Synthesis of Both Enantiomers of Flavanone and 2-Methylchromanone

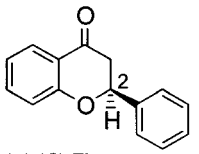
by **Yoshihiro Noda*** and **Morio Watanabe**

Department of Materials Chemistry and Engineering, College of Engineering, Nihon University, Tamura-machi, Koriyama, Fukushima, 963-8642 Japan
(e-mail: noda@chem.ce.nihon-u.ac.jp)

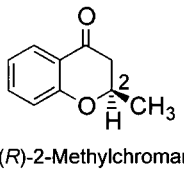
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

An efficient enantiospecific synthesis of the (*R*)- and (*S*)-enantiomers of flavanone and 2-methylchromanone is described. The key steps are a C,C-bond formation by ring opening of a chiral epoxide with a dithiane anion, followed by a *Mitsunobu* cyclization. The products obtained have high enantiomeric purity.

Flavanones (=2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-ones) constitute an important class of the wide group of flavanoids, and 2-methylchromanones (=2,3-dihydro-2-methyl-4*H*-1-benzopyran-4-ones) are also found in several biologically active natural products. A stereogenic center is present in their structures. Notwithstanding that they are crucial substituents in a number of naturally occurring and pharmacologically important compounds, there has been no simple and general method described to obtain optically active flavanones and 2-methylchromanones.



(–)-(*S*)-Flavanone

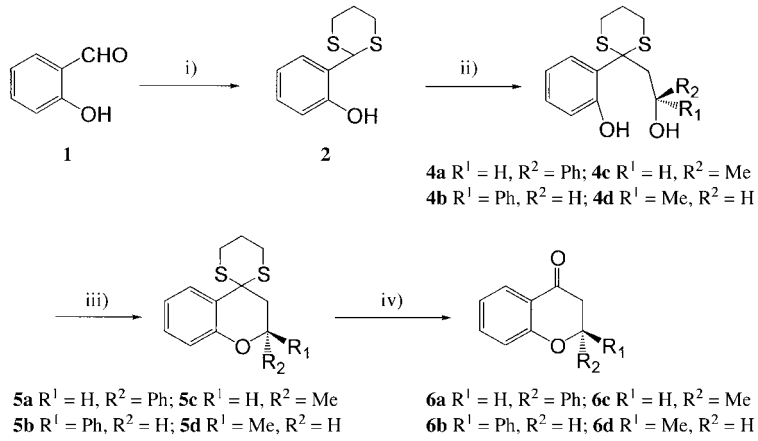


(+)-(*R*)-2-Methylchromanone

Syntheses of optically active flavanones and 2-methylchromanones have been reported by four groups: *a*) *Saengchantara* and *Wallace* reported the synthesis of 2-methylchromanone by the diasteroselective conjugate addition of lithium dimethylcuprate to (*S*)-3-(*p*-tolylsulfinyl)chromanone [1]. Recently, they have prepared the natural products (*S*)-2,6-dimethylchromanone and LL-D253α [2]. *b*) *Solladie et al.* has applied the *Wallace* method, *i.e.*, conjugate addition of PhMgBr to (*S*)-5,7-dimethoxy-8-methyl-3-(*p*-tolylsulfinyl) chromenone in the presence of dilithium tetrachlorocuprate as an efficient catalyst, to synthesize (+)-(*R*)-5-hydroxy-6-(hydroxymethyl)-7-methoxy-8-methylflavanone [3]. *c*) *Rama Rao et al.* reported the synthesis of both enantiomers of 5,7-dimethoxy-2-methylchromanone and (*R*)-7-methoxy-2-methylchromanone by inter- and intramolecular *Houben-Hoesch* reaction [4]. *d*) Recently, *Hodgetts* reported the synthesis of the biologically active natural product (–)-pinostrobin (= (*R*)-5-hydroxy-7-methoxyflavanone) [5].

