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An Asymmetric Synthesis of the Tricyclic Core and a Formal Total Synthesis of Roseophilin via an Enyne Metathesis

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Abstract: A formal synthesis of roseophilin, a novel pentacyclic structure possessing significant antitumor activity, starting from 3-cycloundecenylcarboxylic acid has been completed. The acid was converted diastereoselectively to the corresponding menthol ester via the ketene which, in turn, provided (*S*)-3-cycloundecenylcarboxaldehyde. Diastereoselective propargylation with propargyltriphenylstannane promoted by an asymmetric boron reagent prepared in situ from boron tribromide and the bis-*p*-toluenesulfonamide of (*S,S*)-stilbenediamine gave (1*S*,1′*R*)-1-cycloundec-2′-enylbut-3-yn-1-ol which set the stage for the key metathesis reaction. Platinum-catalyzed enyne metathesis via a formal [2 + 2] cycloaddition to a cyclobutene followed by conrotatory ring opening created the corresponding bicyclo[10.2.1]pentadeca-1(15),2-diene. Regioselective epoxidation of the less reactive double bond of the 1,3-diene was accomplished by 1,4-bromohydrin formation followed by base. Cuprate opening regio- and stereospecifically installed the isopropyl substituent. Standard procedures converted this intermediate to (1*R*,12*R*,13*R*,15*R*)-13-(*tert*-butyldimethylsiloxy)-15-isopropylbicyclo-[10.2.1]pentadecane-3,14-dione. This diketone was converted to the corresponding unstable pyrrole by condensation with ammonium acetate, and the pyrrole nitrogen immediately alkylated with SEM-chloride. The formal synthesis was completed by conversion of the siloxy group to the corresponding ketone which previously had been condensed with the heterocyclic side chain to complete a synthesis of roseophilin. By having access to the tricyclic core asymmetrically for the first time, this route provides the opportunity to establish the absolute configuration of the natural product.

In exploring the culture broth of *Streptomyces griseoviridis*, Hayakawa, Kawakami, and Seto isolated a deeply colored hydrochloride salt that showed significant cytotoxicity against K562 human erythroid leukemia cells and KB human epidermoid carcinoma cells.[1] The structure of the compound, named roseophilin (**1**), was assigned solely by spectroscopy, largely NMR. While the relative stereochemistry was assigned by NMR spectroscopy, the absolute stereochemistry remained unresolved. The unusual nature of the structure makes it an interesting lead structure for exploitation of its biological profile as an antitumor agent. This fact stimulated a number of synthetic efforts, including our own.[2] At the time we embarked upon this synthesis, no synthetic work had been recorded.

Scheme 1 represents our retrosynthetic analysis. An obvious disconnection involves two pieces, the unit **2** that constitutes

(1) Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701.

(2) (a) Nakatani, S.; Kirihara, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1995**, *36*, 8461. (b) Kim, S. H.; Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 2545. (c) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601. (d) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944. (e) Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1998**, *63*, 220. (f) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (g) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911. (h) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (i) Robertson, J.; Hatley, R. J. D. *Chem. Commun.* **1999**, 1455. (j) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649. (k) Fagan, M. A.; Knight, D. W. *Tetrahedron Lett.* **1999**, *40*, 6117.

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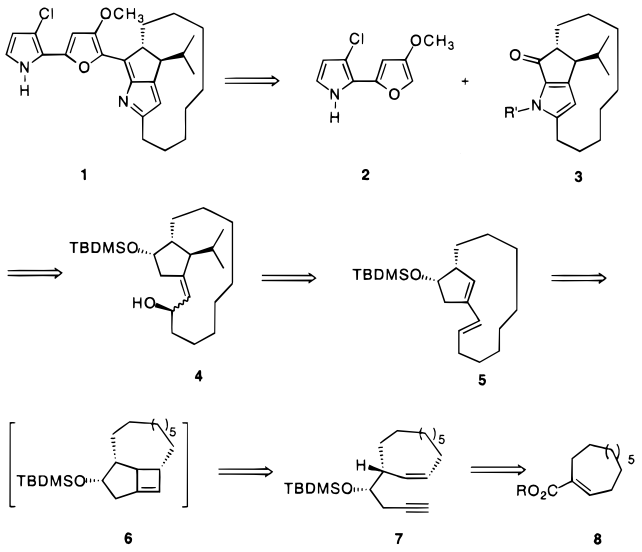
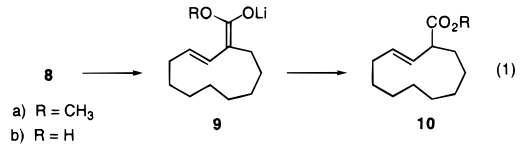
Scheme 1. Retrosynthetic Analysis of Roseophilin



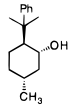
the heterocyclic side chain and the tricyclic core **3**. Several methods including the classical Paal−Knorr condensation can be envisioned to form the pyrrole moiety from the allyl alcohol **4**. Using the macrocyclic bridge to control stereochemistry of introduction of the isopropyl group allows diene **5** to be a precursor of **4**. This bridged bicycle, **5**, may derive from an enyne metathesis of **7** via cyclobutene **6**. Since **7** can derive from a diastereoselective addition of a propargyl anion to an aldehyde and the latter can derive from an ester, the known enoate **8**[3] becomes an attractive starting material. First, it is readily available in two steps from cyclododecanone, a commercially available starting material. Second, the absolute stereochemistry is set during the deconjugation, thus providing access to either enantiomer of the product. Since the stereochemistry of roseophilin is unknown, a strategy which involves de novo creation of the absolute configuration is preferable to one from the chiral pool because it allows access to either enantiomer.

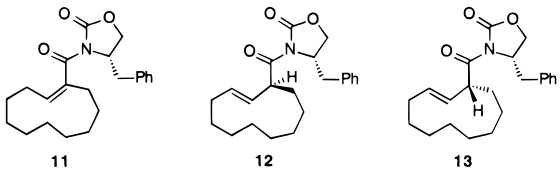
Synthesis of the Metathesis Substrate. The transformation of enoate **8** to enyne **7** requires deconjugation of the double bond and appending a propargyl group. The deconjugation step sets the chirality for the entire synthesis. The enolate from ester **8a** (R = CH_3)[3a] or the dianion from acid **8b** (R = H)[3b] was inversely quenched into aqueous sodium bisulfate which generated the β,γ-unsaturated derivatives **10a** and **10b**.[4] The 15.7 Hz coupling between the vinyl protons indicated an *E*-alkene geometry—in contrast to the normally observed *Z*-alkene geometry in most deconjugations with acyclic esters.



Conversion of the deconjugation into an asymmetric process requires control of the stereochemistry of protonation. Attempts to utilize the method described by Vedejs[5a] employing quenching of a lithium enolate of an amide with a chiral tetrahydroisoquinoline failed. Use of a chiral auxiliary to influence protonation led to the preparation of the *N*-acyloxazolidine-2-one **11**.[5b]

Table 1. Esterification of Deconjugated Acid **10b** with Chiral Alcohols via Ketene

Entry	ROH	Solvent	Temp (°C)	dr
1		CH_2Cl_2	0°	3.8:1
		CH_2Cl_2	-78°	4.7:1
		pentane	-78°	1.5:1
2		CH_2Cl_2	0°	1.5:1
3		CH_2Cl_2	0°	1.5:1
4		CH_2Cl_2	-50°	5:1
5		CH_2Cl_2	0°	1:1
		pentane	-78°	1:1



Unfortunately, the harshness of the conditions required for deprotonation of this conjugated substrate only decomposed it and led to the examination of the corresponding deconjugated derivatives **12** and **13** which derived from the β,γ-unsaturated acid **10b**. Even these derivatives were of insufficient acidity to be enolized without decomposition. On the other hand, they were easily separable and could, therefore, serve as a resolution protocol. However, this avenue was unattractive because of problems in removing the chiral auxiliary.

Additions of chiral alcohols to ketenes may serve as an effective asymmetric synthesis.[6] When the carboxylic acid **10b** was mixed with DCC, elimination of dicyclohexylurea occurred within minutes at 0 °C. Addition of a chiral nonracemic alcohol to the ketene can generate nonequal amounts of diastereomeric esters (see Table 1). The ketene was remarkably unreactive, but in the presence of a catalytic amount of DMAP, the reaction proceeded well. Although pantolactone proved effective for acylketenes,[6b] it was nonselective in this case (entry 5). The best result was obtained with (−)-borneol (entry 4) and (−)-menthol (entry 1). Interestingly, there was a significant solvent effect; dichloromethane proved sufficiently better than the nonpolar pentane. Surprisingly, (−)-menthol was better than 9-phenylmenthol. The dr of menthol ester **14** was enriched to 7:1 by one recrystallization, but enrichment to optical purity

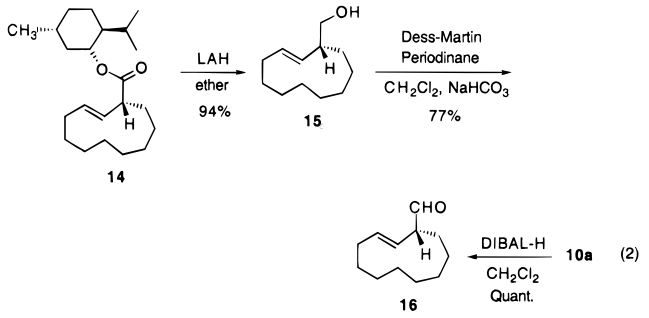
(3) (a) Garbisch, E.; Wohllebe, J. *Chem. Commun.* **1968**, 306. Garbisch, E.; Wohllebe, J. *J. Org. Chem.* **1968**, *33*, 2157. Wohllebe, J.; Garbisch, E. *Org. Synth. 56*, 107. (b) Also see: Ziegenbein, W. *Chem. Ber.* **1961**, *94*, 9.

