The Palladium-Catalyzed Enyne Cycloisomerization Reaction in a General Approach to the Asymmetric Syntheses of the Picrotoxane Sesquiterpenes. Part I. First-Generation Total Synthesis of Corianin and Formal Syntheses of Picrotoxinin and Picrotin

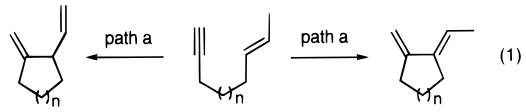
Barry M. Trost,* Curt D. Haffner, David J. Jebaratnam, Michael J. Krische, and Andrew P. Thomas

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received January 19, 1999

Abstract: The palladium-catalyzed enyne cycloisomerization is used as a key ring-forming process for the obtention of the cis-fused hydrindane carbon skeleton characteristic of the picrotoxanes sesquiterpenes. The enyne cycloisomerization product is suitably functionalized so that each carbon of the hydrindane core can be modified to permit access to many members of the picrotoxane family, not only to picrotoxinin itself. Part I of this report describes our first-generation approach to the picrotoxane sesquiterpenes as illustrated by the asymmetric synthesis of corianin and the asymmetric formal syntheses of picrotoxinin and picrotin. A new catalyst system to effect the cycloisomerization emerged from this study. Subsequent work proved the generality of this catalyst system.

The development of new synthetic methodology becomes enabling to devise new synthetic strategies to complex molecules. As part of our program to invent more atom economical reactions,[1] we have been developing the palladium-catalyzed cycloisomerizations and cycloreductions of enynes[2] and diynes.[3] These reactions proceed under very mild conditions to generate five-, six-, and seven-membered rings. The cycloisomerization of enynes to generate cyclic 1,4-dienes may be likened to an Alder ene reaction. However, the ability to use a transition metal should not only lower the temperature for this normally rather high temperature reaction, thus broadening the scope to thermally labile substrates, but should also provide opportunities for enhanced selectivity. For example, by virtue of the mechanism of the thermal Alder ene reaction, only 1,4-dienes may be accessed (eq 1, path a). However, in the palladium-catalyzed



reaction, both 1,4- (eq 1, path a) and 1,3-dienes (eq 1, path b) may be made.[2,4] The catalyst may exercise control of regio-, diastereo-, and enantioselectivity in ways simply not possible thermally.

The true utility of the reaction is defined by its ability to overcome any obstacles that are thrown in its path by the demands of a particular molecular environment of a given substrate. Again, an advantage of the transition-metal catalyzed version is the ability to tune the catalyst, normally by ligand modification, to clear any such hurdles. Transition-metal-catalyzed reactions frequently show a sensitivity to steric effects. The ability to form quaternary centers, a traditionally difficult task, becomes a notable objective. The picrotaxanes offered a structural challenge to this methodology since it required an even more challenging task—i.e., to form two adjacent quaternary centers. Furthermore, they represent a chemoselectivity issue since the substrate must also bear a tertiary allylic alcohol that would be particularly prone to ionization.

The picrotoxane sesquiterpenes are a growing family of natural products with a chemical history extending back to the 1600s where there exist the first written accounts of Indian natives using the poisonous berries of *Menispermum cocculus* to stun fish and kill body lice. In 1811, the poisonous constituent, named picrotoxin, was isolated[5] and 75 years later was realized to be a mixture comprised of a toxic principle, picrotoxinin, and nontoxic picrotin.[6] It was not until 1951 that the correct structure of picrotoxinin was elegantly deduced in the now classical studies of Harold Conroy.[7] The structural assignment and absolute stereochemistry was later verified by X-ray crystallographic analysis.[8] One of the most toxic substances of plant origin known ($LD_{50} = 3.0$ mg/kg),[9] picrotoxinin is a potent

(1) Trost, B. M. *Science* **1991**, *254*, 1471; Trost, B. M. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 259; Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

(2) (a) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255. (b) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. (c) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. (d) For a review, see: Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.

(3) Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146.

(4) For an illustrative application of the resultant 1,3-diene in total synthesis, see: Trost, B. M.; Hipskind, P. A. *Tetrahedron Lett.* **1992**, *33*, 4541; Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. *Angew. Chem., Int. Ed. Eng.* **1989**, *28*, 1502.

(5) Boulley, P. F. G. *Ann. Chim. Phys.* **1811**, *80*, 209.

(6) Barth, L.; Kretschy, M. *Monatsh. Chem.* **1884**, *5*, 65; Meyer, R. J.; Bruger, P. *Chem. Ber.* **1896**, *31*, 2958; Hormann, P. *Chem. Ber.* **1912**, *45*, 2090.

(7) Conroy, H. *J. Am. Chem. Soc.* **1951**, *73*, 1889; Conroy, H. *J. Am. Chem. Soc.* **1952**, *74*, 491, 3046; Conroy, H. *J. Am. Chem. Soc.* **1957**, *79*, 1726, 5550.

(8) Craven, B. M. *Tetrahedron Lett.* **1960**, 21.

(9) Jarboe, C. H.; Porter, L. A.; Buckler, R. T. *J. Med. Chem.* **1968**, *11*, 729.

10.1021/ja9901821 CCC: $18.00
Published on Web 06/19/1999

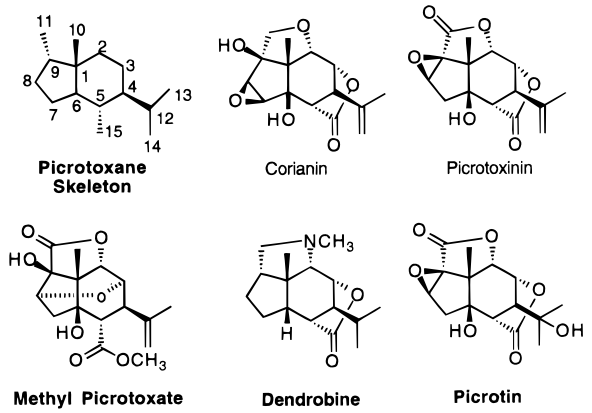


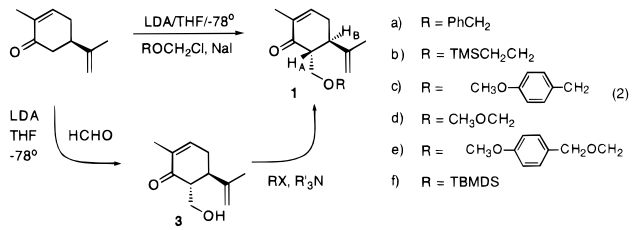
Figure 1. Picrotoxane targets *via* palladium catalyzed cycloisomerization.

and specific antagonist against the neurotransmitter suppressor γ-aminobutyric acid (GABA)[10] and inhibits the opening of chloride ion channels in vivo.[11] To date, over 50 picrotoxane related compounds possessing similar biological activity have been isolated not only from plants, but also from marine and terrestrial animals as well. Their ubiquity, novel structure, and remarkable neurochemical properties have prompted intense investigations which have been reviewed by chemists[12] and biologists alike.[13] The high potency, unusual pentacyclic structure, and density of functionality, characteristic of the picrotoxanes, have made them challenging targets for synthesis.[14] In pursuing our goal of developing a synthetic strategy revolving around palladium-catalyzed cycloisomerization, the structural demands of the picrotoxane skeleton required a modification of the catalyst and led to a novel new family of ligands that are generally effective for palladium-catalyzed cycloisomerizations. Herein, we provide a detailed account of our previously, largely unreported, first-generation approach to the picrotoxane sesquiterpenes (Figure 1).

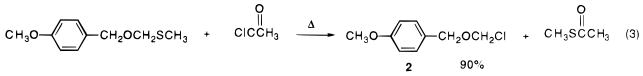
Retrosynthesis. Scheme 1 represents a general retrosynthetic analysis. A key aspect of this approach involves the transfer of stereochemical information around the cyclohexyl core of the hydrindane skeleton by a series of 1,2-asymmetric induction events. In particular, the success of this strategy hinged upon the formation of a quaternary carbon center by use of the palladium-catalyzed enyne cycloisomerization reaction. Thus, representative picrotoxanes corianin and picrotoxinin may be envisioned to derive from the bicycle **II** which possesses all of the carbons required and has the appropriate functionality to adjust the oxidation level as needed to access each of the picrotoxanes illustrated. The bicycle **II** may be accessed via the intramolecular Alder ene reaction of enyne **I** which may, in turn, be obtained from (*R*)-carvone (Scheme 1).

Preparation of Cycloisomerization Substrate. The diastereoselective introduction of the alkoxymethyl group at the α-carbon of carvone to give the trans system is favored sterically (i.e., anti to the isopropenyl group) but disfavored stereoelectronically (i.e., axial attack on the enolate having a pseudochair conformation where the isopropenyl group is equatorial forms the cis product). Equilibration of any kinetic mixture to the thermodynamically preferred trans compound was deemed undesirable because of potential elimination issues. The reaction can be performed either by carbonyl addition to formaldehyde or alkylation of chloromethyl ethers.

