The residue was chromatographed on silica gel (3 g) to give **17b** (18 mg, quantitative).

Reaction of Endoperoxide 3a with Cobalt-Tetraphenylporphine. To a solution of CoTPP (3 mg, 4.5×10^{-3} mmol) in CH_2Cl_2 (1 mL) was added a solution of **3a** (20 mg, 4.8×10^{-2} mmol) in CH_2Cl_2 (1 mL) at −20 °C, and the mixture was stirred at −20 to −10 °C for 5 h. Evaporation of the solvent and chromatography of the residue on silica gel (5 g) with ethyl acetate-hexane (80:20) as the eluent afforded **13a** (15 mg, 75%).

Reaction of Endoperoxides 3a and 4a with Tetrakis(triphenylphosphine)palladium. A solution of **3a** (35 mg, 8.4×10^{-2} mmol) and $Pd(Ph_3P)_4$ (10 mg, 8.7×10^{-3} mmol) in benzene (1 mL) was refluxed for 15 min. The dark red reaction mixture was directly chromatographed on silica gel to afford **15a** (16 mg, 47%) (ethyl acetate–hexane, 20:80) and **13a** (5.5 mg, 16%) (ethyl acetate–hexane, 70:30).

In a similar manner, **4a** (50 mg) was treated with $Pd(Ph_3P)_4$ to give **15a** (25 mg, 52%) and **14a** (8 mg, 16%).

(6*R*)-9,10-Secocholesta-5(10),7-diene-3β,6,19-triol (9). Reduction of Endoperoxide 3a with $LiAlH_4$. A solution of **3a** (118 mg, 0.28 mmol) in dry ether (5 mL) was added to a suspension of $LiAlH_4$ (22 mg, 0.58 mmol) in ether (2 mL) at 0 °C. After 1 h at room temperature, the reaction was quenched with wet Na_2SO_4, and the mixture was filtered and washed with ethyl acetate–methanol (4:1). The combined filtrate and washings were evaporated, and the residue was chromatographed on Sephdex LH-20 (10 g) with hexane–chloroform (35:65) as the eluent to afford triol **9**: 83 mg (70%); MS, *m/e* 418 (M^+), 400, 382, 287, 269, 152, 134; ^1H NMR ($CDCl_3$) δ 0.50 (3 H, s, H-18), 3.88 (1 H, m, H-3), 4.05 (1 H, d, *J* = 12 Hz, H-19), 4.25 (1 H, d, *J* = 12 Hz, H-19), 5.14 (1 H, d, *J* = 8 Hz, H-6 or H-7), 5.34 (1 H, d, *J* = 8 Hz, H-7 or H-6); IR ($CHCl_3$) 3610, 3410, 2960 cm^{-1}.

(6*S*)-9,10-Secocholesta-5(10),7-diene-3β,6,19-triol (10). Reduction of Endoperoxide 4a with $LiAlH_4$. Reduction of **4a** (45 mg) with $LiAlH_4$ was followed the procedure described above to give triol **10**: 23 mg (51%); MS *m/e* 418 (M^+), 400, 287, 269, 153, 152, 135, 134; ^1H NMR ($CDCl_3$) δ 0.57 (3 H, s, H-18), 3.77 (1 H, d, *J* = 12 Hz, H-19), 4.10 (1 H, m, H-3), 4.47 (1 H, d, *J* = 12 Hz, H-19), 5.10 (1 H, d, *J* = 8 Hz, H-6 or H-7), 5.52 (1 H, d, *J* = 8 Hz, H-7 or H-6); IR ($CHCl_3$) 3620, 3410, 2955 cm^{-1}.

Registry No. **1a**, 67-97-0; **1b**, 50-14-6; **2a**, 22350-41-0; **2b**, 51744-66-2; **3a**, 73047-69-5; **3b**, 70779-98-5; **3c**, 70779-97-4; **4a**, 73047-65-1; **4b**, 70779-99-6; **4c**, 70801-88-6; **5a**, 86728-02-1; **5b**, 86728-03-2; **6a**, 86728-04-3; **6b**, 86728-05-4; **7a**, 86728-06-5; **8a**, 86728-07-6; **9a**, 86832-43-1; **10a**, 74532-19-7; **13a** C(19)-(*R*), 86728-08-7; **13a** C(19)-(*S*), 86832-09-8; **13b** C(19)-(*R*), 86832-44-2; **13b** C(19)-(*S*), 86832-45-3; **14a**, 86782-90-3; **14b** C(19)-(*R*), 86832-46-4; **14b** C(19)-(*S*), 86832-47-5; **15a**, 74546-09-1; **15b**, 86728-10-1; **16b**, 86728-11-2; **17a**, 86728-12-3; **17a** semicarbazone, 86728-13-4; **17b**, 86728-14-5; **17c**, 86728-15-6.

Stereoselective Synthesis of (5*E*)- and (5*Z*)-Vitamin D_3 19-Alkanoic Acids via Vitamin D_3–Sulfur Dioxide Adducts

Sachiko Yamada, Takayoshi Suzuki, and Hiroaki Takayama*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

Katsuhito Miyamoto, Isao Matsunaga, and Yoshiharu Nawata

New Drug Research Laboratories, Chugai Pharmaceutical Co., Toshima-ku, Tokyo 171, Japan

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(5*E*)- and (5*Z*)-vitamin D_3 19-alkanoic acids **7** and **8** have been synthesized by a new method starting with vitamin D_3. In this synthesis, sulfur dioxide was utilized innovatively to protect the *s*-cis diene part of vitamin D and at the same time to activate the terminal position (C-19) of the diene group for an electrophilic substitution reaction. The two C-6 epimers of the vitamin D_3–sulfur dioxide adducts **2** and **3** were isolated in pure form, and the structure was determined unambiguously on the basis of X-ray analysis. The reaction of pure adducts **2b** and **3b** with *tert*-butyl ω-iodoalkanoate **4** proceeded with complete regio- and stereoselectivity to afford 19-alkanoic acid derivatives **5** and **6** in which the substituent at C-19 is located trans to that at C-6. Thermolytic desulfonylation of the 19-substituted adducts **5** and **6** in the presence of $NaHCO_3$ afforded (5*E*)-vitamin D_3 19-alkanoic acid derivatives **7** with high selectivity (ca. 93%), contrary to orbital symmetry rules. The (5*E*)-vitamin D derivatives **7** were converted to the corresponding (5*Z*)-vitamin D derivatives **8** in high selectivity (ca. 95%) by photosensitized isomerization.

