with sulfuric acid. The lower layer which formed was separated and mixed with 75 mL of 96% H_2SO_4, and the mixture was distilled at aspirator pressure into a dry ice cooled receiver. This gave a yield of 145.5 g (64.5%) of colorless 1, pure by NMR.

2-*n*-Butoxy-*F*-2-methylpentane. Dimethyl sulfoxide (125 g), alcohol 1 (25.0 g, 0.0744 mol), KOH pellets (9.9 g, 0.115 mol), and 1-iodobutane (18.4 g, 0.100 mol) were combined and stirred at room temperature for 3 days. (When 1 was mixed with Me_2SO, heat was evolved; on a larger scale, provision for cooling should be made.) At the end of the reaction period the mixture was poured into ca. 300 mL of water, and the crude lower layer was separated and dried over solid KOH. Distillation of the crude product at aspirator pressure into a dry ice cooled receiver gave 24.8 g of colorless liquid (84% yield). The analytical sample was obtained by preparative gas chromatography: bp 138 °C (732 mm); d^{21} 1.473 g cm^{-3}.

Anal. Calcd for $C_{10}H_9OF_{13}$: C, 30.63; H, 2.31; O, 4.08; F, 62.98. Found: C, 30.47; H, 2.25.

Note Added in Proof. After submission of this manuscript, preparation of 1 by the method of ref 8 was reported.[16]

Registry No. 1, 67728-22-7; 3, 1584-03-8; 4, 2070-70-4; 5, 67728-23-8; 6, 72939-10-7; *F*-propene, 116-15-4; 2-butoxy-*F*-2-methylpentane, 72939-11-8; 1-iodobutane, 542-69-8.

(16) A. Ya. Zapevalov, T. I. Filyakova, and I. P. Kolenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2620 (1979).

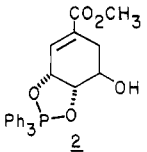
(-)-Methyl *cis*-3-Hydroxy-4,5-oxycyclohex-1-enecarboxylate: Stereospecific Formation from and Conversion to (-)-Methyl Shikimate; Complex Formation with Bis(carbomethoxy)hydrazine

Donald A. McGowan and Glenn A. Berchtold*

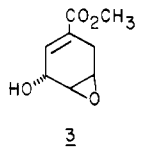
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received January 23, 1981

Our interest in the chemistry of shikimic acid derivatives prompted us to investigate the reaction of (-)-methyl shikimate (1) with triphenylphosphine/azodicarboxylates as a route to triphenylphosphorane derivative **2** that would



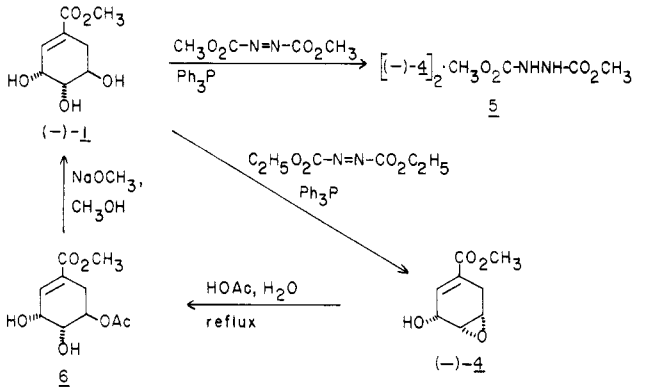
2



3

reasonably be expected to fragment to *anti*-hydroxy epoxide **3**. In cyclic systems, *cis*-1,2-diols afford triphenylphosphoranes under the reaction conditions,[1-3] whereas epoxides are formed from the corresponding reaction of *trans*-1,2-diols.[2-5] Reaction of (-)-1 with triphenylphosphine/dimethyl or diethyl azodicarboxylate did not follow the expected course but gave instead *syn*-hydroxy epoxide (-)-4 which, depending on the azodicarboxylate used, was obtained as such or as a complex with the hydrazine product of the reaction. Described herein are the details of the reaction and a procedure to regenerate (-)-1 from (-)-4 in high optical purity.

