nation[12] (5:3:1 molar ratio of $NiBr_2/Bz_2O_2$/diol, R = C_6H_5) produced a complex mixture of products that included lactone **2** (20% yield) and keto alcohol **3** (9% yield).

Acknowledgment. We thank the Research Corporation for their support of this work. We are grateful to Robert Dow for his preliminary experiments with these selective oxidations.

Registry No. **1** (R = C_6H_5), 4850-50-4; **1** (R = C_4H_9), 51916-47-3; **1** (R = C_6H_{13}), 37810-94-9; **2** (R = C_6H_5), 1008-76-0; **2** (R = C_4H_9), 104-50-7; **2** (R = C_6H_{13}), 706-14-9; nickel(II) 2-ethylhexanoate, 4454-16-4; bromine, 7726-95-6.

Synthesis of 7-Hydroxybicyclo[3.3.0]oct-8-en-2-one Derivatives and Use of Carbonate Participation for Stereospecific Epoxidation

Martin F. Haslanger* and Syed Ahmed

The Squibb Institute for Medical Research, Princeton, New Jersey 08540

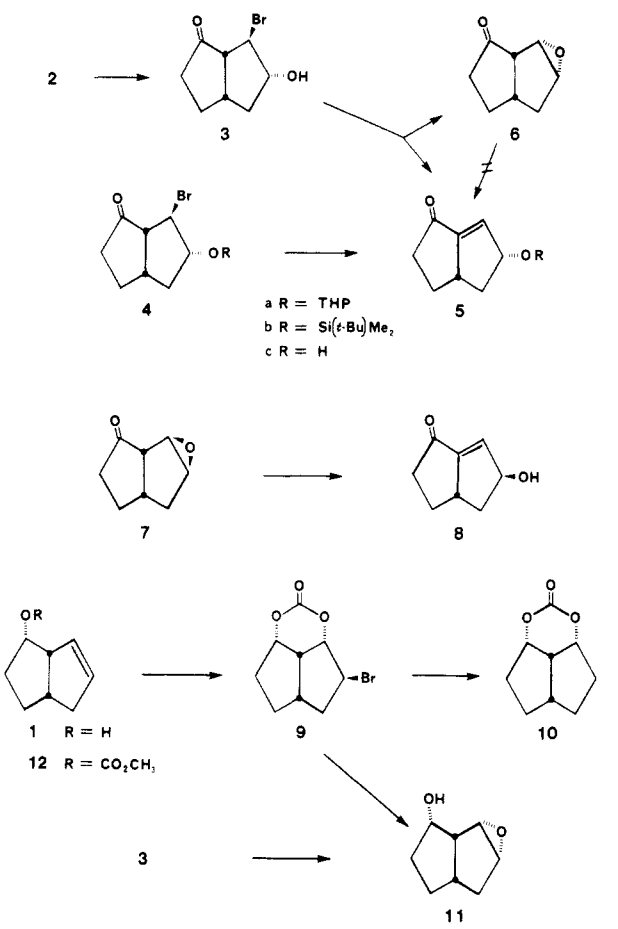
Received May 12, 1981

Bicyclo[3.3.0]oct-7-en-2-ol (**1**) is a readily prepared pentalene derivative which has served as the starting point of several sesquiterpene syntheses[1] and can be obtained in chiral form.[2] We[3] and others[4] have utilized this starting material to synthesize prostacyclin analogues. Bicyclo[3.3.0]octene **5** possesses functionality suitable for the stereocontrolled assembly of prostacyclin analogues[3] and sesquiterpenes such as coriolin.[5] Recent reports[6] on the preparation of enone **5** prompt us to present our work in this area. Herein we report the direct conversion of alcohol **1** to enone **5** and the introduction of a novel oxidative bromocarbonation to demonstrate its relative stereochemistry.