Extensive studies on the metabolism of vitamin D_3 have lead to the discovery of more than 20 metabolites.[1] For clinical studies of the production of the biologically important metabolites, such as 1α,25-dihydroxyvitamin D_3, 24(*R*),25-dihydroxyvitamin D_3, etc., establishment of a sensitive, convenient, and selective analytical method has been needed. Radioimmunoassay has been highly successful for the measurement of steroid hormones. For use as an immunogen, a vitamin D molecule must be converted to a derivative appropriate for combining with a protein. Recently, we have developed a new regioselective method of alkylating vitamin D at the 6- and 19-positions via its sulfur dioxide adducts **2** and **3**.[2] In this method sulfur dioxide is used to protect the *s*-cis diene part of vitamin D, as well as to activate the terminal position of the diene group for electrophilic substitution reaction under basic conditions. We planned to apply the alkylation method to the synthesis of vitamin D_3 19-alkanoic acid derivatives **7** and **8**. The compounds **8** and **7** as components of a hapten are suitable derivatives for inducing antibodies for the radioimmunoassay of vitamin D and its 1α-hydroxylated derivatives, respectively. Because the biologically essential hydroxyl group remains intact[3] in **7** and

(1) (a) DeLuca, H. F.; Schnoes, H. K. *Annu. Rev. Biochem.* **1976**, *45*, 631. (b) Takasaki, Y.; Suda, T.; Yamada, S.; Takayama, H.; Nishii, Y. *Biochemistry* **1981**, *20*, 1681. (c) Tanaka, Y.; Wichmann, J. K.; Schnoes, H. K.; DeLuca, H. F. *Ibid.* **1981**, *20*, 3875. (d) Wichmann, J. K.; Schnoes, H. K.; DeLuca, H. F. *Ibid.* **1981**, *20*, 7385. (e) Ohnuma, N.; Kruse, J. R.; Popjak, G.; Norman, A. W. *J. Biol. Chem.* **1982**, *257*, 5097. (f) Ohnuma, N.; Norman, A. W. *Ibid.* **1982**, *257*, 8261. (g) Yamada, S.; Ohmori, M.; Takayama, H.; Takasaki, Y.; Suda, T. *Ibid.* **1983**, *258*, 457.

(2) Yamada, S.; Suzuki, T.; Takayama, H. *Tetrahedron Lett.* **1981**, *22*, 3085.

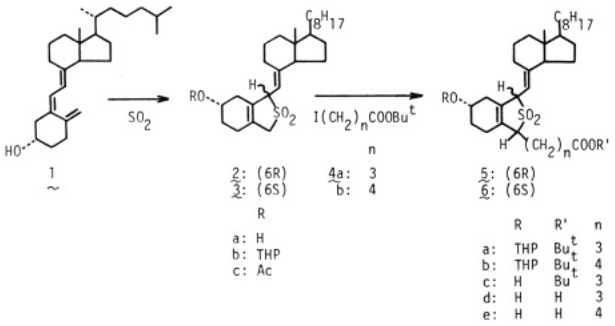
0022-3263/83/1948-3483$01.50/0

Table I. ^{1}H NMR Spectral Data of Vitamin D–Sulfur Dioxide Adducts

compd	shift[a] (multiplicity, J)				
	H-18	H-19	H-6	H-7	t-Bu
2a	0.55 (s)	3.30 (br s)	4.52 (d, 9)	4.78 (d, 9)	
3a	0.70 (s)	3.28 (br s)	4.49 (d, 9)	4.78 (d, 9)	
2b	0.56 (s)	3.32 (br s)	4.50 (d, 9)	4.75 (d, 9)	
3b	0.69 (s)	3.30 (br s)	4.50 (d, 9)	4.77 (d, 9)	
2c	0.56 (s)	3.34 (br s)	4.51 (d, 9)	4.79 (d, 9)	
3c	0.70 (s)	3.32 (br s)	4.51 (d, 9)	4.78 (d, 9)	
5a	0.56 (s)	3.55 (m)	4.55 (d, 9)	4.80 (d, 9)	1.42 (s)
6a	0.65 (s)	3.55 (m)	4.50 (d, 9)	4.70 (d, 9)	1.44 (s)
5b	0.56 (s)	3.52 (m)	4.51 (d, 9)	4.77 (d, 9)	1.46 (s)
5c	0.56 (s)	3.50 (m)	4.50 (d, 9)	4.75 (d, 9)	1.45 (s)
6c	0.67 (s)	3.55 (m)	4.50 (d, 9)	4.78 (d, 9)	1.45 (s)
5d	0.56 (s)	3.53 (m)	4.61 (d, 9)	4.85 (d, 9)	
6d	0.67 (s)	3.55 (m)	4.50 (d, 9)	4.78 (d, 9)	

[a] Shifts in parts per million downfield from Me_4Si in $CDCl_3$ solution. J values are in hertz.

Scheme I



8 and the carboxyl group is firmly connected to the vitamin D molecule via a C–C bond, the vitamin D moiety of the hapten is imparted with selectivity and stability. It is also advantageous that the carboxylic acids **7** and **8** can be prepared from ready-made vitamin D derivatives and that the length of the chain connecting the vitamin D molecule to the terminal carboxyl group can be controlled. Stereoselectivity of the alkylation reactions of the adducts **2** and **3** as well as the thermal desulfonylation reactions of the alkylated adducts **5** and **6** have been studied. We report in detail here the stereoselective synthesis of (5*E*)- and (5*Z*)-vitamin D_3 19-butanoic and -pentanoic acids along with the stereoselectivity of the reactions involved.

Results and Discussion

Except for the stabilized derivatives fused to an aromatic ring,[4] little attention[5] has been given to a practical method for alkylating the labile sulfolene α-carbanion.[6] We have found that alkylation of vitamin D–sulfur dioxide adducts **2** and **3** occurs by generating the unstable carbanion in the presence of alkylating agent.

