Table V. Elemental Analysis of the New Compounds

compd	calcd C	calcd H	calcd N	found C	found H	found N
2a	46.28	7.21	3.85	46.13	7.03	3.52
2b	47.74	7.48	3.71	47.77	7.51	3.34
2c	47.74	7.48	3.71	47.50	7.25	3.64
2d	50.36	7.96	3.45	50.14	7.78	3.37
2e	45.80	7.17	3.56	45.51	7.17	3.28
5a	80.93	10.49	8.58	80.68	10.59	8.61
5b	81.30	10.80	7.90	81.34	11.01	7.88
5c	81.30	10.80	7.90	81.21	10.74	7.88
5d	81.89	11.29	6.82	81.68	11.33	6.70
5e	74.57	9.91	7.25	74.45	10.01	7.22

(200 mL) and was extracted with ether (4 × 100 mL). The ether layer was washed with 1.5% aqueous $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and concentrated. HPLC and ^1H NMR analyses of the residual oils indicated the presence of two isomeric amines, **4a** and **5a** or **4e** and **5e**. Their structures were confirmed by ^1H NMR and UV spectra. The yield of each compound was calculated from the mole ratio based on the proton ratios in ^1H NMR.

4a: ^1H NMR (C_6D_6) δ 1.08 (d, 3 H, J = 6.6 Hz, CH_3), 2.12 (s, 6 H, NCH_3), 2.35–2.40 (m, 1 H, CH), 3.53 (m, 1 H, CH), 4.80 (s, 1 H, $=CH_2$), 5.06 (s, 1 H, $=CH_2$), 5.63–5.66 (m, 1 H, —CH=), 5.90–5.95 (m, 2 H, —CH= × 2), 6.05 (d, 1 H, J = 10.3 Hz, —CH=); UV λ_{max} 311 nm (log ϵ was not determined due to insufficient purity).

4e: ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 6.5 Hz, CH_3), 2.14 (m, 1 H, CH), 2.34 (s, 6 H, NCH_3), 3.58 (s, 3 H, OCH_3), 3.63 (m, 1 H, CH), 4.72 (dd, 1 H, J = 4.9 and 2.2 Hz, —CH=), 4.90 (s, 1 H, $=CH_2$), 5.12 (s, 1 H, $=CH_2$), 5.64 (m, 1 H, —CH=), 6.14 (dd, 1 H, J = 0.7 and 9.9 Hz, —CH=); UV λ_{max} 318 nm (log ϵ 3.58).

Chemical Behavior of 4a and 4e in HMPA. A mixture of **4a** and **5a** or of **4e** and **5e**, obtained in a manner similar to that described above, was dissolved in HMPA (10 mL) and stirred at room temperature. After 19 h for **4a** or 66 h for **4e**, the UV absorption (λ_{max} 310–320 nm) of the solution had disappeared. The solution was poured into 1.5% aqueous $NaHCO_3$ (200 mL), and the mixture was extracted with ether (4 × 100 mL). The ethereal extract was washed with 1.5% aqueous $NaHCO_3$ (2 × 100 mL), concentrated to about 20 mL, and then extracted with 10% HCl (3 × 10 mL). The acid layer was made alkaline with 30% NaOH and extracted with ether (3 × 10 mL). The ether layer was dried ($MgSO_4$), concentrated, and distilled to give a mixture of **5**, **6**, and **7**. The ether layer remaining after the acid extraction was analyzed by GLC and GC mass spectra to determine the presence of **8** and **9**. The yields and ratio of the products were determined in a manner similar described above: **5a**, **6a**, and **7a** (total yield 20%; ratio 90:5:5), **8a** (36%), and **9a** (trace); **5e** and **6e** (total yield 30%; ratio 99:1), **8e** (33%), and **9e** (trace).

***N*,*N*-Dimethyl-1-(2-methylphenyl)ethylamine[11] (6a) and *N*,*N*-Dimethyl-1-(4-methylphenyl)ethylamine[11] (7a).** A mixture of dimethylamine hydrochloride (675 mg, 10 mmol), KOH (450 mg, 8 mmol), and MeOH (5 mL) was stirred for a few minutes. After the addition of 3A molecular sieves (about 1 g), the mixture was allowed to stand for 0.5 h. The supernatant of the above mixture was transferred to another flask, followed by addition of 2- (or 4-) methylacetophenone (268 mg, 2 mmol) and a solution of $NaBH_3CN$ (100 mg, 1.6 mmol) in MeOH (1 mL). After being stirred for 7 days at room temperature, the solution was mixed with 10% HCl (20 mL), and the mixture was washed with ether (2 × 10 mL). The acid layer was neutralized and extracted with ether. The extract was dried ($MgSO_4$), concentrated, and distilled to give **6a** (88 mg, 27%) or **7a** (235 mg, 72%).

6a: bp 115 °C (30 mmHg); ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz, CH_3), 2.16 (s, 6 H, NCH_3), 2.30 (s, 3 H, $PhCH_3$), 3.37 (q, 1 H, J = 6 Hz, CH), 6.99–7.47 (m, 4 H, Ar H).

7a: bp 115–102 °C (20 mmHg); ^1H NMR ($CDCl_3$) δ 1.33 (d, 3 H, J = 7 Hz, CH_3), 2.15 (s, 6 H, NCH_3), 2.29 (s, 3 H, $PhCH_3$), 3.18 (q, 1 H, J = 7 Hz, CH), 7.01 (s, 4 H, Ar H).

Elemental analyses of **2a–e** and **5a–e** are found in Table V.

Acknowledgment. We are grateful to the Ministry of Education, Science, and Culture, Japan, for a Grant-in-Aid (No. 01571160).

