(31), 211 (100), 107 (9), 106 (7), 105 (11), 91 (6), 90 (7), 83 (12), 77 (6); HREIMS, calcd for $C_{28}H_{24}O_4$ m/e 424.1674, found m/e 424.1700.

Riccardin A Diacetate (2). Riccardin A (1, 40 mg) was dissolved in 3 mL of pyridine and 3 mL of acetic anhydride. The mixture was allowed to stand overnight. The reaction mixture was treated in usual manner to give riccardin A diacetate (2): 45 mg; mp 209–210 °C (from petroleum ether); UV λ_{max} 218 nm (log ϵ, 4.62), 250 (4.38); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.96 (s, 6 H), 2.29 (s, 3 H), 2.70, 2.79, 2.93 (m, 8 H), 3.83 (s, 3 H), 5.42 (d, J = 2 Hz, 1 H), 6.43–7.02 (m, 12 H); IR (CCl_4) 1770, 1610, 1505, 1425, 1370, 1270, 1200, 1115; EIMS, m/e (relative intensity) 522 (M^+, 28), 480 (67), 438 (100), 226 (22), 225 (66), 213 (14), 211 (32), 43 (38).

Riccardin A Trimethyl Ether (3). To riccardin A (1, 60 mg) in 5 mL of dry acetone was added 3 mL of MeI and 2 g of dry K_2CO_3. The mixture was kept at reflux for 10 h, and then the reaction mixture was filtered. The solvents were evaporated in vacuo, and the residue was purified by silica gel PLC to afford riccardin A trimethyl ether (3, 40 mg) as viscous liquid: UV λ_{max} 210 nm (log ϵ, 4.77), 280 (3.96); ^{13}C NMR ($CDCl_3$) δ 35.7, 37.2, 38.1, 38.3, 55.2*, 56.2, 111.4, 111.6, 112.2*, 115.5, 116.9, 121.5, 121.8, 122.4, 127.8, 122.4, 127.8, 129.5*, 131.1, 132.5*, 134.0, 139.8, 141.3, 143.4, 147.2, 148.9, 153.0, 156.2, 159.3; IR (CCl_4) 1610, 1580, 1510, 1490, 1455, 1440, 1420, 1265, 1235, 1165, 1130, 1040, 1020, 905, 870, 855 cm^{-1}; EIMS, m/e (relative intensity) 466 (M^+, 90), 240 (20), 239 (100), 233 (14), 227 (12), 225 (15), 211 (16), 105 (11), 90 (18).

Riccardin B Diacetate (5). Riccardin B (4a, 38 mg) was treated in the same manner as described above to yield riccardin B diacetate (5): 40 mg; UV λ_{max} 215 nm (log ϵ, 4.31), 273 (3.50); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.13 (s, 3 H), 2.16 (s, 3 H), 2.80 (s, 8 H), 6.23–7.20 (complex m, 14 H); IR (CCl_4) 1770, 1590, 1505, 1485, 1445, 1425, 1370, 1265, 1240, 1220, 1190, 1170, 1150, 1110, 1010, 900; EIMS, m/e (relative intensity) 508 (M^+, 11), 466 (31), 424 (100), 213 (13), 212 (20), 211 (92), 105 (15), 43 (27).

Riccardin B Dimethyl Ether (6). Riccardin B (4a, 60 mg) was methylated in the same manner as described above to give riccardin B dimethyl ether (6): 58 mg; mp 151–152 °C (petroleum ether); UV λ_{max} 217 nm (log ϵ, 4.41), 277 (3.79); IR (CCl_4) 1607, 1585, 1505, 1470, 1440, 1415, 1265, 1215, 1155, 1125, 1035, 690, 670; EIMS, m/e (relative intensity) 452 (M^+, 100), 239 (11), 226 (19), 213 (11), 211 (25), 105 (11), 90 (24), 85 (17), 83 (28).

Acknowledgment. We thank Dr. S. Hattori of The Hattori Botanical Laboratory, Nichinan, Japan, for his identification of the liverwort and I. Miura for his measurement of 400-MHz NMR spectra. The present work was supported in part by a Grant-in-Aid for Scientific Research (No. 56771051, 1981) from the Ministry of Education and Takeda Science Foundation.

Registry No. 1, 85318-25-8; 2, 85318-26-9; 3, 84575-09-7; 4a, 85318-27-0; 5, 85318-28-1; 6, 85318-29-2.

Supplementary Material Available: Tables II–V containing final atomic and anisotropic thermal parameters for nonhydrogen atoms, bond lengths, and bond angles for compound 2 (5 pages). Ordering information is given on any current masthead page.

A Triply Convergent Total Synthesis of L-(-)-Prostaglandin E_2[1]

R. E. Donaldson,[†,‡] J. C. Saddler,[†,‡] S. Byrn,[§] A. T. McKenzie,[§] and P. L. Fuchs*[†]

Department of Chemistry and Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, Indiana 47907

Received August 18, 1982

This paper details a versatile and efficient total synthesis of *l*-(-)-PGE_2 (3). The key step is a triply convergent conjugate-addition/alkylation reaction involving the 1,4-addition of chiral vinyllithium reagent **7b** to chiral vinyl sulfone D-**47** to afford sulfone-stabilized anion [**57**], which is subsequently alkylated to produce the basic prostaglandin E_2 skeleton **70**. The synthesis of chiral vinyl sulfone D-**47** involves a five-step sequence with an enantioconvergent resolution process as one step and produces vinyl sulfone D-**47** from readily available sulfide alcohol DL-**11** in an overall yield of 36%. The preparation of D-**47** features two steps that utilize stereospecific S_N2' reactions. The synthesis of *l*-(-)-PGE_2 (3) involves a seven-step sequence from vinyl sulfone D-**47** using mild conditions with an overall yield of 40% and features an efficient peracetic acid oxidation of secondary amino acid **120** to oximino acid **121**, which is, in turn, desulfonylated by 1,4-elimination of phenylsulfinic acid to generate a vinyl nitroso species that undergoes stereospecific 1,4-reduction by sodium borohydride to yield oxime **131**. The hydrolysis of oxime **131** to *l*-(-)-PGE_2 (3) using boron trifluoride and paraformaldehyde is the first reported high-yield method (84%). This gives an overall yield for the synthesis of *l*-(-)-PGE_2 (3) from racemic sulfide alcohol DL-**11** of 14.5%, including the resolution process.

The wide range of biological activity exhibited by the prostaglandin family combined with the lack of good natural source has elicited an immense effort dedicated to the total synthesis of these important materials. Particularly important in recent years is prostacyclin (PGI_2, 1)[2] and its analogues[3] because of their ability to inhibit blood platelet aggregation. The efficient conversion of PGE_2 **3** to prostacyclin **1** (through $PGF_{2\alpha}$ **2**) interconnects all three of these important prostaglandin cogeners.

The synthetic activity in the prostaglandin area covers a vast number of papers and has been extensively reviewed.[5] The only previous synthetic efforts that have direct relevance to this paper deal with a strategy involving

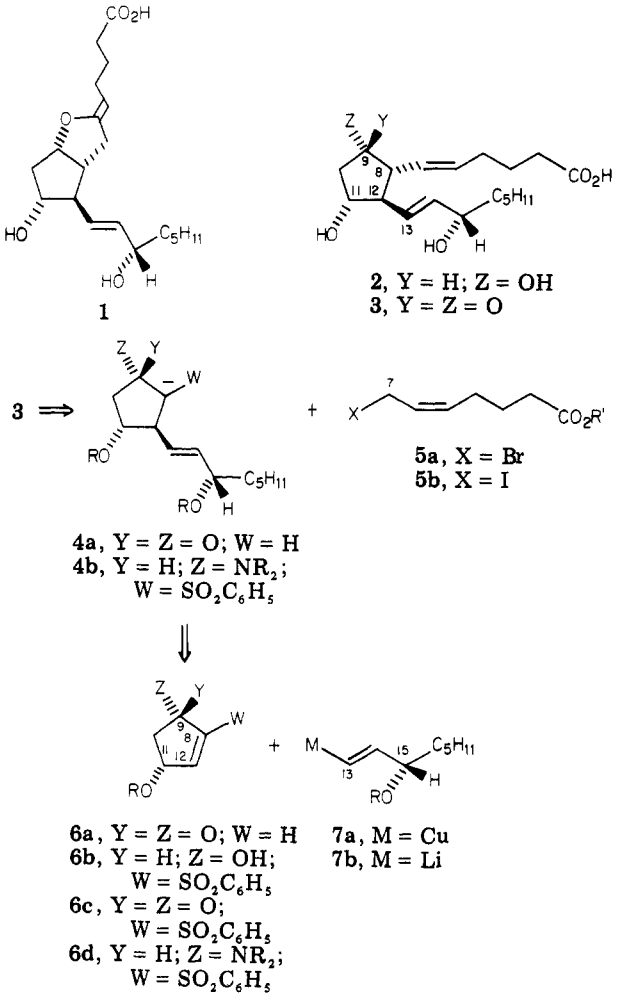
[†] Department of Chemistry.
[‡] Graduate Research Associate.
[§] Department of Medicinal Chemistry.

(1) Syntheses via Vinyl Sulfones. 11. For paper 10, see P. Hamann and P. L. Fuchs, *J. Org. Chem.*, **48**, 914 (1983). Synthetic Utilization of the Imine Moiety. 9. For papers 8, 7, and 6 in this series, see S. G. Pyne; et al., *ibid.*, **104**, 5728 (1982); ref 1a; D. A. Clark, C. A. Bunnell, and P. L. Fuchs, *J. Am. Chem. Soc.*, **100**, 7777 (1978). This work has been published in part: (a) R. E. Donaldson and P. L. Fuchs, *ibid.*, **103**, 2108 (1981); (b) J. C. Saddler, R. E. Donaldson, and P. L. Fuchs, *ibid.*, **103**, 2110 (1981); (c) R. E. Donaldson, Ph.D. Thesis, Purdue University (1981).

(2) (a) R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Son, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, **12**, 915 (1976); (b) E. J. Corey, G. E. Keck, and I. Szekely, *J. Am. Chem. Soc.*, **99**, 2006 (1977); (c) K. C. Nicolaou, *J. Chem. Soc., Chem.* 630 (1977); (d) J. G. Kelton; et al., *Can. Med. Assoc. J.* **122**, 175 (1980).

0022-3263/83/1948-2167$01.50/0

Scheme I

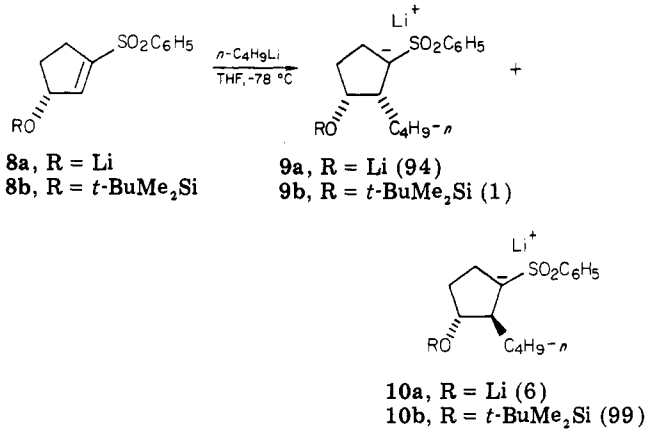


a "triply convergent" approach (Scheme I). Namely, it is highly desirable to effect formation of the C-12–C-13 bond and the C-7–C-8 bond by the sequential addition of the easily available reagents **7**[6] and **5**[7] to a suitably activated, optically active cyclopentene nucleus (**6**). A substantial effort has been investigated in using 4-alkoxycyclopent-2-enone **6a** as the acceptor for such a conjugate-addition/alkylation sequence.[8] Although the conjugate-addition reaction (**6a** + **7**) works well, subsequent enolate alkylation (**4a** + **5**) is totally unsatisfactory.[8] At present, only indirect procedures are available for further elaboration of enolate **4a** to prostaglandin E_2.[4,8]

Our own interest in the triply convergent scenerio was fostered by the possibility of using a vinyl sulfone moiety as the activator for the cyclopentene nucleus (**6b–d**) in the conjugate-addition/alkylation sequence.[1]

Earlier observations from our laboratory regarding conjugate-addition reactions with γ-oxido vinyl sulfones (Scheme II) had demonstrated a useful directing effect manifested by the γ-oxido moiety.[9] Namely, when the γ substituent was present as an alkoxide (**8a**), the incoming anionic nucleophile was strongly directed (presumably via an alkoxide–alkyllithium complex) to occur cis to the alkoxide group (**9a**/**10a** = 94:6), whereas when the oxygen substituent was protected as a *tert*-butyldimethylsilyl group (**8b**), addition occurred on the opposite face of the molecule (**9b**/**10b** = 1:99). We initially therefore elected to examine conjugate additions to vinyl sulfone **6b**, a more highly oxygenated version of **8b**.

Scheme II



Results and Discussion

Synthesis of the Optically Active Cyclopentane Nucleus. The synthesis of **6b** was readily accomplished in the following manner: Epoxidation of cyclopentadiene at 15 °C with 40% peracetic acid[10] (1-mol scale) followed by the addition of triethylamine and thiophenol (1 equiv) produces sulfide alcohol DL-**11** in 67% yield[11] (reactions of up to 5 mol lead to lower yields probably due to the longer times required for addition of the peracetic acid). Phenyl disulfide is also produced as a byproduct in this reaction and may be removed from the crude product by dropwise addition of excess hydrogen peroxide to a stirred

(3) (a) P. A. Aristoff and A. W. Harrison, *Tetrahedron Lett.*, **23**, 2067 (1982); (b) K. C. Nicolaou, W. E. Barnette, and R. L. Magolda, *J. Am. Chem. Soc.*, **103**, 3472 (1981); (c) *ibid.*, 3480 (1981); (d) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **45**, 3802 (1980); (e) M. Shibasaki, J. I. Veda, and S. Ikegam, *Tetrahedron Lett.*, 433 (1979); (f) J. Fried and J. Barton, *Proc. Natl. Acad. Sci. U.S.A.*, *74*, 2199 (1977).

(4) (a) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 4745 (1975); (b) *ibid.*, **97**, 6260 (1975).

(5) (a) J. C. Colbert, "Prostaglandins: Isolation and Synthesis"; Noyes Data Corporation, New Jersey, 1973. (b) U. Axen, J. E. Pike, and W. P. Schneider in "The Total Synthesis of Natural Products", Vol. 1, J. Ap Simon, Ed., Wiley-Interscience, New York, 1973, pp 81–142. (c) G. Pattenden, "Aliphatic Chem", Vol. 2, 1974, pp 258–308. (d) P. H. Bentley, *Chem. Soc. Rev.*, **2**, 29 (1973). (e) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Eds., "Natural Products Chemistry", Vol. 2, Academic Press, New York, 1973, pp 33–48. (f) G. L. Bundy, *Annu. Rep. Med. Chem.*, **7**, 157 (1972). (g) W. P. Schneider, "Prostaglandins: Prog. Res.", S. M. M. Karim, Ed., Wiley-Interscience, New York, 1972, pp 293–319. (h) J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press, New York, 1977. (i) R. Clarkson, *Prog. Org. Chem.*, **8**, 1 (1973). (j) N. M. Weinshenker and N. H. Anderson in "The Prostaglandins", Vol. 1, P. W. Ramwell, Ed., Plenum Press, New York, 1973, pp 5–82. (k) A. Mitra, "The Synthesis of Prostaglandins", Wiley-Interscience, New York, 1977.

(6) The chiral 15-(*S*)-*trans*-vinyl iodide precursor (prostaglandin numbering) to organolithium reagent **7b** is available either by classical resolution of the *trans*-halovinyl alcohol [A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972)] or, more recently, by enantioselective reduction of the trans iodo vinyl ketone with a chiral hydride reducing reagent [R. Noyori, I. Tomino, and M. Nishizawa, *ibid.*, **101**, 5843 (1979)].

(7) (a) J. W. Patterson, Jr., and J. H. Fried, *J. Org. Chem.* **39**, 2506 (1974); (b) J. Martel and E. Toromanoff (Roussel-UCLAF), German Patent 2121 361, 1970. (c) We thank Dr. Patterson for providing us the details of the experimental preparation for this material.

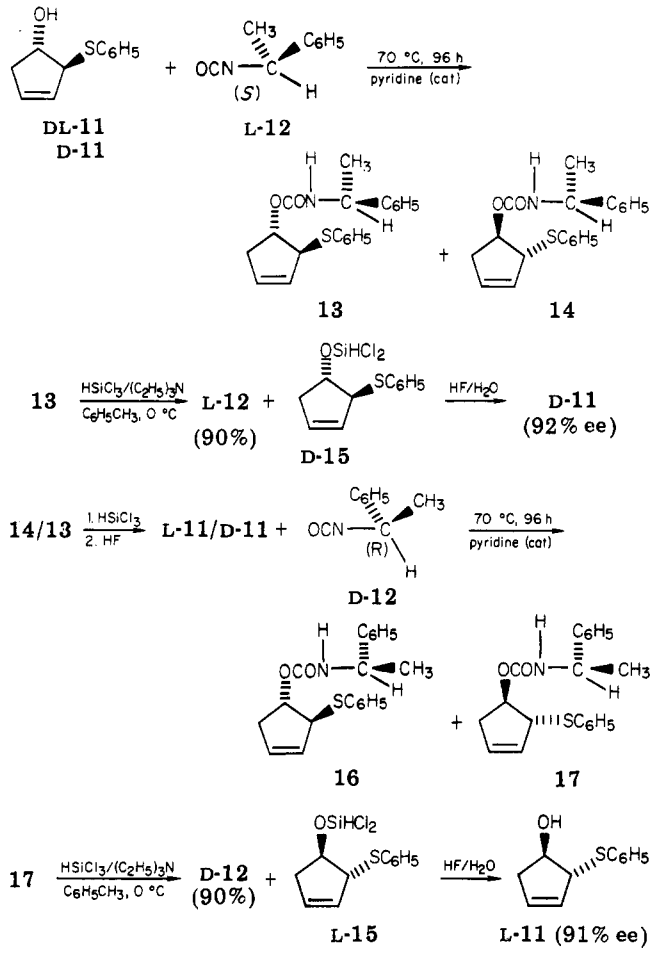
(8) For an indepth discussion of the problem, see (a) R. Davis and K. G. Untch, *J. Org. Chem.*, **44**, 3755 (1979); (b) J. Schwartz, M. J. Loots, and H. Kosugi, *J. Am. Chem. Soc.*, **102**, 1333 (1980).

(9) J. C. Saddler, P. C. Conrad, and P. L. Fuchs, *Tetrahedron Lett.*, 5079 (1978).

(10) J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, **33**, 423 (1968).

(11) D. A. Evans, T. C. Crawford, T. T. Fujimoto, and R. C. Thomas, *J. Org. Chem.*, **39**, 3176 (1974).

Scheme III



solution in basic ethanol (NaOH) at 25 °C followed by sodium bisulfite and neutralization with dry ice.

Racemic sulfide alcohol DL-11 is resolved on the mole scale by a modification of the method of Evans and Thomas.[11,12] Treatment of DL-11 with 1 equiv of *S*-(−)-(α-methylbenzyl)isocyanate (L-12)[13,14] gives a mixture of diastereomeric urethanes **13** and **14** (Scheme III). Crystallization of this mixture from methanol gives pure **13** (mp 115–116 °C, methanol; $[\alpha]^{25}_D$ +142° (*c* 0.447, $CHCl_3$), 40%). Cleavage of urethane **13** is accomplished via the method of Pirkle and Hauske[15] by treatment with trichlorosilane, which allows for greater than 90% recovery of chiral L-12 for recycle purposes. The resulting silyl ether D-15 is then hydrolyzed (without isolation) with dilute aqueous hydrofluoric acid to give optically active sulfide alcohol D-11 (96% from **13**, $[\alpha]^{25}_D$ +116° (*c* 0.308, $CHCl_3$), 92% ee).[12]

Trichlorosilane cleavage of the **14**/**13** crystallization residues returns isocyanate L-12 as well as a sulfide alcohol mixture now enriched in L-11. Treatment of this mixture with the enantiomeric isocyanate D-12 gives urethane diastereomers **16** and **17** from which **17** (mp 115–116 °C (methanol), $[\alpha]^{25}_D$ −133° (*c* 0.314, $CHCl_3$) can be crystallized in an apparent 80% yield and then cleaved with trichlorosilane to give silyl ether L-15 (and recovered D-12).

Three repetitions of the above cycle gives an overall yield of approximately 70% for urethane **13** and approximately 65% for urethane **17**. This corresponds to a 67% yield of sulfide alcohol D-11 and a 62% yield of sulfide alcohol L-11 from racemic DL-11.

Reaction of D-11 with 2 equiv of peracetic acid gives sulfone **18**, which is generally not purified, but directly treated with 1.1 equiv of *m*-chloroperoxybenzoic acid (MCPBA) to produce highly crystalline epoxysulfone D-19 (mp 103–104 °C, hexane; 88% from D-11; $[\alpha^{25}]_D$ +64° (*c* 0.429, $CHCl_3$). On small scale it is more convenient to simply use 3 equiv of MCPBA to obtain D-19 directly. Purification of the mother liquors (plug on silica gel) affords the relatively unstable epoxy sulfone D-20 (mp 101–103 °C (hexane), 3% from D-11; $[\alpha]^{25}_D$ +137° (c 0.439, $CHCl_3$) (Scheme IV).

Treatment of D-19 with catalytic DBU (to produce the dihydroxy vinyl sulfone **21**) followed by in situ silylation of less hindered alcohol moiety (*t*-$BuMe_2SiCl$, imidazole, THF;[16] use of less bulky chlorosilanes, e.g., *i*-$PrMe_2SiCl$, gives no selectivity between C-9 and C-11) gives crystalline monosilyl ether D-**6b** (mp 72–73 °C (hexane), 79% from D-19; $[\alpha]^{25}_D$ +58° (*c* 0.456, $CHCl_3$)). Purification of the mother liquors gives disilyl ether D-22 (9% from D-19; $[\alpha]^{25}_D$ +113° (*c* 0.378, $CHCl_3$)), which can be hydrolyzed back to **21** (CF_3CO_2H, THF, H_2O) in near quantitative yield and recycled in the silylation step.

The structure of D-**6b** was confirmed by proton NMR coupling constants (Table I). The fact that protons on a five-membered ring α to a substituent (such as OH) are more shielded when they are cis to this substituent than when they are trans allows for assignments of H_c and H_d.[17] Studies of the effect of $Eu(fod)_3$ on the chemical shifts of H_b–H_e also allows for their assignments (assuming chelation at the hydroxyl moiety). H_c has a larger relative shift than H_d, and H_e has a larger relative shift than H_b.

The "incorrect" enantiomer L-11 could also be successfully converted to a material (**29**) bearing appropriate C-11 chirality for prostaglandin synthesis[1b] (Scheme V). Oxidation of sulfide alcohol L-11 with *m*-chloroperoxybenzoic acid affords sulfoxide **23** (91%), which has been shown by Evans to be in equilibrium with sulfenate ester **24**.[11] Treatment of sulfoxide **23** with freshly prepared pyridine hydrobromide and pyridine in THF at reflux for 18 h affords a mixture of bromo diol **27** as well as unreacted diol **25** as assayed by thin-layer chromatography. Addition of sodium hydroxide to this reaction mixture affords epoxy alcohol **28** in 39% yield. Alternatively, if after the pyridine hydrobromide step the reaction mixture is cooled to 0 °C and solid phenyl disulfide and bromine are introduced the conversion of diol **25** to bromo diol **28** is complete. Apparently the pyridine hydrobromide serves to effect elec-

Table I. ^{1}H NMR Coupling Data for D-6b

proton	δ from Me_4Si	coupling pattern	*J*, Hz
H_a	6.75	d	2
H_b	4.70	ddd	2, 6, 7
H_c	1.77	ddd	6, 7, 14
H_d	2.80	ddd	6, 7, 14
H_e	4.78	dd	6, 7

(12) Sulfide alcohol 11 has been resolved previously on a smaller scale in a similar manner; see R. C. Thomas, Ph.D. Thesis, University of California, Los Angeles (1976). We thank Professor Evans for helpful discussions.

(13) α-Methylbenzylamine is easily resolved with *d*-(+)-tartaric acid on a 10-mol scale, "Organic Syntheses", Collect. Vol. V, Wiley, New York, 1973, p 932.

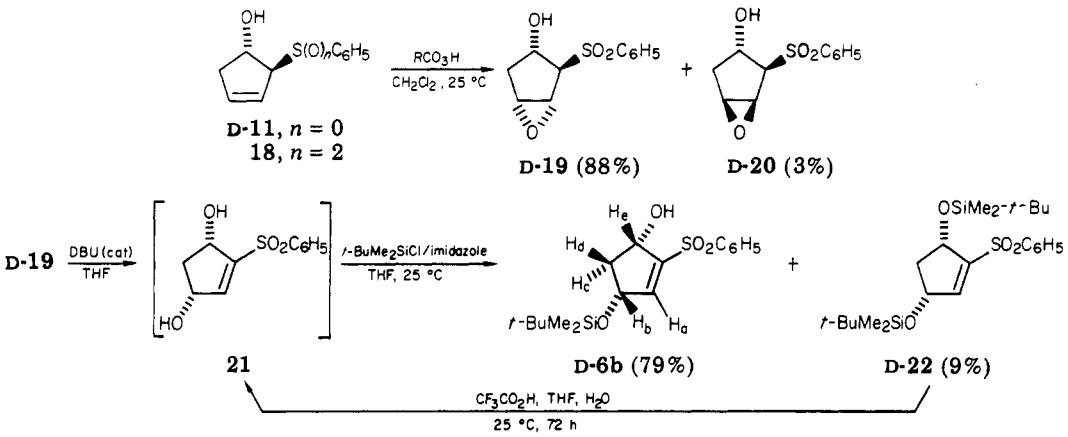
(14) R. A. Gracheva, A. P. Terent'ev, and V. T. Bezruchko, *Zh. Org. Khim.* **5**, 1044 (1969).