Vitamin D_3–sulfur dioxide adducts **2a** and **3a** were prepared in quantitative yield[7] by the reaction of vitamin D_3 with liquid sulfur dioxide (Scheme I). The isomers were cleanly separated into the two C-6 epimers, less polar **2a** and more polar **3a**, in about 1:1 ratio, by silica gel chromatography. The stereochemistry of the two epimeric vitamin D_3–sulfur dioxide adducts **2a** and **3a** at C-6 was determined on the basis of X-ray analysis of crystalline acetyl derivative **2c** of the less polar isomer **2a**.[8] The ORTEP drawing of the molecules is shown in Figure 1. From this result the C-6 configuration of isomer **2a** was

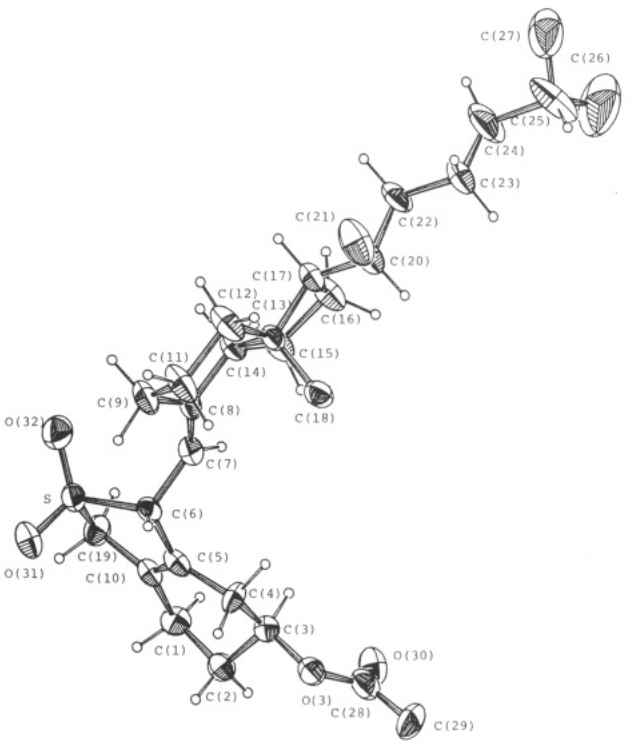


Figure 1. ORTEP drawing of the molecule of **2c** showing atom numbering. The calculated positions of hydrogen atoms (excluding those of methyl groups) are presented.

(3) In most of the previously reported radioimmunoassay methods of vitamin D metabolites, one of the hydroxyl groups of the metabolites is utilized to combine with protein via its hemisuccinate. For example: (a) Bouillon, R.; Moor, P. D.; Baggiolini, E. G.; Uskokovic, M. R. *Clin. Chem.* **1980**, *26*, 562. (b) Clemens, T. L.; Hendy, G. N.; Graham, R. F.; Baggiolini, E. G.; Uskokovic, M. R.; O'Riordan, J. L. H. *Clin. Sci. Mol. Med.* **1978**, *54*, 329. (c) Peacock, M.; Taylor, G. A.; Brown, W. *Clin. Chim. Acta* **1980**, *101*, 93.

(4) (a) Oppolzer, W.; Roberts, D. A.; Bird, T. G. C. *Helv. Chim. Acta* **1979**, *62*, 2017. (b) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463.

(5) (a) Berestovitskaya, V. M.; Speranskii, E. M.; Perekalin, R. V.; Trukhin, E. M. *Zh. Org. Khim.* **1974**, *10*, 1783. (b) Welcher, R. P. *J. Org. Chem.* **1963**, *28*, 1712.

(6) (a) Gaoni, Y. *Tetrahedron Lett.* **1977**, 4521. (b) Krug, R. C.; Rigney, J. S.; Tichelaar, G. R. *J. Org. Chem.* **1962**, 27, 1305.

(7) (a) Yamada, S.; Takayama, H. *Chem. Lett.* **1979**, 583. (b) Reischl, W.; Zbiral, E. *Helv. Chim. Acta*, **1979**, *62*, 1763. The structure of vitamin D_3–sulfur dioxide adducts reported in this literature is incorrect in the stereochemistry at C-6 and in the geometry of the 7(8)-double bond.

(8) The crystals were monoclinic $P2_1$ with cell dimensions of a = 15.448 Å, b = 11.752 Å, c = 7.762 Å, and β = 93.16°. Intensities were measured on a Philips PW1100 four-circle diffractometer using Cu Kα radiation monochromated by a graphite plate, and 1397 independent data were used for the analysis. The structure was elucidated by the direct method with program MULTAN (Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect A* **1971**, *A27*, 368). The positional and the thermal parameters of non-hydrogen atoms were refined by the least-squares method to an R value of 0.082.

Table II. ^{13}C NMR Spectral Data of Vitamin D-Sulfur Dioxide Adducts

atom/ compd	shift[a] (multiplicity)				
	2a	2c	3a	5c	6c
C-3	65.90 (d)	68.05 (d)	65.42 (d)	66.96 (d)	65.99 (d)
C-5	130.63 (s)	126.96 (s)	130.14 (s)	130.02 (s)	130.05 (s)
C-6	67.29 (d)	66.96 (d)	66.97 (d)	66.97 (d)	66.53 (d)
C-7	109.84 (d)	109.64 (d)	109.50 (d)	108.86 (d)	108.87 (d)
C-8	150.84 (s)	150.39 (s)	150.38 (s)	150.77 (s)	150.59 (s)
C-10	126.62 (s)	126.97 (s)	126.82 (s)	130.77 (s)	130.79 (s)
C-19	58.00 (t)	58.20 (t)	58.13 (t)	66.01 (d)	65.98 (d)

[a] Shifts in parts per million downfield from Me_4Si in $CDCl_3$ solution.

determined to be *R* and that of isomer **3a** to be *S*. This assignment is identical with that previously deduced on the basis of CD spectra[2,7a] and is different from that reported by Reischl et al.[7b]

We examined the reaction of *tert*-butyl γ-iodobutyrate (**4a**) with the THP ethers **2b** and **3b**. Treatment of a solution of the adduct **2b** and iodide **4a** in THF–DME with lithium tetramethylpiperidide (LiTMP) at −75 °C afforded a single alkylation product (**5a**) in 56% isolated yield (68% yield based on the consumed starting material). A similar result was obtained by using lithium bis(trimethylsilyl)-amide (LiHMDS) (THF–HMPA, −75 °C) for the alkylation. The 6*S* isomer **3b** reacted with iodide **4a** under similar reaction conditions to give a single alkylation product (**6a**) in 42% yield (62% based on the consumed **3b**).

