Synthesis and X-ray Characterization of 6(*S*)-*epi*-Mevinolin, a Lactone Epimer

G. E. Stokker,* C. S. Rooney, J. M. Wiggins, and J. Hirshfield

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486, and Rahway, New Jersey 07065

Received June 3, 1986

Synthesis of the 6(*S*) epimer of mevinolin has been achieved in four steps from the natural product.

Compactin (**1**, ML-236B)[1] and mevinolin (**2**, MK-803, monacolin K)[2] are highly functionalized fungal metabolites and are potent inhibitors of cholesterol biosynthesis at the level of HMG-CoA reductase.[3] Over the past few years a number of total syntheses of compactin[4] and mevinolin[4f,5] along with their partial syntheses[6] have appeared in the literature. Only two papers have appeared in which modifications of the lactone portion have been described.[4e,7] The recent report by Heathcock,[4e] wherein he described the preparation of 5-*epi*-compactin[8], has prompted us to describe our unequivocal, four-step synthesis of the corresponding diasteromer of mevinolin. This short, relatively simple procedure for inverting C-6 in the lactone moiety of **2** has as its key step the spontaneous, intramolecular displacement of the mesylate group in **4a**.

Silylation of **2** yielded the known *tert*-butyldimethylsilyl ether[4h,7] **3** in quantitative yield. Conversion of **3** to benzylamide **4** was achieved in nearly quantitative yield by heating **3** with an excess of benzylamine with or without a small amount of THF as solvent. The addition of 1 equiv of Me_3Al, a general method of amide formation from esters developed by Weinreb,[9] afforded no advantage in either purity of product, rate of reaction, or yield. Mesylation of benzylamide **4** at ambient temperature provided, after aqueous workup and flash chromatography, epimeric lactone **5** (68%). The intermediate mesylate **4a** may be detected in the crude reaction mixture by ^1H NMR and/or HPLC but, suprisingly, has not been identified in the eluant after chromatography. The conversion of **4a** to **5**, as followed by HPLC, occurs in part during the workup prior to chromatography and is completed during the chromatography step.[10,11] The proportion of imino lactone intermediate **4b**, which is formed through nucleophilic displacement of the 5-mesylate group of **4a** by the amide carbonyl oxygen, was observed by HPLC to increase at the expense of **4a** during workup prior to chromatography. Positive evidence for the presence of the imino lactone intermediate was obtained by field desorption mass spectrometry that showed the presence of a strong peak at 608 mas units coresponding to MH^+. The ^1H NMR spectrum showed an upfield shift from δ 3.05 for the mesylate ester to δ 2.7 for the imino lactone methanesulfonic acid salt.

The final step in the sequence for **2** to **6** involved fluoride-mediated desilylation of **5** under buffered conditions[12] to prevent facile β-elimination to the α,β-unsaturated lactone (Scheme I).

During handling following chromatography, the 6-*epi*-mevinolin (**6**) has displayed an extreme susceptibility to autoxidation. The field ionization mass spectrum of deteriorated samples of **6** showed the presence of significant amounts of MO^+ and MO_2^+ peaks. Changes were also evident in the vinyl region of the ^1H NMR spectrum. Thus, once **6** was obtained as an oil from the chromatographic purification, it was kept in the freezer under an argon atmosphere. Crystallizations from ether–hexane and filtrations were carried out in a glovebox under an argon atmosphere. Crystals formed in this way appear to be stable indefinitely when stored under argon in the freezer. When attempts to obtain an X-ray crystal structure from crystalline **6** proved unsuccessful, the 4-*p*-nitrobenzoate ester derivative **7** of **6** was prepared. Derivative **7**, which was higher melting than **6**, did not exhibit a similar susceptibility to autoxidation and could be handled without problems in the open air. An X-ray crystal structure of **7** was readily obtained (Figure 1). It is of interest to note that the lactone moiety of this derivative exists in a boat

