Stereoselective Synthesis of (±)-Irones[1]

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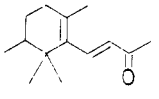
β-, *α-cis*-, and *α-trans*-irones (**1**, **2a**, and **2b**) have been prepared via 2,5,6,6-tetramethyl-1-[(phenylsulfonyl)methyl]cyclohexene (**7**) and 1,4*β*,5,5-tetramethyl-6*β*-[(phenylsulfonyl)methyl]cyclohexene (**8a**) and its C-6 epimer (**8b**). Electrochemical epoxidation of neryl phenyl sulfone (**6a**) provided 6,7-epoxy-3,7-dimethyl-1-(phenylsulfonyl)-2-octene (**9a**) in 85% yield. Conversion of **9a** into 2,6-dimethyl-8-(phenylsulfonyl)-6(*Z*)-octen-3-one (**11a**) was accomplished in formic acid, and then **11a** was transformed into 2,3,6-trimethyl-8-phenylsulfonyl-6(*Z*)-octen-3-ol (**5a**). Dehydration and subsequent cyclization of **5a** with $SnCl_4$ in benzene afforded **7** and **8a** (2:98) in 93% yield; the cyclization of **5b** provided a mixture of **7**, **8a**, and **8b** (12:44:44). The reaction of **7**, **8a**, and **8b** with propylene oxide followed by pyridinium chlorochromate oxidation and desulfonation gave (±)-**1**, **2a**, and **2b**, respectively. The cyclization mechanism of **5** and the stereochemistry of **8a** and **8b** are discussed.

Irones were isolated from orris root by Tiemann and Kruger;[2,3] the fragrant constituents include three isomers (**1**, **2a**, and **2b**). The *α*-cis isomer **2a**, in particular, has



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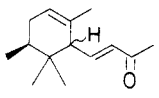
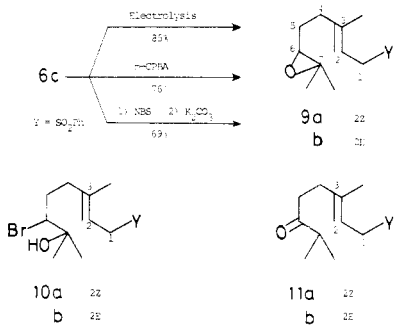


2a cis
b trans

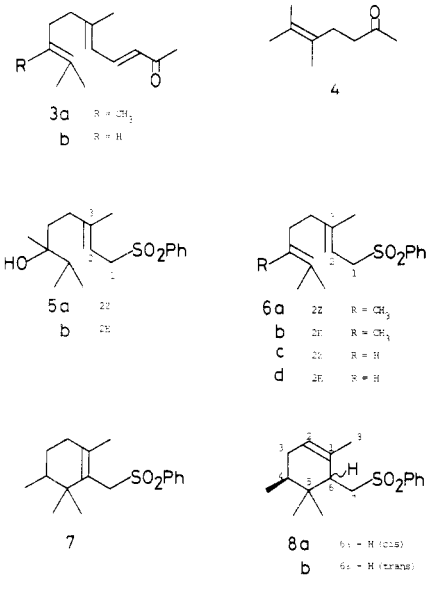
been recognized as an important odorous component. Several attempts to synthesize these compounds involved the acid-catalyzed cyclization of 9-methylpseudoionone (**3a**), derived from 5,6-dimethyl-5-hepten-2-one (**4**),[4,5] and led to a mixture of irones. Introduction of a methyl group at the C-6 position of geraniol and its derivatives has also been examined. Although Friedel–Crafts-type methylation at the double bond of geraniol,[6] citral,[7] and pseudoionone

Scheme I



(**3b**)[8] failed, Simmons–Smith cyclopropanation of **3b** followed by cyclization provided a mixture of irones.[9]

In this paper, we describe a stereoselective synthesis of (±)-irones (**1**, **2a**, and **2b**) via sulfones **7**, **8a**, and **8b**, prepared by acid-catalyzed dehydration of **5a** and **5b** and subsequent cyclization of **6a** and **6b**.



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(5) Eschninazi accomplished an elegant transformation of *α*-pinene into 2-(2,2,3-trimethylcyclobutyl)-hepta-2,4-dien-6-one, which was subjected to ring-opening cyclization resulting in a mixture of irones. (a) Eschinazi, H. E. *J. Am. Chem. Soc.* **1959**, *81*, 2905. (b) Eschinazi, H. E. *J. Org. Chem.* **1961**, *26*, 3140. (c) Eshinazi, H. E. U.S. Patent 3 019 265, Jan 30, 1972, Appl. Apr 2, 1959, 3 pp; *Chem. Abstr.* **1962**, *57*, 876*e*.