(15) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 2781 (1977).

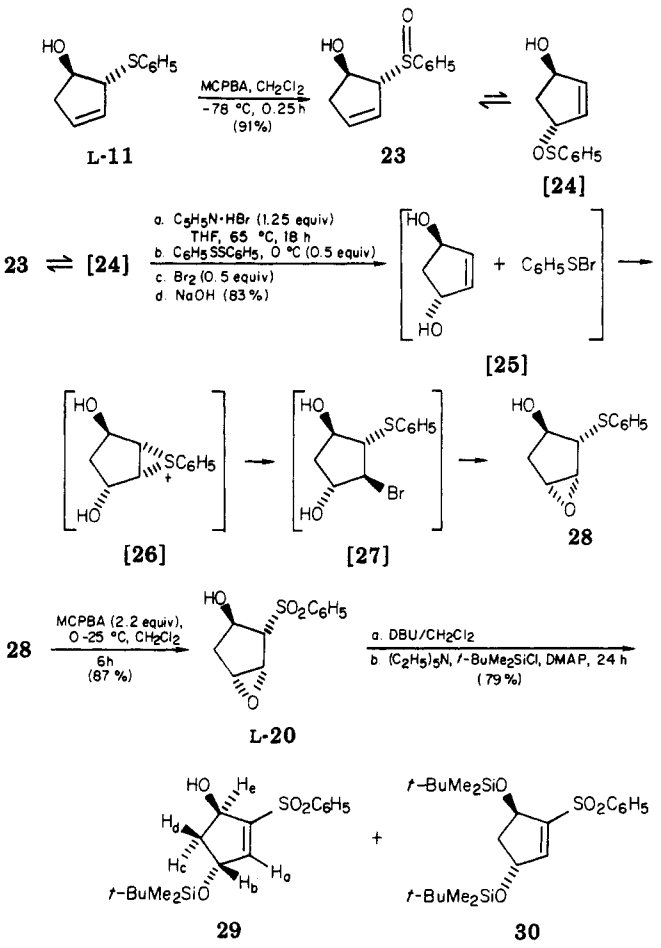
(16) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

(17) H. B. Kagan, Ed., "Stereochemistry: Fundamentals and Methods", Vol. 1, A. Gaudemer, "Spectrometric Methods", Georg Thieme Publishers, Stuttgart, 1977, pp 89–93.

Scheme IV



Scheme V



trophilic cleavage of sulfenate ester **24** to afford diol **25** and benzenesulfenyl bromide. The need for introduction of excess sulfenyl bromide is probably related to a competitive sulfenylation of pyridine. Use of more hindered pyridine hydrohalides such as that derived from 2,4,6-trimethylpyridine resulted in uselessly long reaction times.

It should be noted that sulfenylation of diol **25** from either the α or β face yields a single episulfonium ion [**26**] due to the presence of a C_2 symmetry element in **25**. Bromo diol [**27**] is quite sensitive and is simply cyclized to the epoxide **28** by treatment with aqueous sodium hydroxide solution in the workup in the sulfenylation sequence. Purification of the crude epoxide was effected by plus filtration through silica gel (to remove excess phenyl disulfide) to afford the oily epoxide **28** (83%).

Table II. ^{1}H NMR Coupling Data for 29

proton	δ from Me_4Si	coupling pattern	J, Hz
H_a	6.69	br s	
H_b	5.17	dd	6, 6
H_c	1.97	ddd	6, 7, 15
H_d	2.35	ddd	2, 6, 15
H_e	4.94	dd	2, 7

Oxidation of sulfide alcohol **28** with MCPBA in methylene chloride produces epoxy sulfone L-**20**, which is identical in all respects except sign of rotation with the minor epoxide (D-**20**) prepared by oxidation of the "natural" sulfide alcohol D-**11**.

Conversion of L-**20** to the C-9 *trans*-hydroxy γ-silyloxy vinyl sulfone **29** was accomplished similarly to cis isomer D-**6b**. Namely, treatment of a methylene chloride solution of L-**20** with a catalytic amount of DBU to generate the *trans*-1,4 enediol intermediate followed by (dimethylamino pyridine catalyzed[18] silylation with *tert*-butyldimethylchlorosilane produces monosilyl ether **29** (79%) along with disilyl ether **30** (10%), which can be hydrolized and recycled (Table II).

Attempts to directly employ hydroxy vinyl sulfone D-**6b**, either as its monolithio alkoxide or further protected as the bis(silyl) ether, as a substrate for the conjugate-addition of organolithium reagent **7b** were completely unrewarding. A detailed discussion of this chemistry along with an improved preparation of chiral organolithium reagent **7b** *on the molar scale*, can be found in the supplementary material.

Enantioconvergent Syntheses of C-9 Amino Vinyl Sulfones. On the basis of unsuccessful experiments in the C-9 oxygen series (see supplementary material), it became apparent that the C-9 oxygen moiety of **6** must be replaced by a nonanionic substituent that would not serve as an anion-stabilizing group or be capable of serving as a leaving group β to a sulfonyl anion. One such compound that would fulfill these criteria would be amino vinyl sulfone **6d** (pK_a (α sulfone) = 25, pK_a (dialkylamide) = 35).

(18) S. K. Chandhary and O. Hernandez, *Tetrahedron Lett.*, 99 (1979).
(19) (a) "Organic Syntheses", Collect. Vol. IV, Wiley, New York, (b) Y. K. Yurév and G. B. Elyakov, *Zh. Obshch. Khim.*, **27**, 176 (1957).
(20) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972).
(21) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
(22) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Am. Chem. Soc.*, **92**, 2586 (1970).
(23) P. L. Fuchs, unpublished results.

Scheme VI

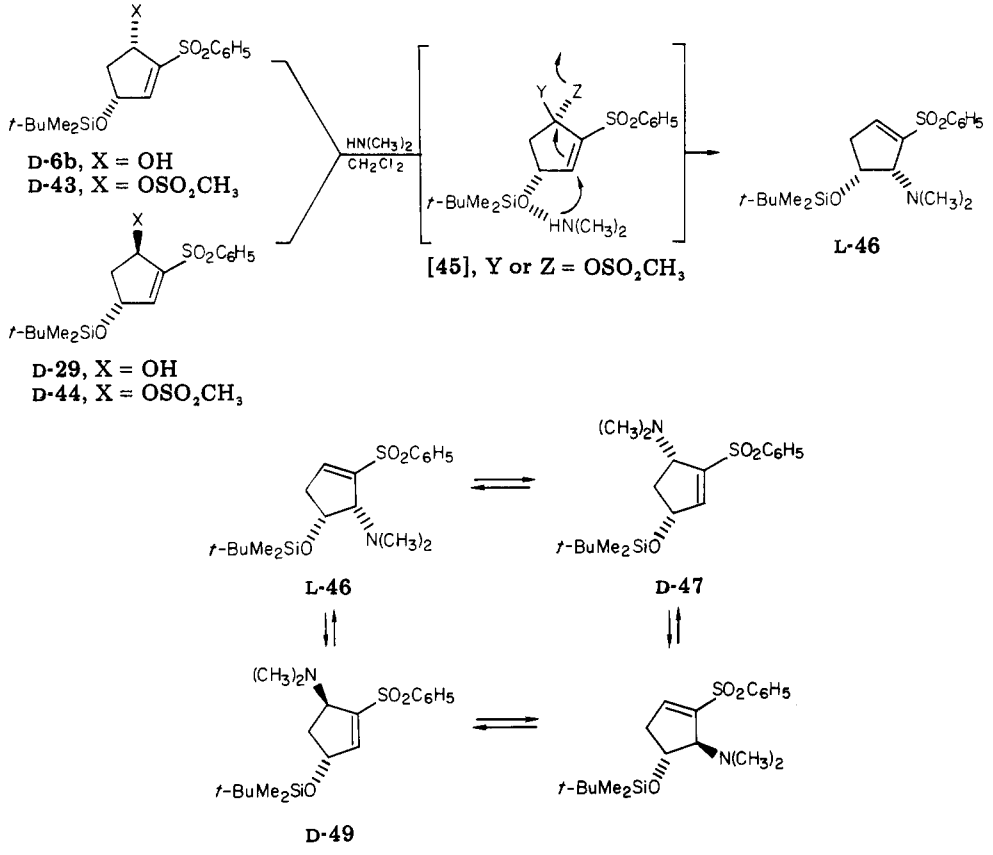


Table III. ^{13}C and ^{1}H NMR Chemical Shift Data for Aminovinyl Sulfones 46-49

compound	$CHNR_2$ (C/H)	CH_2 (C/H)	CHOR (C/H)	vinyl CH (C/H)
D-47 (1,4-*cis*)	67.73/3.93	31.40/1.69, 2.11	73.05/4.71	144.63/6.61
L-46 (1,2-*cis*)	67.98/3.88	41.27/2.31, 2.73	74.75/4.51	141.99/6.68
L-48 (1,2-*trans*)	70.09/3.86	42.38/2.36, 2.80	78.85/4.47	143.75/6.90
D-49 (1,4-*trans*)	68.91/4.23	32.72/1.63, 2.33	76.08/4.93	146.65/6.80

Synthesis of the requisite C-9 amino vinyl sulfone **6d** was accomplished via a pair of polarized-olefin, S_N2' Lawton[24] reactions. Treatment of D-**6b** under the conditions of Crossland and Servis[25] results in the formation of the sensitive mesylate D-**43** (mp 96–97 °C, $[\alpha]^{25}_D$ +109° (*c* 0.442, $CHCl_3$), 94%), which is not routinely isolated but rather treated directly with dimethylamine at −20 °C (<5 min) to give amino vinyl sulfone L-**46** (mp 96–98 °C, $[\alpha]^{25}_D$ −18° (*c* 0.434, $CHCl_3$), 95% from D-**43**) (Scheme VI).

Of equal importance was the observation that the "unnatural" trans alcohol D-**29** could also similarly be converted to the corresponding mesylate D-**44**, which undergoes the Lawton-type reaction with dimethylamine to produce the same vinyl sulfone (L-**46**) as is generated from D-**43**. Apparently in methylene chloride as solvent the silyloxy moiety is instrumental in directing the S_N2' reaction. Mechanistic considerations[24,26] notwithstanding, from a practical point of view, what this reaction sequence accomplishes is the chemical reunification of the two enantiomers that were resolved from racemic sulfide alcohol D-**11**, thus "enantioconvergently"[27] providing chiral vinyl sulfone L-**46**.

When the reaction mixture containing L-**46** is allowed to warm to 25 °C for 12 h, amino vinyl sulfone D-**47** is generated as the major product of a preequilibrium mixture of L-**46** (6%), D-**47** (one member of the **6d** family) (90%) (mp 67–68 °C, pentane; $[\alpha]^{25}_D$ +153° (*c* 0.385, $CHCl_3$)), *trans*-aminovinyl sulfone L-**48** (2%) (mp 74–75 °C, pentane; $[\alpha]^{25}_D$ 25–38 °C (*c* 0.384, $CHCl_3$)), and Δ *trans*-aminovinyl sulfone D-**49** (2%) (mp 68–69 °C, pentane; $[\alpha]_D$ +36° (*c* 0.349, $CHCl_3$)). Apparently the dimethylammonium mesylate produced in the D-**43** to L-**46** reaction serves as acid catalyst for the further interconversion of these four isomers. Use of more polar solvents or vastly extended times establishes an apparent equilibrium mixture of L-**46** (2%), D-**47** (38%), L-**48** (40%), and D-**49** (20%). Compounds D-**47**, L-**46**, and L-**48** of the equilibrium mixture can be isolated by fractional crystallization from pentane.

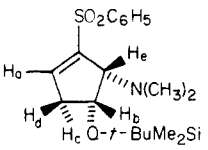
(24) For S_N2' reactions of polarized olefins, see (a) S. Mitra and R. G. Lawton, *J. Am. Chem. Soc.*, **101**, 3097 (1979); (b) D. J. Dunham and R. G. Lawton, *ibid.*, **93**, 2074 (1971); (c) N. H. Cromwell, D. S. Soriano, and E. Doomes, *J. Org. Chem.*, **45**, 4983 (1980); (e) T. Takahashi, K. Hori, and J. Tsuji, *Tetrahedron Lett.*, 119 (1981).

(25) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

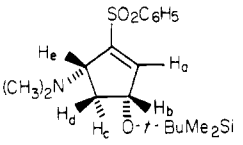
(26) For a discussion of the effects of leaving-group stereochemistry in the normal S_N2' reaction, see R. M. Magid and O. S. Fruchey, *J. Am. Chem. Soc.*, **99**, 8368 (1977), and references contained therein.

(27) In its broadest definitional sense, the term "enantioconvergent" refers to a process in which both enantiomers of a racemic substrate are ultimately converted into a single enantiomeric series. The efficiency of such a process will be inversely related to the number of steps between enantiomer separation and enantioconversion. This term was first applied by Trost to an example involving fractional crystallization of a single diastereomeric allylic urethane followed by "enantioconversion" of the crystallization residues by [3.3] sigmatropic rearrangement: B. M. Trost, J. M. Timko, and J. L. Stanton, *J. Chem. Soc., Chem. Commun*, 436 (1978).

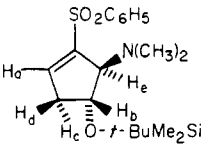
Table IV. ^{1}H NMR Coupling Constants (in Hz) for 46-49



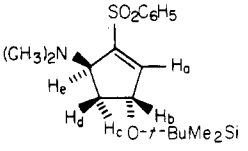
L-46



D-47



L-48



D-49

compound	J_{ab}	J_{ac}	J_{ad}	J_{ae}	J_{bc}	J_{bd}	J_{be}	J_{cd}	J_{ce}	J_{de}
D-47	2.0	<1	<1	1.2	3.9	7.9	<1	14.0	4.3	8.0
L-46	<1	2.3	3.3	<1	7.5	7.8	7.5	18.0	2.3	<1
L-48	<1	2.1	2.1	<1	2.1	6.3	2.0	18.8	<1	2.1
D-49	1	<1	<1	<1	5.6	7.5	1	14.1	2.4	1.5

NMR data for isomers **46–49** are compared in Table III and IV. The structures of isomers **46–49** were confirmed by proton NMR coupling constants (Table IV). In all cases H_c was further upfield than H_d probably due to shielding from the silyloxy moiety.[17] Studies on the effect of Eu(fod)$_3$ on the chemical shifts of H_c and H_d of D-47, L-46, and D-49 confirms the assignments shown in Table IV (assuming chelation at the amino moiety). H_c in D-47 and L-46, and H_d in D-49 all show larger relative shifts than H_d in D-47 and L-46 and H_c in D-49. The coupling constants for L-46 (J_{bd}, J_{bc}, and J_{be}) are all nearly equal (ca. 8 Hz), leading to an apparent quartet for the H_b signal. Also noteworthy is the fact that J_{bc} in L-48 and J_{de} in D-49 are small (2 Hz), indicating a trans relationship for these protons.[17]

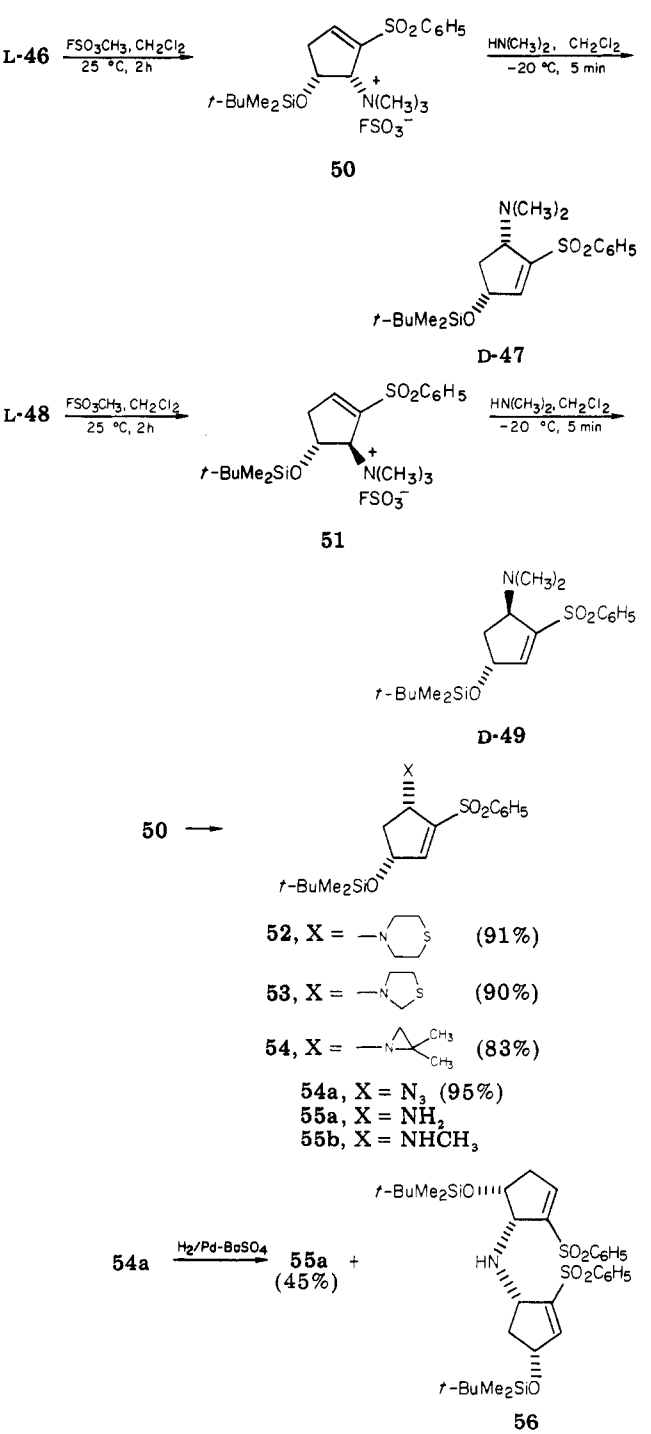
A more expedient preparation of D-47 from L-46 (or D-49 from L-48) involves quaternization of the amine moiety with methyl fluorosulfonate (1.1 equiv, CH_2Cl_2, 25 °C, 2 h) to give the crystalline ammonium salt **50** (or **51**), which is not normally isolated but rather directly treated with dimethylamine at −20 °C (5 min). Use of dimethyl sulfate (4 days, CH_2Cl_2, 25 °C) in place of methyl fluorosulfonate gives slightly lower yields (ca. 90%).

Ammonium salt **50** is also a useful intermediate for preparation of other members of the **6d** amino vinyl sulfone family (Scheme VII). For example, treatment of **50** with thiomorpholine, thiazolidine, dimethylaziridine,[28] or trimethylammonium azide[29] affords vinyl sulfones **52–54**, respectively.

Attempts at direct generation of the primary amine **55a** or the secondary amine **55b** by reaction of **50** with ammonia or methylamine were unsuccessful. In these instances an inseparable mixture of all four cis/trans 1,2/1,4 isomers (plus unidentified dimers) was rapidly formed. A sample of primary amine **55a** could be prepared in 45% yield along with 2:1 adduct **56** (which apparently results from the S_N2' reaction of **55a** with **54a**). Amine **55a** showed a strong tendency to equilibrate to the cis/trans 1,2/1,4 isomers in solution without added catalyst.

The Triply Convergent Conjugate-Addition/Alkylation Sequence. Treatment of amino vinyl sulfone D-47 with optically active vinyllithium reagent **7b** (THF, hexane, −60 °C; the reaction is slow below −70 °C) followed by quenching with water provides a separable 92:5 mixture of 1:1 adducts **59** and **60** (Scheme VIII). The use of large ratios of hexane to THF as solvent lead to lower yields. Conversely, a large ratio of hexane to THF is desirable for the high-yield preparation of the vinyllithium reagent **7b**. Reaction conditions were developed that accommodated both of these requirements (see Experimental Section).

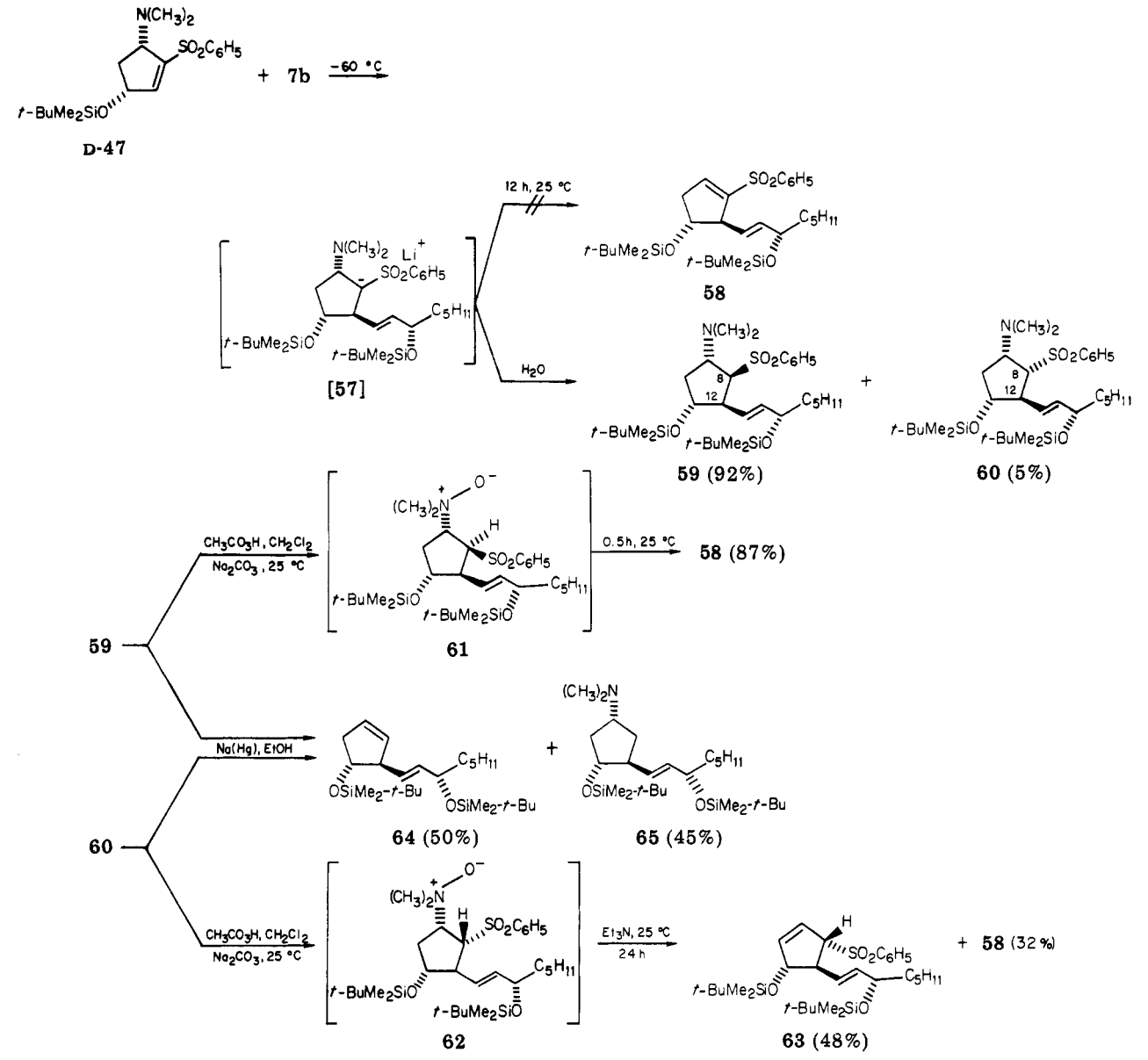
Scheme VII



The preference for protonation from the α face of [**57**] to yield **59** (cf. alkylation reactions that exhibit a strong

(28) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).
(29) For the preparation of triethylammonium azide, see A. Fliri and K. Hohenlohe-Oehringen, *Chem. Ber.*, **113**, 607 (1980).

Scheme VIII



preference for β-face attack) may emanate from both the hydrophilic nature of the α face and the small size of the electrophile, water.

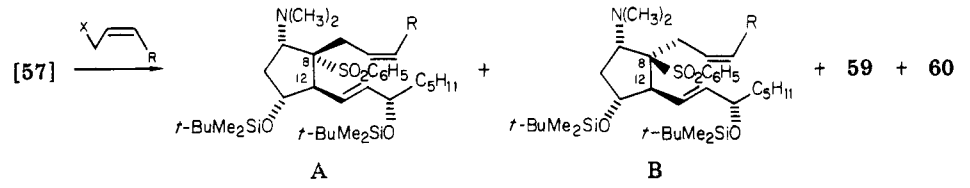
Two additional points about this reaction are worthy of mention: (1) warming a solution of [57] to room temperature for 12 h does not afford *any* detectable amount of vinyl sulfone **58**, thus verifying the expected stability of the β-amino sulfonyl anion [57]; and (2) the stereocontrol at C-12 is at least 97% (the isolated yield of **59** + **60**).