The structure of the alkylation products **5a** and **6a** was based on the spectral data (Tables I and II and Experimental Section). The spectral properties of the corresponding 3β-hydroxyl derivatives **5c** and **6c** are also shown in the Tables to support the structures. The mass spectra show a parent ion at $M^+ - SO_2$. The IR spectra show an absorption due to the ester carbonyl near 1720 cm^{-1}. The ^1H NMR spectra show a pair of doublets for H-6 and H-7 at δ 4.5–5.0, a one-proton multiplet for H-19 at δ 3.5, a nine-proton singlet for the *tert*-butyl group at δ 1.4, and a three-proton singlet for H-18 which is characteristic for each of the C-6 epimers, the signal of the 6*R* isomer appearing at δ 0.55 and that of the 6*S* isomers at δ 0.65–0.70. The ^1H NMR spectral data indicate that in each alkylated adduct (**5a** and **6a**), no epimerization at C-6 occurred. In addition, the epimerization at C-6 was not observed in the recovered starting materials (**2b** and **3b**). The ^{13}C NMR spectra of **5c** and **6c** (Table II) indicate definitely that the alkylation occurred at the 19-position, since the signals of C-10 and C-19 shift downfield compared with those of the starting materials due to the β- and α-effects, respectively, of the newly introduced 19-substituent. The stereochemistry of the substituent introduced at C-19 could not be determined on the basis of the spectral data alone. The stereochemistry was assigned trans to the substituent at C-6 on the basis of examples of alkylation of 3-sulfolene derivatives under similar reaction conditions.[9] The results of desulfonylation of alkylation products **5** and **6** also support the assigned structure (see below). The regio- and stereochemical results of the alkylation of adducts **2b** and **3b** reveal that, of the three active hydrogens adjacent to the sulfonyl group, the bulky base used can abstract only the least hindered proton at C-19 oriented trans to the C-6 substituent and that the carbanion generated reacts rapidly before it undergoes inversion of the configuration.

Table III. Thermolytic Desulfonylation of 5c and 6c

entry	conditions	time,[b] h	substrate	ratio 7c/8c[c]
1	octane, 120 °C, argon bubbling[a]	2	5c	2.3
			6c	2.4
2	95% EtOH, 120 °C, $NaHCO_3$ (20 equiv)	2	5c	4.9
			6c	4.6
3	95% EtOH, 90 °C, $NaHCO_3$ (20 equiv)	3.5	5c	14.8

[a] Reactions were carried out by using a solution of the adduct **5c** or **6c** (25 mg) in a specified solvent (5 mL). [b] Time required to complete the reaction. [c] Product ratio determination based on the peak height at 260 nm on HPLC (Lichrosorb Si-60, 3% *i*-PrOH in hexane).

Treatment of **5a** and **6a** with trifluoroacetic acid (CH_2Cl_2, 0 °C to room temperature) afforded the corresponding carboxylic acids **5d** and **6d** in high yields (~90%).

Thermolytic desulfonylation of the alkylated adducts **5c** and **6c** was studied in some detail. Thermolysis of both adducts **5c** and **6c** yielded (5*E*)-vitamin D (**7c**) as the major product and the 5*Z* isomer (**8c**) as the minor product in 85–95% total yield. The ratio of the two products (**7c** and **8c**) depended somewhat on the reaction conditions as shown in Table III. In octane solution with continuous bubbling of argon gas at 120 °C,[10] the 5*E* isomer **7c** was obtained in about 70% selectivity (entry 1). The selectivity was raised to 80–85% under these conditions by adding $NaHCO_3$ (entry 2), and much higher selectivity was attained under the same conditions at lower temperature (entry 3). No appreciable diference in the stereoselectivity was observed between the two C-6 epimers (**5c** and **6c**). From the results, it appears that the desulfonylation proceeds preferentially in an antarafacial manner with respect to the diene part, clearly in contrast with the well-studied desulfonylation of *cis*- and *trans*-2,5-dimethyl-3-sulfolenes[11] in which the reaction proceeds exclusively in the suprafacial manner. Since the major product **7c** is considered to be the thermodynamically most stable isomer of the four possible products (**7**–**10**) and since

(9) The reaction of 2-*n*-butyl-3-sulfolene with *n*-butyl iodide under similar reaction conditions [LiHMDS, THF–HMPA, −75 °C] was found to give exclusively (ca. 95% selectivity) *trans*-2,5-dibutyl-3-sulfolene, whose structure was confirmed on the basis of spectral data and specific chemical reactions, bromination and thermal desulfonylation. Yamada, S.; Suzuki, T.; Ohsawa, H.; Takayama, H.; Miyamoto, K.; Ochi, K.; Matsunaga, I. "Abstracts of Papers", 5th International Conference on Organic Synthesis, Tokyo, Japan, Aug 1982, p 208. Ohsawa, H.; Suzuki, T.; Yamada, S.; Takayama, H. "Abstracts of Papers", 9th Symposium on Progress in Organic Reactions and Syntheses, Hiroshima, Japan, Nov 1982, p 103. Yamada, S.; Ohsawa, H.; Suzuki, T.; Takayama, H. *Chem. Lett.* **1983**, 1003.

(10) For elimination of the sulfur dioxide formed, which causes undesirable isomerization of vitamin D derivatives, from the reaction medium, continuous bubbling of inert gas or addition of basic substances is necessary.

(11) (a) Mock, W. L. *J. Am. Chem. Soc.* **1966**, *88*, 2857. (b) Mcgregor, S. D.; Lemal, D. M. *Ibid.* **1966**, *88*, 2858. (c) Mock, W. L. *Ibid.* **1975**, *97*, 3666. (d) *Ibid.* **1975**, *97*, 3673. (e) Isaacs, N. S.; Laila, A. A. R. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1470.