The enone **2** is obtained from alcohol **1** by CrO_3–pyridine oxidation.[7] Treatment of bicyclic enone **2** with *N*-

bromoacetamide in aqueous acetone gives crystalline bromohydrin **3** in 82% yield. The anticipated stereochemistry of bromohydrin **3**[8] is supported by the chemical correlation described below. Treatment of bromohydrin **3** with 1,8-diazabicyclo[5.4.0]undecene (DBU) gives a 1:1 mixture of epoxy ketone **6** and hydroxy enone **5c** (Scheme I). Epoxide **6** is not converted to enone **5c** upon further treatment with triethylamine or DBU. However, treatment of epoxy ketone **6** with sodium carbonate results in a low yield of hydroxy enone **5c**.[6b] The stability of *endo*-epoxy ketone **6** contrasts sharply with the reactivity of *exo*-epoxy ketone **7**, prepared as previously described.[6b]

Scheme I



We have found that *exo*-epoxy ketone **7** is rapidly converted to hydroxy enone **8** upon treatment with DBU or triethylamine at room temperature (Scheme I). The bromo ketone **4** and *exo*-epoxide **7** readily undergo elimination, while *endo*-epoxide **6** fragments at a notably slower rate.[9]

Protection of the hydroxyl function as either the tetrahydropyranyl ether[10] **4a** or *tert*-butyldimethylsilyl ether[11] **4b** allows dehydrobromination with DBU to proceed cleanly to give enone **5a** or **5b** in 80% yield after chromatography. In view of a previous report on the relative instability of a bridgehead double bond in bicyclo[3.3.0]-octenes,[12] it is interesting to note that no isomers of enone **5** were detected in the elimination reaction. Thus we have demonstrated that expeditious protection of the hydroxyl group of bromohydrin **3** allows straightforward conversion of ketone **2** to enone **5** in high yield without unnecessary protection and deprotection steps.[6] Synthetic sequences for the further elaboration of enone **5** will generally require hydroxyl protection.[3-5] This protection is conveniently introduced at bromohydrin **3** and, although we have used THP and *tert*-butyldimethylsilyl ethers, presumably any DBU stable protecting group could be employed.

The relative stereochemistry of pentalenone **5** is crucial to its synthetic utility. Prior to the publication of other reports[6] we sought to prove the relative configuration of

(1) J. K. Whitesell and R. S. Matthews, *J. Org. Chem.*, **43**, 1650 (1978); J. K. Whitesell, R. S. Matthews, and A. M. Helbing, *ibid.*, **43**, 784 (1978).
(2) H. Kuritani, Y. Takaoka, and K. Shingu, *J. Org. Chem.*, **44**, 452 (1979).
(3) M. F. Haslanger, U.S. Patent 4 192 891 (1980).
(4) M. Shibasaki, K. Iseki, and S. Ikegami, *Tetrahedron Lett.*, **21**, 169 (1980).
(5) M. Shibasaki, K. Iseki, and S. Ikegami, *Tetrahedron Lett.*, **21**, 3587 (1980).
(6) (a) M. Shibasaki, K. Iseki, and S. Ikegami, *Synth. Commun.*, **10**, 545 (1980); (b) *Chem. Lett.*, 1299 (1979).
(7) J. K. Crandall and L-H. Chang, *J. Org. Chem.*, **32**, 532 (1967).
(8) Z. Grudzinski and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1767 (1975).
(9) The dramatic difference in reactivity of the endo and exo β-epoxy ketones may be peculiar to the bicyclo[3.3.0]octane skeleton. Barton has shown that steroidal β-epoxy ketones of α or β stereochemistry fragment at approximately the same rate. Cf. D. H. R. B. Barton and Y. Houminer, *J. Chem. Soc., Perkin Trans. 1*, 919 (1972).
(10) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).
(11) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(12) W. C. Agosta and S. Wolff, *J. Org. Chem.*, **40**, 1699 (1975).

0022-3263/81/1946-4808$01.25/0

bromohydrin 3 and thus the configuration of enone 5. We developed a novel, unambiguous approach to epoxide 11. Treatment of the lithium alkoxide of alcohol 1 with dry CO_2 in THF followed by the addition of an equivalent of bromine gives bromo carbonate 9 in 79% yield. The structure of bromo carbonate 9 follows from the debromination product. Treatment with tri-*n*-butyltin hydride gives carbonate 10, which possesses a plane of symmetry that is apparent in its six-line ^{13}C NMR spectrum. The relative configuration of bromo carbonate 9 dictates that upon treatment with hydroxide it is converted to epoxy alcohol 11. Reduction of bromohydrin 3 with $NaBH_4$ and treatment with hydroxide gives an epoxy alcohol identical with epoxide 11.[13] Thus this chemical correlation agrees with the previously reported[6] assignments of relative stereochemistry.

