Access to (*S*)-2-Methyloxetane and the Precursor (*S*)-1,3-Butanediol of High Enantiomeric Purity

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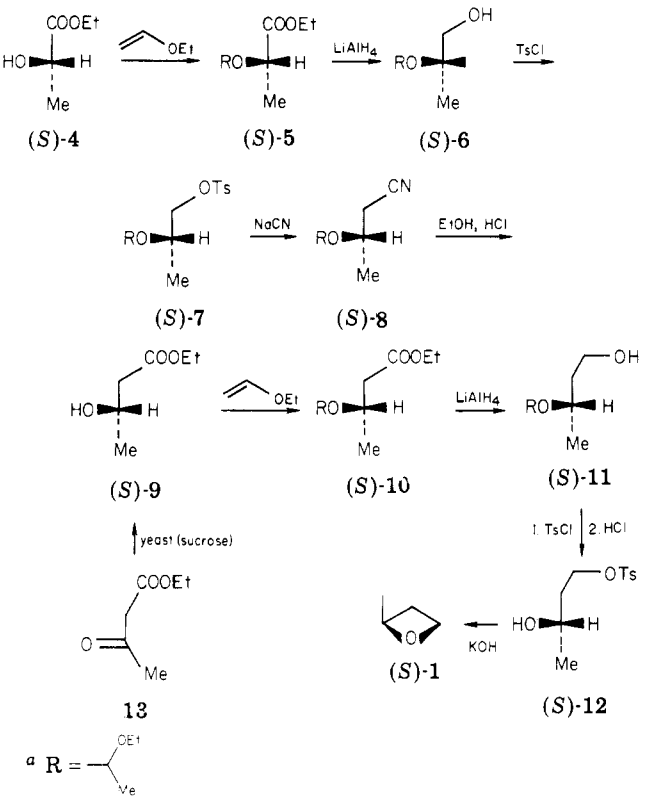
(*S*)-2-Methyloxetane (1) and its precursor (*S*)-1,3-butanediol (2) were prepared in low to moderate chemical yield with less than 0.5% racemization from (*S*)-ethyl lactate (4) and from (2*S*,3*S*)-allothreonine (14b). For the first time the enantiomeric purities of *both* the starting material and the product (1) were carefully determined by high-precision capillary gas chromatography on optically active resolving stationary phases. The validity of the *quadrant rule*, correlating the relative configuration of alkyloxiranes with the order of elution from manganese(II) bis[(1*R*)-3-(heptafluorobutyryl)camphorate] (3) by *complexation gas chromatography*, is also confirmed for 2-methyloxetane (1).

The availability of 2-methyloxetane (1) of quantitative enantiomeric composition is a prerequisite for the study of the chiral properties of optically active poly(2-methyloxetane).[1] The synthetic precursors of 1, i.e., 1,3-butanediol (2) and structurally related 1,3-bifunctional four-carbon-atom fragments, are also versatile building blocks in the design of chiral synthesis, e.g., for the preparation of optically pure natural compounds.[2-5] A precise method capable of determining the enantiomeric composition and absolute configuration of 1 is therefore warranted. We have recently shown[6] that 1 may be quantitatively resolved by *complexation gas chromatography*[7] on optically active manganese(II) bis[(1*R*)-3-(heptafluorobutyryl)camphorate] (3) by direct "head-space" analysis, i.e., without resorting to substrate derivatization, isolation, or purification (cf. Figure 1e). This methodology[8] permits the unambiguous determination of the enantiomeric purity of 1 obtained by various synthetic strategies. In addition, enantiomeric compositions and maximum specific rotations can also be extrapolated to synthetic precursors such as 1,3-butanediol (2) and derivatives, respectively. Finally, the order of chromatographic elution of the enantiomers of 1 on the optically active stationary phase 3 derived from (1*R*)-(+)-camphor can be correlated with the configuration at the chiral carbon atom and compared with that of alkyl-substituted oxiranes. This, eventually, leads to an elaboration of a previously proposed *quadrant rule* for predicting absolute configurations of alkyl-substituted cyclic ethers.[9]

We describe here the preparation of the enantiomers of 1 in low to moderate chemical but high enantiomeric yield from readily available chiral precursors, e.g., from ethyl lactate (4), ethyl 3-hydroxybutanoate (9), threonine (14a), and allothreonine (14b). Novel in the present work is the exact gas chromatographic determination of enantiomeric compositions of *both* the starting materials and target molecules, providing a clear assessment of stereospecificities and of mechanistic aspects.

Scheme I[a]



(*S*)-(+)-1,3-Butanediol (2), the inherent precursor of 1, may be obtained by classical resolution with (−)-camphanic acid[2] or, on a larger scale, via microbial reduction of ethyl acetoacetate (13) by employing baker's yeast[10,11] and subsequent $LiAlH_4$ reduction of (*S*)-ethyl 3-hydroxybutanoate (9).[2,3,5] Unfortunately, an unacceptably high bias for the quoted optical rotations for 9 is found in the literature,[1-3,5,10-13] and the reported *enantiomeric* purity, determined by chiral NMR shift reagents, varies from 70%[13] to >97%.[3] We therefore sought independent evidence for the enantiomeric yield generated in the enzymatic yeast-catalyzed reduction of 13 by the precise determination of the enantiomeric composition of (*S*)-1

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(3) A. I. Meyers and R. A. Amos, *J. Am. Chem. Soc.*, 102, 870 (1980).
(4) K. Hintzer, R. Weber, and V. Schurig, *Tetrahedron Lett.*, 22, 55 (1981).
(5) K. Mori, *Tetrahedron*, 37, 1341 (1981).
(6) V. Schurig and R. Weber, *J. Chromatogr.*, 217, 51 (1981).
(7) V. Schurig, *Chromatographia*, 13, 263 (1980).
(8) V. Schurig, B. Koppenhoefer, and W. Bürkle, *J. Org. Chem.*, 45, 538 (1980).
(9) V. Schurig, B. Koppenhoefer, and W. Bürkle, *Angew. Chem., Int. Ed. Engl.*, 17, 937 (1978).
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(11) B. S. Deol, D. D. Ridley, and G. W. Simpson, *Aust. J. Chem.*, 29, 2459 (1976).
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(13) G. Fráter, *Helv. Chim. Acta*, 62, 2825 (1979).

