Synthesis and Absolute Configuration at C(8) of '*p*-Menthane-3,8,9-triol' Derived from (–)-Isopulegol

by **Yoshifumi Yuasa***[a]) and **Yoko Yuasa**[b])

[a]) Takasago International Corporation, 1-5-1 Nishiyawata, Hiratsuka, Kanagawa, 254-0073, Japan (phone: 81-(0)463-21-7516; fax: 81-(0)463-21-7413; e-mail: yoshifumi_yuasa@takasago.com)

[b]) School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, 192-0392, Tokyo, Japan (e-mail: yuasay@ps.toyaku.ac.jp)

Two diastereoisomers of the new, potentially insecticidal '*p*-menthane-3,8,9-triol' (=(2*S*)- and (2*R*)- 2-[(1*R*,2*R*,4*R*)-2-hydroxy-4-methylcyclohexyl]propane-1,2-diol; (8*S*)- and (8*R*)-**1**), have been synthesized from (–)-isopulegol by both conventional dihydroxylation and catalytic *Sharpless* dihydroxylation (*Scheme*). The absolute configuration at C(8) of the corresponding orthoformate adduct (8*S*)-**3a** was determined by ^{1}H-NMR and X-ray crystallographic analysis (*Figure*).

Introduction. – Dihydroxylated monoterpenes are known to exert a repellent effect on insect pests such as mosquitoes and fleas [1–12]. In particular, '*p*-menthane-3,8-diol', obtained from (–)-citronellal, is being used in this context[1]). In view of this, we report the synthesis and absolute configuration of the unknown *p*-menthane-derived triol **1** (=2-[(1*R*,2*R*,4*R*)-2-hydroxy-4-methylcyclohexyl]propane-1,2-diol), which was prepared by classical dihydroxylation or catalytic *Sharpless* dihydroxylation [13] of (–)-isopulegol (=(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethenyl)cyclohexanol).

Results and Discussion. – The dihydroxylation of (–)-isopulegol was performed with formic acid (HCOOH) and 30% aqueous hydrogen peroxide (H_2O_2), followed by alkaline hydrolysis [14][15]. H_2O_2 was slowly added to a solution of (–)-isopulegol and HCOOH at 50°, and the reaction was monitored by gas chromatography (GC). Upon completion of the reaction, the mixture was hydrolyzed with aqueous 15% NaOH soln. at 50° to afford a diastereoisomeric mixture of (8*S*)-**1**/(8*R*)-**1** in a ratio of 53:47 (*Scheme*), as determined by ^{1}H-NMR spectroscopy. The epimeric mixture was purified by column chromatography (SiO_2) to afford (8*S*)-**1** in pure, crystalline form, together with an enriched, oily mixture of predominantly (8*R*)-**1**.

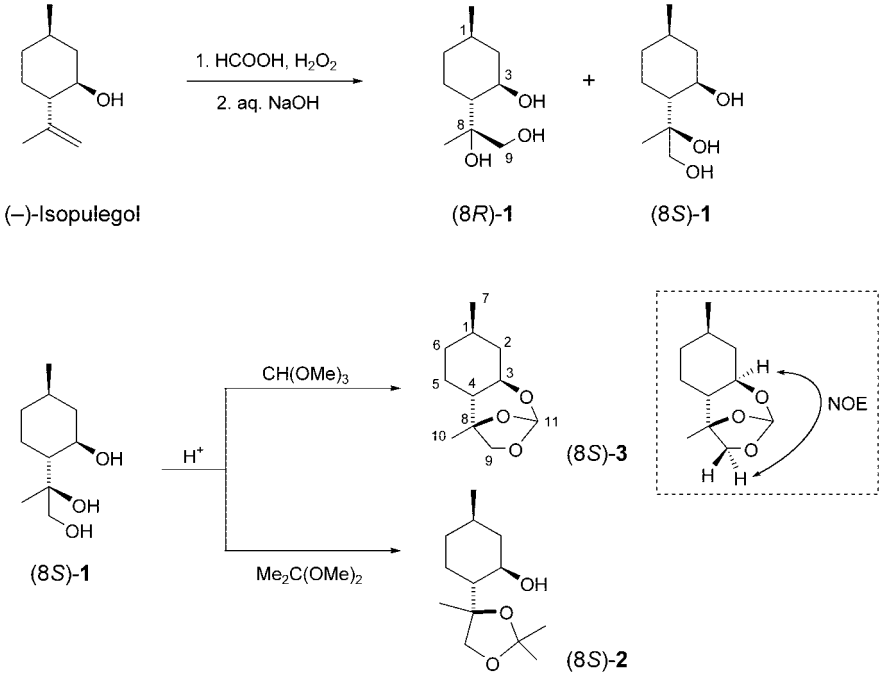
By means of 2D-NMR techniques, all ^{1}H- and ^{13}C-NMR chemical shifts could be assigned for both epimers (*Table 1*). To determine the configuration at the C(8)-atom[2]), crystalline (8*S*)-**1** was converted to the corresponding acetonide (8*S*)-**2** and orthoformate (8*S*)-**3**, respectively, in 66% and 95% yield (*Scheme*). Whereas the absolute configuration could not be derived from NOE studies with (8*S*)-**1** and -**2**, this was possible with (8*S*)-**3**. From the observed NOEs between H–C(3) and one of the H–C(9) H-atoms (see *Scheme*), the (8*S*)-configuration was assigned.

