Total Synthesis of Ostopanic Acid, a Plant Cytotoxin, via Cyclopropanation of 2-*n*-Hexylfuran

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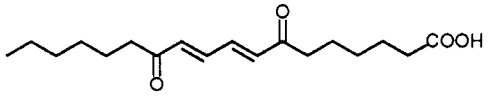
The cyclopropanation of 2-*n*-hexylfuran with ethyl 8-diazo-7-oxooctanoate catalyzed by dirhodium tetraacetate as a key step for the synthesis of ostopanic acid is reported. This reaction allowed the preparation of ethyl ostopanate (**5**) and its unstable regioisomer (**10**) in 58% yield. Exposure of the mixture to a catalytic amount of iodine in dichloromethane afforded pure ethyl ostopanate, which was converted to the target compound in two steps.

Introduction

Ostopanic acid (**1**), a cytotoxic fatty acid which was isolated from the stems and fruits of *ostodes paniculate* Blume (Euphorbiaceae), has been shown to inhibit the growth of P-388 lymphocytic leukemia test system in vitro.[1]



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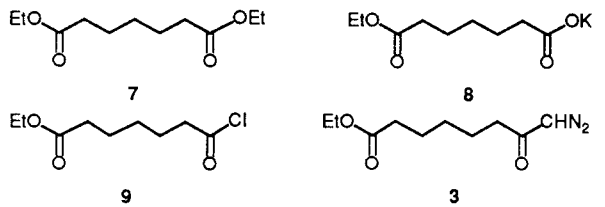
The unique *E,E*-dienyl diketone skeleton structure of ostopanic acid, together with its interesting biological activity, stimulated us to develop a synthetic pathway to this natural product. Our approach was based on the cyclopropanation of furan with α-diazo ketones[2] and α-diazo esters[3] to yield the corresponding cyclopropanes which could be ring opened by iodine catalysis under mild condition. The ring-opened produccts of the furan cyclopropanes possess the desired *E,E*-dienyl dicarbonyl moiety. Even more important, it has been reported that α-diazo carbonyl compounds add selectively to the less substituted double bond of furans.[3c] Clearly it is reasonable to expect that cyclopropanation of 2-*n*-hexylfuran by the rhodium-catalyzed decomposition of 8-diazo-7-oxooctanate would occur at the 4,5-double bond. The cyclopropane **4** obtained should be opened in the presence of iodine to afford ethyl ostopanate (**5**), which could be readily converted to ostopanic acid (Scheme I).

Results and Discussion

Potassium ethyl pimelate (**8**) was prepared by selective hydrolysis of diethyl pimelate (**7**) in 72% yield. Reaction of **8** with oxalyl chloride in benzene solution in the presence of pyridine gave ethyl pimeloyl chloride (**9**).[4] The clear solution of chloride **9** obtained was immediately reacted with 2 equiv of diazomethane to give the desired diazo carbonyl compound **3**.[4] The overall yield from **8** to **3** was 56%. 2-*n*-Hexylfuran (**2**) was prepared by treatment of *n*-hexyl bromide (**6**) with 2-lithium furan[5] in 80% yield.

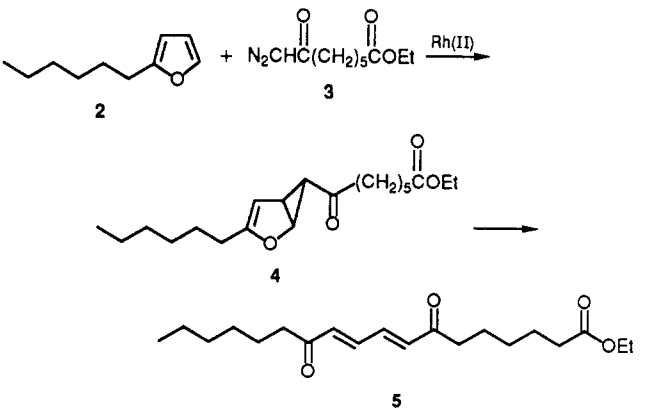


7 **8**

9 **3**

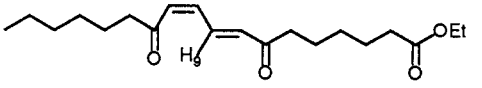
With the appropriate diazo carbonyl compounds **3** and **2** in hand, cyclopropanation was carried out by adding a