Determination of the C-8–C-12 stereochemistry of **59** and **60** was accomplished by spectroscopy in conjunction with the following pair of experiments. Separate treatment of **59** and **60** with 1 equiv of peracetic acid produces amine oxides **61** and **62**, respectively. Amine oxide **61** rapidly (ca. 30 min) undergoes Cope elimination at 25 °C under the reaction conditions to give vinyl sulfone **58** (87% yield, greater than 95% pure), whereas elimination of **62** requires added base (triethylamine, 1.0 equiv), a longer reaction time for completion (24 h), and gives a 3:2 mixture of allyl sulfone **63** and vinyl sulfone **58** (formation of **58** presumably is a base-assisted β-elimination reaction). Treatment of sulfones **59** or **60** with sodium amalgam (6%)[30] in ethanol leads to identical reaction mixtures of olefin **64** (50%, $[\alpha]^{25}_D$ −125° (*c* 0.40, $CHCl_3$)) and amine **65** (45%, $[\alpha]^{25}_D$ −40° (*c* 0.52, $CHCl_3$)), confirming that **59** and **60** are epimeric only at the C-8 sulfone-bearing carbon.

Attention was next turned to the in situ alkylation of α-sulfonyl anion [57]. After conjugate addition of **7b** to D-**47**, the resulting anion [57] was treated with a series of allyl halides (**66**, **5a**, **5b**, **67**[7]) to afford in all instances the β-face alkylated isomers (**68**, **70**, **72**) as the major products along with minor amounts of α-face alkylated isomers (**69**, **71**, **73**) as well as some nonalkylated material (**59**, **60**). Inspection of Table V reveals that relative to the alkylation reaction with allyl bromide (**66**) itself, there is apparently some protonation of α-sulfonyl anion [57] competitive with the desired reaction with the substituted *Z*-allyl halides **5a**, **5b**, and **67**. The exact nature of the proton source in these reactions was not investigated, but inasmuch as the nitrile reagent **67** appeared to provide enhanced yields (relative to esters **5a** and **5b**), it was assumed to have arisen from the methylene group α to the ester moiety.

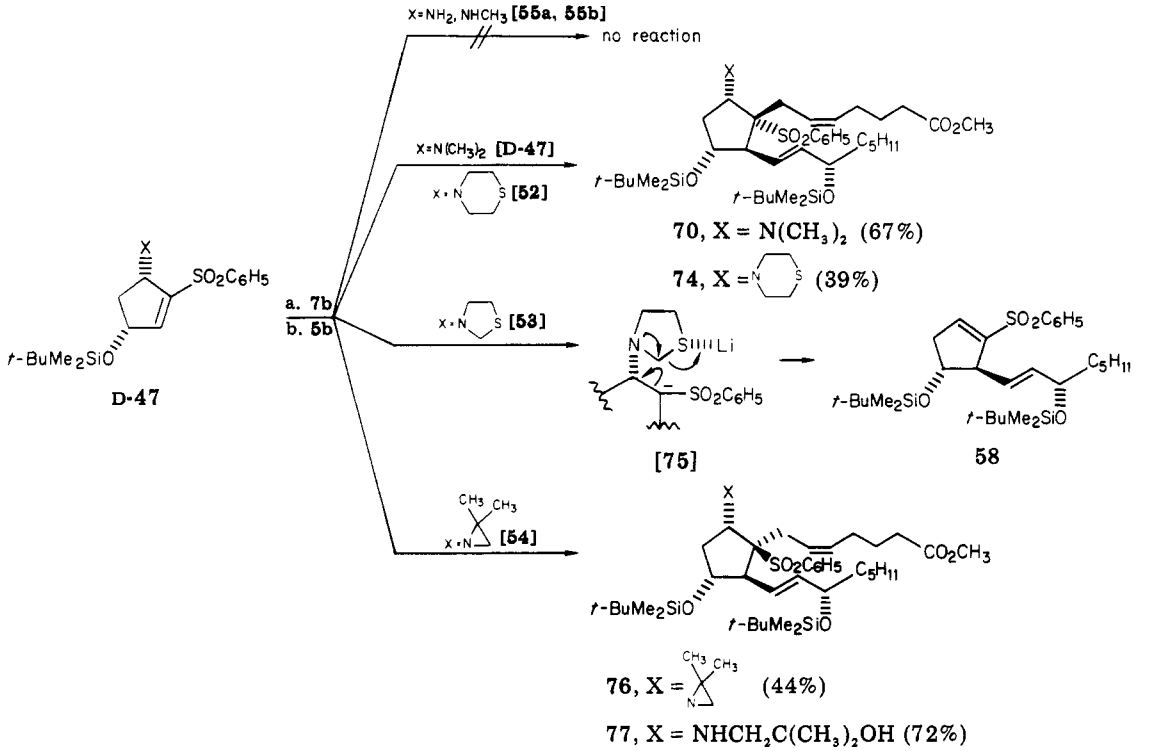
(30) B. M. Trost, H. C. Arndt, P. F. Strege, and T. R. Verhoeven, *Tetrahedron Lett.*, 3477 (1976).

Table V. Alkylation of α-Sulfonyl Anion [57]



allyl halide			allylation product yield, %		quenching product yield, %	
no.	X	R	A	B	59	60
66	Br	H	68, 87	69, <1	10	trace
5a	Br[7]	$(CH_2)_3CO_2CH_3$	70, 54	71, 3	15	4
5b	I	$(CH_2)_3CO_2CH_3$	70, 67	71, 2	8	5
67[1c,7]	Br	$(CH_2)_3CN$	72, 82	73, 7	9	trace

Scheme IX



Although it might appear that the higher yield with nitrile reagent **67** would be most advantageous, it was found later in the synthesis that the nitrile could not be satisfactorily hydrolyzed to the requisite carboxylic acid group. The preferred alkylation route was via allyl iodide **5c**, and the 67% yield reported represents a 75-mmol experiment.

Attention was next turned to exploring the effect of the C-9 amino moiety on the conjugate-addition/alkylation reaction. In this study all alkylations were conducted with the allyl iodide reagent **5b** (Scheme IX). It was found (not surprisingly) that the two proton-bearing amino substrates **55a** and **55b** were returned unchanged from the attepted conjugate-addition reaction with vinyllithium reagent **7b**, thus strongly suggesting that amine deprotonation occurs more rapidly than conjugate addition.

Two unanticipated results were uncovered during this study: (1) although the thiomorpholine-bearing vinyl sulfone **52** reacted analogously to the standard dimethylamino substrate (D-**47**) to afford the 1:1:1 adduct **74** (39%, not optimized), the corresponding thiazolidine analogue **53** rapidly produced vinyl sulfone **58** as the major reaction product (ca. 50%). In view of the successful reactions with D-**47** and **52**, it would seem that the α-amino sulfide moiety of presumed intermediate [**75**] is responsible for "triggering" this unusual fragmentation reaction; and (2) reaction of the dimethyl aziridine-bearing substrate **54** provides adduct **76** in 44% yield. The low yield in this instance is a reflection of the (desired) instability of **76** to acid-catalyzed ring opening (to **77**). Repetition of the conjugate-addition/alkylation reaction followed by acid treatment affords β-amino alcohol **77** in 72% yield. It should be noted that in the case of substrate **54**, the alkylation now occurs from the α face. Apparently the *gem*-dimethyl moiety of aziridine **54** is now discouraging β-face alkylation seen with D-**47** and **52**.

The assigned stereochemistry at the tetrasubstituted C-8 center for adducts **68–76** rests on a combination of X-ray crystallography and ^{13}C NMR analyses. A single-crystal X-ray of the isomer **70** reveals it to have the allyl moiety in the β configuration (see Figure 1 for a stereoview of **70**[31]).

(31) Tables of bond angles and bond distances for adduct **70** can be found in the supplementary material.

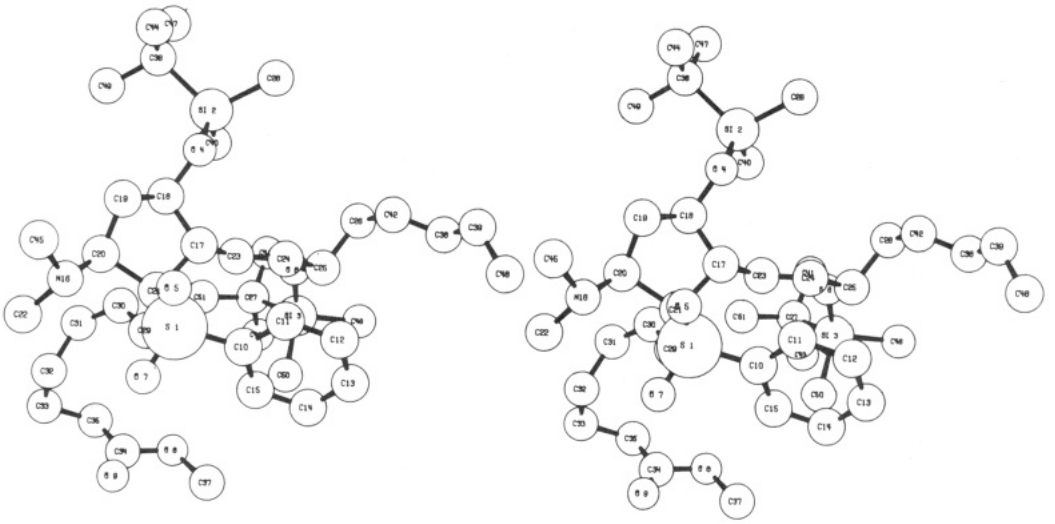
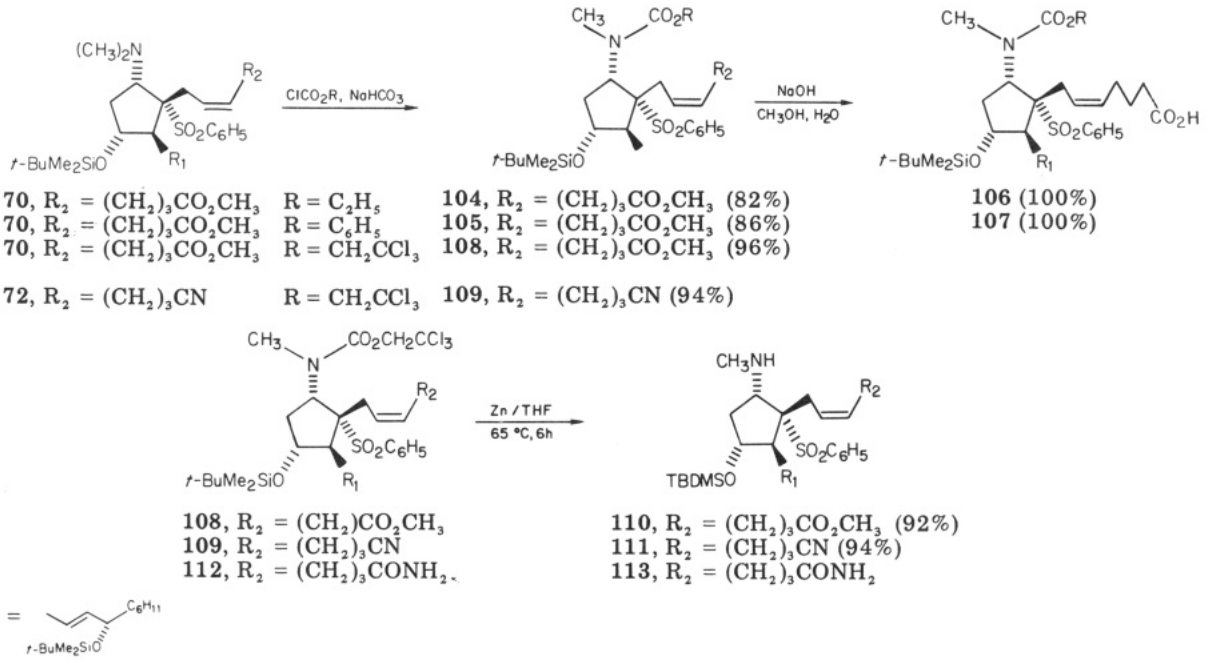


Figure 1. X-ray structure for **70**.

Scheme X[a]



The structure of **71** is secured by converting both it and **70** to a common desulfonylated intermediate (**131**) later in the synthetic sequence.

All other adducts are assigned by analogy based upon

(32) (a) S. S. Rawalay and H. Shechter, *J. Org. Chem.*, **32**, 3129 (1967); (b) E. F. Curragh, H. B. Henbest, and A. Thomas, *J. Chem. Soc.*, 3559 (1960); (c) F. E. Newmann and C. W. Gould, *Anal. Chem.*, **25**, 751 (1953); (d) S. Dunstan and H. B. Henbest, *J. Chem. Soc.*, 4905 (1957); (e) N. C. Deno and R. E. Fruit, Jr., *J. Am. Chem. Soc.*, **90**, 3502 (1968); (f) N. Y. Demŷanov and Z. I. Shuikina, *J. Gen. Chem. USSR.*, **6**, 350 (1936); (g) N. J. Leonard and D. F. Morrow, *J. Am. Chem. Soc.*, **80**, 371 (1958); (h) H. B. Henbest and P. Slade, *J. Chem. Soc.*, 1558 (1960); (i) R. G. R. Bacon and W. J. W. Hanna, *Proc. Chem. Soc., London*, 305 (1959); (j) W. Strecker and M. Baltes, *Ber.*, **54**, 2693 (1921); (k) L. A. Hull, G. T. Davis, D. H. Rosenblatt, H. K. R. Williams, and R. C. Weglein, *J. Am. Chem. Soc.*, **89**, 1163 (1967); (l) Z. I. Shuikina, *J. Gen. Chem. USSR*, **7**, 983 (1937); (m) D. Buckley, S. Dunstan, and H. B. Henbest, *J. Chem. Soc.*, 4901 (1957); (n) H. E. De La Mare, *J. Org. Chem.*, **25**, 2114 (1960); (o) R. J. Kennedy and A. M. Stock, *ibid.*, **25**, 1901 (1960); (p) Y. Ogata, K. Tomizawa, and T. Morikawa, *ibid.*, **44**, 352 (1979); (q) P. A. S. Smith and R. N. Loeppky, *J. Am. Chem. Soc.*, **89**, 1147 (1967); (r) F. E. Scully, Jr., and R. C. Davis, *J. Org. Chem.*, **43**, 1467 (1978); (s) H. E. Zimmerman, K. G. Hancock, and G. C. Licke, *J. Am. Chem. Soc.*, **90**, 4892 (1968); (t) R. V. Hoffman, *ibid.*, **98**, 6702 (1976); (u) G. A. Olah and J. Welch, *ibid.*, **100**, 5396 (1978).

(33) For recent reviews and papers on the Polonovski reaction and modification thereof, see (a) G. A. Russell and G. J. Mikol, *Mech. Mol. Migr.*, **1**, 157 (1968); (b) A. Cave, C. Kan-Fan, P. Potier, and J. LeMan, *Tetrahedron*, **23**, 4681 (1967); (c) P. Potier, *Rev. Latinoam. Quinn.*, **9**, 47 (1978); (d) A Ahond, A. Cave, C. Kan-Fan, H. P. Husson, J. de Rostolan, and P. Potier, *J. Am. Chem. Soc.*, **90**, 5622 (1968); (e) P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Org. Chem.*, **44**, 3765 (1979).

(34) R. A. Grimm and W. A. Bonner, *J. Org. Chem.*, **32**, 3470 (1967).

(35) V. Pascali and A. Urnni-Ronchi, *J. Chem. Soc., Chem. Commun.*, 351 (1973).

(36) P. A. Grieco and Y. Masaki, *J. Org. Chem.* **39**, 2135 (1974).

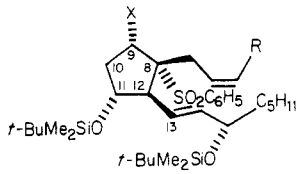
(37) This rapid quenching phenomenon between lithium and an alcohol under Birch-type conditions catalyzed by organosulfur compounds has been observed on other substrates in these laboratories; D. M. Hedstrand and P. L. Fuchs, unpublished results.

(38) E. J. Corey and H. E. Ensley, *J. Org. Chem.*, **38**, 3187 (1973).

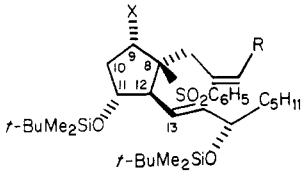
(39) We thank Dr. Gordon Bundy of the Upjohn Co. for generous comparison samples of PGE_2, 8-epi-PGE_2, and PGA_2.

(40) E. G. Daniels, W. C. Krueger, F. P. Kupiecki, J. E. Pike, and W. P. Schneider, *J. Am. Chem. Soc.*, **90**, 5894 (1968).

Table VI. ^{13}C NMR Spectral Data for Conjugate-Addition/Alkylation Products



68, X = $N(CH_3)_2$; R = H
70, X = $N(CH_3)_2$; R = $(CH_2)_3CO_2CH_3$
72, X = $N(CH_3)_2$; R = $(CH_2)_3CN$
74, X =  ; R = $(CH_2)_3CO_2CH_3$



71, X = $N(CH_3)_2$; R = $(CH_2)_3CO_2CH_3$
73, X = $N(CH_3)_2$; R = $(CH_2)_3CN$
76, X =  ; R = $(CH_2)_3CO_2CH_3$

compound	C-8	C-9	C-10	C-11	C-12	C-13
C-8 β-Allyl						
68	76.20	65.79	37.26	73.93	53.75	133.82
70	76.37	66.66	37.56	74.23	54.24	132.10
72	76.28	66.70	37.37	74.22	54.08	130.41
74	75.77	67.69	36.36	74.62	54.34	132.54
C-8 α-Allyl						
71	79.43	66.00	33.22	74.50	59.36	130.19
73	79.35	66.03	33.03	74.61	59.31	128.37
76	79.29	62.73	35.33	74.14	58.00	130.45

their ^{13}C NMR data similarity to either **70** or **71**. (see Table VI). Further confirmation of the "reversed" stereochemistry of adduct **76** is demonstrated by ^{13}C NMR data comparison of a series of secondary amines (Table VII).

Considerable effort was expended at converting tertiary amine **70** to a suitable ketonic prostaglandin precursor. Research along these lines involving Polonovski-type reactions ultimately lead to an unsatisfactory total synthesis of PGE_2. Details of these efforts can be found in the supplementary material.

An Efficient Prostaglandin Synthesis. The unsatisfactory nature of the total synthesis of *l*-(−)-PGE_2 (**3**) that evolved from tertiary amine **70** (supplementary material) demanded an alternate approach. It was felt that a more productive route might be developed via secondary amine **110** prepared by N-demethylation of tertiary amine **70**.

At present there are a large number of published procedures for the demethylation of tertiary methylamines.[43] Most of these procedures are limited in that they either form amides or urethanes that are difficult to hydrolyze or require high temperatures (100–150 °C). More notable are the procedures that use 2,2,2-trichloroethyl chloroformate[43g] or 2,2,2-trichloro-*tert*-butyl chloroformate,[43h] which give carbamate intermediates that can be reductively cleaved with zinc or vinyl chloroformate,[43i] which gives urethane intermediates that can be cleaved by treatment with electrophilic reagents (hydrogen halides or bromine) followed by either methanol or ethanol).

Initial experiments used a large excess of ethyl chloroformate (greater than 20 equiv) in methylene chloride with a trace of sodium bicarbonate for the demethylation of the dimethylamine moiety of **70** to give urethane **104** (82%) after 6 days. A large excess of ethyl chloroformate was necessary, presumably due to competitive nucleophilic attack[43e] of chloride ion on the ethyl group of the intermediate ammonium salt to give ethyl chloride, carbon dioxide, and recovered **70** (Scheme X).

One solution to this problem is the use of phenyl chloroformate in place of ethyl chloroformate. Treatment of **70** with phenyl chloroformate (3 equiv.) in methylene chloride with a trace of sodium bicarbonate over 7 days gives an 86% yield of urethane **105**.

Hydrolysis of urethanes **104** and **105** proved impossible since treatment with either 50% aqueous potassium hydroxide in ethanol[43e] or aqueous hydrazine[43f] gives useless mixtures of products. Hydrolysis of the ester moieties of **104** and **105** with sodium hydroxide in aqueous methanol gives near quantitative yields for the carboxylic acids **106** and **107**. Treatment of **106** and **107** with the reduction conditions used for the removal of the sulfonyl moiety (lithium, ammonia, THF) also gives complicated product mixtures.

An excellent solution to the demethylation problem was provided by the treatment of **70** with 2,2,2-trichloroethyl chloroformate[43g] (2 equiv, neat, 25 °C, 72 h) in the presence of solid sodium bicarbonate to give urethane **108** (96%) as an oil after excess 2,2,2-trichloroethyl chloroformate is removed with a silica gel plug. Treatment of **108** with activated zinc in refluxing THF[44] for 6 h gives a 92% yield of desired secondary amine **110** (mp 50–52 °C (aqueous methanol), $[\alpha]^{25}_D$ −6.2° (*c* 0.431, $CHCl_3$)), which neatly solves the problems associated with hydrolysis of the demethylated urethanes of **70**. These reactions have been easily run on 40-g scale. (The ^{13}C NMR spectra of **108** and **110** are compared with those of similar analogues in Table VII.)

As a potential alternative to ester **70**, nitrile **72** was also treated with 2,2,2-trichloroethyl chloroformate (2 equiv, neat, solid sodium bicarbonate, 25 °C, 72 h) to give urethane nitrile **109** (95% as an oil) followed by reduction with zinc in refluxing THF for 6 h and purification using a silica gel plug to give secondary amine **111** (94% as an oil). (The ^{13}C NMR spectra of **109** or **111** are compared with those of similar analogues in Table VII.)

Due to the higher yields obtained in the conjugate-addition/alkylation reaction using bromo nitrile **67** vs. iodo ester **5b** as alkylating reagents (82% vs. 67%), hydrolysis experiments of the nitrile moiety of **109** and **111** were explored. Treatment of either **109** or **111** with potassium hydroxide in aqueous methanol at various temperatures (25–85 °C) was found to give complex mixtures of products. This was attributed to problems associated with 1,2-elimination of the sulfonyl group since hydrolysis of a very similar nitrile (minus the sulfonyl moiety) has been readily accomplished under similar conditions.[45]

Attempted nitrogen alkylation of nitrile **109** using methyl trifluoromethylsulfonate gives no reaction after 24 h at 25 °C, and longer reaction times give decomposition.[46]

(41) (a) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *J. Am. Chem. Soc.*, **94**, 2123 (1972); (b) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *ibid.*, **94**, 2124 (1972); W. P. Schneider, G. L. Bundy, and F. H. Lincoln, *J. Chem. Soc., Chem. Commun.*, 254, (1973).
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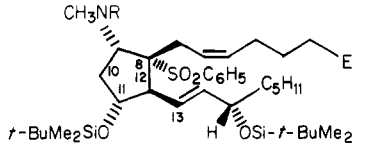
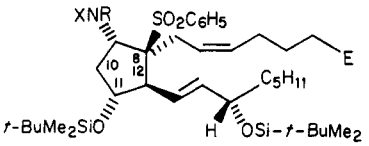
(43) (a) H. A. Hageman, *Org. React. (N.Y.)*, **7**, 198 (1953); G. Fodor, S. Abidi, and T. Carpenter, *J. Org. Chem.*, **39**, 1507 (1974); (b) Y. L. Goldfarb and I. M. Ispiryan, *Bull. Acad. Sci. USSR., Div. Chem. Sci. (Engl. Transl.)*, 839 (1969); (c) R. P. Mariella and K. H. Brown, *Can. J. Chem.*, **49**, 3348 (1971); (d) G. Leclerc, B. Rouot, and C. G. Wermuth, *Tetrahedron Lett.*, 3765 (1974); (e) J. D. Hobson and J. G. McClusky, *J. Chem. Soc.*, 2015 (1967); (f) M. M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, **15**, 208 (1972); K. C. Rice, *J. Org. Chem.*, **40**, 1850 (1975); (g) T. A. Montzka, J. D. Matiskella, and R. A. Partyka, *Tetrahedron Lett.*, 1325 (1974); (h) H. Eckert, M. Listl, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **17**, 361 (1978); (i) R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Lett.*, 1567 (1977); (j) H. J. Reich and M. L. Cohen, *J. Org. Chem.*, **44**, 3148 (1979).
(44) J. L. Isodor and R. M. Carlson, *J. Org. Chem.*, **38**, 554 (1973).
(45) E. J. Corey, N. H. Anderson, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).

