Photolysis of Diazoketone 1b. A. Diazoketone **1b** (50 mg, 0.21 mmol) was irradiated in 50 mL of MeOH with a 100-W medium-pressure lamp (Rayonett reactor) through a Pyrex tube for 7 h. The solution was evaporated and filtered through a short column of silica gel to afford 44 mg (87%) of the Arndt–Eistert product methyl 6-(2-methylcyclopent-1-enyl)-3,3-dimethylhex-5-enoate: IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 6 H), 1.8 (s, 3 H), 1.7–2.6 (m, 8 H), 2.2 (s, 2 H), 3.6 (s, 3 H), 5.4 (m, 1 H), 6.3 (d, 1 H, J = 14 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 21.5 (CH_2), 27.2 (CH_3) (double intensity), 33.1 (CH_2), 34.0 (C), 39.3 (CH_2), 45.7 (CH_2), 46.1 (CH_2), 51.1 (CH_3), 125.5 (CH), 127.9 (CH), 133.6 (C), 136.4 (C), 172.9 (C).

B. An identical procedure was repeated for a solution of **1b** in hexane. After 6 h the solution was evaporated and filtered as above to give 28 mg (64%) of **7b** identical with a sample obtained from cyclopropanation of **1b**. The vinylcyclopropane was inert to the conditions of photolysis.

Acid-Catalyzed Rearrangement of Diazoketone 1b. A solution of boron trifluoride etherate (284 mg, 2 mmol) in 5 mL of benzene was cooled to 6 °C and diazoketone **1b** (232 mg, 1 mmol) in 2 mL of benzene was added during *30 s*. *Immediately* afterward the reaction mixture was quenched with $NaHCO_3$, and the organic phase was separated, washed with brine, dried over Na_2SO_4, and evaporated to yield a yellow oil which was chromatographed to furnish 145 mg (82%) of diene **10d**: IR (neat) 1732, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.12 (s, 3 H), 1.7 (br s, 3 H), 1.4–3.2 (m, 9 H), 4.9–5.2 (m, 1 H), 5.7 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.7 (q), 24.4 (q) (double intensity), 27.2 (t), 30.0 (t), 33.4 (d), 44.5 (t), 45.9 (t), 45.9 (s), 119.5 (d), 133.9 (d), 140.3 (s), 148.5 (s), 222.9 (s); mass spectrum (70 eV), m/e (relative intensity) 204 (M^+) (89), 189 (63), 174 (21), 161 (22), 147 (26), 133 (42), 120 (B), 105 (73), 91 (52).

Simmons-Smith and Bu_3SnH/AIBN Reactions of Dihalides 6a–c. To a stirred solution of diazoketone **1b** (232 mg, 1 mmol) in 10 mL of benzene at 6 °C was added a standard solution (previously titrated) of either Br_2, I_2, or IBr. The reaction mixture was stirred for 15 min at which time TLC analysis indicated complete disappearance of **1b** and formation of the corresponding dihalides **6a**, **6b**, or **6c**, respectively (NMR δ 5.6, 1 H). The dihalides were unstable to any attempts at purification and were therefore generated in situ. To the solution of appropriate dihalide was added either Zn dust or Bu_3SnH (436 mg, 1.5 mmol) and 25 mg of AIBN dropwise over 30 min. The reaction mixture was then refluxed for 30 min, filtered, washed with brine, dried over Na_2SO_4, and evaporated to give brown oils which were chromatographed to afford cyclopropanes **7b** in the yields of 20% from **6a**, **6b**, and 45% from **6c**, respectively. The cyclopropane isolated from these reactions was identical with a sample obtained by cyclopropanation of **1b**. The relatively poor yields reflect the purity of starting dihalides—a better method of their production must therefore be developed.

Photolysis of Enone 8b. Enone **8b** (204 mg, 1 mmol) was irradiated in *either* MeOH *or* hexane (100 mL) as described above. After 20 h, the solution was filtered and evaporated to give 202 mg (98%) of a yellow oil identified as diene **10c**: IR (neat) 1700, 1620, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) 1.05 (d, 3 H, J = 7 Hz), 1.15 (s, 6 H), 1.4–2.7 (m, 8 H), 3.4 (m, 1 H), 5.95 (br s, 1 H), 6.2 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.6 (q), 23.8 (q) (double intensity), 24.1 (t), 24.3 (t), 28.9 (t), 29.8 (d), 42.5 (t), 44.5 (s), 121.9 (d), 123.6 (s), 131.7 (s), 137.8 (s), 201 (s).