(1) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.
(2) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Sconberg, G.; Hensens, O.; Hirschfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.
(3) Rodwell, V. W.; Nordstrom, J. L.; Mitschell, J. J. *Adv. Lipid Res.* **1976**, *14*, 1.
(4) (a) Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538. (b) Hirama, M.; Uei, M. *Ibid.* **1982**, *104*, 4251. (c) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *Ibid.* **1983**, *105*, 1403. (d) Hsu, C. T.; Wang, N. Y.; Latimer, L. H.; Sih, C. J. *Ibid.* **1983**, *105*, 593. (e) Rosen, T.; Heathcock, C. H. *Ibid.* **1985**, *107*, 3731. (f) Hirama, M. *Yuki Gosei Kagaku Kyokaishi* **1983**, *41*, 418; *Chem. Abstr.* **1983**, *99*, 139547 w. (g) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501. (h) Girotra, N. N.; Wendler, N. L. *Ibid.* **1983**, *24*, 3687.
(5) Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811.
(6) (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (c) Deutsch, E. A.; Snider, B. B. *Ibid.* **1982**, *47*, 2682. (d) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *Ibid.* **1984**, *49*, 3994. (e) Hecker, S. J.; Heathcock, C. H. *Ibid.* **1985**, *50*, 5159. (f) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, *23*, 281. (g) Yang, Y. L.; Falck, J. R. *Ibid.* **1982**, *23*, 4305. (h) Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popjak, G. *Ibid.* **1982**, *23*, 4747. (i) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Ibid.* **1983**, *24*, 1373. (j) Deutsch, E. A. Snider, B. B. *Ibid.* **1983**, *24*, 3701. (k) Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Ibid.* **1984**, *25*, 1655. (l) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Ibid.* **1984**, *25*, 2101. (m) Prasad, K.; Repic, O. *Ibid.* **1984**, *25*. 2435.
(7) Lee, T. J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750.
(8) We have chosen to number the lactone as a pyranone derivative rather than retain the numbering scheme of the ring-opened dihydroxy acid. Chemical Abstracts names compactin and mevinolin as pyranyl-substituted butanoic acid derivatives and this particular carbon (i.e., C-6 in this manuscript) as C-2: Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl-1-naphthalenyl ester.
(9) Basha, A.; Lipton, M.; Weinreb, S. *Tetrahedron* Lett. **1977**, *18*, 4171.
(10) In a study of simpler 4,6-disubstituted δ-lactones, small amounts (ca. 10%) of the corresponding *N*-benzyl lactams were isolated as a consequence of nucleophilic attack by the nitrogen instead of the oxygen. Formation of this type of byproduct could be avoided readily by the use of *N*-methylbenzylamine in the amide preparation. In the synthesis of **5** none of the *N*-benzyl lactam was observed in the product mixture.
(11) An analogous intramolecular displacement of a secondary benzylic chloride by an amide carbonyl to give a γ-lactone has been reported: Potsywte, N. K.; Rasteikene, L. P.; Knunyants *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 2363; *Theilheimer's Synthetic Methods* **1980**, *37*, 85.
(12) Willard, A. K.; Smith, R. L. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 337.

