the other hand, are calculated to have triplet ground states.

The effect of *d*-functions on silicon is much greater for the unsaturated than for the saturated silicon molecules.[2] In general, much greater decreases in the silicon bond distances are found in the unsaturated molecules when *d*-functions are added.

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Enantiocontrolled Cycloaddition Approach to (+)-Brefeldin A

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Abstract: The concept of a cycloaddition to form five-membered rings allows a retrosynthetic analysis of the antifungal, antiviral, and antitumor agent (+)-brefeldin A that resolves the problem of relative and absolute stereochemistry. The acetonide of D-glyceraldehyde which provides C-4 of the target transmits its stereochemistry ultimately to C-5, -7, and -9 via a Pd-catalyzed cycloaddition as the key step to form the five-membered ring unit. The last chiral center at C-15 is established by using a microbiological reduction of 1-phenylsulfonyl-5-hexanone with a relatively unknown microorganism *C. guillermonde*. Julia olefination attaches the derived hexanol unit which constitutes the lower side chain to the cyclopentyl unit. Alkylative elimination using the dianion of phenylthioacetic acid introduces the acrylate unit and completes the synthesis of the optically pure natural product.

While the Diels–Alder reaction enjoys unparallel prominence in the formation of six-membered rings for the synthesis of complex natural products, cycloaddition strategy for forming five-membered ring carbocyclic natural products is virtually unknown. The opportunities for selectivity embodied in such a strategy based upon a Pd-catalyzed cycloaddition[1] are revealed in analyzing an approach to (+)-brefeldin A (**1**), a significant target because of its antifungal, antimitotic, antiviral, and antitumor activities.[2,3] This 16-membered macrolide antibiotic, also known as cyanein,[4] decumbin,[5] and ascotoxin, bears a structural resemblance to the prostaglandins. Studies on the biosynthesis of **1**, however, strongly suggest that cyclopentanol formation in **1** does not parallel prostaglandin biosynthesis.[7]

The synthesis[8] of racemic brefeldin A was first reported by Corey and Wollenberg[9] and subsequently by others.[8] Natural (+)-brefeldin A has been prepared by a rather long route from D-mannitol and D-glutamic acid[10] and also more efficiently from an optically active Diels-Alder adduct.[11] Studies directed toward a possibly biomimetic synthesis have also been recently reported.[12]

Previous syntheses of **1** (with one exception[18]) have relied on one of two methods for obtaining the cyclopentanol ring with the correct stereochemistry: one uses *trans* cyclopentanone-3,4-dicarboxylic acid as the starting material; the other uses conjugate addition of an organometallic reagent to a 4-substituted cyclopentenone, giving 3,4-trans substituents.

The approach to (+)-brefeldin A described herein is unique in that the absolute configuration at carbons 4, 5, and 9 (brefeldin numbering) is controlled by the method by which the cyclopentyl ring is constructed.

Scheme I outlines a retrosynthetic analysis. As in almost all previous syntheses,[8] the seco acid **2** was envisioned as the immediate precursor. The concept of alkylative elimination (eq 1)[13,14] allows dissection of the upper side chain between C(2) and C(3) of **3** and requires a leaving group at *pro*-C-3 as exemplified by the epoxide in **4**. Obviously, any vicinal oxygen substitution such as in **5** is easily convertible into an epoxide. At this point, attention turned to the lower side chain which nicely draws upon the Julia olefination[15] which has been shown to be capable of generating (*E*)-olefins with excellent geometrical control.[16] The availability of the requisite β-hydroxy sulfone **6** via the β-keto sulfone **7** suggested acylation of a sulfone-stabilizing anion with the ester

(1) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326. (b) Trost, B. M.; Renaut, P. *Ibid.* **1982**, *104*, 6668.

(2) (a) Betina, V. *Neoplasma* **1969**, *16*, 23. (b) Bacikova, D.; Betina, V.; Nemec, P. *Naturwissenschaften* **1964**, *51*, 445 and earlier references therein. (c) Harri, E.; Loeffler, W.; Sigg, H. P.; Stahelin, H.; Tamm, Ch. *Helv. Chim. Acta* **1963**, *46*, 1235. (d) Hayashi, T.; Takatsuki, A.; Tamura, G. *J. Antibiot., Ser. A* **1974**, *27*, 65. (e) Suzuki, Y.; Tanaka, H.; Aoki, H.; Tamura, T. *Agric. Biol. Chem.* **1970**, *34*, 395.

(3) First isolation: Singleton, V. L.; Bohonos, N.; Ullstrup, A. J. *Nature (London)* **1958**, *181*, 1072. Structure: Weber, H. P.; Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 2763.

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(6) (a) BuLock, J. D.; Clay, P. T. *Chem. Commun.* **1969**, 237. (b) Cross, B. E.; Hendly, P. *Ibid.* **1975**, 124.

(7) (a) Maburi, C. T.; Garlaschelli, L.; Ellison, R. A.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 707. (b) Hutchinson, C. R.; Kurobane, I.; Cane, D. E.; Hasler, H.; McInnes, A. G. *Ibid.* **1981**, *103*, 2477. Hutchinson, C. R.; Kurobrani, I.; Mabuni, C. T.; Kumola, R. W.; McInnes, A. G.; Walter, J. A. *Ibid.* **1981**, *103*, 2474. (c) Yamamoto, Y.; Hori, A.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 2471.

(8) For most recent syntheses, see: (a) Gais, H. J.; Lied, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 145. (b) Koksal, Y.; Raddatz, P.; Winterfeldt, E. *Annalen* **1984**, 450, 462. (c) Marx, K.-H.; Raddatz, P.; Winterfeldt, E. *Ibid.* **1984**, 474. (d) Kitahara, T.; Mori, K. *Tetrahedron* **1984**, *40*, 2935. For references prior to 1984, see citations contained in these publications.

(9) Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4705. Corey, E. J.; Wollenberg, R. H.; Williams, D. R. *Tetrahedron Lett.* **1977**, 2243.

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(11) LeDrian, C.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473.

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(16) Kocienski, P. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829, 834; *Chem. Ind. (London)* **1981**, 548.

(17) See, for example: Bartlett, P. A.; Green, F. R., III; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852.

(18) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.

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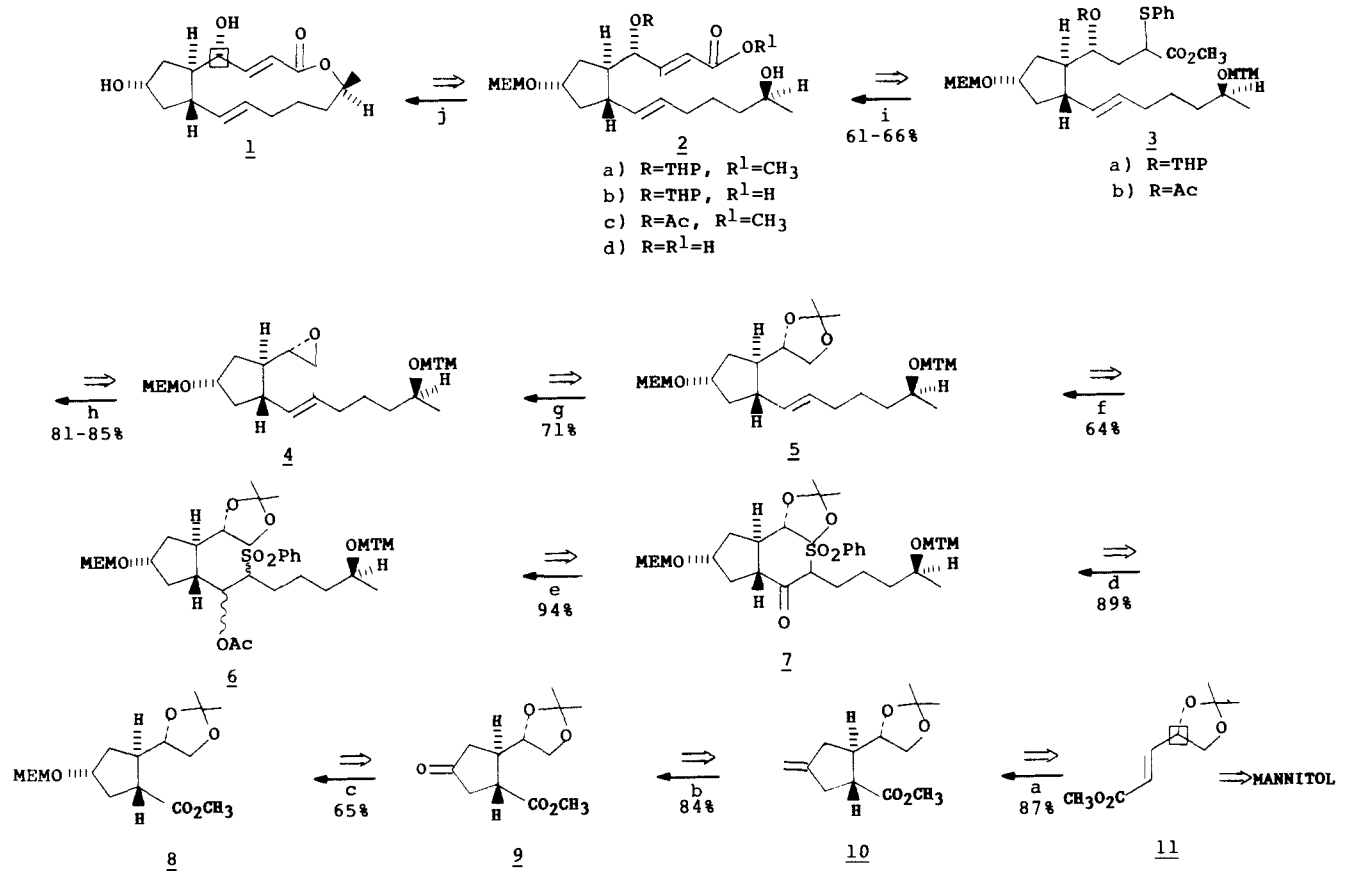
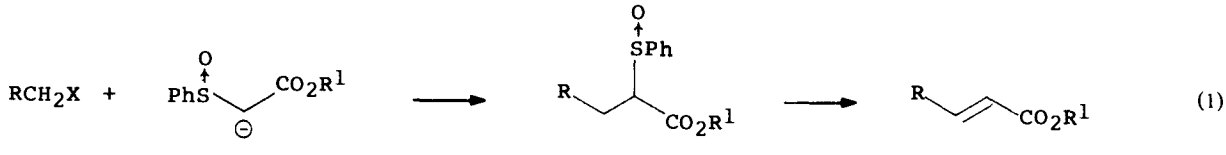
Scheme I. Retrosynthetic Analysis and Synthesis of (+)-Brefeldin A