Here, we describe a novel route to the optically active flavanone and 2-methylchromanone starting from salicylaldehyde (**1**) which was converted to dithiane derivative **2** by BF_3-catalyzed reaction with propane-1,3-dithiol in 95% yield [6] (*Scheme*). Treatment of **2** with 2 equiv. of BuLi in THF and a commercially available optically active epoxide, *e.g.*, (+)-(*R*)- and (−)-(*S*)-styrene oxide (**3a** and **3b**, resp.,) and (+)-(*R*)- and (−)-(*S*)-propylene oxide (**3c** and **3d**, resp.) gave the corresponding diols **4a** (52% yield), **4b** (52%), **4c** (72%), and **4d** (86%). *Mitsunobu* cyclization [7][8] of diols **4a**–**4d** by treating with Ph_3P and diethyl azodicarboxylate (DEAD) in dry THF gave **5a** (68% yield), **5b** (72%), **5c** (85%), and **5d** (91%), respectively. In this cyclization, the absolute configuration was converted completely by an S_N2-type nucleophilic displacement. Each cyclized compound, **5a**–**5d**, was hydrolyzed in aqueous MeCN with $HgCl_2$ in the presence of $CaCO_3$ [6] to afford the flavanones **6a** (70% yield) and **6b** (73%), and 2-methylchromanones **6c** (62% yield) and **6d** (66%), respectively.

Scheme



i) Propane-1,3-dithiol, $BF_3 \cdot Et_2O$, $CHCl_3$, r.t. ii) 2 equiv. BuLi, epoxides ((+)-(*R*)-styrene oxide (**3a**), (−)-(*S*)-styrene oxide (**3b**), (+)-(*R*)-propylene oxide (**3c**), (−)-(*S*)-propylene oxide (**3d**)) THF, −18°. iii) PPh_3, diethyl azodicarboxylate (DEAD), THF, r.t. iv) $HgCl_2$, $CaCO_3$, MeCN/H_2O, r.t.

Our samples of (+)-(*R*)-**6a** (m.p. 77° (hexane/CH_2Cl_2), $[\alpha]_D^{22} = +62.8$ ($c = 0.5$, $CHCl_3$)), (−)-(*S*)-**6b** (m.p. 77–78° (hexane/CH_2Cl_2), $[\alpha]_D^{22} = -63.6$ ($c = 0.5$, $CHCl_3$))[1]), and 2-methylchromanones (−)-(*S*)-**6c** (m.p. 43–44° (hexane/CH_2Cl_2), $[\alpha]_D^{21} = -46.7°$ ($c = 1.4$, $CHCl_3$)), (+)-(*R*)-**6d** (m.p. 43–44° (hexane/CH_2Cl_2), $[\alpha]_D^{19} = +47.9$ ($c = 0.8$, $CHCl_3$))[2]), were shown to be of high enantiomeric purity (flavanone (+)-(*R*)-**6a**: 95% ee, (−)-(*S*)-**6b**: 97% ee, 2-methylchromanone (−)-(*S*)-**6c**: 97% ee,

[1]) Reported data for (+)-(*R*)- and (−)-(*S*)-flavanone [9]: m.p. 77°, $[\alpha]_D = +67.2$ ($c = 0.35$, $CHCl_3$), and m.p. 76–77°, $[\alpha]_D = -64.4$ ($c = 0.35$, $CHCl_3$), resp.; [10]: m.p. 76° (petroleum ether), $[\alpha]_D^{25} = +52$ ($c = 0.75$, $CHCl_3$), and m.p. 77–78° (petroleum ether), $[\alpha]_D^{25} = -53.5$ ($c = 2.27$, $CHCl_3$), resp.; [11]: m.p. 72–74°, $[\alpha]_D = +12.4°$ (benzene), and m.p. 75–76°, $[\alpha]_D = -9.35°$ (benzene), resp.

[2]) Reported data for (−)-(*S*)-2-methylchromanone m.p. 39–40°, $[\alpha]_D^{22} = -50 + -4°$ ($c = 2$, $CHCl_3$), reference [1], (+)-(*R*)-$[\alpha]_D = +51°$ ($c = 1$, $CHCl_3$), reference [5].

(+)-(*R*)-**6d**: 99% ee) by HPLC analysis under optimized conditions for racemic standard on a chiral stationary phase (*Sumichiral OA-7000*).

In conclusion, we have developed a general and efficient synthesis of optically active flavanone and 2-methylchromanone of high enantiomeric purity from readily available starting materials. The method presented may be generally applicable to the synthesis of natural products.

We thank Prof. *Y. Fujimoto* and Dr. *M. Makino*, College of Pharmacy, Nihon University, for mass spectra.