Scheme I



2 **3** **4** **5**

dichloromethane solution of diazo **3** into an excess amount of furan **2** with a catalytic amount of dirhodium tetraacetate. It was not possible to isolate the cyclopropane **4**. However, the isolated product of the reaction was found to be the mixture of ethyl ostopanate (**5**) and its regioisomer **10** in 58% yield. The ratio of isomers **5** and **10** increased as the reaction was carried out over a longer period of time. The structure of 8*E*,10*Z*-diene **10** was proved by its ^{1}H NMR spectrum: δ 8.18 (dd, J = 11, 16 Hz, H_9), and by comparison with the ^{1}H NMR spectral data with those of dienes **12** and **13**.[6]



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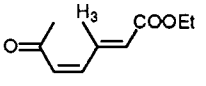
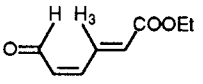


12 H_3 δ 8.18 (J = 11.5, 15.5 Hz)



13 H_3 δ 8.10 (J = 12, 15 Hz)

† Department of Marine Resources.
‡ Department of Chemistry.

(1) Hamburger, M.; Handa, S. S.; Cordell, G. A.; Kinghorn, A. D.; Farnsworth, N. R. *J. Nat. Prod.* **1987**, *50*, 281.
(2) (a) Novak, J.; Sorm, F. *Collect. Czech. Chem. Commum.* **1958**, *23*, 1126. (b) Novak, J.; Ratusky, J.; Sneberk, V.; Sorm, F. *Ibid.* **1957**, *22*, 1836. (c) Nwaji, M. N.; Onyiriuka, O. S. *Tetrahedron Lett.* **1974**, 2255. (d) Rokach, J.; Adams, J. *Acc. Chem. Res.* **1985**, *18*, 87 and references cited therein.
(3) (a) Wenkert, E.; Bakuzis, M. L. F.; Buckwalter, B. L.; Woodgate, P. D. *Synth. Commun.* **1981**, *11*, 533. (b) Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J. G.; Larue, M.; Young, R. N.; Masson, P.; Holme, G. *Tetrahedron Lett.* **1980**, *21*, 1485. (c) Porter, B. Ph.D. Dissertation, University of California, San Diego, 1984.
(4) Wilds, A. L.; Shunk, C. *J. Am. Chem. Soc.* **1948**, *70*, 2427.
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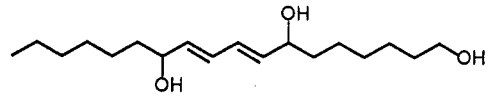
0022-3263/89/1954-5126$01.50/0

The failure to isolate the cyclopropane **4** indicated that the compound was unstable and ring opened immediately upon its formation. Addition of iodine to a dichloromethane solution of the mixture of isomeric dienes **5** and **10** gave pure 8*E*,10*E*-diene **5** in 46% overall yield from diazo **3**. The less stable 8*E*,10*Z*-diene **10** was completely isomerized to **5** in the presence of iodine.

Ethyl ostoponate (**5**) was assumed to give ostopanic acid (**1**) under acid- or base-catalyzed hydrolysis. Unfortunately, attempted hydrolysis of **5** with hydrochloric acid and sulfuric acid or with bases like sodium or potassium hydroxide produced only an intractable product. The failure of this reaction presumably arose from the vulnerable conjugated diene diketone present in compound **5**.

Since direct hydrolysis of ester **5** with acid or base to form acid **1** was unsuccessful, we decided to reduce **5** to the dienyl triol **11**, which could be oxidized back to ostopanic acid.



11

Thus, lithium aluminum hydride reduction of **5** at −10 °C to 25 °C gave triol **11** in 67% yield. The triol obtained was then successfully oxidized by pyridinium dichromate complex in dimethyl formamide[7] to complete the synthesis of ostopanic acid with a yield of 40%.

