Enantiodivergent Total Syntheses of (+)- and (−)-Scopadulcic Acid A

Martin E. Fox,[1a] Chi Li,[1b] Joseph P. Marino, Jr.,[1c] and Larry E. Overman*

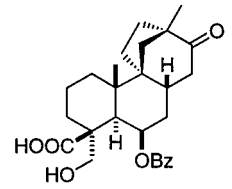
Contribution from the Department of Chemistry, University of California, 516 Rowland Hall, Irvine, California 92697-2025

Received February 8, 1999

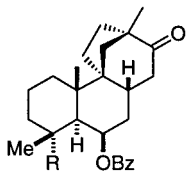
Abstract: The first enantioselective total synthesis of scopadulcic acid A is described. The key step is a cascade intramolecular Heck reaction of a methylenecycloheptene iodide, which generates the B, C, and D rings of the scopadulan ring system in 90% yield as a single stereoisomer. A distinctive feature of these syntheses is the use of stereoselective enolization to dictate which enantiomer of the natural product is produced.

Introduction

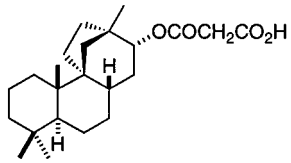
Scoparia dulcis L. (Scrophuraliaceae) is an erect perennial herb growing to a half-meter in size and is found in many tropical countries of the world. There are numerous reports of its use as an herbal remedy of a variety of disorders.[2,3] For example, the Paraguayan crude drug *Typchá-Kuratû* prepared from whole plants of *S. dulcis* L. is claimed by indigenous peoples to improve digestion and protect the gastrointestinal system.[3c,4] During their investigations of this folk medicine, Hayashi and co-workers identified from its pharmacologically active extracts two structurally unique tetracyclic diterpene acids, scopadulcic acids A (**1**, SDA) and B (**2**, SDB).[5,6] Scopadulciol (**3**) was later isolated by these workers from *S. dulcis* indigenous to Taiwan and gives the same triol as **2** when reduced with $LiAlH_4$.[7] A diterpene alcohol originally called dulcinol had been described earlier from a Bangladeshi collection of *S. dulcis*[8] and is believed to be identical with scopadulciol from ^{1}H NMR comparisons.[9] Several years later, three additional diterpene acids, exemplified by thyrsiflorin A (**4**), having the scopadulan ring system (**5**) were isolated from *Calceolaria thyrsiflora L.*, a plant also of the Scrophuraliaceae family.[10]



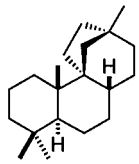
(−)-scopadulcic acid A (**1**)



scopadulcic acid B (**2**) R = CO_2H
scopadulciol (**3**) R = CH_2OH



thyrsiflorin A (**4**)



scopadulan skeleton (**5**)

The scopadulcic acids and some of their semisynthetic analogues exhibit a broad pharmacological profile, including in vitro antiviral activity against herpes simplex virus type 1,[11,12] in vitro and in vivo antitumor activity in various human cell lines,[13,14] and inhibition of tumor promotion by phorbol esters.[15] SDB also shows powerful inhibitory activity against H^+,K^+-adenosine triphosphatase (ATPase), the proton pump for gastric acid secretion.[16−18] Interestingly, SDB inhibits H^+,K^+-ATPase quite differently from Omeprazole, a highly successful clinical proton pump inhibitor.[16] More recently, SDB has been shown to inhibit bone resorption by osteoclast cells, suggesting that the scopadulan diterpenes might be leads for developing therapeutic agents to treat osteoporosis.[19]

(1) Current address: (a) Chiroscience Limited, C. S. P.-M. R., Cambridge, CB4 4WE, U.K. (b) Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543-4000. (c) SmithKline Beecham Pharmaceuticals, P.O. Box 1539, King of Prussia, PA 19406-0939.

(2) Hostettmann, K. *Phytochemistry of Plants Used in Traditional Medicine*; Oxford University Press: New York, 1995.

(3) See, inter alia: (a) Satyanarayana, K. *J. Indian Chem. Soc.* **1969**, *46*, 765−766. (b) Chow, S. Y.; Chen, S. M.; Yang, C. M.; Hsu, H. *J. Formosan Med. Assoc.* **1974**, *73*, 739. (c) Gonzales Torres, D. M. *Catalogo de Plantas Medicinales (y Alimenticias y Utiles) Usada en Paraguay*, Asunción, Paraguay, 1986; p 394.

(4) Shimizu, M.; Horie, S.; Terashima, S.; Ueno, H.; Hayashi, T.; Arisawa, M.; Suzuki, S.; Yoshizaki, M.; Morita, N. *Chem. Pharm. Bull.* **1989**, *37*, 2531−2532.

(5) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Shimizu, M.; Suzuki, S.; Yoshizaki, M.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Berganza, L. H.; Ferro, E.; Basualdo, I. *Tetrahedron Lett.* **1987**, *28*, 3693−3696.

(6) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Morita, N. *J. Nat. Prod.* **1988**, *51*, 360−363.

(7) Hayashi, T.; Asano, S.; Mizutani, M.; Takeguchi, N.; Kojima, T.; Okamura, K.; Morita, N. *J. Nat. Prod.* **1991**, *54*, 802−809.

(8) Ahmed, M.; Jakupovic, J. *Phytochemistry* **1990**, *29*, 3035−3037.

(9) Hayashi, T.; Okamura, K.; Tamada, Y.; Iida, A.; Fujita, T.; Morita, N. *Phytochemistry* **1993**, *32*, 349−352

(10) Chamy, M. C.; Piovano, M.; Garbarino, J. A.; Miranda, C.; Gambaro, V.; Rodriguez, M. L.; Ruiz-Perez, C.; Brito, I. *Phytochemistry* **1991**, *30*, 589−592.

(11) Hayashi, K.; Niwayama, S.; Hayashi, T.; Nago, R.; Ochiai, H.; Morita, N. *Antiviral Res.* **1988**, *9*, 345−354.

(12) Hayashi, T.; Hayashi, K.; Uchida, K.; Niwayama, S.; Morita, N. *Chem. Pharm. Bull.* **1990**, *38*, 239−242.

(13) Hayashi, T.; Kawasaki, M.; Miwa, Y.; Taga, T.; Morita, N. *Chem. Pharm. Bull.* **1990**, *38*, 945−947.

(14) Hayashi, K.; Hayashi, T.; Morita, N. *Phytother. Res.* **1992**, *6*, 6−9.

(15) Nishino, H.; Hayashi, T.; Arisawa, M.; Satomi, Y.; Iwashima, A. *Oncology* **1993**, *50*, 100−103.

(16) Asano, S.; Mizutani, M.; Hayashi, T.; Morita, N.; Takeguchi, N. *J. Biol. Chem.* **1990**, *265*, 22167−22173.

(17) Hayashi, T.; Okamura, K.; Kakemi, M.; Asano, S.; Mizutani, M.; Takeguchi, N.; Kawasaki, M.; Tezuka, Y.; Kikuchi, T.; Morita, N. *Chem. Pharm. Bull.* **1990**, *38*, 2740−2745.

(18) Hayashi, T.; Kawasaki, M.; Okamura, K.; Tamada, Y.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Miwa, Y.; Taga, T. *J. Nat. Prod.* **1992**, *55*, 1748−1755.

10.1021/ja990404v CCC: $18.00
Published on Web 05/20/1999

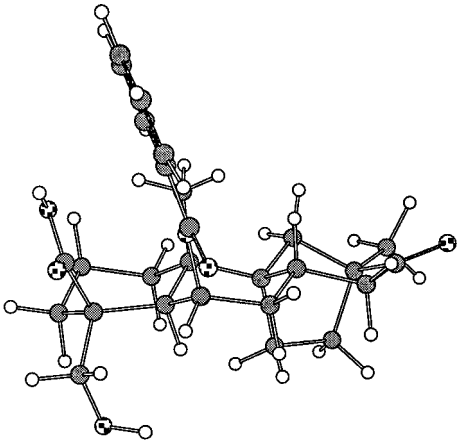


Figure 1. X-ray model of scopadulcic acid A.

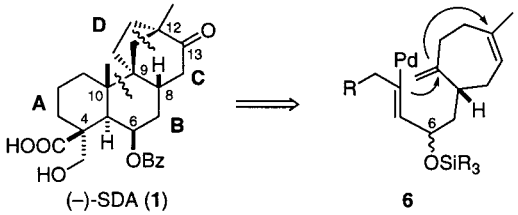


Figure 2. Sequential Heck cyclizations to form the B, C, and D rings of SDA.

Based initially on spectroscopic investigations, **1** and **2** were advanced in 1987 as the structures of SDA and SDB, respectively.[5] Soon thereafter, the relative stereochemistry of SDA was confirmed by single-crystal X-ray analysis of its methanol solvate (Figure 1).[6] The absolute stereochemistry of SDA and SDB depicted in structures **1** and **2** has been proposed on the basis of the positive Cotton effect observed in the CD spectra of each diterpene acid.[5]

In 1993, our group reported the first total syntheses of (±)-SDA[20] and (±)-SDB,[21,22] using in each case a bis-Heck cyclization to create the B, C, and D rings of the scopadulan ring system (Figure 2). The formation of the C9 and C12 quaternary stereocenters efficiently in a single step in these total syntheses showcased the exceptional ability of intramolecular Heck reactions to forge quaternary carbon centers, even in highly congested environments.[23] Ziegler and Wallace subsequently reported total syntheses of (±)-SDA, (±)-SDB, and (±)-scopadulciol using a different strategy.[24] More recently, Zaragozá and co-workers reported the elaboration of (+)-podocarp-8(14)-en-13-one to the methyl ester of the simplest scopadulan diterpene, (−)-thyrsiflorin A (**4**).[25] Approaches to the scopadulan ring system have also been described by several research groups.[26,27]

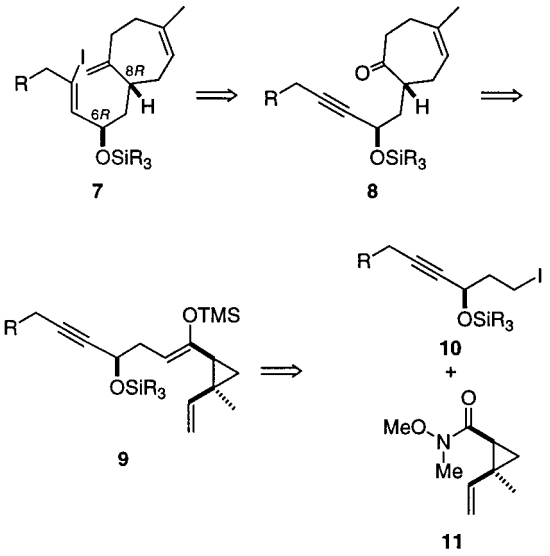


Figure 3. Plan for preparing (*R*,*R*)-**7**.

The unique and synthetically challenging atom connectivity of the scopadulan diterpenes prompted us to extend our studies in this area to develop an enantioselective route to this class of pharmacologically significant natural products. In this paper, we describe enantioselective total syntheses of (+)- and (−)-scopadulcic acid A. Besides constituting the inaugural enantioselective entry to the scopadulcic acids, these syntheses for the first time rigorously establish the absolute configuration of natural (−)-SDA (**1**).

Results and Discussion

A. Synthesis Plan. In our earlier synthesis of (±)-SDA, we first formed the B, C, D rings as depicted in Figure 2, and at a late stage generated the A ring through an aldol cyclization.[20] During an early phase of these studies in the racemic series, we learned that only one of the two C6 siloxy epimers of **6** underwent the pivotal Heck insertion of the exomethylene group from the desired α-face to generate the trans-B/C ring fusion of the scopadulan diterpenes.[28,29] Heck cyclization of the other epimer led to a mixture of products, two of which contain bridged bicyclooctane units having the B/C cis-ring fusion found in tetracyclic diterpenes of the aphidicolin and stemarin families.[30]

Prior to the studies disclosed herein, the methylenecycloheptene diastereomer that cyclized to generate the scopadulan ring system was believed to possess the relative stereochemistry depicted in intermediate **7** (Figure 3).[20,31] As a result, our inaugural studies directed toward (−)-SDA targeted cyclization precursor **7**, having the 6*R*,8*R* absolute configuration. As in our

(19) Miyahara, T.; Hayashi, T.; Matsuda, S.; Yamada, R.; Ikeda, K.; Tonoyama, H.; Komiyama, H.; Matsumoto, M.; Nemoto, N.; Sankawa, U. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1037−1042.

(20) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304−5306.

(21) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042−2044.

(22) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031−12040.

(23) For recent reviews of the use of intramolecular Heck reactions in natural products total synthesis, see: (a) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross Coupling Reactions*; Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 6. (b) Link, J. T.; Overman, L. E. *CHEMTECH* **1998**, *28* (8, August), 19−26.

(24) Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626−3636.

(25) Abad, A.; Agulló, C.; Arnó, M.; Marin, M. L.; Zaragozá, R. J. *Synlett* **1997**, 574−576.

(26) (a) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607−2609. (b) Tagat, J. R.; McCombie, S. W.; Puar, M. S. *Tetrahedron Lett.* **1996**, *37*, 8459−8462. (c) Tagat, J. R.; Puar, M. S.; McCombie, S. W. *Tetrahedron Lett.* **1996**, *37*, 8463−8466. (d) Hall, D. G.; Caille, A. S.; Drouin, M.; Lamothe, S.; Muller, R.; Deslongchamps, P. *Synthesis* **1995**, 1081−1088. (e) Reddy, S. H. K.; Moeller, K. D. *Tetrahedron Lett.* **1998**, *39*, 8027−8030.

(27) The scopadulan skeleton has also been generated by rearrangement of an aphidicolin derivative: Hanson, J. R.; Hitchcock, P. B.; Jarvis, A. G.; Ratcliffe, A. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1773−1778.

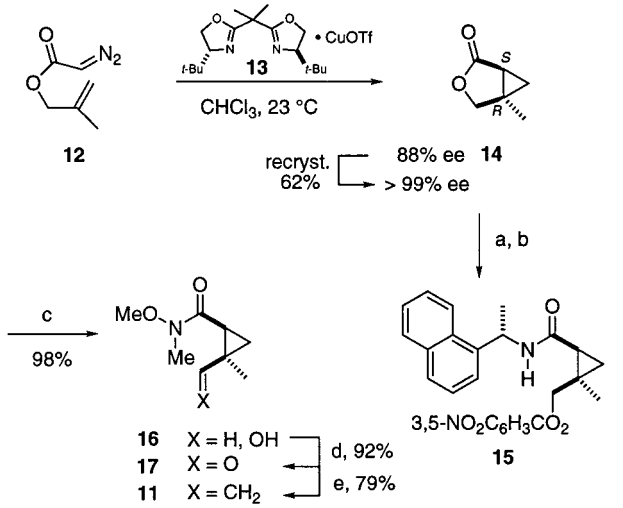
(28) Kucera, D. J. Ph.D. Dissertation, University of California, Irvine, 1991.

(29) The scopadulan numbering system will be employed in the discussion of all synthetic intermediates. Correct IUPAC designations of intermediates are found in the Experimental Section.

(30) Rucker, P. V.; Overman, L. E. Unpublished studies, UCI.

(31) This erroneous assignment resulted in an incorrect specification of the relative stereochemistry at C6 of structures **10**−**13** in ref 20.

Scheme 1[a]



[a] Reaction conditions: (a) (*S*)-(−)-1-(1-naphthyl)ethylamine, Me_3Al, 92%; (b) 3,5-dinitrobenzoyl chloride, DMAP, Et_3N, CH_2Cl_2, 74%; (c) MeNH(OMe)·HCl, Me_3Al; (d) TPAP, NMO; (e) $Ph_3P{=}CH_2$, THF, 0 °C.

earlier investigations in the racemic series, vinyl iodide **7** would derive through standard synthetic transformations from cycloheptenone **8**. This ketone, which contains the critical C6 and C8 stereocenters, was envisaged to arise from divinylcyclopropane rearrangement of (*Z*)-enoxysilane **9**.[32−35] Since divinylcyclopropane sigmatropic rearrangements strictly adhere to a boat topography,[35] the *Z* geometry of the enoxysilane unit would translate to the *R* absolute configuration at C8 of cycloheptenone **8**. Generation of the *Z* enoxysilane stereoisomer from a cyclopropyl ketone precursor seemed plausible on the basis of ample literature guidance on stereoselective enolization of acyclic ketones.[36] Last, the cyclopropyl ketone precursor of **9** would come from coupling the lithium reagent derived from (*R*)-iodide **10** with cyclopropyl amide **11**.