0022-3263/86/1951-4931$01.50/0 © 1986 American Chemical Society

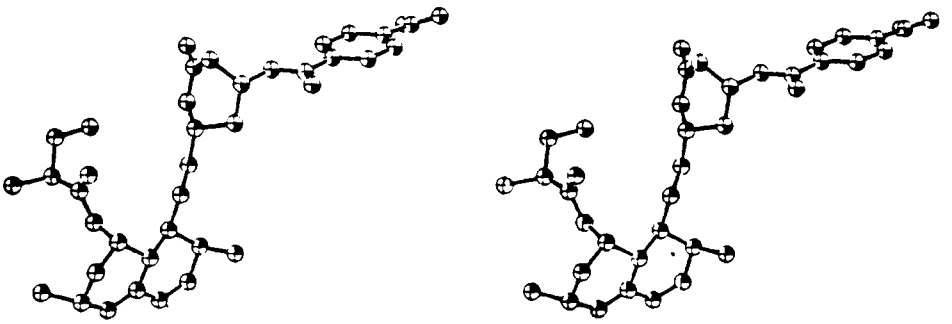
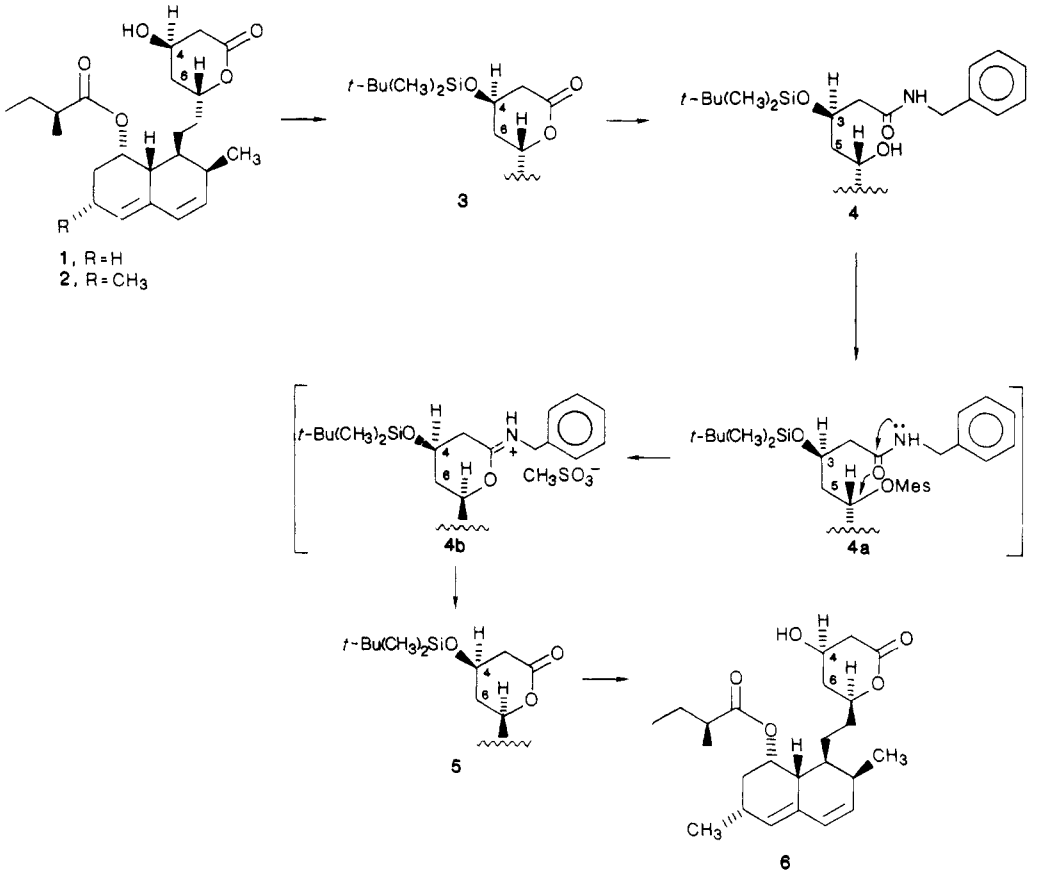


Figure 1. Stereo ORTEP plot of *p*-nitrobenzoate ester **7** with hydrogen atoms omitted for simplicity.

Scheme I



conformation. In contrast, the crystal structure of mevinolin indicates the lactone ring exists in the chair conformation.

Inversion of the configuration from 6(*R*) in **2** to 6(*S*) in **6** results in at least a 10 000-fold decrease in in vitro inhibitory potency against the HMG-CoA reductase enzyme.[13]

Experimental Section

Capillary melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were determined with a Perkin-Elmer Model 240 elemental analyzer. Field desorption (FD) mass spectra were determined on a Model MM 7035 mass spectrometer (VG Instruments Inc.). ^{1}H NMR spectra were recorded in $CDCl_3$ on Nicolet 360-MHz and Varian XL300 spectrometers. TLC analyses were conducted on Analtech silica gel GF with spots detected by UV and PMA solution. HPLC analyses were performed with a Spectra-Physics SP8700 solvent delivery system, employing a Whatman Partisil 5 RAC column and 2-PrOH–hexanes as the developing solvent system. The UV detector was set at 254 nm.