The alkylation route (eq 2) already provides the product in



the desired protected form and might be more sterically demanding in order to provide the trans stereochemistry. Alkylation to form **1a**−**1c** required maintaining the temperature at −78° for good diastereoselectivity (>12:1). Addition of a catalytic amount of sodium iodide was essential to perform the reaction at −78°. Preparation of *p*-methoxybenzyl chloromethyl ether (**2**)[15] to form **1c** deserves comment since it could not be prepared by standard methods. The versatility by which a PMB group can be removed ranging from oxidative, reductive, to solvolytic made this choice significant to pursue. Equation 3



outlines a practical synthesis from the easily accessed methylthiomethyl ether. The sensitivity of this alkylating agent limited the yield of **1c** to less than 50% compared to 75 and 72% yields for **1a** and **1b**, respectively.

Because of the negative influence of any α substituents on the diastereoselectivity of the next step (vide infra), the carbonyl addition, alkoxymethoxy-protecting groups were examined. Their synthesis proved more facile via the hydroxymethyl derivative **3**. Addition of gaseous formaldehyde[16] to the lithium enolate of carvone provided **3** as essentially a single diastereomer reliably in yields of 62 ± 3% under carefully controlled conditions. Generation of gaseous formaldehyde by thermal depolymerization of paraformaldehyde proved critical. The disproportionation products, methanol and formic acid, are notably detrimental to the reaction. To avoid these byproducts, the temperature of the depolymerization should be kept below 200 °C. To minimize condensation and repolymerization of the tubes leading into the reaction flask, they should be kept short

(10) Ticku, M. K.; Burch, T. P.; Davis, W. *Adv. Biochem. Psychopharmacol*. **1981**, *29*, 411.

(11) Nistri, A.; Constanti, A. *Progress in Neurobiology*; Pergamon: New York, 1979; Vol. 13, pp 117−235.

(12) Koike, K.; Suzuki, Y.; Ohmoto, T. *Phytochemistry* **1994**, *35*, 701; Nagahisa, M.; Koike, K.; Narita, M.; Ohmoto, T. *Tetrahedron* **1994**, *50*, 10859 and reference therein; Castaneda, R.; Bachena, A.; Garcia, E.; Chavez, D.; Meta, R. *J. Nat. Prod.* **1993**, *56*, 1575; Ohmoto, T.; Koike, K.; Fukuda, H.; Mitsunaga, K.; Ogata, K.; Kagei, K. *Chem. Pharm. Bull.* **1989**, *37*, 2988; Wakamatsu, K.; Niiyama, K.; Niwa, H.; Yamada, K. *Chem. Lett.* **1984**, 1763; Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 268; Taylor, W. I., Battersby, A. R., Coscia, C. J., Eds. *Cyclopentanoid Terpene Derivatives*; Dekker: New York, 1969, Chapter 2, pp 147−201; Porter, L. A. *Chem. Rev.* **1967**, *67*, 441.

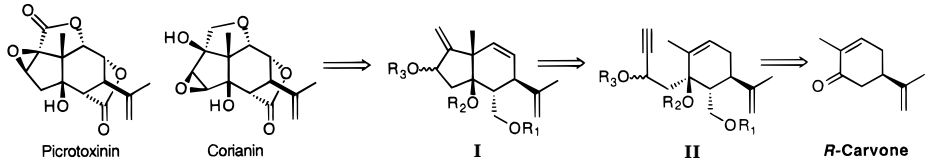
(13) Covey, D. F. *J. Med. Chem.* **1994**, *37*, 275; Nistri, A.; Constantin, A. *Progress in Neurobiology*; Pergamon Press: New York, 1979; Vol. 13, pp 117−235; Narabashi, T. *Physiol. Rev.* **1974**, *54*, 813.

(14) (a) Wakamatsu, K.; Kogoshi, H.; Niiyama, K.; Niwa, H.; Yamada, K. *Tetrahedron* **1986**, *42*, 5551; Niwa, H.; Wakamatsu, K.; Hida, T.; Niiyama, K. Kigoshi, H.; Yamada, M.; Nagase, H.; Suzuki, M.; Yamada, K. *J. Am. Chem. Soc.* **1984**, *106*, 4547. (b) Tanaka, K.; Uchiyama, F.; Sakamoto, K.; Inubishi, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1943, 1948, 1972; Tanaka, K.; Uchiyama, F.; Sakamoto, K.; Inubishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4965. (c) Corey, E. J.; Pearce, H. *J. Am. Chem. Soc.* **1979**, *101*, 5841; Corey, E. J.; Pearce, H. *Tetrahedron Lett.* **1980**, *21*, 1823. (d) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1989**, *111*, 3728.

(15) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762. Kozikowski, A. P.; Wu, J.-P. *Tetahedron Lett.* **1987**, *28*, 5125.

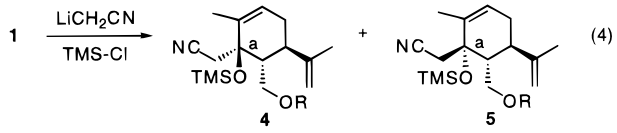
(16) McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *Tetrahedron Suppl.* **1981**, *37*, 319.

Scheme 1. Retrosynthesis of the Picrotoxane Sesquiterpenes



and may be heated to 100°. Alkylation of **3** to form the MOM ether proceeded uneventfully in nearly quantitative yield. We devised a new, more versatile group, the *p*-methoxybenzyloxymethyl (PMBOM) group, to provide the greatest versatility in its removal, especially given the difficulties of removing the MOM ether and the ready access now to **2**. The PMBOM group was also readily introduced to form **1e** in 98% yield by simply stirring an ether solution of the alcohol, PMBOM-Cl, and Hünig's base at room temperature. The TBDMS ether **1f** was also readily available from alcohol **3**.

The addition of an acetaldehyde enolate equivalent must occur axially to create the third contiguous asymmetric center. While torsional strain should favor such a stereochemical outcome, steric strain should favor equatorial attack.[17] Minimizing steric strain requires use of a sterically nondemanding nucleophile. In an ancillary study, we established the viability of metalated acetonitrile to undergo axial attack in both cyclohexanones and cyclohexenones.[18] Addition of lithiated acetonitrile to **1b** gave a 10:1 ratio of **4b:5b** but in only 41% yield (eq 4). A superior

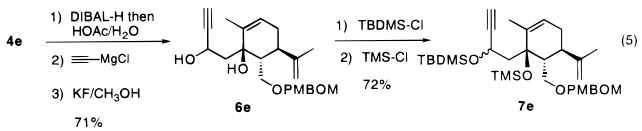


(4)

yield of the adduct was obtained with **1c** (67%) but the **4c:5c** ratio dropped to 5:1. On the other hand, the MOM substrate **1d** gave a 65% isolated yield of **4d** and a 6% isolated yield of **5d**. The PMBOM substrate **1e** proved to be the best, a 75% yield of at least a 14:1 ratio of **4e:5e**. The initial adducts were directly protected as the trimethylsilyl ethers since protection proved necessary for the subsequent addition of an acetylide anion. In the case of the silyl ether protected substrate **1f**, the two alcohols were initially separated to give a 72 and a 14% yield of the axial vs equatorial adducts, respectively. The former was converted quantitatively to its TMS ether **4f**.

The stereochemistry of the major diastereomer was suggested by analogy to our ancillary study and by ^{13}C NMR shifts.[18] In the carbonyl adducts of carvone, C(a) is at a lower field when the alkyl group is axial compared to equatorial. The fact that it appears at δ 97.3 for **4d** and δ 92.9 for **5d** supports the assignment. Obviously, the successful execution of the synthesis provides ultimate verification. While the dominance of torsional strain, even in light of the additional steric hindrance of the α-substituent, explains the results, electronic effects may also account for this stereochemistry.[19]

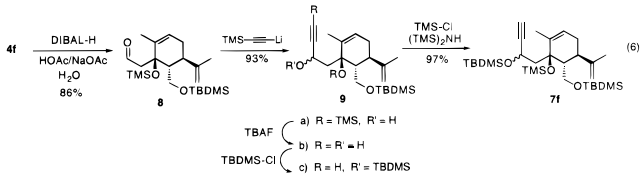
Reduction of the nitrile to the imine followed by in situ hydrolysis with aqueous acetic acid buffered with sodium acetate provides the aldehyde without removal of the TMS ether (eq 5). The aldehyde was directly reacted with ethynylmagnesium



(5)

chloride. Since some silyl migration occurred, the adduct was desilylated with potassium fluoride in methanol to give diol **6e**. Since the stereochemistry at the propargylic center is irrelevant for the synthesis, the fact that a 1:1 mixture of epimers was generated was inconsequential. Silylation with a TBDMS group derivatizes only the secondary alcohol, thereby requiring the sterically less demanding TMS group for the tertiary alcohol and thereby providing the substrate for the cycloisomerization **7e** in nine steps.