---

[1]) '*p*-Menthane-3,8-diol' (systematic name: 2-(1-hydroxy-1-methylethyl)-5-methylcyclohexanol) is a registered pesticide: U.S. EPA pesticide chemical code 011550 (issued: 5/2000).

[2]) Arbitrary atom numbering (see the *Scheme*).

Scheme. *Synthesis of the New Menthane-Derived Epimeric Triols* **1**, *and Conversion of (8*S*)-***1*** to the Corresponding Orthoformate* **2** *and Acetonide* **3**, *Respectively.* The structure of (8*S*)-**1** was secured by NOE measurements (box) and X-ray analysis (see the *Figure*). Arbitrary atom numbering.



The absolute configuration of (8*S*)-**3** was confirmed by X-ray crystal-structure analysis (see *Figure*, and *Table 2* in the *Exper. Part*). In contrast to its precursor (8*S*)-**1**, whose crystal shape was not suited for X-ray analysis, (8*S*)-**3** afforded nice crystals from MeOH. Attempts to prepare other crystalline derivatives of (8*S*)-**1**, *e.g.*, the 4-nitrobenzoate or the 3-nitrophthalate, were unsuccessful.

Table 1. *^{1}H- and ^{13}C-NMR Chemical Shifts of the Epimers (8*R*)- and (8*S*)-***1***.* Recorded at 500/125 MHz in $CDCl_3$; δ in ppm. Arbitrary atom numbering (see the *Scheme*).

	(8*R*)-**1**		(8*S*)-**1**	
	δ(C)	δ(H)	δ(C)	δ(H)
CH(1)	31.23	1.39 – 1.47	31.38	1.38 – 1.48
CH_2(2)	44.70	1.03 – 1.11, 1.89 – 1.97	45.12	0.96 – 1.05, 1.89 – 1,95
CH(3)	72.25	3.80	72.65	3.81
CH(4)	47.75	1.62 – 1.70	52.00	1.49 – 1.55
CH_2(5)	26.23	0.85 – 0.98, 1.89 – 1.97	26.33	0.96 – 1.05, 1.75 – 1.79
CH_2(6)	34.18	1.62 – 1.70	34.55	0.86 – 0.94, 1.66 – 1.72
Me(7)	21.94	0.93	21.88	0.92
C(8)	76.53	–	76.32	–
CH_2(9)	68.67	3.37, 3.53	66.83	3.45, 3.75
Me(10)	19.37	1.14	24.29	1.18

Although the enriched epimer (8*R*)-**1** had been obtained as a viscous oil, the corresponding pure orthoformate (8*R*)-**3** could be readily crystallized from the diastereoisomeric mixture. However, its crystal shape was inconvenient for X-ray crystallographic analysis. Its configuration, however, was in accord with a significant NOE between the H-atoms H–C(4) and H–C(9) (not shown).

