The Total Synthesis of (+)-Totarol and (+)-Podototarin

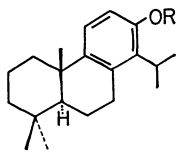
Takashi MATSUMOTO* and Akira SUETSUGU

Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Hiroshima 730

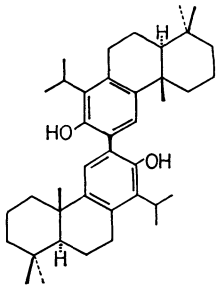
(Received August 28, 1978)

The Grignard reaction of 7-methoxyphthalide with methylmagnesium iodide, followed by acetylation and dehydration, gave 3-acetoxymethyl-2-isopropenylanisole which, on catalytic hydrogenation, afforded 3-acetoxymethyl-2-isopropylanisole. This was then converted into (2-isopropyl-3-methoxybenzyl)triphenylphosphonium chloride (**8**) *via* 3-hydroxymethyl-2-isopropylanisole and 3-chloromethyl-2-isopropylanisole. The Wittig reaction of (*R*)-(−)-α-cyclocitral with **8** in the presence of butyllithium afforded the corresponding styryl derivative, which was converted into the dihydro compound (**19**) by partial catalytic hydrogenation. The intramolecular cyclization of **19** gave (+)-totaryl methyl ether (**20**) along with its *cis*-isomer. The methyl ether **20** was finally demethylated with boron tribromide to give (+)-totarol (**1**), which was further characterized as its acetate. Since the conversion of (+)-**1** into (+)-podototarin has already been reported, the present work can be regarded as the total synthesis of natural (+)-podototarin.

Totarol, a rare tricyclic diterpene phenol possessing an isopropyl group at the C-14 position, was first isolated as a major constituent of the heartwood of *Podocarpus totara* G. Benn. *ex.* D. Don by Easterfield and McDowell.[1] On the basis of chemical and spectroscopic studies, Short and his coworkers[2] deduced the structure of totarol to be **1**; this was confirmed by the synthesis of the racemate by Barltrop and Rogers.[3] The absolute configuration of totarol was determined by ORD measurements and by direct correlation with dehydroabietic acid by Chow and Erdtman.[4] Podototarin (**2**), a novel bisditerpene, was also isolated from the heartwood of P. *totara* by Brandt and Thomas[5] and Cambie and Mander.[6] The structure of podototarin was determined by the synthesis[7–9] of **2** from natural (+)-totarol. However, no investigation on the total synthesis of optically active totarol has hitherto been reported. It is thus still necessary to synthesize the optically active totarol to complete the total synthesis of natural podototarin. This paper describes the simple syntheses of (+)-totarol (**1**) and, consequently, of (+)-podototarin (**2**).



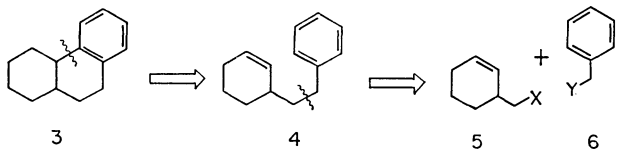
1 R=H
20 R=Me
22 R=Ac



2

Our basic strategy for the synthesis of optically active octahydrophenanthrene backbone (**3**) is shown in Scheme 1. Since there are many precedents for the intramolecular cyclization of phenethylcyclohexene derivatives, the synthetic target is the optically active 3-phenethyl-1-cyclohexene derivative (**4**), which might be constructed by the condensation of optically active cyclohexenylmethyl derivative (**5**) and benzyl derivative (**6**).

In the present study, (*R*)-(−)-α-cyclocitral (**7**)[10,11] and (2-isopropyl-3-methoxybenzyl)triphenylphosphonium chloride (**8**) were chosen as the compounds



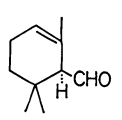
3 4 5 6

Scheme 1.