[a] $AcOCH_2C(=CH_2)CH_2(TMS)$, 33 mol % $(i\text{-}C_3H_7O)_3P$, 7 mol % $Pd(OAc)_2$, $PhCH_3$, 100 °C. [b] O_3, CH_3OH, -78 °C and then $(CH_3)_2S$. [c] (i) DIBAL-H, BHT, $PhCH_3$, -78° → 0 °C. (ii) $(i\text{-}C_3H_7)_2NC_2H_5$, MEM-Cl, CH_2Cl_2. [d] **15**, THF, -78 °C. [e] (i) $NaBH_4$, C_2H_5OH; room temperature. (ii) Ac_2O, DMAP, C_5H_5N, room temperature. [f] 6% Na(Hg), CH_3OH, Na_2HPO_4, -20 °C. [g] (i) HCl, H_2O, THF, room temperature. (ii) TsCl, C_5H_5N, 0 °C. (iii) $NaOCH_3$, CH_3OH, ether, 0 °C. [h] (i) **18**, THF, 0° → room temperature then CH_2N_2, ether. (ii) R = Ac, Ac_2O, DMAP, C_5H_5N, 0 °C or R = THP, DHP, PPTS, CH_2Cl_2, room temperature. [i] (i) NCS, $AgNO_3$, CH_3CN-H_2O, $CaCO_3$. (ii) $PhCH_3$, BSA, room temperature → 95 °C. [j] References 9, 10.



(1)

8.[9] This operation separates one chiral center, that at *pro*-C-15, from the other four and thereby requires an asymmetric synthesis of the sulfone unit (vide infra). Of the remaining four chiral centers, it was felt that those at *pro*-C-4, *pro*-C-5, and *pro*-C-9 could induce the fourth at *pro*-C-7 by diastereoselective reduction of ketone **9**. Recognizing the synthetic equivalence of an exocyclic methylene group and a carbonyl group suggests **10**, a structure that immediately reveals the elements of trimethylenemethane and acrylate **11**.[18] A Pd-catalyzed cycloaddition must extend the one chiral center of **11** to the three of **10**, a type of selectivity at which cycloadditions should excel. The fact that **11** emanates from mannitol means **11** is optically pure. Thus, this asymmetric synthesis elaborates four of the five asymmetric centers of **1** from mannitol, the fifth yet to be established.

Synthesis of the C(11)–C(16) Fragment. The obtention of the lower side chain in optically pure form can most easily be accomplished by asymmetric reduction of the methyl ketone **12**. Microbiological methods are ideal for such a problem. Surprisingly, bakers' yeast totally failed to give any reduction. After screening many microorganisms in collaboration with Prof. C. Sih, we found *C. guillermonde* reduced **12** to give >95% optically pure **13**,[19] $[\alpha]^{24}_D$ +7.91° (*c* 6.5, $CDCl_3$), in 73–98% yield (eq 2). Conversion of the alcohol to the *O*-methylmandelate ester **14** allowed NMR analysis to establish both the optical purity and absolute configuration.[20,21] Using the extended Newman projections of **14a** and **14b** for **14** indicates that the *S* isomer should exhibit a lower field shift for the secondary methyl group than the *R* isomer. The *O*-methylmandelate ester derived from racemic alcohol which gives a 1:1 diastereomeric mixture of **14a** and **14b** shows the methyl group as a doublet at δ 1.06 and 1.18 for the *R* and *S* (with respect to the alcohol epimeric carbon) isomers, respectively. The ^1H NMR spectrum of the *O*-methylmandelate ester from the alcohol **13** obtained by microbiological reduction showed only the methyl doublet at δ 1.18, corresponding to the *SS* diastereomer.

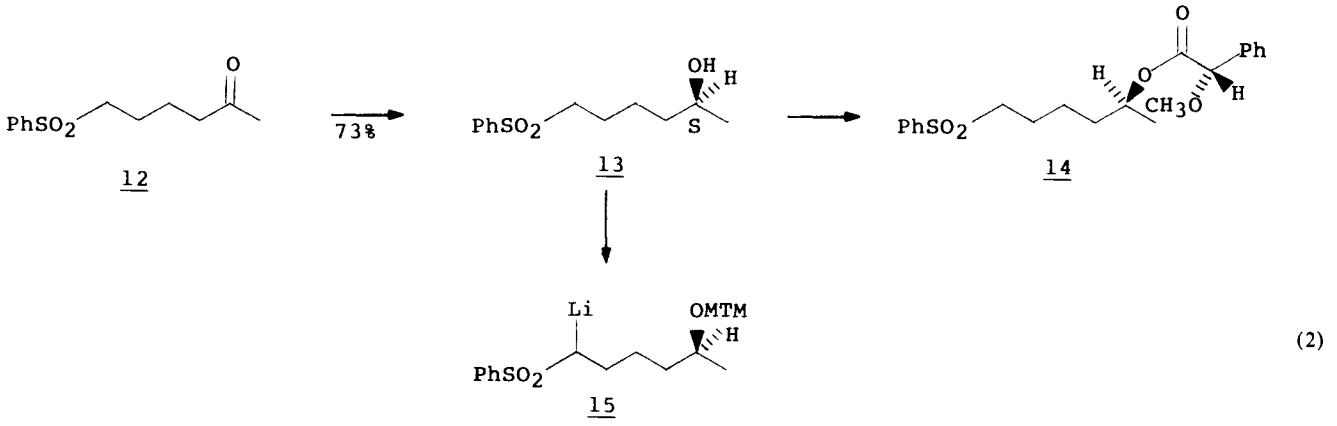
Using the method of Angyal,[22] the alcohol was protected as its methyl thiomethyl ether in 67–73% yield to facilitate metallations. Byproducts in this step proved to be ketone **12**, a result of a Moffatt-type oxidation, and acetoxymethyl ether which can be reconverted to alcohol **13** by treatment with aqueous potassium hydroxide.

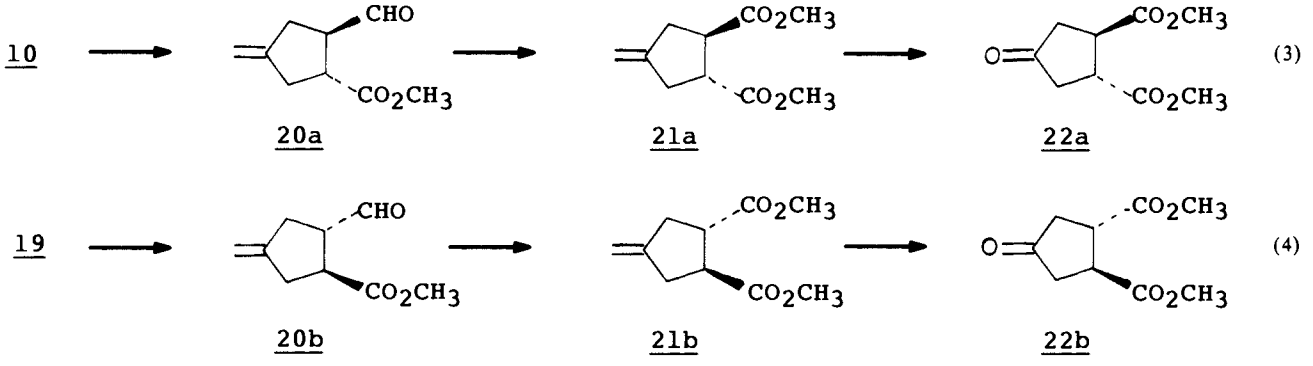
(19) Cf.: Bartlett, P. A.; Green, F. R., III. *J. Am. Chem. Soc.* **1978**, *100*, 4858.

