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Total Synthesis of Cyathin A₃ and Cyathin B₂

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The cyathin diterpenes, isolated from bird's nest fungi by Ayer and co-workers, were known to display a wide range of interesting biological properties.^[1,2] The isolation of many structurally related metabolites such as striatins, scabronines, sarcodonins, erinacines, and cyanthiwigins was reported in recent years. A great majority of these cyathane metabolites possess a unique 5–6–7 tricyclic skeleton with a *trans* 6–7 ring junction, as exemplified by cyathin A₃ (**1**), cyathin B₂ (**2**), erinacine B (**3**), and erinacine E (**4**). Some cyathins were reported to stimulate nerve growth factor synthesis and might thus serve as a useful lead in identifying small molecules having neurotrophic activity with potential application in combating neurodegenerative disorders.^[3] The novel structure and significant bioactivity of these cyathane diterpenoids, coupled with their low natural abundance, spurred synthetic studies, and several elegant syntheses were recently disclosed.^[4–9] We report herein a stereoselective synthesis of cyathin A₃ (**1**) and cyathin B₂ (**2**) by a Prins-type reaction of a cycloalkenyl cyclopropanol and subsequent elaboration of the resulting spirocyclobutanone.

Toward the development of a unified approach to the cyathane diterpenoids, we selected **1** and **2** as our initial targets. The key challenges center around the surprisingly difficult

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diastereocontrol of the *trans* 6–7 ring junction relative to the methyl group at C(9) and the juxtaposition of the remaining functionalities. As outlined retrosynthetically in Scheme 1, we envisioned the construction of a seven-membered core **5** by ring closing metathesis (RCM) of **6** and subsequent elaboration of the resulting product **5**. Substrate **6** could be prepared from spirocyclobutanone **7**, which would be available by a Prins-type reaction of vinylcyclopropanol **8** with a suitable acetal. The use of a spirocyclobutanone as the key quaternary carbon scaffold could present an attractive solution to the requisite diastereocontrol, wherein formation of the two newly formed C–C bonds was anticipated to take place from the opposite side of the angular methyl group.

Our synthesis began with the known dienoate **9** (Scheme 2).^[4b,10] The Kulinkovich cyclopropanation of **9** with EtMgBr, followed by silylation of **10**, delivered **8**.^[11] Treatment of **8** with acetal **11** in the presence of TiCl₄ afforded predominantly (>15:1) two isomers **12β,α** (78%) in a separable 10:3 ratio.^[12] The stereochemistry of the major isomer **12β** was firmly established by a single crystal X-ray analysis. Reductive elimination of both **12β,α** with Zn dust gave cleanly **7** (85%) as the sole product, thus ascertaining the epimeric relationship at C(10) between **12β** and **12α**. It was next necessary to introduce the second alkene moiety from the more hindered face of the cyclobutanone to set the stage for the pivotal RCM reaction.^[13] Toward this end, an aldol reaction of cyclobutanone **7** with benzaldehyde was undertaken to provide **13a**, in 81% yield, essentially as one isomer. The stereochemistry of the aldol product **13a** was assigned on the basis of the Zimmerman-Traxler transition state model. A suitably functionalized allylation reagent was generated from **14**.^[14–16] Subsequent addition of **14** to cyclobutanone **13a** afforded the corresponding adduct **15a** in 76% yield. RCM of **15a** by Grubbs' second-generation catalyst proceeded cleanly to furnish **5a** (81%). Addition of thiophenol^[17] to diene **5a** and subsequent Grob fragmentation of the cyclobutanone ring then provided **16a** in respectable yield.

With the complete tricyclic core **16a**, the remaining tasks entailed cleavage of the styrene moiety and elaboration of the allylic sulfide functionality to complete a total synthesis of **1** and **2** (Scheme 3). Regioselective dihydroxylation of **16a** under Sharpless' asymmetric dihydroxylation conditions^[18] proceeded very slowly to give the corresponding diol (67% brsm). The *p*-methoxystyrene derivative **16b** was thus prepared to avoid cumbersome recycling of recovered **16a**. Osmylation of **16b** was indeed more facile to afford the respective diol in 74% yield. Oxidative cleavage of these diols with lead(IV) acetate, followed by decarbonylation of the resulting aldehyde with the Wilkinson catalyst, delivered **17**. The allylic sulfide functionality of **17** was then elaborated by means of a Pummerer rearrangement of sulfoxide **18**.^[19,20] The latter was next prepared by use of Davis' oxaziridine^[21] as a 1:1 diastereomeric mixture in 96% yield. Exposure of **18** to TFAA produced cyathin B₂ (**2**), along with vinyl sulfides **19** and **20**, in 80–95% combined yield.^[22,23] Most conveniently, the crude mixture (10:3:7) of these products was subjected, without separation, to acetylation and subsequent hydrolysis by Hg(OCOCF₃)₂ to afford **2** in greater than 85% yield.

