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

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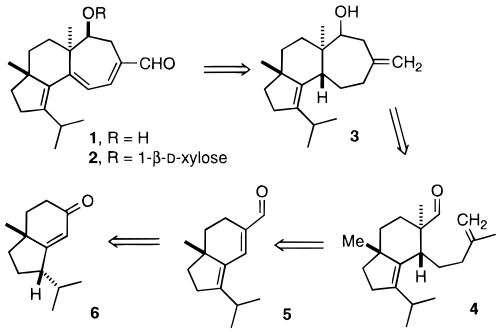
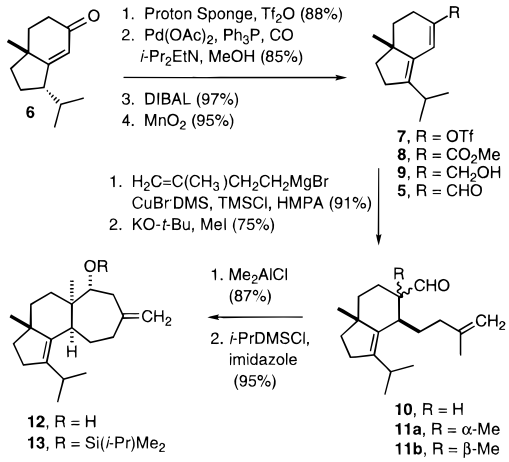
We report here the total synthesis of (±)-allocyathin B_2 (**1**)[1f] and erinacine A (**2**),[2] the 1-β-D-xyloside of (+)-**1**, the first cyathin diterpenes[1] to be prepared. The cyathin antibiotics were first isolated in 1970 by Ayer and Brodie[1a] from *Cyathus helenae* Brodie, a bird nest fungus growing in the Rocky Mountains of Alberta. Allocyathin B_2 (**1**) was later isolated by Ayer[1f] from a related fungus, *Cyathus earlei* Lloyd. More recently, Kawagishi isolated erinacine A (**2**), a potent stimulator of nerve growth factor synthesis, from the mycelia of *Hericum erinaceum*.[2] The unusual 5−6−7 tricyclic ring system and extensive functionality make cyathin synthesis a challenging problem.[3]



We envisioned that **1** could be prepared from cycloheptanol **3**, which should be readily available from aldehyde **4** by an intramolecular carbonyl ene reaction.[4,5] We expected that **4** could be prepared from dienal **5** by the Koga protocol,[6] addition of a Grignard reagent to the *tert*-leucine *tert*-butyl ester imine of **5** followed by methylation, which we used successfully in our synthesis of reiswigin A.[5] Dienal **5** should be readily available by palladium-catalyzed carbonylation of the dienyl triflate **7** prepared from enone **6**. Since enone **6** can be prepared in two steps,[7] this route should provide very efficient access to **3**, which contains the complete carbon skeleton and much of the functionality of the cyathins.

Conversion of **6** to dienyl triflate **7**[8] followed by palladium-catalyzed carbonylation[9] of **7** in methanol gave dienoate **8**. Reduction of **8** with DIBAL followed by MnO_2 oxidation of **9** gave dienal **5**[10] in 69% overall yield from **6**. Attempted addition of isopentenylmagnesium bromide to the *tert*-leucine *tert*-butyl ester imine of **5** by the Koga protocol[6] gave only traces of the desired 1,4-addition product, possibly due to steric hindrance from the isopropyl group. All attempts to introduce the isopentenyl side chain by cuprate addition to dienoate **8** failed. Fortunately, TMS-accelerated cuprate addition to dienal **5** by the Nakamura−Kuwajima procedure[11] gave 91% of **10** 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,[12] while in other cases an axial methyl group forces equatorial cuprate attack.[13] Methylation of **10** using Ireland's procedure[14] with a large excess of MeI (50 equiv) and KO*t*Bu (7 equiv) provided 75% of a 15:1 mixture of α-methylated aldehydes **11a** and **11b**. The stereochemistry of the major product was not obvious since equatorial methylation of cyclohexanecarboxaldehydes, which would give **11b**, is usually observed, while approach from the least hindered face of the enolate of **10** would result in axial methylation to give **11a**. The stereochemistry of the major product was eventually established as **11a** by X-ray crystallographic structure determination of a derivative of **11b**.[15]