Registry No. **1** (R^1 = H, R^2 = R^3 = Me), 123701-29-1; **1** (R^1 = H, R^2 = Me, R^3 = Et), 123701-30-4; **1** (R^1 = H, R^2 = Et, R^3 = Me), 123701-31-5; **1** (R^1 = H, R^2 = Bu, R^3 = Me), 123701-32-6; **1** (R^1 = MeO, R^2 = R^3 = Me), 123701-33-7; **2a**, 123701-34-8; **2b** (diastereoisomer 1), 123701-35-9; **2b** (diastereoisomer 2), 123701-36-0; **2c**, 123701-37-1; **2d**, 123701-38-2; **2e**, 123701-39-3; **4a**, 123701-46-2; **4e**, 123701-47-3; **5a**, 4075-96-1; **5b**, 119290-77-6; **5c**, 2576-14-9; **5d**, 100874-84-8; **5e**, 26070-48-4; **6a**, 42142-24-5; **6b**, 123701-40-6; **6c**, 123701-42-8; **6d**, 123701-44-0; **6e**, 91553-19-4; **7a**, 42142-19-8; **7b**, 123701-41-7; **7c**, 123701-43-9; **7d**, 123701-45-1; **8a**, 108-88-3; **8e**, 104-93-8; 2-methylacetophenone, 577-16-2; 4-methylacetophenone, 122-00-9.

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α-Silyl Sulfones as Latent α-Sulfonyl Anions. Fluoride-Promoted Intramolecular 1,2-Additions to Aldehydes as the Basis of a New Cyclopentenylation Strategy[1]

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Received April 11, 1989

Conjugate addition of allylpotassium to vinyl sulfones **8** and **23** followed by carbon silylation provides α-silyl sulfones **9d** and **24b**. These materials are transformed to aldehydes **11** and **26**, which subsequently undergo smooth fluoride-induced cyclopentannulation giving β-hydroxy sulfones **13a** and **27**. Reductive cleavage of these alcohols affords cyclopentenyl-annulated compounds **14** and **28**.

Introduction

Utilization of the vinyl sulfone moiety as the focal point in a sequence involving conjugate addition (A to B, Scheme I) followed by electrophilic functionalization of the α-sulfonyl anion (B to C) represents a useful strategy for the rapid construction of complex substrates. Recent examples of this protocol are found in the total syntheses of PGE_2,[2] carbacyclin,[3] morphine,[4] and cephalotaxine.[5]

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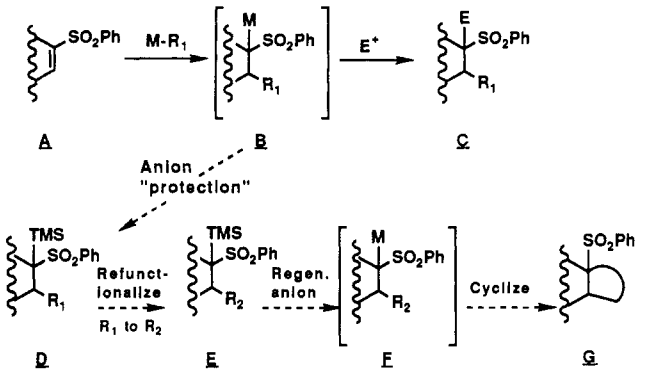
(3) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4755.

(4) Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 4694.

0022-3263/90/1955-0337$02.50/0

Scheme I



A limitation of this strategy is imposed by the sequence of operations. In cases where additional chemistry is required before alkylation of the α-sulfonyl center, it is desirable to have a method for the "delayed derivatization" of the nucleophilic center. A conceptually attractive approach to this problem involves conversion of intermediate B to an α-silyl sulfone (D), which may then be refunctionalized appropriately for intramolecular alkylation. Selective regeneration of the α-sulfonyl anion (E to F) would then provide an intermediate capable of undergoing cyclization (F to G). At the outset of this investigation, few examples were reported of compounds having a group-14 element (silicon, germanium, tin, or lead) α to a sulfone.[6]

A complementary strategy to that shown in scheme I was effectively explored by Isobe.[7] In this application, acyclic α-silylvinyl sulfones 1 (Scheme II) were substrates for conjugate addition reactions, providing α-silyl sulfones 2, which were desilylated to sulfones 3. Isobe did not report utilization of the α-silyl sulfone for regeneration of the α-sulfonyl anion but was concerned with using the silicon moiety as a blocking group to retard deprotonation of the vinyl proton α to the sulfonyl center, so that controlled conjugate additions could be obtained.

The regeneration of α-sulfonyl anions from α-silyl sulfones has been demonstrated by Otto, who showed that bis(silyl) sulfone 4 undergoes fluoride-mediated aldol reaction with acetaldehyde to afford alcohol 6 in addition to the products of desilylation and Peterson olefination (5 and 7).[8]

Although these references contain sufficient information to encourage further investigation, there have been no reports concerning the preparation of α-silyl sulfones originating from conjugate addition to vinyl sulfones that utilize the α-silyl sulfone as a latent α-sulfonyl anion. The first examples of a new cyclopentenyl annulation method based upon the concepts outlined in Scheme I are described below.

Results and Discussion

The initial chemistry involved determining conditions for the addition of allyl anions to vinyl sulfone 8 (Scheme III).[9] Allyllithium generated in situ from tetraallyltin and phenyllithium[10] did not undergo conjugate addition to 8 at −78 °C, 0 °C, or ambient temperature for 18 h; no product **9b** was obtained, and vinyl sulfone 8 was recovered in 90% yield. Our previous finding that organopotassium reagents undergo superior conjugate addition reactions to vinyl sulfones prompted a change of counterion.[11] Generation of the allyllithium at ambient temperature as before followed by transmetalation[12] using potassium *tert*-butoxide at −78 °C afforded a reagent (presumably allylpotassium) that underwent rapid addition to 8 at −78 °C to generate α-sulfonyl anion **9a**. Hydrolytic quench of this intermediate gave the α-proteo sulfone **9b** in 89% yield, while methyl iodide quench gave the α-methyl sulfone **9c** in 92%.[13]

Silylation of anion **9a** was more demanding; successful reaction needed the use of absolutely acid-free TMSCl stored over poly(4-vinylpyridine)[14] and extended reaction time (14–18 h) at ambient temperature. Under these optimal conditions, **9c** was obtained in quantitative yield as a mixture of inseparable diastereomers at the α-sulfonyl center. Although the literature[6a] suggested that the α-silyl sulfone **9d** might be labile under conditions where oxygen anions were present in homogeneous solution, a control reaction where 3% H_2O_2 and 10% NaOH was stirred with a CH_2Cl_2 solution of the alkene **9d** for 2 h at 25 °C showed no proteodesilylation to **9b**.

