Synthesis of (±)-Allocyathin B_2 and (+)-Erinacine A

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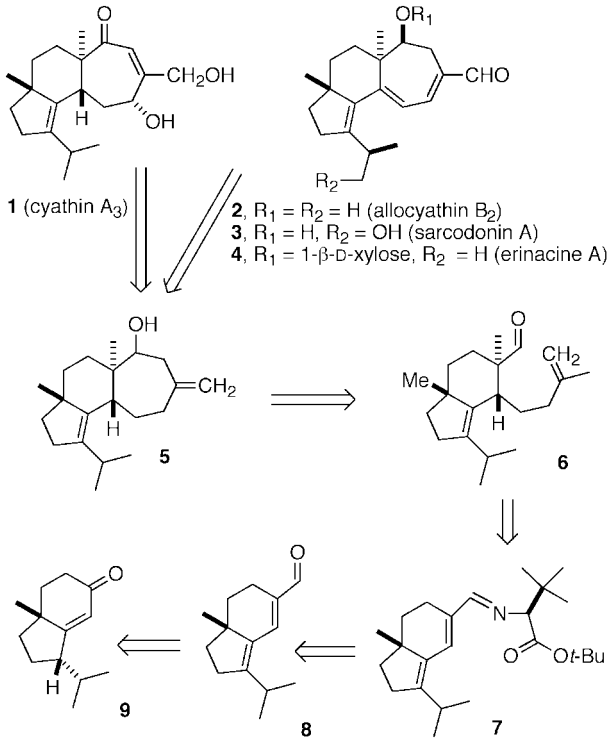
(±)-Allocyathin B_2 (**2**) and (+)-erinacine A (**4**), the 1-β-D-xyloside of (+)-allocyathin B_2, the first cyathin diterpenes to be prepared, have been synthesized using a carbonyl ene reaction of **14a** to construct an appropriately functionalized seven-membered ring and palladium-catalyzed carbonylation of dienyl triflates **10** and **39** as key steps. The entire cyathin carbon skeleton is constructed in seven steps, and allocyathin B_2 is synthesized in only 17 steps (>5% overall yield) from readily available enone **9**.

Introduction

The isolation of the cyathin and cyafrin diterpenes from bird nest fungi and the determination of their structures were reported by Ayer and co-workers in a series of papers published between 1971 and 1979.[1] The compounds were shown to be active against actinomycetes, Gram-positive and Gram-negative bacteria, and some fungi.[1a] These diterpenes have an unusual 5−6−7 tricyclic ring system with a trans 6−7 ring fusion, as shown in cyathin A_3 (**1**, Scheme 1),[1b,c] except for the more highly unsaturated trienal allocyathin B_2 (**2**).[1f] In 1989, Hirota reported the isolation of sarcodonin A (**3**), a hydroxylated allocyathin B_2, from *Sarcodon scabrosus*.[2] In 1994, Kawagishi isolated erinacine A (**4**), a potent stimulator of nerve growth factor synthesis, from the mycelia of *Hericum erinaceum*.[3a]

The novel ring system and extensive functionality make the synthesis of the cyathins a challenging problem that has not been solved in the 25 years since the structure of cyathin A_3 was determined.[4,5] We chose cyathin A_3 (**1**) as our initial target since Ayer and co-workers converted it to many of the other cyathins in the course of their structural determination studies. We envisioned that **1** could be prepared from cycloheptanol

Scheme 1



5, which should be readily available from aldehyde **6** by an intramolecular carbonyl ene reaction.[6,7] We anticipated that **6** could be prepared from dienal **8** by the Koga protocol,[8] addition of a Grignard reagent to *tert*-leucine *tert*-butyl ester imine **7** followed by methylation. We used this procedure in our reiswigin A synthesis to introduce the 3-methyl-3-butenyl and methyl groups from the same face of an enal and demonstrated that an efficient kinetic resolution could be achieved if a racemic enal was used.[7] Dienal **8** should be readily available by palladium-catalyzed carbonylation of the dienyl triflate prepared from enone **9**. Since we developed an efficient two-step route to enone **9** several years ago,[9] this route should

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(2) Shibata, H.; Tokunaga, T.; Karasawa, D.; Hirota, A.; Nakayama, M.; Nozaki, H.; Tada, T. *Agric. Biol. Chem.* **1989**, *53*, 3373.

(3) (a) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569. (b) Kawagishi, H.; Shimada, A.; Shizuki, K.; Mori, H.; Okamoto, K.; Sakamoto, H.; Furukawa, S. *Heterocycl. Commun.* **1996**, *2*, 51. (c) Kawagishi, H.; Shimada, A.; Hosokawa, S.; Mori, H.; Sakamoto, H.; Ishiguro, Y.; Sakemi, S.; Bordner, J.; Kojima, N.; Furukawa, S. *Tetrahedron Lett.* **1996**, *37*, 7399. (d) Hecht, H.-J.; Höfle, G.; Steglich, W.; Anke, T.; Oberwinkler, F. *J. Chem. Soc., Chem. Commun.* **1978**, 665.

(4) For unsuccessful approaches to cyathins see: (a) Ayer, W. A.; Ward, D. E.; Browne, L. M.; Delbaere, L. T. J.; Hoyano, Y. *Can. J. Chem.* **1981**, *59*, 2665. (b) Ward, D. E. *Can. J. Chem.* **1987**, *65*, 2380. (c) Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 885.

(5) (a) For a preliminary communication see: Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644. (b) A second synthesis of allocyathin B_2 has been reported recently: Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306.

(6) Snider, B. B. *Comprehensive Organic Synthesis;* Pergamon: Oxford, 1991; Vol 2, Chapter 2.1, pp 527−561.

(7) Snider, B. B.; Yang, K. *J. Org. Chem.* **1990**, *55*, 4392.

(8) (a) Kogen, H.; Tomioka, K.; Hashimoto, S.-I.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4005. (b) Kogen, H.; Tomioka, K.; Hashimoto, S.-I.; Koga, K. *Tetrahedron* **1981**, *37*, 3951. (c) Tomioka, K.; Masumi, F.; Yamashita, T.; Koga, K. *Tetrahedron* **1989**, *45*, 643.

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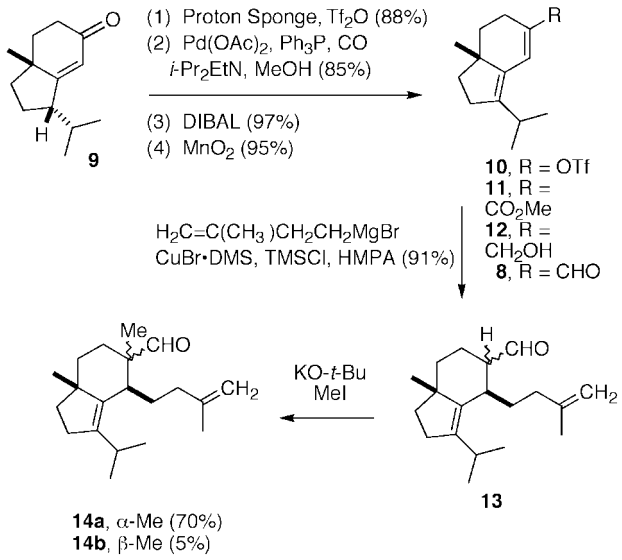
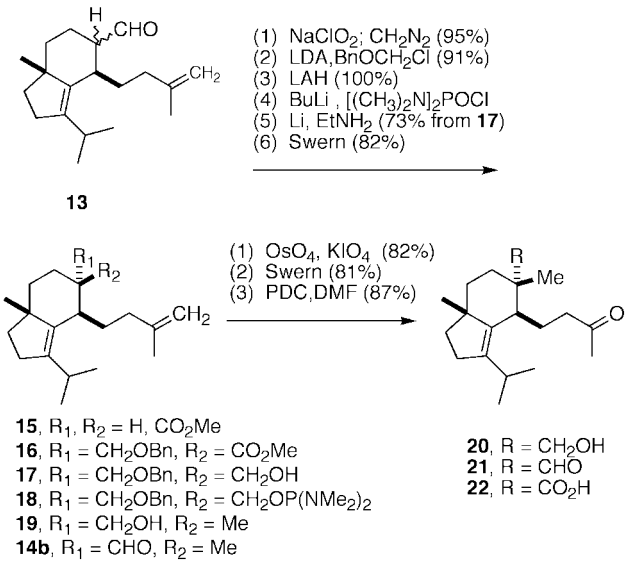
Scheme 2



Scheme 3



provide very efficient access to **5**, which contains the complete carbon skeleton and much of the functionality of the cyathins.

Results and Discussion

Preparation of Dienal 8. Treatment of enone **9**[9] with triflic anhydride and 1,8-bis(dimethylamino)naphthalene at −78 °C[10] provided exclusively conjugated dienyl triflate **10** in 88% yield (Scheme 2). Formylation with a catalytic amount of $Pd(PPh_3)_4$ under a CO atmosphere with slow addition of Bu_3SnH[11] afforded dienal **8** in low yield. Fortunately, palladium-catalyzed carbonylation[12] of **10** in methanol gave 85% of dienoate **11**. Reduction of **11** with DIBAL yielded 97% of alcohol **12**, which was oxidized with MnO_2 to provide 95% of dienal **8**. This four-step sequence afforded 69% of dienal **8** from enone **9** and can easily be carried out on a large scale.