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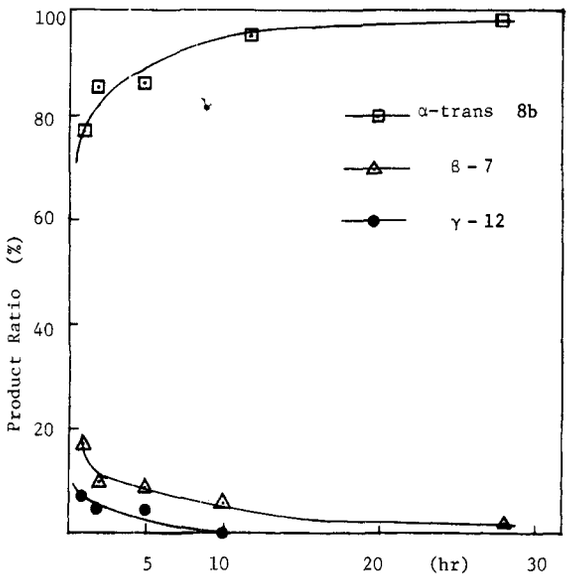


Figure 1. Time-dependent product distribution in the cyclization of **5a** with $SnCl_4$ in $CDCl_3$.

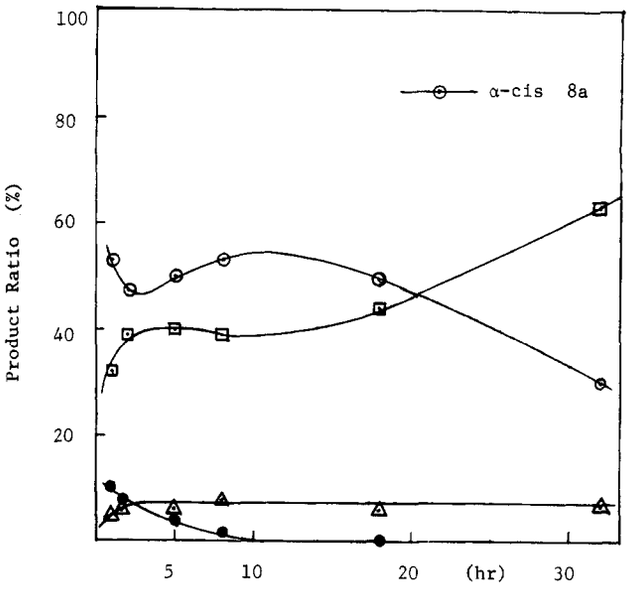


Figure 2. Time-dependent product distribution in the cyclization of **5b** with $SnCl_4$ in $CDCl_3$.

Results and Discussion

Epoxidation via peracid oxidation[10] and halohydrin methods[11] is known to produce some difficulties in large-scale production because of the instability of oxidizing agents and unfavorable economics of scale. Electrochemical epoxidation of simple olefins has been used, but the method has never been applied to regioselective epoxidation of complex molecules.[12] We examined three different methods for the epoxidation of **6c** and found that electrolytic epoxidation provides satisfactory results (Scheme I).

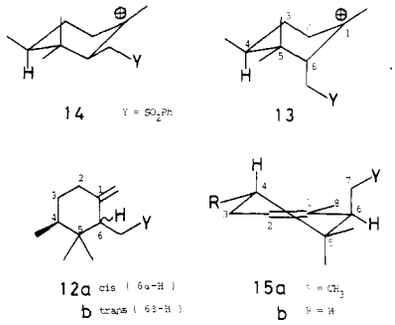
Oxidation of **6c** with *m*-chloroperbenzoic acid in CH_2Cl_2 afforded **9a** (76%) along with the corresponding diepoxide (14%). Reaction of **6c** with 1 equiv of *N*-bromosuccinimide in THF–H_2O (2.5:1) followed by treatment with potassium carbonate in MeOH gave **9a** in 69% yield. In contrast, the electrosynthesis of **9a** was performed in 85% yield using sodium bromide in MeCN–H_2O (7.5:1.5).[13] In the analysis of the product, no appreciable amount of the diepoxide was detected. Similarly, 6,7-epoxygeranyl phenyl sulfone (**9b**) was obtained (88%).

Conversion of **9a** into **11a** was accomplished quantitatively by heating in formic acid. The ketone **11a** was allowed to react with methylmagnesium iodide to give **5a** (85%). Similarly, **5b** was obtained from **9b** (70%).

Previously, we reported that a facile cyclization of **6d** by the action of BF_3 etherate in benzene and sulfuric acid in acetic acid gives cyclogeranyl phenyl sulfones.[14] Therefore, dehydration of **5** and subsequent cyclization of the dehydrates **6a** and **6b** would in principle give the corresponding methyl homologues (**7** and **8**).[15]

Upon treatment with $SnCl_4$ in CH_2Cl_2 at room temperature, **5a** cyclized stereoselectively to afford *trans*-**8b** (91%) and its β-isomer **7** (2%), but the cis-isomer **8a** was not detected at all. Likewise, the treatment of **5a** with BF_3 etherate in refluxing benzene provided a 87% yield of **8b** and **7** (88:12). Cyclization of **5b** was somewhat different from that of **5a**. Thus, **5b** was transformed to a 95% yield of **7**, **8a**, and **8b** (12:44:44) on treatment with BF_3 etherate in refluxing benzene. When **5a** was allowed to react with BF_3 etherate in refluxing benzene for 3 min, **6a** was isolated by high-pressure LC and cyclized into **7** and **8b** by further treatment with the acid. Therefore, **6a** was an intermediate for the transformation of **5a** into **7** and **8b**.