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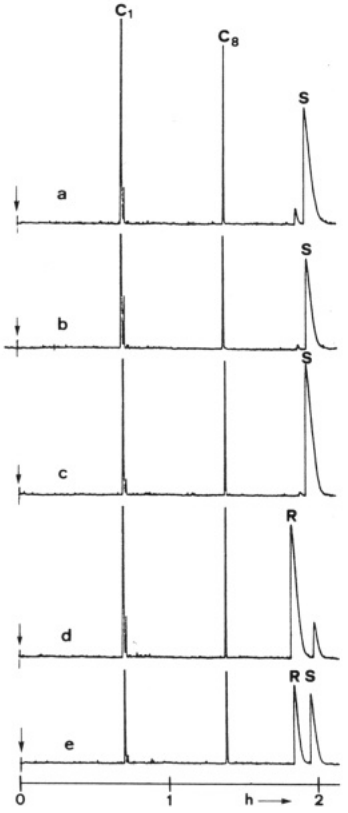


Figure 1. Enantiomer resolution and determination of enantiomeric compositions of 2-methyloxetane (**1**) by complexation gas chromatography on manganese(II) bis[(1*R*)-3-(heptafluorobutyryl)camphorate] (**3**) in squalane at 75 °C: (a) (*S*)-**1** (89.2% ee) obtained from yeast reduction of ethyl acetoacetate (**13**) via (*S*)-ethyl 3-hydroxybutanoate (**9**); (b) (*S*)-**1** (96.1% ee) obtained from (*S*)-ethyl lactate (**4**, 96.6% ee); (c) (*S*)-**1** (99.0% ee) obtained from (2*S*,3*S*)-allothreonine (**14b**, >99.7% ee); (d) (*R*)-**1** (73.6% ee) obtained from (2*S*,3*R*)-threonine (**14a**, >99.8% ee); (e) racemic **1** (peak ratio 1:1); C_1 = methane, C_8 = *n*-octane (coinjected).

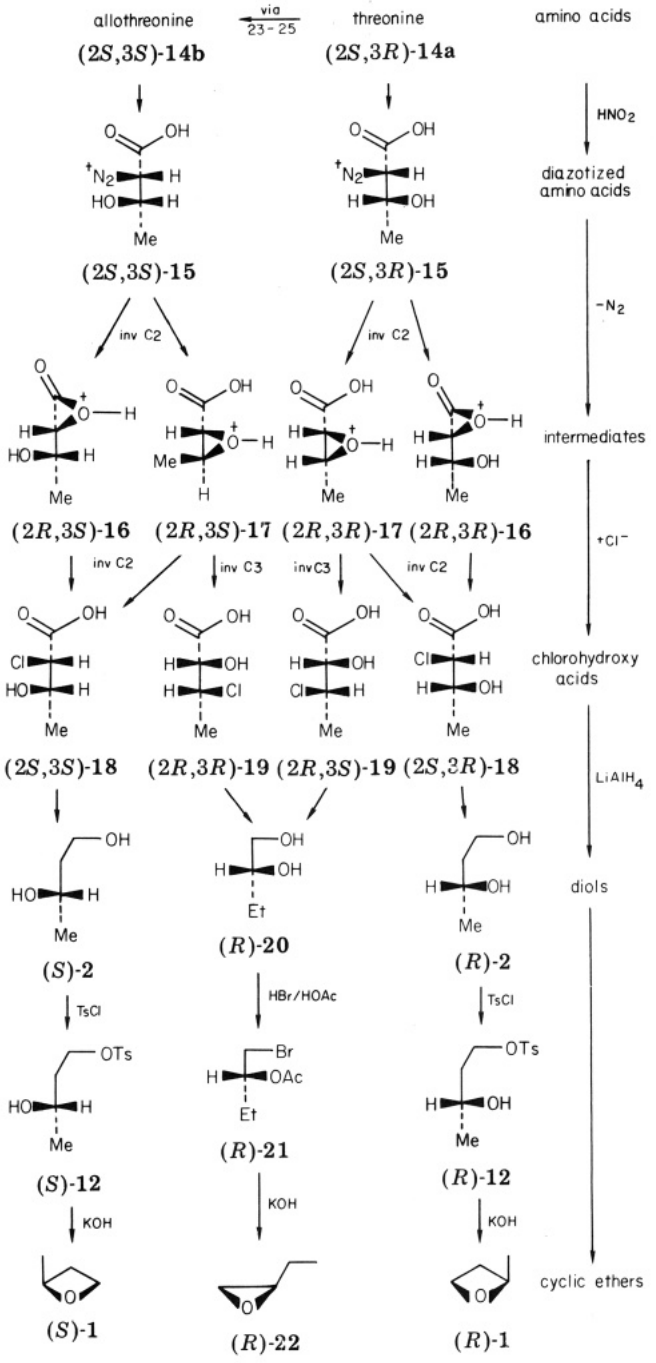
prepared as shown in Scheme I.