Since the stems and fruits of *ostodes paniculate* only contain small amount (0.009%) of ostopanic acid, our synthesis will provide the easy access to this compound for more detailed biological studies.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were obtained at 90 or 300 MHZ.

Ethyl 8-Diazo-7-oxooctanoate (3). A solution of 5.18 g (92 mmol) of potassium hydroxide in 80 mL of absolute alcohol was slowly added to 20 g (92 mmol) of diethyl pimelate at 50 °C. The mixture was stirred overnight at 50 °C. The solution was then evaporated to yield a white solid. This solid was washed with hexane to give 16.3 g (72%) of potassium ethyl pimelate (**8**); mp 273–275 °C. A solution of 4.24 mL (50 mmol) of oxalyl chloride in 10 mL of dry benzene was added dropwise into a mixture of 30 mL of dry benzene and 10.3 g (45.5 mmol) of potassium ethyl pimelate under nitrogen at 0 °C. The mixture was kept at 0 °C for 1 h to form a clear solution and potassium chloride solid. The solution was transfered to an addition funnel and then slowly added to a stirring etheral solution of diazomethane (4.23 g, 100 mmol) at 25 °C under nitrogen. The resulting solution was then stirred for another 2 h. Evaporation of the solution yielded a yellow oil. Chromatography of the residue on silica gel and elution with 3:1 hexane–ethyl acetate gave 5.37 g (56%) of diazo ester **3**: IR (neat) 2110 cm^{-1} (N_2CH); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz, CH_3), 1.33–1.80 (m, 6 H, 3,4,5-H_2), 2.20–2.50 (4 H, m, 2,6-H_2), 4.12 (2 H, t, CH_2O), 5.20 (1 H, s, N_2CH).

2-*n*-Hexylfuran (2). Furan (6.18 g, 0.1 mol) was added dropwise into a stirring mixture of 66.7 mL of *n*-butyllithium (1.6 M in hexane) and 50 mL of tetrahydrofuran at −25 °C. Stirring was continued for 4 h at −15 °C after the completion of addition. A solution of *n*-hexyl bromide (16.51 g, 0.1 mol) in 15 mL of tetrahydrofuran was then added to the mixture. The mixture was stirred for another 1 h at −15 °C, the cooling bath was removed, and the mixture was stirred overnight. It was poured over crushed ice and extracted with ether (30 mL × 2). The extract was washed with water, dried, and then evaporated to give 12.11 g (80% yield) of the known furan **2**.[8] ^{1}H NMR (CCl_4) δ 0.85 (3 H, distorted triplet, J = 6.9 Hz, Me), 1.20–1.87 (8 H, $(CH_2)_4$), 2.57 (2 H, t, J = 7.0 Hz, allylic CH_2), 5.85 (1 H, vinylic CH), 6.13 (1 H, vinylic CH), 7.17 (1 H, vinylic CH).