Scheme I



Reaction of (-)-1 with triphenylphosphine/dimethyl azodicarboxylate in tetrahydrofuran (THF) followed by removal of solvent gave a crude residue, the ^{1}H NMR spectrum of which indicated the absence of epoxy H. It was not possible to isolate a pure product on workup, but distillation of the residue and recrystallization afforded **5** (93% yield), a sharp-melting, 2:1 complex of (-)-4 and bis(carbomethoxy)hydrazine (Scheme I). Complex **5** survived sublimation (75 °C, 0.05 mm) and chromatography (silica gel), but pure (-)-4 could be obtained from complex **5** in 15-25% yield by two-phase distribution in $CHCl_3/H_2O$. The superior procedure for preparation of (-)-4 involved reaction of (-)-1 with triphenylphosphine/diethyl azodicarboxylate. The reaction followed a similar course, but in this case pure (-)-4 was obtained in 77% yield by preparative plate chromatography (silica gel) of the material obtained from distillation of the reaction mixture.

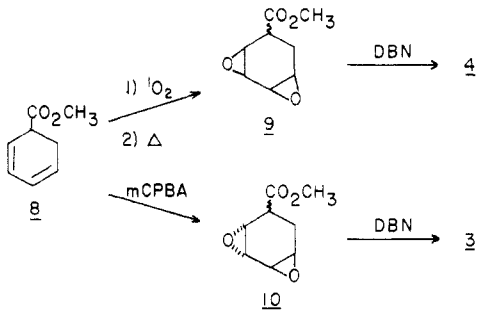
The formation and stability of complex **5** is unusual. That the product is indeed complex **5** and not a covalent adduct from bis(carbomethoxy)hydrazine and (-)-4 (or an intermediate derived from 1) was suggested from comparison of the ^{1}H NMR spectra of (-)-4 and **5**. When the additional absorption for the hydrazine derivative of complex **5** is taken into account, with the exception of the chemical shift position of the hydroxyl proton, the chemical shift positions and line shapes in the spectra of (-)-4 and **5** are virtually identical. Furthermore, if (-)-4 and bis(carbomethoxy)hydrazine (2:1 molar ratio, respectively) are dissolved in diethyl ether with slight warming to effect solution, complex **5** crystallizes in near quantitative yield upon addition of petroleum ether. The melting point and IR and ^{1}H NMR spectra of **5** prepared by the two routes are identical.

The syn relationship of the hydroxyl and epoxide groups of (-)-4 was suggested from the ^{1}H NMR spectrum. The absorption for the hydroxyl proton of (-)-4 and of complex **5** in $CDCl_3$ appears as a sharp doublet with J_{H_3-OH} = 10.7 Hz in each case. Consequently, the conformation of the carbocyclic ring must be such that H_3 and the hydroxyl proton are antiperiplanar, and the hydroxyl proton is hydrogen-bonded to the *syn*-epoxide group.[6] In dimethyl-d_6 sulfoxide the intramolecular hydrogen bonding

(1) Kimura, J.; Fujisawa, Y.; Sawada, T.; Mitsonobu, O. *Chem. Lett.* **1974**, 691-692.
(2) Mitsunobu, O.; Kimura, J.; Inzumi, K.; Yanagida, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 510-513.
(3) Mengel, R.; Bartke, M. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 679-680.
(4) Brandstetter, H. H.; Zbiral, E. *Helv. Chim. Acta* **1980**, *63*, 327-343.
(5) Guthrie, R. D.; Jenkins, I. D.; Yamasaki, R. *J. Chem. Soc., Chem. Commun.* **1980**, 784-785.
(6) Rastetter, W. H.; Adams, J. *J. Org. Chem.* **1980**, *45*, 3534-3535.

0022-3263/81/1946-2381$01.25/0

Scheme II



in (−)-4 is disrupted, and the hydroxyl group is hydrogen bonded to solvent (J_{H_3-OH} = 6.5 Hz). Unambiguous proof of the structure of (−)-4 was established by comparison with authentic samples of racemic 3 and 4 that were prepared as outlined in Scheme II. The solution IR and ^1H NMR spectra of (−)-4 were identical with those of racemic 4 and were distinctly different from those of racemic 3.