Acknowledgment. We thank the National Institutes of Health (AI-19749) and the National Science Foundation (CHE-8102944) for the support of this work. We also express our gratitude to Dr. James Hudson (University of Texas, Austin) and Mr. Kim Harich (Virginia Tech) for their assistance with mass spectral analyses.

Registry No. **1a**, 93453-83-9; **1b**, 93453-84-0; **3**, 81328-61-2; **4**, 93453-85-1; 4 isobutyrate, 93453-86-2; **5a**, 93453-87-3; **5a** ethyl ester, 93454-03-6; **5b** ethyl ester, 93453-88-4; **5c**, 93453-89-5; **5c** ethyl ester, 93454-01-4; **5c** acid chloride, 93454-02-5; **6a**, 93453-90-8; **6b**, 93453-91-9; **6c**, 93453-92-0; **7a**, 93453-93-1; **7b**, 93453-94-2; **8a**, 93453-95-3; **8b**, 93453-96-4; **9a**, 93453-97-5; **9b**, 93453-98-6; **10b**, 93454-04-7; **10c**, 93454-05-8; **10d**, 93473-49-5; CH_2=CHBr, 593-60-2; $(MeO)_2CH(CH_2)_4C(O)CH_3$, 36727-64-7; $CH_3C(O)(CH_2)_4CHO$, 19480-04-7; $(CH_3)_2CHC(O)Cl$, 79-30-1; $CH_3CH_2C(OEt)_3$, 115-80-0; methyl (*E*)-6(2-methylcyclopent-1-enyl)-3,3-dimethylhex-5-enoate, 93453-99-7; 5-(2-methylcyclopent-1-enyl)pent-4-enoyl chloride, 93454-00-3; 1-methylcyclohexene, 591-49-1.

Supplementary Material Available: Experimental and spectral data for compounds **1a**, **5a**, **5b**, **7a**, and **8a** (2 pages). Ordering information is given on any current masthead page.

Convenient Synthesis of (*S*)-Citronellol of High Optical Purity

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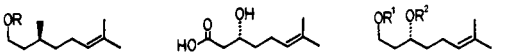
Optically active citronellol has recently attracted much attention as a useful chiral building block in synthetic studies of complex natural products.[1] However, natural citronellol, as well as citronellal and citronellic acid, is known ordinarily to be a mixture of *R* and *S* enantiomers with the optical purity less than 80%.[2] While several routes to citronellol of higher enantiomeric excess, both chemical transformations of other terpenes[2,3] and asymmetric syntheses,[4] have already been developed, there are only a few that can provide virtually enantiomerically pure citronellol in quantity.[3,4c] We now report a convenient chemomicrobiological synthesis applicable for a large-scale preparation of (*S*)-(−)-citronellol (**1**) of at least 96% ee using all commercially available materials and reagents.



1, R=H
2, R=COBu-*t*

3

4, R^1=R^2=H
5, R^1=COBu-*t*, R^2=H
6, R^1=COBu-*t*, R^2=Ts

Enantiomerically pure (*R*)-3-hydroxy-7-methyloct-6-enoic acid (**3**) was readily prepared in 67% crude yield by Baker's yeast reduction of the corresponding potassium β-keto carboxylate.[5,6] Without purification, the crude acid **3** was reduced by $LiAlH_4$ (2 molar equiv) in THF to give the chiral diol **4**, $[\alpha]^{18}_D$ +5.9° (*c* 2.0), in 74% yield. After **4** was selectively acylated to the pivaloyl ester **5** [*t*-BuCOCl (1.0 equiv)/pyridine/room temperature, $[\alpha]^{20}_D$ −2.8°/(*c* 2.0), 81%], **5** was treated with excess tosyl chloride and 1.3 equiv of NEt_3 in pyridine to give the tosylate **6** ($[\alpha]^{20}_D$ −8.9° (*c* 2.0), 82% yield). Substitution of the tosyloxy by

(1) (a) (−)-α-Multistriatin: Cernigliaro, G. J.; Kocienski, P. J. *J. Org. Chem.* **1977**, *42*, 3622. Sex pheromene of beetle: Rossi, R.; Salvadori, P. A.; Carpita, A.; Niccoli, A. *Tetrahedron* **1979**, *35*, 2039. Monensin: Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118. Milbemycin β_3: Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708. (b) Sex pheromone of cockroach: Mori, K.; Masuda, S.; Suguro, T. *Tetrahedron* **1981**, *37*, 1329.

