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A General Approach to Cyathin Diterpenes. Total Synthesis of Allocyathin B_3

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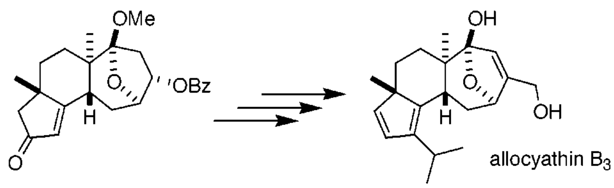
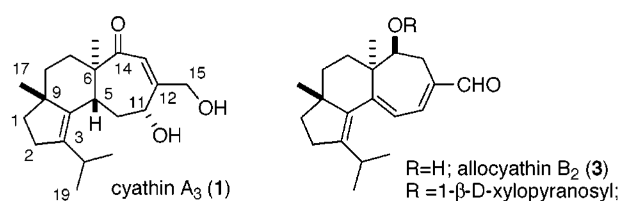
ABSTRACT



The synthesis of allocyathin B_3 from an advanced intermediate possessing the ring system and relative stereochemistry but lacking the isopropyl and hydroxymethyl groups is reported. The isopropyl group was introduced by radical cyclization of a methyl propargyl acetal of an α-bromo ketone, and the hydroxymethyl group was generated by Pd-catalyzed carbonylation of a vinyl triflate. The route provides functionalized intermediates that could allow access to more complex members of the cyathin family of diterpenes.

The cyathins are a unique family of diterpenoids first isolated by Ayer et al. from cultures of bird's nest fungi of the genus *Cyathus*.[1] With the exception of allocyathin B_2 (**3**),[1g] all cyathins possess a trans 6-7 ring fusion as illustrated by cyathin A_3 (**1**) and differ only in the degree of oxidation around the five-membered[2] and seven-membered[3] rings.



cyathin A_3 (**1**)
$\Delta^{1,2}$; allocyathin B_3 (**2**)

R=H; allocyathin B_2 (**3**)
R =1-β-D-xylopyranosyl; erinacine A (**4**)

More recently, several fungal metabolites with structures closely related to those of the cyathins have been reported. For example, the striatins[4] and erinacines[5] are carbohydrate conjugates of cyathins (e.g., **4**), the sarcodonins[6] are cyathins with a C-19 alcohol, and the scabronines[7] are cyathins with a C-17 carboxylic acid. Several cyathins[1a] show strong antibiotic activity, and both the erinacines[5] and scabronines[7] stimulate the synthesis of nerve growth factor. The unique 5-6-7 ring system and biological activities associated with this ever growing family of natural products has attracted the attention of synthetic chemists.[8−10] To date, total

(1) (a) Allbutt, A. D.; Ayer, W. A.; Brodie, H. J.; Johri, B. N.; Taube, H. *Can. J. Microbiol.* **1971**, *17*, 1401. (b) Ayer, W. A.; Taube, H. *Tetrahedron Lett.* **1972**, *19*, 1917. (c) Ayer, W. A.; Taube, H. *Can. J. Chem.* **1973**, *51*, 3842. (d) Ayer, W. A.; Carstens, L. L. *Can. J. Chem.* **1973**, *51*, 3157. (e) Ayer, W. A.; Browne, L. M.; Mercer, J. R.; Taylor, D. R.; Ward, D. E. *Can. J. Chem.* **1978**, *56*, 717. (f) Ayer, W. A.; Yoshida, T.; Van Schie, D. M. J. *Can. J. Chem.* **1978**, *56*, 2113. (g) Ayer, W. A.; Lee, S. P. J. *Can. J. Chem.* **1979**, *57*, 3332.

(2) For example, $\Delta^{1,2}$, 3,4-epoxide, C-1 ketone, C-2 ketone, C-1 β-OH, C-19 OH, C-19 acid.

(3) For example, C-15 aldehyde, C-14 β-OH.

(4) Hecht, H.-J.; Höfle, G.; Steglich, W.; Anke, T.; Oberwinkler, F. *J. Chem. Soc., Chem. Commun.* **1978**, 665.

(5) (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.

