Asymmetric Total Syntheses of (−)- and (+)-Strychnine and the Wieland−Gumlich Aldehyde[1]

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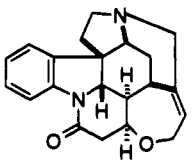
Abstract: The first asymmetric total syntheses of (−)-strychnine, *ent*-strychnine, and the Wieland−Gumlich aldehyde are described with full experimental details. The total synthesis of (−)-strychnine was realized in 24 steps and 3% overall yield from (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate (**28**). This synthesis fully controls the six stereogenic centers and forms the C(20) double bond of (−)-strychnine with high diastereoselection (>20:1). In the first stage of the synthesis, the (*R*)-cyclopentenylstannane **8** is prepared in nine steps and 30% overall yield (40% with one recycle of **38**) as summarized in Scheme 4. Palladium-catalyzed carbonylative coupling of **8** with the 2-iodoaniline derivative **7** provides enone **6**, which is converted to the 2-azabicyclo[3.2.1]octane **5** in seven additional steps. This latter sequence proceeds in 36% overall yield (Scheme 6). The central step of the total synthesis is aza-Cope−Mannich rearrangement of **5** which proceeds in 98% yield to form the pentacyclic intermediate **4** (Scheme 7). In five additional steps **4** is converted to the Wieland−Gumlich aldehyde **2**, which is the ultimate precursor of (−)-strychnine. A slight modification of this synthesis strategy allowed *ent*-strychnine to be prepared and provided the first samples of this unnatural enantiomer for pharmacological studies (Scheme 8). The efficiency and conciseness of this synthesis provide an important benchmark of the power of the aza-Cope rearrangement−Mannich reaction to solve formidable problems in alkaloid construction.

Introduction

Strychnine (**1**), the notorious Southeast Asian poison, occurs in large amounts in the Indian poison nut (*Strychnos nux-vomica*) and the Saint-Ignatiu's bean (*Strychnos ignatii Bergius*).[3] It has a long and mysterious medical history dating from sixteenth century Europe where it gained unwarranted use as a tonic.[4] Although strychnine is reported to stimulate appetite and increase the tone of skeletal musculature, there is no rational therapeutic use for this alkaloid.[4,5] Poisoning from strychnine occurs to this day due to its use as a rat poison.[5,6] A dose of 50−100 mg is lethal for an adult human, with death resulting from asphyxiation caused by intense convulsions that prevent normal respiration.[5] Strychnine toxicity is now known to result from blocking postsynaptic inhibition in the spinal cord and lower brain stem where glycine is the major inhibitory neurotransmitter.[7] It is the best characterized high-affinity antagonist of the inhibitory glycine receptor, often termed the strychnine-sensitive glycine receptor.[7,8] Binding of strychnine abolishes glycinergic inhibition and results in overexcitation of the motor system and muscular convulsions. Strychnine helped establish glycine as an inhibitory neurotransmitter in the spinal cord, and binding of [^{3}H]strychnine has been used to map glycine receptors autoradiographically.[7,8] Since strychnine is covalently attached to the α subunit of the glycine receptor upon UV irradiation, it also played an important role in the recent structural characterization of this important ligand-gated ion channel receptor.[8]



(−)-strychnine (**1**)

Strychnine was isolated by Pelletier and Caventou in 1818, and was one of the first alkaloids to be obtained in pure form.[9] The molecular constitution of strychnine, $C_{21}H_{22}O_2N_2$, was established by Regnault 20 years later.[10] Degradative investigations commenced as early as the 1880s; however, the seven intertwined rings of this alkaloid presented an enormous challenge to classical chemical structure elucidation.[3] The extensive structural investigations early in this century were spearheaded by Leuchs and Robinson whose groups published nearly 400 communications on the strychnine structural problem. The structure proof was finally completed by Woodward and Brehm in 1948.[11-13] This accomplishment marked the end of

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(1) Publication 28 in the series: Synthesis Applications of Cationic Aza-Cope Rearrangements. For part 27, see: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

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(3) For historical surveys, see: (a) Smith, G. F. *Alkaloids* **1965**, *8*, 591. (b) Huisgen, R. *Angew. Chem.* **1950**, *62*, 527. (c) Robinson, R. In *Progress in Organic Chemistry;* Cook, J. W., Ed.; Butterworths: London, 1952; Vol. 1, p 12.

(4) Creasey, W. A. In *The Monoterpene Indole Alkaloids;* Saxton, J. E., Ed.; Interscience: New York, 1983; pp 800−802.

(5) (a) Franz, D. N. In *The Pharmacological Basis of Therapeutics*, 5th ed.; Goodman, L. S., Gilman, H., Eds.; MacMillan: New York, 1975; pp 359-361. (b) Barron, S. E.; Guth, P. S. *Trends Pharm. Sci.* **1987**, *8*, 204.

(6) Van Heerden, P. V.; Edibam, C.; Auguston, B.; Thompson, W. R.; Power, B. M. *Anaesth. Intens. Care* **1993**, *21*, 876.

(7) Aprison, M. H. In *Glycine Neurotransmission*; Otterson, O. P., Storm-Mathisen, J., Eds.; John Wiley: New York, 1990; pp 1−23.

(8) For recent reviews, see: (a) Béchade, C.; Sur, C.; Triller, A. *Bioessays* **1994**, *16*, 735. (b) Betz, H. *Q. Rev. Biophys.* **1992**, *25*, 381. (c) Betz, H.; Becker C.-M. *Neurochem. Int.* **1988**, *13*, 137.

(9) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323.

(10) Regnault, V. *Ann.* **1838**, *26*, 17, 35.

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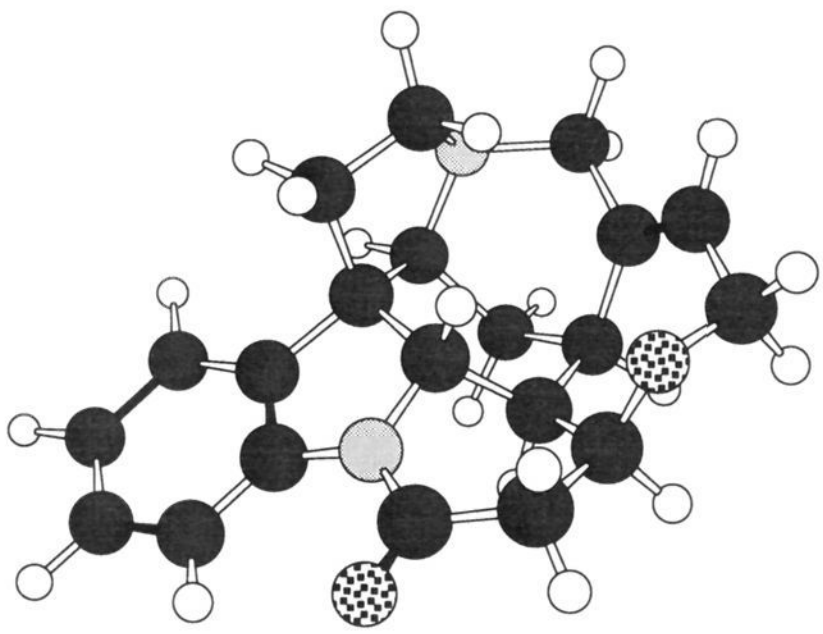


Figure 1. Chem 3D model of (−)-strychnine.

the era of classical structure elucidation,[14] since the relative and absolute stereochemistry of strychnine were determined by single-crystal X-ray crystallography three years later.[15]

The total synthesis of strychnine by Woodward, coming only six years after its structure was established, is a landmark in organic synthesis.[16] Prior to this time no molecule approaching the complexity of strychnine had been prepared by designed total synthesis. That strychnine's seven rings displayed on only 24 skeletal atoms and six stereogenic centers (Figure 1) still represent a formidable challenge for total synthesis is apparent in the nearly 40 years that elapsed between Woodward's seminal synthesis and the recent notable accomplishments in this area: Magnus's relay total synthesis of (−)-strychnine;[17] total syntheses of (±)-strychnine by Kuehne,[18] Rawal[19] and Stork;[20] and the asymmetric total synthesis of (−)-strychnine reported from our laboratory in 1993.[21,22] We record herein the details of the first enantioselective total syntheses of (−)-strychnine and the Wieland−Gumlich aldehyde as well as the extension of our synthesis strategy to prepare *ent*-strychnine.

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

(12) The correct structure of strychnine appeared first in publications from Robinson's laboratory. However, a slightly different structure was favored by this group at the time.[13]

(13) (a) Briggs, L. H.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 903. (b) Robinson, R. *Experientia* **1946**, *2*, 28.

(14) The emerging importance of instrumental methods of structure elucidation is foreshadowed by Woodward's key application of UV spectroscopy to solve a central feature of the strychnine structural challenge.[11b]

(15) (a) Robertson, J. H.; Beevers, C. A. *Acta Crystallogr.* **1951**, *4*, 270. (b) Bokhoven, C.; Schoone, J. C.; Bijvoet, J. M. *Acta Crystallogr.* **1951**, *4*, 275. (c) Peerdeman, A. F. *Acta Crystallogr.* **1956**, *9*, 824.

(16) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.

(17) (a) 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.

(18) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.

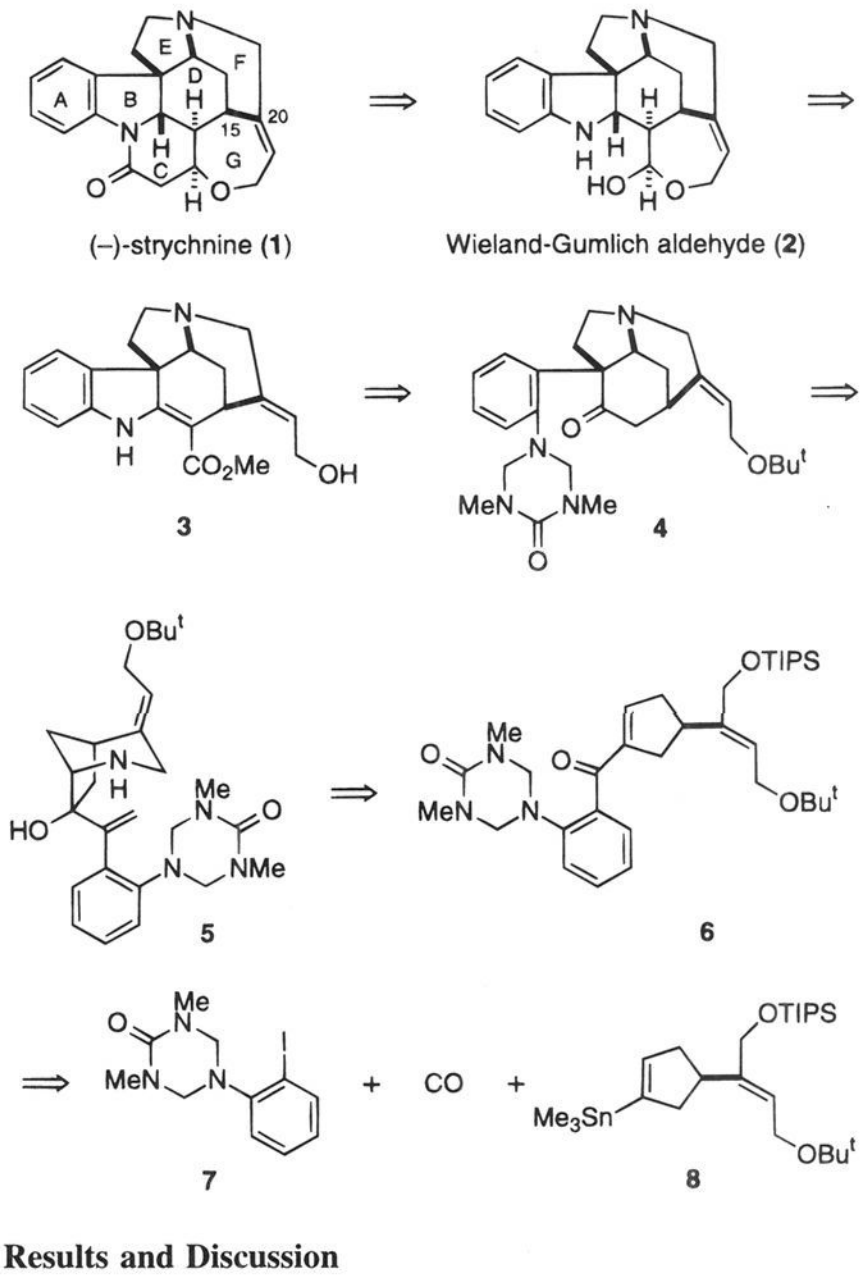
(19) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.

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

(21) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.

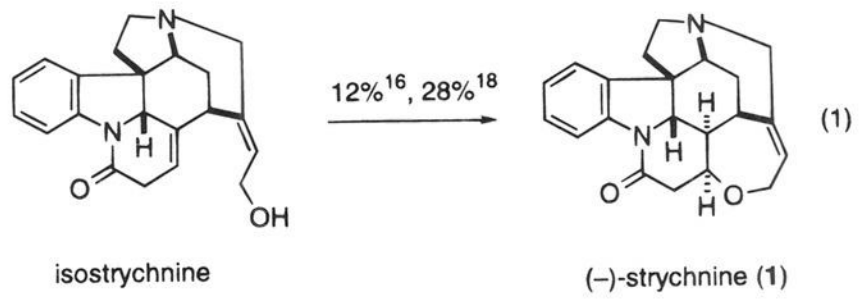
(22) For recent reviews of *Strychnos* alkaloid synthesis, see: (a) Bosch, J.; Bonjoch, J. In *Studies in Natural Product Chemistry Vol. 1, Stereoselective Synthesis (Part A)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; p 31. (b) Massiot, G.; Delaude, C. *Alkaloids* **1988**, *34*, 211. (c) Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1144.

Scheme 1. Synthesis Plan



Results and Discussion

Synthesis Plan. The conversion of isostrychnine to strychnine is known to be an inefficient transformation (eq 1).[16,17b,18]



(1)

As a result, our strychnine synthesis plan focused on the asymmetric construction of the Wieland−Gumlich aldehyde **2** (Scheme 1), whose high-yielding conversion to strychnine had been demonstrated many years ago by Anet and Robinson.[23,24] The major challenge in the synthesis of **1** and **2** is assembly of the congested basket formed by rings D, E, and F (see Figure 1). In our earlier investigations in the *Strychnos* alkaloid area, we had shown that this key subunit of the pentacyclic curane core could be efficiently assembled by the cationic aza-Cope rearrangement−Mannich cyclization reaction.[25,26] In the context

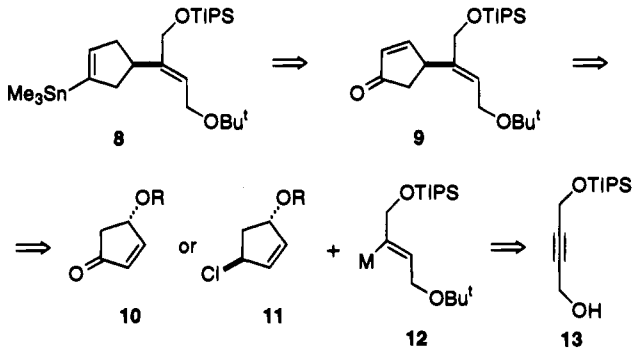
(23) Anet, F. A. L.; Robinson, R. *Chem. Ind.* **1953**, 245.