(2) Valentine, D., Jr.; Chan, K. K.; Scott, C. G.; Johnson, K. K.; Toth, K.; Sancy, G. *J. Org. Chem.* **1976**, *41*, 62 and references therein.

(3) Plesek, J. *Collect. Czech. Chem. Commun.* **1957**, *22*, 644.

(4) (a) Hashimoto, S.; Yamada, S.; Koga, K. *J. Am. Chem. Soc.* **1976**, *98*, 7450. (b) Mori, K.; Sugai, T. *Synthesis* **1982**, *752*. (c) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1982**, 600. (d) Oppolzer, W.; Moretti, R.; Godal, T. *Tetrahedron Lett.* **1983**, *24*, 4971.

(5) Hirama, M.; Shimizu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* **1983**, 599.

(6) Ethyl 7-methyl-3-oxooct-6-enoate was prepared by prenylation of the dianion of ethyl acetonacetate (NaH/*n*-BuLi/THF/1-bromo-3-methyl-2-butene) in 70–96% yield. Cf. Kaiser, E. M.; Petty, J. D.; Knutson, L. A. *Synthesis* **1977**, 509 and references therein.

0022-3263/85/1950-0127$01.50/0

methyl group was performed with $LiCuMe_2$ in ether, affording the pivalate (2) of (S)-(−)-citronellol, $[\alpha]^{18}_D$ −1.0° (c 2.0), in 75% yield. The reaction proceeded cleanly with high stereoselectivity (vide infra) as long as the reaction temperature was kept below −20 °C. Finally, alkaline hydrolysis of 2 with 10% NaOH in MeOH gave rise to (S)-(−)-citronellol (1) with $[\alpha]^{18}_D$ −4.67° (neat)[7] in 94% yield. The product was identical in all respects with authentic citronellol[8] except optical rotation. Total chemical yield in the five steps was about 35% from crude 3.[9] The optical purity of synthetic 1 was determined by converting it to citronellic acid and then to its (R)-(+)-1-(1-naphthylethylamide.[1b] HPLC analysis of the acid amide disclosed the presence of 1.7 ± 0.5% of R enantiomer, assuming that the chiral amine used ((R)-(+)-1-(1-naphthyl)ethylamine, Aldrich Chemical Co.) is enantiomerically pure. Since the optical purity of chiral 3 is known to be higher than 99%,[5] the stereoselectivity of the methyl substitution onto 6 was proved to be greater than 98% inversion.

Experimental Section

All ^1H NMR spectra were run for $CDCl_3$ solutions with Me_4Si as the internal standard on JEOL FX90Q spectrometer. Infrared spectra were recorded on a JASCO IRA-2 diffraction grating spectrophotometer. Electron-impact mass spectra were obtained by Hitachi M52 mass spectrometer at 13.5 eV. Microanalyses were performed at Instrumental Analysis Center for Chemistry, Tohoku University. Optical rotations were recorded for $CHCl_3$ solution unless otherwise stated on a JASCO DIP-181 digital polarimeter. HPLC analysis was performed on a Varian Model 5000 system with JASCO UVIDEC-100 UV detector and Varian CDS 111L. Merck silica gel 60 (70–230 mesh) was used for column chromatography.

