R-32 (90 MHz) spectrometer. Chemical shifts are reported in δ units downfield from internal Me_4Si, and the J values are given in hertz.

Recommended General Procedure for Nitrene Reaction. *N*-Aminophthalimide (0.01 mol) was stirred with dry dichloromethane (15 mL/g), and the olefin (0.011 mol) was added. Lead tetraacetate (0.012 mol) was then added to the stirred suspension at 5–10 °C during 10 min. After being stirred for a further 15 min, the reaction mixture was filtered, and the residue was washed with dichloromethane. The combined filtrate was then washed sequentially with water and with a saturated solution of sodium bicarbonate to remove any traces of acetic acid. The dichloromethane layer was then dried (Na_2SO_4) and evaporated to dryness. The residue was examined by TLC, and the subsequent purification was effected as mentioned for each aziridine.

Reaction of Phthalimidonitrene with 1,4-Dihydronaphthalene 1,4-*endo*-Oxide. Addition of phthalimidonitrene from *N*-aminophthalimide (1.63 g) and lead tetraacetate (5.33 g) to the *endo*-oxide (1.58 g) gave the aziridine **4**: 2.90 g (92%); mp 183 °C; IR (KBr) ν_{max} 1780, 1745, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.3 (2 H, S), 5.7 (2 H, S), 7.2–7.7 (8 H, m); mass spectrum, m/e 304 ($M^{+\cdot}$). Anal. Calcd for $C_{18}H_{12}N_2O_3$: C, 70.8; H, 4.0. Found: C, 70.3; H, 4.1.

Reaction of Phthalimidonitrene with 1,4-Dihydronaphthalene. Addition of phthalimidonitrene from *N*-aminophthalimide (1.63 g) and lead tetraacetate (5.33 g) to 1,4-dihydronaphthalene (1.43 g) gave the aziridine **7**: 2.03 g (70%); mp 180 °C (ethyl acetate–petroleum ether); IR (KBr) ν_{max} 3010, 1750, 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (2 H, J = 9, t), 3.1 (4 H, J = 10 Hz, d), 7.2–7.7 (8 H, m); mass spectrum, m/e 290 ($M^{+\cdot}$). Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.8. Found: C, 74.01; H, 4.5.

Reaction of Aziridine 4 with P_2S_5. A solution of the aziridine **4** (0.50 g) in carbon disulfide (250 mL) was stirred with phosphorous pentasulfide (4.00 g) at room temperature for 2 h. The filtered solution was evaporated to dryness, and the residue was taken up in benzene and purified by chromatography over basic alumina. Crystallization from ethyl acetate–petroleum ether afforded *N*-phthalimido-3-benzazepine: 0.18 g (40%); mp 63 °C; UV (EtOH) λ_{max} 225 nm (ϵ 24170), 290 (1036), 340 (186.6); IR ($CHCl_3$) ν_{max} 1600 cm^{-1}; ^1H NMR (CCl_4) δ 7.1–7.6 (m); mass spectrum, m/e 286 ($M^{+\cdot}$). Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 75.0; H, 4.2. Found: C, 74.6; H, 3.9.

Oxidation of Aziridine 7. To a solution of the aziridine **7** (8.7 g) in dry chloroform (50 mL) was added lead tetraacetate (13.3 g) in small portions at 45 °C. The precipitated lead diacetate was removed by filtration. The residue was washed with water, dried (Na_2SO_4), and evaporated to give a dark-colored oily product which was purified with a column of basic alumina. Elution by ethyl acetate–benzene (1:9) gave *N*-phthalimido-3-benzazepine: 2.3 g (30%); mp 63 °C. The oxidation when carried out with dichlorodicyano-*p*-benzoquinone under similar conditions gave the same azepine **5** in 20% yield.

Synthesis of *N*-Phthalimido-3-benzazepine. The acid chloride prepared from *o*-phenylenediacetic acid (3.86 g) was refluxed for 5 h with *N*-aminophthalimide (3.24 g) in dry benzene (80 mL) with a few drops of pyridine. Benzene was removed, and the residue was extracted with ether (100 mL). The ether layer was washed with water and was concentrated (20 mL), and lithium aluminium hydride (1.55 g) was added to it. The workup gave an oil: IR ν_{max} 3480, 3450, 1780, 1740, 1610 cm^{-1}.

