A Unified Total Synthesis of the Immunomodulators (−)-Rapamycin and (−)-27-Demethoxyrapamycin: Construction of the C(21−42) Perimeters

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Abstract: A total synthesis of the potent, naturally occurring immunomodulators (−)-rapamycin (**1**) and (−)-27-demethoxyrapamycin (**2**) has been achieved via a unified, highly convergent synthetic strategy. Both targets were elaborated from common building blocks A−E, the latter available in decagram quantities. Herein we present the construction of the ABC northern perimeters of **1** and **2**. The accompanying paper describes the preparation of the southern perimeter DE segment, triene and deprotection model studies, and completion of the synthetic venture. Notable features of the approach include stereoselective σ-bond constructions of trisubstituted olefins and the union of advanced intermediates via efficient dithiane couplings.

In 1975, researchers at Ayerst Laboratories (Montréal, Canada) reported the discovery of rapamycin (**1**), an antibiotic produced by *Streptomyces hydroscopicus* (NRRL 5491) endemic to Easter Island soil samples.[1] Structure elucidation via degradation and X-ray crystallography revealed a fundamentally new type of macrocycle, a 31-membered ring containing both lactam and lactone linkages,[2] richly adorned with stereochemical and functional elements. Notwithstanding its challenging architecture, rapamycin attracted little interest until 1986, when the isolation of the structurally related immunosuppressant FK506 (**3**)[3] sparked investigations of the immunosuppressive activity of **1**. Rapamycin proved to be a potent immunomodulator and prospective anti-graft-rejection agent.[4,5] In rats, **1** completely suppressed the development of cellular immunity as well as the formation of an IgE-like antibody.[6]

Both rapamycin and FK506 bind to the cytosolic immunophilin FKBP12, a strict requirement for the observed physiological responses.[7] At this point, however, the immunosuppressive mechanisms diverge. The FK506−FKBP12 complex binds calcineurin,[8,9] whereas a different target for the rapamycin−FKBP12 complex has recently been identified and variously designated as mTOR, RAFT and FRAP.[10,11] Whereas the specific roles of **1** and its complexes in signal transduction and immunosuppression remain unclear, it has been established that rapamycin interferes with a Ca^{2+}-independent signaling pathway emanating from the IL-2 receptor.[12]

Whereas preliminary reports indicated that the naturally occurring congener[13] 27-demethoxyrapamycin (**2**) is 10-fold less active than **1** in the mixed lymphocyte response assay, **2** is

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(1) (a) Vézina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721. (b) Sehgal, S. N.; Baker, H.; Vézina, C. *Ibid.* **1975**, *28*, 727. (c) Baker, H.; Sidorowicz, A.; Sehgal, S. N.; Vézina, C. *Ibid.* **1978**, *31*, 539. (d) Singh, K.; Sun, S.; Vézina, C. *Ibid.* **1979**, *32*, 630.

(2) (a) Swindells, D. C. N.; White, P. S.; Findlay, J. A. *Can. J. Chem.* **1978**, *56*, 2491. (b) McAlpine, J. B.; Swanson, S. J.; Jackson, M.; Whittern, D. N. *Ibid.* **1991**, *44*, 688. (c) McAlpine, J. B.; Swanson, S. J.; Jackson, M.; Whittern, D. N. *Ibid.* **1991**, *44*, C-3 (correction). (d) Findlay, J. A.; Radics, L. *Can. J. Chem.* **1980**, *58*, 579. (e) Findlay, J. A.; Radics, L. *Ibid.* **1981**, *59*, 49 (erratum).

(3) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249.

(4) (a) Luo, H.; Chen, H.; Daloze, P.; Chang, J. Y.; St-Louis, G.; Wu, J. *Transplantation* **1992**, *53*, 1071. (b) Henderson, D. J.; Naya, I.; Bundick, R. V.; Smith, G. M.; Schmidt, J. A. *Immunology* **1991**, *73*, 316. (c) Morris, R. E. *Transplant. Proc.* **1991**, *23*, 2722. (d) Sigal, N. H.; Lin, C. S.; Siekierka, J. J. *Ibid.* **1991**, *23* (Suppl. 2), 1.

(5) Zheng, X. X.; Strom, T. B.; Steele, A. W. *Transplantation* **1994**, *58*, 87.

(6) Martel, R. R.; Klicius, J.; Galet, S. *Can. J. Physiol. Pharmacol.* **1977**, *55*, 48.

(7) (a) Bierer, B. E.; Mattila, P. S.; Standaert, R. F.; Herzenberg, L. A.; Burakoff, G.; Crabtree, G.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9231. (b) Somers, P. K.; Wandless, T. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8045.

(8) (a) Liu, J. *Immunol. Today* **1993**, *14*, 290. (b) Schreiber, S. L.; Crabtree, G. R. *Ibid.* **1992**, *13*, 136. (c) Fruman, D. A.; Klee, C. B.; Bierer, B. E.; Burakoff, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 3686. (d) Liu, J.; Albers, M. W.; Wandless, T. J.; Luan, S.; Alberg, D. G.; Belshaw, P. J.; Cohen, P.; MacKintosh, C.; Klee, C. B.; Schreiber, S. L. *Biochemistry* **1992**, *31*, 3896. (e) Liu, J.; Farmer, J. D., Jr.; Lane, W. S.; Friedman, J.; Weissman, I.; Schreiber, S. L. *Cell* **1991**, *66*, 807.

(9) Griffith, J. P.; Kim, J. L.; Kim, E. E.; Sintchak, M. D.; Thomson, J. A.; Fitzgibbon, M. J.; Fleming, M. A.; Caron, P. R.; Hsiao, K.; Navia, M. *Cell* **1995**, *82*, 507.

(10) (a) Cafferkey, R.; Young, P. R.; McLaughlin, M. M.; Bergsma, D. J.; Koltin, Y.; Sathe, G. M.; Faucette, L.; Eng, W.-K.; Johnson, R. K.; Livi, G. P. *Mol. Cell. Biol.* **1993**, *13*, 6012. (b) Brown, E. J.; Albers, M. W.; Shin, T. B.; Ichikawa, K.; Keith, C. T.; Lane, W. S.; Schreiber, S. L. *Nature* **1994**, *369*, 756. (c) Sabatini, D. M.; Erdjument-Bromage, H.; Lui, M.; Tempst, P.; Snyder, S. H. *Cell* **1994**, *78*, 35. (d) Chen, Y.; Chen, H.; Rhoad, A. E.; Warner, L.; Caggiano, T. J.; Failli, A.; Zhang, H.; Hsiao, C.-L.; Nakanishi, K.; Molnar-Kimber, K. L. *Biochem. Biophys. Res. Commun.* **1994**, *203*, 1. (e) Chiu, M. I.; Katz, H.; Berlin, V. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 12574. (f) Sabers, C. J.; Martin, M. M.; Brunn, G. J.; Williams, J. M.; Dumont, F. J.; Wiederrecht, G.; Abraham, R. T. *J. Biol. Chem.* **1995**, *270*, 815.

(11) For the X-ray structure of the rapamycin−FKBP12 complex interacting with the binding domain of human FRAP, see: Choi, J.; Chen, J.; Schreiber, S. L.; Clardy, J. *Science* **1996**, *273*, 239.

(12) Schreiber, S. L.; Albers, M. W.; Brown, E. J. *Acc. Chem. Res.* **1993**, *26*, 412.

(13) Other natural congeners of **1** include (a) 27-desmethylrapamycin: Ondeyka, J.; Hensens, O.; Liesch, J. U.S. Patent 5,091,389, 1992. (b) 16,27-bis(desmethyl)rapamycin: Byrne, K.; Goegelman, R. T.; Hensens, O.; Kaplan, L.; Liesch, J. M. U.S. Patent 5,093,338, 1992. (c) 2-norrapamycin: Chan, J. A.; Gerber, R.; Johnson, R. K.; Luengo, J. I. U.S. Patent 5,162,333, May 26, 1994.

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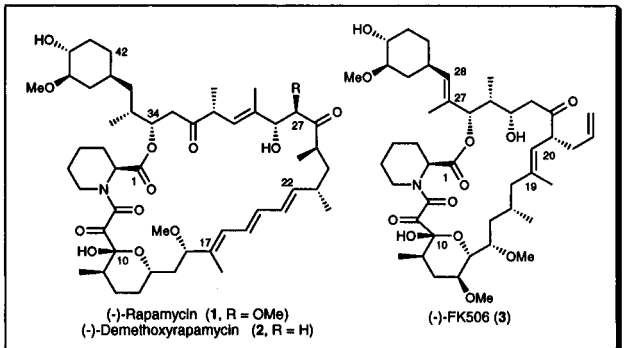


Immunosuppressive macrolides rapamycin (**1**), demethoxyrapamycin (**2**), and FK506 (**3**).

comparable in potency to the clinically important immunomodulator cyclosporin A.[14] Moreover, the assigned structure of **2** was derived solely from NMR comparison with **1**. These considerations prompted us to design a single flexible strategy for the construction of both **1** and **2**.

The unique structure and therapeutic potential[15] of rapamycin have stimulated intensive activity within the synthetic community.[16] Three other laboratories have completed total syntheses of **1**, each representing a significant achievement.[17−19] Here and in the accompanying paper, we describe in full the design and execution of a unified synthetic strategy for (−)-rapamycin and (−)-27-demethoxyrapamycin.[20] Our convergent and flexible approach should also provide access to rationally designed analogs of **1** and **2**.

Initial Retrosynthetic Analysis of (−)-Rapamycin. In planning the synthesis of **1**, we wished to extend our earlier work on σ-bond olefin construction[21] and dithiane coupling reactions, the latter of considerable value both for the generation of protected aldol linkages and as a tactic for the union of major synthetic building blocks. Through the investigation of these key reactions in the rapamycin context, we further developed several themes which have served to unite the individual projects within our immunosuppressant program, including most recently the syntheses of FK506[22] and discodermolide.[23]

The selective generation of *E*- and *Z*-disubstitued olefins in complex targets has traditionally been achieved via π-bond constructions employing the Wittig reaction and its Horner−Wadsworth−Emmons variant.[24] This approach is not generally suitable for trisubstituted olefins, as α,α-disubstituted ylides often furnish unacceptable isomer mixtures. Accordingly, we were eager to explore the applicability of σ-bond constructions[21] to the C(29,30) trisubstituted olefin of rapamycin. We had successfully installed both the C(19,20) and C(27,28) trisubstituted olefins of FK506 in this fashion.[22]

Although couplings of 1,3-dithianes with electrophiles have been exploited in the total syntheses of many natural products,[25−28] most examples have involved relatively simple reactant structures.[29] In contrast with the parent molecule, which readily undergoes deprotonation with *n*-butyllithium, metalation of substituted dithianes has usually required stronger bases,[30] solvent additives, and a myriad of time and temperature regimes. Moreover, the behavior of highly oxygenated d^3 dithiane anions is often capricious,[31,32] consistent with their increased kinetic basicity.[33] In the course of our immunosuppressant synthetic studies, we have demonstrated the generality of the *t*-BuLi−10% HMPA/THF protocol for the rapid metalation of highly functionalized 2-alkyl-1,3-dithianes,[34] as well as their efficient union with structurally complex epoxides, iodo ethers, and aldehydes.[35]

Beyond these two general objectives, our primary concerns a priori included (a) stereocontrolled introduction of the C(17−22) all *trans*-triene, (b) the lability of the C(16) allylic methoxy group,[36] (c) potential β-elimination of the pipecolinate moiety

(14) (a) Sehgal, S. N.; Baker, H.; Eng, C.; Singh, K.; Vézina, C. *J. Antibiot.* **1983**, *36*, 351. (b) Findlay, J. A.; Liu, J. S.; Burnell, D. J.; Nakashima, T. T. *Can. J. Chem.* **1982**, *60*, 2046. (c) Caufield, C. E.; Musser, J. H. *Annu. Rep. Med. Chem.* **1989**, *25*, 195.

(15) Sehgal, S. N.; Molnar-Kimber, K.; Ocain, T. D.; Weichman, B. M. *Med. Res. Rev.* **1994**, *14*, 1.

(16) Synthetic approaches to **1**: (a) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643. (b) Eshelman, J. E.; Epps, J. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 749. (c) Sin, N.; Kallmerten, J. *Ibid.* **1993**, *34*, 753. (d) Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182. (e) Rao, A. V. R.; Desibhatla, V. *Tetrahedron Lett.* **1993**, *34*, 7111. (f) Ny, S.; Kallmerten, J. *Ibid.* **1993**, *34*, 753. (g) Pattenden, G.; Tankard, M.; Cherry, P. C. *Ibid.* **1993**, *34*, 2677. (h) Anderson, J. C.; Ley, S. V.; Marsden, S. P. *Ibid.* **1994**, *35*, 2087. (i) Kouklousky, C.; Ley, S. V.; Marsden, S. P. *Ibid.* **1994**, *35*, 2091. (j) Ley, S. V.; Norman, J.; Pinel, C. *Ibid.* **1994**, *35*, 2095. (k) Norley, M. C.; Kocienski, P. J.; Faller, A. *Synlett* **1994**, 77. (l) Ley, S. V.; Kouklovsky, C. *Tetrahedron* **1994**, *50*, 835. (m) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285.

(17) (a) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318. (b) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. (c) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617. (d) Nicolaou, K. C.; Bertinato, P.; Piscopio, A. D.; Chakraborty, T. K.; Minowa, N. *Ibid.* **1993**, 619.

(18) (a) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906. (b) Meyer, S. D.; Miwa, T.; Nakatsuka, M.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5058. (c) Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *Ibid.* **1992**, *57*, 5060.

(19) (a) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345. (b) Hayward, C. M.; Fisher, M. J.; Yohannes, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 3989. (c) Horvath, R. F.; Linde, R. G., II; Hayward, C. M.; Joglar, J.; Yohannes, D.; Danishefsky, S. J. *Ibid.* **1993**, *34*, 3993. (d) Fisher, M. J.; Myers, C. D.; Joglar, J.; Chen, S.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5826. (e) Chen, S.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *Ibid.* **1991**, *56*, 5834.

(20) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 5407.

(21) Smith, A. B., III; Hale, K. J.; Laakso, L. M.; Chen, K.; Riéra, A. *Tetrahedron Lett.* **1989**, *30*, 6963.

(22) For leading references see: Smith, A. B., III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett.* **1994**, *35*, 4271.

(23) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011.

(24) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948.

(25) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613.

(26) Corey, E. J.; Pan, B.-C.; Hua, D. H.; Deardorff, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816.

(27) Park, P.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205.

(28) (a) Mori, Y.; Asai, M.; Furukawa, H. *Heterocycles* **1992**, *34*, 1281. Also see: (b) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15.

(29) (a) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S. *Angew. Chem., Int Ed. Engl.* **1994**, *33*, 2190. (b) Egbertson, M.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 11. (c) Barrett, A. G. M.; Capps, N. K. *Tetrahedron Lett.* **1986**, *27*, 5571. (d) Redlich, H.; Francke, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 630.

(30) Lipshutz, B. H.; Garcia, E. *Tetrahedron Lett.* **1990**, *31*, 7261.

(31) Oppong, I.; Pauls, H. W.; Liang, D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1241.

(32) Konishita, M.; Taniguchi, M.; Morioka, M.; Takami, H.; Mizusawa, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2147.

(33) (a) De Brabander, J.; Vandewalle, M. *Synthesis* **1994**, 855. (b) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289.

(34) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949.

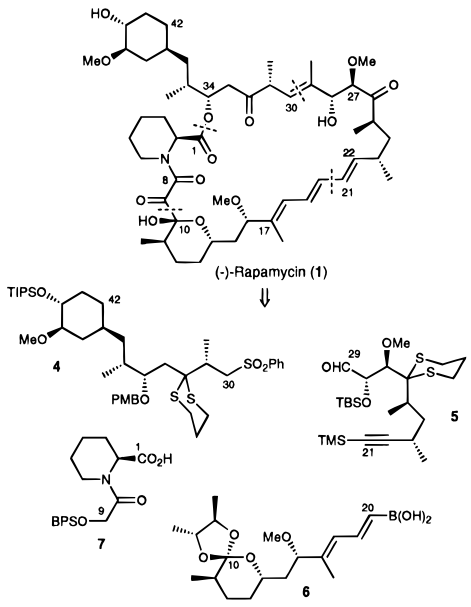
(35) For a related coupling of a dithiane anion with a cyclic sulfate, see: Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**, *118*, 3059.

(36) (a) Grinfeld, A. A.; Caufield, C. E.; Schiksnis, R. A.; Mattes, J. F.; Chan, K. W. *Tetrahedron Lett.* **1994**, *35*, 6835. (b) Luengo, J. I.; Konialian-Beck, A.; Rozamus, L. W.; Holt, D. A. *J. Org. Chem.* **1994**, *59*, 6512. (c) Luengo, J. I.; Yamashita, D. S.; Dunnington, D.; Konialian-Beck, A.; Rozamus, L. W.; Yen, H.-K.; Bossard, M. J.; Levy, M. A.; Hand, A.; Newmann-Tarr, T.; Badger, A.; Faucette, L.; Johnson, R. K.; D'Alessio, K.; Porter, T.; Shu, A. Y. L.; Heys, R.; Choi, J.; Kongsaeree, P.; Clardy, J.; Holt, D. A. *Chem. Biol.* **1995**, *2*, 471.

in advanced intermediates,[37] (d) installation of the C(8−10) tricarbonyl region, common to both rapamycin and FK506,[38] (e) efficient union of the major subtargets, and (f) macrocyclization of the 31-membered ring. At the outset of our work, essentially nothing was known about the relevant chemistry of rapamycin.