Solvolysis of (−)-4 in 80% aqueous HOAc followed by ester interchange ($NaOCH_3/CH_3OH$) of the resulting acetate (6) afforded (−)-1 (97%) that was 89% optically pure after one recrystallization.

Formation of (−)-4 from reaction of (−)-1 with triphenylphosphine/azodicarboxylates must occur by selective activation of the C-5 hydroxyl group. Such selectivity in reactions of shikimate derivatives has not been observed previously and may be unique to the triphenylphosphine/azodicarboxylate reaction. The regiospecific, acid-catalyzed cleavage of oxirane 4 provides a simple, high-yield procedure for preparation of shikimate derivatives from the *syn*-hydroxy epoxide.

Experimental Section

Melting points were determined by using a Thomas-Hoover Unimelt apparatus and are corrected. ^1H NMR spectra were obtained at 250 MHz with a Bruker FT spectrometer. Chemical shift values (δ) are reported in parts per million downfield from tetramethylsilane. Infrared spectra were obtained with a Perkin-Elmer Model 283B spectrometer. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Microanalyses were performed by Galbraith Laboratories.

Reaction of (−)-1 with Triphenylphosphine/Dimethyl Azodicarboxylate. Preparation of Complex 5. Triphenylphosphine (3.83 g, 14.6 mmol) and (−)-1[7] (2.5 g, 13.3 mmol) were dissolved in THF, and the mixture was cooled to 0 °C under N_2. Dimethyl azodicarboxylate (2.14 g, 14.6 mmol) was added dropwise with stirring. The mixture was kept at 0 °C for 30 min and then at room temperature for 1 h. Solvent was removed in vacuo. The residue was distilled (Kugelrohr), and distillate coming over up to 160 °C (0.1 mm) was collected. The distillate was dissolved in the minimum amount of ethyl ether with slight heating and the mixture allowed to cool to deposit 390 mg of bis(carbomethoxy)hydrazine, mp 130 °C (lit.[8] mp 131 °C). The residue from evaporation of the filtrate was recrystallized from ethyl ether/petroleum ether to give two crops of crystalline complex 5: 3.0 g (93%); mp 92–93 °C (after second recrystallization); $[\alpha]^{25}_D$ −29.9° (*c* 4.72, $CHCl_3$); IR (CH_2Cl_2) 3650, 3405, 1740, 1720, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (d, 1 H, OH, *J* = 10.7 Hz), 2.49 (m d, 1 H, *J* = 19.9 Hz), 3.02 (m d, 1 H, *J* = 19.9 Hz), 3.56 (br s, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.56 (m d, 1 H, *J* = 10.7 Hz), 6.70 (br s, 1 H), 6.72 (m, 1 H); integral values are based on a 2:1 ratio of (−)-4 to bis(carbomethoxy)hydrazine; exchange with ^1H_2O removes the OH (δ 2.35) and NH (δ 6.70) absorptions, and the absorption for H_3 (δ 4.56) collapses to an unresolved multiplet. Anal. Calcd for $C_{20}H_{28}N_2O_{12}$: C, 49.18; H, 5.78; N, 5.74. Found: C, 49.19; H, 5.80; N, 5.56.

When complex 5 is sublimed (75 °C, 0.05 mm), the early and the latter fractions of the sublimate are the sharp-melting complex. When (−)-4 (2 parts) and bis(carbomethoxy)hydrazine (1 part) are dissolved in ether with slight warming to effect solution, there is quantitative conversion to complex 5, with a melting point and IR and ^1H NMR spectra identical with those of 5 prepared as described above.