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

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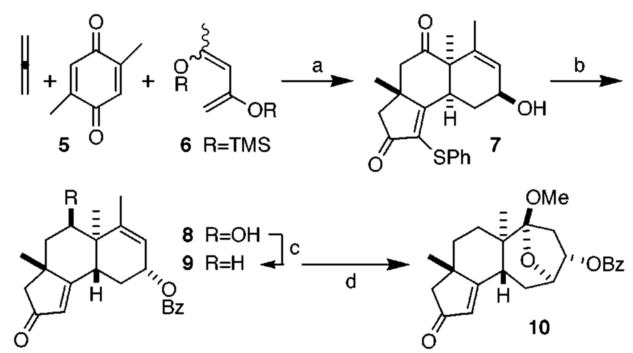
syntheses of both (±)-**3**[9,10] and **4**[9] have been reported; however, modifications of these routes to provide targets with the much more common trans 6-7 ring fusion have not been demonstrated and are far from certain. In this paper we report the first synthesis of a cyathin diterpene with the trans 6-7 ring fusion and fully functionalized seven-membered ring.[11]

Several years ago we reported the synthesis of **10**,[8c] an intermediate possessing the ring system and relative stereochemistry present in cyathin diterpenes (cf. **1**). The preparation of **10** was efficient, proceeding in >10% overall yield from 2,5-dimethylbenzoquinone (**5**) in 17 operations of which only 6 required purification beyond normal workup including only 4 chromatographic separations (Scheme 1).

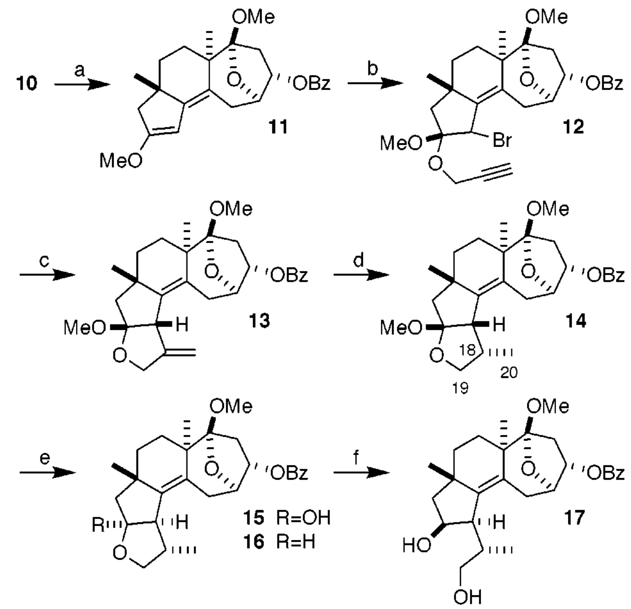
Scheme 1[a]



[a] Reagents: (a) i. **5** + **6**, 140 °C (92%); ii. allene, *hν*; iii. TFA; iv. mCPBA; v. 9-BBN; vi. PhSH, NaOH (50% from **5**). (b) i. PhCOOH, DEAD, Ph_3P; ii. $NaBH_4$, CH_2Cl_2, MeOH, −78 °C; iii. NaOH, MeOH; iv. RaNi; v. NaOH, MeOH, reflux; vi. BzCl, Et_3N, DMAP (60% from **7**). (c) i. MsCl, pyridine, 50 °C, then DBU, toluene reflux (75%); ii. H_2, $RhCl(Ph_3P)_3$ (90%). (d) i. O_3, Sudan III, then Me_2S; ii. TsOH, toluene; iii. MeI, Ag_2O (50% from **9**).

For conversion of **10** into a cyathin diterpene (cf. **1**), a number of methods can be envisaged to generate the required vinyl hydroxymethyl group at C-12 (cyathin numbering); however, strategies to introduce the isopropyl group at C-3 were less obvious. After considerable experimentation, a method was established to introduce a 3-carbon side chain based on radical cyclization (Scheme 2). Treatment of **10**

Scheme 2[a]



[a] Reagents: (a) MeOH, HCl, $(MeO)_3CH$, toluene, reflux. (b) NBS, propargyl alcohol, CH_2Cl_2, −78 °C. (c) Ph_3SnH, AIBN, C_6H_6, reflux (60% from **10**). (d) H_2, Pd−C, EtOAc (90%). (e) 10% HCl, THF (85%). (f) $NaBH_4$, EtOH (85%).

