

# Asymmetric Synthesis of the Tricyclic Core of NGF-Inducing Cyathane Diterpenes via a Transition-Metal-Catalyzed [5 + 2] Cycloaddition

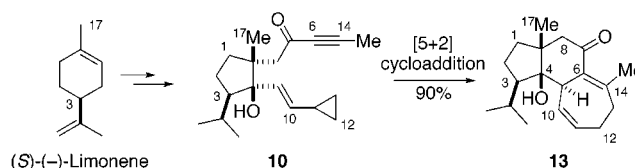
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## ABSTRACT



A concise asymmetric synthesis of the tricyclic core of cyathane diterpenes is described, based on a novel transition-metal-catalyzed intramolecular [5 + 2] cycloaddition of ynone-vinylcyclopropane 10 (assembled from commercially available (S)-(-)-limonene), which proceeds in 90% yield with >95% selectivity. This strategy provides efficient access (14 steps and 13% overall yield) to potential analogues as well as precursors of nerve growth factor (NGF)-inducing diterpenes.

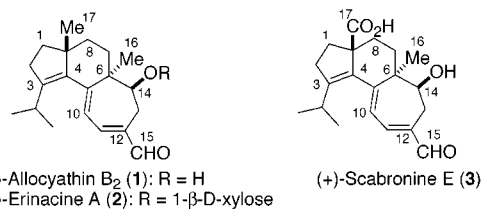
A continuing effort in our laboratory is directed at investigating the use of transition metal catalysts to achieve  $[m + n]$  cycloadditions, particularly those that in the absence of catalyst are theoretically impossible or require harsh conditions. Toward this end, we have reported the first examples of metal-catalyzed [4 + 4] cycloadditions of bisdienes and intramolecular [4 + 2] cycloadditions of dienes and  $\pi$ -systems.<sup>1</sup> More recently, we have described two new reactions: [5 + 2] cycloadditions of vinylcyclopropanes and

$\pi$ -systems and intramolecular [6 + 2] cycloadditions of vinylcyclobutanones and  $\pi$ -systems.<sup>2,3</sup> As part of our interest in further developing the scope and utility of the transition-metal-catalyzed [5 + 2] cycloaddition in complex molecule total synthesis, we have successfully incorporated this new strategy-level reaction into the asymmetric synthesis of the carbocyclic core of cyathane diterpene natural products as described herein.

Cyathane diterpenes exhibiting antibiotic activity were first isolated from fungal sources by Ayer and co-workers in the early 1970s.<sup>4</sup> More recently, Kawagishi et al. and scientists at Pfizer reported the isolation of erinacines A–G from the mycelia of *Hericium erinaceum*.<sup>5</sup> Structurally related scabronines A–F were isolated later by Ohta et al. from the mushroom *Sarcodon scabrosus*.<sup>6</sup> Erinacines and scabronines have attracted medicinal interest because of their ability to stimulate the production of nerve growth factor (NGF). NGF

(1) For [4 + 4] cycloadditions, see: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678–4679. Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904–5906. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089–1094. For more recent studies, see: Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrinho, A.; Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908–4909. Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251–6282. Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, *SI*, 951–953. For [4 + 2] cycloadditions, see: Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432–6434. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843–1844. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824–825. Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255–1275. For more recent studies, see: Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965–4966. McKinsty, L.;

Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145–6154. O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443–445. Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075–2078. Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077–10080.



**Figure 1.** Representative cyathane diterpenes.

is a neurotrophin protein dimer that is essential for the development and maintenance of neuronal cells.<sup>7</sup> Delivery of NGF to the brain represents a potential approach for the treatment of neurodegeneration in Alzheimer, Parkinson, and Huntington diseases; however, it requires invasive surgical techniques because NGF does not cross the blood-brain barrier and is rapidly metabolized in vivo.<sup>8</sup> As an alternative, the use of small-molecule NGF promoters is currently perceived as a promising way to treat these neurodegenerative diseases.<sup>9</sup>

(2) For intramolecular [5 + 2] cycloadditions with alkynes, see: (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720–4721. For more recent reports, see: (b) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442–10443. Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089–2092. For intermolecular [5 + 2] cycloadditions with alkynes, see: (c) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976–10977. Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Scanio, M. J. C. *Org. Lett.* **2000**, *2*, 1609–1611. Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Am. Chem. Soc.* **2001**, *123*, 179–180. For intramolecular [5 + 2] cycloadditions with alkenes, see: (d) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940–1941. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203–7220. For intramolecular [5 + 2] cycloadditions with allenes, see: (e) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348–5349. Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137–139. Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323–2326. For more recent studies using other catalysts, see: (f) Wender, P. A.; Sperandio, D. A. *J. Org. Chem.* **1998**, *63*, 4164–4165. (g) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379–2380.