***N*-Benzyl 7-[1,2,6,7,8,8a(*R*)-Hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutanoyl]oxy]-1(*S*)-naphthyl]-3(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*R*)-hydroxyheptanoic Acid Amide (4).** A mixture of **3** (30.3 g, 0.053 mol), benzylamine (19.9 g, 0.186 mol), and THF (~20 mL) was heated at reflux overnight. When TLC indicated disappearance of starting material [R_f 0.1 vs. 0.65 for **3** (2% acetone/$MeCl_2$) usually by 18–24 h], the reaction mixture was allowed to cool to room temperature and then was diluted with Et_2O (700 mL). The Et_2O solution was washed successively with H_2O (300 mL), 1 N HCl (3 × 300 mL), H_2O (3 × 300 mL), and saturated brine (3 × 200 mL). After drying with $MgSO_4$, the Et_2O was removed by evaporation to give crude amide intermediate **4** as a thick gum, 34.4 g. The product was purified by flash chromatography, employing a 140-mm-diameter column packed with 10 in. of 230–400-mesh silica gel. The column was developed initially with 2% acetone/$MeCl_2$ (4 L), followed by 4% acetone/$MeCl_2$ (4 L). The polarity of the eluting solvent was then increased to 8% acetone/$MeCl_2$, and collection of product commenced. The recovery of amorphous purified product was 32.4 g (~100%): ^{1}H NMR δ 0.10 (s, 3 H), 0.11 (s, 3 H), 0.84 (s, 9 H), 0.88 (t, J = 3, 6.3 Hz, 3 H), 0.88 (d, J = 3, 6.9 Hz, 3 H), 1.08 (d, J = 9.9 Hz, 3 H), 1.11 (d, J = 9.0 Hz, 3 H), 1.12–1.27 (m, 2 H), 1.37–1.72 (m, 8 H), 1.90 (ddd, J = 2.4,

(13) Gilfillan, J. L., private communication.

7.5, 15.0 Hz, 1 H), 1.97 (dm, J = 15.0 Hz, 1 H), 2.23 (dm, J = 12.0 Hz, 1 H), 2.28–2.40 (m, 2 H), 2.40–2.48 (m, 2 H), 2.54 (dd, J = 5.7, 14.4 Hz, 1 H), 3.69 (m, 1 H), 4.32 (m, 1 H), 4.39 (dd, J = 6.0, 14.5 Hz, 1 H),4.49 (dd, J = 6.0, 14.5 Hz, 1 H), 5.38 (m, 1 H), 5.52 (m, 1 H), 5.79 (dd, J = 6.0, 9.0 Hz, 1 H), 5.99 (d, J = 9.0 Hz, 1 H), 6.57 (br t, J = 6.0 Hz, 1 H), 7.24–7.37 (m, 5 H); MS (FD) m/z 626 (MH^+). Anal. Calcd for $C_{37}H_{59}NO_5Si$: C, 71.00; H, 9.50. Found: C, 70.98; H, 9.67.