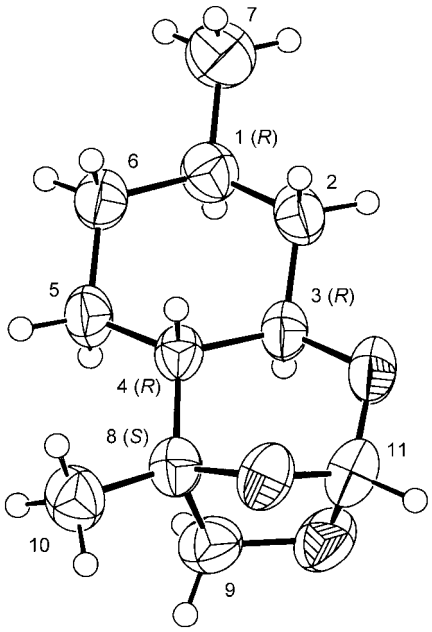


Figure. *X-Ray crystal structure* (ORTEP plot) *of the orthoformate (8*S*)-***3**. Arbitrary atom numbering.

We also examined the application of the asymmetric *Sharpless* dihydroxylation (AD) on (–)-isopulegol, using the commercial catalyst mixtures 'AD-mix-α' and 'AD-mix-β' [16]. However, these reactions were not very successful, with diastereoisomeric ratios of (8*S*)-**1**/(8*R*)-**1** of 59:41 and 43:57, respectively.

Experimental Part

General. All reagents and solvents were obtained from commercial sources and used without further purification. GC: *HP-5890* with an FID detector; column: *Silicon NB-1* (*df* = 0.15 μm; 0.25 mm × 25 m); carrier gas: N_2 (0.1 MPa); oven temp.: 70–200° at 4°/min, injection temp.: 250°, detector temp.: 250°. M.p.: *Yanagimoto* micromelting apparatus; uncorrected. IR Spectra: *Nicolet Avatar-360* FT-IR spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-500* (500/125 MHz) apparatus, in $CDCl_3$; chemical shifts δ in ppm rel. to Me_4Si (= 0 ppm) as internal standard, coupling constants *J* in Hz. EI-MS: *Hitachi M-80A* mass spectrometer, at 70 eV; in *m*/*z*.

*(2*R*)- and (2*S*)-2-[(1*R*,2*R*,4*R*)-2-hydroxy-4-methylcyclohexyl]propane-1,2-diol* ((8*R*)- and (8*S*)-**1**[2]). To a mixture of (–)-isopulegol (65.5 g, 424 mmol) and HCOOH (43.3 g, 943 mmol) was added 30% aq. H_2O_2 (65 g, 573 mmol) dropwise over 4 h at 50°, and the mixture was stirred for another 4 h at this temp. A 15% aq. NaOH soln. (260 ml) was added dropwise at 50°, and the mixture was stirred for 1 h at this temp. Then, AcOEt (200 ml) was added, and the org. phase was washed successively with 10% aq. Na_2SO_3 soln. (100 ml) and brine (100 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give a crude oil (66.63 g), which was distilled under reduced pressure to afford a 53:47 mixture of (8*S*)-**1** and (8*R*)-**1** (49.2 g), boiling at 140–145° (0.08 torr). The distillate

was further purified by column chromatography (CC; SiO_2, hexane/AcOEt 1:2) to afford pure (8*S*)-**1** as a solid (18.1 g, 23%), and impure (8*R*)-**1** (25.2 g, 32%) as an oil containing the (8*S*)-epimer.

*Data for (8*S*)-***1***.* Crystalline solid. M.p. 65.0–65.5°. $[\alpha]_D^{22} = +16.21$ ($c = 1.11$, $CHCl_3$). IR ($CHCl_3$): 3402, 3020, 2955, 2925, 1521, 1452, 1423. ^{1}H-NMR ($CDCl_3$): 0.86–0.94 (*m*, 1 H); 0.92 (*d*, *J* = 6.5, 3 H); 0.96–1.05 (*m*, 2 H); 1.18 (*s*, 3 H); 1.38–1.48 (*m*, 1 H); 1.49–1.55 (*m*, 1 H); 1.66–1.72 (*m*, 1 H); 1.75–1.79 (*m*, 1 H); 1.89–1.95 (*m*, 1 H); 3.45 (*d*, *J* = 11.1, 1 H); 3.75 (*d*, *J* = 11.1, 1 H); 3.81 (*dt*, *J* = 4.3, 10.6, 1 H). ^{13}C-NMR ($CDCl_3$): 21.88, 24.29 (2 Me); 26.33 (CH_2); 31.38 (CH); 34.55, 45.12 (2 CH_2); 52.00 (CH); 66.83 (CH_2); 72.65 (CH); 76.32 (C_q). EI-MS: 157 ($[M-31]^+$), 139, 123, 109, 108, 96, 95, 81, 75, 71, 54, 43. Anal. calc. for $C_{10}H_{20}O_3$: C 63.80, H 10.71; found: C 63.82, H 10.72.