Preparation of Ene Substrates 14a and 14b. Condensation of dienal **8** with L-*tert*-leucine *tert*-butyl ester with azeotropic removal of water gave a quantitative yield of imine **7** as a 1:1 diastereomeric mixture. Unfortunately, imine **7** reacted with isopentenylmagnesium bromide to give a complex mixture containing only a trace of the desired 1,4-addition product, probably due to steric hindrance from the isopropyl group. We then examined cuprate additions to dienoate **11** and dienal **8**. Ester **11** did not react with a variety of cuprates, including those which add to methyl 1-cyclohexenecarboxylate in high yield.[13,14] Fortunately, TMSCl-accelerated cuprate addition to dienal **8** by the Nakamura−Kuwajima procedure[13] gave 91% of **13** as a 4:6 mixture of isomers. The isomers were separated and reequilibrated with Et_3N, establishing that cuprate addition had occurred stereospecifically. The stereochemistry of the cuprate addition could not be established by mechanistic considerations, since there was precedent for axial cuprate addition despite the axial methyl group,[15] while in other cases an axial methyl group forces equatorial cuprate attack.[16]

The structure of the cuprate adduct was eventually established as **13** by X-ray crystallography of **22** (see below), indicating that the axial methyl group did not prevent axial addition of the cuprate from the same face of the enal. Methylation of **13** with a large excess of MeI (50 equiv) and KO*t*-Bu (10 equiv) by Ireland's procedure[17] provided 75% of a 15:1 mixture of α-methylated aldehydes **14a** and **14b**. Once again, the stereochemistry of the major product was not obvious, since equatorial methylation of cyclohexanecarboxaldehydes, which would give **14b**, is usually observed, while approach from the least hindered face of the enolate of **13** would result in axial methylation to give **14a**.[18] The X-ray crystallographic structure determination of **22** eventually established the structure of the major product as **14a**.[5a]

Since we were unsure of the structures of the newly formed chiral centers in **13** and **14** at this point, we developed a sequence that would convert **13** to **14b**, the minor product from the direct methylation of **13**, by alkylation of **13** with a latent formyl group and reduction of the aldehyde of **13** to a methyl group (Scheme 3). Alkylation of **13** with benzyloxymethyl chloride (BOMCl)[19] was unsuccessful, giving a complex mixture containing some *O*-alkylated product. Oxidation of the mixture of **13** with $NaClO_2$, followed by treatment of the acid with CH_2N_2, provided ester **15** in 95% overall yield. Fortunately, alkylation[19] of ester **15** with LDA and BOMCl gave 91% of **16** as single stereoisomer. Reaction of **15**

(9) Snider, B. B.; Rodini D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.
(10) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.
(11) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.
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(13) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.
(14) (a) Yamamoto, Y.; Yamada, J.-I.; Uyehara, T. *J. Am. Chem. Soc.* **1987**, *109*, 5820. (b) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119. (c) Munch-Petersen, J.; Bretting, C.; Jorgensen, P. M.; Refn, S.; Andersen, V. K. *Acta Chem. Scand.* **1961**, *15*, 277.
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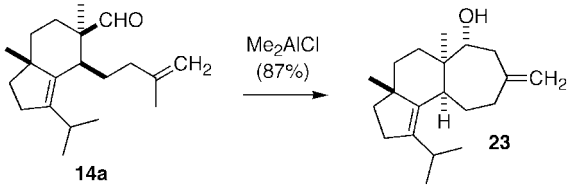
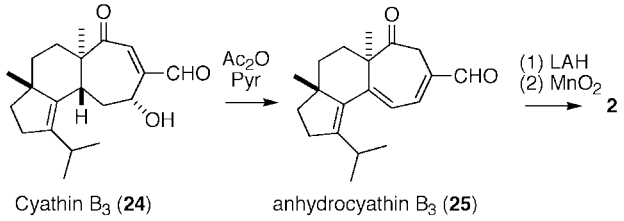
(17) Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1967**, *32*, 689.
(18) Krapcho, A. P.; Dundulis, E. A. *J. Org. Chem.* **1980**, *45*, 3236.
(19) (a) Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Synthesis;* Wiley: New York, 1988; Collect. Vol. 6, p 101. (b) Boeckman, R. K., Jr.; Ramiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1977**, 4485.

Scheme 4



Scheme 5



with LDA in THF for 2 h at 0 °C was necessary for enolate formation. Reduction of ester **16** with LAH provided alcohol **17** quantitatively. Phosphorylation of alcohol **17** with $(Me_2N)_2POCl$ gave phosphoramidate **18**.[20] Reduction of **18** with Li in $EtNH_2$ deprotected the benzyl ether at −78 °C. Reductive cleavage of the phosphoramidate in this reaction occurred readily at temperatures greater than 0 °C. Unfortunately, reduction of the side chain double bond also occurred at these temperatures. Selective reduction of **18** to give 73% of **19** from **17** was eventually achieved by maintaining the temperature at −10 to 0 °C and adding Li slowly to maintain a faint blue color. Swern oxidation of **19** gave 82% of the desired aldehyde **14b**, which was identical to the minor methylation product of **13**.[21]

Intramolecular Ene Reaction of 14a. At this point we had developed efficient routes to ene substrates **14a** and **14b**, although the stereochemistry of these compounds had not been assigned. We were delighted to find that treatment of **14a** with Me_2AlCl at −45 °C for 2 h gave 87% of a single alcohol **23** (Scheme 4).[22] On the other hand, **14b** did not undergo an ene reaction under any conditions. We therefore converted **19** to keto aldehyde **21**, which might form a cycloheptenone by an intramolecular aldol reaction. Cleavage of **19** with a catalytic amount of OsO_4 and KIO_4 selectively oxidized the less hindered side-chain double bond, giving hydroxy ketone **20** (82%), which was subjected to a Swern oxidation to give keto aldehyde **21** (81%). Intramolecular aldol reactions of **21** could not be effected under a variety of acidic and basic conditions, suggesting correctly that the formyl and isopentenyl substituents of **14b** are trans and diaxial on the cyclohexane ring. Oxidation of **21** with PDC in DMF afforded 87% of crystalline **22**, whose stereochemistry was unambiguously assigned by X-ray crystallographic structure determination.[5a] Therefore cuprate addition to **8** occurred axially to give **13**, despite the potential steric hindrance from the methyl group, and methylation of **13a** proceeded axially to give **14a**.

Revision of the Synthetic Plan. Ene adduct **23**, with the complete cyathin skeleton, is available from enone **9** in 38% overall yield in only seven steps. Unfortunately, the stereochemistry of the 6−7 ring fusion in **23** is cis, while it is trans in all of the cyathins except for allocyathin B_2 (**2**). During his structure determination work, Ayer established that treatment of cyathin B_3 (**24**) with acetic anhydride in pyridine afforded anhydrocyathin B_3 (**25**).[1d] Reduction of **25** with LAH afforded a 2:1 mixture of diols with the desired β-diol predominating; MnO_2 oxidation of the major isomer afforded allocyathin B_2.[1f] This established that **25**, with a conjugated trienal and an unconjugated ketone, should be readily available by equilibration. We therefore addressed the question of adjusting the oxidation state of ene adduct **23** to that of **25** so that we could prepare allocyathin B_2 (**2**) (Scheme 5).

Unsuccessful Routes to Allocyathin B_2. Protection of the hydroxyl group of **23** as the TBDMS ether proceeded in quantitative yield. Hydroxylation of the less hindered disubstituted alkene with a catalytic amount of OsO_4 and 2 equiv of NMO in 80% aqueous *tert*-BuOH for 1 d at 25 °C provided a 2:1 mixture of epimeric diols. Selective acetylation of the primary alcohol with Ac_2O and pyridine provided a 2:1 mixture of acetates. Mesylation of the tertiary alcohol with MsCl and Et_3N resulted in elimination of the mesylate to yield a single allylic acetate, which was hydrolyzed with NaOH to give allylic alcohol **26** in 55% overall yield from **23** (Scheme 6). MnO_2 oxidation of crude **26** afforded enal **27** in 95% overall yield. We planned to introduce the additional double bond of allocyathin B_2 (**2**) by oxidation of dienyl ethers such as **32**. Unfortunately, we were unable to convert **27** directly to dienyl silyl ether **32** or analogous alkyl ethers.

Ayer found that treatment of cyathin B_2, which is identical to **29** except for the stereochemistry of the ring fusion, with alkaline H_2O_2 afforded 25% of anhydrocyathin B_3 (**25**).[1f] Desilylation of **26** with 10% HCl provided a diol that was oxidized with excess PDC in CH_2Cl_2 to give 5-epicyathin B_2 (**29**) in 74% yield from **26**. Disappointingly, treatment of **26** with NaOH and H_2O_2 as previously described for cyathin B_2[1f] gave a complex mixture that did not contain anhydrocyathin B_3 (**25**). Apparently, the stereochemistry at the ring fusion effects the reaction of the enal with hydrogen peroxide. We therefore turned to other methods to oxidize **26**.

Hydroxyl-directed epoxidation of allylic alcohol **26** with a catalytic amount of $VO(acac)_2$ and *t*-BuOOH provided a mixture of unstable epimeric epoxides that was treated with TBDMSCl and imidazole to give crude **28** as a 3:1 mixture of epimers. Epoxide opening was accomplished by treatment with sodium phenylselenide;[23] oxidation of the phenylselenide with H_2O_2 afforded the desired bissilyloxy allylic alcohol **30** as an 8:1 mixture of diastereomers in 57% yield from **26**.