Experimental Part

General. M.p.: *Yanako MP-500D* melting-point apparatus; uncorrected. Prep. TLC: *Kieselgel GF254*. Column chromatography (CC): silica gel (*Merck*, *Kieselgel 60*, 70–230 mesh). Specific rotations: *JASCO DIP-360* polarimeter, $CHCl_3$ as solvent; concentration in g/100 ml. IR Spectra: *Perkin-Elmer Paragon 1000 FT-IR* spectrometer, in $CHCl_3$ soln. ^{1}H- and ^{13}C-NMR spectra: *Hitachi R3000* (300- (^{1}H) or 75-MHz (^{13}C)) instrument; all spectra were recorded with TMS as internal standard in $CDCl_3$ as solvent. MS: at 70 eV with a *JEOL GC mate* instrument. Solvent systems used are shown in parentheses. Anh. $MgSO_4$ was employed to dry extracts.

2-(1,3-Dithian-2-yl)phenol (**2**). *Salicylaldehyde* (=*2-hydroxybenzaldehyde*, **1**; 4.88 g, 40 mmol), propane-1,3-dithiol (4.83 g, 45 mmol), and $BF_3 \cdot Et_2O$ (2.00 g, 14 mmol) were stirred in $CHCl_3$ (100 ml) at 25° for 10 h; 10% $NaHCO_3$ (50 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined org. phase washed with sat. NaCl soln. (100 ml), dried ($MgSO_4$), and filtered. Evaporation gave a yellow solid, which was recrystallized (hexane/CH_2Cl_2) to give **2** (8.05 g, 95%). M.p. 138–139° (hexane/CH_2Cl_2), IR ($CHCl_3$): 3590, 3425, 3007, 1578, 1487, 1277, 1227, 1170. ^{1}H-NMR (300 MHz): 1.9–2.2 (*m*, 2 H, dithiane); 3.0 (*m*, 4 H, dithiane); 5.42 (*s*, H–C(4)); 6.04 (br. *s*, OH); 6.8–7.4 (*m*, 4 arom. H). ^{13}C-NMR (75 MHz): 24.8; 31.6; 47.2; 117.2; 120.7; 123.6; 129.0; 130.0; 154.3. EI-MS: 124 (15), 123 (20), 122 (100), 147 (32), 139 (25), 138 (100), 137 (93), 105 (19). HR-MS: 212.03356 ($C_{10}H_{12}OS_2$; calc. 212.03295).

C,C-Bond Formation by Ring Opening of a Chiral Epoxide with **2**. *General Procedure*. Addition of 3.55 ml (5.7 mmol) of a 1.6M BuLi soln. in hexane to 482 mg (2.27 mmol) of **2** in 20 ml of anh. THF at –18° and stirring for 3 h. To a soln. of dithiane anion were added 546 mg (4.55 mmol) of styrene oxide in 5 ml of anh. THF and, after stirring for 3 h, sat. NH_4Cl soln. was added, and the mixture was extracted with Et_2O (3 × 50 ml). The org. layer was dried and evaporated, and the residue purified by CC and prep. TLC to give the alcohol.

*2-[(*S*)-2-(2-Hydroxy-2-phenylethyl)-1,3-dithian-2-yl]phenol* (**4a**). From 492 mg (2.27 mmol) of **2** and 546 mg (4.55 mmol) of *(+)-(*R*)-styrene oxide* (**3a**), 392 mg (52%) of **4a** was obtained. Colorless liquid. $[\alpha]_D^{22} = -4.0$ ($c = 0.8$, $CHCl_3$). IR ($CHCl_3$): 3474, 3195, 3008, 2911, 1605, 1573, 1477, 1457, 1423, 1282, 1226, 1193, 1047, 908. ^{1}H-NMR (300 MHz): 2.0 (*m*, 2 H, dithiane); 2.34–2.6 (*m*, CH_2); 3.0 (*m*, 4 H, dithiane); 4.84 (*d*, $J = 8.7$, C*H*OH); 6.98 (*m*, 2 arom. H); 7.22 (*m*, 6 arom. H); 7.93 (*m*, 1 arom. H); 8.63 (*s*, OH). ^{13}C-NMR (75 MHz): 24.2; 27.7; 28.0; 51.5; 57.0; 70.7; 119.3; 120.6; 123.3; 125.5; 127.3; 128.3; 130.2; 131.5; 143.7; 155.9. EI-MS: 332 (27), 224 (75), 225 (83), 211 (22), 152 (61), 151 (48), 137 (21), 119 (100), 107 (28), 105 (35), 91 (37), 79 (30), 78 (27). HR-MS: 332.08984 ($C_{18}H_{20}O_2S_2$; calc. 332.09046).