6(S)-[2-[8(S)-[[2(S)-Methylbutanoyl]oxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]ethyl]-4-(R)-[(tert-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2H-pyran-2-one (5). To a stirred solution of benzylamide intermediate 4 (44.6 g, 0.071 mol) in $MeCl_2$ (900 mL), cooled in an iceacetone bath and maintained under a nitrogen atmosphere, was added triethylamine (18.2 g, 0.18 mol). Methanesulfonyl chloride (10.3 g, 0.090 mol) was added dropwise over a period of about 5 min. After 2.3 h, because HPLC indicated the presence of a small amount of unchanged starting material, an additional 0.7 mL of methanesulfonyl chloride was added. The cooling bath was removed after 3 h and the mixture stirred at room temperature for 8 h. The reaction flask was then stoppered and left in the refrigerator overnight. The reaction mixture was worked up by washing successively with H_2O (500 mL), 1 N HCl (3 × 300 mL), H_2O (2 × 400 mL), saturated $NaHCO_3$ solution (300 mL), and H_2O (2 × 400 mL). After drying ($MgSO_4$), the $MeCl_2$ was removed by evaporation to give crude product, 43.6 g. Purification by flash chromatography was carried out with a 140-mm column containing 10 in. of 230–400-mesh silica gel, employing 2% acetone/$MeCl_2$ as developing solvent. The product **5** was obtained as an oil [25.1 g (68%)][14] with an HPLC purity exceeding 95%: TLC, R_f 0.60 (2% acetone/$MeCl_2$); ^1H NMR δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.85–0.93 (m, 15 H), 1.09 (d, J = 12.6 Hz, 3 H), 1.11 (d, J = 12 Hz, 3 H), 1.10–1.20 (m, 2 H), 1.39–1.80 (m, 7 H), 1.90 (ddd, J = 2.4, 7.5, 15.0 Hz, 1 H), 2.01 (dm, J = 15 Hz, 1 H), 2.13 (dm, J = 13.5 Hz, 1 H), 2.26 (dm, J = 12 Hz, 1 H), 2.30–2.50 (m, 3 H), 2.80 (ddd, J = 2.1, 6.3, 16.5 Hz, 1 H), 4.07–4.17 (m, 2 H), 5.35 (m, 1 H), 5.54 (m, 1 H), 5.80 (dd, J = 6.0, 9.0 Hz, 1 H), 6.0 (d, J = 9.0 Hz, 1 H); MS (FD) m/z 518 (M^+).

Evidence for the Presence of 4a and 4b Intermediates in the Formation of 5. When the reaction was followed by HPLC (2% 2-PrOH/hexanes, 3 mL/min), an initial major peak was observed at 10.1 min (mesylate ester). Appearance of a second peak at 12.1 min was attributed to formation of imino lactone intermediate **4b**. The relative proportion of the 12.1-min peak to the 10.1-min peak increased during the course of the reaction and the extraction procedure. The amount of product **5** (3.0 min) steadily increased during the whole operation. ^1H NMR of extracted crude product showed singlet peaks at δ 3.05 and 2.7 due to the methyl of the methanesulfonyl group of **4a** and the mesylate anion of **4b**. Field desorption MS of a sample of evaporated Et_2O extract showed a strong peak at m/z 608 (MH^+) corresponding to protonated imino lactone intermediate.

6(S)-[2-[8(S)-[[2(S)-Methylbutanoyl]oxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]ethyl]-4-(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (6). To a stirred solution of intermediate **5** (8.71 g, 0.0168 mol) in THF (450 mL) at room temperature and under nitrogen was added HOAc (9.05 mL) followed by tetra-n-butylammonium fluoride (87.1 mL of a 1.0 M solution in THF). The mixture was stirred for 36–48 h (or until TLC indicated the reaction was complete). The reaction mixture was worked up by pouring into a stirred mixture of Et_2O (500 mL) and H_2O (500 mL). After separation, the Et_2O layer was successively washed with H_2O (400 mL), saturated $NaHCO_3$ (400 mL), H_2O (2 × 400 mL), and saturated brine (3 × 150 mL). After drying over $MgSO_4$, the Et_2O was removed by evaporation to give crude product, 7.0 g. Purification was carried out by flash chromatography on a 100-mm-diameter column, with 8 in. of 230–400-mesh silica gel adsorbent and 15% acetone/$MeCl_2$ as developing solvent. After evaporation of the combined fractions, **6** was obtained as a viscous oil [4.62 g (68%)] that was 98.4% pure by HPLC analysis: TLC, R_f 0.35 (15% acetone/$MeCl_2$). Crystallization from Et_2O–hexanes gave **6** as a colorless solid: mp 70–74 °C;[15] ^1H NMR δ 0.88 (t, J = 7.5 Hz, 3 H), 0.89 (d, J = 7.5 Hz, 3 H), 1.07 (d, J = 12.3 Hz, 3 H), 1.10 (d, J = 12.0 Hz, 3 H), 1.10–1.23 (m, 2 H), 1.39–1.84 (m, 7 H), 1.91 (ddd, J = 2.7, 7.5, 15.0 Hz, 1 H), 1.99 (dm, J = 15.0 Hz, 1 H), 2.20 (d, J = 4.2 Hz, 1 H), 2.26 (dm, J = 12.00 Hz, 1 H), 2.30–2.50 (m, 4 H), 2.90 (ddd, J = 1.2, 5.7, 17.0 Hz, 1 H), 4.13–4.29 (m, 2 H), 5.37 (m, 1 H), 5.54 (m, 1 H), 5.79 (dd, J = 6.0, 9.0 Hz, 1 H), 6.0 (d, J = 9.0 Hz, 1 H); IR (KBr) 3400–3240, 3010, 2950, 2860, 1720, 1450, 1375, 1240, 1180, 1120, 1045, 835 cm^{-1}; MS (FD) m/z 404 (M^+). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.30; H, 9.09.