We expected that elimination of the tertiary alcohol would give one of the two possible cycloheptadienes, which could be converted to anhydrocyathin B_3 (**25**) by

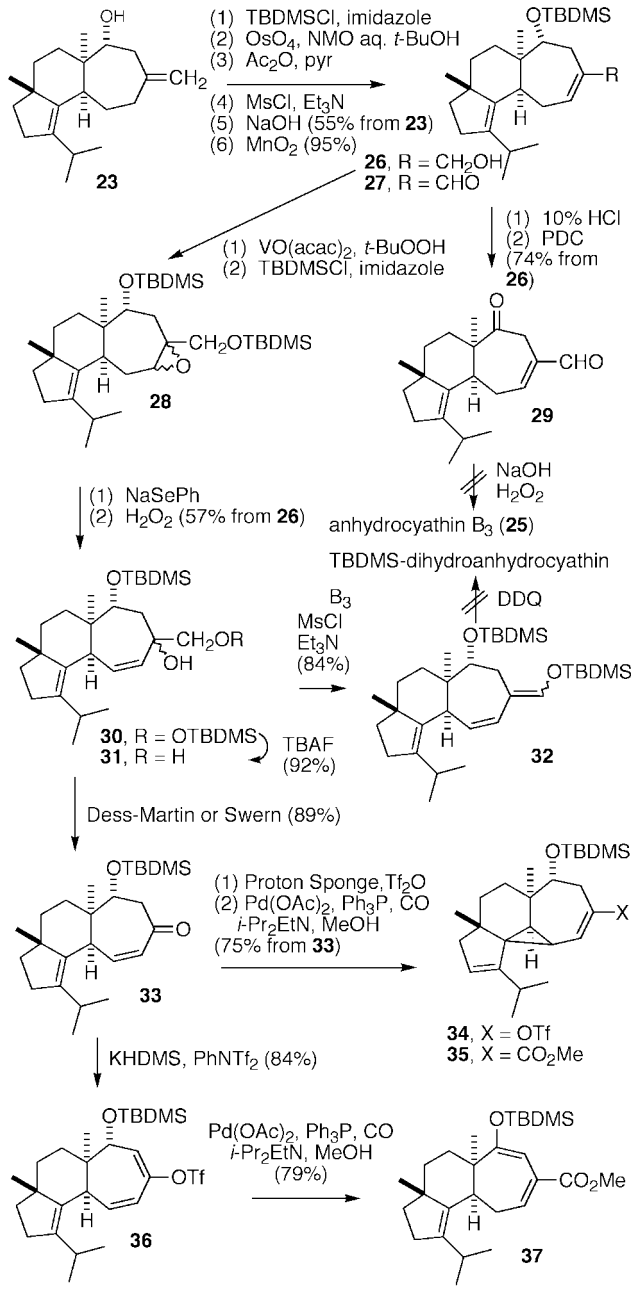
(20) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(21) For an alternative conversion of a benzyloxymethyl carboxaldehyde to a methyl carboxaldehyde, see: Taber, D. F.; Campbell, C.; Gunn, B. P.; Chiu, I.-C. *Tetrahedron Lett.* **1981**, *22*, 5141.

(22) The stereochemistry of the hydroxyl group of **23** was tentatively assigned on the basis of a long-range coupling of 1.0 Hz between the α-proton and one of the α′ protons in enone **38**. A detailed analysis of the ^1H NMR spectrum of 5-methyl-2-cyclohexenone showed a 0.7 Hz coupling between H_2 and H_{6eq} and no coupling between H_2 and H_{6ax}. Molecular mechanics calculations indicate that **38** is rigid and that the pseudoequatorial α′ proton that is long-range coupled to the α proton with $J = 1.0$ Hz should be vicinally coupled to C*H*OSi with a small coupling constant (1.5 Hz), as is observed. In the diastereomer of **38**, the pseudoequatorial α′ proton would be vicinally coupled to C*H*OSi with a large coupling constant.

(23) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

Scheme 6



oxidation to the keto aldehyde and equilibration. We were surprised and disappointed to find that treatment of **30** with MsCl and Et_3N in CH_2Cl_2 gave 84% of dienyl silyl ether **32**, as a 2:1 mixture of stereoisomers. Unfortunately, allylic oxidation of dienol silyl ether **32** with DDQ[24] failed to provide the desired trienal. Hydrolysis to **27** occurred on prolonged reaction.

We next attempted to prevent elimination of **30** to dienyl silyl ether **32** by introduction of the aldehyde before elimination of the tertiary alcohol. Deprotection of **30** with TBAF in THF at 25 °C afforded 92% of diol **31**. More vigorous desilylation conditions, e.g. TBAF, THF, 65 °C, led to decomposition, indicating that a TBDMS group could not be removed from the secondary alcohol. Surprisingly, oxidation of diol **31** with Dess−Martin periodinane[25] afforded 89% of enone **33** rather than the expected α-hydroxyaldehyde. Similar results were obtained under Swern conditions, although successful oxidation of 2,2-dialkyl-1,2-diols to give 2,2-dialkyl-2-hydroxyaldehydes under Swern conditions have been reported.[26]

Palladium-catalyzed carbonylation of the dienyl triflate derived from **33**, as in the conversion of enone **9** to dienoate **11**, should give a cycloheptadienecarboxylate that could be converted to allocyathin B_2. However, treatment of **33** with bis-1,8-(dimethylamino)naphthalene and triflic anhydride provided the unexpected cyclopropyl enol triflate **34**, which was carbonylated to give ester **35** in 75% yield from **33**. The ^{13}C NMR spectrum of **35** shows the presence of only four olefinic carbons. The allylic isopropyl methine hydrogen absorption is shifted upfield from δ 2.60 in **33** to δ 1.63 in **35**, since it is in the shielding region of the cyclopropane ring. The formation of triflate **34** is initiated by triflation of enone **33** with Tf_2O. Abstraction of the hindered ring fusion methine proton by a hindered base is slow, so that addition of the cyclopentane double bond to the β-position of the triflated enone and loss of a less hindered methylene proton to give **34** is the preferred process. Preparation of the triflate from **33** by addition of a triflating agent to a preformed enolate should and does circumvent the undesired formation of the cyclopropane ring. The enolate of enone **33** was generated by treatment with potassium bis(trimethylsilyl)amide at −78 °C. Quenching with $PhNTf_2$[27] provided 84% of triflate **36**. Surprisingly, palladium-catalyzed carbonylation of triflate **36** gave 79% of dienoate **37**, in which double bond migration had accompanied carbonylation. Presumably, the desired dienoate is formed and undergoes palladium-catalyzed double bond isomerization (formally a 1,5-hydrogen shift) to give the undesired dienoate **37**.

Completion of the Synthesis of Allocyathin B_2 (2). We hypothesized that the undesired isomerization leading to **37** could be suppressed by converting the silyl ether of **36** to a ketone (i.e. **39**) prior to the carbonylation. To investigate this, we needed both a more efficient route to the enone from **23** and a more easily removable protecting group, since the TBDMS group could not be removed from **31**. We therefore developed an efficient three-step route to enone **38** from ene adduct **23** (Scheme 7).

Protection of ene adduct **23** with chlorodimethylisopropylsilane and imidazole (95%), followed by oxidative cleavage of the exocyclic double bond (OsO_4/KIO_4, 77%), gave the saturated ketone. Enolization with lithium bis(trimethylsilyl)amide, quenching the enolate with phenylselenyl chloride,[28] subsequent oxidation to the selenoxide with hydrogen peroxide, and elimination (72%) provided a practical route to enone **38**. Desilylation of the dimethylisopropylsilyl ether of **38** in THF:AcOH:H_2O proceeded efficiently. Dess−Martin oxidation[19] of the β-hydroxyketone gave the 1,3-dione, which was treated with KHMDS and then $PhNTf_2$[27] to provide exclusively enol triflate **39** in 54% yield from **38**. The position of

(24) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264.

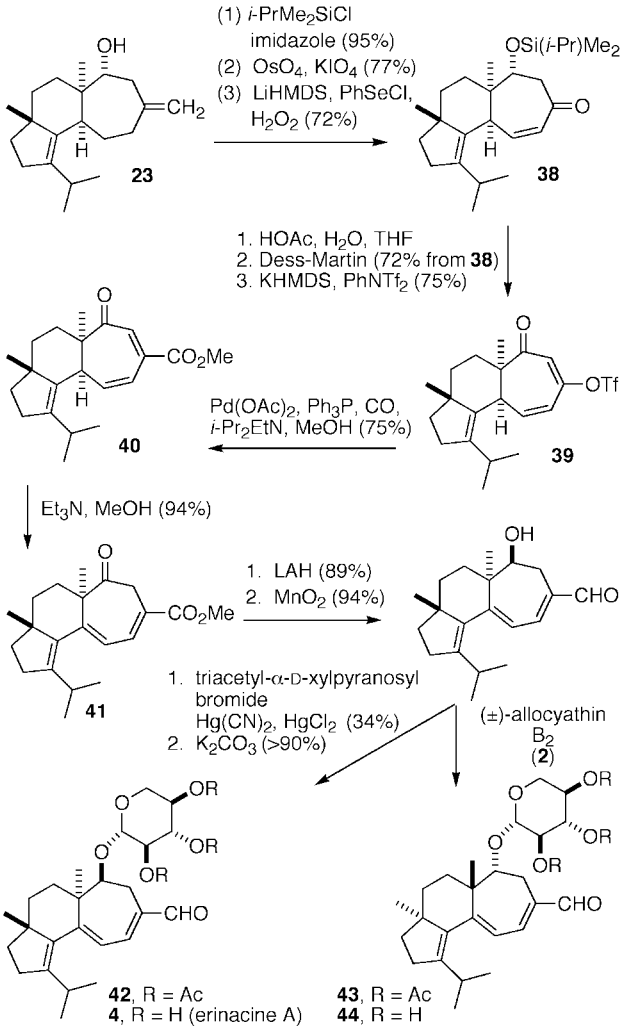
(25) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(26) (a) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 9912. (b) Nakata, T.; Akita, H.; Naito, T.; Oishi, T. *J. Am. Chem. Soc.* **1979**, *101*, 4400.

(27) (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979. (b) García Martínez, A.; Martínez Alvarez, R.; Madueño Casado, M.; Subramanian, L. R.; Hanack, M. *Tetrahedron* **1987**, *43*, 275.

