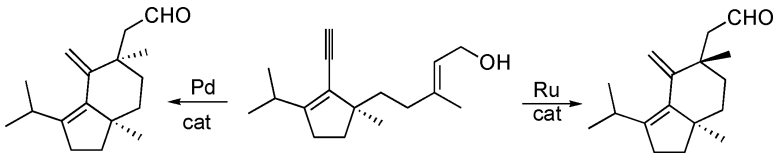
Article

Exploiting the Pd- and Ru-Catalyzed Cycloisomerizations: Enantioselective Total Synthesis of (+)-Allocyathin B

Barry M. Trost, Li Dong, and Gretchen M. Schroeder

J. Am. Chem. Soc., **2005**, 127 (29), 10259-10268• DOI: 10.1021/ja051547m • Publication Date (Web): 28 June 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 5 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 06/28/2005

Exploiting the Pd- and Ru-Catalyzed Cycloisomerizations: Enantioselective Total Synthesis of (+)-Allocyathin B_2

Barry M. Trost,* Li Dong, and Gretchen M. Schroeder

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94301-5080

Received March 10, 2005; E-mail: bmtrost@stanford.edu

Abstract: Pd- and Ru-catalyzed cycloisomerizations of 1,6-enynes are compared and contrasted. Such considerations led to the enantioselective synthesis of a cyathin terpenoid, (+)-allocyathin B_2 (**1**). The synthesis features a Pd-catalyzed asymmetric allylic alkylation (AAA) to install the initial quaternary center, a Ru-catalyzed diastereoselective cycloisomerization to construct the six-membered ring, and a diastereoselective hydroxylative Knoevenagel reaction to introduce the final hydroxyl group. We demonstrate for the first time a mechanism-based stereochemical divergence in Pd- and Ru-catalyzed cycloisomerization reactions as well as in creation of alkene geometry with alkynes bearing a carboalkoxy group. Mechanistic rationalization is proposed for these observations.

Introduction

Cycloisomerizations represent atom economic approaches to ring construction. As a result, we have pioneered metal-catalyzed cycloisomerizations of enynes to form cyclic 1,3- and 1,4-dienes.[1−3] In the Pd-catalyzed reaction (Figure 1), a mechanistic rationale invokes HPd^+ formed by protonation of Pd(0) as the catalytically active species.[4] Preferential hydropalladation of the alkyne and intramolecular carbapalladation of the alkene by the in situ generated vinylpalladium species followed by β-hydrogen elimination complete the cycle. β-Hydrogen elimination toward H_a creates a 1,3-diene, whereas β-hydrogen elimination of H_b provides a 1,4-diene. Experimentally, both pathways have been observed and normally proceed with excellent regioselectivity depending upon the substrate. On the other hand, a Ru-catalyzed process proceeds via a completely different pathway, as shown in Figure 2. This mechanism precludes the formation of 1,3-dienes since β-hydrogen elimination within the metallacycle is geometrically strongly disfavored. Further, the regioselectivity in the β-hydrogen elimination to form 1,4-dienes, where such exists (i.e., with trisubstituted alkenes), also has been complementary. Despite these facts, divergences of the two quite distinct mechanisms remain to be elucidated.

In the course of a total synthesis project, the issue of the differences between these two catalytic systems arose. In 1979, Ayer et al. reported the isolation and structure of (+)-allocyathin B_2 (**1**, Scheme 1),[5] a member of the cyathin terpenoids.[5−13] Compound **1**, a metabolite from the fruit bodies of *Cyathus*

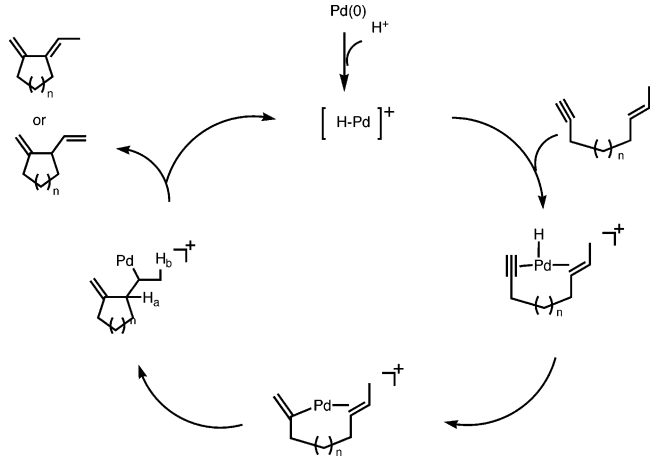


Figure 1. Pd-catalyzed cycloisomerization mechanism.

earlei Lloyd, is distinguished by an angularly fused 5−6−7 tricyclic skeleton with a highly unsaturated trienal motif embedded in the framework and 1,4-anti quaternary methyl groups located at the ring junctions. These terpenoids exhibit interesting biological activities against actinomycetes, Gram-positive and Gram-negative bacteria, as well as some fungi.[6] Metabolites of other fungi[14−17] and liverworts[18] also share the

(1) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1−16.
(2) Trost, B. M.; Surivet, J.-P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15592−15602.
(3) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2002**, *124*, 5025−5036.
(4) Trost, B. M. *Chem.—Eur. J.* **1998**, *4*, 2405−2412.
(5) Ayer, W. A.; Lee, S. P. *Can. J. Chem.* **1979**, *57*, 3332−3337.
(6) Allbutt, A. D.; Ayer, W. A.; Brodie, H. J.; Johri, B. N.; Taube, H. *Can. J. Microbiol.* **1971**, *17*, 1401−1402.
(7) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199−2248.
(8) Ayer, W. A.; Browne, L. M.; Mercer, J. R.; Taylor, D. R.; Ward, D. E. *Can. J. Chem.* **1978**, *56*, 717−721.
(9) Ayer, W. A.; Lee, S. P.; Nakashima, T. T. *Can. J. Chem.* **1979**, *57*, 3338−3343.
(10) Ayer, W. A.; Taube, H. *Tetrahedron Lett.* **1972**, *13*, 1917−1920.
(11) Ayer, W. A.; Taube, H. *Can. J. Chem.* **1973**, *51*, 3842−3843.
(12) Ayer, W. A.; Ward, D. E.; Browne, L. M.; Delbaere, L. T. J.; Hoyano, Y. *Can. J. Chem.* **1981**, *59*, 2665−2672.
(13) Ayer, W. A.; Yoshida, T.; Van Schie, D. M. J. *Can. J. Chem.* **1978**, *56*, 2113−2120.
(14) Kawagishi, H.; Shimada, A.; Hosokawa, S.; Mori, H.; Sakamoto, H.; Ishiguro, Y.; Sakemi, S.; Bordner, J.; Kijima, N.; Furukawa, S. *Tetrahedron Lett.* **1996**, *37*, 7399−7402.
(15) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569−1572.
(16) Kawagishi, H.; Simada, A.; Shizuki, K.; Mori, H.; Okamoto, K.; Sakamoto, H.; Furukawa, S. *Heterocycl. Commun.* **1996**, *2*, 51−54.

10.1021/ja051547m CCC: $30.25

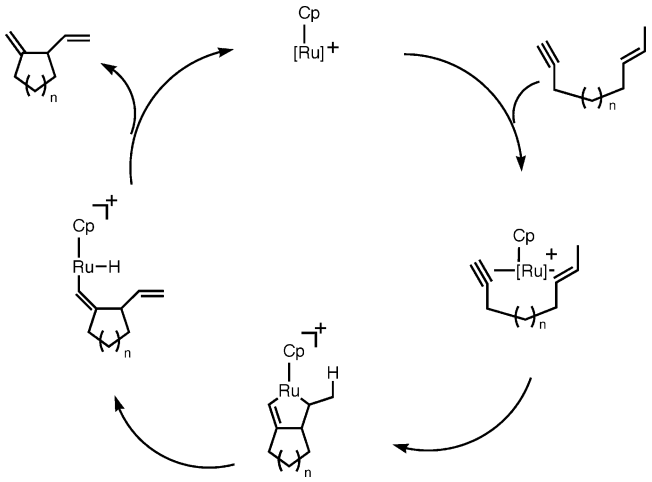
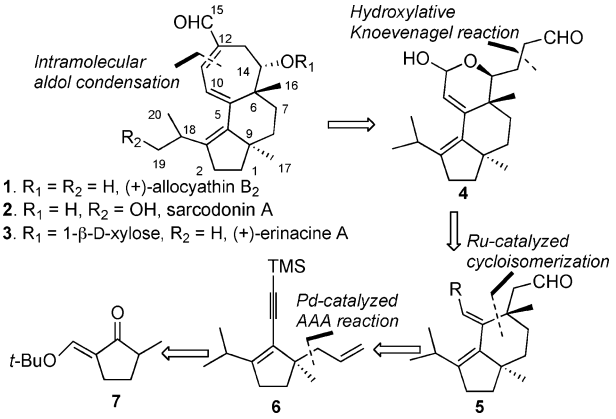


Figure 2. Ru-catalyzed cycloisomerization mechanism.