B. Unanticipated Synthesis of the 8*S* Stereoisomer of the Cycloheptenone Intermediate. Our investigations began with the enantioselective synthesis of 3-oxabicyclo[3.1.0]hexan-1-one (**14**) by catalytic asymmetric intramolecular cyclopropanation of diazoester **12** (Scheme 1). After screening several possible catalysts, we found that the (*R*,*R*)-bis(oxazoline)copper catalyst **13** reported by Evans and Woerpel was optimal.[37] This reaction was best performed by adding diazoacetate **12** slowly using a syringe pump to a dilute chloroform solution of **13** (0.6 mol %). These conditions obviated the formation of the maleate and fumarate byproducts arising from formal dimerization of the ketocarbenoid intermediate. In addition, moisture had to be rigorously excluded to prevent competitive formation of di(2-methyl-2-propenyloxycarbonylmethyl) ether, which arises from the reaction of water with 2 equiv of the ketocarbenoid. When these precautions were taken, **14** could be prepared on multigram scales in 80% yield and 88% ee.[38,39] Even though butyrolactone **14** is a low-melting solid (mp 58−59 °C), the corresponding racemate is a liquid at room temperature, allowing the enantiomeric purity of this intermediate to be enhanced to greater than 99% ee by a single recrystallization. The absolute configuration of **14** was confirmed by single-crystal X-ray analysis of amide **15**, which was formed from the reaction of **14** with (*S*)-(−)-1-(1-naphthyl)ethylamine and acylation of this product with 3,5-dinitrobenzoyl chloride.[40,41] Treatment of lactone **14** with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum provided amide **16** in high yield.[42] Oxidation of this intermediate with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[43] yielded aldehyde **17**, which underwent subsequent Wittig methylenation to give rise to cyclopropyl amide **11** in 43% overall yield from **12**.

The (*R*)-alkyl iodide **23**, which contains 9 of the 10 skeletal carbons of the A and B rings, was next prepared as summarized in Scheme 2. Reaction of 3-(*tert*-butyldimethylsiloxy)propanal (**18**)[44] with the lithium salt of 2-(4′-pentynyl)-1,3-dioxolane[45] provided *rac*-**19**, which was oxidized by the Swern procedure[46] to yield ynone **20**. A variety of asymmetric reducing conditions, including Darvon-alcohol-$LiAlH_4$,[47−50] (*R*)-BINAL-H,[51] and oxazaborolidine-catalyzed borane reduction,[52,53] were screened for enantioselective reduction of **20**; however, either the efficiency of the reaction was poor or the enantiomeric excess

(32) (a) Piers, E.; Nagakura, I. *Tetrahedron Lett.* **1976**, 3237−3240. (b) Piers, E.; Burmeister, M. S.; Ressig, H.-U. *Can. J. Chem.* **1986**, *64*, 180−187.

(33) Marino, J. P.; Browne, L. J. *Tetrahedron Lett.* **1976**, *37*, 3245−3248.

(34) (a) Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976**, *41*, 3490−3491. (b) Wender, P. A.; Eissenstat, M. A.; Filosa, M. P. *J. Am. Chem. Soc.* **1979**, *101*, 2196−2198.

(35) For a brief review, see: Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 971−998.

(36) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, pp 1−110.

(37) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (b) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430−432.

(38) Enantioenriched 5-methyl-2-oxo-3-oxabicyclo[3.1.0]hexane has also been prepared from **12** by Doyle and co-workers.[39] These workers studied the enantioselectivity of this intramolecular cyclopropanation using several asymmetric catalysts [chiral Rh(I) and Rh(II) catalysts and *ent*-**13**]; the copper bis-oxazoline catalyst provides highest enantioselection.[39c] The absolute configuration for the levorotatory (1*S*,5*R*) enantiomer of **14** is incorrectly specified in refs 39a and 39c.

(39) (a) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763−5775. (b) Doyle, M. P.; Zhou, Q. L.; Dyatkin, A. B.; Ruppar, D. A. *Tetrahedron Lett.* **1995**, *36*, 7579−7582. (c) Doyle, M. P.; Peterson, C. S.; Zhou, Q.-L.; Nishiyama, H. *Chem. Commun.* **1997**, *36*, 211−212.

(40) The authors have deposited coordinates for this derivative with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(41) At the time **14** was first prepared, the sense of asymmetric induction with copper(I) complexes of **13** in intramolecular cyclopropanations had not been established. The model advanced by Evans and Woerpel[37] to rationalize bimolecular cyclopropanations brought about with this catalyst correctly predicts the formation of (1*S*,2*R*)-**14**.

(42) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993.

(43) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13−19.

(44) Prepared from 3-buten-1-ol: Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603−3613.

(45) Prepared from 5-hexyn-1-ol by Swern oxidation[46] followed by acetalization.

(46) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(47) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870−1877.

(48) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339−8341.

(49) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582−588.

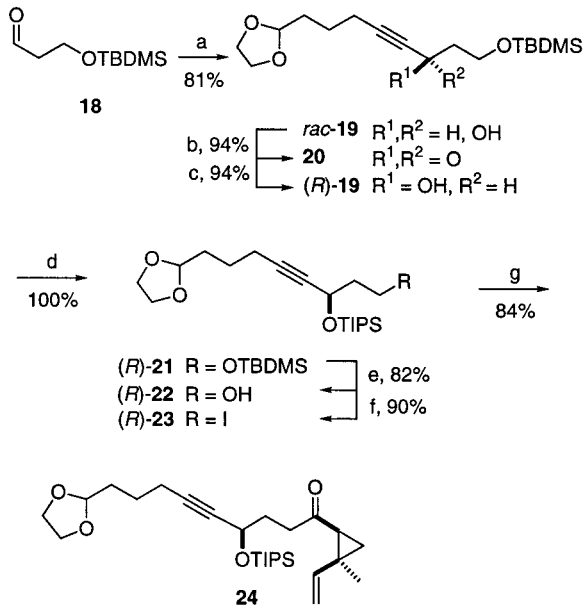
(50) Deeter, J.; Frazier, J.; Staten, G.; Staszak, M.; Weigel, L. *Tetrahedron Lett.* **1990**, *31*, 7101−7104.

(51) Noyori, R.; Tomino, I.; Tanamoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716.

(52) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chung-Pin, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.

(53) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. *J. Org. Chem.* **1993**, *58*, 2880−2888.

Scheme 2[a]

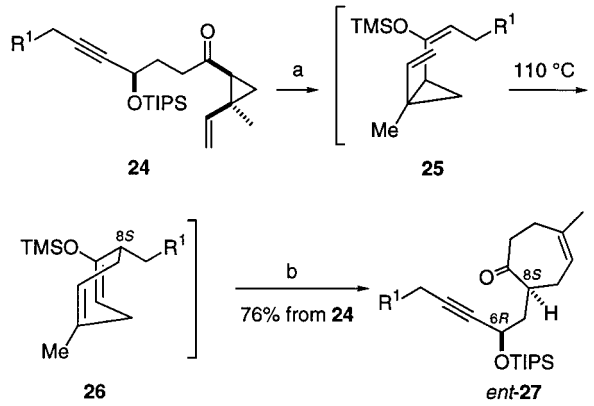


[a] Reaction conditions: (a) $(OCH_2CH_2O)CH(CH_2)_3C{\equiv}CLi$, THF, −78 → 23 °C; (b) TPAP, NMO, 94%; (c) (*R*)-α-pinene, 9-BBN; (d) TIPS-Cl, imidazole; (e) AcOH/H_2O, THF; (f) I_2, Ph_3P, imidazole; (g) *t*-BuLi, −78 °C, **11**.

of **19** thus obtained was low. Asymmetric reduction of **20** was best realized with (*R*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]-nonane [(*R*)-Alpine-Borane] following procedures developed by Brown and Midland[54,55] to generate (*R*)-**19** in 94% yield and 88% ee.[56,57] The assignment of the *R* absolute configuration to this product rested initially upon analogy with the known absolute stereochemical bias for the reduction of ynones by (*R*)-Alpine-Borane.[54,55] Unambiguous confirmation of the absolute configuration of (*R*)-**19** was obtained through ^{1}H NMR analysis of the *R* and *S* Mosher esters of alcohol (*R*)-**19**.[58] Protection of alcohol (*R*)-**19** as its triisopropylsilyl (TIPS) ether, followed by selective cleavage of the TBDMS group with aqueous acetic acid and reaction of the resulting primary alcohol with Ph_3P, I_2, and imidazole, proceeded smoothly to form alkyl iodide (*R*)-**23**. Generation of the organolithium derivative at −78 °C in ether by reaction of (*R*)-**23** with 2 equiv of *t*-BuLi,[59] followed by addition of amide **11**, provided cyclopropyl ketone **24** in 84% yield.

Enolsilylation of cyclopropyl ketone **24** with TMSOTf and Et_3N[60] led to the isolation of a single enoxysilane **25** (Scheme 3). This intermediate showed a ^{1}H NMR signal at δ 5.16 for the vinylic hydrogen of the enoxysilane grouping. However, comparison of this signal with signals of comparable vinylic

Scheme 3[a]



[a] Reaction conditions: (a) TMSOTf, Et_3N, −25 °C; (b) HCl−H_2O. R^1 = $CH_2CH_2CH(OCH_2CH_2O)$.

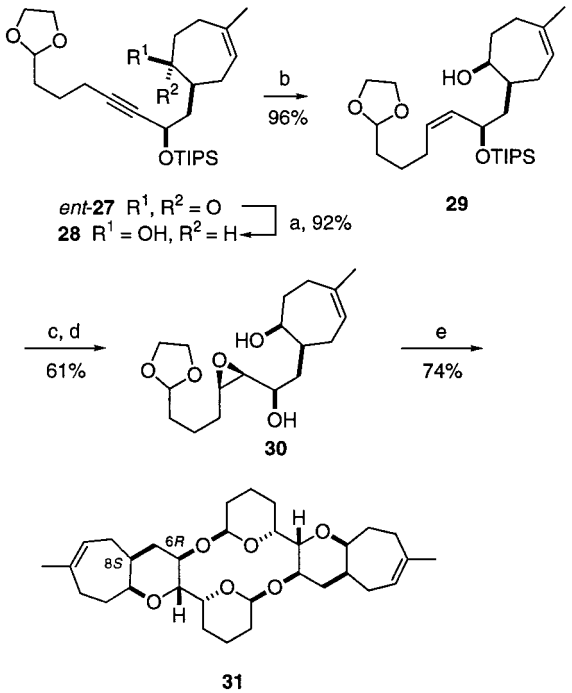
hydrogens in other stereoisomerically pure enoxysilanes failed to offer conclusive evidence for the enoxysilane geometry, an issue we will return to shortly.[61] Heating **25** at 110 °C for 24 h induced smooth Cope rearrangement to generate **26**, and this intermediate upon exposure to dilute aqueous HCl at room temperature furnished a *single* cycloheptenone in 76% overall yield from **24**. The stereochemistry of this product was misassigned at the time and resulted in us initially preparing the unnatural enantiomer of scopadulcic acid A (vide infra). This unexpected result prompted a careful reinvestigation of our scopadulan A synthetic sequence, which, we will see, demonstrated that the product of the sequence summarized in Scheme 3 was *ent*-**27**.[62]

Unable to confirm the relative stereochemistry at C8 of cycloheptenone intermediate produced from **24** by NMR techniques, we attempted to obtain a crystalline derivative. Numerous derivatives of *ent*-**27** were prepared; however, all failed to crystallize. After much experimentation, we succeeded in converting *ent*-**27** to the crystalline hexacyclic polyether **31**, which contains two units of the starting cycloheptenone (Scheme 4). Reduction of *ent*-**27** with lithium tri-*sec*-butylborohydride (L-Selectride) provided a single alcohol,[63] which was semi-hydrogenated to provide **29**. Discharge of the silyl protecting group and hydroxyl-directed epoxidation with $VO(acac)_2$ and *t*-BuO_2H[64] provided epoxy diol **30**. Finally, when this intermediate was exposed to a catalytic amount of *p*-toluenesulfonic acid, hexacyclic polyether **31** was formed in 64% yield. Single-crystal X-ray analysis of this product revealed, to our surprise at the time, that the cycloheptenone product of the Cope rearrangement sequence had the *S* configuration at C8.[40] It was now clear, as is depicted in Scheme 3, that enolsilylation under the Simchen conditions[60] had generated the *E* enoxysilane stereoisomer.

With the relative stereochemistry of the C6 and C8 centers in *ent*-**27** established through X-ray analysis of **31**, we were in a position to establish which C6 epimer of the trienyl iodide intermediate efficiently undergoes bis-Heck cyclization to generate rings B, C, and D of the scopadulan skeleton. To this

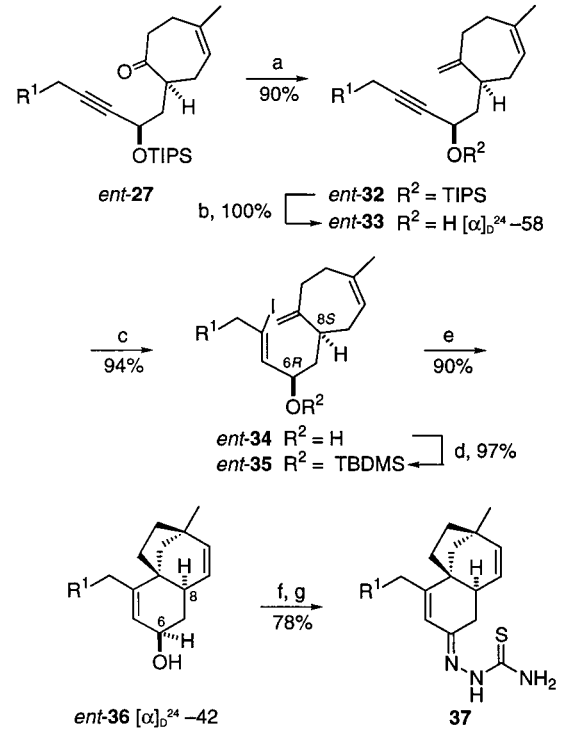
(54) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384−1394.
(55) Midland, M. M.; Graham, R. S. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. 7, pp 402−406.
(56) Enantiomeric purity of this intermediate was determined by ^{1}H NMR analysis of the methyl mandelate derivative.
(57) Asymmetric reducing conditions recently described by Noyori and co-workers, which were published after this phase of our synthesis was completed, would appear to be particularly attractive for the synthesis of (*R*)-**21**: Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739.
(58) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.
(59) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785−2812.
(60) (a) Simchen, G.; Kober, W. *Synthesis* **1976**, 259−261. (b) Kobayashi, M.; Masumoto, K.; Nakai, E.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 3005−3008. (c) For a review of enolsilylation with trialkyllsilyl perfluoroalkanesulfonates, see: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1−26.
(61) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066−1080.
(62) When both enantiomers of an intermediate have been prepared, those in the series leading to unnatural (+)-SDA are specified with the *ent* designation. The preparation of **27**, which is a precursor of natural (−)-SDA, is described in Scheme 8.
(63) Ando, K.; Condroski, K. R.; Houk, K. N.; Wu, Y.-D.; Ly, S. K.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 3196−3203.
(64) Sharpless, B.; K. B.; Michaelson, R. C. *J. Org. Chem.* **1970**, *35*, 6136.

Scheme 4[a]



[a] Reaction conditions: (a) L-Selectride, −25 °C; (b) Pd·$BaSO_4$, H_2, benzene; (c) Bu_4NF; (d) $VO(acac)_2$, *t*-BuO_2H; (e) *p*-TsOH, $CHCl_3$.