Reaction of **9d** (Scheme IV) with *m*-chloroperoxybenzoic acid in sodium bicarbonate buffered methylene chloride

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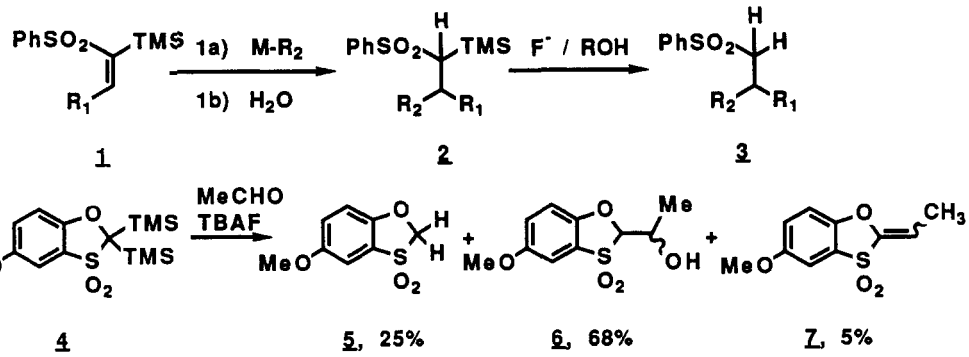
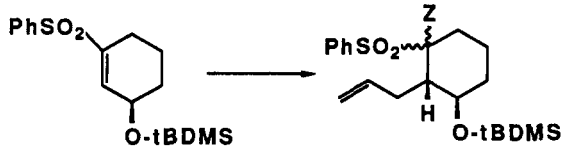
Scheme II



Scheme III



8

9a Z=K
9b Z=H
9c Z=Me
9d Z=SiMe3

afforded epoxide **10**, presumably as a mixture of four diastereomers (92%). Treatment of **10** with $BF_3 \cdot OEt_2$ in ether[15] at ambient temperature gave pure aldehyde **11** in quantitative yield. Because of its lability toward long-term storage, aldehyde **11** was used immediately after its generation. An alternative preparation of aldehyde **11** involved hydroboration of olefin **9a** using borane–methyl sulfide[16] in THF to provide alcohol **12** in 72% yield. This alcohol was a poor substrate for PCC oxidation, but under Swern[17] conditions afforded aldehyde **11** in 99% yield.

Pretreatment (ambient temperature 2 min) of commercial (1.0 M in THF containing about 5% H_2O) tetra-*n*-butylammonium fluoride solution (TBAF) with powdered 4-Å molecular sieves in Et_2O[18] was followed by addition of the aldehyde **11**. Fluoride-mediated cyclization of **11** to **13a** begins at approximately −5 °C and is complete before the reaction reaches 25 °C as assayed by TLC. While the transformation appears essentially quantitative (as assayed by TLC), purification of **13a** by chromatography (78%) showed product decomposition (as assayed by TLC of the residues before and after purification).

Mesylation[19] of **13a** to **13b** was done under the usual conditions, except adding Et_3N last seemed to produce a cleaner product. Reductive cleavage[20] of **13b** resulted in the preparation of alkene **14** in 87% yield. Alternatively, direct desulfonylation[21] of alcohol **13a** gave **14** in quantitative yield.

Mesylation of alcohol **12** (Scheme V) gave a quantitative isolated yield of **15** but slowly suffered cyclization to tetrahydropyran **18** under long-term neat storage in soft glass vials. Control studies suggest that this reaction is acid catalyzed since treatment with methanesulfonic acid in CH_2Cl_2 gave **18** in 86% yield. Efforts to effect an intramolecular alkylation[8] of **15** under the TBAF conditions that were successful for conversion of **11** to **13a** did not afford **16** but quantitatively provided desilylated sulfone **17** as a diastereomeric mixture. Mesylate **17** also underwent cyclization to tetrahydropyran **19** upon storage as a neat material or via treatment with catalytic methanesulfonic acid in CH_2Cl_2.

Acylation of the alcohol **12** using acetic anhydride pyridine and DMAP in CH_2Cl_2 smoothly gave acetate **20** in 91% yield. Attempts to effect intramolecular transacylation by reacting **20** with TBAF did not afford alcohol **21** but supplied sulfone **22** in 91% yield, the product of desilylation.

Applying the successful cyclopentene annulation to the more complicated vinyl sulfone substrate **23** (Scheme VI)[22] provided some interesting results. Addition of the allylpotassium reagent occurred at −78 °C to produce an α-sulfonyl anion which was quenched with either methyl iodide (2 h, −78 to 25 °C) or acid-free TMSCl (18 h, −78 to 25 °C). Both adducts **24a** (91%) and **24b** (92%) appear to be single diastereomers at the α-sulfonyl center. The stereochemistry shown in Scheme VI has been tentatively assigned by NOE studies.