Scheme 1. Retrosynthetic Analysis



cyathane backbone, including a hydroxylated analogue, sarcodonin A (**2**, Scheme 1) from *Sarcodon scabrosus*, which has anti-inflammatory activity,[19] and a D-xylose conjugate of allocyathin B_2, erinacine A (**3**, Scheme 1) from the mycelia of *Hericum erinaceum*, which possesses potent stimulating activity for nerve growth factor (NGF) synthesis in vitro.[15] The imposing structure and potential medicinal importance of these molecules have attracted a great deal of attention from many research teams since the disclosure of their structures,[7,20−26] although only three groups have completed the racemic syntheses of allocyathin B_2[27−29] and sarcodonin A.[30] In this paper, we report our studies contrasting these two metal-catalyzed cycloisomerizations stimulated by this total synthesis. A preliminary report describing only the total synthesis has recently appeared.[31]

Herein, we report an enantioselective total synthesis of (+)-allocyathin B_2. The goal of this synthesis was to develop a catalytic approach to enantioselectively install the first quaternary carbon and relay the stereochemical information to the remaining two stereogenic centers. Strategically, we planned to construct the cycloheptadiene unit of allocyathin B_2 by a late-stage intramolecular aldol condensation from aldehyde **4** (Scheme 1). A transition metal-catalyzed cycloisomerization was envisioned to build the six-membered ring of the 5−6−7 tricyclic cyathin core (compound **5**).[32] At the outset, it was recognized that this key disassembly allows several synthetic parameters, such as catalyst, substrate geometry, and appendage at the alkyne terminus, to be adjusted to achieve the requisite stereochemistry as well as to prepare for subsequent transformations. This disconnection also provides a rare opportunity to explore the Pd- and Ru-catalyzed cycloisomerizations related to the methods developed in this laboratory in a complex setting. The crucial intermediate, enyne **6**, would be prepared through a Pd-catalyzed asymmetric allylic alkylation (AAA) reaction from ketone **7**, another methodology recently developed in this group.[33−35]

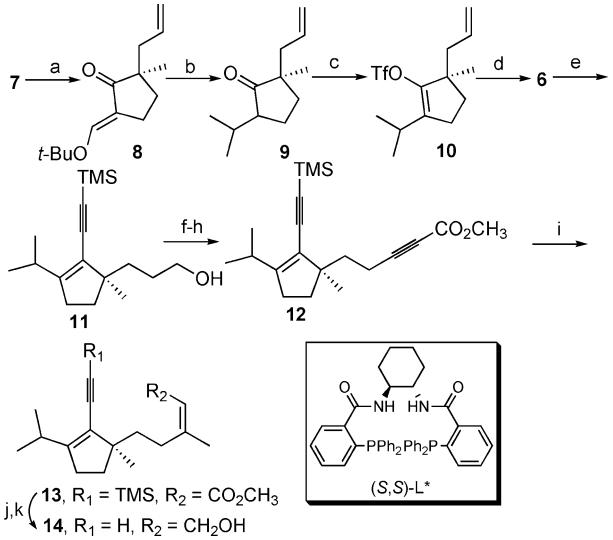
Results and Discussion

Pd-Catalyzed Cycloisomerization of 1,7-Enyne 14. Since we had an efficient and reliable approach to enantioselectively install the C17 methyl group using a Pd-catalyzed enolate AAA reaction (**8**, Scheme 2),[36] it was desirable to design a cyclization substrate from this compound in such a way that both sides of the resulting six-membered ring would be properly functionalized to allow the diastereoselective introduction of the C14 hydroxyl group as well as set the stage for the closure of the final seven-membered ring. With these considerations in mind, compound **14** was conceived as one of the viable substrates for the pivotal transition metal-catalyzed cycloisomerization. It should be noted that the *Z*-geometry of the olefin in compound **14** was chosen at this stage because of its ease of assembly, although we do anticipate that the olefin geometry will be a key factor to determine the stereochemical outcome of this reaction.

Alkyne **6** was synthesized in satisfactory yield through the addition of lithium dimethylcuprate to **8** followed by treatment of the resulting ketone **9** with LDA and $PhNTf_2$[36] followed by a Sonogashira coupling reaction (Scheme 2).[37] The elaboration of the *Z*-alkene **14** involved a straightforward chain elongation protocol[38−40] involving a stereospecific conjugate addition of lithium dimethylcuprate to ynoate **12**.[41]

(17) Lee, E. W.; Shizuki, K.; Hosokawa, S.; Suzuki, M.; Suganuma, H.; Inakuma, T.; Li, J.; Ohnishi-Kameyama, M.; Nagata, T.; Furukawa, S.; Kawagishi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2402−2405.
(18) Toyota, M.; Nakaisi, E.; Asakawa, Y. *Phytochemistry* **1996**, *43*, 1057−1064.
(19) Shibata, H.; Tokunaga, T.; Karasawa, D.; Hirota, A.; Nakayama, M.; Nozaki, H.; Tada, T. *Agric. Biol. Chem.* **1989**, *53*, 3373−3375.
(20) Wright, D. L.; Whitehead, C. R. *Org. Prep. Proc.* **2000**, *32*, 307−320.
(21) Thominiaux, C.; Chiaroni, A.; Desmaele, D. *Tetrahedron Lett.* **2002**, *43*, 4107−4110.
(22) Tekeda, K.; Nakane, D.; Tekeda, M. *Org. Lett.* **2000**, *2*, 1903−1905.
(23) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105−2108.
(24) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535−1538.
(25) Magnus, P.; Shen, L. *Tetrahedron* **1999**, *55*, 3553−3560.
(26) Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 885−899.
(27) Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306−313.
(28) Snider, B. B.; Vo, N. H.; O'Neil, S. V. *J. Org. Chem.* **1998**, *63*, 4732−4740.
(29) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644−7645.
(30) (a) Piers, E.; Cook, K. L. *Chem. Commun.* **1996**, 1879−1880. (b) Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407−1410.
(31) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 2844−2845.
(32) Aubert, C.; Buisine, O.; Malacria, B. *Chem. Rev.* **2002**, *102*, 813−834.
(33) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759−6760.
(34) Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492−3495.
(35) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1−14.
(36) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480−4481.
(37) Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649−651.
(38) Brown, C. A.; Coleman, R. A. *J. Org. Chem.* **1979**, *44*, 2328−2329.
(39) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−168.
(40) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.
(41) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851−1852.

Scheme 2. Synthesis of Substrate **14**[a]



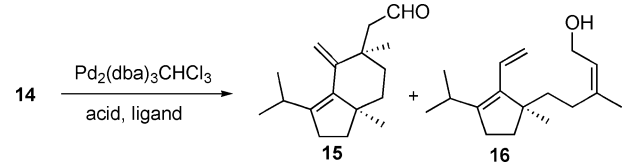
[a] Conditions: (a) LDA, $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.5 mol %), (*S*,*S*)-L* (1 mol %), allyl acetate, Me_3SnCl, *t*-BuOH, 83%, 95% ee; (b) Me_2CuLi, −20 °C to room temperature, 85%; (c) LDA, $PhNTf_2$, 98%; (d) $Pd_2(dba)_3CHCl_3$ (2.5 mol %), PPh_3 (20 mol %), CuI (5 mol %), TMS-acetylene, *n*-$BuNH_2$, 50 °C, 85%; (e) 9-BBN; H_2O_2, NaOH, 87%; (f) $(COCl)_2$, DMSO, Et_3N, −78 °C to room temperature, 84%; (g) CBr_4, PPh_3, 94%; (h) *n*-BuLi, $ClCO_2Me$, −78 °C to room temperature, 99%; (i) Me_2CuLi, −78 °C, 93%; (j) DIBAL-H, −78 °C to room temperature, 94%; (k) TBAF, 97%.

Many transition metals have been reported to catalyze the cycloisomerization of 1,6- and 1,7-enynes, notably Pd, Ru, Rh, and Ti.[1,32] However, 1,7-enynes with trisubstituted olefins are challenges for most of the known methodologies, possibly due to the poor substrate coordination to the catalyst. Not surprisingly, $[Rh(COD)Cl]_2$/BINAP/$AgBF_4$[42,43] and $Cp_2Ti(CO)_2$[44] are ineffective catalysts in the cycloisomerization of **14**. Prior efforts in our laboratory indicate that palladium systems are more tolerant of olefin substitution than ruthenium in these reactions.[45] Therefore, we decided to initially examine palladium catalysts in our cycloisomerization reaction.

Although $Pd_2(dba)_3{\cdot}CHCl_3$/HOAc is known to be effective in catalyzing the formation of six-membered rings, only trace amounts of the cyclization product were obtained along with a significant amount of the starting material when **14** was exposed to the standard conditions (entry 1, Table 1). Despite the low conversion, a single diastereomer was obtained, as demonstrated by NMR analysis. The obvious difficulty in the coordination of this 1,7-enyne to the catalyst prompted us to use the "ligandless" conditions developed in this group.[46] Indeed, the yield significantly improved without the addition of BBEDA [bis(benzylidene)ethylenediamine]. Since the use of HOAc as the cocatalyst led to the formation of an unidentified isomerization product, other acids were surveyed to avoid this problem.