*Data for (8*R*)-***1***.* Viscous oil. ^{1}H-NMR ($CDCl_3$): 0.85–0.98 (*m*, 1 H); 0.93 (*d*, *J* = 6.5, 3 H); 1.03–1.11 (*m*, 1 H); 1.14 (*s*, 3 H); 1.39–1.47 (*m*, 1 H); 1.62–1.70 (*m*, 2 H); 1.89–1.97 (*m*, 2 H); 3.37 (*d*, *J* = 11.2, 1 H); 3.53 (*d*, *J* = 11.2, 1 H); 3.80 (*q*, *J* = 4.3, 10.8, 1 H). ^{13}C-NMR ($CDCl_3$): 19.37, 21.94 (2 Me); 26.23 (CH_2); 31.23 (CH); 34.18, 44.70 (2 CH_2); 47.75 (CH); 68.67 (CH_2); 72.25 (CH); 76.53 (C_q). EI-MS: 157 ($[M-31]^+$), 139, 123, 109, 108, 96, 95, 81, 75, 71, 54, 43.

*(1*R*,2*R*,5*R*)-5-Methyl-2-[(4*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl]cyclohexan-1-ol* ((8*S*)-**2**). Compound (8*S*)-**1** (1.0 g, 5.3 mmol), 4-methylbenzenesulfonic acid (TsOH, 20 mg), and 2,2-dimethoxypropane (5 ml) in CH_2Cl_2 (20 ml) were stirred at r.t. for 1 h. The solvent was evaporated, and the residue was purified by CC (SiO_2; hexane/AcOEt 4:1): 0.8 g (66%). Oil. $[\alpha]_D^{22} = -10.89$ ($c = 1.56$, $CHCl_3$). IR (neat): 3447, 2983, 2922, 1455, 1375. ^{1}H-NMR ($CDCl_3$): 0.84–0.98 (*m*, 2 H); 0.92 (*d*, *J* = 6.5, 3 H); 0.99 (*q*, *J* = 12.3, 23.1, 1 H); 1.30 (*s*, 3 H); 1.38–1.47 (*m*, 1 H); 1.47 (*s*, 3 H); 1.54–1.58 (*m*, 1 H); 1.65–1.67 (*m*, 1 H); 1.80–1.83 (*m*, 1 H); 1.94 (*m*, 1 H); 3.57 (*m*, 1 H); 3.67 (br. *s*, 1 H); 3.74 (*d*, *J* = 8.7, 1 H); 3.94 (*d*, *J* = 8.7, 1 H). ^{13}C-NMR ($CDCl_3$): 21.98, 23.81 (2 Me); 26.37 (CH_2); 26.40, 28.13 (2 Me); 31.19 (CH); 34.22, 43.97 (2 CH_2); 51.42, 70.84 (2 CH); 72.37 (CH_2); 84.83, 108.61 (2 C_q). EI-MS: 213 ($[M-15]^+$), 195, 170, 153, 135, 115, 95, 81, 72, 57, 43.

*(1*R*,2*R*,5*R*)-5-Methyl-2-[(4*S*)-2,2,4-trimethyl-1,3-dioxolan-4-yl]cyclohexan-1-ol* ((8*R*)-**2**). Obtained in analogy to (8*S*)-**2** from an epimeric mixture of **1**. Oil. $[\alpha]_D^{21} = -13.88$ ($c = 0.36$, $CHCl_3$). IR (neat): 3518, 2984, 2926, 2870, 1454, 1378. ^{1}H-NMR ($CDCl_3$): 0.87–1.07 (*m*, 3 H); 0.93 (d, *J* = 6.5, 3 H); 0.99 (*q*, *J* = 12.3, 23.1, 1 H); 1.27 (*s*, 3 H); 1.36 (*s*, 3 H); 1.45 (*s*, 3 H); 1.39–1.51 (*m*, 3 H); 1.61–1.67 (*m*, 1 H); 2.00–2.05 (*m*, 1 H); 3.71 (*dt*, *J* = 4.5, 10.3, 1 H); 3.78 (*d*, *J* = 8.6, 1 H); 3.82 (*d*, *J* = 8.6, 1 H); 4.58 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 20.00, 22.00, 26.56 (3 Me); 27.13 (CH_2); 27.62 (Me); 30.86 (CH); 34.16, 43.50 (2 CH_2); 51.90, 71.05 (2 CH); 74.85 (CH_2); 85.13, 109.97 (2 C_q). EI-MS: 213 ($[M-15]^+$), 195, 170, 153, 135, 115, 95, 81, 72, 57, 43.