Scheme II

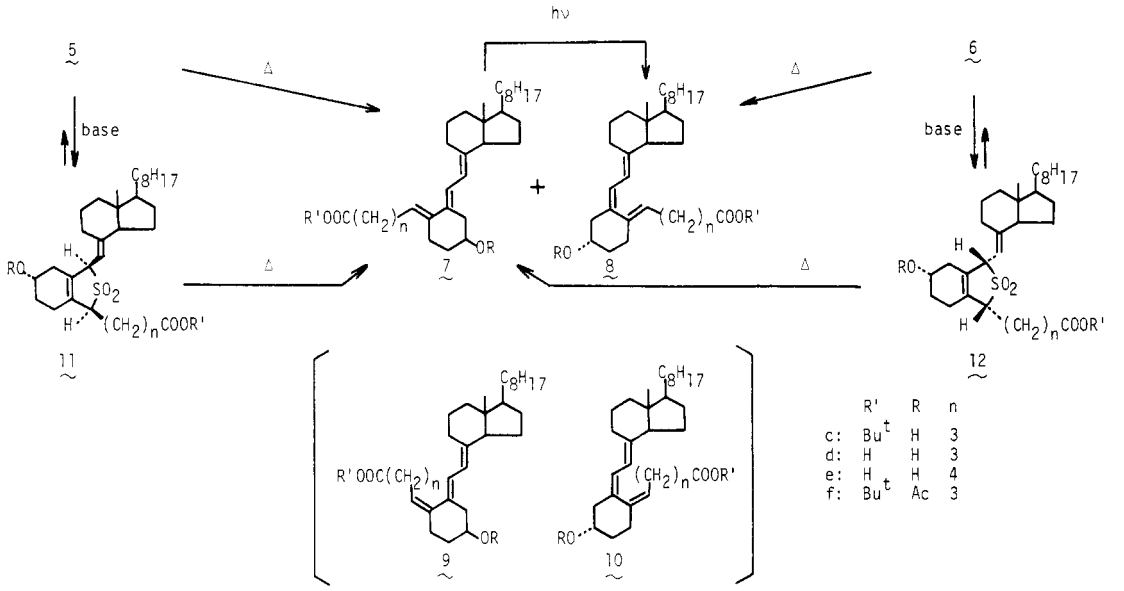


Table IV. ^{1}H NMR Spectral Data of 19-Substituted Vitamin D Derivatives

compd	shift[a] (multiplicity, J)				
	H-18	H-19	H-6	H-7	H-3
7c	0.57 (s)	5.20 (t, 7)	6.23 (d, 12)	5.90 (d, 12)	3.90 (m)
7d	0.57 (s)	5.20 (t, 7)	6.23 (d, 12)	5.89 (d, 12)	3.88 (m)
7f	0.56 (s)	5.18 (t, 7)	6.22 (d, 12)	5.92 (d, 12)	4.92 (m)
8c	0.54 (s)	5.29 (t, 7)	6.17 (d, 12)	5.94 (d, 12)	3.92 (m)
8d	0.55 (s)	5.35 (t, 7)	6.23 (d, 12)	5.95 (d, 12)	3.96 (m)
8f	0.54 (s)	5.32 (t, 7)	6.20 (d, 12)	5.94 (d, 12)	4.93 (m)

[a] Shifts in parts per million downfield from Me_4Si in $CDCl_3$ solution. J values are in hertz.

Table V. ^{13}C NMR Spectral Data of 19-Substituted Vitamin D Derivatives

atom/ compd	shift[a] (multiplicity)					
	7c	7d	7f	8c	8d	8f
C-4	37.40 (t)	37.95 (t)	35.16 (t)	45.95 (t)	45.85 (t)	43.63 (t)
C-5	143.36 (s)	143.25 (s)	143.94 (s)	141.75 (s)	141.65 (s)	142.05 (s)
C-6	123.16 (d)	123.20 (d)	123.89 (d)	121.98 (d)	121.99 (d)	122.65 (d)
C-7	114.94 (d)	114.90 (d)	115.51 (d)	117.63 (d)	117.60 (d)	118.21 (d)
C-8	140.62 (s)	140.59 (s)	140.99 (s)	141.74 (s)	141.70 (s)	141.90 (s)
C-10	131.42 (s)	131.40 (s)	131.42 (s)	128.15 (s)	128.15 (s)	128.19 (s)
C-19	123.00 (d)	122.98 (d)	123.70 (d)	121.98 (d)	121.90 (d)	122.59 (d)

[a] Shifts in parts per million downfield from Me_4Si in $CDCl_3$ solution.

sterically unfavorable isomers **9** and **10** could not be detected in the products, it is likely that in this case the cheletropic reaction yields the thermodynamically more stable products rather than exclusively the products allowed under the symmetry rule.[12] This is probably due to the presence of fairly bulky substituents on the sulfolene ring of adducts **5** and **6**. The effect of $NaHCO_3$ in enhancing the yield of the 5*E* isomer **7c** can be explained by assuming an equilibrium between the trans-substituted sulfolene **5** (or **6**) and the corresponding cis-substituted isomer **11** (or **12**) under basic reaction conditions (Scheme II); the resultant cis isomer (**11** or **12**), in turn, rapidly extrudes sulfur dioxide to yield the (5*E*)-vitamin D (**7**). It has been known in the thermolysis of *trans*- and *cis*-2,5-dimethyl-3-sulfolenes that the cis isomer is the thermodynamically more stable isomer although it extrudes sulfur dioxide more rapidly than the trans isomer. Formation of a considerable amount of (5*Z*)-vitamin D (**8**) in the thermolysis under neutral conditions (entry 1) supports the assigned structure for the alkylation products **5** and **6**, because if the sulfolenes **5** and **6** had the cis structure (**11** and **12**), they would produce only the thermodynamically more stable 5*E* isomer **7**, which is also the product allowed under the symmetry rule.[13]

Structures of **7c** and **8c** were based on the spectral data (Table IV and V and Experimental Section) and on the stereochemical aspect of the desulfonylation reaction. The UV spectrum of the major product **7c** showed an absorption maximum at a longer wavelength (269 nm) with a higher extinction coefficient (25 000) than that of the minor product 8c (λ_{max} 264 nm, ϵ 19 000) in accord with the UV spectra of the corresponding parent vitamin D deriva-

(12) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(13) It is unlikely that (5*E*)-vitamin D (**7**) isomerized to the (5*Z*)-vitamin D (**8**) under the reaction conditions; isomerization of (5*E*)-vitamin D to (5*Z*)-vitamin D has been known only in a photosensitized reaction[15] and in a catalytic reaction with iodine. Acid-catalyzed isomerization of (5*E*)- and (5*Z*)-vitamin D has been known to give isotachysterol and isovitamin D (Inhoffen, H. H.; Quinkert, G.; Hess, H.-J.; Erdmann, H.-M. *Ber.* **1956**, *89*, 2273).