Among the acids assayed, *o*-trifluoromethylbenzoic acid was identified as the best choice (Table 1). Although formic acid was superior in terms of reactivity, the relatively sluggish cycloisomerization reaction allowed the formation of a significant amount of the reduced triene **16**. Using the optimized conditions, compound **15** was obtained in 60% yield as a single diastereomer (entry 6, Table 1). The relative stereochemistry of the newly formed quaternary center was determined at a later stage (vide infra).

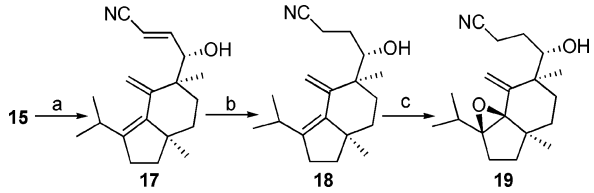
Table 1. Pd-Catalyzed Cycloisomerization of Compound **14**[a]



entry	ligand	acid (mol %)	*T* (°C)	time (h)	yield of **15** (%)
1	BBEDA[b]	HOAc (25 mol %)	60	24	4 (82% **14**)
2	none	HOAc (25 mol %)	60	20	18 (13% **14**)
3	none	TFA (20 mol %)	60	2	19 (8% **14**)
4	none	HCO_2H (200 mol %)	70	0.8	23 (62% **16**)
5	none	HCO_2H (200 mol %)	25	20	22 (64% **16**)
6	none	*o*-CF_3BzOH (20 mol %)	70	12	60

[a] All reactions were performed in toluene (0.1 M) with 2 mol % of $Pd_2(dba)_3CHCl_3$ at the indicated temperature. [b] No conversion was observed with other ligands, such as $(o\text{-Tol})_3P$.

Scheme 3. Synthesis of Epoxide **19**[a]



[a] Conditions: (a) $PhS(O)CH_2CN$, piperidine, 69%; (b) 10% Pd/C, H_2 (1 atm), 98%; (c) *m*CPBA, 76% or NBS, water, 46% or $VO(acac)_2$, TBHP, 80%.

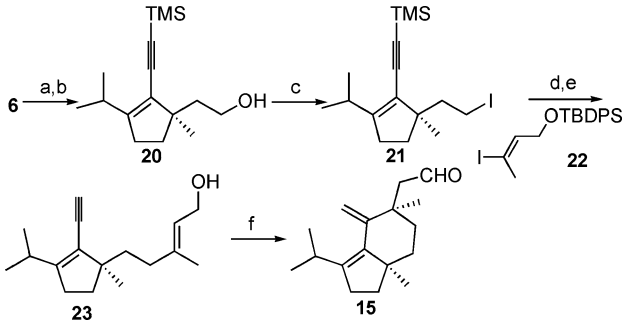
We then turned our attention to the construction of the final seven-membered ring. An interesting methodology developed by Nokami, the hydroxylative Knoevenagel reaction, seemed well suited to our goal of installing the C14 hydroxy group with concomitant extension of the carbon chain.[47] Gratifyingly, after some experimentation, the desired transformation was accomplished to afford alcohol **17** as a single diastereomer (Scheme 3). Compound **17**, which contains all three requisite stereogenic centers, was submitted for X-ray crystallographic structural determination. Unfortunately, the two quaternary methyls are 1,4-syn, while the hydroxyl group possesses the correct configuration (Figure 1). Despite this setback, we decided to pursue our synthesis using compound **17** as a model study and a possible intermediate to an epimer of (+)-allocyathin B_2.

Surprisingly, the 1,4-reduction of the α,β-unsaturated nitrile (C12−C13) of compound **17** did not occur under a variety of conditions known for this purpose.[48] On the other hand, by taking advantage of the unique conformation of nitrile **17**, a chemoselective hydrogenation was achieved with heterogeneous catalysis. Thus, by subjecting compound **17** to 10% Pd/C and 1 atm of hydrogen, a near quantitative yield of the desired dihydro derivative **18** was obtained (Scheme 3).

Having established the requisite oxygen-bearing stereocenter, we found ourselves faced with the task of homologating the

(42) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3457−3460.
(43) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104−4106.
(44) Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976−1977.
(45) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34−42.
(46) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625−6633.
(47) Nokami, J.; Mandai, T.; Imakura, Y.; Nishiuchi, K.; Kawada, M.; Wakabayashi, S. *Tetrahedron Lett.* **1981**, *22*, 4489−4490.
(48) Reduction with in situ generated copper hydride, Mo-catalyzed hydrosilane reduction, or Lindlar's catalyst reduction gave no reaction.

Scheme 4. Pd-Catalyzed Cycloisomerization of Compound **23**[a]



[a] Conditions: (a) OsO_4 (1 mol %), NMO, $NaIO_4$, 84%; (b) $NaBH_4$, 94%; (c) PPh_3, I_2, ImH, 93%; (d) *t*-BuLi, $ZnCl_2$, −78 °C to room temperature, then $Pd(PPh_3)_4$ (5 mol %), **22**; (e) TBAF, 72% from **21**; (f) $Pd_2(dba)_3CHCl_3$, *o*-CF_3BzOH, 70 °C, 54%.

exocyclic olefin to an α,β-unsaturated aldehyde or equivalent. An osmium-catalyzed dihydroxylation of **18** failed to proceed with a number of co-oxidants [NMO, trimethylamine oxide, or $K_3Fe(CN)_6$] and additives (methane sulfonamide or pyridine).[49] On the other hand, exposure of **18** to sterically less sensitive epoxidizing agents, such as *m*CPBA or NBS/water, generated epoxide **19** due to an electron-rich nature of the tetrasubstituted double bond (Scheme 3).[50] As predicted by analysis of a molecular model, a hydroxyl-directed epoxidation [$VO(acac)_2$, TBHP][51] afforded the same product. These results, although discouraging, demonstrated the key role that the C6 stereochemistry plays in affecting the chemoselectivity. We, therefore, tried several approaches to reverse the diastereoselectivity of the cycloisomerization.

Pd-Catalyzed Cycloisomerization of Compounds 23 and 28. As previously mentioned, we anticipate the olefin geometry of the enyne to be a key factor in determining the stereochemical outcome of the cycloisomerization reaction. Thus, *E*-isomer **23** was synthesized from compound **6** as detailed in Scheme 4. The allyl side chain of compound **6** was oxidatively cleaved (OsO_4, NMO; $NaIO_4$), reduced ($NaBH_4$), and iodinated (PPh_3, I_2, imidazole) to furnish compound **21**. A Pd-catalyzed Negishi sp^3-sp^2 coupling reaction of the zinc derivative of alkyl iodide **21** and vinyl iodide **22**[52] followed by TBAF-mediated desilylation provided the desired *E*-allylic alcohol **23**.[53−55] When compound **23** was subjected to the established cycloisomerization conditions, surprisingly, the same aldehyde **15** was obtained in 54% yield.

The outcome observed for both **14** and **23** in the Pd-catalyzed cycloisomerization can be rationalized by the proposed mechanism (Figure 4).[56] For the substrate **24**, after the initial hydropalladation, two intermediates **25** and **26**, which place the bulky Pd catalyst approximately perpendicular to the five-membered ring to minimize steric interactions with the isopropyl

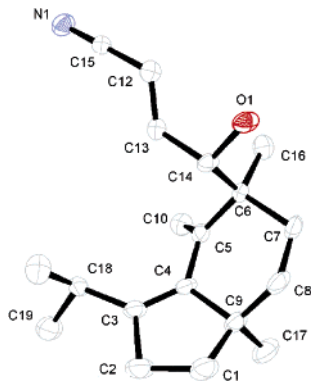


Figure 3. X-ray crystallography of compound **17**.

group, are generated. In intermediate **25**, the C−Pd bond and the π-bond of the acyclic alkene are syn-coplanar as required for the carbametalation. Thus, this orientation is energetically favorable and leads to the observed product. On the other hand, the alternative conformation **26** has the C−Pd and π-bond orthogonal. Such an unfavorable geometry for the carbametalation disfavors this cyclization and precludes formation of the desired stereochemistry. As this picture illustrates, the geometry of the trisubstituted double bond with respect to the product stereochemistry is irrelevant.

