51.7, 39.7, 36.9, 36.0, 34.8, 33.4, 31.4, 25.9, 25.8, 18.2, 18.1, 14.7, 14.6, 12.8, -3.9, -4.1, -4.3; IR ($CHCl_3$) 2920, 2860, 1705, 1460, 1260, 1090 cm^{-1}; MS (FAB) *m/e* 601.4328 (601.4321 calcd for $C_{32}H_{64}O_6Si_2$ + H); $[\alpha]^{23}_D$ -21.1° (*c* 1.4, $CHCl_3$).

Structure Proof for Diol 21. Preparation of Dibenzyl Ether 37. Diol **21** (0.080 g, 0.288 mmol) was dissolved in 2-methoxypropene (5 mL). The resulting solution was treated with Amberlyst -15 (ca. 100 mg) and then stirred at room temperature for 2.5 h. At this time, the mixture was filtered and concentrated. The crude isolate was then taken up in a 1:1 mixture of methanol and CH_2Cl_2 (5 mL) and treated at -78 °C with ozone until the solution remained blue. At this point, the reaction was degassed with argon and treated with $NaBH_4$ (ca. 100 mg). After being stirred at room temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic material was dried (K_2CO_3) and concentrated. The crude material was taken up in DMF (0.5 mL) and treated with benzyl bromide (46 mL, 0.39 mmol), Bu_4NI (cat.), and NaH (ca. 50 mg of a 60% dispersion in oil). This mixture was maintained at room temperature for 16 h. The reaction was quenched with H_2O (10 mL), and the resulting mixture was extracted with hexanes. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (silica gel, 240-400 mesh, 10:1 hexanes/EtOAc) to provide 0.050 g of **37** (47%) as a pure colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5 H), 4.50 (s, 4 H), 3.72 (app q, *J* = 8.0 Hz, 2 H), 3.53 (dd, *J* = 4.5, 9.0 Hz, 2 H), 3.38 (dd, *J* = 6.3, 9.0 Hz, 2 H), 1.85 (m, 2 H), 1.62 (app t, *J* = 8.0 Hz, 2 H), 1.30 (s, 6 H), 0.96 (d, *J* = 6.7 Hz, 6 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 138.9, 128.3, 127.5, 127.4, 100.3, 73.1, 72.2, 67.9, 38.7, 34.0, 24.4, 12.8; IR (film) 2900, 1450, 1380, 1230, 1100 cm^{-1}; MS (EI) *m/e* 397 ($M^+ - CH_3$); $[\alpha]^{23}_D$ -13.7° (*c* 0.35, $CHCl_3$).

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Registry No. **1**, 53123-88-9; **5**, 135708-74-6; **6**, 135708-83-7; α-**8**, 67968-51-8; β-**8**, 131615-73-1; α-**9**, 126373-46-4; β-**9**, 135818-56-3; α-**10**, 18933-65-8; β-**10**, 135708-66-6; α-**11**, 135708-67-7; β-**11**, 135708-68-8; α-**12**, 135708-69-9; β-**12**, 135708-70-2; α-**13**, 135708-71-3; β-**13**, 135708-72-4; **14**, 135708-73-5; *anti*-**16a**, 94233-74-6; *syn*-**16a**, 94233-73-5; *anti*-**16b**, 135708-75-7; *syn*-**16b**, 135708-76-8; α-**17**, 135708-77-9; β-**17**, 135708-78-0; **18**, 99687-40-8; **21**, 135708-79-1; **22**, 135708-80-4; **23**, 135708-81-5; **24**, 135708-82-6; **25**, 135708-84-8; **26**, 135708-85-9; **27** (isomer 1), 135708-86-0; **27** (isomer 2), 135818-57-4; **28** (isomer 1), 135708-87-1; **28** (isomer 2), 135818-58-5; **29** (isomer 1), 135708-88-2; **29** (isomer 2), 135818-59-6; **30** (isomer 1), 135708-89-3; **30** (isomer 2), 135818-60-9; **31**, 135708-90-6; **33**, 135708-91-7; **34**, 135708-92-8; **35**, 2605-68-7; **36**, 135708-93-9; **37**, 135734-22-4.

Supplementary Material Available: NMR spectra for compounds **5**, **6**, **21-25**, **31**, **33**, **34**, **36**, and **37** (12 pages). Ordering information is given on any current masthead page.

Application of the Ibuka-Yamamoto Reaction to a Problem in Stereochemical Communication: A Strategy for the Stereospecific Synthesis and Stabilization of the Triene Substructure of Rapamycin through Sulfone Substitution

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The aldehydes **49** and **55** corresponding to carbons 13-30 in a projected total synthesis of rapamycin have been synthesized. The LACDAC technology was used to elaborate dithiane enal **5**. The aldehyde **4** was synthesized from D-(+)-glucose. A critical element of that construction involved cuprate-induced displacement reactions on enoates **7** and **8** (see formation of esters **9a** and **9b**) to correlate the stereochemistry of carbons 8 and 12. The feasibility of conducting a Nozaki-Kishi reaction between iodosulfone **6** and aldehyde **4** was a major simplification. Julia coupling between sulfone **5** and aldehyde **43** was followed by acetylation and elimination of acetic acid. The triene sulfone **54** was obtained stereospecifically. The C_4 sulfone linkage is a considerable stabilizing element on the C_1-C_6 triene. Its presence allows for removal of the dithiane linkage (see formation of aldehyde **55**). Cleavage of the sulfone is accomplished with sodium analgam without reduction of an aldehyde function at C_{30} (see formation of **49**).

Background of the Problem and Synthetic Planning

In the preceding paper,[1] we reviewed background issues concerning the immunosuppressant rapamycin (**1**)[2] and reported the synthesis of a major segment of the molecule containing C_{47}-C_{28} (see compound **2**).[3] Below, we describe the outcome of a program that focused on generalized system **3**, encompassing C_{30}-C_{13}. In the preliminary stages, the oxygen protecting groups could not be specified and the nature of the acyl carbon at C_{30} was not formulated in detail. To converge on rapamycin, it would be necessary to interpolate the C_{29} methine center (bearing a methoxy group) between C_{30} of **3** and C_{28} of **2**. It would also be necessary to introduce C_{14} and C_{15} as a "C_2 fragment" (presumably via an aldehyde ultimately derived from C_{13})[3,4]

(1) Preceding paper in this issue.
(2) (a) Sehgal, S. N.; Baker, H.; Vézina, C. *J. Antibiot.* **1975**, *28*, 727. (b) Vézina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721. (c) Findlay, J. A.; Radics, L. *Can. J. Chem.* **1980**, *58*, 579. (d) Swindells, D. C. N.; White, P. S.; Findlay, J. A. *Can. J. Chem.* **1978**, *56*, 2491.

(3) The numbering system for rapamycin has been previously defined. See ref 2c.

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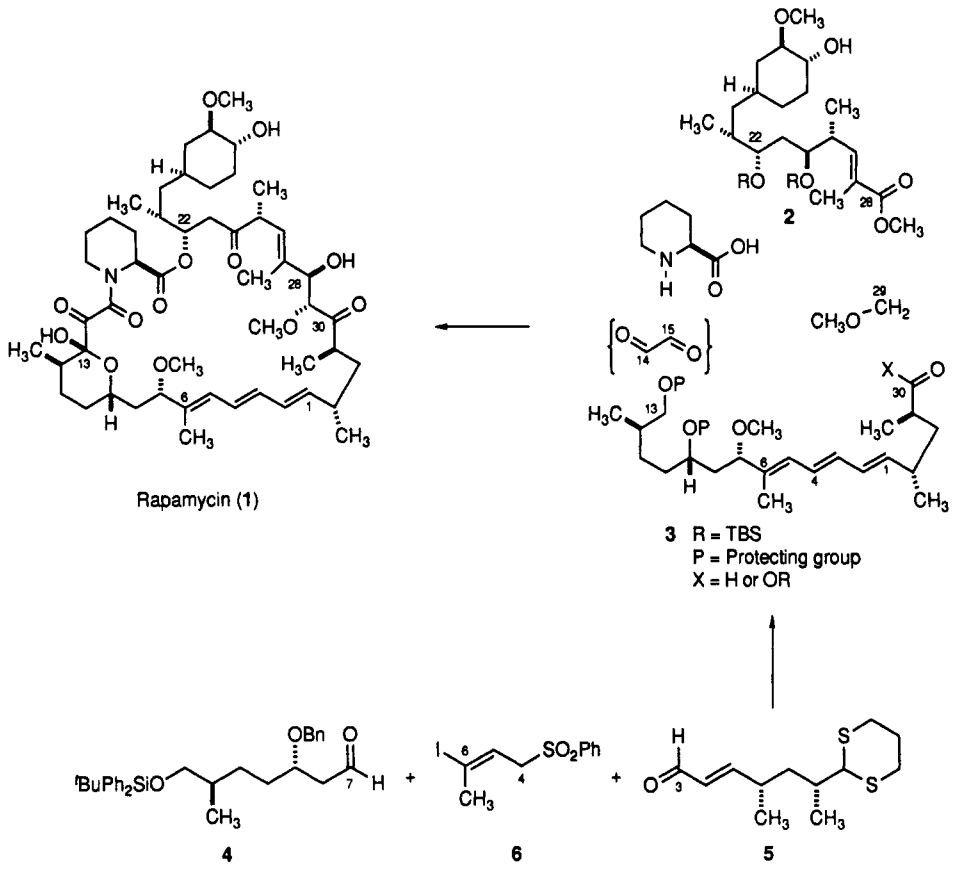


Figure 1.

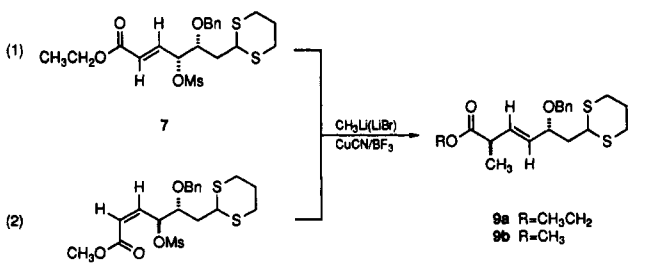
and to make provision for the installation of a pipecolinyl residue at the C_{22} hydroxyl of fragment **2**. Finally, a program for macrocyclization would be required.

In our synthesis strategy for the C_{30}–C_{13} fragment, we would be dealing with the triene array spanning carbons 1–6.[3] This olefinic locus insulates the two chiral domains of fragment **3**. The "triene spacer" represented an opportunity and a challenge. The opportunity resided in the potential use of known olefin-forming reactions for the construction of the C_3–C_4 linkage. *The coupling of properly matched subunits would avoid the need for "long range" asymmetric induction.*[5] The challenge arose from the need to exercise control over the geometry of the three double bonds. As matters transpired (vide infra) we were to be confronted with an unforeseen problem. Various acyclic derivatives containing the triene system manifested only marginal stability toward subsequent reactions. In some instances (cf. **47** and **52**) molecules containing the triene chromophore decomposed during workup and would not tolerate routine purification procedures.

In this paper, we describe a straightforward route to several versions of system **3** (see specific compounds **49** and **55**). This large fragment was assembled from two chiral subfragments **4** and **5** and "spacer" **6** (Figure 1). A highly stereoselective route to the triene was eventually accomplished. During the course of these studies it was found that systems containing trienesulfone (see compounds **54** and **55**) are much more stable than are those that contain a "naked" triene. Chemical steps that were highly problematic when the sulfone was lacking could be conducted in molecules containing a C_4 sulfone moiety. Reductive removal of the sulfone proceeded smoothly and can be accomplished even in the presence of an aldehyde (see transformation **55** → **49**).

Subfragment **4** was viewed as corresponding to carbons C_7–C_{13} of rapamycin.[3] It is expected that at a later stage C_{13} will, after conversion to an aldehyde, couple with a two-carbon nucleophile[4] embodying C_{14} and C_{15} of rapamycin. We considered schemes in which the chirality at C_{12} and C_9 would be controlled in the required sense. Ideally, a suitably chosen starting material could provide convenient access to one of the stereogenic centers, while the second center could be fashioned by intramolecular induction. However, we were not confident that a straightforward way could be found by which one of these two stereogenic elements could instruct the configuration of the other (viz. reduction, alkylation, etc.).

An interesting possibility for addressing this problem was implicit in the work of Ibuka and Yamamoto.[6] As shown in eqs 1 and 2, application of this stereochemical



logic to a cuprate displacement reaction on either of the

(4) For leading references on the synthesis of tricarbonyl systems see: Linde, R. G. III; Jeroncic, L. O.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 2534. Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743. *Schank*, K.; Lick, C. *Synthesis* **1983**, 392. Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785.

(5) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.

(6) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864.

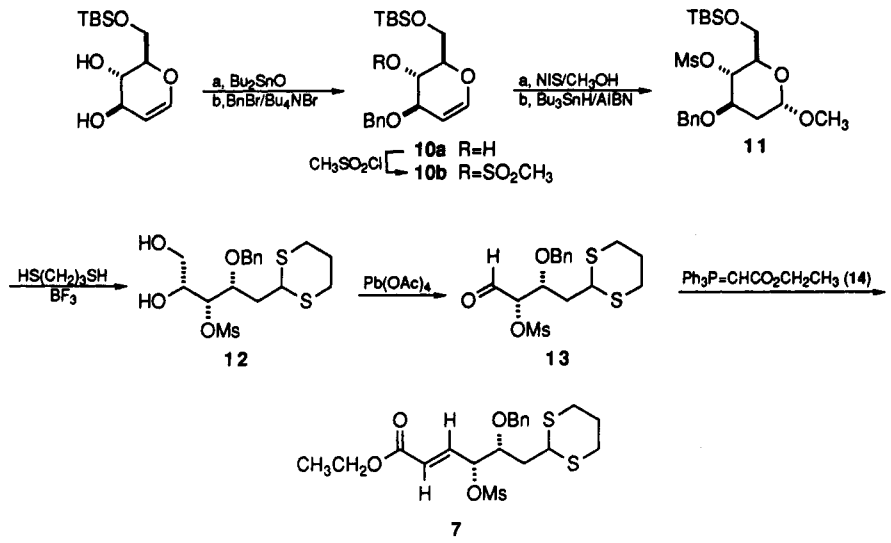


Figure 2.

allylic mesylates **7** or **8** should give rise to an unsaturated ester of the type **9**. Such a product would have obvious possibilities for reaching fragment **4**.