The oily product was refluxed in dry benzene with catalytic amounts of *p*-toluenesulfonic acid for 2 h. Benzene was then removed, and the product was chromatographed on an alumina column. Elution with benzene gave the required azepine: 0.75 g (20%); mp 64 °C.

Acknowledgment. We thank Professor S. Swaminathan, University of Madras, for encouragement and support and Professor K. Griesbaum, Universitat Karlsruhe, for the mass spectral data. P.R.K. thanks the UGC for a fellowship.

Registry No. **1**, 24965-33-1; **3**, 573-57-9; **4**, 84648-94-2; **5**, 84648-95-3; **6**, 612-17-9; **7**, 84648-96-4; *N*-aminophthalimide, 1875-48-5.

Synthesis of Costatolide, a Halogenated Monoterpenoid from the Red Alga *Plocamium costatum*

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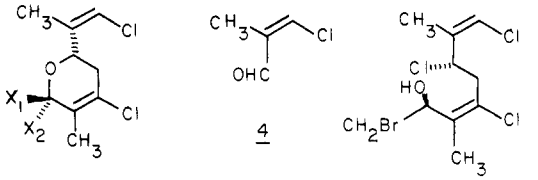
Marine red algae are the source of numerous halogenated products. Excellent reviews of the progress in isolation and structure determination of these compounds are available.[1] Many of these marine metabolites present interesting synthetic targets since the patterns of halogenation which they exhibit are particularly intriguing. Correlation of the structures of many marine natural products reveals that a number of simple building blocks (i.e., four-, five-, and six-carbon pieces) with well-defined patterns of halogenation are found in several different compounds. Recently, we have focused our efforts on the numerous unique, polyhalogenated monoterpenes isolated from various species of red algae belonging to the genus *Plocamium*. We outline below some initial results in this area culminating in the synthesis of the natural product costatolide (**1**).

The structures of the three marine natural products costatolide (**1**),[2a] costatone (**2**),[2a,b] and costatol (**3**)[2b] are given below. The structures and the absolute configura-



4

1 $X_1, X_2 = O$

2 $X_1 = OH$, $X_2 = CHBr_2$

3

tions of compounds **2** and **3** have been confirmed by X-ray diffraction analysis.[2] The key structural feature in all of these compounds is the terminal (*Z*)-chloro olefin. This is depicted in the structures as the uppermost carbon atoms. It appeared to us that a suitable precursor of the (*Z*)-chloro olefin in all of these compounds would be the four carbon unit (*Z*)-3-chloro-2-methylpropenal (**4**). Compound **4** has not been previously characterized in the literature, and thus we sought a convenient preparation of this material.[3,4]

Our preparative route to aldehyde **4** proceeds from 2-methyl-1,2,3-trichloropropane (**5**, Scheme I). Compound **5** is easily obtained by chlorination of methallyl chloride.[5]

(1) (a) Crews, P. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum: New York, 1977; pp 211–224. (b) Sims, J. J.; Rose, A. F.; Izac, R. R. In "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. II, pp 297–378. (c) Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421. (d) Wells, R. J. *Pure Appl. Chem.* **1979**, *51*, 1829.

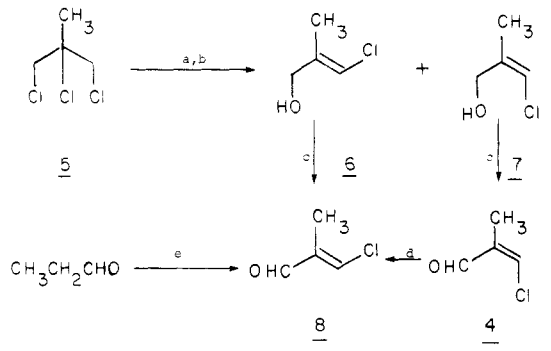
(2) (a) Stierle, D. B.; Wing, R. M.; Sims, J. J. *Tetrahedron Lett.* **1976**, 4455. (b) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Lett.* **1976**, 4451.