The bromocarbonation sequence applied to alcohol 1 is a novel form of neighboring group participation which we employed to control relative stereochemsitry.[14] This sequence is analogous to the oxidative cyclization of homoallyic phosphates developed by Bartlett.[15] In our procedure the bridging carbonate group was introduced in situ rather than as a preformed derivative.[16] Mild alkaline hydrolysis converted bromo carbonate 9 to epoxy alcohol 11 with excision of the bridging carbonate. The homoallylic alcohol 1 was converted stereospecifically to *endo*-epoxide 11 in 75% yield by this route. We have also observed that treatment of the methoxycarbonyl derivative 12 with an equivalent of bromine at 0 °C in CH_2Cl_2 or *N*-bromosuccinimide (NBS) in CH_3CN gives cyclic carbonate 9.

The four-step converstion of the alcohol 1 to enone 5 described herein is the most efficient preparation reported to date for this versatile intermediate. This procedure allows latitude in the choice of the hydroxyl-protecting group and can be used to prepare either enantiomer of enone 5 since alcohol 1 has been resolved.[2]

Experimental Section

Melting points were taken in an open glass capillary and are uncorrected. IR spectra were taken on a Perkin-Elmer 257 spectrophotometer. ^{13}C NMR spectra were taken on a JEOL FX60Q spectrometer at 15 MHZ and chemical shifts are reported in parts per million relative to Me_4Si.

2-Bromo-3-hydroxybicyclo[3.3.0]octan-8-one (3). To an ice-cooled solution of 4.6 g (38 mmol) of bicyclo[3.3.0]oct-7-en-2-one (2)[7] in 80% aqueous acetone (120 mL) was added 8.04 g (58 mmol) of *N*-bromoacetamide in one portion. The reaction mixture was allowed to warm to ambient temperature and stir for 14 h, then concentrated in vacuo, diluted with ether, and partitioned. The ether phase was washed with saturated $NaHSO_3$, saturated $KHCO_3$, and saturated NaCl, dried ($MgSO_4$), and evaporated to yield the crude product, which was crystallized from pentane–ether to yield 6.8 g (82%) of bromohydrin 3: mp 60–61 °C; IR (KBr) 1720 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 218.4, 80.4, 60.8, 57.2, 39.0, 37.2, 36.9, 26.7. Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.85; H, 5.06; Br, 36.48. Found: C, 43.81; H, 5.16; Br, 36.27.

***endo*-7-Hydroxybicyclo[3.3.0]oct-8-en-2-one *tert*-Butyldimethylsilyl Ether (5b).** To an ice-cooled solution of 2.95 g (13.5 mmol) of bromohydrin 3 and 2.24 g (14.8 mmol) of *tert*-butyldimethylsilyl chloride in DMF (15 mL) was added 2 g (29.6 mmol) of imidazole. The reaction mixture was allowed to warm to room temperature and stir for 16 h and then poured into ether–water. The ether phase was washed with water, pH 5.5 buffer, saturated $KHCO_3$, and saturated NaCl and dried ($MgSO_4$). The solvent was evaporated to yield 4.4 g (98%) of silyl ether **4b**.[6b] To a solution of 4.0 g of silyl ether **4b** in toluene (50 mL) was added 1.8 g of 1,8-diazabicyclo[5.4.0]undecene (DBU). The resulting solution was stirred at room temperature for 4 h and then poured into ether and water. The ether phase was washed with pH 5.5 buffer, saturated $KHCO_3$, and saturated NaCl, dried ($MgSO_4$), and evaporated to yield the crude product which was chromatographed on silica with hexane–ethyl acetate to yield 2.4 g (80%) of enone **5b**:[6b] IR (neat) 1715, 1940 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 203.3, 147.3, 136.3, 82.3, 46.8, 46.2, 42.2, 29.2, 25.8, 18.0, -4.8.