(24) Wieland−Gumlich aldehyde is the ultimate precursor of strychnine in the Magnus synthesis,[17] while the Woodward,[16] Kuehne,[18] and Rawal[19] syntheses rely on the isostrychnine → strychnine conversion. For a recent unsuccessful attempt to optimize the conversion of isostrychnine → strychnine, see ref 17b.

(25) (a) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966. (b) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085.

(26) For brief reviews of the aza-Cope−Mannich reaction, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (b) Overman, L. E. *Abstracts, 33rd National Organic Symposium* **1993**, 96.

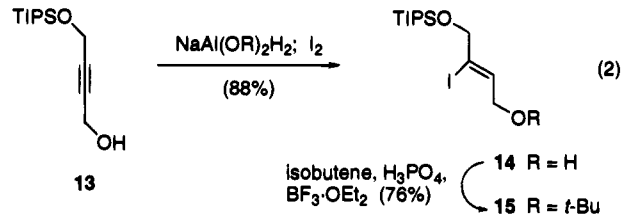
Scheme 2. Initial Plan for the Synthesis of Enone **9**

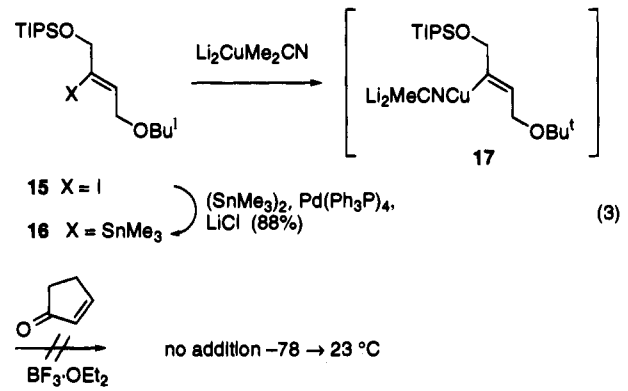


of the total synthesis of (−)-strychnine, aza-Cope−Mannich rearrangement of **5** was envisaged to lead to **4**, which should be readily converted to **3**.[25a] Curane **3**, 18-hydroxyakuammicine, is a likely precursor of the Wieland−Gumlich aldehyde **2**. Following tactics developed in our earlier synthesis of *rac*-akuammicine,[25a] azabicyclooctane **5** would derive from aryl cyclopentenyl ketone **6**, which should itself be accessible by palladium-catalyzed carbonylative cross coupling of the 2-iodoaniline derivative **7** and cyclopentenylstannane **8**. The initial phase of the enantioselective synthesis of (−)-strychnine then reduces to the preparation of (*R*)-**8**. Since the (*E*)-butenyl side chain of **8** would evolve to the F and G rings of (−)-strychnine, stereoselective introduction of this unit would solve the stereochemical problem posed by the allylic ether double bond at C(20).[27]

Initial Unsuccessful Attempts To Prepare Cyclopentenone 9. The (*S*)-cyclopentenone **9** emerges as a likely precursor of vinylstannane **8** (Scheme 2). One reason for targeting this intermediate is the wealth of chemistry extant for assembling enantiopure cyclopentenes, which was developed over several decades during synthesis efforts directed toward the prostaglandins.[28] Although numerous tactics were possible, we initially examined the coupling of a (*Z*)-butenyl organometallic **12** with the enantiopure cyclopentenyl electrophiles **10**[29,30] and **11**.[31] Since the (*Z*)-alkenylmetal reagent would derive directly from antarafacial reduction of a propargyl alcohol precursor, this sequence would nicely establish the stereochemistry of strychnine's allylic ether functionality. Ample precedent suggested that the (*S*) alkoxy substituent of **10** and **11** would exert strong control on face selection in the coupling of the cyclopentenyl and organometallic components.[30,32]

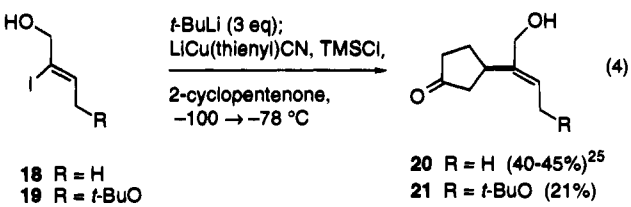
These investigations began with the TIPS-protected butynediol **13**, which is available in 95% yield from the reaction of triisopropylsilyl chloride with 6 equiv of 2-butyne-1,4-diol (eq 2).[33] Standard reduction of **13** with sodium bis(2-methoxyethoxy)aluminum hydride followed by quenching with iodine[34] provided the (*Z*)-butenyl iodide **14**, which was transformed in standard fashion to the *tert*-butyl ether derivative **15**. Since the vinyllithium derived from **15** would be expected to rapidly suffer β-elimination,[25a] we initially examined in situ generation of cuprate **17** from a tin precursor (eq 3).[35] The requisite





vinylstannane **16** was conveniently obtained by palladium-catalyzed cross-coupling of **15** with hexamethylditin.[36] However, transmetalation of **16** to form the butenyl cuprate intermediate **17** and addition of the latter to the model electrophile 2-cyclopentenone could not be accomplished. At temperatures below −20 °C transmetalation does not take place, while at higher temperatures **17** apparently decomposes (presumably by β-elimination) more rapidly than it adds to 2-cyclopentenone.

In our earlier synthesis of (±)-akuammicine we partially solved the β-elimination problem in a related copper nucleophile by generating a higher order cyanocuprate reagent from the dilithium derivative of (*Z*)-2-iodo-2-butenol (**18** → **20**, eq 4).[25] However, application of this protocol to the *tert*-butoxy derivative **19** was less successful and provided the 2-cyclopentenone adduct **21** in an unsatisfactory yield of 21%.



(27) A brief discussion of this problem and an analysis of the published syntheses of (−)- and (±)-strychnine has appeared.[22c]

(28) For reviews of prostanoid synthesis, see: (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977. (b) Mitra, A. *Synthesis of Prostaglandins*; Wiley-Interscience: New York, 1977. (c) Garcia, G. A.; Maldonado, L. A.; Crabbé, P. *Prostaglandin Research*; Crabbè, P., Ed.; Academic Press: New York, 1977; Chapter 6. (d) Roberts, S. M., Scheinmann, F., Eds. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic Press: London, 1982. (e) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.

(29) (a) Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth.* **1995**, *73*, in press. (b) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.

(30) (a) Sugai, T.; Mori, K. *Synthesis* **1988**, 19. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298. (c) Tanaka, T.; Kurozumi, S.; Toru, T.; Miura, S.; Kobayashi, M.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1713. (d) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402. (e) Asami, M. *Tetrahedron Lett.* **1985**, *26*, 5803.

(31) Oppolzer, W.; Gaudin, J.-M.; Birkinshaw, T. N. *Tetrahedron Lett.* **1988**, *29*, 4705.

(32) For representative examples, see: (a) Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755. (b) Suzuki, M.; Kawagishi, T.; Suzuki, T., Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 4057.

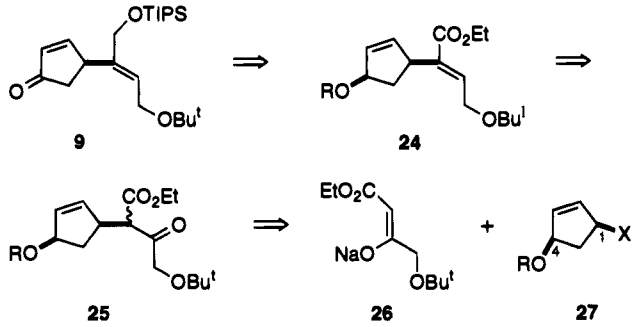
(33) Common abbreviations employed can be found in *J. Org. Chem.* **1994**, *59*, 7A.

(34) (a) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem* **1982**, *47*, 4595.

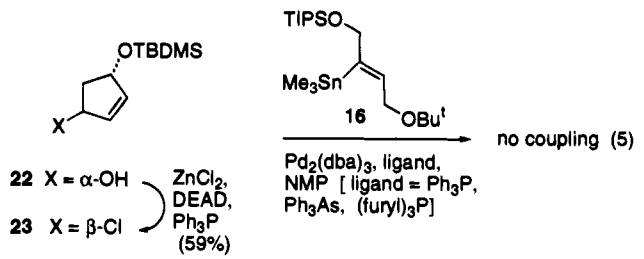
(35) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

(36) 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.

Scheme 3. Revised Plan for the Synthesis of Enone **9**

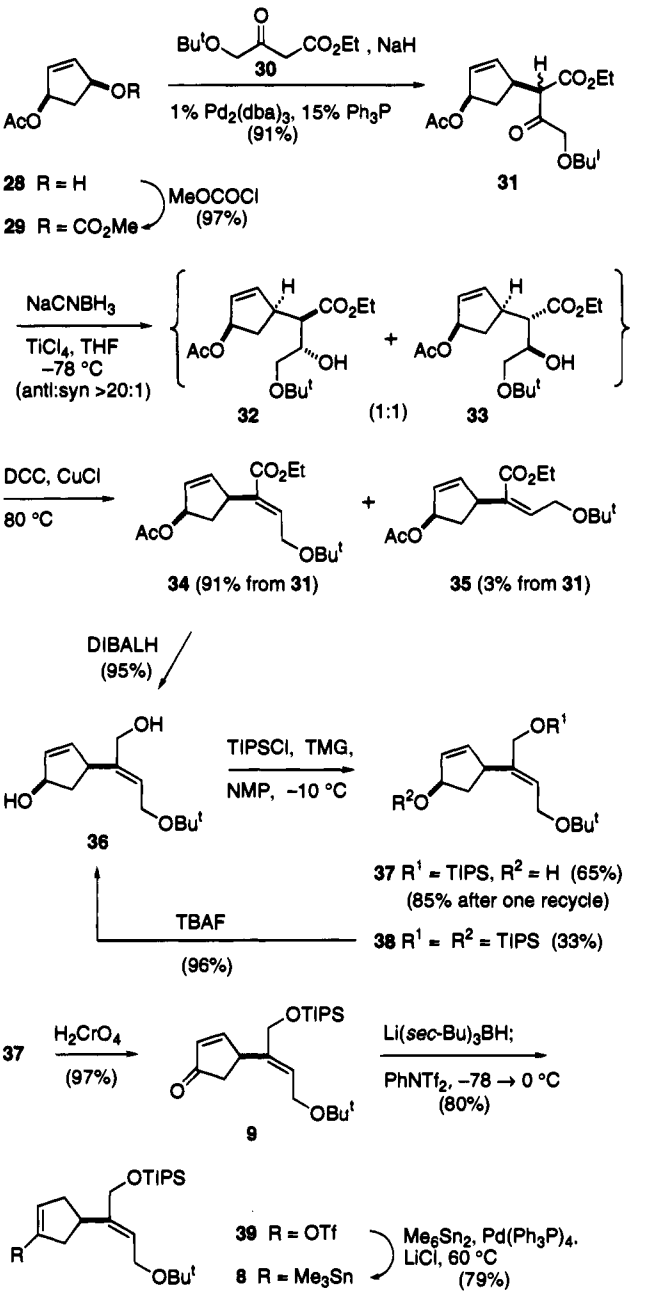


Since cross-coupling of alkenylstannanes with allylic chlorides is well-known,[37] we also examined the reaction of *trans*-siloxycyclopentenyl chloride **23** with vinylstannane **16** (eq 5). This allylic chloride was available by Mitsunobu-type chlorination[38] of (1*R*,4*S*)-*cis*-4-(*tert*-butyldimethylsiloxy)cyclopentenol (**22**).[30a] Disappointingly, however, numerous attempts to cross-couple **23** and **16** using a wide variety of palladium catalysts, including those recently optimized by Farina and co-workers,[39] failed.[40-42]



Successful Preparation of Vinylstannane 8. In light of our inability to introduce the (*Z*)-2-butenyl unit as a vinyl organometallic nucleophile, we turned to a less direct strategy that had precedent from our earliest investigations in the *Strychnos* alkaloid area.[43] As illustrated in Scheme 3, palladium(0)-catalyzed substitution of an allylic electrophile **27** and β-keto ester enolate **26** should provide the cyclopentenyl β-keto ester **25**. Stereoselective reduction of **25** followed by stereospecific dehydration of the derived β-hydroxy ester then would provide the (*E*)-alkenyl ester **24** as long as the stereochemistry of the reduction and elimination processes were properly coordinated.[43] The leaving group X in **27** would have to be chosen such that η^3-allylpalladium formation would take place selectively at carbons 1−3. The exceptional reactivity of allyl carbonates towards Pd(0) nucleophiles suggested that X could be OCO_2-Me.[44] A further attraction to this scheme was the possibility that inversion of the relative reactivity of X and OR would allow the enantiomer of **9** (and eventually *ent*-strychnine) to be prepared using nearly identical chemistry (*vide infra*).

Scheme 4. Preparation of (*R*)-Vinylstannane **8**



The successful synthesis of (*R*)-vinylstannane **8** that emerged from these considerations is summarized in Scheme 4. The synthesis begins with (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate (**28**), which is readily obtained by enantioselective hydrolysis of *cis*-3,5-diacetoxycyclopentene.[29,30ab] We employed the procedure recently documented in *Organic Syntheses*,[29] which utilizes electric eel acetylcholinesterase and conveniently provides **28** on large scales with ≥99% ee. Palladium-catalyzed coupling of the carbonate derivative **29** and the sodium salt of ethyl 4-*tert*-butoxy-3-oxobutanoate (**30**), prepared in one step from commercially available ethyl α-chloroacetoacetate,[45] provided the cis adduct **31** (a 1:1 mixture of ethyl ester epimers) in 91% yield.

Results obtained in the reduction of **31** with several reducing agents are tabulated in Table 1. In all cases there was negligible

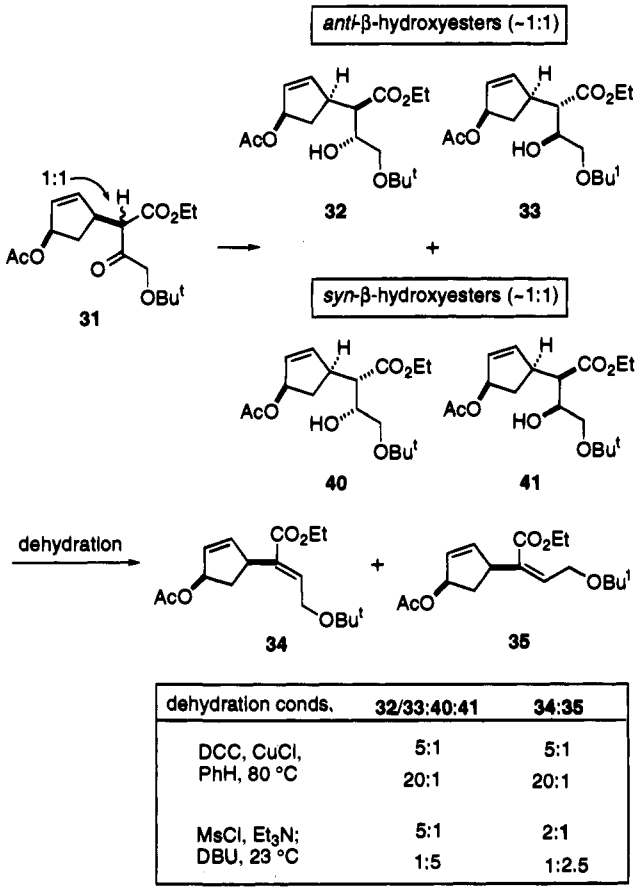
(37) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833.
(38) Ho, P.-T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027.
(39) (a) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, Jr., C. *J. Org. Chem.* **1990**, *55*, 5833. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(40) A number of other approaches to realize the construction of enone **9** projected in Scheme 2 were also explored without success. For example, attempted Heck reaction of 2-cyclopentenone (a model for cyclopentenyl chiron **10**) with alkenyl iodide **19** using a wide variety of Pd(0) catalysts and reaction solvents failed, as did related Ni(0) coupling.[41,42]
(41) For a review of recent advances in the Heck reaction, see: de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.
(42) Sustmann, R.; Hopp, P.; Holl, P. *Tetrahedron Lett.* **1989**, *30*, 689.
(43) Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021.
(44) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809.
(45) A slight modification of a procedure outlined in the patent literature was employed: Raimund, M.; Leander, T. Eur. Pat. Appl. EP 67, 408, 1982; *Chem. Abstr.* **1983**, *98* (21), 179198u. Full details are provided in the Experimental Section.