These considerations outlined above guided our initial retrosynthetic analysis of the rapamycin problem (Scheme 1).

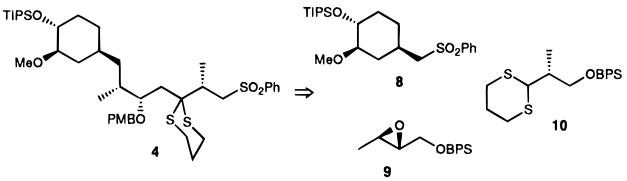
Scheme 1



Disconnection of the macrocyclic lactone followed by excision of the C(1,9) pipecolinate **7** generated fragments **4**, **5**, and **6**. In the synthetic direction, *σ*-bond construction of the C(29,30) trisubstituted olefin would follow addition of the C(30−42) sulfone **4** to the C(21−29) aldehyde **5**. The triene array would arise via palladium-catalyzed Suzuki coupling of **5** with dienyl boronate **6**. Installation of the C(8−10) tricarbonyl region and macrolactonization would then furnish the natural product.

The C(30−42) sulfone **4** would in turn derive from components **8**−**10** (Scheme 2). Sulfone **8** was employed in our recent

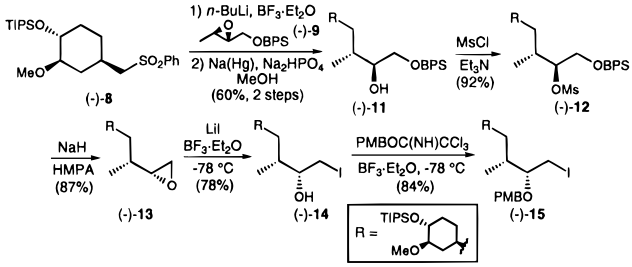
Scheme 2



formal synthesis of FK506.[22] The butene oxide derivative **9** (90% ee) was also prepared earlier, via Sharpless asymmetric epoxidation of (*E*)-crotyl alcohol and in situ derivatization.[39] We envisioned the synthesis of dithiane **10** from methyl *(R)*-3-hydroxy-2-methylpropionate *(vide infra)*.

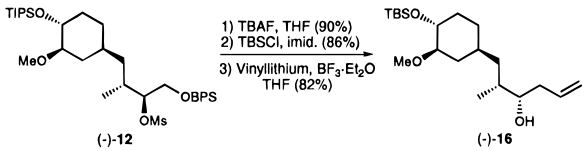
Studies Directed toward the C(30−42) Subunit 4. As our point of departure, sulfone (−)-**8** and epoxide (−)-**9** were coupled by treatment of the admixed components with *n*-BuLi followed by a stoichiometric amount of boron trifluoride etherate (THF, −78 °C; Scheme 3). Desulfonylation with 6% sodium

Scheme 3



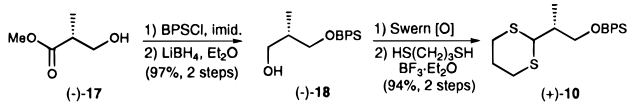
amalgam in buffered methanol then gave the desired alcohol (−)-**11** in 60% yield. Mesylation allowed for oxirane formation upon selective removal of the *tert*-butyldiphenylsilyl (BPS) protecting group in **12** (NaH, anhydrous HMPA).[40] Exposure of epoxide (−)-**13** to LiI and $BF_3{\cdot}Et_2O$ provided iodohydrin (−)-**14**, which was protected as PMB ether (−)-**15** via the trichloroacetimidate method of Bundle.[41] The stereochemistry of (−)-**15** was confirmed by conversion of (−)-**12** to homoallylic alcohol (−)-**16** (Scheme 4), the latter prepared earlier by the Merck group from a degradation product of natural rapamycin.[42]

Scheme 4



The preparation of dithiane **10** began with the conversion of methyl *(R)*-3-hydroxy-2-methylpropionate [(−)-**17**; 97% ee] to the known alcohol (−)-**18**[43,44] (Scheme 5). Swern oxidation followed by dithioacetalization of the crude aldehyde furnished dithiane (+)-**10** in 94% yield for the two steps.

Scheme 5



Invariably we have found that treatment with *t*-BuLi in 10% HMPA/THF at −78 °C is the optimum protocol for generation of 2-substituted dithiane anions *(vide infra)*.[34,45] We routinely add the precooled electrophile immediately thereafter because prolonged stirring (ca. 1 h) of the anion solutions at −78 °C results in loss of reactivity. Kinoshita et al. observed similar decomposition in their work directed toward the total synthesis of amphotericin B.[32] As expected, alkylation of the 2-lithio

(37) Steffan, R. J.; Kearney, R. M.; Hu, D. C.; Failli, A. A.; Skotnicki, J. S.; Schiksnis, R. A.; Mattes, J. F.; Chan, K. W.; Caufield, C. E. *Tetrahedron Lett.* **1993**, *34*, 3699.

(38) (a) Linde, R. G., II; Jeronic, L. O.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 2534. (b) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M.; Hedgecock, C. J. R. *Tetrahedron Lett.* **1993**, *34*, 167. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(39) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(40) Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.

(41) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

(42) (a) Goulet, M. T.; Boger, J. *Tetrahedron Lett.* **1991**, *32*, 6454 (erratum). (b) Goulet, M. T.; Hodkey, D. W. *Ibid.* **1991**, *32*, 4627.

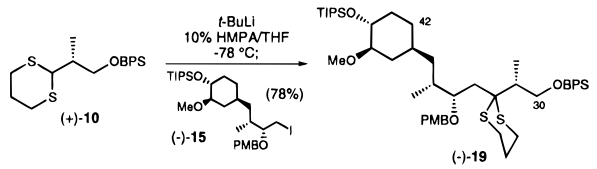
(43) Brandes, E.; Grieco, P. A.; Garner, P. *J. Chem. Soc., Chem. Commun.* **1988**, 500.

(44) Ley, S. V.; Anthony, N. J.; Armstrong, A.; Brasca, M. G.; Clarke, T.; Culshaw, D.; Greck, C.; Grice, P.; Jones, A. B.; Lygo, B.; Madin, A.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1989**, *45*, 7161.

(45) For an insightful discussion of the ion pair structures of 2-lithio-1,3-dithianes in THF and HMPA/THF, see: Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869.

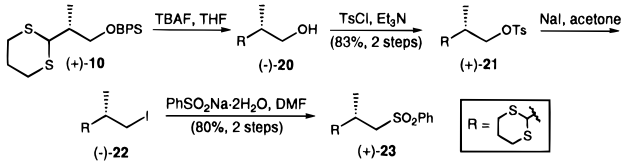
derivative of dithiane (+)-**10** with iodohydrin (−)-**15** uneventfully afforded the C(30-42) fragment **19** in 78% yield (Scheme 6).

Scheme 6



All that remained for completion of subunit **4** was installation of the C(30) sulfone moiety. To gain experience with the requisite transformations, we converted dithiane (+)-**10** to iodide (−)-**22** via alcohol (−)-**20** and tosylate (+)-**21** (Scheme 7).

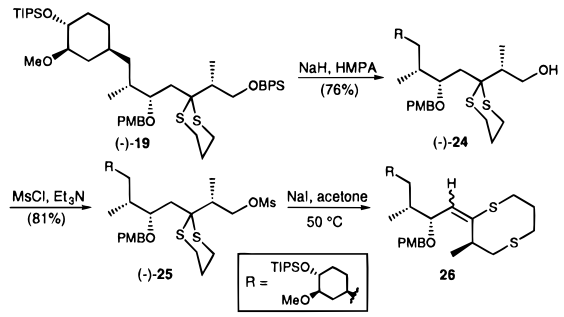
Scheme 7



Displacement with sodium benzenesulfinate provided sulfone (+)-**23** in excellent yield, accompanied by a small quantity of the corresponding sulfinate diastereomers. Noteworthy here is the preparation of **23** in eight steps and 60−65% overall yield from commercially available methyl *(R)*-3-hydroxy-2-methylpropionate (**17**; Scheme 5), on a 50-g scale with only two chromatographic purifications.

Extension of this sequence to the more advanced C(30−42) intermediate entailed selective removal of the BPS group[40] in **19** followed by mesylation of the resultant alcohol (−)-**24** (62% overall yield; Scheme 8). However, standard Finkelstein

Scheme 8

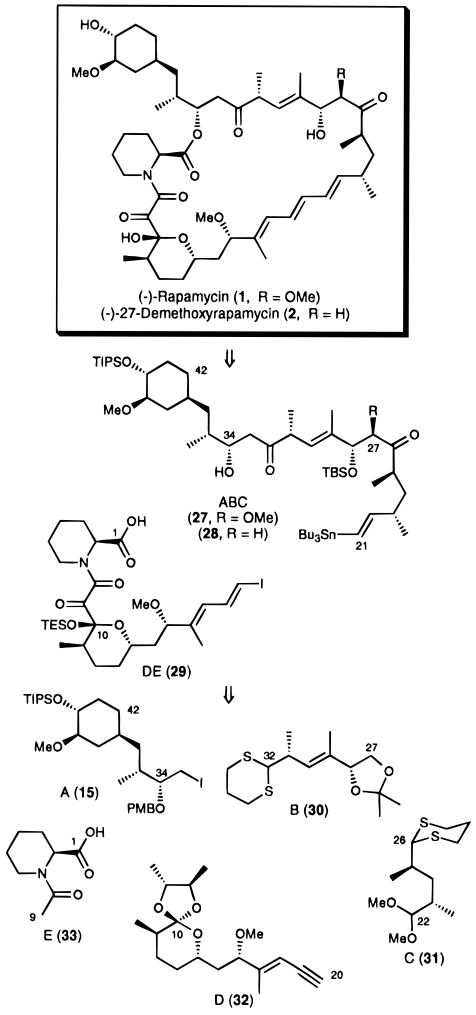


treatment of mesylate (−)-**25** failed to generate the desired iodide. Analysis of the crude reaction mixture via ^{1}H NMR instead suggested formation of the unstable ring-expansion product **26**.

Similar rearrangements of 2,2-disubstituted 1,3-dithianes bearing proximal leaving groups have been observed previously[46] and attributed to the Thorpe−Ingold effect,[47] reflecting steric congestion at C(2) of the dithiane.[48] Our efforts to circumvent this problem by direct conversion of alcohol **24** to the bromide with dibromotriphenylphosphorane were likewise unsuccessful (not shown). Ultimately, the observation that mesylate **25** also rearranged upon exposure to sodium benzenesulfinate or upon heating brought to an end this line of investigation. *Significant differences in the reactivities of pendant functional groups in 2-monosubstituted 1,3-dithianes vis-á-vis related 2,2-disubstituted derivatives, perhaps induced by conformational changes, resurfaced throughout this synthetic investigation (vide infra).*

Second-Generation Retrosynthetic Analysis of Rapamycin and Demethoxyrapamycin. At this juncture we revised our original synthetic plan in order to circumvent the inaccessible sulfonyl dithiane **4**, retaining insofar as possible the effective chemistry developed in our initial studies. To this end we planned to couple the available sulfonyl dithiane (+)-**23** with L-isopropylidene glyceraldehyde, setting the stage for σ-bond construction of the C(29,30) olefin at an earlier point in the synthesis. This change in strategy, with retention of the lactone and C(20,21) disconnections, led to subtargets A, B, and C (Scheme 9). With the advent of the Golec procedure for

Scheme 9



tricarbonyl formation,[38b] we could also employ pipecolinate **33**, rather than a C(9) oxygenated derivative (**7**), as the fifth building block. For simplicity, we chose to protect C(22) in fragment

(46) (a) Marshall, J. A.; Roebke, H. *J. Org. Chem.* **1969**, *34*, 4188. (b) Nickon, A.; Rodriguez, A. D.; Shirhatti, V.; Ganguly, R. *Ibid.* **1985**, *50*, 4218. See also: (c) Seebach, D.; Jones, N. R.; Corey, E. J. *Ibid.* **1968**, *33*, 300. (d) Tsai, Y.-M.; Cherng, C.-D. *Tetrahedron Lett.* **1991**, *32*, 3515. (e) Li, W. L.; Mao, J.; Li, Y.; Li, Y. *OPPI Briefs* **1994**, *26*, 445.

(47) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *Ibid.* **1921**, *119*, 305. (c) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429. (d) Cauwberghs, S.; DeClercq, P.; Tinant, B.; DeClercq, J. P. *Ibid.* **1988**, *29*, 2493.

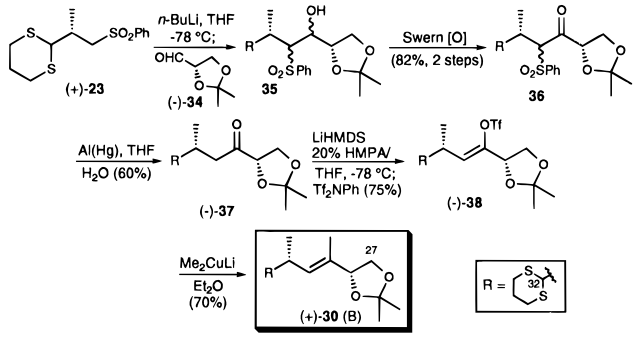
(48) Davey, A. E.; Parsons, A. F.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1853. See also: Keese, R.; Meyer, M. *Tetrahedron* **1993**, *49*, 2055.

C as a dimethyl acetal, deferring elaboration to a suitable Stille coupling partner until the endgame. We also took advantage of this opportunity to expand the scope of our effort, previously focused solely on rapamycin (**1**), by developing a unified strategy for the construction of both **1** and the 27-demethoxy congener **2**. The methoxy and demethoxy series would be differentiated via coupling of suitable electrophiles with dithiane C.

From the retrosynthetic perspective (Scheme 9), we envisioned the elaboration of **1** and **2** from the fully functionalized northern-perimeter ABC fragments **27** and **28** and a common southern-perimeter DE element **29**, all derived in turn from the building blocks A−E (**15**, **30**−**33**).[49] This modular approach would afford considerable flexibility in optimizing the subunit coupling sequence. Rapid conversion of the ABC and DE subtargets to the natural products would require minimal functional group manipulations, with similar endgame chemistry for both **1** and **2**. Final assembly of the macrocycles could in principle be effected via intermolecular acylation at C(34) and intramolecular Pd(0)-catalyzed Stille coupling, or alternatively via initial formation of the triene seco acid followed by macrolactonization, without major modification of the subtargets.

Stereocontrolled *σ*-Bond Olefin Construction: Assembly of Fragment B (30). With subtarget A [(−)-**15**] in hand from our first-generation investigations, we next undertook the synthesis of fragment B (**30**) (Scheme 10), exploiting the

Scheme 10

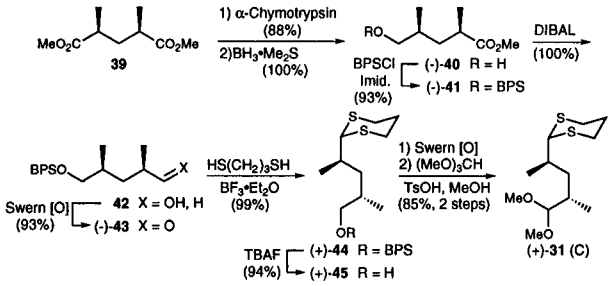


stereocontrolled *σ*-bond construction of olefins which we also employed in our FK506 synthesis.[22] α-Lithiation of sulfone (+)-**23** (cf. Scheme 7) and addition to isopropylidene L-glyceraldehyde (**34**)[50] afforded the diastereomeric *β*-hydroxy sulfones **35**, which furnished a single ketone (−)-**37** after oxidation and desulfonylation.

We anticipated that the C(29,30) trisubstituted olefin could be installed via coupling of the appropriate vinyl triflate with lithium dimethyl cuprate.[51,52] To our surprise, treatment of ketone **37** with LDA in 10% HMPA/THF, under the conditions utilized to great advantage in the FK506 work,[22,53] generated exclusively the undesired enolate regioisomer. After considerable experimentation, the requisite (*Z*)-enolate was secured by slow addition of **37** to a solution of lithium bis(trimethylsilyl)-amide (LiHMDS) in 20% HMPA/THF at −78 °C; trapping with *N*-phenyltrifluoromethanesulfonimide[54] and methylation of the resultant vinyl triflate (−)-**38** (Me_2CuLi, Et_2O, 0 °C) gave the C(27−32) B-fragment (+)-**30** in 70% yield. Only the *Z* isomer was detected by ^1H NMR analysis.