The tetrahydropyranyl ether **4a** was prepared by the usual procedure[10] and treated as above to give enone **5a** in 82% yield: IR (neat) 1710, 1635 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.10. Found: C, 69.90; H, 8.13.

3-Bromo-2,8-dihydroxybicyclo[3.3.0]octane Carbonate (9). To a solution of 2.4 g (20 mmol) of alcohol 1 in dry THF (100 mL) at -78 °C, under argon, was added 25 mL of 1.6 M *n*-butyllithium. Upon completion of addition, dry CO_2 was bubbled into the reaction mixture for 0.5 h, the reaction mixture was allowed to warm to -20 °C, and a solution of 3.2 g (20 mmol) of bromine in CH_2Cl_2 (20 mL) was added over 0.5 h. During the course of the addition the temperature was allowed to rise to 0 °C. The reaction mixture was then diluted with ether, washed with saturated $NaHSO_3$, saturated $KHCO_3$, and saturated NaCl, and dried ($MgSO_4$), and the solvent was evaporated to yield the crude product which was chromatographed on silica with hexane–ethyl acetate to yield 3.9 g (79%) of bromo carbonate 9: mp 86–87 °C; IR (KBr) 1760 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 149.1, 86.3, 81.8, 53.9, 42.6, 42.2, 40.2, 35.4, 28.5. Anal. Calcd for $C_9H_{11}BrO_3$: C, 43.74; H, 4.48; Br, 32.34. Found: C, 43.49; H, 4.64; Br, 32.74. Treatment of methyl carbonate 12 (320 mg, 1.76 mmol) with Br_2 (1.8 mmol) in CH_2Cl_2 at 0 °C followed by isolation as above gave bromo carbonate 9 (220 mg, 51%). Carbonate 12 (182 mg, 1 mmol) was allowed to react with NBS (1.1 mmol) in CH_3CN at ambient temperature for 22 h to give bromo carbonate 9 (153 mg, 62%).

2,8-Dihydroxybicyclo[3.3.0]octane Carbonate (10). To a solution of 0.5 g (2 mmol) of bromo carbonate 9 in benzene (5 mL) at 75 °C was added in solution of 0.6 g (2.1 mmol) of tri-*n*-butyltin hydride and 50 mg of azobis(isobutyronitrile) (AIBN) in benzene (5 mL). Upon completion of addition the reaction mixture was heated at reflux for 2 h. The solvent was evaporated to yield the crude product which was chromatographed on silica with hexane–ethyl acetate and crystallized from ether–pentane to yield 170 mg (50%) of cyclic carbonate 10: mp 74–75 °C; IR (KBr) 1750 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 151.2, 82.4, 44.7, 43.8, 35.0, 29.6. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.97; H, 7.32.

2,3-Epoxybicyclo[3.3.0]octan-8-ol (11). A solution of 245 mg (1 mmol) of bromo carbonate 9 in methanol (2 mL) and 2 N KOH (1 mL) was stirred at ambient temperature for 2 h and then diluted with ether. The ether phase was washed with saturated NaCl, dried ($MgSO_4$), and evaporated to yield 130 mg (94%) of epoxy alcohol 11 (identical with an authentic sample[6]): ^{13}C NMR ($CDCl_3$) δ 74.7, 60.1, 59.9, 49.5, 41.1, 36.5, 34.1, 31.0. Reduction of bromo ketone 3 (200 mg, 0.9 mmol) with $NaBH_4$ (100 mg, 2.6 mmol) in CH_3OH at -20 °C (2 h) followed by treatment with excess KOH at room temperature gave epoxy alcohol 11 (100 mg, 71%).

Treatment of Bromohydrin 3 with DBU. A solution of 356 mg (1.6 mmol) bromohydrin 3 and 0.25 mL (1.7 mmol) DBU in benzene (5 mL) was stirred at ambient temperature for 1.5 h and then partitioned between ether and saturated NaCl. The ether phase was washed with pH 5 acetate buffer, saturated $KHCO_3$, and saturated NaCl and dried ($MgSO_4$). The solvent was evaporated to yield 180 mg (80%) of a 1:1 mixture of epoxy ketone 6 and enone 5c, which separated by chromatography on silica with hexane–ethyl acetate. Epoxy ketone 6 was identical with an authentic sample:[6a] ^{13}C NMR ($CDCl_3$) δ 218.1, 60.3, 59.3, 52.8, 39.6, 38.6, 34.1, 29.7. Enone 5c was identical with an authentic sample:[6b] ^{13}C NMR ($CDCl_3$) δ 203.3, 148.3, 135.5, 82.1, 46.6, 46.1, 42.3, 30.0.