Table 1. Reduction of β-Keto Esters 31[a]

entry	reducing agent	solvent	temp, °C	*anti*:*syn*[b]
1	$Zn(BH_4)_2$	Et_2O	0	1:2
2	$Zn(BH_4)_2$	Et_2O	−4	1:2
3	$Zn(BH_4)_2$	CH_2Cl_2	23	1:3
4	$Zn(BH_4)_2$	THF	23	1:1
5	$NaBH_4$	EtOH	23	1:1
6	$NaBH_4$, $CeCl_3$ (1 equiv)	EtOH	23	1:1
7	$Bu_4N{\cdot}NCBH_3$, $TiCl_4$ (0.1 equiv)	CH_2Cl_2	−78	1:7
8	$NaNCBH_3$ (3 equiv), $TiCl_4$ (0.1 equiv)	THF	−78	10:1
9	$NaNCBH_3$ (3 equiv), $TiCl_4$ (1.0−1.05 equiv)	THF	−78	20:1

[a] Unless noted otherwise, 1 equiv of the reducing agent was employed. [b] See Scheme 5. Isomer ratios were determined by ^1H NMR analysis and confirmed in most cases by *syn* elimination (DCC, CuCl) to form the α,β-unsaturated esters **34** and **35**. [c] Similar results were obtained with $Bu_4N{\cdot}NCBH_3$.

Scheme 5. Reduction of β-Keto Esters **31**



asymmetric induction from the acetate group, so the *anti* and *syn* products were each produced as a 1:1 mixture of diastereomers (Scheme 5). Under no condition examined could *syn*-selective reduction, resulting from conventional chelate organization of the ketone and ester functionalities, be realized with high selectivity.[46,47] This result must arise from competitive chelation of the Lewis acid component of the reducing agent with the *t*-BuO substituent, since reduction of a closely related cyclopentenyl β-keto ester lacking the *t*-BuO group with $Zn(BH_4)_2$ in ether at 0 °C gave exclusively the expected *syn* β-hydroxy ester product.[43] Highest *syn* selectivity (Table 1, entry 7) was realized with a two-component reactant recently described by DiMare and co-workers ($Bu_4N{\cdot}NCBH_3-TiCl_4$),[48]

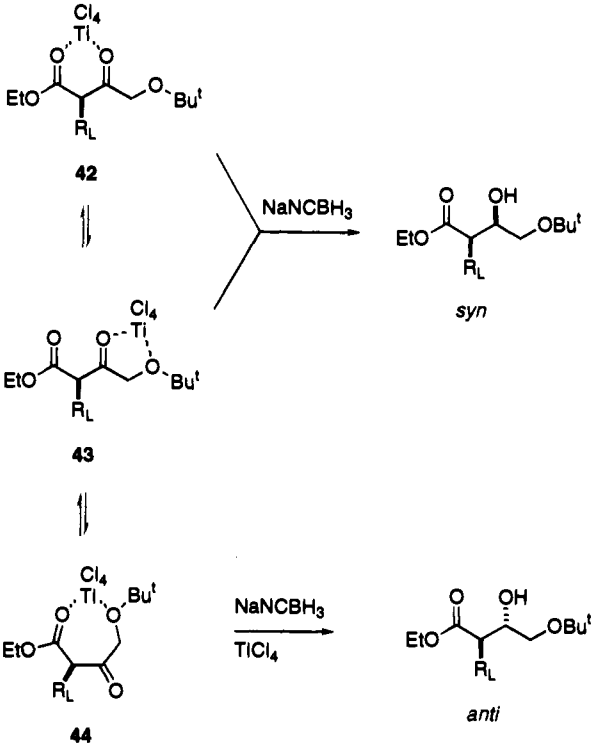


Figure 2. $TiCl_4$ chelates of **31** and their expected reduction products (R_L = 4-acetoxy-2-cyclopentenyl).

which at −78 °C in CH_2Cl_2 gave a 7:1 *syn* preference. Changing the solvent from CH_2Cl_2 to THF with this mixed reductant system had a remarkable effect on facial selectivity, producing the *anti* products **32/33** with high selectivity (Table 1, entries 8 and 9). After careful investigation of this reduction, the following procedure was found to be optimal: a THF solution of **31** and $NaNCBH_3$ (3 equiv) was cooled to −78 °C and a 1 M CH_2Cl_2 solution of $TiCl_4$ (1.03 equiv) was added dropwise over 1 h. This condition resulted in nearly exclusive (>20:1) formation of the *anti* β-hydroxy esters **32/33**.

The structures of the *anti* β-hydroxy esters **32/33** and *syn* stereoisomers **40/41** were assigned by stereocontrolled dehydration to afford the corresponding α,β-unsaturated esters **34** and **35** (Scheme 5). *Syn* elimination of a 5:1 mixture of **32/33**:**40/41** with DCC and CuCl at 80 °C[49] took place stereospecifically in high yield to provide a 5:1 mixture of **34** and **35**, while a >20:1 *anti*:*syn* mixture provided a >20:1 *E*:*Z* mixture of α,β-unsaturated esters. As summarized in Scheme 5, *anti* elimination of the mesylate derivatives was much less stereospecific.

The *t*-OBu substituent is undoubtedly responsible for the *anti* selectivity obtained in the reduction of **31** with $NaNCBH_3-TiCl_4$ in THF, since *syn* selectivity is observed in the reduction of simple β-keto esters under these conditions.[48b] The three $TiCl_4$ chelates that could be formed from **31** are shown in Figure 2. Hydride reduction of chelates **42** and **43** would be expected to lead to the *syn* β-hydroxy ester product.[48,50] However, the 7-membered chelate **44** would be strongly biased toward forming the *anti* product.[51] Reduction of **44** would appear to require prior activation of the ketone carbonyl with $TiCl_4$. Further speculation on the unusual *anti* stereoselective reduction

(46) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.
(47) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641.
(48) (a) Sarko, C. R.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1994**, *59*, 705. (b) DiMare, M. Personal communications with L.E.O.
(49) Alexandre, C.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1971**, 1837.
(50) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(51) A closely related 7-membered $TiCl_4$ chelate of acryloyl ethyl lactate has been characterized by X-ray crystallography: Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112.

of **31** is premature at this point and would require as a prelude a thorough investigation of Lewis acid stoichiometry, solvent, and counterion effects.

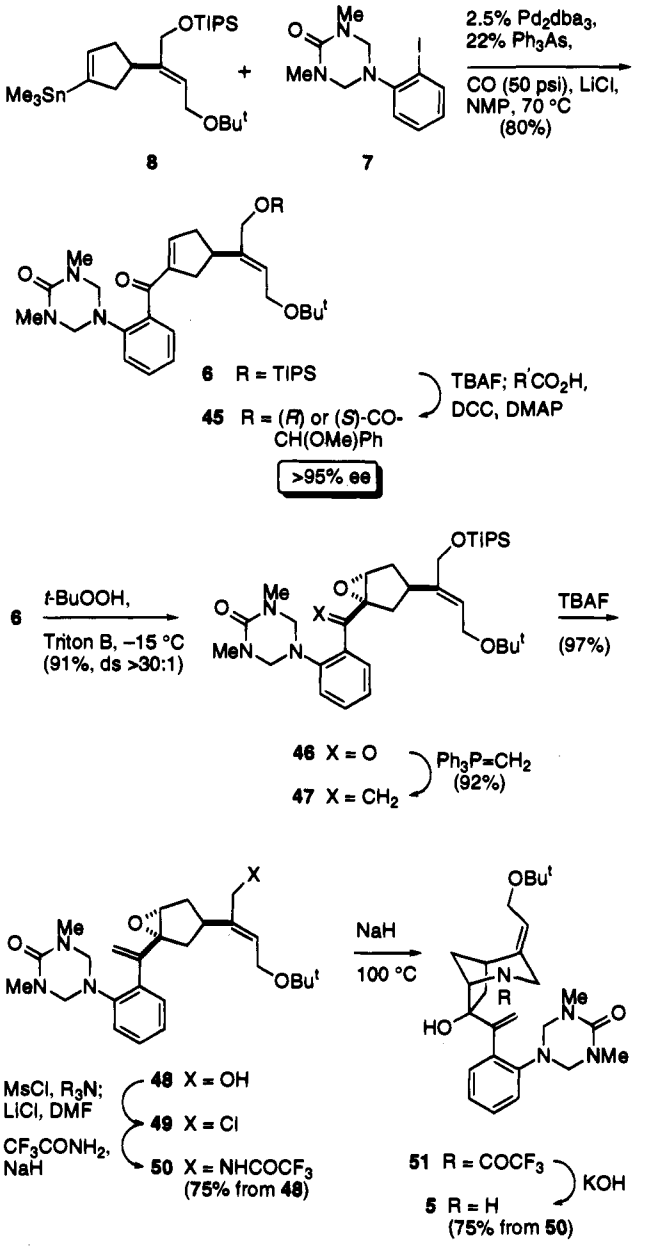
When the reduction of **31** was conducted on a 30 g scale and the resulting mixture of β-hydroxy esters was dehydrated with DCC/CuCl in refluxing benzene, the desired (*E*)-cyclopentenyl ester **34** (vinylic hydrogen δ 6.84) was obtained in 91% overall yield (Scheme 4). Also isolated from this large-scale reaction was 3% of the (*Z*)-ester **35** (vinylic hydrogen δ 6.06). Subsequent reduction of **34** with excess DIBALH provided diol **36** in high yield. Selective protection of the primary alcohol of this intermediate with a TIPS group proved unexpectedly difficult. None of the many conditions examined proved fully satisfactory.[52] The best solution found was to treat **36** with 2 equiv of triisopropylsilyl chloride and 2.2 equiv of 1,1,3,3-tetramethylguanidine (TMG) at 0 °C in *N*-methyl-2-pyrrolidinone (NMP)[53] until diol **36** could no longer be detected by TLC analysis. This treatment provided the readily separable monosilyl ether **37** in 65% yield and the bissilyl ether **38** in 33% yield. Fortunately, this latter product could be efficiently recycled (see Scheme 4), allowing the overall yield for the **36** → **37** conversion to be raised to 85% after a single recycle of **38**.

Jones oxidation of **37** at −5 °C proceeded smoothly to provide cyclopentenone **9** in 97% yield. Reduction of this intermediate with lithium tri-*sec*-butylborohydride and trapping of the resulting enolate with *N*-phenyltriflamide provided enol triflate **39** in 80% yield.[54] Palladium-catalyzed stannylation of **39** by the general procedure described by Wulff and co-workers[36] delivered the desired alkenylstannane **8** in 79% yield. The optimized sequence summarized in Scheme 4 is notably efficient and allows **8** to be prepared on multigram scales in 40% overall yield from (1*R*,4*S*)-4-hydroxy-2-cyclopentenyl acetate (**28**).

Conversion of 8 to Azabicyclooctane 5. Using conditions recently optimized during our total synthesis of (±)-akuammicine,[25a] palladium-catalyzed carbonylative coupling of **8** with the triazone-protected[55] *o*-iodoaniline **7** proceeded smoothly to provide enone **6** in 80% yield. At this point the enantiomeric purity of this key intermediate was confirmed to be >95% ee by ^{1}H NMR analysis of the α-methoxyphenylacetic esters prepared by cleavage of the TIPS ether of **6** with TBAF and subsequent acylation of the liberated primary alcohol with (*R*)- or (*S*)-2-methoxyphenylacetic acid.

Following the strategy developed in our earlier *Strychos* alkaloid studies,[25] the 2-azabicyclo[3.2.1]octane ring system was next assembled by nucleophilic epoxidation of **6** to provide the trans epoxide **46** (Scheme 6). No stereoisomer of **46** was detectable in the 500 MHz ^{1}H NMR spectrum of the crude epoxidation product, indicating that diastereoselection in this step is at least 30:1. Wittig methylenation of **46** and cleavage of the TIPS ether of **47** with TBAF produced the allylic alcohol **48** in 89% overall yield. Conversion of **48** to the allylic trifluoroacetamide **50** then was accomplished in 75% overall yield by treatment of the former with methanesulfonyl chloride and LiCl, followed by displacement of the resulting crude allylic chloride **49** with the sodium salt of trifluoroacetamide.[56] Cyclization of **50** with NaH in benzene at 100 °C and final

Scheme 6. Synthesis of Azabicyclooctane **5**



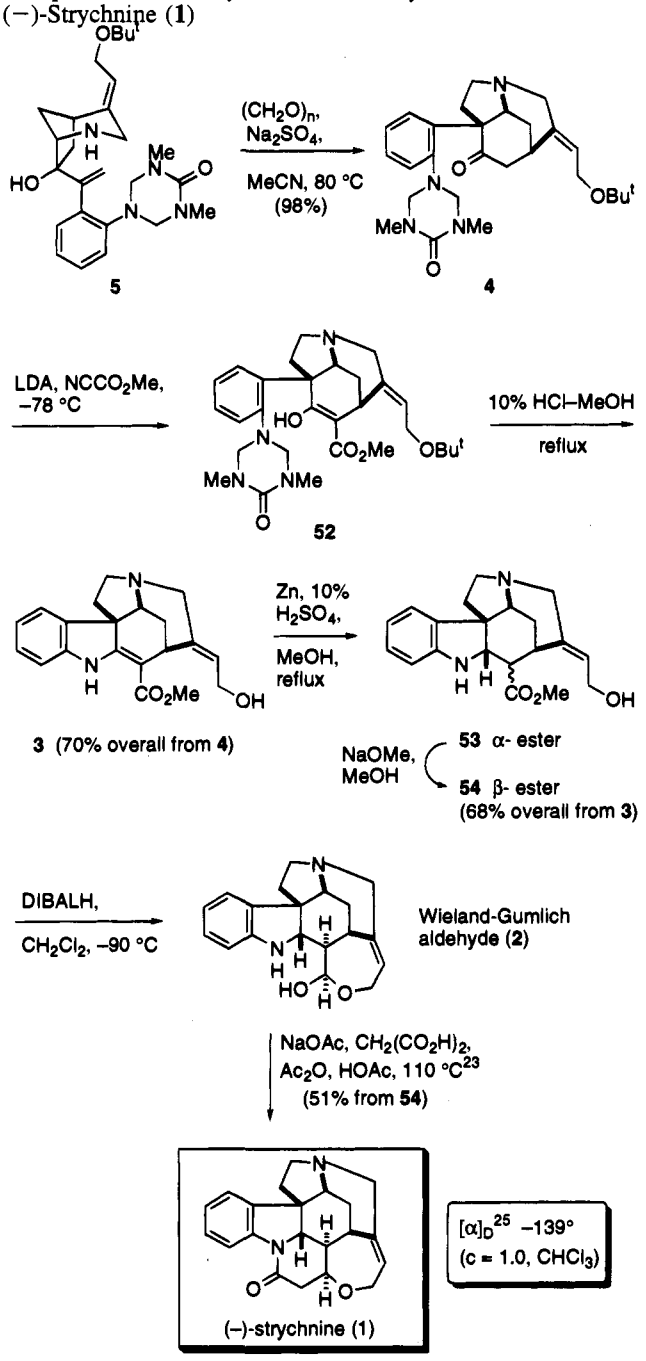
removal of the trifluoroacetyl group of **51** at 60 °C with KOH in EtOH−H_2O provided azabicyclooctane **5** in 45% overall yield from enone **6**.