*(5*S*,5a*R*,8*R*,9a*R*)-4,5,5a,6,7,8,9,9a-Octahydro-5,8-dimethyl-2,5-epoxy-2*H*-[1,3-]benzodioxepine* ((8*S*)-**3**). Compound (8*S*)-**1** (1.0 g, 5.3 mmol), TsOH (20 mg), and trimethyl orthoformate (1.12 g, 10.6 mmol) in CH_2Cl_2 (30 ml) were stirred at r.t. for 30 min. The solvent was evaporated, and the residue was purified by CC (SiO_2; hexane/AcOEt 4:1) to afford a solid (1.0 g, 95%), which was recrystallized from MeOH. M.p. 75–76° (MeOH). $[\alpha]_D^{21} = -66.03$ ($c = 1.06$, $CHCl_3$). IR ($CHCl_3$): 3021, 2894, 1521, 14577, 1385. ^{1}H-NMR ($CDCl_3$): 0.88 (*d*, *J* = 6.6, 3 H); 0.88–0.98 (*m*, 2 H); 1.04 (*q*, *J* = 11.7, 23.5, 1 H); 1.27 (*s*, 3 H); 1.43–1.51 (*m*, 1 H); 1.52–1.58 (*m*, 1 H); 1.59–1.63 (*m*, 1 H); 1.68–1.70 (*m*, 1 H); 1.78–1.81 (*m*, 1 H); 3.30 (*dd*, *J* = 1.3, 7.3, 1 H); 3.60 (*dt*, *J* = 3.8, 9.3, 1 H); 3.95 (*d*, *J* = 7.4, 1 H); 5.95 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 19.11, 22.10 (2 Me); 24.81 (CH_2); 31.33 (CH); 39.47 (CH_2); 49.21 (CH); 69.70 (CH_2); 71.83 (CH); 80.51 (C_q); 112.21 (CH). EI-MS: 197 ($[M-1]^+$), 168, 152, 137, 123, 109, 108, 96, 95, 93, 81, 67, 55, 43, 29. Anal. calc. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.63, H 9.15.

*(5*R*,5a*R*,8*R*,9a*R*)-4,5,5a,6,7,8,9,9a-Octahydro-5,8-dimethyl-2,5-epoxy-2*H*-[1,3-]benzodioxepine* ((8*R*)-**3**). Obtained in analogy to (8*S*)-**3** from an epimeric mixture of **1**. Crystalline solid. M.p. 125–126° (Et_2O). $[\alpha]_D^{21} = +38.82$ ($c = 1.05$, $CHCl_3$). IR ($CHCl_3$): 3021, 2930, 2895, 1521, 1478, 1445, 1385. ^{1}H-NMR ($CDCl_3$): 0.87 (*d*, *J* = 6.6, 3 H); 0.78–0.89 (*m*, 1 H); 0.97 (*q*, *J* = 11.8, 23.7, 1 H); 1.24–1.34 (*m*, 1 H); 1.30 (*s*, 3 H); 1.41–1.51 (*m*, 1 H); 1.60–1.69 (*m*, 3 H); 1.88–1.93 (*m*, 1 H); 3.26 (*d*, *J* = 6.8, 1 H); 3.27 (*dt*, *J* = 3.6, 10.1, 1 H); 3.64 (*d*, *J* = 6.7, 1 H); 6.03 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 16.03, 21.97 (2 Me); 26.38 (CH_2); 31.21 (CH); 34.68, 39.90 (2 CH_2), 52.04, 68.94 (2 CH); 76.64 (CH_2); 79.16 (C_q), 111.54 (CH). EI-MS: 197 ($[M-1]^+$); 168, 152, 137, 123, 109, 108, 103, 95, 93, 81 (100), 67, 55, 43, 29. Anal. calc. for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.6, H 9.13.