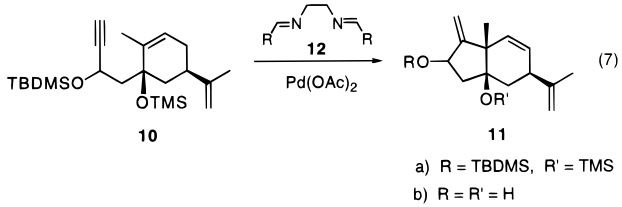
The TBDMS analogues **6f** and **7f** were formed analogously as shown in eq 6. In this case, the aldehyde was isolated and



(6)

reacted with trimethylsilylethynyllithium to give a 3:1 ratio of epimers at the propargylic position. Acetylenic desilylation was accompanied by removal of the TMS group to give diol **9b** which was directly silylated at the propargyl alcohol to give **9c** in 88% yield for the two steps. Final silylation gave the cycloisomerization substrate **7f**. Following a sequence identical to that in eq 5, the MOM ether **4d** was converted to the enyne **7d** in 63% overall yield for the five steps.

Cycloisomerization. Initial efforts for the cycloisomerization were performed with enyne **10**, prepared by a route analogous to that shown in eqs 4 and 6 starting from carvone. Thermal cycloisomerization led only to decomposition. Thus, a catalyzed Alder ene reaction was required. The presence of a tertiary allylic alcohol and the absence of significant Lewis basic sites as part of the ene or enophile make the use of a Lewis acid inoperable. Transition metals which π-coordinate alkynes and alkenes are more neutral catalysts. We were pleased to find that exposure of enyne **10** to bis(triphenylphosphine) palladium acetate in benzene[2a] at 60° effected cyclization to **11** (eq 7).



(7)

Unfortunately, attempts to reproduce that result failed for still inexplicable reasons and subsequently led to only low yields (~10%) of **11** with most of the remaining material resulting from decomposition. Varying the ligand to tri-*o*-tolylphosphine, triphenylarsine, dppb, triisopropyl phosphite, and 2,2′-bipyridyl led to no reaction at room temperature and decomposition upon

(17) Cherest, M.; Felkin, H. *Tetrahedron* **1980**, *36*, 1593; Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.

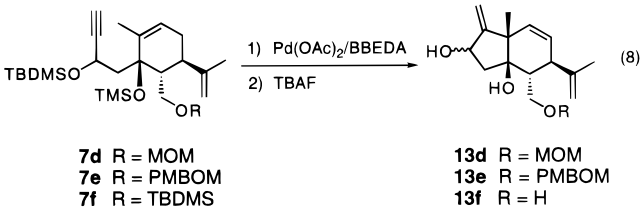
(18) Trost, B. M.; Florez, J.; Jeberatnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613.

(19) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

heating. In the case of dppb, a low yield (~10%) of the desired cycloisomer was observed.

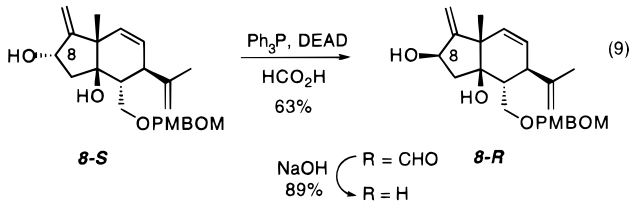
Believing that the main source of the failure was the sensitivity of the product toward the somewhat Lewis acidic catalyst, we buffered the medium with more strongly donating nitrogen ligands such as pyridine derivatives. However, they inhibited the reaction, thereby requiring more forcing conditions to see any reaction which again led to decomposition. Using a nitrogen ligand that could be a reasonable acceptor as well as a donor might better balance the coordinative reactivity of the palladium to permit cycloisomerization but inhibit Lewis acid type decomposition. Imines derived from ethylene diamine and carboxaldehydes including benzaldehyde, furfural, and isobutyraldehyde proved to be effective ligands. Generating a catalyst in situ by mixing equimolar amounts of the bis-imine ligands and palladium acetate (5 mol % of each) effected a clean cyclization to **11** at 50° in either benzene or 1,2-dichloroethane. Ease of preparation, purification by crystallization, and stability led us to favor **12** (R = Ph, BBEDA). Performing the reaction at 0.3−0.5 M in 1,2-dichloroethane at 50° gave a quantitative yield of the cycloisomer **11**, albeit somewhat slowly since 24 h were required.

This set of conditions was then applied to the cyclization of **7d**−**7f**. In each case the crude cyclized product was immediately desilylated to give the diols **13d** and **13e** in 85 and 79% yields, respectively, or the triol **13f** in 75% yield (eq 8). Thus, the fourth

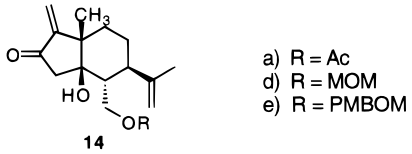


contiguous center is set. The remarkable effect of the ligand on the success of this reaction is to be noted.

The **8*R*-** and **8*S*-** epimer of **13e** are readily separable by flash chromatography and isolated as crystalline solids. They may be interconverted by a Mitsunobu reaction[20] as shown in eq 9.

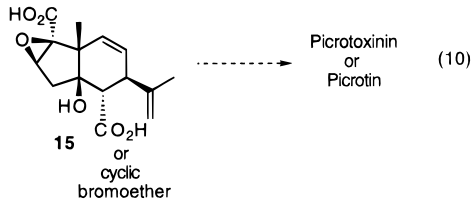


Formal Synthesis of Picrotoxinin and Picrotin. During the course of these studies, Yoshikoshi et al. reported a synthetic approach to the picrotoxane family passing through the intermediate **14a** possessing the full carbocyclic core which they

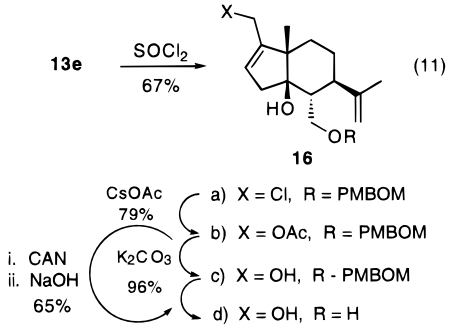


prepared in 27 steps from carvone.[14d] The availability of diol **13** in only 11 steps from carvone by the palladium-catalyzed cycloisomerization strategy made it attractive to correlate it with the Yoshikoshi intermediate which simply required an oxidation of the allylic alcohol to give the MOM- or PMBOM-protected versions, **14d** and **14e**. Manganese dioxide in methylene chloride converted **13d** to **14d** in 65% yield. PDC in DMF proved more effective to convert **13e** to **14e** in 79% yield. In a practical sense, it would be unnecessary to change the protecting groups to complete the total synthesis. Thus, the Yoshikoshi intermediate bearing only a different protecting group is now available in only 12 steps from carvone. However, to be fully correct in completing a formal synthesis, the PMBOM group was converted to the acetate **14a**. Treating ketone **14e** with CAN in aqueous acetonitrile (78%) followed by acetylation (CH_3COCl, DMAP, CH_2Cl_2, 85%) completed this transformation and the synthesis of the identical Yoshikoshi intermediate in 14 steps. While DDQ is normally employed to remove PMB groups[21] and CAN to remove *p*-methoxyphenyl groups,[22] we have found CAN to be the preferred oxidative reagent for removal of the PMB group as well.

A totally different end game from **13** derived from an oxidative bis-lactonization of **15** or its cyclic bromoether as depicted in eq 10 in analogy to the work of Corey and Pearce[14c]



was also envisioned. Isomerization of the allyl alcohol portion of **13** to its allylic isomer **16** which was envisioned to be the most stable isomer proved surprisingly difficult. Attempts to effect "thermodynamic" equilibration failed. The Nozaki protocol of epoxidation−mesylation−reductive cleavage to give triol **16d** proved capricious.[23] Isolated yields ranged as high as 52% but a yield of around 20% was more reproducible. We settled upon the sequence outlined in eq 11. Thionyl chloride



effected replacement of the alcohol by chloride with clean allyl inversion to give **16a**. Displacement by nitrate which has been claimed to be an excellent oxygen nucleophile[24] failed. Use of cesium acetate in DMF at 50 °C to form acetate **16b** proved satisfactory. Hydrolysis to diol **16c** completed the three-step sequence. Attempts to deprotect the PMBOM group of diol **16c** proved unsuccessful. On the other hand, reversing the two steps, i.e., removal of the PMBOM group from acetate **16b** followed

(20) Mitsunobu, O. *Synthesis* **1981**, 1.

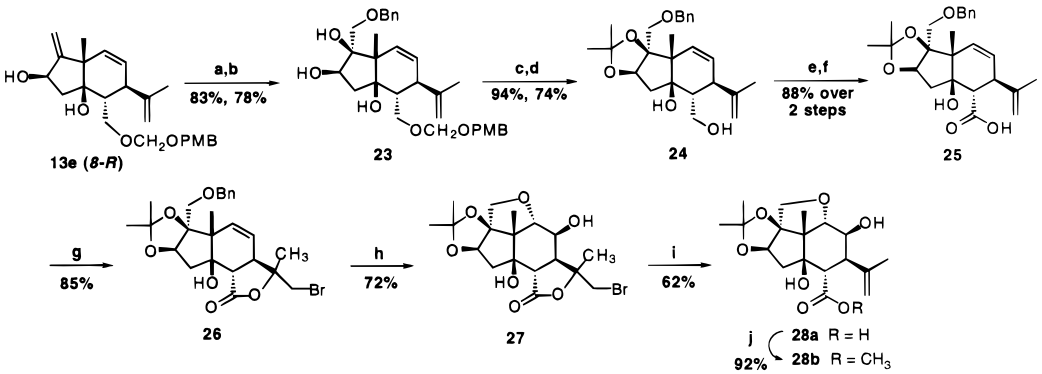
(21) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(22) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.