It was recognized that in either D-(+)-glucose or D-(+)-galactose, the configuration at C_3 and the relationship of this center with the masked aldehyde at C_1 mapped well with the requirements at C_9 and C_7 of our target fragment **4**. A further simplification would be possible by starting with the corresponding glycals. Successful implementation of this strategy would require cleavage of the C_5–C_6 diol of the carbohydrate and transformation of the resulting aldehyde into an enoate. It is interesting to note that by permuting the olefin geometry of the enoate (see **7** or **8**) one could use either sugar, although they differ in their configurations at C_4.

Discussion of Results

The synthesis of **7** (Figure 2) started with the 6-*O*-TBS derivative of D-glucal, which was converted, via its stannyl ether,[7] to the known[8] benzyl ether **10a** and thence to mesylate **10b** (99%). The mesylate survived transformation of the glycal to the α-methyl 2-deoxyglycoside **11** (62% overall) via iodomethoxylation and reduction.[9] Subsequent conversion to the dithianediol **12** was accomplished in 74% yield through the reaction of **11** with BF_3·Et_2O and 1,3-propanedithiol. Oxidation of **12** with lead tetraacetate [$Pb(OAc)_4$][10] provided the labile α-mesyloxy aldehyde **13**, which was allowed to react with (carbethoxymethylene)-triphenylphosphorane (**14**), giving **7** in (45% yield from **12**).

Compound **8** was synthesized by a related route (Figure 3) that started with D-galactal triacetate. This compound was converted to the α-methyl 2-deoxygalactoside **15b** via reduction of the 2-iodo sugar **15a** (72% for two steps).[9] The acetates were cleaved with sodium methoxide in methanol, and a TBS group was introduced onto the primary alcohol C_6 providing **16** in 75% yield. Benzylation of the C_3 hydroxyl group via the corresponding stannyl ether[7] provided compound **17** in 98% yield, which was mesylated at C_4, giving rise to **18** in 80% yield. This compound was subjected to the action of BF_3·Et_2O and 1,3-propanedithiol whereupon dithiane diol **19** was obtained in 73% yield. Cleavage of the vicinal diol with $Pb(OAc)_4$[10] gave **20**, which was immediately subjected to cis olefination under the protocols of Still[11] giving **8**, in 32% overall yield from **19**.

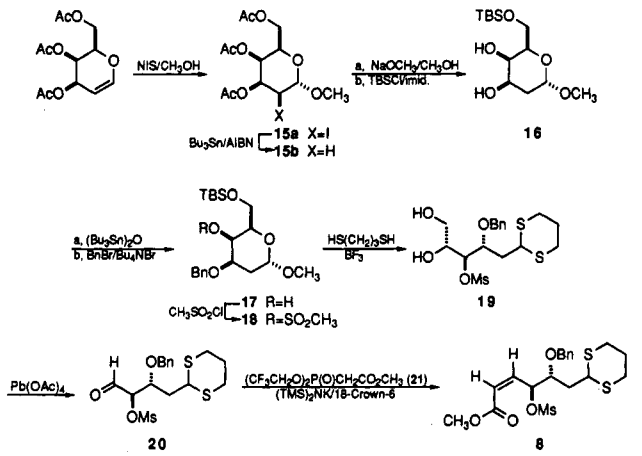


Figure 3.

The stage was set to carry out the cuprate displacement reaction on **7** and **8** (Figure 4). Indeed, reaction of these mesylates under the previously described conditions[6] afforded the closely related esters **9a** and **9b**, respectively, in ca. 75% yield. Reduction of the double bond of these compounds with Wilkinson's catalyst[12] provided **22a** or **22b**, respectively, in 85% to 95% yield. The two series were merged after reduction of the esters with diisobutylaluminum hydride (DIBAH) to afford **23** (about 90% yield in each case). Protection of the primary alcohol as the *tert*-butyldiphenylsilyl ether provided **24** in 100% yield. Finally, liberation of the aldehyde from the dithiane afforded subfragment **4** in 89% yield.[13]

The synthesis of enal **5** (Figure 5) exploited stereochemical findings that we had registered in our studies of the LACDAC reaction.[14,15] We proposed to use as our defining matrix a branched pyranose that would be prepared by total synthesis. The branched pyranose would

(7) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(8) Prandi, J.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4517.
(9) Theim, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.
(10) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439.
(11) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(12) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711.
(13) See: Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357 and references cited therein.
(14) Danishefsky, S. J. *Chemtracts* **1989**, 273.
(15) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.

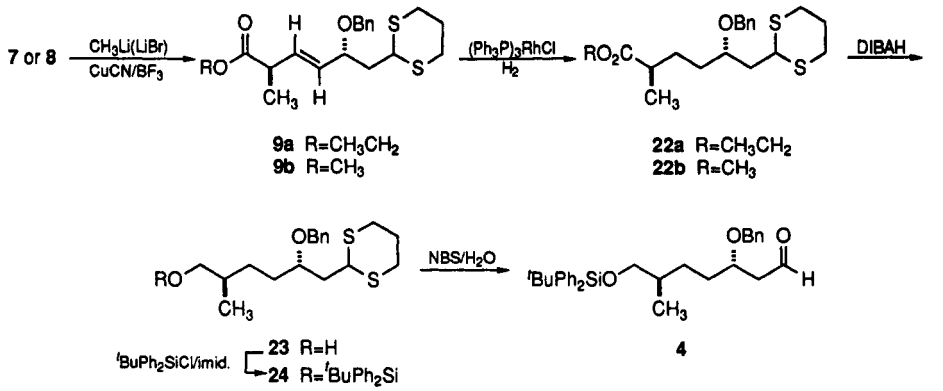


Figure 4.

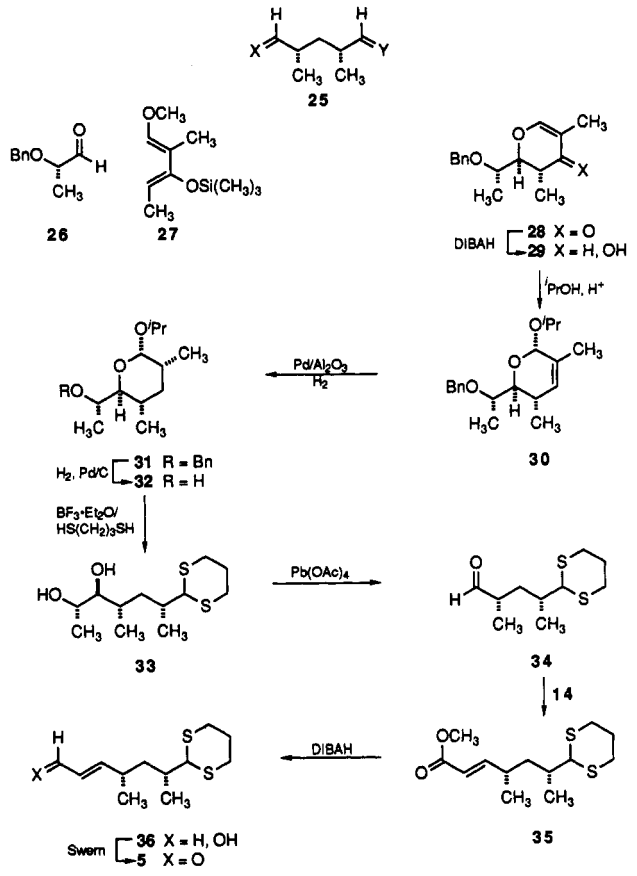


Figure 5.

be a functional equivalent of the formal dialdehyde equivalent **25**, *with the critical proviso that the terminal functions X and Y shall not, at any stage, be identical.* The appropriate absolute configuration of the pyranose ring would be established by suitable communication[16] from a heterodienophile bearing an α stereogenic center. As matters would unfold, neither C_6 of the heptulose, which was initially present in aldehyde **26**, nor C_5, arising in **28** from the stereocontrolled cyclocondensation reaction (vide infra), would be "bequeathed" to the final product **5**. However, their imprints were to be transferred to the methyl-branched centers destined to become carbons 31 and 33 of rapamycin.

The compound that served the synthesis well was (*S*)-2-(benzyloxy)propanal **26**.[17] Chelation-controlled

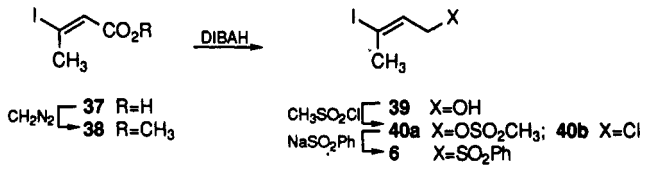


Figure 6.

LACDAC reaction of **26** with diene **27**, modulated by magnesium bromide,[18] afforded a 75% yield of dihydropyrone **28**. Reduction of the carbonyl group with DIBAH afforded the branched glycal **29**. Treatment of **29** with acidic 2-propanol triggered Ferrier rearrangement,[19] thereby providing the branched isopropoxypseudoglycal **30** (88% yield from **28**). Hydrogenation of the double bond, catalyzed by palladium on alumina, was stereospecific in the anticipated[20] sense, affording the branched pyranose derivative **31**. Further hydrogenation with palladium on charcoal cleaved the benzyl ether protecting group, providing **32** in 68% yield from **30**. Compound **32** was treated with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$. In this process (96%), the masked aldehyde at the "reducing" terminus of **32** emerged as a protected dithiane, and a vicinal diol function is liberated. The diol of **33** was cleaved with $Pb(OAc)_4$[10] to afford aldehyde **34** in 60% yield. The latter was condensed with phosphorane **14** to afford the enoate **35** (81% yield). Reduction of the ester function with DIBAH produced alcohol **36**, which upon Swern oxidation[21] afforded the desired enal subfragment **5** (62% from **35**).

The synthesis of the spacer element **6** commenced with known protocols[22] for the addition of hydrogen iodide to tetrolic acid (Figure 6). This reaction produced, after isomerization, the (*E*)-iodocrotonic acid **37**. The latter was subjected to the action of diazomethane, and the resulting ester **38** was reduced with DIBAH affording **39** in 71% yield (from **37**). This alcohol afforded, upon treatment with methanesulfonyl chloride, a mixture of chloride **40a** and mesylate **40b**. Upon reaction of the mixture with sodium phenylsulfinate, the required **6** was obtained in 47% yield from **39**. Apparently, **40a** and **40b** are each converted to **6** by this process. The latter is obtained as a crystalline solid (mp 106.5–107.5 °C), and its ready purification was a significant convenience for the synthesis.

(16) Cf. Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456. Danishefsky, S. J.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360. Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636.

(17) Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247.

(18) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2455.

(19) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.

(20) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

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

(22) LeNoble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897.

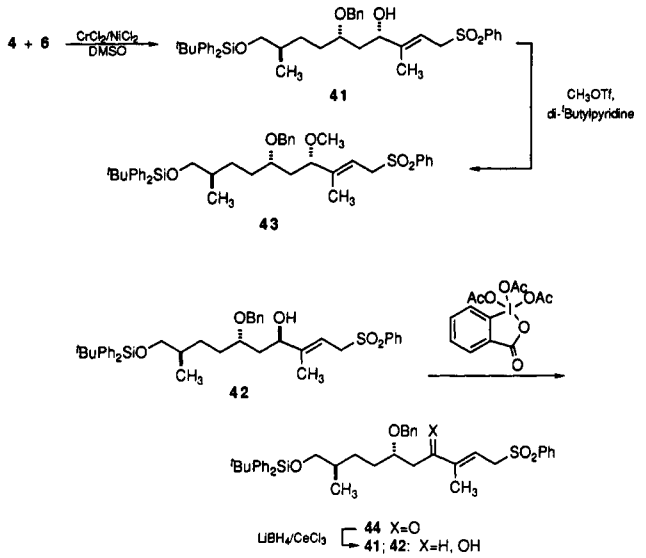


Figure 7.

A variety of possibilities were attempted,[23] unsuccessfully, to achieve stereoselective addition of a relevant nucleophile to the β-benzyloxy aldehyde **4**. As part of this effort we studied a Nozaki–Kishi reaction of the iodo olefin **6** with **4**[24,25] (Figure 7). In the event, a 66% yield of a 1:1 mixture of epimers was obtained. The two compounds could be separated, and the one shown (vide infra) to be **41** was transformed (100%) to methyl ether **43** through the agency of di-*tert*-butylpyridine and methyl triflate.[26] The epimeric alcohol **42** was recycled by oxidation with Dess–Martin reagent[27] to give **44**. The latter, upon reduction with lithium borohydride in the presence of cerium chloride,[28] gave a 1:1 mixture of **41** and **42**, from which additional amounts of the former could be obtained. Obviously, the lack of stereoselectivity in either the addition reaction, or the reduction, is a significant awkwardness, although the yields are high and the recycling process is eminently practical. We shall return to this issue toward the end of this report and describe a prospectus for a solution. For the moment we shall concern ourselves with the all critical Julia[29,30] coupling of compounds **43** and **5**.