(20) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

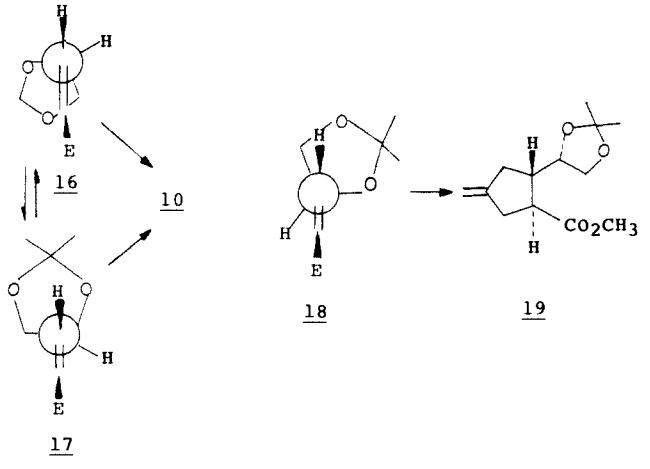
(21) Trost, B. M. In "Asymmetric Reactions and Processes in Chemistry"; Eliel, E. L., Otsuka, S., Eds.; Wiley: New York, 1982; ACS Symp. Ser. No. 185, pp 1–20. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. Trost, B. M.; McDougal, P. G. *Ibid.* **1982**, *23*, 5497.

(22) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.





Preparation of the Cyclopentyl Unit. Cycloaddition of [2-(acetoxymethyl)allyl]silane[23] to the known acrylate **11**[24] has the possibility to generate three of the four remaining stereocenters of brefeldin A with the correct absolute and relative stereochemistry. The availability of **11** in optically pure form from mannitol establishes the absolute stereochemistry. Diastereoselectivity in the cycloaddition extends the stereochemistry of **11** into the absolute stereochemistry of **10**. Extension of the concepts



of Felkin-Ahn[25] to acrylates[26] suggests that **16** should represent the reactive conformer. Nevertheless, the severe nonbonded interactions of **16**, the unfavorable dipole-dipole effect, and the propensity to place an allylic C-O bond close to the plane of an olefin bearing an electron-withdrawing group[27] suggest that **17** may be preferred. Fortunately, both **16** and **17** predict the same diastereomeric product **10**. On the other hand, the conformer **18** leads to the maximum steric hindrance to the approaching nucleophile. In the event, cycloaddition proceeds in 87% isolated yield to a 3–4:1 mixture of the two diastereomeric adducts **10** and **19**.

To establish stereochemistry of the adduct, the degradation outlined in eq 3 and 4 was performed on a 7:3 mixture of **10** and **19**. Hydrolysis of the acetonide (TsOH, CH_3OH, room temperature) followed by diol cleavage with lead tetraacetate (PhH, room temperature) provided the aldehydes **20a** and **20b**. Oxidation with PDC (DMF, room temperature) and esterification with diazomethane (ether) gave the diesters **21a** and **21b** which upon subjection to ozonolysis provided the ketones **22a** and **22b**. The enantiomer **22a** is a known degradation product of brefeldin A.[28] The rotation of the mixture, $[\alpha]^{25}_D$ −44°, indicated the absolute stereochemistry depicted in **22a** for the major component of the

(23) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

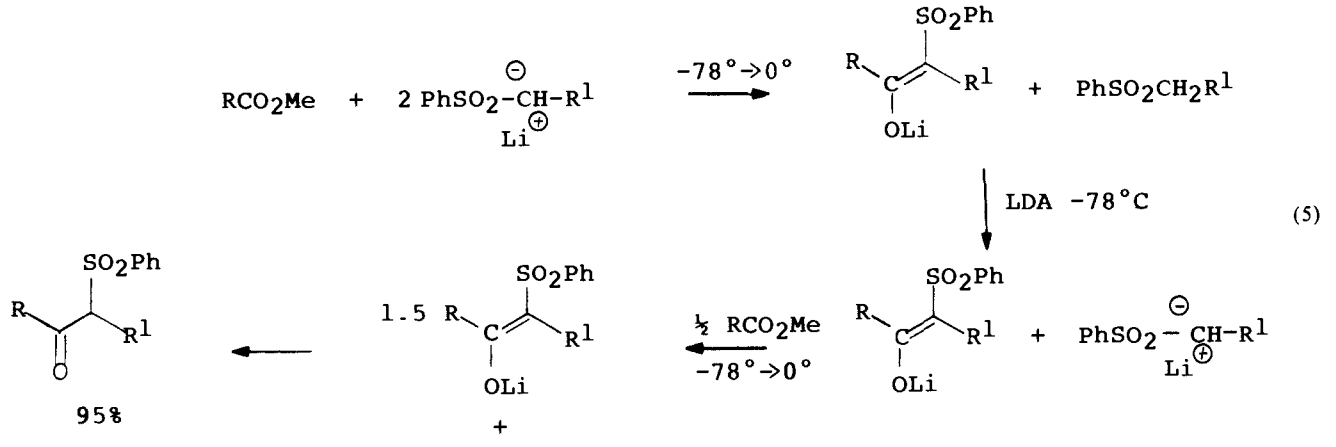
(24) (a) Cf. Ethyl ester: Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (b) For methyl ester, see: Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009.

(25) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2001 and 2205. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(26) (a) Mulzer, J.; Kappert, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 63. (b) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231.

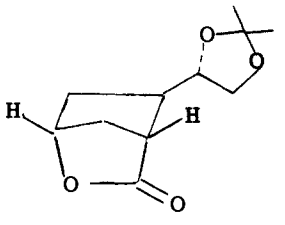
(27) Tronchet, J. M. J.; Xuan, T. N. *Carbohydr. Res.* **1978**, *67*, 469. Lessard, J.; Saunders, J. K.; Viet, M. T. P. *Tetrahedron Lett.* **1982**, *23*, 2059. Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(28) Sigg, H. P. *Helv. Chim. Acta* **1964**, *47*, 1401. Because of the sample size, the magnitude of the rotation is subject to a large error.



mixture. Based upon a maximum rotation of −119° for optically pure **22a**, the calculated optical purity of 40% is consistent with the 7:3 diastereomeric composition of the initial adduct. Having demonstrated that the major [3 + 2] adduct corresponds to **10**, this cycloaddition proceeds preferentially via conformer **16** or, more likely, **17**. This assignment corresponds to the same diastereoselectivity observed in nucleophilic additions to **11**.[24b,26,29,30]

For creation of the fifth and final chiral center, the ketone **9** derived from **10** by ozonolysis was reduced to give a mixture of alcohols, the major one having the 7-epi configuration.[31] This observation implies that the face of the ketone cis to the ester was less-hindered. Using Yamamoto's reagent[32] which may coordinate to the basic ether oxygen to deliver hydride cis to the 1,3-dioxolane, a 6:1 ratio with the major isomer having the stereochemistry depicted in **8**, after protection as the MEM ether, was produced. Lactonization of the alcohol corresponding to **8** with ethyl chlorocarbonate[19] in the presence of triethylamine to form **23** demonstrates the cis relationship of the alcohol and ester in the major epimer. Reconversion of the lactone **23** to the starting hydroxy ester completes the interrelationships and unequivocably establishes the stereochemistry.

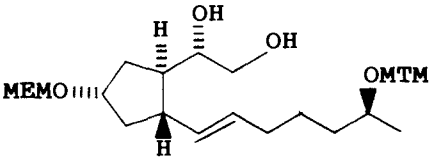


23

Attachment of the Lower Side Chain. Reaction of ester **8** with 2.2 equiv of the lithiated sulfone **15** provided a mixture of diastereomeric keto sulfones **7** in 90–96% yield. Recent experiments have shown that excess **15** can be recycled in situ by adding an appropriate amount of LDA following the reaction with ester **8** and then adding a second portion of **8** without loss of yield as in eq 5.

Conversion of the β-keto sulfone **7** to the (*E*)-olefin via an enol derivative failed.[19] On the other hand, the Julia procedure succeeds admirably.[15,16] The keto sulfone **7** was reduced and acetylated, giving the β-acetoxy sulfone **6** as a complex mixture of diastereomers. Reduction of **6** by Na(Hg)[16] with careful control of pH gave the desired (*E*)-olefin in 65% yield.

Up to this point, it was not convenient to separate the minor isomers from the cycloaddition and reduction steps. However, the major diol **24** obtained by hydrolysis of the acetonide is readily

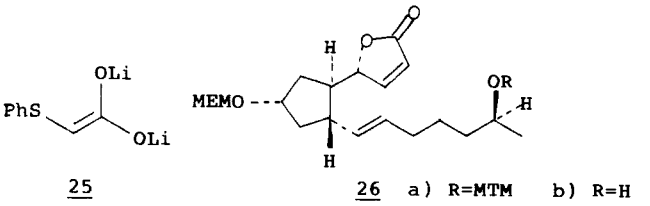


24

isolated by flash chromatography in 56–65% yield from keto sulfone in >94% diastereomeric purity. NMR spectroscopy of this diol clearly established the *E* double bond geometry (δ 5.42, dt, *J* = 16, 7 Hz and δ 5.28, dd, *J* = 16, 8 Hz).

Attachment of Upper Side Chain and Completion. Priming the diol **24** for the alkylative elimination involves forming the corresponding epoxide. Selective monotosylation of **24** gave yields varying from 72% to 89%. In those cases where lower yields were obtained, unreacted diol was recovered and resubjected to tosylation conditions. Treatment of the monotosylate with sodium methoxide gave epoxide **4** in nearly quantitative yield.

Alkylation of the dianion **25** generated from phenylthioacetic acid and 2 equiv of LDA[14] with epoxide **4** gave, after acidification and esterification with diazomethane, an unstable hydroxyester **3**, R = H. Attempts to introduce the 2,3-double bond by sulfoxide thermolysis with the free C(4) alcohol invariably led to substantial production of butenolide **26a**. Therefore, to complete the synthesis, the C(4) hydroxyl group was masked as its THP ether as in **3a** by using a large excess of DHP and PPTS to prevent γ-lactone formation.