with trimethyl orthoformate and methanolic HCl in toluene followed by azeotropic distillation of MeOH produced the dienol ether **11**. Cohalogenation[12] of **11** with *N*-bromosuccinimide (NBS) and propargyl alcohol gave the somewhat unstable **12** as a single diastereomer (^{1}H NMR) which cyclized[13] to **13** (60% overall yield from **10**) on treatment with Ph_3SnH and AIBN in refluxing benzene.[14,15]

Unmasking the isopropyl group present in **13** proved to be difficult. Treatment with protic or Lewis acids led to loss of MeOH and formation of the corresponding furan derivative.[16] Hydrogenation of **13** gave **14**[17] which on exposure to 10% aqueous HCl slowly (ca. 14 h) produced the isomerized hemiacetal **15**[18] without evidence of an intermediate (by TLC). Although various attempts to trap the hydroxy ketone tautomer of **15** by formation of acyl, xanthate, or dithioacetal

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(10) Tori, M.; Toyoda, N. Sono, M. *J. Org. Chem.* **1998**, *63*, 306.

(11) After this paper was submitted, the synthesis of (±)-sarcodonin G, which has a trans 6-7 ring fusion and a C-19 hydroxyl group, was reported. Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407.

(12) Rodriguez, J.; Dulcere, J.-P. *Synthesis* **1993**, 1177.

(13) Giese, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. L.; Trach, F. *Org. React.* **1996**, *48*, 301.

(14) The relative configuration of **13** was assigned on the basis of a positive NOE for HC-3 and H_3C-9 on irradiation of the C-2 methoxy group.

(15) Several examples of this route to 3-methylenetetrahydrofurans can be found in ref 13. For early examples, see: (a) Okabe, M.; Abe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 1775. (b) Moriya, O.; Okawara, M.; Ueno, Y. *Chem. Lett.* **1984**, 1437.

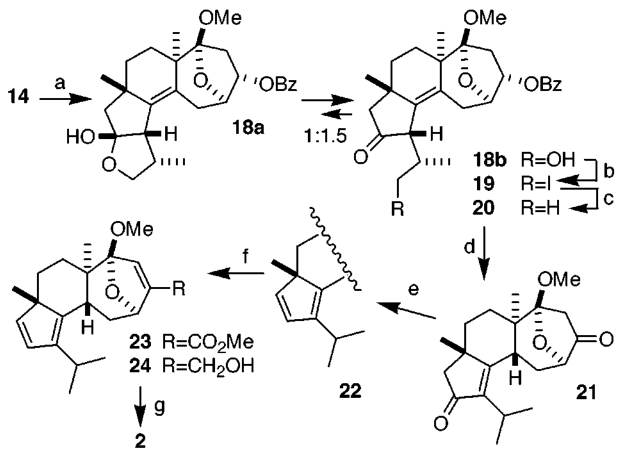
(16) Sirkrishna, A.; Pullaiah, K. C. *Tetrahedron Lett.* **1987**, *28*, 5203.

(17) The relative configuration of **14** was assigned on the basis of the $^3J_{HH}$ coupling constants between H_2C-19 and HC-18 (4, <1 Hz), which are consistent with the dihedral angles (44°, −81°) determined for **14** by molecular mechanics (CaChe, version 3.9), and on the apparent shielding of the C-20 methyl group (*δ* 0.83) by the alkene. This relative configuration at C-18 (cyathin numbering) is the same as that in the sarcodonins A and G (refs 6 and 11) and possibly the cyathins A_4 and C_5 (ref 1e).

(18) The relative configuration of **15** was assigned on the basis of the large changes in the $^3J_{HH}$ coupling constants between H_2C-19 and HC-18 (8, 10.5 Hz) and chemical shift of the C-20 methyl group (*δ* 1.32) compared to those of **14** (and **18a**). These coupling constants are consistent with the dihedral angles (−36°, −161°) for **15** determined by molecular mechanics (CaChe, version 3.9) which also indicated that **15** was 1.3 kcal/mol more stable than **18a**.

derivatives failed, the diol **17** was readily prepared by reaction of **15** with $NaBH_4$. Unfortunately, all efforts to deoxygenate one or both the alcohol groups in **17** were unsuccessful, and several attempts at derivatization led to the tetrahydrofuran **16**.[19] The serendipitous observation that under very mild conditions hydrolysis of **14** would occur without isomerization was crucial for our solution of this problem (Scheme 3).