Treatment of **11a** with Me_2AlCl at −45 °C for 2 h gave 87% of a single alcohol, **12**,[17] with the complete cyathin skeleton, which was protected giving isopropyldimethylsilyl ether **13**. Unfortunately, the stereochemistry of the 6−7 ring fusion in **12** was cis, while it is trans in all of the cyathins except for allocyathin B_2 (**1**). During his structure determination work, Ayer established that treatment of cyathin B_3 (**14**) with acetic anhydride in pyridine afforded anhydrocyathin B_3 (**15**).[1f]

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(9) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(10) Formylation of the dienyl triflate by Stille's procedure gave a low yield of **5**: Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.

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(15) Aldehyde **11b** was prepared efficiently from **10** by the following sequence: $NaClO_2$ then CH_2N_2 (95%); LDA, $PhCH_2OCH_2Cl$ (91%); LAH (100%); BuLi then $[(CH_3)_2N]_2POCl$ followed by Li, $EtNH_2$[16] (73%); Swern oxidation (82%). Oxidative cleavage (OsO_4, KIO_4) of the side chain double bond of **11b** followed by oxidation of the aldehyde ($NaClO_2$) gave a keto acid whose structure was established by X-ray crystallography.

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

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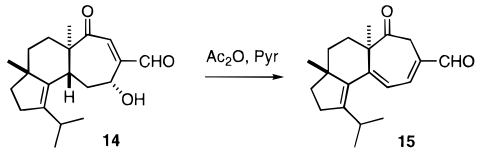
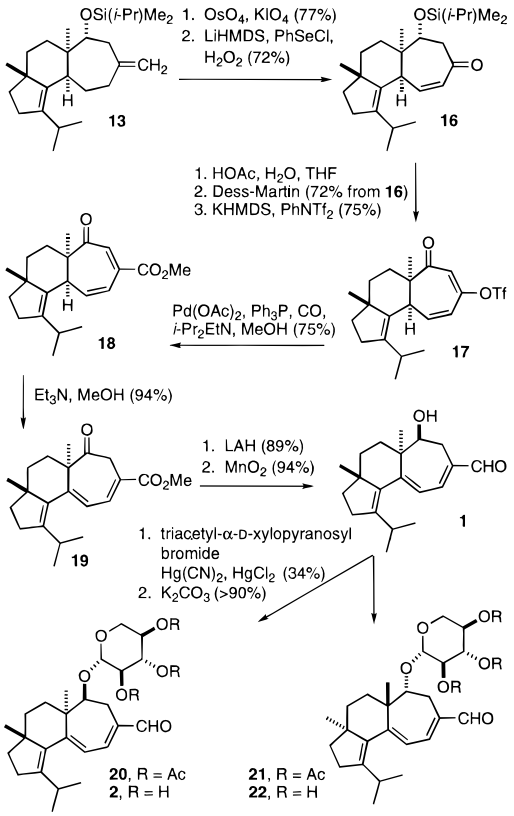
Reduction of **15** with LAH afforded a 2:1 mixture of diols with the desired β-diol predominating; MnO_2 oxidation afforded allocyathin B_2.[1f] This suggested that the conjugated triene moiety of allocyathin B_2 could be prepared by equilibration of keto ester **18**.



14 **15**

The exocyclic alkene of **13** was easily elaborated to a cycloheptenecarboxaldehyde. Unfortunately, all attempts to introduce the third double bond failed. We therefore cleaved the exocyclic double bond (OsO_4/KIO_4, 77%) to give the ketone, which was elaborated to enone **16** in 72% yield via the α-phenylselenide.[18] Desilylation followed by Dess−Martin oxidation[19] gave the dione, which was treated with KHMDS and then $PhNTf_2$[20] to give exclusively enol triflate **17**. The position of triflation follows from the UV spectrum (λ_{max} 274 nm, ϵ 3600) of **17** which is consistent with a β-triflyloxy-conjugated dienone rather than a cross-conjugated dienone.[21] Palladium-catalyzed carbonylation of **17** in methanol[9] gave keto ester **18**, which isomerized quantitatively to keto ester **19** on treatment with Et_3N in MeOH (100 °C, 12 h). We were pleasantly surprised to find that reduction of **19** with LAH at −78 to 0 °C gave exclusively the desired β-diol, which was oxidized with MnO_2 to give (±)-allocyathin B_2 (**1**) with ^1H and ^{13}C NMR and IR spectral data identical to those of natural allocyathin B_2.[23] Presumably the different stereoselectivity in the reduction of the ketones of keto aldehyde **15** and keto ester **19** results from the disparate reactivity of the other carbonyl group. The ketone group of **19** is reduced first selectively from the α-face, while the aldehyde of **15** should be reduced more rapidly so that the ketone group can then be reduced from either face by intramolecular delivery of hydride from $RCH_2OAlH_3^-$.