Scheme 5[a]



[a] Reaction conditions: (a) $Ph_3P{=}CH_2$, THF, 0 °C; (b) TBAF, THF, 23 °C; (c) Red-Al, Et_2O, 23 °C, NIS, −78 → 23 °C; (d) TBDMSCl, imidazole, DMF; (e) 10% $Pd(OAc)_2$, 20% Ph_3P, Ag_2CO_3, THF, reflux, TBAF, THF, 23 °C; (f) TPAP, NMO, 95%; (g) $H_2NCSNHNH_2$, AcOH, 82%. $R^1 = CH_2CH_2CH(OCH_2CH_2O)$.

end, *ent*-**27** was converted to trienyl iodide *ent*-**35** by the four-step sequence summarized in Scheme 5. Wittig methylenation of *ent*-**27** initially provided *ent*-**32**, $[\alpha]^{24}_D$ −58 (*c* 1.0, $CHCl_3$), which was treated with tetrabutylammonium fluoride (TBAF) to remove the TIPS group. Reduction of the resulting propargylic alcohol *ent*-**33** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[65] and reaction of the resulting vinylalane intermediate with *N*-iodosuccinimide (NIS) gave *ent*-**34** in 84% overall yield from *ent*-**27**. To achieve high yields in the reductive iodination step, it was essential to use freshly recrystallized NIS. If any adventitious iodine was present, cyclization of the C6 hydroxyl group and the exomethylene group became a serious side reaction. Protection of the C6 alcohol of *ent*-**34** with a TBDMS group generated the *Z* trienyl iodide cyclization substrate *ent*-**35**. Much to our delight, the critical palladium-catalyzed cyclization of *ent*-**35** proceeded cleanly to afford, after desilylation, a single tricyclic product, *ent*-**36**, $[\alpha]^{24}_D$ −42 (*c* 1.2, $CHCl_3$), in 90% yield. The presence of Ag_2CO_3 in this bis-Heck cyclization was paramount in suppressing migration of the initially formed 1,2-disubstituted double bond of *ent*-**36**. As first revealed in earlier studies in the racemic series,[20] protection of the C6 alcohol is required in order to achieve high yields in the bis-Heck cyclization.

Consistent with the assignment of the C6−C8 relative stereochemistry of *ent*-**27**, the alcohol substituent of *ent*-**36** was pseudoequatorial, as signaled by a 5% $^1H-^1H$ NOE observed between the axial C6 and C8 methine hydrogens. As a final check on the constitution of the tricyclic Heck product, *ent*-**36** was oxidized[43] to the enone, and the corresponding crystalline thiosemicarbazone **37** was subjected to single-crystal X-ray analysis.[40] This examination confirmed both the relative and absolute configuration of the tricyclic Heck product *ent*-**36**.

The high-yielding conversion of the (6*R*,8*S*)-trienyl iodide *ent*-**35** to *ent*-**36** established that our earlier surmise in the racemic series as to which diastereomer undergoes bis-Heck cyclization was incorrect.[20,66] A rationale for the success of this and related Heck cyclizations will be presented later in this paper.

C. An Enantiodivergent Strategy for Preparing Both Enantiomers of the Heck Cyclization Substrate. At this point, we had established that the 6*R*,8*R* enantiomer of the Heck cyclization precursor would be required to access natural (−)-scopadulcic acid A (**1**). We entertained two possibilities for obtaining this intermediate. One approach would be to synthesize the enantiomer of cyclopropyl ketone **24** from the *S* enantiomer of alkyl iodide **23** and the 1*R*,2*S* enantiomer of cyclopropyl amide **11**. However, a more intriguing strategy would be to utilize the *Z* enoxysilane intermediate **40** in the [3,3]-rearrangement step in order to establish the *R* configuration at the pivotal C8 stereocenter (Figure 4). This latter approach had the attraction that we could employ (1*S*,2*R*)-cyclopropyl amide **11**, which was already in hand and would only require that we prepare (*S*)-**23**.

To establish conditions for generating the *Z* enoxysilane stereoisomer from a cyclopropyl ketone intermediate, we examined enolization of the model ketone **44** having a β ethyl, rather than a β vinyl, substituent (Scheme 6). This intermediate was readily accessed from iodide **42** and amide **11**, using Wilkinson's catalyst to selectively hydrogenate the vinyl group of **43**.[67] The Simchen conditions (TMSOTf and Et_3N)[60] generated a 4:1 mixture of enoxysilanes **45** (δ 4.93, ═CH) and **46** (δ 4.58, ═CH). Fortunately, Ireland's conditions, enolization with LDA in 20% HMPA−THF followed by quenching with TMSCl,[68] to the limits of detection by 500-MHz ^1H NMR

(65) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595−4597.

(66) The relative stereochemistry at C6 of *rac*-**36** could easily been established by careful ^1H NMR analysis during our earlier investigations. That the next step in the synthetic sequence was oxidation to the C6 ketone undoubtedly contributed to this oversight.[20]

(67) Zutterman, F.; Krief, A. *J. Org. Chem.* **1983**, *48*, 1135−1137.

(68) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2876.

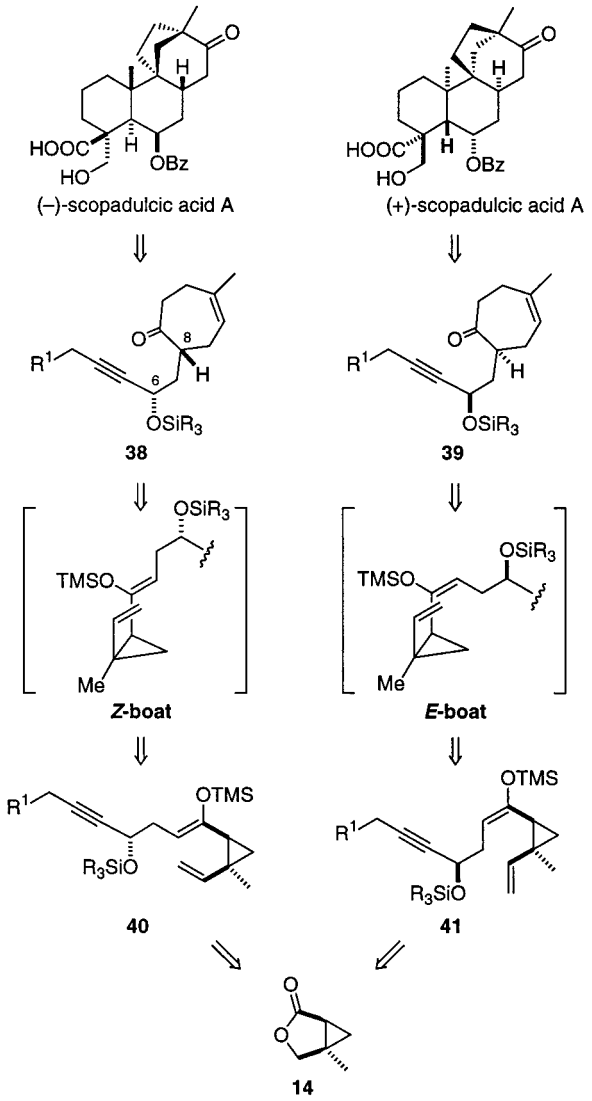
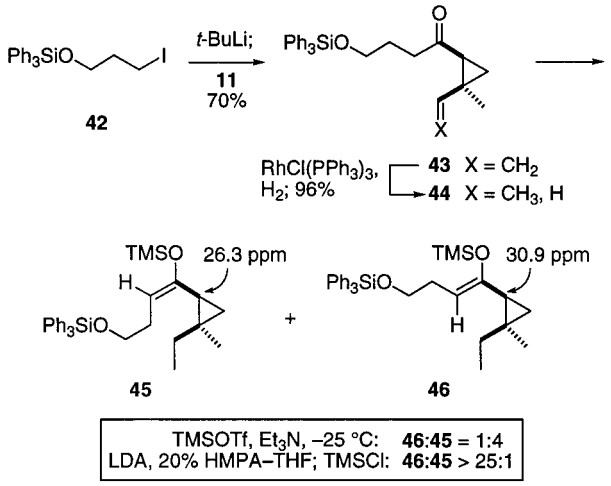


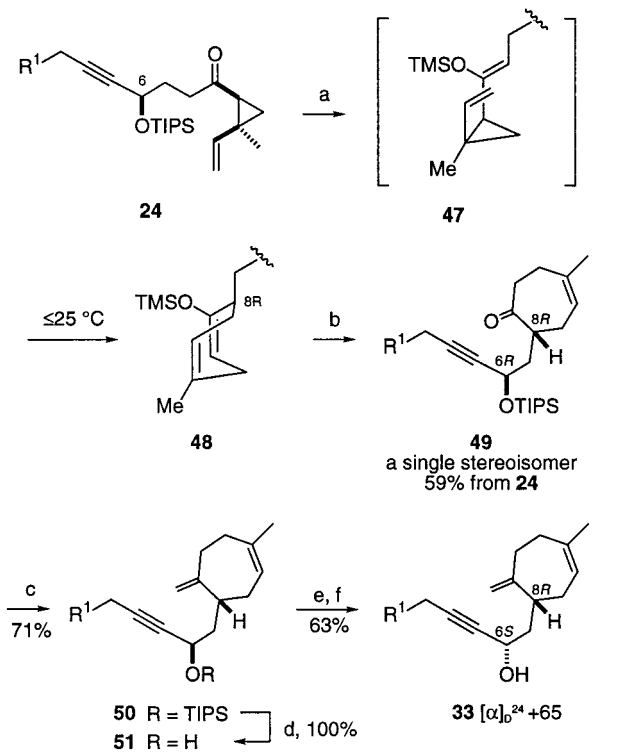
Figure 4. Enantiodivergent strategy for preparing (+)- and (−)-scopadulcic acid A.

Scheme 6



analysis, led to the formation of only the *Z* stereoisomer **46**. Since Heathcock had previously demonstrated that the chemical shift of the β vinylic hydrogen was not a reliable method to assign enoxysilane stereochemistry,[61] the ^{13}C NMR method introduced by these workers was employed; diagnostic carbon shifts are shown in Scheme 6.

Scheme 7[a]

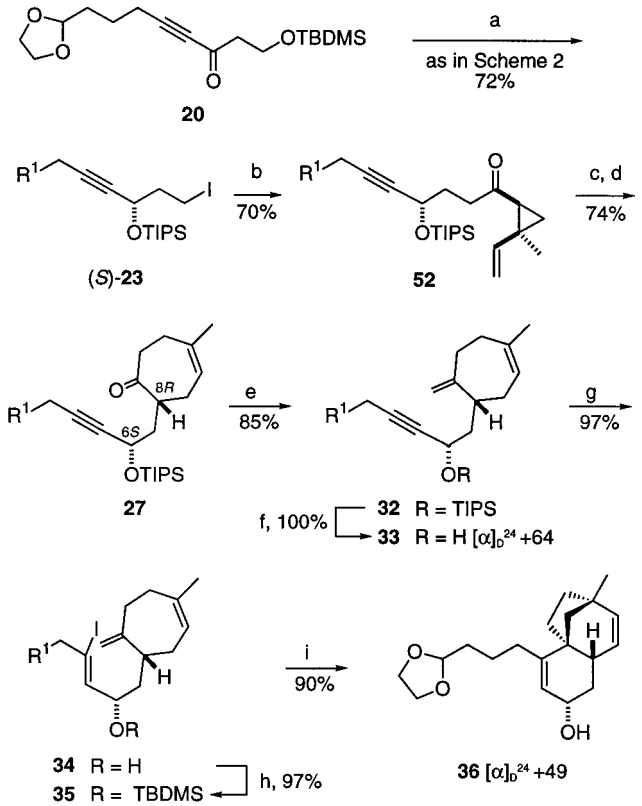


[a] Reaction conditions: (a) LDA, 20% HMPA−THF, −78 °C, TMSCl, −78 → 0 °C; (b) HCl−H_2O; (c) $Ph_3P{=}CH_2$, THF, 0 °C; (d) TBAF, THF, 23 °C; (e) DEAD, PPh_3, *p*-NO_2-$C_6H_4CO_2H$, 0 °C, 67%; (f) NaOH (aq), 23 °C, 94%. R^1 = $CH_2CH_2CH(OCH_2CHO)$.

To examine the divinylcyclopropane rearrangement with a *Z* enoxysilane unit, we treated cyclopropyl ketone **24** at −78 °C sequentially with LDA in 20% HMPA−THF and TMSCl. In this case, the presumed *Z* enoxysilane **47** underwent rearrangement prior to warming to room temperature to furnish siloxy cycloheptadiene **48** (Scheme 7). Hydrolysis of this intermediate then gave rise to (6*R*,8*R*)-cycloheptenone **49**, as a single detectable stereoisomer, in 59% overall yield from **24**. It is reasonable that Cope rearrangement of the *Z* enoxysilane intermediate took place at a temperature at least 80 °C lower than that required for rearrangement of the corresponding *E* enoxysilane intermediate, since boat conformer **47** has a hydrogen (rather than the side chain) thrust over the cyclopropane ring.

Since **49** and diastereomer *ent*-**27** showed nearly identical NMR spectra, we decided to unambiguously confirm that we had finally accessed an intermediate having the *R* configuration at C8. This objective was accomplished in straightforward fashion by conversion of **49** to **33** (Scheme 7). The optical rotation of **33**, $[\alpha]^{24}_D$ +65 (*c* 1.0, $CHCl_3$), was opposite in sign to that of *ent*-**33**, $[\alpha]^{24}_D$ −58 (*c* 1.0, $CHCl_3$), which had been synthesized earlier (Scheme 5). The somewhat higher optical rotation of **33** likely arises from the lower temperature of the Cope rearrangement of the *Z* enoxysilane intermediate. Since the iodide employed to prepare **24** was not enantiopure (88% ee), **24** was contaminated with ~6% of its C6 epimer. Boat topography rearrangement of the *Z* enoxysilane derivative of this minor C6 epimer would lead to **27** and consequently slightly decrease the enantiopurity of *ent*-**27**. In contrast, any *E* enoxysilane derivative of the minor C6 epimer would not rearrange at room temperature; thus, the presence of this minor epimer in **24** would not erode the enantiopurity of **49** produced by the sequence summarized in Scheme 7.

Scheme 8[a]



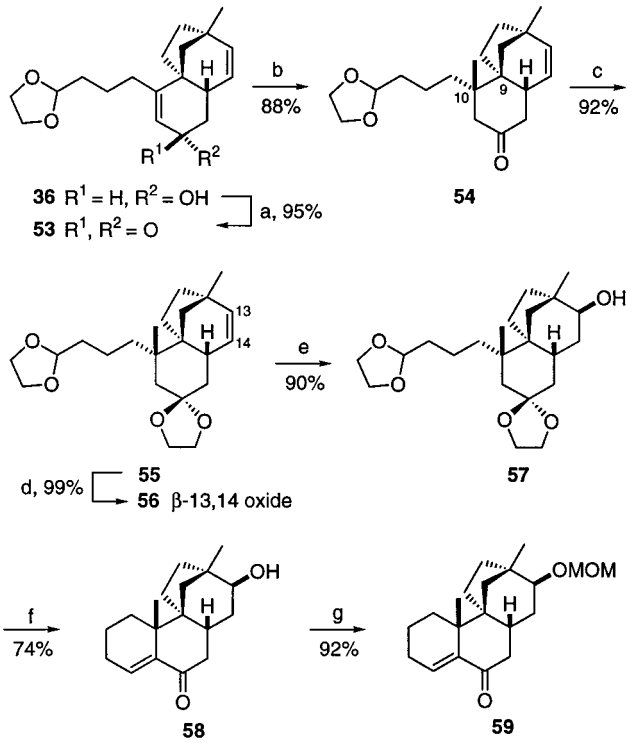
[a] Reaction conditions: (a) steps c−f of Scheme 2 with (*S*)-α-pinene used in step c; (b) *t*-BuLi, Et_2O, −78 °C, **11**, −78 → 0 °C; (c) LDA, 20% HMPA−THF, −78 °C, TMSCl, −78 → 0 °C; (d) HCl−H_2O; (e) $Ph_3P{=}CH_2$, THF, 0 °C; (f) TBAF, THF, 23 °C; (g) Red-Al, Et_2O, 23 °C, NIS, −78 → 23 °C; (h) TBDMSCl, imidazole, DMF; (i) 30% $Pd(OAc)_2$, 60% Ph_3P, Ag_2CO_3, THF, reflux, TBAF, THF, 23 °C. R^1 = $CH_2CH_2CH(OCH_2CH_2O)$.

