A Useful Route to (*R*)-Alkyloxiranes of Defined Enantiomeric Purity from (*S*)-Amino Acids

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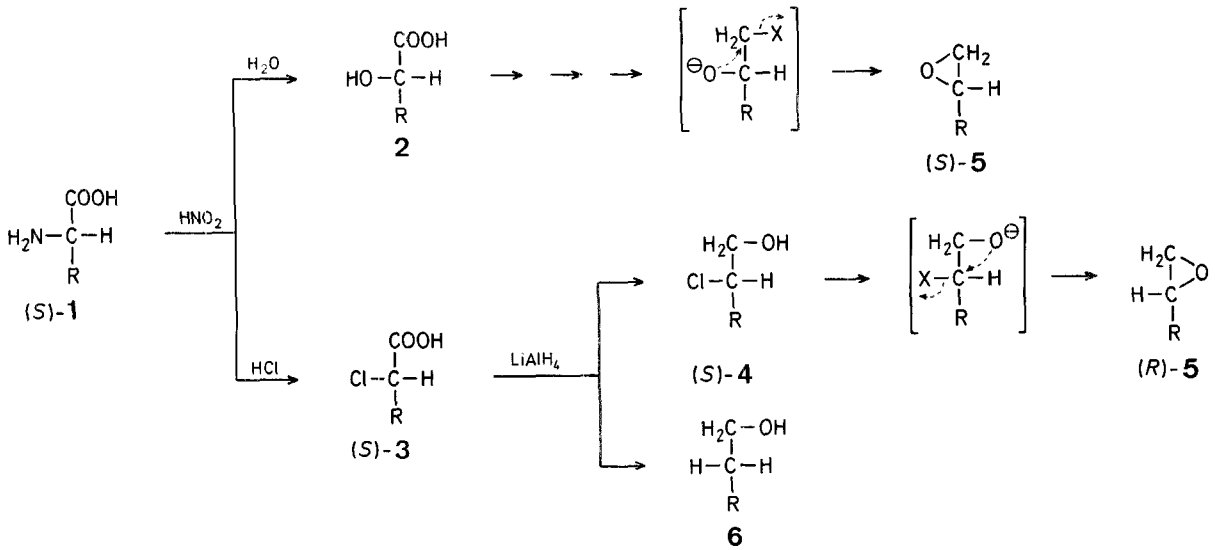
Chiral oxiranes are important building blocks for numerous synthetic purposes (e.g., the preparation of optically active polyoxiranes[1,2] and pheromones[3-6]). The most economic access to simple oxiranes available at present is to exploit naturally occurring compounds as vast "chiral pool"[5], although direct methods such as enantiospecific epoxidation of prochiral unfunctionalized olefins may gain attention[6]. The scope of the "chiral pool" approach may be further extended if chemical transformations are carried out directly at the chiral center in a stereocontrolled fashion. Thus, (*S*)-α-amino acids **(1)** have been transformed with retention of configuration to (*S*)-2-hydroxy acids **(2)**[2,3] which can be converted into (*S*)-alkyloxiranes [(*S*)-**5**] with preservation of the C—O bond at the chiral center. In this strategy it is necessary to substitute regioselectively the terminal hydroxy group of the glycol by a good leaving group X, and the overall chemical yield is not always satisfactory.

A useful three-step alternative providing the *R* antipodes (*R*)-**5** in satisfactory chemical and enantiomeric yields consists of the conversion of the (*S*)-α-amino acid **1** to the (*S*)-2-chloroalkanoic acid (*S*)-**3** with retention of configuration, formation of the chlorohydrin (*S*)-**4** (carrying the leaving group X at the chiral C-atom) by time-controlled reduction with lithium alanate, and subsequent cyclization with inversion of configuration to give the (*R*)-alkyloxirane[7] (*R*)-**5**.



a R = CH_3 (Ala)
b R = *i*-C_3H_7 (Val)
c R = (*S*)-*sec*-C_4H_9 (Ile)

By performing the lithium alanate reduction without quenching, this route may also be used for the preparation of primary alcohols **6** having chiral side-chains R [e.g., (*S*)- or (*R*)-1,3-butanediol from (2*S*,3*S*)-allothreonine or (2*S*,3*R*)-threonine[8], respectively, or (*S*)-3-methylpentanol from (2*S*,3*S*)-isoleucine].