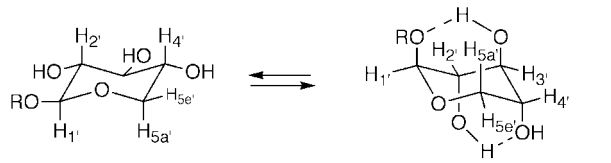
(28) Zipkin, R. E.; Natale, N. R.; Taffer, I. M.; Hutchins, R. O. *Synthesis* **1980**, 1035.

Scheme 7



triflation follows from the UV spectrum (λ_{max} 274 nm, ϵ 3600) of **39**, which is consistent with a β-triflyloxy conjugated dienone rather than a cross-conjugated dienone.[29]

Palladium-catalyzed carbonylation of **39** in methanol[12] now gave exclusively the desired keto ester **40** in 75% yield. As expected from Ayer's conversion of cyathin B_3 (**24**) to anhydrocyathin B_3 (**25**),[1d] treatment of keto ester **40** with Et_3N in MeOH (100 °C, 12 h) afforded 94% of the desired conjugated trienoate **41**. We were pleasantly surprised to find that reduction of **41** with LAH at −78 to 0 °C gave exclusively the desired β-diol, which was oxidized with MnO_2 to give (±)-allocyathin B_2 (**2**) with ^{1}H and ^{13}C NMR and IR spectral data identical to natural allocyathin B_2.[31] Presumably, the different stereoselectivity in the reduction of the ketones of keto aldehyde **25**, which gives a 2:1 mixture of isomers,[1f] and keto ester **41** results from the disparate reactivity of the other carbonyl group. The ketone group of **41** was reduced first selectively from the α-face, while the aldehyde of **25** should be reduced more rapidly so that the ketone group can then be reduced from either face by intramolecular delivery of hydride from $RCH_2OAlH_3^-$.



1-C conformation of erinacine A in 4:1 $CDCl_3/CD_3OD$

$H_{1'}$ δ 4.59 (d, J = 4.4)
$H_{5e'}$ δ 3.82 (dd, J = 12.4, 2.9)
$H_{5a'}$ δ 3.33 (dd, J = 12.4, 6.6)

C-1 conformation of erinacine A in $CDCl_3$

$H_{1'}$ δ 4.77 (d, J = 3.0)
$H_{5a'}$ δ 3.87 (dd, J = 12.6, 1.9)
$H_{5e'}$ δ 3.45 (ddd, J = 12.6, 2.8, 2.2)

Figure 1. Partial spectral data for the xyloside portion of erinacine A in the 1-C conformation in $CDCl_3$ and the C-1 conformation in 4:1 $CDCl_3$:CD_3OD.

Synthesis of Erinacine A (4). Model studies with borneol and 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide[32] suggested that the Helferich method[33] was most suitable for glycosidation of the hindered secondary alcohol of allocyathin B_2. Treatment of (±)-**2**[34] with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide, $Hg(CN)_2$, and $HgCl_2$ in CH_3CN for 3.5 min at 25 °C gave 34% (68% based on recovered **2**) of an easily separable 1:1 mixture of erinacine A triacetate (**42**) from (+)-**2**, and diastereomer **43** from (−)-**2**. Longer reaction times led to complete consumption of **2** but were accompanied by decomposition of **42** and **43**. The spectral data of erinacine A triacetate (**42**) are identical to those of the natural material.[31] Separate hydrolyses of **42** and **43** with potassium carbonate in MeOH provided (+)-erinacine A (**4**) and diastereomer **44**, the 1-β-D-xyloside of (−)-allocyathin B_2, in >90% yield.

Conformation of the Xyloside of 4. We were very surprised to find that the NMR spectral data for a dilute solution of synthetic **4** in $CDCl_3$ are very different than those reported for a more concentrated solution of natural **4** in the same solvent, even though the spectral data for the synthetic and natural triacetates **42** are identical. The anomeric proton of synthetic **4** absorbs at δ 4.77 (d, J = 3.0) while natural **4** was reported to absorb at δ 4.48 (d, J = 5.1). The C-5′ protons of synthetic **4** absorb at δ 3.87 (dd, J = 12.6, 1.9) and δ 3.45 (ddd, J = 12.6, 2.8, 2.2) while natural **4** was reported to absorb at δ 3.74 (dd, J = 11.7, 2.9) and δ 3.45 (dd, J = 11.7, 7.0). The absence of a large vicinal coupling constant to either $H_{5'}$ in synthetic **4** indicates that $H_{4'}$ is equatorial. These data are consistent with the pyranose ring of synthetic **4** existing in the C-1 conformation with all substituents axial. This is confirmed by the long-range *W*-coupling observed for one of the C-5′ protons, which can occur only if $H_{3'}$ is equatorial, as shown in Figure 1.

The spectral differences suggest that the xyloside adopts the C-1 conformation (all substituents axial) in the dilute $CDCl_3$ solution used for obtaining the spectrum of synthetic material and the 1-C conformation (all

(29) 2,4-Cycloheptadienone absorbs with λ_{max} = 292, while the cross conjugated isomer 2,6-cycloheptadienone absorbs with λ_{max} = 235.[30] Since a β-triflate has little effect on the UV absorption of 2-cyclohexenones,[27b] the observed value for **17** is consistent with a 2,4-cycloheptadienone.

(30) Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109.

(31) A sample of natural cyathin A_3 (**1**) was oxidized to cyathin B_3 (**24**) in ether.[1e] Treatment of cyathin B_3 with Ac_2O in pyridine gave anhydrocyathin B_3 (**25**)[1d] that was spectroscopically identical to that obtained by Dess−Martin oxidation of synthetic allocyathin B_2. We are grateful to Prof. William Ayer for a sample of cyathin A_3 and to Prof. Hirokazu Kawagishi for copies of the ^{1}H and ^{13}C NMR spectra of allocyathin B_2, erinacine A, and erinacine A triacetate.

(32) Bock, K.; Pedersen, C.; Rasmussen, P. *Acta Chem. Scand. B* **1975**, *29*, 389.

(33) (a) Helferich, B.; Ost, W. *Chem. Ber.* **1962**, *95*, 2612. (b) Ojika, M.; Wakamatsu, K.; Niwa, H.; Yamada, K. *Tetrahedron* **1987**, *43*, 5275.

(34) All synthetic compounds are racemic, except for **4** and **42**−**44**.

substituents equatorial) in the more concentrated solution used in the isolation work. Professor Kawagishi has kindly established that the NMR spectrum of a dilute solution of natural **4** is very different from that reported in the isolation work and identical to that of synthetic **4**. The NMR spectrum of a dilute solution of synthetic **4** in 4:1 $CDCl_3/CD_3OD$ corresponds closely to that reported for the natural product in $CDCl_3$, with the xyloside in the 1-C conformation (see Figure 1). The xyloside of **4** exists in the C-1 conformation, which is stabilized by intramolecular hydrogen bonding, in very dilute $CDCl_3$ solution, while the 1-C conformation is preferred in more concentrated solution and in alcohol solvents, probably due to intermolecular hydrogen bonding.

Lemieux reported similar conformational changes in 3-deoxyxylosides as a function of solvent.[35] Methyl 3-deoxyxyloside exists primarily in the C-1 conformation with all substituents axial in $CDCl_3$, a poor hydrogen-bonding solvent. As the solvent was changed to better hydrogen-bond-accepting solvents, the chemical shifts and coupling constants changed, as described above for **4**, indicating that the 1-C conformation with all substituents equatorial is now favored.

The unnatural diastereomer of erinacine A **44** does not change conformation as a function of concentration or the ability of the solvent to hydrogen bond. This diastereomer exists in the 1-C conformation with all substituents equatorial, even in dilute $CDCl_3$ solution. The interactions between the diterpene and carbohydrate moieties of **4** and **44** that are responsible for the different conformational preferences in dilute $CDCl_3$ solution are not understood.

In conclusion, (±)-allocyathin B_2 (**2**) and erinacine A (**4**), the 1-β-D-xyloside of (+)-allocyathin B_2, the first cyathin diterpenes to be prepared, have been synthesized using a carbonyl ene reaction of **14a** to construct an appropriately functionalized seven-membered ring and palladium-catalyzed carbonylation of dienyl triflates **10** and **39** as the key steps. The entire cyathin carbon skeleton is constructed in only seven steps and allocyathin B_2 is synthesized in only 17 steps (>5% overall yield) from readily available enone **9**.[9]

Experimental Section

All NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported in δ and coupling constants are reported in hertz. Infrared absorptions are reported in inverse centimeters.

2,6,7,7a-Tetrahydro-7a-methyl-3-(1-methylethyl)-5-trifluoromethylsulfonyl-oxy-1*H*-indene (10). To a solution of enone **9** (4.00 g, 20.8 mmol) and 1,8-bis(dimethylamino)-naphthalenediamine (5.80 g, 27.0 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added triflic anhydride (5.87 g, 20.8 mmol) dropwise via syringe. The reaction mixture was stirred for 5 min and quenched by addition of water. The aqueous layer was separated and further extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (98:2 hexane/Et_3N) provided 5.66 g (88%) of **10**: ^{1}H NMR 6.30 (d, 1, J = 2.2), 2.69 (h, 1, J = 6.8), 2.68−2.58 (m, 1), 2.55−2.27 (m, 3), 1.81 (ddd, 1, J = 1.5, 7.3, 12.7), 1.76 (dd, 1, J = 6.9, 11.9), 1.63−1.41 (m, 2), 1.02 (d, 3, J = 6.8), 0.99 (d, 3, J = 6.8), 0.95 (s, 3); ^{13}C NMR 149.2, 146.9, 133.4, 113.1, 44.3, 38.1, 35.0, 29.6, 26.9, 26.4, 21.5, 21.3, 21.0 (the triflate C was not observed); IR (neat) 1623.