(4) (a) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 743. (b) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, *14*, 4249. (c) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *15*, 2433.

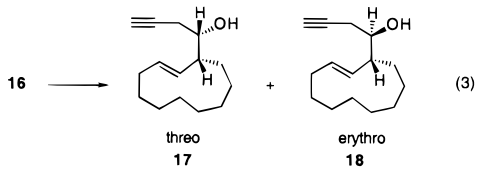
(5) (a) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175. (b) Gosh, A. K.; Liu, W. *J. Org. Chem.* **1995**, *60*, 6198.

(6) (a) Jähme, J.; Rüchardt, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 885. (b) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grawbowski, E. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650. (c) For related work involving thiols, see: Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1044. (d) For an overview, see: Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566.

led to significant loss of material. Thus, further upgrading of the ee was postponed to a later step in the synthesis. LAH reduction led to recovery of the menthol and the desired alcohol **15** (er 7:1) which was oxidized with the Dess−Martin periodinane to give aldehyde **16**. The racemate of aldehyde **16** (*rac*-**16**) was also available quantitatively by direct reduction of methyl ester **10a** with DIBAL-H.



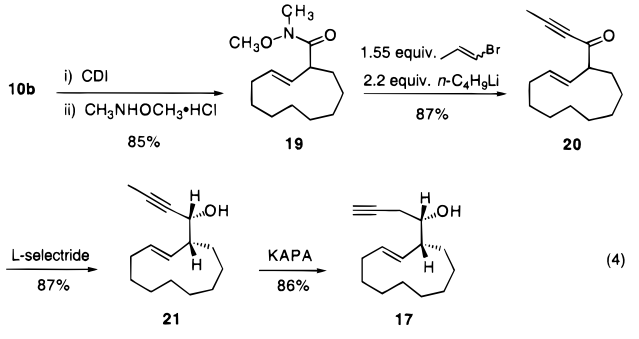
The diastereoselectivity of the propargylation was investigated with allenylmagnesium bromide and allenyltri-*n*-stannane, the latter catalyzed by boron trifluoride (eq 3). Not unexpectedly,



neither method gave any significant selectivity (**17**:**18**, 45:55 and 55:45, respectively). Changing the Lewis acid to MAD[7] did increase the diastereoselectivity but at the expense of yield (15%). In principle, this stereocenter is irrelevant since it is ultimately lost.

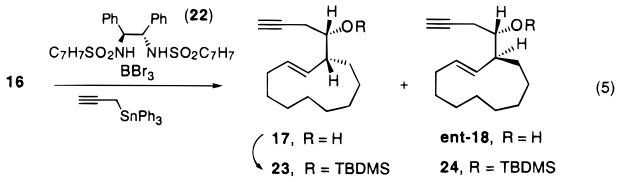
Nevertheless, complications of carrying through a mixture of diastereomers made obtention of a single diastereomer desirable. Attempts to invert one epimer to the other failed due to competing eliminations. Inversion via an oxidation−reduction also failed due to virtually instantaneous isomerization of the propargyl ketone to an allenyl ketone.

An alternative strategy focused on a diastereoselective reduction of an alkynyl ketone as shown in eq 4. The requisite

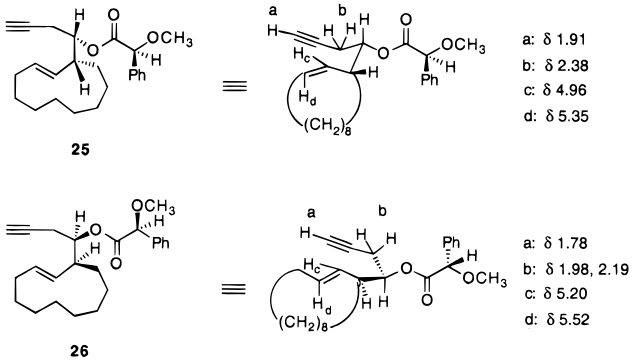


alkynyl ketone **20** was formed via Weinreb amide **19** and 1-propyne which was generated via a convenient in situ procedure.[8] Good diastereoselectivity (9:1) favoring the depicted isomer was observed using L-Selectride. Importantly, zipping the acetylenic linkage to the terminus occurred with no loss of diastereoselectivity.[9] The *erythro* stereochemistry of the product was assigned by comparison to the previously obtained diastereomer. This stereochemistry corresponds to a Felkin-Anh mode of addition.

A diastereocontrolled propargylation of aldehyde **16**, using a reagent-controlled approach, also constitutes a reasonable strategy. The available methods require stoichiometric chiral nonracemic reagents—a fact that indicates there is a need for further developments here. The Yamamoto method based on a chiral boron reagent has the disadvantage of requiring excess aldehyde.[10] On the other hand, the Corey procedure has the disadvantages of preparation of a more complicated reagent and the use of toxic tin reagents.[11] Nonetheless, the more favorable stoichiometry of this process led us to employ it. As shown in eq 5, utilizing the allenylborane derived from the (*S*,*S*)-stein



(**22**) boron tribromide and propynyltriphenylstannane gave two diastereomers in a 7:1 ratio, reflective of the enantiopurity of the starting aldehyde. The major diastereomer, the *erythro*, was separated from the minor diastereomer, the *threo*, by chromatography of the corresponding silyl ethers **23** and **24**. The enantiopurity of silyl ether **23** was determined by conversion to *O*-methylmandelate **25** which indicated an ee of 96%. Mandelate esters **25** and **26** allowed the assignment of the absolute configuration as depicted.[12] In particular, the low-field shifts of the protons of the propynyl group in **25** compared to those in **26** and the reverse for the vinyl protons are consistent with the mnemonic established for the *O*-methylmandelates. The assignment of the *S* configuration for the homopropargylic alcohol also is consistent with the observed stereochemistry in the additions reported by Corey, Yu, and Lee.



As an aside, the two diastereomeric mandelates **25** and **26** obtained as a 1:1 mixture by esterification of racemic alcohol **17** with *S*-*O*-methylmandelic acid were easily separated by column chromatography. Hydrolysis of either one with methanolic sodium hydroxide gave alcohol **17** enantiomerically pure.

(7) Maruoka, K.; Concepcion, A. B.; Murase, N.; Oishi, M.; Hirayama, N.; Yamamoto, H. *J. Am. Soc. Chem. Soc.* **1993**, *115*, 3943.

(8) Suffert, J.; Toussaint, D. *J. Org. Chem.* **1995**, *60*, 3550.

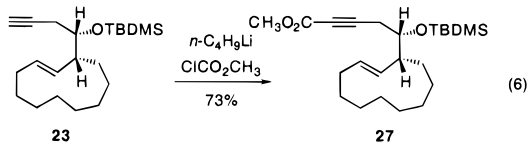
(9) Midland, M. M.; Halterman, R. L. *Tetrahedron Lett.* **1981**, *22*, 4171.

(10) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 438.

(11) Corey, E. J.; Yu, C.-M.; Lee, D.-M. *J. Am. Chem. Soc.* **1990**, *112*, 878.

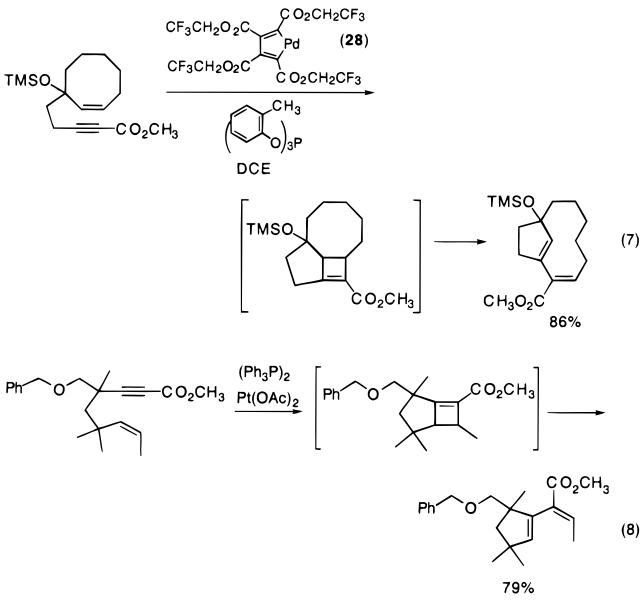
(12) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

While the enynes **17**, **18**, **23**, and **24** constitute valid metathesis substrates, the corresponding ynoate **27** was also considered a desirable target since such ynoates are sometimes better metathesis substrates.[14b] The requisite compound was easily accessed as summarized in eq 6.