We found that the conversion of (*S*)-α-amino acids (**1**) into (*S*)-2-chloroalkanoic acids [(*S*)-**3**] is accompanied by side-reactions and racemization[7] if aqua regia[9] is used; however, satisfactory results were obtained by using sodium nitrite in 6 normal hydrochloric acid according to Ref.[10]. The course of the lithium alanate reduction of **3** was followed by G.L.C. analysis (after hydrolysis). Almost quantitative reduction of the carboxy group within a few minutes was observed when applying a 1:1 molar ratio $LiAlH_4$: **3** in boiling ether. The rate of the subsequent slow hydrogenolysis of the C—Cl bond depends on the nature of R. With a 3:1 molar ratio $LiAlH_4$: **3**, 90% hydrogenolysis (G.L.C. peak ratio of **3** and **4**) required 12 h for **3a** and 72 h for **3c**. As regards the ring closure of the chlorohydrins **4** to the oxiranes **5** in the presence of base, attention should be paid to the expected boiling point difference between oxirane and solvent. No solvent, i.e. anhydrous potassium hydroxide, should be used in the case of less volatile oxiranes (e.g., **5b**) [whereas neat potassium hydroxide reacts too vigorously with **4a**].

In the present investigation it was essential to determine precisely the extent of racemization accompanying substitution at the chiral C-atom (conversions **1**→**3** and **3**→**4** proceeding with retention of configuration, **4**→**5** with inversion). Such determinations have previously been performed[7,8] by chromatography on stationary chiral phases[11]. We determined the enantiomeric purity of the starting (*S*)-α-amino acids **1** by capillary gas chromatography on Chirasil-Val[12] using the *O*-isopropyl-*N*-pentafluoropropanoyl derivatives of **1**; e.e. > 99.5%. The enantiomeric purity of the alkyloxiranes **5** was determined by "complexation gas chromatography" on manganese(II) bis[3-heptafluorobutanoyl-(1*R*)-camphorate][13] (see Figure). The results (lower chromatogram in Figure) show that the overall reaction is only to a minor degree accompanied by racemization (maximum racemization: 2.7% for **5a**, 1.4% for **5b**); product **5c** which contains an additional chiral center is contaminated by only 1.6% of one epimer to which we assign the 2*S*,3*S* configuration since epimerization is likely to occur at C-2 during the first reaction step.

Thus, the overall synthesis described here proceeds with a high degree of stereocontrol, although two consecutive substitutions at the chiral center are involved in the reaction sequence.

(2*S*)-2-Chloroalkanoic Acids [(*S*)-3]:
These compounds are prepared according to the method described in Ref.[10].

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(S)-*2-Chloropropanoic Acid* [(*S*)-**3a**]; yield: 60%; b.p. 75°C/10 torr; $[\alpha]_D^{25}$: −16.9°; $[\alpha]_D^{25}$: −13.5° (neat) [Ref.[10], b.p. 77°C/10 torr; d^{25}: 1.2485; $[\alpha]_D^{25}$: −14.6° (neat)].

(S)-*2-Chloro-3-methylbutanoic Acid* [(*S*)-**3b**]; yield: 57%; b.p. 98°C/16 torr; $[\alpha]_{436}^{20}$: 6.80°; d^{20}: 1.171; $[\alpha]_{436}^{20}$: 5.80° (neat); $[\alpha]_D^{25}$: 2.8° (*c* = 8.7, ethanol) [Ref.[14], $[\alpha]_D^{25}$: 2.12° (8.7% in ethanol)].

(*2S,3S*)-*2-Chloro-3-methylpentanoic Acid* [(2*S*,3*S*)-**3c**]; yield: 42%; b.p. 62°C/0.07 torr; $[\alpha]_D^{20}$: −5.30°; d^{20}: 1.071; $[\alpha]_D^{20}$: −4.95° (neat) (Ref.[15], b.p. 88–90°C/1–2 torr).