In order to elucidate the cyclization mechanism, the reaction was followed by measuring the ^1H NMR signals of products in $CDCl_3$ containing 1 equiv of $SnCl_4$ at 45 °C. The results are given in Figure 1. Under the reaction conditions both **5a** and **5b** disappeared completely within 1 h. In the case of **5a**, the presence of **8b** (77%), **7** (17%), and γ-isomer **12** (6%)[16] was observed by NMR after 1 h.



The amount of **8b** gradually increased, whereas the amounts of both **7** and **12** decreased. After 10 h, **12** disappeared completely and the yield of **8b** reached more than 98% at 29 h. At this stage no other byproduct was observed on the basis of ^1H NMR.[17] Time-dependent product distribution in the case of **5b** is shown in Figure 2. The amount of *cis*-**8a** was more than that of *trans*-**8b**

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(11) (a) van Tamelen, E. E.; Curphey, T. J. *Tetrahedron Lett.* **1962**, 121. (b) van Tamelen, E. E.; Sharpless, K. B. *Ibid.* **1967**, 2655.

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(13) Detailed electrolytic procedures and discussion on the electrolytic epoxidation of polyenes are described in Torii, S.; Uneyama, K.; Ono, M.; Tazawa, Y.; Matsunami, S. *Tetrahedron Lett.*, **1979**, 4661.

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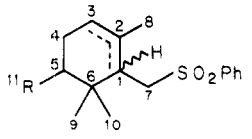
(15) Eschinazi reported a phosphoric acid-catalyzed cyclization of 9-hydroxy-6,9,10-trimethylundeca-3,5-dien-2-one into irones: Eschinazi, E. H.; Cotter, M. L. *Tetrahedron Lett.* **1964**, 3481.

(16) Existence of γ-isomers **12a,b** are assumed by the fact that two pairs of broad singlets, characteristic ^1H NMR signals of olefinic methylene, appeared at δ 4.48, 4.54 and 4.66, 4.76, respectively.

(17) Geminal methyl signal of **7** was observed at δ 0.60, from whose intensity the amount of **7** was estimated.

Table I. ^{13}C and ^{1}H NMR Chemical Shifts of 7, 8a, 8b, and 8c[c]



carbon no.	7[b]	8a[b]	8b[b]	8c[c]
1	138.7	44.1 (2.55)	45.0 (2.25)	42.7 (2.25)
2	126.0	132.5	135.7	134.7
3	31.8	123.5	122.4	121.7
7	58.0 (3.98)	55.7 (3.24) (3.08)	59.0 (3.32) (2.86)	58.5 (3.11) (2.47)
8	21.9 (1.68)	22.4 (1.73)	22.6 (1.63)	22.5 (1.65)
9	22.7 (0.92)	15.6 (0.61)	20.4 (0.82)	26.2 (0.91)
10	27.7 (1.06)	26.1 (0.80)	25.1 (0.92)	27.0 (0.91)
11	16.5 (0.90)	16.2 (0.81)	15.1 (0.82)	

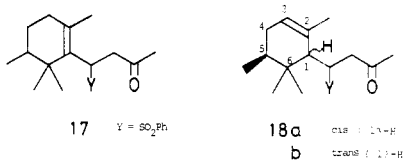
[a] δ (ppm) from Me_4Si in $CDCl_3$. ^{1}H NMR chemical shifts are shown in parentheses. [b] R = Me. [c] α-Cyclogeranyl phenyl sulfone (R = H).

in the beginning of the reaction; however, **8b** increased against a decrease of **8a** with elapsing reaction time.

If it is assumed that cyclization occurs from a cation at C-7 of **6a** and that a chair-type transition state is involved for cyclization, the attack of Lewis acids on **6a** would orient the C-4 methyl toward the equatorial position followed by π-electron participation to give carbonium ion **13**. The intermediate **13** would deprotonate preferentially from C-2 in a kinetically controlled fashion, leading to **8b** and, in part, **7** and **12**. Then, both **7** and **12** would isomerize slowly to the more thermodynamically stable isomer **8b** via **13**. The carbonium ion **14** would be derived from **5b** and would necessarily be a precursor of **7**, **8a**, and **12**. However, **8a** is thermodynamically less stable than **8b** because of eclipsing repulsion between C-1 methyl and sulfonylmethyl groups; therefore, **8a** would isomerize to **8b** via **7**. In fact, upon treating **8a**, **8b**, and **7** with $SnCl_4$ both **7** and **8a** isomerized to **8b**, while **8b** was found to be quite inert.

The isomers **7** and **8b** were separated by repeated column chromatography, whereas separation of **8a** from **7** and **8b** was realized by high-pressure LC.[17] The stereochemistry of **8** was estimated on the basis of ^{1}H and ^{13}C NMR spectra and the transformation of **8a** and **8b** into (±)-**2a** and **2b**, respectively. ^{1}H NMR signals for methine (2.25) on C-1, methyl (1.63) on C-8, and methylene (3.32 and 2.86) on C-7 of **8b** are quite similar to those (2.25, 1.65, and 3.11 and 2.47, respectively) of **8c** (α-cyclogeranyl phenyl sulfone) (see Table I). Similar correspondence between **8b** and **8c** was observed in ^{13}C chemical shifts of C-7 and C-8. Since the sulfonylmethyl groups of both **8b** and **8c** are preferentially situated in quasi-axial positions as shown in **15** to avoid steric repulsion between sulfonylmethyl and 8-methyl, the preferred conformer of **8b** would be that of **15a**. The fact that less shielding of the ^{13}C chemical shifts of C-7 and C-8 occurs with **8b** than with **8a** also supports this assessment of the stereochemistry of **8b**.