6(S)-[2-[8(S)-[[2(S)-Methylbutanoyl]oxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]ethyl]-4-(R)-[(p-nitrobenzoyl)oxy]-3,4,5,6-tetrahydro-2H-pyran-2-one (7). A mixture of **6** (101 mg, 0.25 mmol), p-nitrobenzoyl chloride (51 mg, 0.275 mmol), and pyridine (1 mL) at 0 °C under nitrogen was allowed to warm to room temperature and stirred overnight. The reaction mixture was partitioned between Et_2O and H_2O. The Et_2O phase after washing with dilute HCl, H_2O, saturated $NaHCO_3$, H_2O, and brine and drying ($MgSO_4$) was evaporated to give 114 mg of crude product as a foam. Purification by flash chromatography on a 20-mm-diameter column packed with 6 in. of 230–400-mesh silica gel, with 10% 2-PrOH–hexanes as developing solvent, gave 108 mg of product which crystallized on evaporation. Recrystallization from Et_2O–hexanes gave an analytically pure sample: mp 129–132 °C; ^1H NMR δ 0.89 (t, J = 7.2 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 1.08 (d, J = 10.5 Hz, 3 H), 1.12 (d, J = 9.9 Hz, 3 H), 1.13–1.17 (m, 2 H), 1.45 (septet, J = 7.5 Hz, 1 H), 1.52–1.85 (m, 5 H), 1.91 (ddd, J = 2.4, 7.2, 15.0 Hz, 1 H), 1.99 (dm, J = 15.0 Hz, 1 H), 2.26 (dm, J = 12.0 Hz, 1 H), 2.30–2.50 (m, 3 H), 2.54 (ddd, J = 2.4, 6.0, 13.5 Hz, 1 H), 2.77 (dd, J = 6.0, 16.5 Hz, 1 H), 3.12 (dd, J = 6.0, 16.5 Hz, 1 H), 4.25–4.34 (m, 1 H), 5.37 (m, 1 H), 5.47–5.57 (m, 2 H), 5.79 (dd, J = 6.0, 9.6 Hz, 1 H), 6.01 (d, J = 9.6 Hz, 1 H), 8.21 (dm, J = 9.0 Hz, 2 H), 8.32 (dm, J = 9.0 Hz, 2 H); IR (KBr) 2960, 2930, 2880, 1755, 1720, 1525, 1355, 1285, 1245, 1190, 1160, 1120, 1045, 1020, 870, 720 cm^{-1}; MS (FD) m/z 554 (MH^+). Anal. Calcd for $C_{31}H_{39}NO_8$: C, 67.25; H, 7.10; N, 2.53. Found: C, 67.20; H, 7.45; N, 2.39.