Complexation gas chromatography on optically active complex **3** revealed that (*S*)-**1** derived from **13** was contaminated by 5.4% of the *R* antipode (cf. Figure 1a). Thus, the β-hydroxy ester **9** as well as the derivatives of 1,3-butanediol, i.e., **11** and **12**, were only 89.2 ± 0.5% enantiomerically pure (vide infra). Despite considerable efforts to improve fermentation conditions, we were unable to achieve the high enantiomeric purity of **9** (i.e., >97%) as reported previously.[3] Our results can, however, be reconciled with results of fermentation experiments by Mori,[5] who found 86–87% ee for **9** determined by GLC as well as (lanthanide shifts) ^{1}H NMR for the α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) ester.[14]

At this point it became necessary to establish that no racemization took place during the conversion of (*S*)-**9** to (*S*)-**1** via **11** and **12**. Thus, as shown in Scheme I, the three-carbon building block (*S*)-ethyl lactate (**4**) with known enantiomeric composition (i.e., 96.6 ± 0.2% ee[15]) was converted in five steps by chain extension to (*S*)-ethyl 3-hydroxybutanoate (**9**, overall chemical yield 20%). Alcohol protection, $LiAlH_4$ reduction, and cyclization gave (*S*)-**1** with 96.1 ± 0.5% ee (cf. Figure 1b). This result demonstrated that essentially no racemization occurred during the nine-step transformation of (*S*)-**4** to (*S*)-**1** which is corroborated by the high enantiomeric purity of the insect pheromone (5*S*,7*S*)-7-methyl-1,6-dioxaspiro[4.5]-decane prepared from (*S*)-**4** via (*S*)-**9**.[4]

Recently we have described a useful route to (*R*)-alkyloxiranes from (*S*)-amino acids.[16] Thus, diazotization in the presence of chloride affords 2-chloro carboxylic acids with *retention* of configuration, whereas reduction of the carboxylic group with $LiAlH_4$, followed by alkaline-mediated cyclization of the chlorohydrins, yielded the epoxides with *inversion* of configuration. It has been noted[16]

Scheme II



(14) **9** (94–97% ee) was reported by interrupting fermentation (footnote in ref 5).

(15) Obviously, despite its frequent use for "chiral pool" syntheses, the correct enantiomeric purity of (*S*)-(−)-ethyl lactate (**4**) has never been measured. (*S*)-(−)-**4** (Fluka AG, CH Buchs, labeled $[\alpha]^{20}_D$ −11.0 ± 0.3°) was derivatized with *tert*-butyl isocyanate. Seven GC measurements on Chirasil-Val [cf. H. Frank, G. J. Nicholson, and E. Bayer, *J. Chromatogr. Sci.*, **15**, 174 (1977)] gave 96.6 ± 0.2% ee (J. Gerhard, Diplomarbeit, Universität Tübingen, 1981).

(16) B. Koppenhoefer, R. Weber, and V. Schurig, *Synthesis*, 316 (1982).

that prolonged treatment of the chloro acids with $LiAlH_4$ leads to hydrogenolysis of the halo–carbon bond, affording primary alcohols. This reaction, when applied to 2-amino-3-hydroxy acids with an additional asymmetric center in the side chain, is useful in its own right as it provides a convenient entry to chiral 1,3-diols and their derivatives.

Consequently, we investigated the transformation of (2*S*,3*R*)-threonine (**14a**) and the epimer (2*S*,3*S*)-allothreonine (**14b**)[17] into (*R*)- and (*S*)-1,3-butanediol (**2**) and into (*R*)- and (*S*)-2-methyloxetane (**1**), respectively. As summarized in Scheme II, some peculiarities were encountered in the course of the reaction. Thus, it was observed that nitrosation ($NaNO_2$, KCl, H_2SO_4[18]) of both (2*S*,3*R*)-threonine (**14a**) and (2*S*,3*S*)-allothreonine (**14b**) afforded not only 2-chloro-3-hydroxybutanoic acid (**18**) but also rearranged 3-chloro-2-hydroxybutanoic acid (**19**) (ratio 4:1, determined by ^{13}C NMR). $LiAlH_4$ reduction of the crude mixture of **18** and **19** furnished 1,3-butanediol (**2**) and 1,2-butanediol (**20**) which were separated by Spaltrohr distillation. 1,3-Butanediol (**2**, 18% from **14**) was monotosylated to give 1-(tosyloxy)butan-3-ol (**12**) and 10% of the isomer 3-(tosyloxy)butan-1-ol (**12a**). It was essential for the stereochemical integrity of the subsequent cyclization to remove (**12a**) by liquid chromatography on silica. 1-(Tosyloxy)butan-3-ol (**12**) was reacted with powdered KOH to yield 2-methyloxetane (**1**, 38% from **12**).[19] The side-product 1,2-butanediol (**20**, 3% from **14**) was transformed by the HBr/HOAc method[20] to ethyloxirane (**22**).

Complexation gas chromatography on optically active **3** allowed the precise (i.e., ±0.5%) determination of the enantiomeric purities of the cyclic ethers prepared. Thus, (*R*)-2-methyloxetane (**1**) was formed from (2*S*,3*R*)-threonine (**14a**, >99.8% ee[21]) with an enantiomeric purity of only 73.6%. In contrast, (*S*)-2-methyloxetane (**1**) was obtained from the *epimer* (2*S*,3*S*)-allothreonine (**14b**, >99.7% ee[21]) with almost quantitative enantiomeric yield, i.e., 99.0% ee (cf. Figure 1c; chemical yield 4.9% from **14b**). Likewise, the antipode (*R*)-2-methyloxetane (**1**) was obtained from (2*R*,3*R*)-allothreonine (**14b**, >99.7% ee) with 98.8% ee. As for the side reaction, ethyloxirane (**22**) with the inverted configuration *R* was obtained both from (2*S*,3*R*)-threonine (**14a**) with 96.6% ee and from (2*S*,3*S*)-allothreonine (**14b**) with 98.0% ee. These results merit the following comments.