25 **26** a) R=MTM b) R=H

Oxidation of the sulfide to the sulfoxide with NCS and silver nitrate[33] in the presence of a calcium carbonate buffer simultaneously removed the MTM group which, without isolation, was directly thermolyzed[34] in the presence of BSA to generate (*E*)-olefin **2a**, $[\alpha]^{24}_D$ +4.90° (*c* 0.245, $CHCl_3$) (two epimers at THP group, δ 6.93 and 6.78, each dd, *J* = 16, 6–7 Hz, total 1 H and δ 6.02 and 5.90, each d, *J* = 16 Hz, total 1 H). Hydrolysis of the ester **2a** to the corresponding acid **2b** with methanolic

(29) Mulzer, J.; Kappert, M.; Huttner, G.; Jibul, I. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 704.
(30) For an exception, see ref 26a.
(31) 7-*epi* Brefeldin A is also a natural product and thus available by this route. Gorst-Allman, C. P.; Steyn, P. S.; Rabie, C. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2387.
(32) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363.
(33) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(34) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

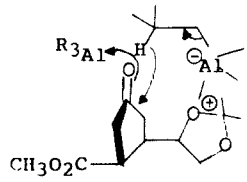
potassium carbonate (97% yield) completes the synthesis since this acid has already been transformed to (+)-brefeldin A.[9,10,35]

An alternative approach to (+)-brefeldin A envisioned the direct cyclization of the MEM ether of secobrefeldinoic acid, **2d**. In pursuing this avenue, the hydroxysulfide **3**, R = H, was capped by acetylation with acetic anhydride in pyridine to give **3b** in 85% overall yield from epoxide **4**. As in the case of the THP ether **3a**, oxidation of the phenyl sulfide to the sulfoxide was accompanied by removal of the MTM group. Thermolysis in the same fashion as for the THP ether gave the (*E*)-olefin as a single diastereomer since it lacks the creation of a chiral center in the protecting group as in the case of the THP ether (δ 6.83, dd, J = 15, 6 Hz and δ 5.87, d, J = 15 Hz). Hydrolysis of **2c** (LiOH, CH_3OH, H_2O, room temperature, 99%) generated the 7-MEM ether of secobrefeldinoic acid **2d**. In spite of the fact that the C(2)–C(3) double bond is clearly *E*, all attempts to generate the macrolactone led either to formation of the butenolide **26b** or decomposition. For example, formation of the mixed anhydride with diphenyl chlorophosphate and triethylamine[36] in THF at 0 °C followed by adding this activated substrate to a benzene solution of DMAP at 80 °C led only to the butenolide which was isolated in 50% yield. Formation of the butenolide requires double bond isomerization prior to lactonization which thwarts macrocyclization of a substrate bearing a free hydroxyl group at C(4).

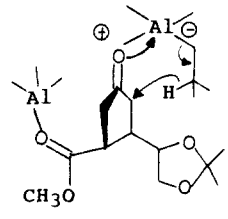
Discussion

Cycloaddition represents an important approach to diastereocontrolled formation of six-membered rings. It appears that such a strategy can extend to five-membered rings using this palladium-catalyzed [3 + 2] cycloaddition. The center that ultimately resides at C(4) of (+)-brefeldin A now sets the stage via the cycloaddition for the stereochemistry at C(5) and C(9). Further work to define the scope and basis of the diastereoselectivity as well as refine the degree of diastereoselectivity of palladium-mediated TMM additions is the object of future investigations.

The stereochemistry of the normal reduction of the carbonyl group of **9** reveals an easy approach to (+)-7-epibrefeldin A, a recently discovered metabolite from the same organism Penicillium brefeldianum.[31] The source of the change in diastereoselectivity with the Yamamoto reagent is unclear. Yamamoto reports that esters do not complex the reagent. If so, then delivery of the hydride on the more-hindered face syn to the acetonide would suggest an internal delivery as in **27**. On the other hand, it would



27

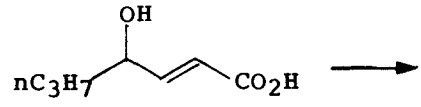


28

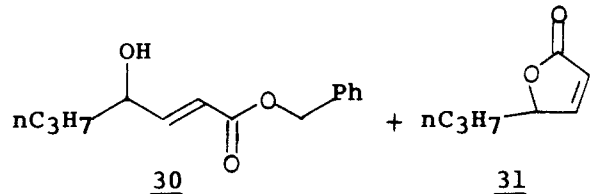
seem more probable that a normal Meerwein–Verley–Ponndorf[37] type of reduction occurs as in **28**. By making the α-face (i.e., syn to the ester) more hindered by complexation with 1 mol of the reagent to the ester, reduction occurs by a second mole from the opposite face. Thus, 1 mol of reagent serves as a temporary diastereoselectivity control element and, thereby, changes the intrinsic relative steric congestion of the two faces of the carbonyl group.

The establishment of the fifth and final asymmetric center at C(15) required the use of an uncommonly used microorganism *C. guillermonde*. It shows the same bias of generating *S* alcohols as the common yeasts. The failure of the bakers' yeast to effect reduction is surprising in light of its normal compatibility with sulfur substituents.[38] It should be pointed out that even the sulfide corresponding to **12** failed to reduce. The ability of *C. guillermonde* to accomplish this reduction where bakers' yeast fails suggests it may prove to be more general.

The failure of the MEM ether of secobrefeldinoic acid to cyclize because of its facile *E* to *Z* isomerization of the C(2)–C(3) double bond led us to explore this effect in a simpler system. Indeed, esterification of the hydroxyacid **29** led to varying amounts of the lactone **31** in addition to the expected ester **30**. For example,

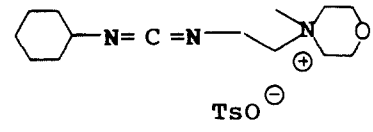


29



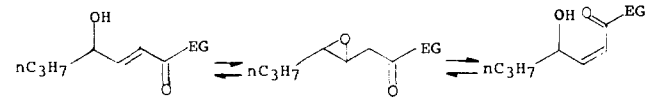
30 31

use of the carbodiimide **32**[39] with pyridine or DMAP led only to **31**. *N*-Methyl-2-chloropyridinium iodide produces only the lactone **31** when DABCO was employed as the base but generated the ester **30** when diisopropylethylamine was used as the base. A



32

possible explanation of the facility of the double bond isomerization under esterification conditions is the enhanced Michael reactivity of **29** when the carboxylic acid is activated by an electronegative group (EG) which enhances the electron-withdrawing effect of the carbonyl group as in **33**. An intramolecular addition of the



33 34 35

γ-hydroxy group to form the epoxide **34** then allows β-elimination either back to **33** or to the (*Z*)-olefin **35** which would rapidly lactonize. It is also possible that an external nucleophile serves to equilibrate the olefin geometry by a similar addition–elimination sequence but such an explanation does not adequately account for the enhancement seen for the hydroxy group.

Experimental Section

Methyl (*S*)-(+)-(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)propenoate, 11. Methyl (diisopropylphosphono)acetate (92.8 g, 390 mmol) was added to 39.6 g (353 mmol) of potassium *tert*-butoxide in 300 mL of dry THF at 0 °C under nitrogen. The solution was stirred 40 min at 0 °C and then cooled to −78 °C. (*R*)-(+)-2,3-Isopropylidineglyceraldehyde[40] (12.7 g, 97.6 mmol) in 50 mL of dry THF was added dropwise. After stirring 40 min further, 150 mL of saturated aqueous ammonium chloride was added. The mixture was allowed to warm to room temperature, and the aqueous layer was extracted with ether. The combined organic solution was dried ($MgSO_4$), concentrated, and distilled, giving a 1:1 mixture of **11** and starting phosphonate (bp 108–127 °C/15 mm Hg). This mixture was chromatographed (silica gel, 7:3 hexane/ether), giving 12.84 g (70%) of pure **11** as a clear liquid, bp 90 °C/2.8 mmHg, $[\alpha]^{22}_D$ + 33.6° (*c* 10, $CDCl_3$): IR 1710, 1440, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82 (dd, J = 15.5, 5.5 Hz, 1 H), 6.03 (dd, J = 15.5, 1.5 Hz, 1 H), 4.59

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(m, 1 H), 4.10 (dd, J = 8.2, 6.6 Hz, 1 H), 3.66 (s, 3 H), 3.59 (dd, J = 8.2, 6.9 Hz, 1 H), 1.36 (s, 3 H), 1.32 (s, 3 H); MS (% int), 171 (38), 129 (11), 98 (21), 97 (37), 72 (22). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.94; H, 7.60.

4(*S*),1′(*R*),2′(*R*)-2,2-Dimethyl-4-(2-carbomethoxy-4-methylenecyclopentyl)-1,3-dioxolane, 10. To 160 mg (0.71 mmol) of palladium acetate in 11 mL of dry toluene under nitrogen was added 726 mg (3.48 mmol) of triisopropyl phosphite, 2.00 g (10.7 mmol) of 2-[(trimethylsilyl)methyl]allyl acetate,[23] and 2.00 g (10.7 mmol) of **11**. The resulting solution was heated at 100 °C under nitrogen for 16 h. After cooling, the solution was concentrated. Flash chromatography (4:1 hexane/ether) gave 2.260 g (87%) of **10** and its 1′(*S*),2′(*S*) diastereomer as a colorless liquid at room temperature which crystallizes at −25 °C: IR ($CDCl_3$) 1730, 1650, 1430, 1375, 1365 cm^{-1}; ^1H NMR (270 MHz) ($CDCl_3$) δ 4.84 (br s, 2 H), 4.16–3.90 (m, 2 H), 3.66 (s), 3.65 (s) [3 H, overall], 3.53 (m, 1 H), 2.76–2.21 (m, 6 H), 1.36 (s), 1.34 (s) [3 H, overall], 1.30 (s), 1.28 (s) [3 H overall]; ^{13}C NMR ($CDCl_3$) 175.5, 175.1, 148.3, 108.9, 108.6, 106.5, 106.3, 78.3, 76.7, 67.6, 67.4, 51.5, 46.9, 46.7, 45.8, 45.4, 36.9, 34.7, 33.9, 26.4, 26.1, 25.3, 25.1 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: 240.1361. Found: 240.1361.