Construction of Subunit C (31). The synthesis of **31**, the C(22−26) C fragment, began with the enzymatic desymmetrization of meso diester **39** (Scheme 11).[55] Thus, hydrolysis with

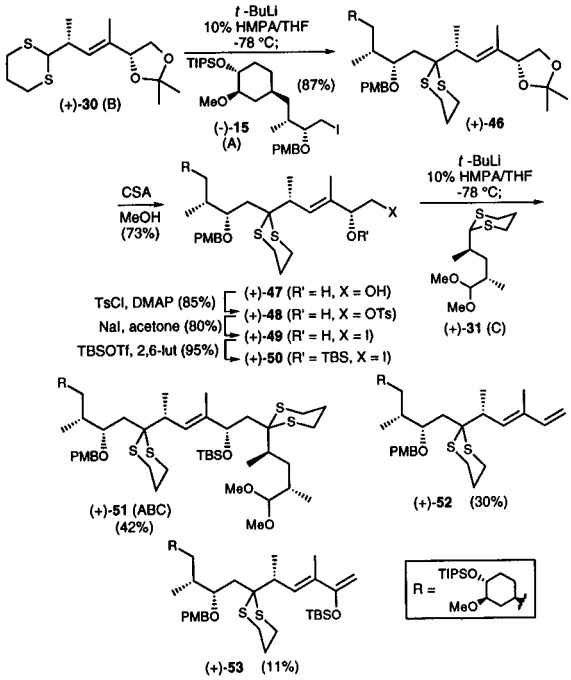
Scheme 11



α-chymotrypsin via a modified procedure of Tamm provided the half acid in 88% yield and 94% ee, and carboxyl reduction with borane methyl sulfide[56] cleanly afforded the primary alcohol (−)-**40**. Following protection as the BPS ether (−)-**41**, the ester was converted to the corresponding aldehyde (−)-**43** via DIBAL reduction and Swern oxidation of alcohol **42** (86% yield, three steps). Interestingly, **42** displayed negligible optical rotation. Exposure of **43** to 1,3-propanedithiol and boron trifluoride etherate then furnished dithiane (+)-**44** (99%). Desilylation to alcohol (+)-**45** (94% yield), Swern oxidation, and dimethyl acetal formation (85%, two steps) generated the C-fragment (+)-**31**.

Fragment Coupling for Demethoxyrapamycin: A + B → AB + C → ABC. Confident in our ability to prepare large quantities of the three subtargets, we began to investigate the assembly of the demethoxyrapamycin backbone. Union of the A and B-fragments entailed metalation of dithiane (+)-**30** with *t*-BuLi and alkylation with precooled iodide (−)-**15** (10% HMPA/THF, −78 °C), affording (+)-**46** in 87% yield (Scheme 12). Acetonide hydrolysis and selective tosylation of the

Scheme 12



primary alcohol gave (+)-**48**; the derived iodohydrin (+)-**49**

(49) (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leahy, J. W.; Leazer, J. L., Jr.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1994**, *35*, 4907. (b) Smith, A. B., III; Maleczka, R. E., Jr.; Leazer, J. L., Jr.; Leahy, J. W.; McCauley, J. A.; Condon, S. M. *Ibid.* **1994**, *35*, 4911.

(50) (a) MaloneyHuss, K. E. *Synth. Commun.* **1985**, *15*, 273. (b) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1993**, *72*, 1.

(51) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313.

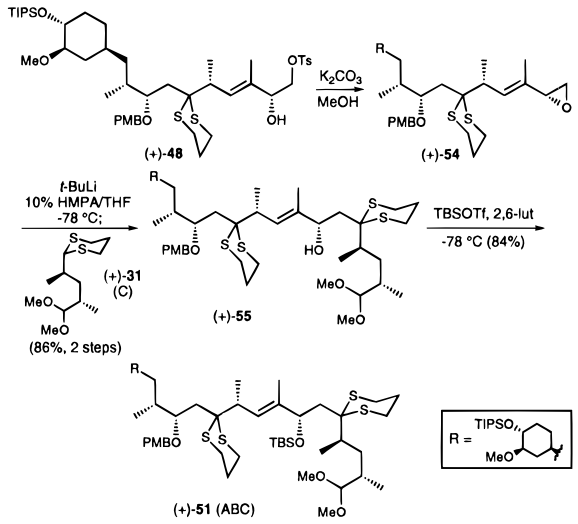
(52) Synthetic applications of aryl and vinyl triflates have been recently reviewed: Ritter, K. *Synthesis* **1993**, 735.

(53) Chen, K. Ph.D. Thesis, University of Pennsylvania, 1991.

was then smoothly protected as the TBS ether (+)-**50**. Lithiation of the C-subunit dithiane **31** and alkylation with the AB iodide **50** generated a three-component mixture in good yield (ca. 80%). The desired ABC segment (+)-**51** predominated in all of our experiments, but formation of the elimination products (+)-**52** and (+)-**53** in significant amounts precluded further development of this route.

We turned instead to the epoxide (+)-**54**, available quantitatively from hydroxy tosylate **48** (Scheme 13). The very acid-

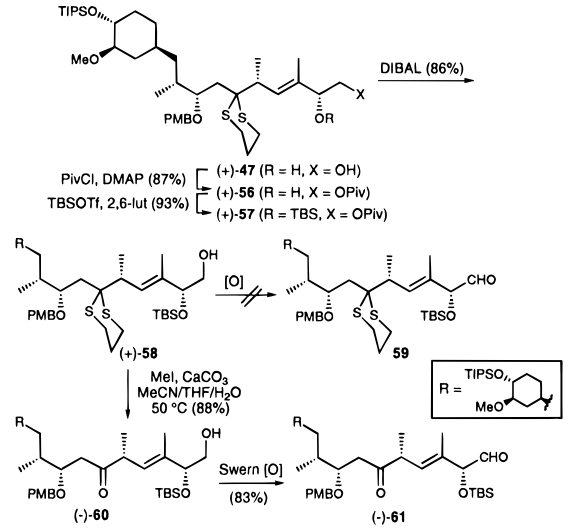
Scheme 13



sensitive epoxide was used without purification. Coupling with the lithio derivative of dithiane (+)-**31** (*t*-BuLi, 10% HMPA/THF) and silylation afforded the advanced ABC intermediate (+)-**51**, isolated in 72% yield overall from **48**. Completion of the demethoxyrapamycin C(21−42) backbone (i.e., **28**) merely entailed installation of the vinyl stannane moiety *(vide infra)*.

An Initial Approach to the Rapamycin AB Aldehyde 59. In seeking to extend the successful strategy employed for the 27-demethoxy intermediate (i.e., A + B → AB + C → ABC) to the corresponding segment of rapamycin, we planned to establish the C(27) stereocenter by adding the lithio derivative of dithiane (+)-**31** to AB aldehyde **59** (Scheme 14). The

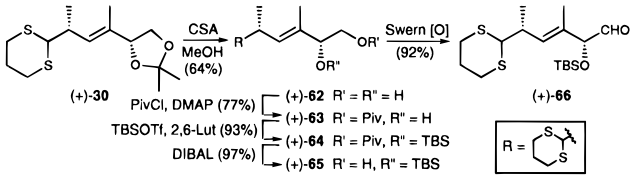
Scheme 14



aldehyde in turn was expected to derive from diol **47** via standard manipulations, whereas the requisite β-configuration of the C(27) hydroxyl was both predicted by Felkin−Anh analysis[57] and supported by literature precedent for dithiane additions to D-isopropylideneglyceraldehyde *(vide infra)*.[58] Selective protection of **47** as pivaloate (+)-**56** followed by silylation and reduction of the ester in (+)-**57** readily afforded primary alcohol (+)-**58**. Unfortunately, a variety of oxidation protocols all failed to provide aldehyde **59**. Suspecting that an unfavorable conformation imparted by the 2,2-disubstituted 1,3-dithiane might be responsible, we unmasked the C(34) ketone by exposure of **58** to MeI in 4:1:1 MeCN/THF/H_2O.[59] In support of our hypothesis, keto alcohol (−)-**60** underwent facile Swern oxidation to aldehyde (−)-**61**. However, coupling of dithiane (+)-**31** with **61** not unexpectedly furnished a complex mixture of products (not shown).

An Alternative Coupling Sequence for 1: B + C → BC + A → ABC. The flexibility of our synthetic scheme allowed for the ready pursuit of an alternative strategy, involving initial union of fragments B and C and subsequent alkylation with subunit A. In this approach the C(27) hydroxyl would be installed via the B−C coupling step; the reduced complexity of the latter products (vis-á-vis ABC intermediates) was expected to facilitate stereochemical analysis. Preliminary investigations began with the conversion of (+)-**30** (B) to a suitable electrophile, aldehyde **66** (Scheme 15). By analogy

Scheme 15



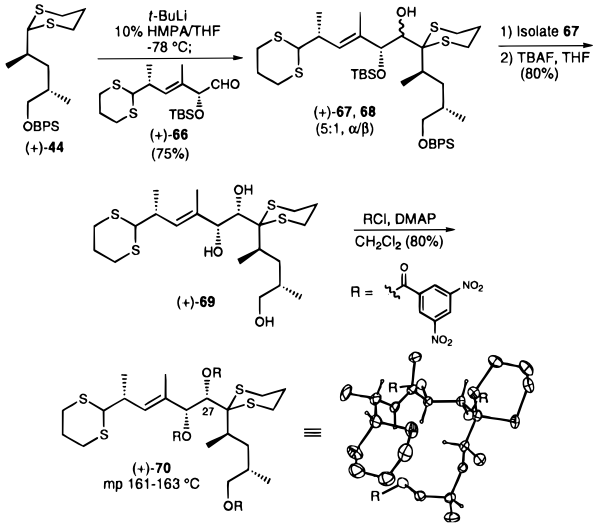
with the attempted preparation of aldehyde **59**, the acetonide moiety in **30** was hydrolyzed and the resultant diol (+)-**62** selectively protected as pivaloate (+)-**63**. A minor bispivaloate by-product (5−15%) could be reconverted to **62** with DIBAL. Silylation of **63** and DIBAL reduction of (+)-**64** then provided alcohol (+)-**65**. Under Swern conditions **65** uneventfully furnished aldehyde (+)-**66**, providing further support for the contention that the unsuccessful oxidation of alcohol **58** was specifically attributable to the 2,2-disubstituted dithiane moiety, and not simply to the presence of sulfur. Single-crystal X-ray analysis confirmed the stereochemistry and olefin geometry of (+)-**66**.[49a]

The reaction of aldehyde **66** with the lithio derivative of dithiane **44** was complicated by competitive proton transfer from the 1,3-dithiane moiety in **66**. This problem was overcome by addition of the precooled aldehyde to 5 equiv of preformed dithiane anion at −78 °C; a 5:1 mixture of C(27) epimers (+)-**67** and **68** was isolated in 75% yield, with 76% recovery of unreacted **44** (Scheme 16). The Felkin−Anh model,[57] with the α-carbon−oxygen bond orthogonal to the carbonyl group, indicated that the requisite *(R)*-alcohol should predominate *(vide infra)*.

For elucidation of the C(27) stereochemistry, we recognized that comparison of NMR coupling constants would be inconclusive. Mosher analysis of hindered alcohols can likewise be

(54) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(55) Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501.
(56) Seebach, D.; Maestro, M. A.; Sefkow, M.; Neidlein, A.; Sternfeld, F.; Adam, G.; Sommerfeld, T. *Helv. Chim. Acta* **1991**, *74*, 2112.
(57) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (c) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(58) David, S.; Estramareix, B.; Fischer, J.-C.; Thérisod, M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2131.
(59) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.

Scheme 16



problematic;[60] moreover, generation of the diastereomeric Mosher esters was not straightforward.[61] These considerations prompted us to prepare a crystalline derivative; the major epimer **67** was thus converted to tris(3,5-dinitrobenzoate) (+)-**70** via triol (+)-**69** (Scheme 16). X-ray analysis of (+)-**70** revealed that the major product was, in fact, the undesired *(S)*-alcohol.

Stereoselectivity of Dithiane Additions to Aldehyde 66. Preferential formation of the α-epimer (+)-**67** is consistent with the Felkin−Anh model[57] only if the vinyl moiety is oriented as the large group (conformers I and II, Figure 1). We had

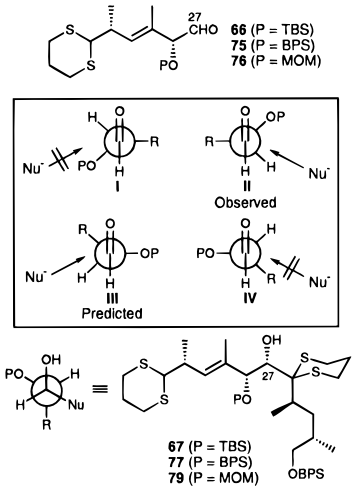


Figure 1. Felkin−Anh analysis of dithiane additions to C(27) aldehydes.

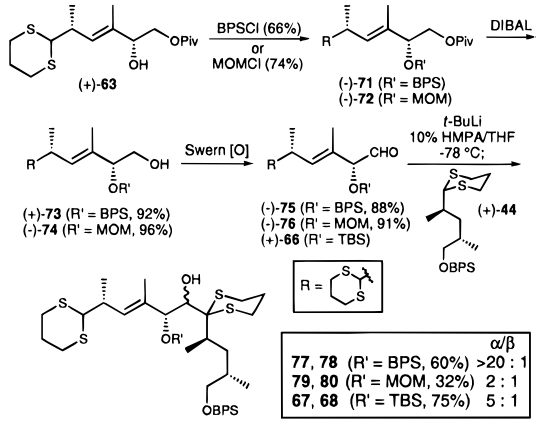
anticipated that both steric and stereoelectronic interactions involving the OTBS group would control the stereochemistry of addition, as illustrated in conformers III and IV.[62] Variation of the α-hydroxyl protecting group did yield some interesting results (Scheme 17). The very bulky *tert*-butyldiphenylsilyl (BPS) moiety caused a marked increase in selectivity: only the undesired epimer (+)-**77**[63] was detected! Whereas we expected a larger OR group to give predominantly the *β*-alcohol via conformer III, the observed effect was just the opposite.

(60) (a) Kusumi, T.; Fujita, Y.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2923. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(61) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(62) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

Scheme 17



Apparently, the bulkier OBPS moiety led to enhanced discrimination between conformers I and II, with the vinyl side chain perpendicular to the carbonyl. This hypothesis suggested that a smaller protecting group would result in diminished α-selectivity. Indeed, coupling of dithiane **44** with the MOM ether **76** furnished a 2:1 mixture of **79** and **80**, albeit in low yield.[64]

We also determined the X-ray structure of aldehyde **66** (Figure 2), which revealed that the solid-state conformation most

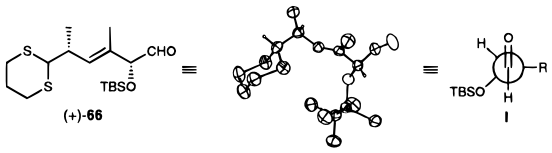
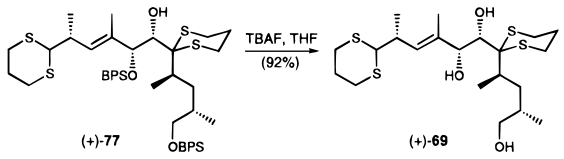


Figure 2. Solid-state conformation of aldehyde (+)-**66**.

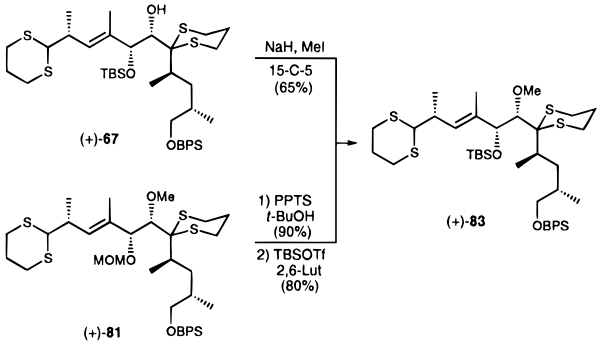
closely resembles conformation I. Thus, the olefin moiety is orthogonal to the carbonyl plane both in crystalline **66** and apparently in the reactive solution conformation. Presumably, the steric influence of the trisubstituted olefin overrides the stereoelectronic effect of the α-alkoxy substituent.[65]

The substitution of dithiane (+)-**31** for (+)-**44** in the coupling reaction with **66** had little effect on the yield and selectivity,

(63) The stereochemistry of (+)-**77** was determined by conversion to (+)-**69**.



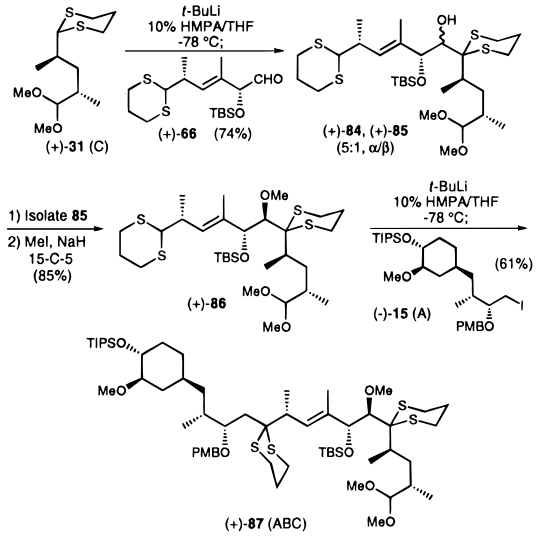
(64) The stereochemistry of (+)-**81** was elucidated by conversion to (+)-**83**, identical to an authentic sample prepared from (+)-**67**.