D. Total Synthesis of (−)- and (+)-Scopadulcic Acid A. With our ability to establish the C8 *R* stereochemistry of a Heck cyclization precursor through divinylcyclopropane rearrangement of a *Z* enoxysilane intermediate established, and the knowledge that the 6*S*,8*R* stereochemistry is required for efficient bis-Heck cyclization, we turned to the total synthesis of (−)-SDA. The synthesis began with the preparation of iodide (*S*)-**23** from ketone **20** (Scheme 8). This iodide was available in 85−89% ee[69] by the sequence described in Scheme 2, with an important exception that reduction of **20** was accomplished with (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane.[54,55] Lithiation of (*S*)-**23** with *t*-BuLi, followed by condensation of the resulting organolithium intermediate with amide **11**, provided cyclopropyl ketone **52** in good yield. Careful purification of **52** by flash chromatography employing a solvent gradient allowed the minor C6 epimer to be removed to provide **52** on multigram scale as a *single* stereoisomer.

Ketone **52** was then added dropwise at −78 °C to 1.25 equiv of LDA in 20% HMPA−THF and quenched with 3.0 equiv of TMSCl, and after the solution warmed to room temperature, the resulting siloxy cycloheptadiene was hydrolyzed with dilute aqueous HCl to provide (6*S*,8*R*)-cycloheptenone **27** in 75% overall yield (Scheme 8). Following exactly the sequence optimized in the enantiomeric series, this intermediate was converted to **33**, $[\alpha]^{24}_D$ +64 (*c* 1.0, $CHCl_3$).[70] Transformation of **33** to **35**, Heck cyclization of **35**, and discharge of the alcohol protecting group provided the key tricyclic intermediate **36**, $[\alpha]^{24}_D$ +49 (*c* 1.2, $CHCl_3$), in 90% yield.

(69) Determined for alcohol precursor (*S*)-**19**.[56]

Scheme 9[a]



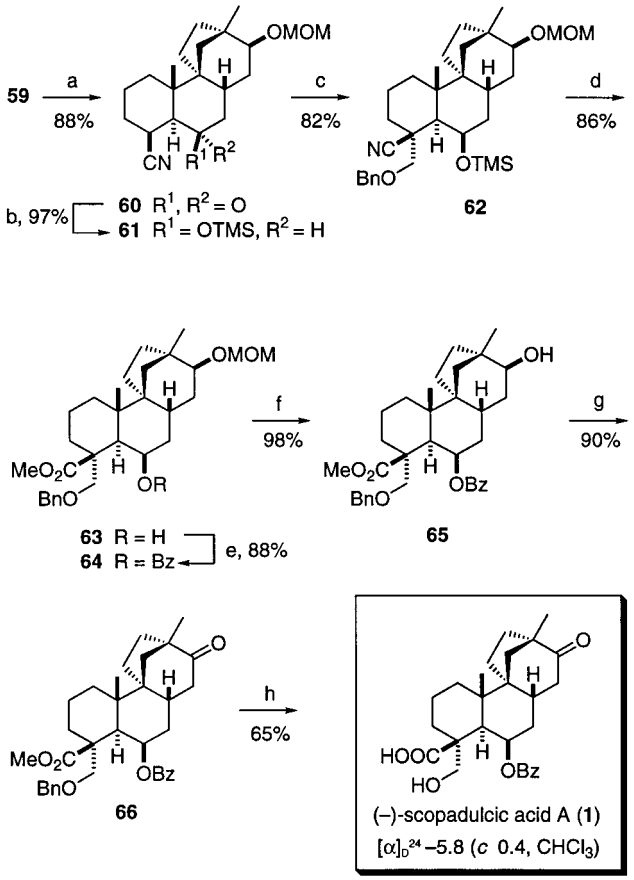
[a] Reaction conditions: (a) TPAP, NMO; (b) Me_2Zn, $Ni(acac)_2$, 0 → 23 °C; (c) $(CH_2OH)_2$, $(OCH_2CH_2O)CHOMe$, Amberlyst 15; (d) *m*-CPBA, $NaHCO_3$, 0 °C; (e) $LiAlH_4$, 23 °C; (f) 20% aqueous HCl, THF, 50 °C; (g) MOM-Cl, $(i\text{-}Pr)_2NEt$.

From this stage on, the synthesis of (−)-SDA (**1**) was accomplished by an optimized version of the sequence employed in our earlier synthesis of (±)-SDA.[20] Since the synthesis of (±)-SDA has been described in communication format only, key problems that were overcome in developing the ultimately successful sequence for preparing scopadulcic acid A from a tricyclic Heck product will be briefly noted. A challenging aspect of this sequence was introducing the angular methyl group at C10, since C10 is contiguous to the C9 quaternary center. Oxidation of allylic alcohol **36** with TPAP and NMO provided enone **53** (Scheme 9), which was a much better Michael acceptor than a related tetrasubstituted enone that was an intermediate in our synthesis of (±)-SDB.[21,22] Thus, **53** did react with Me_2CuLi to provide **54**; however, in some runs the product of 1,2-addition was a significant byproduct. More reliable was $Ni(acac)_2$-catalyzed addition of Me_2Zn,[71] which provided **54** in 88% yield. As expected, conjugate addition of the methyl group was highly stereoselective and occurred from the face opposite the axial ethano bridge. The oxygen functionality at C13 was next introduced by protecting the C6 ketone as a 1,3-dioxolane and oxidation of the resulting bis-ketal **55** with *m*-chloroperbenzoic acid, which also occurred selectively from the *β*-face, to deliver **56** in excellent overall yield. Reduction of **56** with $LiAlH_4$ led to a single secondary alcohol **57**. That this product arose from axial hydride delivery was readily confirmed by the absence of

(70) The enantiopurity of **33** should be at least 99.8%, since it derives from combination of fragments of 88 and >99% ee. Two factors, each of which alone would have been sufficient, dictate that there would have been no loss in enantiopurity in the conversion of **52** → **27**: (a) the sample of **52** employed in the Cope rearrangement step contained no detectable C6 epimer, and (b) any (*E*)-enoxysilane produced upon enolization of **52** would not undergo Cope rearrangement at room temperature.

(71) Luche, J.-L.; Petrier, C.; Lansard, J.-P.; Greene, A. E. *J. Org. Chem.* **1983**, *48*, 3837−3839.

Scheme 10[a]



[a] Reaction conditions: (a) Et_2AlCN, TMSCl, THF, 0 °C; (b) $LiAlH_4$, −78 °C, TMSCl, DMAP, pyridine−CH_2CH_2; (c) LDA, THF, 0 °C, $BnOCH_2Br$, −78 → 0 °C; (d) KOH, K_2CO_3, 140 °C; CH_2N_2, Et_2O, 0 → 23 °C; (e) BzCl, DMAP, pyridine, 100 °C; (f) HCl, MeOH, 70 °C; (g) PCC, 4-Å molecular sieves, 23 °C; (h) *n*-PrSLi, HMPA, 23 °C, 72%; H_2, 10% Pd−C, MeOH, 90%.

coupling in the ^{1}H NMR spectrum between the C8 and C13 methine hydrogens.

Exposure of **57** to 10% aqueous HCl−THF at room temperature selectively cleaved the C6 dioxolane, while the use of 20% aqueous HCl−THF led to cleavage of both dioxolane groups. The keto aldehyde produced under these second conditions could be isolated and subsequently treated with acid at higher temperature to close the A ring. However, we found that the conversion of **57** to the crystalline tetracyclic enone **58** was most efficiently accomplished in one step by heating a 4:1 solution of THF and 20% aqueous HCl at 50 °C, which provided **58** in 74% yield. At this point, the C13 alcohol was protected as a methoxymethyl (MOM) ether to furnish **59**.

After examining several strategies for elaborating the remaining functionality at carbons 4 and 6, a quite direct strategy emerged (Scheme 10). Conjugate addition of Et_2AlCN[72] to enone **59** took place solely from the β-face; however, quenching of the resulting aluminum enolate with acid provided some of the A/B cis product in addition to **60**. Fortunately, if the addition of Et_2AlCN was conducted in the presence of freshly purified TMS−Cl and the resulting $\Delta^{5,6}$ enoxysilane was hydrolyzed with dilute aqueous HCl, the trans-fused ketone **60** was generated cleanly in 88% yield. Reaction of this intermediate with $LiAlH_4$ at −78 °C selectively reduced the C6 ketone, exclusively from the face opposite to the C10 methyl group, to provide the C6 axial alcohol, which was silylated to furnish **61**. The remaining substituent at C4 was introduced with complete stereocontrol by deprotonation of **61** with LDA followed by quenching with (benzyloxy)methyl bromide (BOM-Br) to give **62** in 82% yield. To ensure the success of this reaction, BOM-Br must be freshly prepared and purified by distillation prior to use.[73] Again, the angular methyl group at C10 regulated facial selectivity and the alkoxymethyl group was introduced exclusively from the α face.

Hydrolysis of the axial, tertiary carbinyl nitrile was accomplished under forcing conditions by heating **62** at 140 °C with KOH. Acidification of this product and esterification of the resulting carboxylic acid with diazomethane provided **63** in high yield. At this point, the axial C6 benzoate was introduced by reaction of **63** with benzoyl chloride and 4-(dimethylamino)-pyridine (DMAP) in pyridine at 100 °C to provide benzoate **64** in an optimized overall yield of 76% from **62**. The MOM ether was then cleaved in excellent yield with hot methanolic HCl, and the resulting alcohol **65** was oxidized with pyridinium chlorochromate (PCC)[74] to furnish **66**. Finally, the methyl ester was cleaved with lithium *n*-propylmercaptide[75] and the benzyl ether cleaved by conventional catalytic hydrogenolysis to furnish (−)-scopadulcic acid A (**1**), $[\alpha]^{24}_D$ −5.8 (*c* 0.4, $CHCl_3$), in 65% yield. Since the reported rotation of natural SDA at the sodium D line is small, $[\alpha]^{24}_D$ −5.7 (*c* 0.1, $CHCl_3$), confirmation of the identity of synthetic (−)-SDA with a sample of the natural product was unambiguously secured by circular dichroism spectra: synthetic (−)-SDA, $[\Theta]^{24}_{292}$ +8230 (*c* 0.71 mM, MeOH); natural (−)-SDA, $[\Theta]^{24}_{292}$ +6140 (*c* 0.7 mM, MeOH).

Following exactly the sequence described for the natural series, *ent*-**36** was converted to (+)-scopadulcic acid. Synthetic (+)-SDA (**1**) showed $[\alpha]^{24}_D$ +5.4° (*c* 0.4, $CHCl_3$) and $[\Theta]^{24}_{291}$ −6620 (*c* 0.7 mM, MeOH).

E. Stereoselection in the Bis-Heck Cyclization. The stereochemical requirements for the central bis-Heck cyclization of our scopadulan diterpene synthesis approach are now clearly defined; the analysis that follows corrects the erroneous[31] brief discussion of this issue in our preliminary communication.[20] As illustrated for the 6*S*,8*R*-enantiomer in Figure 5, the B, C, and D rings of the scopadulan skeleton are generated when the C6 and C8 stereocenters of the cyclization precursor have opposite absolute configurations. In this series, the C6 siloxy substituent of intermediates **68** and **69**, and tricyclic product **70**, would be quasi-equatorial. Examination of molecular models suggests that insertion topography **67**, which involves reaction of the *Si* face of the exomethylene group and has a favored (nearly coplanar) orientation of the Pd−C σ bond and the C−C π bonds,[76] would have the nascent B ring coiled in a twist conformation in which the siloxy substituent would be quasi-equatorial.[77]

Under identical Heck reaction conditions, the diastereomeric cyclization precursor (illustrated in Figure 5 for the 6*R*,8*R* enantiomer **71**) cyclizes to form a complex mixture of polycyclic products.[20] Although this mixture has not been resolved for

(72) Nagata, W. In *Organic Reactions*; Wiley: New York, 1977; Vol. 25, pp 255−476.

(73) Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckmann, R. K., Jr.; Medwid, J. B. *Orgaic Syntheses*; Wiley: New York, 1988; Collective Volume 6, pp 101−103.

(74) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(75) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459.

(76) (a) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959. (b) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813.

(77) That the nascent B ring would adopt a twist conformation was missed in our earlier analysis of insertion topographies and contributed to our initial misassignment[20] of which diastereomer would lead to the scopadulan ring system.

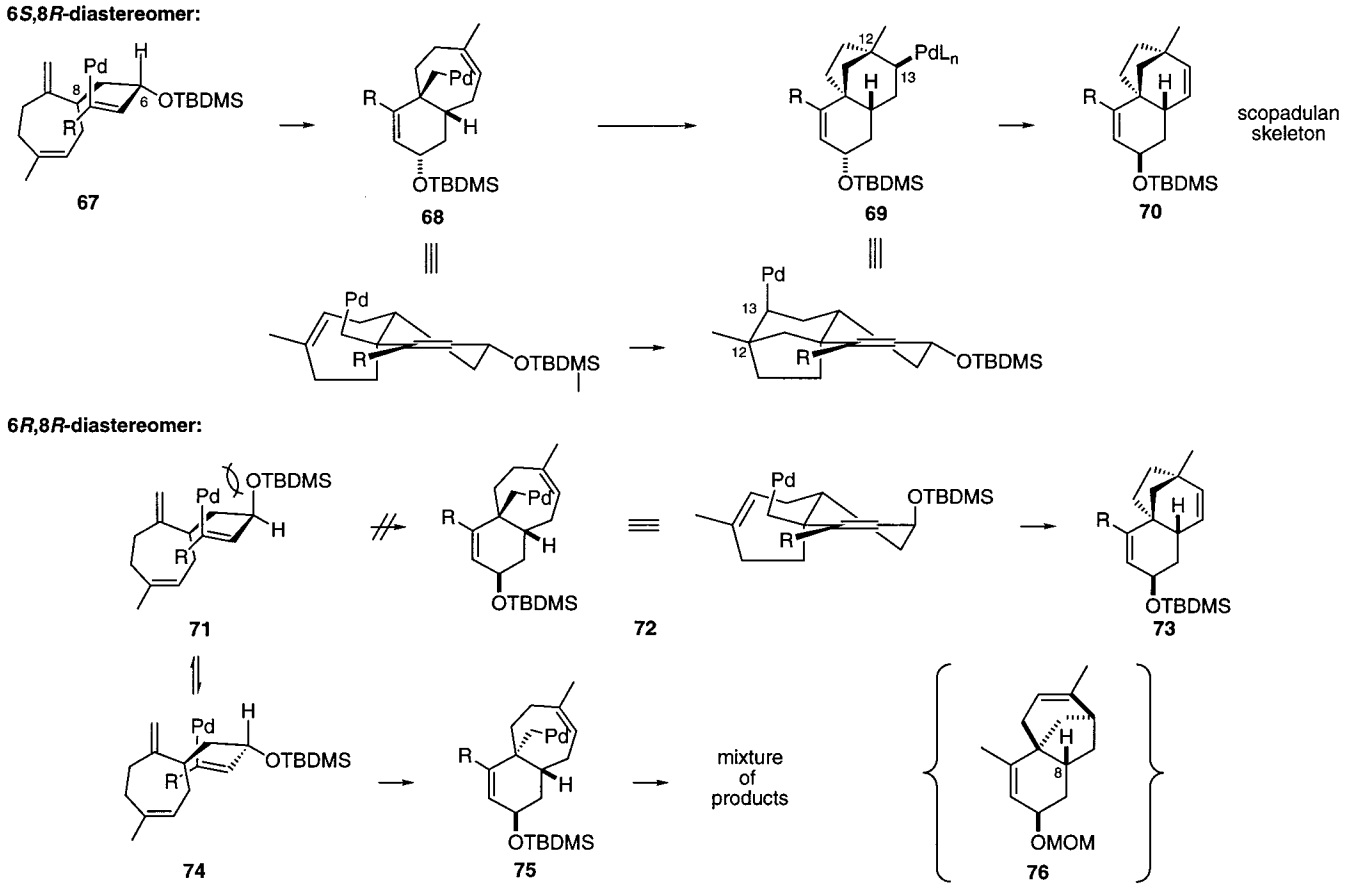


Figure 5. Bis-Heck cyclizations of the 6*S*,8*R*- and 6*R*,8*R*-diastereomers; ligands on palladium are not shown.

cyclization substrates having R = $(OCH_2CH_2O)CH_2CH_2CH_2$, in a model series (R = Me) that will be described elsewhere,[78] the major product **76** has a trans relationship of the 1 carbon bridge and the C8 hydrogen. Since **76** would derive from initial insertion into the Re face of the exomethylene group (**74** → **75**, R = Me), and since the initial insertion step is not likely to be reversible,[79,80] we conclude that the disparate outcome of Heck cyclizations in the two diastereomeric series arises in the initial insertion step. As suggested in Figure 5, a destabilizing interaction between the palladium substituent and the siloxy group in **71** could direct the 6*R*,8*R* diastereomer toward the **74** → **75** pathway and, thus, away from forming the scopadulan skeleton.