Extension of the C_3 unit to **7** and **8** was accomplished by reaction with propylene oxide. Thus, **8a** was treated with BuLi in THF at −50 °C followed with propylene oxide at room temperature to give the corresponding alcohol (85%), whose oxidation with pyridinium chlorochromate in CH_2Cl_2 afforded **18a** (89%). The ketone **18a** was



17 Y = SO_2Ph 18a b

transformed into the (±)-α-*cis*-irone **2a** in 85% yield on treatment with sodium methoxide in *t*-BuOH.[19] Similarly, (±)-**1** and **2b** were prepared in 55 and 58% yields from **7** and **8b**, respectively.

Experimental Section

Melting points are uncorrected. The IR spectra were obtained with a JASCO IRA-1 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JNM FX-100 Fourier transform spectrometer at 100 MHz in $CDCl_3$ using Me_4Si as an internal standard.

3,7-Dimethyl-1-(phenylsulfonyl)-2(*Z*),6-octadiene (6c). Phosphorus tribromide (0.42 mL, 4.4 mmol) was added dropwise into a dry ethereal solution (15 mL) of nerol (620 mg, 4.0 mmol) under ice cooling, and the mixture was stirred for 3 h at room temperature. After the reaction was quenched with saturated $NaHCO_3$, the ether layer was washed twice with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. The oil was added into sodium benzenesulfinate (660 mg, 4 mmol) dissolved in dry DMF (10 mL), and the mixture was stirred at room temperature under N_2 in the dark for 20 h.[20] After addition of brine, the organic substances were extracted with ether, and the usual workup gave an oil (1.1 g) which contained **6c** and **6d** (95:5, by high-pressure LC). The column chromatography (SiO_2, *n*-hexane–AcOEt (10:1)) gave **6c** (834 mg, purity 98% more by high-pressure LC μ-Porasil, *n*-hexane–AcOEt (5:1)) as a colorless oil: IR (neat) 1655 (C=C), 1585, 1300, 1140 (SO_2) cm^{-1}; ^{1}H NMR δ 1.55 (br s, 3, CH_3), 1.66 (br s, 3, CH_3), 1.73 (br s, 3, CH_3), 1.76–2.06 (m, 4, CH_2), 3.79 (d, J = 7.8 Hz, 2, CH_2), 4.95 (m, 1, CH=), 5.19 (t, J = 7.8 Hz, 1, CH=), 7.40–7.96 (m, 5, Ar H). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.97. Found: C, 68.90; H, 7.75.

6,7-Epoxy-3,7-dimethyl-1-(phenylsulfonyl)-2(*Z*)-octene (9a) Electrolysis of 6c. The mixture of **6c** (56 mg, 0.2 mmol) and NaBr (30 mg, 0.3 mmol) in CH_3CN (7.5 mL)–H_2O (1.5 mL) was electrolyzed at 25–28 °C under a constant current (10 mA for 2 h, applied voltage 2–3 V) using a platinum electrode (2 × 1.5 cm^2) in an undivided cell. Most of the CH_3CN being evaporated in vacuo, the organic substances were extracted with ether, and the extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (SiO_2, hexane–AcOEt (5:1)) to give **9a** (51 mg, 85%) as a colorless oil: IR (neat) 3050, 1662 (C=C), 1587, 1307, 1150 (SO_2) cm^{-1}; ^{1}H NMR δ 1.12 (s, 3, CH_3), 1.16 (s, 3, CH_3), 1.10–1.54 (m, 2, CH_2), 1.68 (s, 3, CH_3), 1.70–2.12 (m, 2, CH_2), 2.49 (t, J = 7.0 Hz, 1, CH), 3.78 (d, J = 8.0 Hz, 2, CH_2SO_2), 5.16 (t, J = 8.0 Hz, 1, CH=), 7.35–8.00 (m, 5, Ar H). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.36; H, 7.61.

6,7-Epoxy-3,7-dimethyl-1-(phenylsulfonyl)-2(*E*)-octene (9b): IR (neat) 1665 (C=C), 1590, 1450, 1310, 1155 (SO_2) cm^{-1}; ^{1}H NMR δ 1.26 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.40 (s, 3, CH_3), 1.74–1.52 (m, 2, CH_2), 2.16 (t, J = 7.0 Hz, 2, CH_2), 2.66 (t, J = 6.0 Hz, 1, epoxy CH), 3.83 (d, J = 8.0 Hz, 2, CH_2SO_2), 5.26 (t, J = 8.0 Hz, 1, CH=), 7.44–8.08 (m, 5, Ar H). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.36; H, 7.61.