To further test this mechanistic proposal and provide an alternative strategy for our synthesis, we decided to prepare the demethylated substrate **28** and subject this compound to the Pd-catalyzed cycloisomerization reaction (Scheme 5). Toward this end, Moffatt−Swern oxidation of compound **11** followed by a Wittig reaction with PPh_3CHCO_2Et furnished *E*-olefin **27** as the only product.[39] Reduction of the ester and desilylation produced alcohol **28**. The Pd-catalyzed cycloisomerization of enyne **28** proceeded smoothly under the previously established conditions to afford aldehyde **29** in 54% yield as a single diastereomer. As expected, the same stereoselectivity was achieved as in the case of *E*-olefin **23**.[57] This result provides further evidence to support our rationale that the interaction between the fused five-membered ring and the vinyl substituent dominates the stereo-determining step. It is also noteworthy that, in this transformation, no 1,3-diene **30** was detected (Scheme 5). Previous studies show that Pd-catalyzed enyne cycloisomerizations of disubstituted olefins often generate mixtures of 1,4- and 1,3-dienes.[58] Further, the presence of an allylic hydroxyl substituent tends to favor the 1,3-diene (i.e., **30**).[59] Presumably, the overwhelming bias toward the formation of a nonconjugated 1,4-diene in this reaction is derived from the conformational restriction of the bicyclic system and the strain associated with placing a double bond exocyclic to a six-membered ring.[58−60] We observed a similar effect in our application of this cycloisomerization in our synthesis of saponaceolide.[60]

Ru-Catalyzed Cycloisomerization. Because the Pd-catalyzed cycloisomerization only generated the cyclized product with a 1,4-syn relationship, we considered employing $CpRu(CH_3CN)_3PF_6$ as the catalyst.[61,62] This choice was based on the

(49) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766−768.
(50) Sato, T.; Nagata, T.; Maeda, K.; Ohtsuka, S. *Tetrahedron Lett.* **1994**, *35*, 5027−5030.
(51) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690−7692.
(52) Nesnas, N.; Rando, R. R.; Nakanishi, K. *Tetrahedron* **2002**, *58*, 6577−6584.
(53) Gagneur, S.; Montchamp, J. L.; Negishi, E. *Organometallics* **2000**, *19*, 2417−2419.
(54) Negishi, E.-I.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298−3299.
(55) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406−5409.
(56) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268−4278.
(57) The relative stereochemistry was assigned by comparison of the NMR spectra of compound **29** with those of compound **15**.
(58) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651−654.
(59) Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586−4588.
(60) Trost, B. M.; Corte, J. R.; Gudiksen, M. S. *Angew. Chem., Int. Ed.* **1999**, *38*.
(61) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096.

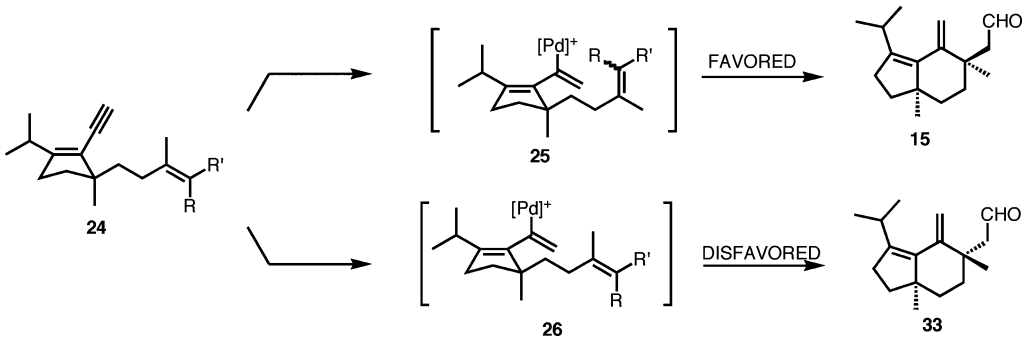
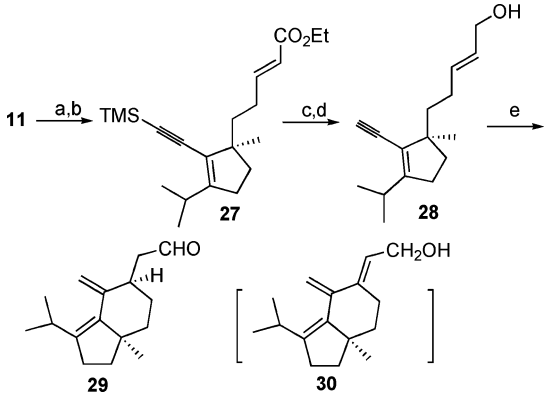


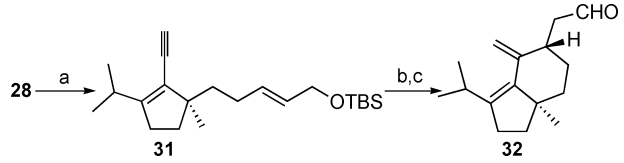
Figure 4. Proposed rationale for the palladium-catalyzed cycloisomerization of compound **24**.

Scheme 5. Pd-Catalyzed Cycloisomerization of Compound **28**[a]



[a] Conditions: (a) $(COCl)_2$, DMSO, NEt_3, 88%; (b) Ph_3PCHCO_2Et, 98%; (c) DIBAL-H, −78 °C to room temperature, 96%; (d) TBAF, 92%; (e) $Pd_2(dba)_3CHCl_3$, *o*-CF_3BzOH, 70 °C, 54%.

Scheme 6. Ru-Catalyzed Cycloisomerization of Compound **31**[a]

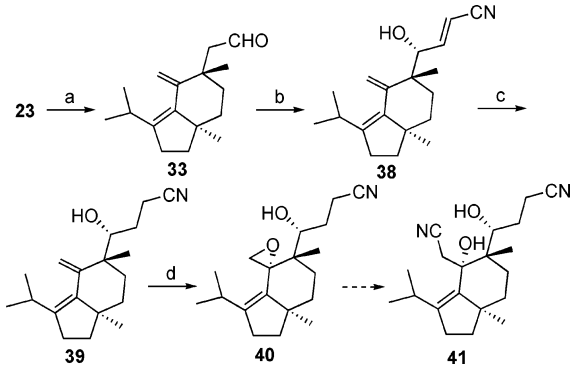


[a] Conditions: (a) TBSCl, ImH, 99%; (b) $CpRu(CH_3CN)_3PF_6$ (10 mol %), 53%; (c) TFA, H_2O, 0 °C to room temperature, 83%.

notion that Pd- and Ru-catalyzed cycloisomerizations undergo different reaction mechanisms.[32] Unfortunately, precedent indicated that this cycloisomerization is sensitive to olefin substitution, and that 1,7-enynes with trisubstituted olefins are not particularly good substrates. Consequently, we first carried out a model study with compound **31** to establish the diastereoselectivity of this process and as proof of concept. Previous efforts in our group suggested the use of an allylic silyl ether as the substrate.[2] Indeed, no reaction occurred with compound **28** under standard conditions with $CpRu(CH_3CN)_3PF_6$ (10 mol %), while the reaction of silyl ether **31** cleanly generated an enol ether,[63] which was hydrolyzed (TFA, H_2O) to deliver aldehyde **32** as a single diastereomer (Scheme 6). To our delight, comparison of the spectral data of compound **29** with those of **32** clearly indicated that the opposite diastereoselectivity was achieved with Ru catalysis. This result provided support to our hypothesis that different reaction mechanisms might induce complementary diastereoselectivity in transition metal-catalyzed cycloisomerization reactions.

(62) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714−715.

Scheme 7. Synthesis of Epoxide **40**[a]



[a] Conditions: (a) $CpRu(CH_3CN)_3PF_6$ (35 mol %), 29%; (b) $PhS(O)CH_2CN$, piperidine, 44%, dr > 20:1; (c) 10% Pd/C, H_2 (1 atm), 87%; (d) $VO(acac)_2$, TBHP, 52%.

Encouraged by this result, compounds **14** and **23** as well as their silyl ethers were subjected to the Ru-catalyzed reaction. Unlike the disubstituted model **31**, the silyl-protected derivatives of **14** and **23** did not give any desired product.[64] With some optimization, we found that exposure of compound **23** to $CpRu(CH_3CN)_3PF_6$ (20 mol %) in 2-butanone generated a cyclization product in 15% yield. Gratifyingly, comparison of NMR data of this product with those of compound **15** indicates that only the desired diastereomer **33** was obtained (Scheme 7). This result agreed with our observations in the reactions of disubstituted substrates. The excellent diastereoselectivity was certainly exciting. However, improvement on the conversion was desirable to render the reaction synthetically practical.[65] A yield of 29% was achieved by increasing the catalyst loading to 35 mol %. Further increase of the catalyst was detrimental due to significant decomposition of the starting material. On the other hand, the best yield (41%) was obtained upon addition of 100 mol % of DMF with 20 mol % of catalyst (vide infra).

(63) The enol ether was obtained as a single *E*-isomer based on the NMR analysis.

(64) A rapid decomposition was observed with TBS-protected compounds in the presence of $CpRu(CH_3CN)_3PF_6$ in acetone, while a clean desilylation occurred in DMF after 4 h. On the other hand, TBDPS derivatives are very stable and were quantitatively recovered in both solvents. Protection of the free hydroxyl group as an acetate led to no reaction.

(65) We attempted to use CpRu(COD)Cl, which is an effective catalyst in the intermolecular Alder-ene reaction. There was no reaction with this catalyst alone, and a complex mixture was obtained with the addition of AgOTf as the cocatalyst. Since the free allylic alcohol was perceived as a potential problem due to its possible coordination with Ru, some additives were added to tentatively mask the hydroxyl group. However, no reaction occurred when the substrate was premixed with $AlMe_3$ before the addition of the catalyst. On the other hand, TMS-protected starting material was isolated if BSA was added.