Regioselection in the second insertion step is undoubtedly influenced by the dramatically decreasing stability of metal−C σ bonds as the degree of substitution at carbon increases.[81,82] Product **70**, which is formed exclusively, would arise from insertion of **68** to generate cyclohexylpalladium intermediate **69**, having palladium attached to the secondary carbon center C13.

Conclusion

Total syntheses of (−)- and (+)-scopadulcic acid A (**1** and *ent*-**1**) were completed in 27 steps and with an overall yield of ~1% from (1*S*,5*R*)-γ-butyrolactone **14**, which is available in two steps and 60% yield from methallyl alcohol. These inaugural enantioselective total syntheses of the scopadulan diterpenes, moreover, rigorously establish the absolute configuration of scopadulcic acid A. The central transformation is a palladium-catalyzed bis-Heck cyclization of a 5-methylenecycloheptenyl iodide, which occurs with complete stereo- and regioselectivity, to construct the B, C, and D rings of the scopadulan skeleton (Figure 2). An additional notable feature of these syntheses is the use of enolization stereoselection to dictate which enantiomer of the natural product is produced (Figure 4). We anticipate that the enantioselective synthesis strategy detailed here could be used to prepare other scopadulan diterpenes and analogues, as well as to access different polycyclic structures containing a bicyclo[3.2.1]octane substructure.

Experimental Section[83]

(1*S*,5*R*)-5-Methyl-2-oxo-3-oxabicyclo[3.1.0]hexane (14). The (*R*,*R*)-bis(oxazoline) catalyst **13**[37] (130 mg, 0.26 mmol) was weighed in a glovebox and added to a reaction flask; the flask was purged with argon, and freshly distilled $CHCl_3$ (415 mL) was added under an argon atmosphere. A solution of diazoester **12** (5.52 g, 39.4 mmol)[84] and $CHCl_3$ (100 mL) then was added by syringe pump (2.3 mL/min) at room temperature. After the addition was complete, the reaction solution was washed with aqueous EDTA (0.1 M, 100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic

(78) Overman, L. E.; Rucker, P. V.; O'Connor, S. J. Manuscript to be submitted for publication.

(79) We are not aware of documented examples of β-alkyl elimination of alkylpalladium complexes. Heck insertions to generate cyclopropylcarbinylpalladium complexes are reversible.[80]

(80) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091.

(81) Jones, W. D., Feher, F. J. *Acc. Chem. Res.* **1989**, *22*, 91.

(82) More than this factor is obviously involved, since stereoisomer **75** (R = Me) preferentially inserts to form **76**.[78]

(83) General experimental details have been described: Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379. Optical rotations were measured with a Jasco DIP-360 polarimeter. *N*-Iodosuccinimide was purified by recrystallization from CCl_4−1,4-dioxane, and LiBr was dried by placing it in an evacuated flask and heating with a heat gun until the solid just began to melt.

(84) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.*, **1990**, *112*, 1906−1912.

layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (1:1 hexanes−Et_2O) to give 3.55 g (80%) of lactone **14** as a colorless solid, which was recrystallized from hexanes to give 2.20 g (62%) of enantiomerically pure (>99% ee, GLC analysis of **16** using a cyclodextrin column) **14** as long colorless needles:[38] mp 58−59 °C; $R_f = 0.25$ (1:1 hexanes−Et_2O); $[\alpha]^{26}_D$ −53.3, $[\alpha]^{26}_{577}$ −59.6, $[\alpha]^{26}_{546}$ −71.2, $[\alpha]^{26}_{435}$ −162, $[\alpha]^{26}_{405}$ −226 (*c* 1.0, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (d, $J = 9.1$ Hz, 1H), 4.09 (d, $J = 9.1$ Hz, 1H), 1.85 (dd, $J = 9.0$, 3.3 Hz, 1H), 1.39 (s, 3H), 1.19 (dd, $J = 9.0$, 4.7 Hz, 1H), 1.03 (dd, $J = 4.6$, 3.3 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.7, 73.5, 25.3, 23.7, 19.0, 17.0; IR (KBr) 1751 cm^{-1}. Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.28; H, 7.18.

(1*S*,2*R*)-1-(*N*,*O*-Dimethylhydroxamido)-2-hydroxymethyl-2-methylcyclopropane (16). Trimethylaluminum (2.0 M in toluene, 21.4 mL) was added dropwise to a stirring suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (4.18 g, 42.8 mmol)[42] in toluene (72 mL) at 0 °C. The mixture was allowed to warm to room temperature for 30 min. It then was recooled to 0 °C, and a solution of lactone **14** (2.40 g, 21.4 mmol) and toluene (24 mL) was added dropwise. The reaction was warmed to room temperature and maintained at room temperature for 30 min before being transferred into a solution of saturated aqueous potassium sodium tartrate−H_2O (1:1, 240 mL). The resulting mixture was extracted with CH_2Cl_2 (240 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give 3.62 g (98%) of amide **16** as a colorless oil: $R_f = 0.20$ (Et_2O); $[\alpha]^{24}_D$ +49.8, $[\alpha]^{24}_{577}$ +45.0, $[\alpha]^{24}_{546}$ +61.4, $[\alpha]^{24}_{435}$ +101, $[\alpha]^{24}_{405}$ +121 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 3.77−3.74 (m, 2H), 3.19 (s, 3H), 2.93 (t, $J = 6.1$ Hz, 1H), 2.89 (s, 3H), 1.89 (br s, 1H), 1.50 (t, $J = 5.0$ Hz, 1H), 1.05 (s, 3H), 0.58 (dd, $J = 8.2$, 4.3, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.2, 64.9, 61.5, 33.0, 29.2, 24.5, 23.1, 18.6; IR (film) 1635 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 174.1123 (174.1130 calcd for $C_8H_{16}NO_3$, MH). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.21; H, 8.80; N, 8.01.

(1*S*,2*R*)-1-(*N*,*O*-Dimethylhydroxamido)-2-formyl-2-methylcyclopropane (17). A suspension of alcohol **16** (6.14 g, 35.5 mmol), *N*-methylmorpholine *N*-oxide (NMO, 6.24 g, 53.2 mmol), 4-Å molecular sieves (6.2 g, powdered, activated), and CH_2Cl_2−MeCN (9:1, 220 mL) was stirred for 30 min at room temperature, and then tetra-*n*-propylammonium perruthenate (TPAP, 310 mg, 0.89 mmol) was added portionwise.[43] The resulting mixture was stirred at room temperature for 30 min and filtered through a short silica gel column (Et_2O). The filtrate was carefully concentrated at room temperature, and the residue was purified by flash chromatography (2:1 Et_2O−pentane) to give 5.56 g (92%) of aldehyde **17** as a colorless oil: $R_f = 0.45$ (Et_2O); $[\alpha]^{24}_D$ +102, $[\alpha]^{24}_{577}$ +105, $[\alpha]^{24}_{546}$ +119, $[\alpha]^{24}_{435}$ +232, $[\alpha]^{24}_{405}$ +296 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 9.44 (s, 1H), 2.97 (s, 3H), 2.76 (s, 3H), 2.19 (br s, 1H), 1.96 (dd, $J = 6.6$, 4.9 Hz, 1H), 1.05 (s, 3H), 0.74 (dd, $J = 7.8$, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 169.3, 61.8, 35.2, 32.5, 28.1, 19.5, 17.2; IR (film) 1707, 1654 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 172.0975 (172.0973 calcd for $C_8H_{14}NO_3$, MH). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.91; H, 7.61; N, 8.12.

(1*S*,2*R*)-1-(*N*,*O*-Dimethylhydroxamido)-2-ethenyl-2-methylcyclopropane (11). Potassium hexamethyldisilazide (0.5 M in toluene, 78 mL) was added dropwise to a rapidly stirring suspension of methyltriphenylphosphonium bromide (15.1 g, 42.3 mmol) in THF (75 mL) at 0 °C. The resulting yellow suspension was warmed to room temperature for 30 min and then cooled to −78 °C. A solution of aldehyde **17** (5.56 g, 32.5 mmol) and THF (75 mL) was added by cannula. The reaction was warmed to 0 °C for 1 h and quenched with saturated aqueous NH_4Cl (0.75 mL). The mixture was diluted with pentane (300 mL) and filtered, and the filtrate was cooled to −30 °C. The resulting suspension was filtered, and the filtrate was concentrated (trituration with pentane was repeated 3 times). The remaining liquid was purified by bulb-to-bulb distillation (100 °C, 0.5 mm) to give 4.34 g (79%) of **11** as a colorless liquid: $R_f = 0.57$ (Et_2O); $[\alpha]^{24}_D$ +77.0, $[\alpha]^{24}_{577}$ +81.0, $[\alpha]^{24}_{546}$ +92.2, $[\alpha]^{24}_{435}$ +163, $[\alpha]^{24}_{405}$ +201 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (dd, $J = 17.4$, 10.8 Hz, 1H), 5.08 (dd, $J = 17.4$, 1.2 Hz, 1H), 5.02 (dd, $J = 10.8$, 1.2 Hz, 1H), 3.65 (s, 3H), 3.19 (s, 3H), 2.25 (br s, 1H), 1.53 (dd, $J = 5.8$, 4.6, 1H), 1.31 (s, 3H), 1.04 (dd, $J = 7.8$, 4.6, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 139.7, 113.0, 61.5, 32.5, 27.2, 27.1, 21.7, 20.2; IR (film) 1655, 993 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 170.1176 (170.1181 calcd for $C_9H_{16}NO_2$, MH). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.69; H, 9.00; N, 8.25.

(1*S*,2*R*,2′*S*-1-[1′-Oxo-4′-(triisopropylsiloxy)-10′-(1,3-dioxolanyl)-5′-decynyl]-2-ethenyl-2-methylcyclopropane (52). A solution of iodide (**S**)-**23** (12.3 g, 25.7 mmol) and Et_2O (25 mL) was added dropwise by cannula to a solution of *tert*-butyllithium (1.58 M in pentane, 34.2 mL) and Et_2O (25 mL) at −78 °C. The resulting solution was maintained at −78 °C for 30 min, and then a solution of amide **11** (4.79 g, 28.2 mmol) and Et_2O (25 mL) was added dropwise. After being stirred for 10 min, the reaction was warmed to 0 °C, maintained at 0 °C for 1.5 h, and quenched with saturated aqueous NH_4Cl (25 mL) and H_2O (300 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 250 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (12:1 hexanes−EtOAc) to yield 8.2 g (70%) of cyclopropyl ketone **52** as a clear oil: $R_f = 0.30$ (12:1 → 10:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +75.7, $[\alpha]^{24}_{577}$ +81.2, $[\alpha]^{24}_{546}$ +94.8, $[\alpha]^{24}_{435}$ +196, $[\alpha]^{24}_{405}$ +259 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dd, $J = 17.4$, 10.8 Hz, 1H), 5.02 (dd, $J = 17.4$, 1.4 Hz, 1H), 4.98 (dd, $J = 10.8$, 1.4 Hz, 1H), 4.84 (t, $J = 4.6$ Hz, 1H), 4.50 (m, 1H), 3.95−3.89 (m, 2H), 3.86−3.80 (m, 2H), 2.72−2.62 (m, 2H), 2.22 (td, $J = 7.0$, 1.8 Hz, 2H), 2.12 (dd, $J = 7.4$, 6.1 Hz, 1H), 1.91−1.85 (m, 2H), 1.75−1.70 (m, 2H), 1.62−1.56 (m, 3H), 1.30 (s, 3H), 1.10−1.04 (m, 22H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 138.5, 113.3, 104.1, 84.3, 81.6, 64.8, 62.1, 40.0, 37.0, 32.9, 32.8, 30.7, 23.0, 22.7, 22.1, 18.6, 18.0, 12.2; IR (film) 1698 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 462.3155 (462.3165 calcd for $C_{27}H_{46}O_4Si$, M).

(2*R*,2′*S*-2-[2′-(Triisopropylsiloxy)-8′-(1,3-dioxolanyl)-3′-octynyl]-5-methyl-cyclohept-4-en-1-one (27). *n*-Butyllithium (2.47 M in hexanes, 1.6 mL) was added dropwise to stirring diisopropylamine (0.51 mL, 3.9 mmol) at 0 °C, and the concentrated hexane solution of LDA was maintained for 10 min at 0 °C. Tetrahydrofuran (52 mL) was added, the resulting solution was cooled to −78 °C, and freshly distilled HMPA (17.5 mL) was then added.[68] After the mixture was stirred for 15 min, a solution of ketone **52** (1.4 g, 3.0 mmol) and THF (18 mL) was added dropwise. After 5 min, TMSCl (1.2 mL, 9.0 mmol) was added, and the reaction was stirred for 15 min at −78 °C. The reaction was then warmed to 0 °C and, after 45 min, was poured into saturated aqueous $NaHCO_3$ (100 mL), and the aqueous solution was extracted with pentane (4 × 75 mL). The pentane extracts were then washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated to provide the crude siloxy cycloheptadiene intermediate as a yellow oil.

A solution of this material (1.6 g, 2.9 mmol), 5% aqueous HCl (1 mL), and a 10:1 solution of THF/H_2O (22 mL) was maintained at room temperature for 1 h and then diluted with H_2O (10 mL). The reaction mixture was extracted with $CHCl_3$ (4 × 25 mL), the $CHCl_3$ extracts were dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (7:1 → 5:1 → 4:1 petroleum ether−Et_2O) to provide 1.04 g (74%) of cycloheptenone **27** as a clear oil: $R_f = 0.30$ (5:1 petroleum ether−Et_2O); $[\alpha]^{24}_D$ −1.9, $[\alpha]^{24}_{577}$ −1.0, $[\alpha]^{24}_{546}$ +0.5, $[\alpha]^{24}_{435}$ +13.6, $[\alpha]^{24}_{405}$ +27.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48−5.45 (m, 1H), 4.85 (t, $J = 4.6$ Hz, 1H), 4.49 (t, $J = 6.5$ Hz, 1H), 3.98−3.81 (m, 4H), 3.17−3.09 (m, 1H), 2.70−2.65 (m, 1H), 2.64−2.45 (m, 2H), 2.36−2.03 (m, 7H), 1.78−1.69 (m, 2H), 1.74 (br s, 3H), 1.65−1.56 (m, 2H) and 1.09−1.03 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 137.4, 122.5, 104.2, 84.4, 82.1, 64.9, 61.4, 47.0, 41.8, 40.0, 33.0, 31.2, 29.2, 26.2, 23.0, 18.6, 18.1, 12.3; IR (film) 1706 cm^{-1}; HRMS (EI) *m*/*z* 462.3149 (462.3165 calcd for $C_{27}H_{46}O_4Si$, M). Anal. Calcd for $C_{27}H_{46}O_4Si$: C, 70.08; H, 10.02. Found: C, 70.16; H, 9.97.