(23) Yasuda, A.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1976**, 2621.

(24) Cainelli, G.; Manescalchi, F.; Martelli, G.; Panunzio, M.; Plessi, L. *Tetrahedron Lett.* **1985**, *26*, 3369.

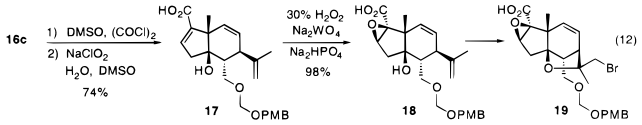
Scheme 2. Chemo- and Stereoselective Oxygenation of Key Intermediate 5[a]



[a] (a) $VO(acac)_2$, ^tBuOOH, DCM, room temperature. (b) $Ti(OBn)_4$, BnOH, 60 °C. (c) DMP, TsOH, acetone, room temperature. (d) DDQ, DCM−H_2O, room temperature. (e) $(COCl)_2$, DMSO, TEA, −78 °C to room temperature. (f) $NaClO_2$, NaH_2PO_4, H_2O−^tBuOH, 2-Methyl-but-2-ene, room temperature. (g) Pyr·HBr_3, $NaHCO_3$, THF, room temperature. (h) CF_3CO_3H, $NaHCO_3$, DCM, room temperature. (i) Zn, NH_4Cl, EtOH, reflux. (j) CH_2N_2, ether, room temperature.

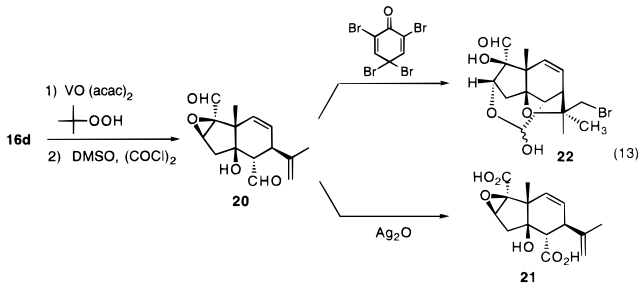
by base hydrolysis (NaOH, CH_3OH), provided the triol **16d** satisfactorily.

Because it was known that the ring conformation influenced the ability to form the final lactones, we wondered whether initial closure of the fused five-membered ring lactone, from a carboxylic acid unit at C-9, might be sufficient to promote the formation of the bridged lactone as well. To explore just the formation of the fused lactone, diol **16c** was converted to the monocarboxylic acid as shown in eq 12. Chemoselective



epoxidation of the *least* electron-rich double bond of the triene **17** was accomplished in excellent yield with pertungstic acid by maintaining the pH around 5−6.[25] Not only was the chemoselectivity with respect to the alkene outstanding, but the PMBOM group, which is oxidatively sensitive, is also compatible. Only a single diastereomer was observed and is assigned as the exo epoxide based upon the strong bias for attack on the convex face of this polyhydroindane skeleton. Attempts to initiate halolactonization of **18** generally failed. With 2,4,4,6-tetrabromocyclohexadiene, only bromoetherification to **19** occurred, but further halolactonization still failed.

The labile diacid **21** could be prepared from triol **16d** as shown in eq 13. Initially, the triol **16d** was oxidized to its



corresponding dialdehyde under Moffatt−Swern[26] conditions. However, further oxidation to the diacid led mainly to decomposition. A more successful strategy initiated the sequence as shown in eq 13 whereby chemoselective epoxidation of the double bond preceded oxidation of the hydroxyl groups to give epoxy-dialdehyde **20**. Oxidation with silver oxide in aqueous *tert*-butyl alcohol proceeded cleanly to the diacid **21** which, however, was difficult to work with. Unfortunately, attempts to perform the oxidative bis-lactonization failed. Haloetherification of diacid **21** also failed. Bromoetherification at the dialdehyde stage appeared to proceed but was accompanied by epoxide ring opening to give **22**. The extraordinarily low reactivity of the 2,3-double bond made electrophically initiated reactions difficult. The oxidative bis-lactonization does not appear to be a general route to the bis-lactones of the picrotaxane type. Our second-generation approach reported in the accompanying manuscript addressed this issue.

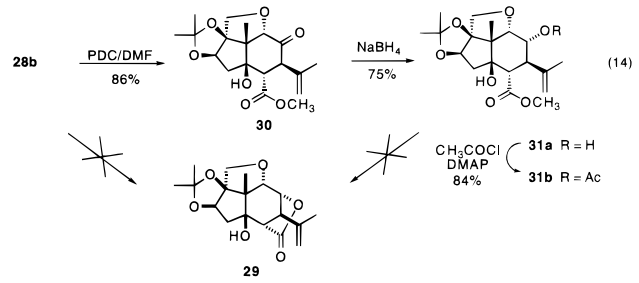
Total Asymmetric Synthesis of Corianin. Since we did complete a formal synthesis of picrotoxinin and picrotin and wanted to show the general versatility of our strategy, we chose to use our key intermediates **13** to approach another member of the picrotoxane family. Corianin, which shows promise as a possible therapeutic agent for schizophrenia and has never been accessed synthetically, seemed a formidable target.[27] Not least among the challenges lay the establishment of nine contiguous chiral centers around a hydrindane skeleton in which every carbon is asymmetrically substituted.

The total synthesis of corianin from key intermediate **13e** (**8-*R***), requires the chemo- and stereoselective dihydroxylation of the C2−C3 and C9−C11 olefins and oxidation of the C15 hydroxyl group to the corresponding carboxylic acid (see Scheme 2). Hydroxy-directed epoxidation of the C9−C11 olefin[28] followed by titanium(IV)benzyloxide-mediated[29] epoxide ring opening[30] proceeded in 83 and 78% yields, respectively, thus accomplishing the stereocontrolled installation of the vicinal hydroxyl functionality at C9 and C11 to provide the partially protected pentol **23** as a single stereoisomer. Exposure of triol **23** to 2,2-dimethoxypropane and catalytic acid which effected conversion of the C8 and C9 vicinal diol functionality to the corresponding acetonide in 94% yield was followed by selective cleavage of the PMBOM at C15 to give the primary alcohol **24** in 74% yield. Conversion to the acid **25** required use of a two-step oxidation sequence—Moffatt−Swern oxidation to the aldehyde followed by chlorite oxidation[31] to the acid. Selective oxidation of the C2−C3 olefin required that the

(25) Kirshenbaum, K. S.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1979.
(26) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
(27) Okuda, T.; Yoshida, T.; Chen, X. M.; Jing, X.; Fukushima, M. *Chem. Pharm. Bull.* **1987**, *35*, 182.
(28) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
(29) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schurrenburger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.
(30) Sharpless, K. B.; Caron, M. *J. Org. Chem.* **1985**, *50*, 1560.

isopropenyl moiety at C4 be masked. Thus, bromolactonization of **25** gave the olefin **26** in 85% yield. Upon exposure to MCPBA or peroxytrifluoroacetic acid, **26** underwent tandem epoxidation−debenzylative cycloetherification to provide a 72% yield of the tetrahydrofuran **27**. Finally, zinc-induced cleavage of the β-halolactone unmasked the C4 isopropenyl moiety, giving the hydroxy acid **28** in 62% yield.

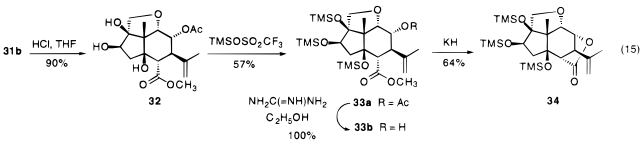
With the bulk of the oxygen functionality installed, the next step taken toward corianin involved formation of the bridged lactone **29** (eq 14). The most direct means of lactonization



(14)

involved activation of the C3 hydroxyl of hydroxy acid **28** as a leaving group to be internally displaced by the C15 carboxylic acid. However, exposure of **28** to Mitsunobu conditions resulted only in recovered starting material. Attempts at derivatizing the C3 alcohol as an alkyl or aryl sulfonate gave similar results. The fact that **28** would not undergo acylation made it clear that the C3 hydroxyl was not easily accessible to external reagents. This prompted us to investigate use of the epimeric C3 alcohol **31** as an internal nucleophile which was prepared by esterifying **28** with diazomethane, followed by oxidization to the ketone **30** in 86% yield. It was our hope that ketone reduction would occur with concomitant lactonization in analogy to the reaction of similar ketoesters found in Roush's,[32a] Kende's,[32b] and Inubishi's[32c] syntheses of (±)-dendrobine. Sodium borohydride reduction did produce the desired α-alcohol **31a** in 75% yield and returned the original β-alcohol **28b** in 10% yield, but lactonization of the former did not occur. All attempts at base-promoted lactonization of **31a**, or the related carboxylic acid and its derivatives, resulted in decomposition or unreacted **31a**.