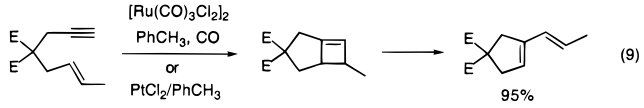


(6)

Enyne Metathesis. There are two mechanistic paths for an enyne metathesis. The common metathesis reactions using alkylidene metal complexes of ruthenium and molybdenum normally proceed via a metalacyclobutene intermediate.[13] An alternative mechanism involving palladium and platinum complexes invokes a formal [2 + 2] cycloaddition to a cyclobutene followed by a [2 + 2] cycloreversion (eqs 7 and 8).[14] These

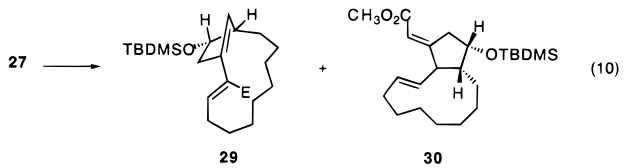


reactions, which invoke a metallacyclopentene intermediate, also appear to involve a series of potential equilibria involving valence isomerization of the metallacycle and thus account for the diverse array of possible products observed. One of these paths is a collapse to a cyclobutene which then represents an equivalent of a [2 + 2] process. After the completion of our work, Murai developed both a ruthenium and a platinum catalyst that appears to involve a similar mechanism (eq 9).[15]



(9)

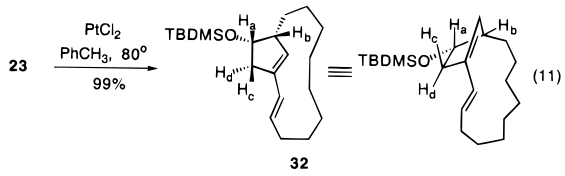
Studies were initiated with ynoate **27** as substrate. Using the palladacycle **28** as catalyst, the metathesis product (**29**) was not observed at temperatures up to 60 °C. At 100−110 °C in 1,2-



(10)

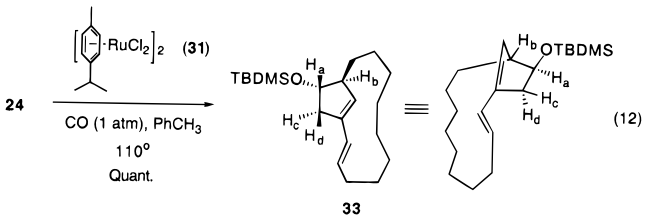
dichloroethane or toluene, the Alder ene product **30** was the exclusive product. A similar result was obtained with (*p*-cymene) ruthenium dichloride dimer (**31**) and tri-*o*-tolyl phosphite; only **30** was observed. On the other hand, the same catalyst in toluene at 80 °C gave a 25:75 ratio of **29** and **30** which increased in favor of the methathesis product **29** as the temperature was increased ($PhCH_3$ at 110 °C, 95:5, *p*-cymene at 130 °C, 98:2).

Both the ruthenium and platinum catalyst systems converted substrates **23** (eq 11) and **24** (eq 12) to the metathesis products **32** and **33**, respectively, essentially quantitatively. It was at this



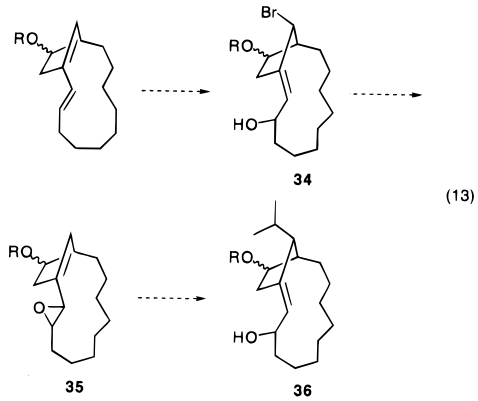
(11)

point that the relative stereochemistry of the propargyl addition product could be established. H_a in diastereomer **32** appeared as a quartet ($J = 7.7$ Hz) at δ 4.68, whereas this proton appeared as a doublet ($J = 6.0$ Hz) at δ 4.15 in **33**. A molecular mechanics calculation on **32** revealed a dihedral angle of nearly 0° between H_a-H_b and H_a-H_d and one of 145° between H_a-H_d, creating a quartet as expected. On the other hand, the same calculation on diastereomer **33** revealed a dihedral angle of about 90° between H_a-H_b and H_a-H_c but one of about 0° between H_a-H_d. A doublet with coupling only to H_d was then consistent.



(12)

1,4-Hydroxyalkylation of Diene. The next step requires a regio- and diastereocontrolled addition of a hydroxyl and an isopropyl group across the diene. To effect this transformation, cuprate addition from the least hindered face of monoepoxide **35** was envisioned (eq 13). This selectivity required a chemose-

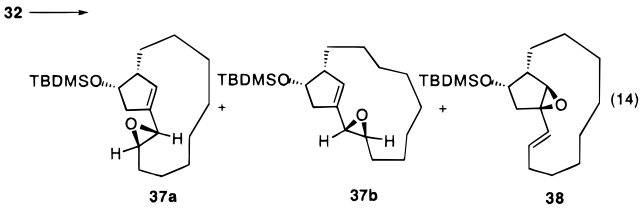


(13)

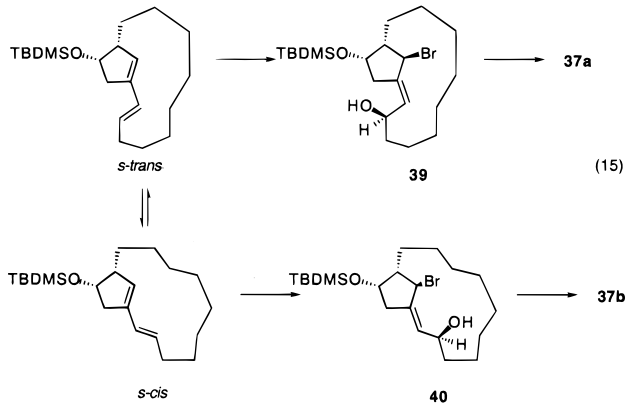
lective epoxidation of the less reactive double bond of the dienes **32** and **33**. For this selectivity, we envisioned a 1,4-halohydrin formation initiated by attack of the bromonium ion on the more reactive double bond to give **34** followed by base-catalyzed elimination as shown in eq 13.

In the event, diene **32** was treated with NBS in wet THF to give the bromohydrin(s). The instability of these adducts led

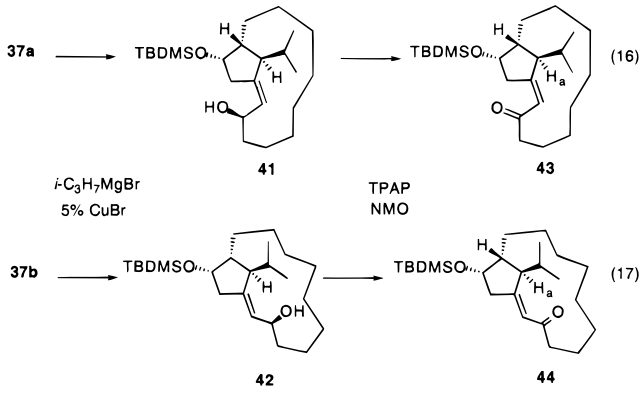
us to treat them directly with aqueous sodium hydroxide to form the two regioisomeric epoxides, **37** and **38**, in a 9:1 ratio (as determined by the ratio of the vinyl protons). Further, the regioisomeric epoxide **37** was a 75:25 ratio of diastereomers tentatively assigned as **37a** and **37b** (eq 14). Curiously, the alternative diastereomer **33** gave a 55:45 ratio of the two regioisomeric epoxides. Since **32** was available stereoselectively, it was employed for the synthesis.



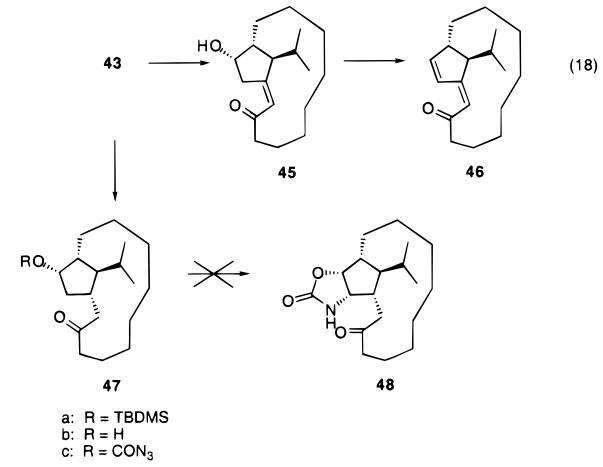
Both diastereomeric epoxides **37** are *trans* as determined by the 2.2 Hz coupling between the epoxide hydrogens in the ^{1}H NMR spectra. Thus, they must represent the two facial isomers. Molecular modeling showed that diene **32** possessed an inner and outer face with respect to the chain of carbons constituting the ring with only the outer face accessible for attack. A *syn* selectivity for the addition of the elements of HOBr in a 1,4 fashion in analogy to 1,4-bromination of dienes[16] led us to suggest that the two diastereomeric bromohydrins are **39** and **40** which arose from addition to the *s-trans* and *s-cis* conformers of the diene (eq 15). Base treatment then generated the two diastereomeric epoxides **37a** and **37b**, respectively.



Since cuprate additions to vinyl epoxides occur *syn* to the epoxide oxygen,[17] the isopropyl group was introduced on the same face of the cyclopentene of both diastereomeric epoxides which generated different alkene geometries as depicted in eqs 16 and 17. In practice, the crude mixture of **37a**, **37b**, and **38** (eq 14) was directly subjected to a copper-catalyzed addition of isopropylmagnesium chloride. The very minor product which arose from reaction of **38** was easily removed, and the two desired isomers **41** and **42** were easily separated chromatographically. Oxidation of the allylic hydroxyl group in both products produced the corresponding ketones **43** and **44**. H_a appeared as a doublet (**43**, δ 2.09, $J = 9.7$ Hz; **44**, δ 2.90, $J = 9.1$ Hz) in both cases which revealed no coupling to the bridgehead hydrogen. This same pattern was observed in roseophilin. The lower field shift of this proton in **44** compared to that in **43** is in agreement with the assignment of the alkene geometry as depicted.