(2*R*,2′*S*)-2-[2′-Triisopropylsilyloxy-8′-(1,3-dioxolanyl)-3′-octynyl]-5-methyl-1-methylenecyclohept-4-ene (32). *sec*-Butyllithium (1.3 M in cyclohexane, 16.4 mL) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (10.1 g, 28.3 mmol) in THF (40 mL) at 0 °C. The resulting solution was maintained at 0 °C for 30 min and then cooled to −78 °C, and a solution of ketone **27** (3.28 g, 7.09 mmol) and THF (28 mL) was added dropwise by cannula. The

reaction was allowed to warm to 0 °C over 1 h and was quenched with saturated aqueous NH_4Cl (100 mL). The resulting mixture was extracted with CH_2Cl_2 (100 mL and 2 × 50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (32:1 → 19:1 hexanes−EtOAc) to give 2.79 g (85%) of diene **32** as a colorless oil: R_f = 0.25 (19:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +16.7, $[\alpha]^{24}_{577}$ +15.9, $[\alpha]^{24}_{546}$ +18.5, $[\alpha]^{24}_{435}$ +33.4, $[\alpha]^{24}_{405}$ +41.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 5.45 (t, *J* = 6.6 Hz, 1H), 4.92 (d, *J* = 2.2 Hz, 1H), 4.79 (d, *J* = 2.6 Hz, 1H), 4.74 (t, *J* = 4.6 Hz, 1H), 4.67 (t, *J* = 7.0, Hz, 1H), 3.51−3.49 (m, 2H), 3.34−3.31 (m, 2H), 2.24−1.90 (m, 11H), 1.81−1.77 (m, 2H), 1.67−1.61 (m, 2H), 1.63 (s, 3H), 1.11−1.06 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.0, 140.0, 122.7, 110.4, 104.4, 84.7, 83.0, 64.8, 62.0, 43.1, 42.1, 35.0, 33.4, 32.4, 32.4, 25.9, 23.6, 18.9, 18.5, 12.9; IR (film) 884 cm^{-1}; HRMS (CI, NH_3) *m*/*z* 461.3440 (461.3451 calcd for $C_{28}H_{49}O_3Si$, MH). Anal. Calcd for $C_{28}H_{48}O_3Si$: C, 72.99; H, 10.50. Found: C, 72.77; H, 10.53.

(2*R*,2′*S*)-2-[2′-Hydroxy-8′-(1,3-dioxolanyl)-3′-octynyl]-5-methyl-1-methylenecyclohept-4-ene (33). A solution of **32** (2.79 g, 6.07 mmol), tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 6.7 mL) and THF (30 mL) was maintained at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl (100 mL). The mixture was extracted with CH_2Cl_2 (100 mL and 2 × 50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (3:1 hexanes−EtOAc) to afford 1.84 g (100%) of propargyl alcohol **33** as a pale yellow oil: R_f = 0.25 (3:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +64.3, $[\alpha]^{24}_{577}$ +66.6, $[\alpha]^{24}_{546}$ +76.9, $[\alpha]^{24}_{435}$ +134, $[\alpha]^{24}_{405}$ +164 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, *J* = 12.5 Hz, 1H), 5.42 (t, *J* = 6.4 Hz, 1H), 4.86 (t, *J* = 4.6 Hz, 1H), 4.75−4.73 (m, 2H), 4.28 (t, *J* = 6.6 Hz, 1H), 3.97−3.92 (m, 2H), 3.87−3.82 (m, 2H), 2.73−2.69 (m, 1H), 2.27−2.26 (m, 2H), 2.25−2.04 (m, 6H), 1.80−1.60 (m, 6H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 140.3, 121.9, 110.8, 104.1, 84.7, 81.9, 64.8, 60.9, 41.6, 40.8, 34.5, 32.8, 32.2, 31.5, 25.8, 23.1, 18.6; IR (film) 3448, 894 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 305.2118 (305.2116 calcd for $C_{19}H_{29}O_3$, MH). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.01; H, 9.32.

(2*R*,2′*S*)-(*Z*)-2-[2′-Hydroxy-8′-(1,3-dioxolanyl)-4′-iodo-3′-octenyl]-5-methyl-1-methylenecyclohept-4-ene (34). A solution of the propargyl alcohol **33** (0.44 g, 1.46 mmol) and Et_2O (5 mL) was added dropwise by cannula to a solution of sodium bis(2-methoxyethoxy)-aluminum hydride (3.5 M in THF, 0.66 mL)[65] and Et_2O (30 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and, after 15 h, was cooled to −78 °C. A solution of freshly purified *N*-iodosuccinimide (0.82 g, 3.6 mmol) and THF−Et_2O (10:7, 17 mL) was then added dropwise by cannula. The solution was maintained at 0 °C for 5 min, allowed to warm to room temperature, and then quenched by sequential addition of saturated aqueous Na_2SO_3−H_2O (1:1, 20 mL) and H_2O (50 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (3:1 hexanes−EtOAc) furnished 0.61 g (97%) of **34** as a colorless oil: R_f = 0.20 (3:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +38.7, $[\alpha]^{24}_{577}$ +42.2, $[\alpha]^{24}_{546}$ +49.1, $[\alpha]^{24}_{435}$ +89.8, $[\alpha]^{24}_{405}$ +111 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (d, *J* = 7.5 Hz, 1H), 5.44 (t, *J* = 6.3 Hz, 1H), 4.86 (t, *J* = 3.7 Hz, 1H), 4.76−4.72 (m, 2H), 4.24 (m, 1H), 3.99−3.82 (m, 4H), 2.62−2.49 (m, 3H), 2.26−2.04 (m, 6H), 1.83−1.45 (m, 7H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 140.4, 134.9, 122.1, 110.5, 108.4, 104.1, 74.8, 64.9, 45.0, 41.3, 38.4, 34.5, 32.9, 32.3, 31.7, 25.8, 23.6; IR (film) 3417, 843 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 433.1239 (433.1239 calcd for $C_{19}H_{30}IO_3$, MH).

(2*R*,2′*S*)-(*Z*)-2-[2′-(*tert*-Butyldimethylsilyloxy)-8′-(1,3-dioxolanyl)-4′-iodo-3′-octenyl]-5-methyl-1-methylenecyclohept-4-ene (35). A solution of alcohol **34** (1.74 g, 4.0 mmol), imidazole (0.77 g, 11.4 mmol), *tert*-butyldimethylsilyl chloride (0.86 g, 5.7 mmol), and DMF (25 mL) was maintained at room temperature for 8.5 h and then quenched with H_2O (50 mL). The resulting mixture was extracted with hexanes (3 × 75 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (19:1 hexanes−EtOAc) to afford 2.15 g (97%) of vinyl iodide **35** as a colorless oil: R_f = 0.35 (95:5 hexanes−EtOAc); $[\alpha]^{24}_D$ +45.8, $[\alpha]^{24}_{577}$ +48.7, $[\alpha]^{24}_{546}$ +56.8, $[\alpha]^{24}_{435}$ +108, $[\alpha]^{24}_{405}$ +136 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (d, *J* = 7.6 Hz, 1H), 5.44 (t, *J* = 7.6 Hz, 1H), 4.88−4.84 (m, 1H), 4.75−4.67 (m, 2H), 4.22−4.15 (m, 1H), 3.99−3.82 (m, 4H), 2.57−2.49 (m, 3H), 2.28−2.01 (m, 6H), 1.74 (s, 3H), 1.64−1.63 (m, 4H), 1.61−1.37 (m, 2H), 0.87 (s, 9H), 0.06 (s, 3H) and 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 139.9, 139.2, 122.6, 110.0, 105.7, 104.2, 76.0, 64.8, 45.0, 40.8, 40.2, 34.7, 33.8, 32.4, 26.0, 23.6, 18.0, −3.7, −4.5; IR (film) 888, 835, 811 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 547.2086 (547.2106 calcd for $C_{25}H_{44}IO_3Si$, MH).

(2*S*,4a*S*,7*S*,9a*S*)-4-[4-(1,3-Dioxolanyl)butyl]-7-methyl-1,2,5,6,7,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2-ol (36). A solution of vinyl iodide **35** (740 mg, 1.35 mmol) and THF (75 mL) was degassed (Ar, evacuate−refill), and Ph_3P (107 mg, 0.41 mmol), Ag_2CO_3 (410 mg, 1.5 mmol), and $Pd(OAc)_2$ (46 mg, 0.20 mmol) were added. The resulting suspension was stirred at room temperature for 15 min and then heated at 65 °C in a sealed tube for 12 h. A black suspension resulted after 10−20 min at 65 °C. After GC analysis of a filtered aliquot showed that the reaction had not proceeded to completion, additional Ph_3P (107 mg, 0.41 mmol), Ag_2CO_3 (411 mg, 1.49 mmol), and $Pd(OAc)_2$ (46 mg, 0.20 mmol) were added, and the black suspension was stirred in a sealed tube at 65 °C for an additional 6 h. The suspension was then cooled to room temperature and filtered through a plug of silica gel (1.5 cm × 12 cm, EtOAc), and the filtrate was concentrated to give the crude Heck product as a yellow oil.

This sample was dissolved in THF (4 mL), and TBAF (1.0 M solution in THF, 2.0 mL) was added. The resulting solution was maintained at room temperature for 20 h and quenched with saturated aqueous NH_4Cl (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (4:1 hexanes−EtOAc) to provide 370 mg (90%) of tricyclic allylic alcohol **36** as a pale yellow oil: R_f = 0.25 (5:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +49.5, $[\alpha]^{24}_{577}$ +53.9, $[\alpha]^{24}_{546}$ +61.6, $[\alpha]^{24}_{435}$ +109, $[\alpha]^{24}_{405}$ +133 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (d, *J* = 9.5 Hz, 1H), 5.32 (br s, 1H), 5.19 (dd, *J* = 9.5, 1.6 Hz, 1H), 4.87 (t, *J* = 4.5 Hz, 1H), 4.33 (t, *J* = 7.5 Hz, 1H), 4.00−3.83 (m, 4H), 2.50 (d, *J* = 13.3 Hz, 1H), 2.52−1.25 (m, 15H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 137.2, 127.7, 125.0, 104.4, 68.4, 64.8, 47.3, 46.4, 45.2, 42.4, 41.3, 34.0, 33.6, 32.4, 30.6, 23.9, 22.8; IR (film) 3390, 1652 cm^{-1}; HRMS (EI) *m*/*z* 304.2042 (304.2038 calcd for $C_{19}H_{28}O_3$, M).

(4a*S*,7*S*,9a*S*)-4-[4-(1,3-Dioxolanyl)butyl]-7-methyl-1,2,5,6,7,9a-hexahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one (53). Alcohol **36** (170 mg, 0.56 mmol) was oxidized with TPAP (10 mg, 0.03 mmol) and NMO (130 mg, 1.1 mmol) as described for the preparation of **17** to provide the crude enone, which was then purified by flash chromatography (5.7:1 hexanes−EtOAc) to give 160 mg (95%) of enone **53** as a colorless oil: R_f = 0.40 (3:2 hexanes−EtOAc); $[\alpha]^{24}_D$ +56.2, $[\alpha]^{24}_{577}$ +60.8, $[\alpha]^{24}_{546}$ +73.2, $[\alpha]^{24}_{435}$ +188, $[\alpha]^{24}_{405}$ +308 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (s, 1H), 5.61 (d, *J* = 9.5 Hz, 1H), 5.20 (dd, *J* = 9.4, 1.7 Hz, 1H), 4.88 (t, *J* = 4.3 Hz, 1H), 4.00−3.82 (m, 4H), 2.98 (br d, *J* = 13.0 Hz, 1H), 2.49−2.08 (m, 5H), 1.92 (d, *J* = 10.6 Hz, 1H), 1.78−1.40 (m, 8H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 170.5, 137.8, 125.9, 124.9, 104.0, 64.9, 48.1, 46.1, 45.3, 42.4, 40.5, 38.6, 33.3, 31.7, 28.8, 23.8, 21.5; IR (film) 1674, 1602 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 303.1960 (303.1946 calcd for $C_{19}H_{27}O_3$, MH). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66. Found: C, 75.35; H, 8.93.

(4*S*,4a*S*,7*S*,9a*S*)-4-[4-(1,3-Dioxolanyl)butyl]-4,7-dimethyl-1,2,3,4,5,6,7,9a-octahydro-4a,7-methano-4a*H*-benzocyclohepten-2(1*H*)-one (54). Using a glovebox, a flask was charged with dry LiBr (650 mg, 7.5 mmol) and $Ni(acac)_2$ (7 mg, 0.03 mmol) and then flushed with Ar, and dry Et_2O was added. Dimethylzinc (0.26 mL, 3.8 mmol) was added dropwise to this stirred suspension at 0 °C under Ar.[71] The brown heterogeneous mixture was stirred at 0 °C for 10 min, and then a solution of enone **53** (280 mg, 0.93 mmol) and Et_2O (6 mL) was added by cannula. The reaction was allowed to warm to room temperature and stirred at room temperature for 17 h. This mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (14

mL). Saturated aqueous EDTA (5 mL) was then added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (5.7:1 hexanes−EtOAc) afforded 258 mg (88%) of ketone **54** as a colorless oil: $R_f = 0.45$ (3:2 hexanes−EtOAc); $[\alpha]^{24}_D$ +47.2, $[\alpha]^{24}_{577}$ +49.7, $[\alpha]^{24}_{546}$ +57.2, $[\alpha]^{24}_{435}$ +108, $[\alpha]^{24}_{405}$ +136 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (d, $J = 9.3$ Hz, 1H), 5.14 (dd, $J = 9.4$, 1.1 Hz, 1H), 4.85 (t, $J = 4.5$ Hz, 1H), 3.97−3.83 (m, 4H), 3.00 (br d, $J = 13.5$ Hz, 1H), 2.35 (t, $J = 14.2$ Hz, 1H), 2.24 (dd, $J = 14.8$, 4.4 Hz, 1H), 2.18 (d, $J = 13.9$ Hz, 1H), 2.12 (d, $J = 13.9$ Hz, 1H), 1.86−1.22 (m, 12H), 1.11 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 138.1, 127.6, 104.9, 65.5, 51.0, 50.8, 44.6, 44.5, 43.3, 42.7, 42.6, 41.9, 35.9, 35.3, 26.2, 24.4, 21.2, 18.9; IR (film) 1706, 1668, 1656 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.26; H, 9.50.

(4*S*,4a*S*,7*S*,9a*S*)-2-(1,3-Dioxolanyl)-4-[4-(1,3-dioxolanyl)butyl]-4,7-dimethyl-1,2,3,4,5,6,7,9a-octahydro-4a,7-methano-4a*H*-benzocycloheptene (55). A mixture of ketone **54** (150 mg, 0.47 mmol), ethylene glycol (0.25 mL, 5 mmol), 2-methoxy-1,3-dioxolane (0.16 mL, 1.7 mmol), Amberlyst-15 acidic resin (44 mg), and MeCN (4 mL) was stirred at room temperature for 12 h and then filtered. The Amberlyst resin was thoroughly washed with CH_2Cl_2 (20 mL), the combined filtrates were concentrated, and the residue was purified by flash chromatography (9:1 hexanes−EtOAc) to provide 157 mg (92%) of **55** as a colorless oil: $R_f = 0.45$ (4:1 hexanes−EtOAc); $[\alpha]^{23}_D$ +63.2, $[\alpha]^{23}_{577}$ +67.3, $[\alpha]^{23}_{546}$ +77.5, $[\alpha]^{23}_{435}$ +140, $[\alpha]^{23}_{405}$ +174 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (d, $J = 9.6$ Hz, 1H), 5.11 (d, $J = 9.5$ Hz, 1H), 4.83 (t, $J = 4.8$ Hz, 1H), 3.96−3.80 (m, 8H), 2.86 (br d, $J = 12.8$ Hz, 1H), 1.70−1.47 (m, 9H), 1.42−1.24 (m, 7H), 1.05 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 128.4, 109.2, 104.5, 64.8, 64.4, 63.4, 50.1, 44.3, 42.5, 42.1, 41.4, 37.6, 36.9, 36.0, 34.9, 24.1, 23.8, 20.5, 18.6; IR (film) 1086, 1063 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 363.2533 (363.2536 calcd for $C_{22}H_{35}O_4$, MH).