(3) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815–7816.

(4) (a) Ayer, W. A.; Taube, H. *Tetrahedron Lett.* **1972**, 1917–1920. (b) Ayer, W. A.; Taube, H. *Can. J. Chem.* **1973**, *51*, 3842–3854. (c) Brodie, H. J. *Can. J. Bot.* **1966**, *44*, 1235–1237. (d) Allbutt, A. D.; Ayer, W. A.; Brodie, H. J.; Johri, B. N.; Taube, H. *Can. J. Microbiol.* **1971**, *17*, 1401–1407.

(5) For the isolation of erinacines A–C, see: Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569–1572. For Erinacine D, see: Kawagishi, H.; Shimada, A.; Shizuki, K.; Mori, H.; Okamoto, K.; Sakamoto, H.; Furukawa, S. *Heterocycl. Commun.* **1996**, *2*, 51–54. For erinacines E–G, see: Kawagishi, H.; Shimada, A.; Satoshi, H.; Hironobu, M.; Sakamoto, H.; Ishiguro, Y.; Sakemi, S.; Bordner, J.; Kojim, N.; Furukawa, S. *Tetrahedron Lett.* **1996**, *37*, 7399–7402. For the isolation of erinacine P, see: Kenmoku, H.; Sassa, T.; Kato, N. *Tetrahedron Lett.* **2000**, *41*, 4389–4393.

(6) For scabronine A, see: Ohta, T.; Kita, T.; Kobayashi, N.; Obara, Y.; Nakahata, N.; Ohizumi, Y.; Takaya, Y.; Oshima, Y. *Tetrahedron Lett.* **1998**, *39*, 6229–6232. For scabronines B–F, see: Kita, T.; Takaya, Y.; Oshima, Y.; Ohta, T.; Aizawa, K.; Hirano, T.; Inakuma, T. *Tetrahedron* **1998**, *54*, 11877–11886.

(7) (a) Greene, L. A.; Shooter, E. M. *Annu. Rev. Neurosci.* **1980**, *3*, 353–402. (b) Yankner, B. A.; Shooter, E. M. *Annu. Rev. Biochem.* **1982**, *51*, 845–868.

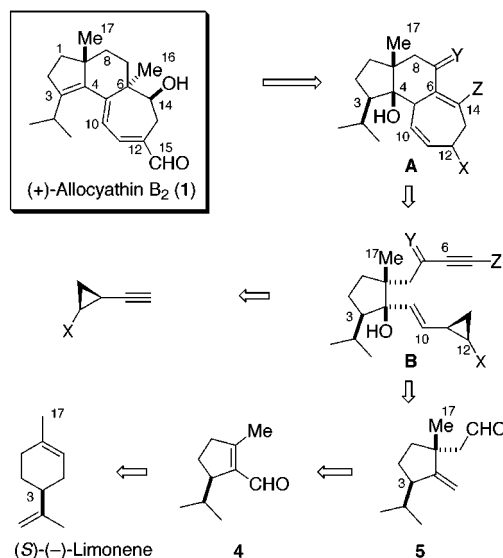
(8) Dijkhuizen, P. A.; Verhaagen, J. *Neuro. Res. Commun.* **1999**, *24*, 1–10.

(9) (a) Rosenberg, S. *Annu. Rep. Med. Chem.* **1992**, *27*, 41–48. (b) Bigge, C. F.; Boxer, P. A. *Annu. Rep. Med. Chem.* **1994**, *29*, 13–22. (c) Saragovi, H. U.; Burgess, K. *Exp. Opin. Ther. Patents* **1999**, *9*, 737–751.

The structural complexity and biological activity of the cyathane family of diterpenes has stimulated considerable interest from synthetic chemists. Testimony to this has been recorded in the number and diversity of approaches that have been developed to construct these fascinating natural products.<sup>10</sup>

Our own strategy for cyathane synthesis is based on the retrosynthetic analysis illustrated in Scheme 1. We reasoned

**Scheme 1**



that the tricyclic core of cyathanes shown here with (+)-alloxyathin B<sub>2</sub> could be derived from tricycle A. This precursor could in turn originate from a transition-metal-catalyzed intramolecular [5 + 2] cycloaddition of a vinylcyclopropane with a  $\pi$ -system as found in B. Further analysis suggests that B could be elaborated from cyclopentane carboxaldehyde 5, which could ultimately be traced back to commercially available and inexpensive (S)-(-)-limonene.