Aza-Cope−Mannich Rearrangement of 5 and Conversion of 4 to the Wieland−Gumlich Aldehyde and (−)-Strychnine. The central aza-Cope−Mannich reorganization was accomplished in nearly *quantitative yield* by heating **5** in acetonitrile with excess paraformaldehyde and anhydrous Na_2SO_4 (Scheme 7). These conditions provided the crystalline pentacyclic diamine **4** (mp 151−152 °C) in 98% yield on a multigram scale. This pivotal conversion forms, with complete stereocontrol, the critical D, E, and F rings of (−)-strychnine (Figure 3).

Carbomethoxylation of **4** with methyl cyanoformate[57] delivered the β-keto ester derivative **52**, which exists largely in the enol form. Direct treatment of this intermediate with refluxing methanolic HCl resulted in removal of both the triazone and *tert*-butyl protecting groups to yield 18-hydroxyakuammicine (**3**) after dehydration. Rapid elution of this product through a short plug of silica gel provided **3** in 70% overall yield from **4**.

(52) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Syntheses*, 2nd ed.; John Wiley: New York, 1991; pp 74−75.
(53) (a) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797. (b) Kim, S.; Chang, H. *Synth. Commun.* **1984**, *14*, 899.
(54) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.
(55) (a) Knapp, S.; Hale, J. J.; Bastos, M.; Molina, A.; Chen, K. Y. *J. Org. Chem.* **1992**, *57*, 6239. (b) Knapp, S.; Hale, J. J.; Bastos, M.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109.
(56) (a) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820. (b) Albanese, D.; Landini, D.; Penso, M. *J. Org. Chem.* **1992**, *57*, 1603.
(57) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

Scheme 7. Aza-Cope–Mannich Rearrangement and Completion of the Asymmetric Total Synthesis of (−)-Strychnine (**1**)



Due to the slight instability of **3** on silica gel, this intermediate was typically not purified but directly used in the next step.

With a sufficient supply of 18-hydroxyakuammicine in hand, our attention turned to the conversion of **3** to the Wieland–Gumlich aldehyde **2**. The first task was to reduce the double bond of the vinylogous carbamate functionality. The reduction of akuammicine and related alkylideneindolines with either $NaNCBH_3$ in HOAc[58] or zinc dust in acidic MeOH[59] has been described. In the case at hand, reaction of **3** with $NaNCBH_3$ in HOAc proceeded readily at room temperature, however an inseparable 1:1 mixture of the α-ester **53** and an unidentified indole byproduct was obtained (eq 6). Although the structure

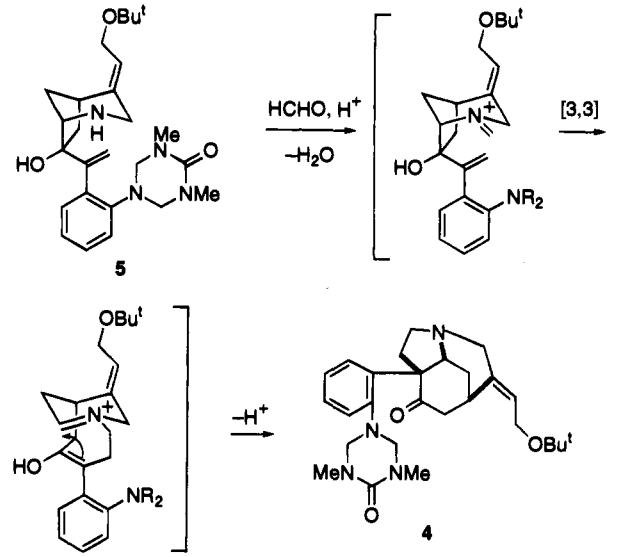
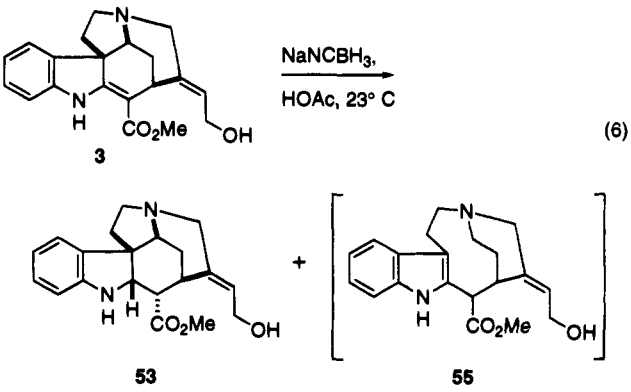


Figure 3. Stereochemistry of the aza-Cope–Mannich step.

of this byproduct was not established rigorously, reductions of similar indole alkaloids under neutral conditions, or in the presence of weak acids, often results in the formation of "cleavamine" products related to **55**.[60,61]



Reduction of the 2,16-double bond of **3** was easily accomplished, however, by treatment of **3** with zinc dust in 10% methanolic sulfuric acid. After 45 min at reflux, the α-ester **53**, contaminated with a small amount (<10%) of the β-ester **54** that likely was formed during the basic workup, was obtained. Complete epimerization of the ester could be realized by exposure of the crude reduction product to NaOMe in MeOH at room temperature to furnish the β-ester **54** in 68% overall yield from **3**. At this point the identity of our synthetic material was rigorously established by direct comparison with a sample of **54** prepared by degradation of strychnine.[59a]

The stereochemical outcome of this reduction–epimerization sequence is readily understood.[59a] Upon protonation of the vinylogous urethane grouping of **3**, the C ring must adopt a boat conformation as depicted in Figure 4. Thus protonation of **3** favors the formation of **56** in which the methyl ester is in a pseudoequatorial position. Reduction of the iminium ion from the β-face then generates **53**, in which the C ring can now adopt a chair conformation that places the ester into an axial orientation. Epimerization of **53** with base then affords the equatorial β-ester **54**.

(58) Mirand, C.; Massiot, G.; Le Men-Olivier, L.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 1257.

(59) (a) Edwards, P. N.; Smith, G. F. *J. Chem. Soc.* **1961**, 152. (b) Wenkert, E.; Sklar, R. *J. Org. Chem.* **1966**, *31*, 2689. (c) Hymon, J. R.; Schmid, H. *Helv. Chim. Acta* **1966**, 49, 2067.

(60) See, e.g.: (a) Kutney, J. P.; Fuller, G. B. *Heterocycles* **1975**, *3*, 197. (b) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977.

(61) The ^1H NMR spectrum of the crude reaction mixture did not show the presence of the known β-ester **51**.

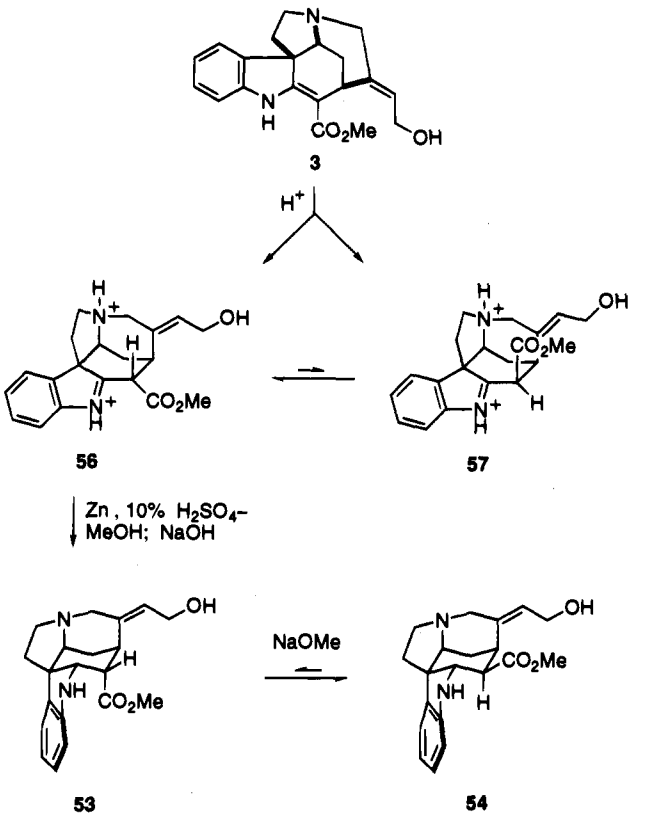
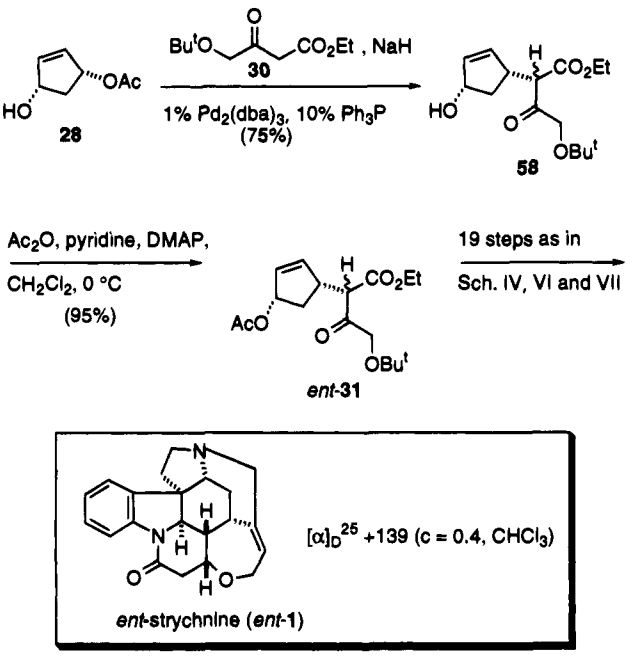


Figure 4. Stereorationale for reduction−epimerization steps.

All that now remained to complete the total synthesis of the Wieland−Gumlich aldehyde was to reduce the ester functionality of **54** to an aldehyde. To our delight this conversion could be directly accomplished with DIBALH at low temperature (Scheme 7) without having to protect the indoline NH group. The optimum procedure was to cool a CH_2Cl_2 solution of **54** to −90 °C and then add 3 equiv of DIBALH. Reduction appeared to be instantaneous and furnished the Wieland−Gumlich aldehyde **2**,[62] contaminated with a small amount (~10%) of the corresponding diol, in ~75% yield. Since separation of the diol impurity was difficult, this crude product was treated directly with malonic acid under the Perkin condensation conditions previously developed by Anet and Robinson[23] to furnish (−)-strychnine in 51% overall yield from ester **54**. Synthetic (−)-strychnine was identical in all respects with a sample of the natural alkaloid: mp 278−285 °C (EtOH), mixed mp 278−285 °C, lit.[16] mp 275−285 °C; $[\alpha]^{25}_D$ −139° (c = 0.4, $CHCl_3$), lit.[23] $[\alpha]^{25}_D$ −139° (c = 2.0, $CHCl_3$).

Enantioselective Total Synthesis of *ent*-Strychnine (*ent*-1). Bäckvall has recently illustrated how enantioselective hydrolysis of *meso*-2-alken-1,4-diol derivatives can be coupled with η^3-allylpalladium chemistry to prepare either enantiomer of a substitution product.[63] Application of this strategy in the cyclopentenyl series readily allowed *ent*-strychnine (*ent*-**1**) to be prepared for the first time (Scheme 8). Palladium-catalyzed coupling of hydroxy acetate **28** with the sodium salt of ethyl 4-*tert*-butoxy-3-oxobutanoate (**30**) in refluxing THF occurred cleanly at the allylic acetate functionality to provide the cis adduct **58** (a 1:1 mixture of ester epimers) in 75% yield. Acetylation of **58** delivered the cyclopentenyl keto ester *ent*-**31** (95% yield), which is enantiomeric with an early intermediate

Scheme 8. Asymmetric Total Synthesis of *ent*-Strychnine (*ent*-**1**)



in our total synthesis of (−)-strychnine. Following the chemistry developed in the natural series, *ent*-**31** was readily converted to *ent*-strychnine (*ent*-**1**). *ent*-Strychnine showed $[\alpha]^{25}_D$ + 139° (c = 0.4, $CHCl_3$), which was identical in magnitude but opposite in sign to the rotation observed for natural (−)-strychnine.

Conclusion

The first asymmetric total syntheses of (−)-strychnine, *ent*-strychnine, and the Wieland−Gumlich aldehyde have been achieved. The synthesis of (−)-strychnine was realized in 24 steps and 3% overall yield (Schemes 4, 6, and 7) from readily available[29a] (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate (**28**).[64] This synthesis fashioned the six stereogenic centers of (−)-strychnine with complete stereocontrol and formed the C(20) double bond with high diastereoselection (>20:1). The defining step is aza-Cope−Mannich rearrangement of the 2-azabicyclo-[3.2.1]octane **5** which proceeded in essentially quantitative yield to form the pentacyclic intermediate **4** (Scheme 7 and Figure 3). A slight modification of the synthesis strategy allowed *ent*-strychnine to be prepared and provided the first samples of this unnatural enantiomer for pharmacological studies. Although biological studies are at an early stage, they have already established that *ent*-strychnine is about a 1000-fold weaker antagonist of the inhibitory glycine receptor than natural (−)-strychnine, thus demonstrating that three-dimensional interactions are critical in binding of (−)-strychnine to this ion channel receptor.[65]

The strychnine synthesis strategy developed during this investigation provides an important benchmark of the power of the aza-Cope rearrangement−Mannich cyclization reaction to solve formidable problems in alkaloid construction. The synthesis is sufficiently concise that the preparation of 50 mg of *ent*-strychnine from **28** was accomplished in its entirety in less than six weeks.

The enantioselective total syntheses of (−)- and (+)-strychnine recorded here, and the recent accomplishments of

(62) (a) Wieland, H., Gumlich, W. *Liebigs Ann. Chem.* **1932**, *494*, 191. (b) Hymon, J. R.; Schmid, H.; Karrer, P.; Boller, A.; Els, H.; Fahrni, P; Fürst, A. *Helv. Chim. Acta* **1969**, *52*, 1564.

(63) (a) Bäckvall, J.-E.; Gatti, R.; Schink, H. E. *Synthesis* **1993**, 343. (b) Schink, H. E. Bäckvall, J.-E. *J. Org. Chem.* **1992**, *57*, 1588.

(64) The overall yield is raised to 3.8% when the bis-silyl ether **38** is recycled one time in the conversion of **36** → **37** (Scheme 4).