Hydroboration of **24b** followed by oxidative workup gave the alcohol **25** in 55–82% yield. This variation in yield appears due to lability of the alcohol; in practice it is expedient to carry the crude alcohol onto the next step without purification. Swern oxidation of **25** resulted in the desired aldehyde **26** in 85–99% yield. Fluoride-induced cyclization of **26** required the use of specially activated powdered 4-Å molecular sieves (see Experimental Section) to avoid the production of some recovered desilylated aldehyde which was especially troublesome to separate from the desired β-sulfonyl alcohol **27**. Purification of **27** for characterization purposes could best be done using acetone-deactivated silica gel for chromatography (78%). Reductive cleavage of **27** using the method of Trost[21] gave the olefin **28** as a clear, colorless oil in 70% yield.

The above method shows one use of α-silyl sulfones as latent anions and suggests considerably broader potential once the experimental difficulties associated with quenching of the α-sulfonyl anions can be addressed. This paper shows some of the reaction conditions under which α-silylsulfones are stable prior to latent regeneration of the

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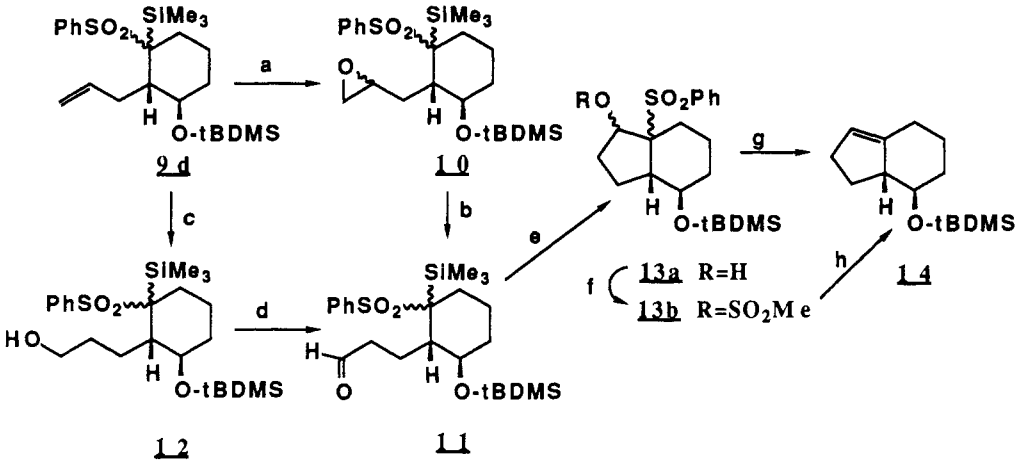
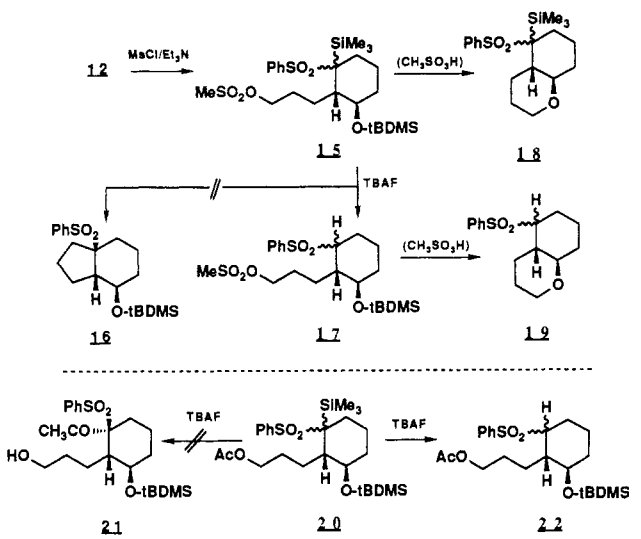
Scheme IV

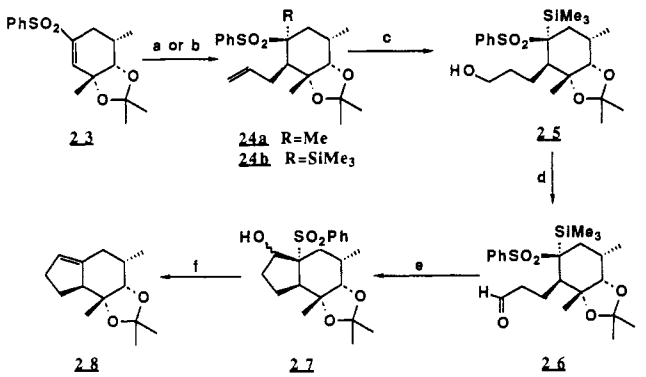


[a] (i) **9d** in CH_2Cl_2; (ii) MCPBA and $NaHCO_3$, 25 °C, 10 h (92%). [b] (i) **10** in Et_2O; (ii) BF_3OEt_2, 25 °C, 5 min (quantitative). [c] (i) **9d** in THF; (ii) BH_3SMe_2, 0 to 25 °C, 0.5 h; (iii) add CH_2Cl_2, 10% H_2O_2, and 10% NaOH, 0 to 25 °C, 1 h (72%). [d] (i) $(COCl)_2$ in CH_2Cl_2 then cool to −78 °C; (ii) DMSO, 10 min; (iii) add **12**, 20 min; (iv) add Et_3N, 10 min then warm to 25 °C, 4 h (99%). [e] (i) powdered 4-Å molecular sieves in Et_2O; (ii) TBAF, 2–8 min; (iii) add **11**, 25 °C, 1.5 h (78%). [f] (i) **13a** in CH_2Cl_2; (ii) $MeSO_2Cl$; (iii) Et_3N, 25 °C, 2 h (quantitative). [g] (i) **13a** in MeOH, (ii) 6% Na(Hg) and Na_2HPO_4, reflux, 1 h (quantitative); [h] (i) **13b** in MeOH (ii) 6% Na(Hg) and Na_2HOP_4, reflux, 2 h (87%).