Table VII. ^{13}C NMR Chemical Shift Data for Urethane and Secondary Amine Derivatives





108, R = $CO_2CH_2CCl_3$; E = CO_2CH_3
109, R = $CO_2CH_2CCl_3$; E = CN
112, R = $CO_2CH_2CCl_3$; E = $CONH_2$
110, R = H; E = CO_2CH_3
111, R = H; E = CN
113, R = H; E = $CONH_2$
120, R = H; E = CO_2H

141, R = $CO_2CH_2CCl_3$; X = CH_3; E = CO_2CH_3
142, R = H; X = CH_3; E = CO_2CH_3
143, R = H; X = CH_3; E = CO_2H
77, R = H; X = $CH_2C(CH_3)_2OH$; E = CO_2CH_3
78, R = H; X = $CH_2C(CH_3)_2Cl$; E = CO_2CH_3
144, R = H; X = $CH_2C(CH_3)_2OH$; E = CO_2H

	β-allyl						α-allyl						
compd	C-8	C-9	C-10	C-11	C-12	C-13	compd	C-8	C-9	C-10	C-11	C-12	C-13
						Urethanes							
108	74.12	58.48	37.59	74.12	55.12	133.45	**141**	81.19	61.39	38.00	76.51	60.73	130.54
109	73.87	58.34	37.63	74.05	54.95	132.09							
112	74.13	59.68	37.79	74.39	55.40	133.53							
						Secondary Amines							
110	75.31	64.22	40.51	73.92	54.96	132.92	**142**	76.46	60.69	40.81	73.72	58.25	132.02
111	75.83	64.58	40.28	74.19	54.94	130.94	**143**	76.12	60.86	39.79	73.82	58.46	132.33
113	75.47	63.82	39.54	74.24	54.83	133.48	**77**	76.53	59.19	41.93	73.64	58.43	132.28
120	74.91	63.33	40.00	74.07	54.99	134.31	**78**	76.77	58.08	41.85	73.50	58.32	132.26
							144	76.28	59.26	41.60	73.71	58.49	132.14

Likewise, reaction of **109** (or **111**) with anhydrous hydrogen bromide in methanol at −20 °C gives no reaction with the nitrile group after 4 h;[47] however, rapid hydrolysis of the silyl protecting groups is observed, leading to potential problems with epimerization of the 15-(*S*)-hydroxyl moiety.[48]

Partial hydrolysis of nitriles **109** and **111** to amides **112** and **113** can be accomplished in high yield by using a modified alkaline hydrogen peroxide procedure.[49] Treatment of **109** and **111** with potassium hydroxide, excess ethanolamine (ca. 10 equiv), and excess 30% hydrogen peroxide (ca. 10 equiv) in aqueous 2-methoxyethanol for 4 h gives amides **112** (92%) and **113** (94%), respectively. Longer reaction times (greater than 24 h) lead to complex mixtures of products presumably due to 1,2-elimination of the sulfonyl moiety as described previously. The use of ethanolamine in the reaction is critical since the reaction is very slow in its absence (greater than 24 h). The (^{13}C NMR spectra of **112** and **113** are compared with those of similar analogues in Table VII).

Attempted diazotization of amide **112** with excess nitrosyl chloride in a heterogeneous mixture of 10% sodium carbonate and methylene chloride at 0 °C and also at ambient temperatures gives a complex mixture of products after 1 h,[50] thereby exhausting the number of simple procedures for nitrile hydrolysis.

A number of reagents were tried for the oxidation of amine **110**, including hydrogen peroxide, hydrogen peroxide/sodium tungstate,[32s] alkaline hydrogen peroxide/acetonitrile,[51] sodium *m*-peroidate, benzoyl peroxide/vanadium oxyacetylacetonate,[32m] *tert*-butyl hydroperoxide-/vanadium oxyacetylacetonate,[35n] *m*-chloroperbenzoic acid, peracetic acid/sodium carbonate, bis(*m*-nitrobenzenesulfonyl)peroxide,[35t] hydrogen peroxide/molybdenum hexacarbonyl,[52] hydrogen peroxide/molybdenum trioxide,[52] peracetic acid/sodium tungstate/sodium carbonate, peracetic acid/sodium tungstate/potassium carbonate, and potassium permanganate.[35a] Although all of the above reagents give varying amounts of oxime **115**, most are either very slow (greater than 48 h) or give low yields of product (Scheme XI). In our hands, the best procedure involved addition of 40% peracetic acid (10 equiv) to a solution of amine **110** in wet methanol containing solid sodium carbonate (15 equiv) and a catalytic amount of sodium tungstate (0.1 equiv) to give oxime **115** (68%) and an 18% yield of a mixture of more polar products that are presumed to arise from nitrone **116**, which is the major constituent of this mixture.[53] In point of fact, nitrone **116** can be isolated pure and does slowly give the same mixture upon standing at 25 °C for ca. 1 week. Nitrone **116** cannot be hydrolyzed and is stable to dilute hydrochloric acid, sodium borohydride, and peracetic acid. Nitrone **116** decomposes on treatment with base (sodium hydroxide). The nitrone stereochemistry of **116** is expected to be similar to that of oxime **115** since the C-8 and C-10 signals in the ^{13}C NMR spectrum of **116** are both shifted downfield by equal amounts (4–5 ppm) from those of oxime **115**, a result not expected for the opposite stereochemistry.[53]

Treatment of nitrile **111** with 40% peracetic acid (7 equiv) in wet methanol containing solid sodium carbonate (15 equiv) and a catalytic amount of sodium tungstate (0.1 equiv) for 5 h affords oximino nitrile **117** (74%), a nitrone mixture tentatively assigned structure **118** (19%), and an epoxide (**119**) (2%) tentatively assigned as the C-5,C-6 epoxide of **117**.

(46) (a) J. L. Fry, *J. Chem. Soc., Chem. Commun.*, 45 (1974); (b) M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Witing, *Chem. Commun.*, 1533 (1968).
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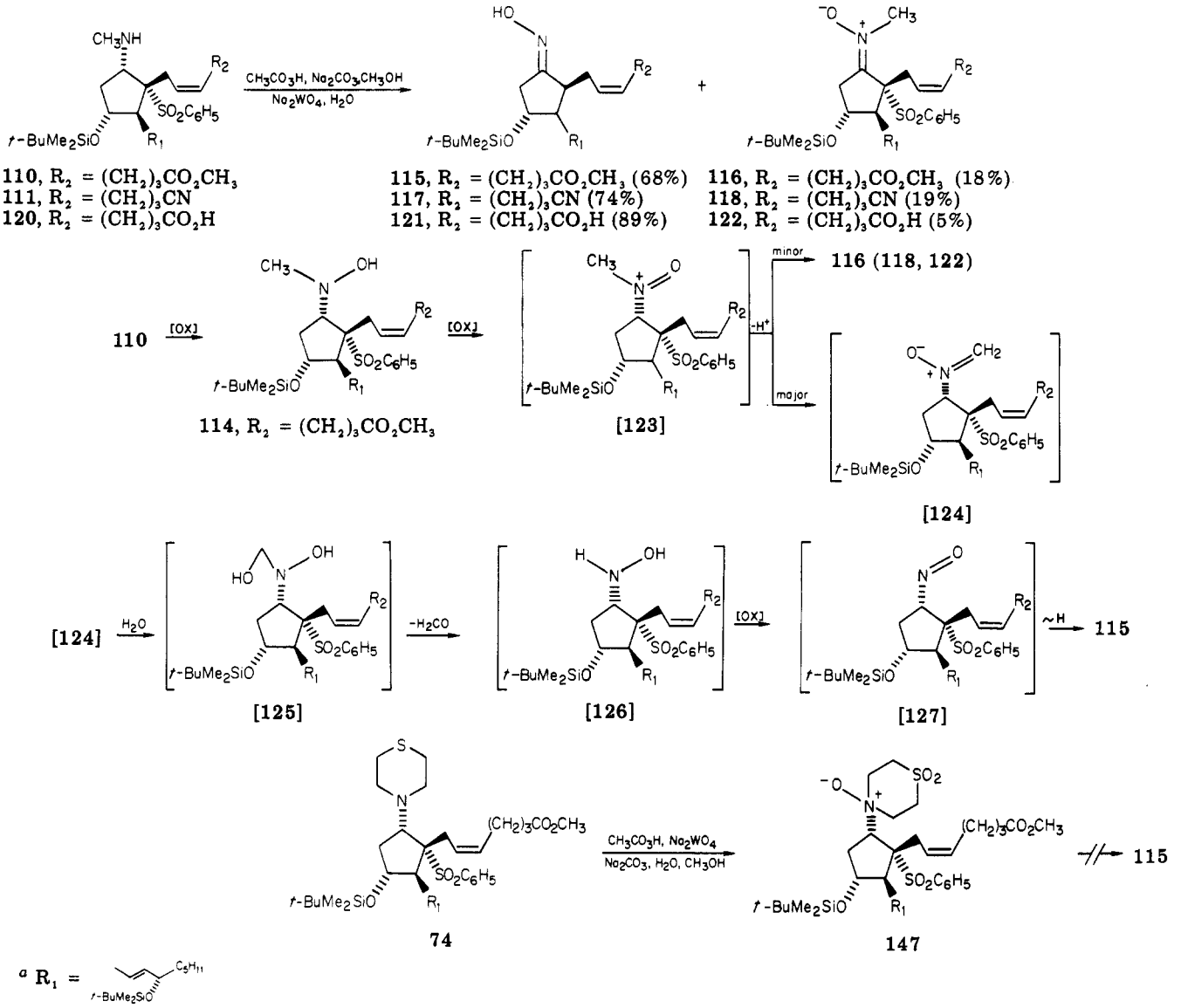
(52) K. Kahr and C. Berther, *Chem. Ber.*, **93**, 132 (1960).
(53) The oxime stereochemistry of **128** and **131** is assigned by ^{13}C NMR; see C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, **42**, 2614 (1977).

Scheme XI[a]



[a] R_1 =

Repetition of the oxidation procedure described above on amino acid **120** provides the most satisfactory results. Ester hydrolysis of **110** is easily accomplished by treatment with sodium hydroxide (3 equiv) in 2% aqueous methanol for 48 h followed by evaporation of one-half of the solvent and partitioning the resulting mixture between 10% sodium bicarbonate and ethyl acetate to give amino acid **120** as a yellowish foam (99%).

Addition of 40% peracetic acid (6 equiv) to a solution of **120** in wet methanol containing solid sodium carbonate (15 equiv) and a catalytic amount of sodium tungstate (0.1 equiv) yields oximino acid **121** as an oil (89%) after purification with a silica gel plug using 2% methanol/49% ethyl acetate/49% methylene chloride. The yield is substantially higher when using acid **120** as the reaction substrate than when ester **110** (89% vs. 68%) is used. This reaction has been easily run on a 30-g scale.

The mechanism of oxidation of **110** (**111**, **120**) presumably involves initial formation of hydroxylamine **114** with the first equivalent of oxidant. The second equivalent of oxidant probably forms ion [**123**], which can then lose an α-proton in either of two directions to give nitrones **116** and [**124**]. Nitrone [**124**] is then hydrated to give aminal intermediate [**125**], which then loses formaldehyde to yield hydroxylamine [**126**]. Hydroxylamine [**126**] is then rapidly oxidized with a third equivalent of oxidant to afford nitroso compound [**127**], which tautomerizes to oxime **115**. The formaldehyde formed by cleavage of aminal [**125**] is probably also oxidized to formic acid by using another equivalent of oxidant, which means the reaction requires a total of 4 equiv of oxidizing reagent (Scheme XI).

Although this mechanism only represents a reasonable working hypothesis, it is consistent with several observations. It is known that hydroxylamine **114** is an intermediate of the above oxidation and can be isolated as the major product under certain controlled conditions such as treatment of amine **110** with hydrogen peroxide in the presence of acetonitrile and potassium carbonate at 0 °C for 5 h.[51] Oxidation of hydroxylamine **114** with the same conditions used for the oxidation of amine **110** to oxime **115** gives the same ratio of products (**115** to **116**).

In an effort to develop a procedure for the preparation of oxime **115** without recourse to the haloformate dealkylation of a tertiary amine, oxidations of thiomorpholine **74** were examined (see also Scheme XIV for the oxidation of the secondary amines **77** and **144** derived from aziridine **76**). Although oxidation of **74** proceeded smoothly to the stage of sulfone amine oxide **147**, apparently the requisite β-elimination of the hydroxylamine moiety is not occurring under sufficiently mild conditions, since no oxime **115** (or

145) could be isolated from this reaction.

Oximino sulfone **115** is readily desulfonylated by treatment with 2 equiv of sodium methoxide in methanol in the presence of sodium borohydride (8 hydride equivalents) for 30 min at 25 °C. Subsequent purification by chromatography (silica gel) gives oxime **128**[53] (82%) and oximino alcohol **129** (11%). Evidently, ester reduction with sodium borohydride is competitive with the desulfonylation reaction, and larger amounts of alcohol **129** are observed for longer reaction times. Large excess of base is avoided to minimize formation of α,β-unsaturated oxime **130**, which is the major product (90%) in the absence of sodium borohydride. The C-8 stereochemistry of oxime **128** is confirmed by independent synthesis of **128** from PGE_2 methyl ester by sequential silylation (t-$BuMe_2SiCl$, 2,4,6-collidine, DMF, 0 °C[38]) and oximation (NH_2OH,-CH_3OH,H_2O[48]).

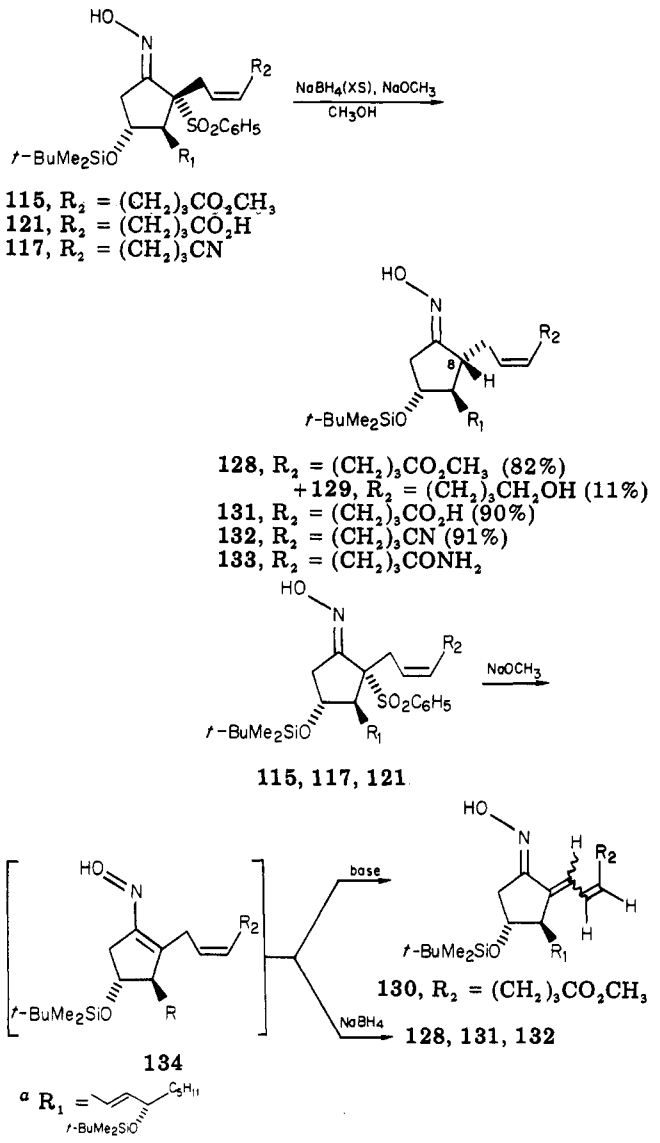
Use of oximino acid **121** avoids the problem of ester reduction observed with oximino ester **115**. Treatment of **121** with 1 equiv of sodium methoxide in methanol at −30 °C (to deprotonate the carboxylic acid moiety) followed by excess sodium borohydride (16 hydride equivalents), warming to 25 °C, and finally slow addition of sodium methoxide over an additional 5 h gives oxime **131**[53] (90%) as an oil after purification via a silica gel plug. This reaction has been easily run on 20-g scale. The C-8 stereochemistry of oxime **131** is confirmed by independent synthesis of **131** from l-(−)-PGE_2 (**3**) by sequential disilylation (t-$BuMe_2SiCl$, 2,4,6-collidine, DMF, −20 °C[38]) and oximination (NH_2OH,CH_3OH,H_2O[48]).

Treatment of oximino nitrile **117** with sodium borohydride (16 hydride equivalents) in methanol followed by 1.2 equiv of sodium methoxide at 25 °C for 1 h gives oximino nitrile **132** (91%) as an oil after purification with a silica gel plug. Nitrile **132** decomposed during attempted hydrolysis to carboxylic acid **131**; however, treatment with a solution of potassium hydroxide, ethanolamine (ca. 10 equiv), and 30% hydrogen peroxide (ca. 10 equiv) in aqueous 2-methoxyethanol for 3 h gives amide **133** (79%) as an oil after column chromatography.

The desulfonylation reaction presumably occurs via 1,4-addition of hydride to vinyl nitroso intermediate [**134**], which is produced by 1,4-elimination of phenylsulfinic acid from the starting oximino sulfones (**115**, **117**, **121**).[54] The very high C-8 stereospecificity observed in this reaction may be a consequence of enhanced α-face shielding afforded by a folded conformation of the hydrophobic alkyl groups of C-11 silyloxy moiety in the methanol as solvent, (Scheme XII).

At this stage in the synthesis a mild and convenient method for the generation of a ketone from an oxime is required. There are presently three general classes of procedures reported for this transformation.[55-57]

Scheme XII[a]



The hydrolysis of l-PGE_1 methoxime using nitrous acid has been reported; however, the yields were unsatisfactorily low (21%).[58] The hydrolysis of the methoximes of 11-deoxyprostaglandin precursors, have also been recently reported;[59] however the sensitive β-hydroxy ketone system found in using acetone and hydrochloric acid at reflux l-(−)-PGE_2 (**3**) would certainly not survive the strongly acidic conditions.

Treatment of oxime **128** with 20% titanium trichloride (3 equiv) in a solution of acetone, acetic acid, and water buffered with ammonium acetate[57b] for 4 h gives a 41% yield of disilyl-PGE_2 methyl ester **135** after column chromatography (silica gel). Longer reaction times lead to polymerization products (Scheme XIII).

A more satisfactory procedure that has been used successfully for the regeneration of ketones from p-toluenesulfonic acid hydrazones involves use of paraformaldehyde

(54) Vinyl nitroso and vinyl azo species have been shown to be powerful acceptors of nucleophiles in similar reactions. (a) E. J. Corey, M. Petrizilka, and Y. Ueda, *Tetrahedron Lett.*, 4343 (1975); (b) C. E. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975); (c) P. L. Fuchs, *J. Org. Chem.*, **41**, 2935 (1976).

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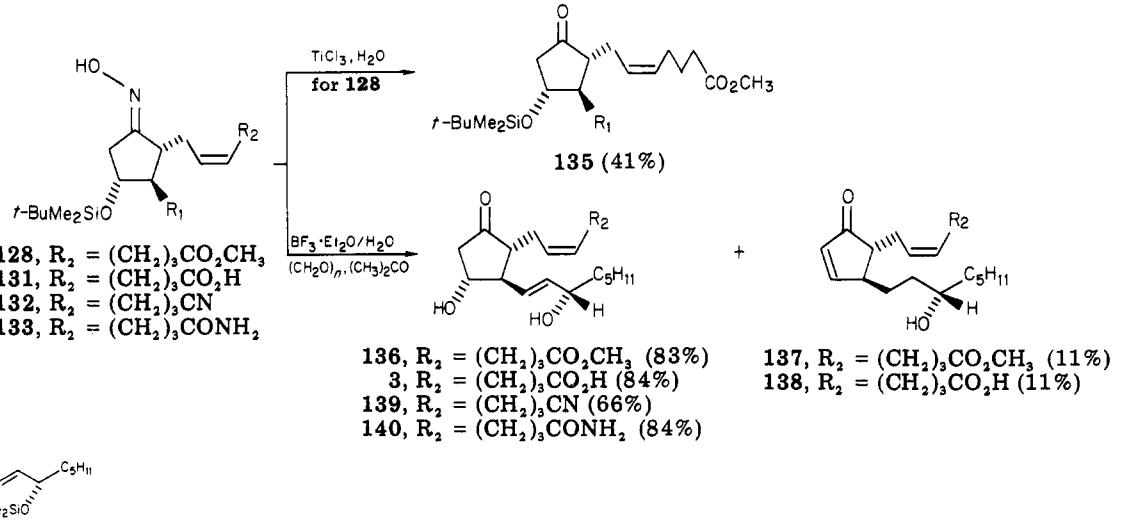
(57) (a) E. J. Corey and J. E. Richman, *J. Am. Chem. Soc.*, **92**, 5276 (1970); (b) H. H. Timms, E. Wildsmith, *Tetrahedron Lett.*, 195 (1971); (c) G. A. Olah, J. Welch, G. K. S. Prakash, and T. L. Ho, *Synthesis*, 808 (1976); (d) M. S. Ahmed and A. H. Siddiqui, *J. Indian Chem. Soc.*, **46**, 44 (1969); (e) H. Alper and J. T. Edward, *J. Org. Chem.*, **32**, 2938 (1967); (f) G. A. Olah, M. Arvanaghi, and G. K. S. Prakash, *Synthesis*, 220 (1980).

(58) N. Finch, L. D. Vecchia, J. J. Fitt, R. Stephani, and I. Vlattas, *J. Org. Chem.*, **38**, 4412 (1973).

(59) K. F. Bernady, J. F. Poletto, J. Nocera, P. Mirando, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.*, **45**, 4702 (1980).

Scheme XIII[a]



[a] R_1 =

in aqueous acetone with boron trifluoride etherate added as catalyst.[60] Treatment of oxime **128** with a 1:1 solution of acetone and aqueous 40% paraformaldehyde (acetone alone gives very little reaction) in the presence of boron trifluoride (0.7 equiv) as catalyst for 5 days at ambient temperature gives an 83% yield of PGE_2 methyl ester **136** as well as an 11% yield of PGA_2 methyl ester (**137**) after column chromatography (silica gel). On a small scale, larger amounts of boron trifluoride catalyst lead to shorter reaction times. Desilation also occurs under the reaction conditions and it is presently not known whether the responsible reagent is boron trifluoride[61] or aqueous hydrofluoric acid[62] produced under the reaction conditions. The ^{13}C NMR spectra of **136** and **137** are identical with those obtained from authentic material.[63] The ^{13}C NMR spectrum of **137** indicates the presence of ca. 20% of another epimer (presumably the C-8 epimer).

Treatment of oximino acid **131** with a 1:1 solution of acetone and aqueous 40% paraformaldehyde in the presence of boron trifluoride catalyst (0.7 equiv) for 5 days gives crude *l*-(−)-PGE_2 (**3**). Commercial 40% aqueous formaldehyde is less satisfactory for the reaction since it contains methanol, which leads to partial esterification of *l*-(−)-PGE_2 (**3**). The 40% solution used is prepared by briefly heating paraformaldehyde in water to 100 °C, cooling, and using the resulting colorless supernatant solution, which is decanted from a minor amount of residual polymer. The crude prostaglandin product obtained contains some ether-soluble paraformaldehyde residues and is purified by extraction of an ether solution with saturated sodium bicarbonate followed by regeneration of the prostaglandin acids by acidifying the aqueous phase with acetic acid to pH 5.5. Purification by column chromatography (silica gel) give *l*-(−)-PGE_2 (**3**) as an oil (84%) and PGA_2 (**138**) also as an oil (11%). Recrystallization (ethyl acetate/hexane) gives crystalline *l*-(−)-PGE_2 (mp 64–66 °C, $[\alpha]^{25}_D$ −64° (*c* 1.03, THF)),[65] which is confirmed by 360-MHz proton NMR and ^{13}C NMR analysis and by direct comparison with an authentic sample.[39] The above hydrolysis reaction has been run on 14-g scale and gives an overall yield of 40% for the synthesis of PGE_2 **3** from chiral vinyl sulfone D-**47** (67 × 96 × 92 × 99 × 89 × 90 × 84%). Treatment of authentic 8-epi-PGE_2[39] under the same reaction conditions described above (minus the paraformaldehyde) for 5 days gives about a 1:1 mixture of 8-epi-PGE_2 and PGE_2 **3**. Since the equilibrium mixture of PGE_2 **3** to 8-epi-PGE_2 would be expected to contain greater than 90% PGE_2 **3**,[40] approximately 1 half-life for C-8 epimerization is observed from the reaction conditions. Assuming equilibration of pure PGE_2 **3**, only trace amounts (less than 5%) of 8-epi-PGE_2 would be expected in the crude product from hydrolysis of oxime **131**. 8-Epi-PGE_2 is not observed by a ^{13}C NMR analysis of the crude PGE_2 **3**.

Treatment of oximino nitrile **132** and oximino amide **133** with the hydrolysis conditions gives a 66% yield of PGE_2 nitrile **139** and an 84% yield of PGE_2 amide **140**, respectively. Crude PGE_2 nitrile **139** contains a large amount of ether-soluble paraformaldehyde residues that cannot be removed by direct column chromatography and is purified by silylation (isopropyldimethyl silyl chloride, 2,4,6-collidine, DMF, 0 °C[38]), column chromatography (silica gel), and then desilation (boron trifluoride, acetone, water[61]). This gives an overall yield of 35% (89 × 95 × 94 × 74 × 91 × 66%) for PGE_2 nitrile **139** and 42% (89 × 95 × 94 × 92 × 74 × 91 × 84%) for amide **140** from chiral vinyl sulfone D-**47**.

The only remaining questions to be answered concerned proving the C-8 stereochemistry of minor alkylation product **71** and the possibility of using the proton-cleaved secondary amine **77** (from aziridine **76**) in the oxidation reaction. Since the C-8 stereochemistry of **71** did not rest on X-ray data, it was deemed appropriate to verify the assigned stereochemistry by converting it to PGE_2 **3**, (Scheme XIV). Additionally it was highly desirable to prepare the attendant series of transformation products (**141–143**, **145**) to enhance the ^{13}C NMR data set bearing the scarce C-8 α-allyl configuration.