Ethyl Ostopanate (5). A solution of 4.24 g (20.0 mmol) of diazo ketone **3** in 20 mL of dichloromethane was added dropwise into a stirring mixture of 5.30 g of 2-*n*-hexylfuran (34.9 mmol) and 88 mg (0.01 equiv) of dirhodium tetraacetate in 10 mL of dichloromethane under nitrogen at room temperature over a period of 2 h. Stirring was continued for another 10 h, and the solution was evaporated to give a crude product. Chromatography on silica gel and elution with 3:1 hexane–ethyl acetate led to the isolation of 3.90 g (58%) of the mixture of ethyl ostopanate and its 10*Z*-isomer **10**. The mixture was added to a solution of 10 mg of iodine in 30 mL of dichloromethane and stirred at room temperature for 2 h. The solution was washed with saturated aqueous sodium thiosulfate. The mixture was then extracted with ether. The extract was dried and evaporated. Chromatography of the residue on silica gel and elution with 3:1 hexane–ethyl acetate gave 3.12 g (46% overall yield) of colorless, crystalline ethyl ostopanate: mp 87–88 °C; UV (MeOH) λ_{max} 278.8 nm (log ϵ 4.46); IR (CCl_4) 2960–2840, 1730, 1682, 1583, 1466, 1388, 1357, 1290, 1240, 1080, 988 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 6.8 Hz, 18-H_3), 1.23 (3 H, t, J = 6.9 Hz, CH_3 of OEt), 1.33 (8 H, m, 4, 15,16,17-H_2), 1.60 (6 H, m, 3,5,14-H_2), 2.34 (2 H, t, J = 7.5 Hz, 2-H_2), 2.55 (2 H, t, J = 7.3 Hz, 6-H_2 or 13-H_2), 2.57 (2 H, t, J = 7.3 Hz, 13-H_2 or 6-H_2), 4.09 (2 H, q, J = 6.9 Hz, OCH_2), 6.42 (1 H, m, 8-H or 11-H), 6.48 (1 H, m, 11-H or 8-H), 7.12 (1 H, m, 9-H or 10-H), 7.16 (1 H, m, 10-H or 9-H); ^{13}C NMR ($CDCl_3$), 14.0 (C-18), 14.2 (CH_3 of OEt), 22.4 (C-17), 23.5 (C-5 or C-14), 24.0 (C-14 or C-5), 24.6 (C-3), 28.6 (C-15 or C-16), 28.8 (C-16 or C-15), 31.5 (C-4), 34.0 (C-2), 40.9 (C-6 or C-13), 41.3 (C-13 or C-6), 60.2 (OCH_2), 135.9 (C-8 or C-11), 136.1 (C-11 or C-8), 138.8 (C-9 or C-10), 139.0 (C-10 or C-9), 173.7 (C-1), 199.7 (C-7 or C-12), 200.2 (C-12 or C-7); MS m/e (rel intensity), 336 (M^+, 11), 291 (16), 223 (18), 191 (16), 171 (43), 165 (78), 138 (55), 125 (100), 113 (39), 95 (41), 85 (17), 71 (4), 57 (6), 55 (33), 43 (18), 41 (16); exact mass 336.2302 (calcd for $C_{20}H_{32}O_4$ 336.2299). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.43; H, 9.52. Found: C, 71.35; H, 9.48.

(8*E*,10*E*)-8,10-Octadecadiene-1,7,12-triol (11). A solution of 2.88 g (8.57 mmol) of ethyl ostopanate in 10 mL of dry ether was added to a stirring mixture of 0.65 g (17.1 mmol) of lithium aluminum hydride in 50 mL of dry ether under nitrogen at −10 °C. The mixture was stirred at −10 to −5 °C for 2 h and then at room temperature for 2 h.[9] Water (0.71 g) was slowly added, followed by the addition of 10% NaOH(aq) (2.1 mL) into the mixture. The organic layer was filtered and evaporated to give 1.70 g (67%) of triol **11**: mp 86–88 °C; UV (MeOH) λ_{max} 226.8 nm (log ϵ 4.14); IR (KBr) 3100–3600, 2960–2860, 1635, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, distorted triplet, CH_3), 1.10–1.85 (20 H, br, 2,3,4,5,6,13,14,15,16,17-H_2), 2.27 (br, OH), 3.60 (2 H, t, J = 6.0 Hz, 1-H_2), 4.08 (2 H, q, J = 6.0 Hz, 7,12-H), 5.45–6.33 (4 H, m, 8,9,10,11-H).

Ostopanic Acid (1). A solution of triol **11** (1.63 g, 5.47 mmol) in 10 mL of dimethylformamide was added to the solution of pyridinium dichromate in 80 mL of dimethylformamide. The mixture was stirred for 4 h at room temperature. The reaction mixture was then poured into 600 mL of water and extracted with ether. The extract was dried and evaporated to give a solid product. Recrystallization from ether gave 675 mg (40%) of ostopanic acid: mp 132–133 °C;[10] UV (MeOH) λ_{max} 278.4 nm (log ϵ 4.31); IR (KBr) 2960–2850, 1715, 1683, 1580, 1470, 1380, 1354, 1293, 1215, 990 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 0.86 (3 H, t, J = 6.7 Hz, CH_3), 1.30 (8 H, m, 4, 15, 16, 17-H_2), 1.64 (6 H, m, 3,5,14-H_2), 2.36 (2 H, t, J = 7.4 Hz, 2-H_2), 2.57 (2 H, t, J = 7.4 Hz, 13-H_2 or 6-H_2), 2.59 (2 H, t, J = 7.0 Hz, 6-H_2 or 13-H_2), 6.43 (1 H, m, 8-H or 11-H), 6.50 (1 H, m, 11-H or 8-H), 7.13 (1 H, m, 9-H or