*2-[(*R*)-2-(2-Hydroxy-2-phenylethyl)-1,3-dithian-2-yl]phenol* (**4b**). From 469 mg (2.21 mmol) of **2** and 530 mg (4.42 mmol) *(−)-(*S*)-styrene oxide* (**3b**), 382 mg (52%) of **4b** was obtained. Colorless liquid. $[\alpha]_D^{22} = +3.7$ ($c = 0.8$, $CHCl_3$).

*2-[(*R*)-2-(2-Hydroxypropyl)-1,3-dithian-2-yl]phenol* (**4c**). From 759 mg (3.58 mmol) of **2** and 415 mg (7.2 mmol) *(+)-(*R*)-propylene oxide* (**3c**), 696 mg (72%) of **4c** was obtained. Colorless liquid. $[\alpha]_D^{22} = +6.3$ ($c = 1.3$, $CHCl_3$). IR ($CHCl_3$): 3197, 3008, 2911, 1605, 1573, 1477, 1456, 1423, 1281, 1225, 1152, 1047. ^{1}H-NMR (300 MHz): 1.09 (*d*, $J = 6$, Me); 1.95–2.05 (*m*, 2 H, dithiane); 2.06–2.17 (*m*, CH_2); 2.85 (*m*, 4 H, dithiane); 4.0 (br., C*H*OH); 6.95 (*m*, 2 arom. H); 7.27 (*t*, $J = 7.5$, 1 arom. H); 7.90 (*d*, $J = 7.5$, 1 arom. H); 8.61 (*s*, OH). ^{13}C-NMR (75 MHz): 24.3; 24.7; 28.0; 28.4; 51.2; 57.3; 65.0; 120.0; 121.0; 123.8; 130.6; 131.8; 156.4. MS: 270 (96), 211 (28), 195 (35), 178 (28), 163 (100), 152 (45), 151 (46), 145 (22), 137 (30), 91 (58). HR-MS: 270.07477 ($C_{13}H_{18}O_2S_2$; calc. 270.07481).

*2-[(*S*)-2-(2-Hydroxypropyl)-1,3-dithian-2-yl]phenol* (**4d**). From 759 mg (3.58 mmol) of **2** and 415 mg (7.2 mmol) *(−)-(*S*)-propylene oxide* (**3d**), 831 mg (86%) of **4d** was obtained. Colorless liquid. $[\alpha]_D^{22} = -6.6$ ($c = 1.2$, $CHCl_3$).

Mitsunobu *Cyclization. General Procedure.* To a soln. of 957 mg (3.65 mmol) Ph_3P in 10 ml of anh. THF was added at r.t. 1.6 g (1.66 mmol) of diethyl azodicarboxylate (DEAD), and, after stirring 1 h, the mixture was added to 303 mg (0.91 mmol) of **4a**. After 2 h, the reaction was monitored by TLC, then the mixture was diluted with H_2O (30 ml) and extracted with Et_2O (3 × 50 ml). The combined Et_2O extracts were dried and evaporated. Purification (TLC) and recrystallization (hexane/CH_2Cl_2) afforded the cyclized compound **5a**.

*(*R*)-2,3-Dihydro-2-phenylspiro[4*H*-[1]benzopyran-4,2′-[1,3]dithiane]* (**5a**). From 303 mg (0.91 mmol) of **4a**, 195 mg (68%) of **5a** was obtained. M.p. 147–148° (hexane/CH_2Cl_2). $[\alpha]_D^{22} = -63.5$ ($c = 0.6$, $CHCl_3$). IR ($CHCl_3$): 3010, 1606, 1578, 1480, 1453, 1220, 1041, 916. ^{1}H-NMR (300 MHz): 1.98–2.2 (*m*, 2 H, dithiane); 2.5–2.6 (*m*, CH_2(3)); 2.6–2.8 (*m*, 2 H, dithiane); 3.05–3.15 (*m*, 2 H, dithiane); 5.32 (*d*, $J = 10.2$, H–C(2)); 6.8–7.8 (*m*, 9 arom. H). ^{13}C-NMR (75 MHz): 24.7; 27.8; 27.9; 43.8; 48.5; 75.5; 117.3; 121.0; 123.6; 126.4; 128.2; 128.6; 129.6; 129.7; 140.3; 154.7. EI-MS: 332 (27), 224 (75), 225 (83), 211 (22), 152 (61), 151 (48), 137 (21), 119 (100), 107 (28), 105 (35), 91 (37), 79 (30), 78 (27). HR-MS: 332.09046 ($C_{18}H_{20}O_2S_2$; calc. 332.09046).