4(*S*),3′(*R*),4′(*R*)-2,2-Dimethyl-4-(4-carbomethoxycyclopentan-1-on-3-yl)-1,3-dioxolane, 9. A slow stream of ozone was bubbled through a solution of 1.584 g (6.6 mmol) of **10** in 60 mL of dry methanol at −78 °C until a blue color persisted. Excess ozone was removed by a stream of nitrogen, and 8 mL of dimethyl sulfide in 20 mL of methanol was added dropwise. The solution was allowed to warm to room temperature and was concentrated. Flash chromatography (1:1 hexane/EtOAc) gave 1.346 g (84%) of **9** as a mixture with its 3′(*S*),4′(*S*) diastereomer as a crystalline solid, mp 34–48 °C. IR ($CDCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 (m, 1 H), 4.08 (m, 1 H), 3.76 (s), 3.74 (s) [3 H, overall], 3.59 (m, 1 H), 3.09 (m, 1 H), 2.79–2.27 (m, 5 H), 1.40 (s), 1.39 (s), 1.35 (s), 1.33 (s), [6 H, overall]. Anal. Calcd or $C_{12}H_{18}O_5$: 242.1154. Found: 241.1154.

4(*S*),2′(*R*),1′(*R*),4′(*R*)-2,2-Dimethyl-4-(2-carbomethoxy-4-hydroxycyclopentan-1-yl)-1,3-dioxolane. Diisobutylaluminum hydride (23 mmol) in toluene was added dropwise to 7.18 g (27.3 mmol) of 2,6-di-*tert*-butyl-4-methylphenol in 21 mL of dry toluene at 0 °C.[16] After stirring 1.5 h at 0 °C, the solution was cooled to −78 °C, and 0.644 g (2.66 mmol) of ketone **9** in 28 mL of dry toluene was added dropwise. The resulting bright-yellow solution was stirred 1 h at −78 °C, allowed to warm and maintained at −30 °C for 0.75 h (yellow disappears), and allowed to warm to 0 °C. After stirring at 0 °C for 0.5 h, 17 g of silica gel was added, and the mixture was allowed to warm to room temperature. The mixture was concentrated to a dry solid which was placed on top of a column of silica gel. Elution with chloroform/acetone (9:1) gave 494 mg (76%) of the titled alcohol as a clear oil and as a 3:1 mixture with its 4(*S*),2′(*S*),1′(*S*),4′(*S*) diastereomer: IR (neat) 3600–3400 (s), 1735 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.3 (br s, 1 H), 4.18 (q, J = 6 Hz, 0.75 H), 3.9 (t, J = 7 Hz, 1.25 H), 3.67 (s, 3 H), 3.7–3.5 (m, 1 H), 3.0–2.5 (m, 3 H), 2.2–1.89 (m, 3 H), 1.8–1.4 (m, 1 H), 1.38 (s, 3 H), 1.32 (s, 3 H). Anal. Calcd for $C_{12}H_{20}O_5$: 244.1311. Found: 244.1311.

1(*R*),2(*R*),4(*R*),4′(*R*)-Methyl 2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-[(methoxyethoxy)methoxy]cyclopentanecarboxylate, 8. Diisopropylethyl amine (1.00 g, 7.69 mmol) was added to 936 mg (3.83 mmol) of the above alcohol in 10 mL of dry CH_2Cl_2 at 0 °C under nitrogen. (Methoxyethoxy)methyl chloride (469 mg, 3.76 mmol) was added dropwise and the solution was allowed to warm to room temperature. After stirring for 20 h, the solution was recooled to 0 °C and 1.00 g (7.69 mmol) of diisopropylethyl amine and (methoxyethoxy)methyl chloride were added in succession. After 21 h at room temperature, the solution was chromatographed directly (1:1 hexane/EtOAc). Concentration and distillation [bp 135–140 °C/0.03 mm Hg (Kugelrohr)] gave 1.081 g (85%) of **8** as a colorless oil: IR (neat) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.64 (ABq, J = 7 Hz, 2 H), 4.11 (m, 2 H), 3.94 (dd, J = 8.0, 6.25 Hz, 1 H), 3.62 (s, 3 H), 3.63–3.59 (m, 2 H), 3.49 (m, 3 H), 3.32 (s, 3 H), 2.57 (m, 2 H), 2.20–1.60 (m, 4 H), 1.33 (s), 1.31 (s), 1.30 (s), 1.27 (s), 1.25 (s) [6 H, overall]; ^{13}C NMR ($CDCl_3$, major isomer only) δ 173.3, 107.0, 92.5, 75.8, 75.5, 70.3, 66.3, 57.3, 50.2, 43.0, 41.5, 35.0, 32.5, 25.0, 23.9. Anal. Calcd for $C_{16}H_{28}O_7$: C, 57.81; H, 8.49; M_r, 332.1835. Found: C, 57.76; H, 8.30; M_r, 332.1833.

(*S*)-(+)-6-(Phenylsulfonyl)-2-hexanol, 12. 6-(Phenylsulfonyl)-2-hexanone[17] (2.7 g, 11.2 mmol) was reduced by a yeast culture, *C. guillermonde*, in 4 L of broth. The broth was extracted with 2 vol of ethyl acetate; the extract was dried ($MgSO_4$) and concentrated to give 5.05 g of a brown oil. Flash chromatography (1:2 hexane/ethyl acetate) gave 1.98 g (73% yield) of the alcohol as a clear oil $[\alpha]^{24}_D$ +7.91° (*c* 6.5, $CDCl_3$). The spectral properties matched those previously recorded for the racemic series.

(*S*)-(+)-6-(Phenylsulfonyl)-2-hexyl (Methylthio)methyl Ether, 13. Acetic acid (4.5 mL) and acetic anhydride (12 mL) were added to 1.343 g (5.54 mmol) of alcohol **12** in 16 mL of Me_2SO. The solution was stirred under nitrogen for 44 h, poured into 250 mL of saturated aqueous sodium bicarbonate, and the resulting mixture extracted with 1:1 methylene chloride/hexane (3 × 50 mL). The combined extract was washed with 40 mL of aqueous sodium bicarbonate, 3 × 40 mL of water, and brine and then dried (Na_2SO_4) and concentrated to give 3.01 g of a yellow oil. Flash chromatography (5:2 hexane/EtOAc) gave 1.212 g (72% yield) of **13** as a clear oil. In addition, a small amount of the acetoxymethyl ether (185 mg, 9.6%) and 6-(phenylsulfonyl)-2-hexanone was obtained: $[\alpha]^{22}_D$ +56.70 (*c* 2.4, $CDCl_3$); IR ($CDCl_3$) 2960, 2920, 2860, 1450, 1380, 1310, 1150, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (m, 2 H), 7.70–7.53 (m, 3 H), 4.58 (ABq, J = 11.4 Hz, 2 H), 3.71 (sex, J = 6 Hz, 1 H), 3.09 (t, J = 7.7 Hz, 2 H), 2.11 (s, 3 H), 1.81–1.36 (m, 6 H), 1.10 (d, J = 5 Hz, 3 H). Anal. Calcd for $C_{14}H_{22}O_3S_2$: 302.1010. Found: 302.1009.

4(*S*),1′(*R*),2′(*R*),4′(*R*),6′(*S*)-4-[4-[(4-methoxyethoxy)methoxy]-2-(6-[(methylthio)methoxy]-1-oxo-2-(phenylsulfonyl)heptyl)cyclopentyl]-1,3-dioxolane, 7. *n*-Butyllithium (3.94 mmol) in hexane was added to 1.310 g (4.33 mmol) of phenyl sulfone **13** in 8 mL of THF at −78 °C under nitrogen. After 20 min, 574 mg (1.73 mmol) of methyl ester **8** in 5 mL of THF was added dropwise. The solution was stirred 40 min at −78 °C and allowed to warm to room temperature. Water (3 mL) and 10% aqueous sodium diacid phosphate (3 mL) were added, the aqueous layer was extracted with ether (3 × 7 mL), and the combined organic solution was dried ($MgSO_4$) and concentrated to 1.778 g of pale-yellow oil. Flash chromatography (1:1 hexane/ethyl acetate) gave 0.696 g (89% recovery) of phenyl sulfone **13** and 0.926 g (89% yield) of the keto sulfone **7**: IR ($CDCl_3$) 1720, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–7.50 (m, 5 H), 4.80–4.45 (m), 4.32–3.88 (m), 3.76–3.50 (m), [14 H, overall], 3.37 (s), 3.38 (s) [3 H, overall], 2.10 (s), 2.08 (s) [3 H, overall], 1.95–1.19 (m, 12 H), 1.48 (s), 1.47 (s), 1.43 (s), 1.38 (s), 1.37 (s), 1.34 (s) [6 H, overall], 1.05 (m, 3 H). Anal. Calcd for $C_{29}H_{46}O_9S_2$: C, 57.78; H, 7.96. Found: C, 57.94; H, 7.70.