Construction of Pyrrole and Completion of the Roseophilin Core. The completion of the synthesis requires the construction of the pyrrole unit. Fortunately, there are many ways to achieve this task. An attractive method considers the introduction of the requisite amino group via an intramolecular insertion of an acylnitrene.[18] We initially targeted formation of the azidoformate derived from **45** but were thwarted by its ease of dehydration to dienone **46** upon attempted derivatization of the hydroxyl group (eq 18). After saturation of the double bond (H_2, 5% Pd/C, 95%) to form **47a**, the corresponding saturated alcohol **47b** (HF, CH_3CN, 71%) readily formed the azidoformate **47c** ($Cl_3COCO_2CCl_3$, then LiN_3). However, neither photolysis nor thermolysis afforded any oxazolidine **48**.



Our discovery that the mixture of alcohols **41** and **42** smoothly underwent regioselective elimination to diene **49** upon attempted alcohol displacement led to our exploration of the dihydroisoxazines **50** as suitable pyrrole precursors.[19] Preparatively, the

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(14) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850. (c) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647. (d) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824. (e) Trost, B. M.; Yanai, M.; Hoogsteen *J. Am. Chem. Soc.* **1993**, *115*, 9294. (f) Trost, B. M.; Hashmi, S. K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1085.

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(16) Heasley, G. E.; Heasley, V. L.; Manatt, S. C.; Day, H. A.; Hodges, R. V.; Kroon, P. A.; Redfield, D. A.; Rold, T. L.; Williamson, D. E. *J. Org. Chem.* **1973**, *38*, 4109.

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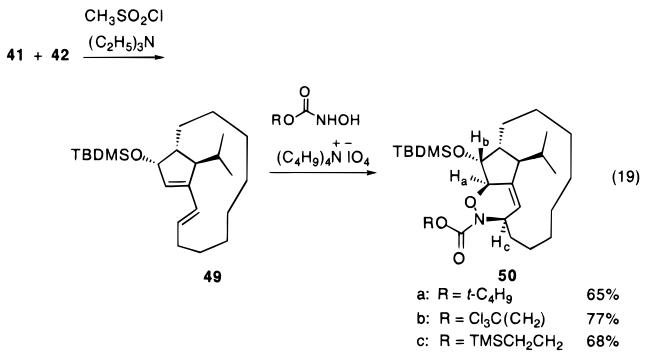
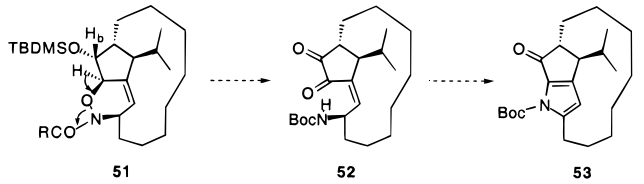
(18) (a) Edwards, O. E.; Paryzek, Z. *Can. J. Chem.* **1973**, *51*, 3866. (b) Wright, J. J.; Morton, J. B. *Chem. Commun.* **1976**, *116*, 668.

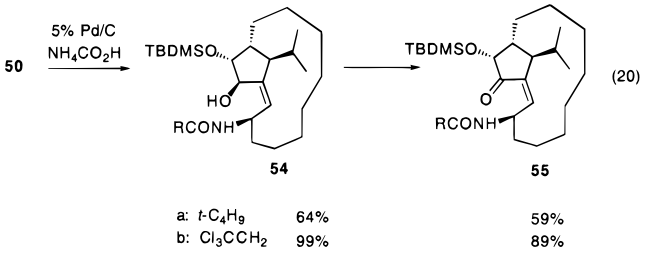
(19) Kresze, G.; Firl, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 382.



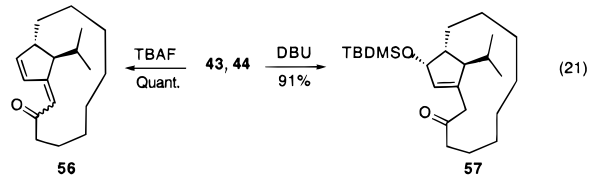
elimination proceeded readily by treating alcohols **41** and **42** with methanesulfonyl chloride. The coupling pattern of the three vinyl protons of the diene [δ 6.18, d, $J = 15.4$ Hz; δ 5.71, ddd, $J = 15.4$, 10.5, 4.1 Hz; δ 5.44, bs] and the collapse of the methine proton adjacent to the siloxy group to a broad doublet (δ 5.08, d, $J = 5.5$ Hz) verified the position of the double bonds. Oxidation of the hydroxamic acids with periodate in the presence of the diene gave the cycloadducts as single regio- and diastereomers.[20] For adduct **50a**, the proton adjacent to the oxygen of the dihydroisoxazine, H_a (δ 4.66, dd, $J = 7.5$, 2.7 Hz), showed coupling to H_b (δ 4.50, t, $J = 7.1$ Hz), whereas the proton adjacent to nitrogen, H_c (δ 3.62, dd, $J = 9.2$, 5.4 Hz, 1H), did not. Thus, the regioisomer was the one depicted. Blocking of the α-face of the diene by the ring carbons directed addition to the β-face. The regioselectivity then derived from unfavorable steric interactions between the nitrogen substituent and the isopropyl group that would have developed in forming the other isomer. Conversion of the siloxy group to ketone **51**



was envisioned to set the stage for a fragmentation to diketone **52** which could then ring close to give pyrrole **53**. Unfortunately, ketone **51** spontaneously underwent a cycloreversion to the diene. Hydrogenolysis to **54** followed by oxidation generated the desired ketones **55a**,**b**. However, all attempts to convert amidoketone **55** to pyrroles failed.

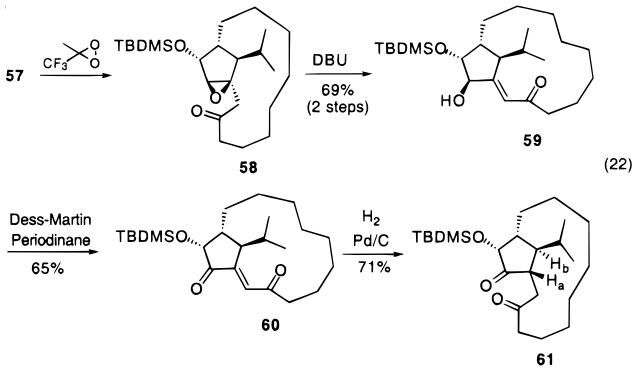


While additional sequences can be readily envisioned and several more explored, we focused on the classical Paal−Knorr condensation of an amine and a 1,4-diketone.[21] The regioselectivity of the elimination to the diene induced us to ascertain the equilibrium between the α,β- and β,γ-unsaturated ketones. Such a route was initially rejected because of our fear of β-elimination of the siloxy group, a fear fully verified by the obtention of diene **56** upon treatment of **43**−**44** with TBAF in quantitative yield (eq 21). On the other hand, heating an



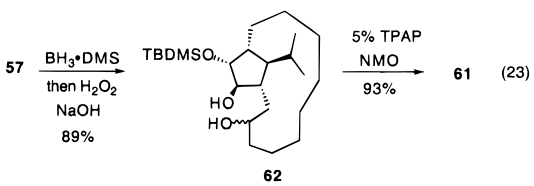
acetonitrile solution of a mixture of **43** and **44** with 50 mol % of DBU at 80 °C gave a 75:25 mixture of deconjugated ketone **57** and conjugated enone **44**. Surprisingly, elimination to diene **56** was not a problem at all under these conditions.

Enone **57** proved remarkably inert toward epoxidation, resisting MCPBA, trifluoroperacetic acid,[22] and dimethyldioxirane.[23] However, it succumbed to epoxidation with methyl trifluoromethyldioxirane[24] to give epoxide **58** (eq 22). Base-



catalyzed elimination to enone **59** followed by standard oxidation then puts the second carbonyl group in place (i.e., **60**). Hydrogenation occurred from the outside face of the alkene to give saturated diketone **61** even though it is *cis* to the isopropyl group. The absence of observable coupling between H_a and H_b supported this assignment.

A shorter sequence employed hydroboration as a key step (eq 23). Borane added to both the alkene and the carbonyl group to give diol **62** as a diastereomeric mixture after the usual work up with basic hydrogen peroxide. Upon oxidation with catalytic TPAP,[25] this stereocenter was destroyed and the single diketone **61** was obtained in excellent overall yield.



Initial experiments to form the parent pyrrole **63a** misled us to believe that the reaction proceeded poorly because of the

(20) (a) Baldwin, J. E.; Adlington, R. M.; Mellor, L. C. *Tetrahedron* **1994**, *50*, 5049. (b) Kirby, G. W.; McGuigan, H.; MacKinnon, J. W. M.; McLean, D.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1437. (c) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.

(21) (a) Paal, G. *Chem. Ber.* **1884**, *17*, 2756. (b) Knorr, L. *Chem. Ber.* **1884**, *17*, 2863.

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(24) Mello, R.; Fiorentino, M. Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3891.