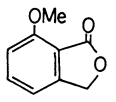
corresponding to **5** and **6**. Thus, the first synthetic goal was to prepare the phosphonium salt **8**. This was successfully achieved in the following manner. The Grignard reaction of 7-methoxyphthalide (**9**)[12] in tetrahydrofuran with methylmagnesium iodide in ether afforded the corresponding diol (**10**), which was converted into a monoacetate (**11**). The treatment of **11** with *p*-toluenesulfonic acid in hot benzene gave a mixture of the desired 3-acetoxymethyl-2-isopropenylanisole (**12**) and 7-methoxy-1,1-dimethyl-1,3-dihydroisobenzofuran (**13**) in a ratio of *ca.* 2 : 1. Since the separation of **12** and **13** was somewhat difficult, the mixture was directly oxidized with Jones reagent and then purified by column chromatography on silica gel to afford **12** and 4-methoxy-3,3-dimethylphthalide (**14**), which was easily converted into **10** by reduction with lithium aluminium hydride. The catalytic hydrogenation of **12** in ethanol over PtO_2 gave 3-acetoxymethyl-2-isopropylanisole (**15**) which, on reduction with lithium aluminium hydride, afforded 3-hydroxymethyl-2-isopropylanisole (**16**). The alcohol **16** was treated at room temperature with thionyl chloride in ether and the resulting benzyl chloride derivative (**17**), without purification, was converted into the phosphonium salt **8**, by treatment with triphenylphosphine in refluxing benzene. The Wittig reaction of **7** with **8** in benzene in the presence of butyllithium gave 6-(2-isopropyl-3-methoxystyryl)-1,5,5-trimethylcyclohexene (**18**). The NMR spectrum of **18** showed signals at δ 5.63 (dd, J=9 and 15 Hz) and 6.68 ppm (d, J=15 Hz) due to the newly formed olefinic protons. These vicinal coupling constants (J=15 Hz) suggested the presence of a *trans*-disubstituted double bond in **18**. The compound **18** in ethanol was submitted to partial catalytic hydrogenation over Pd–C to afford the corresponding phenethyl derivative (**19**). The intramolecular cyclization of **19** with anhydrous aluminium chloride in dichloro-

methane afforded (+)-totaryl methyl ether (**20**), $[\alpha]_D$ +23.3°(EtOH), as the major product and its *cis*-isomer (**21**), $[\alpha]_D$ −44.3°(EtOH), as the minor one. The *cis*-configuration of the A/B ring junction in **21** was supported by its NMR spectrum, which showed a high field signal, δ 0.41 ppm, due to the $C_{4\beta}$ methyl group and the shielding effect of the aromatic ring. Since the optical rotation of **20** was somewhat lower than that of the natural derivative,[6] it was further purified by crystallization to give the optically pure compound, $[\alpha]_D$ +40.6°(EtOH). The demethylation of **20** with boron tribromide in dichloromethane gave (+)-totarol (**1**), which was characterized as its acetate (**22**).

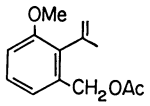
As has been described above, the partial synthesis of (+)-podototarin from (+)-totarol has already been reported.[7-9] Consequently, the present synthesis of (+)-totarol can be regarded as the total synthesis of (+)-podototarin.



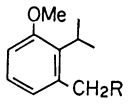
7



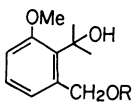
9



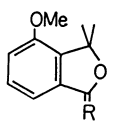
12



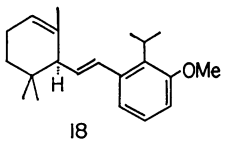
8 R=$\overset{+}{P}Ph_3Cl^-$
15 R=OAc
16 R=OH
17 R=Cl



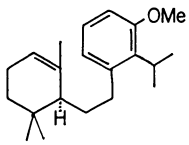
10 R=H
11 R=Ac



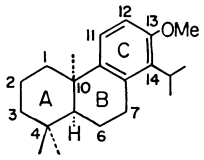
13 R=H2
14 R=O



18



19



21

Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform, and the NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as the internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, dd: double doublet, m: multiplet. Column chromatography was performed using Merck silica gel (0.063 mm).

