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Enantioselective Total Synthesis of Cyathin A_3†

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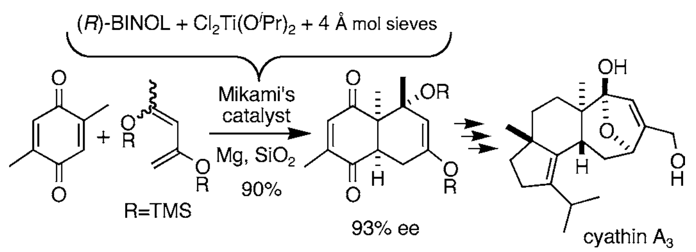
ABSTRACT



The total synthesis of (−)-cyathin A_3 is described. The key step involves an unusual enantioselective Diels−Alder reaction of 2,5-dimethyl-1,4-benzoquinone with 2,4-bis(trimethylsilyloxy)-1,3-pentadiene, using Mikami's catalyst [(*R*)-BINOL + $Cl_2Ti(O^iPr)_2$ + 4 Å mol sieves] modified by addition of Mg and SiO_2. Because cyathin A_3 is easily transformed into allocyathin B_3, cyathin B_3, cyathin C_3, and neoallocyathin A_4, this route also constitutes formal syntheses of these natural products.

The cyathanes are a family of diterpenoids whose members possess a (3a*R*,5a*R*)-3a,5a,8-trimethyl-1-(1-methylethyl)cyclohept[*e*]indene (**1**; cyathane) carbon skeleton.[1] They are isolated from various mushrooms and related basidiomycetes and include the cyathins (e.g., **2**−**6**) (from *Cyathus helenae*), the erinacines (e.g., **8**, **9**) (from *Hericium erinaceum*), the sarcodonins (e.g., **10**), and the scabronines (e.g., **11**) (from *Sarcodon scabrosus*), among others (Figure 1).[1,2] Diverse biological activities have been noted among the cyathanes. In particular, the discovery that certain members can stimulate the production of nerve growth factor (NGF) has generated substantial interest in the synthesis of these compounds.[1,3] Several total syntheses have been reported to date;[4−7] however, the majority of these concern allocyathin

† Dedicated to the memory of William A. Ayer (1932−2005).

(1) Review: Wright, D. L.; Whitehead, C. R. *Org. Prep. Proced. Int.* **2000**, *32*, 307, 309−330.

(2) Recent examples: (a) Marcotullio, M. C.; Pagiott, R.; Maltese, F.; Obara, Y.; Hoshino, T.; Nakahata, N.; Curini, M. *Planta Med.* **2006**, *72*, 819−823. (b) Kawagishi, H.; Masui, A.; Tokuyama, S.; Nakamura, T. *Tetrahedron* **2006**, *62*, 8463−8466. (c) Ma, B.-J.; Liu, J.-K. *J. Basic Microbiol.* **2005**, *45*, 328−330. (d) Curini, M.; Maltese, F.; Marcotullio, M. C.; Menghini, L.; Pagiotti, R.; Rosati, O.; Altinier, G.; Tubaro, A. *Planta Med.* **2005**, *71*, 488. (e) Ma, B.-J.; Zhu, H.-J.; Liu, J.-K. *Helv. Chim. Acta* **2004**, *87*, 2877−2881. (f) Kenmoku, H.; Tanaka, K.; Okada, K.; Kato, N.; Sassa, T. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 1786−1789. (g) Kamo, T.; Imura, Y.; Hagio, T.; Makabe, H.; Shibata, H.; Hirota, M. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 1362−1365.

(3) (a) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569−1572. (b) Kawagishi, H.; Shimada, A.; Hosokawa, S.; Mori, H.; Sakamoto, H.; Ishiguro, Y.; Sakemi, S.; Bordner, J.; Kojima, N.; Furukawa, S. *Tetrahedron Lett.* **1996**, *37*, 7399−7402. (c) Obara, Y.; Nakahata, N.; Kita, T.; Takaya, Y.; Kobayashi, H.; Hosoi, S.; Kiuchi, F.; Ohta, T.; Oshima, Y.; Ohizumi, Y. *Eur. J. Pharmacol.* **1999**, *370*, 79−84. (d) Obara, Y.; Kobayashi, H.; Ohta, T.; Ohizumi, Y.; Nakahata, N. *Mol. Pharmacol.* **2001**, *59*, 1287−1297. Also see ref 2a.