(3) An obvious method for the preparation of β-halo α,β-unsaturated carbonyl compounds utilizes the Vilsmeier–Haack–Arnold acylation. Cf.: Jutz, C. In "Advances in Organic Chemistry: Methods and Results"; Boehme, H., Viehe, H. G., Eds.; Wiley: New York, 1976; Vol IX, pp 225–342.

(4) The reaction of propionaldehyde with the phosphorus oxychloride–dimethyformamide adduct is described; cf.: Arnold, A.; Zemlicka, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2385. The major isomer (>97%) formed in this reaction corresponds to (*E*)-3-chloro-2-methylpropenal (**8**; see Scheme I).

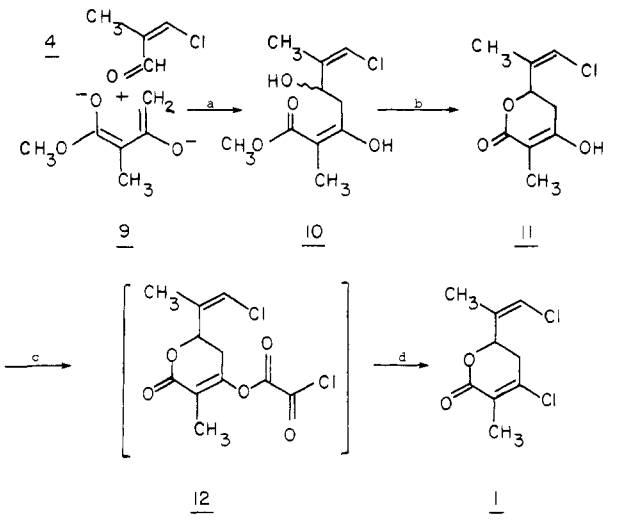
0022-3263/83/1948-1123$01.50/0

Scheme I[a]



[a] (a) 10% NaOH; (b) spinning-band distillation; (c) MnO_2, Et_2O; (d) H^+; (e) $POCl_3$; dimethylformamide.

Scheme II[a]



[a] (a) −78 to 0 °C; (b) NaOH; (c) oxalyl chloride, Et_2O; (d) dimethylformamide, tetrabutylammonium chloride.

Vigorous treatment of **5** with 10% NaOH leads to a 1:1 mixture of the isomeric allylic alcohols **6** and **7** in good yield.[6] In contrast to the literature report, we were quite pleasantly surprised to find that the alcohols **6** and **7** are easily separable by a spinning-band distillation at reduced pressure.[7] The desired Z isomer **7** distills off almost completely before the E isomer **6** begins to distill. Structural assignments of alcohols **6** and **7** were based upon analysis of the NMR spectra.[8,9] The chloro aldehyde **4** is prepared in 54% yield immediately before use by the MnO_2 oxidation of alcohol **7**.[10]

Dianion **9** is prepared by the Weiler procedure[11] in THF at −5 °C at which time a slight excess of freshly distilled aldehyde **4** is added. After the mixture warmed to 0 °C, it was possible to isolate the aldol product **10** in 60% yield[12] (Scheme II). However, we find it more convenient simply to add the reaction mixture to ice–water and then stir it for several hours to obtain lactone **11** directly. Crystalline lactone **11** can be obtained from this one pot procedure in over 66% yield from **9** and is suitable for use in the next step without further purification.[13]