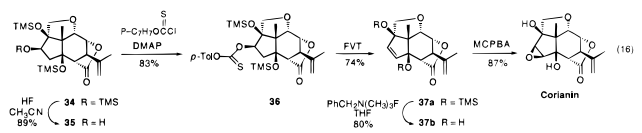
We questioned whether the acetonide moiety might have an adverse effect on the conformational mobility of the system. It was thought that in order to alleviate any disfavorable transannular interactions that might prevent adoption of the requisite conformation for lactonization, a conformationally more mobile system was needed. For this purpose, we chose the differentially protected hydroxyester **33** as our substrate. As shown in eq 15,



(15)

acid hydrolysis of the acetonide **31b** provided the triol monoacetate **32**. Exhaustive silylation with trimethylsilyl triflate and chemoselective deacetylation with guanidine and ethanol in dichloromethane[33] set the stage for lactonization. Gratifyingly, the long sought-after lactone **34** was obtained in 64% yield upon exposure of hydroxyether **33** to potassium hydride in THF at 0 °C. The trimethylsilyloxy substitution in the five-membered ring may play several roles including greater conformational mobility, destabilization of the nonproductive equatorial conformer, and prevention of degradative cleavage between C6 and C5 via a retro-aldol reaction, which has been documented in related systems.

Completion of the synthesis entailed placement of the C7−C8 epoxide. We envisioned carrying out this transformation through the use of the C8 hydroxyl to effect an elimination−epoxidation sequence. To isolate the functionality upon which we desired to act, selective removal of the secondary trimethylsilyl group at C8 was performed in 84% yield by exposure of **34** to aqueous HF in acetonitrile (eq 16). Initial attempts at



(16)

eliminating the C8 alcohol of **35** involved conversion to the mesylate and subsequent treatment with bases such as DBU, potassium *tert*-butoxide, or LDA.[34] Under these conditions, recovered mesylate and degradation were observed. Other attempts to generate the olefin employed Burgess' salt,[35] Martin's sulfurane,[36] copper sulfate on silica gel[37] and copper triflate in Decalin.[38] All met with failure. Realizing that steric approach of a base as required for trans-elimination not only must come from the concave face of the hydrindane but would also be impeded by the presence of the bridged lactone prompted us to investigate the possibility of effecting a cis-elimination. Thus, derivatization of the C8 hydroxyl group as the *p*-tolylthionocarbonate **36** was accomplished in 83% yield.[39] Again, the presence of the silyl-protecting group proved beneficial since it prevented formation of the cyclic thionocarbonate which would be useless. Passing this material through a quartz tube at 500 °C cleanly provided the olefin in 74% yield. At lower temperatures (e.g., 220 °C) distillation of **36** occurred without elimination. Fluorodesilylation of the remaining trimethylsilyl-protecting groups allowed access to the olefinic diol **37** in 80% yield. Hydroxyl group directed epoxidation was envisioned to resolve the required chemoselectivity since, for electronic reasons, reaction at the isopropenyl double bond should have been favored. Indeed, MCPBA at 0° in methylene chloride accomplished this task with complete selectivity to deliver corianin in 87% yield.

Discussion

The palladium-catalyzed cycloisomerization reaction constitutes an increasingly valuable approach for construction of five-, six-, and seven-membered rings. At the present time, the greatest scope has been demonstrated for five-membered ring formation, and the example reported herein dramatically illustrates its

(31) Bal., B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091; Dalcanle, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

(32) (a) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599; Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390; Roush, W. R.; Gills, H. R. *J. Org. Chem.* **1980**, *45*, 4283. (b) Kende, A.; Bently, T. J.; Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332. (c) Inubishi, Y.; Kikuchi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1252.

(33) Kunesch, N.; Miet, C.; Poisson, J. *Tetrahedron Lett.* **1987**, *28*, 3569.

(34) Compare: Tanaka, K. Uchiyana, F.; Sakamoto, K.; Inubushi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4965.

(35) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *36*, 26.

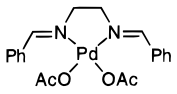
(36) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

(37) Nichiguchi, T.; Machida, N.; Yamamoto, E. *Tetrahedron Lett.* **1987**, *28*, 4565.

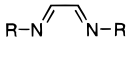
(38) Laali, K.; Gerzina, R. J.; Flajnik, C. M.; Geric, C. M.; Dombroski A. M. *Helv. Chim. Acta* **1987**, *70*, 607.

(39) Gerlach, H.; Huong, T. T.; Muller, W. *J. Chem. Soc., Chem. Commun.* **1972**, 1215.

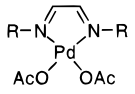
utility. A synthesis of a functionalized bicyclic core of the picrotoxanes has now been constructed in less than half the number of steps previously reported by a completely different route. Our strategy only becomes possible by the palladium-catalyzed cycloisomerization reaction since the thermal reaction of enynes **7** completely fail. The new class of bis-imine ligands represented by **12** presumably form Pd(+2) complexes such as **38**. On the other hand, the bis-imine ligands such as **39** would generate complexes such as **40**, which are not catalysts for this



38



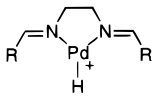
39



40

reaction. Thus, it appears the stronger σ-donation in complexes such as **38** compared to **40** might account for this difference. If a Pd(+2)−Pd(+4) cycle is involved, stronger σ-donation by nitrogen ligands may stabilize such a high oxidation state of the metal.[40] Simple amines and pyridines are too strong σ-donors, which simply inhibits enyne coordination. The bis-imine ligand **39** is too weak a σ-donor and too good a π-acceptor and thereby does not stabilize the Pd(+4) species adequately. In this sense, ligands such as **12** generate complexes such as **38** which have the right balance of σ-donation to stabilize the forming Pd(+4) intermediate as well as sufficient π-acceptor capability that enynes are still capable of coordinating.

On the other hand, we cannot rule out a Pd(0) pathway invoking a hydridopalladium catalyst such as **41**.[2] Once again,



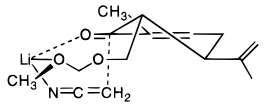
41

ligands such as **12** would have sufficient ability to coordinate to palladium to prefer protonation at palladium rather than nitrogen, in contrast to more basic amine ligands, and be good enough σ-donors to promote the protonation reaction. On the other hand, the bis-imine ligands **39** may not be good enough σ-donors or too strong π-acceptors to permit protonation at palladium in their Pd(0) complexes. Ligands such as **12** can be sterically and electronically tuned by variation of R or the linker between the two nitrogens. Thus, this class may prove to be more generally useful in metal-catalyzed reactions.

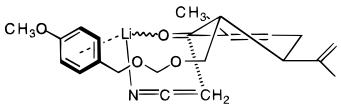
This new family of palladium catalysts has proven to be exceptionally effective for the cycloisomerization of substrates **7d**−**f** and **10** where the more common ligands have failed. They have overcome both the high lability of the substrate as well as the steric congestion. The success of eqs 6 and 7 clearly attest to the power of this method.

Several other features of this synthesis are noteworthy. The use of PMBOM as a protecting group is one aspect. It is easy to put on, has good stability, and most importantly, has a sufficiently diverse range of methods for its removal so that it almost assuredly can also be readily removed in almost any molecular environment. It was for the latter reason that we turned to it. Oxidative cleavage with CAN proved to be the method of choice for its removal herein.

The axial selectivity for the addition of lithiated acetonitrile tests the limits of this diastereoselectivity. We had previously noted[18] that, with this class of nucleophile for carbonyl addition, torsional strain dominated over steric strain, leading to a selectivity for axial attack. However, in the case of **1**, axial attack is further sterically stressed by the presence of the adjacent alkoxymethyl substituent. The validity of this statement is reflected by the effect of the R group of **1** on this reaction. With benzyl, alky, and silyl groups, the axial/equatorial selectivity was typically about 5:1 (the ratio in the case of benzyl itself must be viewed critically since the yield of the adduct was rather low). On the other hand, the MOM-like side chains in the case of **1d** and **1e** gave good ratios. Lithium coordination depicted in **42** and **43** may account for their counter-influence of simple



42



43

steric repulsion disfavoring axial attack. The fact that the PMBOM group gave the best diastereoselectivity may suggest the ability of lithium to coordinate to the π-cloud of a benzene ring, as depicted in **43**. In the case of the simple benzyl-protecting groups (**1a** and **1c**), the tether length is simply too short to permit such π-complexation to lithium.

In the synthesis itself, formation of the bis-lactone rings proved to be very sensitive to the choice of substrate. Remarkably, the choice of the protecting group for the 8,9-diol proved critical. Although, it clearly suggests a conformational effect on the ring system, molecular modeling did not reveal any significant issue wherein the acetonide disfavored the bis-lactone or the bis-silyl ether favored it. More detailed conformational studies of these molecules would be warranted to understand these significant effects.