*3-Hydroxymethyl-2-(1-hydroxy-1-methylethyl)anisole (**10**).* A solution of 7-methoxyphthalide (**9**)[12] (mp 108—109 °C, 3.347 g) in dry tetrahydrofuran (60 ml) was added dropwise to a stirred solution of methylmagnesium iodide prepared from magnesium (1.239 g) and methyl iodide (3.80 ml) in dry ether (20 ml), with cooling in an ice–water bath. The mixture was stirred at room temperature for 4 h, poured into aqueous ammonium chloride, and extracted with ether. The ether extract was washed successively with aqueous sodium thiosulfate and water, dried over sodium sulfate, and evaporated to give an oil. The crude product was purified by column chromatography on silica gel (100 g) using ether–chloroform (3 : 97) as the eluent to give **10** (2.058 g: 52%), which was recrystallized from hexane–ether: mp 63—64 °C; IR: 3607, 3386 cm^{-1}; NMR: 1.60 (6H, s, $-\overset{|}{C}(CH_3)_2$), 3.78 (3H, s, $-OCH_3$), 4.68 (2H, s, $-CH_2OH$). Found: C, 67.26; H, 8.23%. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%.

*3-Acetoxymethyl-2-(1-hydroxy-1-methylethyl)anisole (**11**).* A solution of **10** (345 mg), acetic anhydride (0.4 ml), and pyridine (0.2 ml) was allowed to stand at room temperature for 15 h and diluted with ether. The ether solution was washed successively with dilute hydrochloric acid, aqueous sodium hydrogencarbonate, and water. After drying over sodium sulfate, the solvent was evaporated to dryness and the residue was chromatographed on silica gel (20 g) using ether–benzene (1 : 9) as the eluent to give a monoacetate (**11**) (352 mg: 84%) which was then recrystallized from petroleum benzin; mp 61—62 °C; IR: 3585, 3511, 1733 cm^{-1}; NMR: 1.63 (6H, s, $-\overset{|}{C}(CH_3)_2$), 2.02 (3H, s, $-OCOCH_3$), 3.00 (1H, bs, –OH), 3.82 (3H, s, $-OCH_3$), 5.48 (2H, s, $-CH_2O-$). Found: C, 65.61; H, 7.58%. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%.

*3-Acetoxymethyl-2-isopropenylanisole (**12**) and 4-Methoxy-3,3-dimethylphthalide (**14**).* A solution of **11** (1.880 g) and *p*-toluenesulfonic acid (200 mg) in dry benzene (20 ml) was heated at 60 °C for 10 min, cooled to room temperature, and then diluted with ether. The solution was washed with aqueous sodium hydrogencarbonate and water, dried over sodium sulfate, and evaporated *in vacuo* to give an oil (1.812 g), whose NMR spectrum suggested the presence of the isopropenyl compound (**12**) and 7-methoxy-1,1-dimethyl-1,3-dihydroisobenzofuran (**13**); NMR: 1.47 (6H, s, $-\overset{|}{C}(CH_3)_2$), 3.83 (3H, s, $-OCH_3$), 4.94 (2H, s, $-OCH_2-$). Since the separation of **12** and **13** was unsuccessful, the above crude oil (1.812 g) was immediately oxidized with Jones reagent (8 N, 3.0 ml) in acetone (8.0 ml) at 16 °C for 1 h. The reaction mixture was diluted with ether, washed with water, and then dried over sodium sulfate. After the solvent had been evaporated, the residue was purified by column chromatography on silica gel (60 g) using benzene as the eluent to give **12** (764 mg: 44%) as an oil. IR: 1731, 1642 cm^{-1}; NMR: 2.00 (6H, s, $=\overset{|}{C}CH_3$ and $-OCOCH_3$), 3.78 (3H, s, $-OCH_3$), 4.79 and 5.23 (each 1H and bs, $-\overset{|}{C}=CH_2$), 5.01 (2H, s, $-CH_2O-$). Found: C, 70.84; H, 7.47%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

Further elution with ether–benzene (1 : 9) gave a phthalide (**14**) (323 mg: 21%) which was recrystallized from hexane: mp 88—89 °C; IR: 1751 cm^{-1}; NMR: 1.65 (6H, s, $-\overset{|}{C}(CH_3)_2$), 3.95 (3H, s, $-OCH_3$). Found: C, 68.90; H, 6.35%. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29%.