Thus, using the chemistry already established for the major leading isomer (**70**), minor isomer **71** was treated

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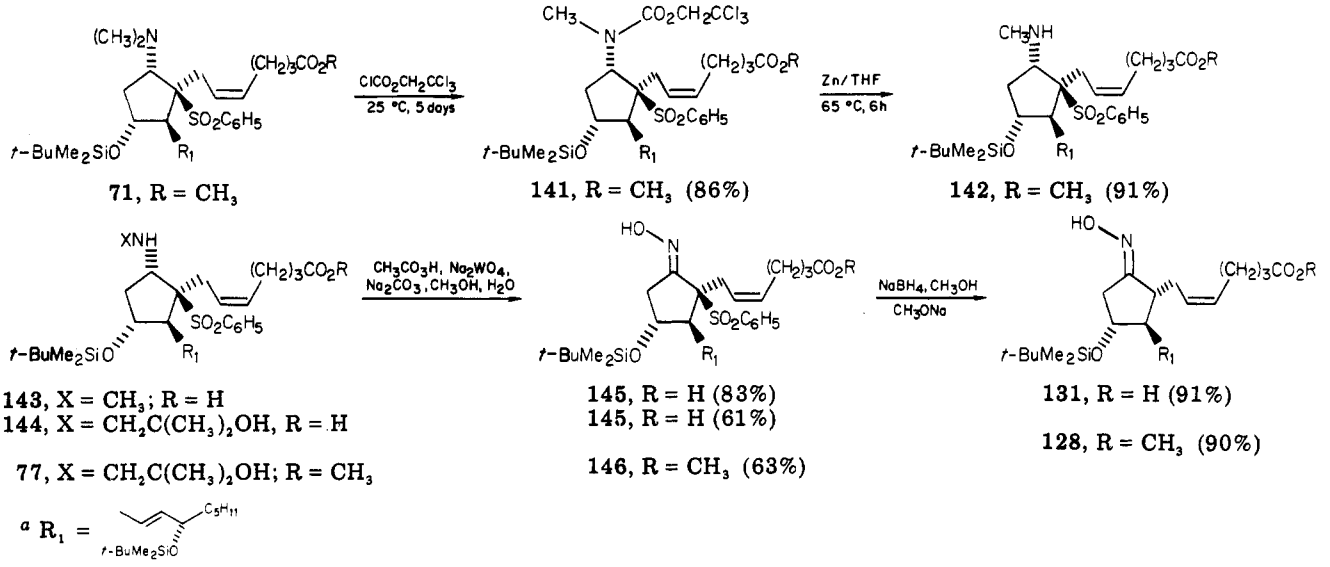
Scheme X IV[a]



71, R = CH_3

141, R = CH_3 (86%)

142, R = CH_3 (91%)

143, X = CH_3; R = H
144, X = $CH_2C(CH_3)_2OH$, R = H

77, X = $CH_2C(CH_3)_2OH$; R = CH_3

145, R = H (83%)
145, R = H (61%)

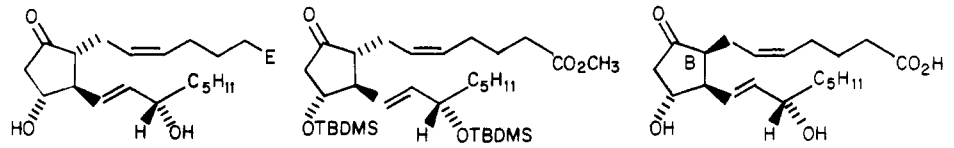
146, R = CH_3 (63%)

131, R = H (91%)

128, R = CH_3 (90%)

[a] R_1 =

Table VIII. ^{13}C NMR Chemical Shifts for E_2 Prostaglandins



136, E = CO_2CH_3
3, E = CO_2H
139, E = CN
140, E = $CONH_2$

135

8-epi-3

compd	chemical shift, ppm						
	C-5	C-7	C-8	C-10	C-11	C-12	C-13
136	130.84	25.19	53.90	46.14	71.97	54.62	131.96
3	130.92	25.20	53.50	46.21	72.13	54.54	131.52
139	129.18	25.12	53.78	46.05	72.01	54.49	131.27
140	131.03	25.14	53.11	46.41	72.16	54.35	131.03
135	128.69	25.29	52.74	47.75	72.67	53.97	130.74
8-epi-3	129.95	23.39	50.95	44.90	72.48	51.45	128.00

with 2,2,2-trichloroethyl chloroformate (2 equiv, neat, 25 °C, 5 days) in the presence of solid sodium bicarbonate to give urethane **141** (86%) followed by reduction with activated zinc in refluxing THF[44] for 6 h and purified with a silica gel plug to give secondary amine **142** (91%) as an oil.

Ester hydrolysis of **142** with sodium hydroxide (3 equiv) in 2% aqueous methanol (48 h) gives acid **143** (99%), which is, in turn, oxidized with 40% peracetic acid (6 equiv) in wet methanol containing solid sodium carbonate (15 equiv) and a catalytic amount of sodium tungstate (0.1 equiv) to give oxime **145** (83%).

Desulfonylation of oximino acid **145** is accomplished by treatment with sodium methoxide and sodium borohydride in methanol by using the procedure described previously for the desulfonylation of oximino acid **121** to give 91% of an oxime (**131**) that is identical in all respects with that obtained from reduction of **121**. Moreover, hydrolysis of this oxime (boron trifluoride, paraformaldehyde, aqueous acetone) gives *l*-(−)-PGE_2 (**3**) that is identical in all respects with an authentic sample of *l*-(−)-PGE_2 (**3**), thus confirming minor alkylation isomer **71** as the C-8 epimer of **70**.

Finally, oxidation of secondary amines **77** and **144** from the aziridine route affords oximes **146** and **145**, respectively (63, 61% yield). Reductive desulfonylation of **145** and **146** under the borohydride/methanol conditions provides an alternate route to oximes **131** and **128** (90%).

As can be readily seen from inspection of Table VIII (and Tables VI and VII), the C-8 stereochemistry of the various adducts can readily be assigned on the basis of the chemical shifts of the cyclopentene ring carbons (particularly C-8, C-9, C-12).

Conclusion

Seven major contributions have been described in this study: (1) provision for the first efficient triply convergent total synthesis of prostaglandin E_2, (2) demonstration of a series of stereospecific "Lawton-type" S_N2' reactions of cyclopentenyl sulfones, (3) development of an enantioconvergent synthesis of a chiral cyclopentenyl sulfone, (4) development of a new "Polonovski-like" method for oxidation of tertiary amines to ketones, (5) development of a new method of oxidation of secondary amines to oximes, (6) development of a stereospecific method for reductive desulfonylation of α-sulfonyl oximes involving the 1,4-addition of hydride to vinyl nitroso species, and (7) provision of a ^{13}C NMR method for the assignment of C-8 stereochemistry of prostanoids.

Experimental Section

General Procedures. Melting points were measured on a Fisher-Johns melting-point apparatus. All melting and boiling points are uncorrected. Infrared spectra were recorded neat (NaCl) or as KBr pellets on a Perkin-Elmer 137 sodium chloride

or a 267 grating infrared spectrophotometer. NMR spectra were determined in chloroform-*d* solution with tetramethylsilane as an internal reference unless otherwise stated. NMR instrumentation included Varian A-60A, Perkin-Elmer R-32, Varian CFT-20, and Nicolet 360 or 470 spectrometers. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra and exact mass determinations were obtained by using a CEC-21-110-B high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 μA.

All experiments were carried out under a positive pressure of nitrogen in dry flasks equipped with rubber stoppers for introduction of reagents via syringe. All solvents used for workup or recrystallization were distilled. Reactions were monitored by TLC on precoated thin-layer (0.25 mm) Silica Gel 60 F-254 plates obtained from EM Reagents. Thick-layer plates (2 mm) used were Silica Gel 60 F_{254} or were made by using silica gel PF-254 containing $CaSO_4$, both from EM Reagents. Column chromatography was done on silica gel (60–200 mesh) obtained from either Sargent-Welch or Davison Chemical, 230–400 mesh silica gel from EM Reagents, or on 80–200 mesh alumina from Fisher. Gas chromatographic analyses were performed on a Varian Aerograph Model 920. Solvents were evaporated on a Büchi Rotovapor R at aspirator pressure (~20 mm) fitted with a constant-temperature bath and/or a duo-seal vacuum pump (~0.1 mm) from Welch Scientific Co.

Normal reaction solvents were purified as follows: THF, DMF, and ethyl ether were distilled from sodium/benzophenone; toluene, methylene chloride, ethyl acetate, Me_2SO, HMPA, and DMF were distilled from CaH_2 and stored over 4-Å molecular sieves. All other solvents and reagents were purified as described in ref 66. Lithium diisopropylamide (LDA) was routinely prepared by adding *n*-butyllithium to a solution of diisopropylamine in THF at −78 °C and stirring for 45 min. Stock solutions of organolithium reagents were titrated in benzene at 25 °C with menthol, with 2,2′-bipyridyl as an indicator.

TLC data for compounds are reported as (solvent, R_f) by using the following solvent systems: (1) 10% THF/hexane, (2) 20% ether/chloroform, (3) 3:1:2:2 hexane/ether/chloroform/methanol, (4)[67] 20:3:10:1 ethyl acetate/acetic acid/hexane/water. Mass spectral data are reported as *m/e* (relative intensity). IR data are reported in microns. ^{13}C NMR data are reported in ppm with tetramethylsilane as internal standard.

Microanalyses were performed by Ching Siang Yeh and Margaret Lam, Department of Chemistry, Purdue University.

Experimental conditions for preparation of the following compounds can be found in the supplementary material: DL-11; resolution of DL-11 (D-11, L-11); L-12; 13; 31; 32; DL-33; resolution of DL-33 (D-33); L-34; L-35; 37–39; 52–54; 55a; 56; 58; 64; 65; 17; 67; 68; 72–74; 76–78; 81; 85; 86; 88; 89a; 89b; 91; 92; 93a; 93b; 95a; 95b; 96–99; 102; 104–107; 109; 111–113; 117–119; 132; 133; 135–137; 141–146; 139, 140.

Synthesis. *l*-(−)-PGE$_2$ (3). To 15.39 g (25.8 mmol) of bis(*tert*-butyldimethylsilyl)-PGE$_2$ oxime (131) was added 330 mL of acetone, 330 mL of 40% aqueous paraformaldehyde (prepared by dissolution of paraformaldehyde in water at reflux), and 2.3 mL (8.0 M, 18 mmol) of boron trifluoride etherate. The solution was stirred for 5 days at ambient temperature and then partitioned between 600 mL of brine and 600 mL of ethyl acetate. The aqueous phase was extracted twice with 400-mL portions of ethyl acetate, and the organic fractions were combined, dried (Na_2SO_4), and evaporated (15 mm). To remove ether-soluble paraformaldehyde residues, the crude product was dissolved in 500 mL of ether and extracted with three 500-mL portions of 10% sodium bicarbonate. The aqueous layers were combined, carefully acidified to pH 5.5 with acetic acid (~100 mL), and extracted with three 500-mL portions of ether. The ether fractions were combined, dried (Na_2SO_4), and evaporated to give 8.77 g of crude product, which was purified by column chromatography (SiO_2, 60–200 mesh, 500 g, 50% ethyl acetate/methylene chloride to 45% ethyl acetate/5% acetic acid/methylene chloride gradient) to give 0.95 g (11%) of PGA$_2$ (138) (identical in all respects with an authentic sample[39] except ^{13}C NMR data, which showed ~20% of another epimer, presumably the C8 epimer) and 7.67 g (84%) of 3. An analytical sample of 3 was obtained by recrystallization from ethyl acetate/hexane: mp 64–66 °C; $[\alpha]^{25}_D$ −64° (*c* 1.03, THF);[65] TLC (3, 0.3); IR (melt) 3.0 (OH) 5.75 (C=O, COOH); NMR ($CDCl_3$) δ 5.67 (dd, *J* = 6.6, 15.4, 1, 14-CH), 5.57 (dd, *J* = 8.1, 15.4, 1.13, CH), 5.40 (m, 2, 5, 6-CH), 4.12 (q, *J* = 6.5, 6.7, 6.8, 1, 15-CH), 4.06 (q, *J* = 8.1, 8.2, 8.3, 1, 11-CH), 2.74 (dd, *J* = 7.5, 18.3, 1, 10β-CH), 2.15 (m, 5, 2, 7-CH_2, 12-CH), 2.13 (dd, *J* = 9.9, 18.5, 1, 10α-CH), 2.1 (m, 3, 4-CH_2 and 8-CH), 1.7 (m, 2, 3-CH_2) 1.5, 1.6 (m, 2, 16-CH_2), 1.3 (br s, 6, 17, 18, 19-CH_2), 0.9 (m, 3, 20-CH_3); ^{13}C NMR 214.71 (C9), 178.39 (C1), 136.62 (C14), 131.52 (C13), 130.91 (C5), 126.69 (C6), 73.19 (C15), 72.13 (C11), 54.55 (C12), 53.51 (8), 46.23 (C10), 37.00 (C16), 33.56 (C2), 31.73 (C18), 26.47 (C4), 25.20 (C7, 17), 24.60 (C3), 22.64 (C19), 14.04 (C20); exact mass, calcd $C_{20}H_{32}O_5$ (M − H_2O) 334.214; found, 334.213.

Anal. Calcd for $C_{20}H_{32}O_5$; C, 68.18; H, 9.09. Found: C, 68.38; H, 9.29.

Methyl 7-Iodo-*cis*-5-heptenoate (5b).[7,68] To a stirred solution of methyl 7-bromo-*cis*-5-heptenoate (5a)[31] (18.4 g, 83 mmol) in 150 mL of acetone with a trace of anhydrous sodium carbonate in a 1-L flask was added rapidly a solution of 14.5 g (93 mmol) of sodium iodide in 150 mL of acetone. The solution immediately clouded with a precipitate, and after being stirred for 2 min, the mixture was diluted with 500 mL of ether and filtered. A trace (ca. 0.001 g) of anhydrous sodium carbonate was added to the filtrate, which was evaporated in vacuo (<30 °C) to give a light brown mixture. Addition of 500 mL of ether, filtration, and evaporation in vacuo gave 21 g (95%) of **5b** as an unstable red oil that must be protected from light and kept over anhydrous sodium carbonate at all times to prevent olefin isomerization: TLC (2, 0.07); IR (neat) 5.76 (C=O) 13.6 (cis olefin); NMR ($CDCl_3$) δ 5.2–6.0 (m, 2, HC=CH), 3.90 (d, 2, CH_2I), 3.68 (s, 3, OCH_3), 1.4–2.5 (m, 6, CH_2).

(1*S*,4*R*)-*cis*-4-(*tert*-Butyldimethylsiloxy)-1-hydroxy-2-(phenylsulfonyl)-2-cyclopentene (D-6b) and (1*S*,4*R*)-*cis*-1,4-Bis(*tert*-butyldimethylsiloxy)-2-(phenylsulfonyl)-2-cyclopentene (D-22). To a mechanically stirred solution of 182 g (0.76 mol) of epoxide D-19 in 1.8 L of THF in a dry 3-L flask was added 1 mL (1.02 g, 0.007 mol) of DBU. After 2 h, the solution was cooled to −20 °C and 115 g (1.7 mol) of imidazole added. To this solution was added 121 g (0.80 mol) of *tert*-butyldimethylchlorosilane in 500 mL of THF over 2 h at −20 °C. After being stirred an additional 15 h at 25 °C, the mixture was filtered and the filtrate evaporated at 15 mm of pressure. The resulting oil was partitioned between 1.5 L of ether, 1.5 L of hexane, and 1.5 L of 5% hydrochloric acid and washed with 1 L of 5% hydrochloric acid, 1 L of water, 1 L of 10% sodium bicarbonate, and 1 L of brine. After drying ($MgSO_4$) and evaporation of the solvent in vacuo, the residue was dissolved in 200 mL of ether, added dropwise to 4 L of hexane, and cooled to −20 °C. The crystals were collected and dried in vacuo to give 188 g (70%) of D-6b: mp 72–73 °C; $[\alpha]^{25}_D$ +58.2° (c 0.456, $CHCl_3$); TLC (2.03); IR (melt) 2.8 (OH) 6.2, 6.3, 6.8 (Ar), 7.95 ($SiCH_3$), 7.7, 8.7 (SO_2), 13.2, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.6 (m, 3, *m*- and *p*-Ar), 6.75 (br s, 1, vinyl CH), 4.75 (m, 2, CHOR), 2.82 (ddd, 1, methylene-β), 2.8 (br s, 1, OH), 1.80 (ddd, 1, methylene-α), 0.89 (s, 9, *t*-Bu), 0.10 (s, 6, $SiCH_3$); ^{13}C NMR, 147.41 (C–S), 146.25 (vinyl C), 140.03 (i), 133.78 (*p*), 129.28 (*m*), 128.13 (*o*), 72.55 (COSi), 72.34 (COH), 44.92 (CH_2), 25.76 (*t*-Bu), 18.06 (*t*-Bu), −4.73 ($SiCH_3$); exact mass, calcd $C_{17}H_{26}O_4SiS$ (M − C_4H_9) 297.062, found 267.060.

Anal. Calcd for $C_{17}H_{26}O_4SiS$: C, 57.62; H, 7.34; S, 9.04; Si, 7.91. Found: C, 57.97; H, 7.31; S, 9.04; Si, 7.91.

Plug filtration of the mother liquor residues (SiO_2, 60–200 mesh, 500 g, 20:80 ether/hexane and then 1:1:2 ether/chloroform/hexane) gave 24 g (9%) of D-6b and 26 g (7%) of D-22: mp 54–55 °C; $[\alpha]^{25}_D$ +113° (*c* 0.378, $CHCl_3$); TLC (2, 0.7); IR (melt) 6.8 (C=C) 7.6, 8.65 (SO_2), 7.95 ($SiCH_3$), 13.2, 14.5 (monosubstituted Ar); NMr ($CDCl_3$) δ 7.9 (m, 2, *o*-Ar), 7.5 (m, 3, *m*- and *p*-Ar), 6.7 (m, 1, vinyl CH), 4.97 (dd, 1, 1-CHOSi), 4.69 (dd, 1,4-CHOSi), 2.80 (ddd, 1, methylene-β), 1.74 (ddd, 1, methylene-α), 0.89 (s, 9, 4-$OSiC_4H_9$), 0.71 (s, 9, 1-$OSiC_4H_9$), 0.1 (s, 6, 4-$OSiCH_3$), 0.02

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(s, 6, 1-OSiCH_3); ^{13}C NMR 147.47 (C–S), 147.23 (vinyl C), 141.23 (i), 133.03 (*p*), 128.84 (*m*), 127.63 (*o*), 72.71 (4-COSi), 72.18 (1-COSi), 46.50 (CH_2), 25.75 (*t*-Bu), 18.12, 17.84 (*t*-Bu), −4.70 ($SiCH_3$); exact mass, calcd $C_{23}H_{40}O_4Si_2S$ (M − C_4H_9) 411.148, found 411.150.

(1*S*,2*R*,3*R*,4*R*)-*cis*-3,4-Epoxy-*trans*-2-(phenylsulfonyl)-cyclopentan-1-ol (D-19) and (1*S*,2*R*,3*S*,4*S*)-*trans*-3,4-Epoxy-*trans*-2-(phenylsulfonyl)cyclopentan-1-ol (D-20). To a cooled (ice bath) stirred solution of 151.3 g (0.788 mol) of chiral sulfide alcohol D-11 in 1.6 L of methylene chloride in a 5-L flask was added 280 mL (1.6 mol) of 40% peracetic acid (pretreated with 16 g of anhydrous sodium acetate) over 2 h. After being stirred for an additional 5 h at 25 °C, 1.6 L of 5% sodium carbonate was added carefully (caution, foaming!), and to the resulting mixture was added anhydrous sodium carbonate to pH 7 (~170 g, 1.6 mol). The layers were separated, and the aqueous phase was extracted with 100 mL of methylene chloride. The organic fractions were combined, dried ($MgSO_4$), and filtered. To this solution was added 163 g (0.8 mol) of MCPBA (85%) and the mixture stirred for 72 h at 25 °C. To this mixture was added 50 mL of saturated sodium thiosulfate and 600 mL of 10% sodium carbonate (caution, foaming!) (pH of aqueous phase should be 7–8). The layers were separated, and the aqueous phase was extracted with 100 mL of methylene chloride. The organic fractions were combined, dried ($MgSO_4$), and evaporated in vacuo to give a pale yellow oil. This oil was dissolved in 300 mL of methylene chloride and added to 2 L of ether. After cooling to −20 °C, the crystals were collected and dried in vacuo to give 139 g of D-19. A second (22.7 g) and third crop (6.2 g) of crystals were obtained to give a total of 168 g (88%) of D-19: mp 103–104 °C; $[\alpha]^{25}_D$ +64° (*c* 0.429, $CHCl_3$); TLC (2, 0.2); IR (KBr) 2.9 (OH), 6.3, 6.75 (Ar), 7.6, 8.7 (SO_2), 13.1, 14.5 (monosubstituted d Ar); NMR ($CDCl_3$) δ 7.9 (m, 2, *o*-Ar), 7.6 (m, 3, *m*- and *p*-Ar), 4.45 (m, 1, CHOH) 3.8 (m, 3, $CHSO_2$ and CH epoxide), 2.55 (d, 1, methylene-β), 2.15 (d, 1, methylene-α), 2.13 (s, 1, OH); ^{13}C NMR 138.08 (i), 134.52 (*p*), 129.72 (*m*), 128.49 (*o*), 72.40 (C–S), 70.44 (COH), 58.43 (C3-epoxide), 56.34 (C4-epoxide), 37.38 (CH_2); exact mass, calcd $C_{11}H_{12}O_4S$ 240.046, found 240.044.

Anal. Calcd for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.04; S, 13.32. Found: C, 54.96; H, 5.23; S, 13.40.

Purification of the mother liquor by plug filtration (SiO_2, 60–200 mesh, 200 g, 10% ether/chloroform) gave 3.0 g (3%) of relatively unstable epoxide D-20: mp 101–103 °C; $[\alpha]^{25}_D$ +137° (*c* 0.439, $CHCl_3$); TLC (2, 0.15); IR (KBr) 2.9 (OH), 6.15, 6.3, 6.75 (Ar), 7.6, 8.7 (SO_2), 13.1, 14.4 (monosubstituted Ar); NMR ($CDCl_3$) δ 8.0 (, 2, *o*-Ar) 7.6 (m, 3, *m*- and *p*-Ar) 4.25 (m, 1, CHOH) 3.4–3.8 (m, 4, $CHSO_2$, CH epoxide, and OH), 2.55 (dd, 1, methylene-β), 1.78 (ddd, 1, methylene-α); ^{13}C NMR 137.82 (i), 134.21 (*p*), 129.28 (*m*), 128.94 (*o*), 72.60 (C–S), 67.96 (COH), 53.81 (C3-epoxide), 53.14 (C4-epoxide), 35.24 (CH_2); exact mass, calcd $C_{11}H_{12}O_4S$ 240.046, found 240.047.

(1*S*,4*R*)-*cis*-1,4-Dihydroxy-2-(phenylsulfonyl)-2-cyclopentene (21). To 28.1 g (60 mmol) of D-22 under nitrogen were added 60 mL of THF, 3.0 mL of trifluoroacetic acid, and 6 mL of water. The solution was stirred for 5 days at 25 °C and then evaporated in vacuo to give 14.5 g (101%) of diol **21** as a water-soluble crystalline mass: mp ~100 °C; TLC [2 and 3 (1:1), 0.2]; IR (KBr) 2.9 (OH), 6.15, 6.3, 6.75 (Ar), 7.7, 8.7 (SO_2), 13.3, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.6 (m, 3, *m*- and *p*-Ar), 6.72 (br s, 1, vinyl CH), 4.7 (m, 2, CHOR), 3.7 (br s, 2, OH), 2.80 (ddd, 1, methylene-β), 1.82 (ddd, 1, methylene-α); exact mass, calcd $C_{11}H_{12}O_4S$ 240.046, found 240.044.

Monosilylation of this product as described previously gave 16.3 g (77%) of D-6b.

(1*R*,2*R*)-*trans*-2-(phenylsulfinyl)-3-cyclopenten-1-ol (23). To a solution of 43.2 g (225 mmol) sulfide L-11 in 800 mL of methylene chloride at −78 °C was added dropwise a solution of 72.8 g (338 mmol) *m*-chloroperbenzoic acid in 800 mL of methylene chloride over 1 h. The mixture was quenched after the addition of 8 mL (109 mmol) of methyl sulfide at −78 °C. The slurry was filtered and the filtrate washed twice with saturated sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation in vacuo gave 42.64 g (91%) of **23**[11] as one major diastereomer: mp 95–100 °C; $[\alpha]^{25}_D$ −331° (*c* 2.00, $CHCl_3$); TLC (20% $Et_2O/CHCl_3$, 0.1); NMR ($CDCl_3$) δ 7.5–7.8 (m, 5, aryl), 6.1 (m, 1, C4H), 5.4 (m, 1, C3H), 5.0 (m, 1, CHOH), 3.9 (m, 1, C2H), 2.9 (m, 1, methylene *syn*-OH), 2.4 (m, 1, methylene anti-OH), 3.0 (br s, 1, OH); ^{13}C NMR ($CDCl_3$) 142.1 (s, i), 131.5 (d, *p*), 129.2 (d, *o*), 125.0 (d, m), 137.4 (d, C3), 122.5 (d, C4), 81.2 (d, C1), 71.0 (d, C2), 42.0 (t, C5); IR ($CHCl_3$) 3.0 (OH), 6.8, 6.9 (aryl), 9.6 (SO), 14.5 (aryl); exact mass, calcd $C_{11}H_{12}SO_2$ 208.056, found 208.058.