The current strategy resulted in an efficient synthesis of the core ring system of the picrotoxanes. It led to a formal synthesis of picrotoxinin and picrotin as well as a total synthesis of corianin. It set the stage for our second-generation strategy which culminated in total syntheses of all of these compounds as well as that of methyl picrotoxate via a key common intermediate.

Experimental Section

General. All reactions were run under an atmosphere of nitrogen passed through a tube of calcium carbonate, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe or cannula. Flasks were flame-dried and cooled under a stream of nitrogen. Acetonitrile, benzene, dichloromethane, dichloroethane, hexane, pyridine, triethylamine, and diisopropylamine were distilled from calcium hydride. Dimethyl sulfoxide (DMSO) was distilled at 60 °C at 0.1 mmHg. Dimethylformamide (DMF) was distilled from barium hydroxide at reduced pressure. Ether, tetrahydrofuran (THF), and toluene were distilled from sodium benzophenone ketyl. Methanol and ethanol were distilled from magnesium methoxide and magnesium ethoxide, respectively.

Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. Solvents for chromatography are listed as volume/volume ratios.

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer or a Nicolet 205 1420 spectrophotometer. Elemental analyses were performed by Robertson Laboratories, Madison, New Jersey and M-H-W Laboratories Pheonix, Arizona. High-resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco on a Kratos MS9 and are reported as *m/e* (relative intensity. Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion.

(40) For a review, see: Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian XL-400 (400 MHz), Varian Gemini 200 (200 MHz), or Varian Gemini 300 (300 MHz) spectrometer. Chemical shifts are reported in delta (d) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz).

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian XL-400 (100 MHz), Varian Gemini 200 (50 MHz) or Varian Gemini 300 (75 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center line of the triplet at 77.00 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

Chloro(4-methoxybenzyloxy)methane (2). 4-Methoxybenzyl alcohol (23.0 mL, 0.185 mol) was carefully added dropwise to a slurry of sodium iodide (27.78 g, 0.185 mol) and sodium hydride (8.89 g, 37.0 mmol) in THF (200 mL) under nitrogen at room temperature. After addition when hydrogen evolution had ceased, the mixture was cooled to 0 °C, and chloromethyl methyl sulfide (15.5 mL, 0.185 mol) in THF (50 mL) was added dropwise over 20 min. The reaction mixture was stirred at 0 °C for 2 h and then warmed to room temperature and stirred a further 6 h. Water (300 mL) was carefully added and then ether (150 mL). The organic phase was separated and the aqueous layer extracted with ether (2 × 150 mL). The combined extracts were dried (K_2CO_3) and evaporated in vacuo. The residue was filtered through silica gel, eluting with hexane/ (6:1) to give 4-methoxy-benzyloxymethyl methyl sulfide as an oil, R_f (hexanes/ethyl acetate, 5:1) 0.23. IR ($CDCl_3$) 1614, 1512, 1465, 1439, 1381, 1301 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, 8.7 Hz, 2H), 6.88 (d, 8.7 Hz, 2H), 4.66 (s, 2H), 4.55 (s, 2H), 3.80 (s, 3H), and 2.18 (s, 3H). Calcd for $C_9H_{14}OS$ (M^+): 198.0714. Found: 198.0710. The sulfide then was dissolved in dichloromethane (50 mL) and acetyl chloride (21 mL, 0.278 mol) added to the stirred solution under nitrogen at room temperature. After 4 h, the solvent was evaporated in vacuo and the residue heated to 45 °C at 1 mmHg for 30 min. The residue was redissolved in dichloromethane (20 mL) and stirred under nitrogen at room temperature, and an additional batch of acetyl chloride (7 mL, 0.093 mol) was added. After 2 h, the solvent was evaporated in vacuo and again heated to 45 °C at 1 mmHg for 30 min. The residue was distilled under reduced pressure to give the chloride (**2**) (30.28 g, 88% over two steps) as an oil, bp 110−115 °C at 0.05 mmHg. IR ($CDCl_3$) 1620, 1519, 1472, 1309 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (d, 8.7 Hz, 2H), 6.90 (d, 8.7 Hz, 2H), 6.90 (d, 8.7 Hz, 2H), 5.49 (s, 2H), 4.68 (s, 2H) and 3.81 (s, 3H). HRMS Calcd for $C_9H_{11}ClO_2$ (M^+): 186.0448. Found: 186.0448.

(4*R*,5*R*,6*S*)-1-Methyl-4-isopropenyl-5-(4′-methoxybenzyloxy)-methoxymethyl-6-cyanomethyl-6-trimethylsilyloxycyclohex-1-ene, (4e). *n*-Butyllithium (12.2 mL of a 1.59 M hexane solution, 19.4 mmoL) was added dropwise to a −78 °C THF solution (30 mL) containing acetonitrile (1.08 mL, 797 mg, 19.4 mmol). The reaction was stirred for 40 min at −78 °C, and then enone **1e** (3.37 g, 10.2 mmol) in THF (6 mL) was added dropwise to the reaction via an addition funnel. The mixture was stirred at −78 °C for 2 h and then was carefully quenched with saturated NH_4Cl, poured into saturated NH_4Cl (50 mL) and ether (100 mL) added. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residual oil was dissolved in pyridine (10 mL). Hexamethyldisilizane (1.65 g, 10.2 mmol) and chlorotrimethylsilane (1.66 g, 15.3 mmol) were added. After the mixture stirred at room temperature for 18 h, water and ether were added. The organic layer was separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residual yellow oil was purified via column chromatography (hexanes/ethyl acetate 6:1) yielding 3.45 g (7.8 mmol, 76% yield) of nitrile **4e**, R_f = 0.63 (2:1 hexanes/ethyl acetate), $[\alpha]_D = -15.6°$ (c = 2.41, $CHCl_3$). IR ($CDCl_3$) 3046, 3031, 2952, 2836, 2245, 1613, 1513, 1380, 1301, 1244, 1172, 1087, 1043, 881, 844 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.64 (m, 1H), 4.9−4.8 (m, 2H), 4.71 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.52 (m, 2H), 3.90−3.70 (m, 1H), 3.80 (s, 3H), 3.63 (dd, J = 10.1, 3.8 Hz, 1H), 2.91 (ddd, J = 12.3, 10.0, 6.7 Hz, 1H), 2.70 (s, 2H), 2.20−1.90 (m, 3H), 1.77 (m, 3H), 1.73 (s, 3H), 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.2, 146.1, 135.1, 129.9, 129.3, 126.5, 118.1, 113.8, 112.5,95.3, 69.3, 65.2, 55.1, 48.0, 42.1, 31.1, 26.8, 18.7, 17.5, 1.6. HRMS: Calcd for $C_{25}H_{37}NO_4Si$ [M^+]: 443.2492, found 443.2492. Calcd for $C_{25}H_{37}NO_4$: C, 67.71; H, 8.35; N, 3.16; MW: 443.2492. Found: C, 67.66; H, 8.61; N, 3.13; MW: 443.2492.

(4*R*,5*R*,6*S*,1′*RS*)-1-Methyl-4-isopropenyl-5-(4″-methoxybenzyloxy)methoxymethyl-6-(2′-hydroxybut-3′-yn-1-yl)-6-hydroxylcyclohex-1-ene (6e). To a toluene solution (12 mL) containing nitrile **4e** (4.3 g, 9.7 mmol) at −78 °C was added dropwise via addition funnel DIBAL (9.7 mL of a 1.5 M toluene solution, 14.6 mmol). After addition, the reaction mixture was stirred at −78 °C for 2.5 h. A solution containing acetic acid (2.5 g, 41.7 mmol, 2.4 mL), sodium acetate (2.4 g, 29.1 mmol) and THF (9.5 mL) in water (40 mL) was added dropwise at −78 °C. The flask was warmed to room temperature and kept there for 20 min at which time Celite was added and stirring continued an additional 5 min. The mixture was filtered through a Celite bed with the Celite bed being rinsed thoroughly with ether. The aqueous layer was separated and extracted with ether (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. In a separate flask, butylmagnesium chloride (8.1 mL of a 1.8 M THF solution, 14.6 mmoL) was added dropwise to a saturated solution of acetylene in THF (20 mL) (the acetylene gas was passed through a dry ice acetone trap, a concentrated sulfuric acid trap, and finally a KOH tube before being bubbled into the THF solution), while acetylene continued to bubble through the solution at 0 °C. After the addition of the Grignard reagent was complete, acetylene gas continued to bubble through the solution for 20 min at which time the atmosphere was changed to nitrogen. The crude aldehyde obtained above was dissolved in THF (10 mL) and was added dropwise to the solution at 0 °C. After 1.5 h at 0 °C, saturated NH_4Cl (25 mL) and ether (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residual oil was dissolved in methanol (25 mL), and anhydrous KF (681 mg, 11.7 mmol) was added. The reaction mixture was stirred at room temperature for 5 h, and then the solvent was removed in vacuo. The residue was added to water, the organic layer was extracted with ether (3 × 25 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by column chromatography (2:1 hexanes/ethyl acetate) to yield 2.72 g (6.8 mmol, 70% yield) of diol **6e**. R_f = 0.26 (2:1 hexanes/ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz) **2′*R* epimer** δ 7.30−7.20 (m, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.50−5.30 (m, 1H), 5.00−4.40 (m, 7H), 3.80 (s, 3H), 3.80−3.50 (m, 2H), 2.45 (d, J = 2.1 Hz, 1H), 2.50−1.80 (m, 5H), 1.90 (m, 3H), 1.63 (s, 3H); **2′*S* epimer** δ 7.30−7.20 (m, 2H), 6.88 (d, 2H, J = 8.6 Hz), 5.50−5.30 (m, 1H), 5.00−4.40 (m, 7H), 3.80 (s, 3H), 3.80−3.50 (m, 2H), 2.45 (d, 1H, J = 2.1 Hz), 2.50−1.80 (m, 5H), 1.77 (m, 3H), 1.69 (s, 3H). IR ($CDCl_3$) 3432, 3304, 3069, 2931, 2840, 1613, 1513, 1444, 1379, 1301 cm^{-1}. HRMS Calcd for $C_{24}H_{31}O_4$ [M^+− OH]: 383.2222. Found: 383.2224.