*Conversion of the Phthalide (**14**) into the Diol (**10**).* A mixture of **14** (1.020 g), lithium aluminium hydride (302 mg), and dry tetrahydrofuran (35 ml) was refluxed for 3 h. The reaction mixture was decomposed with aqueous ammonium chloride, extracted with ether, and the extract was washed with water. After drying over sodium sulfate, the solvent was evaporated *in vacuo* to give the diol (**10**) (968 mg: 93%) as a solid. The IR and NMR spectra were identical with those of the above authentic diol (**10**).

*3-Acetoxymethyl-2-isopropylanisole (**15**).* A mixture of **12** (2.988 g) and PtO_2 (170 mg) in ethanol (10 ml) was subjected to catalytic hydrogenation at room temperature for *ca.* 25 min. After the usual work-up, the crude product was purifi-

ed by column chromatography on silica gel (50 g) using benzene as the eluent to give **15** (2.733 g: 91%), which was recrystallized from methanol: mp 31.5—32 °C; IR: 1731 cm^{-1}; NMR: 1.32 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.99 (3H, s, $-OCOCH_3$), 3.18 (1H, m, $-C\underline{H}(CH_3)_2$), 3.80 (3H, s, $-OCH_3$), 5.05 (2H, s, $-CH_2O-$). Found: C, 70.48; H, 8.25%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

*3-Hydroxymethyl-2-isopropylanisole (**16**).* A mixture of **15** (2.544 g), lithium aluminium hydride (434 mg), and dry ether (40 ml) was stirred at room temperature for 1.5 h, and then decomposed with aqueous ammonium chloride. The mixture was extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and then evaporated to give an alcohol (**16**) (2.036 g: 99%), which was used directly in the subsequent reaction. For microanalysis an aliquot of the crude product (157 mg) was purified by column chromatography on silica gel (20 g) using ether–benzene (5 : 95) as the eluent to give the pure alcohol (147 mg). IR: 3618, 3415 cm^{-1}; NMR: 1.30 (6H, d, J= 7 Hz, $-CH(C\underline{H}_3)_2$), 1.95 (1H, bs, –OH), 3.29 (1H, m, $-C\underline{H}(CH_3)_2$), 3.80 (3H, s, $-OCH_3$), 4.51 (2H, s, $-CH_2O-$). Found: C, 73.45; H, 9.02%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%.

*3-Chloromethyl-2-isopropylanisole (**17**).* A solution of **16** (2.156 g) and thionyl chloride (1.7 ml) in dry ether (5.0 ml) was stirred at room temperature for 2 h, and then evaporated *in vacuo*. The residue was dissolved in dry benzene and the solution was evaporated *in vacuo* to afford **17** (2.278 g: 96%) which, without purification, was used in the next reaction. NMR: 1.36 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.22 (1H, m, $-C\underline{H}(CH_3)_2$), 3.82 (3H, s, $-OCH_3$), 4.53 (2H, s, $-CH_2-$).

*(2-Isopropyl-3-methoxybenzyl)triphenylphosphonium Chloride (**8**).* A solution of **17** (2.595 g) and triphenylphosphine (3.444 g) in dry benzene (10 ml) was refluxed for 16 h. The precipitates (**8**) (2.627 g, mp 239—241 °C) were filtered and washed with dry benzene. The filtrate was further refluxed for 14 h to give an additional salt (2.299 g, mp 239—242 °C).

