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Studies Related to β-Lactam Antibiotics. IX.[1] Alcoholysis of a 4-Oxa-1-azabicyclo[3.2.0]heptane-3,7-dione

MAGOICHI SAKO, KAZUKI AKIRA, KOSAKU HIROTA, and YOSHIFUMI MAKI*

Gifu College of Pharmacy, 6–1, Mitahora-higashi 5-chome, Gifu 502, Japan

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Thermal reactions of (2*R*, 5*S*, 6*S*)-2-(1-methylethenyl)-6-phenylacetamido-4-oxa-1-azabicyclo[3.2.0]heptane-3,7-dione (**1**) with alcohols gave 2-phenylmethyl-4-{*N*-[(1*R*)-1-carboxy-2-methylprop-2-enyl]}carbamoyloxazole (**2a**), (3*S*, 4*S*)-4-alkoxy-1-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-3-phenylacetamidoazetidin-2-ones (**3a**, **c**), and (2*S*)-*N*-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-3,3-dialkoxy-2-phenylacetamidopropionamides (**4a**, **c**), probably *via* an intramolecular ring transformation of **1** into (1*S*, 5*R*)-3-phenylmethyl-6-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (**5a**) in the initial stage of the reaction.

Keywords——(5*S*, 6*S*)-4-oxa-1-azabicyclo[3.2.0]heptane-3,7-dione; alcoholysis; oxazole; (3*S*, 4*S*)-4-alkoxyazetidin-2-one; 3,3-dialkoxypropionamide; (1*S*, 5*R*)-4-oxa-2,6-diazabicyclo-[3.2.0]hept-2-en-7-one; intramolecular ring transformation

Our previous work[1] demonstrated the acid-catalyzed ring transformation of (2*R*, 5*S*, 6*S*)-2-(1-methylethenyl)-6-phenylacetamido-4-oxa-1-azabicyclo[3.2.0]heptane-3,7-dione (**1**) (azetidinone-lactone) into oxazolinones; this transformation could be initiated by protonation at the carbonyl group of the lactone ring followed by cleavage of the bicyclic ring.

We now report a facile ring transformation of **1** in alcohols under thermal conditions. The present results indicate that the alcoholysis of **1** causes ring cleavage in a manner different from that in the case of the acid-catalyzed ring transformation.

A solution of the azetidinone-lactone **1** in methanol was refluxed for 1 h. After removal of the solvent under reduced pressure, the reaction mixture was chromatographed on silica gel to give three crystalline products, 2-phenylmethyl-4-{*N*-[(1*R*)-1-carboxy-2-methylprop-2-enyl]}-carbamoyloxazole (**2a**, 23%) (oxazole), (3*S*, 4*S*)-1-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-4-methoxy-3-phenylacetamidoazetidin-2-one (**3a**, 27%)(4α-methoxyazetidinone), and (2*S*)-*N*-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-3,3-dimethoxy-2-phenylacetamidopropionamide (**4a**, 4%) (3,3-dimethoxypropionamide). The starting material **1** was recovered unchanged in 35% yield in this reaction. No other products were detected by thin-layer chromatography (TLC) analysis and nuclear magnetic resonance (NMR) spectroscopy of the reaction mixture. The structures of the products **2a**, **3a**, and **4a** were supported by microanalytical and spectral data[2] and by chemical conversion of the compounds to the corresponding methyl esters **2b**, **3b**, and **4b** (see the experimental section).

In a similar manner, thermolysis of **1** in ethanol gave **2a**, the 4α-ethoxyazetidinone **3c**, and the 3,3-diethoxypropionamide **4c** in 35, 19, and 35% yields, respectively.

When a solution of **1** in methanol was stirred at room temperature for 1 d a small amount of (1*S*, 5*R*)-3-phenylmethyl-6-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-4-oxa-2,6-diazabicyclo-[3.2.0]hept-2-en-7-one (**5a**)[3] (oxazolinoazetidinone) was isolated as a new product in addition to the compounds **2a**, **3a**, and **4a** described above. Treatment of **5a** thus obtained with refluxing methanol for 30 min afforded **2a**, **3a**, and **4a** in 40, 35, and 8% yields, respectively. The product distribution of **2a**, **3a**, and **4a** was similar to that of methanolysis of the azeti-