Scheme V



Scheme VI



[a] (i) $Sn(CH_2CH{=}CH_2)_4$ in Et_2O at 25 °C; (ii) PhLi, 0.5 h then cool to −78 °C; (iii) Me_3COK in Et_2O, 0.5 h; (iv) add **23**, 0.5 h; (v) MeI −78 to 25 °C, 2 h (91%). [b] (i) $Sn(CH_2CH{=}CH_2)_4$ in Et_2O at 25 °C; (ii) PhLi, 1.08 h then cool to −78 °C; (iii) Me_3COK in Et_2O, 1 h; (iv) add **23**, 0.5 h; (iv) add TMSCl at −78 °C then warm to 25 °C, 19 h (92%). [c] (i) **24b** in THF; (ii) BH_3SMe_2, at 0 °C then warm to 25 °C, 1.2 h; (iii) add CH_2Cl_2, 10% H_2O_2, and 10% NaOH, cool to 0 °C then warm to 25 °C, 0.75 h (82%). [d] (i) $(COCl)_2$ in CH_2Cl_2 and cool to −78 °C; (ii) DMSO, 20 min; (iii) add **25**, 20 min; (iv) Et_3N, −78 °C, 0.5 h then warm to 25 °C, 2 h (99%). [e] (i) 4-Å powdered molecular sieves in Et_2O; (ii) add TBAF, 8 min; (iii) add **26** 25 °C, 0.75 h (78%). [f] (i) **27** in MeOH; (ii) 6% Na(Hg) and Na_2HPO_4 reflux, 2.17 h (70%).

nucleophilic center.[23] Research concerning the scope and limitation of α-silyl sulfones in underway.

Experimental Section

General Procedures. Reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis Ltd. and were used as received. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride, and methanesulfonyl chloride was distilled from P_2O_5. Tetra-*n*-butylammonium fluoride (TBAF 1.0 M in THF, from Lancaster) was stored over 4-Å molecular sieves. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl, and CH_2Cl_2 was distilled from calcium hydride, all under nitrogen. Reactions were done under a positive pressure of argon, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or flame dried. Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 F 254 plates (EM reagents, 0.25 mm) and eluted with (v/v) ethyl acetate in hexane solutions and are designated as tlc system A or B (A = 10%; B = 30%). Visualization of the TLC plates was done with a *p*-anisaldehyde spray reagent activated with heat.

Analytical samples were obtained from flash[24] column chromatography (silica gel from Davison Chemical, 60–200 mesh, using a ratio of 100:1 unless otherwise stated) or from multiply eluted TLC or prep plates (EM reagents). Deactivation of silica gel columns was done by slurry packing with either 50% acetone/hexane (best results) or 50% acetone/ethyl acetate and washed with hexane and then the desired elution solvent. Melting points were obtained on a MEL-TEMP apparatus and are uncorrected. ^1H NMR spectra were recorded on a General Electric QE-300 instrument operating at 300 MHz. ^{13}C NMR spectra were also recorded on a General Electric QE-300 instrument operating at 75 MHz. NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), with chloroform as the reference standard (7.26 and 77.00 ppm). When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). For the carbon spectra, e and o are used

(23) For an example of a metallation promoted cyclization of an α-sulfonyl anion to an ester bearing no α-hydrogens, see: Kang, S. H., Kim, W. J., Chae, Y. B. *Tetrahedron Lett.* **1988**, *29*, 5169.

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to denote even and odd, respectively. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer or Perkin-Elmer 1800 FT IR spectrometer as neat oils or as $CDCl_3$ solutions and are reported in micrometers. The mass spectra were obtained on a Finnigan 4000 mass spectrometer using electron impact and chemical ionization (isobutane) methods with the molecular ion as $(M)^+$ and $(M + H)^+$. Compounds characterized by exact mass were shown being greater than 95% pure by TLC and NMR analysis. Powdered 4-Å molecular sieves (Lancaster) were oven and/or flame activated under vacuum (0.2 Torr) before use. Reagents and substrates are listed in order of addition. Yields given are for pure homogeneous materials unless otherwise stated. Experimental procedures including partial NMR and IR data for compounds **9–22** and mass spectroscopy data are available in the supplementary material (see the paragraph at the end of the paper).

Preparation of α-Methyl Sulfone 24a. A solution of tetraallyltin (25 mg, 0.089 mmol) in Et_2O (1 mL, 0.08 M) was treated with phenyllithium (166 μL of 2.09 M in Et_2O, 0.347 mmol) at ambient temperature, and the reaction contents were stirred for 30 min before being cooled to −78 °C. A slurry of potassium *tert*-butoxide (46 mg, 0.413 mmol) in Et_2O (750 μL, slurry 0.55 M) was added, and the reaction contents were stirred for 30 min at −78 °C. A solution of vinyl sulfone **23** (58 mg, 0.181 mmol) in Et_2O (1 mL, 0.17 M) was added, and the yellow solution was stirred for 0.5 h at −78 °C, before being quenched at −78 °C with methyl iodide (70 mg, 0.496 mmol). The low-temperature cooling bath was removed, and the reaction contents were allowed to warm to ambient temperature over 2 h, TLC system A. The reaction was terminated with the addition of saturated NH_4Cl (5 mL) and by dilution with Et_2O (5 mL). The heterogeneous layers were separated, and the organic phase was washed (×2) successively with aqueous portions of saturated NH_4Cl and brine and dried over Na_2SO_4. The solvent was removed in vacuo which afforded an oil that was flash chromatographed on 60–200 mesh silica gel and eluted with hexane and then 30% (v/v) ethyl acetate in hexane. Concentration in vacuo afforded 62 mg of **24a** as a solid (mp 51–53 °C, 91%): ^1H NMR δ 7.78 (d, 2 H, J = 7.1 Hz), 7.59 (t, 1 H, J = 7.1 Hz), 7.49 (t, 2 H, J = 7.9 Hz), 5.91 (m, 1 H), 5.03 (d, 1 H, J = 17.1 Hz), 4.87 (d, 1 H, J = 9.6 Hz), 3.76 (d, 1 H, J = 2.7 Hz), 2.84 (m, 1 H), 2.70 (m, 2 H), 2.06 (dd, 1 H, J = 5.6 Hz), 1.67 (s, 3 H), 1.59 (m, 2 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.02 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 140.16 (o), 138.15 (e), 133.51 (o), 129.84 (o), 128.75 (o), 114.32 (e), 107.13 (e), 83.62 (o), 82.84 (e), 67.25 (e), 53.25 (o), 37.30 (e), 31.02 (e), 28.42 (o), 28.38 (o), 27.30 (o), 26.70 (o), 20.85 (o), 18.41 (o); IR ($CDCl_3$) 6.11 μm (C=C); exact mass (EI) calculated for $C_{21}H_{30}O_4S$ 378.1864, found 378.1864.