(1*R*,2*S*,3*R*,4*R*)-3,4-Epoxy-2-(phenylthio)-1-cyclopentanol (28). To a stirred slurry of 19.6 g (94.2 mmol) of sulfoxide **23** and 10 g (125 mmol) of anhydrous pyridium bromide in 1.5 L of dry tetrahydrofuran at room temperature was added 0.8 mL (9.4 mmol) of pyridine, and the mixture was heated to reflux. After 9 h, the solution was cooled to −78 °C, and 10.2 g (47 mmol) of phenyl disulfide was added. To this was added 2.2 mL (44.6 mmol) of bromine dropwise, after which the solution was allowed to warm to room temperature over 1 h. The mixture was filtered, evaporated in vacuo, and redissolved in 1.5 L of Et_2O. This was washed with 1.5 L of water, and the aqueous solution was extracted 2 times with 750 mL of Et_2O. The organic layers were combined, washed with water, and stirred over 1 L of 10% NaOH at room temperature until complete conversion to the epoxide (ca. 1 h). The organic layer was separated, washed twice with water, dried ($MgSO_4$), and evaporated in vacuo to give a crude oil. Plug filtration on silica first with ca. 3 L of chloroform (to remove the phenyl disulfide and the brown band) and second with 5 L of Et_2O gave 16.34 g (83%) of a yellow liquid **28**: $[\alpha]^{25}_D$ −134° (*c* 2.24, $CHCl_3$); TLC (20% $Et_2O/CHCl_3$, 0.27); NMR ($CDCl_3$) δ 7.85 (m, 2, aryl *o*), 7.6 (m, 3, aryl *m* and *p*), 4.15 (dd, $J_1 = J_2 = 7$, 1, CHOH), 3.8 (m, 2, both epoxy H), 3.65 (d, $J = 7$, 1, CHS), 3.15 (br s, 1, OH), 2.83 (dd, $J = 7$, 14, 1, methylene *syn*-OH), 2.0 (ddd, $J = 1$, 7, 14, 1, methylene anti-OH); ^{13}C NMR ($CDCl_3$) 134.2 (s, i), 132.4 (d, *o*), 129.1 (d, *m*), 127.5 (d, *p*), 73.1 (d, C1), 57.7 (d, C2), 56.8 (d, C3), 55.1 (d, C4), 35.5 (t, C5); IR ($CHCl_3$) δ 3.0 (OH), 3.4 (CH), 6.3, 6.8, 7.0 (aryl), 8.0, 10.8, 11.8 (epoxide), 14.5 (–S–); exact mass, cald $C_{11}H_{12}SO_2$ 208.056, found 208.056.

(1*R*,2*S*,3*R*,4*R*)-3,4-Epoxy-2-(phenylsulfonyl)-1-cyclopentanol (L-20). To a slurry of 12.56 g (62 mmol) of *m*-chloroperbenzoic acid in 100 mL of methylene chloride at 0 °C was added dropwise 5.85 g (28 mmol) of sulfide **28** in 50 mL of methylene chloride over 20 min. The reaction was allowed to stir for 3 h at room temperature, and was filtered and then diluted with 150 mL of CH_2Cl_2. The solution was washed once with water, the aqueous layer was extracted with 100 mL of CH_2Cl_2, and the organic layers were combined. Washing with saturated sodium bicarbonate and brine, drying ($MgSO_4$), and evaporation in vacuo gave 5.84 g (87%) of L-20: mp 101–103 °C; $[\alpha]^{25}_D$ −133° (*c* 2.53, $CHCl_3$); TLC (10% MeOH/$CHCl_3$, 0.4); NMR ($CDCl_3$) 8.0 (m, 2, aryl *o*), 7.6 (m, 3, aryl *m* and *p*), 4.25 (q, $J = 8$, 1, CHOH), 3.4–3.7 (m, 3, C2H, C3H, C4H), 2.6 (ddd, $J = 15$, 8, 1, 1, methylene syn-OH), 1.8 (ddd, $J = 15$, 8, 2, 1, methylene anti-OH); ^{13}C NMR ($CDCl_3$) 137.7 (s, i), 134.3 (d, *p*), 129.3 (d, o), 129.0 (d, m), 72.7 (d, Cl), 68.0 (d, C2), 53.8 (d, C3), 53.1 (d, C4), 35.1 (t, C5); IR ($CHCl_3$) 3.0 (OH), 3.4 (CH), 6.3, 6.8, 6.9, 14.5 (aryl), 7.7, 8.7 (SO_2); exact mass, calcd $C_{11}H_{12}SO_4$ 240.046, found 240.053.

(1*R*,4*R*)-*trans*-4-(*tert*-butyldimethylsiloxy)-1-hydroxy-2-(phenylsulfonyl)-2-cyclopentene (29) and (1*R*,4*R*)-*trans*-1,4-Bis(*tert*-butyldimethylsiloxy)-2-(phenylsulfonyl)-2-cyclopentene (30). To a stirred solution of 0.240 g (1.00 mmol) of *trans*-epoxy alcohol L-20 in 5 mL of methylene chloride was added 1 drop of DBU. After 15 min, 0.42 mL (0.303 g, 3.0 mmol) of triethylamine 0.21 g (1.4 mmol) of *tert*-butyldimethylchlorosilane, and 0.03 g (0.25 mmol) of 4-(dimethylamino)pyridine were added, and the mixture was stirred for 15 h. The mixture was partitioned between 50 mL of 5% hydrochloric acid and 50 mL of methylene chloride, and the aqueous phase was extracted with 10 mL of methylene chloride. The combined organic fractions were washed with 20 mL of 10% sodium bicarbonate, dried (Na_2SO_4), and evaporated in vacuo to give a light brown oil. The crude product was purified by plug filtration (SiO_2, 30 g, 30% ether/hexane and then 50% ether/hexane) to give 0.28 g (79%) of **29** and 0.04 g (10%) of **30** as crystalline compounds.

Crystallization of **29** from hexane gave an analytical sample: mp 76–77 °C; $[\alpha]^{25}_D$ +147° (*c* 0.360, $CHCl_3$); TLC (2, 0.3); IR (melt) 2.93 (OH), 6.2, 6.9 (C=C), 7.7, 8.7 (SO_2), 7.95 ($SiCH_2$), 9.2 (C-O), 13.7, 14.6 (monosubstituted Ar); NMR ($CDCl_3$) δ 7.9 (m, 2, *o*-Ar) 7.6 (m, 3, *m*- and *p*-Ar), 6.75 (d, $J = 2$, 1, vinyl CH), 5.22 (m, 1, CHOSi), 4.98 (d, $J = 6$, 1, CHOH), 3.0 (br s, 1, OH), 2.35 (ddd, $J = 2$, 6, 14, 1, CH_2-β), 1.98 (ddd, $J = 6$, 6, 14, 1, CH_2-α), 0.86 (s, 9, *t*-Bu), 0.07 (s, 6, $SiCH_3$); ^{13}C NMR 147.60 (vinyl CH), 146.62

(CS), 139.06 (i), 133.99 (*p*), 129.43 (*m*), 128.17 (*o*), 75.28 (COSi), 73.29 (COH), 44.65 (CH_2), 25.75, 18.11 (*t*-Bu), −4.80 ($SiCH_3$); exact mass, calcd $C_{17}H_{26}O_4SiS$ (M − C_4H_9) 297.062, found 297.059.

Anal. Calcd for $C_{17}H_{26}O_4SiS$: C, 57.62; H, 7.34; S, 9.04; Si, 7.91. Found: C, 57.79; H, 7.31; S, 8.96; Si, 8.02.

30: mp 85–88 °C; $[\alpha]^{25}_D$ +31° (*c* 0.232, $CHCl_3$); TLC (2, 0.6); IR (melt) 6.14, 6.90 (C=C), 7.6, 8.7 (SO_2), 7.95 ($SiCH_3$), 9.2 (C—O), 13.7, 14.4 (monosubstituted Ar); NMR ($CDCl_3$) δ 7.9 (m, 2, *o*-Ar), 7.55 (m, 3, *m*- and *p*-Ar), 7.78 (d, *J* = 1, 1, vinyl CH), 3.2 (m, 2, CHOR), 2.1 (m, 2, CH_2), 0.86 (s, 9, *t*-Bu), 0.74 (s, 9, *t*-Bu), 0.0 (m, 12, $SiCH_3$); exact mass, calcd $C_{23}H_{40}O_4Si_2S$ (M − C_4H_9) 411.148, found 411.151.

(1*S*,4*R*)-*cis*-4-(*tert*-Butyldimethylsiloxy)-1-(methanesulfonoxy)-2-(phenylsulfonyl)-2-cyclopentene (D-43). The procedure of Crossland and Servis was used.[25] To a cooled (ice bath), stirred solution of alcohol D-**6b** (7.08 g, 20 mmol) and triethylamine (4.05 g, 5.5 mL, 40 mmol) in 150 mL of methylene chloride in a 250-mL flask was added 1.85 mL (2.75 g, 24 mmol) of methanesulfonyl chloride over 30 min. After stirring for an additional 30 min at 5 °C, the solution was partitioned between 400 mL of 10% sodium bicarbonate and 600 mL of methylene chloride. The aqueous phase was extracted with 100 mL of methylene chloride. The organic fractions were combined, dried ($MgSO_4$), decolarized (activated carbon), and evaporated in vacuo. The crude oil was dissolved in 25 mL of chloroform and added dropwise to 700 mL of hot hexane, which had been seeded with pure D-**43** (obtained by purification of a small amount by column chromatography, SiO_2, 60–200 mesh, 30% ether/hexane). After cooling to −20 °C, the crystals were collected by filtration and dried in vacuo to give 5.81 g of pure D-**43**. Purification of the mother liquor residues by column chromatography (SiO_2, 60–200 mesh, 100 g, 30% ether/hexane) gave an additional 2.33 g (94% total) of pure D-**43**: mp 96–97 °C; $[\alpha]^{25}_D$ +109° (*c* 0.442, $CHCl_3$); TLC (2, 0.7); IR (melt) 6.2, 6.8 (Ar) 7.4, 8.5 (SO_2OR), 7.6, 8.7 (SO_2R), 7.95 ($SiCH_3$), 13.1, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.6 (m, 3, *m*- and *p*-Ar), 6.9 (m, 1, vinyl CH), 5.6 (m, 1, $CHOSO_2$), 4.8 (m, 1, CHOSi), 3.05 (ddd, 1, methylene-β), 2.97 (s, 3, CH_3), 2.03 (ddd, 1, methylene-α), 0.88 (s, 9, *t*-Bu), 0.09 (s, 6, $SiCH_3$); ^{13}C NMR 149.94 (vinyl C), 143.65 (C–SO_2), 140.28 (i), 133.91 (*p*) 129.34 (*m*), 128.23 (*o*), 78.89 (CO-SO_2), 72.80 (COSi), 43.51 (CH_2), 38.53 (SCH_3), 25.76 (*t*-Bu), 18.02 (*t*-Bu), −4.70 ($SiCH_3$); mass spectrum, *m/e* (rel intensity) 375 (<1), 337 (<1), 301 (1).

(1*R*,4*R*)-*trans*-4-(*tert*-Butyldimethylsiloxy)-1-(methanesulfonoxy)-2-(phenylsulfonyl)-2-cyclopentene (D-44). Using the procedure described previously for the synthesis of D-**43**,[25] a solution of 0.55 g (1.55 mmol) of D-**29** and 0.43 mL (3.1 mmol) of triethylamine in 5 mL of methylene chloride was treated with 0.15 mL (1.9 mmol) of methanesulfonyl chloride (added over 15 min) at 0 °C. After another 15 min the mixture was worked up as previously described to give 0.61 g (91%) (recrystallized from hexane) of pure D-**44**: mp 90–92 °C; $[\alpha]^{25}_D$ +63° (*c* 0.513, $CHCl_3$); TLC (2, 0.5); IR (melt) 6.15, 6.89 (C=C), 7.35, 8.50 (SO_2OR), 7.6, 8.65 (SO_2), 7.95 ($SiCH_3$), 9.2 (C—O), 13.7, 14.4 (monosubstituted Ar); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.6 (m, 3, *m*- and *p*-Ar), 6.98 (d, *J* = 1, 1, vinyl CH), 5.80 (d, *J* = 6, 1, $CHOSO_2$), 5.23 (m, 1, CHOSi), 3.01 (s, 3, SO_2CH_3), 2.73 (dd, *J* = 7, 14, 1, CH_2-β), 2.19 (ddd, *J* = 6, 6, 14, 1, CH_2-α), 0.92 (s, 9, *t*-Bu), 0.07 (s, 6, $SiCH_3$); ^{13}C NMR 153.08 (vinyl CH), 143.29 (CS), 139.75 (i), 134.07 (*p*), 129.48 (*m*), 128.41 (*o*), 81.40 ($COSO_2$), 75.03 (COSi), 44.27 (CH_2), 38.69 (SCH_3), 25.77, 18.09 (*t*-Bu), −4.73 ($SiCH_3$); mass spectrum, *m/e* (rel intensity) 249 (50), 222 (100), 218 (20).

(1*S*,4*R*)-*cis*-4-(*tert*-Butyldimethylsiloxy)-1-(dimethylamino)-2-(phenylsulfonyl)-2-cyclopentene (D-47) via [(1*R*,5*R*)-*cis*-5-(*tert*-Butyldimethylsiloxy)-2-(phenylsulfonyl)-2-cyclopentenyl]trimethylammonium Fluorosulfonate (50). To a solution of 0.382 g (1.00 mmol) of (1*R*,2*R*)-*cis*-1-(*tert*-butyldimethylsiloxy)-2-(dimethylamino)-3-(phenylsulfonyl)-3-cyclopentene (L-**46**) in 5 mL of methylene chloride was added 0.090 mL (0.125 g, 1.1 mmol) of methyl fluorosulfonate. After stirring for 2 h, the solvent was removed in vacuo to give salt **50** as an hygroscopic, low-melting solid: TLC (3, 0.2); IR (melt) 7.7, 8.7 (SO_2), 7.9 ($SiCH_2$); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.65 (m, 3, *m*- and *p*-Ar), 6.95 (m, 1, vinyl CH), 4.75 (m, 2, CHOR and CHN^+R_3), 3.4 (s, 9, $N(CH_3)_3$), 2.8 (m, 2, CH_2), 0.9 (s, 9, *t*-Bu), 0.15 (d, 6, $SiCH_3$); ^{13}C NMR 155.42 (vinyl C), 141.46 (vinyl CS), 139.08 (i), 134.71 (*p*), 129.99 (*m*), 128.44 (*o*), 75.70 (COR), 74.21 (CNR_3), 53.63 ($N(CH_3)_3$), 40.62 (CH_2), 25.79, 17.88 (*t*-Bu), −4.87 ($SiCH_3$). Salt **50** was normally not isolated but treated directly with excess gaseous dimethylamine at −20 °C and, after 3 min, rapidly added to a mixture of 20 mL of 10% sodium bicarbonate and 20 mL of methylene chloride. The aqueous layer was extracted with 10 mL of methylene chloride, and the organic fractions were combined, dried ($MgSO_4$), and evaporated in vacuo to give 0.374 g (98%) of D-**47** as an oil. An analytical sample was obtained by crystallization from 10 mL of hexane at −30 °C: mp 67–68 °C; $[\alpha]^{25}_D$ +153° (*c* 0.385, $CHCl_3$); TLC (2, 0.4); IR (melt) 7.6, 8.7 (SO_2), 7.95 ($SiCH_2$), 11.9 (trisubstituted C=C), 13.2 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 7.97 (br d, 2, *o*-Ar), 7.56 (br t, 1, *p*-Ar), 7.47 (br t, 2, *m*-Ar), 6.67 (t, *J* = 1.2, 2.0, 1, vinyl CH), 4.68 (ddd, *J* = 2.0, 3.9, 7.8, 1, CHOR), 3.96 (ddd, *J* = 1.2, 4.3, 8.1, 1, $CHNR_2$), 2.18 (ddd, *J* = 8.0, 8.0, 14.0, 1, CH_2-β), 1.89 (s, 6, NMe_2), 1.73 (ddd, *J* = 3.9, 4.3, 14.0, 1, CH_2-α), 0.83 (s, 9, *t*-Bu), 0.03 (s, 6, $SiCH_3$); ^{13}C NMR 147.57 (CS), 144.63 (vinyl C), 140.19 (i), 133.23 (*p*), 128.92 (*o*), 128.46 (*m*), 73.05 (COR), 67.73 (CNR_2), 40.12 (NMe), 31.41 (CH_2), 25.74, 18.02 (*t*-Bu), −4.76 ($SiCH_3$); exact mass, calcd $C_{19}H_{31}NO_3SiS$ 381.179, found 381.180.

Anal. Calcd for $C_{19}H_{31}NO_3SiS$: C, 59.84; H, 8.14; N, 3.67; S, 8.40; Si, 7.35. Found: C, 59.95; H, 8.12; N, 3.91; S, 8.33; Si, 7.20.

***cis*-1,4-Amino Vinyl Sulfone D-47, (1*R*,2*R*)-*cis*-1-(*tert*-Butyldimethylsiloxy)-2-(dimethylamino)-3-(phenylsulfonyl)-3-cyclopentene (L-46) and (1*R*,2*S*)-*trans*-1-(*tert*-Butyldimethylsiloxy)-2-(dimethylamino)-3-(phenylsulfonyl)-3-cyclopentene (L-48) via Mesylate D-43.** To a 5-L flask fitted with a 100-mL addition funnel and a magnetic stirrer were added 212 g (0.60 mol) of alcohol D-**6b**, 3.5 L of methylene chloride, and 165 mL (121 g, 1.2 mol) of triethylamine. The system was flushed with nitrogen and cooled to 0 °C (ice bath). To this stirred solution was added 56 mL (82.5 g, 0.72 mol) of methanesulfonyl chloride over 1 h. After stirring an additional hour at 0 °C, the solution was treated with 1 L of 10% sodium bicarbonate. The aqueous phase was extracted with 500 mL of methylene chloride. The combined organic fractions were washed with 500 mL of brine, dried ($MgSO_4$), decolorized (activated carbon), and evaporated in vacuo to give mesylate D-**43** as a light yellow oil. This product was dissolved in 2.5 L of methylene chloride, cooled to −20 °C, and treated with approximately 1.22 mol of gaseous dimethylamine (starting material disappearance was monitored by TLC, 20% ether/chloroform) to produce *cis*-1,2-amino vinyl sulfone L-**46**, which was not isolated at this point (isolation gives >95% L-**46** and 1–4% D-**47**). The reaction mixture was allowed to warm to ambient temperature for 24 h and then treated with 2 L of 10% sodium bicarbonate. The aqueous phase was extracted with 500 mL of methylene chloride, and the organic fractions were combined, dried (K_2CO_3), and evaporated in vacuo to give 228 g (99%) of crude D-**47** (ca. 90% pure, impure with L-**46**, L-**48**, and D-**49**). The product was purified by fractional recrystallization from (initially) 2 L of hexane at −25 °C. The 1,2-amino vinyl sulfones L-**46** and L-**48** tended to crystallize out first, even when present in small amounts (ca. 1%), giving small crystalline needles. The desired product D-**47** crystallized in very large prisms (>3-cm crystals were common). *trans1*,4-Amino vinyl sulfone D-**49** would not crystallize from the mixture. The recrystallization process gave 187 g (82%) of pure D-**47**, 11 g (5%) of pure L-**46**, and 4 g (2%) of pure L-**48**.

L-**46**: mp 96–98 °C; $[\alpha]^{25}_D$ −18° (*c* 0.434, $CHCl_3$); TLC (2, 0.5); IR (melt) 7.7, 8.7 (SO_2), 7.95 ($SiCH_3$), 11.9 (trisubstituted C=C), 13.1, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 7.93 (br d, 2, *o*-Ar), 7.57 (br t, 1, *p*-Ar), 7.48 (br t, 2, *m*-Ar), 6.82 (m, *J* = 2.3, 3.3, 1, vinyl CH), 4.50 (ddd, *J* = 7.5, 7.5, 7.8, 1, CHOR), 3.92 (dd, *J* = 3.3, 7.8 1, $CHNR_2$), 2.71 (ddd, *J* = 3.3, 7.8, 18.0, 1, CH_2-β), 2.37 (dddd, *J* = 2.3, 2.3, 7.5, 18.0, 1, CH_2-α), 2.17 (s, 6, NCH_3), 0.87 (s, 9, *t*-Bu), 0.06 (d, 6, $SiCH_3$); ^{13}C NMR 143.71 (C5, 142.00 (vinyl CH), 140.92 (i), 132.91 (*p*), 128.51 (*o*), 128.36 (*m*), 74.75 (CHOR), 67.99 (CNR_2), 41.27 (CH_2), 40.33 (NMe_2), 25.87, 17.93 (*t*-Bu), −4.95 ($SiCH_3$); exact mass, calcd $C_{19}H_{31}NO_3SiS$ 381.179, found 381.177.

Anal. Calcd for $C_{19}H_{31}NO_3SiS$: C, 59.84; H, 8.14; N, 3.67; S, 8.40; Si, 7.35. Found: C, 59.76; H, 7.89; N, 3.62; S, 8.37; Si, 7.11.

L-**48**: mp 74–75 °C; $[\alpha]^{25}_D$ −38° (*c* 0.384, $CHCl_3$); TLC (2, 0.4); IR (melt) 6.20 (C=C) 7.7, 8.7 (SO_2), 7.95 ($SiCH_3$), 11.9 (trisub-

stituted C=C), 13.1, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 7.93 (br d, 2, *o*-Ar), 7.55 (br t, 1, *p*-Ar), 7.46 (br t, 2, *m*-Ar), 6.83 (br s, 1, vinyl CH)$_2$ 4.38 (ddd, J = 2.0, 2.1, 6.3, 1, CHOR), 3.77 (br s, 1, $CHNR_2$), 2.67 (dddd, J = 2.1, 2.1, 6.3, 18.8, 1, CH_2-β), 2.32 (ddd, J = 2.1, 2.1, 18.8, 1, CH_2-α), 1.54 (s, 6, NCH_3), 0.79 (s, 9, *t*-Bu), −0.005 (s, 6, $SiCH_3$); ^{13}C NMR 143.78 (vinyl CH), 143.53 (CS), 140.28 (i), 133.09 (*p*), 128.51 (*o*, *m*), 78.86 (CHOR), 70.10 ($CHNR_2$), 42.38 (CH_2), 40.43 (NMe_2), 25.65, 17.72 (*t*-Bu), −4.45, −4.78 ($SiCH_3$); exact mass, calcd $C_{19}H_{31}NO_3SiS$ 381.179, found 381.180.

Anal. Calcd for $C_{19}H_{31}NO_3SiS$: C, 59.84; H, 8.14; N, 3.67; S, 8.40; Si, 7.35. Found: C, 59.56; H, 8.35; N, 3.92; S, 8.25; Si, 7.10.

(1*R*,4*R*)-*trans*-4-(*tert*-Butyldimethylsiloxy)-1-(dimethylamino)-2-(phenylsulfonyl)-2-cyclopentene (D-49). With the procedure described previously for the preparation of D-47 from L-46 using methyl fluorosulfonate, D-49 was prepared in 98% yield from L-48: mp 68–69 °C; $[\alpha]^{25}_D$ +36° (*c* 0.349, $CHCl_3$); TLC (2, 0.4); IR (melt) 7.6, 8.7 (SO_2), 7.95 ($SiCH_3$), 11.9 (trisubstituted C=C), 13.2, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 7.99 (br d, 2, *o*-Ar), 7.55 (br t, 1, *p*-Ar), 7.46 (br t, 2 *m*-Ar), 6.62 (br s, 1, vinyl CH), 4.87 (br dd, J = 5.6, 7.5, 1, CHOR), 4.16 (br d, J = 8.4, 1, $CHNR_2$), 2.25 (ddd, J = 1.5, 7.5, 14.1 1, CH_2-β), 1.88 (s, 6, NCH_3), 1.57 (ddd, J = 5.6, 8.4, 14.1, 1, CH_2-α), 0.83 (s, 9, *t*-Bu), 0.01 (s, 6, $SiCH_2$); ^{13}C NMR 146.65 (vinyl CH), 146.19 (CS), 139.89 (i), 133.33 (*p*), 128.84 (*o*), 128.56 (*m*), 75.49 (COR), 68.91 (CNR_2), 39.98 (NCH_3), 32.72 (CH_2), 25.76, 18.08 (*t*-Bu), −4.73 ($SiCH_3$); exact mass, calcd $C_{19}H_{31}NO_3SiS$ 381.179, found 381.177.

Anal. Calcd for $C_{19}H_{31}NO_3SiS$: C, 59.84, H, 8.14; N, 3.67; S, 8.40; Si, 7.35. Found: C, 60.01; H, 8.04; N, 3.86; S, 8.59; Si, 7.10.