(4) Total syntheses of (±)-**7**: (a) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644−7645. (b) Snider, B. B.; Vo, N. H.; O'Neil, S. V. *J. Org. Chem.* **1998**, *63*, 4732−4740. (c) Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306−313. Total syntheses of (+)-**7**: (d) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 2844−2845. (e) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 10259−10268. (f) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897−4900. For the conversion of (±)-**7** into (+)-**8**, see refs 4a and 4b.

(5) Total synthesis of (±)-**3**: (a) Ward, D. E.; Gai, Y.; Qiao, Q. *Org. Lett.* **2000**, *2*, 2125−2127. (b) Ward, D. E.; Gai, Y.; Qiao, Q.; Shen, J. *Can. J. Chem.* **2004**, *82*, 254−267.

(6) Total synthesis of (−)-**9** via a protected cyathatriol intermediate: Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2007**, *9*, 359−362.

(7) Total synthesis of (±)-**10**: Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407−1410. Total synthesis of (−)-**11**: Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514−13515.

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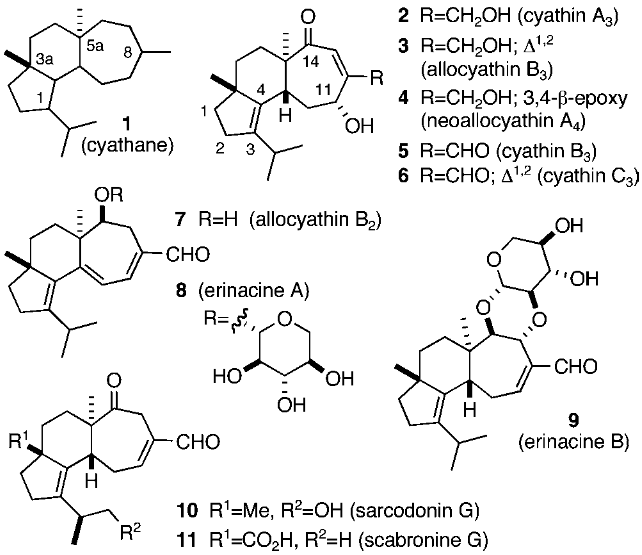
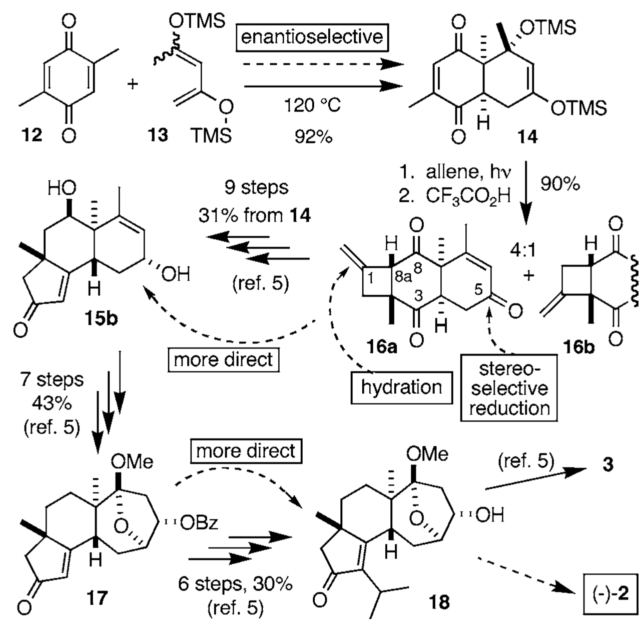


Figure 1. Selected cyathane diterpenes.

Scheme 1. Goals for a Second-Generation Synthesis (dashed arrow)



B$_2$ (**7**),[4] a nonprototypical cyathane.[8] Cyathin A$_3$ (**2**) is a synthetic precursor to several cyathanes including **3**−**9**[4b,6,9] and cyathatriol (the 14-β-alcohol derivative of **2**)[9b] has been proposed[10] as a (bio)synthetic precursor of the erinacines.[6] In this paper, we report the enantioselective synthesis of cyathin A$_3$ (**2**)[11] via a second-generation route based on our earlier synthesis[5] of (±)-**3** (Scheme 1).