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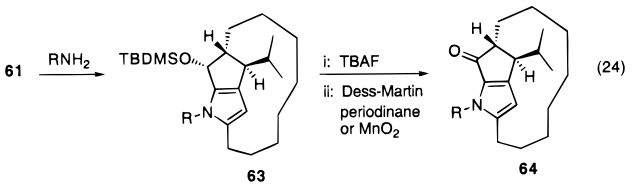
instability of the product. Thus, substituted amines were employed that could be appropriately deprotected subsequently with the belief that these *N*-alkylpyrroles would be more stable. Indeed, the pyrroles **63b**−**d** formed smoothly under a standard set of reaction conditions (eq 24, HOAc, 4 Å MS, CH_3OH, 50



(24)

a: R = H	see text		
b: R = CH_2Ph	60%	b: R = CH_2Ph	87% x 79%
c: R = PMB	61%	c: R = PMB	76% x 64%
d: R = 3,4-DMB	58%	d: R = R = 3,4-DMB	46% x 87%
e: R = $TsCH_2CH_2$	40%	f: R = SEM	54% (2 steps)
f: R = SEM	76%		

°C). Removal of the silyl ether proceeded smoothly with **63b**−**d**, and the resulting alcohols were oxidized to the desired ketones **64b**−**d**. The data of the benzyl derivative prepared herein, **64b**, were identical to those reported by Fürstner and Weintritt.[2f] While the benzyl derivative **64b** had been converted to the parent pyrrole **64a** using calcium in liquid ammonia, the process also reduced the ketone, thereby necessitating a reoxidation. The fact that it proceeded in only 50% yield at 69% conversion led us to synthesize the methoxylated benzyl derivatives **64b** and **64c** in the hope of improving their removal by alternative methods. Unfortunately, this did not prove to be the case. The ability to remove the arylsulfonylethyl substituent with base led to the synthesis of the corresponding pyrrole **63e**. However, attempts to effect desilylation only led to decomposition.

As a result, we returned to the parent pyrrole **63a**. Monitoring the reaction revealed that using ammonium acetate and catalytic CSA in methanol at 50 °C generated **63a** in 86% crude yield with minimal workup. Immediate protection with SEM-Cl gave a stable pyrrole **63f** that was isolated pure in 54% yield for the two steps. Desilylation and MnO_2 oxidation gave the ketone **64f** whose data are in full accord with those recorded for the racemic compound.

Discussion

The enyne metathesis proceeding via a metallacyclopentene that results in a formal [2 + 2] cycloaddition followed by an electrocyclic ring opening of the cyclobutene constitutes a useful method for making bridged bicycles.[26] As noted earlier, previous observations in the case of Pd indicate that this initial palladacycle does exist in equilibria with cyclopropylalkylidene complexes that can lead to other products as well as metathesis type products involving skeletal rearrangements. Similar skeletal rearrangements are observed with all three systems, palladium, ruthenium, and platinum. The fact that cyclobutenes can be isolated in good yield in the case of palladium leads us to favor this mechanistic manifold at present.[14] Among the three methods available, the platinum-based method appears to be the mildest in terms of temperature and the most convenient. Ligandless platinum (+2) is more effective than using a salt in the presence of triphenylphosphine. This method should prove to be generally useful.

A new strategy for the equivalent of a diastereoselective propargylation of an aldehyde has been developed. Diastereoselective reductions of alkynyl ketones proceed readily. Combining this result with the ease of zipping an acetylene then constitutes an equivalent of such a diastereoselective addition. This strategy serves as an alternative to a reagent-controlled diastereoselective addition. While it requires more steps, it does not require stoichiometric amounts of chiral reagents that themselves may not be so readily available and also may be expensive. The chemoselective epoxidation of the less reactive double bond of a 1,3-diene has also been accomplished using a simple protocol.

The current route to the macrocyclic core of roseophilin also constitutes a formal total synthesis since it intersects the same intermediate employed by Fürstner and Weintritt.[2f] Since our route provides the macrocyclic core enantiomerically pure and of known configuration, it offers the opportunity to define the absolute stereochemistry of roseophilin, a subject for future studies. Our route provides the first asymmetric synthesis of the core primed for coupling in 17 steps and 4.4% overall yield from the known acid **8b**.

Experimental Section

Preparation of (1*S*,1′*R*)-1-Cycloundec-2′-enylbut-3-yn-1-ol (17) and *erythro*-1-Cycloundec-2′-enylbut-3-yn-1-ol (18). From the Allenyltin Addition to Cycloundec-2-enylcarboxaldehyde (16). Boron trifluoride diethyl etherate (3.40 mL, 26.83 mmol) was added dropwise to a solution of cycloundec-2-enylcarboxaldehyde **16** (4.15 g, 23.02 mmol) and allenyltributyltin[27] (8.33 g, 25.33 mmol) in 50 mL of methylene chloride at −78 °C. After the addition of ∼50% of the Lewis acid, the reaction was judged complete by thin-layer chromatography. The reaction was allowed to warm to room temperature and diluted with 50 mL of diethyl ether. The reaction was washed with 1 N sodium hydroxide (3 × 100 mL) and a saturated sodium chloride solution (100 mL), dried over magnesium sulfate, and concentrated in vacuo to give 6.619 g of a yellow oil. ^{1}H NMR indicated that a 55:45 diastereomeric mixture resulted. Upon sitting at 0 °C, the oil solidified. The solid was recrystallized from pentane to give 2.12 g (9.60 mmol) of ***rac*-18** as a white solid, mp 76−77 °C (pentane). The pentane was concentrated in vacuo and chromatographed over silica gel (hexane/ethyl acetate 10:1) to give 1.92 g (8.70 mmol) of ***rac*-17** as a colorless oil. The total yield was 4.03 g (18.30 mmol, 80%).

From the Asymmetric Propargylation of (1*S*)-Cycloundec-2-enylcarboxaldehyde (16). The bis-*p*-toluenesulfonamide of (*S*,*S*)-1,2-diphenyl-1,2-diaminoethane (*S*,*S*-stein, 1.85 g, 3.57 mmol) was suspended in 10 mL of methylene chloride and cooled to 0 °C. Boron tribromide (3.40 mL, 3.43 mmol, 1.0 M in methylene chloride) was added dropwise. After 15 min of stirring at 0 °C, the reaction was allowed to warm to room temperature and stirred for an additional 45 min. The solvent was removed in vacuo through a needle inserted through the septum. The resulting yellow solid was dissolved in 5 mL of methylene chloride, and the solvent was removed again as above. The resulting solid was dissolved in 10 mL of methylene chloride and cooled to 0 °C. Propargyltriphenyltin (1.28 g, 3.29 mmol) in 2 mL of methylene chloride was added and the reaction stirred at room temperature for 4 h. The solution was cooled to −78 °C and (1*S*)-cycloundec-2-enylcarboxaldehyde **16** (0.36 g, 2.02 mmol) in 2 mL of methylene chloride was added. After 2 h at −78 °C, the reaction was quenched with 10% aqueous sodium bisulfate (10 mL) and the product extracted into methylene chloride (25 mL). The organic layer was concentrated in vacuo followed by the addition of 3:1 hexane/ethyl acetate which led to the precipitation of the (*S*,*S*)-stein which was collected by filtration. The resulting solution was stirred with aqueous potassium fluoride which caused a precipitate to form. The resulting solid was removed by filtration, and the resulting solution was washed with aqueous potassium fluoride, dried over magnesium sulfate, and concentrated in vacuo. Chromatography over silica gel (petroleum ether/

(26) Murai and co-workers prefer a mechanism invoking a slipped η^1-alkyne−metal bond creating a positive charge at the B vinylic carbon.[15a,b] Also, see: ref 15c for an alternative mechanism.

(27) Carofiglio, T.; Marton, D.; Tagliavini, G. *Organometallics* **1992**, *11*, 2961.

ethyl acetate 10:1) yielded 0.36 g (1.62 mmol, 80%) of a pale yellow oil as a 6.8:1 mixture of **17**, $[\alpha]^{25}_D$ −36.6 (c = 1.15, $CHCl_3$), and **18**.

From *threo*-Cycloundec-2′-enylbut-2-yn-1-ol (21). Potassium hydride (4.92 g, 122.85 mmol) was added to 150 mL of 1,3-diaminopropane (freshly distilled from calcium hydride) at room temperature. After 2 h, the brownish-yellow solution was cooled to 0 °C and a solution of *threo*-cycloundec-2′-enylbut-2-yn-1-ol **21** (6.77 g, 30.71 mmol) in 10 mL of THF was added which caused a deep red color to form. After 1 h, the reaction was quenched by being poured into 250 mL of water and the product was extracted into methylene chloride (3 × 100 mL). The combined organic layers were washed with water (150 mL) and saturated aqueous sodium chloride (150 mL), dried over magnesium sulfate, and concentrated in vacuo. Chromatography over silica gel (petroleum ether/ethyl acetate 5:1) yielded 5.85 g (26.55 mmol, 86%) of ***rac*-17** as a yellow oil.

From (*S*)-Methoxyphenylacetic Acid (1*S*,1′*R*)-1-Cycloundec-2′-enylbut-3-ynyl Ester (25*). Sodium hydroxide (0.5 mL, 1.5 mmol, 3 N) was added to a solution of (*S*)-methoxyphenylacetic acid (1*S*,1′*R*)-1-cycloundec-2′-enylbut-3-ynyl ester **25** (0.34 g, 0.921 mmol) in 2 mL of methanol. After 12 h at room temperature, the reaction was diluted with 20 mL of ethyl ether, washed with 1 N sodium hydroxide (10 mL) and saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, and concentrated in vacuo to give 0.20 g (0.91 mmol, 99%) of **17** as a colorless oil.

Physical Data for (1*S*,1′*R*)-1-Cycloundec-2′-enylbut-3-yn-1-ol (17). IR (neat): 3310, 2926, 2857, 2127, 1462, 1041, 983 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.57 (ddd, J = 4.7, 9.8, 14.8 Hz, 1H), 5.30 (dd, J = 9.9, 15.3 Hz, 1H), 3.57 (dd, J = 5.3, 10.4 Hz, 1H), 1.9−2.5 (m, 7H), 1.1−1.7 (m, 14H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 134.5, 129.6, 72.6, 70.2, 50.4, 34.0, 29.7, 26.5, 26.4, 25.7, 25.6, 25.4, 25.1, 24.9, 24.4. HRMS: calcd for $C_{15}H_{24}O$ (M^+) 220.1819. Found: 220.1827.