(3R)-7-Methyl-3-hydroxyoct-6-enoic Acid (3). Ethyl 7-methyl-3-oxooct-6-enoate (28.7 g) was reduced according to the procedure reported.[5] The acidified filtrate was extracted continuously with Et_2O to afford the crude oily 3 (16.6 g, 67%): ^1H NMR ($CDCl_3$) δ 1.44–1.84 (2 H, m, H-4), 1.63 (3 H, s, 7-CH_3), 1.70 (3 H, d, J = 1.1 Hz, 7-CH_3), 2.11 (2 H, br q, J = 7.2 Hz, H-5), 2.56 (2 H, m, ABX, H-2), 4.08 (1 H, br quintet, J = 5.8 Hz, H-3), 5.16 (1 H, br t, J = 7.2 Hz, H-6), 6.09 (2 H, br, OH); IR (liquid film) ν 3100–3600, 1705, 1435, 1065 cm^{-1}.

(3R)-1,3-Dihydroxy-7-methyloct-6-ene (4). To a stirred suspension of $LiAlH_4$ (2.23 g, 0.059 mol) in dry THF (50 mL) was added dropwise a solution of crude 3 (5.00 g, 0.029 mol) in dry THF (100 mL) at 0 °C under Ar. The reaction mixture was stirred at room temperature overnight and then heated under reflux for 2 h. After the decomposition of excess $LiAlH_4$ by water, addition of 2 N NaOH (200 mL) and evaporation of THF in vacuo, the aqueous solution was continuously extracted with Et_2O for 2 days. The organic extract was washed with saturated NH_4Cl solution and dried over $MgSO_4$. Evaporation of the solvent and SiO_2 column chromatography of the residue gave 4 (3.40 g, oil) in 74% yield: $[\alpha]^{18}_D$ +5.9° (c 2.0); ^1H NMR δ 1.47–1.80 (4 H, m, H-2 and H-4), 1.63 (3 H, s, 7-CH_3), 1.69 (3 H, d, J = 1.1 Hz, 7-CH_3), 2.10 (2 H, br q, J = 7.2 Hz, H-5), 2.22 (2 H, br s, OH), 3.76–4.03 (3 H, m, H-1 and H-3), 5.14 (1 H, br t, J = 7.2 Hz, H-6); IR (liquid film) ν 3320, 2950, 1670, 1445, 1055, 840 cm^{-1}; MS, m/z 158 (M^+, 6), 107 (100). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.76; H, 11.43.

(3R)-3-Hydroxy-7-methyloct-6-enyl Pivalate (5). To a stirred solution of 4 (11.6 g, 0.073 mol) in dry pyridine (150 mL) was added dropwise pivaloyl chloride (8.8 g, 0.073 mol) at 0 °C over a period of 40 min. After the mixture was stirred for further 1.5 h, a small amount of pivaloyl chloride (0.4 g, 0.003 mol) was added to complete the reaction. After 30 min, a few drops of water was added, the reaction mixture was diluted with Et_2O and washed with 2 N HCl, saturated $NaHCO_3$, and saturated NH_4Cl. The dried organic layer was concentrated and the residue was chromatographed on SiO_2 column: 14.3 g of 5 (oil, 81%); $[\alpha]^{20}_D$ −2.8° (c 2.0); ^1H NMR δ 1.20 (9 H, s, $COC(CH_3)_3$), 1.38–1.91 (4 H, m, H-2 and H-4), 1.62 (3 H, s, 7-CH_3), 1.68 (3 H, d, J = 1.1 Hz, 7-CH_3), 1.98–2.23 (3 H, m, OH and H-5), 3.52–3.80 (1 H, m, H-3), 3.98–4.52 (2 H, m, H-1), 5.12 (1 H, br t, J = 7.2 Hz); IR (liquid film) ν 3450, 2960, 2920, 2870, 1725, 1705, 1480, 1460, 1285, 1160, 1110 cm^{-1}; MS, m/z 242 (M^+, 2), 122 (100). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.45; H, 10.88.