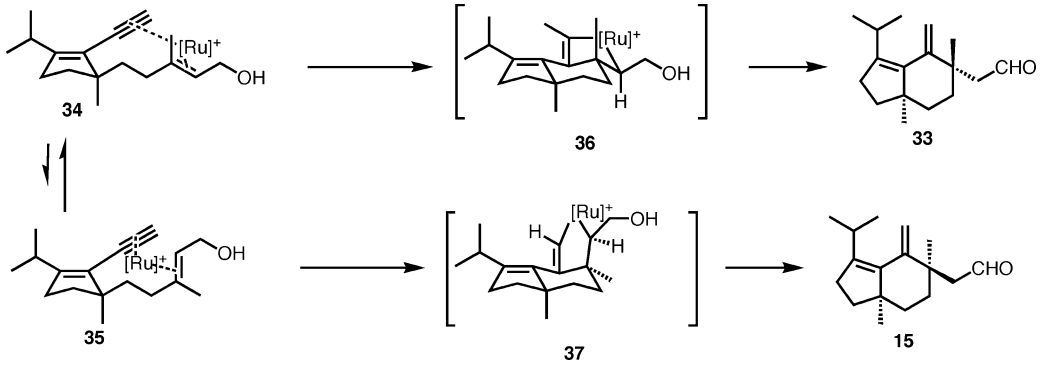


Figure 5. Mechanistic rationale for the Ru-catalyzed cycloisomerization of compounds **14** and **23**.

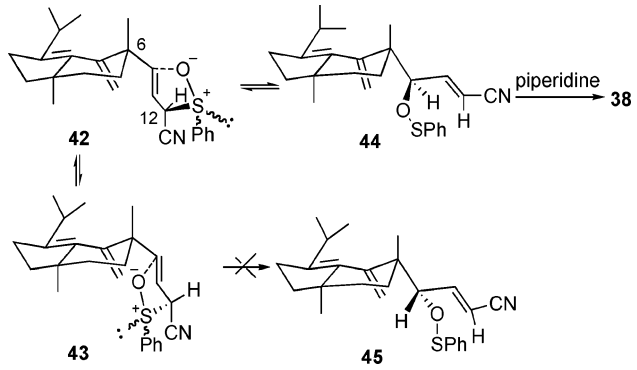
Although there was no difference in reactivity or diastereoselectivity in the Pd-catalyzed cycloisomerization of *Z*- and *E*-isomers **14** and **23**, this was the not case in the Ru-catalyzed reaction. In fact, only a small amount of cyclization product (5%) was obtained when compound **14** was subjected to the optimized cycloisomerization conditions (20 mol % of catalyst).[66] More surprisingly, examination of the NMR spectra revealed that a 1:1 mixture of both diastereomers, compounds **33** and **15**, was obtained.

To explain our observations in the Ru-catalyzed cycloisomerization of compounds **14** and **23**, especially the difference in diastereoselectivity, the following mechanistic rationale was proposed (Figure 5). Presumably, after the initial chelation of the coordinatively unsaturated Ru catalyst to the enyne, the rate-limiting formation of a ruthenacyclopentene intermediate occurs.[3,61] Between the two conformers **34** and **35**, the syncoplanar orientation of the alkene and alkyne in the former compared to an orthogonal orientation in the latter should favor formation of ruthenacycle **36** over **37**. In the case of *Z*-substrate **14**, the intermediates derived from the corresponding to the *Z*-geometrical isomer of **34** and **35** lead to bad steric interactions in both **36** and **37**, leading to both being disfavored. Thus, the reaction is poorer and both products are observed. With the *E*-substrate **23**, the upper pathway via **36** is now favored since it is devoid of most bad inter-reactions.

With these results, we demonstrate for the first time a mechanism-based stereochemical divergence in Pd- and Ru-catalyzed cycloisomerizations. By varying substrate geometry and, more importantly, catalyst choice, we can enable access to all four diastereomers with excellent stereocontrol. The complementarity of Pd and Ru catalysts revealed by our study further broadens the scope of transition metal-catalyzed cycloisomerization reactions and provides valuable insight into the mechanistic aspects of these interesting transformations.

With aldehyde **33** available, it was subjected to the hydroxylative Knoevenagel reaction to furnish nitrile **38** with excellent diastereoselectivity (dr > 20:1, Scheme 7).[67] On the basis of previous results, the stereochemistry of the hydroxyl group was assigned as *R* and would have to be inverted at a later stage. After the selective hydrogenation of the C13−C14 double bond to produce diene **39**, we were again in a position to address the homologation of the exocyclic olefin. As observed with

Scheme 8. Mechanistic Rationale for the Hydroxylative Knoevenagel Reaction to Form **38**

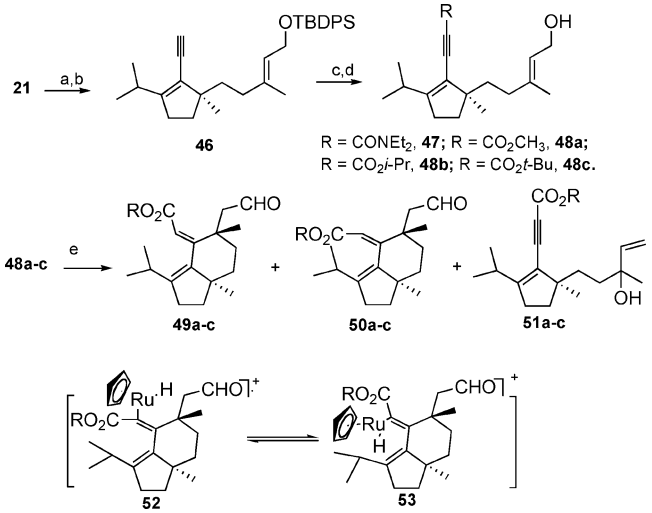


compound **18** (vide supra), no reaction occurred under osmium-catalyzed dihydroxylation conditions. We anticipated that, by changing the stereochemistry at C6, the chemoselectivity of the hydroxyl-directed epoxidation would be different since the tetrasubstituted olefin is no longer accessible from the bottom face. Indeed, treatment of compound **39** with $VO(acac)_2$/TBHP furnished the desired epoxide **40** as the only product. However, our attempts to open the epoxide with a cyanide source (KCN; TMSCN)[68] were thwarted by the poor stability of the substrate. In appraisal of the difficulty of this route, we decided to pursue a more feasible alternative.

Before discussing the revised approach, it is necessary to examine the unusual diastereoselectivity in the formation of compound **38.** The accepted mechanism of the transformation from **42** to **43** involved the initial Knoevenagel reaction followed by double bond migration, sulfoxide−sulfenate 2,3-sigmatropic rearrangement, and desulfurization.[69] We believe that, in this case, the double bond migration generates an olefin that is oriented perpendicular to the plane of the bicyclic system to avoid the steric interaction with the exocyclic olefin (Scheme 8). By analogy to previous studies in this group, a quickly equilibrating mixture of roughly equal amounts of two diastereomers **42** and **43** is expected.[70] Since the nitrile group has to be situated to lead to an *E* double bond, each diastereomer can only rearrange as depicted in Scheme 8.[71] Intermediate **42** rearranges much faster to **44** from the front than from the back due to the steric interaction with the exocyclic olefin. Since

(66) The rest of the mass is recovered starting material along with some of the corresponding allylic aldehyde. Rigorous exclusion of oxygen from the solvent minimized the formation of the oxidation byproduct. This is also true for the reaction of compound **23**.
(67) Ono, T.; Tamaoka, T.; Yuasa, Y.; Matsuda, T.; Nokami, J.; Wakabayashi, S. *J. Am. Chem. Soc.* **1984**, *106*, 7890−7893.
(68) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *36*, 4775−4778.
(69) Trost, B. M.; Flemming, I.; Paquette, L. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Elsevier: Oxford, 1991; Vol. VI, pp 899−904.
(70) Trost, B. M.; Mallert, S. *Tetrahedron Lett.* **1993**, *34*, 8025−8028.
(71) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1979**, *18*, 563−572.

