward this end, benzyloxycrotonyl chloride (**29**) was prepared in three steps by treating methyl bromocrotonate with benzyl alcohol in the presence of silver(I) oxide, followed by ester saponification and reaction of the intermediate acid with oxalyl chloride. The vinylogous Mannich addition of 1-trimethylsilyloxybutadiene to the *N*-acyl iminium ion that was generated in situ upon reaction of **29** with **6** then delivered **30**. Heating **30** induced a facile intramolecular hetero Diels−Alder reaction to give **31** in 67% overall yield from **6**. The conversion of **31** into amine **34** (46% overall yield) followed prior art, thereby setting the stage for the key skeletal rearrangement. Indeed, treatment of **34** with $SnCl_4$ and *tert*-butyl hypochlorite followed by reaction of the mixture of chloroindolenines thus obtained with LHMDS gave **35** in 25−30% yield. To our dismay, however, a number of preliminary attempts to effect the selective O-debenzylation by catalytic hydrogenolysis or by reaction with trimethylsilyl iodide were not promising, and we elected to use another hydroxyl-protecting group.

The possibility of introducing alternative protecting groups including *tert*-butyldimethylsilyl, *p*-methoxybenzyl, or methoxymethyl on the hydroxy crotonyl acylating agent used at the outset of the synthesis was explored. However, we encountered difficulties arising from incompatibilities of these protecting groups with the reaction conditions at various subsequent steps. The expedient of replacing the benzyl group at a more advanced stage of the synthesis was therefore examined. After testing several possibilities, we concluded that this exchange of protecting groups would be best performed on the lactone **32.** However, deprotection of **32** to give **37** by catalytic hydrogenolysis also proved somewhat troublesome, as variable quantities of the ring-cleaved product **38** were often obtained (Scheme 8). Eventually we found that hydrogenolysis (1 atm H_2) of **32** in the presence of Pearlman's catalyst in EtOAc/EtOH (2:1) furnished **37** in 67% yield. Opening the lactone ring of **37** by base-induced β-elimination and acid-catalyzed formation of the methyl ester, followed by protection of the primary alcohol moiety as its *tert*-butyldimethylsilyl ether afforded **39** in 53% overall yield. Selective reduction of the lactam function in **39** as before then provided the amine **40**. Compound **40** was subjected to the oxidation−rearrangement protocol previously developed for **34**, and the hydroxyl-protecting group was then removed to furnish **36** in 22% (unoptimized) overall yield. The synthetic **36** thus obtained gave spectral data (^{1}H NMR, ^{13}C NMR, IR) identical with that of an authentic sample. Because Overman had previously converted **36** into **1** in four steps,[13] its preparation constitutes a formal synthesis of **1**.

Conclusions. Concise syntheses of the two complex indole alkaloids **1** and **2** have been completed using a novel biomimetic approach that features the skeletal reorganizations of the tetracyclic corynantheoid derivatives **40** and **11**, which were quickly assembled by exploiting vinylogous Mannich and intramolecular hetero Diels−Alder reactions as key steps. The total synthesis of **2** required only 10 steps from commercially available tryptamine and proceeded in an overall yield of 8%. Notwithstanding the need to exchange hydroxyl-protecting groups at an advanced stage in the formal synthesis of strychnine, **36** was nevertheless prepared via a longest linear sequence requiring only 12 steps and proceeding in 2.8% overall yield from tryptamine. Other applications of vinylogous Mannich, Diels−Alder, and related biomimetic transformations to the syntheses of indole alkaloids are currently being investigated on a broad front, and the results of these investigations will be reported in due course.