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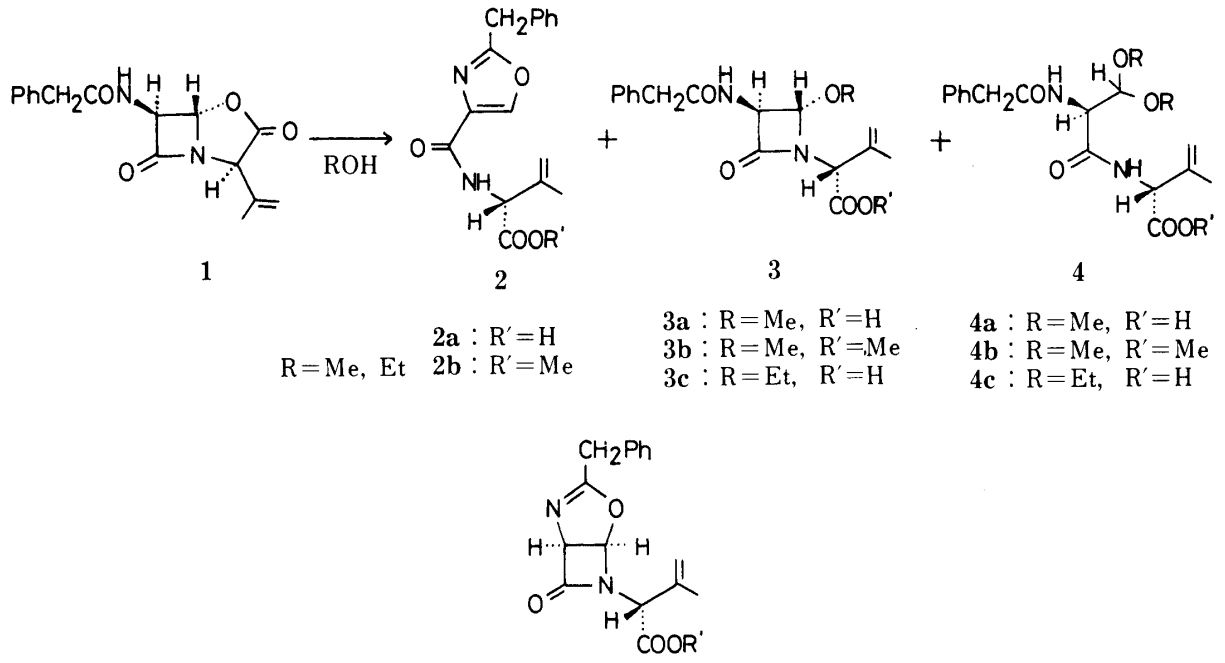


1

2

3

4

R=Me, Et

2a : R′=H
2b : R′=Me

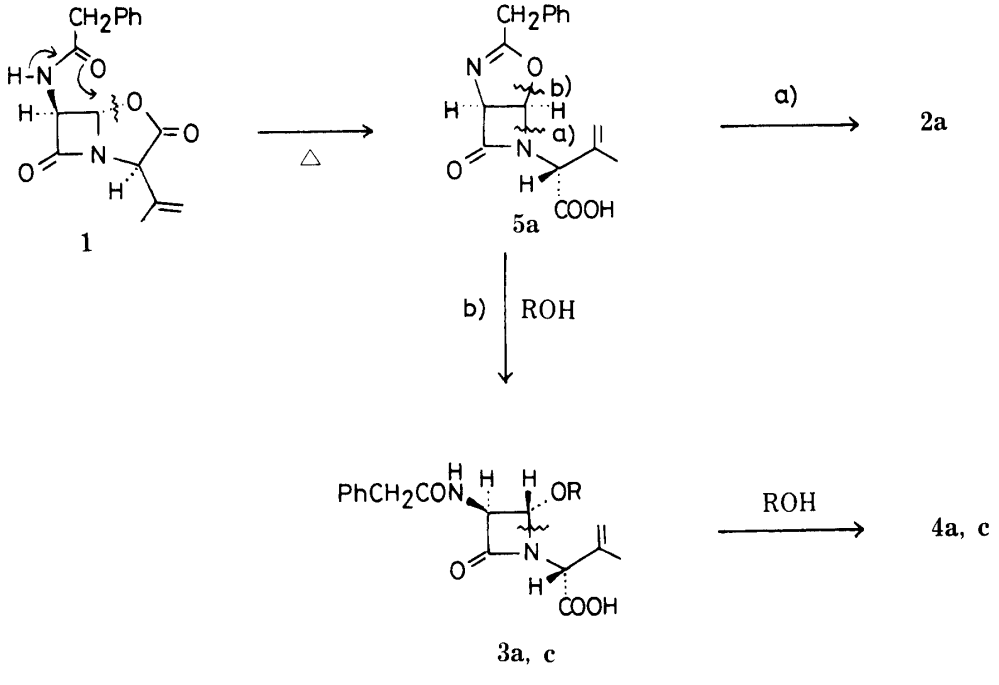
3a : R=Me, R′=H
3b : R=Me, R′=Me
3c : R=Et, R′=H