Treatment of *exo*-Epoxide 7 with DBU. Epoxy ketone 7 was prepared as previously described:[6b] ^{13}C NMR ($CDCl_3$) δ 218.2, 57.7, 57.3, 55.1, 36.8, 35.4, 32.8, 25.0. By the same procedure

(13) M. Shibasaki, J. I. Ueda, and S. Ikegami, *Tetrahedron Lett.*, **20**, 433 (1979).
(14) P. A. Bartlett, *Tetrahedron*, **36**, 2 (1980).
(15) P. A. Bartlett and K. K. Jernstedt, *J. Am. Chem. Soc.*, **99**, 4829 (1977).
(16) The use of chloral for the in situ generation of a bridging group in an alternative strategy has been described: L. E. Overman and C. B. Campbell, *J. Org. Chem.*, **39**, 1474 (1974).

applied above, 170 mg (1.2 mmol) of epoxy ketone 7 was converted in 80% yield to enone 8 which was identical with an authentic sample:[6a] ^{13}C NMR ($CDCl_3$) δ 203.4, 153.5, 131.1, 81.2, 46.0, 43.8, 42.5, 29.0.

Bicyclo[3.3.0]oct-7-en-2-ol Methyl Carbonate (12). Methyl carbonate 12 was prepared from alcohol 1 by a standard procedure: ^{13}C NMR ($CDCl_3$) δ 155.4, 132.7, 127.6, 81.0, 54.4, 53.6, 41.3, 39.2, 30.9, 30.7. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.67; H, 7.61.

Registry No. 1, 41164-15-2; 2, 10095-78-0; 3, 79068-87-4; 4a, 79068-88-5; 4b, 79068-89-6; 5a, 79068-90-9; 5b, 72397-63-8; 5c, 72397-62-7; 6, 72397-61-6; 7, 79120-22-2; 8, 79068-91-0; 9, 79068-92-1; 10, 79068-93-2; 11, 79120-23-3; 12, 79068-94-3.

Regioselective Reduction of Anhydrides by L-Selectride

Mansour A. Makhlouf and Bruce Rickborn*

Department of Chemistry, University of California, Santa Barbara, California 93106

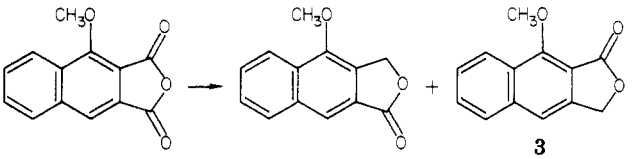
Received May 14, 1981

Cyclic anhydrides are useful precursors to lactones via reduction. An older procedure involving zinc/acetic acid appears to be nonselective with unsymmetrical anhydrides[1] and has been largely supplanted by borohydride reduction. With this reagent, the initially formed hydroxy carboxylate product is usually considered to be resistant to further reduction and is converted to lactone by acidification/dehydration. There are intriguing reports[2,3] of selective reduction of the apparently most hindered carbonyl group by $NaBH_4$ and at least one example[4] of selectivity in the opposite sense. Additional examples and a discussion of mechanistic possibilities are found in recent work by Kayser and Morand.[5] A troublesome feature of several examples of reported regioselectivity is the modest yield of isolated lactone.[2-5]

Results and Discussion

We have recently described[6] an approach to 1-alkoxy-2,3-naphthoic anhydride via 1-alkoxyisobenzofuran that should be general for more highly substituted analogues. Similar work has been reported by MacLean and co-workers.[7] Further synthetic utility would be enhanced by selective reduction to one or the other possible lactone. Consequently, we treated naphthoic anhydride 1 with $NaBH_4$ in the expectation that behavior similar to that reported by McCrindle and co-workers[3] for 3-methoxyphthalic anhydride 4a might obtain. The reduction of 1 proved, however, to be essentially devoid of selectivity with this reagent; similar results were obtained with $LiBH_4$. In contrast, L-Selectride provided significant regioselectivity, giving 90% (of total lactone) isomer 3, from hydride attack