X-Ray Crystal-Structure Analysis. The crystal data for (8*S*)-**3** are collected in *Table 2*, and a representation can be found in the *Figure*. All diagrams and calculations were performed with maXus on a *Bruker Nonius* apparatus (*Delft & MacScience*, Japan).

Table 2. *Crystallographic Data of (8S)-***3**[a])

Crystallized from	MeOH
Empirical formula	$C_{11}H_{18}O_3$
Formula weight [g mol^{-1}]	198.262
Crystal color, habit	Colorless, prism
Crystal dimensions [mm]	$0.50 \times 0.25 \times 0.25$
Temperature [K]	296
Crystal system	Monoclinic
Space group	$P\,2_1$
Z	2
Reflections for cell determination	1070
2θ-Range [°]	6.28 – 54.26
Unit-cell parameters:	
a [Å]	6.504(2)
b [Å]	7.056(4)
c [Å]	11.832(5)
α [°]	90.00
β [°]	94.10(2)
γ [°]	90.00
V [Å^3]	541.6(4)
D_x [g cm^{-3}]	1.216
μ(MoK_α) [mm^{-1}]	0.087
$2\theta_{max}$ [°]	54.26
Total reflections	measured
1070	
Independent reflections	1070
Reflections used ($I > 2\sigma(I)$)	931
Parameters refined	
130	
Final R	0.0452
wR	0.1134
Extinction coefficient	0.142(19)
Δ_{max}/σ	0.000
Δ/ρ (max; min) [e Å^{-3}]	0.141; −0.150
Flack parameter	−1 (2)

[a]) Crystallographic data, excluding structure factors, for the structure of (8*S*)-**3** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-215546. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

REFERENCES

[1] H. Nishimura, K. Kaku, T. Nakamura, Y. Fukuzawa, J. Mizutani, *J. Agric. Biol. Chem.* **1982**, *46*, 319.
[2] H. Nishimura, K. Kobayashi, T. Unno, Jap. Pat. 60199804, 1985 (*Chem. Abstr.* **1986**, *104*, 83820g).
[3] Y. Asakawa, R. Matsuda, M. Tori, T. Hashimoto, *Phytochemistry* **1988**, *27*, 3861.
[4] Y. Asakawa, H. Takahashi, M. Toyota, Y. Noma, *Phytochemistry* **1991**, *30*, 3981.
[5] Y. Shono, K. Watanabe, H. Sekihachi, A. Kakimizu, M. Suzuki, N. Matsuo, U.S. Pat. 5130136, 1992 (*Chem. Abstr.* **1992**, *117*, 207191t).
[6] Y. Yamamoto, M. Kobayashi, Jap. Pat. 03133906, 1991 (*Chem. Abstr.* **1991**, *115*, 226183s).
[7] B. D. Lett, H. S. Kraus, PCT Int. Appl. WO9202136, 1992 (*Chem. Abstr.* **1992**, *117*, 2827h).
[8] K. Watanabe, Y. Shono, A. Kakimizu, A. Okada, N. Matsuo, A. Satoh, H. Nishimura, *J. Agric. Biol. Chem.* **1993**, *41*, 2164.

[9] A. Sato, H. Utamura, T. Nakada, H. Nishimura, *Biotech. Biochem*. **1995**, *59*, 1139.
[10] Y. Shono, Y. Takebayashi, T. Ishiwatari, Can. Pat. 2157955, 1995 (*Chem. Abstr*. **1996**, *125*, 3619h).
[11] H. Nishimura, Y. Noma, *ACS Symp. Ser*. **1996**, *637*, 173 (*Chem. Abstr*. **1996**, *125*, 299509u).
[12] Y. Yuasa, H. Tsuruta, Y. Yuasa, *Org. Process Res. Dev.* **2000**, *4*, 159.
[13] H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[14] O. Mancera, G. Rosenkranz, C. Djerassi, *J. Org. Chem*. **1951**, *16*, 192.
[15] D. Swern, J. T. Scanlan, G. B. Dickel, *Org. Synth*. **1963**, *IV*, 317.
[16] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang, *J. Org. Chem,* **1992**, *57*, 2768.

Received July 8, 2004