(35) Lemieux, R. U.; Pavia, A. A. *Can. J. Chem.* **1969**, *47*, 4441.

Methyl 2,6,7,7a-Tetrahydro-7a-methyl-3-(1-methylethyl)-1*H*-indene-5-carboxylate (11). To a solution of **10** (5.56 g, 17.9 mmol) and *N,N*-diisopropylethylamine (3.47 g, 26.9 mmol) in MeOH (20 mL) was added triphenylphosphine (469 mg, 1.79 mmol) and $Pd(OAc)_2$ (201 mg, 0.90 mmol). CO gas was bubbled through the solution for 24 h. The reaction mixture was diluted with ether, washed with 1 N HCl, H_2O, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (49:1 hexane/EtOAc) of the residue on silica gel provided 3.58 g (85%) of pure **11**: ^{1}H NMR 7.43 (d, 1, J = 2.0), 3.76 (s, 3), 2.95 (h, 1, J = 6.8), 2.60−2.27 (m, 4), 1.82 (ddd, 1, J = 1.5, 5.6, 12.4), 1.78 (dd, 1, J = 6.9, 11.5), 1.51−1.33 (m, 2), 1.04 (d, 3, J = 6.8), 1.01 (d, 3, J = 6.8), 0.90 (s, 3); ^{13}C NMR 168.6, 151.1, 136.8, 129.6, 126.9, 51.5, 44.3, 38.8, 35.3, 29.1, 26.9, 23.0, 21.6 (2C), 21.1; IR (neat) 1711, 1633, 1594. Anal. Calcd for $C_{15}H_{22}O$: C, 76.88; H, 9.46. Found: C, 76.50; H, 9.79.

2,6,7,7a-Tetrahydro-5-hydroxymethyl-7a-methyl-3-(1-methylethyl)-1*H*-indene (12). To a solution of ester **11** (2.51 g, 10.7 mmol) in THF (40 mL) at 0 °C was added dropwise a 1 M solution of DIBAL in hexane (24.6 mL, 24.6 mmol). The reaction mixture was stirred for 30 min at 0 °C and quenched by addition of 10% NaOH (40 mL). The resulting solution was extracted with ether. The combined ether extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure, giving 2.14 g (97%) of pure **12**: ^{1}H NMR 6.30 (br s, 1), 4.12 (br s, 2), 2.82 (h, 1, J = 6.8), 2.48−2.36 (m, 1), 2.35−2.07 (m, 3), 1.78 (ddd, 1, J = 1.5, 5.6, 12.6), 1.73 (dd, 1, J = 6.8, 11.9), 1.52−1.38 (m, 3), 1.01 (d, 3, J = 6.8), 0.97 (d, 3, J = 6.8), 0.90 (s, 3); ^{13}C NMR 141.5, 137.5, 136.3, 116.7, 67.3, 44.8, 39.0, 35.8, 28.4, 26.5, 24.6, 21.5, 21.4, 21.3; IR (neat) 3298, 1650, 1620.

2,6,7,7a-Tetrahydro-7a-methyl-3-(1-methylethyl)-1*H*-indene-5-carboxaldehyde (8). A solution of **12** (2.10 g, 10.2 mmol) and MnO_2 (10.4 g, 102 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 20 h. The suspension was filtered through a thin layer of silica and rinsed with additional CH_2Cl_2. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (98:2 hexane/EtOAc) gave 1.98 g (95%) of pure **8**: ^{1}H NMR 9.51 (s, 1), 7.18 (d, 1, J = 2.0), 2.98 (h, 1, J = 6.9), 2.62−2.50 (m, 1), 2.53 (br d, 1, J = 17.8), 2.38 (dd, 1, J = 8.8, 17.8), 2.33−2.18 (m, 1), 1.90−1.79 (m, 2), 1.53 (ddd, 1, J = 10, 10, 11.5), 1.35 (ddd, 1, J = 5.6, 12.7, 12.7), 1.08 (d, 3, J = 6.9), 1.06 (d, 3, J = 6.9), 0.92 (s, 3); ^{13}C NMR 194.2, 154.7, 139.0, 137.8, 137.5, 45.4, 38.8, 34.6, 29.6, 27.3, 21.8, 21.6, 21.1, 20.1; IR (neat) 2713, 1682, 1626, 1589.

2,4,5,6,7,7a-Hexahydro-7aα-methyl-4α-(3-methyl-3-butenyl)-3-(1-methylethyl)-1*H*-indene-5-carboxaldehyde (13). To a solution of $CuBr{\cdot}Me_2S$ (150 mg, 0.73 mmol) and HMPA (8.25 mL, 51.4 mmol) in THF (350 mL) at −78 °C was added a solution of 1.1 M isopentenylmagnesium bromide in THF (20 mL, 22.0 mmol). To the resulting solution was added dropwise a solution of dienal **8** (1.50 g, 7.34 mmol) and TMSCl (6.36 mL, 51.4 mmol) in THF (10 mL). The reaction mixture was stirred for 30 min at −78 °C and quenched by addition of 20 mL of 10% HCl. The resulting solution was stirred at room temperature for 1 h and extracted with ether. The combined ether extracts were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (49:1 hexane/EtOAc) of the residue on silica gel provided 1.83 g (91%) of a 4:6 mixture of the two stereoisomers of **13**: ^{1}H NMR 9.77 (s, 0.6 × 1), 9.60 (s, 0.4 × 1), 4.71 (br s, 0.4 × 1), 4.67 (br s, 1), 4.62 (br s, 0.6 × 1), 3.20 (ddd, 0.6 × 1, J = 4.8, 4.8, 11.5), 3.11 (br dd, 0.4 × 1, J = 7.9, 7.9), 2.74 (h, 1, J = 6.8), 2.38−2.06 (m, 3), 2.04−1.36 (series of m, 10), 1.73 (br s, 0.4 × 3), 1.67 (br s, 0.6 × 3), 1.09 (s, 3), 0.99 (d, 0.6 × 6, J = 6.8), 0.97 (d, 0.4 × 6, J = 6.8); ^{13}C NMR (both) (205.6, 204.9), (145.85, 145.78), (142.9, 142.4), (136.8, 135.8), (109.9, 109.6), (55.5, 51.9), (46.9, 46.0), 41.9, 41.7, 41.0, 38.0, 36.25, 36.16, 34.9, 33.9, 33.0, 28.1, 27.5, 27.2, 26.5, 26.4, 25.1, 24.9, 22.6, 22.5, 21.7, 21.4, 20.9, 20.8, 19.1, 18.2; IR (neat) 3073, 2703, 1724, 1649.

2,4,5,6,7,7a-Hexahydro-5β,7aα-dimethyl-4α-(3-methyl-3-butenyl)-3-(1-methylethyl)-1*H*-indene-5α-carboxalde-

hyde (14a). An epimeric mixture of aldehydes **13** (1.20 g, 4.37 mmol) in MeI (31.0 g, 219 mmol) was added dropwise to a solution of KO-*t*-Bu (3.62 g of 95% pure, 30.6 mmol) in 1,2-dimethoxyethane (220 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Additional KO-*t*-Bu (1.55 g, 13.1 mmol) was added in three portions over 30 min. The mixture was diluted with ether, washed with ice cold H_2O and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 1.35 g of crude product, which was used directly in the following reaction without further purification. The crude mixture can be purified by flash chromatography on silica gel (49:1 hexane/EtOAc) to give 4−6% of **14b** and 69−76% of **14a**: ^{1}H NMR 9.55 (s, 1), 4.64 (br s, 1), 4.59 (br s, 1), 2.68 (h, 1, J = 6.8), 2.60 (dd, 1, J = 4.1, 11.4), 2.33 (ddd, 1, J = 7.5, 10.5, 15.6), 2.20 (ddd, 1, J = 1.4, 9.2, 15.6), 2.12−2.01 (m, 1), 1.97−1.81 (m, 2), 1.78−1.20 (series of m, 7), 1.65 (br s, 3), 1.08 (s, 3), 0.99 (s, 3), 0.97 (d, 6, J = 6.8); ^{13}C NMR 206.9, 145.8, 145.1, 134.2, 109.6, 49.9, 46.5, 42.5, 41.1, 36.3, 36.1, 29.4, 27.7, 26.4, 25.5, 23.5, 22.5, 21.5, 20.6, 19.7; IR (neat) 2691, 1727, 1649.

(3aα,5a*β*,6*β*,10a*β*)-2,3,3a,4,5,5a,6,7,8,9,10,10a-Dodecahydro-3a,5a-dimethyl-8-methylene-1-(1-methylethyl)cyclohept[*e*]inden-6-ol (23). To a solution of a 15:1 mixture of crude **14a** and **14b** (1.35 g) in CH_2Cl_2 (450 mL) at −45 °C was added Me_2AlCl (8.74 mL of 1.0 M in hexane, 8.74 mmol). The reaction mixture was kept at −45 °C for 2 h and quenched by addition of 50 mL of 10% NaOH. The CH_2Cl_2 layer was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (49:1 hexane/EtOAc) afforded 70 mg (6%) of unreacted **14b**, and 761 mg (60% for 2 steps) of **23** as a white solid: mp 107−108 °C; ^{1}H NMR 4.76 (br s, 1), 4.72 (br s, 1), 3.54 (d, 1, J = 9.5), 2.64 (h, 1, J = 6.8), 2.63 (dd, 1, J = 12.3, 12.3), 2.45 (br d, 1, J = 14.4), 2.37−2.10 (m, 5), 1.80−1.35 (m, 8), 1.25 (br d, 1, J = 14.4), 0.97 (s, 3), 0.98 (d, 3, J = 6.8), 0.93 (d, 3, J = 6.8), 0.83 (s, 3); ^{13}C NMR 148.1, 141.9, 139.6, 111.6, 79.7, 46.1, 43.3, 41.3, 40.7, 40.4, 38.7, 36.4, 30.7, 30.0, 27.7, 26.4, 24.8, 21.4, 21.1, 18.8; IR (CCl_4) 3630, 1640. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 82.89; H, 10.90.