Table I. Reductions of 1



1 2 3

reagent	% yield (2 + 3)	% 2	% 3
$NaBH_4$	80	58	42
$LiBH_4$	87[a]	55	45
L-Selectride	90	10	90

[a] Corrected for 35% recovered starting material.

at the *least* hindered carbonyl. The results are given in Table I.

The absence of selectivity in the $NaBH_4$ reduction of 1 led us to reexamine the reactions of 4a (R = OCH_3) and 4b (R = CH_3) with this reagent. Contrary to the earlier report[3] for 4a (5a/6a = 87/13), but in close agreement with the low selectivity reported[3] for 4b (5b/6b = 57/43), we find both substrates giving nearly equal mixtures of the two lactones. We suggest that the differences between our observations and those of McCrindle et al. are due to selective loss of material, probably at the hydroxy acid stage, in the earlier work. McCrindle gives overall lactone yields of 52% for 5a,6a, and 77% for 5b,6b. We find that yields are significantly lower for the product from 4a if the evaporation-extraction procedure described in the Experimental Section is not followed.

Lithium triethylborohydride (Superhydride) has recently been shown to give phthalide from phthalic anhydride, in high yield.[8] Application of this reagent to 4a indicates that, like $NaBH_4$, it shows little selectivity; because of cost and workup factors, it offers no advantages over the simpler hydride. L-Selectride reductions of 4a and 4b exhibit regioselection similar to that found in the naphthalene system. The ratio of lactones from 4a does not change significantly when the reduction with L-Selectride is carried out at -78 °C (initial, allowed to warm to ambient), 0 °C, or room temperature.

Although the selectivity observed with this bulky reagent is not exceptionally high, the increase in one isomer can be useful in further synthetic applications, and the product is more easily purified than from the near 50/50 mixtures obtained with $NaBH_4$. Selective reduction of the least hindered carbonyl group is most simply rationalized on steric grounds, although electronic factors may also play a role.

Experimental Section

The preparation of 1-methoxy-2,3-naphthalenedicarboxylic anhydride 1 has been described previously.[6] The procedure of Newman and Kanakarajan[9] was followed to prepare dimethyl 3-methoxyphthalate, mp 76-77 °C, using dimethyl acetylenedicarboxylate and trifluoroacetic acid as catalyst. This ester was hydrolyzed, and the diacid dehydrated in refluxing acetic anhydride to give 4a, mp 162-163 °C (lit.[10] mp 160-161 °C). The anhydride 4b was a commercial sample purified by sublimation and recrystallization from hexane, mp 117.5-119 °C (lit.[11] mp 116-117 °C).

(1) For example, see Brewster, J. H.; Fusco, A. M. *J. Org. Chem.* **1963**, *28*, 501.
(2) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574.
(3) McAlees, A. J.; McCrindle, R.; Sneddon, D. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2037.
(4) Vaughan, W. R.; Goetschel, C. T.; Goodrow, M. H.; Warren, C. L. *J. Am. Chem. Soc.* **1963**, *85*, 2282.
(5) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1980**, *58*, 2484.
(6) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 2734.
(7) Contreras, L.; Slemon, C. E.; MacLean, D. B. *Tetrahedron Lett.* **1978**, 4237. Contreras, L.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2573, 2580.
(8) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.
(9) Newman, M. S.; Kanakarajan, K. *J. Org. Chem.* **1980**, *45*, 3523. See also Rao, G. S. R. S.; Kumar, V. P. S. *Indian J. Chem., Sect. B* **1979**, *18*, 543.
(10) Profitt, J. A.; Jones, T.; Watt, D. S. *Synth. Commun.* **1975**, *5*, 457.
(11) Jurgens, V. *Chem. Ber.* **1907**, *40*, 4413.

0022-3263/81/1946-4810$01.25/0