(65) See ref 62 for a discussion of steric vs stereoelectronic effects in nucleophilic addition reactions of α-substituted aldehydes.

affording the desired alcohol (+)-**85**[66] as the minor component of a separable 5:1 epimer mixture (Scheme 18). Nonetheless,

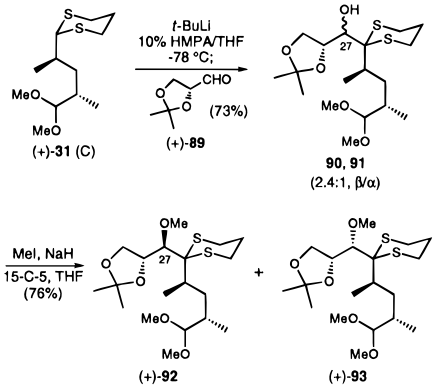
Scheme 18



it seemed prudent to test the viability of our strategy by coupling this intermediate with fragment A. Following *O*-methylation, alkylation of dithiane (+)-**86** with iodide (−)-**15** gave the rapamycin ABC segment (+)-**87** in 61% yield.

To explore further the dominant influence of the C(29,30) trisubstituted olefin on the stereoselectivity of dithiane additions to aldehydes **66**, **75**, and **76**, we coupled the lithio derivative of dithiane (+)-**31** with D-isopropylideneglyceraldehyde [(+)-**89**],[67] obtaining an inseparable 2.4:1 mixture of epimeric alcohols **90** and **91** in good yield (Scheme 19). The derived methyl ethers

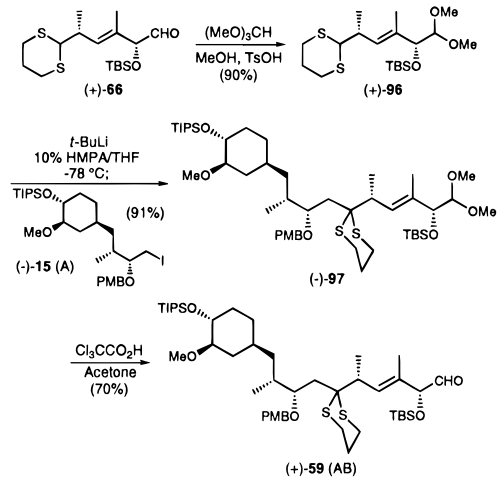
Scheme 19



(+)-**92** and (+)-**93** were readily purified by chromatography, and the C(27) *β*-configuration of the major product **92** was established by conversion of **92** to a substance of known stereochemistry.[68] The anticipated predominance of **90** is in accord with a perpendicular orientation of the α-carbon−oxygen bond and the carbonyl moiety as well as literature precedent.[58] Efforts to convert **92** to the rapamycin intermediate **86** were unsuccessful.[69]

Assembly of the Rapamycin ABC Backbone Segment: Aldehyde 59 Revisited. At this point we recalled the markedly divergent behavior of alcohols **58** and **65** toward oxidizing reagents (cf. Schemes 14 and 15) and wondered whether the 2,2-disubstituted dithiane moiety in aldehyde **59** might influence the stereochemical outcome of dithiane addition as well. In devising an alternate route to **59** (Scheme 20), we circumvented

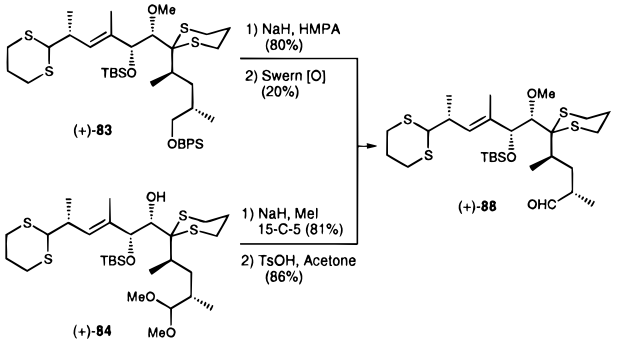
Scheme 20



the problematic oxidation of an advanced intermediate (e.g., **58**) by protecting aldehyde **66** as an acetal. Alkylation of (+)-**96** with the A-fragment iodide (−)-**15** was effected under our standard conditions in excellent yield. Hydrolysis of acetal (−)-**97** then furnished the elusive aldehyde (+)-**59** (70%).

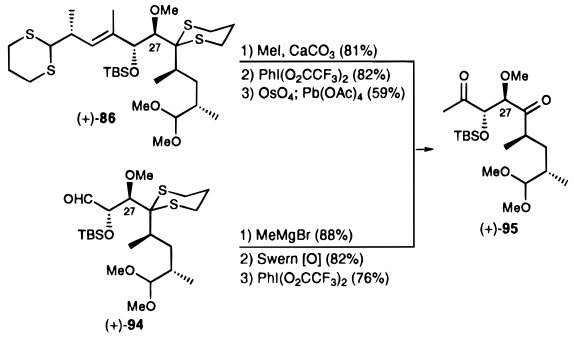
In the event, addition of the lithio derivative of fragment-C dithiane (+)-**31** to the AB aldehyde (+)-**59** generated a 1.2:1 mixture of alcohols (+)-**98** and (+)-**99** in 65% yield, with the undesired α-epimer in slight excess (Scheme 21). This result offered a significant improvement in material throughput. *O*-Methylation of (+)-**99** then afforded (+)-**87** (88%), identical to the material prepared earlier (Scheme 18). It is noteworthy that our modular synthetic design furnished the rapamycin

(66) The stereochemistry of (+)-**84** was determined by conversion to (+)-**88**, identical to a sample prepared from (+)-**83**.



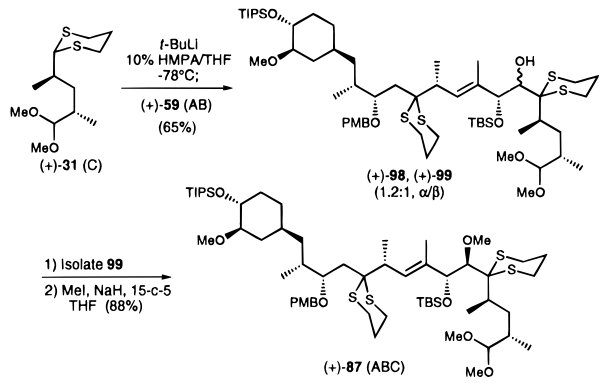
(67) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1993**, *72*, 6.

(68) The stereochemistry of (+)-**94**, a derivative of (+)-**92**,[69] was elucidated via conversion to (+)-**95**, identical to a sample prepared from (+)-**86**.



(69) McCauley, J. A. Ph.D. Thesis, University of Pennsylvania, 1996.

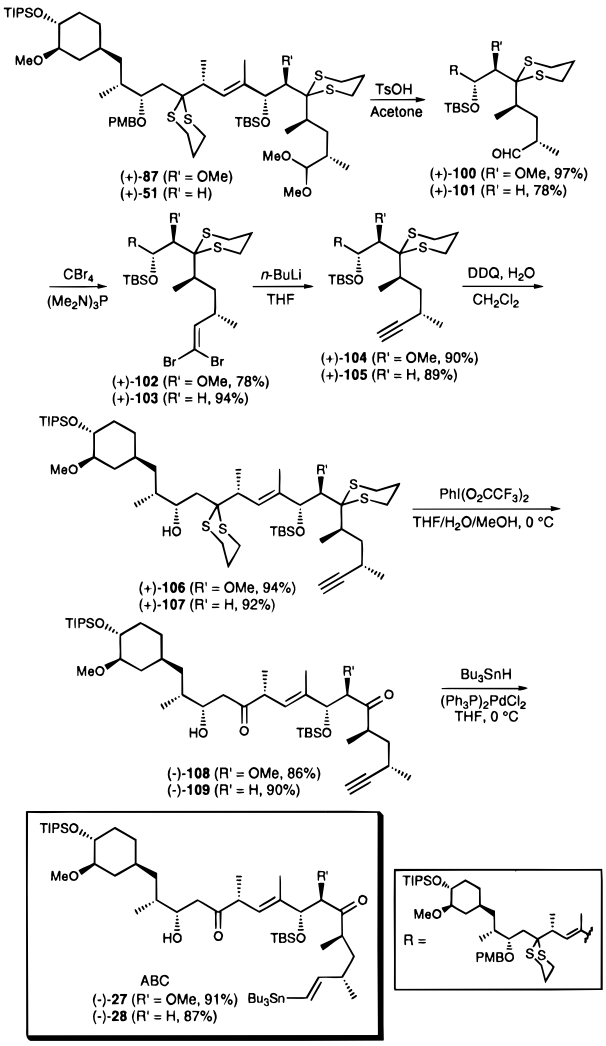
Scheme 21



C(22−42) ABC segment **87** via two different assembly strategies *without significant modifications of the initial building blocks*.

Completion of the Rapamycin and 27-Demethoxyrapamycin ABC Vinylstannanes. Final elaboration of the methoxy and 27-demethoxy intermediates **87** and **51** to the targeted C(21−42) northern perimeters proceeded along parallel lines (Scheme 22). Unmasking of the C(22) aldehydes and homologation via a modification of the two-step Corey−Fuchs protocol[70] provided acetylenes (+)-**104** and (+)-**105** in good overall yields. DDQ-induced oxidative removal of the PMB group gave the C(34) alcohols (+)-**106** and (+)-**107** (92−94%);[71] dithiane cleavage with bis(trifluoroacetoxy)iodobenzene then led to aldols (−)-**108** and (−)-**109** (86−90%).[72] Finally, palladium-mediated hydrostannylation[73] produced the requisite ABC vinylstannanes (−)-**27** and (−)-**28** in 91 and 87% yields.[74]

Scheme 22



Summary. We have presented herein a unified synthetic approach to the complete C(21−42) ABC segments of rapamycin and its 27-demethoxy congener [(−)-**27** and (−)-**28**, respectively], poised for union with a common DE fragment. The successful strategy exploited and extended our earlier investigations of σ-bond olefin construction to generate the C(29,30) trisubstituted alkene in stereocontrolled fashion. We have again efficiently coupled highly functionalized dithiane anions with diverse electrophilic subunits in the assembly of complex structures. In addition, we have discovered that a second C(2) appendage in a substituted dithiane can exert dramatic effects on the reactivity of ϵ side-chain functionalities, five bonds removed. In the following paper we describe the preparation of the DE segment and completion of the rapamycin synthetic venture.

Experimental Section[75]

Alcohol (−)-11. A solution of sulfone (−)-**8**[22] (18.0 g, 40.8 mmol) and epoxide (−)-**9**[39] (13.0 g, 40.8 mmol) in THF (250 mL) was cooled

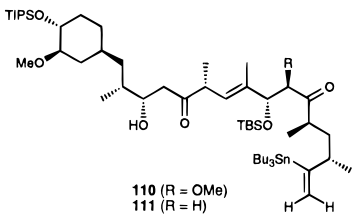
(70) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(71) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(72) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

(73) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(74) Minor amounts (ca. 5% total) of internal stannanes **110** and **111** were formed in the hydrostannylation reaction.



(75) **Materials and Methods.** Reactions were carried out in oven- or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Dichloromethane, benzene, diisopropylamine, and hexamethylphosphoramide (HMPA) were freshly distilled from calcium hydride. Triethylamine and diisopropylethylamine were distilled from calcium hydride and stored over potassium hydroxide. Anhydrous pyridine, *N*,*N*-dimethylformamide, and dimethyl sulfoxide were purchased from Aldrich and used without purification. *n*-Butyllithium and *tert*-butyllithium were purchased from Aldrich and standardized by titration with diphenylacetic acid. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography with Whatman 0.25-mm precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.023−0.040 mm) supplied by E. Merck. Radial chromatography was performed with a Chromatotron (Harrison Research, Inc., Palo Alto, CA) and silica gel rotors supplied by Analtech (Newark, DE). High-performance liquid chromatography (HPLC) was performed with a Ranin component analytical/semiprep system. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Melting points were determined on a Bristoline heated-stage microscope or a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrometer with polystyrene as external standard. Proton NMR spectra were recorded on a Bruker AM-500 spectrometer. Carbon-13 NMR spectra were recorded on a Bruker AM-500 or AM-250 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00) for ^{1}H and chloroform (δ 77.0) or benzene (δ 128.0) for ^{13}C. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center with either a VG Micromass 70/70H or VG ZAB-E spectrometer. Microanalyses were performed by Robertson Laboratories, Madison, NJ. Single-crystal X-ray structure determinations were performed at the University of Pennsylvania with an Enraf Nonius CAD-4 automated diffractometer.

to −78 °C. *n*-BuLi (1.7 M in hexanes, 24.0 mL, 40.8 mmol) was added dropwise from an addition funnel and the resultant yellow solution stirred for 30 min. Boron trifluoride etherate (5.00 mL, 40.8 mmol) was then introduced dropwise via a syringe. After an additional 2 h at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl (100 mL), warmed to ambient temperature, and partitioned between ether (300 mL) and water (300 mL). The organic phase was washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated. Following flash chromatography (hexanes/ethyl acetate, 5:1), the fractions containing the diastereomeric sulfones were combined and concentrated. This material was used without further purification.

Dibasic sodium phosphate (83 g, 0.58 mol) was added to a solution of the sulfones in methanol (750 mL), and the white, heterogeneous mixture was stirred for 30 min at ambient temperature. Na(Hg) (6%) (80 g, 0.19 mol) was added in 5-g portions over 15 min, and the reaction was monitored closely by TLC. Upon completion (ca. 30 min), the mixture was filtered through Celite and the solids were washed with ethyl acetate (300 mL). The clear filtrate was concentrated until it became cloudy and then partitioned between ethyl acetate (300 mL) and water (300 mL). The organic phase was washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) followed by HPLC (Waters Prep 500; hexanes/ethyl acetate, 10:1, 0.2 L/min) provided (−)-**11** (15 g, 60% yield) as a colorless oil: $[\alpha]_D^{23}$ −12° (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.63 (m, 4 H), 7.48−7.33 (m, 6 H), 3.64 (dd, J = 9.8, 3.9 Hz, 1 H), 3.58 (d, J = 9.8 Hz, 1 H), 3.57−3.48 (m, 2 H), 3.36 (s, 3 H), 2.88 (ddd, J = 11.3, 8.2, 4.4 Hz, 1 H), 2.38 (br s, 1 H), 2.03 (qd, J = 13.0, 4.1 Hz, 1 H), 1.88 (qd, J = 13.1, 4.5 Hz, 1 H), 1.67−1.58 (m, 1 H), 1.57−1.52 (m, 1 H), 1.39−1.16 (m, 4 H), 1.14−1.01 (m, 31 H), 0.83 (d, J = 6.7 Hz, 3 H), 0.68 (q, J = 12.0 Hz, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 135.5, 133.1, 129.8, 127.7, 84.7, 75.4, 74.9, 66.2, 57.4, 39.9, 35.8, 34.2, 32.9, 32.2, 31.5, 26.8, 19.1, 18.0, 14.4, 12.6; high-resolution mass spectrum (CI, NH_3) *m/z* 627.4296 $[(M + H)^+$; calcd for $C_{37}H_{63}O_4Si_2$, 627.4264]. Anal. Calcd for $C_{37}H_{62}O_4Si_2$, C, 70.92; H, 10.03. Found: C, 70.76; H, 10.11.

Epoxide (−)-13. A solution of mesylate (−)-**12** (392 mg, 0.55 mmol) in HMPA (2 mL) was added to a mixture of sodium hydride (60% oil dispersion; 0.11 g, 2.77 mmol) and HMPA (2 mL) at 5 °C. The reaction mixture was stirred at ambient temperature for 6 h and then recooled to 5 °C and quenched by the cautious addition of water (2 mL). The reaction mixture was partitioned between ether (100 mL) and water (100 mL), and the organic phase was washed with 1 N HCl (100 mL), water (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution, hexanes → hexanes/ethyl acetate, 50:1) afforded (−)-**13** (181 mg, 87% yield) as a colorless oil: $[\alpha]_D^{23}$ −29° (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53 (ddd, J = 10.9, 8.4, 4.8 Hz, 1 H), 3.38 (s, 3 H), 2.92 (ddd, J = 11.2, 8.4, 4.5 Hz, 1 H), 2.71−2.66 (m, 2 H), 2.45 (dd, J = 4.7, 3.0 Hz, 1 H), 2.05 (dq, J = 12.7, 4.1 Hz, 1 H), 1.91 (dq, J = 13.1, 4.6 Hz, 1 H), 1.73−1.66 (m, 1 H), 1.57−1.48 (m, 1 H), 1.47−1.31 (m, 3 H), 1.26−1.18 (m, 1 H), 1.10−1.00 (m, 22 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.78 (q, J = 12.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.7, 75.5, 57.4, 57.1, 45.4, 41.7, 36.4, 34.2, 33.5, 33.2, 31.2, 18.0, 16.2, 12.6; high-resolution mass spectrum (CI, NH_3) *m/z* 371.2981 $[(M + H)^+$; calcd for $C_{21}H_{43}O_3Si$, 371.2981].

Iodohydrin (−)-14. At −78 °C a solution of epoxide (−)-**13** (270 mg, 0.72 mmol) in ether (5 mL) was treated with LiI (0.32 g, 2.39 mmol) in one portion. Boron trifluoride etherate (90 μL, 0.72 mmol) was then added dropwise, and after an additional 5 min the reaction was quenched with water (5 mL), warmed to ambient temperature, and partitioned between ether (100 mL) and water (100 mL). The organic phase was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) furnished (−)-**14** (285 mg, 78% yield) as a colorless oil: $[\alpha]_D^{23}$ −25° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3600−3300 (br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (ddd, J = 10.6, 8.4, 4.7 Hz, 1 H), 3.45−3.39 (m, 4 H), 3.38−3.34 (m, 1 H), 3.28 (dd, J = 9.8, 7.6 Hz, 1 H), 2.92 (ddd, J = 11.1, 8.3, 4.5 Hz, 1 H), 2.14−2.06 (m, 1 H), 1.98 (d, J = 5.0 Hz, 1 H), 1.96−1.90 (m, 1 H), 1.81−1.73 (m, 1 H), 1.66−1.59 (m, 2 H), 1.47-1.31 (m, 4 H), 1.17−1.05 (m, 21 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.76 (q, J = 11.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.7, 75.6, 75.3, 57.5, 38.7, 35.9, 35.5, 34.0, 33.3, 31.9, 18.1, 15.7, 14.6, 12.6; high-resolution mass spectrum (CI, NH_3) *m/z* 499.2086 $[(M + H)^+$; calcd for $C_{21}H_{44}IO_3Si$, 499.2104].