Preparation of α-Trimethylsilyl Sulfone 24b. A solution of tetraallyltin (2.23 g, 7.81 mmol) in Et_2O (98 mL, 0.08 M) was treated with phenyllithium (18.9 mL of 1.60 M in Et_2O, 30.5 mmol) at ambient temperature, and the reaction contents were stirred for 1.1 h before being cooled to −78 °C. A slurry of potassium *tert*-butoxide (4.06 g, 36.2 mmol) in Et_2O (66 mL, slurry 0.55 M) was added, and the reaction contents were stirred for 1 h at −78 °C. A solution of vinyl sulfone **23** (2.55 g, 7.91 mmol) in Et_2O (43 mL, 0.17 M) was added, and the yellow solution stirred for 0.5 h at −78 °C before being quenched at −78 °C with acid-free[14] trimethylchlorosilane (9.43 g, 86.8 mmol), TLC system A. The low-temperature cooling bath was removed, and the reaction contents were allowed to warm to ambient temperature over 19 h (over which time the reaction mixture turned white). The reaction was terminated by dilution with Et_2O (40 mL) and then poured into 100 mL of aqueous NH_4Cl. The heterogeneous layers were separated, and the organic phase was washed with aqueous portions of saturated NH_4Cl and brine and dried over Na_2SO_4. The crude product was plug filtered through a pad of silica gel and eluted with Et_2O. The solvent was removed in vacuo and the crude product was then diluted with hexanes and plug filtered on 60–200 mesh silica gel to remove some higher R_f impurities. The crude product was eluted off the silica gel with ethyl acetate. The solvent was removed in vacuo, which afforded an oil that was flash chromatographed on 60–200 mesh silica gel and eluted with 3% (v/v) ethyl acetate in hexane. Concentration in vacuo afforded 3.16 g of **24b** (92%; yields range from 83 to 92%): ^1H NMR δ 7.85 (d, 2 H, J = 7.5 Hz), 7.64 (t, 1 H, J = 7.2 Hz), 7.54 (t, 2 H, J = 7.8 Hz), 6.06 (m, 1 H), 5.03 (d, 1 H, J = 17.0 Hz), 4.93 (d, 1 H, J = 9.9 Hz), 3.78 (d, 1 H, J = 2.8 Hz), 3.10 (m, 1 H), 2.86 (m, 1 H), 3.76 (dd, 1 H, J = 6.8 Hz), 2.47 (d, 1 H, J = 12.4 Hz), 1.71 (m, 2 H), 1.67 (s, 3 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.06 (d, 3 H, J = 7.1 Hz), 0.02 (s, 9 H); ^{13}C NMR δ 140.93 (e), 139.67 (o), 133.43 (o), 129.45 (o), 128.67 (o), 113.37 (e), 106.68 (e), 83.50 (o), 82.92 (e), 65.66 (e), 46.54 (o), 34.61 (e), 31.11 (e), 28.18 (o), 27.26 (o), 26.10 (o), 20.81 (o), 18.64 (o), −0.01 (o); IR ($CDCl_3$) 6.11 μm (C=C); exact mass (EI) calculated for $C_{23}H_{36}O_4SSi$ 436.2104, found 436.2100.

Hydroboration–Oxidation of Alkene 24b to Alcohol 25. A solution of **24b** (642 mg, 1.47 mmol) in THF (7 mL, 0.2 M) was cooled to 0 °C and treated with borane–methyl sulfide complex (123 mg, 1.62 mmol of 10 M in BH_3) by careful addition via syringe. The reaction contents were stirred for 10 min at 0 °C before being warmed to ambient temperature, and the reaction contents stirred 1 h, TLC system B. The reduction was terminated by careful dilution of the contents into 50 mL of CH_2Cl_2 and then addition of 3% H_2O_2 (84 mL) and 10% NaOH (84 mL) at ambient temperature. An ice bath was added, and the contents were stirred for 0.75 h at 0 °C. The reaction was terminated by the separation of the heterogeneous layers, and the organic phase was washed with brine and dried over Na_2SO_4. The crude product was plug filtered through a pad of silica gel and eluted with ethyl acetate. The solvent was removed in vacuo, which afforded an oil that was flash chromatographed on 60–200 mesh deactivated silica gel with a gradient of 15% then 20% (v/v) ethyl acetate in hexane. Concentration in vacuo afforded 550 mg of **25** (82%, yields range from 55 to 82%): ^1H NMR δ 7.84 (d, 2 H, J = 7.5 Hz), 7.63 (t, 1 H, J = 7.2 Hz), 7.54 (t, 2 H, J = 7.7 Hz), 3.81 (d, 1 H, J = 2.4 Hz), 3.65 (m, 2 H), 2.86 (m, 1 H), 2.49 (s, 1 H), 2.32 (d, 1 H, J = 11.9 Hz), 2.19 (q, 1 H, J = 12.9 Hz), 2.06 (m, 1 H), 2.00 (d, 1 H, J = 12.1 Hz), 1.65 (AB, 2 H, J_{AB} = 12.4 Hz), 1.58 (s, 3 H), 1.44 (s, 3 H), 1.25 (s, 3 H), 1.00 (d, 3 H, J = 6.8 Hz), −0.04 (s, 9 H); ^{13}C NMR δ 140.81 (e), 133.28 (o), 129.33 (o), 128.52 (o), 106.47 (e), 83.49 (o), 82.80 (e), 66.12 (e), 62.84 (e), 46.29 (o), 33.18 (e), 30.84 (e), 28.17 (o), 26.99 (o), 26.32 (e), 25.96 (o), 20.88 (o), 18.51 (o), −0.06 (o); IR ($CDCl_3$) R-*OH* 2.73–3.13 μm; exact mass (CI) calculated for $C_{22}H_{38}O_5SSi$ 455.2287, found 455.2295.