Physical Data for *erythro*-1-Cycloundec-2′-enylbut-3-yn-1-ol (18). IR ($CDCl_3$): 3574, 3307, 2250, 2121, 1462.8, 1263 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.54 (ddd, J = 5.0, 9.6, 14.8 Hz, 1H), 5.18 (dd, J = 9.9, 15.4 Hz, 1H), 3.4−3.6 (m, 1H), 2.48 (ddd, J = 2.7, 3.6, 17.0 Hz, 1H), 2.27 (ddd, J = 2.6, 7.4, 16.8 Hz, 1H), 1.9−2.2 (m, 5H), 1.0−1.7 (m, 14H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 133.3, 130.6, 81.4, 72.8, 70.6, 51.2, 34.0, 29.0, 26.5, 26.3, 25.8 (2C), 25.5, 25.4, 24.3. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.57; H, 10.73.

Preparation of (12*R*,13*S*)-13-(*tert*-Butyldimethylsilyloxy)bicyclo-[10.2.1]pentadeca-1(15),2-diene (32). Platinum chloride (0.035 g, 0.133 mmol, 5%) was added to a solution of (1*S*,1′*R*)-1-(*tert*-butyldimethylsilyloxy)-1-cycloundec-2′-enylbut-3-yne **23** (0.891 g, 2.664 mmol) in 5 mL of toluene. The solution was heated to 80 °C and stirred for 1 h. The solution was cooled and filtered through Florisil (petroleum ether). Concentration in vacuo yielded 0.874 g (2.612 mmol, 98%) of the metathesis product **32** as a pale yellow oil, $[\alpha]^{24}_D$ 13.3° (c = 0.35, $CHCl_3$). IR (neat): 1462, 1257, 1251 cm^{-1}. ^{1} H NMR (300 MHz, $CDCl_3$): δ 6.18 (d, J = 15.7 Hz, 1H), 5.48 (s, 1H), 5.40 (ddd, J = 4.4, 10.7, 15.3 Hz, 1H), 4.68 (q, J = 7.7 Hz, 1H), 2.79 (s, 1H), 2.60 (dd, J = 8.8, 15.9 Hz, 1H), 2.48 (dd, J = 7.8, 15.7 Hz, 1H), 2.3−2.4 (m, 1H), 2.0−2.1 (m, 1H), 1.7−1.85 (m, 2H), 1.0−1.4 (m, 12H), 0.9 (s, 9H), 0.1 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.4, 130.9, 129.6, 128.4, 73.5, 48.6, 41.6, 34.0, 29.4, 28.65, 58.57, 27.9, 26.9, 26.5, 26.3, 25.9 (3), 18.4, −4.8, −5.0.

Preparation of *anti*-13-(*tert*-Butyldimethylsilyloxy)bicyclo[10.2.1]-pentadeca-1(15),2-diene (33). [(*p*-cymene)$RuCl_2$]$_2$ (46 mg, 0.075 mmol, 1.25%) was added to a solution of *erythro*-1-(*tert*-butyldimethylsilyloxy)-1-cycloundec-2′-enylbut-3-yne **24** (2.011 g, 5.997 mmol) in 30 mL of toluene. The reaction was placed under carbon monoxide at 1 atm and submersed in an oil bath preheated to 110 °C. As the solution warmed, the catalyst dissolved and the solution went from a red to a yellow color. After 15 min, the solution was cooled, filtered through a short plug of silica gel (pentane), and then concentrated in vacuo to yield 2.118 g (6.330 mmol, 100%) of **33** as a pale yellow solid, mp 74−76 °C (toluene). IR ($CDCl_3$): 1471, 1457, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.26 (d, J = 15.7 Hz, 1H), 5.50 (s, 1H), 5.38 (ddd, J = 4.4, 10.9, 15.4 Hz, 1H), 4.15 (d, J = 6.0 Hz, 1H), 2.91 (dd, J = 6.9, 17.1 Hz, 1H), 2.78 (s, 1H), 2.35−2.4 (m, 1H), 2.27 (d, J = 17.0 Hz, 1H), 1.7−1.9 (m, 3H), 1.0−1.4 (m, 12H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.9, 130.8, 129.4, 128.1, 77.3, 55.8, 43.6, 34.1, 32.0, 29.5, 28.6, 27.8, 26.4, 26.0(3), 25.9, 25.5, 18.4, −4.5, −4.6. Anal. Calcd for $C_{21}H_{38}OSi$: C, 75.38; H, 11.45. Found: C, 75.37; H, 11.24.

Preparation of (3*R*,12*R*,13*S*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-ol (41) and (3*S*,12*R*,13*S*,-15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]-pentadec-1-en-3-ol (42). *N*-Bromosuccinimide (0.58 g, 3.27 mmol) was added to a solution of *rac*-(12*R*,13*S*)-13-(*tert*-butyldimethylsilyloxy)-bicyclo[10.2.1]pentadeca-1(15),2-diene **32** (1.00 g, 2.97 mmol) in 6 mL of THF/water (5:1) at 0 °C. The resulting yellow solution was stirred for 3 h at this temperature. Sodium hydroxide (0.60 g, 14.86 mmol) was added, and the resulting solution was vigorously stirred for 3 h. The solution was diluted with 25 mL of ether and washed with water (25 mL), saturated aqueous sodium bicarbonate (25 mL), and saturated aqueous sodium chloride (25 mL). The organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo to give 1.04 g of a yellow oil. This oil was dissolved in 5 mL of THF and cooled to 0 °C. CuBr·DMS (61 mg, 0.30 mmol, 1%) was added followed by the dropwise addition of 2.2 mL of a 2.0 M solution of isopropylmagnesium chloride in THF. After a total reaction time of 30 min, the reaction was quenched with 5 mL of water. The product was extracted into ether (25 mL) and washed with 10% aqueous sodium bisulfate solution (25 mL) and saturated aqueous sodium chloride (25 mL). The organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo. Chromatography over silica gel (hexane/ethyl acetate 15:1−10:1) yielded 0.73 g (1.84 mmol, 62%) of a mixture of **41** and **42** as a sticky oil. Careful chromatography of the mixture of **41** and **42** over silica gel (hexane/ethyl acetate 15:1−10:1) yielded a small sample of each diastereomer. The same reaction performed using enantiomerically pure **32** (0.87 g, 2.61 mmol) gave 0.45 g (44%) of enantiomerically pure **41** and **42**.

Physical Data for (3*R*,12*R*,13*S*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-ol (41) (Major Diastereomer). IR (neat): 3343, 1463, 1251, 1100, 836, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.19 (d, J = 10.2 Hz, 1H), 4.40 (td, J = 7.1, 9.3 Hz, 1H), 4.29 (td, J = 3.9, 10.4 Hz, 1H), 2.71 (ddd, J = 1.7, 8.7, 17.4 Hz, 1H), 2.29 (d, J = 9.9 Hz, 1H), 2.10 (dd, J = 7.4, 17.7 Hz, 1H), 1.93 (dd, J = 6.4, 11.3 Hz, 1H), 1.65−1.75 (m, 1H), 1.2−1.5 (m, 17H), 0.95 (d, J = 5.0 Hz, 3H), 0.93 (d, J = 4.8 Hz, 3H), 0.89 (s, 6H), 0.42 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 146.6, 127.9, 78.0, 69.5, 53.3, 47.8, 39.3, 38.1, 30.8, 30.4, 29.9, 29.4, 26.6, 26.5(3), 25.4, 24.0, 22.8, 22.7, 21.8, 18.8, −4.25, −4.35. HRMS: calcd for $C_{24}H_{46}O_3Si$ (M^+) 394.3267. Found: 394.3274.

Physical Data for (3*S*,12*R*,13*S*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-ol (42) (Minor Diastereomer). IR (neat): 3332, 1462, 1385, 362, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.17 (d, J = 9.6 Hz, 1H), 4.41 (q, J = 8.2 Hz, 1H,), 4.19 (dt, J = 3.8, 9.7 Hz, 1H), 2.62 (ddd, J = 2.5, 9.3, 17.6 Hz, 1H), 2.19 (ddd, J = 2.5, 7.8, 17.6 Hz, 1H), 2.00 (d, J = 9.3 Hz, 1H), 1.90−2.0 (m, 1H), 1.0−1.5 (m, 15H), 0.90 (d, J = 5.8 Hz, 3H), 0.89 (s, 9H), 0.86 (d, J = 6.7 Hz, 3H), 0.04 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 145.3, 127.8, 73.3, 71.0, 57.1, 44.9, 36.6, 35.9, 30.0, 28.7, 28.2, 27.2, 25.8(3), 25.6, 25.4, 24.8, 22.5, 21.7, 20.7, 18.1, −4.9, −5.0. HRMS: calcd for $C_{24}H_{46}O_2Si$ 394.3267. Found: 394.3252.

Preparation of (12*R*,13*S*,15*R*,1*E*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-one (43) and (12*R*,13*S*,-15*R*,1*Z*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]-pentadec-1-en-3-one (44). TPAP (1 mg, 0.029 mmol, 2.5%) was added to a solution of a mixture of (3*R*,12*S*,13*S*,15*R*)-13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-ol **41** and (3*S*,-12*R*,13*S*,15*R*)-13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]-pentadec-1-en-3-ol **42** (0.451 g, 1.143 mmol), NMO (0.161 g, 1.372 mmol), and 4 Å molecular sieves (0.500 g) in 2 mL of methylene chloride. The reaction was stirred at room temperature for 2.5 h. The reaction was filtered through silica gel (methylene chloride) and concentrated in vacuo to give the crude product. Chromatography over silica gel (petroleum ether/ethyl acetate 10:1) yielded 0.392 g (0.998 mmol, 87%) of a colorless oil as a mixture of **43** and **44**. Additional silica gel chromatography allowed the isolation of a pure sample of **43**

as a colorless oil, $[\alpha]^{20}_D$ 22.4° (c = 0.88, $CHCl_3$), and **44** as a colorless oil, $[\alpha]^{20}_D$ −77.6° (c = 1.12, $CHCl_3$), with the minor diastereomer **44** eluting first.