Numerous attempts to introduce a chlorine atom into **11** were unsuccessful. The conversion of **11** into **1** is successfully effected by a modification of the Heathcock procedure.[14] Thus after complete conversion of **11** into the chloro oxalate ester **12** with excess oxalyl chloride, anhydrous DMF is carefully added to react with all of the acyl chloride present. A quantity of tetrabutyl ammonium chloride and a trace of boron trifluoride etherate are also required for the formation of **1**. It is possible to observe the disappearance of the starting material and the concomitant appearance of costatolide (**1**) while monitoring this reaction by TLC. Costatolide (**1**) is obtained in 70% yield from (**11**) as a colorless oil following chromatography on silica gel. The spectra (NMR, IR, UV, and mas) of our synthetic material correspond in all respects to those reported for the natural product. The synthesis of other compounds in this series is being carried out in our laboratories.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on either a Varian EM-360, a Varian EM-390, or a Bruker WM-250 spectrometer in $CDCl_3$ solution with Me_4Si as an internal standard. IR spectra were recorded in $CHCl_3$ solution, and mass spectra were recorded on a Hitachi RMU-6 spectrometer. Microanalysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

(*Z*)-3-Chloro-2-methylpropenal (4). To a stirred solution of manganese dioxide[10,15] (10 g) in dry ether (25 mL) was added (*Z*)-3-chloro-2-methylpropen-1-ol (1.0 g). The reaction mixture was stirred for 10 h at room temperature. The mixture was filtered through Celite, and the manganese dioxide was washed with ether (2 × 10 mL). The filtered washings were combined with filtrate and evaporated in vacuo to afford 0.55 g (54%) of **4**. Compound **4** was used immediately without further purifcation: ^1H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 7.03 (q, 1 H), 10.27 (s, 1 H); mass spectrum, *m/e* 105, 104, 89, 39.

6-[2-(*Z*)-(1-Chloropropenyl)]-5,6-dihydro-4-hydroxy-3-methyl-2(*H*)-pyran-2-one (11). To a solution containing 18.5 mmol of sodium hydride (NaH 60% oil dispersion) in 40 mL of dry THF at −5 °C under N_2 was added 2-methyl methylacetoacetate (2.41 g, 18.5 mmol) in 5 mL of THF dropwise over 5 min. After the mixture was stirred for 10 min at −5 °C, 12.8 mL of 1.44 M *n*-butyllithium was added and the solution stirred an additional 10 min. (*Z*)-3-Chloro-2-methylpropenal (**4**; 0.968 g, 9.2 mmol) in 2 mL of dry THF was then added, and the reaction mixture was

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(6) Hatch, L. F.; Ross, J. J.; Gordon, L. B. *J. Am. Chem. Soc.* **1947**, *69*, 2614.
(7) The 60-MHz ^1H NMR shifts (δ) for **6** and **7** are given as follows. Compound **6**: CH_3, 1.8; CH_2, 1.8; CH_2OH, 4.02; H, 6.1. Compound **7**: CH_3, 1.85; CH_2OH, 4.32; CH_2OH, 4.32; H, 5.85.
(8) The ^{13}C NMR spectra of alcohols **6** and **7** were obtained by employing a single frequency for resonance decoupling which was set to irradiate only the protons on the methyl group. The ^{13}C resonance for the hydroxy methyl carbons of **6** and **7** appeared as a doublets of triplets (*dt*) centered at 60.8 and 65.65 ppm with coupling constants of 106, 3.5, and 102, 6 Hz, respectively. The 3.5- and 6-Hz coupling constants are attributed to the three-bond coupling $J(^{13}CCCH)$ between the hydroxymethyl carbon and the olefinic hydrogen. The analogous three-bond proton–proton coupling $J(HC{=}CH)$ is well established (i.e., $J_{cis} < J_{trans}$).[9a] This conclusion has been drawn for the analogous $^{13}CCCH$ three bond coupling.[9b,c] Hence it is possible to assign the correct stereochemistry to the alcohols **6** and **7** by analysis of these coupling constants.
(9) (a) Jackman, L. M.; Sternhell, S., Eds. In "Applications of NMR Spectroscopy in Organic Chemistry"; Pergamon: New York, 1969; Vol V, pp 301–302. (b) Brouwer, H.; Stothers, J. B. *Can. J. Chem.* **1972**, 50, 1361. (c) Vogeli, V.; von Philipsborn, W. *Org. Magn. Reson.* **1975**, 7, 617.
(10) It is important to use base-washed MnO_2[15] in this oxidation otherwise an appreciable quantity of the isomeric aldehyde **8** is obtained. Traces of acid catalyze the isomerization of **4** and **8**. This isomerization if effectively inhibited by addition of minute quantities of either propylene oxide or styrene oxide. This acid sensitivity leads to formation of exclusively the *E* isomer **8** in the Vilsmeier–Haack–Arnold reaction on propanal (see ref 4).
(11) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(12) A similar dianion condensation reaction has been utilized in the synthesis of the monoterpenoid antibiotic nectriapyrone. See: Reffstrup, T.; Boll, P. M. *Tetrahedron Lett.* **1976**, 1903.
(13) All new compounds were characterized by ^1H and ^{13}C NMR, IR, UV, and mass spectroscopy. Yields reported refer to distilled or chromatographically pure, isolated material.
(14) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636.
(15) Attenburrow, J.; et al. *J. Chem. Soc.* **1952**, 1094.