(4*S*,4a*S*,7*S*,8*R*,9*S*,9a*S*)-8,9-Epoxy-2-(1,3-dioxolanyl)-4-[4-(1,3-dioxolanyl)butyl]-4,7-dimethyl-1,2,3,4,5,6,7,8,9,9a-decahydro-4a,7-methano-4a*H*-benzocycloheptene (56). A mixture of **55** (200 mg, 0.55 mmol), $NaHCO_3$ (56 mg, 0.67 mmol), and CH_2Cl_2 (6.9 mL) was cooled to 0 °C, and *m*-chloroperbenzoic acid (95%, 143 mg, 0.79 mmol) was added. The reaction was allowed to warm to room temperature over 3 h. This mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with 5% aqueous NaOH (10 mL), saturated aqueous Na_2SO_3 (10 mL), and 5% aqueous NaOH (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by flash chromatography (17:3 hexanes−EtOAc) to give 206 mg (99%) of epoxide **56** as a colorless oil: $R_f = 0.40$ (2:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +18.0, $[\alpha]^{24}_{577}$ +19.7, $[\alpha]^{24}_{546}$ +22.9, $[\alpha]^{24}_{435}$ +40.4, $[\alpha]^{24}_{405}$ +48.6 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (t, $J = 4.5$ Hz, 1H), 3.97−3.78 (m, 8H), 2.80 (d, $J = 3.3$ Hz, 1H), 2.60 (d, $J = 3.8$ Hz, 1H), 2.36 (dd, $J = 13.3$, 4.3 Hz, 1H), 1.78−1.54 (m, 7H), 1.44−1.08 (m, 9H), 1.14 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.0, 104.4, 64.8, 64.5, 63.5, 60.8, 55.1, 48.8, 42.2, 40.8, 38.7, 38.3, 37.6, 36.9, 36.4, 35.6, 34.9, 24.6, 22.2, 20.6, 18.5; IR (film) 1247 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 379.2473 (379.2484 calcd for $C_{22}H_{35}O_5$, MH). Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.13. Found: C, 69.94; H, 9.13.

(4*S*,4a*S*,7*S*,8*S*,9a*S*)-2-(1,3-Dioxolanyl)-4-[4-(1,3-dioxolanyl)butyl]-4,7-dimethyl-1,2,3,4,5,6,7,8,9,9a-decahydro-4a,7-methano-4a*H*-benzocyclohepten-8-ol (57). A solution of epoxide **56** (235 mg, 0.62 mmol) and Et_2O (4.2 mL) was added dropwise to a solution of $LiAlH_4$ (1.0 M in THF, 1.2 mL) and Et_2O (0.4 mL). The reaction was stirred vigorously at room temperature for 14 h. After the mixture was cooled to 0 °C, a solution of EtOAc (1.3 mL) and Et_2O (6.6 mL) was added dropwise. The resulting suspension was warmed to room temperature, and 15% aqueous NaOH (0.2 mL) and H_2O (0.4 mL) were added. The mixture was stirred vigorously for 15 min, and Na_2SO_4 (2.6 g) was added. After being stirred for 15 min, the mixture was filtered through a plug of Celite (1 cm × 5 cm). The plug was washed with Et_2O (50 mL), and the filtrate was concentrated. Purification of the residue by flash chromatography (4:1 hexanes−EtOAc) afforded 212 mg (90%) of alcohol **57** as a viscous colorless oil: $R_f = 0.38$ (1:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +8.6, $[\alpha]^{24}_{577}$ +9.3, $[\alpha]^{24}_{546}$ +10.4, $[\alpha]^{24}_{435}$ +18.1, $[\alpha]^{24}_{405}$ +22.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (t, $J = 4.7$ Hz, 1H), 3.96−3.77 (m, 8H), 3.38 (br s, 1H), 2.18 (m, 1H), 1.73−1.12 (m, 19H), 0.99 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.7, 104.5, 74.7, 64.7, 64.4, 63.2, 50.6, 43.7, 42.5, 38.5, 38.4, 37.6, 36.4, 36.3, 34.9, 32.5, 23.9, 21.8, 21.6, 18.6; IR (film) 3480 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 381.2627 (381.2641 calcd for $C_{22}H_{37}O_5$, MH).

(6a*S*,8*S*,9*S*,11a*S*,11b*S*)-8-Hydroxy-9,11b-dimethyl-1,2,3,6a,7,8,9,-10,11,11b-decahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalen-5(6*H*)-one (58). A solution of alcohol **57** (150 mg, 0.39 mmol), 20% aqueous HCl (2.6 mL), and THF (7.8 mL) was maintained at room temperature for 12 h and then heated at 50 °C for an additional 12 h. The resulting yellow solution was cooled to room temperature, poured into ice-cold saturated aqueous $NaHCO_3$ (15 mL), and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (4:1 hexanes−EtOAc) to provide 80 mg (74%) of **58** as a colorless solid. Recrystallization from hexanes−Et_2O provided analytically pure **58** as colorless needles: mp 146 °C; $R_f = 0.50$ (3:2 hexanes−EtOAc); $[\alpha]^{25}_D$ +72.3, $[\alpha]^{25}_{577}$ +76.6, $[\alpha]^{25}_{546}$ +87.6, $[\alpha]^{24}_{435}$ +125, $[\alpha]^{24}_{405}$ +102 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (dd, $J = 5.7$, 2.1 Hz, 1H), 3.48 (br s, 1H), 2.57 (dd, $J = 19.0$, 7.5 Hz, 1H), 2.46 (m, 1H), 2.19−2.12 (m, 1H), 2.07−1.99 (m, 1H), 1.97 (dd, $J = 19.1$, 9.0 Hz, 1H), 1.75−1.39 (m, 10H), 1.25−1.22 (m, 2H), 1.19 (d, $J = 11.2$ Hz, 1H), 1.09 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 142.6, 134.6, 74.5, 50.6, 44.5, 42.5, 38.5, 37.7, 37.5, 36.3, 31.9, 29.3, 25.5, 24.5, 24.2, 23.9, 18.2; IR (film) 3460, 1686, 1672, 1617 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 275.1994 (275.2011 calcd for $C_{18}H_{27}O_2$, MH). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.52; H, 9.59.

(6a*S*,8*S*,9*S*,11a*S*,11b*S*)-8-(Methoxymethyl)oxy-9,11b-dimethyl-1,2,3,6a,7,8,9,10,11,11b-decahydro-9,11a-methano-11a*H*-cyclohepta-[*a*]naphthalen-5(6*H*)-one (59). *N*,*N*-Diisopropylethylamine (0.4 mL, 2.3 mmol) and chloromethyl methyl ether (0.12 mL, 1.6 mmol) were added to a solution of enone **58** (149 mg, 0.54 mmol) and CH_2Cl_2 (2.5 mL) at 0 °C. The reaction was maintained at room temperature for 7 h and then diluted with CH_2Cl_2 (5 mL). The resulting mixture was washed sequentially with 1 M HCl (2 × 2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The organic extracts were dried ($NaSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (9:1 hexanes−EtOAc) to give 159 mg (92%) of **59** as a colorless solid. Recrystallization from hexanes produced analytically pure **59** as colorless needles: mp 87−87.5 °C; $R_f = 0.77$ (3:2 hexanes−EtOAc); $[\alpha]^{24}_D$ +106, $[\alpha]^{24}_{577}$ +109, $[\alpha]^{24}_{546}$ +123, $[\alpha]^{24}_{435}$ +190, $[\alpha]^{24}_{405}$ +191 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (dd, $J = 5.5$, 2.0 Hz, 1H), 4.71 (d, $J = 6.9$ Hz, 1H), 4.57 (d, $J = 6.9$ Hz, 1H), 3.38 (s, 3H), 3.31 (s, 1H), 2.57 (dd, $J = 19.1$, 7.5 Hz, 1H), 2.39 (m, 1H), 2.20−1.96 (m, 2H), 1.99 (dd, $J = 19.1$, 9.2 Hz, 1H), 1.83 (ddd, $J = 14.6$, 5.1, 1.2 Hz, 1H), 1.78−1.41 (m, 8H), 1.21−1.17 (m, 3H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 142.7, 134.4, 95.5, 79.9, 55.5, 50.2, 44.2, 42.6, 38.5, 38.3, 36.4, 34.3, 32.4, 29.4, 25.4, 24.5, 24.3, 24.1, 18.3; IR (film) 1684, 1619 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 319.2273 (319.2273 calcd for $C_{20}H_{31}O_3$, MH).

(4*S*,4a*S*,6a*S*,8*S*,9*S*,11a*S*,11b*S*)-4-Cyano-8-(methoxymethyl)oxy-9,-11b-dimethyl-1,2,3,4,6,6a,7,8,9,10,11,11b-dodecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalen-5(4a*H*)-one (60). Diethyl aluminum cyanide (1.0 M in toluene, 1.1 mL) was added dropwise to a solution of enone **59** (170 mg, 0.53 mmol) and THF (11 mL) at 0 °C.[72] After 10 h at 0 °C, a viscous solution of Et_3N (0.75 mL, 5.4 mmol), TMSCl (0.34 mL, 2.7 mmol), and THF (0.5 mL) was added using a 16−18-gauge cannula. The resulting mixture was allowed to warm to room temperature, and Et_2O (30 mL) and saturated aqueous $NaHCO_3$ (10 mL) were added. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL), dried (K_2CO_3), and filtered through a short column of silica gel (Et_2O) to provide the crude $\Delta^{5,6}$-enoxysilane.

A solution of this material, 10:1 THF−H_2O (5 mL), and 1 M HCl (0.05 mL) was maintained at room temperature for 15 min and then diluted with Et_2O (15 mL), and K_2CO_3 (150 mg) was added. The

resulting mixture was stirred for 10 min, dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (4:1 hexanes−EtOAc) afforded 162 mg (88%) of **60** as a colorless solid. Recrystallization from hexanes−Et_2O provided analytically pure **60** as colorless needles: mp 168 °C; $R_f = 0.37$ (3:2 hexanes−EtOAc); $[\alpha]^{24}_D$ +72.2, $[\alpha]^{24}_{577}$ +74.3, $[\alpha]^{24}_{546}$ +84.8, $[\alpha]^{24}_{435}$ +149, $[\alpha]^{24}_{405}$ +183 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (d, $J = 6.9$ Hz, 1H), 4.54 (d, $J = 6.9$ Hz, 1H), 3.34 (s, 3H), 3.29 (br s, 1H), 2.96 (br s, 1H), 2.38−2.30 (m, 2H), 2.22 (d, $J = 4.6$ Hz, 1H), 2.08−1.95 (m, 2H), 1.87−1.44 (m, 10H), 1.38 (tt, $J = 13.8$, 4.1 Hz, 1H), 1.28 (ddd, $J = 18.2$, 11.8, 3.6 Hz, 1H), 1.20 (d, $J = 11.4$ Hz, 1H), 1.13 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 122.0, 95.5, 79.7, 55.5, 53.4, 51.8, 43.9, 43.9, 41.8, 37.7, 35.9, 35.0, 33.5, 30.3, 28.6, 24.0, 23.9, 23.3, 18.1, 18.0; IR (film) 2233, 1701 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 346.2372 (346.2383 calcd for $C_{21}H_{32}NO_3$, MH). Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04. Found: C, 72.74; H, 9.06.

(4*S*,4a*S*,5*R*,6a*S*,8*S*,9*S*,11a*S*,11b*S*)-4-Cyano-8-(methoxymethyl)-oxy-9,11b-dimethyl-5-trimethylsiloxy-1,2,3,4,4a,5,6,6a,7,8,9,10,11,-11b-tetradecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalene (61). Lithium aluminum hydride (1.0 M in THF, 0.48 mL) was added dropwise to a solution of ketone **60** (158 mg, 0.46 mmol) and THF (5.5 mL) at −78 °C. The reaction was maintained at −78 °C for 30 min and was quenched by sequential additions of H_2O (0.02 mL), 15% aqueous NaOH (0.02 mL), and H_2O (0.06 mL). The mixture was warmed to room temperature and diluted with Et_2O (15 mL), and $MgSO_4$ (750 mg) was then added. After being stirred vigorously for 10 min, the mixture was filtered through a plug of silica gel (1 cm × 4 cm, Et_2O), and the filtrate was concentrated. The residue was purified by flash chromatography (4:1 hexanes−EtOAc) to give 143 mg (90%) of (4*S*,4a*S*,5*R*,6a*S*,8*S*,9*S*,11a*S*,11b*S*)-4-cyano-8-(methoxymethyl)oxy-9,11b-dimethyl-1,2,3,4,4a,5,6,6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalen-5-ol as a colorless solid: mp 129−130 °C; $R_f = 0.53$ (1:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +58.6, $[\alpha]^{24}_{577}$ +59.5, $[\alpha]^{24}_{546}$ +67.5, $[\alpha]^{24}_{435}$ +110, $[\alpha]^{24}_{405}$ +130 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (d, $J = 6.9$ Hz, 1H), 4.54 (d, $J = 6.9$ Hz, 1H), 3.91 (br s, 1H), 3.36 (s, 3H), 3.26 (br s, 1H), 2.76 (br s, 1H), 2.33 (m, 1H), 2.15−2.02 (m, 2H), 1.95−1.78 (m, 1H), 1.72−1.09 (m, 15H), 1.43 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.3, 95.1, 79.6, 71.4, 55.5, 52.0, 44.7, 43.1, 38.3, 38.2, 37.8, 36.2, 33.0, 32.6, 31.0, 29.3, 29.0, 24.1, 21.7, 19.8, 18.8; IR (film) 3483, 2232 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 348.2536 (348.2538 calcd for $C_{21}H_{34}NO_3$, MH). Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57. Found: C, 72.68; H, 9.63.

Pyridine (0.5 mL), DMAP (4.5 mg, 0.037 mmol), and freshly distilled TMSCl (0.07 mL, 0.55 mmol) were added sequentially to a solution of this alcohol (51 mg, 0.147 mmol) and CH_2Cl_2 (0.5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 2 h and then partitioned between saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (19:1 hexanes−Et_2O) yielded 60 mg (97%) of **61** as a colorless solid. Recrystallization from hexanes afforded analytically pure **61** as colorless needles: mp 141 °C; $R_f = 0.55$ (8:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +42.1, $[\alpha]^{24}_{577}$ +45.2, $[\alpha]^{24}_{546}$ +50.7, $[\alpha]^{24}_{435}$ +84.0, $[\alpha]^{24}_{405}$ +99.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, $J = 7.0$ Hz, 1H), 4.60 (d, $J = 7.0$ Hz, 1H), 3.82 (br s, 1H), 3.39 (s, 3H), 3.25 (br s, 1H), 2.60 (br s, 1H), 2.31 (m, 1H), 2.05 (br d, $J = 12.9$ Hz, 1H), 1.95−1.87 (m, 1H), 1.70−1.10 (m, 15H), 1.41 (s, 3H), 1.02 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.8, 95.7, 80.5, 71.5, 55.5, 52.0, 45.3, 43.1, 38.5, 38.4, 37.9, 36.3, 33.2, 33.1, 31.8, 29.9, 29.1, 24.2, 21.8, 19.6, 19.0, 0.09; IR (film) 2360 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 420.2929 (420.2935 calcd for $C_{24}H_{42}NO_3Si$, MH).