Physical Data for (12*R*,13*S*,15*R*,1*E*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-one (43) (Major Diastereomer). IR (neat): 1683, 1619, 1471, 1462, 1251 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.27 (s, 1H), 4.51 (td, J = 6.8, 9.4 Hz, 1H), 2.96 (ddd, J = 2.5, 9.4, 20.4 Hz, 1H), 2.53 (dt, J = 5.2, 13.8 Hz, 1H), 2.44 (dd, J = 6.8, 20.6 Hz, 1H), 2.1−2.2 (m, 2H), 2.08 (d, J = 9.7 Hz, 1H), 1.6−1.7 (m, 2H), 1.0−1.5 (m, 13H), 0.90 (d, J = 6.6 Hz, 3H), 0.85 (s, 9H), 0.83 (d, J = 7.1 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 202.6, 164.9, 123.3, 72.9, 60.3, 44.2, 43.3, 39.9, 29.7, 29.1, 28.6, 27.3, 27.2, 26.5, 25.9, 25.7(3), 24.0, 21.4, 21.0, 17.9, −5.0, −5.2. HRMS: calcd for $C_{24}H_{44}O_2Si$ (M^+) 392.3111. Found: 392.3116.

Physical Data for (12*R*,13*S*,15*R*,1*Z*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-one (44) (Minor Diastereomer). IR (neat): 1685, 1620, 1462, 1251 cm^{-1}. ^1H NMR (300 MHz, CDC_3): δ 6.24 (s, 1H), 4.50 (dt, J = 6.5, 9.7 Hz, 1H), 2.90 (d, J = 9.1 Hz, 1H), 2.85 (dd, J = 9.9, 19.8 Hz, 1H), 2.50 (ddd, J = 4.6, 8.8, 12.9 Hz, 1H), 2.25 (ddd, J = 4.6, 7.9, 12.6 Hz, 1H), 2.18 (dd, J = 6.5, 18.7 Hz, 1H), 1.93 (ddd, J = 2.5, 6.4, 8.9 Hz, 1H), 1.0−1.8 (m, 15H), 0.97 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 202.7, 164.5, 125.4, 70.8, 54.3, 46.8, 44.5, 40.7, 30.7, 29.6, 27.0, 26.2, 25.8(3), 25.0, 24.3, 23.4, 23.2, 21.2, 21.1, 18.1, −5.0, −5.1. HRMS: calcd for $C_{24}H_{44}O_2Si$ (M^+) 392.3111. Found: 392.3107.

Preparation of (12*R*,13*R*,15*R*)-13-*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1(14)-en-3-one (57). DBU (33 μL, 0.222 mmol, 0.5 equiv) was added to a solution of *rac*-(12*R*,13*S*,-15*R*,1*E*)-13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]-pentadec-1-en-3-one **43** and (12*R*,13*S*,15*R*,1*Z*)-13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-en-3-one **44** (0.175 g, 0.445 mmol) in 1 mL of acetonitrile at 75 °C. After 4 h, the reaction was cooled and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/ethyl acetate 50:1) to yield 0.119 g (0.303 mmol, 68%, 91% brsm) of the product as a colorless oil along with 0.044 g (0.112 mmol, 25%) of the starting material. Performing the reaction with DBU (75 μL, 0.499 mmol, 0.5 equiv) and enantiomerically pure **43**−**44** (0.392 g, 0.992 mmol) in 1 mL of acetonitrile at 60 °C gave 0.265 g (0.674 mmol, 68%) of the product as a colorless oil which solidified upon sitting, mp 50 °C $[\alpha]^{24}_D$ 1.1° (c = 1.05, $CHCl_3$). IR (neat): 1717, 1462, 1365, 1251 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.53 (s, 1H), 4.84 (m, 1H), 3.26 (d, J = 12.0 Hz, 1H), 2.89 (d, J = 12.0 Hz, 1H), 2.79 (ddd, J = 3.6, 10.2, 19.0 Hz, 1H), 2.32 (dt, J = 5.1, 18.9 Hz, 1H), 2.23 (s, 1H), 2.10−2.18 (m, 1H), 1.85−2.0 (m, 2H), 1.05−1.5 (m, 13H), 0.96 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.69 (d, J = 6.9 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 208.1, 139.9, 134.3, 78.1, 57.0, 45.2, 43.0, 38.9, 28.4, 28.2, 27.1, 25.9(3), 25.7, 25.1, 23.6, 22.9, 21.5, 20.6, 18.2, 17.3, −4.9, −5.1. Anal. Calcd for $C_{24}H_{44}O_2Si$: C, 73.41; H, 11.29. Found: C, 73.52; H, 11.27.

Preparation of (1*R*,3*R*,12*R*,13*R*,14*R*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-diol (62a) and (1*R*,3*S*,12*R*,13*R*,14*R*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-diol (62b). Borane dimethyl sulfide complex (0.127 mL, 1.273 mmol, 10.0 M) was added to a solution of (12*R*,13*R*,15*R*)-13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1(14)-en-3-one **57** (100 mg, 0.255 mmol) in 5 mL of ethyl ether. After 22 h of stirring, the reaction was carefully quenched by the addition of 0.25 mL of methanol. Sodium hydroxide (0.85 mL, 2.546 mmol, 3 N) and hydrogen peroxide (0.22 mL, 6.366 mmol, 30% aqueous solution) were added, and stirring was continued for an additional 20 h at room temperature. The product was extracted into ethyl ether (4 × 5 mL), dried over magnesium sulfate, and concentrated in vacuo. Chromatography over silica gel (petroleum ether/ethyl acetate 2:1) yielded 57 mg of **62a** and 36 mg of **62b** for a total yield of 93 mg (0.226 mmol, 89%).

The reaction was performed with borane dimethyl sulfide complex (0.170 mL, 1.69 mmol, 10.0 M) and enantiomerically pure **57** (265 mg, 0.675 mmol) in 1 mL of ethyl ether. After 16 h of stirring, the reaction was carefully quenched by the addition of 5 mL of water. Sodium bromate 0.125 g (0.810 mmol) was added, and the reaction was heated to 50 °C for 2.5 h. The product was extracted into ethyl ether (10 mL), washed with water (2 × 10 mL) and saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, and concentrated in vacuo. Chromatography over silica gel (petroleum ether/ethyl acetate 2:1) yielded 197 mg 0.477 mmol, 70%) of a white solid containing a mixture of the two epimeric diols **62**. Additional chromatography over silica gel (petroleum ether/ethyl acetate 2:1) allowed the isolation of a pure sample of **62a** as a white solid, mp 122−123 °C, $[\alpha]^{24}_D$ 37.5° (c = 1.02, $CHCl_3$), and pure sample of **62b** as a white solid, mp 125 °C, $[\alpha]^{24}_D$ −24.0° (c = 0.86, $CHCl_3$).

Physical Data for (1*R*,3*R*,12*R*,13*R*,14*R*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-diol (62a). IR (neat): 3361, 1463, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.92 (t, J = 9.3 Hz, 1H), 3.73 (t, J = 8.0 Hz, 1H), 3.60−3.70 (b, 1H), 2.90 (b, 1H), 2.40 (b, 1H), 1.85 (d, J = 8.3 Hz, 1H), 1.0−1.7 (m, 18H), 0.89 (s, 9H), 0.83−0.89 (m, 6H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 78.9, 77.1, 68.8, 47.7, 42.7, 41.8, 38.0, 36.3, 33.2, 26.3, 26.0(3), 25.9, 25.0, 24.0, 22.4, 22.1, 22.0, 20.5, 20.4, 18.3, −4.6, −4.7. Anal. Calcd for $C_{24}H_{48}O_3Si$: C, 69.84; H, 11.72. Found: C, 69.70; H, 11.62.

Physical Data for (1*R*,3*S*,12*R*,13*R*,14*R*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-diol (62b). IR (KBr): 3386, 1465, 1251 cm^{-1}. ^{1} H NMR (300 MHz, $CDCl_3$): δ 3.88 (t, J = 7.3 Hz, 1H), 3.81 (b, 1H), 3.71 (t, J = 6.8 Hz, 1H), 2.0 (b, 1H), 1.1−1.9 (m, 32H), 0.94 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.88 (d, J = 6.3 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 84.5, 80.1, 68.9, 48.3, 43.8, 42.7, 41.6, 37.2, 32.8, 27.3, 26.8, 26.6, 25.9(3), 24.24, 24.18, 23.4, 22.4, 21.5, 20.5, 18.2, −4.7(2). Anal. Calcd for $C_{24}H_{46}O_3Si$: C, 39.84; H, 11.72. Found: C, 69.63; H, 11.57.

Preparation of (1*R*,12*R*,13*R*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-dione (61). From the Reduction of *rac*-(1*Z*,12*R*,13*R*,15*R*)-13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-ene-3−14-dione (60). Palladium on carbon (10 mg, 10%) was added to a solution of 13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadec-1-ene-3,14-dione 60 (25 mg, 0.062 mmol) in 0.5 mL of ethyl acetate. The reaction was stirred at room temperature under hydrogen at 1 atm. After 30 min at room temperature, the reaction was filtered through Florisil (ethyl acetate) and concentrated in vacuo. The product, which has the same R_f as the substrate but is not UV active, was purified by Florisil chromatography (hexane/ethyl acetate 50:1) to yield 19 mg (0.046 mmol, 74%) of *rac*-**61** as a colorless oil.