Scheme 9. Preparation of Substrates **47** and **48a**−**c** and Their Cycloisomerization Reactions[a]



[a] Conditions: (a) *t*-BuLi, $ZnCl_2$, −78 °C to room temperature, then $Pd(PPh_3)_4$ (5 mol %), **22**; (b) K_2CO_3, MeOH, 68% from **21**; (c) *n*-BuLi, $ClCO_2NEt_2$ (**47**); $ClCO_2CH_3$ (**48a**); $ClCO_2i$-Pr (**48b**); $ClCO_2$, *t*-Bu (**48c**), 99%; (d) TBAF, 52−55%; (e) $CpRu(CH_3CN)_3PF_6$ (20 mol %).

only the final S−O bond cleavage by piperidine is irreversible, it does not matter which intermediate, **44** or **45**, is favored in the equilibrium. Only the relative rate of the sigmatropic rearrangement controls the diastereoselectivity, which represents a Curtin−Hammett situation (Scheme 8). It is worth noting that in similar instances, only 50−75% de was obtained through the β-chiral carbon induction.[70]

Revised Strategy. To avoid the difficulty in the homologation of the exocyclic double bond, we decided to introduce the requisite carbon as an alkynyl substituent before the cyclization. However, this strategy has several potential drawbacks. First, after the initial ruthenacyclopentene formation, significant steric interaction between the extra carbon at the terminus of the alkyne and the isopropyl group might slow the already sluggish reaction. Furthermore, the mechanism of both the Pd- and Ru-catalyzed cycloisomerizations indicates that the *E*-geometry of the exocyclic olefin should form exclusively, which will require a subsequent isomerization in some way to allow the intramolecular aldol reaction to form a seven-membered ring. On the other hand, the introduction of an alkynyl substituent might benefit the cycloisomerization. The presence of a terminal alkyne in the substrate slows the Ru-catalyzed cyclization since the Ru catalyst gets tied up in formation of a vinylidene complex. While this is reversible, the rates of these steps are not so fast compared to the cycloisomerization. Preventing such a pathway should, therefore, speed up the cycloisomerization as well as shut down decomposition pathways via the reactive vinylidene intermediates. While the cycloisomerization might suffer from the strain between the substituent at the alkyne and the isopropyl group, the same strain might promote the isomerization of the resulting exocyclic olefin to give the desired *Z*-product. The fact that the initial C-bound Ru enolate can slip to form an O-bound enolate may provide a kinetic pathway for equilibration (see Scheme 9).[3,61]

Four derivatives of compound **23** were prepared in a straightforward fashion by monodesilylation of the Negishi coupling product followed by acylation and deprotection to remove the TBDPS group (**47**,**48a**−**c**, Scheme 9). When amide **47** was subjected to the standard Ru-catalyzed cycloisomerization conditions, no reaction occurred, presumably due to the conformation rigidity associated with amides and the coordination of the amide moiety to the ruthenium catalyst.[72] Reaction of ester **48a** produced three compounds along with some recovered starting material. We identified two separable cyclization products **49a** and **50a** in a ratio of 1.8:1 as well as a hydroxyl group transposition product **51a** (Scheme 9). Satisfactorily, both **49a** and **50a** constitute only the desired diastereomer. It is worth noting that this is the first reported double bond isomerization in enyne cycloisomerization reactions to form six-membered rings.[73]

Table 2. Ru-Catalyzed Cycloisomerization of Compounds **48a**−**c**[a]

entry	substrate	additive	yield (**49**+**50**) (%)[b]	ratio (**49**/**50**)[c]
1	**48a**	none	23 (30% **51a**)	1.8:1
2	**48a**	4Å mol. sieves	14	1:8.2
3	**48a**	water (100 mol %)	54	1.2:1
4	**48a**	DMF (50 mol %)	29	1.2:1
5	**48a**	DMF (100 mol %)	62	1.2:1
6	**48b**	DMF (100 mol %)	60	1.5:1
7	**48c**	DMF (100 mol %)	55	6.7:1

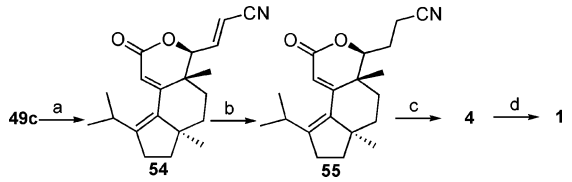
[a] All reactions were performed with 20 mol % of $CpRu(CH_3CN)_3PF_6$ in 2-butanone (0.1 M) at room temperature for 2 h. [b] Yields of **51a**−**c** were not determined except entry 1. [c] Ratio was determined upon isolation. Both geometric isomers were obtained as single diastereomers.

While we were certainly delighted to observe the excellent diastereoselectivity and the isomerization of the exocyclic double bond, the poor yield and the low geometric selectivity represent two major hurdles to overcome. The issue of conversion was addressed first using compound **48a** as a model. Previous experiences in this laboratory with $CpRu(CH_3CN)_3PF_6$ indicate that the reaction can be sensitive to the water content of the solvent. However, no significant change was observed when freshly distilled 2-butanone was used. Interestingly, the conversion deteriorated with the addition of 4 Å molecular sieves, and the ratio of compound **48a** to **49a** was completely reversed (entry 2, Table 2). On the other hand, adding water (100 mol %) to the reaction actually doubled the yield, although the selectivity of the two geometric isomers dropped slightly (entry 3, Table 2). We ascribe the beneficial effect of water to its function as a weak ligand. Following this lead, we assayed a variety of ligands[74] and improved the yield to 62% with DMF as an additive (100 mol %), although the product ratio is still poor (entry 5, Table 2).[75] It is noteworthy that the conversion-promoting effect of DMF was also observed in the reaction of compound **23** as the yield increased from 29% with 35 mol % of catalyst to 41% with 20 mol % of catalyst with 100 mol % of DMF as the additive.

As *E*-isomer **50** is not a viable candidate for the intramolecular aldol cyclization to form a seven-membered ring, we attempted to further increase the ratio of compound **49**.[76] Using the proposed rationale as a guide, we reasoned that by increasing

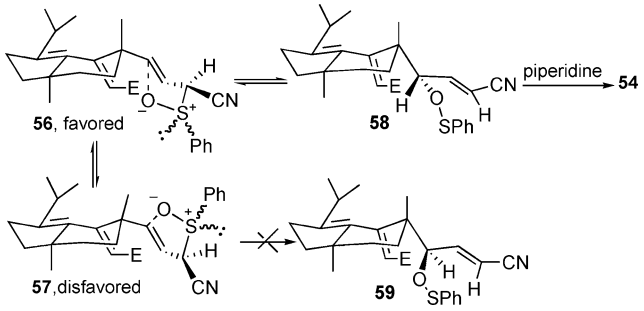
(72) We also synthesized the corresponding unsaturated nitrile and aldehyde. The reaction of the nitrile derivative gave recovered starting material because of its strong coordination with Ru and subsequent deactivation of the catalyst. The aldehyde derivative generated a cyclization product which is too labile to be isolated.
(73) For complete double bond isomerization in seven-membered ring formation, see ref 61.
(74) Other weak phosphorus-containing ligands, such as triphenylphosphine oxide and phosphonate, suppressed the conversion to less than 3%.
(75) No reaction was observed with DMF as solvent.
(76) Attempts to isomerize the double bond by treatment with diphenyl disulfide in the presence of light led to decomposition of the starting material.

Scheme 10. Synthesis of (+)-Allocyathin B_2[a]



[a] Conditions: (a) $PhS(O)CH_2CN$, piperidine, 75%; (b) 10% Pd/C, H_2, 83%; (c) DIBAL-H; (d) KOH, MeOH, 60 °C, 51% from **55**.

Scheme 11. Mechanistic Rationale for the Hydroxylative Knoevenagel Reaction to Form **54**



the size of the ester we might be able to accentuate the strain and thus promote the double bond isomerization. Indeed, we observed a drastic improvement in the ratio of compound **49** by changing methyl ester (**48a**) to *tert*-butyl ester (**48c**) as the most relief was achieved in the latter case (Table 2). In the event, a 55% combined yield of the 6.7:1 ratio of products **49c** and **50c** was obtained, and the pure diastereomer **49c** was isolated in 48% yield.

In the next hydroxylative Knoevenagel reaction, we obtained lactone **54** in good yield as one diastereomer instead of the expected alcohol (Scheme 10).[67] Although *tert*-butyl esters have been used to block the possible lactonization, the rigid conformation of our substrates greatly accelerated the cyclization process. The C12−C13 double bond was then selectively hydrogenated to generate compound **55** in satisfactory yield.

The absolute configuration of the oxygen-bearing stereocenter was later shown to be *S* by comparison to the final product. This stereochemical outcome is the opposite of what was expected based on the results of compound **38**. The rationale for this unusual observation is outlined in Scheme 11. We propose that the *E*-vinyl ester forces the migrated olefin to be parallel to the plane of the bicycle instead of perpendicular, as in the previous case shown in Scheme 8. The preferred route of sigmatropic rearrangement would be from the bottom (intermediate **56**) instead of from the top (intermediate **57**), where a quaternary methyl group interferes (Scheme 11). The altered rearrangement trajectory leads to a reversal from the stereoselectivity predicted by previous experiments.

With the stage set for the endgame, we attended to the closure of the final seven-membered ring through an intramolecular aldol condensation of lactol−aldehyde **4**, as summarized in Scheme 10.[77,78] The spectroscopic properties of the synthetic sample were in full agreement with those reported in the literature.[27−29] Since the preparation of erinacine A (**3**) through the glycosidation of **1** has been described by Snider et al.,[28,29] this asymmetric route also constitutes a formal synthesis of this natural product. An alternative approach for the asymmetric synthesis of allocyathin B_2 also appeared recently.[79]

Summary. We demonstrate for the first time a mechanism-based stereochemical divergence in Pd- and Ru-catalyzed cycloisomerizations. Building upon these enyne cycloisomerizations, we have achieved an efficient enantioselective synthesis of a cyathin diterpene, (+)-allocyathin B_2 (**1**). Additional highlights of this route include a Pd-catalyzed enolate AAA reaction to build the first quaternary carbon and a unique hydroxylative Knoevenagel reaction to stereoselectively introduce the oxygen-bearing center. The unusual olefin isomerization in the Ru-catalyzed cycloisomerization was also investigated and exploited. The synthesis consists of a longest linear sequence of 17 steps and a total of 19 steps from 2-methylcyclopentanone.