*(−)-6-(2-Isopropyl-3-methoxystyryl)-1,5,5-trimethylcyclohexene (**18**).* A solution of butyllithium in hexane (15%; 4.5 ml) was added at room temperature to a stirred suspension of **8** (4.16 g) in dry benzene (25 ml) in a stream of nitrogen. The mixture was stirred at room temperature for 1.5 h and a solution of (*R*)-(−)-α-cyclocitral (**7**)[10,11] (860 mg), $[\alpha]_D$ −710° (EtOH), in dry benzene (5.0 ml) was added. After stirring at room temperature for 4 h, the reaction mixture was poured into a mixture of ice and aqueous ammonium chloride, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and then evaporated. The residue was triturated with hexane and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (100 g) using hexane–benzene (9 : 1) as the eluent to give **18** (733 mg: 44%) as an oil. $[\alpha]_D$ −248°; NMR: 0.92 and 0.96 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.30 (6H, d, J= 7 Hz, $-CH(C\underline{H}_3)_2$), 1.68 (3H, bs, $=\dot{C}CH_3$), 3.38 (1H, m, $-C\underline{H}(CH_3)_2$), 3.80 (3H, s, $-OCH_3$), 5.43 (1H, m, $-CH=\dot{C}-$), 5.63 (1H, dd, J=9 and 15 Hz, $-\dot{C}H-C\underline{H}=CH-$), 6.68 (1H, d, J=15 Hz, $-\dot{C}H-CH=C\underline{H}-$). Found: C, 84.72; H, 10.16%. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13%.

*(−)-2-(2,6,6-Trimethyl-2-cyclohexenyl)-1-(2-isopropyl-3-methoxyphenyl)ethane (**19**).* A suspension of **18** (1.550 g) and 5% Pd–C (700 mg) in ethanol (6.0 ml) was stirred at room temperature in an atmosphere of hydrogen. After one mole equivalent of hydrogen had been absorbed (*ca.* 80 min), the mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (150 g) using hexane and then hexane–benzene (7 : 3) as the eluents to give the dihydro compound (**19**) (1.253 g: 80%) as an oil. $[\alpha]_D$ −99.7°; NMR: 0.91 and 1.01 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.33 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.73 (3H, bs, $=\dot{C}CH_3$), 3.18 (1H, m, $-C\underline{H}(CH_3)_2$), 3.78 (3H, s, $-OCH_3$), 5.29 (1H, m, $-CH=\dot{C}-$). Found: C, 84.24; H, 10.79%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

*Intramolecular Cyclization of **19**.* Anhydrous aluminium chloride (450 mg) was added at 35 °C to a solution of **19** (1.015 g) in dichloromethane (10 ml). The reaction mixture was stirred at 35 °C for 20 min, poured into ice–water, and then extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The crude product was chromatographed on silica gel (120 g) using hexane as the eluent to give the *cis*-isomer (**21**) (305 mg: 30%). $[\alpha]_D$ −44.3° (EtOH); NMR ($CDCl_3$): 0.41 (3H, s, $C_{4\beta}-CH_3$), 0.94 (3H, s, $C_{4\alpha}-CH_3$), 1.15 (3H, s, $C_{10}-CH_3$), 1.24 and 1.33 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.42 (1H, m, $-C\underline{H}(CH_3)_2$), 3.79 (3H, s, $-OCH_3$), 6.70 and 7.13 (each 1H, d, and J=9 Hz, $C_{11}-H$ and $C_{12}-H$). Found: C, 83.86; H, 10.74%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

Further elution gave the *trans*-isomer (**20**) (565 mg: 56%), $[\alpha]_D$ +23.3° (EtOH), which was recrystallized from ethanol to give pure totaryl methyl ether. Mp 91—93 °C; $[\alpha]_D$ +40.6° (EtOH) [lit,[6] mp 91—92 °C, $[\alpha]_D$+42° (EtOH)]; NMR ($CDCl_3$): 0.94 (6H, s, $-\dot{C}(CH_3)_2$), 1.20 (3H, s, $C_{10}-CH_3$), 1.31 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.29 (1H, m, $-C\underline{H}(CH_3)_2$), 3.77 (3H, s, $-OCH_3$), 6.72 and 7.12 (each 1H, d, and J=9 Hz, $C_{11}-H$ and $C_{12}-H$). Found: C, 83.72; H, 10.80%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