Single-Crystal X-ray Diffraction Analysis of p-Nitrobenzoate Ester 7. The unit cell parameters are a = 13.985 (5) Å, b = 5.545 (2) Å, c = 20.028 (8) Å, β = 105.65 (3)°, and V = 1496 (2) Å^3 in the noncentrosymmetric space group $P2_1$ (Z = 2). The empirical formula is $C_{31}H_{39}NO_8$, molecular weight is 553.66, and calculated density is 1.229 g/cm^3. Data were collected on a Syntex $P2_1$ fully automated diffractometer ($2\theta/\theta$ mode) using nonmonochromated Cu Kα radiation (λ = 1.5418 Å) up to a maximum 2θ of 115°. Of 2255 total symmetry-independent reflections, 1446 (64.1%) were considered observed at the level $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for absorption using the SDP[16] series of computer programs. A suitable trial structure was obtained from MULTAN[17] and expanded to a complete structure by a series of difference electron density syntheses. Final refinement was carried out by full-matrix least squares, minimizing the function $\sum w(|F_o| - |F_c|)^2$ where w $1/\sigma(F)^2$. Hydrogen atoms were assigned equivalent isotropic temperature factors of the atoms to which bound and refined for positional parameter variant only. All other atoms were refined freely with anisotropic temperature factors. The final unweighted residual index $(\sum||F_o| - |F_c||/\sum|F_o|$ was 0.041. The highest calculated peak from a final difference electron density synthesis was 0.135 (0.024) e/Å^3.

Acknowledgment. We extend our appreciation to Drs.

(14) The isolated yield from this step has proven variable in our experience. This value represents the highest yield that has been obtained.

(15) Successful recrystallization of **6** could be achieved consistently only if oxygen-free solvents were employed and if the operations were carried out in an argon atmosphere (glovebox). The presence of small quantities of autoxidation products were found to interfere with crystallization.

(16) Okaya, Y.; Frenz, B.; Brice, M.; Corfield, P.; Hodgson, K.; Rohrer, D.; Linn, E. Enraf-Nonius Structure Determination Package Plus, Version 1.1A; Jan 19, 1984. An integrated set of computer programs written for use on PDP-11 series of computers.

(17) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. *Multan. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; Universities of York and Louvain: York, England, and Louvain, Belgium, 1980.

S. M. Pitzenberger and S. L. Varga for the 360-MHz ^1H NMR spectral determinations, to Dr. H. Ramjit for the field desorption mass spectra, to J. P. Moreau for elemental analysis, and to M. Z. Banker for manuscript preparation.

Registry No. 3, 79902-36-6; 4, 102963-74-6; 5, 105227-50-7; 6, 105227-51-8; 7, 105227-52-9.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, and interatomic angles for 7 (5 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of (*E*)-, (*E,Z*)-, and (*E,E*)-Conjugated Dienes via Alkylation of 3-Sulfolenes as the Key Step

Sachiko Yamada, Hideto Ohsawa, Takayoshi Suzuki, and Hiroaki Takayama*

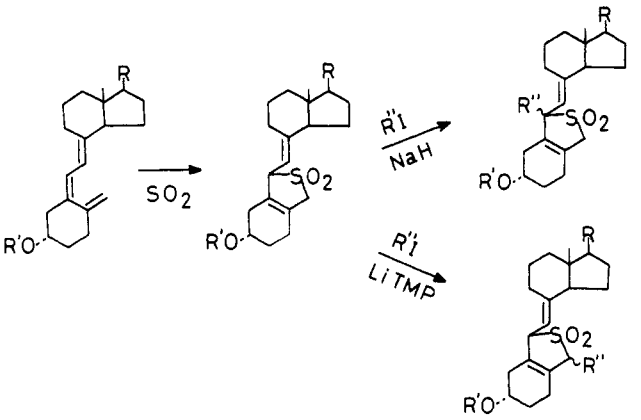
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

Received April 8, 1986

A new stereoselective method is presented for synthesizing (*E*)-, (*E,Z*)-, and (*E,E*)-conjugated dienes via alkylation of 3-sulfolenes as the key step. Direct alkylation of 3-sulfolene at the 2-position proceeds with good yields when labile sulfolene α-carbanion is generated in the presence of alkyl iodides in THF–HMPA solution at −78 °C. Alkylation of 2-alkyl-3-sulfolenes gives *trans*-2,5-dialkyl-3-sulfolenes with 100% regioselectivity and more than 90% stereoselectivity. Desulfonylation of trans-2,5-disubstituted 3-sulfolenes is examined in detail, and the conditions to give stereoselectively the corresponding (*E,Z*)- and (*E,E*)-conjugated dienes are found. Applying the method, three insect pheromones, (*E*)-9,11-dodecadien-1-yl acetate, a sex pheromone of the red bollworm moth, (*E,E*)-8,10-dodecadien-1-ol, a sex pheromone of the codling moth, and (*E,E*)-11,13-hexadecadienal, a sex pheromone of the cabbage webworm, are easily synthesized by starting with 3-sulfolene with nearly 100% stereoselectivity. Synthesis of cis-3,4,5-trisubstituted cyclohexenes using 2-substituted 3-sulfolenes as the diene synthons is also described.