(3R)-7-Methyl-3-(tosyloxy)oct-6-enyl Pivalate (6). Tosyl chloride (7.91 g, 41 mmol) was added at 0 °C in small portions to a solution of 5 (1.00 g, 4.1 mmol) and NEt_3 (0.75 mL, 5.4 mmol) in dry pyridine (44 mL). After being stirred at room temperature overnight, the reaction mixture was diluted with AcOEt and washed with 2 N HCl, saturated $NaHCO_3$, and saturated NH_4Cl. The organic layer was dried over $MgSO_4$ and concentrated. SiO_2 column chromatography of the residue gave 6 (1.35 g, oil, 82%): $[\alpha]^{20}_D$ −8.9° (c 2.0); ^1H NMR δ 1.18 (9 H, s, $COC(CH_3)_3$), 1.48–1.75 (2 H, m), 1.53 (3 H, s, 7-CH_3), 1.64 (3 H, s, 7-CH_3), 1.94 (4 H, br q, J = 6.5 Hz), 2.45 (3 H, s, $C_6H_4CH_3$), 4.00 (1 H, ddd, J = 17.4, 11.2, 6.2 Hz, H-1), 4.05 (1 H, ddd, J = 17.4, 11.2, 6.2 Hz, H-1), 4.69 (1 H, quintet, J = 5.7 Hz), 4.88–5.04 (1 H, m), 7.32 (2 H, d, J = 10 Hz), 7.82 (2 H, d, J = 10 Hz); IR (liquid film) ν 2970, 2930, 2870, 1725, 1600, 1495, 1480, 1460, 1360, 1285, 1190, 1175, 1140, 905, 815 cm^{-1}; MS, m/z 224 (59), 122 (100), 107 (82). Anal. Calcd for $C_{21}H_{32}O_5S$: C, 63.61; H, 8.14; S, 8.07. Found: C, 63.19; H, 8.29; S, 7.87.

(3S)-3,7-Dimethyloct-6-enyl Pivalate (2). To a stirred suspension of CuI [20.6 g, 0.107 mol; powdered CuI (Nakarai Chem. Co.) was washed thoroughly with hexane and dried in vacuo] in dry Et_2O (1 L) ws added dropwise 143 mL (0.214 mol) of 1.5 M MeLi·LiBr in Et_2O (Aldrich) at 0 °C under Ar. After 10 min, the resulting $LiCuMe_2$ solution was cooled to −78 °C, and 6 (7.03 g, 0.0177 mol) in dry Et_2O (200 mL) was added dropwise. The reaction mixture was kept at −78 °C for 0.5 h, warmed slowly to −20 °C over a period of 2 h, and kept at the temperature for 2 h; then saturated aqueous NH_2Cl solution (1 L) was added. The organic phase was separated, washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and evaporated. The residue was chromatographed on SiO_2 column to afford oily 2 (3.18 g, 75%): $[\alpha]^{18}_D$ −1.0° (c 2.0); ^1H NMR δ 0.92 (3 H, d, J = 5.8 Hz, 3-CH_3), 1.19 (9 H, s, $COC(CH_3)_3$), 1.25–1.72 (5 H, m, H-2, -3 and H-4), 1.60 (3 H, s, 7-CH_3), 1.68 (3 H, d, J = 1.1 Hz, 7-CH_3), 1.96 (2 H, br q, J = 7.2 Hz, H-5), 4.10 (2 H, t, J = 7.2 Hz, H-1), 5.09 (1 H, br t, J = 7.2 Hz, H-6); IR (liquid film) ν 2970, 2930, 2875, 1730, 1480, 1460, 1285, 1160 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.74. Found: C, 75.00; H, 11.72.

(S)-(−)-Citronellol (1). A sample of 2 (2.60 g, 0.011 mol) was stirred overnight in 150 mL of 10% NaOH in MeOH solution at room temperature. The reaction mixture was concentrated in vacuo at 30 °C to remove most of MeOH. The alkaline residue (ca. 35 mL) was diluted with 250 mL of water and extracted with Et_2O twice (350 mL and then 120 mL). The combined Et_2O solution was washed with aqueous 1 N NaOH (120 mL) and saturated aqueous NH_4Cl (120 mL) solutions, dried over $MgSO_4$, and concentrated in vacuo to give 1 (1.59 g, 94%) as a colorless liquid of >99% purity by GLC analysis [SE-30, capillary column (50 m), 140 °C, He, 58 mL/min]. An analytically pure sample was obtained by distillation: bp 109–110 °C (10 mmHg); $[\alpha]^{18}_D$ −4.67° (neat); ^1H NMR δ 0.92 (3 H, d, J = 6.8 Hz, 3-CH_3), 1.17–1.75 (6 H, m, H-2, -3, -4 and OH), 1.61 (3 H, s, 7-CH_3), 1.69 (3 H, d, J = 1.1 Hz, 7-CH_3), 1.96 (2 H, br q, J = 7.2 Hz,H-5), 3.68 (2 H, t, J = 6.4 Hz, H-1), 5.10 (1 H, br t, J = 7.2 Hz, H-6); IR (liquid film) ν 3320, 2920, 1450, 1375, 1055, 825 cm^{-1}; MS, m/z 156 (M^+, 66), 91 (100). Anal. Calcd for $C_{10}H_{20}O$: C, 76.85; H, 12.89. Found: C, 76.85, H, 13.04.