Swern Oxidation of 25 to Aldehyde 26. A solution of oxalyl chloride (154 mg, 1.21 mmol) in CH_2Cl_2 (12 mL, 0.1 M) was cooled to −78 C and treated with dimethyl sulfoxide (184 mg, 2.42 mmol). The reaction contents were stirred for 20 min at −78 °C, then a solution of alcohol **25** (250 mg, 0.550 mmol) in CH_2Cl_2 (28 mL, 0.02 M overall) was added, and the reaction contents were again stirred for 20 min at −78 °C. After the addition of Et_3N (557 mg, 5.50 mmol), the reaction contents were stirred for 30 min at −78 °C. The low-temperature cooling bath was removed, and reaction contents were allowed to warm to ambient temperature over 2 h, TLC system B. The reaction was terminated by dilution with CH_2Cl_2 (28 mL) and the careful addition of H_2O. The heterogeneous layers separated, and the organic phase was washed with aqueous portions of saturated NH_4Cl and brine and dried over Na_2SO_4. The crude product was plug filtered through a pad of silica gel and eluted with ethyl acetate. The solvent was removed in vacuo, which afforded an oil that was flash chromatographed on 60–200 mesh deactivated silica gel with 20% (v/v) ethyl acetate in hexane. Concentration in vacuo afforded 245 mg of **26** as a white foam (mp 107–109 °C, 99%): ^1H NMR δ 9.80 (s, 1 H), 7.84 (d, 2 H, J = 7.5 Hz), 7.63 (t, 1 H, J = 7.2 Hz), 7.54 (t, 2 H, J = 7.6 Hz), 3.80 (d, 1 H, J = 2.4 Hz), 2.80 (m, 2 H), 2.50 (m, 1 H), 2.38 (m, 2 H), 1.70 (m, 2 H), 1.65 (s, 3 H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.30 (m, 1 H), 1.06 (d, 3 H, J = 7.0 Hz), 0.04 (s, 9 H); ^{13}C NMR δ 202.32 (o), 140.77 (e), 133.39 (o), 129.40 (o), 128.59 (o), 106.78 (e), 83.44 (o), 82.60 (e), 65.75 (e), 45.19 (o), 43.22 (e), 30.69 (e), 28.14 (o), 26.93 (o), 25.86 (o), 22.02 (e), 21.04 (o), 18.50 (o), −0.22 (o); IR ($CDCl_3$) 5.78 μm (C=O); exact mass (EI) calculated for $C_{23}H_{36}O_5SSi$ 452.2052, found 452.2049.

Fluoride-Induced Cyclization of Aldehyde 26 to β-Hydroxy Sulfone 27. A suspension of oven- and flame-dried powdered 4-Å molecular sieves (1.41 g, using a ratio of 1.33 g of powdered 4-Å molecular sieves/mmol of TBAF in THF 1.0 M) in Et_2O (20 mL) was stirred for 8 min at 25 °C after TBAF (1.1 mL of 1.0 M in THF, 1.1 mmol) was added. The suspension was treated at ambient temperature with a solution of aldehyde **26** (120 mg, 0.265 mmol) in Et_2O (7 mL, 0.01 M), and the reaction

contents were stirred for 0.75 h at ambient temperature, TLC system B. The reaction was terminated by dilution with Et_2O (27 mL) and the addition of H_2O. The layers were separated, and the organic phase was washed with H_2O and brine and dried over Na_2SO_4. The crude product was plug filtered through a pad of silica gel and eluted with ethyl acetate. The solvent was removed in vacuo which afforded an oil that was flash chromatographed on 60–200 mesh deactivated silica gel with 20% (v/v) ethyl acetate in hexane. Concentration in vacuo afforded 79 mg of **27** as a white foam (78%): ^1H NMR (partial of stereomeric mixture in a ratio of approximately 1:3) δ 7.88 (d, 2 H, J = 7.2 Hz), 7.80 (d, 2 H, J = 7.4 Hz), 7.62 (d, 1 H, J = 7.0 Hz), 7.55 (t, 2 H, J = 7.8 Hz), 4.31 (d, 1 H, J = 6.3 Hz), 3.89 (d, 1 H, J = 3.4 Hz), 3.17 (m, 1 H), 1.68 (s, 3 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.10 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (peaks of stereomeric mixture) δ 138.50 (e), 133.58 (o), 130.89 (o), 129.69 (o), 129.02 (o), 128.72 (o), 106.75 (e), 82.85 (o), 81.40 (e), 78.15 (e), 74.87 (o), 50.70 (o), 33.92 (e), 30.15 (e), 28.61 (o), 26.90 (o), 19.99 (o), 18.43 (o); IR ($CDCl_3$) R-*OH* 2.70–3.23 μm, exact mass (CI) calculated for $C_{20}H_{28}O_5S$ 381.1735, found 381.1727.