Reaction of (−)-1 with Triphenylphosphine/Diethyl Azodicarboxylate. Preparation of (−)-Methyl *cis*-3-Hydroxy-4,5-oxycyclohex-1-enecarboxylate [(−)-4]. Reaction of (−)-1[7] (220 mg, 1.06 mmol) with triphenylphosphine (557 mg, 2.12 mmol) and diethyl azodicarboxylate (370 mg, 2.12 mmol) was effected in a similar fashion to the preceeding experiment. Material distilling (Kugelrohr) up to 165 °C (0.1 mm) was collected and taken up in ethyl ether. Cooling of the solution deposited 190 mg of bis(carboethoxy)hydrazine, mp 133 °C. The filtrate was concentrated and chromatographed (preparative plate, silica gel, ethyl ether) to afford 140 mg (77%) of (−)-4 as an oil that crystallized on being allowed to stand: mp 81–82 °C (ethyl ether/petroleum ether); $[\alpha]^{25}_D$ −55.4° (*c* 4.04, $CHCl_3$); IR (CH_2Cl_2) 3550, 3450, 1715, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (m d, 1 H, H-6β, *J* = 19.9 Hz), 2.60 (d, 1 H, OH, exchanges with ^2H_2O, *J* = 10.7 Hz), 3.01 (m d, 1 H, H-6α, *J* = 19.9 Hz), 3.55 (br s, 2 H, H-4 and H-5), 3.76 (s, 3 H, OCH_3), 4.56 (md, 1 H, H-3, *J* = 10.7 Hz), 6.71 (br s, 1 H, H-2); mass spectrum (70 eV), *m/e* (relative intensity) 169 (1.1, M − 1^+), 155 (15), 138 (29), 121 (3.6), 111 (49), 93 (11), 81 (53), 71 (32), 65 (29), 53 (100), 39 (89). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.55; H, 5.93.

Preparation of (−)-Methyl Shikimate [(−)-1] from (−)-4. Hydroxy epoxide (−)-4 (132 mg, 0.77 mmol) was dissolved in 80% acetic acid and stirred at room temperature overnight. The mixture was then heated under reflux for 1 h. The solvent was removed in vacuo to give crude monoacetate 6 as an oil that was dissolved in 10 mL of dry CH_3OH to which a small piece of Na had been added. The mixture was stirred at room temperature overnight, acidified with acetic acid, and concentrated in vacuo. The residue was dissolved in CH_3OH/H_2O (1:1) and stirred with a small amount of Dowex 50-W (acid form). Filtration and removal of solvent gave 142 mg (97%) of (−)-1 as an oil that crystallized on standing. Recrystallization from ethyl acetate (Norit) afforded pure (−)-1: mp 111–112.5 °C; $[\alpha]^{25}_D$ −142° (*c* 4.5, H_2O). There was no depression of the mixture melting point with authentic (−)-1 which had the following: mp 114–115 °C (lit.[7] mp 113–114 °C); $[\alpha]^{25}_D$ −159° (*c* 4.5, H_2O).

Racemic 4. A solution of 8[9-11] (1 g, contaminated with ~30% methyl benzoate) and Rose Bengal (4 mg) in dry acetone at −10 °C was irradiated with a 300-W lamp while O_2 was bubbled through the solution over a period of 7 h. The solvent was removed in vacuo to afford a crude mixture of isomeric *endo*-peroxides that were dissolved in toluene and heated under reflux for 6 h. Removal of the solvent in vacuo and chromatography (silica gel, $CHCl_3$) of the residue afforded 438 mg of isomers 9 (~1:1) which were dissolved in 20 mL of dry ethyl ether. To the solution was added 345 mg (2.78 mmol) of 1.5-diazabicyclo[4.3.0]non-5-ene (DBN). The mixture was stirred at room temperature for 1.5 h, heated under reflux for 0.5 h, and allowed to cool. The solution was extracted with concentrated, aqueous NaH_2PO_4, and the ether layer was separated. The aqueous layer was extracted with ether. The combined ether layers were washed (aqueous NaH_2PO_4, H_2O, and saturated NaCl), dried (Na_2SO_4), and evaporated to afford 167 mg of an oil. Preparative plate chromatography (silica gel, ethyl ether) gave 4 as a colorless oil which crystallized on standing: 104 mg (overall 12%, reaction conditions not optimized); mp 75–76.5 °C (ethyl ether/petroleum ether). The IR (CH_2Cl_2), ^1H NMR, and mass spectra of racemic 4 were identical with those of (−)-4.