Treatment of **43** with 1 equiv of *n*-butyllithium in THF at −78 °C generated its presumed α-lithiosulfonyl derivative (Figure 8). To the latter was added dithiane enal **5**. Chromatographic and spectroscopic analysis indicated that coupling had occurred, though a homogeneous β-hydroxy sulfone was not isolated. Instead, the crude product, presumed to consist of stereoisomers **45**, was acetylated (Ac_2O, Et_3N, DMAP). Some difficulties were experienced in obtaining the purified acetate epimer mixture **46** from **45** (85%). In crude form, the acetate mixture **46** was unstable, though the purified product exhibited greater stability. Treatment of **46** with 5% sodium amalgam in THF afforded the triene dithiane **47**. Unfortunately the material so obtained was an inseparable ca. 1:1 mixture of presumed *E* and *Z* isomers (**47** and **48**) in 65% yield. Moreover, silica gel chromatography failed to resolve the mixture. A further serious reverse was incurred when a variety of attempted deprotection reactions[31] designed to obtain a triene aldehyde (see compounds **49** and **50**) resulted in extensive decomposition with formation of unidentifiable products. The apparent instability of the triene chromophore to the seemingly mild conditions employed for the removal of the dithiane was also mirrored in its poor "shelf life" under essentially neutral conditions.

We next explored the possibility that the dithiane deprotection could be accomplished on the β-hydroxy acetate mixture **46**. This in fact was possible. Treatment of **47** with NCS and $AgNO_3$[13] indeed afforded aldehyde **51** in 66% yield. This compound was reduced with sodium borohydride. The resultant product was subjected to the action of 5% sodium amalgam to afford a mixture (ca. 1:1 ratio) of **52** and **53**, which were inseparable. While these results did demonstrate that the dithiane could be cleaved at a stage when the triene was absent, they did not identify a solution to the problem of the apparent lack of selectivity in the construction of the C_3–C_4 double bond.

A simultaneous solution to both the selectivity and stability problems was achieved through a phenylsulfonyl triene.[32] Thus, treatment of sulfonyl acetates **46** with DBU in THF generated compound **54** as apparently a single geometric isomer (shown arbitrarily in the *Z* form) in 89% yield. In contrast to **47**, **54** was a reasonably stable product. Treatment of this compound with NCS and $AgNO_3$[13] did indeed produce aldehyde **55**. The sodium amalgam method for desulfonylation is sufficiently selective that it can be conducted in the presence of an aldehyde. Thus, reaction of **55** with sodium amalgam afforded the trienealdehyde **49** as substantially a single *E* product.[33]

We now return to the issue of the assignment of stereochemistry at C_7 in structure **41** (the assignment of the configuration at this center in the terminal product **49** rests on the correct assignment at the stage of **41**). While persuing this stereochemical question, we also addressed the lack of stereoselectivity in addition reactions to aldehyde **4**. In this connection we studied (Figure 9) the reaction of **4** with (*E*)-crotyl boronate **56** (derived from (*S*,*S*)-diisopropyl tartrate). It was hoped that auxiliary-mediated crotyl boronate addition[34,35] would provide the desired level of stereoselectivity.

In practice, a mixture (ca. 2.5:1) of two addition products was generated. The alcohol functions of the resulting products were methylated through the agency of methyl triflate and di-*tert*-butylpyridine.[26] At this point, the methyl ethers could be separated by silica gel chromatography. On the basis of the extensive investigations of

(23) (a) Attempted addition of the organo lithium reagent derived from a vinyl bromide prepared from tetrolic acid[22] resulted in significant elimination of the β-benzyloxy group of **4**. A variety of cuprates[23b] derived from the latter vinyl bromide gave similar results. (b) For a successful example of this type of transformation see: Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863.

(24) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

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(26) Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1990**, *55*, 5192 and references cited therein.

(27) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(28) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

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(31) Deprotection methods included the reagents NCS/$AgNO_3$, Me_3OBF_4, $C_6H_5I(OCOCF_3)_2$/MeOH/H_2O, $C_6H_5I(OCOCF_3)_2$/CH_3CN/H_2O, and $Hg(OAc)_2$.

(32) For a review on the chemistry of vinyl sulfones, see: Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951.

(33) While sulfone aldehyde **55** is a single entity, triene aldehyde **49**, arising from the sodium amalgam reduction, is obtained as a 5.3:1 mixture. The minor impurity is not compound **50**. We assume it to have arisen from small amounts of epimerization at C_{31}.

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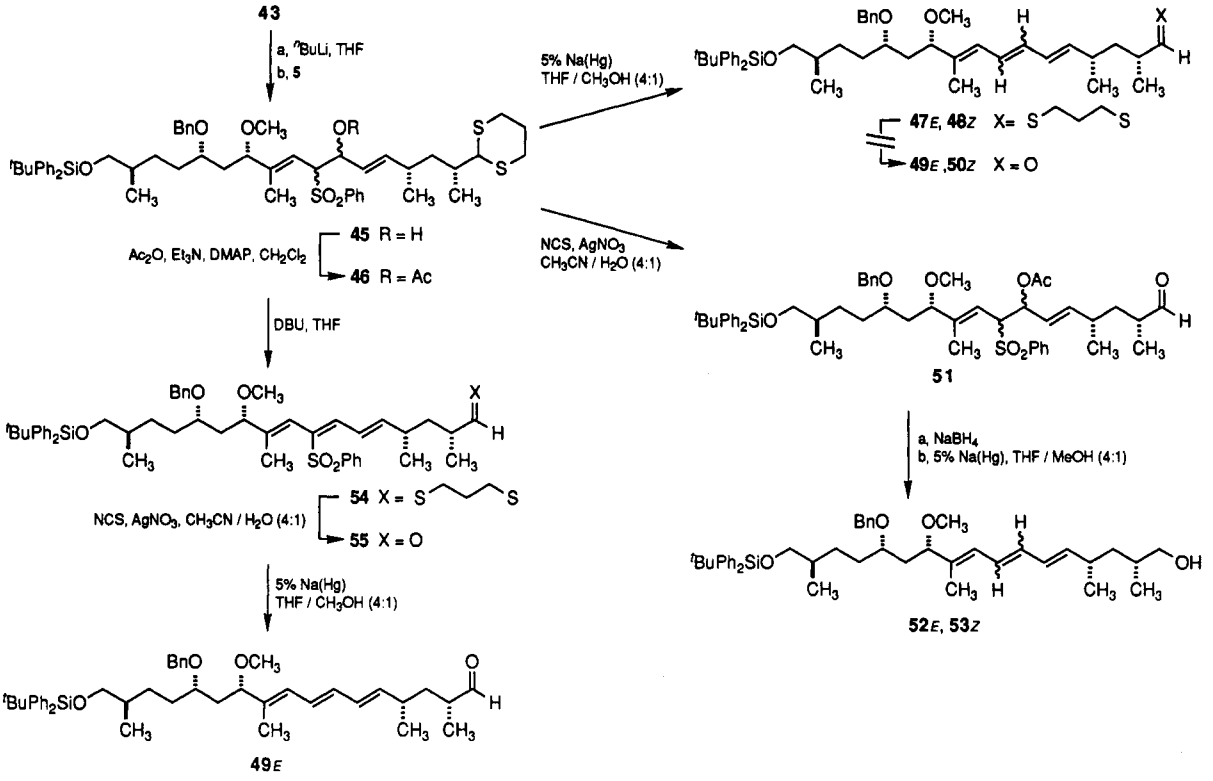

Figure 8.

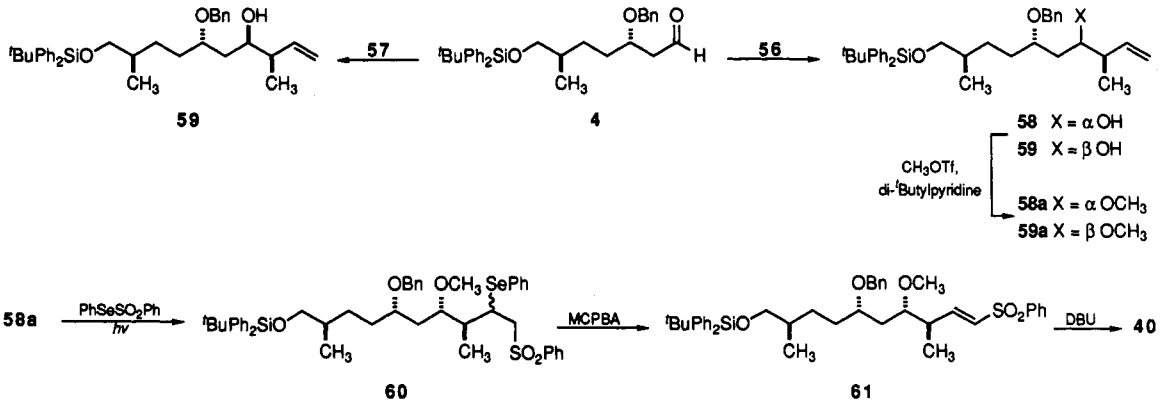

Figure 9.

Roush, recently corroborated in a related case in our laboratory,[1] the major product was assigned to be **58** and the minor **59**. The methyl ethers are correspondingly formulated as **58a** and **59a**.

It became clear that in the reaction of **4** with **56** we were dealing in the "mismatched" series.[36a] Thus, reaction of the same aldehyde with (*E*)-crotyl boronate **57** (derived from (*R*,*R*)-diisopropyl tartrate) gave compound **59** in nearly quantitative yield. Thus far, attempted Mitsonobu[36b] inversion reactions of compound **59**, designed to produce esters related to **58**, have been unsuccessful.

It proved possible to convert **58a** to the unsaturated sulfone **43**. The sequence passed through photoadduct[37] **60** and conjugated sulfone[38] **61** en route to **43**. While a greater degree of stereoselectivity had been attained through the crotyl boronate route, this advantage did not render it competitive with the earlier and much shorter sequence (i.e., reductive coupling of aldehyde **4** with iodosulfone **6**). However, use of the boronate endeavor does provide strong support for the assignment of methyl ether **43**.[39] For the moment, a stereospecific route leading to **41** has not been achieved.

Conclusions

The chemistry described above illustrates several potentially powerful methods in stereospecific synthesis and assembly. The integration of the Ibuka–Yamamoto reaction[6] with straightforward chemical manipulations of glycals[14-16] provides new possibilities for addressing long-range connectivities in goal systems wherein stereogenic centers are separated by spacer elements whose incorporation by synthesis would otherwise be awkward (see routes leading to **9**). Furthermore, the LACDAC reaction (conducted on enantiomerically pure heterodieneophiles) when

(36) Similar problems were experienced in attempts to invert C_7 stereochemistry for compound **42**. For a review on inversion reactions see: Mitsonobu, O. *Synthesis* **1981**, 1.

(37) Gancarz, R. A.; Kice, J. L. *Tetrahedron Lett.* **1980**, *21*, 4155. Gancarz, R. A.; Kice, J. L. *J. Org. Chem.* **1981**, *46*, 4899. Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, *21*, 2213.

(38) Kobayashi, T.; Tanaka, Y.; Ohtani, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1987**, 1209.

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followed by simple pyran-based manipulations, provides versatile routes to carbon-branched targets where the branching carbons are separated by a single methylene group (see synthesis of compound 5). Finally, the finding that the phenylsulfonyl group at C_4 exerts a stabilizing influence in the critical C_1–C_6 triene linkage and can be reductively cleaved is a potentially important enabling advance for a total synthesis of rapamycin. We are continuing to pursue that goal.

Experimental Section

Glucal 10b. To a solution of **10a** (12.5 g, 35.7 mmol) in pyridine (400 mL), cooled to 0 °C, was added methanesulfonyl chloride (3.0 mL, 38.8 mmol). The solution was warmed to 23 °C while being stirred for 12 h. The solution was concentrated and diluted with CH_2Cl_2. This solution was successively washed with 0.1 N HCl, saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (9:1 hexanes/EtOAc) yielding 15.2 g (99%) of **10b** as a white solid. The product can be recrystallized from hot EtOAc and hexanes: mp 77–78 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H), 6.45 (dd, J = 6.2, 1.3 Hz, 1 H), 5.05 (dd, J = 7.3, 5.7 Hz, 1 H), 4.89 (dd, J = 6.2, 3.2 Hz, 1 H), 4.63 (AB, J = 11.4 Hz, $\Delta\nu$ = 19.1 Hz, 2 H), 4.28 (m, 1 H), 4.13 (m, 1 H), 3.94 (ABX, J = 11.4, 5.6, 3.8 Hz, $\Delta\nu$ = 19.5 Hz, 2 H), 3.05 (s, 3 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 145.2, 137.9, 128.5, 128.0, 127.9, 98.8, 77.4, 75.3, 72.4, 70.1, 61.4, 39.0, 25.9, 18.4, –5.3; IR ($CHCl_3$) 2920, 2860, 1645, 1460, 1360, 1250, 1200, 1180, 1105, 1005, 970, 840 cm^{-1}; HRMS (FAB) m/e 429.1771 (429.1768 calcd for $C_{20}H_{32}O_6SSi$ + H); $[\alpha]^{23}_D$ 14.4° (c 0.45, $CHCl_3$). Anal. Calcd for $C_{20}H_{32}O_6SSi$: C, 56.04; H, 7.53. Found: C, 56.17; H, 7.45.

Methyl 2-Iodoglycoside 10c. To a solution of **10b** (15.2 g, 35.5 mmol) in anhydrous acetonitrile (400 mL) was added *N*-iodosuccinimide (9.6 g, 42.7 mmol) and dry methanol (2.2 mL, 54.3 mmol). The reaction was stirred at 23 °C in the dark for 12 h. The solution was concentrated then diluted with EtOAc and successively washed with 10% $Na_2S_2O_3$ solution, saturated $CuSO_4$ solution, and brine. The organic layer was dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (9:1 then 4:1 hexanes/EtOAc), yielding 18.4 g (88%) of **10c**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5 H), 5.11 (br s, 1 H), 4.74 (t, J = 9.1 Hz, 1 H), 4.68 (d, J = 10.7 Hz, 1 H), 4.50 (dd, J = 4.2, 1.1 Hz, 1 H), 4.34 (d, J = 10.7 Hz, 1 H), 3.99–3.91 (m, 1 H), 3.90–3.79 (m, 2 H), 3.40 (dd, J = 9.1, 4.2 Hz, 1 H), 3.38 (s, 3 H), 2.86 (s, 3 H), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.4, 128.6, 128.4, 128.3, 102.0, 82.9, 78.0, 74.2, 72.0, 70.6, 61.9, 55.1, 38.7, 31.3, 25.9, 18.3, –5.3; IR ($CHCl_3$) 2930, 2850, 1460, 1360, 1255, 1200, 1180, 1130, 1080, 1060, 1010, 965, 840 cm^{-1}; HRMS (FAB) m/e 587.1002 (587.0997 calcd for $C_{21}H_{35}IO_7SSi$ + H); $[\alpha]^{23}_D$ 8.8° (c 0.35, $CHCl_3$). Anal. Calcd for $C_{21}H_{35}IO_7SSi$: C, 43.00; H, 6.01. Found: C, 43.29; H, 5.84.