Nucleophilic displacement of dinitrogen from diazotized α-amino acids by fluoride[22] or chloride[23] is known to proceed with nearly complete[24] (net) retention of configuration through anchimeric assistance of the carboxylic group via a (protonated) α-lactone (**16**;[25] cf. Scheme II). In the nitrosation of 2-amino-3-hydroxy carboxylic acids such as **14** the hydroxy group may also participate as a neighboring group, giving rise to the intermediate formation of an (protonated) oxirane (**17**)[26] as indicated in Scheme II. Stereospecific back-side attack of chloride on the oxirane at C2 leads to **18** with (net) retention of configuration at C2. Likewise, chloride attack at C3 provides a mechanistic rationale for the observed occurrence of the rearranged acid **19** with inverted configuration at C2, eventually leading to the formation of (*R*)-ethyloxirane (**22**) both from (2*S*,3*R*)-threonine (**14a**) and from (2*S*,3*S*)-allothreonine (**14b**).

In the synthesis of 2-methyloxetane (**1**) from **14a** or **14b** one is only concerned with the stereochemistry at C3. The striking *diastereoselective* effect, i.e., the observation of almost complete stereointegrity in the conversion of allothreonine (**14b**) to 2-methyloxetane (**1**) (as demonstrated for both enantiomers) vs. 13.2% racemization in the transformation of the epimer threonine (**14a**) to **1** is not fully comprehended at present and therefore awaits further mechanistic investigations.[27] GC/MS analysis of the methyl esters of **18** and **19** showed the following results: from threonine (**14a**) 75.5% *threo*-**18**, 6.5% *erythro*-**18**, and 18% *threo*-**19** were formed, whereas from allothreonine (**14b**) 81% *erythro*-**18** and 19% *erythro*-**19** were formed.

The synthesis of (*S*)-2-methyloxetane (**1**) and of the precursor (*S*)-1,3-butanediol (**2**) from (2*S*,3*S*)-allothreonine (**14b**) is suited for practical purposes (although the chemical overall yield is low) as it is free of experimental difficulties and since it affords essentially enantiomerically pure compounds. From the precise knowledge of the enantiomeric purity of 2-methyloxetane (**1**, 99.0% ee) determined via **3** the maximum optical rotation can now be extrapolated to α^{20}_D +34.7 ± 0.5° (neat) for (*S*)-2-methyloxetane (**1**) and to α^{20}_D +31.2 ± 0.9° (neat) or $[\alpha]^{20}_D$ +30.5 ± 0.6° (*c* 1, EtOH), [lit.[2] $[\alpha]^{20}_D$ +29° (*c* 1, EtOH)] for (*S*)-1,3-butanediol (**2**).

Recently we have correlated the molecular configuration of chiral alkyl-substituted oxiranes, i.e., of methyloxirane and *trans*-2,3-dimethyloxirane, with the order of elution from a gas chromatographic column containing an optically active metal chelate of defined chirality.[9,16] The validity of an empirical *quadrant rule*,[9] predicting *S* configuration to the oxirane having longer retention times than the *R* enantiomers on **3** (or the corresponding nickel chelate) derived from (1*R*)-(+)-camphor, has since been confirmed for additional substrates [viz., ethyloxirane,[28] isopropyloxirane,[16] *sec*-butyloxirane (both diastereomers),[16] *tert*-butyloxirane,[29] and trimethyloxirane[30]]. One objective of the present work was to test the applicability of the *quadrant rule* to oxetanes such as **1**. As shown in Figure 1, (*S*)-2-methyloxetane (**1**), when prepared from (*S*)-ethyl lactate (**4**) or from (2*S*,3*S*)-allothreonine (**14b**) via transformations of established stereochemistry (vide supra), is eluted as the second peak from **3** derived from (1*R*)-(+)-camphor. Thus, the *quadrant rule*, within certain

(17) (2*S*,3*S*)-Allothreonine (**14b**) is obtained from (2*S*,3*R*)-threonine (**14a**) in a convenient four-step procedure (chemical yield 67%); see the Experimental Section [cf.: D. F. Elliot, *J. Chem. Soc.*, 62 (1950); J. L. Morell, P. Fleckenstein, and E. Gross, *J. Org. Chem.*, **42**, 355 (1977)].

(18) H. Shimasaki, *Nippon Kagaku Zasshi*, **87**, 459 (1966); *Chem. Abstr.*, **65**, 15299 (1966).

(19) Oguni[1] prepared (*R*)-**1** from (*R*)-**2** (optical purity 76%) via a mixture of 1-chloro-3-acetoxybutane and isomeric 3-chloro-1-acetoxybutane [cf. S. Searles, K. A. Pollart, and F. Block, *J. Am. Chem. Soc.*, **79**, 952 (1957)]. We found by complexation gas chromatography of **1** on optically active **3** that this route was accompanied by approximately 1% racemization.

(20) B. T. Golding, D. R. Hall, and S. Sakrikar, *J. Chem. Soc., Perkin Trans. 1*, 1214 (1973).

(21) Determined on Chirasil-Val according to H. Frank, W. Woiwode, G. Nicholson, and E. Bayer, *Liebigs Ann. Chem.*, 354 (1981).

(22) G. A. Olah and J. Welch, *Synthesis*, 652 (1974); R. Keck and J. Rétey, *Helv. Chim. Acta*, **63**, 769 (1980); F. Faustini, S. DeMunari, A. Panzeri, V. Villa, and C. A. Gandolfi, *Tetrahedron Lett.*, **22**, 4533 (1981).

(23) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. Rao, *Nature (London)*, **166**, 179 (1950); S.-C. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.*, **76**, 6054 (1954).

(24) It has been proved[9,16] that racemization does not exceed 2.7% in the conversion (with retention of configuration) of 2-amino carboxylic acids to 2-chloro carboxylic acids.

(25) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939).

(26) M. Ketola, M. Lyytinen, M. Hotokka, and K. Pihlaja, *Acta Chem. Scand., Ser. B*, **32**, 743 (1978).

(27) The authors are indebted to one referee and to Professor Dr. W. Kirmse, University of Bochum, West Germany, for valuable comments.

(28) B. Koppenhoefer, K. Hintzer, R. Weber, and V. Schurig, *Angew. Chem., Int. Ed. Engl.*, **19**, 471 (1980).