C(33-42) Subtarget (−)-15 (A). A solution of iodohydrin (−)-**14** (536 mg, 1.07 mmol) and *p*-methoxybenzyl trichloroacetimidate (350 mg, 1.23 mmol) in dichloromethane (6 mL) was cooled to −78 °C and boron trifluoride etherate catalyst (ca. 10 μL) was added. After 30 min the white, heterogeneous mixture was diluted with ether (100 mL) and water (50 mL) and warmed to ambient temperature. The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 15:1) provided (−)-**15** (A) (560 mg, 84% yield) as a colorless oil: $[\alpha]_D^{23}$ −18° (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.50 (ABq, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 65.6 Hz, 2 H), 3.80 (s, 3 H), 3.53 (ddd, J = 10.9, 8.4, 4.8 Hz, 1 H), 3.40 (s, 3 H), 3.32−3.20 (m, 3 H), 2.89 (ddd, J = 11.2, 8.4, 4.5 Hz, 1 H), 2.09−2.05 (m, 1 H), 1.95−1.88 (m, 2 H), 1.57−1.54 (m, 1 H), 1.38−1.24 (m, 4 H), 1.16−1.00 (m, 22 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.72 (q, J = 11.6 Hz, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 130.1, 129.5, 113.7, 84.7, 82.5, 75.4, 71.9, 57.6, 55.2, 38.5, 35.7, 34.2, 33.6, 33.3, 31.8, 18.1, 15.5, 12.6, 7.3; high-resolution mass spectrum (CI, NH_3) *m/z* 636.2911 $[(M + NH_4)^+$; calcd for $C_{29}H_{55}INO_4Si$, 636.2945].

***β*-Hydroxy Sulfones 35.** A solution of sulfone (+)-**23** (33.3 g, 110 mmol) in THF (400 mL) was cooled to −78 °C, and *n*-BuLi (1.6 M in hexanes, 75.6 mL, 121 mmol) was added dropwise from an addition funnel. After 30 min, the brilliant yellow reaction mixture was warmed to −55 °C and treated dropwise with a solution of freshly distilled L-isopropylideneglyceraldehyde (**34**) (21.5 g, 166 mmol) in THF (75 mL), premixed, and stored for 1 h over activated 4 Å molecular sieves. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with ether (1 L). The organic phase was washed with water (500 mL) and brine (500 mL), dried over $MgSO_4$, filtered, and concentrated. Following flash chromatography (hexanes/ethyl acetate, 4:1) the fractions containing the diastereomeric products were combined, concentrated, and carried forward without further purification.

***β*-Keto Sulfones 36.** A solution of oxalyl chloride (5.2 mL, 60 mmol) in dichloromethane (400 mL) was cooled to −78 °C, and dimethyl sulfoxide (9.2 mL, 119 mmol) in dichloromethane (50 mL) was added dropwise via a syringe. After 15 min, a solution of the β-hydroxy sulfones **35** (21.5 g, 49.6 mmol) in dichloromethane (150 mL) was introduced at a moderate rate. After an additional 15 min triethylamine (34.6 mL, 248 mmol) was added, and the mixture was warmed to 0 °C and partitioned between ether (1 L) and water (1 L). The organic phase was washed with water (500 mL) and brine (500 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 3:1) furnished **36** (17.6 g, 82% from **23**) as a mixture of diastereomers. An analytical sample of the *S* isomer was obtained by washing the crude solid with cold ether followed by recrystallization from ether to yield clear crystals: mp 124−126 °C; $[\alpha]_D^{23}$ −121° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 1720 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 7.1 Hz, 2 H), 7.70 (t, J = 7.5 Hz, 1 H), 7.59 (t, J = 7.5 Hz, 2 H), 5.56 (d, J = 9.2 Hz, 1 H), 4.69 (d, J = 3.1 Hz, 1 H), 4.46 (dd, J = 7.8, 5.0 Hz, 1 H), 4.16 (dd, J = 8.8, 8.0 Hz, 1 H), 4.06 (dd, J = 8.8, 5.0 Hz, 1 H), 2.97 (td, J = 11.7, 1.7 Hz, 1 H), 2.86−2.79 (m, 2 H), 2.73 (td, J = 12.0, 2.3 Hz, 1 H), 2.65−2.61 (m, 1 H), 2.10−2.07 (m, 1 H), 1.79 (qt, J = 14.1, 2.3 Hz, 1 H), 1.52 (s, 3 H), 1.36 (s, 3 H), 1.02 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 202.7, 137.5, 134.3, 129.4, 129.0, 111.3, 80.6, 69.4, 66.1, 52.1, 37.7, 31.2, 30.3, 26.1, 25.7, 24.4, 14.3; high-resolution mass spectrum (CI, NH_3) *m/z* 431.1013 $[(M + H)^+$; calcd for $C_{19}H_{27}O_5S_3$, 431.1020].

Desulfonylated Ketone (−)-37. A solution of mercury(II) chloride (60.3 g, 222 mmol) in water (1.2 L) was added to a vigorously stirred suspension of aluminum powder (11.9 g, 449 mmol) in water (50 mL). The supernatant was decanted and the amalgam washed with methanol (3 × 50 mL) followed by THF (3 × 50 mL). A suspension of the amalgam in THF (50 mL) was poured through a funnel into a solution of the β-keto sulfones **36** (4.80 g, 11.1 mmol) in THF (70 mL). A reflux condenser was then fitted, and water (5 mL) was added. After ca. 5 min, the reaction mixture began to reflux. Stirring was continued for 1 h, and the mixture was then filtered through a pad of Celite and

sand on a sintered-glass funnel. The solids were rinsed with ethyl acetate (300 mL), and the filtrate was washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 3:1) provided (−)-**37** (1.9 g, 60% yield) as a colorless oil: $[\alpha]_D^{23}$ −15° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 1715 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (dd, J = 7.7, 5.5 Hz, 1 H), 4.16 (dd, J = 8.6, 7.7 Hz, 1 H), 4.07 (d, J = 4.8 Hz, 1 H), 3.97 (dd, J = 8.6, 5.5 Hz, 1 H), 2.95 (dd, J = 17.7, 4.6 Hz, 1 H), 2.81 (m, 4 H), 2.58 (dd, J = 17.7, 7.9 Hz, 1 H), 2.55 (m, 1 H), 2.06 (m, 1 H), 1.82 (m, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.07 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 209.2, 110.9, 80.2, 66.3, 53.9, 42.9, 33.1, 30.4, 30.2, 26.0, 24.9, 17.6; high-resolution mass spectrum (CI, NH_3) *m/z* 291.1063 [$(M + H)^+$; calcd for $C_{13}H_{23}O_3S_2$, 291.1088].

Enol Triflate (−)-38. A mixture of HMPA and THF (1:4, 20 mL) was cooled to −78 °C, and LHMDS (1.0 M in THF, 3.84 mL, 3.84 mmol) was added. A solution of ketone (−)-**37** (860 mg, 2.96 mmol) in 1:4 HMPA/THF (6 mL), precooled to −78 °C, followed by a solution of *N*-phenyltrifluoromethanesulfonimide (1.27 g, 3.55 mmol) in 1:4 HMPA/THF (6 mL) was then introduced dropwise via a cannula. After 5 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and partitioned between water (100 mL) and ether (100 mL). The organic phase was washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) gave (−)-**38** (937 mg, 75% yield) as a pale yellow oil: $[\alpha]_D^{23}$ −19° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (d, J = 10.5 Hz, 1 H), 4.65 (t, J = 6.5 Hz, 1 H), 4.15 (ABq, J_{AB} = 6.6 Hz, $\Delta\nu_{AB}$ = 8.5 Hz, 1 H), 4.01 (d, J = 6.0 Hz, 1 H), 3.89 (ABq, J_{AB} = 6.5 Hz, $\Delta\nu_{AB}$ = 8.5 Hz, 1 H), 3.09−3.04 (m, 1 H), 2.86−2.83 (m, 4 H), 2.10−2.06 (m, 1 H), 1.88−1.84 (m, 1 H), 1.49 (s, 3 H), 1.38 (s, 3 H), 1.23 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 144.8, 125.5, 118.4 (q, J_{CF} = 319 Hz), 110.8, 74.4, 67.4, 52.7, 35.7, 30.2, 30.1, 25.9, 25.7, 25.2, 17.6; high-resolution mass spectrum (CI, NH_3) *m/z* 422.0513 [M^+; calcd for $C_{14}H_{21}F_3O_5S_3$, 422.0503].

C(27−32) Subtarget (+)-30 (B). At −15 °C a suspension of CuI (1.7 g, 9.0 mmol) in ether (200 mL) was treated with MeLi (1.1 M in ether, 15.0 mL, 18.0 mmol). The resultant clear, colorless solution was cooled to −78 °C, and a solution of vinyl triflate (−)-**38** (1.9 g, 4.5 mmol) in ether (50 mL) was added dropwise. After 10 min the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and 10% aqueous NH_4OH (20 mL), and the organic phase was washed with 10% aqueous NH_4OH (30 mL), water (30 mL), and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) afforded (+)-**30** (B) (0.91 g, 70% yield) as a colorless oil: $[\alpha]_D^{23}$ +15° (*c* 2.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, J = 10.0 Hz, 1 H), 4.51 (t, J = 7.0 Hz, 1 H), 4.08 (dd, J = 8.2, 6.8 Hz, 1 H), 4.01 (d, J = 6.8 Hz, 1 H), 3.67 (dd, J = 8.0, 7.8 Hz, 1 H), 2.85−2.78 (m, 5 H), 2.09−2.06 (m, 1 H), 1.85−1.75 (m, 1 H), 1.66 (d, J = 1.3 Hz, 3 H), 1.45, (s, 3 H), 1.38 (s, 3 H), 1.15 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 133.3 (s), 130.2 (d), 109.0 (s), 80.9 (d), 67.8 (t), 54.3 (d), 37.3 (d), 30.7 (t), 30.5 (t), 26.2 (t), 25.9 (q), 25.3 (q), 18.1 (q), 11.3 (q); high-resolution mass spectrum (CI, NH_3) *m/z* 288.1218 [M^+; calcd for $C_{14}H_{24}O_2S_2$, 288.1234]. Anal. Calcd for $C_{14}H_{24}O_2S_2$, C, 58.29; H, 8.38. Found: C, 58.59; H, 8.74.

Dithiane Alcohol (+)-45. At 0 °C a solution of silyl ether (+)-**44** (1.80 g, 3.92 mmol) in THF (30 mL) was treated slowly with TBAF (1.0 M in THF, 4.7 mL, 4.7 mmol). After removal of the cooling bath, the reaction mixture was stirred for 16 h at ambient temperature and then poured into a mixture of water and ether (1:1, 100 mL). The organic phase was washed with 1 N HCl (50 mL), water (50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1, then 1:1) provided (+)-**45** (816 mg, 94% yield) as a colorless oil: $[\alpha]_D^{23}$ +11° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3630 (m), 3590−3320 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (d, J = 3.7 Hz, 1 H), 3.49 (dd, J = 10.5, 4.8 Hz, 1 H), 3.40 (dd, J = 10.5, 6.0 Hz, 1 H), 2.87 (dq, J = 14.1, 2.5 Hz, 1 H), 2.82 (m, 3 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.80 (m, 1 H), 1.70 (m, 2 H), 1.43 (br s, 1 H), 1.10 (m, 1 H), 1.07 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 67.8, 55.0, 37.7, 35.9, 33.2, 31.1, 30.7, 26.3, 17.7, 17.3; high-resolution mass spectrum (CI, NH_3) *m/z* 220.0931 [M^+; calcd for $C_{10}H_{20}OS_2$, 220.0956]. Anal. Calcd for $C_{10}H_{20}OS_2$, C, 54.50; H, 9.15. Found: C, 54.58; H, 9.47.

C(22−26) Subtarget (+)-31 (C). A solution of oxalyl chloride (0.14 mL, 1.6 mmol) in dichloromethane (4 mL) was cooled to −78 °C, and dimethyl sulfoxide (0.23 mL, 3.21 mmol) in dichloromethane (1 mL) was added dropwise. After 15 min, a solution of alcohol (+)-**45** (295 mg, 1.33 mmol) in dichloromethane (2 mL) was introduced at a moderate rate. The mixture was stirred for 15 min further, treated with triethylamine (0.93 mL, 6.69 mmol), warmed to 0 °C for 15 min, and partitioned between ether (50 mL) and water (50 mL). The organic phase was washed with 1 N HCl (25 mL), water (25 mL), and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The crude aldehyde was dried azeotropically with benzene (20 mL) and used without further purification.

A solution of the above aldehyde and *p*-TsOH (1 mg) in trimethyl orthoformate (3 mL) and MeOH (3 mL) was stirred for 1 h at ambient temperature and then quenched with saturated aqueous $NaHCO_3$ (2 mL). The mixture was extracted with ether (50 mL), and the organic phase was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1, containing 1% triethylamine) furnished (+)-**31** (C) (302 mg, 85%yield) as a clear, colorless oil: $[\alpha]_D^{23}$ +2.6° (*c* 3.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.15 (d, J = 3.5 Hz, 1 H), 4.01 (d, J = 5.7 Hz, 1 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 2.94−2.83 (m, 4 H), 2.12−2.03 (m, 2 H), 1.87−1.80 (m, 4 H), 1.10 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 108.8, 54.5, 54.4, 54.0, 36.4, 35.7, 33.2, 31.1, 30.6, 26.3, 17.7, 14.7; high-resolution mass spectrum (CI, CH_4) *m/z* 264.1206 [M^+; calcd for $C_{12}H_{24}O_2S_2$, 264.1218].

Alkylated Dithiane (+)-46. A solution of dithiane (+)-**30** (B) (200 mg, 0.69 mmol) in 10% HMPA/THF (3 mL) was cooled to −78 °C, and *t*-BuLi (1.5 M in pentane, 0.46 mL, 0.69 mmol) was added dropwise. Immediately thereafter a precooled (−78 °C) solution of iodide (−)-**15** (A) (320 mg, 0.51 mmol) in 10% HMPA/THF (3 mL) was added dropwise via a cannula. The reaction was immediately quenched with saturated aqueous NH_4Cl (2 mL), diluted with ether (50 mL), and warmed to ambient temperature. The layers were separated, and the organic phase was washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) gave (+)-**46** (350 mg, 87% yield) as a white foam: $[\alpha]_D^{23}$ +14° (*c* 3.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.5 Hz, 2 H), 5.70 (d, J = 9.6 Hz, 1 H), 4.52 (t, J = 7.0 Hz, 1 H), 4.46 (ABq, J_{AB} = 10.3 Hz, $\Delta\nu_{AB}$ = 37.7 Hz, 2 H), 4.03 (t, J = 7.2 Hz, 1 H), 3.78 (s, 3 H), 3.66−3.63 (m, 2 H), 3.55 (ddd, J = 10.9, 8.4, 4.7 Hz, 1 H), 3.40 (s, 3 H), 3.16 (dq, J = 9.6, 6.9 Hz, 1 H), 2.94−2.70 (m, 5 H), 2.11−1.88 (m, 7 H), 1.66−1.59 (m, 1 H), 1.61 (s, 3 H), 1.46−1.20 (m, 2 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 1.19−0.85 (m, 24 H), 1.13 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.77 (q, J = 12.0 Hz, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 158.8, 131.9, 131.1, 130.1, 129.5, 113.4, 108.9, 84.7, 81.4, 80.3, 75.5, 70.7, 67.6, 57.5, 57.2, 55.1, 39.7, 38.7, 36.2, 36.0, 34.1, 33.3, 32.5, 31.6, 26.4, 26.2, 25.9, 25.2, 24.9, 18.0, 15.8, 14.2, 12.5, 10.9; high-resolution mass spectrum (FAB, NBA) *m/z* 777.4583 [$(M - H)^+$; calcd for $C_{43}H_{73}O_6S_2Si$, 777.4618]. Anal. Calcd for $C_{43}H_{74}O_6S_2Si$, C, 66.28; H, 9.57. Found: C, 65.94; H, 9.43.