Cyathin B₂ (**2**) was next converted to cyathin A₃ (**1**) by standard methods (Scheme 4). Chemoselective reduction of **2** by L-Selectride and subsequent epoxidation of the resulting allylic alcohol gave the β-epoxide in >10:1 selectivity. Protection of the primary alcohol, followed by ring opening of the epoxide with DBU, afforded **21** in 61% overall yield. The Mitsunobu inversion of **21** with benzoic acid proceeded cleanly to give **22** in 85% yield. Cyathin A₃ (**1**) was then secured by sequential removal of the two protecting groups and its *bis*-acetate was also prepared for additional characterization.^[1,8,24]

In summary, cyathin A₃ (**1**) and cyathin B₂ (**2**) have been synthesized by utilizing a Prins-type reaction of a vinyl cyclopropanol as the stereocontrolling step and the resulting

spirocyclobutanone in an efficient RCM reaction to stereoselectively construct a suitably functionalized seven-membered ring. Additional studies on erinacines and congeners, as well as enantioselective syntheses of **1–4**, will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. a) Ayer WA, Taube H. Tetrahedron Lett. 1972; 13:1917. b) Ayer WA, Taube H. Can. J. Chem. 1973; 51:3842. c) Ayer WA, Nakashima TT, Ward DE. Can. J. Chem. 1978; 56:2197. d) Allbutt AD, Ayer WA, Brodie HJ, Johri BN, Taube H. Can. J. Microbiol. 1971; 17:1401. [PubMed: 5156938]
2. Ayer WA, Lee SP. Can. J. Chem. 1979; 57:3332.
3. See *inter alia*: Kawagishi H, Shimada A, Shirai R, Okamoto K, Ojima F, Sakamoto H, Ishiguro Y, Furukawa S. Tetrahedron Lett. 1994; 35:1569. Kita T, Takaya Y, Oshima Y, Ohta T, Aizawa K, Hirano T, Inakuma T. Tetrahedron. 1998; 54:11877. Obara Y, Kobayashi H, Ohta T, Ohizumi Y, Nakahata N. Mol. Pharmacol. 2001; 59:1287. [PubMed: 11306714] Obara Y, Hoshino T, Marcotullio MC, Pagiotti R, Nakahata N. Life Sci. 2007; 80:1669. [PubMed: 17337280]
4. *allocyathin B* and *erinacine A*: Snider BB, Vo NH, O'Neil SV, Foxman BM. J. Am. Chem. Soc. 1996; 118:7644. Snider BB, Vo NH, O'Neil SV. J. Org. Chem. 1998; 63:4732. Tori M, Toyoda N, Sono M. J. Org. Chem. 1998; 63:306. Takano M, Umino A, Nakada M. Org. Lett. 2004; 6:4897. [PubMed: 15606094] Trost BM, Dong L, Schroeder GM. J. Am. Chem. Soc. 2005; 127:2844. [PubMed: 15740107] Trost BM, Dong L, Schroeder GM. J. Am. Chem. Soc. 2005; 127:10259. [PubMed: 16028937]
5. *sarcodonin G*: Piers E, Gilbert M, Cook KL. Org. Lett. 2000; 2:1407. [PubMed: 10814459]
6. *scabronine G*: Waters SP, Tian Y, Li Y-M, Danishefsky SJ. J. Am. Chem. Soc. 2005; 127:13514. [PubMed: 16190712] See also: Wilson RM, Danishefsky SJ. Acc. Chem. Res. 2006; 39:539. [PubMed: 16906750]
7. *cyanthiwiggins*: Pfeiffer MWB, Phillips AJ. J. Am. Chem. Soc. 2005; 127:5334. [PubMed: 15826167] Reddy TJ, Bordeau G, Trimble L. Org. Lett. 2006; 8:5585. [PubMed: 17107078] Enquist JA Jr, Stoltz BM. Nature. 2008; 453:1228. [PubMed: 18580947] See also: Miller LC, Ndungu JM, Sarpong R. Angew. Chem. 2009; 121:2434. *Angew. Chem. Int. Ed.* **2009**, *48*, 2398.
8. *allocyathin B*: Ward DE, Gai Y, Qiao Q. Org. Lett. 2000; 2:2125. [PubMed: 10891246] Ward DE, Gai Y, Qiao Q, Shen J. Can. J. Chem. 2004; 82:254. *cyathin A*: Ward DE, Shen J. Org. Lett. 2007; 9:2843. [PubMed: 17580883]
9. *erinacine B*: Watanabe H, Takano M, Umino A, Ito T, Ishikawa H, Nakada M. Org. Lett. 2007; 9:359. [PubMed: 17217304] *erinacine E*: Watanabe H, Nakada M. J. Am. Chem. Soc. 2008; 130:1150. [PubMed: 18181632]
10. Snider BB, Rodini DJ, van Straten J. J. Am. Chem. Soc. 1980; 102:5872. Cf. Paquett LA, Heidelbaugh TM. Synthesis. 1998:495.
11. For reviews, see: Kulinkovich OG, de Meijere A. Chem. Rev. 2000; 100:2789. [PubMed: 11749306] Kulinkovich OG. Russ. Chem. Bull., Int. Ed. 2004; 53:1065.
12. For recent stereochemical studies, see: Lysenko IL, Oh H-S, Cha JK. J. Org. Chem. 2007; 72:7903. [PubMed: 17850161]
13. For recent reviews on RCM, see: Grubbs RH. Handbook of Metathesis. 2003; Vol. Germany John Wiley, Weinheim:1–3.
14. For reviews, see: Sato F, Urabe H, Okamoto S. Chem. Rev. 2000; 100:2835. [PubMed: 11749307] Sato F, Urabe H, Marek I. Titanium and Zirconium in Organic Synthesis. 2002 New York Wiley-VCH:319–354.