4a : R=Me, R′=H
4b : R=Me, R′=Me
4c : R=Et, R′=H

5

5a : R′=H
5b : R′=Me

Chart 1



1

5a

3a, c

Chart 2

dinone-lactone **1**. Compounds **2a** and **4a**, **c** were very stable in refluxing alcohols even after a prolonged reaction time (for 5 h). The 4α-alkoxyazetidinones **3a** and **3c**, however, changed gradually into **4a** and **4c** under analogous conditions. These results indicate that **5a** is a key intermediate for the formation of **2a**, **3a**, **c**, and **4a,c** in the thermal reactions of **1** with alcohols and that the formation of **4a**, **c** occurs as a result of the degradation of **3a**, **c**.

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On the basis of the above results, we propose the reaction sequence depicted in Chart 2 for the present alcoholysis of **1**.

The reaction could be initiated by the intramolecular ring transformation of **1** into the oxazolinoazetidinone **5a** under the thermal conditions. The C_5–N_6 bond cleavage in **5a** results in the formation of **2a**. Nucleophilic attack of alcohols at position 5 of **5a** produces competitively the 4α-alkoxyazetidinones **3a, c**, which undergo subsequent degradation of the β-lactam ring to give **4a, c**.

The formation of **2**, **3**, and **4** from the oxazolinoazetidinone **5** without any acid catalyst[4,5] is of interest from a mechanistic point of view.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer in potassium bromide discs. ^{1}H-NMR spectra were recorded on a Hitachi R-24 B (60 Hz) spectrometer in deuteriodimethyl sulfoxide or deuteriochloroform containing tetramethylsilane as an internal standard. Mass spectra (MS) were measured at 75 eV with a JEOL JMS-D300 spectrometer. The specific rotations were measured with a JASCO DIP-4 polarimeter. Column chromatography was performed on silica gel (Wako gel C-300). TLC analyses were carried out by using silica gel plates (Merck pre-coated plates Silica gel 60 F-254).

Alcoholysis of (2*R*, 5*S*, 6*S*)-2-(1-Methylethenyl)-6-phenylacetamido-4-oxa-1-azabicyclo[3.2.0]heptane-3,7-dione (1)——a) In Refluxing Methanol: A solution of **1** (300 mg, 1.0 mmol) in methanol (20 ml) was refluxed for 1 h. After removal of the solvent under reduced pressure, the residue was chromatographed over silica gel (eluant, chloroform : methanol = 30 : 1) to give 2-phenylmethyl-4-{*N*-[(1*R*)-1-carboxy-2-methylprop-2-enyl]}-carbamoyloxazole (**2a**) (70 mg, 23%), (3*S*, 4*S*)-1-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-4-methoxy-3-phenylacetamidoazetidin-2-one (**3a**) (89 mg, 27%), and (2*S*)-*N*-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-3,3-dimethoxy-2-phenylacetamidopropionamide (**4a**) (16 mg, 4%), together with unchanged starting material **1** (105 mg, 35%). **2a**: mp 150—151 °C (from diethyl ether). IR (KBr): 3380 (NH), 1730 (C=O), 1630 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.80 (3H, br s, =C–Me), 4.25 (2H, s, phenylmethyl protons), 4.97 (1H, d, J = 8 Hz, –CH–NH–), 5.05 (2H, br, –C=CH$_2$), 7.37 (5H, s, phenyl ring protons), 8.00 (1H, br d, J = 8 Hz, NH), 8.63 (1H, s, oxazole ring proton). MS *m/e*: 300 (M$^+$), 282, 255, 186. *Anal.* Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.89; H, 5.34; N, 9.31. $[\alpha]_D^{19}$ −46° (c = 0.1, methanol). **3a**: mp 84—86 °C (from diethyl ether–*n*-hexane). IR (KBr): 3300 (NH), 1760 (C=O), 1650 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.91 (3H, br s, =C–Me), 3.44 (3H, s, C_4-OMe), 3.60 (2H, s, phenylmethyl protons), 4.65 (1H, dd, J = 1.0 and 6.5 Hz, C_3–H), 4.71 (1H, br s, –CH–COOH), 4.95 (1H, d, J = 1.0 Hz, C_4–H), 5.05—5.35 (2H, m, –C=CH$_2$), 7.29 (5H, s, phenyl ring protons), 7.50 (1H, br d, J = 6.5 Hz, NH), 8.87 (1H, br, COOH). MS *m/e*: 332 (M$^+$), 287. *Anal.* Calcd for $C_{17}H_{20}N_2O_5 \cdot H_2O$: C, 58.27; H, 6.33; N, 8.00. Found: C, 58.03; H, 5.95; N, 7.82. **4a**: mp 191 °C (from tetrahydrofuran). IR (KBr): 3300 (NH), 1740 (C=O), 1660 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.73 (3H, br s, =C–Me), 3.25 (3H, s, –OMe), 3.26 (3H, s, –OMe), 3.55 (2H, s, phenylmethyl protons), 4.43—5.05 (3H, m, 3×–CH–), 4.97 (2H, br s, –C=CH$_2$), 7.26 (5H, s, phenyl ring protons), 8.25 (1H, br d, J = 8.5 Hz, NH), 8.31 (1H, br d, J = 7.5 Hz, NH). MS *m/e*: 364 (M$^+$). *Anal.* Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.35; H, 6.75; N, 7.69. $[\alpha]_D^{19}$ −43° (c = 0.1, methanol).