The main objectives for our second-generation synthetic route are outlined in Scheme 1. Developing an enantioselective version of the key Diels−Alder (DA) reaction of **12** with **13** was a significant challenge. To the best of our knowledge, enantioselective DA reactions of Danishefsky-type dienes (e.g., **13**) are unknown,[12] presumably due to their sensitivity to Lewis acids.[13] Similarly, enantioselective DA reactions of quinone dienophiles was an unsolved problem that only recently has been addressed successfully.[14−16] Despite these advances, no examples using quinone **12** with unsymmetrical dienes have been reported. Indeed, reactions of **12** gave poor regioselectivities with use of the otherwise very effective cationic oxazaborolidine-type catalysts developed by Corey et al.[16,17]

In a preliminary study, we screened a variety of catalysts for efficacy in the enantioselective DA reaction of **12** with **13** (Table 1). Diene **13** was not stable to **19** and no DA adducts were obtained under conditions validated by using 1,3-cyclohexadiene (entry 1).[16a] Low yields of **14** with modest ee values were obtained with **20**[18] using Rawal's procedure;[12b] however, the diene **13** did not survive the conditions (entries 2 and 3). An excellent yield was obtained by using the catalyst prepared from BINOL and AlMe$_3$ (1:1) but with moderate enantioselectivity (entry 4).[19]

Although **14** was obtained with good ee by using Mikami's catalyst (**21**),[15e,20] yields were poor because of diene decomposition (Table 1, entries 5−8).[21] Diene **13** was stable to

(8) The vast majority of cyathanes have a trans 6,7-ring fusion.

(9) (a) Ayer, W. A.; Browne, L. M.; Mercer, J. R.; Taylor, D. R.; Ward, D. E. *Can. J. Chem.* **1978**, *56*, 717−721. (b) Ayer, W. A.; Lee, S. P. *Can. J. Chem*. **1979**, *57*, 3332−3337.

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(12) Enantioselectvive hetero-DA reactions of these dienes are well-known; for example, see: (a) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558−3588. For enantioselective DA reactions of 1-amino-3-silyloxy dienes, see inter alia: (b) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843−7844. (c) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846−5850.

(13) Inokuchi, T.; Okano, M.; Miyamoto, T. *J. Org. Chem.* **2001**, *66*, 8059−8063.

(14) (a) Engler, T. A.; Letavic, M. A.; Lynch, K. O., Jr.; Takusagawa, F. *J. Org. Chem.* **1994**, *59*, 1179−1183. (b) White, J. D.; Choi, Y. *Helv. Chim. Acta* **2002**, *85*, 4306−4327. (c) Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359−5371. (d) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162−10163. (e) Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6043−6046. (f) Boezio, A. A.; Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6046−6050.

(15) Quinone monoketals: (a) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559−1562. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993. Naphthoquinones: (c) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510−3512. (d) Maruoka, K.; Sakurai, M.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4895−4898. (e) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820. (f) Brimble, M. A.; McEwan, J. F. *Tetrahedron*: *Asymmetry* **1997**, *8*, 4069−4078.

(16) (a) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390. (b) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800−4802. (c) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708−13713. (d) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498−1499.

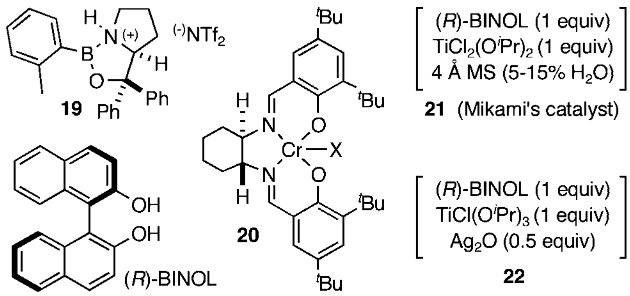
(17) This problem was solved by using 3-iodo-2,5-dimethylbenzoquinone (ref 16a).; however, the regioselectiviy obtained with unsymmetrical dienes is opposite to our requirements

(18) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898.

(19) Ward, D. E.; Souweha, M. S. *Org. Lett.* **2005**, *7*, 3533−3536.

(20) The structure of Mikami's catalyst is unknown. For a review of Ti(IV)-based enantioselective catalysts, see: Ramon, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126−2208.