(4*R*,5*R*,6*S*,1′*RS*)-1-Methyl-4-isopropenyl-5-[(4″-methoxybenzyloxy)-methoxymethyl]-6-(1′−*tert*-butyldimethylsiloxyprop-3′-ynyl)methyl-6-trimethylsilyloxycyclohex-1-ene (7e). To a DMF solution (45 mL) containing enyne **6e** (7.97 g, 19.9 mmol) was added *tert*-butyldimethylsilyl chloride (3.6 g, 23.9 mmoL) and imidazole (2.7 g, 39.8 mmol). The reaction was heated to 60 °C, after 2.5 h the reaction was cooled to room temperature, and then pyridine (20 mL), trimethylsilyl chloride (3.0 g, 27.9 mmol), and hexamethyldisilizane (3.2 g, 19.9 mmol) were added. The heterogeneous yellow mixture was stirred at room temperature for 6.5 h. Water (50 mL) and ether (50 mL) were added, the organic layer was separated, and the aqueous layer was extracted with ether (2 × 75 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residual yellow oil was purified via column chromatography (10:1 hexanes/ethyl acetate), yielding 8.41 g (14.3 mmol, 72% yield) of enyne **7e**. R_f = 0.47 (5:1 hexanes/ethyl acetate). IR ($CDCl_3$) 3301, 2950, 2928, 2853, 1613, 1512, 1468, 1439, 1378, 1250, 1171, 1037, 839 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 5.50−5.30 (m, 1H), 4.81 (s(br), 1H), 4.73 (m, 2H), 4.60 (m, 2H), 4.50 (s, 2H), 3.80 (s, 3H, $-OCH_3$), 3.90−3.50 (m, 2H), 2.70−1.70 (m, 6H), 3.36 (d, 1H, J = 2.1 Hz), 3.32 (d, 1H, J = 2.1 Hz), 1.74 (s(br), 6H), 0.88 (s, 9H), 0.20−0.00 (m, 15H).

(1*R*,4*S*,5*S*,6*S*,8*RS*)-1-Methyl-4-isopropenyl-5-[(4′-methoxybenzyloxy)-methoxymethyl]-6,8-dihydroxy-9-methylene-*cis*-bicyclo[4.3.0.^{1,6}]-non-2-ene (13e). To a freshly distilled dichloroethane solution (30 mL) containing enyne **7e** (10.29 g, 17.6 mmol) was added at room temperature a prestirred dichloroethane solution (10 mL) containing palladium acetate (197 mg, 0.88 mmol) and *N*,*N*-bis(phenylmethylene)-1,2-ethylene diamine (228 mg, 0.96 mmol). The reaction was heated at 56 °C for 23 h at which time the solvent was removed in vacuo, and the residual dark oil was purified via column chromatography (15:1 hexanes/ethyl acetate). The resultant product was dissolved in 40 mL of acetonitrile, followed by the addition of potassium fluoride dihydrate (6.6 g, 70.4 mmol) and tetra-*n*-butylammonium chloride (978 mg, 3.52 mmol) were added. The reaction was heated under reflux for 24 h. Water (25 mL) was added, and the mixture was poured into ether (50 mL). The organic layer was separated, and the aqueous layer was extracted with ether (75 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residual oil was purified via column chromatography (1:1 hexanes/ethyl acetate), yielding 4.53 g (11.3 mmoL, 64% yield) of diol **13e** as a 1:1 diastereomeric mixture.

8*S* Diastereomer: Mp = 94−95 °C. R_f = (hexanes/ethyl acetate, 1:1) 0.41. $[\alpha]_D = -143.1°$ (c = 2.405, $CHCl_3$). IR ($CDCl_3$) 3518 (br), 3480(br), 1615, 1514, 1452, 1399, 1377, 1301 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.42 (dd, J = 9.8, 2.4 Hz, 1H), 5.33 (d, J = 2.0 Hz, 1H), 5.20−5.10 (m, 2H), 4.90−4.70 (m, 1H), 4.86 (m, 1H), 4.81 (m, 1H), 4.80−4.75 (m, 2H), 4.55 (m, 2H), 3.92 (s, 1H), 3.81 (s, 3H), 3.90−3.60 (m, 2H), 2.50 (m, 1H), 2.22 (dd, J = 12.6, 7.7 Hz, 1H), 2.25−2.00 (m, 1H), 1.67 (s, 3H), 1.70−1.50 (m, 3H), 1.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.8, 159.4, 145.3, 137.4, 129.5, 125.1, 113.9, 108.9, 94.6, 81.5, 72.8, 69.7, 69.3, 55.2, 50.5, 47.0, 41.9, 38.5, 21.5, 18.6. HRMS: Calcd for $C_{24}H_{30}O_4$: [$M^+ - H_2O$] = 382.2144. Found: 382.2139.

8*R* Diastereomer: Mp = 41−43 °C. R_f = 0.48 (1:1 hexanes/ethyl acetate). $[\alpha]_D = -161.6°$ (c = 5.875, $CHCl_3$). IR ($CDCl_3$) 3453(br), 1611, 1510, 1373 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.6 Hz), 5.45 (s, 1H), 5.31 (dd, 1H, J = 9.8, 2.4 Hz), 5.23 (s, 1H), 5.11 (dd, 1H, J = 9.8, 2.0 Hz), 4.86 (s, 1H), 4.80 (s, 1H), 4.74 (s, 2H), 4.56 (s, 2H), 4.46 (d, 1H, J = 5.5 Hz), 3.87 (dd, 1H, J = 10.0, 5.6 Hz), 3.81 (s, 3H), 3.80−3.60 (m, 1H), 2.52 (m, 1H), 2.20−1.80 (m, 3H), 1.67 (s, 3H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.0, 159.3, 145.2, 137.0, 129.4, 125.4, 113.8, 111.1, 94.5, 84.1, 73.2, 69.4, 68.7, 55.1, 51.4, 46.6, 40.7, 38.4, 21.6, 18.4. HRMS: Calcd for $C_{24}H_{30}O_4$ [$M^+ - H_2O$]: 382.2144. Found: 382.2126.

Hydroxy Ester (33b). To a 9:1 ethanol dichloromethane solution (3 mL) containing acetate **33a** (165.2 mg, 0.28 mmol) was added an ethanol solution containing guanidine (0.56 mmol, prepared by neutralization of the hydrochloride with sodium methoxide in a known amount of ethanol, filtration, and direct use of an aliquot of this standard solution at room temperature). After 1.5 h, the slightly yellow solution was poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated $NaHSO_4$ (20 mL) and dried ($MgSO_4$) and the solvent was removed in vacuo, yielding 140.4 mg (0.26 mmol) of hydroxyester **33b** plus 13.9 mg of lactone **34** in quantitative yield. The hydroxyester and lactone were not separated but taken directly into the next step; nevertheless, the hydroxy ester **33b** was characterized, mp = 104 °C, $R_f = 27.4°$ (c = 2.0, $CHCl_3$). IR(film) 3456, 1731, 1452, 1436, 1386, 1380 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.94 (t, J = 1.49 Hz, 1H), 4.84 (bs, 1H), 3.99 (t, J = 5.74 Hz, 1H), 3.86 (d, J = 8.85 Hz, 1H), 3.78 (d, J = 4.04 Hz, 1H), 3.70 (m, 1H), 3.61 (s, 3H), 3.50 (d, J = 8.99 Hz, 1H), 2.80 (d, J = 12.6 Hz, 1H), 2.62 (dd, J = 12.4, 11.1 Hz, 1H), 2.38 (dd, J = 13.9, 5.78 Hz, 1H), 2.05 (d, J = 7.7 Hz, 1H), 1.98 (dd, J = 6.95, 5.66 Hz, 1H), 1.75 (s, 3H), 0.99 (s, 3H), 0.15 (s, 9H), 0.14 (s, 9H), 0.09 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.1, 144.2, 114.8, 92.0, 88.2, 84.1, 77.3, 76.5, 70.6, 58.4, 57.8, 50.8, 47.7, 43.3, 19.4, 18.5, 2.86, 2.54, 0.57. HRMS Calcd for $C_{25}H_{48}O_2Si_3$ [M^+]: 544.2708. Found: 544.2723.