b) In Methanol at Room Temperature: A solution of **1** (300 mg, 1.0 mmol) in methanol (20 ml) was stirred at room temperature for 1 d. After the same procedure as described above, (1*S*, 5*R*)-3-phenylmethyl-6-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (**5a**) (15 mg, 5%), **2a** (50 mg, 17%) **3a** (61 mg, 18%), and **4a** (trace) were obtained, along with the starting material **1** (130 mg, 43%). The product **5a** was identical with an authentic sample.[3]

c) In Refluxing Ethanol: A solution of **1** (300 mg, 1.0 mmol) in ethanol (20 ml) was refluxed for 1 h. After the procedure described in the preceding section, **2a** (106 mg, 35%), (3*S*, 4*S*)-1-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-4-ethoxy-3-phenylacetamidoazetidin-2-one (**3c**) (67 mg, 19%) and (2*S*)-*N*-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-3,3-diethoxy-2-phenylacetamidopropionamide (**4c**) (139 mg, 35%) were isolated. **3c**: Oil IR (KBr): 3300 (NH), 1755 (C=O), 1655 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, C_4–OEt), 1.94 (3H, br s, =C–Me), 3.65 (2H, s, phenylmethyl protons), 3.75 (2H, q, C_4–OEt), 4.61 (1H, dd, J = 1.0 Hz and 6.5 Hz, C_3–H), 4.74 (1H, br s, –CH–COOH), 5.01 (1H, d, J = 1.0 Hz, C_4–H), 5.15—5.30 (2H, br s, –C=CH$_2$), 7.10 (1H, br d, J = 6.5 Hz, NH), 7.30 (5H, s, phenyl ring protons), 7.78 (1H, br, COOH). MS *m/e*: 346 (M$^+$), 301. **4c**: mp 182—184 °C (from tetrahydrofuran). IR (KBr): 3300 (NH), 1735 (C=O), 1650 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (6H, br t, 2×–OEt), 1.72 (3H, br s, =C–Me), 3.20—3.80 (4H, m, 2×–OEt), 3.51 (2H, s, phenylmethyl protons), 4.50—4.80 (3H, m, 3×–CH–), 5.00 (2H, br s, –C=CH$_2$), 7.26 (5H, s, phenyl ring protons). MS *m/e*: 363 (M$^+$ −29), 347, 302, 232, 205. *Anal.* Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 60.93; H, 7.23; N, 7.26.

Methylation of the Oxazole 2a, the 4α-Methoxyazetidin-2-one 3a, and the 3,3-Dimethoxypropionamide 4a——

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Methylation of **2a**, **3a**, and **4a** with diazomethane gave the corresponding methyl esters **2b**, **3b**, and **4b** in almost quantitative yields.