Racemic 3. Diepoxidation of 8[9-11] (1.35 g, contaminated with 30% methyl benzoate) by the same procedure for diepoxidation of dimethyl *trans*-1,2-dihydrophthalate[12] afforded the mixture

(7) Fischer, H. O. L.; Dangschat, G. *Helv. Chim. Acta* **1934**, *17*, 1200–1207.
(8) Diels, O.; Fritzsche, P. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 3018–3027.
(9) Bailey, W. J.; Barclay, R.; Baylouny, R. A. *J. Org. Chem.* **1962**, *27*, 1851–1855.
(10) Boeckman, R. K.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1977**, 4485–4488.
(11) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.*, **1979**, 2301–2304.

of isomers 10 that, on reaction with DBN as described for the preparation of 4, afforded racemic 3: 113 mg (overall 9%, reaction conditions not optimized); mp 54-55 °C (ethyl ether/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 2.67 (m d, 1 H, J = 19.8 Hz), 2.71 (br s, 1 H), 2.95 (d, 1 H, J = 19.8 Hz), 3.30 (br s, 1 H), 3.44 (br s, 1 H), 3.76 (s, 3 H), 4.64 (br s, 1 H), 6.80 (br s, 1 H).

Acknowledgment. We are grateful to the National Institutes of Health, Grant GM 19103, for financial support.

Registry No. (-)-1, 40983-58-2; (±)-3, 76947-23-4; (-)-4, 76985-84-7; (±)-4, 76985-85-8; 5, 77026-72-3; 6, 76947-24-5; (±)-8, 76947-25-6; (±)-9 (isomer 1), 76947-26-7; (±)-9 (isomer 2), 76985-86-9; (±)-10 (isomer 1), 76985-87-0; (±)-10 (isomer 2), 76985-88-1; dimethyl azodicarboxylate, 2446-84-6; bis(carbomethoxy)hydrazine, 17643-54-8; diethyl azodicarboxylate, 1972-28-7; bis(carboethoxy)hydrazine, 4114-28-7.

(12) Chiasson, B. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1974**, *96*, 2898-2901.

3-Oxo-(*Z*)-9-hexadecenal: An Unusual Enolic β-Keto Aldehyde from a Termite Soldier Defense Secretion

Glenn D. Prestwich*[1]

Department of Chemistry, State University of New York, Stony Brook, New York 11794

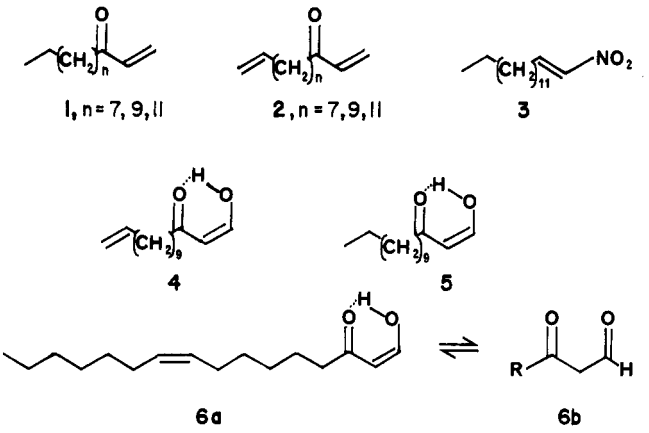
Margaret S. Collins

Department of Zoology, Howard University, Washington, DC 20059

Received October 15, 1980

Chemical defense by soldier termites of the advanced subfamilies Prorhinotermitinae and Rhinotermitinae (Isoptera, Rhinotermitidae) is effected by the topical application of large quantities of a lipophilic contact insecticide to the surface of an attacking arthropod.[2,3] The primary evolutionary trend in soldier morphology in the subfamily Rhinotermitinae is the development of a minor soldier caste with reduced mandibles, an elongated labrum (the "upper lip") used as a paint brush for dispensing the contact poison, and the hypertrophy of the cephalic frontal gland to include a voluminous abdominal reservoir.[4] We have proposed[5] that the evolution of the defense chemistry of these termites has resulted in the production of increasingly reactive electrophiles in the more advanced genera. Thus, vinyl ketones (e.g., **1**),[6] α,ω-dienones (e.g., **2**),[7] and nitroolefin **3**[8] (Chart I) have been found in termites along this phyletic line. In addition, our recent discovery of the highly reactive enolized β-keto aldehydes **4** and **5** in *Rhinotermes hispidus*[5] supports this hypothesis. We

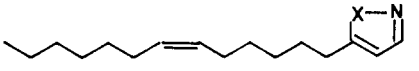
Chart I. Defense Secretions of Rhinotermitidae



now report that the most advanced termite of this subfamily, *Acorhinotermes subfusciceps*, possesses the 16-carbon β-keto aldehyde **6** as the major component of its defense secretion.