Experimental Section

(±)-(19α,20α)-19-Methyloxayohimban-17,21-dione (9). A solution of the cycloadduct **8** (1.616 g, 5.24 mmol) in a mixture of THF (28 mL) and H_2O (8 mL) containing 70% aqueous $HClO_4$ (6 drops) was heated at 80 °C for 6 h. EtOAc (80 mL) was added, and the organic layer was separated and washed with $NaHCO_3$ (20 mL). The combined aqueous phases were extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in toluene (80 mL) containing Et_3N (0.17 mL, 0.123 g, 0.64 mmol), 4-phenyl-3-butene-2-one (0.918 g, 6.28 mmol), and tris(triphenylphosphine)ruthenium(II) chloride (0.48 g, 0.50 mmol), and the resulting slurry was heated at 120 °C for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:50) to give 1.34 g (79%) of **9** as a gray solid: mp 251−252 °C; ^{1}H NMR (DMSO-d_6) δ 10.98 (s, 1 H), 7.40 (d, J = 7.6 Hz, 1 H), 7.31 (d, J = 7.9 Hz, 1 H), 7.06 (t, J = 7.2 Hz, 1 H), 6.97 (t, J = 7.3 Hz, 1 H), 4.92−4.78 (m, 2 H), 4.67 (dd, J = 7.7, 6.3 Hz, 1 H), 2.89 (td, J = 12.2, 4.0 Hz, 1 H), 2.77−2.41 (m, 6 H), 2.38 (m, 1 H), 1.61 (dt, J = 10.5, 2.3 Hz, 1 H), 1.41 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 170.6, 167.1, 136.2, 133.8, 126.2, 121.1, 118.7, 117.8, 111.1, 107.0, 74.3, 52.2, 45.0, 37.2, 33.9, 32.5, 26.9, 21.3, 20.6; IR 3140, 1715, 1635 cm^{-1}; mass spectrum (EI) *m*/*z* 324.1472 ($C_{19}H_{20}N_2O_3$ requires 324.1474), 324, 308 (base), 265, 237, 139.

(±)-(19*E*)-19,20-Didehydro-21-oxocorynan-17-oic Acid, Methyl Ester (10). A suspension of **9** (1.10 g, 3.40 mmol) in MeOH (25 mL) containing NaOMe (0.724 g, 13.4 mmol) was stirred at room temperature for 24 h. The solution was cooled to 0 °C, and oxalyl chloride (2.42 mL, 3.52 g, 27.7 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for 5 h. CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL) were added, and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:50) to furnish 1.05 g (92%) of **10** as a pale yellow solid: mp 210−211 °C; ^{1}H NMR (300 MHz) δ 8.16 (s, 1 H), 7.51 (d, J = 7.5 Hz, 1 H), 7.34 (d, J = 7.5 Hz, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.14 (t, J = 7.5 Hz, 1 H), 6.89 (q, J = 7.4 Hz, 1 H), 5.14−5.07 (m, 1 H), 4.84 (t, J = 5.4 Hz, 1 H), 3.58 (s, 3 H), 3.43 (ddd, J = 16.0, 5.4, 4.9 Hz, 1 H), 3.03 (dd, J = 11.4, 3.9 Hz, 1 H), 2.92 (ddd, J = 11.4, 3.9, 2.0 Hz, 1 H), 2.86−2.78 (m, 1 H), 2.51 (dt, J = 11.4, 4.1 Hz, 1 H), 2.33 (dt, J = 8.2, 3.1 Hz, 1 H), 2.27 (d, J = 16.4 Hz, 1 H), 2.11 (dd, J = 16.4, 11.1 Hz, 1 H), 1.82 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.9, 165.8, 136.6, 134.7, 133.6, 133.2, 127.4, 122.3, 121.0, 118.5, 111.2, 109.8, 51.8, 51.6, 41.7, 38.1, 31.8,

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30.0, 21.2, 13.8; IR 3460, 3080, 2970, 2940, 1725, 1660, 1605, 1440 cm^{-1}; mass spectrum (CI) *m*/*z* 338.1623 ($C_{20}H_{22}N_2O_3$ requires 338.1630), 338 (base), 265, 237, 169.