(3aα,5a*β*,6*β*,10a*β*)-2,3,3a,4,5,5a,6,7,8,9,10,10a-Dodecahydro-3a,5a-dimethyl-8-methylene-1-(1-methylethyl)-6-(dimethyl-1-methylethylsilyloxy)cyclohept[*e*]indene. To a solution of **23** (350 mg, 1.21 mmol) in DMF (1 mL) was added imidazole (247 mg, 3.63 mmol) and chlorodimethylisopropylsilane (0.57 mL, 3.63 mmol). The reaction mixture was stirred at room temperature for 1 d, diluted with ether, washed with saturated NH_4Cl solution, H_2O, and brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure followed by flash chromatography on silica gel (199:1 hexane/EtOAc) gave 449 mg (95%) of pure silyl ether: ^{1}H NMR 4.67 (br s, 1), 4.66 (br s, 1), 3.49 (d, 1, J = 9.0), 2.64 (h, 1, J = 6.8), 2.63 (dd, 1, J = 10.7, 13.5), 2.39 (br d, 1, J = 14.1), 2.32 (d, 1, J = 10.0), 2.25 (ddd, 1, J = 7.5, 10.4, 15.6), 2.18−2.08 (m, 3), 1.77−1.63 (m, 2), 1.55−1.33 (m, 5), 1.27−1.18 (m, 1), 1.0−0.80 (m, 1), 0.98 (d, 6, J = 6.9), 0.96 (d, 3, J = 6.8), 0.96 (s, 3), 0.93 (d, 3, J = 6.8), 0.77 (s, 3), 0.09 (s, 3), 0.05 (s, 3); ^{13}C NMR 149.2, 142.4, 139.2, 110.7, 80.4, 46.1, 43.3, 41.3, 41.0, 40.9, 39.3, 36.7, 30.9, 30.3, 27.7, 26.4, 24.7, 21.4, 21.2, 19.1, 17.1 (2C), 15.0, −2.8, −3.9; IR (CCl_4) 1639. Anal. Calcd for $C_{25}H_{44}OSi$: C, 77.25; H, 11.41. Found: C, 77.04; H, 11.14.

(3aα,5a*β*,6*β*,10a*β*)-2,3,3a,4,5,5a,6,7,8,9,10,10a-Dodecahydro-3a,5a-dimethyl-1-(1-methylethyl)-6-(dimethyl-1-methylethylsilyloxy)cyclohept[*e*]inden-8-one. To a solution of silyl ether (210 mg, 0.54 mmol) in *tert*-butyl alcohol (10 mL) was added H_2O (2 mL), $NaHCO_3$ (454 mg, 5.40 mmol), KIO_4 (745 mg, 3.24 mmol), and OsO_4 (55 mg of 2.5% in *tert*-butyl alcohol, 5.4×10^{-3} mmol). The mixture was stirred at room temperature for 2 d and quenched by addition of 10 mL of 10% $Na_2S_2O_3$. After 30 min, the mixture was diluted with ether, washed with H_2O and brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure followed by flash chromatography on silica gel (97:3 hexane/EtOAc) gave 163 mg (77%) of pure ketone: ^{1}H NMR 3.60 (d, 1, J = 8.1), 3.02−2.86 (m, 1), 2.62 (h, 1, J = 6.8), 2.60−2.51 (m, 1), 2.50 (dd, 1, J = 3.2, 11.9), 2.43 (ddd, 1, J = 3, 6.1, 16.9), 2.25 (ddd, 1, J = 6.9, 10.6, 15.6), 2.13 (dd, 1, J = 9, 15.6), 2.10−1.94 (m, 1), 1.93−1.79 (m, 1), 1.69 (dd, 1, J = 6.2, 11.8), 1.64−1.22 (series of m, 6), 1.03 (s, 3), 0.95 (d, 3, J = 6.8), 0.94 (d, 3, J = 6.4), 0.93 (d, 3, J = 6.8), 0.92 (d, 3, J = 6.4), 0.88 (s, 3), 0.82−0.72 (m, 1), 0.05 (s, 3), 0.04 (s, 3); ^{13}C NMR 212.4, 141.3, 140.1, 76.1, 46.1, 45.6, 43.9, 42.6, 42.4, 41.5, 36.3, 28.0, 27.8, 27.2, 26.2, 26.1, 21.2, 21.1, 17.0, 16.9, 14.9, −3.3, −4.1 (one carbon not observed); IR (neat) 1710.

(3aα,5a*β*,6*β*,10a*β*)-2,3,3a,4,5,5a,6,7,8,10a-Decahydro-3a,-5a-dimethyl-1-(1-methylethyl)-6-(dimethyl-1-methylethylsilyloxy)cyclohept[*e*]inden-8-one (38). To a solution of LiHMDS (0.28 mL of 1.0 M solution in THF, 0.28 mmol) in THF (1.0 mL) at −78 °C was added dropwise a solution of *β*-silyloxy ketone (55 mg, 0.14 mmol) in THF (1.0 mL). The mixture was stirred at −78 °C for 30 min and solid phenylselenyl chloride (55 mg, 0.28 mmol) was added. The reaction mixture was gradually warmed to 0 °C over 1 h. Addition of 2 mL of saturated NH_4Cl solution was followed by addition of H_2O_2 (0.30 mL of 30%, 2.9 mmol). The resulting solution was stirred for 30 min in a warm H_2O bath (40 °C), diluted with ether, washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (49:1 hexane/EtOAc) provided 39 mg (72%) of pure **38**: ^{1}H NMR 6.16 (dd, 1, J = 4.1, 12.2), 5.86 (ddd, 1, J = 1.0, 2.8, 12.2), 3.72 (dd, 1, J = 1.5, 8.2), 3.36−3.32 (m, 1), 2.88 (dd, 1, J = 8.2, 17.7), 2.71 (ddd, 1, J = 1.0, 1.2, 17.7), 2.56 (h, 1, J = 6.8), 2.32 (ddd, 1, J = 7.4, 10.3, 15.6), 2.21 (ddd, 1, J = 1.2, 9.2, 15.6), 1.74 (ddd, 1, J = 1.5, 7.2, 12.1), 1.67−1.33 (m, 5), 1.03 (s, 3), 0.97 (d, 3, J = 6.8), 0.94 (d, 9, J = 6.8), 0.89 (s, 3), 0.82−0.75 (m, 1), 0.06 (s, 3), 0.05 (s, 3); ^{13}C NMR 201.6, 149.9, 142.7, 137.3, 130.3, 75.7, 47.9, 46.7, 43.0, 41.0, 40.2, 36.2, 30.4, 27.9, 26.3, 24.5, 21.2, 21.2, 21.1, 16.9 (2 C), 15.0, −3.2, −4.0; IR (CCl_4) 1675.

(3aα,5a*β*,10a*β*)-2,3,3a,4,5,5a,6,7,8,10a-Decahydro-3a,5a-dimethyl-1-(1-methylethyl)cyclohept[*e*]indene-6,8-dione. A solution consisting of 310 mg (0.80 mmol) of enone **38**, 15 mL of THF, 15 mL of H_2O, and 30 mL of HOAc was stirred at 45 °C for 2.25 h. The resulting solution was diluted with Et_2O, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 251 mg of crude hydroxy enone as a clear viscous oil: ^{1}H NMR 6.20 (dd, 1, J = 4.4, 12.1), 5.91 (ddd, 1, J = 1.0, 2.7, 12.1), 3.81 (m, 1), 3.35 (m, 1), 2.95 (dd, 1, J = 8.5, 17.8), 2.79 (ddd, 1, J = 1.1, 1.8, 17.8), 2.59 (h, 1, J = 6.8), 2.34 (ddd, 1, J = 7.2, 10.4, 15.8), 2.23 (ddd, 1, J = 1.1, 9.0, 15.8), 2.01 (m, 1, OH), 1.80−1.45 (m, 6), 1.05 (s, 3), 0.98 (d, 3, J = 6.8), 0.97 (s, 3), 0.94 (d, 3, J = 6.8); ^{13}C NMR 201.5, 149.6, 143.4, 136.7, 130.5, 75.1, 47.6, 46.6, 42.8, 41.0, 39.6, 35.9, 30.6, 27.9, 26.3, 24.4, 21.2, 21.1, 20.3; IR (neat) 3452, 1741, 1658.

To a solution of 251 mg of crude hydroxy enone in 50 mL of CH_2Cl_2 was added 410 mg (0.96 mmol) of Dess−Martin reagent. The solution was stirred at room temperature under N_2 for 15 min and quenched by the addition of 30 mL of 10% $Na_2S_2O_3$. The resulting two-phase solution was stirred rapidly until the organic layer cleared. The solution was diluted with 50 mL of CH_2Cl_2 and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography on silica gel (10:1 hexane/EtOAc) gave 165 mg (72% for two steps) of pure crystalline dione: mp (recrystallized from hexane) 116.5−117.5 °C; ^{1}H NMR 6.55 (dd, 1, J = 4.7, 11.9), 6.00 (ddd, 1, J = 2.2, 2.2, 11.9), 4.38 (d, 1, J = 12.8), 3.87 (m, 1), 3.48 (dd, 1, J = 2.2, 12.8), 2.66 (h, 1, J = 6.8), 2.41 (ddd, 1, J = 7.3, 10.3, 15.9), 2.29 (ddd, 1, J = 1.2, 9.2, 15.9), 1.94−1.43 (m, 6), 1.10 (s, 3), 1.08 (s, 3), 1.03 (d, 3, J = 6.8), 0.98 (d, 3, J = 6.8); ^{13}C NMR 206.7, 190.7, 153.0, 145.5, 135.2, 131.9, 56.4, 50.2, 46.2, 41.4, 41.1, 35.3, 28.2, 26.4, 26.3, 24.6, 22.1, 21.4, 21.2; IR (neat) 1712, 1677. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.60; H, 9.30.