stirred for 5 min at −5 °C. The reaction mixture was poured into 300 mL of ice–water and stirred for 2 h. The solution was then washed with ether (50 mL), acidified to pH 1 with 1 N HCl, and extracted with ethyl acetate (3 × 150 mL). The organic phase was washed with water and brine and dried over $MgSO_4$. Removal of solvent in vacuo and washing of the solid with ether afforded 1.224 g (66%) of compound 11: ^1H NMR (CD_3COCD_3) δ 1.65 (s, 3 H), 1.82 (s, 3 H), 2.65 (m, 3 H) 4.88 (q, 1 H), 6.10 (s, 1 H); IR (1705) cm^{-1}; mp 183–184 °C. Anal. Calcd for $C_9H_{11}ClO_3$: C, 53.39; H, 5.47; Cl, 17.50. Found: C, 53.42; H, 5.64; Cl, 17.44.

Costatolide (1). To a solution of 11 (0.25 g, 1.25 mmol) in dry ether (25 mL) at room temperature under N_2 was added oxalyl chloride (1.1 mL, 12.5 mmol). After the mixture was stirred for 5 h, dimethyl formamide (0.97 mL, 12.5 mmol) was added dropwise over 5 min at 0 °C. Stirring was continued for 10 min, and then tetrabutylammonium chloride (1.74 g, 6.3 mmol) followed by boron trifluoride etherate (0.15 mL, 1.2 mmol) was added at room temperature. The mixture was then stirred 60 h under N_2. The reaction mixture was poured into ice-cooled (0 °C) 10% $NaHCO_3$. The aqueous layer was extracted with ether (3 × 15 mL), and the organic layers were combined, washed with water and brine, and dried over magnesium sulfate. Removal of solvent in vacuo followed by column chromatography (20% ethyl acetate–petroleum ether) on silica gel afforded 0.193 (70%) of costatolide (1): ^1H NMR ($CDCl_3$, 60 MHz) δ 1.88 (m, 3 H), 2.07 (m, 3 H), 2.80 (m, 2 H), 5.60 (q, 1 H), 6.01 (s, 1 H); IR 3018, 1720, 1643, 1120, 825 cm^{-1}; ^{13}C NMR ($CDCl_3$, 250 MHz) δ 13.8, 16.1, 35.1, 220, 222, 224; mass spectrum, *m/e* 187 (M^+ − Cl), 85.

Acknowledgment. We thank Professor James J. Sims (University of California, Riverside) for sending us a copy of the 90-MHz ^1H NMr spectrum of costatolide and Dr. Jeff Barton (USV Laboratories, Tuckahoe, NY) for recording the 90-MHz ^1H NMR of our synthetic material. The ^{13}C NMR spectra were recorded at Brown University on a Bruker WM-250 spectrometer purchased by a grant from NSF and from the Montedison Group of Milan. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No. (±)-1, 84926-48-7; 4, 84895-35-2; 5, 1067-09-0; 6, 37428-54-9; 7, 37428-47-0; 8, 84895-36-3; 9, 84895-37-4; (±)-10, 84895-38-5; (±)-11, 84895-39-6; (±)-12, 84895-40-9; methyl 2-methylacetoacetate, 17094-21-2; oxalyl chloride, 79-37-8.