(±)-(19*E*)-19,20-Didehydrocorynan-17-oic Acid, Methyl Ester (11). To a solution of **10** (0.740 g, 2.19 mmol) in CH_2Cl_2 (20 mL) was added trimethyloxonium tetrafluoroborate (0.811 g, 5.48 mmol) and 2,6-di-*tert*-butylpyridine (1.72 mL, 1.47 g, 7.66 mmol), and the resulting slurry was stirred for 24 h at room temperature. The mixture was then cooled to 0 °C, and anhydrous MeOH (30 mL) was added. Solid $NaBH_4$ (0.495, 13.1 mmol) was then added, and the mixture was stirred at 0 °C for 10 min. The mixture was poured into saturated $NaHCO_3$ (20 mL), and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (3% MeOH/CH_2Cl_2) to provide 0.646 g (91%) of **11** as a white foam that gave spectral properties identical with those published.[28]

Akuammicine (2). A 1 M solution of $SnCl_4$ in heptane (0.84 mL, 0.84 mmol) was added to a solution of amine **11** (248 mg, 0.76 mmol) in toluene (25 mL) at −15 °C, and the resulting yellow solution was stirred vigorously for 30 min. *tert*-BuOCl (125 μL, 1.09 mmol) was added, and the reaction mixture was stirred for 10 min. The mixture was poured into a saturated solution of K_2CO_3 (30 mL), and the biphasic mixture was shaken vigorously until both layers were clear. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with NH_4Cl (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The oily residue was dried under high vacuum for 30 min and then dissolved in THF (50 mL). The solution was cooled to −15 °C, and a 1 M solution of LHMDS in THF (2.3 mL, 2.3 mmol) was added. The mixture was stirred for 2 h, and then saturated aqueous NH_4Cl (20 mL) was added. The layers were separated, and the aqueous layer was back extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude material was purified by flash column chromatography eluting with $CHCl_3$/MeOH (70:1) to give 128 mg (52%) of **2** that was identical (TLC, ^1H and ^{13}C NMR) with an authentic sample.

(±)-1*H*-Pyrido[3,4-*b*]indole, 2,3,4,9-tetrahydro-1-(4-oxo-2-butenyl)-2-[1-oxo-4-(phenylmethoxy)-2-butenyl]-, (*E*,*E*)- (30). To a solution of 4-(phenylmethoxy)-2-butenoic acid (3.34 g, 17.4 mmol) in CH_2Cl_2 (35 mL) was added freshly distilled oxalyl chloride (7.6 mL, 11 g, 87 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure to give the acid chloride **29**. A solution of crude **29** was dissolved in THF (25 mL) and added dropwise to a solution of **6** (2.67 g, 15.7 mmol) and 1-trimethylsiloxybutadiene (13.5 g, 15.0 mL, 95.1 mmol) in THF (35 mL) at −78 °C. The reaction mixture was stirred 1 h at −78 °C, allowed to warm to room temperature, and stirred at room temperature for 1 h. The mixture was partitioned between CH_2Cl_2 (60 mL) and saturated $NaHCO_3$ (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a gum that was purified by flash chromatography eluting with $CHCl_3$/EtOAc (3:1) to afford 5.13 g (79%) of **30** as a pale yellow solid: mp 118−119 °C; ^1H NMR (300 MHz) δ 9.25 (d, J = 7.9 Hz, 1 H), 9.10 (s, 1 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.39−7.35 (comp, 5 H), 7.32 (d, J = 7.5 Hz, 1 H), 7.19−7.08 (comp, 2 H), 6.99 (dt, J = 15.1, 3.8 Hz, 1 H), 6.82 (dt, J = 15.6, 7.4 Hz, 1 H), 6.71 (d, J = 15.1 Hz, 1 H), 6.09 (dd, J = 8.3, 5.1 Hz, 1 H), 5.99 (dd, J = 15.6, 7.9 Hz, 1 H), 4.62 (s, 2 H), 4.25−4.22 (comp, 3 H), 3.49−3.42 (m, 1 H), 2.98−2.78 (comp, 4 H); ^{13}C NMR (75 MHz) δ 193.8, 166.2, 153.0, 142.9, 137.7, 136.3, 134.8, 132.4, 128.5, 127.8, 127.7, 126.4, 122.1, 119.7, 119.6, 118.1, 111.2, 108.1, 72.9, 69.0, 48.8, 40.7, 37.9, 22.2; IR ($CHCl_3$) 3265, 3296, 3065, 3032, 2919, 2849, 2248, 1686, 1661, 1608, 1440 cm^{-1}; mass spectrum (CI) *m*/*z* 415.2015 ($C_{26}H_{27}N_2O_3$ requires 415.2021), 415, 346 (base), 308, 290.