Model studies with borneol and 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide[24] suggested that the Helferich method[25] was most suitable for glycosidation of the hindered secondary alcohol of allocyathin B_2. Treatment of (±)-**1** 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 **1**) of an easily separable 1:1 mixture of erinacine A triacetate (**20**) from (+)-**1**,[26] with spectral data identical to those of natural material,[23] and the diastereomer **21** from (−)-**1**.[26] Separate hydrolyses with potassium carbonate in MeOH provided (+)-erinacine A (**2**)[23,27] and diastereomer **22**, the 1-β-D-xyloside of (−)-**1**, in >90% yield.

In conclusion, (±)-allocyathin B_2 (**1**) and erinacine A (**2**), 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 **11a** to construct an appropriately functionalized seven-membered ring and palladium-catalyzed carbonylation of dienyl triflates **7** and **17** as key steps. The entire cyathin carbon skeleton is constructed in only 7 steps and allocyathin B_2 is synthesized in only 17 steps (>5% overall yield) from readily available enone **6**.[7]

Acknowledgment. We are grateful to the National Institutes of Health for generous financial support. We are grateful to Professor William Ayer for a sample of cyathin A_3 and to Professor Hirokazu Kawagishi for copies of the ^1H and ^{13}C NMR spectra of allocyathin B_2, erinacine A, and erinacine A triacetate.

Supporting Information Available: Complete experimental procedures; X-ray structural information, including tables of crystal and intensity collection data, positional and thermal parameters, and interatomic distances and angles (25 pages). See any current masthead page for ordering and Internet access instructions.

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(17) The stereochemistry of the hydroxyl group of **12** 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 **16**. 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 **16** is rigid and that the pseudo equatorial 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 **16**, the pseudo equatorial α′ proton would be vicinally coupled to C*H*OSi with a large coupling constant.

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(21) 2,4-Cycloheptadienone absorbs with $\lambda_{max} = 292$, while the cross-conjugated isomer 2,6-cycloheptadienone absorbs with $\lambda_{max} = 235$.[22] Since a β-triflate has little effect on the UV absorption of 2-cyclohexenones,[20b] the observed value for **17** is consistent with a 2,4-cycloheptadienone.

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(23) A sample of natural cyathin A_3 was oxidized to cyathin B_3 (**14**) in ether.[1e] Treatment of cyathin B_3 with Ac_2O in pyridine gave anhydrocyathin B_3 (**15**)[1d] that was spectroscopically identical to that obtained by Dess−Martin oxidation of synthetic allocyathin B_2. We are grateful to Professor William Ayer for a sample of cyathin A_3 and to Professor Hirokazu Kawagishi for copies of the ^1H and ^{13}C NMR spectra of allocyathin B_2, erinacine A, and erinacine A triacetate.

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(26) All synthetic compounds are racemic except for **2** and **20**−**22**.

(27) The NMR data for a dilute solution of synthetic **2** in $CDCl_3$ are very different than those reported for a more concentrated solution of natural **2** in the same solvent. The spectral differences suggest that the xyloside adopts the C-1 conformation (all substituents axial) in dilute solution and the 1-C conformation (all substituents equatorial) in more concentrated solution. Professor Kawagishi has kindly established that the NMR spectrum of a dilute solution of natural **2** is very different from that of a more concentrated solution and identical to that of synthetic **2**. The NMR spectrum of a dilute solution of synthetic **2** in $CDCl_3$ containing 20% CD_3OD corresponds closely to that reported for the natural product in $CDCl_3$ with the xyloside in the 1-C conformation. It appears that **2** 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. Similar solvent effects on conformation been observed for 3-deoxyxylosides.[28]

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