Oxidative Cyclization of Dicarboxylate Dienolates as a New Cyclization Method

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On consideration of the abundance of rings in organic compounds, synthetic methods leading to cyclic structures are of obvious importance in organic synthesis.[1] In principle, the cyclic structures may be constructed either by cyclization of acyclic precursors, whereby one bond is formed, or by cycloaddition reactions in which two or more bonds are simultaneously formed. The Dieckmann[2] and the acyloin cyclizations[3] are most commonly used for the cyclization of dicarboxylic esters into the carbocyclic or heterocyclic ketone systems. The Dieckmann cyclization has been found to be useful for the preparation of cyclic ketones of a ring size of five or larger, although it is almost ineffective for the cyclic systems in the range of 9–12-membered rings. The acyloin cyclization appears to be the method of choice for the preparation of the medium- to large-sized ring systems.

Scheme I

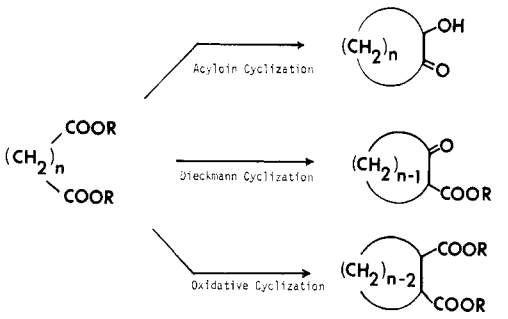

Table I. Oxidative Cyclization of Dimethyl Glutarate to Dimethyl Cyclopropanedicarboxylate

run	metal salt (molar equiv)	% yield (cis/trans ratio[a])
1	Ag_2O (2.5)	0
2	$AgClO_4$ (2.5)	7 (1.0)
3	$FeCl_3$ (2.5)	0
4	$NiCl_2$ (2.5)	0
5	$CuBr_2$ (2.5)	99 (1.2)
6	$CuCl_2$ (2.5)	99 (3.3)
7	$Cu(OAc)_2$ (2.5)	24 (1.4)
8	$CuSO_4$ (2.5)	0
9	CuI	0
10	CuI (1.1), $CuBr_2$ (2.5)	78 (1.7)
11	CuCl (1.1), $CuBr_2$ (2.5)	81 (1.9)

[a] Determined by GC analysis on a 15-ft column of 10% FFAP on Anakrom 60/70 mesh.

Oxidative coupling of metalated organic species has received increasing attention in the recent years for its synthetic utility.[4] For example, the ligand coupling can be effected either thermally or oxidatively in the reactions of organolithiums or Grignard reagents with copper salts. Although copper and silver salts are most extensively used in the oxidative coupling, other metal salts such as Au, Ni, Co, and Pt have also been found useful in certain cases. The coupling may occur via a radical or a nonradical mechanism, perhaps depending on the nature of the metal–carbon bond as well as on the reaction conditions.[4] The ligand coupling may proceed either monocentrically or dicentrically on the metal cluster.[5] The oxidative coupling has been successfully extended to the carbanionic species which are stabilized by a carbonyl,[5,6] alkoxycarbonyl,[7] phosphoryl,[8] or thioamidyl[9] functional group. The cyclization of diketones by intramolecular oxidative coupling has recently been exploited in the syntheses of 1,3-cyclopentanediones[10] and 1,4-cyclohexanediones.[11]

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(2) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* 1967, *15*, 1.
(3) Bloomfield, J. J.; Owsley, D. C.; Ainsworth, C.; Robertson, R. E. *J. Org. Chem.* **1975**, *40*, 393. Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976**, *23*, 259.
(4) Noyori, R. In "Transition Metal Organometallics in Organic Synthesis"; Alper, H., Ed.; Academic Press: New York, 1976; Vol. 1.
(5) Kauffman, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 291.
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(9) Tamaru, Y.; Harada, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1978** *100*, 1923.

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