(±)-(19α,20α)-16,17-Didehydro-19-[(phenylmethoxy)methyl]oxayohimban-21-one (31). A solution of **30** (1.24 g, 3.00 mmol) in mesitylene (150 mL) was degassed and heated at 160 °C in a sealed tube for 72 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to yield 1.05 g (85%) of **31** as a light yellow solid: mp 236−238 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.42 (d, J = 7.4 Hz, 1 H), 7.27−7.15 (comp, 6 H), 7.14−7.02 (comp, 2 H), 6.37 (dd, J = 6.0, 1.0 Hz, 1 H), 5.09−5.04 (m, 1 H), 4.66 (dd, J = 6.0, 5.1 Hz, 1 H), 4.63−4.60 (m, 1 H), 4.55 (d, J = 11.9 Hz, 1 H), 4.49 (d, J = 11.9 Hz, 1 H), 4.02−3.95 (m, 1 H), 3.88 (dd, J = 10.8, 2.9 Hz, 1 H), 3.76 (dd, J = 10.8, 7.2 Hz, 1 H), 2.83−2.76 (m, 2 H), 2.72−2.68 (m, 2 H), 2.56−2.50 (m, 1 H), 2.39 (td, J = 13.6, 3.4 Hz, 1 H), 1.70−1.58 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 144.2, 138.0, 136.2, 132.7, 128.2, 127.8, 127.5, 126.6, 122.1, 119.7, 118.3, 111.0, 109.0, 102.1, 73.5, 72.3, 71.2, 53.6, 42.4, 40.5, 33.9, 27.8, 21.0; IR ($CHCl_3$) 3470, 3064, 2925, 2247, 1636, 1433 cm^{-1}; mass spectrum (CI) *m*/*z* 415.2024 ($C_{26}H_{27}N_2O_3$ requires 415.2021), 415, 397, 307.

(±)-(19α,20α)-19-[(Phenylmethoxy)methyl]oxayohimban-17,21-dione (32). A slurry of **31** (0.97 g, 2.2 mmol) in a mixture of THF (25 mL) and water (5 mL) containing 70% aqueous $HClO_4$ (4 drops) was stirred at 80 °C for 12 h. The mixture was cooled to room temperature and then added to a separatory funnel containing CH_2Cl_2 (30 mL) and saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:20) to give 0.94 g (93%) of anomeric lactols as an off-white mixture that was not characterized but used immediately in the next step.

A solution containing a portion of the mixture of the above lactols (0.537 g, 1.19 mmol), 4-phenyl-3-butene-2-one (0.192 mg, 1.28 mmol), Et_3N (0.45 mg, 0.45 mmol), and tris(triphenylphosphine)ruthenium(II) chloride (82 mg, 0.08 mmol) in toluene (40 mL) was heated under reflux for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:50) to give 0.422 g (79%) of lactone **32** as a gray solid: mp 210−212 °C; ^1H NMR (300 MHz) δ 8.06 (s, 1 H), 7.50 (d, J = 7.3 Hz, 1 H), 7.38−7.29 (comp, 6 H), 7.21−7.16 (m, 1 H), 7.15−7.10 (m, 1 H), 5.08−5.02 (m, 1 H), 4.89−4.84 (m, 1 H), 4.70 (dt, J = 7.2, 2.6 Hz, 1 H), 4.60 (s, 2 H), 3.91 (d, J = 2.6 Hz, 2 H), 3.22 (dt, J = 7.0 Hz, 1 H), 2.98−2.91 (m, 1 H), 2.86−2.75 (comp, 3 H), 2.69−2.62 (m, 1 H), 2.43 (m, 2 H), 1.81−1.69 (m, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.1, 168.6, 139.1, 137.1, 134.7, 129.2, 128.3, 127.3, 127.1, 122.0, 119.6, 118.7, 112.1, 108.0, 78.0, 73.2, 72.7, 53.0, 40.5, 39.6, 35.0, 33.2, 27.9, 21.4; IR ($CHCl_3$) 3468, 2925, 2868, 2247, 1740, 1640, 1434 cm^{-1}; mass spectrum (CI) *m*/*z* 431.1969 ($C_{26}H_{27}N_2O_4$ requires 431.1970), 431 (base), 339.