tives.[14] In the ^1H NMR spectra, the proton at C-7 is slightly more deshielded in **8c** than in **7c** by the anisotropic effect of the 10(19)-double bond, while the proton at C-6 is more deshielded in **7c** than in **8c** by the same effect. In the ^{13}C NMR spectra, the signal of the carbon at the 4-position is useful in differentiating the geometrical isomers at the 5,6-double bond. Due to the γ-effect of the C(7)-H group, the signal of the 5*E* isomer appears at a field higher than that of the 5*Z* isomer.[15] The two desulfonylation products (**7c** and **8c**) show distinct difference in their C-4 chemical shifts: the signal of the major isomer **7c** appears at δ 37 whereas that of the minor isomer **8c** appears at δ 46. The assignment of the ^{13}C NMR signals of **7c** and **8c** were confirmed by comparison with those of the corresponding 3-acetoxy derivatives **7f** and **8f**. All of these spectral data indicate that the stereochemistry of the 5,6-double bond is *E* in the major product **7c** and *Z* in the minor product **8c**. Structure **10c** for the minor 5*Z* isomer was excluded for stereochemical reason. The compound **10c** is sterically severely congested, and formation of which is unlikely under the conditions of the desulfonylation. The structure **9c** is not appropriate for the major 5*E* isomer because it is unlikely that the thermolytic desulfonylation of **5c** (or **6c**) produces exclusively the thermodynamically less stable **9c** rather than more stable **8c**. The fact that the major isomer **7c** isomerized exclusively to the minor isomer **8c** by photosensitized reaction also indicates structure **7c** rather than **9c** for the major product (see below).[16]

Thermolysis of the carboxylic acid **5d** proceeded similarly to afford the 5*E* isomer **7d** as the major product (~93% selectivity) together with a minor amount of the 5*Z* isomer **8d** in 85–95% total yield under the same reaction conditions as entry 4. Spectral properties of **7d** and **8d** (Tables IV and V and Experimental Section) were in good agreement with the assigned structure.

(5*Z*)-Vitamin D derivatives **8** were obtained selectively by photosensitized isomerization[16] of the 5*E* isomers **7** or a mixture of the two isomers (**7** and **8**) obtained by the thermolysis. Thus, irradiation (halogen lamp) of an ethanol solution of **7c** in the presence of Rose Bengal afforded **8c** in 89% yield. In this reaction, no other product was detected on TLC or HPLC. At the photostationary state under the conditions with Rose Bengal as the sensitizer, the ratio 8:7 was more than 20. Similarly, photochemical isomerization of 5*E* carboxylic acid **7d** gave 5*Z* isomer **8d** in good yield (90%).

Alkylation of **2b** with *tert*-butyl δ-iodovalerate (**4b**) gave **5b** as a single product in 62% isolated yield. The adduct **5b** was transformed into (5*E*)-vitamin D_3 19-pentanoic acid (**7e**) in good overall yield (60%) by applying the methods described above.

Thus we have established a convenient and stereoselective method for synthesizing (5*E*)- and (5*Z*)-vitamin D_3 19-alkanoic acids starting with vitamin D_3. The preparation of the protein conjugate of the carboxylic acids (**7** and **8**) and the production of antibodies for radioimmunoassay are progressing.

Experimental Section

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Hitachi 215 spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were recorded with a Varian XL-100 spectrometer with tetramethylsilane as an internal standard and $CDCl_3$ as solvent. Carbon magnetic resonance (^{13}C NMR) spectra were recorded with a Varian XL-100 spectrometer at 25.16 MHz. The solvent for ^{13}C NMR spectra was $CDCl_3$ with tetramethylsilane as an internal reference; with deuterated solvent providing the internal lock signal. Mass spectra were recorded with a JEOL JMS-D300 GC-MS instrument with interfaced computer. Ultraviolet (UV) spectra were recorded with a Union Giken SM-401 spectrophotometer and 95% ethanol as solvent.

Sulfur Dioxide Adducts of Vitamin D_3 (2a and 3a). Vitamin D_3 (**1**) (5.0 g, 13.0 mmol) was dissolved in liquid sulfur dioxide (~30 mL), and the solution was refluxed at the boiling temperature of sulfur dioxide for 30 min. The sulfur dioxide was evaporated, and the residue was chromatographed on silica gel (150 g) with $CHCl_3$–acetone (19:1) as eluent to afford less polar **2a** (2.80 g, 48%) and more polar **3a** (2.68 g, 46%). **2a**: IR ($CHCl_3$) 1310, 1148 cm^{-1}; mass spectrum, *m/e* 384 ($M^+ - SO_2$). **3a**: IR ($CHCl_3$) 1308, 1150 cm^{-1}; mass spectrum, *m/e* 384 ($M^+ - SO_2$).

Sulfur Dioxide Adducts of Vitamin D_3 3-Acetate (2c and 3c). To a solution of **2a** (449 mg, 1 mmol) in pyridine (2 mL) was added acetic anhydride (225 mg, 2.2 mmol) at 0 °C under argon, and the solution was stirred for 3 h at room temperature. The resulting mixture was evaporated, and the residue was chromatographed on silica gel (10 g) with ethyl acetate–hexane (1:4) as eluent to afford **2c** (437 mg, 89%): mp 123–126 °C dec (recrystallized from diisopropyl ether–hexane); IR ($CHCl_3$) 1719, 1310, 1148 cm^{-1}; mass spectrum, *m/e* 426 ($M^+ - SO_2$).

Acetylation of **3a** (224 mg, 0.5 mmol) followed the procedure described above to give **3c** (225 mg, 92%): IR ($CHCl_3$) 1721, 1305, 1150 cm^{-1}; mass spectrum, *m/e* 426 ($M^+ - SO_2$).

Sulfur Dioxide Adducts of Vitamin D_3 3-Tetrahydropyranyl Ether (2b and 3b). To a solution of **2a** (2.56 g, 5.71 mmol) and dihydropyran (720 mg, 8.57 mmol) in CH_2Cl_2 (15 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (143 mg, 0.57 mmol) at room temperature under argon, and the solution was stirred for 4 h at room temperature. The solvent was evaporated, and the residue was chromatographed on silica gel (50 g) with hexane–ethyl acetate (4:1) as eluent to afford **2b** (2.85 g, 94%): IR ($CHCl_3$) 1310, 1150 cm^{-1}; mass spectrum, *m/e* 468 ($M^+ - SO_2$), 384 (468 – dihydropyran).