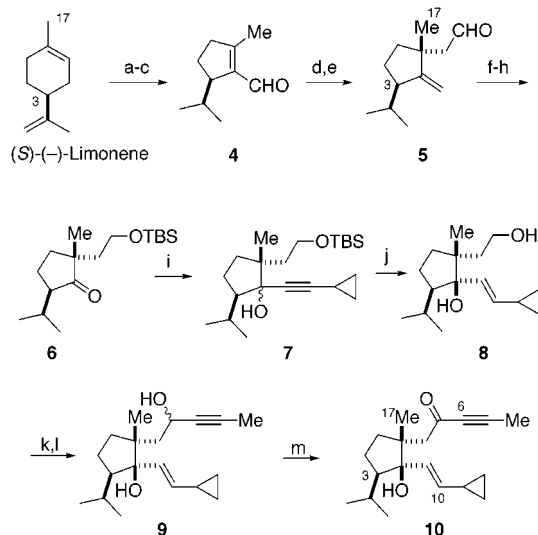
Following this plan, the synthesis of the cyclopentanone 6 was achieved through a shortening of previously published routes.<sup>11</sup> Aldehyde 4 was obtained in three steps and 68% yield by partial hydrogenation of (S)-(-)-limonene over

(10) Reviewed in: Wright, D. L.; Whitehead, C. R. *Org. Prep. Proc. Int.* **2000**, *32*, 307–330. For total syntheses of cyathane diterpenes, see: (a) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644–7645. (b) Tori, M.; Toyoda, N.; Sono, S. *J. Org. Chem.* **1998**, *63*, 306–313. (c) Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407–1410. (d) Ward, D. E.; Gai, Y. Z.; Qiao, Q. *Org. Lett.* **2000**, *2*, 2125–2127. For synthetic approaches to cyathanes, see: (a) Ayer, W. A.; Ward, D. E.; Browne, L. M.; Delbaere, L. T.; Hoyano, Y. *Can. J. Chem.* **1981**, *59*, 2665–2672. (b) Ward, D. E. *Can. J. Chem.* **1987**, *65*, 2380–2384. (c) Paquette, L. A.; Dahnke, K. R. *J. Org. Chem.* **1994**, *59*, 885–899. (d) Magnus, P.; Shen, L. *Tetrahedron* **1999**, *55*, 3553–3560. (e) Wright, D. L.; Whitehead, C. R.; Sessions, H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535–1538. (f) Takeda, K.; Nakane, D.; Takeda, M. *Org. Lett.* **2000**, *2*, 1903–1905.

(11) (a) van Tamelen, E. E.; Milne, G. M.; Suffness, M. I.; Rudler Chauvin, M. C.; Anderson, R. J.; Achini, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 7202–7204. (b) Lange, G. L.; Neidert, E. E.; Orrom, W. J.; Wallace, D. J. *Can. J. Chem.* **1978**, *56*, 1628–1633. (c) White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1813–1821. (d) Mehta, G.; Krishnamurthy, N. *Tetrahedron Lett.* **1987**, *28*, 5945–

platinum oxide, followed by Johnson–Lemieux oxidation<sup>12</sup> and intramolecular aldol condensation, overall requiring two fewer steps from the original five-step route. Reduction of enal **4** with DIBAL-H in diethyl ether followed by vinylation and Claisen rearrangement gave aldehyde **5** in 90% yield as a >10:1 mixture of inseparable diastereomers favoring the one shown in Scheme 2. The stereochemical assignment was

Scheme 2<sup>a</sup>



<sup>a</sup> (a) H<sub>2</sub>, PtO<sub>2</sub>, 94%; (b) 1 mol % OsO<sub>4</sub>, NaIO<sub>4</sub>, THF/H<sub>2</sub>O, 97%; (c) piperidine, AcOH, PhH, Δ, 75%; (d) DIBAL-H, Et<sub>2</sub>O, 0 °C, 96%; (e) EtOCH=CH<sub>2</sub>, Hg(OAc)<sub>2</sub>, Δ, then PhCH<sub>3</sub>, Δ, 90%; (f) NaBH<sub>4</sub>, MeOH/H<sub>2</sub>O, 95%; (g) TBSCl, imidazole, DMF, 90%; (h) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, Me<sub>2</sub>S, 65%; (i) 1-ethynylcyclopropane, *n*-BuLi, CeCl<sub>3</sub>, 0 °C, 91%; (j) LiAlH<sub>4</sub>, MeONa, THF, Δ, 69%; (k) DMP, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (l) MeCCMgBr, THF, 75% over two steps; (m) DMP, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 93%.