3-Bromo-2,6-dimethyl-8-(phenylsulfonyl)-6(*Z*)-octen-2-ol (10a). A solution of NBS (200 mg, 1.12 mmol) dissolved in THF (1.5 mL) was added to a mixture of **6c** (156 mg, 0.56 mmol) in THF (1 mL) and H_2O (1 mL), and the mixture was stirred at room temperature for 20 min. Usual workup and chromatography (SiO_2, benzene–AcOEt (10:1)) of the products gave **10a** (154 mg, 81%) as a colorless oil. The treatment of **10a** with K_2CO_3 in dry methanol at room temperature for 4.5 h afforded **9a** (85%): IR

(18) We are grateful to Dr. M. Ueda and Messrs. I. Akuta, Y. Fujita, T. Onishi, and T. Nishida, Central Research Laboratories, Kuraray Co., Ltd., for the support of a preparative high-pressure LC and a generous supply of geraniol and the related acyclic terpenoids.

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(neat) 3570 (OH), 3020, 1660 (C=C), 1585, 1305, 1147 (SO_2) cm^{-1}; ^1H NMR (CCl_4) δ 1.23 (s, 3, CH_3), 1.27 (s, 3, CH_3), 1.72 (br s, 3, CH_3), 1.50–2.30 (m, 4, CH_2), 2.33 (br s, 1, OH), 3.57–3.87 (m, 1, CHBr), 3.73 (d, J = 8.0 Hz, 2, CH_2SO_2), 5.15 (t, J = 8.0 Hz, 1, CH=), 7.30–7.94 (m, 5, Ar H). Anal. Calcd for $C_{16}H_{23}O_3SBr$: C, 51.20; H, 6.18. Found: C, 51.00; H, 6.32.

3-Bromo-2,6-dimethyl-8-(phenylsulfonyl)-6(*E*)-octen-2-ol (10b), colorless oil: IR (neat) 3480 (OH), 3048, 1665 (C=C), 1588, 1308, 1150 (SO_2) cm^{-1}; ^1H NMR δ 1.34 (s, 6, CH_3), 1.43 (s, 3, CH_3), 1.55–2.35 (m, 4, CH_2), 2.65 (s, 1, OH), 3.72–3.96 (m, 3, CH_2SO_2, CHBr), 5.27 (t, J = 8.0 Hz, 1, CH=), 7.40–8.08 (m, 5, Ar H). Anal. Calcd for $C_{16}H_{23}O_3SBr$: C, 51.20; H, 6.18. Found: C, 51.04; H, 6.39.

***m*-CPBA Oxidation of 6c.** A solution of **6c** (36 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added to *m*-CPBA (29 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) under ice cooling, and the mixture was stirred at room temperature for 7 h. After evaporation of the solvent, the residue was dissolved in ether, and the ether layer was washed with aqueous $Na_2S_2O_3$ followed by 5% NaOH and then by brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (SiO_2, benzene–AcOEt (5:1)) to give **9a** (29 mg, 75%).

2,6-Dimethyl-8-(phenylsulfonyl)-6(*Z*)-octen-3-one (11a). A mixture of **9a** (20 mg, 0.07 mmol) and formic acid (1 mL) was stirred at 100 °C for 2 h under N_2. After evaporation of formic acid in vacuo followed by addition of saturated $NaHCO_3$ (5 mL), the organic substances were extracted with AcOEt. The usual workup and chromatography (SiO_2, benzene–AcOEt (10:1)) gave **11a** (20 mg, quantitative) as a colorless oil: IR (neat) 1708 (C=O), 1603, 1585, 1305, 1150 (SO_2) cm^{-1}; ^1H NMR δ 1.06 (d, J = 6.8 Hz, 6, CH_3), 1.73 (s, 3, CH_3), 2.05 (t, J = 7.3 Hz, 2, CH_2), 2.24–2.65 (m, 3, CH_2, CH), 3.86 (d, J = 7.8 Hz, 2, CH_2SO_2), 5.23 (t, J = 7.8 Hz, 1, CH=), 7.40–7.96 (m, 5, Ar H). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.29; H, 7.53. Found: C, 65.25; H, 7.70.

2,6-Dimethyl-8-(phenylsulfonyl)-6(*E*)-octen-3-one (11b), colorless oil: IR (neat) 1705 (C=O), 1662 (C=C), 1586, 1305, 1150 (SO_2) cm^{-1}; ^1H NMR δ 1.10 (d, J = 6.2 Hz, 6, CH_3), 1.34 (s, 3, CH_3), 2.02–2.80 (m, 5, CH_2, CH), 3.78 (d, J = 8.0 Hz, 2, CH_2SO_2), 5.18 (t, J = 8.0 Hz, 1, CH=), 7.20–7.96 (m, 5, Ar H). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.29; H, 7.53. Found: C, 65.22; H, 7.80.

2,3,6-Trimethyl-8-(phenylsulfonyl)-6(*Z*)-octen-3-ol (5a). The usual Grignard reaction of **11a** with methylmagnesium iodide in ether–THF (5:1) at 5–10 °C gave **5a** (85%) as a colorless oil: IR (neat) 3500 (OH), 1660 (C=C), 1590, 1305, 1150 (SO_2) cm^{-1}; ^1H NMR δ 0.84 (d, J = 6.6 Hz, 3, CH_3), 0.89 (d, J = 6.6 Hz, 3, CH_3), 1.16–2.04 (m, 6, CH_2, CH, OH), 3.82 (d, J = 8.1 Hz, 2, CH_2SO_2), 5.16 (t, J = 8.1 Hz, 1, CH=), 7.40–7.96 (m, 5, Ar H). Anal. Calcd for $C_{17}H_{26}O_3S$: C, 65.78; H, 8.44. Found: C, 65.81; H, 8.20.