(6) Porter, B. Ph.D. Dissertation, University of California, San Diego, 1984, p 113 and 120.

(7) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(8) Mamdai, T.; Hashio, S.; Goto, J.; Kawada, M. *Tetrahedron Lett.* **1981**, *22*, 2187.

(9) The lithium aluminum hydride reduction of ethyl ostopanate was carried out at −10 to −5 °C in the beginning to prevent the possible reduction of double bonds in conjugation with carbonyl groups.

(10) Cordell reported that the natural product has a melting point of 122–123 °C which is lower in comparison with our result. Other than this discrepancy, our synthetic material is identical spectroscopically with the natural product.

10-H), 7.19 (1 H, m, 10-H or 9-H); ^{13}C NMR δ ($CDCl_3$), 14.0 (C-18), 22.4 (C-17), 23.5 (C-5 or C-14), 24.0 (C-14 or C-5), 24.4 (C-3), 28.5 (C-15 or C-16), 28.8 (C-16 or C-15), 31.5 (C-4), 33.7 (C-2), 40.7 (C-6 or C-13), 41.6 (C-13 or C-6), 135.8 (C-8 or C-11), 136.1 (C-11 or C-8), 138.7 (C-9 or C-10), 139.0 (C-10 or C-9), 178.3 (C-1), 199.7 (C-7 or C-12), 200.2 (C-12 or C-7); MS *m/e* (rel intensity) 308 (M^+, 23), 290 (4), 237 (2), 223 (4), 207 (4), 205 (8), 165 (100), 138 (53), 125 (78), 123 (39), 95 (76), 85 (34), 81 (52), 55 (77), 43 (73), 41 (50); exact mass 308.1988 (calcd for $C_{18}H_{28}O_4$ 308.1986). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.13; H, 9.09. Found: C, 70.01; H, 9.06.

Acknowledgment. We thank the National Science Council of Taiwan, ROC, for the financial support of this research.

Supplementary Material Available: ^1H NMR spectra of synthetic and natural ostopanic acid (2 pages). Ordering information is given on any current masthead page.

Synthesis of Bicyclo[2.1.0]pentanoid-Containing Prostaglandins[1]

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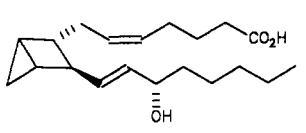
Received December 23, 1987

The synthesis of (5*Z*,13*E*,15*S*)-15-hydroxy-9α,11α-cycloprosta-5,13-dien-1-oic acid and its 9β,11β epimer was accomplished in 21 steps from cyclopentadiene with an efficiency of 0.75%. Although the strain (almost 48 kcal/mol of the 56 kcal/mol total by MMX calculation) in the 9,11 bridging bond renders its susceptible to electrophilic opening, these compounds were not found to inhibit platelet aggregation by blocking any of the prostaglandin biosynthetic pathways in the arachidonic acid cascade. Specific inhibition (IC_{50} at 3.2×10^{-6} M) of TXA_2-stimulated platelet aggregation, however, suggests that they are weak TXA_2 antagonists.

Prostaglandin endoperoxide (PGH_2) is the key member of the arachidonic acid cascade that leads to the formation (Scheme I) of prostacyclin (PGI_2) and thromboxane A_2 (TXA_2).[2] Since these natural compounds have been implicated to be intimately involved in many of the pulmonary–cardiovascular disorders that account for over a million deaths (USA) each year,[3] it is not surprising that they continue to be the focus of intensive study by synthetic organic chemists.