(3aα,5a*β*,10a*β*)-2,3,3a,4,5,5a,6,10a-Octahydro-3a,5a-dimethyl-1-(1-methylethyl)-8-trifluoromethylsulfonyloxycyclohept[*e*]inden-6-one (39). To a solution containing 1 mL of 0.5 M KHMDS (0.5 mmol) in 5 mL of THF was added 70 mg (0.25 mmol) of the above dione in 5 mL of THF over a 15 min period at −78 °C. The solution was stirred at −78 °C

for an additional 10 min, and 357 mg (1.0 mmol) of $PhNTf_2$ in 20 mL of THF was added rapidly. The solution was warmed to room temperature, diluted with Et_2O, washed with saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (hexane followed by 100:1 hexane/EtOAc) gave 76 mg (75%) of pure **39**: ^{1}H NMR 6.32 (d, 1, J = 2.6), 6.11 (dd, 1, J = 4.6, 11.7), 5.90 (ddd, 1, J = 2.6, 2.6, 11.7), 3.52 (m, 1), 2.56 (h, 1, J = 6.8), 2.35 (ddd, 1, J = 7.0, 10.4, 15.9), 2.24 (ddd, 1, J = 1.4, 9.3, 15.9), 1.93 (ddd, 1, J = 4.2, 13.9, 13.9), 1.79 (ddd, 1, J = 1.4, 7.0, 12.2), 1.69−1.45 (m, 4), 1.10 (s, 3), 1.07 (s, 3), 0.99 (d, 3, J = 6.8), 0.95 (d, 3, J = 6.8); ^{13}C NMR 203.0, 151.8, 144.7, 135.1, 122.3, 121.4, 56.7, 46.3, 42.7, 41.5, 34.9, 28.1, 26.4, 25.9, 25.1, 22.2, 21.3, 21.2 (2 carbons not observed); IR (neat) 1686, 1639; UV (EtOH) λ_{max} (ϵ) 274 nm (3600).

Methyl (3aα,5a*β*,10a*β*)-2,3,3a,4,5,5a,6,10a-Octahydro-3a,5a-dimethyl-1-(1-methylethyl)-6-oxocyclohept[*e*]indene-8-carboxylate (40). CO gas was bubbled through a stirred solution containing 72 mg (0.17 mmol) of triflate **39**, 0.1 mL (0.76 mmol) of diisopropylethylamine, 3 mg (0.013 mmol) of $Pd(OAc)_2$, and 7 mg (0.027 mmol) of Ph_3P in 15 mL of MeOH at room temperature for 2.5 h. The solution was diluted with Et_2O, washed with 1 N HCl and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (25:1 hexane/EtOAc) gave 42 mg (75%) of pure **40**: ^{1}H NMR 7.22 (d, 1, J = 1.6), 6.31 (ddd, 1, J = 1.6, 2.6, 11.3), 5.99 (dd, 1, J = 5.0, 11.3), 3.83 (s, 3), 3.43 (m, 1), 2.56 (h, 1, J = 6.9), 2.34 (ddd, 1, J = 7.1, 10.3, 15.6), 2.22 (ddd, 1, J = 1.2, 9.2, 15.6), 1.89 (ddd, 1, J = 1.2, 13.8, 13.8), 1.77 (ddd, 1, J = 1.2, 7.1, 12.1), 1.73−1.43 (m, 4), 1.12 (s, 3), 1.05 (s, 3), 0.96 (d, 3, J = 6.9), 0.93 (d, 3, J = 6.9); ^{13}C NMR 207.4, 166.1, 144.3, 140.8, 137.3, 135.6, 134.0, 123.3, 59.4, 52.5, 46.4, 42.3, 41.6, 34.8, 28.0, 26.2, 25.1, 24.9, 21.8, 21.4, 21.1; IR (neat) 1727, 1682; UV (EtOH) λ_{max} (ϵ) 286 nm (1900).

Methyl (3aα,5a*β*)-2,3,3a,4,5,5a,6,7-Octahydro-3a,5a-dimethyl-1-(1-methylethyl)-6-oxocyclohept[*e*]indene-8-carboxylate (41). A solution containing 35 mg (0.11 mmol) of **40** and 0.2 mL of Et_3N in 5 mL of MeOH was heated at 100 °C in a sealed tube for 12 h. The solution was cooled, diluted with Et_2O, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated to give 34 mg of nearly pure **41**. Further purification by flash chromatography on silica gel (25:1 hexane/EtOAc) gave 33 mg (94%) of pure **41** as a yellow oil: ^{1}H NMR 7.27 (ddd, 1, J = 0.7, 1.9, 6.3), 5.95 (d, 1, J = 6.3), 3.86 (d, 1, J = 11.0), 3.80 (s, 3), 3.39 (ddd, 1, J = 1.0, 1.9, 11.0), 2.87 (h, 1, J = 6.9), 2.41 (m, 2), 2.02 (ddd, 1, J = 4.6, 13.0, 13.0), 1.81−1.57 (m, 4), 1.44 (ddd, 1, J = 4.0, 4.0, 13.4), 1.17 (s, 3), 1.05 (d, 3, J = 6.9), 1.02 (s, 3), 1.00 (d, 3, J = 6.9); ^{13}C NMR 205.2, 166.1, 148.7, 144.2, 139.8, 135.8, 123.7, 121.9, 56.9, 52.3, 49.3, 40.6, 38.6, 36.0, 34.2, 28.6, 26.8, 23.8, 22.4, 21.5, 21.5; IR (neat) 1715, 1587; UV (EtOH) λ_{max} (ϵ) 314 nm (9100), 261 nm (5500).

(3aα,5a*β*,6α)-2,3,3a,4,5,5a,6,7-Octahydro-6-hydroxy-3a,5a-dimethyl-1-(1-methylethyl)cyclohept[*e*]indene-8-methanol. To a solution containing 21 mg (0.064 mmol) of **41** in 10 mL of Et_2O was added 10 mg (0.26 mmol) of LAH at −78 °C. The reaction was stirred for 10 min at −78 °C and the solution was warmed to room temperature. The solution was quenched by the addition of 2 mL of H_2O, diluted with Et_2O, washed with H_2O and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 20 mg of crude diol as a single isomer. Flash chromatography of the residue on silica gel (5:1 followed by 2:1 hexane/EtOAc) gave 17 mg (89%) of pure diol as a clear viscous oil: ^{1}H NMR 6.04 (dddd, 1, J = 1.3, 1.3, 2.5, 8.0), 5.59 (d, 1, J = 8.0), 4.11 (br s, 2), 3.59 (m, 1), 2.83 (h, 1, J = 6.9), 2.72 (br d, 1, J = 17.5), 2.59 (dd, 1, J = 5.9, 17.5), 2.46 (ddd, 1, J = 9.2, 13.7), 2.34 (m, 2), 1.75−1.54 (m, 4), 1.24 (ddd, 1, J = 3.6, 3.6, 12.6), 1.00 (d, 3, J = 6.9), 0.95 (s, 3), 0.94 (d, 3, J = 6.9), 0.93 (s, 3); ^{13}C NMR 143.8, 143.1, 141.9, 138.0, 121.5, 119.3, 74.5, 68.8, 48.3, 47.2, 38.4, 36.8, 34.1, 32.9, 28.5, 26.7, 26.2, 23.9, 21.6, 21.5; IR (neat) 3377, 1596.

Allocyathin B_2 (2). A suspension of 43 mg (0.5 mmol) of MnO_2 in a solution containing 15 mg (0.05 mmol) of diol in 10 mL of CH_2Cl_2 was stirred under N_2 at room temperature for 12 h. The solution was filtered, dried ($MgSO_4$), and concentrated under reduced pressure to give 18 mg of crude **2**. Flash chromatography of the residue on silica gel (10:1 hexane/EtOAc) gave 14 mg (94%) of pure allocyathin B_2: ^{1}H NMR 9.45 (s, 1), 6.82 (dd, 1, J = 2.5, 8.3), 5.9 (d, 1, J = 8.3), 3.72 (m, 1), 3.16 (dd, 1, J = 5.8, 18.2), 2.83 (h, 1, J = 6.8), 2.55 (br d, 1, J = 18.2), 2.53 (m, 1), 2.41 (m, 2), 1.76−1.63 (m, 4), 1.34 (ddd, 1, J = 3.5, 3.7, 13.7), 1.05 (d, 3, J = 6.8), 1.00 (s, 3), 0.97 (d, 3, J = 6.8), 0.96 (s, 3); ^{13}C NMR 194.1, 155.1, 146.4, 144.3, 141.8, 137.7, 119.3, 74.0, 49.1, 48.2, 38.3, 36.5, 33.7, 29.2, 29.0, 27.0, 26.5, 23.9, 21.5, 21.5; IR (CCl_4) 3588, 1683, 1570; UV (EtOH) λ_{max} (ϵ) 338 (17 000), 201 (7700). The ^{1}H and ^{13}C NMR spectral data are identical to those provided by Professor Kawagishi.