(65) Knight, S. D.; Miledi, R.; Overman, L. E.; Pairaudeau, G. *Biomed. Chem. Lett.* **1995**, *5*, 749.

the Magnus, Kuehne, Rawal, and Stork groups, provide striking testimony to the enormous progress realized in synthetic organic chemistry during the past 40 years. Although the number of steps in our synthesis of (−)-strychnine is only slightly less than employed in the Woodward synthesis, the overall yield is nearly 100 000 times greater. It is instructive to note that less than half of the steps employed in our synthesis would have been available to Woodward in the early 1950s. In addition to the central role of the aza-Cope−Mannich reaction in our total synthesis of (−)-strychnine, organopalladium chemistry was indispensable and was employed in three different steps.

Experimental Section[66]

Ethyl 4-*tert*-butoxy-3-oxobutanoate (30). A slight modification of a literature procedure was employed.[45] A suspension of sodium hydride (36.0 g, 60% suspension in mineral oil, 0.85 mol) was washed three times with hexanes (50 mL), and DME (600 mL) was added. Ethyl α-chloroacetoacetate (58.0 mL, 0.42 mol) was then added dropwise over 30 min at 0 °C. *tert*-Butyl alcohol (27.7 mL, 0.48 mol) was then added, and the resulting solution was maintained at 0 °C for 14 h. The brown reaction mixture then was poured into 2 M HCl−ice (500 mL), and the resulting mixture was extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (200 mL), dried ($MgSO_4$), and concentrated. The residue was passed through a short plug of silica gel (100 g) with 70:30 Et_2O−hexanes, the eluent was concentrated, and the residue was distilled (95−100 °C, 4 mm) to give **30** (60.2 g, 71%) as a colorless oil. This material was homogeneous by TLC analysis and had spectral and physical data in agreement with those reported in the literature:[45] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (q, J = 7.1 Hz, 2H, CH_2), 4.07 (s, 2H, CH_2O), 3.56 (s, 2H, CH_2CO), 1.32 (t, J = 7.1 Hz, 3H, Me), 1.26 (s, 9H, *t*-Bu); MS (CI, isobutane) *m/e* 203 (MH), 187, 147.

Methyl (1*S*,4*R*)-4-Acetoxy-2-cyclopentenylcarbonate (29). Methyl chloroformate (20 g, 230 mmol) was added dropwise over 1 h at 0 °C to a stirred solution of (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate[29a] (**28**, 19 g, 140 mmol), pyridine (40 mL, 500 mmol), and CH_2Cl_2 (300 mL). After 2 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with 1 M HCl (2 × 200 mL), saturated aqueous $NaHCO_3$ (2 × 200 mL), and brine (200 mL). The resulting solution was dried ($MgSO_4$), passed through a short plug of silica gel (150 g) with CH_2Cl_2 (500 mL), and concentrated to afford **29**[69] as a colorless oil (26.5g, 97%) that was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 2H, CH=CH), 5.45 (dd, J = 7.5, 3.8 Hz, 1H, C*H*OAc), 5.37 (dd, J = 7.5, 3.7 Hz 1 H, C*H*OCO_2Me), 3.65 (s, 3H, Me), 2.83 (app quintet, J = 7.5 Hz, 1H, CH_2), 1.98 (s, 3H, Ac), 1.74 (dt, J = 15.0, 3.8 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 170.3, 155.0, 135.0, 133.7, 79.9, 76.1, 54.5, 36.8, 20.8; IR (film) 2962, 1743, 1450, 1375, 1275, 1237, 1075 cm^{-1}; MS (CI isobutane) *m/e* 201.0827 (201.0763 calcd for $C_9H_{13}O_5$, MH), 141, 125, 97; $[\alpha]^{20}_D$ −1.5°, $[\alpha]_{405}$ −0.8°, $[\alpha]_{435}$ −1.5°, $[\alpha]_{546}$ −2.5°, $[\alpha]_{577}$ −1.2° (c = 1.0, $CHCl_3$).

Ethyl 2-[(1*S*,4*R*)-4-Acetoxy-2-cyclopentenyl]-4-*tert*-butoxy-3-oxobutanoate (31). To a suspension of washed (3 × 50 mL of pentane) NaH (4.4 g, 60% dispersion in oil, 110 mmol) in THF (200 mL) at room temperature was added β-keto ester **30** (22 g, 110 mmol) dropwise over 20 min. In a separate flask a mixture of carbonate **29** (20.6 g, 103 mmol), Pd_2dba_3 (1.0 g, 1.1 mmol), PPh_3 (4.0 g, 15 mmol), and THF (400 mL) was stirred for 10 min at room temperature. The solution of sodium salt **23** then was added with a cannula to the yellow green solution of the catalyst and carbonate. The reaction mixture then was maintained at room temperature for 2 h, quenched with saturated aqueous NH_4Cl (500 mL), and extracted with EtOAc (2 × 500 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residual oil was purified by flash chromatography (75:25 hexanes−EtOAc) to afford **31** (30.7 g, 91%) as a colorless oil. This material, a 1:1 mixture of epimers at C-2 (^{1}H NMR analysis), was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (br d, J = 5.7 Hz, 0.5H, CH=C*H*), 5.95 (br d, J = 5.7 Hz, 0.5H, CH=C*H*), 5.8−5.9 (m, 1H, C*H*=CH), 5.58−5.63 (m, 1H, C*H*OAc), 4.10−4.22 (m, 2H, OCH_2Me), 3.95−4.05 (m, 2H), 3.70 (dd, 1H, J = 2.2, 8.9 Hz), 3.30−3.40 (m, 1H), 2.50-2.65 (m, 1H), 2.04 (s, 3H, MeCO), 1.4−1.7 (m, 1H), 1.26 (m, 3H, CH_3CH_2), 1.2 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 137.8, 137.6, 130.7, 78.9, 74.2, 67.7, 61.1, 59.8, 42.3, 42.0, 34.7, 33.9, 26.9, 21.0, 14.0; IR (film) 2981, 1743, 1725, 1468, 1443, 1368, 1193, 1106, 1025 cm^{-1}; HRMS (FAB) *m/e* 327.1807 (327.1807 calcd for $C_{17}H_{27}O_6$, MH); MS (CI, isobutane) 267, 211, 152. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.55; H, 8.03. Found: C, 62.40; H, 7.98.

Ethyl 2-[(1*S*,4*R*)-4-(Acetyloxy)-2-cyclopentenyl]-4-*tert*-butoxy-3-hydroxybutanoates (32 and 33). A 1 M CH_2Cl_2 solution of $TiCl_4$ (92 mL) was added dropwise over 1 h to a solution of keto ester **31** (29.2 g, 89.5 mmol), $NaNCBH_3$ (18 g, 290 mmol), and THF (500 mL) while maintaining the temperature below −75 °C. The resulting orange solution was maintained at −78 °C for 24 h, HCl (300 mL of a 1 N solution) was then added, and the resulting mixture was stirred rapidly for 20 min. This mixture was extracted with EtOAc (3 × 400 mL), and the extracts were washed with saturated aqueous $NaHCO_3$ solution (200 mL) and brine (200 mL). Drying ($MgSO_4$), concentration, and purification of the residue by flash chromatography (50:50 hexanes−Et_2O) gave a 1:1 mixture of the *anti* β-hydroxyesters **32** and **33** (28.6 g, 97%) as a colorless oil. This material was homogeneous by TLC analysis; approximately 5% of the corresponding *syn* stereoisomers were apparent in the 500 MHz ^{1}H NMR spectrum of this sample. **32/33**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (br d, J = 5.7 Hz, 0.5H, CH=C*H*), 5.87 (br d, J = 5.7 Hz, 0.5H, CH=C*H*), 5.75−5.85 (m, 1H, C*H*=CH), 5.54−5.62 (m, 1H, C*H*OAc), 4.1−4.2 (m, 2H, CH_2Me), 3.7−3.8 (m, 1H, C*H*OH), 3.35−3.40 (m, 2H), 3.10−3.20 (m, 2H), 2.30−2.60 (m, 2H), 2.03 (s, 3H, MeCO), 1.50−1.60 (m, 1H), 1.20−1.30 (m, 3H, CH_3-CH_2), 1.20 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 173.0, 170.7, 137.8, 130.5, 130.4, 79.0, 73.1, 70.5, 69.9, 64.3, 64.2, 60.4, 52.6, 52.5, 43.7, 43.3, 34.9, 34.3, 27.3, 21.1, 14.2; IR (film) 3506, 2981, 1743, 1481, 1450, 1368, 1243, 1193 cm^{-1}; HRMS (CI isobutane) *m/e* 329.1971 (329.1964 calcd for $C_{17}H_{29}O_6$, MH), 269, 213, 195, 181, 167. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59; Found: C, 61.82; H, 8.60.

Ethyl 2-[(1*S*,4*R*)-4-Acetoxy-2-cyclopentenyl]-4-*tert*-butoxy-2(*E*)-butenoate (34). A solution of a portion of this sample of **32/33** (27 g, 82 mmol, previously dried by azeotroping three times with toluene at room temperature) and benzene (200 mL) was added by cannula to a mixture of DCC (20.6 g, 100 mmol), freshly prepared[70] CuCl (10.5 g, 105 mmol), and benzene (300 mL). The resulting mixture was heated at reflux overnight and allowed to cool to room temperature, and EtOAc (500 mL) was added. The organic layer was washed with brine (2 × 300 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (75:25 hexanes−EtOAc) afforded 24.1 g (91% from **31**) of **34** together with 756 mg (3% from **31**) of the (*Z*)-stereoisomer **35**. Data for **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (t,

(66) General experimental details: Tetrahydrofuran (THF) and Et_2O were distilled from Na and benzophenone. Dimethylformamide (DMF) was distilled from CaH_2 at 20 mm, while CH_2Cl_2, benzene, toluene, and diisopropylamine were distilled from CaH_2 at atmospheric pressure. The molarities indicated for organolithium reagents were established by titration with 2,5-dimethoxybenzyl alcohol.[67] ^{1}H NMR and ^{13}C NMR were measured at 300 and 75, and 500 and 125 MHz, respectively, with Nicolet Omega 500, Nicolet GN-500, Varian AC 300, or Nicolet QE 300 spectrometers. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to TMS. ^{1}H NMR coupling constants are reported in hertz and refer to apparent multiplicities and not true coupling constants. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); etc. Mass spectra were measured using a VG Analytical 7070E or Fisons Autospec spectrometer. Infrared spectra were recorded with a Nicolet 5DBX FTIR spectrometer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter; concentration c is reported in g/100 mL. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. TLC and column chromatography were typically performed as described by Still[68] using E. Merck silica gel. Radial chromatography was done with a Harrison Research Chromatotron. All reactions were conducted under nitrogen or argon and concentrations were performed under reduced pressure using a Büchi rotary evaporator.

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J = 6.0 Hz, C=C*H*), 5.95 (app dt, J = 5.6, 1.8 Hz, CH=C*H*), 5.83 (app dt, J = 5.5, 2.5 Hz, C*H*=CH), 5.65−5.75 (m, 1H, C*H*OAc), 4.10−4.25 (m, 4H), 3.80−3.90 (m, 1H), 2.77 (app dt, J = 13.8, 8.4 Hz, 1H), 2.08 (s, 3H, CH_3CO), 1.71 (ddd, J = 13.5, 7.3, 6.1 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H, CH_3CH_2), 1.21 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 166.9, 141.8, 138.3, 133.2, 129.3, 79.6, 73.5, 60.6, 58.2, 42.4, 37.3, 27.4, 21.2, 14.1; IR (film) 2981, 1737, 1712, 1650, 1475, 1443, 1362, 1237, 1193, 1137 cm^{-1}; HRMS (CI isobutane) *m/e* 311.1778 (311.1858 calcd for $C_{17}H_{27}O_5$, MH), 251, 195, 177, 149; $[\alpha]^{25}_D$ −60.2°, $[\alpha]_{405}$ −165.2°, $[\alpha]_{435}$ −132.8°, $[\alpha]_{546}$ −73.8°, $[\alpha]_{577}$ −63.0° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.84; H, 8.52. (*Z*)-Stereoisomer **35**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (t, J = 4.7 Hz, C=C*H*), 5.8−5.95 (m, 2H, CH=CH), 5.6−5.7 (m, 1H, C*H*OAc), 4.1−4.4 (m, 4H), 3.6−3.7 (m, 1H), 2.70 (app dt, J = 14, 8 Hz, 1H), 2.03 (s, 3H, CH_3CO), 1.5−1.6 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H, CH_3CH_2), 1.20 (s, 9H, *t*-Bu).

Optical rotation data for *ent*-**34**: $[\alpha]^{25}_D$ +60.3°, $[\alpha]_{405}$ +165.9°, $[\alpha]_{435}$ +133.5°, $[\alpha]_{546}$ +73.2°, $[\alpha]_{577}$ +63.8° (c = 1.0, $CHCl_3$).

4-*tert*-Butoxy-2-[(1*S*,4*R*)-4-hydroxy-2-cyclopentenyl]-2(*E*)-buten-1-ol (36). A solution of **34** (28 g, 90 mmol) and CH_2Cl_2 (600 mL) at −78 °C was treated dropwise with neat DIBALH (78 mL, 460 mmol) over 20 min. After the resulting solution was maintained at −78 °C for 2 h, EtOAc (500 mL) was added cautiously, followed by a saturated aqueous solution of Rochelle's salt (400 mL). The resulting biphasic mixture was stirred rapidly for 4 h, at which time two clear layers had formed. The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 500 mL), and the extracts were dried ($MgSO_4$) and concentrated to an oil. This crude product (19.4 g, 95%), which was homogeneous by TLC analysis, was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (app dt, J = 5.2, 2.1Hz, CH=C*H*), 5.83 (dd, J = 5.5, 2.4 Hz, C*H*=CH), 5.59 (app t, J = 6.5 Hz, C=C*H*), 4.75 (d, J = 7.5 Hz, C*H*OH), 3.9−4.2 (m, 4H, OCH_2), 3.60−3.70 (m, 1H), 2.45−2.55 (m, 1H), 1.75 (app dt, J = 14.5, 2.4 Hz, 2H), 1.20 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 136.1, 134.8, 126.6, 76.5, 73.4, 66.1, 57.7, 43.4, 39.1, 27.5; IR (film) 3356, 2981, 2875, 1462, 1393, 1363, 1193, 1062, 1006 cm^{-1}; HRMS (CI isobutane) *m/e* 209.1531 (209.1541 calcd for $C_{13}H_{21}O_2$, M − OH), 152, 134, 106.