(29) Prepared according to M. Sepulchre, A. Khalil, and N. Spassky, *Makromol. Chem.*, **180**, 131 (1979).

(30) By indirect evidence via asymmetric epoxidation of 2-methyl-2-butene: H. B. Kagan, H. Mimoun, C. Mark, and V. Schurig, *Angew. Chem., Int. Ed. Engl.*, **18**, 485 (1979).

limitations,[31] permits the gas chromatographic correlation and assignment of molecular configurations for three- and four-membered cyclic ethers with a minute amount of sample (~1 ng), independently of chiroptical evidence.

Experimental Section

Instrumentation. ^{13}C NMR spectra were recorded on a Bruker HFX-90 and on a WP-80 spectrometer (δ values are given in parts per million from Me_4Si). Mass spectra were recorded on a Varian MAT-711 spectrometer. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Gas chromatography was performed with a Carlo-Erba Fractovap 2101, provided with an FID and suitable for open-tubular column operation. Enantiomeric compositions of amino and hydroxy carboxylic acids were measured after appropriate derivatization[15,21] on a 20 m × 0.3 mm glass capillary column coated with Chirasil-Val,[15,21] which was kindly provided by Professor E. Bayer and G. J. Nicholson, University of Tübingen. Peaks were integrated with a Spectra Physics (System I) electronic integrator. Enantiomeric compositions of cyclic ethers were measured on a 160 m × 0.4 mm stainless-steel capillary column coated with 0.13 *m* manganese(II) bis[(1*R*)-3-(heptafluorobutyryl)camphorate] in squalane at 75 °C[6] injector temperature 150 °C, flow rate 4.5 mL of N_2/min). Peak areas were measured by Xeroxing the chromatograms (obtained with increased chart speed and increased electrometer attenuation to produce large and broad peak recordings) and weighing the paper corresponding to the respective peak areas. The relative error of area measurement was at the most ±1%.

(*S*)-Ethyl 2-(1-Ethoxyethoxy)propanoate (5). (*S*)-Ethyl lactate (**4**: 88.5 g, 0.75 mol; Fluka; $[\alpha]^{20}_D$ −11.0 ± 0.3°; 96.6 ± 0.2% ee[15]) was protected[12] with ethyl vinyl ether (260 mL, 2.7 mol) to give **5**: 135 g (95%); bp 74 °C (12 mmHg); α^{20}_D −80.6° (neat), $[\alpha]^{20}_D$ −78.9° (*c* 4.4, $CHCl_3$); 55:45 mixture of diastereomers; MS, *m/e* (relative intensity) 175 (M − 15), 73 (100); ^{13}C NMR ($CDCl_3$) 172.0, 171.7, 98.3, 98.1, 68.7, 59.7, 59.3, 59.0, 18.9, 18.6, 17.7, 14.2, 13.1.

(*S*)-2-(1-Ethoxyethoxy)propan-1-ol (6). Compound **5** (125 g, 0.66 mol) was reduced[12] with $LiAlH_4$ (16 g, 0.42 mol) in 1 L of diethyl ether under dry N_2 to give **6**: 95 g (97%); bp 71 °C (12 mmHg); α^{20}_D +21.7° (neat) [lit.[12] $[\alpha]^{20}_D$ +11.2° (neat)]; MS, *m/e* (relative intensity) 133 (M − 15), 73 (100); ^{13}C NMR ($CDCl_3$) 99.4, 75.2, 73.0, 66.8, 66.5, 60.7, 60.5, 20.5, 20.3, 17.5, 17.0, 15.1.

(*S*)-1-Tosyl-2-(1-ethoxyethoxy)propane (7). A solution of tosyl chloride (120 g, 0.63 mol) in 400 mL of dichloromethane was added to a solution of **6** (89 g, 0.6 mol) in 200 mL of pyridine at −5 °C. Stirring was continued for 2 h at −5 °C and for 10 h at 20 °C. The mixture was poured into ice–water and extracted with dichloromethane. The organic layer was washed with water and dried over $MgSO_4$. Concentration in vacuo afforded **7** as a colorless oil: 153 g (84%); MS, *m/e* (relative intensity) 287 (M − 15), 91 (100); ^{13}C NMR ($CDCl_3$) 144.1, 132.7, 129.2, 127.1, 99.0, 97.8, 72.3, 68.7, 68.1, 59.6, 59.3, 20.5, 19.6, 17.1, 16.3, 14.4.

(*S*)-3-(1-Ethoxyethoxy)butyronitrile (8). To a solution of **7** (75.3 g, 0.25 mol) in 450 mL of dimethyl sulfoxide was carefully added 23.8 g (0.49 mol) of finely powdered sodium cyanide under dry N_2. The temperature was kept below 27 °C, and the addition required 10 h. After being stirred for an additional 80 h at 20 °C, the reaction mixture was poured into 2.2 L of ice–water and extracted thoroughly with 4.5 L of dichloromethane. The organic layer was washed three times with water, dried over $MgSO_4$, and distilled to give **8**: 19 g (49%); bp 93 °C (17 mmHg); α^{20}_D −17.5° (neat), $[\alpha]^{20}_D$ −9.5° (*c* 1, $CHCl_3$); IR (film) $\nu_{C\equiv N}$ 2250 cm^{-1}; ^{13}C NMR ($CDCl_3$) 116.4, 97.5, 96.9, 66.0, 65.7, 58.6, 58.3, 24.2, 23.6, 19.5, 18.9, 18.5, 13.8.