2,3,6-Trimethyl-8-(phenylsulfonyl)-6(*E*)-octen-3-ol (5b), colorless oil: IR (neat) 3500 (OH), 3060, 1660 (C=C), 1588, 1305, 1150 (SO_2) cm^{-1}; ^1H NMR δ 0.89 (d, J = 6.5 Hz, 3, CH_3), 0.93 (d, J = 6.5 Hz, 3, CH_3), 1.08 (s, 3, CH_3), 1.35 (s, 3, CH_3), 1.20–1.90 (m, 4, CH_2, CH, OH), 1.96–2.24 (m, 2, CH_2), 3.81 (d, J = 8.0 Hz, 2, CH_2SO_2), 5.24 (t, J = 8.0 Hz, 1, CH=), 7.40–8.04 (m, 5, Ar H). Anal. Calcd for $C_{17}H_{26}O_3S$: C, 65.78; H, 8.44. Found: C, 65.59; H, 8.25.

2,5,6,6-Tetramethyl-1-[(phenylsulfonyl)methyl]cyclohexene (7), 1,4α,5,5-Tetramethyl-1α-[(phenylsulfonyl)methyl]cyclohexene (8a), and Its C-6 Epimer (8b) (Cyclization of 5b with BF_3 Etherate). To a benzene solution (5 mL) of **5b** (87 mg, 0.28 mmol) was added BF_3 etherate (58 mg, 0.4 mmol) at room temperature. The mixture was stirred at 100 °C under N_2 for 1 h. After cooling in ice water, the mixture was quenched with saturated $NaHCO_3$, and the organic substances were extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (SiO_2, hexane–AcOEt (20:1)) to give a mixture of **7**, **8a**, and **8b** (77 mg, **7**:**8a**:**8b** (12:44:44) from high-pressure LC and ^1H NMR). The isomers **7** and **8b** were separated by repeated chromatography, and **8a** was obtained by high-pressure LC (Waters, LC-500, hexane–AcOEt (97:3)): **7** mp 81.5–82.0 °C; IR (Nujol) 1590, 1315, 1155 (SO_2) cm^{-1}; ^1H NMR δ 0.90 (d, J = 6.3 Hz, 3, CH_3), 0.92 (s, 3, CH_3), 1.06 (s, 3, CH_3), 1.20–1.80 (m, 3, CH_2, CH), 1.68 (s, 3, CH_3), 1.94–2.16 (m, 2, CH_2), 3.98 (s, 2, CH_2SO_2), 7.40–8.00 (m, 5, Ar H). Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.84; H, 8.27. Found: C, 69.88; H, 8.19. **8a**: mp 121.0–121.5 °C; IR (Nujol) 1590, 1315, 1155 (SO_2) cm^{-1}; ^1H NMR δ 0.61 (s, 3, CH_3), 0.80 (s, 3, CH_3), 0.81 (d, J = 6.0 Hz, 3, CH_3), 1.30–2.10 (m, 3, CH_2, CH), 1.73 (br s, 3, CH_3), 2.55 (m, 1, CH), 3.08 (dd, J_1 = 4.9 Hz, J_2 = 15.1 Hz, 1, CH_2SO_2), 3.24 (dd, J_1 = 3.4 Hz, J_2 = 15.1 Hz, 1, CH_2SO_2), 5.42 (m, 1, CH=), 7.40–8.00 (m, 5, Ar H). Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.84; H, 8.27. Found: C, 69.70; H, 8.03. **8b**: mp 76.0–76.5 °C; IR (Nujol) 1590, 1310, 1150 (SO_2) cm^{-1}; ^1H NMR δ 0.82 (d, J = 6.2 Hz, 3, CH_3), 0.82 (s, 3, CH_3), 0.92 (s, 3, CH_3), 1.20–2.80 (m, 3, CH_2, CH), 1.63 (s, 3, CH_3), 2.25 (t, J = 4.0 Hz, 1, CH), 2.86 (dd, J_1 = 4.0 Hz, J_2 = 15.0 Hz, 1, CH_2SO_2), 3.32 (dd, J_1 = 4.0 Hz, J_2 = 15.0 Hz, 1, CH_2SO_2), 5.27 (m, 1, CH=), 7.40–8.04 (m, 5, Ar H). Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.84; H, 8.27. Found: C, 69.76; H, 8.27.

Cyclization of 5a with $SnCl_4$. Stannic chloride (52 mg, 0.21 mmol) was added to **5a** (62 mg, 0.21 mmol) dissolved in 10 mL of dry CH_2Cl_2 at room temperature under N_2, and the mixture was stirred at 35 °C for 30 h. After addition of water (5 mL), the organic substances were extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil, which was chromatographed (SiO_2, benzene–AcOEt (10:1)) to yield a slight yellow oil (54 mg, 93%, **8a**:**7** = 98:2).