(1*R*,4*S*)-4-[1-((Triisopropylsiloxy)methyl)-3-*tert*-butoxy-1(*E*)-propenyl]-2-cyclopentenol (37). A solution of the crude diol **36** (3.2 g, 14 mmol), tetramethylguanidinine (4.4 mL, 35 mmol), and *N*-methylpyrrolidinone (60 mL) was cooled to 0 °C and treated dropwise with TIPSCl (6.3 mL, 29 mmol) over 2 h. The resulting solution was maintained at 0 °C and monitored by TLC until **36** was consumed (ca. 8 h). The solution was then diluted with Et_2O (200 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL), and dried ($MgSO_4$). Concentration followed by purification of the residue by flash chromatography (75:25 hexanes−Et_2O) gave 3.54 g (65%) of **37** as a colorless oil that was homogeneous by GLC analysis (30 m, SPB-1 fused silica capillary column, 100 °C initial temperature, 10 °C min^{-1}, retention time = 10.4 min). Also isolated was 2.56 g (33%) of the bis(triisopropylsilyl) ether **38**. Data for **37**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (app dt, J = 5.2, 2.1 Hz, C*H*=CH), 5.82 (dd, J = 5.2, 2.0 Hz, CH=C*H*), 5.64 (app t, J = 6.4 Hz, C=C*H*), 4.70−4.75 (m, 1H, C*H*OH), 4.16 (AB q, J_{AB} = 12.6 Hz, $\Delta\nu_{AB}$ = 14.8 Hz, 1H, CH_2OTIPS), 4.07 (dd, J = 11.6, 7.0 Hz, 1H, CH_2O-*t*-Bu), 3.96 (dd, J = 11.6, 6.1 Hz, 1H, CH_2O-*t*-Bu), 3.58−3.65 (m, 1H), 2.75 (broad s, 1H, O*H*), 2.45−2.58 (m, 1H), 1.74 (app dt, J = 14.1, 3.8 Hz, 1H), 1.24 (s, 9H, *t*-Bu), 1.0−1.1 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 135.9, 134.7, 125.7, 76.8, 73.2, 66.3, 57.7, 43.6, 39.6, 27.6, 18.0, 11.9; IR (film) 3418, 2968, 2868, 1462, 1362, 1250, 1193, 1106, 1062, 1012 cm^{-1}; HRMS (CI isobutane) *m/e* 365.2876 (365.2875 calcd for $C_{22}H_{41}O_2Si$, MH − H_2O), 308, 291, 266, 247; $[\alpha]^{25}_D$ −34.3°, $[\alpha]_{405}$ −99.2°, $[\alpha]_{435}$ −78.7°, $[\alpha]_{546}$ −40.0°, $[\alpha]_{577}$ −35.9° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{42}O_3Si$: C, 69.05; H, 11.07. Found: C, 68.91; H, 10.99.

Optical rotation data for *ent*-**37**: $[\alpha]^{25}_D$ +34.6°, $[\alpha]_{405}$ +99.3°, $[\alpha]_{435}$ +79.4°, $[\alpha]_{546}$ +41.9°, $[\alpha]_{577}$ +36.8° (c = 1.0, $CHCl_3$).

Data for **38**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.7−5.8 (m, 3H, CH=CH), 4.9 (app t, J = 5.7 Hz, 1H, CHOTIPS), 4.13 (d, J = 6.5 Hz, 2H, CH_2OTIPS), 4.08 (dd, J = 6.5, 3.5 Hz, 2H, CH_2O-*t*-Bu), 3.59 (app t, J = 6.8 Hz, 1H), 2.54 (dt, J = 13.3, 8.2 Hz, 1H), 1.5−1.6 (m, 1H), 1.2 (s, 9H, *t*-Bu), 1.0−1.1 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 135.1, 134.7, 122.4, 77.3, 73.0, 64.1, 57.9, 43.4, 40.9, 27.7, 18.1, 18.0, 12.1, 12.0; IR (film) 2925, 1468, 1362, 1256, 1192; HRMS (CI isobutane) *m/e* 539.4108 (539.4316 calcd for $C_{31}H_{63}O_3Si_2$, MH), 495, 465, 422, 292.

Recycling the Bis(triisopropylsilyl ether) 38. A solution of the bis(silyl ether) **38** (9.1 g, 17 mmol), THF (100 mL), and TBAF (35 mL of a 1 M solution in THF) was maintained at room temperature for 3 h. Brine (200 mL) was added, the resulting mixture was extracted with EtOAc (2 × 200 mL), and the extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (Et_2O) afforded diol **36** (3.6 g, 96%) as a colorless oil that was homogeneous by TLC analysis.

(4*S*)-4-[3-*tert*-Butoxy-1-((triisopropylsiloxy)methyl)-1(*E*)-propenyl]-2-cyclopentenone (9). Jones reagent (4 mL of a solution prepared from 6.7 g of CrO_3, 6 mL of H_2SO_4, and 50 mL of H_2O) was added dropwise at −5 °C to a solution of **37** (2.75 g, 7.2 mmol) and acetone (100 mL). After 10 min, the reaction was quenched with 1 M aqueous $NaHSO_3$ (50 mL), followed by saturated aqueous Na_2CO_3 (100 mL). The resulting green mixture was extracted with EtOAc (3 × 100 mL) using a little brine to break up the emulsions that formed. The organic extract was dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (70:30 hexanes−Et_2O) to afford 2.68 g (98%) of enone **9** as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, J = 5.6, 2.5 Hz, CH=C*H*), 6.25 (dd, J = 5.6, 2.3 Hz, C*H*=CH), 5.78 (app t, J = 6.5 Hz, C=C*H*), 4.08 (s, 2H, CH_2OTIPS), 3.95−4.08 (m, 2H, CH_2O-*t*-Bu), 2.63 (dd, J = 18.9, 6.9 Hz, 1H), 2.38 (dd, J = 19.0, 2.7 Hz, 1H), 1.20 (s, 9H, *t*-Bu), 1.0−1.1 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 166.8, 139.5, 133.9, 126.3, 73.2, 65.5, 57.5, 41.2, 40.6, 27.5, 17.9, 11.8; IR (film) 2950, 2875, 1718, 1587, 1462, 1362, 1200, 1100, 1056 cm^{-1}; HRMS (CI, isobutane) *m/e* 307.2093 (307.2096 calcd for $C_{18}H_{31}O_2Si$, MH−*t*-BuOH); $[\alpha]^{25}_D$ −97.5°, $[\alpha]_{405}$ −205.9°, $[\alpha]_{435}$ −188.8°, $[\alpha]_{546}$ −113.5°, $[\alpha]_{577}$ −100.2° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{40}O_3Si$: C, 69.42; H, 10.59. Found: C, 69.53; H, 10.64.

Optical rotation data for *ent*-**9**: $[\alpha]^{25}_D$ +96.8°, $[\alpha]_{405}$ +204.1°, $[\alpha]_{435}$ +84.3°, $[\alpha]_{546}$ +111.7°, $[\alpha]_{577}$ +98.4° (c = 1.0, $CHCl_3$).

(4*R*)-1-[((Trifluoromethyl)sulfonyl)oxy]-4-[1-((triisopropylsiloxy)-methyl)-3-*tert*-butoxy-1(*E*)-propenyl]-1-cyclopentene (39). The general procedure of Crisp and Scott was employed.[54] To a −78 °C solution of lithium tri-*sec*-butylborohydride (L-Selectride (Aldrich), 3 mL of a 1 M solution in THF) and THF (20 mL) was added a solution of enone **9** (1.10 g, 2.89 mmol) and THF (15 mL) over 30 min. The resulting solution was maintained at −78 °C for 20 min, $PhNTf_2$ (1.09 g, 3.05 mmol, recrystallized from hexanes prior to use) was added in one portion, and the reaction was allowed to warm to room temperature over 4 h. The reaction mixture then was diluted with 1:4 EtOAc−hexanes (100 mL), and the organic layer was separated, washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (96:2:2 hexanes−EtOAc−Et_3N) provided 1.19 g (80%) of enol triflate **39** as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (t, J = 6.6 Hz, CH=C*H*), 5.61 (app t, J = 2.0 Hz, TfOC=C*H*), 4.22 (app s, 2H, CH_2OTIPS), 3.96 (d, J = 6.6 Hz, 2H, CH_2O-*t*-Bu), 3.49 (quintet, J = 8.4), 2.5−2.8 (m, 4H), 1.23 (s, 9H, *t*-Bu), 1.0−1.1 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 141.9, 125.6, 117.5, 73.4, 66.0, 58.0, 36.3, 35.6, 34.1, 27.8, 18.3, 12.2; IR (film) 2937, 2868, 1662, 1468, 1418, 1362, 1212, 1150, 1112, 1056 cm^{-1}; HRMS (CI isobutane) *m/e* 515.2475 (515.2474 calcd for $C_{23}H_{42}O_5SiSF_3$, MH); MS (EI) *m/e* 471, 397, 265, 181; $[\alpha]^{25}_D$ +7.3°, $[\alpha]_{405}$ +18.4°, $[\alpha]_{435}$ +13.9°, $[\alpha]_{546}$ +8.3°, $[\alpha]_{577}$ +7.5° (c = 1.0, $CHCl_3$).

Optical rotation data for *ent*-**39**: $[\alpha]^{25}_D$ −7.2°, $[\alpha]_{405}$ −18.7°, $[\alpha]_{435}$ −14.1°, $[\alpha]_{546}$ −8.1°, $[\alpha]_{577}$ −7.3° (c = 1.0, $CHCl_3$).

(4*R*)-1-(Trimethylstannyl)-4-[1-((triisopropylsiloxy)methyl)-3-*tert*-butoxy-1(*E*)-propenyl]cyclopentene (8). Following the general procedure of Wulff,[36] LiCl (2.6 g, 61 mmol) was placed in a two-necked flask equipped with a reflux condenser and dried under vacuum with a hot-air gun. A solution of triflate **39** (5.5 g, 10.7 mmol), hexamethylditin (4.0 g, 12 mmol), $Pd(PPh_3)_4$ (1.2 g, 1.3 mmol), and degassed THF (100 mL) was then added. The resulting mixture was heated at reflux for 2 h, at which time the reaction mixture had changed color from pale yellow to black. Hexanes (300 mL) were then added, and

the organic phase was washed with water (2 × 200 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (98:2 hexanes−Et_3N) afforded 4.45 g (81%) of the vinylstannane **8** as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (s, 1H, C*H*=CSn), 5.63 (app t, J = 6.6 Hz, 1H, C=C*H*), 4.16 (s, 2H, CH_2OTIPS), 3.98 (d, J = 6.6 Hz, 2H, CH_2O-*t*-Bu), 3.27 (quintet, J = 4.4 Hz, 1H), 2.3−2.7 (m, 4H), 1.20 (s, 9H, *t*-Bu), 1.00−1.08 (m, 21H, TIPS), 0.10 (s, 9H, $SnMe_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 143.8, 139.8, 122.3, 72.7, 64.7, 57.9, 44.3, 39.8, 37.6, 27.6, 17.9, 11.9, −10.3; IR (film) 2975, 2875, 1587, 1468, 1393, 1362, 1231, 1193, 1106, 1056 cm^{-1}; HRMS (CI isobutane) *m/e* 526.2544 (526.2601 calcd for $C_{25}H_{50}O_2SiSn$, M), 457, 293, 164; $[\alpha]^{25}_D$ +14.8°, $[\alpha]_{405}$ +46.0°, $[\alpha]_{435}$ +36.9°, $[\alpha]_{546}$ +20.6°, $[\alpha]_{577}$ +17.8° (c = 1.0, $CHCl_3$).

Optical rotation data for *ent*-**8**: $[\alpha]^{25}_D$ −14.5°, $[\alpha]_{405}$ −44.8°, $[\alpha]_{435}$ −34.6°, $[\alpha]_{546}$ −18.5°, $[\alpha]_{577}$ −15.0° (c = 1.0, $CHCl_3$).

(4*R*)-4-[1-((Triisopropylsiloxy)methyl)-3-*tert*-butoxy-1(*E*)-propenyl]-1-[1(*E*)-(2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]-benzoyl)]cyclopentene (6). To a Fisher Porter pressure bottle containing LiCl (2.0 g, 47 mmol, dried *in situ* under vacuum with a heat gun) was added a solution of Pd_2dba_3·$CHCl_3$ (261 mg, 0.28 mmol), Ph_3As (685 mg, 2.27 mmol), and *N*-methyl-2-pyrrolidinone (NMP, 50 mL) with a cannula. A solution of the triazone-protected iodide **7**[54b] (3.8 g, 11.6 mmol), stannane **8** (6.0 g, 11.4 mmol), and NMP (50 mL) was then added dropwise. The pressure vessel was evacuated and filled to 50 psi with CO and then heated at 65 °C for 8 h. After this time, Et_2O (300 mL) was added and the organic solution was washed twice with brine (100 mL). The organic portion was dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (50:50 hexanes−EtOAc) to provide 5.5 g (80%) of **6** as a viscous yellow oil that was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dt, J = 7.5, 1.4 Hz, 1H, Ar*H*), 7.15−7.25 (m, 2H, Ar*H*), 7.14 (t, J = 7.4 Hz, 1H, Ar*H*), 6.30 (s, *H*C=CCO), 5.64 (t, J = 6.5Hz, C=C*H*), 4.44 (s, 4H, NCH_2N), 4.23 (AB q, J_{ab} = 11.7 Hz, $\Delta\nu$ = 17 Hz, 2H, CH_2O-*t*-Bu), 3.97 (d, J = 6.5 Hz, 2H, CH_2OTIPS), 3.42 (quintet, 1H), 2.82 (s, 6H, Me), 2.6−2.8 (m, 4H), 1.19 (s, 9H, *t*-Bu), 1.00−1.05 (m, 21H, TIPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 156.1, 147.7, 146.6, 145.5, 141.5, 135.9, 130.6, 128.3, 124.3, 122.7, 73.0, 68.6, 65.7, 57.7, 39.1, 37.7, 35.7, 32.0, 27.5, 18.0, 11.8; IR (film) 2967, 2944, 1660, 1646, 1514, 1302, 1198, 1055 cm^{-1}; MS *m/e* 598.3999 (598.4037 calcd for $C_{34}H_{56}N_3O_4Si$, MH); $[\alpha]^{25}_D$ +17.3°, $[\alpha]_{435}$ +63.4°, $[\alpha]_{546}$ +23.5°, $[\alpha]_{577}$ +17.4° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{34}H_{55}N_3O_4Si$: C, 68.19; H, 9.43; N, 7.02. Found: C, 68.03; H, 9.43; N, 6.95.

Optical rotation data for *ent*-**6**: $[\alpha]^{25}_D$ −18.0°, $[\alpha]_{435}$ −64.6°, $[\alpha]_{546}$ −22.6°, $[\alpha]_{577}$ −18.4° (c = 1.0, $CHCl_3$).

Conversion of 6 to the (*R*)- and (*S*)-2-Methoxyphenylacetic Acid Esters 45. A solution of enone **6** (50 mg, 0.083 mmol), TBAF (0.1 mL of a 1 M solution in THF), and THF (1 mL) was maintained at −78 °C for 1 h. Brine (10 mL) then was added, and the mixture was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (95:5 $CHCl_3$−MeOH) to afford 10 mg (26%) of the corresponding primary alcohol, (4*R*)-4-[1-(hydroxymethyl)-3-*tert*-butoxy-1(*E*)-propenyl]-1-[1-(2-[5-(1,3-dimethyl-hexahydro-2-oxo-1,3,5-triazinyl)]benzoyl)]cyclopentene, as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.4 (m, 4H, Ar), 6.35 (s, 1H, C=CHCO), 5.70 (t, J = 6 Hz, 1H, CH=C), 4.40 (s, 4H, CH_2N),4.15 (s, 2H, CH_2OH), 4.00 (d, J = 6 Hz, 2H, CH_2O-*t*-Bu), 3.45−3.55 (m, 1H), 2.80 (s, 6H, Me), 2.60−2.75 (m, 4H), 1.20 (s, 9H, *t*-Bu).

A solution of this alcohol (4 mg, 0.009 mmol), (*R* or *S*)-α-methoxyphenylacetic acid (2.2 mg, 0.013 mmol), DCC (2.7 mg, 0.013 mmol), DMAP (0.5 mg, 0.5 mmol), and CH_2Cl_2 (0.2 mL) was maintained at room temperature for 2 h, at which time a white precipitate had formed. The reaction then was quenched with saturated aqueous $NaHCO_3$ (2 mL) and extracted with ether (2 mL). The organic extracts were washed with saturated aqueous NH_4Cl (2 mL) and dried ($MgSO_4$). Analysis of the crude esters **45** by ^{1}H NMR at 500 MHz showed resolvable signals for the side chain vinylic hydrogens of the two diastereomers: δ 6.19 for the (*S*)-ester and δ 6.10 for the (*R*)-ester. Integration of these signals showed that the enantiomeric excess of **6** was at least 95%.