15. Cf. Lee J, Cha JK. *Tetrahedron Lett.* 1996; 37:3663.
16. a) Krug RC, Yen TF. *J. Org. Chem.* 1956; 21:1082. b) Bertolini TM, Nguyen QH, Harvey DF. *J. Org. Chem.* 2002; 67:8675. [PubMed: 12444658]
17. Cf. Cristol SJ, Nagpal KL. *J. Org. Chem.* 1961; 26:365. Oswald AA, Griesbaum K, Thaler WA, Hudson BE Jr. *J. Am. Chem. Soc.* 1962; 84:3897. Wender PA, Howbert JJ. *Tetrahedron Lett.* 1982; 23:3983.
18. Cf. McKee BH, Gilheany DG, Sharpless KB. *Org. Synth. Coll. Vol.* 1998; 9:383.
19. For recent reviews, see: Padwa A, Gunn DE Jr, Osterhout MH. *Synthesis.* 1997:1353. Bur SK, Padwa A. *Chem. Rev.* 2004; 104:2401. [PubMed: 15137795]
20. The 2,3-sigmatropic rearrangement of **18** in the presence of a thiophile (e.g., trimethylphosphite) gave a 3:1 mixture of two allylic alcohols in quantitative yield: the α -alcohol exists predominantly as the hemiacetal.
21. Vishwakarma LC, Stringer OD, Davis FA. *Org. Synth. Coll. Vol.* 1993; 8:546.
22. The double bond geometry of the vinyl sulfides was determined by NOE measurements.
23. The configuration of the C(11) alcohol was tentatively assigned by the known preference of cyathin A₃ for the hemiacetal form and also confirmed by X-ray analysis of a related compound.
24. Stereoselective reduction of **22** was achieved by L-Selectride to afford the corresponding β -alcohol at C14, the spectral data of which were in excellent agreement with those of Nakada's.^[9] Interestingly, this stereochemical outcome contrasts with Nakada's procedure under the aegis of the CBS reagent.^[25] Reduction of **2** with an excess of L-Selectride gave small amounts of the corresponding β -diol at C14, along with large amounts of the primary alcohol (without ketone reduction; Cf. Scheme 4). DIBAL reduction of **2** gave a 1:3 mixture of the corresponding β - and α -diol, respectively.
25. The enantiopure β -alcohol obtained from **22** was recently converted by the Nakada group to (–)-**3** and (–)-**4**.^[9] Albeit our alcohol product is racemic, this work can be viewed as a formal synthesis of **3** and **4**.

Scheme 1.
Retrosynthetic analysis.

Scheme 2.
Construction of the tricyclic core.

Scheme 3.
Total synthesis of cyathin B₂ (**2**).

Scheme 4.
Total synthesis of cyathin A₃ (1).