Diol (+)-47. A solution of acetonide (+)-**46** (450 mg, 0.57 mmol) in methanol (15 mL) was treated with camphorsulfonic acid (13 mg, 0.05 mmol), stirred at ambient temperature for 2 h, quenched with saturated aqueous $NaHCO_3$ (10 mL), and partitioned between ether (50 mL) and water (50 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) gave recovered (+)-**46** (57 mg, 13% yield) in addition to (+)-**47** (312 mg, 73% yield), a white foam: $[\alpha]_D^{23}$ +19° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3600−3100 (br, w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 5.66 (d, J = 9.7 Hz, 1 H), 4.43 (ABq, J_{AB} = 10.4 Hz, $\Delta\nu_{AB}$ = 19.4 Hz, 2 H), 4.12 (t, J = 6.2 Hz, 1 H), 3.76 (s, 3 H), 3.60 (m, 1 H), 3.55−3.48 (m, 2 H), 3.38 (s, 3 H), 3.06 (m, 1 H), 2.91−2.65 (m, 5 H), 2.29 (m, 1 H), 2.14−1.83 (m, 7 H), 1.71−1.60 (m, 2 H), 1.59 (d, J = 1.1 Hz, 3 H), 1.42−1.28 (m, 2 H), 1.20−0.85 (m, 4 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.05 (s, 21 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.75 (q, J = 11.8 Hz, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 158.9, 134.1, 131.0, 129.5, 128.8, 113.6, 84.7, 80.3, 77.5, 75.5, 70.7, 64.5, 57.6, 55.2, 39.9,

38.5, 36.2, 34.1, 33.3, 32.4, 31.6, 26.4, 25.8, 25.0, 18.0, 15.7, 14.2, 12.6, 11.7; high-resolution mass spectrum (FAB, NBA) *m/z* 737.4281 [(M − H)$^+$; calcd for $C_{40}H_{69}O_6S_2Si$, 737.4305].

Tosylate (+)-48. A solution of alcohol (+)-**47** (272 mg, 0.36 mmol), triethylamine (0.5 mL, 3.67 mmol), and DMAP (5 mg, 0.03 mmol) in dichloromethane (5 mL) was cooled to 0 °C. TsCl (70 mg, 0.36 mmol) was added in one portion, and the reaction mixture was warmed to ambient temperature, stirred for 16 h, and then poured into a mixture of ether and water (1:1, 40 mL). The organic phase was washed with 1 N HCl (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) provided starting material (+)-**47** (30 mg, 11% yield) and tosylate (+)-**48** (279 mg, 85% yield), a white foam: $[\alpha]_D^{23}$ +10° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3650−3100 (br), 1740 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2 H), 7.26 (d, J = 8.2 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.69 (d, J = 9.8 Hz, 1 H), 4.45 (ABq, J_{AB} = 10.3 Hz, $\Delta\nu_{AB}$ = 27.1 Hz, 2 H), 4.23 (dd, J = 8.1, 2.8 Hz, 1 H), 4.08 (dd, J = 10.3, 3.2 Hz, 1 H), 3.96 (dd, J = 10.2, 8.2 Hz, 1 H), 3.78 (s, 3 H), 3.62 (m, 1 H), 3.55 (ddd, J = 10.9, 8.2, 4.7 Hz, 1 H), 3.40 (s, 3 H), 3.11 (dd, J = 9.7, 6.9 Hz, 1 H), 2.91 (ddd, J = 11.1, 8.3, 4.4 Hz, 1 H), 2.84−2.82 (m, 1 H), 2.74−2.71 (m, 3 H), 2.43 (s, 3 H), 2.07−1.80 (m, 10 H), 1.64 (m, 1 H), 1.43−1.08 (m, 3 H), 1.07 (s, 27 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.77 (q, J = 11.9 Hz, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 158.9, 144.9, 132.9, 131.7, 131.1, 130.0, 129.8, 129.5, 127.9, 113.5, 84.7, 80.3, 75.5, 74.7, 72.7, 70.6, 57.7, 57.2, 55.2, 39.8, 38.5, 36.3, 36.1, 34.2, 33.4, 32.4, 31.6, 26.5, 25.9, 24.9, 21.6, 18.0, 15.8, 14.2, 12.6, 12.5; high-resolution mass spectrum (FAB, NBA) *m/z* 894.4460 [M$^+$; calcd for $C_{47}H_{76}O_8S_3Si$, 894.4472]. Anal. Calcd for $C_{47}H_{76}O_8S_3Si$, C, 63.19; H, 8.57. Found: C, 63.34; H, 8.38.

Epoxide (+)-54. A solution of tosylate (+)-**48** (0.90 g, 1.0 mmol) in anhydrous MeOH (30 mL) was treated with K_2CO_3 (0.40 g, 3.2 mmol). The heterogeneous mixture was stirred at ambient temperature for 1 h and then partitioned between ether (100 mL) and water (100 mL). The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude epoxide was dried azeotropically with benzene (50 mL) and used without further purification in the next reaction. Flash chromatography (hexanes/ethyl acetate, 20:1, containing 1% triethylamine) provided an analytical sample of (+)-**54** as a colorless oil: $[\alpha]_D^{23}$ +12° (*c* 0.7, CCl_4); ^{1}H NMR (500 MHz, C_6D_6) δ 7.37 (d, J = 8.6 Hz, 2 H), 6.80 (d, J = 8.6 Hz, 2 H), 6.07 (d, J = 9.7 Hz, 1 H), 4.64 (ABq, J_{AB} = 10.4 Hz, $\Delta\nu_{AB}$ = 67.9 Hz, 2 H), 3.92 (d, J = 8.2 Hz, 1 H), 3.67 (ddd, J = 10.9, 8.3, 4.8 Hz, 1 H), 3.33 (dd, J = 9.8, 6.9 Hz, 1 H), 3.30 (s, 3 H), 3.29 (s, 3 H), 3.15 (dd, J = 3.9, 2.7 Hz, 1 H), 2.95 (ddd, J = 11.1, 8.4, 4.5 Hz, 1 H), 2.56 (ddd, J = 9.7, 8.0, 3.6 Hz, 1 H), 2.43−2.37 (m, 5 H), 2.34 (dd, J = 15.5, 7.4 Hz, 1 H), 2.17−2.10 (m, 2 H), 2.08 (dd, J = 15.5, 1.5 Hz, 1 H), 1.97 (dq, J = 13.1, 4.5 Hz, 1 H), 1.58−1.47 (m, 3 H), 1.45 (d, J = 1.3 Hz, 3 H), 1.42−1.33 (m, 2 H), 1.30 (d, J = 6.9 Hz, 3 H), 1.25−1.22 (m, 24 H), 1.02 (d, J = 6.8 Hz, 3 H), 0.83 (q, J = 11.2 Hz, 1 H); ^{13}C NMR (62.8 MHz, C_6D_6) δ 159.6 (s), 131.9 (s), 131.8 (s), 131.7 (d), 129.8 (d), 113.9 (d), 85.0 (d), 80.5 (d), 75.8 (d), 71.2 (t), 57.8 (s), 57.0 (q), 56.0 (d), 54.7 (q), 45.5 (t), 40.3 (t), 39.5 (d), 36.8 (t), 36.4 (t), 34.7 (t), 33.7 (d), 33.0 (d), 31.8 (t), 26.6 (t), 26.2 (t), 25.3 (t), 18.5 (q), 16.4 (q), 14.7 (q), 13.0 (d), 10.2 (q); high-resolution mass spectrum (FAB, NBA) *m/z* 743.4152 [(M + Na)$^+$; calcd for $C_{40}H_{68}O_5S_2SiNa$, 743.4175]. Anal. Calcd for $C_{40}H_{68}O_5S_2Si$, C, 66.62; H, 9.50. Found: C, 66.83; H, 9.54.

Dithiane Alcohol (+)-55. At −78 °C a solution of dithiane (+)-**31** (C) (1.7 g, 6.4 mmol) in 10% HMPA/THF (17 mL) was treated with *t*-BuLi (1.7 M in pentane, 3.0 mL, 5.3 mmol). Immediately thereafter a precooled (−78 °C) solution of crude epoxide (+)-**54** in 10% HMPA/THF (7 mL) was added via a cannula. The reaction mixture was rapidly warmed to −55 °C and then quenched with saturated aqueous NH_4Cl (10 mL). At ambient temperature the mixture was partitioned between ether (30 mL) and water (30 mL), and the organic phase was washed with water (3 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. A second reaction was performed on the same scale, and the combined products were subjected to flash chromatography (hexanes/ethyl acetate, 20:1, containing 1% triethylamine, then 4:1, containing triethylamine), affording (+)-**55** (1.8 g, total yield 86% from **48**) as a white foam: $[\alpha]_D^{23}$ +16° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3440 (br) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.40 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 6.01 (d, J = 9.7 Hz, 1 H), 4.79 (d, J = 9.0 Hz, 1 H), 4.66 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 80.8 Hz, 2 H), 4.06 (d, J = 5.7 Hz, 1 H), 3.96 (d, J = 7.9 Hz, 1 H), 3.77 (d, J = 1.6 Hz, 1 H), 3.67 (ddd, J = 10.9, 8.4, 4.8 Hz, 1 H), 3.35 (m, 1 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 3.20 (s, 3 H), 3.17 (s, 3 H), 2.95 (ddd, J = 11.1, 8.3, 4.4 Hz, 1 H), 2.75−2.69 (m, 2 H), 2.64−2.55 (m, 3 H), 2.46 (d, J = 14.2 Hz, 1 H), 2.45−2.41 (m, 2 H), 2.36 (dd, J = 15.3, 7.1 Hz, 1 H), 2.24−2.13 (m, 2 H), 2.10 (d, J = 14.2 Hz, 1 H), 1.96 (m, 1 H), 1.92 (d, J = 1.1 Hz, 3 H), 1.55−1.40 (m, 6 H), 1.39 (d, J = 6.9 Hz, 3 H), 1.34 (d, J = 6.7 Hz, 3 H), 1.33−1.24 (m, 2 H), 1.24−1.21 (m, 29 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.83 (apparent q, J = 11.9 Hz, 1 H); ^{13}C NMR (62.8 MHz, C_6D_6) δ 159.6, 138.4, 131.9, 129.7, 126.7, 113.9, 109.5, 85.0, 80.5, 75.9, 74.7, 71.0, 59.2, 58.5, 57.0, 54.7, 54.6, 53.4, 42.0, 40.2, 39.2, 38.5, 36.8, 36.5, 36.4, 35.2, 34.7, 33.7, 33.1, 31.8, 26.6, 26.3, 25.6, 25.4, 18.5, 17.1, 16.7, 15.5, 14.8, 13.0, 12.2. Anal. Calcd for $C_{52}H_{92}O_7S_4Si$, C, 63.37; H, 9.41. Found: C, 63.08; H, 9.42.

Alcohols (+)-84 and (+)-85. A solution of dithiane (+)-**31** (C) (280 mg, 1.06 mmol) in 10% HMPA/THF (5 mL) was cooled to −78 °C, and *t*-BuLi (1.5 M in pentane, 0.61 mL, 0.92 mmol) was added dropwise. A precooled (−78 °C) solution of aldehyde (+)-**66** (100 mg, 0.28 mmol) in 10% HMPA/THF (3 mL) was immediately added dropwise via a cannula. The reaction was then immediately quenched with saturated aqueous NH_4Cl (5 mL), diluted with ether (20 mL), and warmed to ambient temperature. The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 15:1, containing 1% triethylamine) furnished a 5:1 mixture of (+)-**84** and (+)-**85** (128 mg, 74% yield). Radial chromatography (silica; 1-mm layer, hexanes/ethyl acetate, 15:1, containing 1% triethylamine) then gave pure (+)-**84** (95 mg, 55% yield) and (+)-**85** (20 mg, 12% yield) as colorless oils.

(+)-**84**: $[\alpha]_D^{23}$ +39.2° (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) 3450 (br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (d, J = 9.6 Hz, 1 H), 4.53 (s, 1 H), 4.11 (d, J = 5.7 Hz, 1 H), 4.00 (d, J = 6.0 Hz, 1 H), 3.99 (m, 1 H), 3.81 (d, J = 6.6 Hz, 1 H), 3.39 (s, 6 H), 3.36 (d, J = 4.4 Hz, 1 H), 3.19 (br m, 1 H), 3.04 (apparent t, J = 9.7 Hz, 1 H), 2.86−2.67 (series of m, 7 H), 2.43 (dd, J = 8.0, 6.3 Hz, 1 H), 2.13 (apparent t, J = 6.9 Hz, 1 H), 2.06 (dt, J = 13.8, 3.5 Hz, 1 H), 2.04−1.95 (m, 2 H), 1.84−1.75 (m, 2 H), 1.66 (d, J = 1.2 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.91 (s, 9 H), 0.20 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 138.3 (s), 129.8 (d), 109.4 (d), 79.5 (d), 76.3 (d), 62.4 (s), 54.8 (q), 54.6 (d), 54.2 (q), 37.4 (d), 37.2 (t), 37.1 (d), 35.1 (d), 30.7 (t), 30.5 (t), 27.6 (t), 26.6 (t), 26.1 (t), 25.9 (q), 25.2 (t), 18.2 (q), 17.6 (s), 16.3 (q), 15.8 (q), 11.4 (q), −4.1 (q), −4.6 (q); high-resolution mass spectrum (CI, NH_3) *m/z* 647.2753 [(M + Na)$^+$; calcd for $C_{29}H_{56}O_4S_4Si$, 647.2729].

(+)-**85**: $[\alpha]_D^{23}$ +29° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3500 (br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (d, J = 9.9 Hz, 1 H), 4.49 (d, J = 6.1 Hz, 1 H), 4.15 (dd, J = 6.1, 2.9 Hz, 1 H), 4.08 (d, J = 5.3 Hz, 1 H), 4.02 (d, J = 6.9 Hz, 1 H), 3.36 (s, 6 H), 3.34 (m, 1 H), 3.10 (ddd, J = 13.6, 10.0, 3.4 Hz, 1 H), 2.87−2.79 (m, 5 H), 2.70−2.62 (m, 3 H), 2.40 (apparent t, J = 6.8 Hz, 1 H), 2.14 (dd, J = 12.1, 6.4 Hz, 1 H), 2.08 (dt, J = 13.8, 3.7 Hz, 1 H), 2.01 (m, 1 H), 1.90−1.81 (m, 3 H), 1.76 (d, J = 1.2 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 1.16 (d, J = 6.7 Hz, 3 H), 1.08 (ddd, J = 14.4, 7.8, 6.3 Hz, 1 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 132.1, 108.8, 80.8, 79.3, 62.6, 55.1, 54.1, 54.0, 37.8, 37.2, 35.6, 35.2, 30.7, 30.3, 27.7, 26.7, 26.1, 26.0, 24.7, 18.2, 17.7, 17.4, 15.6, 12.7, −4.4 (2 C); high-resolution mass spectrum (CI, NH_3) *m/z* 647.2741 [(M + Na)$^+$; calcd for $C_{29}H_{56}O_4S_4Si$, 647.2729].

Methyl Ether (+)-86. At ambient temperature a solution of alcohol (+)-**85** (16 mg, 0.03 mmol) in THF (1 mL) was treated with sodium hydride (60% oil dispersion; 5 mg, 0.13 mmol), 15-crown-5 (5 μL, 0.03 mmol), and methyl iodide (25 μL, 0.26 mmol). The reaction mixture was stirred for 4 h and then partitioned between ether (10 mL) and saturated aqueous NH_4Cl (10 mL). The organic layer was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 15:1, containing 1% triethylamine) afforded (+)-**86** (14 mg, 85% yield) as

a colorless oil: $[\alpha]_D^{23}$ +9.8° (*c* 0.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.43 (d, J = 9.3 Hz, 1 H), 4.45 (d, J = 5.4 Hz, 1 H), 4.12 (d, J = 5.6 Hz, 1 H), 4.07 (d, J = 5.4 Hz, 1 H), 3.77 (d, J = 5.5 Hz, 1 H), 3.58 (s, 3 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 3.24 (apparent t, J = 9.7 Hz, 1 H), 3.15 (apparent t, J = 10.6 Hz, 1 H), 2.88 (dq, J = 11.8, 2.3 Hz, 1 H), 2.85−2.79 (m, 4 H), 2.63 (t, J = 4.4 Hz, 1 H), 2.60 (t, J = 4.5 Hz, 1 H), 2.33 (m, 1 H), 2.11−2.00 (m, 3 H), 1.87−1.81 (m, 3 H), 1.79 (d, J = 1.2 Hz, 3 H), 1.23 (d, J = 6.7 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.04 (ddd, J = 15.5, 8.7, 6.8, 1 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 131.1, 108.6, 91.7, 81.0, 63.5, 61.6, 55.2, 54.6, 53.8, 37.7, 37.5, 35.7, 34.7, 31.1, 30.6, 27.7, 27.2, 26.2, 26.0, 24.6, 18.2, 17.7, 17.1, 15.5, −4.5 (2 C).