The ability to selectively modulate the biological conversion of PGH_2 into TXA_2 has important therapeutic value, and several analogues of PGH_2 have been investigated for this purpose.[2] Recent mechanistic studies[4] suggest that the synthetase enzymes involved in the arachidonic acid cascade are electrophilic in nature, and since the strain (almost 48 kcal/mol of the 56 kcal/mol total by MMX[5] calculation) in the bridging bond in bicyclo[2.1.0]pentane renders it susceptible to electrophilic opening,[6] we felt that the novel prostanoids **1** and **2**



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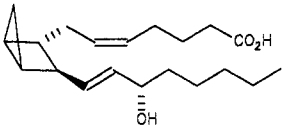

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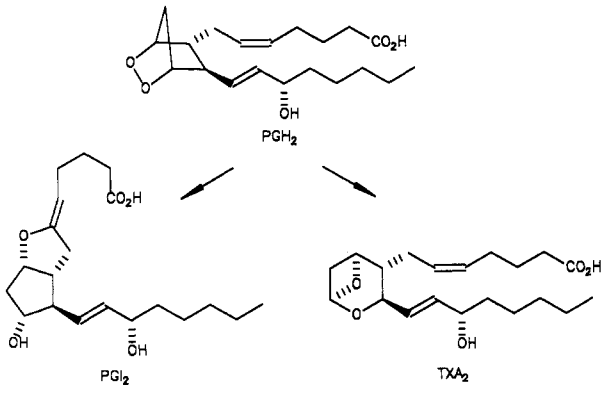
Scheme I



[(5*Z*,13*E*,15*S*)-15-hydroxy-9α,11α-cycloprosta-5,13-dien-1-oic acid and its 9β,11β epimer] would be suitably functionalized to intercept and block some of these enzymatic processes. Furthermore, since Gassman,[6a] Noyori,[6b] and others[6c] have shown that bicyclo[2.1.0]pentanoid intermediates (under controlled conditions) can be converted into bicyclo[2.2.1]heptanoids, **1** and **2** have the potential of being common precursors to many of the important PGH_2 analogues that presently are available only through independent multistep total syntheses. Herein, we describe the total synthesis of **1** and its epimer **2** and report on their biological properties.

Our strategy for the synthesis of **1** and **2** (Scheme II) was designed to profit from the elegant work outlined by Corey and his group in their total synthesis of the 9,11-azo analogue of PGH_2.[7] Early removal of the labile azo functionality and obtaining the appropriately fuctionalized chiral bicyclo[2.1.0]pentane derivatives **8a** and **8b**, both

(1) Dedicated to Prof. E. C. Taylor on the occasion of his 65th birthday.

(2) For an excellent description of prostaglandin chemistry, see: Taylor, R. K. In *Prostaglandins and Thromboxanes*; Newton, R. F., Roberts, S. M., Eds.; Butterworths: New York, 1982, and references cited therein; *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Pike, J. E.; Morton, D. R., Jr., Eds.; Raven Press: New York, 1985; Vol. 14, and references cited therein. See also: Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372 and references cited therein. Hall, S. E.; Han, W. C.; Haslanger, M. F.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1986**, *29*, 2335.

(3) Taylor, M. D.; Sircar, I.; Steffen, R. P. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: New York, 1987; Vol. 22, Chapter 9; *Time* **1987**, *130*(21), 58. Stinson, S. *Chem. Eng. News* **1988** October 3, p 35.

(4) Corey, E. J. *Pure Appl. Chem.* **1987**, *59*, 269.

(5) Obtained from Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076.

(6) See for example: (a) Gassman, P. G. *Acc. Chem. Res.* **1971**, *4*, 128 and references cited therein. (b) Suzuki, T.; Kumagai, Y.; Yamakawa, M.; Noyori, R. *J. Org. Chem.* **1981**, *46*, 2846 and references cited therein. (c) Bloodworth, A. J.; Hargreeves, N. *Tetrahedron Lett.* **1987**, *28*, 2783.

(7) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417.

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