(4*S*,4a*S*,5*R*,6a*S*,8*S*,9*S*,11a*S*,11b*S*)-4-(Benzyloxymethyl)oxy-4-cyano-8-(methoxymethyl)oxy-9,11b-dimethyl-5-trimethylsiloxy-1,2,3,4,-4a,5,6,6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalene (62). *n*-Butyllithium (2.0 M in hexanes, 0.14 mL) was added dropwise to a solution of diisopropylamine (0.04 mL, 0.31 mmol) and THF (0.6 mL) at −78 °C, and the solution of LDA was warmed to 0 °C for 30 min. A solution of nitrile **61** (56 mg, 0.133 mmol) and THF (0.50 mL) was then added dropwise by cannula. After being stirred for 15 min at 0 °C, the yellow solution was cooled to −78 °C, and freshly distilled benzyl bromomethyl ether[73] (65 μL, 0.5 mmol) was added rapidly. The reaction was maintained at 0 °C for 2 h, quenched with saturated aqueous $NaHCO_3$ (1.5 mL), and warmed to room temperature, and then additional saturated aqueous $NaHCO_3$ (10 mL) was added. This mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography (99:1 → 98:2 hexanes−EtOAc) afforded 59 mg (82%) of ether **62** as a colorless oil: $R_f = 0.29$ (15:1 hexanes−EtOAc); $[\alpha]^{24}_D$ +13.8, $[\alpha]^{24}_{577}$ +14.0, $[\alpha]^{24}_{546}$ +15.9, $[\alpha]^{24}_{435}$ +26.5, $[\alpha]^{24}_{405}$ +31.0 (*c* 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.60 (d, $J = 7.0$ Hz, 1H), 4.60 (d, $J = 12.1$ Hz, 1H), 4.43 (d, $J = 12.3$ Hz, 1H), 3.90 (m, 1H), 3.53 (d, $J = 9.0$ Hz, 1H), 3.39 (m, 1H), 3.39 (s, 3H), 3.25 (br s, 1H), 2.26 (m, 1H), 2.00−1.87 (m, 2H), 1.72−1.58 (m, 6H), 1.48−1.40 (m, 3H), 1.43 (s, 3H), 1.36 (t, $J = 7.7$ Hz, 2H), 1.30 (d, $J = 2.0$ Hz, 1H), 1.31−1.10 (m, 3H), 1.02 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 128.4, 127.9, 127.8, 124.0, 95.8, 80.8, 73.3, 72.8, 66.3, 55.4, 52.3, 45.3, 43.1, 38.7, 38.6, 38.4, 37.6, 36.2, 36.0, 33.3, 33.2, 28.6, 24.2, 21.9, 20.0, 19.0, 0.32; IR (film) 2231 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 540.3490 (540.3509 calcd for $C_{32}H_{50}NO_4Si$, MH).

(4*S*,4a*S*,5*R*,6a*S*,8*S*,9*S*,11a*S*,11b*S*)-4-(Benzyloxymethyl)oxy-5-hydroxy-4-methoxycarbonyl-8-(methoxymethyl)oxy-9,11b-dimethyl-1,2,3,4,4a,5,6,6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalene (63). A mixture of K_2CO_3 (33 mg, 0.24 mmol), KOH (78 mg, 1.4 mmol), nitrile **62** (17 mg, 0.031 mmol), and MeOH (1 mL) was concentrated to dryness under a stream of N_2, and the residue was heated at 140 °C for 24 h. After being cooled to room temperature, the resulting solid mass was dissolved in H_2O (3.5 mL) and cooled to 0 °C. Ether (3.5 mL) was added, and the mixture was carefully acidified to pH 2 with 1 M aqueous HCl. The layers were separated, and the aqueous layer was extracted with Et_2O (5 × 7 mL). The combined organic layers were washed with saturated aqueous 1:1 NaCl−H_2O (7 mL), dried ($MgSO_4$), filtered, and concentrated to afford the corresponding carboxylic acid.

The crude acid was dissolved in Et_2O (2 mL), and excess diazomethane (generated from 70 mg of 1-methyl-5-nitro-1-nitrosoguanidine) was added at 0 °C. The resulting solution was allowed to stand at 0 °C for 30 min until a pale yellow color persisted. Excess diazomethane was removed with a stream of N_2, the solution was concentrated, and the residue was purified by flash chromatography (4:1 hexanes−EtOAc) to provide 13.5 mg (86%) of ester **63** as a colorless oil: $R_f = 0.60$ (3:2 hexanes−EtOAc); $[\alpha]^{24}_D$ +34.9, $[\alpha]^{24}_{577}$ +36.4, $[\alpha]^{24}_{546}$ +41.8, $[\alpha]^{24}_{435}$ +69.6, $[\alpha]^{24}_{405}$ +82.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 7.28−7.24 (m, 3H), 5.21 (s, 1H), 4.72 (d, $J = 7.0$ Hz, 1H), 4.53 (d, $J = 7.0$ Hz, 1H), 4.50 (d, $J = 12.4$ Hz, 1H), 4.42 (d, $J = 12.4$ Hz, 1H), 4.23 (br s, 1H), 3.76 (s, 3H), 3.74 (d, $J = 8.4$ Hz, 1H), 3.37 (s, 3H), 3.36 (d, $J = 8.4$ Hz, 1H), 3.28 (br s, 1H), 2.41 (dd, $J = 13.3$, 1.1 Hz, 1H), 2.35 (m, 1H), 1.82−1.72 (m, 2H), 1.69−1.48 (m, 5H), 1.44−1.24 (m, 6H), 1.17−1.08 (m, 3H), 1.09 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 138.0, 128.3, 127.6, 127.2, 94.8, 79.4, 78.0, 73.3, 65.4, 55.5, 52.8, 52.7, 50.9, 49.7, 43.0, 39.0, 38.6, 37.7, 36.6, 34.0, 33.8, 32.2, 28.5, 24.3, 22.3, 20.9, 19.3; IR (film) 1728, 1696 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 501.3199 (501.3216 calcd for $C_{30}H_{45}O_6$, MH).

(4*S*,4a*S*,5*R*,6a*S*,8*S*,9*S*,11a*S*,11b*S*)-5-Benzoyloxy-4-(benzyloxymethyl)oxy-4-methoxycarbonyl-8-(methoxymethyl)oxy-9,11b-dimethyl-1,2,3,4,4a,5,6,6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalene (64). A solution of alcohol **63** (54 mg, 0.11 mmol), freshly distilled benzoyl chloride (54 mg, 0.11 mmol), DMAP (130 mg, 1.1 mmol), and pyridine (1.2 mL) was heated at 100 °C for 5 h and then cooled to room temperature. The reaction was diluted with CH_2Cl_2 (4 mL) and then cooled to 0 °C, and ethylenediamine (0.2 mL, 3 mmol) was added. The resulting suspension was stirred at 0 °C for 30 min, diluted with CH_2Cl_2 (24 mL), and poured into H_2O (24 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 24 mL). The combined organic layers were washed sequentially with 5% aqueous HCl (24 mL) and saturated aqueous $NaHCO_3$ (24 mL), dried ($MgSO_4$), filtered, and concentrated. The solid residue was washed thoroughly with Et_2O (5 × 10 mL), and the combined ether extracts were concentrated ($BzNHCH_2CH_2NH_2$

is insoluble in Et_2O at room temperature). The residue was purified by flash chromatography (9:1 hexanes−EtOAc) to give 57 mg (88%) of **64** as a colorless oil: $R_f = 0.41$ (4:1 hexanes−EtOAc); $[\alpha]^{24}_D$ −20.9, $[\alpha]^{24}_{577}$ −21.7, $[\alpha]^{24}_{546}$ −24.5, $[\alpha]^{24}_{435}$ −44.7, $[\alpha]^{24}_{405}$ −54.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.3$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.36−7.33 (m, 2H), 7.29−7.26 (m, 3H), 5.47 (br s, 1H), 4.65 (d, $J = 6.9$ Hz, 1H), 4.50 (ABq, $J = 12.4$ Hz, 2H), 4.50 (d, $J = 7.1$ Hz, 1H), 3.57 (s, 2H), 3.31 (s, 3H), 3.27 (br s, 1H), 3.07 (s, 3H), 2.31−2.14 (m, 2H), 2.04 (d, $J = 12.1$ Hz, 1H), 1.86−1.73 (m, 3H), 1.65−1.11 (m, 12H), 1.49 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 166.0, 138.4, 132.8, 130.6, 129.6, 128.4, 128.3, 127.4, 127.2, 95.1, 79.5, 75.6, 73.1, 69.7, 55.5, 52.7, 51.6, 47.5, 44.4, 43.3, 38.6, 38.5, 36.4, 34.7, 33.8, 33.4, 32.5, 29.7, 24.3, 22.2, 21.3, 18.8; IR (film) 1727, 1717 cm^{-1}; HRMS (FAB, NBA) *m*/*z* 605.3473 (605.3478 calcd for $C_{37}H_{49}O_7$, MH).

(4*S*,4a*S*,5*R*,6a*S*,8*S*,9*S*,11a*S*,11b*S*)-5-Benzoyloxy-4-(benzyloxymethyl)oxy-8-hydroxy-4-methoxycarbonyl-9,11b-dimethyl-1,2,3,4,4a,5,6,6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalene (65). A solution of **64** (56 mg, 0.093 mmol) and acidic MeOH (4 mL, prepared by adding 2 drops of concentrated aqueous HCl to 5 mL of MeOH) was heated at 70 °C for 45 min. The reaction was cooled to room temperature and partitioned between saturated aqueous $NaHCO_3$ (15 mL) and CH_2Cl_2 (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the crude residue by flash chromatography (17:3 hexanes−EtOAc) afforded 51 mg (98%) of alcohol **65** as a colorless solid, which was recrystallized from hexanes−Et_2O: mp 79−81 °C dec; $R_f = 0.36$ (3:1 hexanes−EtOAc); $[\alpha]^{24}_D$ −64.5, $[\alpha]^{24}_{577}$ −68.0, $[\alpha]^{24}_{546}$ −78.0, $[\alpha]^{24}_{435}$ −136, $[\alpha]^{24}_{405}$ −164 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.3$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 2H), 7.36−7.33 (m, 2H), 7.29−7.27 (m, 3H), 5.45 (br s, 1H), 4.50 (ABq, $J = 12.3$ Hz, 2H), 3.57 (ABq, $J = 9.2$ Hz, 2H), 3.42 (br s, 1H), 3.07 (s, 3H), 2.28−2.23 (m, 2H), 2.04 (d, $J = 12.1$ Hz, 1H), 1.87−1.74 (m, 3H), 1.63−1.22 (m, 13H), 1.49 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 166.0, 138.5, 132.9, 130.6, 129.7, 128.4, 128.3, 127.5, 127.2, 75.6, 74.7, 73.1, 69.6, 53.1, 51.6, 47.5, 44.4, 43.6, 38.6, 37.7, 36.2, 36.0, 34.7, 33.8, 33.4, 29.3, 23.9, 22.0, 21.3, 18.8; IR (film) 3541, 1715 cm^{-1}; HRMS (FAB, NBA) *m*/*z* 561.3204 (561.3216 calcd for $C_{35}H_{45}O_6$, MH).

(4*S*,4a*S*,5*R*,6a*S*,9*S*,11a*S*,11b*S*)-5-Benzoyloxy-4-(benzyloxymethyl)oxy-4-methoxycarbonyl-9,11b-dimethyl-8-oxo-1,2,3,4,4a,5,6,6a,7,8,9,10,11,11b-tetradecahydro-9,11a-methano-11a*H*-cyclohepta[*a*]naphthalene (66). A mixture of Celite (100 mg), 4-Å molecular sieves (40 mg, powdered, activated), pyridinium chlorochromate (32 mg, 0.15 mmol), a portion of alcohol **65** (28 mg, 0.05 mmol), and CH_2Cl_2 (4 mL) was stirred at room temperature for 2.5 h.[74] The resulting suspension was diluted with Et_2O (15 mL) and filtered through a plug of silica gel (1 cm × 5 cm, Et_2O). The filtrate was concentrated, and the residue was purified by flash chromatography (17:3 hexanes−EtOAc) to afford 25 mg (90%) of ketone **66** as a colorless foam: $R_f = 0.43$ (3:1 hexanes−EtOAc); $[\alpha]^{24}_D$ −22.3, $[\alpha]^{24}_{577}$ −23.4, $[\alpha]^{24}_{546}$ −25.5, $[\alpha]^{24}_{435}$ −35.6, $[\alpha]^{24}_{405}$ −36.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, $J = 7.5$ Hz, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.44 (t, $J = 7.7$ Hz, 2H), 7.38−7.34 (m, 2H), 7.31−7.26 (m, 3H), 5.50 (br s, 1H), 4.52 (ABq, $J = 12.2$ Hz, 2H), 3.66 (d, $J = 9.2$ Hz, 1H), 3.53 (d, $J = 9.2$ Hz, 1H), 3.08 (s, 3H), 2.44 (m, 1H), 2.31 (m, 1H), 2.23−2.15 (m, 2H), 2.05−1.95 (m, 3H), 1.87−1.82 (m, 2H), 1.78−1.48 (m, 9H), 1.26 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 176.0, 165.9, 138.3, 133.0, 130.3, 129.6, 128.5, 128.4, 127.5, 127.3, 74.9, 73.1, 69.2, 52.8, 52.2, 51.7, 47.4, 45.3, 44.0, 42.4, 38.8, 36.6, 35.7, 34.7, 33.9, 33.2, 23.3, 20.7, 19.7, 18.7; IR (film) 1726, 1711 cm^{-1}; HRMS (CI, isobutane) *m*/*z* 559.3048 (559.3059 calcd for $C_{35}H_{43}O_6$, MH).

(−)-Scopadulcic acid A (1). Ester **66** (20 mg, 0.036 mmol) was azeotropically dried with benzene (3 × 2 mL), and freshly prepared lithium *n*-propylmercaptide (ca. 0.5 M in HMPA, 0.5 mL) was then added dropwise under Ar at room temperature. The yellow solution was maintained at room temperature for 8 h, cooled to 5 °C, and quenched with 1 M aqueous HCl (1 mL) and H_2O (10 mL). The resulting mixture was extracted with EtOAc (5 × 15 mL), and the combined organic layers were washed with saturated aqueous NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (17:3 → 4:1 hexanes−EtOAc) to provide 14 mg (72%) of the derived carboxylic acid as a colorless solid. It was critical for the success of this reaction to prepare[75] *n*-PrSLi in a Schlenk flask so that excess LiH could be removed by Schlenk filtration.

A flask containing the crude acid (14 mg) and 10% Pd on activated carbon (10 mg) was evacuated and then flushed with H_2 (3 ×). Freshly distilled MeOH (1.4 mL) was added, H_2 was bubbled into the stirring mixture for 2 min, and the reaction was stirred at room temperature under a H_2 atmosphere for 9 h. The mixture was filtered through a plug of silica gel (1 cm × 4 cm, EtOAc), and the filtrate was concentrated to give 12 mg of crude **1** as a colorless solid. Recrystallization from methanol provided 10.5 mg (90%) of analytically pure (−)-scopadulcic acid A **(1)** as colorless prisms: mp 171−173 °C (MeOH); $R_f = 0.67$ (4:1 EtOAc−hexanes); $[\alpha]^{24}_D$ −5.8, $[\alpha]^{24}_{577}$ −5.58, $[\alpha]^{24}_{546}$ −7.5, $[\alpha]^{24}_{435}$ +10.8, $[\alpha]^{24}_{405}$ +32.4 (*c* 0.4, MeOH); $[\Theta]^{24}_{292}$ +8230 (*c* 0.73 mM, MeOH). This sample was identical to an authentic specimen of natural (−)-SDA by ^{1}H NMR, ^{13}C NMR, IR, MS, and TLC comparisons.

Acknowledgment. This research was supported by grants from NIGMS (GM-30859) and through postdoctoral fellowships to M.E.F. (SmithKline Beecham) and J.P.M. (NIH CA-71099). Additional support was provided by Merck, Pfizer, Roche Biosciences, SmithKline Beecham, and Zeneca. We particularly thank Professor David A. Evans for detailed experimental procedures for preparing the (*R*,*R*)-bis(oxazoline) catalyst **13**, Professor Toshimitsu Hayashi for providing a sample of natural (+)-SDA, and Professor Larry Vickery for access to a CD spectrometer. NMR and mass spectra were determined at UCI using instruments acquired with the assistance of shared instrumentation grants from NSF and NIH. We are grateful to Dr. Joseph Ziller for single-crystal X-ray analyses and Dr. John Greaves for mass spectrometric analyses.

Supporting Information Available: Experimental procedures and characterization data for new compounds not described in the Experimental Section and optical rotation data for compounds in the *ent* series (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA990404V