4(*S*),1′(*R*),2′(*R*),4′(*R*),6′(*S*)-4-[4-[(methoxyethoxy)methoxy]-2-(1-hydroxy-6-[(methylthio)methoxy]-2-(phenylsulfonyl)heptyl)cyclopentyl]-1,3-dioxolane. Sodium borohydride (110 mg, 2.9 mmol) was added to 790 mg (1.32 mmol) of ketone **7** in 10 mL of ethanol at room temperature; after stirring 40 min, 2 mL of acetone was added. The solution was concentrated to a white solid which was partitioned between 10 mL of water and 20 mL of ether. The aqueous layer was extracted with 2 × 5 mL of ether and the combined organic solution was washed with 2 × 10 mL of brine, dried ($MgSO_4$), and concentrated to give 769 mg (97% yield) of a clear oil: IR ($CDCl_3$) 3200, 2920, 2880, 1450, 1375, 1300, 1220, 1050, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.87 (m, 2 H), 7.68–7.47 (m, 3 H), 4.78–3.49 (m, 14 H), 3.39 (s, 3 H), 2.13 (s), 2.11 (s), 2.10 (s) [3 H, overall], 2.01–1.25 (m, 14 H), 1.47 (s), 1.36 (s) [6 H, overall], 1.05 (m, 3 H). Anal. Calcd for $C_{29}H_{48}O_9S_2$: C, 57.59; H, 8.00. Found: C, 57.51; H, 7.83.

4(*S*),1′(*R*),2′(*R*),4′(*R*),6′(*S*)-4-(2-(1-Acetoxy-6-[(methylthio)methoxy]-2-(phenylsulfonyl)heptyl)-4-[(methoxyethoxy)methoxy]cyclopentyl)-1,3-dioxolane, 6. Acetic anhydride (1 g, 10 mmol) was added to 758 mg (1.25 mmol) of the above alcohol in 5 mL of dry pyridine at room temperature under nitrogen. (Dimethylamino)pyridine (50 mg, 0.41 mmol) was added, and the solution was stirred for 3 h; it was poured into 75 mL of ether and was washed with 25 mL of aqueous saturated cupric sulfate and 2 × 5 mL of aqueous sodium bicarbonate dried ($MgSO_4$), and concentrated to give 790 mg of a pale-yellow oil. Flash chromatography (1:1 hexane/ethyl acetate) gave 781 mg (97% yield) of **6** as a clear oil: IR ($CDCl_3$) 1745 (s), 1450 (s), 1375 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9 (m, 2 H), 7.68–7.45 (m, 3 H), 5.25 (m, 1 H), 4.68 (s, 2 H), 4.7–4.44 (m, 2 H), 4.27–4.05 (m, 1 H), 4.05–3.80 (m, 2 H), 3.75–3.47 (m, 5 H), 3.36 (s, 3 H), 3.35–3.20 (m, 2 H), 2.8 (m, 1 H), 2.1 (s, 3 H), 1.78 (s, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 2.3–1.2 (m, 11 H), 1.07 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_{31}H_{50}O_{10}S_2$: C, 57.56; H, 7.79. Found: C, 57.62; H, 8.04.

4(*S*),1′(*R*),2′(*R*),4′(*R*),6′(*S*)-4-(4-[(Methoxyethoxy)methoxy]-2-((*E*)-6-[(methylthio)methoxy]heptenyl)cyclopentyl)-1,3-dioxolane, 5. Disodium acid phosphate (1.52 g, 10.7 mmol) was added to 646 mg (1.0 mmol) of acetoxy sulfone **6** in 5 mL of ethyl acetate. After cooling the mixture to −20 °C, 4.2 g of 6% sodium amalgam and 0.5 mL of methanol were added. The mixture was stirred at −20 °C for 2.25 h followed by adding an additional 1.5 g (11 mmol) of disodium acid phosphate and 3.15 g of 6% sodium amalgam. After stirring 2 h further, 4.5 mL of methanol was added. The mixture was stirred 1.25 h followed by additional portions of 0.3 g of disodium acid phosphate and 0.3 g of 6% sodium amalgam. The mixture was stirred 1 h after which it was allowed to warm to room temperature and filtered through silica gel. The silica gel plug was washed with 10 × 10 mL of ethyl acetate and the milky filtrate was concentrated. The white residue was triturated with ether, the ether was dried ($MgSO_4$), filtered through a sintered glass funnel,

and concentrated to give 439 mg of a clear oil. Flash chromatography gave 284 mg (64.2% yield) of **5** (along with its 1′(*S*),2′(*S*),4′(*R*) diastereomer) as a clear oil: IR ($CDCl_3$) 2970, 1450 (m), 1375 (s), 1300 (w), 1240 (m), 1215 (m), 1050 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4–5.2 (m, 2 H), 4.69 (s, 2 H), 4.60 (AB, J = 11 Hz, 2 H), 4.17 (m, 2 H), 3.93 (m, 2 H), 3.8–3.6 (m, 3 H), 3.6–3.45 (m, 2 H), 3.38 (s, 3 H), 2.3–1.2 (m, 12 H), 2.15 (s, 3 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.12 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_{23}H_{42}O_6S$: C, 61.85; H 9.48; M_r, 446.2702. Found: C, 62.27; H 9.41; M_r, 446.2703.

1(*R*),2(*S*),4(*S*),1′(*S*),6′(*S*)-1-(1,2-Dihydroxyethyl)-2-(6-[(methylthio)methoxy]-(*E*)-1-heptenyl)-4-[(methoxyethoxy)methoxy]cyclopentane, 24. Aqueous hydrochloric acid (1 N, 5 mL) was added to 284 mg (0.636 mmol) of acetonide **5** in 5 mL of THF. The solution was stirred at room temperature for 2.25 h followed by portionwise addition of 1 g of potassium carbonate. The aqueous layer was saturated with sodium chloride and was extracted with 4 × 10 mL of ether. The combined organic solution was dried ($MgSO_4$) and concentrated to give 250 mg of a clear oil. Flash chromatography on 150 g of silica gel deactivated with 17 g of water (97:3 $CHCl_3$/MeOH) gave 39 mg of what is assumed to be the 1(*S*),2(*R*),4(*R*),1′(*S*),6′(*S*) diastereomer (15%), 17 mg of a mixture of this diastereomer and its isomer (7%), and 164 mg of titled diol (64%): $[\alpha]^{23}_D$ +15.9° (*c* 7.6, ether); IR (CCl_4) 3700–3200 (s), 2965 (s), 1550 (w), 1460 (m), 1440 (m), 1378 (m), 1300 (m), 1200 (m), 1100 (s), 1050 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42 (dt, J = 16, 7 Hz, 1 H), 5.28 (dd, J = 16, 8 Hz, 1 H), 4.70 (s, 2 H), 4.61 (AB, J = 11 Hz, 2 H), 4.17 (m, 1 H); 3.8–3.4 (m, 8 H), 3.38 (s, 3 H), 2.3–1.2 (m, 14 H), 2.14 (s, 3 H), 1.13 (d, J = 16 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 133.6, 129.9, 93.8, 77.0, 72.1, 72.0, 71.5, 66.5, 66.0, 58.7, 15.7, 43.4, 40.1, 35.7, 33.0, 32.2, 25.2, 19.2, 13.8. Anal. Calcd for $C_{20}H_{38}O_6S$: 406.2390. Found: 406.2390.

1′(*R*),2′(*S*),4′(*S*),2(*S*),6′(*S*)-2-Hydroxy-1-[1-(2-(6-[(methylthio)-methoxy]-(*E*)-1-heptenyl)-4-[(methoxyethoxy)methoxy]cyclopentyl)-ethyl]-*p*-toluene Sulfonate. Toluenesulfonyl chloride (89 mg, 0.47 mmol) was added to 128 mg (0.29 mmol) of the diol **24** in 2 mL of dry pyridine at 0 °C. The solution was allowed to warm slowly to room temperature as the cooling bath melted and warmed. After 10 h at room temperature, the solution was stored at −25 °C for 11 h. Ether (20 mL) and water (5 mL) were added. The ether layer was washed with 5 mL of brine, dried ($MgSO_4$), and concentrated to a yellow oil which partially solidified. This mixture was triturated with ether, and the supernatant ether solution was filtered through silica gel. The filtrate was concentrated to 157 mg (89%) of an oil: $[\alpha]^{23}_D$ +16° (*c* 1.2, $CHCl_3$); IR (CCl_4) 3610 (w), 2970 (s), 1600 (w), 1460 (m), 1375 (s), 1185 (s), 1050 (s); ^1H NMR ($CDCl_3$) δ 5.38 (dt, J = 16, 7 Hz, 1 H), 5.21 (dd, J = 16, 8 Hz, 1 H), 4.66 (s, 2 H), 4.61 (AB, J = 11 Hz, 2 H), 4.20–4.05 (7m, 1 H), 4.00 (t, J = 7 Hz, 1 H), 3.90–3.57 (m, 5 H), 3.50 (m, 2 H), 3.36 (s, 3 H), 2.44 (s, 3 H), 2.35–1.2 (m, 17 H); 2.13 (s, 3 H), 1.12 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.4, 132.9, 132.3, 130.5, 129.4, 127.5, 93.8, 76.6, 73.6, 72.1, 71.8, 71.5, 68.8, 66.6, 58.8, 45.3, 43.3, 40.0, 35.8, 32.2, 25.1, 21.5, 19.3, 13.8. Anal. Calcd for $C_{27}H_{44}O_8S_2$: C, 57.83; H, 7.91. Found: C, 57.74; H, 7.79.