*(*S*)-2,3-Dihydro-2-phenylspiro[4*H*-[1]benzopyran-4,2′-[1,3]dithiane]* (**5b**). From 214 mg (0.64 mmol) of **4b**, 148 mg (73%) of **5b** was obtained. M.p. 147–148° (hexane/CH_2Cl_2). $[\alpha]_D^{22} = +61.1$ ($c = 0.6$, $CHCl_3$).

*(*S*)-2,3-Dihydro-2-methylspiro[4*H*-[1]benzopyran-4,2′-[1,3]dithiane]* (**5c**). From 620 mg (2.3 mmol) of **4c**, 492 mg (85%) of **5c** was obtained. M.p. 118–119° (hexane/CH_2Cl_2). $[\alpha]_D^{23} = -167.5$ ($c = 1.4$, $CHCl_3$). IR ($CHCl_3$): 3008, 2979, 2908, 1579, 1480, 1455, 1279, 1230, 1125, 1069. ^{1}H-NMR (300 MHz): 1.46 (*d*, $J = 6.6$, Me); 1.95 (*m*, CH_2(3)); 2.6–2.8 (*m*, 2 H, dithiane); 2.8–3.0 (*m*, 2 H, dithiane); 4.42 (*m*, H–C(2)); 6.80 (*d*, $J = 8.1$, 1 arom. H); 6.92 (*t*, $J = 7.5$, 1 arom. H); 7.19 (*t*, $J = 7.5$, 1 arom. H); 7.82 (*d*, $J = 8.1$, 1 arom. H). ^{13}C-NMR (75 MHz): 20.7; 24.7; 27.8; 27.9; 42.9; 48.2; 69.6; 117.0; 120.6; 123.6; 129.6; 129.7; 154.8. EI-MS: 253 (17), 252 (85), 237 (43), 179 (24), 178 (100), 177 (45), 163 (58), 145 (66), 131 (15). HR-MS: 252.06412 ($C_{13}H_{16}OS_2$; calc. 252.06425).

*(*R*)-2,3-Dihydro-2-methylspiro[4*H*-[1]-benzopyran-4,2′-[1,3]dithiane]* (**5d**). From 720 mg (2.67 mmol) of **4d**, 611 mg (91%) of **5d** was obtained. M.p. 116–117° (hexane/CH_2Cl_2). $[\alpha]_D^{22} = +171.7$ ($c = 0.1$, $CHCl_3$).

Hydrolysis of Dithianes. General Procedure. A suspension of 314 mg (1.16 mmol) of $HgCl_2$, 116 mg (1.16 mmol) of $CaCO_3$, and 146 mg (0.46 mmol) of **5a** in 10 ml of MeCN/H_2O 4 :1 were stirred at r.t. After 3 h, the mixture was filtered off and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layer was dried and evaporated. Purification (prep. TLC) and recrystallization (hexane/CH_2Cl_2) afforded flavanone (and 2-methylchromanone).

*(+)-(*R*)-Flavanone* (= *(+)-(*R*)-2,3-Dihydro-2-phenyl-4*H*-1-benzopyran*; **6a**). From 146 mg (0.46 mmol) of **5a**, 73 mg (70%) of **6a** was obtained. M.p. 77° (hexane/CH_2Cl_2). $[\alpha]_D^{22} = +62.8$ ($c = 0.5$, $CHCl_3$). HPLC (*Sumichiral OA-7000* column, 20 mM phosphate buffer (pH 2.0), MeCN/H_2O 60 : 40): 8.7 min (97.4%), 16.5 min (2.6%), 95% ee. IR ($CHCl_3$): 3013, 1689, 1606, 1463, 1306, 1228, 1116, 906. ^{1}H-NMR (300 MHz): 3.0 (*dd*, *ABX*, $J = 17$, 13, 2, CH_2(3)); 5.48 (*dd*, *ABX*, $J = 13$, 3, H–C(2)); 7.07 (*m*, 2 arom. H); 7.3–7.6 (*m*, 6 arom. H); 7.93 (*d*, $J = 8.1$, 1 arom. H). ^{13}C-NMR (75 MHz): 44.7; 79.6; 118.1; 120.9; 121.6; 127.0; 128.7; 128.8; 136.1; 138.7; 161.5; 191.9.