Compound **6** was obtained by hexane extraction of whole minor soldiers, and the presence of doublets (J = 4.3 Hz) at δ 7.92 (H-1a) and 5.52 (H-2a) in the ^{1}H NMR signaled the presence of a long-chain enolic β-keto aldehyde.[5] The dicarbonyl form was also present (<10%), showing ^{1}H resonances at δ 9.69 (t, J = 3 Hz, H-1b) and 3.44 (d, J = 3 Hz, H-2b). The nature of the long chain was suggested by the absorption of vinylic protons (δ 5.34, t, J = 5.3 Hz, H-9,10), the methylene protons adjacent to the C-3 ketone (δ 2.34, t, J = 7.2 Hz, H-4), four allylic methylene protons (δ 2.0, br m, H-8, 11), and a terminal methyl group (δ 0.88, t, J = 5 Hz, H-16). Gas chromatography–electron-impact mass spectroscopy of this crude secretion showed a single (>85%) major component [m/z (relative intensity) 252 (M^+, 1), 234 ($M^+ - H_2O$, 2), 86 ($\cdot H_2CC(^+OH)CH{=}CH_2$, 90), 71 ($H_2C{=}CHC{\equiv}O^+$, 100)] consistent with an unsaturated 16-carbon-chain β-keto aldehyde ($C_{16}H_{28}O_2$). The major fragments at m/z 86 and 71 can be attributed to the McLafferty-type rearrangement and α cleavage, respectively, both of which are known to occur in analogous substances.[5,7]

The unstable[9] β-keto aldehyde was not chromatographed but was converted to the pyrazole **7** by treatment with



7, X = NH
8, X = O

hdyrazine in ethanolic sodium hydroxide and to the isoxazole **8** by condensation with hydroxylamine in ethanol with potassium carbonate as the base. The pyrazole derivatives have the advantage of reasonably strong parent peaks in the mass spectra; however, they exist as slowly equilibrating tautomers which give broad GC peaks and broadened ^{1}H and ^{13}C NMR reasonances. Gas chromatographic–high-resolution mass spectroscopic analysis of pyrazole **7** showed m/z 248.2223 (4.7%) (calcd for $C_{16}H_{28}N_2$, 248.2252), confirming the presence of a tridecenyl side chain on a pyrazole nucleus. The isoxazoles are formed exclusively as the 5-substituted isomers as shown, and give sharp GC peaks and NMR resonances. In this case, it was clear that a single β-keto aldehyde was present, with a single isoxazole evident by capillary GC.

(1) Fellow of the Alfred P. Sloan Foundation, 1981-1983.
(2) (a) Prestwich, G. D. *Sociobiology* **1979**, *4*, 127-138; (b) Prestwich, G. D. *J. Chem. Ecol.* **1979**, *5*, 459-480.
(3) Quennedey, A. *La Recherche* **1975**, *6*, 274-277.
(4) Quennedey, A.; Deligne, J. *Insectes Soc.* **1975**, *22*, 243-263.
(5) Prestwich, G. D.; Collins, M. S. *Tetrahedron Lett.* **1980**, *21*, 5001-5002.
(6) Quennedey, A.; Brule, G.; Rigaud, J.; Dubois, P.; Brossut, R. *Insect Biochem.* **1973**, *3*, 67-74.
(7) Prestwich, G. D.; Kaib, M.; Wood, W. F.; Meinwald, J. *Tetrahedron Lett.* **1975**, 4701-4704.
(8) Vrkoč, J.; Ubik, K. *Tetrahedron Lett.* **1974**, 1463-1464.
(9) Rothmann, E. S.; Moore, G. G. *J. Org. Chem.* **1970**, *35*, 2351-2353.

0022-3263/81/1946-2383$01.25/0