(1*S*,2*S*,3*S*,4*R*)-*cis*-4-(*tert*-Butyldimethylsiloxy)-*trans*-3-[(*E*,*S*)-3′-(*tert*-butyldimethylsiloxy)-1′-octenyl]-1-(dimethylamino)-*trans*-2-(phenylsulfonyl)cyclopentane (59) and (1*S*,2*R*,3*S*,4*R*)-*cis*-4-(*tert*-Butyldimethylsiloxy)-*trans*-3-[(*E*,*S*)-3′-(*tert*-butyldimethylsiloxy)-1′-octenyl]-1-(dimethylamino)-*cis*-2-(phenylsulfonyl)cyclopentane (60). To a dry solution of 2.0 mL of 20% THF/hexane under nitrogen at −78 °C was added 0.184 g (0.50 mmol) of vinyl iodide L-35. To this solution was added 1.00 mmol of *tert*-butyllithium in pentane (1.82 M, 0.55 mL) over 3 min and then 3 mL of THF. A bright yellow solution indicated excess *tert*-butyllithium and was removed by addition of one or two drops of vinyl iodide L-35 (*tert*-butyllithium and THF form a bright yellow complex at −78 °C, which was used as an indicator at this point; however, excess THF was avoided during the bulk of the metalation reaction because it lowered the yield substantially). To this mixture was added 0.172 g (0.45 mmol) of vinyl sulfone D-47 in 2 mL of THF. The mixture was warmed to −55 °C and quenched with 10 mL of water with vigorous stirring. This mixture was partitioned between 20 mL of hexane and 20 mL of water. The aqueous phase was extracted with 10 mL of hexane, and the hexane fractions were combined, dried ($MgSO_4$), and evaporated in vacuo. The crude oil was purified by column chromatography (SiO_2, 230–400 mesh, 50 g, 10% ether/chloroform) to give 0.288 g (92%) of **59** (eluted first) and 0.015 g (5%) of **60** as oils.

59: TLC (2, 0.4); IR (neat) 7.7, 8.7 (SO_2), 7.95 ($SiCH_3$), 9.2 (C—O), 10.3 (trans C=C), 13.5, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 7.9 (m, 2, *o*-Ar), 7.55 (m, 3, *m*- and *p*-Ar), 5.63 (dd, J = 8, 16, 1, 14-CH), 5.41 (dd, J = 6, 16, 1, 13-CH), 3.8–4.2 (m, 4, 8, 9, 11, 15-CH), 2.7 (m, 1, 12-CH), 2.2 (m, 1, 10-CH_2-β), 2.15 (s, 6, NCH_3), 1.2–1.9 (m, 9, 16, 17, 18, 19-CH_2, and 10-CH_2-α), 0.9 (2 s, 21, *t*-Bu, and 20-CH_3), 0.03 (m, 12, $SiCH_3$); ^{13}C NMR (141.20 (i), 137.92 (C14), 132.91 (*p*), 128.42 (*o*), 128.30 (*m*), 124.82 (C13), 76.21 (C11), 73.49 (C15), 66.21 (C8)8 63.80 (C9)8 53.48 (C12), 40.32 (NCH_3), 38.18 (C16), 31.88 (C18), 31.42 (C10), 25.92, 25.79 (*t*-Bu), 24.83 (C17), 22.64 (C19), 18.20, 17.95 (*t*-Bu), 14.05 (C20), −4.18, −4.63, −4.79, −4.87 ($SiCH_3$); exact mass, calcd $C_{33}H_{61}NO_4Si_2S$ 623.386, found 623.383. See experimental data of **70** for characterization data for **60**.

(1*S*,2*R*,3*S*,4*R*)-*cis*-4-(*tert*-Butyldimethylsiloxy)-*trans*-3-[(*E*,*S*)-3′-(*tert*-butyldimethylsiloxy)-1′-octenyl]-1-(dimethylamino)-*cis*-2-(phenylsulfonyl)cyclopentane (60), Methyl (5*Z*,13*E*,8*R*,9*S*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(dimethylamino)-8-(phenylsulfonyl)-5,13-prostadienoate (70), and Methyl (5*Z*,13*E*,8*S*,9*S*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(dimethylamino)-8-(phenylsulfonyl)-5,13-prostadienoate (71). To a dry solution of 60 mL of 20% THF/hexane under nitrogen at −78 °C was added 30.0 g (82 mmol) of vinyl iodide L-35. To this solution was added 160 mmol of *tert*-butyllithium in pentane (2.0 M, 80 mL) over 15 min. An additional 270 mL of THF was added over 10 min, and the resulting mixture was titrated with additional *tert*-butyllithium (~1 mL, 2.0 M, 2 mmol) (*tert*-butyllithium and THF form a bright yellow complex at −78 °C, which was used as an indicator at this point; however, excess THF was avoided during the bulk of the metalation reaction because it lowered the yield substantially). The yellow color caused by excess *tert*-butyllithium was removed by addition of one or two drops of vinyl iodide L-35. To this solution was added a cooled (−50 °C) mixture of 28.6 g (75 mmol) of vinyl sulfone D-47, ca. 0.02 g of sodium hydride (to remove any water that may have been present in crystalline D-47), and 180 mL of THF. The resulting mixture was warmed to −40 °C, and 22 g (82 mmol) of allyl iodide **5b** (prepared immediately before use as described previously) in 150 mL of THF was added rapidly. The cold bath was removed and the mixture allowed to warm to 0 °C (ca. 1 h). The mixture was then partitioned between 1 L of hexane and 1 L of 10% sodium bicarbonate and the aqueous phase extracted with 500 mL of hexane. The combined hexane fractions were dried (Na_2SO_4) and evaporated (15 mm) to give a light brown oil. The crude product was immediately purified by plug filtration (Al_2O_3, 80–200 mesh, 1.2 kg, 5–15% ethyl acetate/hexane gradient) to remove nonpolar impurities related to the side-chain reagents L-35 and **5b** and gave partially separated **59**, **71**, **60**, and **70** (in order of elution). Crystallization of the fractions containing **70** from aqueous methanol at −20 °C gave 34.1 g of pure **70**. Evaporation of the mother liquors, plug filtration (Al_2O_3, 80–200 mesh, 300 g, 10–15% ethyl acetate/hexane gradient), and another crystallization from aqueous methanol gave a second crop of 4.1 g (67% overall) of **70**. Purification of the fractions containing **59**, **71**, and **60** and the mother liquors from crystallization by column chromatography (SiO_2, 230–400 mesh, 20–30% ether/hexane) gave 3.7 g (8%) of **59**, 2.3 g (5%) of **60**, and 1.1 g (2%) of **71** as oils.

60: TLC (2, 0.5); IR (neat) 7.7, 8.7 (SO_2), 7.95 ($SiCH_3$), 9.2 (C—O), 10.3 (trans C=C), 13.5, 14.5 (monosubstituted Ar); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.55 (m, 3, *m*- and *p*-Ar), 5.42 (dd, J = 7, 16, 1, 14-CH), 5.15 (dd, J = 5, 16, 1, 13-CH), 3.93 (m, 1, 15-CH), 3.89 (m, 1, 11-CH), 3.37 (m, 1, 8-CH), 3.09 (m, 1, 9-CH), 2.68 (m, 1, 10 CH_2-β), 2.17 (s, 6, NCH_3), 1.9–2.2 (m, 2, 12-CH and 10CH_2-α), 1.1–1.6 (m, 8, 16, 17, 18, 19-CH_2), 0.9 (2 s, 21, *t*-Bu, and 20-CH_3), 0.01 (s, 12, $SiCH_3$); ^{13}C NMR 140.86 (i), 135.10 (C14), 132.84 (*p*), 129.48 (*m*), 129.31 (C13), 128.37 (*o*), 75.59 (C11), 72.49 (C15), 70.35 (C8), 51.50 (C12), 44.62 (NCH_3), 38.26 (C16), 38.09 (C10), 31.80 (C18), 25.91, 25.79 (*t*-Bu), 24.86 (C17), 22.60 (C19), 18.20, 17.87 (*t*-Bu), 14.03 (C20), −4.19, −4.36, −4.66 ($SiCH_3$); exact mass, calcd $C_{33}H_{61}NO_4Si_2S$ 623.386, found, 623.385.

70: mp 60–62 °C; $[\alpha]^{25}_D$ −20.0° (*c* 0.429, $CHCl_3$); TLC (2, 0.5); IR (melt) 5.74 (CO_2R), 7.7–8.7 (SO_2), 8.00 ($SiCH_3$), 9.2 (C—O), 10.3 (trans C=C), 13.2, 14.4 (monosubstituted Ar), 13.9 (cis C=C); NMR $CDCl_3$ δ 8.0 (m, 2, *o*-Ar), 7.55 (m, 3, *m*- and *p*-Ar), 5.1–5.6 (m, 4, olefins), 3.95 (m, 1, 15-CH), 3.79 (m, 1, 11-CH), 3.67 (s, 3, OCH_3), 2.9–3.5 (m, 3-, 9-, 12-CH and 10CH_2-β), 1.8–2.6 (m, 7-, 2-, 7-, 4-CH_2, and 10-CH_2-α), 2.17 (s, 6, NCH_3), 1.7 (m, 2, 3CH_2), 1.1–1.5 (m, 8-, 16-, 17-, 18-, 19-CH_2) 0.87 (2 s, 21, *t*-Bu, 20-CH_3), 0.00 (m, 12, $SiCH_3$); ^{13}C NMR 173.62 (C1), 139.82 (i), 138.92 (C14), 132.71 (*p*), 132.08 (C13), 131.21 (*m*), 127.92 (*o*), 125.42 (C5), 124.36 (C6), 76.46 (C8), 74.27 (C11), 72.40 (C15), 66.68 (C9), 54.20 (C12), 51.46 (OCH_3), 44.85 (NCH_3), 38.47 (C16), 37.53 (C10), 33.46 (C2), 31.93 (C18), 30.22 (C7), 26.96 (C4), 25.91 (*t*-Bu), 24.87 (C17), 24.45 (C3), 22.61 (C19), 18.12, 17.95 (*t*-Bu), 14.06 (C20), −4.15, −4.50, −4.76 ($SiCH_3$); exact mass, calcd $C_{41}H_{73}NO_6Si_2S$ 763.470, found 763.472.

Anal. Calcd for $C_{41}H_{73}NO_6Si_2S$: C, 64.48; H, 9.57; N, 1.83; S, 4.19; Si, 7.34. Found: C, 64.63; H, 9.41; N, 1.81; S, 4.25; Si, 7.11.

71: TLC (2, 0.6); IR (neat) 5.74 (CO_2R), 7.7, 8.7 (SO_2), 7.95 ($SiCH_3$), 9.2 (C—O), 10.25 (trans C=C), 13.2, 14.4 (monosubstituted Ar), 13.7 (cis C=C); NMR ($CDCl_3$) δ 7.9 (m, 2, *o*-Ar), 7.55 (m, 3, *m*- and *p*-Ar), 5.3–6.1 (m, 4, olefin CH), 4.31 (m, 1, 11-CH), 4.17 (m, 1, 15-CH), 3.67 (s, 3, OCH_3), 3.6 (m, 1, 9-CH), 2.7 (m, 3, 7-CH_2 and 10-CH_2-β), 1.9–2.5 (m, 6, 2, 4, 10-CH_2-α and 9, 12-CH), 1.7 (m, 2, 3CH_2), 1.1–1.5 (m, 8, 16, 17, 18, 19-CH_2), 0.86 (2 s, 21, *t*-Bu, 20-CH_3), 0.02 (m, 12, $SiCH_3$); ^{13}C NMR 173.76 (C1),

139.11 (i), 138.10 (C14), 133.20 (*p*), 130.51 (*m*), 130.19 (C13), 128.29 (*o*), 126.42 (C5), 126.09 (C6), 79.43 (C8), 74.60 (C11), 72.88 (C15), 66.00 (C9), 59.36 (C12), 51.33 (OCH_3), 44.15 (NCH_3), 38.40 (C16), 33.49 (C2), 33.22 (C10), 32.00 (C18), 30.09 (C7), 26.73 (C4), 25.97 (*t*-Bu), 24.85 (C17), 24.57 (C3), 22.66 (C19), 18.16, 18.02 (*t*-Bu), 14.07 (C20), -4.16, -4.34, -4.54, -4.66 ($SiCH_3$); exact mass, calcd $C_{41}H_{73}NO_6Si_2S$ (M - C_4H_9) 706.400, found 706.396.

Methyl (5*Z*,13*E*,8*R*,9*S*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-[[carbo(2′,2′,2′-trichloroethoxy)]-methylamino]-8-(phenylsulfonyl)-5,13-prostadienoate (108). To 37.3 g (48.8 mmol) of **70** was added 13.8 mL (21.2 g, 100 mmol) of 2,2,2-trichloroethyl chloroformate,[43g] 2 g (24 mmol) of sodium bicarbonate, and 5 mL of methylene chloride. This mixture was stirred at ambient temperature (ca. 30 °C) for 72 h and 20 mL of hexane added. After stirring for another 30 min, the mixture was directly purified by plug filtration (SiO_2, 60–200 mesh, 1 kg, 15% ether/hexane) to give 43.1 g (96%) of **108** as an oil: TLC (2, 0.6); IR (neat) 5.80 (C=O), 7.6 (N—C), 7.7, 8.7 (SO_2), 7.99 ($SiCH_3$), 9.2 (C—O), 10.23 (trans C=C), 13.2, 14.4 (monosubstituted Ar) 13.8 (cis C=C); NMR ($CDCl_3$) δ 7.9 (m, 2, *o*-Ar), 7.6 (m, 3, m- and *p*-Ar), 5.5, 5.15 (m, 4, olefin CH), 4.5–5.0 (m, 3, 9-CH and Cl_3CCH_2), 3.2–4.2 (m, 4, 11, 12, 15-CH and 10-CH_2-β), 3.70 (s, 3, OCH_3), 3.25 (s, 3, NCH_3), 2.0–2.5 (m, 7, 2-, 4-, 7-CH_2 and 10-CH_2-α), 1.75 (m, 2, 3-CH_2), 1.2 (m, 8, 16, 17, 18, 19-CH_2), 0.88, 0.82 (2 s, 21, *t*-Bu, and 20-CH_3), 0.07, 0.03, -0.07, -0.19 (4 s, 12, $SiCH_3$); ^{13}C NMR 174.00 (C1), 155.71 (NCO_2), 139.55 (C14), 138.35 (i), 133.46 (C13, *p*), 130.79 (*m*), 128.59 (*o*), 124.02 (C5), 122.80 (C6), 95.66 (CCl_3), 75.50 (OCH_2), 74.12 (C8,11), 71.83 (C15), 58.48 (C9), 55.12 (C12), 51.42 (OCH_3), 38.13 (C16), 37.59 (C10), 33.55 (C2), 32.12 (NCH_3), 31.85 (C18), 30.62 (C7), 27.06 (C4), 25.85 (*t*-Bu), 24.87 (C17), 24.43 (C3), 22.57 (C19), 17.99 (*t*-Bu), 14.05 (C20), -4.55, -4.81 ($SiCH_3$); exact mass, calcd $C_{43}H_{72}NO_8Si_2SCl_3$ (M - $C_6H_6O_2S$ and $C_6H_{16}OSi$) 649.253, found 649.252.

Methyl (5*Z*,13*E*,8*R*,9*S*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(methylamino)-8-(phenylsulfonyl)-5,13-prostadienoate (110). To a stirred solution of 39.9 g (43.2 mmol) of trichloroethyl carbamate **108** in 350 mL of dry THF was added 40 g (600 mmol) of powdered zinc activated by washing with 200 mL of 5% hydrochloric acid, 200 mL of water, 200 mL of ethanol, and finally 200 mL of ether.[44] The mixture was heated to reflux for 3 h, cooled, and filtered. The zinc was washed with 50 mL of ether and the filtrate evaporated. The residue was partitioned between 400 mL of 1% hydrochloric acid and 400 mL of hexane. The aqueous phase was extracted with 100 mL of ether, and the combined organic fractions were washed with 100 mL of brine, 100 mL of 10% sodium bicarbonate, and another 100 mL of brine. The organic phase was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by plug filteration (SiO_2, 60–200 mesh, 500 g, 15–50% ether/hexane gradient) (excess 2,2,2-trichloroethyl chloroformate was eluted first) followed by addition to 300 mL of methanol and cooling to 0 °C. To this cold solution was added water to the cloud point, and the mixture was cooled to 0 °C for 12 h and then -20 °C for 24 h to give 20.4 g (63%) of crystalline **110**. A second crop (3.2 g, 10%) was obtained similarly. Purification of the mother liquor residues by column chromatography (SiO_2, 60–200 mesh, 200 g, 45% ether/hexane) gave 2.9 g (9%, 92% overall) of pure **110**: mp 50–52 °C; $[\alpha]^{25}_D$ -6.2° (*c* 0.431, $CHCl_3$), TLC (2, 0.2); IR (melt) 5.74 (COOR), 7.7, 8.7 (SO_2), 7.99 ($SiCH_3$), 9.2 (C—O) 10.22 (trans C=C), 13.2, 14.4 (monosubstituted Ar), 13.78 (cis C=C); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.5, 7.6 (m, 3, *m*- and *p*-Ar), 5.5, 5.0 (m, 4, olefin CH), 3.7 (m, 2, 11-, and 15-CH), 3.67 (s, 3, OCH_3), 2.8–3.3 (m, 3-, 9-, 12-CH and 10-CH_2-β), 2.48 (s, 3, NCH_3), 1.5–2.5 (m, 9, 2, 3, 4, 7-CH_2 and 10-CH_2-α), 1.2 (m, 8, 16, 17, 18, 19-CH_2) 0.82 (br s, 21, *t*-Bu, 20-CH_3), 0.01, -0.05, -0.11 (3 s, 12, $SiCH_3$); ^{13}C NMR 173.70 (C1), 138.71 (C14), 138.32 (i), 133.25 (*p*), 132.94 (C13), 130.99 (*m*), 128.54 (*o*), 124.96 (C5), 123.76 (C6), 75.32 (C8), 73.93 (C11), 72.29 (C15), 64.23 (C9), 54.96 (C12), 51.47 (OCH_3), 40.52 (C10), 38.37 (C16), 36.13 (NCH_3), 33.48 (C2), 31.87 (C18), 30.89 (C7), 26.81 (C4), 25.87 (*t*-Bu), 24.89 (C17), 24.68 (C3), 22.63 (C19), 18.10, 17.96 (*t*-Bu), 14.06 (C20), -4.19, -4.49, -4.75 ($SiCH_3$); exact mass, calcd $C_{40}H_{71}NO_6Si_2S$ 749.454 found 749.455.

Anal. Calcd for $C_{40}H_{71}NO_6Si_2S$: C, 64.08; H, 9.48; N, 1.87; S, 4.27; Si, 7.48. Found: C, 64.15; H, 9.75; N, 1.73; S, 4.19; Si, 7.20.

Methyl (5*Z*,13*E*,8*R*,9*S*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(methylhydroxyamino)-8-(phenylsulfonyl)-5,13-prostadienoate (114) and Methyl (5*Z*,13*E*,8*R*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(*anti*-oximino)-8-(phenylsulfonyl)-5,13-prostadienoate (115). To a stirred solution of 0.225 g (0.30 mol) of **110** in 10 mL of methanol, 3 mL of acetonitrile, and 1 mL (9 mmol) of 30% hydrogen peroxide at 0 °C (ice bath) was added a solution of 0.4 g (3 mmol) of potassium carbonate in 1 mL of water. The mixture was stirred for 5 h at 0 °C and partitioned between 100 mL of 5% sodium bicarbonate and 100 mL of ether. The aqueous phase was extracted with 20 mL of ether, and the combined ether fractions were dried ($MgSO_4$) and evaporated in vacuo. The resulting oil was purified by column chromatography (SiO_2, 60–200 mesh, 50 g, 20–35% ether/hexane gradient) to give (in order of elution) 0.131 g (57%) of hydroxylamine **114** 0.018 g (8%) of oxime **115**, and 0.063 g (28%) of starting material **110** all as oils.

114: TLC (2, 0.6); IR (neat) 2.95 (OH), 5.73 (COOR), 7.7, 8.8 (SO_2), 7.97 ($SiCH_3$), 9.27 (C—O), 10.24 (trans C=C), 13.1, 14.4 (monosubstituted Ar), 13.80 (cis C=C); NMR ($CDCl_3$) δ 8.0 (m, 2, *o*-Ar), 7.6 (m, 3, *m*- and *p*-Ar), 7.01 (s, 1, OH), 5.1–5.8 (m, 4, olefin CH), 3.75 (m, 2, 11- and 15-CH), 3.69 (s, 3, OCH_3), 3.1–3.5 (m, 3, 9, 12-CH and 10-CH_2-β), 2.60 (s, 3, NCH_3), 1.5–2.5 (m, 9, 2-, 3-, 4-, 7-CH_2 and 10-CH_2-α), 1.2 (m, 8, 16-, 17-, 18-, 19-CH_2), 0.82 (br s, 21, *t*-Bu, and 20-CH_3), 0.00, -0.04, -0.12 (3 s, 12, $SiCH_3$); ^{13}C NMR 174.23 (C1), 139.16 (C14), 137.96 (i), 134.03 (C13), 133.60 (*p*), 131.51 (*m*), 128.57 (*o*), 124.28 (C5), 123.35 (C6), 75.99 (C8), 74.10 (C11), 72.17 (C15), 70.55 (C9), 55.03 (C12), 51.54 (OCH_3), 46.41 (NCH_3), 38.31 (C10, 16), 33.56 (C2), 31.84 (C18), 29.92 (C7), 26.89 (C4), 25.82 (*t*-Bu), 24.88 (C17), 24.47 (C3), 22.60 (C19), 18.06, 17.89 (*t*-Bu), 14.03 (C20), -4.23, -4.56, -4.81 ($SiCH_3$); mass spectrum, *m/e* (rel intensity) 750 (2), 749 (2), 748 (3), 708 (5), 633 (3), 522 (7), 521 (15), 445 (100).

115: TLC (2, 0.3); IR (neat) 3.01 (OH), 5.76 (COOR), 7.7, 8.7 (SO_2), 7.98 ($SiCH_3$), 9.21 (C—O), 10.27 (trans C=C), 13.2, 14.4 (monosubstituted Ar), 13.9 (cis C=C); NMR ($CDCl_3$) δ 8.83 (s, 1, OH), 7.87 (d, *J* = 7, 2 *o*-Ar), 7.63 (t, *J* = 7, 1, *p*-Ar), 7.54 (t, *J* = 7, 2, *m*-Ar), 5.72 (dd, *J* = 6, 15, 1, 14CH), 5.56 (dd, *J* = 8, 15, 1, 13CH), 5.39 (m, 1, 5CH), 5.17 (m, 1, 6CH), 4.06 (q, *J* = 3, 1, 15CH), 3.92 (q, *J* = 6, 1, 11CH), 3.67 (s, 3, OCH_3), 3.42 (t, *J* = 8, 1, 12CH), 3.08 (dd, *J* = 6, 18, 1, 10CH_2-β), 3.02 (dd, *J* = 10, 15, 1, 7CH), 2.49 (dd, *J* = 2, 15, 1, 7CH), 2.30, 2.23 (m, 2, 2CH_2), 2.04, 1.82 (m, 2, 4CH_2), 1.86 (dd, *J* = 10, 15, 1, 10CH_2-α), 1.6 (m, 2, 3CH_2), 1.43 (m, 2, 16CH_2), 1.25 (m, 6, 17, 18, 19CH_2) 0.89, 0.82 (2 s, 21, *t*-Bu, and 20-CH_3), 0.05, 0.03, 0.01, -0.01 (4 s, 12, $SiCH_3$); ^{13}C NMR 174.59 (C1), 156.47 (C9), 140.00 (C14), 136.01 (i), 133.72 (*p*), 133.47 (C13), 131.27 (m), 128.63 (*o*), 123.29 (C5), 123.04 (C6), 74.78 (C8), 73.41 (C11), 72.67 (C15), 53.14 (C12), 51.72 (OCH_3), 38.49 (C16), 36.19 (C10), 33.58 (C2), 31.96 (C18), 28.47 (C7), 26.94 (C4), 25.91, 25.77 (*t*-Bu), 24.95 (C17), 24.47 (C3), 22.67 (C19), 18.18, 17.88 (*t*-Bu), 14.09 (C20), -4.34, -4.56, -4.56, -4.69, -4.98 ($SiCH_3$); mass spectrum, *m/e* (rel intensity) 691 (20), 590 (100), 550 (70), 531 (80).