Methoxy-Alkylated Dithiane (+)-87. A. From (+)-86. A solution of dithiane (+)-**86** (15 mg, 0.024 mmol) in 10% HMPA/THF (1.5 mL) was cooled to −78 °C, and *t*-BuLi (1.1 M in pentane, 44 μL, 0.068 mmol) was added dropwise. Immediately thereafter a precooled (−78 °C) solution of iodide (−)-**15** (A) (42 mg, 0.048 mmol) in 10% HMPA/THF (2 mL) was introduced dropwise via a cannula. The reaction mixture was immediately quenched with saturated aqueous NH_4Cl (10 mL), diluted with ether (20 mL), and warmed to ambient temperature. The layers were separated, and the organic phase was washed with saturated aqueous $Na_2S_2O_3$ (10 mL), water (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) gave (+)-**87** (16.3 mg, 61% yield) as a colorless oil: $[\alpha]_D^{23}$ +12° (*c* 0.38, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 5.55 (d, J = 9.2 Hz, 1 H), 4.50 (ABq, J_{AB} = 10.5 Hz, $\Delta\upsilon_{AB}$ = 69.2 Hz, 2 H), 4.42 (d, J = 8.1 Hz, 1 H), 4.03 (d, J = 6.5 Hz, 1 H), 3.78 (s, 3 H), 3.74 (d, J = 6.4 Hz, 1 H), 3.73 (m, 1 H), 3.55 (s, 3 H), 3.55 (m, 1 H), 3.40 (s, 3 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 3.32−3.25 (m, 2 H), 3.16 (m, 1 H), 2.92 (ddd, J = 11.2, 8.4, 4.5 Hz, 1 H), 2.87−2.79 (m, 3 H), 2.68 (m, 1 H), 2.61−2.56 (m, 2 H), 2.38 (apparent t, J = 6.6 Hz, 1 H), 2.12−1.80 (complex series of m, 10 H), 1.79 (d, J = 1.0 Hz, 3 H), 1.64 (dq, J = 10.2, 2.9 Hz, 1 H), 1.40 (m, 1 H), 1.35 (dq, J = 10.9, 3.6 Hz, 1 H), 1.26 (d, J = 6.7 Hz, 3 H), 1.21 (m, 1 H), 1.14 (d, J = 6.9 Hz, 3 H), 1.12−1.03 (m, 4 H), 1.08 (s, 21 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.77 (q, J = 12.0 Hz, 1 H), 0.11 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 158.9, 136.2, 131.5, 130.6, 129.5, 113.5, 108.6, 90.7, 84.9, 82.1, 80.2, 75.6, 70.8, 63.6, 61.5, 57.7, 57.6, 55.2, 55.1, 53.8, 39.7, 38.7, 37.8, 36.4, 36.3, 36.0, 34.3, 33.5, 33.1, 31.7, 28.0, 27.2, 26.5, 26.3, 26.1, 25.0, 24.6, 18.2, 18.1 (2 C), 17.9, 16.1, 15.5, 14.7, 13.1, 12.7, −4.1, −4.3; high-resolution mass spectrum (FAB, NBA) *m/z* 1151.6336 [$(M + Na)^+$; calcd for $C_{59}H_{108}O_8S_4Si_2Na$, 1151.6364]. Anal. Calcd for $C_{59}H_{108}O_8S_4Si_2$: C, 64.51; H, 9.52. Found: C, 64.89; H, 9.66.

Dimethyl Acetal (+)-96. At ambient temperature a solution of aldehyde (+)-**66** (200 mg, 0.55 mmol) in methanol (6 mL) and trimethyl orthoformate (6 mL) was treated with *p*-toluenesulfonic acid monohydrate (20 mg, 0.11 mmol). The reaction mixture was stirred for 30 min, quenched with saturated aqueous Na_2CO_3 (5 mL), and partitioned between ether (50 mL) and water (50 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromtography (hexanes/ethyl acetate, 20:1) afforded (+)-**96** (202 mg, 90% yield) as a colorless oil: $[\alpha]_D^{23}$ +2.8° (*c* 0.88, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (d, J = 9.6 Hz, 1 H), 4.18 (d, J = 6.7 Hz, 1 H), 4.01 (d, J = 6.5 Hz, 1 H), 3.92 (d, J = 6.7 Hz, 1 H), 3.42 (s, 3 H), 3.33 (s, 3 H), 2.88−2.76 (m, 5 H), 2.10−2.04 (m, 1 H), 1.86−1.77 (m, 1 H), 1.65 (d, J = 1.3 Hz, 3 H), 1.13 (d, J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8 (s), 130.2 (d), 106.2 (d), 79.0 (d), 55.6 (q), 54.6 (d), 54.0 (q), 37.4 (d), 30.8 (t), 30.5 (t), 26.1 (t), 25.8 (q), 18.2 (s), 18.0 (q), 12.3 (q), −4.8 (q), −4.9 (q); high-resolution mass spectrum (CI, NH_3) *m/z* 375.1858 [$(M - OMe)^+$; calcd for $C_{18}H_{35}O_2S_2Si$, 375.1848]. Anal. Calcd for $C_{19}H_{38}O_3S_2Si$, C, 56.11; H, 9.42. Found: C, 56.27; H, 9.53.

AB-Alkylated Dithiane (−)-97. Dithiane (+)-**96** (200 mg, 0.49 mmol) was dried azeotropically with benzene (2 × 20 mL) and dissolved in 10% HMPA/THF (4 mL). The solution was cooled to −78 °C and treated with *t*-BuLi (1.6 M in pentane, 0.31 mL, 0.49 mmol). Iodide (−)-**15** (A) (256 mg, 0.41 mmol), dried azeotropically with benzene (2 × 20 mL) was dissolved in 10% HMPA/THF (4 mL); the precooled (−78 °C) solution was immediately added via a cannula to the dark orange anion mixture, and the flask and cannula were rinsed with 10% HMPA/THF (2 × 0.5 mL). The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ether (20 mL). The organic layer was washed with water (10 mL), saturated aqueous $Na_2S_2O_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 30:1) gave recovered (+)-**96** (32 mg, 16% yield) and dithiane (−)-**97** (337 mg, 91% yield), a pale yellow oil: $[\alpha]_D^{23}$ −1.6° (*c* 0.87, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2 H), 6.38 (d, J = 8.6 Hz, 2 H), 5.54 (d, J = 9.6 Hz, 1 H), 4.48 (ABq, J_{AB} = 10.4 Hz, $\Delta\upsilon_{AB}$ = 69.1 Hz, 2 H), 4.21 (d, J = 6.7 Hz, 1 H), 3.96 (d, J = 6.7 Hz, 1 H), 3.79 (s, 3 H), 3.68 (d, J = 5.4 Hz, 1 H), 3.55 (ddd, J = 10.8, 6.2, 3.8 Hz, 1 H), 3.41 (s, 3 H), 3.40 (s, 3 H), 3.29 (s, 3 H), 3.22 (dd, J = 9.6, 6.9 Hz, 1 H), 2.92 (ddd, J = 12.8, 8.4, 4.4 Hz, 1 H), 2.82−2.70 (m, 4 H), 2.09−1.89 (m, 6 H), 1.85 (d, J = 14.6 Hz, 1 H), 1.64 (d, J = 1.0 Hz, 3 H), 1.49−1.45 (m, 1 H), 1.35 (dq, J = 10.9, 3.5 Hz, 1 H), 1.25−1.12 (m, 3 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.08 (s, 21 H), 1.02−0.94 (m, 1 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.86 (s, 9 H), 0.77 (q, J = 12.0 Hz, 1 H), 0.05 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9 (s), 134.4 (s), 131.4 (s), 129.5 (d), 129.5 (d), 113.5 (d), 105.7 (d), 84.8 (d), 80.2 (d), 79.1 (d), 75.6 (d), 70.6 (t), 57.6 (q), 57.5 (s), 55.7 (q), 55.2 (q), 52.8 (q), 39.8 (t), 38.7 (d), 36.4 (t), 36.3 (t), 34.3 (t), 33.4 (d), 32.7 (d), 31.7 (t), 26.6 (t), 25.9 (t), 25.8 (q), 25.0 (t), 18.2 (s), 18.1 (q), 16.0 (q), 14.4 (q), 12.6 (d), 11.9 (q), −4.7 (q), −4.9 (q); high-resolution mass spectrum (FAB, NBA) *m/z* 919.5421 [$(M + Na)^+$; calcd for $C_{48}H_{88}O_7S_2Si_2Na$, 919.5408]. Anal. Calcd for $C_{48}H_{88}O_7S_2Si_2$: C, 64.31; H, 9.78. Found: C, 64.52; H, 10.12.

AB Aldehyde (+)-59. At ambient temperature a solution of dimethyl acetal (−)-**97** (220 mg, 0.24 mmol) in acetone (10 mL) was treated with trichloroacetic acid (1.5 g, 9.6 mmol). The reaction mixture was stirred for 16 h, quenched with saturated aqueous $NaHCO_3$ (25 mL), and extracted with ether (50 mL). The organic layer was washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) provided (+)-**59** (141 mg, 70% yield) as a pale yellow oil: $[\alpha]_D^{23}$ +27.2° (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 2970 (s), 2920 (s), 2860 (s), 1730 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, J = 1.6 Hz, 1 H), 7.27 (d, J = 8.7 Hz, 2 H), 6.38 (d, J = 8.7 Hz, 2 H), 5.87 (d, J = 9.9 Hz, 1 H), 4.46 (ABq, J_{AB} = 10.4 Hz, $\Delta\upsilon_{AB}$ = 50.4 Hz, 2 H), 4.34 (s, 1 H), 3.79 (s, 3 H), 3.65 (dd, J = 7.4, 2.7 Hz, 1 H), 3.55 (ddd, J = 10.9, 8.4, 4.8 Hz, 1 H), 3.40 (s, 3 H), 3.20 (dd, J = 9.8, 6.9 Hz, 1 H), 2.91 (ddd, J = 11.2, 8.4, 4.4 Hz, 1 H), 2.85 (dt, J = 14.9, 6.4 Hz, 1 H), 2.78−2.73 (m, 4 H), 2.12−2.00 (m, 4 H), 1.96−1.88 (m, 4 H), 1.67−1.61 (m, 1 H), 1.55 (d, J = 1.2 Hz, 3 H), 1.51−1.41 (m, 1 H), 1.35 (ddd, J = 24.1, 13.5, 3.8 Hz, 1 H), 1.20−1.14 (m, 1 H), 1.12 (d, J = 6.8 Hz, 3 H), 1.07 (s, 21 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.90 (s, 9 H), 0.77 (q, J = 12.0 Hz, 1 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 158.9, 131.3, 131.0, 129.8, 129.5, 113.5, 84.8, 83.2, 80.3, 75.6, 70.7, 57.6, 57.4, 55.2, 39.9, 38.9, 36.3, 36.2, 34.3, 33.5, 32.6, 31.7, 26.5, 26.0, 25.8, 25.0, 18.3, 18.1, 16.1, 14.3, 12.7, 12.5, −4.8, −5.1; high-resolution mass spectrum (FAB, NBA) *m/z* 873.4981 [$(M + Na)^+$; calcd for $C_{46}H_{82}O_6S_2Si_2Na$, 873.4989]. Anal. Calcd for $C_{46}H_{82}O_6S_2Si_2$: C, 64.89; H, 9.71. Found: C, 65.14; H, 9.72.

Alcohols (+)-98 and (+)-99. Via the procedure described above for the preparation of (−)-**97**, a solution of aldehyde (+)-**59** (31 mg, 0.036 mmol) in 10% HMPA/THF (1.5 mL) was added to the lithio derivative generated by the reaction of dithiane (+)-**31** (C) (80 mg, 0.30 mmol), dissolved in 10% HMPA/THF (1.5 mL) with *t*-BuLi (1.0 M in pentane, 0.25 mL, 0.25 mmol). Work-up and flash chromatography (hexanes/ethyl acetate, 10:1, containing 1% triethylamine) furnished a mixture of (+)-**98** and (+)-**99** (26 mg, 65% yield). Radial chromatography (silica; 1-mm layer, hexanes/ethyl acetate, 10:1) then gave pure (+)-**98** (14 mg, 35% yield) and (+)-**99** (12 mg, 30% yield).

(+)-**98**: white foam; $[\alpha]_D^{23}$ +26° (*c* 0.37, $CHCl_3$); IR ($CHCl_3$) 3460 (w), 2960 (s), 2940 (s), 2880 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 5.56 (d, J = 9.7 Hz, 1 H), 4.64 (s, 1 H), 4.46 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 55.4 Hz, 2 H), 4.08 (d, J = 5.8 Hz, 1 H), 3.91 (d, J = 7.5 Hz, 1 H), 3.79 (s, 3 H), 3.78 (m, 1 H), 3.65 (d, J = 4.8 Hz, 1 H), 3.55 (ddd, J = 11.0, 8.4,

4.7 Hz, 1 H), 3.40 (s, 3 H), 3.37 (s, 6 H), 3.36 (m, 1 H), 3.14 (dd, J = 9.7, 7.0 Hz, 1 H), 3.03 (m, 1 H), 2.93−2.68 (m, 8 H), 2.44−2.40 (m, 2 H), 2.22 (m, 1 H), 2.07−1.73 (series of m, 12 H), 1.63 (d, J = 0.9 Hz, 3 H), 1.43−1.15 (m, 5 H), 1.13 (d, J = 6.8 Hz, 3 H), 1.12 (d, J = 6.9 Hz, 3 H), 1.08 (s, 21 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.91 (s, 9 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.77 (q, J = 12.1 Hz, 1 H), 0.20 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 137.7, 131.5, 129.5, 128.8, 113.6, 109.5, 84.9, 80.2, 76.2, 75.6, 70.7, 62.9, 57.9, 57.6, 55.2, 54.7, 54.1, 39.8, 38.8, 37.9, 37.5, 36.4, 36.3, 35.2, 34.3, 33.5, 32.9, 31.7, 26.5, 26.2, 26.0, 25.2, 25.0, 18.2, 18.1 (2 C), 16.5, 16.0, 15.7, 14.7, 12.7, 11.3, −3.9, −4.5; high-resolution mass spectrum (FAB, NBA) *m/z* 1137.6235 [(M + Na)$^+$; calcd for $C_{58}H_{106}O_8S_4Si_2Na$, 1137.6206].

(+)-**99**: white foam; $[\alpha]_D^{23}$ +28° (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 3480 (w), 2960 (s), 2930 (s), 2860 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 5.63 (d, J = 9.9 Hz, 1 H), 4.57 (d, J = 6.9 Hz, 1 H), 4.46 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 52.8 Hz, 2 H), 4.06 (m, 1 H), 4.05 (d, J = 5.5 Hz, 1 H), 3.78 (s, 3 H), 3.64 (br d, J = 5.1 Hz, 1 H), 3.55 (ddd, J = 10.9, 8.5, 4.8 Hz, 1 H), 3.40 (s, 3 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.26 (apparent t, J = 9.7 Hz, 1 H), 3.15 (dd, J = 9.7, 6.8 Hz, 1 H), 3.03 (m, 1 H), 2.91 (ddd, J = 11.2, 8.3, 4.4 Hz, 1 H), 2.84−2.70 (series of m, 4 H), 2.68 (d, J = 4.0 Hz, 1 H), 2.63 (dt, J = 13.7, 4.2 Hz, 1 H), 2.44 (apparent t, J = 6.6 Hz, 1 H), 2.20 (dd, J = 12.0, 3.8 Hz, 1 H), 2.13−1.86 (series of m, 7 H), 1.81 (quintet, J = 6.4 Hz, 1 H), 1.74 (d, J = 1.0 Hz, 3 H), 1.66−1.52 (m, 2 H), 1.35 (dq, J = 11.4, 3.9 Hz, 1 H), 1.28 (d, J = 6.8 Hz, 3 H), 1.25−1.02 (series of m, 6 H), 1.14 (d, J = 6.9 Hz, 3 H), 1.08 (s, 21 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.1 Hz, 3 H), 0.88 (s, 9 H), 0.78 (q, J = 12.0 Hz, 1 H), 0.14 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 136.9, 131.6, 131.3, 129.4, 113.6, 108.9, 84.9, 82.0, 80.0, 78.3, 75.5, 70.7, 62.9, 57.6, 55.2, 54.9, 53.9, 39.7, 38.5, 38.0, 36.4, 36.3, 35.9, 35.3, 34.3, 33.5, 32.9, 31.7, 26.6, 26.5, 26.1, 26.0, 25.0, 24.8, 18.2, 18.1 (2 C), 17.9, 15.6, 15.0, 14.6, 12.7, 12.2, −4.2 (2 C); high-resolution mass spectrum (FAB, NBA) *m/z* 1137.6239 [(M + Na)$^+$; calcd for $C_{58}H_{106}O_8S_4Si_2Na$, 1137.6206]. Anal. Calcd for $C_{58}H_{106}O_8S_4Si_2$: C, 62.43; H, 9.57. Found: C, 62.65; H, 9.54.

Methoxy-Alkylated Dithiane (+)-87. B. From (+)-99. At ambient temperature a solution of alcohol (+)-**99** (11 mg, 0.01 mmol) in THF (0.3 mL) at ambient temperature was treated with sodium hydride (60% oil dispersion; 4 mg, 0.1 mmol), 15-crown-5 (4 μL, 0.02 mmol), and methyl iodide (18 μL, 0.20 mmol). The reaction mixture was stirred for 6 h and partitioned between ether (10 mL) and saturated aqueous NH_4Cl (10 mL). The organic phase was washed with saturated aqueous $Na_2S_2O_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1, containing 1% triethylamine) provided (+)-**87** (9.7 mg, 88% yield) identical to the material prepared from (+)-**86**.