Lactone 34. To a THF suspension (0.5 mL) containing potassium hydride (0.2 mL of a 35% mineral oil suspension, rinsed twice with THF) at 0 °C was added hydroxyester **33b** (19.4 mg, 0.036 mmol) in THF (2 mL). After 10 min, the reaction was quenched dropwise with saturated aqueous sodium bisulfate until the foaming subsided. The mixture was poured into saturated brine (10 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, and the residual material was purified via column chromatography (15:1 hexanes/EtOAc), yielding 11.9 mg (0.023 mmoL, 64% yield) of lactone **34**, mp = 186−189 °C, R_f = 0.44 (8:1 hexanes/ethyl acetate), $[\alpha]_D = 47.8°$ (c = 1.16, $CHCl_3$). IR(film) 1776 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.96−4.94 (m, 2H), 4.80 (bs, 1H), 4.06 (d, J = 4.58 Hz, 1H), 3.77 (d, J = 8.30 Hz, 1H), 3.74 (dd, J = 12.5, 6.00 Hz, 1H), 3.31 (d, J = 8.54 Hz, 1H), 3.26 (bs, IH), 2.80 (d, J = 4.03 Hz, 1H), 2.52 (dd, J = 11.8, 6.02 Hz, 1H), 2.21 (t, J = 12.1 Hz, 1H), 1.84 (s, 3H), 1.00 (s, 3H), 0.18 (s, 9H), 0.15 (s, 9H), 0.089 (s, 9H). ^{13}C NMR (C_6D_6, 100.6 MHz) δ 175.3, 139.8, 113.1, 90.5, 82.1, 77.5, 71.6, 70.4, 55.0, 54.2, 49.4, 45.6, 22.4, 21.1, 2.40, 2.15, 0.086. HRMS Calcd for $C_{24}H_{44}O_6Si_3$ [M^+]: 512.2446. Found: 512.2452.

Alkene 37a. To an acetonitrile solution (0.4 mL) containing lactone **34** (8.2 mg, 0.016 mmol) was added 13 μL of a 48% HF solution at room temperature. After 5 min, solid sodium bicarbonate (approximately 10 mg) was added and the mixture immediately subjected to column chromatography (5:1 hexanes/EtOAc), yielding 6.3 mg (89% yield) of hydroxy lactone **35**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.98−4.96 (m, 2H), 4.80 (d, J = 2.30 Hz, 1H), 4.11 (d, J = 4.58 Hz, 1H), 3.91 (d, AB, J = 8.54 Hz, 1H), 3.823.75 (m, 1 H), 3.49 (d, J = 8.27 Hz, 1H), 3.27 (bs, 1 H), 2.82 (d, J = 3.97 Hz, 1H), 2.73 (dd, J = 12.1, 6.02 Hz, 1H), 2.11 (t, J = 12.2 Hz, 1H), 1.85 (s, 3H), 1.64 (d, J = 9.70 Hz, 1H), 1.05 (s, 3H), 0.19 (s, 9H), 0.17 (s, 9H).

DMAP (3.5 mg, 0.029 mmol), pyridine (50 μL), and 4-*p*-totylthionochloroformate (32.0 mg, 0.17 mmol) were added to a dichloromethane solution (0.4 mL) of hydroxylactone **35** (6.3 mg, 0.014 mmol). The yellow solution was then heated to 40 °C for 22.5 h and immediately subjected to column chromatography (6:1 hexanes/EtOAc), yielding 7.1 mg (84% yield) of thionocarbonate **36**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, J = 8.01 Hz, 1H), 6.98 (d, J = 8.47 Hz, 1H), 5.61 (dd, J = 12.8, 6.30 Hz, 1H), 5.03 (t, J = 4.42 Hz, 1H), 4.98 (bs, 1H), 4.83 (bs, 1H), 4.19 (d, J = 8.54 Hz, 1H), 4.13 (d, J = 4.51 Hz, 1H), 3.47 (d, J = 8.78 Hz, 1H), 3.32 (bs, 1H), 2.95 (dd, J = 11.8, 6.20 Hz, 1H), 2.89 (d, J = 3.97 Hz, 1H), 2.58 (t, J = 12.3 Hz, 1H), 2.36 (s, 3H), 1.87 (s, 3H), 1.08 (s, 3H), 0.23 (s, 9H), 0.20 (s, 9H).

In a FVT apparatus, thionocarbonate **36** (21.1 mg, 0.036 mmol) was volatilized into a quartz tube in a 500° oven at 0.02 mmHg by heating with a Bunsen burner. After approximately 5 min, the collected flask and the tube were rinsed with chloroform. The solvent was then removed in vacuo and the residue purified via column chromatography (4:1 hexanes/EtOAc) to provide 11 mg (73% yield) of the alkene **36**, R_f = 0.43 (4:1 hexanes/ethyl acetate), $[\alpha]_D = 31°$ (0.8% in chloroform). IR (neat) 1786, 1647, 1454, 1360 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.10 (d, J = 5.80 Hz, 1H), 5.89 (d, J = 5.80 Hz, 1H), 5.02−5.00 (m, 2H), 4.88 (bs, 1H), 4.27 (d, J = 4.27 Hz, 1H), 3.98 (d, J = 9.46 Hz, 1H), 3.77 (d, J = 9.46 Hz, 1H), 3.29 (bs, 1H), 3.03 (d, J = 4.20 Hz, 1H), 1.90 (s, 3H), 1.07 (s, 3H), 0.14 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 139.5, 137.3, 134.5, 113.5, 95.1, 83.8, 82.9, 79.6, 77.8, 58.3, 53.1, 49.2, 22.5, 20.9, 2.2, 1.9. HRMS Calcd for $C_{21}H_{34}O_5Si_2$ [M^+]: 422.1944. Found: 422.1935.

Alkene diol 37b. To a THF solution (200 μL) containing lactone **37b** (2.3 mg, 0.005 mmol) was added benzyltrimethylammonium fluoride hydrate (15.2 mg, 0.090 mmol) at room temperature. After 2.5 h, a small amount of water was added and the reaction immediately subjected to column chromatography (2:1 EtOAc/hexanes), yielding 1.2 mg (80% yield) of diol lactone **37b**, R_f = 0.25 (2:1 ethyl acetate/hexanes), $[\alpha]_D = 27°$ (1.24% in methanol). IR(film) 3415 (br), 1783, 1764, 1648, 1450, 1379, 1362 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.02 (d, J = 5.73 Hz, 1H), 5.89 (d, J = 5.73 Hz, 1H), 5.07 (bs, 1H), 5.05 (t, J = 4.58 Hz, 1H), 4.97 (d, J = 1.76 Hz, 1H), 4.37 (d, J = 4.27 Hz, 1H), 4.06 (d, J = 10.1 Hz, 1H), 3.89 (d, J = 10.1 Hz, 1H), 3.35 (bs, 1H), 3.16 (d, J = 4.27 Hz, 1H), 1.94 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 139.5, 138.3, 133.8, 114.0, 94.8, 84.0, 81.6, 80.1, 78.1, 57.2, 50.6, 49.2, 22.6, 19.5. HRMS Calcd for $C_{15}H_{18}O_5$ [M^+]: 278.1154. Found: 278.1152.

Corianin. To a solution of the diene bis-lactone **37b** (9.0 mg, 0.032 mmol) in dichloromethane (640 μL) was added MCPBA (27 mg of 60% MCPBA, 0.096 mmol). After 2.5 h at 0 °C, the reaction mixture was charged onto a chromatographic column (40 → 70% ethyl acetate/hexanes) to provide 8.2 mg (87% yield) of corianin, $R_f = 0.3$ (60% ethyl acetate in hexane), $[\alpha]_D = 22°$ (0.44% in methanol). IR(film) 3481, 1761, 1739, 1645, 1382, 1351, 1304 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (dd, $J_1 = J_2 = 4.12$ Hz, 1H), 4.99 (bs, 1H), 4.80 (bs, 1H), 4.24 (d, $J = 4.12$ Hz, 1H), 4.01 (m, 3H), 3.60 (d, $J = 2.54$ Hz, 1H), 3.26 (bm, 1H), 3.19 (d, $J = 4.12$ Hz, 1H), 2.38 (s, 1H), 2.33 (bs, 1H), 1.91 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (100 MHz, d^6-Acetone) δ 175.2, 141.5, 112.5, 90.5, 85.5, 81.9, 77.6, 76.0, 64.1, 60.9, 55.6, 49.9, 49.0, 22.9, 21.7. Anal. Calcd for $C_{15}H_{18}O_6$ [M$^+$]: 294.1103. Found: 294.1103.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were obtained from the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures for preparation of **3**, **1e**, **14a**, **14e**, **23**−**28**, **30**−**32**, **33a** and inversion of **8-*S*** to **8-*R*** epimer of **13f** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA9901821