Table 1. Enantioselective Diels−Alder Reactions of **12** with **13** under Various Conditions



entry	catalyst (equiv)[a]	conditions[b]	% yield of **14** (% ee)[c]
1	**19** (0.2)	−78 °C (ref 16a)	NR[d]
2	**20** (0.1; X = Cl)	−40 to 0 °C (ref 12b)	40 (−33)[d]
3	**20** (0.1; X = SbF_6)	−40 to 0 °C (ref 12b)	20 (−60)[d]
4	(*S*)-BINOL/$AlMe_3$ (1:1; 1.2 equiv)[e]	Tol, rt, 24 h (ref)	90 (−50)
5	**21** (0.2)	Tol, rt, 48 h (ref 14b)	NR[d]
6	**21** (0.05)	rt, 48 h (ref 15a)	25 (67)[d]
7	**21** (0.1)	rt, 48 h (ref 15a)	42 (86)[d]
8	**21** (0.2)	rt, 48 h (ref 15a)	20 (86)[d]
9	**22** (0.1)	rt, 72 h (ref 22)	87 (70)
10	**21** (0.05)	+Mg; rt, 48 h	65 (83)
11	**21** (0.05)	+SiO_2; rt, 48 h	72 (75)
12	**21** (0.05)	+Mg + SiO_2; rt, 48 h	93 (90)
13	**21** (0.05)[e,f]	+Mg + SiO_2; rt, 24 h	93 (95)
14	**21** (0.05)[e−g]	+Mg + SiO_2; rt, 24 h	90[h] (93)

[a] On the basis of Ti(IV) for **21** and **22**. [b] Reactions were in CH_2Cl_2 (except entries 4−5) with ca. 25 mg of **12** (0.2 M) and 5 equiv of **13** (a 1:1 mixture of isomers). [c] Isolated yield and ee based on the enone resulting from acid hydrolysis of **14**; see the Supporting Information for details. [d] **13** decomposes under the reaction conditions. [e] 10 equiv of **13**. [f] Neat. [g] 1.0 g of **12**. [h] Isolated yield of **14**.

22[22] and a much improved yield of **14** was obtained by using this catalyst, albeit with moderate ee (entry 9). With this lead, we tested a variety of additives to increase the stability of **13** to **21**. Excellent results were obtained with Mg powder and silica gel (entries 10−14) providing the DA adduct **14** in 90% yield and >90% ee under optimized conditions (1−5 g scale).[23]

It is noteworthy that adduct **14** results from addition of (*E*)-**13** to the *si* face[24] of **12** and is favored with the Mikami catalyst prepared from (*R*)-BINOL.[20] In all previous examples of **21**-catalyzed DA reactions of quinone-type dienophiles,[14b,c,15a,e] preferential *si* face attack was observed with (*S*)-BINOL-derived catalyst. Although alternative models have been proposed[14b,c] to rationalize the observed enantioselectivity, we believe that the TS model **24** can accommodate all the reported examples (i.e., formation of adducts **23**) (Figure 2). This model is fully consistent[25] with Corey's

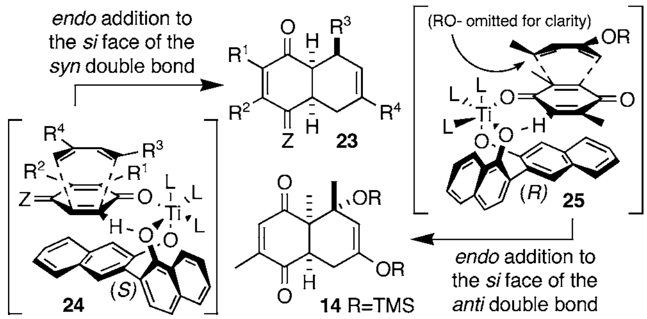
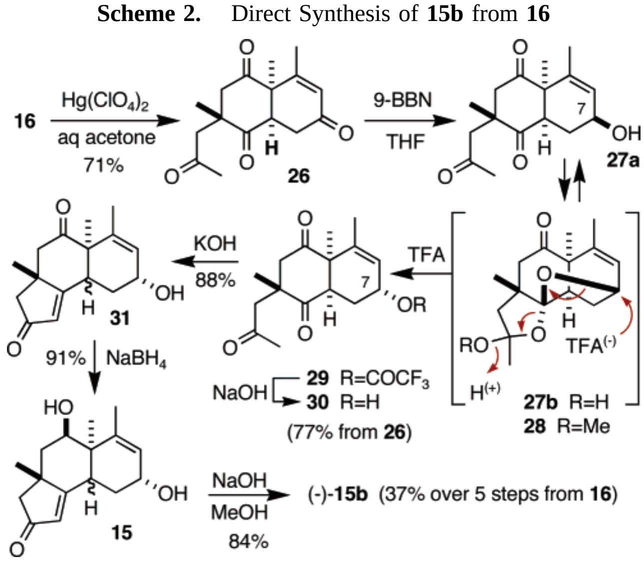