(±)-(19α,20α)-19-(Hydroxymethyl)oxayohimban-17,21-dione **(37).** A solution of the ester **32** (200 mg, 0.465 mmol) in a mixture of EtOAc (14.0 mL) and EtOH (7.0 mL) containing 20% Pd(OH)2/C (32 mg, 46 μmol) was stirred under H_2 (1 atm) at room temperature until starting material was consumed (∼5 h). The catalyst was removed by vacuum filtration through Celite, and the filter pad w×88as washed with hot MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford a yellow solid that was purified by flash chromatography eluting with $CHCl_3$/MeOH (20:1) to give 106 mg (67%) of **37** as a white solid: mp 264−265 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.12 (br s, 1 H), 6.58 (d, J = 7.6 Hz, 1 H), 6.49 (d, J = 8.0 Hz, 1 H), 6.23 (m, 1 H), 6.14 (m, 1 H), 4.22 (t, J = 5.8 Hz, 1 H), 4.11−4.06 (m, 1 H), 4.01−3.96 (m, 1 H), 3.72−3.67 (m, 1 H), 2.93−2.88 (m, 1 H), 2.87−2.80 (m, 1 H), 2.15−2.04 (comp, 2 H), 1.93−1.72 (comp, 4 H), 1.67−1.65 (m, 1 H), 1.48 (dd, J = 16.4, 6.6 Hz, 1 H), 0.78−0.66 (m, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.1, 168.0, 136.2, 133.7, 126.2, 121.0, 118.6, 117.1, 111.1, 106.9, 79.0, 63.2, 52.1, 40.3, 34.0, 32.0, 31.7, 26.8, 20.4; IR 3690, 3606, 3019, 2925, 2254, 1602, 1218 cm^{-1}; mass spectrum (CI) *m*/*z* 341.1501 ($C_{19}H_{21}N_2O_4$ requires 341.1501), 341 (base), 199.

(±)-(19*E*)-19,20-Didehydro-21-oxo-18-hydroxycorynan-17-oic Acid, Methyl Ester. A suspension of **37** (75 mg, 0.22 mmol) in MeOH (10 mL) containing NaOMe (36 mg, 0.66 mmol) was stirred at room temperature for 24 h. The solution was cooled to 0 °C, *p*-toluenesulfonic acid (189 mg, 1.1 mmol) was added, and the mixture was stirred at 0 °C for 1 h and then at room temperature for 5 h. The reaction mixture was transferred to a separatory funnel containing CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic

layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (20:1) to deliver 58 mg (74%) of product as a white solid: mp 337−339 °C; ^{1}H NMR (300 MHz) δ 8.28 (br s, 1 H), 7.50 (d, J = 7.7 Hz, 1 H), 7.33 (d, J = 7.4 Hz, 1 H), 7.12−7.02 (comp, 2 H), 6.86 (t, J = 6.4 Hz, 1 H), 5.10−5.07 (m, 1 H), 4.86 (br t, J = 5.3 Hz, 1 H), 4.36 (d, J = 6.4 Hz, 2 H), 3.54 (s, 3 H), 3.53−3.48 (m, 1 H), 2.99−2.79 (comp, 3 H), 2.52 (dt, J = 14.3, 5.7 Hz, 1 H), 2.32−2.12 (comp, 3 H); ^{13}C NMR (75 MHz) δ 172.7, 168.3, 137.3, 136.3, 133.8, 133.1, 127.2, 122.3, 120.0, 118.4, 111.0, 109.7, 59.1, 51.7, 51.6, 41.8, 40.6, 38.1, 31.4, 30.1, 21.0; IR ($CHCl_3$) 3689, 3609, 3465, 2930, 2852, 2248, 1727, 1662, 1612, 1438 cm^{-1}; mass spectrum (CI) m/z 355.1655 ($C_{20}H_{23}N_2O_4$ requires 355.1658), 355 (base), 323.