Determination of the Optical Purity of 1. The alcohol 1 (53 mg, 0.34 mmol) was oxidized with PDC (256 mg, 0.68 mmol)

(7) The optical rotation of analytically pure sample of 96.6 ± 1.0% ee after distillation: the highest rotation previously reported for (S)-(−)-citronellol is $[\alpha]_D$ −4.9° (neat) [Fluka Catalogue 14, p 291 (1984/85)] to our knowledge, although that for (R)-(+)-enantiomer, prepared from (+)-pulegon,[2] is much higher, +5.37°. The reason for this discrepancy is not apparent at this stage.

(8) We are grateful to Mr. Koichi Tanaka of Nippon Terpene Chemical Co. Ltd. for a gift of natural citronellol.

(9) It should also be possible to prepare (R)-(+)-citronellol of high optical purity conveniently via the S enantiomer of 6, since one-step synthesis of tosylates from secondary alcohols with inversion of the stereochemistry was reported: Galynker, I.; Still, W. C. *Tetrahedron Lett.* **1982**, *23*, 4461.

in dry DMF (0.5 mL) at room temperature. After being kept overnight, the reaction mixture was diluted with ether and filtered through SiO_2, and the filtrate was evaporated. The remaining DMF and unreacted 1 were removed by SiO_2 column chromatography to give citronellic acid (31 mg, 0.18 mmol).

(*R*)-(+)-1-(1-Naphthyl)ethylamide of the acid was prepared by the procedure described in ref 1b. HPLC analysis (column: Varian Micro Pak Si5 50 cm × 8 mm; solvent, hexane/Et_2O = 2/1, 2 mL/min; pressure: 54–56 kg/cm^2; detector 270 nm) showed the diastereomer ratio of [*SR* acid amide (t_R 52.9 min)] vs. [*RR* acid amide (t_R 47.4 min)] was 98.3 ± 0.5:1.7 ± 0.5. The optical purity is therefore 96.6 ± 1.0%.

Registry No. 1, 7540-51-4; 2, 93041-00-0; 3, 93041-01-1; 4, 93041-02-2; 5, 93041-03-3; 6, 93041-04-4; pivaloyl chloride, 3282-30-2; tosyl chloride, 98-59-9.

Oxidative Elimination of Nitrous Acid from Nitrate Esters. Preparation of Mecadox

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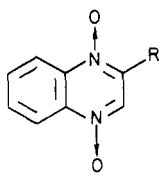
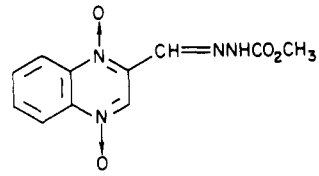
We report a new synthesis of the carbazate derivative of 2-formylquinoxaline 1,4-dioxide (**2**), the highly effective antibacterial and growth-promoting agent[1] marketed under the trade name of Mecadox or Carbadox.