Reductive Elimination of β-Hydroxy Sulfone 27 to Alkene 28 Using 6% Na(Hg). A solution of alcohol **27** (51 mg, 0.134 mmol) in methanol (13.4 mL, 0.01 M) was treated with solid Na_2HPO_4 (76 mg, 0.537 mmol), 6% Na(Hg) (650 mg, 3.22 mmol) at ambient temperature, and then warmed to reflux for 2.2 h, TLC system B. The reaction was terminated by cooling the reaction contents to ambient temperature, then dilution with Et_2O (13 mL), and then careful addition of H_2O. The heterogeneous layers were separated, and the organic phase was washed (×2) with aqueous portions of saturated NH_4Cl and brine and dried over Na_2SO_4. The crude product was plug filtered through a pad of silica gel and eluted with Et_2O. The solvent was removed in vacuo which afforded an oil that was flash chromatographed on 60–200 mesh silica gel and eluted with pentanes and then CH_2Cl_2. Concentration in vacuo afforded 21 mg of **28** as an oil (70%): ^1H NMR δ 5.24 (br, 1 H), 3.66 (d, 1 H, J = 3.2 Hz), 2.87 (br, 1 H), 2.30 (m, 3 H), 1.95 (m, 3 H), 1.75 (m, 1 H), 1.52 (s, 3 H), 1.36 (s, 3 H), 1.13 (d, 3 H, J = 7.1 Hz), 1.11 (s, 3 H); ^{13}C NMR δ 171.79 (e), 143.10 (e), 121.23 (o), 84.70 (o), 76.58 (e), 52.02 (o), 32.97 (o), 32.23 (e), 30.92 (e), 28.56 (o), 27.13 (o), 23.01 (e), 18.30 (o), 17.66 (o); IR ($CDCl_3$) 6.85 (C=C, w), 3.31 μm (C=C*H*, m), exact mass (EI) calculated for $C_{14}H_{22}O_2$ 222.1619, found 222.1614.

Acknowledgment. We thank the National Institute of Health (GM 32693) for their generous support of this work. Thanks also to the Purdue University Magnetic Resonance Laboratory (RR 01077) for access to the 300-MHz high-field spectrometer. We are grateful to K. V. Wood and A. Rothwell for supplying mass spectra and helpful discussions about the fragmentations of α-silyl sulfones. Thanks to Gilbert Emeric for a 200 MHz 2-D NOE ^1H NMR of compound **24b**.

Registry No. (±)-8, 123538-62-5; (±)-**9b** (isomer 1), 123567-93-1; (±)-**9b** (isomer 2), 123670-07-5; (±)-**9c** (isomer 1), 123568-10-5; (±)-**9c** (isomer 2), 123670-08-6; (±)-**9d** (isomer 1), 123568-11-6; (±)-**9d** (isomer 2), 123670-09-7; (±)-**10** (isomer 1), 123567-94-2; (±)-**10** (isomer 2), 123670-17-7; (±)-**10** (isomer 3), 123670-18-8; (±)-**10** (isomer 4), 123670-19-9; (±)-**11** (isomer 1), 123567-95-3; (±)-**11** (isomer 2), 123670-11-1; (±)-**12** (isomer 1), 123567-96-4; (±)-**12** (isomer 2), 123670-10-0; **13a**, 123567-97-5; **13b**, 123568-12-7; (±)-**14**, 123567-98-6; (±)-**15** (isomer 1), 123567-99-7; (±)-**15** (isomer 2), 123670-12-2; (±)-**17** (isomer 1), 123568-00-3; (±)-**17** (isomer 2), 123670-13-3; (±)-**18** (isomer 1), 123568-01-4; (±)-**18** (isomer 2), 123568-13-8; (±)-**19** (isomer 1), 123568-02-5; (±)-**19** (isomer 2), 123568-15-0; (±)-**20** (isomer 1), 123568-03-6; (±)-**20** (isomer 2), 123670-14-4; (±)-**22** (isomer 1), 123568-04-7; (±)-**22** (isomer 2), 123670-15-5; (±)-**23**, 82769-83-3; (±)-**24a**, 123568-05-8; (±)-**24b**, 123568-14-9; (±)-**25**, 123568-06-9; (±)-**26**, 123568-07-0; (±)-**27** (isomer 1), 123568-08-1; (±)-**27** (isomer 2), 123670-16-6; (±)-**28**, 123568-09-2; $Sn(CH_2CH{=}CH_2)_4$, 7393-43-3.

Supplementary Material Available: Experimental procedures including NMR, IR, and mass spectroscopy data for compounds **9–22** (15 pages). Ordering information is given on any current masthead page.

Notes

The Structures of Cardionine and 11-Acetylcardionine, New C_{20}-Diterpenoid Alkaloids, from the Selective INAPT NMR Technique

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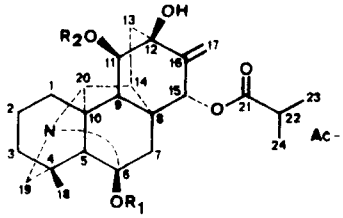
Received April 6, 1989

Discussion

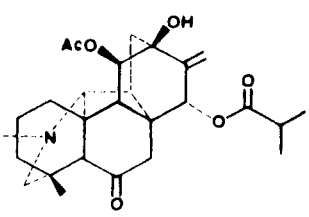
Plants of the *Aconitum*, *Delphinium*, and *Consolida* genera are recognized as rich sources of biologically active and structurally complex diterpenoid alkaloids.[1] In this paper we report on the structure of cardionine (**1**) and 11-acetylcardionine (**2**), isolated from *Delphinium cardiopetalum* DC[2,3] and *D. gracile* DC,[4] respectively.



1 R_1=H, R_2=H

2 R_1=H, R_2=Ac

3 R_1=R_2=Ac



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11-Acetylcardionine (**2**) had a molecular formula $C_{26}H_{35}NO_6$ determined by HREIMS. Its ^1H and ^{13}C NMR spectra, among other characteristic features of a C_{20}-diterpenoid alkaloid with a hetisine-type skeleton,[2,5-8]

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(2) González, A. G.; de la Fuente, G.; Reina, M.; Jones, P. G.; Raithby, P. R. *Tetrahedron Lett.* **1983**, *24*, 3765.

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