From the Oxidation of 13-(*tert*-Butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-diol (62). TPAP (2 mg, 0.002 mmol, 5%) was added to a solution of a diastereomeric mixture of diols **62** (50 mg, 0.121 mmol), NMO (35 mg, 0.303 mmol), and 4 Å molecular sieves (100 mg) in 0.25 mL of methylene chloride. After 8 h at room temperature, the reaction was placed onto silica gel and eluted with petroleum ether/ethyl acetate (10:1) to yield 46 mg (0.113 mmol, 93%) of a colorless oil.

Performing the same reaction using TPAP (2.9 mg, 0.008 mmol, 5%), enantiomerically pure diol **62** (70 mg, 0.170 mmol), NMO (50 mg, 0.424 mmol), and 4 Å molecular sieves (100 mg) in 0.5 mL of methylene chloride yielded 54 mg (0.132 mmol, 78%) of a colorless oil, $[\alpha]^{20}_D$ −19.2° (c = 1.81, $CHCl_3$). IR (neat): 1752, 1711, 1463, 1366, 1362 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.39 (dd, J = 2.0, 8.3 Hz, 1H), 2.76 (d, J = 5.2 Hz, 1H), 2.83 (d, J = 1.7 Hz, 1H), 2.48 (ddd, J = 3.6, 8.2, 14.8 Hz, 1H), 2.38−2.45 (m, 1H), 2.23 (ddd, J = 3.4, 9.4, 14.9 Hz, 1H), 1.9−2.3 (m, 2H), 1.75−1.9 (m, 1H), 1.69 (dd, J = 3.5, 5.8 Hz, 1H), 1.5−1.6 (m, 2H), 1.1−1.5 (m, 11H), 1.02 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.13 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 216.2, 210.6, 78.0, 45.5, 44.2, 43.7, 42.3, 40.0, 32.3, 26.7, 27.0, 25.9, 25.7(3), 24.7, 23.6, 23.1, 22.8, 21.2, 19.6, 16.4, −4.8, −5.5. HRMS: calcd for $C_{24}H_{44}O_3Si$ ($M^+ - CH_3$) 393.2826. Found: 393.2833.

Preparation of (12*R*,13*R*,15*R*)-2-Benzyl-15-(*tert*-butyldimethylsilyloxy)-13-isopropyl-2-azatricyclo[10.2.1.1^{13,14}]hexadeca-1(14),3-(16)-diene (63b).. Benzylamine (0.038 mL, 0.350 mmol) was added

to a solution of *rac*-(1*R*,12*R*,13*R*,15*R*)-13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-dione **62** (29 mg, 0.070 mmol), glacial acetic acid (20 μL, 0.350 mmol), and 4 Å molecular sieves (100 mg) in 0.25 mL of methanol. The reaction was heated to 50 °C for 3 h and then allowed to proceed at room temperature for 12 h. The reaction was filtered through silica gel using petroleum ether/ethyl acetate (10:1) and concentrated in vacuo. Chromatography over silica gel (petroleum ether/ethyl acetate 50:1) yielded 20 mg (0.042 mmol, 60%) of a colorless oil. The enantiomerically pure sample had $[\alpha]^{20}_D$ −59.4° (*c* = 1.77, $CHCl_3$). IR (neat): 1456, 1361, 1257 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ7.14−7.27 (m, 3H), 6.85 (d, *J* = 7.3 Hz, 2H), 5.74 (s, 1H), 5.42 (d, *J* = 6.3 Hz, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 4.94 (d, *J* = 17.1 Hz, 1H), 2.60−2.62 (m, 1H), 2.42−2.76 (m, 3H), 1.80−1.92 (m, 1H), 1.68−1.80 (m, 1H), 0.8−1.5 (m, 13H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 4.9 Hz, 3H), 0.89 (s, 9H), −0.002 (s, 3H), −0.33 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.9, 137.5, 134.3, 128.5(2), 126.6, 125.8, 125.4(2), 106.6, 72.8, 54.2, 51.3, 46.4, 32.8, 29.8, 28.2, 28.0, 27.6, 26.9, 26.4, 25.9(3), 25.3, 25.0, 21.6, 20.3, 17.9, −4.4, −5.9. HRMS: calcd for $C_{31}H_{49}NOSi$ (M^+) 479.3583. Found: 479.3584.

Preparation of (12*R*,13*R*,15*R*)-15-(*tert*-Butyldimethylsilyloxy)-13-isopropyl-2-(2-trimethylsilanylethoxymethyl)-2-azatricyclo[10.2.1.1^{3,14}]-hexadeca-1(14),3(16)-diene (63f). Ammonium acetate (97 mg, 1.350 mmol) was added to a solution of (1*R*,12*R*,13*R*,15*R*)-13-(*tert*-butyldimethylsilyloxy)-15-isopropylbicyclo[10.2.1]pentadecane-3,14-dione **62** (55 mg, 0.135 mmol), camphorsulfonic acid (3 mg, 0.135 mmol, 0.1 equiv), and 4 Å molecular sieves (100 mg) in 0.5 mL of methanol. The reaction was heated to 50 °C for 5 h. The reaction was cooled to room temperature, filtered through Florisil (petroleum ether/ethyl acetate 10:1), and concentrated in vacuo to give 45 mg (0.115 mmol, 85.5%) of a colorless oil. This oil was immediately dissolved in 0.5 mL of DMF, cooled to 0 °C, and treated with potassium hydride (9.1 mg, 0.228 mmol). After 10 min, 2-(trimethylsilyl)ethoxymethyl chloride (38 mg, 0.040 mL, 0.228 mmol) was added and the reaction was allowed to warm to room temperature and stirred for 40 min. The reaction was quenched with 1 mL of saturated aqueous sodium bicarbonate and the product extracted into ether (3 × 1 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Chromatography over silica gel (petroleum ether/ethyl acetate 50:1) yielded 45 mg (0.087 mmol 76%) of a colorless oil, $[\alpha]^{20}_D$ −36° (*c* = 0.77, $CHCl_3$). IR (neat): 1472, 1367, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.69 (s, 1H), 5.55 (d, *J* = 5.9 Hz, 1H), 5.36 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 10.7 Hz, 1H), 3.30−4.58 (m, 2H), 2.69 (td, *J* = 7.2, 14.7 Hz, 1H), 2.60−2.65 (m, 1H), 2.53 (td, *J* = 7.3, 14.7 Hz, 1H), 2.39 (d, *J* = 7.1 Hz, 1H), 1.80−1.95 (m, 1H), 1.60−1.75 (m, 1H), 1.1−1.6 (m, 5H), 0.8−1.1 (m, 22H), 0.15 (s, 3H), 0.10 (s, 3H), −0.02 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 138.1, 135.1, 126.4, 107.3, 72.9, 72.6, 64.6, 54.3, 51.4, 32.7, 29.7, 28.1, 28.0, 27.8, 26.9, 26.4, 26.0(3), 25.5, 24.9, 21.7, 20.3, 18.0, 17.9, −1.5(3), −4.2, −5.0. HRMS: calcd for $C_{30}H_{57}NO_2Si_2$ (M^+) 519.3928. Found: 519.3929.

Preparation of (12*R*,13*R*)-13-Isopropyl-2-(2-trimethylsilanyl-ethoxymethyl)-2-azatricyclo[10.2.1.1^{3,14}]hexadeca-1(14),3(16)-dien-15-one (64f). TBAF (0.26 mL, 0.26 mmol, 1.0 M in THF) was added to a solution of (12*R*,13*R*,15*R*)-15-(*tert*-butyldimethylsilyloxy)-13-isopropyl-2-(2-trimethylsilanylethoxymethyl)-2-azatricyclo[10.2.1.1^{3,14}]-hexadeca-1(14),3(16)-diene **63f** (45 mg, 0.087 mmol) and 4 Å molecular sieves (50 mg) in 0.1 mL of THF. The reaction was stirred at room temperature for 14 h and then filtered through Florisil and concentrated in vacuo. The resulting alcohol was immediately dissolved in 0.2 mL of methylene chloride and treated with manganese dioxide (75 mg, 0.863 mmol). The reaction was stirred at room temperature for 1 h after which time it was filtered through a plug of silica gel (ethyl ether) and concentrated in vacuo. Chromatography over silica gel (petroleum ether/ethyl acetate 10:1) yielded 18 mg (0.046 mmol, 54%) of a colorless oil with an identical ^1H NMR spectrum to that of the compound reported by Fürstner:[2f] $[\alpha]^{20}_D$ −66.0° (*c* = 0.28, $CHCl_3$). IR (neat): 1678, 1471, 1248.4 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.99 (s, 1H), 5.66 (d, *J* = 10.7 Hz, 1H), 5.31 (d, *J* = 11.0 Hz, 1H), 3.64 (td, *J* = 5.6, 10.5 Hz, 1H), 3.51 (td, *J* = 6.3, 9.8 Hz, 1H), 2.70−2.76 (m, 3H), 2.60 (d, *J* = 6.1 Hz, 1H), 2.0−1.40 (m, 5H), 1.30−0.45 (m, 12H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), −0.02 (s, 9H).

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Supporting Information Available: Procedures for the preparation of **10a**, **10b**, **14**−**16**, **19**−**21**, **23**-**27**, **29**, **50a**, **54a**, **55a**, **59**, **60**, and **64b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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