(*S*)-Ethyl 3-Hydroxybutanoate (9). A stream of dry hydrogen chloride was passed for 3 h into the solution of **8** (32 g, 0.2 mol) in 500 mL of ethanol containing 3.5 mL of water. The solvent was removed by distillation within 3 h. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with aqueous $NaHCO_3$ solution and with water and dried over Na_2SO_4. Distillation provided **9**: 12.5 g, (47%); bp 71 °C (12 mmHg); purity 99.5% (by GLC); α^{20}_D +16.6° (neat), $[\alpha]^{20}_D$ +41.6° (*c* 1, $CHCl_3$) [lit.[3] $[\alpha]^{20}_D$ +41.7° ($CHCl_3$).

Fermentation of 80 mL of ethyl acetoacetate (**13**) by baker's yeast (400 g) and sucrose (1000 g) according to the literature procedure[10-13] afforded **9**: 47 g (56%); purity 99.4% (by GLC); α^{20}_D +16.0° (neat), $[\alpha]^{20}_D$ +39.5° (*c* 1.3, $CHCl_3$); ^{13}C NMR ($CDCl_3$) 172.0, 63.7, 59.9, 42.9, 22.1, 13.5.

(*S*)-Ethyl 3-(1-Ethoxyethoxy)butanoate (10). Trifluoroacetic acid (0.25 mL) was added dropwise to the solution of **9** (9.3 g, 0.07 mol) in ethyl vinyl ether (30 mL, 0.31 mol) at −5 °C under dry N_2. After the mixture was stirred for 18 h at −5 °C and 2 h at 20 °C, 9 mL of triethylamine was added, and stirring was continued for 1 h. The ethyl vinyl ether was removed in vacuo, and the reaction mixture was dissolved in diethyl ether. The ether solution was washed with water and brine and dried over $MgSO_4$. Distillation afforded **10**: 13.3 g (93%); bp 94 °C (12 mmHg); α^{20}_D +7.6° (neat), $[\alpha]^{20}_D$ +7.0° (*c* 2.3, $CHCl_3$).

In the same way, the fermentation product (**9**) furnished **10**: α^{20}_D +7.3° (neat), $[\alpha]^{20}_D$ +6.8° (*c* 2.4, $CHCl_3$); MS, *m/e* (relative intensity) 189 (M − 15), 73 (100); ^{13}C NMR ($CDCl_3$) 171.2, 99.6, 98.1, 69.8, 68.2, 60.1, 59.9, 42.6, 42.2, 21.2, 20.5, 20.3, 15.0, 14.0.

(*S*)-3-(1-Ethoxyethoxy)butan-1-ol (11). A solution of **10** (12.5 g, 61 mmol) in 100 mL of diethyl ether was added carefully to a slurry of $LiAlH_4$ (2.7 g, 71 mmol) in 200 mL of diethyl ether under dry N_2. After being refluxed with stirring for 5 h, the mixture was quenched by addition of 3 mL of water (**Caution!**), 3 mL of 2 N KOH, and 6 mL of water. The white precipitate was filtered and thoroughly extracted by refluxing with diethyl ether. The combined ether solution was dried over $MgSO_4$ and K_2CO_3. Distillation provided **11**: 8.7 g (88%); bp 95 °C (12 mmHg); α^{20}_D +40.8° (neat), $[\alpha]^{20}_D$ +68.7° (*c* 1, $CHCl_3$).

Compound **10** obtained from the fermentation product (**9**) was reduced in the same way to give **11**: α^{20}_D +40.4° (neat), $[\alpha]^{20}_D$ +68.0° (*c* 1.1, $CHCl_3$); MS, *m/e* (relative intensity) 147 (M − 15), 73 (100); ^{13}C NMR ($CDCl_3$) 99.0, 97.7, 70.4, 69.3, 60.3, 59.7, 58.8, 58.5, 39.0, 20.6, 20.2, 20.0, 19.7, 14.7.

(*S*)-1-(Tosyloxy)butan-3-ol (12). Tosyl chloride (9.5 g, 50 mmol) was added in portions to a solution of **11** (8.1 g, 50 mmol) in 35 mL of dry pyridine and 60 mL of dichloromethane at −10 °C. After being stirred for 10 h at 0 °C and for 5 h at 20 °C, the reaction mixture was poured into chilled diluted hydrochloric acid. The mixture was then extracted with dichloromethane. The organic layer was washed with water, aqueous $NaHCO_3$ solution, and brine and then concentrated in vacuo. The residue was dissolved in 100 mL of tetrahydrofuran, and 15 mL 2 N hydrochloric acid was added to remove the protecting group. After being stirred for 7 h at 20 °C (deprotection was monitored by TLC), the reaction mixture was concentrated. The residue was diluted with chloroform, washed with aqueous $NaHCO_3$ solution and with brine, and then dried over $MgSO_4$. Chromatography on silica (*n*-hexane/ethyl acetate, 3:2) afforded **12**: 9.6 g (79%); MS, *m/e* (relative intensity) 244 (M^+), 172 (100); ^{13}C NMR ($CDCl_3$) 144.7, 132.9, 129.7, 127.7, 67.8, 63.9, 37.8, 23.4, 21.5.

(2*S*,3*R*)-Threonine Methyl Ester Hydrochloride (23). To 1700 mL of methanol was added dropwise thionyl chloride (200 g, 1.68 mol) at −10 °C. (2*S*,3*R*)-Threonine (**14a**; 200 g, 1.68 mol) was added to the mixture in portions at −10 °C. After being stirred for 72 h at 20 °C, the reaction mixture was concentrated in vacuo. The colorless oil (**23**, 284 g) was used without purification: ^{13}C NMR (CH_3OD) 168.7, 65.5, 58.9, 53.0, 19.7.

(2*S*,3*R*)-*N*-Benzoylthreonine Methyl Ester (24). Crude **23** (284 g, 1.68 mol) in 1800 mL of chloroform was treated with triethylamine (170 g, 1.68 mol) at −5 °C. After 1.5 h of vigorous stirring, triethylamine (187 g, 1.85 mol) and then benzoyl chloride (235.6 g, 1.68 mol) were added at −5 °C. Stirring was continued for 7 h, after which time the temperature was allowed to increase to 2 °C. The reaction mixture was washed with water, three times with aqueous citric acid, twice with aqueous $NaHCO_3$ solution, and with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the residue was recrystallized from chloroform and diethyl ether to give **24**: 351 g (88%); mp 97 °C; $[\alpha]^{20}_D$ +23.8° (*c* 1, EtOH) [lit.[17] $[\alpha]^{20}_D$ +23.2° (EtOH)].