R

1a, CH_3
b CH_2Br
c CH_2ONO_2
d CHO

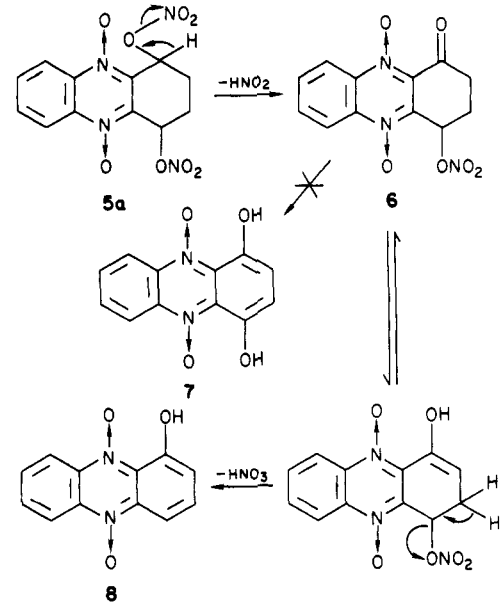


2

Treatment of 2-methylquinoxaline 1,4-dioxide (**1a**) with bromine in ethyl acetate[2] gave the bromomethyl derivative **1b** which reacted with silver nitrate in acetonitrile to give the nitrate ester **1c** (recognizable by the characteristic nitrate ester bands at 1640 and 1285 cm^{-1} and by the NMR singlet at δ 5.9). When a solution of **1c** in dichloromethan e was treated with methyl carbazate and allowed to stand overnight at room temperature, it gave directly Mecadox (**2**, 96% yield from **1c**), presumably via the aldehyde **1d** arising from **1c** by oxidative elimination of nitrous acid.

The transformation of **1a** to **2** entails a two-level increase in oxidation (**1a** to **1b** and **1c** to **1d**). In view of the greatly enhanced antibacterial potency of quinoxaline di-*N*-oxides carrying hydroxymethyl or acyl substituents at positions 2 or 3,[4] we tested the generality of this oxidation on a number of readily available precursors of the type defined by **3a** to **3e**. These were converted to the corresponding nitrate esters (**5a** to **5e**) via the bromo derivatives **4a–e** (Table I).

Scheme I



5a **6** **7** **8**

Attempts to effect elimination of nitrous acid from nitrate esters **5c** and **5e** gave intractable mixtures. Nitrate ester **5b**, which failed to undergo elimination of nitrous acid even in the presence of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol, decomposed when treated with 5% methanolic potassium hydroxide. On the other hand, treatment of **5d** with triethylamine affected smooth oxidative elimination of nitrous acid to give the expected 2-benzoyl-3-phenylquinoxaline 1,4-dioxide (**9**) in 72% yield. Nitrate ester **5a** displayed a remarkable behavior: when treated with triethylamine it gave 1-hydroxyphenazine 9,10-dioxide (**8**) rather than the expected 1,4-dihydroxyphenazine 9,10-dioxide (**7**). Scheme I suggests a plausible pathway for the formation of **8** from **5a** by two successive eliminations: loss of HNO_2 (oxidative) followed by rapid loss of HNO_3 (nonoxidative).

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide disks on a Perkin-Elmer Model 398 grating infrared spectrophotometer. Proton nuclear magnetic resonance spectra were taken on a Varian EM 360L spectrometer in $CDCl_3$ with $(CH_3)_4Si$ as internal reference. Thick layer chromatography was run on silica gel Merck 60_{259}. Elemental analyses were performed by E. Pascher, Bonn, Germany.

All quinoxaline 1,4-dioxides were prepared according to literature methods.[4,5] Bromoketoquinoxaline 1,4-dioxides **4c** and **4e** were prepared according to ref 6.

6,10-Dibromo-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoxaline 5,11-Dioxide (4b). A solution of 7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoxaline 5,11-dioxide (**3b**, 2.3 g) in ethyl acetate (50 mL) was heated at reflux temperature during which a solution of bromine (3.2 g, in 20 mL of ethyl acetate) was added dropwise. The solution was heated for 4 h after which the solvent was evaporated and the product **4b** was collected and recrystallized from $CHCl_3$–CH_3OH: 2.9 g (74%); mp 179–181 °C; IR (cm^{-1}) 2920, 1490, 1450, 1345, 1325, 1310, 1050, 920, 765. The analytical sample was purified by TLC.

2-(Bromomethyl)quinoxaline 1,4-Dioxide (1b). The same procedure as for **4b** was followed, starting with 2-methylquinoxaline 1,4-dioxide (**1a**, 2.64 g, in 50 mL of ethyl acetate) and bromine (2.4 g in 15 mL of ethyl acetate); reaction time 2.5 h. **1b**: 2.10 g (55%); mp 160–162 °C (lit.[7] mp 162–164 °C).

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