Erinacine A Triacetate (42). To a solution containing 8 mg (0.027 mmol) of racemic allocyathin B_2 (**2**) in 2 mL of CH_3CN was added 92 mg (0.27 mmol) of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide followed by 8 mg (0.032 mmol) of $Hg(CN)_2$ and 8 mg (0.030 mmol) of $HgCl_2$ at room temperature. The solution was stirred at room temperature for 3.5 min and diluted immediately with 40 mL of benzene. The solution was washed three times with H_2O and once with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 68 mg of a crude yellow oil. Flash chromatography of the residue on silica gel (5:1 hexane/EtOAc) gave 4 mg (50%) of recovered allocyathin B_2 followed by 5 mg (34%, 68% from recovered allocyathin B_2) of a 1:1 mixture of **42** and **43**. The diastereomeric glycosides were efficiently separated by further chromatography on silica gel (5:1 hexane/EtOAc).

Data for erinacine A triacetate diastereomer **43**: ^{1}H NMR 9.39 (s, 1), 6.69 (dd, 1, J = 2.0, 8.1), 5.80 (d, 1, J = 8.1), 5.12 (dd, 1, J = 9.0, 9.0), 4.94 (ddd, 1, J = 5.1, 9.0, 9.2), 4.82 (dd, 1, J = 6.9, 9.0), 4.39 (d, 1, J = 6.9), 4.08 (dd, 1, J = 5.1, 11.6), 3.83 (d, 1, J = 6.1), 3.32 (dd, 1, J = 9.2, 11.6), 3.17 (dd, 1, J = 6.1, 18.5), 2.80 (h, 1, J = 6.9), 2.50−1.25 (series of m, 9), 2.04 (s, 3), 1.99 (s, 3), 1.94 (s, 3), 1.02 (d, 3, J = 6.9), 0.99 (s, 3), 0.98 (s, 3), 0.95 (d, 3, J = 6.9); ^{13}C NMR 193.6, 169.9, 169.9, 168.9, 155.1, 146.0, 145.1, 142.2, 137.1, 119.6, 96.8, 71.7, 71.0, 69.2, 62.2, 49.4, 47.0, 38.3, 36.5, 33.5, 28.9, 26.9, 26.6, 23.7, 23.5, 21.5, 21.5, 20.7, 20.7, 20.7, one carbon not observed.

Data for synthetic erinacine A triacetate (**42**): 9.39 (s, 1), 6.72 (dd, 1, J = 1.9, 8.2), 5.82 (d, 1, J = 8.2), 5.08 (dd, 1, J = 8.1, 8.1), 4.87 (dd, 1, J = 6.4, 8.1), 4.85 (ddd, 1, J = 5.0, 7.8, 8.1), 4.57 (d, 1, J = 6.4), 3.96 (dd, 1, J = 5.0, 11.8), 3.57 (d, 1, J = 6.3), 3.31 (dd, 1, J = 7.8, 11.8), 3.22 (dd, 1, J = 6.3, 17.8), 2.81 (h, 1, J = 6.7), 2.53 (br d, 1, J = 17.8), 2.43−1.24 (series of m, 8), 2.03 (s, 3), 2.01 (s, 3), 1.99 (s, 3), 1.02 (d, 3, J = 6.7), 0.98 (s, 3), 0.95 (d, 3, J = 6.7), 0.93 (s, 3); ^{13}C NMR 193.7, 170.0, 169.7, 169.0, 152.8, 145.1, 145.0, 141.8, 138.5, 120.1, 102.2, 84.9, 71.4, 71.0, 68.7, 61.7, 49.2, 47.7, 38.3, 36.6, 33.0, 28.9, 27.0, 26.9, 26.5, 23.8, 21.5, 21.5, 20.8, 20.7, 20.7. The ^{1}H and ^{13}C NMR spectral data are identical to those of an authentic sample.

(+)-Erinacine A Diastereomer 44 and (+)-Erinacine A (4). To 3 mg of each triacetate diastereomer **42** and **43** in 2 mL of MeOH was added 5 mg of K_2CO_3. Each solution was stirred at room temperature for 1 h, diluted with 20 mL of EtOAc, and washed twice with H_2O. The combined aqueous washings were extracted three times with EtOAc and all organic extracts were combined, washed with brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the pure deprotected glycosides **4** and **44** in 90−100% yield. Further purification was achieved by flash chromatography on silica gel (EtOAc).

Data for (+)-erinacine A diastereomer **44**: ^{1}H NMR 9.41 (s, 1), 6.80 (dd, 1, J = 2.3, 8.1), 5.87 (d, 1, J = 8.1), 4.23 (d, 1, J = 6.8), 4.02 (dd, 1, J = 4.9, 11.6), 3.89 (d, 1, J = 5.9), 3.70 (m, 1), 3.49 (br dd, 1, J = 9.1, 9.2), 3.30 (dd, 1, J = 6.2, 18.1), 3.30 (dd, 1, J = 9.2, 11.6), 3.22 (ddd, 1, J = 2.4, 6.8, 9.1), 2.87 (m, 1, OH), 2.83 (h, 1, J = 6.8), 2.54−2.40 (m, 2), 2.40 (m, 2), 2.25 (d, 1, J = 2.4, OH), 1.76−1.60 (m, 4), 1.33 (ddd, 1, J = 3.2, 3.7, 13.5), 1.04 (d, 3, J = 6.8), 1.02 (s, 3), 0.97 (s, 3), 0.96 (d, 3, J = 6.8); ^{13}C NMR 193.9, 155.3, 145.8, 145.8, 142.0, 137.5, 119.6, 99.2, 75.3, 73.1, 69.6, 65.1, 49.3, 47.1, 38.3, 36.4, 33.5, 29.0,

27.0, 27.0, 23.9, 23.8, 21.5, 21.5, one carbon not observed; IR (CCl_4) 3607, 3417, 1676, 1573; UV (EtOH) λ_{max} (ϵ) 339 (11 500), 202 (5400); $[\alpha]_D$ +165 (c = 0.18, MeOH).

Data for (+)-erinacine A (**4**): ^{1}H NMR ($CDCl_3$) 9.43 (s, 1), 6.79 (dd, 1, J = 2.5, 8.3), 5.89 (d, 1, J = 8.3), 4.77 (d, 1, J = 3.0), 3.87 (dd, 1, J = 1.9, 12.6), 3.70 (m, 3), 3.61 (m, 1), 3.45 (ddd, 1, J = 2.2, 2.8, 12.6), 3.35 (dd, 1, J = 6.0, 18.3), 3.32 (d, 1, J = 8.3, OH), 3.15 (d, 1, J = 7.9, OH), 2.82 (h, 1, J = 6.9), 2.55 (br d, 1, J = 18.3), 2.41 (m, 2), 2.32 (dd, 1, J = 6.0, 13.2), 1.79−1.62 (m, 4), 1.35 (ddd, 1, J = 3.2, 3.8, 13.5), 1.03 (d, 3, J = 6.9), 0.99 (s, 3), 0.98 (s, 3), 0.96 (d, 3, J = 6.9); (10% $CD_3OD/CDCl_3$) 9.38 (s, 1), 6.80 (dd, 1, J = 2.2, 8.3), 5.89 (d, 1, J = 8.3), 4.59 (d, 1, J = 4.4), 3.82 (dd, 1, J = 2.9, 12.4), 3.67 (d, 1, J = 5.9), 3.54 (m, 2), 3.45 (dd, 1, J = 4.4, 6.9), 3.33 (dd, 1, J = 6.6, 12.4), 3.29 (dd, 1, J = 5.9, 18.1), 2.83 (h, 1, J = 6.8), 2.55 (br d, 1, J = 18.1), 2.44 (m, 1), 2.41 (m, 2), 1.75−1.63 (m, 4), 1.36 (br d, 1, J = 13.0), 1.04 (d, 3, J = 6.8), 1.00 (s, 3), 1.00 (s, 3), 0.96 (d, 3, J = 6.8); (20% $CD_3OD/CDCl_3$) 9.37 (s, 1), 6.81 (dd, 1, J = 2.2, 8.2), 5.89 (d, 1, J = 8.2), 4.53 (d, 1, J = 4.9), 3.81 (dd, 1, J = 3.4, 11.9), 3.67 (br d, 1, J = 6.0), 3.52 (m, 1), 3.49 (dd, 1, J = 6.3, 6.9), 3.41 (br dd, 1, J = 4.9, 6.3), 3.31 (dd, 1, J = 6.8, 11.9), 3.27 (dd, 1, J = 6.0, 18.1), 2.84 (h, 1, J = 6.8), 2.56 (br d, 1, J = 18.1), 2.47 (m, 1), 2.42 (m, 2), 1.78−1.64 (m, 4), 1.37 (br d, 1, J = 13.3), 1.04 (d, 3, J = 6.8), 1.01 (s, 3), 1.01 (s, 3), 0.97 (d, 3, J = 6.8); ^{13}C NMR ($CDCl_3$) 194.1, 154.0, 146.6, 145.1, 141.4, 138.4, 119.8, 104.2, 84.1, 70.1, 69.7, 69.5, 61.8, 49.0, 48.1, 38.2, 36.4, 33.8, 29.0, 27.9, 27.0, 26.3, 23.9, 21.5, 21.5; (20% $CD_3OD/CDCl_3$) 195.0, 154.8, 146.4, 146.1, 141.9, 138.8, 120.0, 105.0, 84.5, 73.2, 71.5, 69.5, 63.7, 38.5, 36.7, 33.7, 29.2, 27.9, 27.2, 26.5, 23.9, 21.7, 21.7; IR (CCl_4) 3419, 1676, 1651, 1576, 1557; UV (EtOH) λ_{max} (ϵ) 338 (12 000), 201 (6100); $[\alpha]_D$ +515 (c = 0.15, MeOH); lit. $[\alpha]_D$ +216 (c = 0.28, MeOH). The ^{1}H and ^{13}C NMR spectral data are identical to those of an authentic sample in dilute $CDCl_3$ solution.

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Supporting Information Available: Experimental procedures for other compounds and copies of ^{1}H and ^{13}C NMR spectra of compounds not characterized by elemental analyses (66 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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