Experimental Procedures

[(5*S*,7*aS*)-3-Isopropyl-5,7*a*-dimethyl-4-methylene-2,4,5,6,7,7*a*-hexahydro-1*H*-inden-5-yl]acetaldehyde (15). To a solution of compound **14** (55.0 mg, 0.224 mmol) in toluene (2.2 mL) were added $Pd_2(dba)_3{\cdot}CHCl_3$ (3.5 mg, 0.00335 mmol) and *o*-trifluoromethylbenzoic acid (6.3 mg, 0.0335 mmol) at room temperature. The mixture was stirred at 70 °C for 15 h and cooled to room temperature. The mixture was directly purified by column chromatography (5% ether in petroleum ether) to afford compound **15** as a clear oil (33.1 mg, 60%): $[\alpha]_D$ = +206.3° (*c* 3.1, 24.4 °C, CH_2Cl_2); IR (neat) 2959, 1723, 1459, 1370, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.60 (dd, J = 4.4, 4.0 Hz, 1 H), 5.02 (d, J = 1.6 Hz, 1 H), 4.79 (d, J = 1.6 Hz, 1 H), 2.81 (sept, J = 7.2 Hz, 1 H), 2.56 (dd, J = 14.8, 1.2 Hz, 1 H), 2.04 (dd, J = 14.4, 4.8 Hz, 1 H), 1.79 (m, 1 H), 1.64−1.57 (m, 6 H), 1.49 (m, 1 H), 1.22 (s, 3 H), 1.00 (dd, J = 6.8, 1.6 Hz, 3 H), 0.93 (m, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.2, 148.4, 142.3, 139.1, 110.2, 50.0, 48.7, 39.6, 39.5, 37.8, 36.8, 28.2, 26.4, 25.1, 23.1, 21.6, 21.4. HRMS calcd for $C_{17}H_{26}O$ [M^+]: 246.1984. Found: 246.1990.

(*E*)-(*S*)-4-Hydroxy-4-[(5*S*,7*aR*)-3-isopropyl-5,7*a*-dimethyl-4-methylene-2,4,5,6,7,7*a*-hexahydro-1*H*-inden-5-yl]but-2-ene nitrile (17). To a solution of compound **15** (30.0 mg, 0.122 mmol) in benzene (1 mL) was added phenylsulfinyl acetonitrile (24.1 mg, 0.146 mmol) followed by piperidine (12.5 mg, 0.146 mmol) at room temperature. The mixture was stirred at room temperature for 15 h and was directly purified by column chromatography (30% ether in petroleum ether) to afford compound **17** as white crystals (23.9 mg, 69%): mp 181−182 °C; $[\alpha]_D$ = +102.3° (*c* 0.72, 23.5 °C, CH_2Cl_2); IR (neat) 3455, 2232, 1630, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.70 (dd, J = 16.0, 3.0 Hz, 1 H), 5.67 (dd, J = 16.0, 2.5 Hz, 1 H), 5.02 (d, J = 1.5 Hz, 1 H), 4.85 (d, J = 1.5 Hz, 1 H), 4.46 (m, 1 H), 2.82 (sept, J = 7.0 Hz, 1H), 2.33 (m, 2 H), 1.85 (m, 1 H), 1.78 (m, 1 H), 1.65 (m, 1 H), 1.56−1.53 (m, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.93 (m, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.5, 147.0, 142.5, 139.5, 118.0, 112.4, 99.4, 71.7, 49.0, 45.5, 39.9, 36.7, 33.6, 28.4, 26.7, 23.3, 21.8, 21.6, 18.7. HRMS calcd for $C_{19}H_{27}NO$ [M^+]: 285.2093. Found: 285.2083.

(*E*)-(*R*)-5-(2-Ethynyl-3-isopropyl-1-methylcyclopent-2-enyl)-3-methylpent-2-en-1-ol (23). To a solution of the compound **21** (110 mg, 0.293 mmol) and anhydrous $ZnCl_2$ (39.8 mg, 0.293 mmol) in THF (3 mL) was added *t*-BuLi (1.4 M in pentane, 0.627 mL, 0.818 mmol) at −78 °C in 10 min. The mixture was stirred for 5 min at this temperature and warmed to room temperature for 1 h. The resulting yellow solution was transferred through cannular to a mixture of vinyl iodide **22** (100.4 mg, 0.322 mmol) and $Pd(PPh_3)_4$ (16.9 mg, 0.146 mmol) at room temperature. The reaction mixture was stirred overnight before the addition of ether (30 mL) and water (15 mL). After separation of the layers, the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried

(77) Various conditions were attempted, including CSA/benzene reflux, L-proline, pyrrolidine/acetic acid, as well as alumina.
(78) Ho, P.-T. *Tetrahedron Lett.* **1978**, *19*, 1623−1626.
(79) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897−4990.

($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was *immediately* purified with column chromatography (3% ether in petroleum ether) to furnish the coupled product as a light yellow liquid, which was contaminated with traces of unreacted vinyl iodide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (m, 4 H), 7.36 (m, 6 H), 5.27 (t, J = 4.2 Hz, 1 H), 4.15 (d, J = 6.0 Hz, 2 H), 2.92 (sept, J = 7.0 Hz, 1H), 2.27 (m, 2 H), 1.90 (m, 1 H), 1.77 (m, 1 H), 1.44 (m, 1 H), 1.38 (s, 3 H), 1.21−1.06 (m, 3 H), 1.00 (m, 3 H), 0.99 (s, 9 H), 0.98 (m, 6 H), 0.15 (s, 6 H).

To a solution of the above product in THF (2 mL) was added TBAF (1 M in THF, 0.585 mL, 0.585 mmol) at room temperature. The mixture was stirred for 1 h and treated with brine (5 mL) and ether (15 mL). After separation of the layers, the aqueous phase was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (25% ether in petroleum ether) to provide compound **23** (51.8 mg, 72%) as a light yellow liquid: $[\alpha]_D$ = + 2.26 (*c* 0.53, 23.3 °C, dichloromethane); IR (neat) 2960, 2137, 1458, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.40 (t, J = 4.2 Hz, 1 H), 4.11 (d, J = 6.9 Hz, 2 H), 3.08 (s, 1H), 2.94 (sept, J = 6.6 Hz, 1H), 2.39 (t, J = 7.8 Hz, 2 H), 1.94 (m, 2 H), 1.82 (m, 1 H), 1.67 (s, 3 H), 1.62−1.41 (m, 4 H), 1.07 (s, 3 H), 1.01 (d, J = 1.5 Hz, 3 H), 0.98 (d, J = 1.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 140.7, 123.6, 122.9, 81.8, 79.6, 59.4, 49.9, 38.3, 34.8, 34.7, 29.2, 28.8, 26.0, 21.0, 20.8, 16.4. HRMS calcd for $C_{17}H_{26}O$ [M$^+$]: 246.1984. Found: 246.1975.

(5*S*,7*aR*)-(3-Isopropyl-5,7*a*-dimethyl-4-methylene-2,4,5,6,7,7*a*-hexahydro-1*H*-inden-5-yl)acetaldehyde (33). To a solution of compound **23** (165 mg, 0.67 mmol) and DMF (49.0 mg, 0.67 mmol) in 2-butanone (7 mL) was added $CpRu(CH_3CN)_3PF_6$ (58 mg, 0.134 mmol) in one portion at room temperature. The mixture was stirred for 2 h and concentrated under reduced pressure. The crude material was purified by column chromatography (8% ether in petroleum ether) to provide compound **33** (67.6 mg, 41%) as a clear liquid: $[\alpha]_D$ = +120.0° (*c* 1.2, 26.3 °C, dichloromethane); IR (neat) 2927, 1727, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.88 (m, 1 H), 4.78 (d, J = 1.0 Hz, 1 H), 4.65 (d, J = 1.0 Hz, 1 H), 2.77 (sept, J = 7.0 Hz, 1 H), 2.50 (dd, J = 15.5, 3.0 Hz, 1 H), 2.42 (dd, J = 15.5, 3.0 Hz, 1 H), 2.27 (m, 2 H), 1.80 (m, 2 H), 1.69 (m, 1 H), 1.54 (m, 3 H), 1.42 (m, 1 H), 1.03 (s, 3 H), 0.92 (d, J = 7.0 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.86 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.2, 149.9, 142.5, 139.3, 108.9, 53.5, 39.9, 39.4, 37.0, 35.8, 29.9, 28.5, 26.7, 25.3, 23.4, 21.8, 21.6. HRMS calcd for $C_{17}H_{26}O$ [M$^+$]: 246.1984. Found: 246.1990.