Oxime 115 and Methyl (5*Z*,13*E*,8*R*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(*E*-methylnitrono)-8-(phenylsulfonyl)-5,13-prostadienoate (116). To a stirred solution of 6.00 g (8.0 mmol) of amine **110** in 350 mL of methanol were added 0.2 g (0.6 mmol) of sodium tungstate dihydrate in 5 mL of water and 13 g (120 mmol) of anhydrous sodium carbonate. To this mixture was added slowly 40 mL (80 mmol) of 40% peracetic acid over 10 h at 25 °C. The mixture was partitioned between 700 mL of saturated ammonium chloride and 700 mL of ethyl acetate. The aqueous phase was extracted with 300 mL of ethyl acetate, and the organic fractions were combined, washed with 100 mL of saturated sodium thiosulfate, dried (Na_2SO_4), and evaporated in vacuo to give a light brown oil. The crude product was purified by column chromatography (SiO_2, 60–200 mesh, 500 g, 20% ether/hexane to ether and then ethyl acetate) to give (in order of elution) 4.1 g (68%) of pure oxime **115** and 1.1 g (18%) of nitrone mixture, which was purified further by column chromatography (SiO_2, 60–200 mesh, 100 g, 20–60% ethyl acetate/methylene chloride gradient) to give 0.48 g (8%) of pure nitrone **116**: TLC (2, 0.1); IR (neat) 5.73 (COOR), 6.23 (nitrone), 7.7, 8.7 (SO_2), 7.96 ($SiCH_3$), 9.2 (C—O), 10.21 (trans C=C), 13.2, 14.5 (monosubstituted Ar) 13.9 (cis C=C); NMR ($CDCl_3$) δ 7.93 (d, *J* = 7.3, 2, *o*-Ar) 7.56 (t, *J* = 7.3, 1, *p*-Ar), 7.46 (t, *J* = 7.3, 2, *m*-Ar), 5.74 (dd, *J* = 4.7, 15.3, 1, 14-CH), 5.54 (dd, *J* = 7.9, 15.3, 1, 13-CH), 5.37 (m, 1, 5-CH), 5.05 (m, 1, 6-CH), 4.08 (q, *J* = 4.8, 1, 15-CH),

3.99 (dd, J = 7.3, 9.0, 1, 11-CH), 3.66 (m, J = 10, 1, 7-CH_2), 3.60 (t, J = 8.7, 1, 12-CH), 3.60 (s, 3, OCH_3), 3.50 (s, 3, NCH_3), 2.73 (dd, J = 7.3, 16.5, 1, 10CH_2-β), 2.47 (dd, J = 9.5, 16.5, 1, 10CH_2-α) 2.32 (dm, J = 11, 1, 7-CH_2), 2.17 (m, 2, 2-CH_2), 1.95 (m, 2, 4-CH_2), 1.53 (m, 2, 3-CH_2), 1.43 (m, 2, 16-CH_2), 1.25 (m, 6, 17-, 18-, 19-CH_2), 0.862, 0.835 (2 s, 21, t-Bu, and 20-CH_3), 0.22, 0.20 (2 s, 12, $SiCH_3$); ^{13}C NMR 173.82 (C1), 141.40 (C9), 140.54 (C14), 140.09 (i), 133.73 (C13), 133.41 (p), 130.14 (m), 128.14 (o), 123.50 (C5), 123.30 (C6), 78.76 (C8), 72.61 (C11,15), 54.59 (C12), 51.32 (OCH_3), 51.07 (NCH_3), 40.95 (C10), 38.57 (C16), 33.42 (C2), 31.98 (C18), 26.70 (C4), 25.91, 25.78 (t-Bu), 25.02 (C17), 24.74 (C3), 22.65 (C19), 18.16, 17.89 (t-Bu), 14.06 (C20), −4.41, −4.67 ($SiCH_3$).

(5*Z*,13*E*,8*R*,9*S*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(methylamino)-8-(phenylsulfonyl)-5,13-prostadienoic Acid (120). Following the procedure described previously for the synthesis of **92**, 27.4 g (36.6 mmol) of **110** in 350 mL of methanol was treated with 9 mL of 10% sodium hydroxide and 3.5 g of solid sodium hydroxide for 48 h. Workup as previously described gave 27.2 g (101%) of **120** as a foam: TLC [2 and 3 (1:1), 0.3]; IR (neat) 5.83 (C=O), 7.4 (C—N), 7.7, 8.8 (SO_2), 7.98 ($SiCH_3$), 9.2 (C—O) 10.24, (trans C=C) 13.2, 14.5 (monosubstituted Ar) 13.8 (cis C=C); NMR ($CDCl_3$) δ 8.0 (m, 2, o-Ar), 7.6 (m, 3, m- and p-Ar), 7.15 (br s, 2, NH, CO_2H), 4.8–5.7 (m, 4, olefin CH), 3.6–3.9 (m, 2, 11 and 15 CH), 3.0–3.4 (m, 3, 9, 12 CH, and 10CH_2-β), 2.53 (s, 3, NCH_3), 1.5–2.5 (m, 9, 2, 3, 4, 7 CH_2 and 10CH_2-α), 1.2 (m, 8, 16, 17, 18, 19 CH_2), 0.83 (br s, 21, t-Bu, and 20-CH_3), 0.05, 0.03, −0.06, −0.12 (4 s, 12, $SiCH_3$); ^{13}C NMR 179.22 (C1), 138.68 (C14), 138.06 (i), 134.31 (C13), 133.52 (p), 130.96 (m), 128.73 (o), 123.95 (C5), 123.32 (C6), 74.91 (C8), 74.07 (C11), 72.08 (C15), 63.33 (C9), 54.99 (C12), 39.9 (C10), 38.30 (C16), 35.67 (NCH_3), 34.90 (C2), 31.83 (C18), 30.2 (C7), 26.93 (C4), 25.87 (t-Bu), 24.87 (C3, 17), 22.59 (C19), 18.02 (t-Bu), 14.04 (C20), −4.19, −4.51, −4.78 ($SiCH_3$); mass spectrum, m/e (rel intensity) 735 (1), 707 (40), 706 (40), 678 (3), 585 (5), 352 (100).

(5*Z*,13*E*,8*R*,11*R*,12*S*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(*anti*-oximino)-8-(phenylsulfonyl)-5,13-prostadienoic Acid (121). Following the procedure previously described for the synthesis of oxime **115**, 26.9 g (36.6 mmol) of acid **120**, 60 g (570 mmol) of anhydrous sodium carbonate, and 1 g (3 mmol) of sodium tungstate dihydrate in 10 mL of water were added to 800 mL of methanol. To this stirred mixture was added slowly 110 mL (220 mmol) of 40% peracetic acid over 10 h at 25 °C. The mixture was worked up as previously described, and the crude product was purified by column chromatography (SiO_2, 60–200 mesh, 1 kg, 50% ethyl acetate/methylene chloride to 2% methanol/48% ethyl acetate/methylene chloride) to give 24.0 g (89%) of pure oxime **121** as an oil: TLC [2 and 3 (1:1), 0.3]; IR (neat) 3.08 (OH), 5.85 (COOH), 7.7, 8.7 (SO_2), 7.97 ($SiCH_3$), 9.21 (C—O), 10.29 (trans C=C), 13.2, 14.5 (monosubstituted Ar), 13.8 (cis C=C); NMR ($CDCl_3$) δ 8.6 (br m, 2, NOH and COOH), 7.9 (m, 2, o-Ar), 7.6 (m, 3, m- and p-Ar), 5.0–5.7 (m, 4, olefin CH), 4.0 (m, 2, 11 and 15 CH), 2.9–3.4 (m, 3, 7, and 12 CH, 10CH_2-β), 2.6 (m, 1, 7CH), 2.2–2.5 (m, 2, 2CH_2), 1.7–2.1 (m, 3, 4CH_2 and 10CH_2-α), 1.6 (m, 2, 3CH_2), 1.3 (m, 8, 16, 17, 18, 19 CH_2), 0.87, 0.82 (2 s, 21, t-Bu, and 20-CH_3), 0.0, −0.02, −0.03 (3 s, 12, $SiCH_3$); ^{13}C NMR 179.98 (C1), 156.76 (C9), 139.96 (C14), 135.85 (i), 134.54 (C13), 133.91 (p), 131.14 (m), 128.85 (o), 122.76 (C6), 121.92 (C5), 74.93 (C8), 73.44 (C11), 72.36 (C15), 53.69 (C12), 38.39 (C16), 36.7 (C10), 34.23 (C2), 31.92 (C18), 28.26 (C7), 27.13 (C4), 25.88, 25.74 (t-Bu), 24.93 (C17), 24.5 (C3), 22.62 (C19), 18.13, 17.84 (t-Bu), 14.05 (C20), −4.35, −4.49, −4.58, −4.72 ($SiCH_3$); mass spectrum, m/e (rel intensity) 518 (10), 461 (7), 460 (8), 446 (8), 445 (8), 444 (11), 443 (10), 398 (100), 396 (100).

Methyl (5*Z*,13*E*,8*R*,11*R*,12*R*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(*anti*-oximino)-5,13-prostadienoate (128) and (5*Z*,13*E*,8*R*,11*R*,12*R*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(*anti*-oximino)-5,13-prostadienol (129). To a stirred solution of oxime **115** (1.88 g, 2.5 mmol) and 0.189 g (5.0 mmol) of sodium borohydride in 25 mL of methanol was added 5 mL of 1 M sodium methoxide in methanol (prepared by addition of sodium to methanol) over 15 min. The solution was stirred another 15 min and then partitioned between 200 mL of saturated ammonium chloride and 200 mL of hexane (caution, foaming!). The aqueous phase was extracted with 100 mL of 50% ether in hexane, and the combined organic fractions were dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil. The crude product was purified by column chromatography (SiO_2, 60–200 mesh, 300 g, 20–40 ether/hexane gradient) to give in order of elution 1.26 g (82%) of oxime **128** and 0.16 g (11%) of **129** as oils.

128: TLC (2, 0.5); IR (neat) 3.02 (OH), 5.76 (COOR), 7.98 ($SiCH_3$), 9.1 (C—O), 10.27 (trans C=C), 13.8 (cis C=C); NMR ($CDCl_3$) δ 8.4 (br s, 1, OH), 5.5 (m, 4, olefin CH), 4.10 (m, 1, 15 CH), 3.93 (q, 1, 11 CH), 3.65 (s, 3, OCH_3), 3.00 (dd, J = 8, 16, 1, 10CH_2-β), 2.0–2.5 (m, 9, 2, 4, 7 CH_2 and 8, 12, 10CH_2-α), 1.7 (m, 2, 3 CH_2), 1.3 (m, 8, 16, 17, 18, 19 CH_2), 0.89 (br s, 21, t-Bu, and 20-CH_3), 0.05 (m, 12, $SiCH_3$); ^{13}C NMR 174.28 (C1), 163.23 (C9), 136.66 (C14), 130.28 (C13), 128.81 (C5), 127.40 (C6), 75.19 (C11), 72.74 (C15), 54.14 (C12), 51.47 (OCH_3), 45.90 (C8), 38.62 (C16), 36.42 (C10), 33.59 (C2), 31.90 (C18), 27.34 (C7), 26.89 (C4), 25.89 (t-Bu), 25.10 (C17), 24.77 (C3), 22.64 (C19), 18.22, 18.06 (t-Bu), 14.03 (C20), −4.26, −4.58 ($SiCH_3$); exact mass, calcd $C_{33}H_{63}NO_5Si_2$ (M − C_4H_9) 552.354, found 552.357.

129: TLC (2, 0.1); IR (neat) 3.07 (OH), 7.97 ($SiCH_3$), 9.15 (C—O), 10.28 (trans C=C), 13.6 (cis C=C); NMR ($CDCl_3$) δ 8.3 (br m, 2, OH, NOH), 5.5 (m, 4, olefin CH), 4.10 (m, 1, 15 CH), 3.95 (m, 1, 11 CH), 3.68 (m, 2, CH_2OH), 3.00 (dd, J = 8, 16, 1, 10CH_2-β), 2.0–3.5 (m, 9, 2, 4, 7 CH_2, 8, 12 CH, and 10CH_2-α), 1.55 (m, 2, 3CH_2), 1.3 (m, 8, 16, 17, 18, 19CH_2), 0.9 (br s, 21, t-Bu, and 20-CH_3), 0.03, −0.01 (2 s, 12, $SiCH_3$); mass spectrum, m/e (rel intensity) 581 (1), 564 (5), 524 (5), 523 (5), 510 (4), 506 (7), 449 (10), 392 (100).

Methyl (5*Z*,13*E*,11*R*,12*R*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(*anti*-oximino)-5,7,13-prostatrienoate (130). To a stirred solution of 0.10 g (0.125 mmol) of oxime **115** in 10 mL of methanol was added 0.25 mL of 1.0 M sodium methoxide in methanol. After 30 min, the solution was partitioned between 50 mL of saturated ammonium chloride and 50 mL of hexane. The aqueous phase was extracted with 20 mL of 50% ether in hexane, and the combined organic fractions were dried (Na_2SO_4) and evaporated in vacuo to give 0.07 g (90%) of **130** as an oil: TLC (2, 0.4); IR (neat) 3.11 (OH), 5.78 (COOR), 7.99 ($SiCH_3$), 9.3 (C—O), 10.3 (trans C=C), 13.6 (cis C=C); NMR ($CDCl_3$) δ 8.16 (d, J = 11, 1, 7CH), 6.17 (t, J = 11, 1, 6CH), 5.7 (m, 1, 5CH), 5.5 (m, 2, 13 and 14CH), 4.05 (m, 2, 11 and 15CH), 3.64 (s, 3, OCH_3), 3.46 (m, 1, 12 CH), 2.7 (dd, J = 4, 15, 1, 10CH_2-β), 2.1–2.5 (m, 5, 2, 4CH_2 and 10CH_2-α), 3.77 (m, 2, 3 CH_2), 1.25 (m, 8, 16, 17, 18, 19CH_2), 0.86 (s, 21, t-Bu, and 20-CH_3), 0.07, 0.00 (2 s, 12, $SiCH_3$); ^{13}C NMR 173.91 (C1), 156.68 (C9), 136.18 (C14), 135.54 (C7), 133.44 (C8), 132.19 (C13), 127.71 (C5), 127.52 (C6), 75.11 (C11), 73.22 (C15), 55.15 (C12), 51.46 (OCH_3), 40.00 (C10), 38.41 (C16), 33.36 (C2), 31.81 (C18), 27.34 (C4), 25.89 (t-Bu), 24.90 (C17), 24.64 (C3), 22.62 (C19), 18.26, 18.17 (t-Bu), 14.01 (C20), −4.29, −4.64 ($SiCH_3$); exact mass, calcd $C_{33}H_{61}NO_5Si_2$ (M − C_4H_9) 550.338, found 550.339.

(5*Z*,13*E*,8*R*,11*R*,12*R*,15*S*)-11,15-Bis(*tert*-butyldimethylsiloxy)-9-(*anti*-oximino)-5,13-prostadienoic Acid (131). Following a procedure similar to that previously described for the synthesis of oxime **128**, 22.0 g (30 mmol) of **121** in 500 mL of methanol was cooled to −30 °C and 120 mL (30 mmol) of 0.25 M sodium methoxide in methanol added over 20 min. To this mixture was added 4.54 g (120 mmol) of solid sodium borohydride and the mixture warmed to 25 °C. To this mixture was added 160 mL (40 mmol) of 0.25 M sodium methoxide in methanol over 1 h, and the mixture was stirred an additional 5 h at 25 °C. Most of the solvent was removed on a rotary evaporator (<30 °C), and the resulting mixture was partitioned between 400 mL of saturated ammonium chloride and 400 mL of ethyl acetate (caution, foaming!). The aqueous phase was extracted twice with 200-mL portions of ethyl acetate, and the combined organic fractions were dried (Na_2SO_4) and evaporated in vacuo to give a yellow oil. The crude product was purified by plug filtration (SiO_2, 60–200 mesh, 1 kg, 60% ethyl acetate in methylene chloride and then ethyl acetate) to give 16.0 g (90%) of pure **131** as a pale yellow oil: TLC [2 and 3 (1:1), 0.4]; IR (neat) 3.10 (OH), 5.85 (C=O), 7.97 ($SiCH_3$), 9.1 (C—O), 10.27 (trans C=C), 13.5 (cis C=C); NMR ($CDCl_3$) δ 5.57 (dd, J = 5.1, 15.3, 1, 14CH), 5.38 (m, 3, 5, 6, 13CH), 4.08 (m, 1, 15CH), 3.91 (m, 1, 11CH), 2.99 (dd, J = 7.4, 18.3, 1, 10CH_2-α), 2.0–2.4 (m, 9, 2, 4, 7CH_2, 8, 12CH, and 10CH_2-β), 1.69 (m, 2, 3CH_2), 1.45 (m, 2, 16CH_2), 1.27 (m, 6, 17, 18, 19CH_2), 0.84, 0.88 (2 s, 21, t-Bu, and 20-CH_3), 0.0 (m, 12, $SiCH_3$); ^{13}C NMR 178.96 (C1), 163.40 (C9), 136.72 (C14), 130.63 (C13), 128.66 (C5), 126.96 (C6), 75.16 (C11), 72.70 (C15), 54.18 (C12), 45.88 (C8), 38.58

(C16), 36.90 (C10), 33.44 (C2), 31.91 (C18), 27.41 (C7), 26.81 (C4), 25.88 (*t*-Bu), 25.06 (C17), 24.59 (C3), 22.63 (C19), 18.22, 18.04 (*t*-Bu), 14.04 (C20), −4.27, −4.61 ($SiCH_3$); exact mass, calcd $C_{32}H_{61}NO_5Si_2$ (M − H_2O, C_4H_9) 520.328, found 520.327.

Acknowledgement is given to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of early phases of this research. We also thank the National Institute of Health for their generous support of this research (Grants CA-19689 and CA-21840). The ^{13}C NMR spectrum used in this investigation was obtained on the departmental CFT-20 instrument provided by NSF Grant 7842. We thank the Purdue University Biological Magnetic Resonance Laboratory (NIH RR01077) for access to the 360-MHz ^1H NMR spectrometer and John Saddler for providing those spectra.

Registry No. **3**, 363-24-6; 8-epi-**3**, 27415-25-4; 11-epi-**3**, 38310-90-6; 8,11-*epi*-**3**, 85548-91-0; **5a**, 51751-83-8; **5b**, 64493-06-7; D-**6b**, 77520-20-8; DL-**6b**, 85548-61-4; DL-**6c**, 85453-04-9; DL-**7a**, 85548-60-3; **7b**, 41138-68-5; DL-**11**, 85548-62-5; D-**11**, 77520-17-3; L-**11**, 77520-12-8; D-**12**, 33375-06-3; L-**12**, 14649-03-7; **13**, 85453-05-0; **14**, 85548-63-6; D-**15**, 85453-06-1; L-**15**, 85548-64-7; **16**, 85548-65-8; **17**, 85548-66-9; **18**, 85453-07-2; D-**19**, 77520-18-4; D-**20**, 85548-67-0; L-**20**, 77493-65-3; L-**20** (enediol), 77493-66-4; **21**, 77520-19-5; D-**22**, 85453-08-3; **23**, 77520-13-9; **24**, 85548-68-1; **25**, 61348-02-5; **27**, 77493-63-1; **28**, 77493-64-2; **29**, 77493-67-5; **30**, 85548-69-2; **31**, 39198-04-4; **32**, 39178-64-8; DL-**33**, 39647-88-6; DL-**33** (hemiphthalate ester), 60457-57-0; D-**33**, 39647-93-3; L-**33**, 42541-99-1; L-**34**, 60498-28-4; L-**35**, 41138-67-4; **36**, 85548-70-5; **37**, 85453-09-4; **38**, 85453-10-7; **39**, 85453-11-8; **40**, 85453-12-9; **41a**, 85479-31-8; **41b**, 85479-32-9; **41c**, 85479-33-0; D-**43**, 77520-21-9; D-**44**, 77493-68-6; L-**46**, 77493-69-7; D-**47**, 77493-70-0; L-**48**, 85610-67-9; D-**49**, 85548-71-6; **50**, 77494-45-2; **51**, 85548-73-8; **52**, 85453-13-0; **53**, 85453-14-1; **54**, 85453-15-2; **54a**, 85453-16-3; **55a**, 85453-17-4; **55b**, 85453-18-5; **56**, 85453-19-6; **57**, 85453-20-9; **58**, 85453-21-0; **59**, 77494-46-3; **60**, 77520-22-0; **61**, 85453-22-1; **62**, 85548-74-9; **63**, 85479-34-1; **64**, 85548-75-0; **65**, 85453-23-2; **66**, 106-95-6; **67**, 85453-24-3; **68**, 85453-25-4; **69**, 85548-76-1; **70**, 77506-98-0; **71**, 85548-77-2; **72**, 85453-26-5; **73**, 85548-78-3; **74**, 85453-27-6; **76**, 85453-28-7; **77**, 85453-29-8; **78**, 85479-28-3; **79a**, 85453-30-1; 8β-**79b**, 85548-79-4; 8α-**79b**, 85610-68-0; **80**, 85453-31-2; **81**, 85453-32-3; **82**, 85453-33-4; **83**, 85453-34-5; **84**, 85453-35-6; **85**, 85453-36-7; **86**, 85453-37-8; **87**, 85548-80-7; **88**, 85453-38-9; **88b**, 85453-39-0; **89a**, 85453-40-3; **89b**, 85548-81-8; **90**, 85453-41-4; **91**, 85453-42-5; **92**, 85453-43-6; **93a**, 85453-44-7; **93b**, 85548-82-9; **94**, 85453-45-8; **95a**, 85453-46-9; **95b**, 85548-83-0; **97**, 85453-47-0; **99**, 85453-48-1; **102**, 85453-77-6; **104**, 85453-49-2; **105**, 85453-50-5; **106**, 85453-51-6; **107**, 85453-52-7; **108**, 77506-99-1; **109**, 85453-53-8; **110**, 77494-47-4; **111**, 85453-54-9; **112**, 85453-55-0; **113**, 85453-56-1; **114**, 85453-57-2; **115**, 85453-58-3; **116**, 85453-59-4; **117**, 85453-60-7; **118**, 85453-61-8; **119**, 85453-62-9; **120**, 77494-48-5; **121**, 85548-84-1; **122**, 85453-63-0; **123**, 85453-64-1; **124**, 85453-65-2; **125**, 85453-66-3; **126**, 85453-67-4; **127**, 85453-68-5; **128**, 85453-69-6; **129**, 85453-70-9; **130**, 85453-71-0; **131**, 85548-85-2; **132**, 85453-72-1; **133**, 85453-73-2; **135**, 66602-10-6; **136**, 31753-17-0; **137**, 31753-19-2; 8-epi-**137**, 85548-90-9; **138**, 13345-50-1; **139**, 85453-74-3; **139** (bis(isopropyldimethylsilyl) ether), 85453-78-7; **140**, 57021-16-6; **141**, 85548-86-3; **142**, 85548-87-4; **143**, 85548-88-5; **144**, 85453-75-4; **145**, 85610-69-1; **146**, 85548-89-6; **147**, 85453-76-5; cyclopentadiene, 542-92-7; cyclopentadiene monoepoxide, 7129-41-1; 2,2,2-trichloroethyl chloroformate, 17341-93-4; hexanoyl chloride, 142-61-0; acetylene, 74-86-2; (*Z*)-7-hydroxy-5-heptenenitrile, 85453-79-8.

Supplementary Material Available: Experimental details for the resolution of DL-**11** and DL-**33** and the preparation of the compounds not described in the Experimental Section as well as a table of X-ray data of **70** (75 pages). Ordering information is given on any current masthead page.

Thermolysis of Benzopyranone–Indenone Adducts: A New Route to the C-Nor-D-Homo Steroid Skeleton

Dirk J. Vanderzande,[1a,b] Roger A. Ceustermans,[1a,b] Henri J. Martens,*[1c] Suzanne M. Toppet,[1b] and Georges J. Hoornaert*[1b]

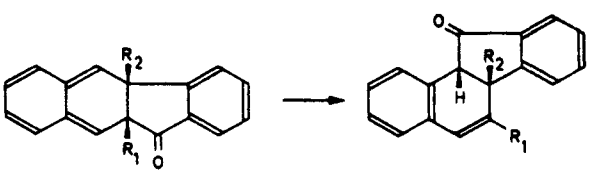
Department of Chemistry, K. U. Leuven, Celestijnenlaan 200 F, 3030 Leuven, Belgium, and Limburgs Universitair Centrum, Universitaire Campus, 3610 Diepenbeek, Belgium

Received October 22, 1982

Generation of *o*-quinodimethane systems and their rearrangement reactions during thermolysis of benzopyranone–indenone adducts **9** have been studied. Three products have been obtained: a C-nor-D-homo steroid, **12**, a benzo[*c*]fluorenone, **13**, and a benzo[*b*]cyclopropa[*lm*]fluorenone, **14**. Their formation and relative distribution on thermolysis of different adducts **9** has been rationalized by mechanisms proceeding via an intermediate *o*-quinodimethane system, **17**, the presence of which has been established by trapping with tetracyanoethylene.

In previous papers we reported the photochemical transformation of truxones to C-nor-D-homo steroid systems.[2] One of the possible mechanisms for this transformation included the intermediacy of *o*-quinodimethane systems like **1** that could rearrange to C-nor-D-homo steroid systems **2** by a 1,5-sigmatropic benzoyl shift

Scheme I



1 **2**

(Scheme I). Therefore we investigated also the possibility of generating these *o*-quinodimethane systems via a nonphotochemical reaction. *o*-Quinodimethanes are now un-

(1) (a) Predoctoral Fellow of the Instituut tot Aanmoediging van Wetenschappelijk Onderzoek in Nijverheid en Landbouw (IWONL). (b) Leuven. (c) Diepenbeek.

(2) (a) G. Jammaer, H. Martens, and G. Hoornaert, *J. Org. Chem.*, **39**, 1325 (1974); (b) R. Ceustermans, H. J. Martens, and G. J. Hoornaert, *ibid.*, **44**, 1388 (1979).

0022-3263/83/1948-2188$01.50/0