Methyl 2-Deoxyglycoside 11. To a solution of **10c** (18.4 g, 31.4 mmol) in benzene was added tributyltin hydride (10.1 mL, 37.5 mmol) and AIBN (0.52 g, 3.17 mmol). Nitrogen gas was bubbled through the solution for 5 min. The reaction was then heated to reflux temperature for 5 h. Upon cooling, a saturated KF solution was added to the reaction. The mixture was stirred vigorously for 12 h. White solid precipitate formed and was removed by filtration through Celite. The aqueous phase of the filtrate was partitioned and extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (9:1 hexanes/EtOAc), yielding 10.2 g (71%) of **11**: mp 79–80 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5 H), 4.83 (br d, J = 2.5 Hz, 1 H), 4.58 (AB, J = 11.3 Hz, $\Delta\nu$ = 40.1 Hz, 2 H), 4.48 (t, J = 9.4 Hz, 1 H), 4.08–3.91 (m, 2 H), 3.81–3.72 (m, 2 H), 3.34 (s, 3 H), 2.93 (s, 3 H), 2.36 (m, 1 H), 1.69 (m, 1 H), 0.91 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.7, 128.3, 127.7, 97.7, 79.5, 74.6, 71.0, 70.9, 62.4, 54.4, 38.5, 35.2, 25.8, 18.2, –5.4, –5.5; IR ($CHCl_3$) 2930, 2860, 1460, 1360, 1255, 1200, 1180, 1130, 1095, 1060, 1000, 975, 890, 840 cm^{-1}; HRMS (FAB) m/e 461.2038 (461.2030 calcd for $C_{21}H_{36}O_7SSi$ + H); $[\alpha]^{23}_D$ 60.7° (c 1.30, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}O_7SSi$: C, 54.75; H, 7.88. Found: C, 55.01; H, 7.86.

Diol 12. To a solution of **11** (6.52 g, 14.2 mmol) and 1,3-propanedithiol (1.4 mL, 13.9 mmol) in CH_2Cl_2 (120 mL), cooled to 0 °C, was added BF_3·OEt_2 (1.7 mL, 13.8 mmol). The solution was warmed to 23 °C while being stirred for 24 h. The reaction was quenched with saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined extract was washed with more saturated $NaHCO_3$ solution then brine and subsequently dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (1:1 then 3:7 hexanes/EtOAc) yielding 4.46 g (74%) of **12**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5 H), 4.78 (dd, J = 8.4, 3.5 Hz, 1 H), 4.72 (AB, J = 11.2 Hz, $\Delta\nu$ = 6.9 Hz, 2 H), 4.32 (m, 1 H), 4.03 (dd, J = 8.3, 6.5 Hz, 1 H), 3.95 (m, 1 H), 3.79 (m, 2 H), 3.25 (br d, J = 5.0 Hz, 1 H), 3.11 (s, 3 H), 2.86–2.66 (m, 4 H), 2.27 (br t, J = 6.3 Hz, 1 H), 2.17–2.07 (m, 3 H), 1.98–1.80 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.3, 128.6, 128.5, 128.2, 77.7, 75.4, 73.6, 70.2, 62.3, 43.3, 38.5, 36.1, 30.0, 29.6, 25.8; IR ($CHCl_3$) 3560, 3420, 2940, 1365, 1205, 1185, 1100, 1050, 970, 850 cm^{-1}; HRMS (FAB) m/e 423.1001 (423.0971 calcd for $C_{17}H_{26}O_6S_3$+H); $[\alpha]^{23}_D$ 22.2° (c 2.25, $CHCl_3$).

Aldehyde 13. To a solution of **12** (9.8 g, 23.2 mmol) in benzene (300 mL) under vigorous mechanical stirring was quickly added lead tetraacetate (11.3 g, 25.5 mmol) in small portions. After 15 min the reaction was filtered through Celite and washed with EtOAc. The unstable product was concentrated (with no heating) and purified by silica gel chromatography (3:7 hexanes/EtOAc). A yield of 6.5 (72%) of **13** was obtained, which was used immediately: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.59 (s, 1 H), 7.41–7.31 (m, 5 H), 5.09 (d, J = 3.7 Hz, 1 H), 4.63 (AB, J = 11.4 Hz, $\Delta\nu$ = 15.8 Hz, 2 H), 4.39 (dt, J = 6.8, 3.7 Hz, 1 H), 4.07 (t, J = 7.4 Hz, 1 H), 3.22 (s, 3 H), 2.87–2.78 (m, 4 H), 2.16–2.07 (m, 3 H), 1.98–1.79 (m, 1 H).

(*E*)-Ethyl Enoate 7. To a solution of **13** (4.60 g, 11.8 mmol) in CH_2Cl_2 (115 mL), cooled to 0 °C, was added (carbethoxymethylene)triphenylphosphorane (**14**, 4.51 g, 12.9 mmol) the reaction was stirred for 15 min and then concentrated while still cold. The crude product was quickly flashed through a short length (3 in.) of silica gel (7:3 hexanes/EtOAc) to yield 3.34 g (62%) of highly unstable **7**, which was used immediately: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5 H), 6.94 (dd, J = 15.7, 5.3 Hz, 1 H), 6.15 (dd, J = 15.7, 1.6 Hz, 1 H), 5.28 (dt, J = 5.3, 1.6 Hz, 1 H), 4.71 (AB, J = 11.4 Hz, $\Delta\nu$ = 12.2 Hz, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.11–4.02 (m, 2 H), 3.02 (s, 3 H), 2.86–2.65 (m, 4 H), 2.18–1.80 (m, 4 H), 1.32 (t, J = 7.2 Hz, 3 H).

2-Iodogalactose 15a. A solution of tri-*O*-acetyl-D-galactal (30.5 g, 112.2 mmol) and CH_3CN (375 mL) was allowed to react in the dark with NIS (30.4 g, 134.7 mmol) and MeOH (6.7 mL, 168.4 mmol) at 23 °C for 16 h. The reaction mixture was then concentrated, and the resulting residue was dissolved in EtOAc (600 mL). This solution was washed with 10% aqueous $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography (5:1 hexanes/EtOAc) giving 38.8 g (80%) of **15a** as a 7:1 mixture of α and β anomers. Data for the major (α) anomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.35 (d, J = 3.5 Hz, 1 H), 5.20 (d, J = 0.4 Hz, 1 H), 4.89 (m, 1 H), 4.26–4.11 (m, 4 H), 3.38 (s, 3 H), 2.16 (s, 3 H), 2.05 (s, 3 H), 2.04 (m, 3 H); IR ($CDCl_3$) 1735, 1345, 1245, 1070 cm^{-1}; HRMS (CI) m/e 431.0182 (431.0203 calcd for $C_{13}H_{19}O_8I$ + H). Anal. Calcd for $C_{13}H_{19}O_8I$: C, 36.30; H, 4.45. Found: C, 36.86; H, 4.37.

2-Deoxygalactose 15b. A solution of **15a** (22.0 g, 51.2 mmol) and dry toluene (200 mL) was allowed to react with AIBN (0.84 g, 5.1 mmol) and *n*-Bu_3SnH (20.5 mL, 76.7 mmol) at reflux for 5 h. At this time, the reaction mixture was allowed to cool to 23 °C where it was treated a saturated aqueous solution of KF (50 mL). This mixture was stirred for 16 h and then filtered through Celite. The aqueous layer was separated and extracted with EtOAc (3 × 100 mL). The organic material was combined, dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel chromatography (3:2 hexanes/EtOAc) giving 14.5 g (93%) of **15b** as a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.30–5.20 (m, 2 H), 4.87 (d, J = 3.1 Hz, 1 H), 4.09–4.04 (m, 3 H), 3.33 (s, 3 H), 2.10 (s, 3 H), 2.02 (s, 3 H), 1.95 (s, 3 H), 1.88–1.80 (m, 1 H), 1.34–1.26 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.1, 170.0, 169.6, 98.3, 66.5, 66.4, 65.9, 62.2, 54.7, 29.9, 20.5, 20.4; IR ($CDCl_3$) 3020–2850, 1750, 1450, 1380, 1260, 1140, 1060 cm^{-1}; HRMS (CI) m/e 305.1258 (305.1236 calcd for $C_{13}H_{20}O_8$ + H). Anal. Calcd

for $C_{13}H_{20}O_6$: C, 51.31; H, 6.62. Found: C, 51.63; H, 6.50.

Diol 16. A solution of **15b** (27.5 g of a 7:1 mixture of α and β anomers, 90.5 mmol) and MeOH (180 mL) was allowed to react with NaOMe (0.486 g, 9.05 mmol) at 23 °C. After 2 h, the reaction mixture was concentrated. The residue was coevaporated once with benzene (50 mL) and maintained at high vacuum for 2 h. The crude isolate was dissolved in DMF (100 mL) and allowed to react with imidazole (9.1 g, 135 mmol) and TBSCl (13.5 g, 90 mmol) at 23 °C. After 16 h, the reaction was concentrated in vacuo at 100 °C. The crude isolate was dissolved in EtOAc/Et_2O (8:2, 100 mL) and washed with H_2O (3 × 40 mL). The resulting aqueous material was extracted with EtOAc (2 × 100 mL). The combined organic material was washed with H_2O (2 × 50 mL) and brine (1 × 40 mL), dried ($MgSO_4$), and concentrated. The crude isolate was purified by silica gel chromatography (7:3 hexanes/EtOAc) giving 19.7 g (75%) of **16** as a 7:1 mixture of α and β anomers. Characteristic data for the α (major) anomer: ^{1}H NMR (490 MHz, $CDCl_3$) δ 4.77 (m, 1 H), 3.94–3.79 (m, 4 H), 3.66 (t, J = 5.2 Hz, 1 H), 3.29 (s, 3 H), 2.89 (d, J = 8.1 Hz, 1 H), 1.88–1.84 (m, 2 H), 0.88 (s, 9 H), 0.072 (s, 3 H), 0.070 (s, 3 H); IR ($CDCl_3$) 3540, 3430 (br), 3000–2880, 1520, 1510, 1390, 1370, 1350, 1200, 1120, 1040, 1000, 840, 780 cm^{-1}; HRMS (CI) m/e 293.1789 (293.1785 calcd for $C_{13}H_{28}O_5Si$ + H). Anal. Calcd for $C_{13}H_{28}O_5Si$: C, 53.39; H, 9.65. Found: C, 53.34; H, 9.67.

Benzyl Ether 17. A solution of diol **16** (10.46 g of a 7:1 mixture of α and β anomers, 35.8 mmol) and toluene (200 mL) was treated with (n-Bu_3Sn)$_2O$ (27.6 mL, 53.7 mmol). The resulting mixture was maintained at reflux, and the toluene/H_2O azeotrope was removed with the aid of a Dean-Stark trap. After 4 h, the resulting clear mixture was allowed to cool to 80 °C where it was treated with benzyl bromide (4.2 mL, 35.8 mmol) and Bu_4NBr (11.4 g, 35.8 mmol). The reaction mixture was maintained at 80 °C for 5 h and then concentrated. The crude isolate was purified by silica gel chromatography (9:1 then 4:1 hexanes/EtOAc) giving 13.5 (98%) of **17** as a 7:1 mixture of α and β anomers. Characteristic data for the α (major) anomer: ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5 H), 4.83 (m, 1 H), 4.58 (s, 2 H), 4.02 (s, 1 H), 3.89–3.77 (m, 3 H), 3.67 (t, J = 5.8 Hz, 1 H), 3.31 (s, 3 H), 2.44 (m, 1 H), 2.03–1.92 (m, 2 H), 0.907 (s, 9 H), 0.086 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.1, 128.4, 127.7, 127.6, 98.6, 72.8, 70.0, 65.5, 63.0, 54.5, 30.2, 25.8, 18.2, –6.0; IR ($CHCl_3$) 3550, 3100–2800, 1490, 1465, 1380, 1350, 1250, 1200, 1120, 1090, 1050, 1010, 970, 840, 780 cm^{-1}; HRMS (CI) m/e 383.2255 (383.2254 calcd for $C_{20}H_{34}O_5Si$ + H). Anal. Calcd for $C_{20}H_{34}O_5Si$: C, 62.79; H, 8.96. Found: C, 63.03; H, 8.90.

Mesylate 18. A solution of **17** (24.6 g of a 7:1 mixture of α and β anomers, 64.4 mmol) and CH_2Cl_2 (60 mL) was allowed to react with pyridine (120 mL), methanesulfonyl chloride (9.84 mL, 128.8 mmol) and a catalytic amount of DMAP at 23 °C. After 24 h, the reaction mixture was concentrated. The crude residue was taken up in 4:1 mixture of EtOAc and Et_2O (1.25 L). The resulting solution was washed with H_2O (3 × 75 mL), saturated aqueous $CuSO_4$ (2 × 75 mL), and brine (1 × 100 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude isolate was purified by silica gel chromatography (4:1 hexanes/EtOAc) giving 23.6 g (80%) of **18** as a 7:1 mixture of α and β anomers. Characteristic data for the α (major) isomer: ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.50–7.27 (m, 5 H), 5.20–5.19 (m, 1 H), 4.88–4.87 (m, 1 H), 4.65 (AB, J = 11.3 Hz, $\Delta\nu$ = 96.4 Hz, 2 H), 3.94 (m, 1 H), 3.85–3.74 (m, 3 H), 3.35 (s, 3 H), 3.04 (s, 3 H), 2.03–1.98 (m, 2 H), 0.93 (m, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.5, 128.5, 127.9, 98.5, 76.2, 71.7, 70.9, 69.8, 61.9, 54.9, 39.0, 31.2, 25.8, 18.2, –5.4, –5.5; IR ($CHCl_3$) 3000–2800, 1460, 1310, 1250, 1200, 1180, 1170, 1125, 1090, 1050, 955, 840, 790 cm^{-1}; HRMS (CI) m/e 461.2025 (461.2030 calcd for $C_{21}H_{36}O_7SiS$ + H). Anal. Calcd for $C_{21}H_{36}O_7SiS$: C, 54.75; H, 7.88. Found: C, 54.66; H, 7.77.