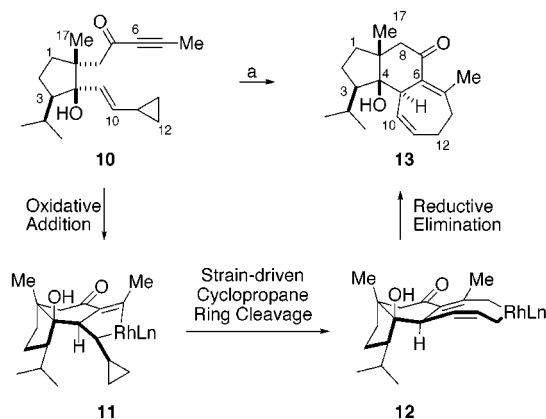
made on the basis of analogy with literature precedent and was ultimately confirmed by X-ray structural analysis of an advanced intermediate.<sup>11</sup> Reduction of the aldehyde with sodium borohydride, protection of the primary alcohol as its *tert*-butyldimethylsilyl ether, and ozonolysis of the exocyclic olefin afforded the desired ketone **6** in 56% yield over three steps.

Introduction of the vinylcyclopropane subunit proceeded in two steps and 66% yield by sequential 1,2-addition of the organocerium reagent<sup>13</sup> derived from lithium cyclopropylacetylide and cerium trichloride, followed by stereospecific reduction of alkyne **7** with LiAlH<sub>4</sub>/NaOMe in THF.<sup>14</sup> At this stage the major diastereomer **8** was readily separated from the other minor diastereomers<sup>15</sup> and was oxidized with

Dess–Martin periodinane.<sup>16</sup> Introduction of the alkyne moiety to the resultant aldehyde was achieved by 1,2-addition of 1-propynylmagnesium bromide to give **9** in 75% yield over two steps.

Attempts to effect a [5 + 2] cycloaddition of vinylcyclopropane **9** with 5 mol % [Rh(CO)<sub>2</sub>Cl]<sub>2</sub><sup>2f</sup> in 1,2-dichloroethane at 80 °C yielded a complex mixture of products. *In dramatic contrast, treatment of the corresponding ketone 10, obtained by oxidation of 9 with Dess–Martin periodinane, with 5 mol % [Rh(CO)<sub>2</sub>Cl]<sub>2</sub> in 1,2-dichloroethane gave cycloadduct 13 (Scheme 3) in 90% yield and in analytically pure form after simple filtration through a plug of neutral alumina.*<sup>17</sup>

Scheme 3<sup>a</sup>



<sup>a</sup> (a) 5 mol % [Rh(CO)<sub>2</sub>Cl]<sub>2</sub>, 1,2-dichloroethane (0.02 M), 80 °C, 3.5 h, 90%.

Structural assignment of cycloadduct **13** was initially obtained through COSY and NOESY NMR experiments and showed that the key [5 + 2] cycloaddition proceeded with >95% chemo-, regio-, and diastereoselectivity. Recrystallization of **13** from diethyl ether/petroleum ether gave colorless needles that were analyzed by single-crystal X-ray crystallography.<sup>18</sup> The ORTEP projection of the resultant structure (Figure 2) confirmed our structural assignment as given in cycloadduct **13**.

(15) Only major diastereomer **8** (isolated in 69% yield) was carried on to test the feasibility of the key cycloaddition.