(±)-(19*E*)-19,20-Didehydro-21-oxo-18-(*tert*-butyldimethylsilyloxy)-corynan-17-oic Acid, Methyl Ester (39). A mixture of alcohol from the preceding experiment (60 mg, 0.17 mmol) in pyridine (10 mL) containing DMAP (100 mg, 0.84 mmol) and TBSCl (127 mg, 0.85 mmol) was stirred at room temperature for 24 h. The reaction mixture was partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:20) to deliver 56 mg (71%) of **39** as a white solid: mp 200−201 °C; ^{1}H NMR (300 MHz) δ 7.96 (br s, 1 H), 7.50 (d, J = 7.4 Hz, 1 H), 7.34−7.31 (m, 1 H), 7.22−7.10 (comp, 2 H), 6.85−6.80 (m, 1 H), 5.11−5.07 (m, 1 H), 4.87−4.83 (m, 1 H), 4.41 (dd, J = 14.7, 7.1 Hz, 1 H), 4.31 (dd, J = 14.7, 4.9 Hz, 1 H), 3.55 (s, 3 H), 3.45−3.40 (m, 1 H), 3.01−2.93 (comp, 2 H), 2.83−2.79 (m, 1 H), 2.53−2.46 (m, 1 H), 2.32−2.23 (comp, 2 H), 2.14 (dd, J = 16.6, 10.6 Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (75 MHz) δ 172.6, 165.0, 138.3, 136.3, 133.1, 132.8, 127.2, 122.2, 119.9, 118.3, 111.0, 109.6, 107.2, 59.7, 51.6, 41.6, 38.1, 31.2, 30.3, 25.8, 21.0, 18.3, −5.3; IR ($CDCl_3$) 3155, 2253, 1816, 1794, 1727, 1651, 1614, 1464, 1380, 1097, 912 cm^{-1}; mass spectrum (CI) m/z 469.2511 ($C_{26}H_{37}N_2O_4$Si requires 469.2522), 469 (base), 453, 411.

(±)-(19*E*)-19,20-Didehydro-18-(*tert*-butyldimethylsilyloxy)corynan-17-oic Acid, Methyl Ester (40). A mixture of **39** (0.56 g, 1.2 mmol) in CH_2Cl_2 (15 mL) containing trimethyloxonium tetrafluoroborate (0.43 g, 3.1 mmol) and 2,6-di-*tert*-butylpyridine (1.1 mL, 0.83 g, 4.2 mmol) was stirred for 24 h at room temperature, whereupon it was cooled to 0 °C and anhydrous MeOH (30 mL) added. Solid $NaBH_4$ (0.23 g, 6 mmol) was added, and the mixture was stirred for 15 min. Saturated $NaHCO_3$ (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (1:30) to provide 0.45 g (83%) of amine **40** as a yellow gum: mp 43 °C; ^{1}H NMR (300 MHz) δ 8.48 (br s, 1 H), 7.48 (d, J = 7.1 Hz, 1 H), 7.34 (d, J = 7.3 Hz, 1 H), 7.17−7.07 (comp, 2 H), 5.54 (t, J = 6.2 Hz, 1 H), 4.29−4.17 (comp, 3 H), 3.69 (s, 3 H), 3.57 (d, J = 12.5 Hz, 1 H), 3.29−3.20 (m, 1 H), 3.14−3.06 (comp, 3 H, C5−H), 2.98 (d, J = 12.5 Hz, 1 H), 2.70−2.62 (m, 1 H), 2.31−2.12 (comp, 4 H), 0.89 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz) δ 173.5, 140.1, 138.5, 134.1, 128.7, 122.6, 121.3, 119.4, 118.5, 111.1, 108.0, 65.2, 53.0, 51.4, 51.0, 37.6, 33.2, 31.1, 25.8, 19.5, 18.1, −4.1; IR ($CHCl_3$) 3470, 3350, 3025, 3008, 2954, 2930, 2857, 1726, 1463 cm^{-1}; mass spectrum (CI) m/z 455.2721 ($C_{26}H_{39}N_2O_3$Si requires 455.2730), 455 (base), 323.