Diol 19. A solution of **18** (23.6 g, 51.3 mmol) and CH_2Cl_2 (270 mL) was allowed to react with 1,3-propanedithiol (5.47 mL, 53.6 mmol) and BF_3·Et_2O (6.7 mL, 53.6 mmol) at 0 °C. The resulting solution was allowed to warm to 23 °C. After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous material was separated and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic material was washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. The crude material was purified by silica gel chromatography (7:3 hexanes/EtOAc) giving 15.7 g (73%) of **19** as a pale yellow oil: ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5 H), 5.03 (dd, J = 5.2, 2.3 Hz, 1 H), 4.67 (AB, J = 11.0 Hz, $\Delta\nu$ = 100.3 Hz, 2 H), 4.10–4.06 (m, 2 H), 3.91–3.87 (m, 1 H), 3.79–3.67 (m, 2 H), 3.45 (d, J = 4.9 Hz, 1 H), 3.09 (s, 3 H), 2.86–2.79 (m, 4 H), 2.73–2.67 (m, 1 H), 2.13–2.01 (m, 3 H), 1.90–1.86 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.1, 128.6, 128.5, 128.1, 82.5, 75.7, 72.8, 70.6, 62.7, 43.3, 38.8, 36.2, 30.0, 29.5, 25.8; IR ($CHCl_3$) 3600–3200, 3040–2800, 1740, 1450, 1420, 1350, 1240, 1210, 1190, 1170, 1070, 1045, 970 cm^{-1}; HRMS (CI) m/e 423.0966 (423.0971 calcd for $C_{17}H_{28}O_6S_3$ + H). Anal. Calcd for $C_{17}H_{28}O_6S_3$: C, 48.32; H, 6.20. Found: C, 48.60; H, 6.28.

(*Z*)-Methyl Enoate 8. A solution of diol **19** (14.7 g, 34.8 mmol) and benzene (300 mL) was allowed to react with $Pb(OAc)_4$ (15.4 g, 34.8 mmol) at 23 °C for 0.5 h. At this time the reaction mixture was filtered through Celite, and the filtrate was concentrated. The crude isolate was passed through a plug of silica gel (1.5:1 hexanes/EtOAc) giving 10.0 g (74%) of **20** as an unstable oil. This material (10.0 g, 25.6 mmol) was immediately dissolved in THF (400 mL) and allowed to react with the potassium salt of bis(2,2,2-trifluoroethyl)[(methoxycarbonyl)methyl]phosphonate prepared from KHMDS (51.3 mL, 0.5 M in toluene), bis(2,2,2-trifluoroethyl)[(methoxycarbonyl)methyl]phosphonate (8.16 g, 25.6 mmol), and 18-crown-6 (33.7g, 128.2 mmol) at –78 °C. After 45 min at –78 °C the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL). Extractive workup (EtOAc) gave the crude material, which was purified by silica gel chromatography (2.3:1 hexanes/EtOAc), giving 6.75 g (59%) of **8** as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 490 MHz) δ 7.46–7.30 (m, 5 H), 6.59–6.56 (m, 1 H), 6.25 (dd, J = 11.6, 7.4, Hz, 1 H), 5.99 (dd, J = 11.6, 1.6 Hz, 1 H), 4.82 (AB, J = 11.1 Hz, $\Delta\nu$ = 117.0 Hz, 2 H), 4.09 (dt, J = 10.6, 2.2 Hz, 1 H), 4.05 (dd, J = 10.8, 3.8 Hz, 1 H), 3.79 (s, 3 H), 3.01 (s, 3 H), 2.84–2.81 (m, 2 H), 2.78–2.73 (m, 1 H), 2.68–2.62 (m, 1 H), 2.14–2.06 (m, 2 H), 1.86–1.75 (m, 2 H); IR ($CHCl_3$) 3100–2800, 1735, 1650, 1460, 1440, 1430, 1405, 1360, 1240, 1210, 1185, 1080, 1050, 1000, 975, 840 cm^{-1}; HRMS (CI) m/e 447.0952 (447.0971 calcd for $C_{19}H_{28}O_6S_3$ + H).

Homoallylic Ethyl Ester 9a. To a slurry of dried CuCN (0.407 g, 4.54 mmol) in anhydrous THF (23 mL), cooled to –78 °C, was added MeLi·LiBr (3.0 mL, 1.5 M in Et_2O). The mixture was stirred for 10 min and warmed to 0 °C. A homogeneous solution was obtained in about 5 min. The cuprate reagent was cooled to –78 °C, treated with BF_3·OEt_2 (0.56 mL, 4.55 mmol), and stirred for another 5 min. Compound **7** (0.697 g, 1.51 mmol) was dissolved in THF (7 mL) and added dropwise to the prepared cuprate reagent. The reaction was stirred at –78 °C for 0.5 h then quenched (2:1 saturated NH_4Cl solution and 28% NH_4OH solution). The mixture was exposed to the air and stirred at 23 °C for 0.5 h. The blue mixture was extracted with ether. The extract was washed successively with 0.1 N HCl, saturated $NaHCO_3$ solution, and water. The extract was dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (9:1 hexanes/EtOAc) to yield 0.432 g (75%) of **9a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5 H), 5.85 (dd, J = 15.7, 7.7 Hz, 1 H), 5.48 (ddd, J = 15.7, 7.9, 1.1 Hz, 1 H), 4.46 (AB, J = 11.6 Hz, $\Delta\nu$ = 52.7 Hz, 2 H), 4.19–4.05 (m, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 3.19 (dt, J = 15.8, 7.9 Hz, 1 H), 2.87–2.79 (m, 4 H), 2.19–2.05 (m, 2 H), 1.98–1.82 (m, 2 H), 1.29 (d, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.2, 138.9, 133.1, 131.4, 128.3, 127.9, 127.5, 76.5, 70.6, 60.6, 43.6, 42.5, 41.6, 30.1, 29.9, 26.2, 17.1, 14.2; IR ($CHCl_3$) 2990, 2940, 2910, 1730, 1460, 1380, 1200, 1100, 1075, 1030, 980, 915, 870 cm^{-1}; HRMS (EI) m/e 380.1481 (380.1481 calcd for $C_{20}H_{28}O_3S_2$); $[\alpha]^{23}_D$ 10.0° (c 0.49, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_3S_2$: C, 63.12; H, 7.42. Found: C, 63.40; H, 7.33.

Homoallylic Methyl Ester 9b. A mixture of dry CuCN (4.07 g, 45.4 mmol) and dry THF (250 mL) was allowed to react with MeLi·LiBr (30.3 mL, 1.5 M in Et_2O) at –78 °C. After 10 min, the cooling bath was removed for 5 min. The resulting mixture was recooled to –78 °C and then was treated with BF_3·Et_2O (5.6 mL, 45.4 mmol). After 5 min, a solution of **8** (6.75 g, 15.1 mmol) in THF (50 mL) was added. After 30 min at –78 °C, the reaction was quenched with 28% aqueous NH_4OH (30 mL) and saturated aqueous NH_4Cl (60 mL). The organic layer was separated, and the aqueous material was extracted with Et_2O (6 × 150 mL). The organic material was combined and washed with 1 M HCl (100

mL), H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (100 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude isolate was purified by silica gel chromatography (5.6:1 hexanes/EtOAc) giving 4.1 g (74%) of **9b** as a pale yellow oil: ^1H NMR (490 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5 H), 5.84 (ddd, J = 15.6, 7.6, 0.7 Hz, 1 H), 5.48 (ddd, J = 15.6, 7.7, 1.2 Hz, 1 H), 4.46 (AB, J = 11.7 Hz, $\Delta\nu$ = 97.3 Hz, 2 H), 4.14 (dd, J = 8.8, 5.8 Hz, 1 H), 4.11–4.07 (m, 1 H), 3.71 (s, 3 H), 3.23–3.20 (m, 1 H), 2.87–2.80 (m, 4 H), 2.12–2.07 (m, 2 H), 1.91–1.65 (m, 2 H), 1.29 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.6, 138.4, 132.8, 131.1, 128.2, 127.8, 127.4, 76.1, 70.4, 51.8, 43.4, 42.2, 41.2, 30.0, 29.7, 26.0, 17.0; IR ($CDCl_3$) 3100–2800, 1735, 1495, 1460, 1440, 1330, 1280, 1250, 1200, 1175, 1100, 1075, 1030, 980, 800 cm^{-1}; HRMS (CI) m/e 367.1397 (367.1403 calcd for $C_{19}H_{26}O_3S_2$ + H). Anal. Calcd for $C_{19}H_{26}O_3S_2$: C, 62.26; H, 7.15. Found: C, 62.21; H, 7.21.

Ethyl Ester 22a. Typically, to a solution of **9a** (0.621 g, 1.63 mmol) in dry benzene (15 mL) was added Wilkinson's catalyst (0.302 g, 0.32 mmol). The reddish brown solution was degassed and stirred for 3 days at 23 °C under an atmosphere of H_2 gas. The product was concentrated and purified by chromatography on silica gel (9:1 hexanes/EtOAc) to yield 0.517 g (83%) of **22a**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5 H), 4.54 (AB, J = 11.4 Hz, $\Delta\nu$ = 13.3 Hz, 2 H), 4.16 (m, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.74 (m, 1 H), 2.94–2.79 (m, 4 H), 2.41 (m, 1 H), 2.19–1.40 (m, 8 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.15 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.7, 138.4, 127.8, 127.4, 127.0, 75.0, 70.9, 59.6, 43.6, 39.8, 39.0, 31.0, 29.9, 29.6, 28.5, 25.6, 16.7, 13.9; IR (film) 2980, 2940, 2910, 1730, 1500, 1460, 1430, 1380, 1355, 1280, 1250, 1185, 1100, 1070, 1035, 915, 865, 745, 710 cm^{-1}; HRMS (FAB) m/e 383.1733 (383.1716 calcd for $C_{20}H_{30}O_3S_2$ + H); $[\alpha]^{23}_D$ 12.1° (c 1.72, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}O_3S_2$: C, 62.79; H, 7.90. Found: C, 62.93; H, 8.06.

Alcohol 23 from Ester 22a or 22b. Typically, to a solution of **22a** (0.759 g, 1.98 mmol) in dry toluene (20 mL) at 0 °C was added DIBAH (5.0 mL, 1.0 M in hexanes). The reaction was stirred for 0.5 h and quenched with saturated sodium potassium tartrate solution. The mixture was stirred for 3 h. The aqueous layer was separated and extracted with ether. The combined extract was dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (7:3 hexanes/EtOAc), yielding 0.608 g (90%) of **23**: ^1H NMR (490 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5 H), 4.56 (AB, J = 11.4 Hz, $\Delta\nu$ = 23.7 Hz, 2 H), 4.18 (dd, J = 9.2, 5.2 Hz, 1 H), 3.75–3.70 (m, 1 H), 3.52–3.43 (m, 2 H), 2.92–2.78 (m, 4 H), 2.14–2.09 (m, 1 H), 2.03–1.98 (m, 1 H), 1.93–1.84 (m, 2 H), 1.67–1.47 (m, 4 H), 1.30–1.27 (m, 1 H), 1.22–1.14 (m, 1 H), 0.93 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 131.8, 128.3, 127.9, 127.6, 75.9, 71.5, 68.1, 44.1, 40.3, 35.8, 31.4, 30.5, 30.1, 28.4, 26.0, 16.6; IR (film) 3600, 3000–2800, 1450, 1420, 1345, 1190, 1065, 1020, 785 cm^{-1}; HRMS (CI) m/e 341.1588 (341.1611 calcd for $C_{18}H_{28}O_2S_2$ + H); $[\alpha]^{23}_D$ 25.4° (c 2.05, $CHCl_3$). Anal. Calcd for $C_{18}H_{28}O_2S_2$: C, 63.48; H, 8.29. Found: C, 63.33; H, 8.09.

Dithiane 24. To a solution of **23** (0.795 g, 2.34 mmol) in DMF (6 mL) was added imidazole (0.238 g, 3.51 mmol) and *tert*-butylchlorodiphenylsilane (638 μL, 2.46 mmol). The reaction was stirred for 3 h at 23 °C then concentrated. The residue was diluted with 1:2 EtOAc/ether and washed with water three times and then with brine. The organic layer was dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (4:1 hexanes/EtOAc), yielding 1.35 g (100%) of **24**; ^1H NMR (490 MHz, $CDCl_3$) δ 7.73–7.71 (m, 4 H), 7.48–7.27 (m, 11 H), 4.57 (AB, J = 11.4 Hz, $\Delta\nu$ = 32.0 Hz, 2 H), 4.20 (dd, J = 9.3, 5.1 Hz, 1 H), 3.80–3.75 (m, 1 H), 3.58–3.50 (m, 2 H), 2.93–2.81 (m, 4 H), 2.17–2.12 (m, 1 H), 2.07–2.01 (m, 1 H), 2.00–1.88 (m, 2 H), 1.85–1.78 (m, 1 H), 1.77–1.58 (m, 2 H), 1.24–1.10 (m, 11 H), 0.98 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.8, 135.6, 134.0, 129.5, 128.3, 127.8, 127.5, 127.4, 75.9, 71.4, 68.7, 44.0, 40.3, 35.8, 31.4, 30.3, 30.0, 28.5, 26.9, 26.0, 19.3, 16.8; IR (film) 3075–2800, 1700, 1575, 1460, 1450, 1445, 1420, 1380, 1350, 1270, 1185, 1105, 820, 785 cm^{-1}; HRMS (CI) m/e 579.2809 (579.2789 calcd for $C_{34}H_{46}O_2S_2Si$ + H); $[\alpha]^{23}_D$ 15.7° (c 1.85, $CHCl_3$). Anal. Calcd for $C_{34}H_{46}O_2S_2Si$: C, 70.54; H, 8.01. Found: C, 70.32; H, 8.03.