Methoxy Aldehyde (+)-100. At ambient temperature a solution of dimethyl acetal (+)-**87** (15 mg, 0.013 mmol) in acetone (4 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid (ca. 1 mg). The reaction mixture was stirred for 5 h and then partitioned between ether (20 mL) and water (20 mL). The organic phase was washed with water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) gave (+)-**100** (14 mg, 97% yield) as a white foam: $[\alpha]_D^{23}$ +21° (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 1725 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, J = 1.9 Hz, 1 H), 7.28 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 5.52 (d, J = 9.2 Hz, 1 H), 4.48 (ABq, J_{AB} = 10.4 Hz, $\Delta\nu_{AB}$ = 60.0 Hz, 2 H), 4.46 (d, J = 5.3 Hz, 1 H), 3.80 (d, J = 5.3 Hz, 1 H), 3.79 (s, 3 H), 3.71 (br d, J = 6.8 Hz, 1 H), 3.59 (s, 3 H), 3.55 (ddd, J = 10.9, 8.4, 4.7 Hz, 1 H), 3.40 (s, 3 H), 3.26 (dd, J = 9.0, 6.7 Hz, 1 H), 3.20−3.15 (m, 2 H), 2.92 (ddd, J = 11.3, 8.4, 4.5 Hz, 1 H), 2.88−2.82 (m, 2 H), 2.77−2.72 (m, 1 H), 2.64−2.57 (m, 3 H), 2.37−2.30 (m, 2 H), 2.15 (apparent t, J = 11.3 Hz, 1 H), 2.09 (br d, J = 12.0 Hz, 1 H), 2.04−1.82 (m, 6 H), 1.81 (s, 3 H), 1.79−1.60 (m, 2 H), 1.48−1.20 (m, 7 H), 1.19 (d, J = 6.5 Hz, 3 H), 1.12 (d, J = 6.9 Hz, 3 H), 1.08 (s, 21 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.78 (q, J = 12.0 Hz, 1 H), 0.08 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 158.9, 136.0, 131.6, 131.0, 129.6, 113.5, 92.1, 84.9, 81.4, 79.9, 75.6, 70.5, 62.4, 62.0, 57.6, 55.3, 44.4, 39.7, 38.1, 37.1, 36.3, 36.0, 34.3, 33.5, 33.0, 31.7, 27.5, 27.2, 26.4, 26.2, 26.1, 25.0, 24.4, 18.2, 18.1 (2 C), 16.4, 16.0, 15.2, 14.6, 13.1, 12.7, −4.3, −4.4; high-resolution mass spectrum (FAB, NBA) *m/z* 1105.5922 [(M + Na)$^+$; calcd for $C_{57}H_{102}O_7S_4Si_2Na$, 1105.5945]. Anal. Calcd for $C_{57}H_{102}O_7S_4Si_2$: C, 63.17; H, 9.48. Found: C, 63.47; H, 9.60.

Methoxy Vinylidene Dibromide (+)-102. A solution of carbon tetrabromide (215 mg, 0.65 mmol) in THF (10 mL) was cooled to −25 °C, and hexamethylphosphortriamide (HMPT) (0.24 mL, 1.3 mmol) was added. After 5 min the yellow heterogeneous mixture turned beige. A solution of aldehyde (+)-**100** and its C(27) epimer (1:1 mixture, 140 mg, 0.13 mmol) in THF (3 mL) was then introduced via a cannula. The reaction mixture was stirred for 30 min further, quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with ether (30 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (10 mL), water (10 mL), and brine, dried over $MgSO_4$, filtered, and concentrated. A second reaction was performed on the same scale, and the combined products were purified by flash chromatography (hexanes/ethyl acetate, 10:1), furnishing a 1:1 mixture of (+)-**102** and its C(27) epimer (250 mg, 78% total yield) as a white foam. Radial chromatography (silica; 2-mm layer, hexanes/ether, 10:1) afforded (+)-**102** (120 mg, 36%) as a white foam: $[\alpha]_D^{23}$ +12° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 2930 (s), 2860 (s), 1720 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.17 (d, J = 9.4 Hz, 1 H), 5.57 (d, J = 9.4 Hz, 1 H), 4.49 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 67.3 Hz, 2 H), 4.37 (d, J = 5.8 Hz, 1 H), 3.78 (s, 3 H), 3.72 (br d, J = 4.6 Hz, 1 H), 3.64 (d, J = 6.9 Hz, 1 H), 3.58−3.52 (m, 2 H), 3.55 (s, 3 H), 3.40 (s, 3 H), 3.26 (dd, J = 8.1, 7.1 Hz, 1 H), 3.12 (apparent t, J = 10.0 Hz, 1 H), 3.04 (apparent t, J = 10.0 Hz, 1 H), 2.92 (ddd, J = 11.0, 7.8, 4.8 Hz, 1 H), 2.86−2.77 (m, 3 H), 2.69−2.52 (m, 4 H), 2.23 (br m, 1 H), 2.09−2.05 (m, 2 H), 1.97−1.81 (m, 5 H), 1.86 (d, J = 14.4 Hz, 2 H), 1.78 (s, 3 H), 1.72 (d, J = 15.4 Hz, 1 H), 1.65 (d, J = 13.1 Hz, 1 H), 1.43−1.31 (m, 3 H), 1.24 (d, J = 6.7 Hz, 3 H), 1.23−1.16 (m, 2 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.08 (s, 21 H), 1.04 (d, J = 6.7 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.77 (q, J = 12.1 Hz, 1 H), 0.11 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 144.1, 135.9, 131.6, 130.9, 129.8, 129.5, 113.5, 90.2, 88.2, 84.9, 81.7, 80.2, 75.6, 70.7, 62.8, 61.8, 57.9, 57.6, 55.2, 39.7, 38.8, 37.5, 37.0, 36.4, 36.3, 34.3, 33.5, 33.1, 31.7, 27.4, 26.8, 26.5, 26.3, 26.1, 25.0, 24.4, 20.5, 18.3, 18.1 (2 C), 16.5, 16.2, 14.7, 12.7, −4.1, −4.3. Anal. Calcd for $C_{58}H_{102}Br_2O_6S_4Si_2$: C, 56.20; H, 8.29. Found: C, 55.81; H, 8.04.

Methoxy Alkyne (+)-104. A solution of vinylidene dibromide (+)-**102** (103 mg, 0.83 mmol) in THF (5 mL) was cooled to −78 °C and treated dropwise with *n*-BuLi (1.6 M in hexanes, 0.25 mL, 0.40 mmol). The reaction mixture was stirred for 5 min further, quenched with saturated aqueous NH_4Cl (5 mL), and extracted with ether (30 mL). The organic phase was washed with water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography with (hexanes/ethyl acetate, 15:1) gave (+)-**104** (81 mg, 90% yield) as a white foam: $[\alpha]_D^{23}$ +19° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3300 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 5.65 (d, J = 8.9 Hz, 1 H), 4.49 (ABq, J_{AB} = 10.6 Hz, $\Delta\nu_{AB}$ = 79.1 Hz, 2 H), 4.46 (d, J = 4.0 Hz, 1 H), 3.90 (d, J = 4.0 Hz, 1 H), 3.79 (s, 3 H), 3.69 (d, J = 4.5 Hz, 1 H), 3.66 (s, 3 H), 3.55 (ddd, J = 10.9, 8.3, 2.6 Hz, 1 H), 3.40 (s, 3 H), 3.32−3.20 (m, 3 H), 2.92 (ddd, J = 12.6, 8.4, 4.4 Hz, 1 H), 2.87−2.76 (m, 3 H), 2.65−2.61 (m, 2 H), 2.57−2.45 (m, 3 H), 2.24 (d, J = 2.2 Hz, 1 H), 2.08−1.91 (m, 8 H), 1.85 (s, 3 H), 1.79 (d, J = 14.9 Hz, 2 H), 1.70 (m, 1 H), 1.64 (m, 2 H), 1.56−1.25 (series of m, 4 H), 1.23 (d, J = 6.5 Hz, 3 H), 1.19 (d, J = 6.8 Hz, 3 H), 1.10 (d, J = 7.0 Hz, 3 H), 1.08 (s, 21 H), 0.89 (s, 9 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.76 (q, J = 12.0 Hz, 1 H), 0.11 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 136.3, 131.6, 130.7, 129.6, 113.4, 96.5, 87.8, 84.9, 80.3, 80.0, 75.6, 70.7, 70.5, 62.1, 60.7, 57.7, 57.5, 55.2, 39.7, 38.1, 38.0, 37.4, 36.3, 36.2, 34.3, 33.5, 33.1, 31.7, 27.5, 26.5, 26.2, 26.1, 25.0, 24.5, 24.1, 22.0, 18.1 (2 C), 15.7, 15.5, 14.6, 14.1, 13.2, 12.8, −4.1, −4.3; high-resolution mass spectrum (FAB, NBA) *m/z* 1101.5985 [(M + Na)$^+$; calcd for $C_{58}H_{102}O_6S_4Si_2Na$, 1101.5996]. Anal. Calcd for $C_{58}H_{102}O_6S_4Si_2$: C, 64.51; H, 9.52. Found: C, 64.89; H, 9.66.

Methoxy Alcohol (+)-106. A solution of PMB ether (+)-**104** (31 mg, 0.03 mmol) in dichloromethane (4 mL) was treated with water (0.2 mL) and the biphasic mixture cooled to 0 °C. DDQ (7 mg, 0.03

mmol) was added portionwise over 5 min. The yellow-brown reaction mixture was stirred at 0 °C for 30 min and then directly subjected to flash chromatography (hexanes/ethyl acetate, 6:1), affording (+)-**106** (26 mg, 94% yield) as a white foam: $[\alpha]_D^{23}$ +9.1° (*c* 0.64, $CHCl_3$); IR ($CHCl_3$) 3620 (w), 3440 (br), 3310 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (d, J = 9.7 Hz, 1 H), 4.49 (d, J = 3.3 Hz, 1 H), 3.95 (d, J = 3.3 Hz, 1 H), 3.86 (m, 1 H), 3.68 (s, 3 H), 3.54 (ddd, J = 12.3, 8.5, 3.6 Hz, 1 H), 3.45 (br s, 1 H), 3.39 (s, 3 H), 3.31 (apparent t, J = 11.0 Hz, 1 H), 3.22 (br t, J = 10.9 Hz, 1 H), 3.14 (ddd, J = 7.4, 7.0, 7.0 Hz, 1 H), 2.97−2.83 (m, 3 H), 2.77−2.70 (m, 2 H), 2.65 (dt, J = 13.5, 4.2 Hz, 1 H), 2.58−2.54 (m, 2 H), 2.43 (ddd, J = 9.8, 6.6, 6.6 Hz, 1 H), 2.32 (d, J = 1.8 Hz, 1 H), 2.21 (dd, J = 15.4, 9.3 Hz, 1 H), 2.11 (br d, J = 9.5 Hz, 1 H), 2.06 (d, J = 15.4 Hz, 1 H), 2.03−1.97 (m, 2 H), 1.93−1.88 (m, 2 H), 1.84 (s, 3 H), 1.81 (m, 1 H), 1.69−1.62 (m, 3 H), 1.57 (d, J = 2.5 Hz, 1 H), 1.52 (dt, J = 12.2, 4.2 Hz, 1 H), 1.43−1.29 (m, 4 H), 1.27 (d, J = 6.5 Hz, 3 H), 1.22 (d, J = 7.3 Hz, 3 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.07 (s, 21 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.73 (q, J = 12.0 Hz, 1 H), 0.12 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 130.2, 87.8, 84.9, 79.9, 75.6, 72.4, 70.6, 65.8, 62.3, 60.3, 57.8, 57.4, 39.0, 38.8, 38.7, 37.5, 36.8, 35.9, 34.3, 33.4, 32.1, 28.3, 27.5, 26.3, 26.0, 24.8, 24.5, 24.1, 22.0, 18.1 (2 C), 15.5, 15.1, 13.3, 12.7, −4.1, −4.3; high-resolution mass spectrum (CI, NH_3) *m/z* 981.5415 [(M + Na)$^+$; calcd for $C_{50}H_{94}O_5S_4Si_2Na$, 981.5421].

Methoxy Aldol (−)-108. A solution of dithiane (+)-**106** (9.9 mg, 0.01 mmol) in THF/MeOH/H_2O (10:9:1, 2 mL) was cooled to 0 °C and treated with $PhI(O_2CCF_3)_2$ (21 mg, 0.05 mmol). After 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), and the resultant mixture was partitioned between ether (10 mL) and water (5 mL). The organic phase was washed with saturated aqueous $Na_2S_2O_3$ (5 mL), water (5 mL), and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 6:1) gave (−)-**108** (6.9 mg, 86% yield) as a colorless oil: $[\alpha]_D^{23}$ −106° (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 3680 (w), 3510 (br), 3310 (w), 1720 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.32 (d, J = 9.9 Hz, 1 H), 4.24 (d, J = 7.0 Hz, 1 H), 3.93 (d, J = 7.0 Hz, 1 H), 3.84 (m, 1 H), 3.53 (ddd, J = 11.0, 8.4, 4.8 Hz, 1 H), 3.41 (dd, J = 9.7, 6.8 Hz, 1 H), 3.38 (s, 3 H), 3.29 (s, 3 H), 3.11 (ddd, J = 11.0, 6.7, 3.1 Hz, 1 H), 2.95 (d, J = 4.1 Hz, 1 H), 2.90 (ddd, J = 11.2, 7.4, 4.5 Hz, 1 H), 2.58 (dd, J = 17.4, 2.2 Hz, 1 H), 2.56 (m, 1 H), 2.46 (dd, J = 17.4, 9.9 Hz, 1 H), 2.09 (d, J = 2.4 Hz, 1 H), 2.07 (m, 1 H), 1.91 (dq, J = 13.1, 4.7 Hz, 1 H), 1.77−1.71 (m, 1 H), 1.75 (d, J = 1.3 Hz, 3 H), 1.67−1.58 (m, 2 H), 1.36−1.13 (m, 4 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.07 (s, 21 H), 0.98−0.88 (m, 2 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.85 (s, 9 H), 0.69 (q, J = 11.6 Hz, 1 H), 0.01 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8 (s), 212.6 (s), 137.8 (s), 127.9 (d), 87.5 (d), 84.9 (d), 84.8 (d), 78.7 (d), 75.5 (d), 71.7 (d), 69.4 (s), 58.1 (q), 57.4 (q), 46.9 (d), 43.5 (t), 42.9 (d), 39.0 (t), 38.7 (t), 35.7 (t), 35.4 (d), 34.3 (t), 33.3 (d), 32.0 (t), 25.8 (q), 23.7 (d), 21.5 (q), 18.1 (s), 18.1 (q), 15.6 (q), 15.3 (q), 14.0 (q), 12.7 (d), 12.2 (q), −4.6 (q), −5.0 (q); high-resolution mass spectrum (FAB, NBA) *m/z* 801.5491 [(M + Na)$^+$; calcd for $C_{44}H_{82}O_7Si_2Na$, 801.5496].

Methoxy ABC Vinylstananne (−)-27. A solution of alkyne (−)-**108** (7.5 mg, 10 μmol) and bis(triphenylphosphine)palladium(II) dichloride (1 mg, 20 mol %) in THF (1.5 mL) was cooled to 0 °C, and tri(*n*-butyl)tin hydride (13 μL, 50 μmol) was added dropwise. After 5 min, the reaction mixture was directly subjected to flash chromatography (hexanes/ethyl acetate, 10:1, containing 1% triethylamine). The resultant impure stannane was rechromatographed (hexanes/ethyl acetate, 10:1, containing 1% triethylamine), affording (−)-**27** (9.4 mg, 91% yield) as a colorless oil: $[\alpha]_D^{23}$ −62° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 1710 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.07 (d, J = 19.0 Hz, 1 H), 5.96 (dd, J = 19.0, 7.5 Hz, 1 H), 5.34 (d, J = 9.4 Hz, 1 H), 4.49 (d, J = 6.9 Hz, 1 H), 3.97 (m, 1 H), 3.88 (d, J = 7.0 Hz, 1 H), 3.66 (ddd, J = 11.1, 6.2, 4.1 Hz, 1 H), 3.29 (s, 3 H), 3.28−3.20 (m, 2 H), 3.20 (s, 3 H), 2.93−2.87 (m, 3 H), 2.52 (dd, J = 17.2, 2.3 Hz, 1 H), 2.42 (dd, J = 17.2, 9.8 Hz, 1 H), 2.31 (m, 1 H), 2.14 (m, 1 H), 1.96 (dq, J = 12.9, 3.5 Hz, 1 H), 1.85 (ddd, J = 13.8, 8.4, 4.3 Hz, 1 H), 1.72 (d, J = 1.3 Hz, 3 H), 1.67−1.51 (m, 9 H), 1.44−1.26 (m, 10 H), 1.24−1.15 (complex series of m, 36 H), 1.14 (d, J = 6.6 Hz, 3 H), 1.12 (d, J = 6.4 Hz, 3 H), 1.05−0.89 (m, 6 H), 0.95 (s, 9 H), 0.77 (q, J = 12.0 Hz, 1 H), 0.11 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.6, 211.1, 154.5, 137.8, 128.5, 126.8, 85.6, 85.0, 78.4, 75.9, 71.9, 58.0, 56.9, 47.1, 44.1, 42.6, 39.7, 39.5, 38.9, 36.0, 35.9, 34.7, 33.7, 32.3, 29.6, 27.6, 26.1, 21.5, 18.5, 18.4, 15.8, 15.3, 13.9, 13.1, 12.4, 9.8, −4.3, −4.7; high-resolution mass spectrum (FAB, NBA) *m/z* 1093.6736 [(M + Na)$^+$; calcd for $C_{56}H_{110}O_7Si_2SnNa$, 1093.6709].

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Supporting Information Available: Experimental procedures and characterization data for **10**, **12**, **16**, **19**−**25**, **41**−**44**, **49**−**53**, **56**−**58**, **60**−**67**, **69**−**77**, **79**−**83**, **88**, **90**−**93**, **95**, **101**, **103**, **105**, **107**, **109**, and **28** and X-ray data for (+)-**66** and (+)-**70** (51 pages). See any current masthead page for ordering and Internet access instructions.

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