(±)-(19*E*)-2,16,19,20-Tetradehydro-18-(*tert*-butyldimethylsilyloxy)-curan-17-oic Acid, Methyl Ester. A 1 M solution of $SnCl_4$ in heptane (160 μL, 0.16 mmol) was added to a solution of amine **40** (65 mg, 0.15 mmol) in toluene (5.0 mL) at −15 °C, and the resulting solution was stirred for 30 min. *tert*-Butyl hypochlorite (32 μL, 0.30 mmol) was added, and the reaction mixture was stirred for an additional 30 min. The mixture was poured into a separatory funnel containing CH_2Cl_2 (20 mL) and saturated K_2CO_3 (10 mL). The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in THF (5 mL) and cooled to −15 °C. A 1 M solution of LHMDS in THF (620 μL of a 1.0 M solution in THF, 0.62 mmol) was added, and the reaction was stirred at −15 °C for 30 min and then at room temperature for 3 h. The mixture was transferred to a separatory funnel containing CH_2Cl_2 (5 mL) and saturated $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with $CHCl_3$/MeOH (50:1) to give 17 mg (26%) of product as an off-white residue: mp 147−149 °C; ^{1}H NMR (300 MHz) δ 9.05 (br s, 1 H), 7.25 (d, J = 7.6 Hz, 1 H), 7.16 (td, J = 7.6, 0.8 Hz, 1 H), 6.90 (t, J = 7.4 Hz, 1 H), 6.82 (d, J = 7.7 Hz, 1 H), 5.43−5.41 (m, 1 H), 4.38 (dd, J = 15.6, 6.2 Hz, 1 H), 4.18−4.12 (comp, 2 H), 4.00−3.89 (comp, 2 H), 3.81 (s, 3 H), 3.36 (td, J = 12.6, 5.6 Hz, 1 H), 3.08−2.98 (comp, 2 H), 2.53−2.41 (comp, 2 H), 1.87 (dd, J = 12.6, 5.5 Hz, 1 H), 1.31 (m, 1 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz) δ 168.3, 167.4, 143.2, 138.4, 136.4, 127.6, 124.6, 121.3, 120.9, 109.6, 100.8, 67.5, 61.4, 57.4, 56.2, 55.9, 51.1, 45.8, 30.5, 29.8, 26.0, 18.3, −5.2; IR ($CHCl_3$) 3469, 3332, 3022, 2954, 2930, 2857, 2426, 1730, 1640, 1463, 1328, 1258 cm^{-1}; mass spectrum (CI) m/z 453.2561 ($C_{26}H_{37}N_2O_3$Si requires 453.2573), 453 (base), 395, 323, 263.

(±)-(19*E*)-2,16,19,20-Tetradehydro-18-hydroxycuran-17-oic Acid, Methyl Ester (36). A solution of protected alcohol from the preceding experiment (17 mg, 38 μmol) in MeOH (3 mL) containing 2 N HCl (7 drops) was stirred overnight at room temperature. The reaction was transferred to a separatory funnel containing 20% Na_2CO_3 (5 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (1 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with $CHCl_3$/MeOH (10:1) to afford 10.5 mg (83%) of **36** as an off-white solid that gave spectra identical with that of an authentic sample.[13]

Acknowledgment. We are grateful to the National Institutes of Health (GM 25439) and The Robert A. Welch Foundation for their generous support of this research program. We also thank Professor Larry E. Overman (University of California, Irvine) for supplying a generous sample of authentic (±)-akuammicine (**2**) and complete spectral data for **36**.

Supporting Information Available: Experimental procedures and complete characterization (^{1}H and ^{13}C NMR and IR spectra and mass spectral data) for new compounds not included in the Experimental Section. See any current masthead page for ordering information and Web access instructions. This material is available free of charge via the Internet at http://pubs.acs.org.

JA010935V