Aldehyde 4. A solution of **24** (1.219 g, 2.11 mmol) in 95:5 acetone/water (20 mL) was gradually added to a solution of *N*-bromosuccinimide (3.0 g, 16.9 mmol) in 95:5 acetone/water (50 mL) at −20 °C. The yellow solution was stirred for 5 min, and then 10% $NaHSO_3$ solution was added until the solution became colorless. The solution was extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel chromatography (9:1 hexanes/EtOAc), yielding 0.920 g (89%) of **4**: ^1H NMR (490 MHz, $CDCl_3$) δ 9.81–9.80 (m, 1 H), 7.78–7.27 (m, 15 H), 4.56 (AB, J = 11.4 Hz, $\Delta\nu$ = 21.7 Hz, 2 H), 3.96–3.93 (m, 1 H), 3.55–3.52 (m, 2 H), 2.70–2.65 (m, 1 H), 2.58–2.54 (m, 1 H), 1.74–1.60 (m, 3 H), 1.23–1.13 (m, 2 H), 1.08 (s, 9 H), 0.97 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.6, 138.2, 135.6, 135.2, 134.8, 134.0, 129.6, 129.5, 128.4, 127.7, 127.6, 127.5, 105.9, 74.6, 71.2, 68.6, 48.2, 35.7, 31.6, 28.5, 26.9, 26.5, 19.3, 19.0, 16.8; IR (film) 3080–2800, 2710, 1715, 1460, 1420, 1385, 1355, 1190, 1110, 1060, 820 cm^{-1}; HRMS (CI) m/e 489.2836 (489.2826 calcd for $C_{31}H_{40}O_3Si$ + H); $[\alpha]^{23}_D$ 15.0° (c 1.17, $CHCl_3$). Anal. Calcd for $C_{31}H_{40}O_3Si$: C, 76.18; H, 8.25. Found: C, 75.78; H, 8.17.

Pyrone 28. A solution of $MgBr_2$ (1.0 M in 4:1 benzene/ether, 53.3 mL, 53.3 mmol) was added to a solution of (*S*)-2-(benzyloxy)propanal[17] (8.75 g, 53.3 mmol) and THF (100 mL) at 23 °C. The resulting yellow mixture was stirred at 23 °C for 10 min and then treated with (*E,Z*)-1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene[40] (11.1 g, 53.3 mmol). After 24 h, HOAc (5 mL) and H_2O (5 mL) were added. The resulting clear yellow solution was then diluted with H_2O (300 mL) and extracted with EtOAc. The organic extracts were washed with saturated aqueous $NaHCO_3$ and brine. The resulting material was dried ($MgSO_4$) and concentrated. The crude material was purified by silica gel chromatography (10:1 hexanes/EtOAc) to provide 10.4 g of **28** (75%) as a clear oil: ^1H NMR ($CDCl_3$, 490 MHz) δ 7.46–7.27 (m, 5 H), 7.23 (s, 1 H), 4.56 (AB, J = 11.8 Hz, $\Delta\nu$ = 75.7 $[\alpha]^{23}_D$ 2 H), 3.86 (dd, J = 12.7, 2.2 Hz, 1 H), 3.74 (qd, J = 6.4, 2.2 Hz, 1 H), 2.83 (dq, J = 12.8, 6.9 Hz, 1 H), 1.64 (d, J = 1.1 Hz, 3 H), 1.37 (d, J = 6.4 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 195.6, 158.3, 137.7, 128.3, 127.9, 127.8, 112.4, 85.9, 71.7, 70.8, 40.1, 15.0, 10.5, 9.67; IR ($CDCl_3$) 3080–2700, 1650, 1615, 1480, 1440, 1365, 1290, 1170, 1145, 1090, 1050, 775 cm^{-1}; HRMS (CI) m/e 261.1471 (261.1491 calcd for $C_{16}H_{20}O_3$ + H); $[\alpha]^{23}_D$ 203.4° (c 1.8, $CHCl_3$).

Pseudoglycal 30. A solution of **28** (1.50 g, 5.75 mmol) and benzene (50 mL) was allowed to react with DIBAH (11.5 mL, 1.0 M in hexanes) at 23 °C. After 0.5 h, a saturated aqueous solution of sodium potassium tartrate (50 mL) was cautiously added. The resulting mixture was stirred vigorously for 1 h, and then the phases were separated. The aqueous material was extracted with EtOAc (×2) and the combined extracts were dried ($MgSO_4$) and concentrated. The resulting residue was taken up in *i*-PrOH (25 mL) and treated with $TsOH \cdot H_2O$ (0.10 g, 0.57 mmol). After 4 h this solution was concentrated. The crude material was dissolved in EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crude material was purified by silica gel chromatography (6:1 hexanes/EtOAc) to provide 1.53 g (88%) of **30** as a clear oil: ^1H NMR ($CDCl_3$, 490 MHz) δ 7.38–7.27 (m, 5 H), 5.43 (s, 1 H), 4.93 (s, 1 H), 4.60 (AB, J = 12.1 Hz, $\Delta\nu$ = 137.3 Hz, 2 H), 4.07 (quintet, J = 6.2 Hz, 1 H), 3.74 (ddd, J = 10.5, 4.1, 1.8 Hz, 1 H), 3.38 (dd, J = 10.0, 1.8 Hz, 1 H), 2.75–2.68 (m, 1 H), 1.71–1.70 (m, 3 H), 1.36 (d, J = 6.4 Hz, 3 H) 1.26 (d, J = 6.3 Hz, 3 H), 1.20 (d, J = 5.4 Hz, 3 H), 0.77 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 138.3, 130.9, 130.2, 128.0, 127.4, 95.7, 75.2, 71.4, 70.6, 69.0, 29.5, 23.6, 21.4, 18.3, 16.0, 15.5; IR ($CHCl_3$) 3100–2800, 1710, 1450, 1370, 1285, 1140, 1120, 1075, 1030, 1000, 945, 790 cm^{-1}; HRMS (CI) m/e 305.2093 (305.2117 calcd for $C_{19}H_{28}O_3$ + H); $[\alpha]^{23}_D$ 66.6° (c 2.8, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.30; H, 9.21.

Alcohol 32. A mixture of **30** (4.28 g, 14.13 mmol), EtOAc (100 mL), and 5% Pd/Al_2O_3 (4.3 g) was hydrogenated at 50 psi for 4 h. At this time, the catalyst was removed by filtration. The resulting solution was then treated with Pd/C (4.3 g) and subjected to further hydrogenation at 50 psi for 8 h. The catalyst was then removed by filtration. The filtrate was concentrated affording

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2.07 g (68%) of **32** as a clear oil. The material prepared in this fashion was sufficiently pure for further use. Chromatography (silica gel, 2:1 hexanes/EtOAc) provided an analytical sample: ^{1}H NMR (490 MHz, $CDCl_3$) δ 4.70 (d, J = 3.4 Hz, 1 H), 3.95–3.87 (m, 1 H), 3.85 (quintet, J = 6.2 Hz, 1 H), 3.90 (d, J = 10.3 Hz, 1 H), 2.03–1.87 (m, 1 H), 1.83–1.72 (m, 2 H), 1.43 (dt, J = 4.0, 12.8 Hz, 1 H), 1.28–1.24 (m, 1 H), 1.24 (d, J = 6.4 Hz, 3 H), 1.18 (d, J = 6.3 Hz, 3 H), 1.10 (d, J = 6.1 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 98.4, 76.5, 68.3, 66.1, 35.0, 34.9, 31.0, 23.4, 21.4, 20.9, 17.4, 16.5; IR ($CDCl_3$) 3600–3300, 2980–2770, 1445, 1365, 1170, 1110, 1015, 995, 805, 780 cm^{-1}; HRMS (CI) m/e 217.1809 (217.1804 calcd for $C_{12}H_{24}O_3$ + H); $[\alpha]^{23}_D$ 134.3° (c 1.3, $CHCl_3$).

Diol Dithiane 33. A solution of **32** (1.00 g, 4.63 mmol) and CH_2Cl_2 (10 mL) was treated at −78 °C with BF_3·Et_2O (0.63 mL, 5.09 mmol) and 1,3-propanedithiol (0.51 mL, 5.09 mmol). After 0.5 h, the reaction mixture was allowed to warm to −20 °C. After 24 h, additional BF_3·Et_2O (0.15 mL, 1.27 mmol) was added. Addition of BF_3·Et_2O (0.15 mL, 1.27 mmol) was continued at 24-h intervals for the next 72 h. At this time, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the resulting mixture was extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and concentrated. The crude isolate was chromatographed (silica gel, 1:1 hexanes/EtOAc) giving 1.29 g (96%) of **33** as a clear oil: ^{1}H NMR (490 MHz, $CDCl_3$) δ 4.20 (d, J = 3.4 Hz, 1 H), 3.86 (quintet, J = 6.3 Hz, 1 H), 3.16 (br d, J = 5.0 Hz, 1 H), 2.97–2.76 (m, 4 H), 2.33–2.20 (m, 1 H), 2.16–1.76 (m, 6 H), 1.25 (d, J = 6.3 Hz, 3 H), 1.11 (d, J = 6.9 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 80.4, 68.0, 54.2, 36.0, 35.5, 32.9, 31.3, 30.7, 26.4, 20.1, 18.3, 17.2; IR ($CDCl_3$) 3640–3300, 3000–2800, 1720, 1460, 1425, 1380, 1280, 1050, 990 cm^{-1}; HRMS (CI) m/e 265.1310 (265.1297 calcd for $C_{12}H_{24}O_2S_2$ + H); $[\alpha]^{23}_D$ −10.2° (c 2.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{24}O_2S_2$: C, 54.50; H, 9.15. Found: C, 54.69; H, 9.10.

Aldehyde 34. Diol **33** (1.29 g, 4.89 mmol) was dissolved in CH_3CN (25 mL) and treated with KOAc (0.962 g, 9.80 mmol) and $Pb(OAc)_4$ (2.17 g, 4.90 mmol) at −20 °C. After 5 min, the reaction mixture was diluted with Et_2O (100 mL) and the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated, and the crude isolate was purified by silica gel chromatography (3:1 hexanes/EtOAc) giving 0.64 g (60%) of **34** as a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.55 (d, J = 2.5 Hz, 1 H), 4.09 (d, J = 3.8 Hz, 1 H), 2.89–2.77 (m, 4 H), 2.47–2.38 (m, 1 H), 2.12–1.74 (m, 4 H), 1.35–1.22 (m, 1 H), 1.08 (d, J = 7.0 Hz, 3 H), 1.07 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 204.4, 54.8, 44.1, 36.0, 35.0, 30.9, 30.6, 26.2, 17.2, 14.1; IR ($CDCl_3$) 3020–2800, 2710, 1720, 1445, 1420, 1380, 1280, 1200, 1185, 910 cm^{-1}; HRMS (CI) m/e 219.0888 (219.0878 calcd for $C_{10}H_{18}OS_2$ + H); $[\alpha]^{23}_D$ 10.7° (c 2.7, $CHCl_3$). Anal. Calcd for $C_{10}H_{18}OS_2$: C, 55.00; H, 8.31. Found: C, 55.04; H, 8.31.

Enoate 35. A solution of **34** (0.640 g, 2.93 mmol) and CH_2Cl_2 (10 mL) was treated with methyl (triphenylphosphoranylidene)acetate (1.47 g, 4.40 mmol) at 23 °C. The resulting solution was maintained at 23 °C for 16 h and then concentrated. The crude residue was purified by silica gel chromatography (10:1 hexanes/EtOAc) providing 0.65 g (81%) of **35** as a clear oil: ^{1}H NMR (490 MHz, $CDCl_3$) δ 6.76 (dd, J = 15.7, 8.7 Hz, 1 H), 5.79 (dd, J = 15.7, 0.8 Hz, 1 H), 4.06 (d, J = 4.0 Hz, 1 H), 3.70 (s, 3 H), 2.90–2.79 (m, 4 H), 2.42–2.34 (m, 1 H), 2.10–2.05 (m, 1 H), 1.86–1.75 (m, 2 H), 1.66 (ddd, J = 13.0, 9.8, 4.4 Hz, 1 H), 1.38 (ddd, J = 14.2, 9.8, 4.9 Hz, 1 H), 1.04 (d, J = 6.7 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.8, 153.7, 119.9, 55.6, 51.3, 40.4, 36.0, 34.3, 31.0, 30.7, 26.2, 20.4, 16.6; IR ($CDCl_3$) 3040–2800, 1720, 1660, 1465, 1445, 1360, 1290, 1240, 1205, 1190, 1155, 1030, 995, 800 cm^{-1}; HRMS (EI) m/e 274.1059 (274.1063 calcd for $C_{13}H_{22}O_2S_2$); $[\alpha]^{23}_D$ 29.0° (c 2.5, $CHCl_3$). Anal. Calcd for $C_{13}H_{22}O_2S_2$: C, 56.90; H, 8.08. Found: C, 56.69; H, 8.00.