Isolation of 6a by High-Pressure LC. A mixture of **5a** (87 mg, 0.28 mmol) and BF_3 etherate (58 mg, 0.4 mmol) in dry benzene (5 mL) was heated at 80 °C for 3 min. The mixture was worked up as usual and chromatographed (SiO_2, *n*-hexane–AcOEt (5:1)) to give a slight yellow oil, which contained **8b**, **7**, **12b**, **6a**, and others. The olefin **6a** was separated as an oil by high-pressure LC (μ-Porasil, *n*-hexane–AcOEt–ether (100:5:1)); IR (CCl_4) 1660 (C=C), 1310, 1140 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 3, CH_3), 1.60 (s, 3, CH_3), 1.75 (br s, 3, CH_3), 1.84 (br s, 3, CH_3), 1.32–2.00 (m, 4, CH_2), 3.76 (d, J = 7.8 Hz, 2, CH_2SO_2), 5.17 (t, J = 7.8 Hz, 1, CH=), 7.40–8.00 (m, 5, Ar H).

4β-(2,5β,6,6-Tetramethyl-2-cyclohexenyl)-4-(phenylsulfonyl)-2-butanone (18a). BuLi (0.6 mmol) was added to **8a** (58 mg, 0.2 mmol) dissolved in THF (1.5 mL) at −50 °C under N_2, and the mixture was stirred for 30 min. Then, propylene oxide (0.2 mL) was added to the mixture at −50 °C, and the temperature was allowed to rise to room temperature. After being stirred for 20 h, the mixture was quenched with saturated NH_4Cl. Usual workup and chromatography (SiO_2, benzene–AcOEt (10:1)) gave the corresponding alcohol (60 mg, 85%) as a diastereomeric mixture. The alcohol (60 mg, 0.17 mmol) in dry CH_2Cl_2 (0.5 mL) was added to pyridinium chlorochromate (71 mg, 0.33 mmol) dissolved in CH_2Cl_2 (1 mL), and the mixture was stirred vigorously at room temperature for 8 h. After quenching with water (1 mL) followed by extraction with $CHCl_3$, the extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (SiO_2, benzene–AcOEt (10:1)) to give **18a** (53 mg, 89%, 76% from **8a**) as colorless crystals: mp 77.0–78.0 °C (benzene–hexane (1:10)); IR (neat) 1723 (C=O), 1590, 1308, 1150 (SO_2) cm^{-1}; ^1H NMR δ 0.72 (d, J = 6.2 Hz, 3, CH_3), 0.78 (s, 3, CH_3), 0.80 (s, 3, CH_3), 1.78 (br s, 3 CH_3), 1.97 (s, 3, CH_3), 2.50 (br s, 1, CH), 2.68 (dd, J_1 = 2.2 Hz, J_2 = 19.4 Hz, 1, CH_2CO), 3.10 (dd, J_1 = 7.6 Hz, J_2 = 19.4 Hz, 1, CH_2CO), 4.30 (d, J = 7.6 Hz, 1, $CHSO_2$), 5.52 (br s, 1, CH=), 7.40–8.00 (m, 5, Ar H). Anal. Calcd for $C_{20}H_{28}O_3S$: C, 68.94; H, 8.10. Found: C, 68.92; H, 8.37.

4α-(2,5β,6,6-Tetramethyl-2-cyclohexenyl)-4-(phenylsulfonyl)-2-butanone (18b). The ketone **18b** was prepared under the same reaction conditions as employed for **18a** (76% from **8b**): mp 96.0–97.0 °C; IR (neat) 1723 (C=O), 1587, 1305, 1150 (SO_2) cm^{-1}; ^1H NMR δ 0.46 (s, 3, CH_3), 0.64 (s, 3, CH_3), 0.75 (d, J = 6.3 Hz, 3, CH_3), 1.20–1.90 (m, 3, CH_2, CH), 1.86 (s, 3, CH_3), 2.08 (s, 3, CH_3), 2.54 (d, J = 19.4 Hz, 1, CH_2CO), 2.78 (br s, 1, CH), 3.42 (dd, J_1 = 8.4 Hz, J_2 = 19.4 Hz, 1, CH_2CO), 4.32 (d, J = 8.4 Hz, 1, $CHSO_2$), 5.62 (br s, 1, CH=), 7.40–8.04 (m, 5, Ar H). Anal. Calcd for $C_{20}H_{28}O_3S$: C, 68.94; H, 8.10. Found: C, 68.69; H, 7.89.

4-(2,5,6,6-Tetramethylcyclohexenyl)-4-(phenylsulfonyl)-2-butanone (17). The ketone **17** was obtained as a diastereomeric mixture in the same condition as employed for **18a** (67% from **7**): IR (neat) 1723 (C=O), 1640 (C=C), 1590, 1300, 1150 (SO_2) cm^{-1}; ^1H NMR δ 0.63–0.98 (m, 9, CH_3), 1.10–1.72 (m, 5, CH_2, CH), 1.92 (s, 3, CH_3), 2.10 (s, 3, CH_3), 2.56–2.84 (m, 1, CH_2CO), 3.76–4.06 (m, 1, CH_2CO), 4.68–4.85 (m, 1, $CHSO_2$), 7.36–7.92 (m, 5, Ar H). Anal. Calcd for $C_{20}H_{28}O_3S$: C, 68.94; H,