2b: Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (3H, br s, =C–Me), 3.76 (3H, s, COOMe), 4.10 (2H, s, phenylmethyl protons), 5.00—5.20 (2H, m, –C=CH_2) 5.17 (1H, d, J=8 Hz, –C<u>H</u>–COOMe), 7.28 (5H, s, phenyl ring protons), 7.64 (1H, br d, J=8 Hz, NH), 8.09 (1H, s, oxazole ring proton). MS *m/e*: 314 (M^+). **3b**: Oil. IR (neat): 3300 (NH), 1775 (C=O), 1745 (C=O), 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (3H, br s, =C–Me), 3.44 (3H, s, C_4–OMe), 3.58 (2H, s, phenylmethyl protons), 3.74 (3H, s, COOMe), 4.53 (1H, dd, J=1.0 and 6.5 Hz, C_3–H), 4.73 (1H, br s, –C<u>H</u>–COOMe), 4.85 (1H, d, J=1.0 Hz, C_4–H), 6.79 (1H, br d, J=6.5 Hz, NH), 7.28 (5H, s, phenyl ring protons). MS *m/e*: 346 (M^+). **4b**: mp 177 °C (from ethyl acetate–diethyl ether). IR (KBr): 3300 (NH), 1740 (C=O), 1640 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.70 (3H, br s, =C–Me), 3.26 (6H, s, 2×–OMe), 3.48 (2H, s, phenylmethyl protons), 3.65 (3H, s, COOMe), 4.40—5.00 (3H, m, 3×–CH–), 4.93 (2H, br s, –C=CH_2), 7.26 (5H, s, phenyl ring protons), 8.15 (1H, br d, J=8 Hz, NH), 8.40 (1H, br d, J=8 Hz, NH). MS *m/e*: 378 (M^+), 363, 346. *Anal.* Calcd for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.35; H, 7.05; N, 7.52. $[\alpha]_D^{19}$ −35 (c=0.1, methanol).

Methanolysis of (1*S*, 5*R*)-3-Phenylmethyl-6-[(1*R*)-1-carboxy-2-methylprop-2-enyl]-4-oxa-2,6-diazabicyclo[3.2.0]-hept-2-en-7-one (5a)——A solution of **5a** (300 mg, 1.0 mmol) in methanol (20 ml) was refluxed for 30 min. After removal of the solvent under reduced pressure, the residual oil was chromatographed over silica gel (eluant, chloroform : methanol = 30 : 1) to afford **2a** (120 mg, 40%), **3a** (116 mg, 35%), and **4a** (30 mg, 8%). No other products were detected by TLC analysis and NMR spectroscopy of the reaction mixture.

Methanolysis of the 4α-Methoxyazetidin-2-one 3a—— A solution of **3a** (166 mg, 0.5 mmol) in methanol (20 ml) was refluxed for 26 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (eluant, chloroform : methanol = 30 : 1) to give **4a** (164 mg, 90%).

References and Notes

1) M. Sako, K. Akira, K. Hirota, and Y. Maki, *Heterocycles*, **1983**, 1001.
2) The *trans* orientation of the β-lactam ring in **3a** was established on the basis of NMR spectroscopy ($J_{3,4}$ = 1.0 Hz). *Cf.*, P. V. Demarco and R. Nagarajan, "Cephalosporins and Penicillins Chemistry and Biology," ed. by E. H. Flynn, Academic Press, New York and London, 1972, p. 311.
3) Y. Maki, N. Mitsumori, M. Sako, and M. Suzuki, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2087.
4) Methanolysis of the oxazolinoazetidinone methyl ester **5b**[3] under more drastic conditions (reflux for 34 h) also gave **2b** and **4c** in 37 and 35% yields, respectively. Therefore, the carboxyl group of **5a** does not play a significant role in the thermal reaction of **5a** with alcohols.
5) There are ample precedents for acid-catalyzed ring cleavage of oxazolinoazetidinones involving nucleophilic attack at the 5-position, leading to 4-substituted azetidinones. *Cf.*, R. J. Stoodley and N. R. Whitehouse, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 181; D. F. Corbett and R. J. Stoodley, *ibid.*, **1974**, 185; *idem, ibid.*, **1975**, 432; C. U. Kim and D. N. McGregor, *Tetrahedron Lett.*, **1978**, 409; Y. Hamashima, T. Kubota, K. Ishikura, and W. Nagata, *ibid.*, **1979**, 4943; S. Kamata, S. Yamamoto, N. Haga, and W. Nagata, *J. Chem. Soc., Chem. Commun.*, **1979**, 1106; S. Uyeo, I. Kikkawa, Y. Hamashima, H. Ona, Y. Nishitani, K. Okada, T. Kubota, K. Ishikura, Y. Ide, K. Nakano, and W. Nagata, *J. Am. Chem. Soc.*, **101**, 4403 (1979); A. C. Kaura, C. D. Maycock, and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, **1980**, 34; M. Yoshioka, T. Tsuji, S. Uyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi, and W. Nagata, *Tetrahedron Lett.*, **1980**, 351.

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