Alcohol 36. A solution of **35** (0.808 g, 2.95 mmol) and toluene (5 mL) was treated with DIBAH (6.2 mL, 1 M in hexanes) at −78 °C. The solution was then allowed to warm to 23 °C where it was quenched with a saturated aqueous solution of sodium potassium tartrate (5 mL). The resulting mixture was stirred vigorously for 2 h and then extracted with EtOAc. The organic extracts were dried ($MgSO_4$) and concentrated affording 0.68 g (95%) of **36** as a pure clear oil: ^{1}H NMR (490 MHz, $CDCl_3$) δ 5.61 (dt, J = 15.3, 5.9 Hz, 1 H), 5.47 (dd, J = 15.5, 8.1 Hz, 1 H), 4.15–4.07 (m, 3 H), 2.91–2.81 (m, 4 H), 2.27–2.17 (m, 1 H), 2.13–2.07 (m, 1 H), 1.92–1.78 (m, 2 H), 1.58 (ddd, J = 13.8, 10.2, 4.1 Hz, 1 H), 1.52–1.46 (br s, 1 H), 1.31 (ddd, J = 14.0, 9.8, 4.7 Hz, 1 H), 1.05 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.9, 128.3, 63.6, 56.0, 41.1, 36.1, 34.3, 31.1, 30.8, 26.4, 21.5, 16.8; IR ($CDCl_3$) 3600, 3450, 3000–2800, 1460, 1425, 1380, 1280, 1190, 1080, 980, 780 cm^{-1}; HRMS (CI) m/e 247.1188 (247.1191 calcd for $C_{12}H_{22}OS_2$ + H); $[\alpha]^{23}_D$ 8.8° (c 1.5, $CHCl_3$). Anal. Calcd for $C_{12}H_{22}OS_2$: C, 58.49; H, 8.99. Found: C, 58.49; H, 8.87.

Enal 5. Alcohol **36** (0.297 g, 1.21 mmol) was oxidized in CH_2Cl_2 (7.5 mL) at −78 °C with oxalyl chloride (0.15 mL, 1.70 mmol), DMSO (0.14 mL, 1.82 mmol), and Et_3N (0.50 mL, 3.64 mmol) following the procedure described by Swern.[21] The reaction mixture was allowed to warm to 23 °C, diluted with Et_2O, and washed with water and brine. The organic material was dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography (5:1 hexanes/EtOAc) giving 0.191 g (65%) of **5** as a clear oil: ^{1}H NMR (490 MHz, $CDCl_3$) δ 9.52 (d, J = 7.9 Hz, 1 H), 6.68 (dd, J = 15.6, 8.3 Hz, 1 H), 6.11 (ddd, J = 15.6, 7.8, 0.9 Hz, 1 H), 4.11 (d, J = 4.0 Hz, 1 H), 2.93–2.83 (m, 4 H), 2.62–2.53 (m, 1 H), 2.15–2.09 (m, 1 H), 1.90–1.75 (m, 3 H), 1.46 (ddd, J = 14.0, 9.6, 5.0 Hz, 1 H), 1.13 (d, J = 6.7 Hz, 3 H), 1.10 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 194.0, 162.9, 131.9, 55.5, 40.3, 36.3, 35.0, 31.0, 30.8, 26.3, 20.3, 17.0; IR ($CDCl_3$) 3000–2800, 2740, 1690, 1630, 1450, 1420, 1275, 1215, 980 cm^{-1}; HRMS (CI) m/e 245.1045 (245.1034 calcd for $C_{12}H_{20}OS_2$ + H); $[\alpha]^{23}_D$ 2.3° (c 3.7, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}OS_2$: C, 58.97; H, 8.25. Found: C, 58.96; H, 7.99.

Vinyl Iodide 38. To a solution of **37** (10 g, 47.2 mmol) in ether (100 mL) at 0 °C was added an etheral solution of diazomethane (100 mL, 0.9 M). The yellow solution was stirred until gas evolution ceased. The solution was quenched by slowly adding glacial acetic acid until the yellow color faded. The solution was stirred for 0.5 h then washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated to yield 8.6 g (81%) of **38**, which was clean by ^{1}H NMR: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.63 (q, J = 1.5 Hz, 1 H), 3.70 (s, 3 H), 2.98 (d, J = 1.5 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 163.8, 130.7, 119.6, 50.8, 30.5; HRMS (EI) m/e 225.9476 (225.9491 calcd for $C_5H_7IO_2$).

Sulfone Iodide 6. To a solution of **38** (8.6 g, 38.0 mmol) in dry toluene (190 mL) at 0 °C was added DIBAH (85 mL, 1.0 M in hexanes). The reaction was stirred for 0.5 h and worked up, as described above (preparation of compound **23**), to yield 6.6 g (88%) of **39**, which was pure by ^{1}H NMR. Compound **39** (1.0 g, 5.0 mmol), triethylamine (1.1 mL, 7.9 mmol), and DMAP (65 mg, 0.53 mmol) were dissolved in CH_2Cl_2 (25 mL). Methanesulfonyl chloride (0.45 mL, 5.8 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred for 1 h, diluted with CH_2Cl_2, and poured in to ice–water. The organic layer was separated and washed successively with 0.1 N HCl, saturated $NaHCO_3$ solution, and brine and then dried and concentrated. The products, **40a** and **40b**, were dissolved in DMF (20 mL), and sodium benzenesulfinic acid (1.7 g, 10.4 mmol) was added. The reaction was stirred for 0.5 h at 23 °C. The solution was poured into water and extracted with ether. The ether layer was washed with brine, then dried ($MgSO_4$), and concentrated. The product was purified by silica gel chromatography (4:1 hexanes/EtOAc), yielding 0.77 g (47% from **39**) of **6** as a white solid. The product was recrystallized from hot EtOAc and hexanes: mp 106.5–107.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2 H), 7.72–7.54 (m, 3 H), 6.18 (tq, J = 8.4, 1.4 Hz, 1 H), 3.73 (d, J = 8.4 Hz, 2 H), 2.05 (d, J = 1.4 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.2, 133.8, 129.1, 128.2, 126.4, 103.8, 56.9, 27.5; IR ($CHCl_3$) 3020, 1635, 1450, 1320, 1315, 1200, 1170, 1150, 1090 cm^{-1}; HRMS (EI) m/e 321.9546 (321.9525 calcd for $C_{10}H_{11}IO_2S$). Anal. Calcd for $C_{10}H_{11}IO_2S$: C, 37.28; H, 3.44. Found: C, 37.59; H, 3.11.

Nozaki–Kishi Coupling of 4 and 6. Aldehyde **4** (1.94 g, 3.98 mmol), azeotroped three times from toluene, and recrystallized sulfone iodide **6** (1.79 g, 5.56 mmol) were separately placed under high vacuum (0.05 mmHg) for 12 h then dissolved in degassed DMSO (35 mL, 99%+, Aldrich) under an atmosphere of nitrogen. To this solution was added $CrCl_2$ (0.68 g, 5.53 mmol, 99.9%, Cerac) mixed with about 0.1% $NiCl_2$ (99%, Alpha), which resulted in the formation of a dark, avocado green color. The reaction was

stirred at 23 °C for 24 h and poured into saturated NH_4Cl solution. The products were extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated. The products **41** and **42** were separated by medium-pressure liquid chromatography (LiChroprep Si60 40–63 μm, 7:3 hexanes/EtOAc) to yield a total of 1.32 g (66% based on recovered **4** and **6**) of material. Data for **41**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H), 7.70–7.67 (m, 4 H), 7.62–7.29 (m, 14 H), 5.51 (br t, J = 8.1 Hz, 1 H), 4.52 (AB, J = 11.2 Hz, $\Delta\nu$ = 51.6 Hz, 2 H), 4.15 (dd, J = 9.0, 2.6 Hz, 1 H), 3.84 (d, J = 8.1 Hz, 2 H), 3.72–3.61 (m, 2 H), 3.52 (dd, J = 5.9, 1.6 Hz, 2 H), 1.75–1.42 (m, 6 H), 1.34 (s, 3 H), 1.23–1.11 (m, 1 H), 1.08 (s, 9 H), 0.97 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 147.7, 139.5, 138.2, 135.6, 134.2, 133.4, 129.5, 128.9, 128.4, 127.8, 127.7, 127.6, 111.2, 79.6, 77.2, 75.9, 70.8, 69.0, 55.9, 39.9, 36.0, 31.1, 29.6, 28.4, 27.0, 19.4, 16.8, 12.3; IR (film) 3480, 2940, 2860, 1960, 1890, 1815, 1740, 1590, 1450, 1430, 1395, 1375, 1310, 1250, 1155, 1115, 1090, 945, 910, 830, 750, 710 cm^{-1}; HRMS (FAB) m/e 685.3403 (685.3385 calcd for $C_{41}H_{52}O_5SSi$ + H); $[\alpha]^{23}_D$ 23.5° (c 3.86, $CHCl_3$). Data for **42**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.90–7.87 (m, 2 H), 7.69–7.29 (m, 18 H), 5.57 (br t, J = 8.1 Hz, 1 H), 4.52 (AB, J = 11.3 Hz, $\Delta\nu$ = 23.6 Hz, 2 H), 4.24 (br m, 1 H), 3.85 (d, J = 8.1 Hz, 2 H), 3.63 (m, 1 H), 3.49 (br d, J = 5.8 Hz, 2 H), 3.11 (br m, 1 H), 1.71–1.45 (m, 6 H), 1.36 (s, 3 H), 1.22–1.11 (m, 1 H), 1.06 (s, 9 H), 0.94 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 148.0, 139.2, 138.4, 135.4, 133.9, 133.2, 129.4, 128.8, 128.2, 127.6, 127.4, 110.2, 72.9, 71.1, 68.7, 60.0, 55.6, 38.6, 35.7, 30.8, 28.6, 26.8, 20.6, 19.1, 16.7, 14.0, 12.6; IR (film) 3480, 3060, 2920, 2850, 1950, 1885, 1810, 1730, 1580, 1445, 1430, 1390, 1370, 1300, 1240, 1100, 940, 900, 825, 740, 705 cm^{-1}; HRMS (FAB) m/e 685.3405 (685.3385 calcd for $C_{41}H_{52}O_5SSi$ + H); $[\alpha]^{23}_D$ 17.9° (c 3.33, $CHCl_3$).

Ketone 44. To a solution of Dess–Martin periodinane[27] (0.570 g, 1.34 mmol) and pyridine (0.11 mL, 1.36 mmol) in CH_2Cl_2 (6 mL) was added dropwise a solution of **42** (0.460 g, 0.671 mmol) in CH_2Cl_2 (6 mL). The reaction was stirred at 23 °C for 1 h then diluted with ether and quenched with a 1:1 mixture of saturated $NaHCO_3$ solution and saturated $NaHSO_3$ solution. The mixture was stirred for 5 min. The organic phase was separated and washed successively with saturated $NaHCO_3$ solution, saturated $CuSO_4$ solution, and brine. The solution was dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (4:1 hexanes/EtOAc) to yield 0.414 g (90%) of **44**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.88–7.84 (m, 2 H), 7.71–7.23 (m, 18 H), 6.49 (dt, J = 8.0, 1.5 Hz, 1 H), 4.48 (AB, J = 11.3 Hz, $\Delta\nu$ = 13.9 Hz, 2 H), 3.99 (d, J = 8.0 Hz, 2 H), 3.95 (m, 1 H), 3.50 (m, 2 H), 3.02 (dd, J = 16.0, 7.5 Hz, 1 H), 2.63 (dd, J = 16.0, 4.7 Hz, 1 H), 1.70–1.47 (m, 4 H), 1.51 (d, J = 1.1 Hz, 3 H), 1.19–1.08 (m, 1 H) 1.07 (s, 9 H), 0.95 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 198.9, 144.1, 138.9, 138.6, 135.3, 134.0, 133.5, 129.2, 128.9, 127.9, 127.3, 127.1, 125.6, 77.2, 76.3, 71.4, 68.6, 56.3, 42.8, 35.6, 31.9, 28.6, 26.8, 19.1, 16.6, 11.4; IR (film) 3070, 3030, 2940, 2860, 1960, 1890, 1820, 1740, 1680, 1590, 1450, 1430, 1390, 1365, 1335, 1310, 1240, 1160, 1115, 1090, 940, 830, 750, 710 cm^{-1}; HRMS (FAB) m/e 683.3226 (683.3228 calcd for $C_{41}H_{50}O_5SSi$ + H); $[\alpha]^{23}_D$ 2.0° (c 20.7, $CHCl_3$). Anal. Calcd for $C_{41}H_{50}O_5SSi$: C, 72.10; H, 7.38. Found: C, 71.88; H, 7.49.

Recycling of Ketone 44. To a solution of **44** (11.9 mg, 0.017 mmol) and $CeCl_3 \cdot 7H_2O$ (9.7 mg, 0.026 mmol) in 1:1 THF/methanol at −78 °C was added $LiBH_4$ (1.5 mg, 0.069 mmol). The reaction was stirred for 15 min and carefully quenched with NH_4Cl solution. The mixture was poured into brine and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated. The total yield of products **41** and **42** was 10.1 mg (85%). The isomers were separated by MPLC, as described above (see Nozaki–Kishi coupling procedure).