For **23** from (2*R*,3*S*)-threonine (**14a**): $[\alpha]^{20}_D$ −23.6° (*c* 1, EtOH); MS, *m/e* (relative intensity) 220 (M − 17), 193 (M − 44), 105 (100); ^{13}C NMR ($CDCl_3$) 171.0, 168.1, 133.3, 131.5, 128.2, 126.9, 67.5, 57.9, 52.1, 19.8. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37;

(31) An inconsistency of the *quadrant rule* has been observed for methyl- vs. *trans*-2,3-dimethylthiirane (V. Schurig and W. Bürkle, *J. Am. Chem. Soc.*, in press.

N, 5.90. Found: C, 60.96; H, 6.46; N, 5.94.

(4*S*,5*S*)-4-(Methoxycarbonyl)-5-methyl-2-phenyl-Δ^2-oxazoline (25). According to the literature[17] **24** (310 g, 1.31 mol) was treated carefully with 150 mL of thionyl chloride to give **25**: 267 g (92%); mp 74–75 °C; $[\alpha]^{20}_D$ +63.3° (*c* 1.1, EtOH) [lit.[17] $[\alpha]^{20}_D$ +69.2° (EtOH)].

For **24** from (2*R*,3*S*)-threonine (**14a**): $[\alpha]^{20}_D$ −62.9° (*c* 1.1, EtOH); MS, *m/e* (relative intensity) 219 (M^+), 160 (100); ^{13}C NMR ($CDCl_3$) 170.3, 166.0, 131.6, 128.3, 128.2, 127.1, 77.5, 71.5, 51.8, 16.0. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.79; H, 6.01; N, 6.42.

(2*S*,3*S*)-Allothreonine (14b). According to the literature[17] **25** (235 g, 1.15 mol) was hydrolyzed in 1 L of 6 N hydrochloric acid to give **14b**: 127 g (92%); $[\alpha]^{20}_D$ +9.6° (*c* 1, water), $[\alpha]^{20}_D$ +32.3° (*c* 1, 1 N HCl) [lit.[17] $[\alpha]^{20}_D$ +32.5° (*c* 8.2, 1 N HCl)]; >99.7% ee.[21]

(2*R*,3*R*)-Allothreonine (14b) was prepared from (2*R*,3*S*)-**14a** in the same way: $[\alpha]^{20}_D$ −9.9° (*c* 1; water), $[\alpha]^{20}_D$ −33.2 (*c* 1, 1 N HCl); >99.7% ee;[21] ^{13}C NMR (1 N DCl) 172.7, 67.7, 61.0, 19.5. Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.44; H, 7.70; N, 11.47.

(*S*)-1,3-Butanediol (2) and (*R*)-1,2-Butanediol (20). A solution of sodium nitrite (60 g, 0.87 mol) in 100 mL of water was added within 2 h to a mixture of (2*S*,3*S*)-**14b** (59.6 g, 0.5 mol)and 125 g of potassium chloride in 900 mL of 1 N sulfuric acid at −3 °C. The mixture was stirred for 3 h at −3 °C, and again a solution of sodium nitrite (6 g) in 10 mL of water was added. Stirring was continued for 18 h, after which time the reaction temperature was allowed to increase to 20 °C. $NaHCO_3$ (150 g) was added to the solution (foaming by gas evolution) until pH 1.5 was reached. Water was removed in vacuo at 40 °C. The residue was extracted thoroughly by refluxing with ethyl acetate (2 L). The organic phase was concentrated in vacuo to yield 42.5 g of a yellow oil. As determined by ^{13}C NMR, the crude mixture contained 2-chloro-3-hydroxybutanoic acid [18: ^{13}C NMR (CD_3OD) 171.7, 69.4, 62.9, 18.9] and 3-chloro-2-hydroxybutanoic acid [19: ^{13}C NMR (CD_3OD) 175.5, 75.4, 69.7, 17.4]; derivatization of the crude mixture of **18** and **19** with diazomethane and GC/MS analysis showed the following results. For the methyl ester of **18**: 81%; MS, *m/e* (relative intensity) 108, 110 (2:1, 1 Cl, McLafferty, 100). For the methyl ester of **19**: 19%; MS, *m/e* (relative intensity) 122, 124 (2:1, 1 Cl, M + 1 − CH_3O), 94, 96 (2:1, 1 Cl 100).

The yellow oil (42.5 g) was dissolved in 200 mL of tetrahydrofuran, and the solution was added dropwise to a vigorously stirred suspension of $LiAlH_4$ (45 g, 1.18 mol) in 800 mL of tetrahydrofuran under dry N_2. After being refluxed for 40 h with stirring, the mixture was cooled and quenched by addition of 45 mL of water (**Caution**!), 45 mL of 2 N KOH, and 90 mL of water. The white precipitate was extracted in a Soxhlet apparatus with tetrahydrofuran. The solution was dried over Na_2SO_4 and concentrated in vacuo, and the two diol fractions were distilled by means of a Spaltrohr column (HMS 300; Fischer, D 5309 Meckenheim, West Germany; approximately 50 theoretical plates). Between 92 and 99 °C (12 mmHg) a mixture of **2** and **20** was collected. At 99–100 °C (12 mmHg) **2** (7.5 g) was obtained. For separation of the mixed fraction monobenzoylation was carried out (molar ratio of diol/benzoyl chloride was 1:1 in pyridine; stirring for 12 h at 25 °C). Chromatography on silica (*n*-hexane/ethyl acetate, 3:2) gave (*R*)-1-(benzoyloxy)-2-ol and (*S*)-1-(benzoyloxy)butan-3-ol. Reductive cleavage with $LiAlH_4$ (50% molar excess, refluxing in diethyl ether for 8 h) furnished **2** (0.7 g) and **20** (1.2 g). The chemical yield with respect to **14b** was 18% of **2** and 3% of the side product **20**.