Figure 2. Models to rationalize observed enantioselectivity in quinone DA reactions with use of Mikami's catalyst (R^1 = H, alkyl, OMe; $R^{2,3}$ = H, alkyl; R^4 = H, alkyl, OTBS; Z = O, $-O(CH_2)_2O-$).

prediction rules,[16b] including preferential activation of the *syn* alkene via H-bonding.[16] In contrast, DA reaction of the *syn* alkene in quinone **12** (cf. **25**) is strongly attenuated by the β-methyl substituent resulting in addition to the *anti* alkene, and preferential *si* face attack now requires the (*R*)-BINOL-derived catalyst.[26]

Enantioenriched **14** was converted to a 4:1 mixture of **16a** and **16b**, respectively, by established procedures (Scheme 1).[5] Tetraone **26** ($[\alpha]_D$ −3.7; *c* 1.3, CH_2Cl_2) was obtained by reaction of the **16a/16b** mixture with $Hg(ClO_4)_2$ in aqueous acetone (Scheme 2). Chemoselective reduction of the enone carbonyl in **26** was achieved with 9-BBN to give the expected β-alcohol that was a 1:1.5 mixture of **27a** and **27b** (3:1 mixture of anomers), respectively, in $CDCl_3$

Scheme 2. Direct Synthesis of **15b** from **16**



(21) Control experiments showed that the reaction was strongly inhibited by the presence of 2,4-pentandione or the corresponding TMS enol ether (i.e., putative byproducts from decomposition of **13**).

(22) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem. Eur. J.* **2003**, *9*, 4405−4413. A mono-μ-oxo Ti-O-Ti catalyst structure is proposed: [BINOLateTi(O^{i}Pr)]$_2$O.

(23) The precise role of the additives is unknown. Mg powder was added to remove HCl. SiO_2 may preferentially absorb diene decomposition products (ref 21) or improve catalyst performance by immobilization; for example, see: Coperet, C.; Chabanas, M.; Saint-Arroman, R. P.; Basset, J.-M. *Angew. Chem., Int. Ed.* **2003**, *42*, 156−181.

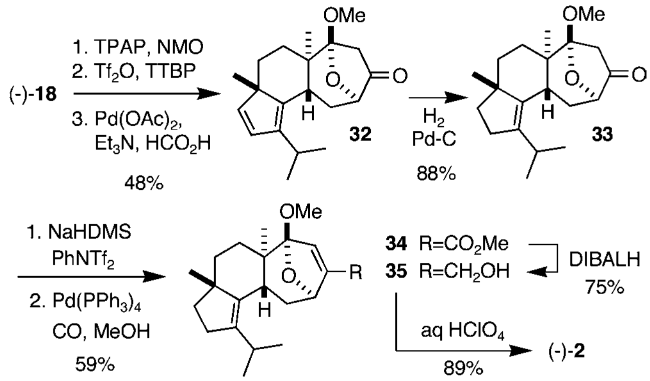
(24) The face designation is according to the carbon adjacent to the activated carbonyl.

solution. Interestingly, merely quenching the 9-BBN reduction with methanol gave **28** (single anomer) in excellent yield. Both **27** and **28** were very sensitive to acid, presumably a result of the almost perfect alignment of the allylic C−O bond with the π-bond. After much experimentation we found that brief exposure of **28** to TFA gave the trifluoroacetate **29** where the configuration at C-7 was inverted compared to that in **27**. Addition of aqueous NaOH to **29** gave the corresponding alcohol **30**. Thus, simply by altering the workup procedure (i.e., (i) MeOH, (ii) TFA, (iii) NaOH) for the β-selective reduction of **26** with 9-BBN, the α-alcohol **30** could be obtained in good yield. Treatment of **30** with KOH in refluxing MeOH gave **31** that was selectively reduced[27] to give **15**, both as ca. 1:1 mixtures of diastereomers. The diastereomers **15** were interconverted by NaOH in refluxing MeOH where the equilibrium was strongly in favor (>30:1)[5] of **15b** ($[\alpha]_D$ −110; *c* 0.9, CH_2Cl_2).