1(*R*),2(*S*),4(*S*),1′(*S*),6′(*S*)-(+)-4-[(Methoxyethoxy)methoxy]-2-(6-[(methylthio)methoxy]-1(*E*)-heptenyl)-1-(oxacyclopropyl)cyclopentane, 4. Sodium methoxide (0.6 mmol) in 1.2 mL of methanol was added to 229 mg (0.401 mmol) of the above tosylate in 40 mL of ether at 0 °C. A gelatinous precipitate formed. After stirring 15 min, 5 mL of water was added and the mixture was stirred vigorously until two clear layers formed. The ether layer was washed with 5 mL of brine, dried ($MgSO_4$), and concentrated to 157 mg of a clear liquid. Flash chromatography (1:1 hexane/ethyl acetate) gave 147 mg (93% yield) of a clear liquid: $[\alpha]^{22}_D$ +25.7° (*c* 2.0, THF); IR ($CDCl_3$) 2920 (s), 1600 (w), 1450 (m), 1375 (m), 1300 (m), 1260 (m), 1050 (s) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 132.8, 130.4, 94.0, 76.8, 72.3, 72.1, 71.7, 66.7, 59.0, 53.6, 46.2, 45.5, 45.0, 40.4, 36.1, 34.7, 32.5, 25.4, 19.4; ^1H NMR ($CDCl_3$) δ 5.44 (dt, J = 16, 7 Hz, 1 H), 5.31 (dd, J = 11, 8 Hz, 1 H), 4.69 (s, 2 H), 4.60 (AB, J = 11 Hz, 2 H), 4.18 (m, 1 H), 3.73 (m, 1 H), 3.66 (m, 2 H), 3.53 (m, 2 H), 3.38 (s, 3 H), 2.83 (m, 1 H), 2.71 (t, J = 5 Hz, 1 H), 2.48 (dd, J = 5, 3 Hz, 1 H), 2.25 (m, 2 H), 2.14 (s, 3 H), 2.00 (q, J = 7 Hz, 2 H), 1.79 (m, 2 H), 1.62 (m, 1 H), 1.45 (m, 5 H), 1.1 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_{20}H_{36}O_5S$: C, 61.82; H, 9.34. Found: C, 61.72; H, 9.20.

4(*S*),2(*R*,*S*),1′(*R*),2′(*S*),4′(*S*),6′(*S*)-Methyl 4-(4-[(Methoxyethoxy)methoxy]-2-(6-[(methylthio)methyl]-(*E*)-hept-1-en-1-yl)cyclopent-1-yl)-2-(phenylthio)-4-(tetrahydropyranyloxy)butanoate, 3a. (Phenylthio)acetic acid, *freshly crystallized from pentane* and dried in vacuo over phosphorus pentoxide for 20 h (220 mg, 1.31 mmol) in 3 mL of THF, was added dropwise to a solution of 2.43 mmol of lithium diisopropylamide in 3 mL of THF at 0 °C under nitrogen. The solution was stirred at 0 °C for 0.5 h, producing a milky suspension. This suspension (4 mL, 0.58 mmol of dianion) was added to 76 mg (0.20 mmol) of epoxide **4** in 0.20 mL of THF at 0 °C. The mixture was allowed to warm to room temperature and was stirred under nitrogen for 18 h. Ether (70 mL) and 1 N aqueous sulfuric acid (5 mL) were added. The aqueous layer was extracted with 2 × 5 mL of ether and the combined ether solution was treated with ethereal diazomethane, dropwise, until the yellow color persisted. The solution was dried ($MgSO_4$), concentrated, and dissolved in 1.25 mL of dry methylene chloride. Dihydropyran (230 mg, 2.7 mmol) and PPTS (50 mg, 0.20 mmol) were added, and the solution was stirred under nitrogen for 0.5 h. Ether (25 mL) was added, the solution was washed with 5 mL of aqueous sodium bicarbonate, dried ($MgSO_4$), concentrated, and flash-chromatographed (2.5:1 hexane/EtOAc) to give 104 mg (81% yield) of **3a** as a pale-yellow oil: IR ($CDCl_3$) 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.43 (m, 2 H), 7.26 (m, 3 H), 5.3 (m, 2 H), 4.68 (s, 2 H), 4.60 (ABq, J = 12.5 Hz, 2 H), 4.13 (m, 1 H), 3.64 (s), 3.63 (s) [total 3 H], 3.9–3.4 (m, 7 H), 3.38 (s, 3 H), 2.14 (s, 3 H), 2.1–1.1 (m, 23 H), 1.10 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_{34}H_{54}O_8S_2$: C, 62.35; H, 8.31. Found: C, 62.71; H, 7.92.

4(*S*),1′(*R*),2′(*S*),4′(*S*),6′(*S*)-Methyl 4-(4-[(methoxyethoxy)methoxy]-2-(6-hydroxy-(*E*)-hept-1-en-1-yl)cyclopent-1-yl)-2-(phenylsulfinyl)-4-(tetrahydropyranyloxy)butanoate. NCS (51 mg, 0.38 mmol) and silver nitrate (64 mg, 0.38 mmol) in 0.20 mL of 4:1 v/v acetonitrile–water were added to 62 mg (0.095 mmol) of disulfide **3a** and 57 mg (0.57 mmol) of calcium carbonate in 0.10 mL of the same solvent using 0.10 mL of additional solvent to aid transfer. After 1.5 h at room temperature, 0.2 mL of aqueous saturated sodium sulfite followed by 0.2 mL of brine was added. The solution was filtered, and the solids were washed thoroughly with 3 mL of the above solvent. Ether (20 mL) was added to the filtrate and then washed with 2 × 2 mL of saturated aqueous sodium carbonate, dried ($MgSO_4$), and concentrated to give 57 mg of a yellow oil. Flash chromatography (1:1 ethyl acetate/ether) gave 40 mg (69% yield) of a clear oil: IR ($CDCl_3$) 3610 (w), 3600–3300 (br), 2940 (s), 1730 (s), 1040 (s) cm^{-1}; partial ^1H NMR (200 MHz, $CDCl_3$) δ 7.64–7.48 (m, 5 H), 5.28 (m, 2 H), 4.76 (m), 4.09 (m), 3.34 (s, 3 H), 1.11 (m, 3 H). Anal. Calcd for $C_{32}H_{50}O_9S$: C, 62.92; H, 8.25. Found: C, 62.66; H, 8.08.

4(*S*),1′(*R*),2′(*S*),4′(*S*),6′(*S*)-Methyl 4-(4-[(Methoxyethoxy)methoxy]-2-(6-hydroxy-(*E*)-hept-1-en-1-yl)cyclopent-1-yl)-4-(tetrahydropyranyloxy)-(*E*)-but-2-enoate, 2a. The above sulfoxide (39 mg, 0.064 mmol) in 4 mL of dry toluene containing 1 mL of BSA was heated slowly from room temperature to 95 °C over 1 h under nitrogen. After 3 h at 95 °C, the solution was allowed to cool and was concentrated. Flash chromatography of the residue (3:1 hexanes/EtOAc) gave 27 mg (76%) of the silyl ether of **2a** and further elution with EtOAc gave 5 mg (16%) of **2a**: partial ^1H NMR (200 MHz, $CDCl_3$) δ 6.98 (dd, J = 16, 6 Hz) 6.80 (dd, J = 16, 7 Hz) [total 1 H], 6.05 (d, J = 16 Hz), 5.93 (d, J = 16 Hz) [total 1 H], 5.35 (m, 2 H), 4.71 (br s, 2 H), 4.18 (m, 2 H), 3.73 (br s, 3 H), 3.39 (s, 3 H), 1.13 (d, J = 7 Hz, 3 H), 0.12 (s, 9 H). Anhydrous potassium carbonate (35 mg, 0.25 mmol) was added to 20 mg (0.036 mmol) of the TMS ether in 0.50 mL of dry methanol. After 0.5 h at room temperature, 10 mL of ether was added. The solution was washed with 3 mL of water and 2 × 5 mL of brine, dried ($MgSO_4$), and concentrated to give 17 mg (quantitative yield) of **2a** or an overall 92% yield from the sulfoxide: $[\alpha]^{24}_D$ +4.90 (*c* 0.245, $CHCl_3$); IR ($CDCl_3$) 3610 (w), 2940 (s), 1715 (s), 1655 (m); ^1H NMR (200 MHz, $CDCl_3$) 6.93 (dd, J = 16, 6 Hz), 6.78 (dd, J = 16, 7 Hz) [total 1 H], 6.02 (dd, J = 16, 1 Hz), 5.90 (d, J = 16 Hz) [total 1 H], 5.32 (m, 2 H), 4.68 (s, 2 H), 4.80–4.45 (7, 1 H), 4.30–4.03 (m, 2 H), 3.71 (s, 3 H), 3.72–3.58 (m, 4 H), 3.58–3.40 (m, 3H), 3.35 (s, 3 H), 2.3–1.2 (m, 19 H), 1.15 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_{26}H_{44}O_8$: C, 64.44; H, 9.25. Found: C, 64.26; H, 9.08.