1,3-Butanediol (2): from (2*S*,3*S*)-allothreonine (**14b**), $[\alpha]^{20}_D$ +29.8° (*c* 1, EtOH), α^{20}_D +30.0° (neat); from (2*R*,3*R*)-allothreonine (**14b**), $[\alpha]^{20}_D$ −29.9° (*c* 1.2, EtOH), α^{20}_D −30.3° (neat); from (2*S*,3*R*)-threonine (**14a**), $[\alpha]^{20}_D$ −21.5° (*c* 1, EtOH), α^{20}_D −22.2° (neat); from (*S*)-ethyl 3-hydroxybutanoate [**9**, obtained by yeast reduction of ethyl acetoacetate (**13**)], $[\alpha]^{20}_D$ +28.1° (*c* 1, EtOH), α^{20}_D +28.9° (neat); from (*S*)-ethyl lactate (**4**), $[\alpha]^{20}_D$ +29.1° (*c* 1.1, EtOH), α^{20}_D +29.9° (neat); ^{13}C NMR ($CDCl_3$) 67.0, 60.5, 40.1, 23.4.

1,2-Butanediol (20) from (2*S*,3*S*)-allothreonine (**14b**): $[\alpha]^{20}_D$ +15.0° (*c* 1.7, EtOH) [lit.[32] $[\alpha]^{20}_D$ +14.5° (*c* 6, EtOH); ^{13}C NMR ($CDCl_3$) 73.6, 66.1, 25.9, 9.8.

(*S*)-1-(Tosyloxy)butan-3-ol (12). Tosyl chloride (14.1 g, 74 mmol) in 30 mL of pyridine was added within 30 min to a solution of (*S*)-**2** (6.2 g, 68 mmol) in 20 mL of pyridine at −20 °C. The mixture was stirred for 1 h at −25 °C. Water (2 mL) was added, and stirring was continued for 20 min. The reaction mixture was diluted with 350 mL of benzene and washed with 2 N sulfuric acid. The organic layer was washed with aqueous Na_2CO_3 solution and with brine. Drying over Na_2SO_4 and concentration in vacuo afforded a colorless oil. After chromatography on silica (*n*-hexane/ethyl acetate, 3:2) to remove the side products (*S*)-3-(tosyloxy)butan-1-ol (**12a**) and (*S*)-1,3-ditosyloxybutane, (*S*)-1-(tosyloxy)butan-3-ol (**12**; 11.9 g, 72%) was collected. For removal of the volatiles, the oil was repeatedly dissolved in xylene and concentrated in vacuo.

2-Methyloxetane (1). Powdered potassium hydroxide (9 g) was added quickly to **12** (8.9 g, 36 mmol) with vigorous stirring. After the reaction mixture became solid, the temperature was raised to 80 °C, and **1** was collected in a −70 °C trap (Hg valve!) at reduced pressure (50 mmHg). Redistillation from CaH_2 afforded a colorless liquid (**1**; 1.0 g, 38%): from (2*S*,3*S*)-allothreonine (**14b**), α^{20}_D +34.4° (neat), 99.0% ee (Figure 1c); from (2*R*,3*R*)-allothreonine (**14b**), 98.8% ee; from (2*R*,3*R*)-allothreonine (**14b**) without separation of (*R*)-**12** and (*R*)-**12a** 96.0% ee; from (2*S*,3*R*)-threonine (**14a**), α^{20}_D −24.1° (neat), 73.6% ee (Figure 1d); from (*S*)-ethyl 3-hydroxybutanoate (**9**) via yeast reduction, α^{20}_D +30.6° (neat), 89.2% ee (Figure 1a); from (*S*)-ethyl lactate (**4**), α^{20}_D +34.0° (neat), 96.1% ee (Figure 1b); all samples were at least 99.5% pure (by GLC; cf. Figure 1a–d); MS, *m/e* (relative intensity) 72 (M^+), 43 (100); ^{13}C NMR ($CDCl_3$) 79.1, 67.4, 29.2, 23.9.

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Registry No. (*S*)-**1**, 75492-29-4; (*R*)-**1**, 81244-76-0; (*S*)-**2**, 24621-61-2; (*S*)-**2** (1-benzoate), 82659-86-7; (*R*)-**2**, 6290-03-5; (*S*)-**4**, 687-47-8; **5** (isomer 1), 64028-91-7; **5** (isomer 2), 64028-81-5; **6**, 82614-85-5; **7**, 64028-83-7; **8**, 77669-83-1; (*S*)-**9**, 56816-01-4; **10**, 82614-86-6; **11**, 82614-87-7; (*S*)-**12**, 82614-88-8; **13**, 141-97-9; (2*S*,3*R*)-**14a**, 72-19-5; (2*R*,3*S*)-**14a**, 632-20-2; (2*S*,3*S*)-**14b**, 28954-12-3; (2*R*,3*R*)-**14b**, 24830-94-2; (2*S*,3*S*)-**18**, 36977-29-4; (2*S*,3*S*)-**18** methyl ester, 82659-85-6; (2*S*,3*R*)-**19**, 82614-89-9; (2*S*,3*R*)-**19** methyl ester, 82614-90-2; (*R*)-**20**, 40348-66-1; (*R*)-**20** (1-benzoate), 82614-91-3; (2*S*,3*R*)-**23**, 39994-75-7; (2*S*,3*R*)-**24**, 79893-89-3; (4*S*,5*S*)-**25**, 82659-84-5; ethyl vinyl ether, 109-92-2.

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