*(−)-(*S*)-Flavanone* (= *(−)-(*S*)-2,3-Dihydro-2-phenyl-4*H*-1-benzopyran*; **6b**): From 129 mg (0.41 mmol) of **5b**, 67 mg (73%) of **6b** was obtained. M.p. 77–78° (hexane/CH_2Cl_2). $[\alpha]_D^{22} = -63.6$ ($c = 0.5$, $CHCl_3$). HPLC: 8.8 min (1.4%), 16.6 min (98.6%), 97% ee.

*(−)-(*S*)-2-Methylchromanone* (= *(−)-(*S*)-2,3-Dihydro-2-methyl-4*H*-1-benzopyran*; **6c**). From 346 mg (1.37 mmol) of **5c**, 134 mg (62%) of **6c** was obtained. M.p. 43–44° (hexane/CH_2Cl_2). $[\alpha]_D^{21} = -46.7$ ($c = 1.4$, $CHCl_3$). HPLC (*Sumichiral OA-7000* column, 20 mM phosphate buffer (pH 2.0), MeCN/H_2O 60 : 40): 48.1 min (1.5%), 51.4 min (98.5%), 97% ee. IR ($CHCl_3$): 3013, 2982, 1693, 1608, 1577, 1473, 1464, 1386, 1349, 1309, 1229, 1153, 1122, 877. ^{1}H-NMR (300 MHz): 1.52 (*d*, $J = 5.7$, Me); 2.68 (*d*, $J = 7.5$, CH_2(3)); 4.59 (*dd*, $J = 7.5$, 5.7, H–C(2)); 6.9–7.0 (*m*, 2 arom. H); 7.47 (*t*, $J = 7.5$, 1 arom. H); 7.87 (*d*, $J = 7.5$, 1 arom. H). ^{13}C-NMR (75 MHz): 21.0; 44.6; 74.2; 117.8; 120.7; 121.1; 126.9; 135.9; 161.6; 192.3.

*(+)-(*R*)-2-Methylchromanone* (= *(+)-(*R*)-2,3-Dihydro-2-methyl-4*H*-1-benzopyran*; **6d**). From 569 mg (2.26 mmol) of **5d**, 241 mg (66%) of **6d** was obtained. M.p. 43–44° (hexane/CH_2Cl_2). $[\alpha]_D^{19} = +47.9$ ($c = 0.8$, $CHCl_3$). HPLC: 48.4 min (99.7%), 51.2 min (0.3%), 99% ee.

REFERENCES

[1] S. T. Saengchantara, T. W. Wallace, *J. Chem. Soc. Chem. Commun.* **1986**, 1592; S. T. Saengchantara, T. W. Wallace, *Tetrahedron* **1990**, *46*, 6553.

[2] K. J. Hodgetts, K. I. Maragkou, T. W. Wallace, R. C. R. Wootton, *Tetrahedron* **2001**, *57*, 6793.

[3] G. Solladie, N. Gehrold, J. Maignan, *Tetrahedron: Asymmetry* **1999**, *10*, 2739.
[4] A. V. Rama Rao, A. S. Gaitonde, K. R. C. Prakash, S. Prahlada Rao, *Tetrahedron Lett*. **1994**, *35*, 6347.
[5] K. J. Hodgetts, *Tetrahedron Lett*. **2001**, *42*, 3763.
[6] D. Seebach, *Synthesis* **1969**, 17.
[7] S. Yamaguchi, K. Furihata, M. Miyazawa, H. Yokoyama, Y. Hirai, *Tetrahedron Lett*. **2000**, *41*, 4787, and refs. cit. therein.
[8] O. Mitsunobu, *Synthesis* **1981**, 1.
[9] M. Rakosi, A. L. Tokes, R. Bognar, *Tetrahedron Lett*. **1970**, 2305.
[10] E. J. Corey, R. B. Mitra, *J. Am. Chem. Soc*. **1962**, *84*, 2938.
[11] M. Kotake, G. Nakaminami, *Proc. Japan Acad*. **1953**, *29*, 56.

Received May 24, 2002