Sulfone 43. A solution of **41** (0.135 g, 0.197 mmol), methyl trifluoromethanesulfonate (33 mL, 0.292 mmol), and 2,6-di-*tert*-butylpyridine (111 μL, 0.494 mmol) in CH_2Cl_2 (1.0 mL) was heated to reflux temperature for 18 h. The solution was concentrated, and the product was purified by silica gel chromatography (4:1 hexanes/EtOAc) to yield 0.138 g (100%) of **43**: ^1H NMR (490 MHz, $CDCl_3$) δ 7.91–7.27 (m, 20 H), 5.36–5.33 (m, 1 H), 4.46 (AB, J = 11.5 Hz, $\Delta\nu$ = 39.6 Hz, 2 H), 3.91 (dd, J = 14.3, 8.1 Hz, 1 H), 3.83 (dd, J = 14.3, 7.6 Hz, 1 H), 3.63 (t, J = 6.7 Hz, 1 H), 3.55 (dd, J = 9.9, 5.7 Hz, 1 H), 3.49 (dd, J = 9.8, 4.2 Hz, 1 H), 3.36–3.33 (m, 1 H), 3.07 (s, 3 H), 1.88–1.82 (m, 1 H), 1.76–1.49 (m, 5 H), 1.38 (d, J = 1.1 Hz, 3 H), 1.21–1.10 (m, 1 H), 1.09 (s, 9 H), 0.97 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 145.3, 139.0, 138.8, 135.5, 134.0, 133.6, 129.5, 129.1, 129.0, 128.3, 128.2, 127.7, 127.5, 127.4, 113.8, 83.4, 76.1, 70.4, 68.8, 56.0, 55.6, 37.9, 35.9, 30.9, 28.5, 26.9, 19.3, 16.9, 10.9; IR (film) 3100–2800, 1740, 1580, 1440, 1420, 1300, 1190, 1150, 1110, 1090, 1070, 820 790 cm^{-1}; HRMS (CI) m/e 699.3537 (699.3540 calcd for $C_{42}H_{54}O_5SSi$ + H); $[\alpha]^{23}_D$ 12.6° (c 1.18, $CHCl_3$). Anal. Calcd for $C_{42}H_{54}O_5SSi$: C, 72.17; H, 7.79. Found: C, 71.98; H, 7.74.

Trienedithiane 47*E*, 48*Z*. To a solution of **46** (15 mg, 0.015 mmol) in dry THF (1.2 mL) and dry MeOH (0.3 mL) was added KH_2PO_4 (10 mg), and the mixture was cooled to −20 °C. Then 5% sodium amalgam (42 mg) was added, and the reaction mixture was stirred at −20 °C for 45 min and then quenched with pH 7 buffer solution (2 mL). The resulting mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was purified by silica gel chromatography (4:1 hexanes/EtOAc) giving 7.8 mg (65%) of **47*E*** and **48*Z*** as a ca. 3:2 mixture of isomers: ^1H NMR (490 MHz, $CDCl_3$) δ 7.74–7.25 (m, 15 H), 6.44–6.34 (m, 2 H), 6.14–6.09 (m, 1 H), 6.01–5.92 (m, 1 H), 5.54–5.50 (m, 1 H), 4.52–4.36 (m, 2 H), 4.10–4.07 (m, 2 H), 3.83–3.69 (m, 1 H), 3.53–3.44 (m, 2 H), 3.36–3.30 (m, 1 H), 3.19 and 3.14 (s, 3 H), 2.93–2.78 (m, 4 H), 2.34–0.75 (m, 33 H); IR ($CDCl_3$) 2950, 2920, 2850, 1725, 1425, 1250, 1110 cm^{-1}; HRMS (FAB) m/e 784.4382 (784.4382 calcd for $C_{48}H_{68}O_3S_2Si$).

Aldehyde 51. To a solution of **46** (22.9 mg, 0.023 mmol) and CH_3CN (0.7 mL) was added a solution of *N*-chlorosuccinimide (24.8 mg, 0.18 mmol), $AgNO_3$ (32 mg, 0.19 mmol), and CH_3CN/H_2O (1:1, 0.5 mL) at 23 °C. After 15 min, the reaction was quenched by the addition of saturated aqueous Na_2SO_3 (1 mL), saturated aqueous Na_2CO_3 (1 mL), and brine (1 mL). This mixture was filtered through Celite, and the filtrate was extracted with EtOAc (4 × 5 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude isolate was chromatographed (silica gel, 7:3 hexanes/EtOAc) giving 13.7 mg (66%) of **51** as a mixture of isomers. Characteristic data for the product mixture: ^1H NMR (490 MHz, $CDCl_3$) δ 9.59–9.50 (m, 1 H), 7.91–7.24 (m, 20 H), 6.03–5.20 (m, 4 H), 4.62–4.22 (m, 3 H), 4.10–3.95 (m, 1 H), 3.75–3.36 (m, 4 H), 3.16–2.94 (m, 3 H), 2.45–2.11 (m, 2 H), 1.97–0.75 (m, 32 H); IR ($CDCl_3$) 2860, 2820, 2750, 1730, 1720, 1710, 1305, 1260, 1235, 1150, 1110, 1085 cm^{-1}; HRMS (FAB) m/e 917.4461 (917.4460 calcd for $C_{53}H_{70}O_8SSi$+Na).

Triene Alcohol 52*E*, 53*Z*. A solution of **51** (13 mg, 0.014 mmol) in CH_2Cl_2/EtOH (1:1, 2 mL) was allowed to react with $NaBH_4$ (2.2 mg, 0.058 mmol) at 0 °C. After 0.5 h, this solution was diluted with Et_2O (75 mL) and filtered through a plug of silica gel. The filtrate was concentrated, and the crude material was dissolved in THF/MeOH (4:1, 1.5 mL). The resulting mixture was treated with several crystals of KH_2PO_4 and then cooled to −20 °C. This mixture was allowed to react with 5% sodium amalgam (43 mg, 0.093 mmol) at −20 °C for 1 h and then was quenched by the addition of pH 7 buffer (2 mL). The resulting mixture was extracted with Et_2O (4 × 5 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. The crude material was purified by silica gel chromatography (7:3 hexanes/EtOAc) giving 8.0 mg (79%) of **52*E*** and **53*Z*** as a 1:1 mixture. Characteristic data for the product mixture: ^1H NMR (250 MHz, $CDCl_3$) δ 7.75–7.25 (m, 15 H), 6.48–6.32 (m, 2 H), 6.20–5.90 (m, 2 H), 5.60–5.47 (m, 1 H), 4.56–4.33 (m, 2 H), 3.86–3.25 (m, 6 H), 3.21 and 3.14 (s, 3 H), 2.40–0.75 (m, 33 H).

Acetoxy Sulfone 46. A solution of **43** (54 mg, 77 μmol) and dry THF (0.7 mL) was treated with *n*-BuLi (49 μL, 1.6 M in hexanes, 77 μmol) at −78 °C. After 20 min, a solution of **5** (20 mg, 81 μmol) in dry THF (0.3 mL) was added. After 30 min at −78 °C the reaction was quenched with the addition of saturated aqueous NH_4Cl (2 mL) and brine (2 mL). The resulting mixture was allowed to warm to 23 °C and then extracted with Et_2O (4 × 5 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated. The crude isolate was then taken up in CH_2Cl_2 (5 mL) and allowed to react with Et_3N (43 μL, 309 μmol), Ac_2O (15 μL, 154 μmol), and a catalytic amount of DMAP at 23 °C. After 1.5 h, the mixture was diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed (silica gel, 3:1 hexanes/EtOAc) giving 64.7 mg (85%) of **46** as a mixture of diastereomers: ^1H NMR (250 MHz, $CDCl_3$)

δ 7.92–7.28 (m, 20 H), 6.05–5.20 (m, 4 H), 4.55–4.32 (m, 3 H), 4.10–3.28 (m, 9 H), 3.18–2.80 (m, 7 H), 2.25–0.80 (m, 37 H); IR ($CDCl_3$) 2960, 2930, 2855, 1735, 1450, 1425, 1305, 1235, 1150, 1110, 1085 cm^{-1}; HRMS (FAB) *m/e* 985.4597 (985.4604 calcd for $C_{56}H_{76}O_7S_3Si$ + H).

Vinyl Sulfone 54. A solution of **46** (40.4 mg, 41 μmol) and THF (0.8 mL) was allowed to react with DBU (37 μL, 246 μmol) at 23 °C. After 1 h this solution was diluted with EtOAc (100 mL) and washed with saturated aqueous $CuSO_4$ (3 × 5 mL), H_2O (3 × 5 mL), and brine (1 × 5 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude material was purified by chromatography (silica gel, 4:1 hexanes/EtOAc) giving 33.9 mg (89%) of **54** as a clear oil: ^1H NMR (490 MHz, $CDCl_3$) δ 7.82–7.26 (m, 21 H), 6.14 (dd, *J* = 15.3, 8.4 Hz, 1 H), 5.87 (dd, *J* = 15.1, 11.0 Hz, 1 H), 5.84 (s, 1 H), 4.45 (AB, *J* = 11.6 Hz, Δν = 34.2 Hz, 2 H), 4.08 (d, *J* = 4.0 Hz, 1 H), 3.67 (t, *J* = 6.7 Hz, 1 H), 3.55–3.44 (m, 2 H), 3.34–3.32 (m, 1 H), 3.04 (s, 3 H), 2.91–2.80 (m, 4 H), 2.36–2.28 (m, 1 H), 2.14–2.07 (m, 1 H), 1.91–1.76 (m, 2 H), [1.71–0.80 (m), 1.14 (s), 1.06 (s), 1.04 (d, *J* = 2.7 Hz), 1.03 (d, *J* = 2.6 Hz), 0.95 (d, *J* = 6.7 Hz), 30 H]; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.4, 147.0, 139.9, 138.7, 137.6, 136.2, 135.6, 134.0, 133.0, 129.5, 128.9, 128.8, 128.3, 128.0, 127.7, 127.6, 127.5, 124.5, 117.4, 76.2, 70.7, 68.8, 56.1, 55.7, 40.9, 38.3, 36.2, 35.9, 35.5, 31.0, 30.8, 29.7, 28.5, 26.9, 26.3, 21.0, 16.9, 16.8, 12.1, 1.0; IR ($CDCl_3$) 3060, 2960, 2935, 2860, 1725, 1630, 1445, 1425, 1305, 1150, 1115, 1090 cm^{-1}; HRMS (FAB) *m/e* 925.4381 (925.4393 calcd for $C_{54}H_{72}O_5S_3Si$ + H); $[\alpha]^{23}_D$ 3.8° (*c* 1.05, $CDCl_3$).

Sulfone Aldehyde 55. A solution of **54** (17.0 mg, 18.4 μmol) and CH_3CN (0.5 mL) was added to a solution of *N*-chlorosuccinimide (20.0 mg, 147 μmol), $AgNO_3$ (26 mg, 148 μmol), H_2O (0.2 mL), and CH_3CN (0.3 mL) at 23 °C. After 20 min, the reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (1 mL), saturated aqueous Na_2CO_3 (1 mL), and brine (1 mL). This mixture was stirred at 23 °C for 1 min and then it was extracted with Et_2O (4 × 5 mL). The organic extracts were dried and concentrated. The crude material was purified by chromatography (silica gel, 7:3 hexanes/EtOAc) giving 10.2 mg (66%) of **55** as a clear oil: ^1H NMR (490 MHz, $CDCl_3$) δ 9.58 (d, *J* = 1.5 Hz, 1 H), 7.82–7.25 (m, 25 H), 6.13 (dd, *J* = 15.2, 8.3 Hz, 1 H), 5.88 (dd, *J* = 15.2, 11.1 Hz, 1 H), 5.85 (s, 1 H), 4.45 (AB, *J* = 11.4 Hz, Δν = 34.8 Hz, 2 H), 3.67 (t, *J* = 6.6 Hz, 1 H), 3.54–3.43 (m, 4 H), 3.36–3.30 (m, 1 H), 3.03 (s, 3 H), 2.38–2.30 (m, 2 H), 1.88–1.78 (m, 2 H), [1.70–0.70 (m), 1.14 (d, *J* = 0.9 Hz), 1.06 (s), 1.06 (d, *J* = 2.6 Hz), 1.05 (d, *J* = 2.6 Hz), 0.95 (d, *J* = 6.7 Hz), 26 H]; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 204.1, 150.4, 147.1, 139.7, 138.6, 137.3, 136.6, 135.6, 134.0, 133.1, 129.5, 128.9, 128.3, 128.0, 127.7, 127.6, 127.5, 124.7, 117.3, 106.4, 76.2, 70.6, 68.8, 56.1, 44.2, 38.3, 36.8, 35.9, 35.1, 31.0, 28.5, 26.9, 20.6, 20.5, 16.9, 13.3, 12.1; IR ($CDCl_3$) 2960, 2920, 2855, 1725, 1305, 1150, 1115, 1090 cm^{-1}; HRMS (FAB) *m/e* 835.4462 (835.4430 calcd for $C_{51}H_{66}O_6SSi$ + H); $[\alpha]^{23}_D$ 16.7° (*c* 1.26, $CHCl_3$).

Triene Aldehyde 49*E*. A solution of **55** (7.0 mg, 8.4 μmol) and 4:1 THF/MeOH (0.88 mL) was treated with several crystals of KH_2PO_4 and 5% sodium amalgam (23 mg, 50 μmol) at −20 °C. After 1 h, the reaction was quenched by the addition of a pH 7 buffer (2.0 mL). The resulting mixture was extracted with Et_2O (4 × 5 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (9:1:3 hexanes/EtOAc/toluene) giving 5.0 mg (85%) of **49*E*** as a clear oil. ^1H NMR indicated that the product was composed of a 5:1 mixture of C_{31} epimers. Data for the major epimer: ^1H NMR (490 MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.6 Hz, 1 H), 7.68–7.27 (m, 20 H), 6.43–6.35 (m, 1 H), 6.16–6.08 (m, 2 H), 5.94 (br d, *J* = 10.9 Hz, 1 H), 5.56–5.48 (m, 1 H), 4.43 (AB, *J* = 11.4 Hz, Δν = 60.1 Hz, 2 H), 3.70 (br t, *J* = 6.8 Hz, 1 H), 3.53–3.44 (m, 2 H), 3.35–3.30 (m, 1 H), 3.14 (s, 3 H), 2.38–2.28 (m, 2 H), 1.96–1.88 (m, 1 H), 1.80–1.73 (m, 1 H), [1.67–0.80 (m), 1.26 (s), 1.06 (s), 0.93 (d, *J* = 6.6 Hz), 23 H]; IR ($CDCl_3$) 2960, 2920, 2850, 1715, 1110, 1090, 990 cm^{-1}; HRMS (FAB) *m/e* 694.4412 (694.4420 calcd for $C_{45}H_{62}O_4Si$).

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Supplementary Material Available: NMR spectra for compounds **8**, **12**, **13**, **28**, **32**, **41**, **46–49**, and **51–55** (15 pages). Ordering information is given on any current masthead page.