8.10. Found: C, 68.65; H, 8.39.

4β-(2,5β,6,6-Tetramethyl-2-cyclohexenyl)-3(*E*)-buten-2-one (2a,*cis*-α-Irone). The ketone **18a** (35 mg, 0.09 mmol) in dry THF (3 mL) was added to MeONa (30 mg, 0.57 mmol) dissolved in *t*-BuOH (6 mL) at 5 °C under N_2. The mixture was stirred at room temperature for 7 h. The usual workup and chromatography (SiO_2, benzene–AcOEt (10:1)) provided **2a** (16 mg, 86%) as a colorless oil. The synthetic **2a** was homogeneous on VPC (SE-30, 4φ-3m, 170 °C), and its IR and NMR spectra were superimposable with those of the authentic sample (Shinetsu). Similarly, **1** and **2b** were prepared from **17** and **18b** in 84 and 85% yield, respectively. The published spectral data of **1**, **2a**, and **2b** were in agreement with those of the synthetic samples.[19]

Registry No. (±)-**1**, 72074-84-1; (±)-**2a**, 72074-85-2; (±)-**2b**, 72074-86-3; (±)-**5a**, 72049-66-2; (±)-**5b**, 72049-67-3; **6a**, 72049-68-4; **6c**, 56881-52-8; **6d**, 56691-80-6; (±)-**7**, 72049-69-5; (±)-**8a**, 72049-70-8; (±)-**8b**, 72049-71-9; (±)-**8c**, 64418-55-9; (±)-**9a**, 72049-72-0; (±)-**9b**, 72049-73-1; (±)-**10a**, 72049-74-2; (±)-**10b**, 72065-27-1; **11a**, 72049-75-3; **11b**, 72049-76-4; (±)-**17**, isomer 1, 72049-77-5; (±)-**17**, isomer 2, 72049-78-6; (±)-**18a**, isomer 1, 72049-79-7; (±)-**18a**, isomer 2, 72074-87-4; (±)-**18b**, isomer 1, 72074-88-5; (±)-**18b**, isomer 2, 72074-89-6; nerol, 106-25-2; methyl iodide, 74-88-4; propylene oxide, 75-56-9; 4-(2,5,6,6-tetramethyl-2-cyclohexenyl)-4-(phenylsulfonyl)-2-butanol, 72049-80-0.

Methylation and Hydroxylation Studies on Aloe-emodin

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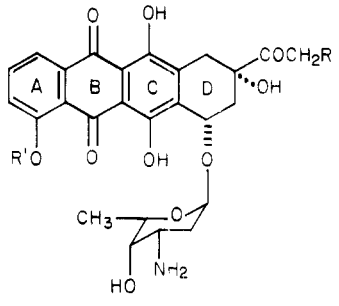
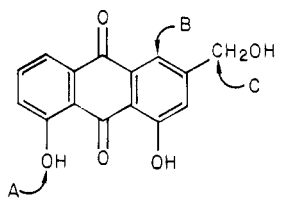
The chemistry of aloe-emodin (**3**) has been explored with a view toward its use as a synthon for the regiospecific synthesis of adriamycin and analogues of it. Routes for satisfactory large-scale monomethyl ether formation at C_8 (**4**) and regiospecific introduction of a phenolic oxygen function at C_4 (**21**) are described. Interesting side reactions were encountered, including an apparent peri O to O acyl wandering reaction during methylation and a reductive debromination reaction during displacement of an aryl bromide by methanolic methoxide.

The anthracycline antibiotics adriamycin (doxorubicin) (**1**) and daunomycin (**2**) are clinically effective antitumor



1, R = OH, R^1 = CH_3
2, R = H, R^1 = CH_3



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agents of considerable contemporary interest.[1] Despite their gratifying spectrum, potency, and clinical acceptance, they are not perfect drugs because of their costliness and toxicity and the resistance which is developed by some cell lines. As a consequence, there have been numerous attempts to solve one or more of these problems by the chemical synthesis of suitable aglycones.[1,2]

Many of the syntheses published to date suffer at a fairly advanced stage from a lack of regiospecificity in joining the AB and CD or ABC and D rings because of the inherent symmetry of ring C. The regiospecificity problem can be overcome, and the production of novel analogues can be achieved, in principle, through the use of starting materials which incorporate at the outset as many asymmetric features of the final target antibiotics as possible. These considerations have led to a considerable recent resurgence of interest in the chemistry of anthraquinones.[3-14]

One of our approaches to anthracyclines has been to explore the chemistry of aloe-emodin (**3**), readily available from oxidation of aloin, a *C*-glycoside present in substantial quantity in aloes, the dried juice of the leaves of various succulent tropical plants of the family Lilaceae. This material is available inexpensively in quantity because of its venerable medicinal use as a carthartic. Three essential problems must be addressed successfully if aloe-emodin is to be used for adriamycin synthesis: (A) one must be able to methylate selectively the phenolic OH group in the future A ring, (B) one must introduce a phenolic OH group into the future C ring, and (C) one must add additional carbons to the benzyl alcohol moiety such that the future D ring can be assembled and still retain suitable functionality for completion of the synthetic sequence. Some of our experiences in finding solutions to problems A and B are reported here.

Results

A. Monomethylation of Aloe-emodin. The two phenolic hydroxyls of aloe-emodin are of similar reactivity so that direct methylation with either Me_2SO_4–K_2CO_3 or, less effectively, with diazomethane, when stopped at the monomethylation stage, produces a nearly equimolar

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