*(+)-Totarol (**1**).* A mixture of **20** (45 mg) and boron tribromide (0.04 ml) in dichloromethane (1.5 ml) was stirred at 0—5 °C for 15 min and then at room temperature for 2 h. The reaction mixture was poured into ice–water and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and then evaporated to dryness. The crude product was purified by column chromatography on silica gel (10 g) using hexane–benzene (3 : 7) as the eluent to afford totarol (**1**) (38 mg: 88%) which was recrystallized from petroleum ether: mp 132—133 °C; $[\alpha]_D$+41.5° (lit,[13] mp 131—132 °C, $[\alpha]_D$+42°); IR: 3608, 3352 cm^{-1}; NMR ($CDCl_3$): 0.93 and 0.95 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.18 (3H, s, $C_{10}-CH_3$), 1.33 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 4.50 (1H, bs, –OH), 6.49 and 7.01 (each 1H, d, and J=9 Hz, $C_{11}-H$ and $C_{12}-H$). Found: C, 83.71; H, 10.63%. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56%.

*(+)-Totaryl Acetate (**22**).* A solution of **1** (60 mg), acetic anhydride (0.2 ml), and pyridine (0.8 ml) was heated at 75—80 °C for 2 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (10 g) using hexane–benzene (1 : 1) as the eluent to give the acetate (**22**) (56 mg: 82%) which was recrystallized from ethanol: mp 122—124 °C (lit,[6] mp 122—124 °C); $[\alpha]_D$+46.0°; IR: 1751 cm^{-1}; NMR: 0.95 (6H, s, $-\dot{C}(CH_3)_2$), 1.20 (3H, s, $C_{10}-CH_3$), 1.21 and 1.24 (each 3H, d, and J= 7 Hz, $-CH(C\underline{H}_3)_2$), 2.21 (3H, s, $-OCOCH_3$), 3.21 (1H, m, $-C\underline{H}(CH_3)_2$), 6.65 and 7.05 (each 1H, d, and J=9 Hz, $C_{11}-H$ and $C_{12}-H$). Found: C, 80.64; H, 9.89%. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83%.

References

1) T. H. Easterfield and J. C. McDowell, *Trans. New Zealand Inst.*, **43**, 55 (1911); **48**, 578 (1915).
2) W. F. Short and H. Wang, *J. Chem. Soc.*, **1951**, 2979, and references cited therein.
3) J. A. Barltrop and N. A. J. Rogers, *J. Chem. Soc.*, **1958**, 2566.
4) Y-L. Chow and H. Erdtman, *Acta Chem. Scand.*, **14**, 1852 (1960); **16**, 1305 (1962); *Chem. Abstr.*, **59**, 1689e (1963).
5) C. W. Brandt and B. R. Thomas, *New Zealand J. Sci. Tech.*, **33B**, 950 (1951).
6) R. C. Cambie and L. N. Mander, *Tetrahedron*, **18**, 465 (1962).
7) R. C. Cambie, W. R. J. Simpson, and L. D. Colebrook, *Tetrahedron*, **19**, 209 (1963).
8) C. P. Falshaw, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, **1963**, 2422.
9) A. C. Day, *J. Chem. Soc.*, **1964**, 3001.
10) C. H. Eugster, R. Buchecker, Ch. Tscharner, G. Uhde, and G. Ohloff, *Helv. Chim. Acta*, **52**, 1729 (1969).
11) T. Matsumoto and S. Usui, *Bull. Chem. Soc. Jpn.*, **52**, 212 (1979).
12) M. Uemura, S. Tokuyama, and T. Sak n, *Chem. Lett.*, **1975**, 1195.
13) R. Hodges, *J. Chem. Soc.*, **1961**, 4247.