(*E*)-(*R*)-4-Hydroxy-4-[(5*S*,7*aR*)-(3-isopropyl-5,7*a*-dimethyl-4-methylene-2,4,5,6,7,7*a*-hexahydro-1*H*-inden-5-yl)]but-2-enenitrile (38). To a solution of compound **33** (66.0 mg, 0.268 mmol) and phenylsulfinyl acetonitrile (53.1 mg, 0.322 mmol) in benzene (2.7 mL) was added piperidine (27.4 mg, 0.322 mmol) dropwise at room temperature. The mixture was stirred for 24 h and purified directly by column chromatography (2:1, petroleum ether/ether) to give compound **38** as a pale yellow solid (33.6 mg, 44%): $[\alpha]_D$ = +150.6° (*c* 1.16, 22.7 °C, dichloromethane); IR (neat) 3476, 2225, 1678, 1450, 1257 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (dd, J = 16.0, 4.0 Hz, 1 H), 5.79 (dd, J = 16.0, 2.5 Hz, 1 H), 4.98 (s, 1 H), 4.79 (s, 1 H), 4.54 (m, 1 H), 2.83 (sept, J = 7.0 Hz, 1H), 2.34 (m, 2 H), 1.96 (d, J = 5.0 Hz, 1 H), 1.74 (m, 2 H), 1.59 (m, 3 H), 1.03 (s, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.4, 148.0, 142.6, 139.3, 117.6, 109.1, 100.6, 76.1, 48.6, 48.2, 45.4, 43.1, 39.0, 36.2, 31.3, 28.4, 26.5, 26.3, 25.0, 24.1, 23.1, 21.6, 21.4, 20.4. Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 80.12; H, 9.54; N, 4.78.

(*E*)-[(5*S*,7*aR*)-3-Isopropyl-5,7*a*-dimethyl-5-(2-oxoethyl)-1,2,5,6,7,7*a*-hexahydroinden-4-ylidene]acetic acid *tert*-butyl ester (49c). To a solution of compound **48c** (184.5 mg, 0.533 mmol) in 2-butanone (5.3 mL) and DMF (38.9 mg, 0.533 mmol) was added $CpRu(CH_3CN)_3PF_6$ (46.3 mg, 0.107 mmol). The yellow solution was stirred at room temperature for 2 h and concentrated under reduced pressure. The crude material was purified by column chromatography (4% ether in petroleum ether) to give compounds **49c** (less polar) and **50c** (more polar). Compound **49c** (88.6 mg, 48%, light yellow oil): $[\alpha]_D$ = +266.0° (*c* 1.80, 23.7 °C, dichloromethane); IR (neat) 2959, 1750, 1708, 1456, 1368, 1143 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.83 (t, J = 3.6 Hz, 1 H), 5.51 (s, 1 H), 3.06 (dd, J = 18.0, 4.0 Hz, 1 H), 2.91 (dd, J = 18.0, 4.0 Hz, 1 H), 2.86 (sept, J = 6.8 Hz, 1H), 2.34 (m, 2 H), 1.71 (m, 2 H), 1.62 (m, 2 H), 1.51 (m, 1 H), 1.48 (s, 9 H), 1.42 (m, 1 H), 1.32 (s, 3 H), 1.01 (m, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 0.98 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.3, 166.4, 154.2, 145.8, 140.9, 118.7, 80.6, 51.1, 48.2, 40.3, 38.9. 36.2, 35.3, 28.5, 28.1, 26.5, 25.5, 24.5, 21.6, 21.4. HRMS calcd for $C_{22}H_{34}O_3$ [M$^+$]: 346.2508. Found: 346.2508.

(*E*)-(3*S*,3*aR*,5*aR*)-3-(1-Isopropyl-3*a*,5*a*-dimethyl-8-oxo-2,3,3*a*,4,5,5*a*,6,8-octahydro-7-oxacyclopenta[*a*]naphthalen-6-yl)-acrylonitrile (54). To a solution of compound **49c** (20.7 mg, 0.060 mmol) and phenylsulfinyl acetonitrile (13.8 mg, 0.084 mmol) in benzene (0.6 mL) was added piperidine (7.1 mg, 0.084 mmol) at room temperature. The mixture was stirred for 36 h and directly purified by column chromatography (petroleum ether/ether, 2:1) to give compound **54** as a white solid (13.9 mg, 75%): mp 130−131 °C, $[\alpha]_D$ = +667.9° (*c* 0.57, 24.6 °C, dichloromethane); IR (neat) 2957, 2227, 1724, 1678, 1451, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.71 (dd, J = 16.0, 3.5 Hz, 1 H), 5.95 (dd, J = 16.0, 2.0 Hz, 1 H), 5.77 (s, 1 H), 4.75 (dd, J = 4.0, 2.0 Hz, 1 H), 2.89 (sept, J = 6.5 Hz, 1 H), 2.48 (m, 2 H), 1.84 (m, 2 H), 1.76 (m, 2 H), 1.65 (m, 2 H), 1.57 (s, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 0.99 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 160.0, 153.1, 146.3, 133.8, 130.3, 116.7, 113.7, 103.1, 82.8, 48.4, 40.1, 39.0, 35.4, 32.3, 29.3, 27.1, 23.4, 21.6, 21.4, 17.8. HRMS calcd for $C_{20}H_{25}NO_2$ [M$^+$]: 311.1885. Found: 311.1865.

(+)-Allocyathin B$_2$ (1). To a solution of compound **55** (10.0 mg, 0.032 mmol) in CH_2Cl_2 (0.5 mL) was added DIBAL-H (1 M in hexanes, 0.128 mL, 0.128 mmol) at −78 °C. The mixture was stirred at this temperature for 2 h and quenched with the addition of 1 M $NaHSO_4$ (0.4 mL). The suspension was warmed to room temperature for 15 min and extracted with ether (2 × 5 mL). The organic layer was washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude aldehyde **4** was used directly for the next step. Aldehyde **4**: ^{1}H NMR ($CDCl_3$, 500 MHz, mixture of two diastereomers) major: δ 9.88 (s, 1 H), 5.88 (m, 1 H), 5.22 (m, 1 H), 3.85 (d, J = 6.5 Hz, 1 H), 3.74 (m, 1 H), 3.66 (m, 1 H), 2.86 (m, 1 H), 2.57−2.39 (m, 4 H), 2.33 (m, 2 H), 1.98 (m, 1 H), 1.72 (m, 1 H), 1.67 (m, 2 H), 1.52 (m, 3 H), 1.35 (m, 2 H), 1.03 (m, 3 H), 0.99−0.96 (m, 6 H), 0.94 (s, 3 H); minor: δ 9.88 (s, 1 H), 5.37 (m, 1 H), 5.09 (m, 1 H), 3.87 (d, J = 6.5 Hz, 1 H), 3.75 (m, 1 H), 3.58 (m, 1 H), 2.86 (m, 1 H), 2.33 (m, 2 H), 1.98 (m, 1 H), 1.72 (m, 1 H), 1.67 (m, 2 H), 1.52 (m, 3 H), 1.35 (m, 2 H), 1.03 (m, 3 H), 0.99−0.96 (m, 6 H), 0.92 (s, 3 H).

To a solution of the crude dialdehyde **4** in MeOH (1.0 mL) was added 5% KOH in MeOH (1.0 mL). The mixture was stirred at 60 °C for 1 h. The reaction was quenched with the addition of 10% citric acid solution (3 mL) and was concentrated under reduced pressure. The aqueous residue was extracted with ether (2 × 5 mL). The combined organic layers were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5:1 EtOAc/petroleum ether) to give (+)-allocyathin B$_2$ (**1**, 4.9 mg, 51%) as a pale yellow oil: $[\alpha]_D$ = +482.3° (*c* 0.18, 23.6 °C, methanol); lit. $[\alpha]_D$ = +144° (*c* 0.18, methanol);[15,79] IR (neat) 3442, 1668, 1571, 2959 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.45 (s, 1 H), 6.82 (dd, J = 8.0, 6.5 Hz, 1 H), 5.94 (d, J = 8.0 Hz, 1 H), 3.73 (m, 1 H), 3.16 (dd, J = 18.5, 6.0 Hz, 1 H), 2.83 (sept, J = 6.5 Hz, 1 H), 2.55 (br, d, J = 18.5 Hz, 2 H), 2.53 (m, 1 H), 2.42 (dd, J = 9.5, 2.5 Hz, 1 H), 2.41 (d, J = 13.5 Hz, 1 H), 1.74 (ddd, J = 12.5, 7.5, 5.0 Hz, 1 H), 1.69−1.65 (m, 3 H), 1.61 (br, m, 1 H), 1.34 (dt, J = 14.0, 3.5 Hz), 1.05 (d, J = 7.0 Hz, 3 H), 1.00

(s, 3 H), 0.97 (d, $J = 7.0$ Hz, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.2, 155.1, 146.5, 144.4, 151.8, 137.7, 119.3, 74.0, 49.1, 48.2, 38.2, 36.5, 33.9, 29.2, 29.0, 27.0, 26.5, 23.9, 21.5, 21.5. HRMS calcd for $C_{20}H_{28}O_2$ [M^+]: 300.2089. Found: 300.2077.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their generous support of our program. Mass spectra were provided by the Mass Spectrometry Facility, University of California, San Francisco, supported the NIH Division of Research Resources. We are grateful to Prof. H. Kawagishi for sharing the optical rotation and NMR spectra of (+)-allocyathin B_2.

Supporting Information Available: Full experimental procedures and characterization data as well as copies of the NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA051547M