4(*R*),1′(*R*),2′(*S*),6′(*S*)-Methyl 4-Acetoxy-4-(4-[(methoxyethoxy)-methoxy]-2-(6-[(methylthio)methoxy]-1(*E*)-heptenyl)cyclopentyl)-2-(phenylthio)butanoate, 3b: *n*-Butyllithium (2.43 mmol) in hexane was added to diisopropylamine (250 mg, 2.50 mmol) in dry THF (3 mL) under N_2 at 0 °C. (Phenylthio)acetic acid (220 mg, 1.31 mmol) in 3 mL of THF was added dropwise to 2.43 mol of LDA in 3 mL of THF at 0 °C under nitrogen. A 3.2-mL aliquot (approximately 0.42 mmol of dianion) of the resulting milky suspension was added to 78 mg (0.20 mmol) of the epoxide **4** in 0.2 mL of THF at 0 °C under nitrogen. The mixture was allowed to warm and stirred 20 h at room temperature. The resulting solution was poured into 30 mL of ether, and 10 mL of 1 N aqueous sulfuric acid was added. The aqueous layer was extracted with 5 mL of ether, and the combined ether solution was treated with excess diazomethane, dried ($MgSO_4$, foaming) and concentrated. Pyridine (2 mL), 40 mg of DMAP, and 0.4 mL of acetic anhydride (0.4 mL) were added to the residue dissolved in 4 mL of methylene chloride at 0 °C. After stirring 3 h, the solution was poured into 25 mL of ether, washed with 10 mL of saturated aqueous sodium bicarbonate, 3 × 10 mL of 10% aqueous sodium bisulfate, dried ($MgSO_4$), and concentrated. Flash chromatography (3:2 hexane/ethyl acetate) gave 105 mg (85% yield) of

3b: IR 1740 (s), 1585 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.31 (m, 3 H), 5.31 (m, 2.5 H), 4.99 (m, 0.5 H), 4.79 (s, 2 H), 4.72 (AB, J = 12 Hz), 4.11 (m, 1 H), 3.8-3.5 (m), 3.68 (s), 3.64 (s) [9 H, overall], 3.39 (s, 3 H), 2.15 (s, 3 H), 2.05 (s), 1.98 (s), [3 H, overall], 2.2-1.2 (m, 14 H), 1.13 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{31}H_{48}O_8S_2$: 612.2791. Found: 612.2791.

4(*R*),1′(*R*),2′(*S*),4′(*S*),6′(*S*)-Methyl 4-Acetoxy-4-(2-(6-hydroxy-1-(*E*)-heptenyl)-4-[(methoxyethoxy)methoxy]cyclopentyl)-2-(phenylsulfinyl)butanoate. NCS (93 mg, 0.70 mmol) and $AgNO_3$ (119 mg, 0.70 mmol) in 0.5 mL of 5:1 v/v acetonitrile-water was added to 106 mg (0.173 mmol) of **3b** in 0.25 mL of 5:1 v/v acetonitrile-water using an additional 0.25 mL of solvent to aid transfer. The mixture (immediate silver chloride precipitate on mixing) was stirred at room temperature for 1.3 h. Saturated aqueous solutions of sodium sulfite, sodium carbonate, and sodium chloride (0.2 mL each) were added successively. The mixture was stirred vigorously with 3 × 10 mL of 1:1 hexane/methylene chloride with decantation of the organic layer each time. The organic layer was then dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 ethyl acetate/hexane) gave 121 mg of an oil, obviously contaminated by succinimide. The mixture was dissolved in 25 mL of 1:1 hexane/methylene chloride, washed with 2 × 5 mL of water, dried (Na_2SO_4), and concentrated to give 74 mg (75%) of a clear oil: IR (neat) 3700-3200 (m), 2930 (s), 1740 (s), 1450 (m), 1375 (m), 1245 (s), 1050 (s) cm^{-1}; partial ^1H NMR ($CDCl_3$) δ 7.5 (m, 5 H), 5.46-5.02 (m, 2.4 H), 4.93 (m, 0.6 H), 4.68 (s, 2 H), 4.09 (m, 1 H), 3.84-3.42 (m), 3.56 (s), 3.47 (s) [9 H, overall], 3.38 (s, 3 H), 1.97 (s), 1.80 (s), 1.16 (d), 1.15 (d). Anal. Calcd for $C_{29}H_{44}O_9S$: C, 61.24; H, 7.80. Found: C, 61.34; H, 7.88.

4(*R*),1′(*R*),2′(*S*),4′(*S*),6′(*S*)-Methyl 4-Acetoxy-4-(2-(6-hydroxy-1-(*E*)-heptenyl)-4-[(methoxyethoxy)methoxy]cyclopentenyl)-2-(*E*)-butenoate, 2c, and 7-MEM-secobrefeldinoic Acid, 2d. The above sulfoxide (65 mg, 0.11 mmol) and 3.25 mL of BSA were heated in 13.5 mL of dry toluene at 80 °C for 4.5 h. The solution was evaporated to a yellow solid which was dissolved in 3 mL of methanol. Silica gel was added and the mixture stirred for 1 h. Flash chromatography (3:2 ethyl acetate/hexane) gave 37 mg (73% yield) of **2c** and 9 mg of its silyl ether. The latter was dissolved in 1 mL of ether and stirred with 1 mL of 1 N aqueous sulfuric acid for 0.5 h. The ether layer was dried ($MgSO_4$) and concentrated. Preparative layer chromatography gave an additional 4 mg (total yield 81%) of **2c**: $[\alpha]^{22}_D$ -6.44°; IR (neat) 3600-3200 (m), 2920 (s), 1740 (s), 1725 (s), 1710 (m); ^1H NMR ($CDCl_3$) (partial) δ 6.83 (dd, J = 15, 6 Hz, 1 H), 5.87 (d, J = 15 Hz, 1 H), 5.5-5.1 (m, 3 H), 4.68 (s, 2 H), 4.15 (m, 1 H), 3.73 (s), 3.87-3.47 (m), [overall, 9 H], 3.39 (s, 3 H), 2.10 (s, 3 h), 1.09 (d, J = 7 Hz, 3 H). Anal. Calcd for $C_{23}H_{38}O_8$: C, 62.42; H, 8.66. Found: C, 61.91; H, 8.55. The diester **2c** (5.60 mg, 0.0013 mmol) was dissolved in 0.15 N LiOH in 0.30 mL (0.045 mmol) of a 3:1 methanol/water solution of 0.15 N lithium hydroxide at room temperature. After stirring 16 h, 30 mg (0.2 mmol) of sodium bisulfate in 0.5 mL of water was added. The solution was extracted with 4 × 2 mL of ethyl acetate and the combined extract was washed with 3 mL of brine, dried ($MgSO_4$), and concentrated to 4.84 mg (99% yield) of **2d** as a clear oil: partial ^1H NMR ($CDCl_3$) 7.05 (dd, J = 16, 5 Hz, 1 H), 6.04 (d, J = 16 Hz, 1 H), 5.2-5.5 (m, 3 H), 4.80 (s, 3.4 H), 3.40 (s, 6 Hz), 1.2 (d, J = 7 Hz).

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Communications to the Editor

Microheterogeneous Photooxidation

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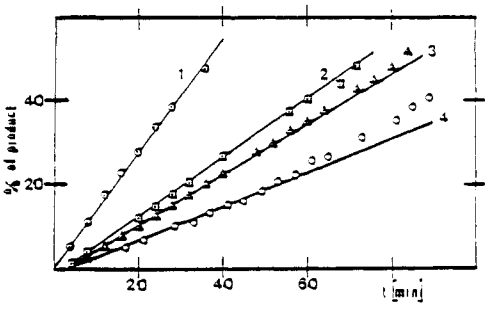
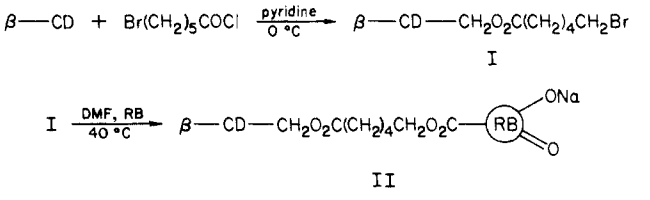
Singlet oxygen lifetimes vary from 1 μs in water to several hundred microseconds in halocarbon solvents. This work demonstrates that one can enhance the reactivity of an acceptor or quencher of singlet oxygen by covalently bonding a sensitizer to a ligand which complexes the acceptor.† We call this effect a microheterogeneous photochemical effect, for the reagents are prevented from being freely dispersed in fluid solution by the ligand and the covalent bonding of the ligand to the sensitizer, respectively.[6] Microheterogeneous effects in photosensitized processes enhance the observed reactivity of an excited state with an acceptor by increasing the effective local concentration of the acceptor.



1. RB (2.9×10^{-4} m)
2. RB (2.9×10^{-4} m) + β-cyclodextrin (2.9×10^{-4} m) + β-carotene (9.0×10^{-6} m)
3. II (RB = 2.9×10^{-4} m) + β-carotene
4. II (RB = 2.9×10^{-4} m) + β-carotene (9.0×10^{-6} m) - 1,2-diphenyl-p-dioxene added directly before photooxidation

Figure 1. Photooxidation of 1,2-diphenyl-*p*-dioxene (4.0×10^{-3} M) in EtOH.

Scheme I



To illustrate the principle, we modified rose bengal[7] through its tethering to β-cyclodextrin. This has been made possible by the work of Lamberts and Neckers,[8-10] who showed that the C-2′

† The key role of distance in electron transfer has been studied between porphyrins and quinones as photosynthetic models. See ref 2-5 and citations therein.

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