Scheme 3[a]



[a] Reagents: (a) PPTS, acetone, H_2O, rt, 12 d (75%; quantitative based on conversion). (b) i. Ph_2PCl, pyridine, toluene. ii. I_2. (c) H_2, Pd−C (65% from **18**. (d) i. NaOH, MeOH, reflux; ii. NMO, TPAP (85%). (e) i. Tf_2O, 2,6-di *tert*-butyl-4-methylpyridine; ii. Bu_3SnH, LiCl, $Pd(Ph_3P)_4$, THF (50%). (f) i. $NaN(TMS)_2$, THF, −78 °C; ii. $PhNTf_2$; iii. CO, DIEA, $Pd(Ph_3P)_4$, THF (50%); iv. DIBAL-H (50%). (g) 1 N $HClO_4$, THF (80%; see ref 1e).

Reaction of **14** with pyridinium 4-methylbenzenesulfonate (PPTS) in aqueous acetone for 12 days gave **18** (75%) along with recovered **14** (25%) (Scheme 3). In contrast to **15**, ^{1}H and ^{13}C NMR (in $CDCl_3$) of **18** indicated a 1.5:1 mixture of the hydroxy ketone (**18b**) and hemiacetal (**18a**) tautomers, respectively. Importantly, esters of the hydroxy ketone tautomer **18b** could be prepared in good yield. Intermediate **18** has functionality that potentially can provide access to any of the various oxidation patterns present on the A (i.e., five-membered) ring of cyathin and related diterpenes.[2] For many of the possible synthetic targets, deoxygenation of the C-19 alcohol group is required; this was readily accomplished by reaction of **18** with Ph_2PCl followed by I_2 and reduction of the resulting iodide[20] **19** with H_2 over Pd−C to give **20** (65% overall from **18**).

Treatment of **20** with NaOH in MeOH served to hydrolyze the benzoate ester with concomitant isomerization of the C-4,5 double bond into conjugation with the ketone, thereby reestablishing the desired trans 6-7 ring fusion.[21] To avoid unnecessary protection/deprotection schemes, the resulting alcohol was directly oxidized to ketone **21** with NMO/TPAP[22] (85% from **20**). Selective deoxygenation of the cyclopentenone carbonyl was achieved by reaction of **21** with triflic anhydride (Tf_2O) in the presence of the hindered base 2,6-di-*tert*-butyl-4-methylpyridine[23] to give the dienol triflate which was reduced to cyclopentadiene **22** by Pd-catalyzed reaction with Bu_3SnH (50% from **21**).[24,25] Finally, introduction of the vinyl hydroxymethyl group was achieved by Pd-catalyzed carbonylation[26] of the vinyl triflate derived from **22** followed by DIBAL-H reduction of the resulting **23** to give (±)−**24** (50% from **22**). Spectral data (^{1}H and ^{13}C NMR, UV, MS) for (±)−**24** closely matched that previously reported[1c,27] for (−)−**24**. Hydrolysis of **24** to allocyathin B_3 (**2**; a mixture of hydroxy ketone and hemiacetal tautomers) proceeds readily in THF solution on exposure to aqueous $HClO_4$.[1e]

In conclusion, the synthesis of allocyathin B_3 (**2**) was achieved by introduction of the required isopropyl and vinyl hydroxymethyl groups onto an advanced intermediate (**10**) already possessing the correct ring system and relative stereochemistry. This is the first synthesis of a cyathin diterpene incorporating the trans 6-7 ring fusion and a fully functionalized seven-membered ring. Although introduction of the isopropyl group proved difficult (i.e. **10** → **21**; 8 steps, 35% yield), the reported solution provides intermediates with potentially useful functionality. Indeed, simple modifications of the route reported herein can be contemplated that might lead to *any* of the known cyathin diterpenes and several related natural products.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council of Canada and the University of Saskatchewan is gratefully acknowledged. We thank Prof. W. A. Ayer for samples of cyathins and for his continuing interest in this work.

Supporting Information Available: Spectroscopic data for **11**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Classon, B.; Liu, Z. *J. Org. Chem.* **1988**, *53*, 6126.

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(23) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

(24) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(25) For a review on the preparation and reactions of enol triflates, see: Ritter, K. *Synthesis* **1993**, 735.

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

(27) Ayer, W. A.; Nakashima, T. T.; Ward, D. E. J. *Can. J. Chem.* **1978**, *56*, 2197.