Tetrahydropyranylation of **3a** (2.11 g, 4.69 mmol) followed the procedure described above to give **3b** (2.37 g, 95%): IR ($CHCl_3$) 1307, 1148 cm^{-1}; mass spectrum, *m/e* 468 ($M^+ - SO_2$), 384 (468 – dihydropyran).

6*R* Sulfur Dioxide Adduct of *tert*-Butyl Vitamin D_3 19-Butanoate 3-Tetrahydropyranyl Ether (5a). A. To a solution of tetramethylpiperidine (514 μL, 3.05 mmol) in pentane (1.2 mL) was added a 1.40 M hexane solution of *n*-butyllithium (1.82 mL, 2.54 mmol) at –75 °C under argon, and the solution was stirred at that temperature for 2 h. The cold (–75 °C) solution of LiTMP was added via stainless tubing in one portion to a solution of **2b** (1.08 g, 2.03 mmol) and *tert*-butyl γ-iodobutylate (**4a**) (527 μL, 2.54 mmol) in THF–DME (1:3, 8 mL) at –75 °C under argon. The resulting mixture was stirred for 1 h at –75 °C, and then ethyl acetate (15 mL) was added. The solution was allowed to warm to room temperature and was washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (60 g) with hexane–ethyl acetate (4:1) as eluent to yield **5a** (765 mg, 56%) and the starting material **2b** (198 mg, 18%). **5a**: IR ($CHCl_3$) 1710, 1310, 1148 cm^{-1}; mass spectrum, *m/e* 610 ($M^+ - SO_2$), 526 (610 – dihydropyran), 508 (526 – H_2O), 451 (508 – *t*-Bu).

B. A solution of lithium bis(trimethylsilyl)amide (prepared from hexamethyldisilazane and *n*-butyllithium, and purified by distillation) (174 mg, 1.05 mmol) in THF (1 mL) was cooled to –75 °C and added to a solution of **2b** (194 mg, 0.364 mmol), iodide **4a** (114 μL, 0.55 mmol), and HMPA (120 μL, 0.73 mmol) in THF (3 mL) at –75 °C under argon. After workup and chromatographic purification as above, **5a** (75 mg, 31%) and the starting material **2b** (42 mg, 22%) were obtained.

6*S* Sulfur Dioxide Adduct of *tert*-Butyl Vitamin D_3 19-Butanoate 3-Tetrahydropyranyl Ether (6a). A cold (–75 °C) solution of LiTMP prepared from *n*-butyllithium (1.4 M hexane

(14) The UV spectra are not correlated to those of 19-methyl analogues reported in the previous paper.[2] Explanation awaits further investigation.

(15) (a) Berman, E.; Luz, Z.; Mazur, Y.; Sheves, M. *J. Org. Chem.* **1977**, *42*, 3325. Tsukida, K.; Akutsu, K.; Saiki, K. *J. Nutr. Sci. Vitaminol.* **1975**, *21*, 411.

(16) Gielen, J. W. J.; Koolstra, R. B.; Jacobs, H. J. C.; Havinga, E. *Recl. Trav. Chim. Pay-Bas* **1980**, 99, 306.

solution, 200 μL, 0.28 mmol) and tetramethylpiperidine (57 μL, 0.34 mmol) was added in one portion to a solution of **3b** (120 mg, 0.23 mmol) and iodide **4a** (58.5 μL, 0.28 mmol) in THF–DME (1:3, 2 mL) at −75 °C under argon, and the mixture was stirred at that temperature for 1 h. The reaction mixture was worked up as above, and the products were chromatographed on silica gel (10 g) with hexane–ethyl acetate (4:1) as eluent to yield **6a** (64 mg, 42%) and **3b** (40 mg, 33%). **6a**: IR ($CHCl_3$) 1720, 1315, 1148 cm^{-1}; mass spectrum, m/e 610 ($M^+ - SO_2$), 526, 508, 451.

6*R* Sulfur Dioxide Adduct of *tert*-Butyl Vitamin D_3 19-Pentanoate 3-Tetrahydropyranyl Ether (5b). A cold (−75 °C) solution of LiTMP prepared from *n*-butyllithium (2.33 M hexane solution, 210 μL, 0.49 mmol) and tetramethylpiperidine (107 μL, 0.64 mmol) in pentane (0.8 mL) was added to a solution of **2b** (200 mg, 0.38 mmol) and *tert*-butyl δ-iodopentanoate (**4b**) (139 mg, 0.49 mmol) in THF–DME (3:1, 2 mL) at −75 °C under argon. After 1 h the mixture was worked up as above and the products were chromatographed on silica gel (10 g). Elution with hexane–ethyl acetate (4:1) yielded **5b** (126 mg, 49%) and the starting material **2b** (44 mg, 22%). **5b**: IR ($CHCl_3$) 1715, 1310, 1148 cm^{-1}; mass spectrum, m/e 624 ($M^+ - SO_2$), 540 (624 − dihydropyran), 522 (540 − H_2O), 465 (522 − *t*-Bu).

6*R* Sulfur Dioxide Adduct of *tert*-Butyl Vitamin D_3 19-Butanoate (5c). A solution of **5a** (510 mg, 0.76 mmol) and PPTS (250 mg, 1 mmol) in EtOH (10 mL) was stirred at 40–45 °C for 2 h. The solvent was evaporated, and the residue was chromatographed on silica gel (30 g) with hexane–ethyl acetate (1:1) as eluent to yield **5c** (408 mg, 91%): IR ($CHCl_3$) 1710, 1310, 1150 cm^{-1}; mass spectrum, m/e 526 ($M^+ - SO_2$), 469; high-resolution mass spectrum, $C_{35}H_{58}O_3$ requires m/e 526.6496, found 526.6450.

6*S* Sulfur Dioxide Adduct of *tert*-Butyl Vitamin D_3 19-Butanoate (6c). Deprotection of **6a** (50 mg) followed the procedure described above to yield **6c** (41 mg, 94%): IR ($CHCl_3$) 1720, 1312, 1148 cm^{-1}; mass spectrum, m/e 526 ($M^+ - SO_2$), 469; high-resolution mass spectrum, $C_{35}H_{58}O_3$ requires m/e 526.6496, found 526.6461.