(1*S*,3*R*,5*R*)-3-[1(*E*)-(1-[((Triisopropylsilyl)oxy)methyl]-3-*tert*-butoxypropenyl)]-1-[2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]-benzoyl]-6-oxabicyclo[3.1.0]hexane (46). To a cooled (−23 °C) solution of enone **6** (12.3 g, 20.6 mmol) and THF (200 mL) was added *tert*-butyl hydroperoxide (11.4 mL of a 90% solution, 102 mmol) and Triton-B (9.3 mL of a 40% methanolic solution, 21 mmol). The resulting solution was maintained at −23 °C for 2 h and then allowed to warm to 0 °C. The solution was diluted with Et_2O (500 mL), washed with brine (2 × 250 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (1:1 EtOAc−hexanes → 4:1 EtOAc−hexanes) gave 11.5 g (91%) of epoxide **46** as a slightly yellow oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.39 (m, 1 H, ArH), 7.19−7.22 (m, 3 H, ArH), 5.61 (q, J = 6.3 Hz, 1 H, C=CH), 4.51 (AB, J = 11.9 Hz, 2 H, NCH_2N), 4.38 (AB, J = 11.9 Hz, 2 H, NCH_2N), 4.19 (app d, J = 8.8 Hz, 2 H, CH_2OTIPS), 3.93 (app d, J = 6.3 Hz, 2 H, CH_2O-*t*-Bu), 3.49 (s, 1 H, epoxide H), 2.82−2.87 (m, 1 H), 2.81 (s, 6 H, NMe), 2.48−2.54 (m, 1 H), 2.02−2.08 (m, 2 H), 1.90−1.95 (m, 1 H), 1.19 (s, 9 H, O-*t*-Bu), 0.98−1.14 (m, 21 H, TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 155.9, 147.1, 138.4, 134.8, 131.2, 126.7, 126.1, 125.2, 123.1, 72.9, 69.2, 68.6, 66.1, 63.3, 57.6, 32.8, 32.1, 31.9, 30.8, 27.4, 17.9, 11.7; IR (film) 2967, 2944, 2865, 1684, 1652, 1515, 1302, 835 cm^{-1}; MS (CI) *m/e* 614.3991 (614.3986 calcd for $C_{34}H_{56}N_3O_5Si$, MH); $[\alpha]^{25}_D$ +21.5° (c = 2.0, $CHCl_3$).

Optical rotation data for *ent*-**46**: $[\alpha]^{25}_D$ −21.3° (c = 0.6, $CHCl_3$).

(1*S*,3*R*,5*R*)-3-[1(*E*)-(1-((Triisopropylsilyl)oxy)methyl)-3-*tert*-butoxypropenyl)]-1-[1-[2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]phenyl]ethenyl]-6-oxabicyclo[3.1.0]hexane (47). To a cooled (0 °C), rapidly stirred suspension of methyltriphenylphosphonium bromide (33 g, 92 mmol) in THF (100 mL) was added KHMDS (170 mL of 0.5 M solution in toluene, 84 mmol). The resulting bright yellow mixture was allowed to warm to room temperature and was maintained at room temperature for 0.5 h, at which time it was recooled to 0 °C and a solution of epoxide **46** (10.3 g, 17.0 mmol) and THF (50 mL) was added with a cannula. The resulting mixture was allowed to warm to room temperature with stirring, and after 4 h the reaction was quenched with H_2O (100 mL) and the mixture extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (1:1 EtOAc−hexane → 4:1 EtOAc−hexane) gave 9.4 g (92%) of **47** as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (td, J = 7.6, 1.8 Hz, 1 H, ArH), 7.06−7.14 (m, 3 H, ArH), 5.60 (t, J = 6.2 Hz, 1 H, C=CH), 5.57 (d, J = 1.5 Hz, 1 H, C=CH_2), 5.24 (d, J = 1.5 Hz, 1 H, C=CH_2), 4.43−4.50 (m, 4 H, NCH_2N), 4.06 (m, 2 H, CH_2OTIPS), 3.91 (dd, J = 6.2, 2.4 Hz, 2 H, CH_2O-*t*-Bu), 3.35 (s, 1 H, epoxide H), 2.89−2.95 (m, 1 H), 2.83 (s, 6 H, NMe), 2.01−2.05 (m, 1 H), 1.90−1.94 (m, 1 H), 1.73−1.82 (m, 2 H), 1.18 (s, 9 H, *t*-Bu), 0.98−1.14 (m, 21 H, OTIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 146.1, 145.8, 138.3, 134.5, 130.8, 128.8, 125.6, 124.5, 121.2, 116.1, 72.7, 67.6, 66.7, 65.1, 64.8, 57.6, 33.1, 32.8, 31.8, 31.7, 27.3, 17.8, 11.6; IR (film) 2970, 2960, 2945, 2866, 1652, 1515, 1301 cm^{-1}; MS (CI) *m/e* 612.4229 (612.4193 calcd for $C_{35}H_{58}N_3O_4Si$, MH). Anal. Calcd for $C_{35}H_{57}N_3O_4Si$: C, 68.70; H, 9.39; N, 6.87. Found: C, 68.59; H, 9.35; N, 6.82.

(1*S*,3*R*,5*R*)-3-[1(*E*)-(1-(Hydroxymethyl)-3-*tert*-butoxypropenyl)]-1-[1-[2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]phenyl]-ethenyl]-6-oxabicyclo[3.1.0]hexane (48). To a cooled (−15 °C) solution of silyl ether **47** (8.8 g, 14 mmol) and THF (120 mL) was added tetrabutylammonium fluoride (43 mL of a 1.0 M solution in THF). The reaction mixture was maintained at −15 °C for 1 h, at which time it was poured into saturated aqueous NaCl (200 mL) and extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (2% MeOH−$CHCl_3$) afforded 6.3 g (97%) of **48** as a colorless amorphous solid that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (td, J = 7.9, 1.5 Hz, 1 H, ArH), 7.18 (dd, J = 7.5, 1.5 Hz, 1 H, ArH), 7.11 (t, J = 7.5 Hz, 1 H, ArH), 7.06 (d, J = 7.9 Hz, 1 H, ArH), 5.58 (m, 1 H, C=CH), 5.57 (d, J = 1.6 Hz, 1 H, C=CH_2), 5.26 (d, J = 1.6 Hz, 1 H, C=CH_2), 4.47 (s, 4 H, NCH_2N), 3.97 (s, 2 H, CH_2OH), 3.87−3.94 (m, 2 H, CH_2O-

t-Bu), 3.35 (s, epoxide H), 2.90−2.94 (m, 1H, C=CCH), 2.83 (s, 6 H, NMe), 2.03−2.08 (m, 1 H), 1.88−1.92 (m, 1 H), 1.70−1.81 (m, 2 H), 1.18 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 146.0, 145.8, 139.5, 134.3, 130.9, 128.8, 126.5, 124.5, 120.9, 115.9, 72.7, 67.4, 66.6, 65.9, 64.5, 57.3, 33.3, 32.9, 31.7, 27.2, 12.0; IR (film) 3411, 2973, 2929, 2872, 1652, 1635, 1521, 1306, 1197, 754 cm^{-1}; MS (CI) *m/e* 456.2839 (456.2860 calcd for $C_{26}H_{38}N_3O_4Si$, MH); $[\alpha]^{25}_D$ +24.0° (*c* = 1.3, $CHCl_3$).

Optical rotation data for *ent*-**48**: $[\alpha]^{25}_D$ −24.1° (*c* = 1.3, $CHCl_3$).

(1*S*,3*R*,5*R*)-3-[1(*E*)-(1-((Trifluoroacetamido)methyl)-3-*tert*-butoxypropenyl)]-1-[1-[2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]-phenyl]ethenyl]-6-oxabicyclo[3.1.0]hexane (50). Diisopropylethylamine (12 mL, 69 mmol) and MsCl (2.7 mL, 35 mmol) were added dropwise sequentially over 10 min to a cooled (−23 °C) solution of alcohol **48** (6.3 g, 14 mmol) and CH_2Cl_2 (100 mL). The resulting solution was maintained at −23 °C for 1 h, at which time DMF (100 mL) and LiCl (5.9 g, 140 mmol) were added and the reaction was allowed to warm to room temperature. The resulting solution was maintained at room temperature for 3 h and then diluted with Et_2O (800 mL), washed with H_2O (2 × 500 mL) and brine (500 mL), dried ($MgSO_4$), and concentrated to provide the crude allylic chloride **49**.

To a suspension of NaH (1.1 g of a 60% dispersion in mineral oil, 28 mmol, washed with hexane) and DMF (60 mL) was added trifluoroacetamide (3.9 g, 35 mmol). The resulting mixture was maintained at room temperature for 30 min, producing a clear colorless solution to which a solution of the crude allylic chloride **49** in DMF (40 mL) was added by cannula. The resulting solution was maintained at room temperature for 12 h and then poured into 20% brine solution (100 mL) and extracted with ether (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (2:1 EtOAc−hexane → 4:1 EtOAc−hexane) gave 5.7 g (75% from **48**) of amide **50** as a colorless solid: mp 135.5−137 °C (EtOAc−hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.9 Hz, 1 H, ArH), 7.17 (d, *J* = 7.6 Hz, 1 H, ArH), 7.06−7.11 (m, 2H, ArH), 6.80 (broad s, NH), 5.56 (d, *J* = 1.2 Hz, 1 H, C=CH_2), 5.52 (t, *J* = 6.2 Hz, C=CH), 5.24 (d, *J* = 1.2 Hz, 1 H, C=CH_2), 4.48−4.52 (m, 4 H, NCH_2N), 3.91 (t, *J* = 6.2 Hz, 2 H, CH_2O-*t*-Bu), 3.70 and 3.79 (ABX, J_{AB} = 14.7 Hz, J_{AX} = 5.7 Hz, J_{BX} = 5.2 Hz, 2 H, $CH_2NHCOCF_3$), 3.36 (s, epoxide H), 2.91−2.96 (m, 1 H, C=CC*H*), 2.82 (s, 6 H, NMe), 2.00−2.05 (m, 1 H), 1.82 (m, 1 H), 1.48−1.58 (m, 2 H), 1.17 (s, 9 H, O-*t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (q, *J* = 6.8 Hz, $COCF_3$), 156.0, 146.1, 135.1, 134.5, 131.2, 129.3, 129.2, 128.1, 124.8, 121.4, 116.2, 115.6 (q, *J* = 288 Hz, $COCF_3$), 73.2, 67.8, 66.6, 65.5, 57.5, 41.7, 33.6, 33.3, 31.9, 31.8, 27.4; IR (film) 3250, 2973, 2932, 2875, 1717, 1635, 1522, 1197 cm^{-1}; MS (CI) *m/e* 551.2829 (551.2843 calcd for $C_{28}H_{38}F_3N_4O_4$, MH); $[\alpha]^{25}_D$ +41.6° (*c* = 2.0, $CHCl_3$). Anal. Calcd for $C_{28}H_{37}F_3N_4O_4$: C, 61.08; H, 6.77; N, 10.18. Found: C, 61.03; H, 6.77; N, 9.99.

Optical rotation data for *ent*-**50**: $[\alpha]^{25}_D$ −41.8° (*c* = 1.3, $CHCl_3$).

(1*R*,5*S*,7*S*)-4-((2-*tert*-Butoxy)-1(*E*)-ethylidene)-7-hydroxy-7-[1-[2-[5-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl)]phenyl]ethenyl]-2-azabicyclo[3.2.1]octane (5). To a solution of amide **50** (3.0 g, 5.4 mmol) and benzene (100 mL) in a resealable pressure tube was added NaH (650 mg of a 60% dispersion in mineral oil, 16 mmol). After H_2 evolution had ceased, the reaction mixture was heated to 100 °C for 48 h and then allowed to cool to room temperature and concentrated to afford the crude azabicyclooctane **51**.

A solution of the resulting residue in 5:1 EtOH−H_2O (75 mL) containing KOH (12 g, 210 mmol) was heated to 70 °C for 3 h and then diluted with H_2O (200 mL) and extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (9:1 $CHCl_3$−MeOH) gave 1.9 g (75%) of **5** as a colorless solid: mp 144−145 °C (EtOAc−hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.26 (m, 1 H, ArH), 7.15−7.19 (m, 3 H, ArH), 5.71 (s, 1 H, C=CH_2), 5.37 (s, 1 H, C=CH_2), 5.13 (t, *J* = 6.2 Hz, 1 H, C=CH), 4.48 (br s, 4 H, NCH_2N), 3.91−3.95 (m, 1 H, CH_2O-*t*-Bu), 3.83−3.84 (m, 1 H, CH_2O-*t*-Bu), 3.22−3.43 (br m, 1 H), 3.16−3.21 (m, 1 H), 3.07 (app d, *J* = 13.2 Hz, 1 H), 2.84 (s, 6 H, NMe), 2.28−2.32 (m, 1 H), 1.65−2.01 (br m, 3 H), 1.54−1.58 (m, 1 H), 1.18 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 152.7, 144.9, 142.9, 138.5, 131.8, 129.0, 126.5, 122.6, 120.1, 117.2, 84.4, 72.8, 67.9, 63.4, 57.1, 47.1, 43.6, 37.1, 36.3, 32.3, 27.4; MS (CI) *m/z* 455.3035 (455.3020 calcd for $C_{26}H_{39}N_4O_3$, MH); $[\alpha]^{25}_D$ +39.7° (*c* = 1.5, $CHCl_3$). Anal. Calcd for $C_{26}H_{38}N_4O_3$: C, 68.69; H, 8.42; N, 12.32. Found: C, 68.71; H, 8.39; N, 12.24.

Optical rotation data for *ent*-**5**: $[\alpha]^{25}_D$ −39.4° (*c* = 1.0, $CHCl_3$).