(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

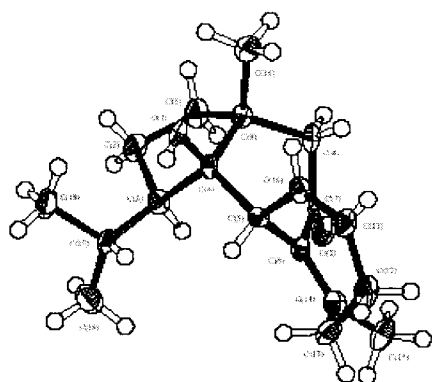
(17) **Typical Procedure.** A solution of **10** (30 mg, 0.104 mmol) in dry 1,2-dichloroethane (5.0 mL) was purged with argon for 15 min, and [Rh(CO)<sub>2</sub>Cl]<sub>2</sub> (2 mg, 0.005 mmol) was added in one portion. The reaction vessel was sealed and heated at 80 °C for 3.5 h. After the mixture cooled to room temperature, the solvent was removed in vacuo, and the residue was dissolved in diethyl ether and filtered through a plug of neutral alumina. Evaporation of the filtrate afforded **13** as a white solid (27 mg, 90%): mp 108.5–109.0 °C, *R*<sub>f</sub> 0.44 (1:9 EtOAc/petroleum ether); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.13–6.17 (m, 1 H), 5.47 (ddd, 1 H, *J* = 11.3, 7.0, 4.0), 4.35 (m, 1 H), 3.14 (dt, 1 H, *J* = 13.4, 4.7), 2.57 (d, 1 H, *J* = 13.0), 2.32–2.38 (m, 1 H), 2.21 (d, 1 H, *J* = 13.0), 2.11–2.19 (m, 1 H), 2.17 (s, 3 H), 2.03 (ddd, 1 H, *J* = 13.4, 4.0, 1.0), 1.81 (dsep, 1 H, *J* = 7.0, 2.0), 1.38–1.67 (m, 5 H), 1.20 (s, 3 H), 0.98 (d, 3 H, *J* = 7.0), 0.95 (d, 3 H, *J* = 7.0); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 201.7, 147.7, 139.4, 128.6, 128.2, 82.0, 54.8, 54.4, 47.8, 43.9, 39.4, 33.6, 27.0, 25.8, 25.0, 24.4, 24.2, 21.2, 20.7; IR (neat, cm<sup>-1</sup>) 3359, 2950, 1674, 1620, 1429, 1294, 1154, 1115, 824; HRMS calcd for C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>: 288.2089, found 288.2093. Anal. Calcd for C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>: C, 79.12; H, 9.78. Found: C, 79.05; H, 9.71.

5948. (e) Wright, J.; Drtina, G. J.; Roberts, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5806–5817. (f) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1990**, *112*, 3252–3253. (g) Mehta, G.; Krishnamurthy, N.; Karra, R. S. *J. Am. Chem. Soc.* **1991**, *113*, 5765–5775.

(12) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.

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(14) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. A. *J. Am. Chem. Soc.* **1967**, *89*, 4245–4247.



**Figure 2.** ORTEP projection of cycloadduct **13**. Ellipsoids drawn at 50% probability level.

The stereochemical outcome of the [5 + 2] cycloaddition was found to be consistent with our previously reported hypotheses.<sup>19</sup> As illustrated in Scheme 3, initial complexation of the alkyne and vinylcyclopropane moieties with the metal, followed by oxidative addition, would lead to formation of a metallacyclopentene intermediate **11**. Strain-driven cleav-

(18) The data collection was carried out at the University of California-Berkeley X-ray facility using direct methods (SIR92) and refined with teXsan:  $C_{19}H_{28}O_2$ ;  $M_r = 288.43$ ; rhombic, colorless crystal; space group  $P2_12_12_1$ ; unit cell dimension ( $\text{\AA}$ )  $a = 6.8941(8)$ ,  $b = 12.995(1)$ ,  $c = 19.155(2)$ ; volume of unit cell ( $\text{\AA}^3$ )  $1716.0(3)$ ;  $Z = 4$ ;  $R_1 = 0.071$  for  $I > 3\sigma(I)$ ,  $\omega R_2 = 0.085$  for all data; GOF = 1.17. The author has deposited the atomic coordinates for the structure of **13** with the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(19) For a more detailed mechanistic interpretation see, for example, ref 2b.

age of the cyclopropane ring would lead to a metallacyclooctadiene **12**, which after reductive elimination would afford the expected cycloadduct **13**. Alternatively, the metallacyclooctadiene intermediate **12** could also be derived through initial formation of and alkyne insertion into a metallacyclohexene intermediate.

In summary, we have developed a concise route to the tricyclic core of the cyathane diterpenes. Further elaboration of cycloadduct **13** should provide access to novel erinacine analogues. Work is in progress to apply this methodology to the total synthesis of erinacines and more significantly their analogues.

**Acknowledgment.** This research was supported by a grant (CHE-9800445) from the National Science Foundation. Mass spectra were provided by the Mass Spectrometry Facility, University of California-San Francisco. We thank Adam P. Cole of Stanford University for solving the X-ray crystallographic structure of **13**. Graduate fellowship support from Roche Bioscience (F.C.B.) as well as postdoctoral fellowship support from the National Institute of Health (M.A.B.) and the Natural Sciences and Engineering Research Council of Canada (F.G.) is gratefully acknowledged.

**Note added after ASAP:** The version published on ASAP 6/8/01 contained an error in the footnote of Scheme 2. The printed version is correct.

**Supporting Information Available:** IR, NMR, and mass spectroscopic data for compounds **4–10** and **13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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