6*R* Suflur Dioxide Adduct of Vitamin D_3 19-Butanoic Acid (5d). Trifluoroacetic acid (1 mL) was added dropwise to a solution of **5a** (95.4 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and then at room temperature for 1.5 h. Water (100 μL) was added, and the mixture was stirred for a further 1 h at room temperature. The mixture was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on Sephadex LH-20 (10 g) with hexane–$CHCl_3$–MeOH (100:300:6) as eluent to afford **5d** (68 mg, 90%): IR ($CHCl_3$) 1710, 1310, 1150 cm^{-1}; mass spectrum, m/e 470 ($M^+ - SO_2$), 452 (470 − H_2O), 222.

6*S* Sulfur Dioxide Adduct of Vitamin D_3 19-Butanoic Acid (6d). Hydrolysis of **6a** (100 mg, 0.15 mmol) followed the procedure described above to yield **6d** (62 mg, 78%): IR ($CHCl_3$) 1708, 1310, 1148 cm^{-1}; mass spectrum, m/e 470 ($M^+ - SO_2$), 452, 222.

Thermolysis of 5c. A suspension of **5c** (10 mg, 1.7×10^{-2} mmol) and $NaHCO_3$ (28 mg, 0.34 mmol) in 95 EtOH (3 mL) was heated at 90–95 °C with stirring in a sealed tube under argon for 3.5 h. The mixture was cooled to room temperature, and the $NaHCO_3$ was filtered and washed with ethyl acetate. The combined filtrate and washings were evaporated. The residue was chromatographed on silica gel (10 g) with hexane–ethyl acetate (4:1) as eluent to afford **7c** (8.0 mg, 90%) and **8c** (ca. 120 μg based on the UV spectrum). **7c**: IR ($CHCl_3$) 1715 cm^{-1}; mass spectrum, m/e 526 (M^+), 469 (M^+ − *t*-Bu), 451 (469 − H_2O), 278 [A ring + C(6) + C(7) + C(19)]; high-resolution mass spectrum, $C_{35}H_{58}O_3$ requires m/e 526.6496, found 526.6468; UV (95% EtOH) 269 nm (ε 25 000).

Thermolysis of 6c. A suspension of **6c** (35 mg, 5.9×10^{-2} mmol) and $NaHCO_3$ (80 mg, 0.95 mmol) in 95% EtOH (5 mL) was heated with stirring at 120 °C in a sealed tube under argon for 3.5 h. The solvent was evaporated, and the residue was chromatographed on silica gel (9 g) with hexane–ethyl acetate (4:1) as eluent to afford **7c** (22 mg, 71%) and **8c** (5 mg, 15%). **8c**: IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 526 (M^+), 469, 451, 278; high-resolution mass spectrum, $C_{35}H_{58}H_3$ requires m/e 526.6496, found 526.6477; UV (95% EtOH) 264 nm (ε 19 000).

Thermolysis of 5d. A mixture of **5d** (17.4 mg, 3.2×10^{-2} mmol) and $NaHCO_3$ (54 mg, 0.65 mmol) suspended in 95% EtOH (5 mL) was heated with stirring at 90–95 °C under argon in a sealed tube for 3.5 h. The mixture was diluted with ethyl acetate, washed with 1% HCl and water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on Sephadex LH-20 (10 g) with hexane–$CHCl_3$–MeOH (100:300:6) as eluent to yield **7d** (12 mg, 77%) and a mixture of **7d** and **8d** (2.3 mg). **7d**: IR ($CHCl_3$) 1705 cm^{-1}; mass spectrum, m/e 470 (M^+), 452 ($M^+ - H_2O$), 222 [A ring + C(6) + C(7) + C(19)]; UV (95% EtOH) 264 nm.

(5*E*)-Vitamin D_3 19-Pentanoic Acid (7e). A solution of **5b** (63 mg, 9.2×10^{-2} mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic acid (1 mL) as described above. After workup and chromatographic purification, **5e** (42 mg, 83%) was obtained. The acid **5e** was dissolved in 95% EtOH (5 mL) and heated in a sealed tube at 95 °C in the presence of $NaHCO_3$ (64 mg, 0.76 mmol) for 3.5 h. The mixture was worked up as described above in the thermolysis of **5d**. Chromatography of the products on Sephadex LH-20 with hexane–$CHCl_3$–MeOH (100:300:6) as eluent afforded **7e** (27 mg, 73%) and a mixture of **7e** and **8e** (6 mg). **7e**: IR ($CHCl_3$) 1705 cm^{-1}; mass spectrum, m/e 484 (M^+); UV (95% EtOH) 269 nm.

Photochemical Isomerization of 7c to 8c. A solution of **7c** (5.4 mg, 10 μmol) and Rose Bengal (2 mg) in 95% EtOH (10 mL) was irradiated under argon with a halogen lamp (Ushio 200W) for 3 min. The mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (5 g) with hexane–ethyl acetate (1:1) as eluent to afford **8c** (4.8 mg, 89%).

Photochemical Isomerization of 7d to 8d. A solution of **7d** (3 mg, 6.4 μmol) and Rose Bengal (1.3 mg) in 95% EtOH (10 mL) was irradiated as described above. After workup and chromatographic purification on Sephadex LH-20 with hexane–$CHCl_3$–MeOH (100:300:6) as eluent, **8d** (2.6 mg, 87%) was obtained: IR ($CHCl_3$) 1705 cm^{-1}; mass spectrum, m/e 470 (M^+), 452, 222; UV (95% EtOH) 264 nm.

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Registry No. 1, 67-97-0; **2a**, 71726-03-9; **2b**, 80666-49-5; **2c**, 86853-48-7; **3a**, 71726-02-8; **3b**, 80666-50-8; **3c**, 86853-49-8; **4a**, 6182-78-1; **4b**, 56198-37-9; **5a**, 86847-13-4; **5b**, 86847-14-5; **5c**, 86940-47-8; **5d**, 87036-80-4; **5e**, 86847-15-6; **6a**, 86847-16-7; **6c**, 86940-48-9; **6d**, 87036-79-1; **7c**, 86900-16-5; **7d**, 86900-17-6; **7e**, 86900-18-7; **7f**, 86847-17-8; **8c**, 84458-83-3; **8d**, 84458-81-1; **8e**, 84458-86-6; **8f**, 86847-18-9; sulfur dioxide, 7446-09-5.