Conjugated dienes are versatile building blocks in the syntheses of organic natural products, especially as a component of the Diels–Alder reaction in the synthesis of 6-membered cyclic compounds. Recent advances in the intramolecular Diels–Alder approach[1] to the synthesis of bicyclic natural products further increased the utility of conjugated dienes. A number of new methods for preparing conjugated dienes have appeared in recent years utilizing reagents such as organoaluminum,[2] -boron,[3] -cobalt,[4] -palladium,[5] -copper,[6] -nickel,[7] and -mercury.[8] The scope of many of these reactions is limited by the nature of the organometallic involved or the procedure employed. 3-Sulfolene, the 1,3-butadiene–sulfur dioxide adduct (1), and its derivatives are attractive as masked diene synthons, since they generate dienes readily by thermal desulfonylation under relatively mild conditions (120 °C) and the terminal CH bonds of the original dienes are activated by the adjacent sulfonyl group, suggesting the possibility of modifying the terminal positions of the dienes. Thus, if the introduction of variable electrophiles to the 2- or 5-position is possible, a variety of 1,4-disubstituted conjugated dienes are made available via the modification of 3-sulfolene. However, the lability of the sulfolene α-carbanion, which readily undergoes ring opening, has prohibited that possibility.[9] For that reason, no general alkylation method for 3-sulfolenes has been known except for the sulfolenes whose double bond constitutes a part of an aromatic ring.[10] Bloch et al.[11] protected the double bond of 3-sulfolene as a cyclopentadiene adduct to prevent the cycloreversion and successfully introduced electrophiles to the terminal position of the masked diene group. The method may not be suitable for compounds having a thermally labile group, because it requires high tempera-

Scheme I



(1) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.
(2) Zweifel, G.; Polston, N. L.; Whitney, C. C. *J. Am. Chem. Soc.* **1968**, *90*, 6243. Zweifel, G.; Miller, R. L. *Ibid.* **1970**, *92*, 6678.
(3) Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 4068. Negishi, E.; Yoshida, T. *J. Chem. Soc., Chem. Commun.* **1973**, 606. Negishi, E.; Lew, G.; Yoshida, T. *Ibid.* **1973**, 874. Negishi, E.; Abramovitch, A. *Tetrahedron Lett.* **1977**, 411. Brown, H. C.; Ravindran, N. *J. Org. Chem.* **1973**, *38*, 1617.
(4) Denny, D. B.; Davis, W. R. *J. Organomet. Chem.* **1970**, *24*, 537.
(5) Diek, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083.
(6) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379. Buchi, G.; Carlson, J. A. *Ibid.* **1969**, *91*, 6470. Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *Ibid.* **1972**, *94*, 4395. Claesson, A.; Quader, A.; Sahlberg, C. *Tetrahedron Lett.* **1983**, *24*, 1297.
(7) Semmelhack, M. F.; Helquist, P. M.; Gorzynski, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 9234.
(8) Larock, R. C. *J. Org. Chem.* **1976**, *41*, 2241.
(9) Krug, R. C.; Rigney, J. A.; Tichelaar, G. R. *J. Org. Chem.* **1962**, *27*, 1305.
(10) (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.
(11) Bloch, R.; Abecassis, J. *Tetrahedron Lett.* **1982**, *23*, 3277; *Ibid.* **1983**, *24*, 1247. Bloch, R.; Hassan, D.; Mandard, X. *Ibid.* **1983**, *24*, 4691. Bloch, R.; Abecassis, J.; Hassan, D. *Can. J. Chem.* **1984**, *62*, 2019.

0022-3263/86/1951-4934$01.50/0 © 1986 American Chemical Society