The key 5-6-7 tricyclic intermediate **17** ($[\alpha]_D$ −120; *c* 1.0, CH_2Cl_2) was obtained from (−)-**15b** as described for the racemic series (Scheme 1).[5] Introduction of the required isopropyl group to **17** is challenging. Previously, an efficacious though moderately efficient route (30% over 6 steps) based on radical cyclization of a propargyl α-bromoacetal was developed.[5] Unfortunately, our plans to explore cross-coupling approaches for a more direct introduction of the isopropyl group have been thwarted by our inability to obtain a suitable α-halo enone precursor.[28] Consequently, **17** was converted to **18** ($[\alpha]_D$ −48; *c* 2.9, CH_2Cl_2) by the former route (6 steps, 30%).[5]

Oxidation[29] of **18** followed by selective enol triflation of the cyclopentenone- and Pd-catalyzed reduction[30a] of the resulting triflate gave the diene **32** ($[\alpha]_D$ −70; *c* 0.9, CH_2Cl_2) (Scheme 3). Selective hydrogenation of the less substituted olefin in **32** was easily effected over Pd−C to obtain **33** ($[\alpha]_D$ −58; *c* 1.7, CH_2Cl_2). Finally, introduction of the vinyl hydroxymethyl group was achieved by Pd-catalyzed carbonylation[30b] of the enol triflate derived from **33** followed by DIBALH reduction of the resulting methyl ester **34** to give (−)-**35**. Spectral data (^{1}H and ^{13}C NMR, IR, MS) for (−)-**35** ($[\alpha]_D$ −150; *c* 0.8, MeOH) were essentially identical with those reported[11b] ($[\alpha]_D$ −154; *c* 0.24, MeOH). Synthetic cyathin A_3 (**2**; a mixture of hydroxy ketone and hemiacetal tautomers) ($[\alpha]_D$ −160; *c* 0.5, MeOH; lit.[11b] $[\alpha]_D$ −155; *c* 0.26, MeOH) was obtained from **35** on exposure to aqueous $HClO_4$ in THF solution.

Scheme 3. Synthesis of Cyathin A_3 (**2**)



In summary, an enantioselective total synthesis of cyathin A_3 (**2**) has been achieved in 28 steps (0.65% overall yield) starting with the DA reaction of **12** with **13** by using Mikami's catalyst (**21**) modifed by addition of Mg powder and silica gel. To the best of our knowledge, this is the first example of an enantioselective DA reaction both of quinone **12** and of a Danishefsky-type diene (e.g., **13**). The conversion of **26** to **30** via reduction with inversion of configuration on workup is noteworthy. Because cyathin A_3 (**2**) is easily transformed into allocyathin B_3 (**3**), neoallocyathin A_4 (**4**), cyathin B_3 (**5**), cyathin C_3 (**6**), and allocyathin B_2 (**7**),[9,31] this route also constitutes a formal synthesis of these natural products. Similarly, several erinacines (e.g., **8** and **9**) can be prepared from a protected derivative of **2** by Nakada's elegant route.[6,10]

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available: Determination of the ee and absolute configuration of **14**; experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all new compounds (**26**−**35**); and experimental procedures and ^{1}H spectra for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) However, activation of the less basic carbonyl predominates where R[1] is OMe (e.g., ref 14c), presumably because coordination of **21** to the more basic carbonyl is not sufficiently activating. Because the presence of the potentially coordinating OMe group does not alter the sense of enantioselectivity, activation without chelation is implied. For related examples with other catalysts, see refs 14a,e,f.

(26) In **19**-catalyzed DA reactions of **12** with unsymmetrical dienes, poor regioselelctivity results from selective addition to both the *syn* and *anti* alkenes giving regioisomeric adducts each with high ee (ref 16a).

(27) Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206−1211.

(28) For a review on synthesis of α-substituted α,β-enones, see: Rezgui, F.; Amri, H.; El Gaied, M. M. *Tetrahedron* **2003**, *59*, 1369−1380.

(29) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(30) (a) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541−5544. (b) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109−1112.

(31) Cyathins **3** and **6** are available more directly from (−)-**18** (ref 5).