(1*R*,7*R*,8*S*)-2-((2-*tert*-Butoxy)-1(*E*)-ethylidene)-7-[2-[5-(1,3-dimethylhexahydro-2-oxa-1,3,5-triazinyl)]phenyl]-4-azatricyclo[5.2.2.0^{4,8}]-undecan-11-one (4). A mixture of azabicyclooctane **5** (1.6 g, 3.5 mmol), Na_2SO_4 (4.9 g, 35 mmol), paraformaldehyde (320 mg, 11 mmol), and MeCN (40 mL) was heated at reflux for 10 min and then concentrated. Purification of the residue by flash chromatography (19:1 $CHCl_3$−MeOH) gave 1.6 g (98%) of **4** as a colorless solid: mp 151−152 °C (EtOAc−hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.9 Hz, 1H, ArH), 7.21−7.30 (m, 2 H, ArH), 7.19 (dd, *J* = 7.5, 1.2 Hz, 1 H, ArH), 5.43 (t, *J* = 6.2 Hz, 1 H, C=CH), 4.11 and 4.52 (AB, J_{AB} = 12.2 Hz, 2 H, NCH_2N), 3.98 (app dd, *J* = 11.2, 2.2 Hz, 1 H), 3.91−3.93 (m, 2 H), 3.80 (app s, 1 H), 3.54 (app d, *J* = 15.2 Hz, 1 H, NCH_2), 3.51 (app dd, *J* = 12.2, 2.2 Hz, 1 H), 3.23−3.26 (m, 1 H, C=C*CH*), 3.21 (app d, *J* = 5.0 Hz, 1 H), 2.94−3.00 (m, 2 H), 2.92 (s, 3 H, NMe), 2.86−2.91 (m, 1 H), 2.76 (s, 3 H, NMe), 2.73 (app d, *J* = 5.8 Hz, 1 H), 2.44 (app td, *J* = 14.7, 2.1 Hz, 1 H), 2.03−2.10 (m, 2 H), 1.87 (app d, *J* = 13.9 Hz, 1 H), 1.20 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 155.8, 146.7, 140.4, 138.6, 128.2, 128.1, 127.6, 125.9, 123.6, 73.1, 69.4, 68.9, 68.7, 61.8, 57.1, 54.0, 53.8, 46.9, 39.1, 32.7, 32.5, 31.8, 27.4, 25.9; IR (film) 2973, 2936, 2874, 1690, 1652, 1520, 1491, 1420, 1306, 752 cm^{-1}; MS (CI) *m/z* 467.2968 (467.3020 calcd for $C_{27}H_{39}N_4O_3$, MH); $[\alpha]^{25}_D$ +39.0° (*c* = 1.1, $CHCl_3$). Anal. Calcd for $C_{27}H_{38}N_4O_3$: C, 69.50; H, 8.21 N, 12.01. Found: C, 69.54; H, 8.19; N, 11.90.

Optical rotation data for *ent*-**4**: $[\alpha]^{25}_D$ −39.1° (*c* = 1.0, $CHCl_3$).

18-Hydroxyakuammicine (3). To a cooled (0 °C) solution of diisopropylamine (1.6 mL, 12 mmol) and THF (20 mL) was added *n*-BuLi (4.7 mL of a 2.2 M solution in hexanes, 10 mmol). This solution was maintained at 0 °C for 0.5 h and then cooled to −78 °C. A solution of ketone **4** (1.6 g, 3.4 mmol) and THF (20 mL) then was added by cannula, and the resulting solution was allowed to warm to 0 °C. After 0.5 h the reaction was recooled to −78 °C and methyl cyanoformate (3.3 mL, 41 mmol) was added dropwise.[57] The resulting solution was maintained at −78 °C for 2 h and then quenched with H_2O (20 mL) and allowed to warm to room temperature. This mixture was extracted with ether (3 × 100 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to afford the crude β-keto ester **52**, which exists as a mixture of the keto and enol forms. Characterization data for major enol form: ^{1}H NMR (500 MHz) δ 7.36 (d, 7.3 Hz, 1 H, ArH), 7.19−7.25 (m, 3 H, ArH), 5.48 (t, *J* = 6.1 Hz, 1 H, C=CH), 4.59 (d, *J* = 11.7 Hz, 1 H, NCH_2N), 4.54 (d, *J* = 11.0 Hz, 1 H, NCH_2N), 4.14 (dd, *J* = 11.6, 6.1 Hz, 1 H, CH_2O-*t*-Bu), 4.07 (dd, *J* = 11.6, 6.1 Hz, 1 H, CH_2O-*t*-Bu), 3.93−4.01 (m, 2 H, NCH_2N), 3.80 (s, 3 H, OMe), 3.77−3.79 (m, 1 H), 3.23−3.29 (m, 4 H), 2.99−3.05 (m, 2 H), 2.88 (s, 3 H, NMe), 2.86 (s, 3 H, NMe), 2.81−2.84 (m, 1H), 2.62 (dd, *J* = 14.3, 6.9 Hz, 1 H), 1.82−1.85 (m, 1 H), 1.24 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz) δ 177.4, 172.3, 156.0, 147.6, 141.3, 136.3, 130.1, 128.3, 128.2, 127.4, 122.7, 99.6, 72.9, 69.5, 69.3, 68.5, 57.7, 55.5, 53.8, 51.7, 38.8, 32.2, 32.1, 28.8, 27.6, 27.5, 25.6; MS (CI) *m/e* 525.3095 (525.3076 calcd for $C_{29}H_{41}N_4O_5$, MH).

This residue was dissolved in 10% HCl−MeOH (100 mL), and the resulting solution was heated at reflux for 12 h, allowed to cool to room temperature, and concentrated. The resulting residue was partitioned between 20% aqueous Na_2CO_3 (100 mL) and EtOAc (4 × 100 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (12:1 $CHCl_3$−MeOH) gave 810 mg (70%) of 18-hydroxyakuammicine (**3**) as a beige solid,[59a] which was contaminated with ~5% of an unidentified byproduct: ^{1}H NMR (500 MHz) δ 8.90 (s, 1 H, NH) 7.22 (d, *J* = 7.4 Hz, 1 H, ArH), 7.15 (td, *J* = 7.7, 1.1 Hz, 1 H, ArH), 6.91 (td, *J* = 7.4, 0.7 Hz, 1 H, ArH), 6.83 (d, *J* = 7.7 Hz, 1 H, ArH), 5.53 (t, *J* = 6.6 Hz, 1 H, C=CH), 4.21 (d, *J* = 6.6 Hz, 2 H, CH_2OH), 4.02 (app s, 1 H), 3.97 (app s, 1 H), 3.83 (s, 3 H, OMe), 3.82−3.84 (m, 1 H), 3.23 (m, 1 H), 2.98−3.03 (m, 2 H), 2.50−2.56 (m, 1 H), 2.35 (ddd, *J* = 13.4, 3.6, 2.5 Hz, 1 H), 1.82−1.86 (m,

1 H), 1.32 (dt, J = 13.4, 2.9 Hz, 1 H); ^{13}C NMR (125 MHz) δ 168.8, 167.6, 143.2, 141.3, 136.4, 127.7, 124.8, 121.1, 120.5, 109.4, 100.4, 61.4, 58.2, 57.6, 56.1, 55.8, 51.2, 45.9, 30.7, 29.8; MS (CI) *m/e* 339.1699 (339.1707 calcd for $C_{20}H_{23}N_2O_3$, MH); $[\alpha]^{25}_D$ −544° (c = 0.4, $CHCl_3$).

Methyl 18-Hydroxy-2β,16α-cur-19-en-17-oate (54). To a solution of **3** (800 mg, 2.4 mmol) and 10% H_2SO_4−MeOH (300 mL) was added Zn dust (100 g), and the resulting mixture was heated at reflux for 45 min with vigorous stirring. After cooling to room temperature, the reaction mixture was filtered through a course glass fritted funnel and the filtrate concentrated. The resulting residue was diluted with H_2O (150 mL) and treated with 20% aqueous Na_2CO_3 until turbid. The resulting mixture was further basified with NH_4OH (60 mL) and extracted with EtOAc (4 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), and concentrated to afford the α-ester **53**, which was contaminated with a small amount (~10%) of the β-epimer **54**. Characterization data for the α-ester **53**: ^{1}H NMR (500 MHz) δ 7.03−7.07 (m, 2 H, ArH), 6.78 (t, J = 7.2 Hz, 1 H, ArH), 6.60 (d, J = 7.7 Hz 1 H, ArH), 5.48 (t, J = 6.8 Hz, 1 H, C=CH), 4.14−4.22 (m, 4 H), 3.79 (s, 3 H, OMe), 3.58 (AB, J_{AB} = 15.2 Hz, 1 H, NCH_2), 3.55 (d, J = 3.0 Hz, 1 H), 3.25 (AB, J_{AB} = 15.2 Hz, 1 H, NCH_2), 3.14−3.17 (m, 2 H), 2.94−2.99 (m, 1 H), 2.62−2.69 (m, 2 H), 2.39−2.45 (m, 1 H), 2.24−2.28 (m, 1 H), 2.09−2.13 (m, 1 H), 1.67 (app ddd, J = 13.8, 4.3, 2.7 Hz, 1 H); ^{13}C NMR (125 MHz) δ 174.3, 149.2, 142.9, 134.7, 127.8, 123.1, 122.3, 119.6, 109.8, 64.8, 63.8, 57.7, 54.1, 53.9, 52.3, 51.7, 46.0, 37.7, 27.4, 23.0; MS (EI) *m/e* 340.1763 (340.1787 calcd for $C_{20}H_{24}N_2O_3$, M); IR (film) 3350, 2956, 2931, 2881, 1739, 1733, 1608, 1487, 1256, 755 cm^{-1}.

This residue was dissolved in a solution of NaOMe−MeOH (20 mL, prepared by dissolving 190 mg of Na in 20 mL of MeOH), degassed under Ar, and maintained at room temperature for 9 h. To re-esterify any acid resulting from adventitious hydrolysis, 10% HCl−MeOH (50 mL) was added and the resulting solution was heated at reflux for 8 h. After cooling to room temperature the reaction mixture was concentrated and basified with 10% aqueous Na_2CO_3 (100 mL) and the resulting mixture extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (9:1 MeOH−$CHCl_3$) gave 550 mg (68%) of β-ester **54** as a brownish solid. Spectral and TLC data of this material were indistinguishable from that of **54** prepared[59a] from (−)-strychnine: ^{1}H NMR (500 MHz) δ 7.03−7.08 (m, 2 H, ArH), 6.76 (t, J = 7.4 Hz, 1 H, ArH), 6.63 (d, J = 7.7 Hz, 1 H, ArH), 5.67 (t, J = 7.1 Hz, 1 H, C=CH), 4.24 (s, 1 H), 4.04−4.13 (m, 2 H, CH_2OH), 3.93 (app d, J = 9.9 Hz, 1 H, NHC*H*), 3.75 (s, 3 H, OMe), 3.48−3.55 (m, 2 H), 3.24−3.26 (m, 1 H), 3.15−3.20 (m, 1 H), 3.09 (app d, J = 14.5 Hz, 1 H), 2.82−2.87 (m, 1 H), 2.53−2.59 (m, 2 H), 2.07 (dt, J = 14.5, 3.5 Hz, 1 H), 1.75−1.84 (m, 2 H); ^{13}C NMR (125 MHz) δ 173.7, 148.3, 143.0, 132.0, 127.9, 126.9, 121.7, 118.9, 109.4, 66.3, 60.6, 57.6, 57.4, 53.6, 53.3, 52.7, 52.0, 42.0, 30.3, 28.1.

Preparation of (−)-Strychnine (1) and the Wieland−Gumlich Aldehyde (2). To a cooled (−90 °C) solution of the β-ester **54** (40 mg, 0.12 mmol) and CH_2Cl_2 (1.0 mL) was added dropwise a solution of DIBALH (1 M in CH_2Cl_2, 360 μL, 0.36 mmol) until the ester was completely consumed (by TLC analysis; ~3 equiv of DIBALH were required; the reaction was virtually instantaneous). The reaction was then quenched with EtOAc, the cooling bath was removed, and 1 M HCl (5 mL) was added. The resulting mixture was stirred at room temperature for 12 h, and the layers were separated, Concentrated NH_4-OH (1 mL) was added, and the basified mixture was extracted with EtOAc (4 × 15 mL). The combined EtOAc portions were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to give the (−)-Wieland−Gumlich aldehyde (**2**)[62] (an ~8:1 mixture of anomers by ^{1}H NMR analysis), which was contaminated with a small amount (<10%) of the corresponding diol.

Following the procedure of Anet and Robinson,[23] a solution of this crude product, HOAc (1.5 mL), NaOAc (200 mg, 2.4 mmol), malonic acid (200 mg, 1.9 mmol), and Ac_2O (40 mg, 0.4 mmol) was heated at 110 °C for 2 h. The reaction mixture then was allowed to cool to room temperature, diluted with H_2O (15 mL), basified with 50% NaOH, and extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (9:1 $CHCl_3$−MeOH) gave 20 mg (51%) of (−)-strychnine (**1**): mp 278−285 °C (EtOH), mixture mp 278−285 °C (lit.[16] mp 275−285 °C); $[\alpha]^{25}_D$ −139° (c = 0.4, $CHCl_3$); lit.[23] $[\alpha]^{25}_D$ −139° (c = 2.0, $CHCl_3$); 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, and TLC (MeOH−$CHCl_3$) data for this material were indistinguishable from those of natural strychnine.

Optical rotation data for *ent*-strychnine: $[\alpha]^{25}_D$ +139° (c = 1.0, $CHCl_3$).

Ethyl 2-[(1*R*,4*S*)-4-Hydroxy-2-cyclopentenyl]-4-*tert*-butoxy-3-oxobutanoate (58). β-Keto ester **30** (37.5 g, 0.189 mol) was added dropwise over 20 min at room temperature to a rapidly stirred suspension of washed (3 × 20 mL pentane) NaH (7.5 g, 0.187 mol, 60% dispersion in oil) in THF (300 mL). In a separate flask, a mixture of **28** (25 g, 0.176 mol), Pd_2dba_3·$CHCl_3$ (1.6 g, 1.7 mmol), Ph_3P (5.2 g, 18.5 mmol), and THF (400 mL) was stirred at room temperature for 10 min. The solution of the sodium enolate **26** then was added by cannula to the yellow green solution of catalyst and carbonate. The reaction then was heated at reflux for 12 h before quenching with saturated aqueous NH_4Cl (500 mL) and extracting with EtOAc (2 × 500 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (25:75 hexanes−Et_2O) to give **55** (37.3 g, 75%) as a colorless oil that was homogeneous by TLC analysis, but a 1:1 mixture of ester epimers by ^{1}H NMR analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.7−5.85 (m, 2H), 4.7−4.75 (m, 1H, CH), 4.1−4.2 (m, 2H, Et), 3.95−4.05 (m, 2H, CH_2O-*t*-Bu), 3.7−3.8 (m, 1H, C*H*OH), 3.2−3.3 (m, 1H, CH), 2.45−2.55 (m, 1H, CH_2), 1.4−1.6 (m, 1H, CH_2), 1.2−1.25 (m, 3H, Et), 1.15 (s, 9H, t-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 204.4, 168.7, 135.1, 135.0, 134.7, 76.6, 74.3, 68.0, 67.9, 61.2, 59.4, 59.2, 42.7, 42.5, 37.9, 37.0, 27.1, 14.3; IR (film) 3418, 2981, 1718, 1643, 1482, 1387, 1368 cm^{-1}; HRMS (EI) *m/e* 284.1624 (284.1619 calcd for $C_{15}H_{24}O_{5y}$, M), 210, 152, 123.

Ethyl 2-[(1*R*,4*S*)-4-(Acetyloxy)-2-cyclopentenyl]-4-*tert*-butoxy-3-oxobutanoate (*ent*-31). A solution of alcohol **55** (7.5 g, 25 mmol), acetic anhydride (3.0 mL, 30 mmol), DMAP (300 mg, 2.5 mmol), pyridine (5 mL), and CH_2Cl_2 (300 mL) was maintained at 0 °C for 4 h before diluting with CH_2Cl_2 (300 mL) and washing sequentially with 1 M HCl, saturated aqueous $NaHCO_3$, and brine (300 mL each). The organic portion was then dried ($MgSO_4$) and concentrated and the residue purified by flash chromatography (50:50 hexanes−Et_2O) to afford 7.9 g (95%) of *ent*-**31** (a 1:1 mixture of ester epimers) as a colorless oil that was homogeneous by TLC analysis and showed spectral properties identical to those of **31**.

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Supplementary Material Available: Experimental details for the preparation of **13**−**16** and **23** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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