(*S*)-2-Chloroalkanols [Chlorohydrins (*S*)-4]; General Procedure:

A solution of the (*S*)-2-chloroalkanoic acid **3** (0.2 mol) in dry ether (100 ml) is added within 10 min *(caution!)* to a stirred slurry of lithium alanate (7.6 g, 0.2 mol) in dry ether (200 ml) at 0°C. The mixture is refluxed for an additional 10 min (5 min for **4a**), and then cooled to 0°C. Water (20 ml) is added *(caution!)* and the resultant white precipitate is dissolved by addition of 2 normal sulfuric acid. The aqueous layer is extracted with ether (3 × 100 ml). The combined organic layers are washed with water (50 ml) and with aqueous sodium carbonate (50 ml), and the aqueous layers are extracted with ether (3 × 100 ml). The combined organic layers are dried with sodium sulfate and distilled. Less than 5% of the corresponding alcohols **6** are formed, and fraction of the chlorohydrins **4** usually exhibiting a purity of 98–99% (G.L.C., OV 17 on Chromosorb P AW-DMCS).

(S)-*2-Chloropropanol* [(*S*)-**4a**]; yield: 56%; b.p. 131°C/730 torr; $[\alpha]_D^{25}$: 19.92° (neat); $[\alpha]_D^{25}$: 18.07° (neat) [Ref.[16], d^{25}: 1.1025; $[\alpha]_D^{25}$: 17.39° (neat)].

(S)-*2-Chloro-3-methylbutanol* [(*S*)-**4b**]; yield: 68%; b.p. 80°C/60 torr; $[\alpha]_D^{20}$: 3.75° (neat); d^{20}: 1.044; $[\alpha]_D^{20}$: 3.58° (neat).

(*2S,3S*)-*2-Chloro-3-methylpentanol* [(2*S*,3*S*)-**4c**]; yield: 60%; b.p. 77°C/10 torr; $[\alpha]_D^{20}$: −7.32°; d^{20}: 0.971; $[\alpha]_D^{20}$: −7.54° (neat).

$C_6H_{13}ClO$	calc.	C 52.75	H 9.59	Cl 25.95
(136.6)	found	53.05	9.69	26.23

(*R*)-Alkyloxiranes [(*R*)-5]; General Procedures:

The syntheses are carried out in a well ventilated hood.

Method A: Oxiranes of high volatility (i.e., **5a**, b.p. 34°C/728 torr) are prepared by addition of the chlorohydrin **4** (0.1 mol) to an aqueous 50% solution of potassium hydroxide (0.15 mol). With vigorous stirring of the mixture at 60°C, the oxirane is distilled through a Vigreux column to a −75°C trap (Hg valve) at reduced pressure. The oxirane is redistilled from potassium hydroxide pellets.

Method B: Oxiranes of low volatility (i.e., **5c**, b.p. 109°C/726 torr) are purified by freezing out the codistilled water and decanting the oxirane prior to the final distillation from potassium hydroxide pellets. Alternatively, the oxirane (i.e., **5b**, b.p. 82°C/730 torr) is prepared by addition of powdered potassium hydroxide (0.2 mol) to the vigorously stirred chlorohydrin **4** (0.1 mol) and worked up as in Method A. – Oxiranes with an expected b.p. > 120°C/760 torr may be isolated by extraction of the reaction mixture with ether, drying, and distillation.

(R)-*1,2-Epoxypropane* [(*R*)-**5a**]; yield: 90%; $[\alpha]_D^{20}$: 11.48°; d^{20}: 1.171; $[\alpha]_D^{20}$: 13.88° (neat); e.e. (by G.L.C.)[7]: 94.6% [in accordance with the previously determined optical rotation for pure (*S*)-**5a**, i.e., $[\alpha]_D^{20}$: −14.65 ± 0.05° (neat)[7]].

(R)-*1,2-Epoxy-3-methylbutane* [(*R*)-**5b**]; yield: 75%; $[\alpha]_{436}^{20}$: −11.60°; d^{20}: 0.801; $[\alpha]_{436}^{20}$: −14.60° (neat); $[\alpha]_D^{25}$: −4.6° (*c* 1.91, cyclohexane); e.e. (by G.L.C.): 97.2% [Ref.[2], b.p. 81.5°C; $[\alpha]_D^{25}$: 3.1° (*c* 1.91, cyclohexane) for (*S*)-**5b**].

(*2R,3S*)-*1,2-Epoxy-3-methylpentane* [(2*R*,3*S*)-**5c**]; yield: 55%; $[\alpha]_D^{20}$: 11.38°; d^{20}: 0.7598; $[\alpha]_D^{20}$: 14.98° (neat); configurational purity (by G.L.C.): <0.1% (2*R*,3*R*)-**5c**, 1.6% (2*S*,3*S*)-**5c**, 98.3 ± 0.1% (2*R*,3*S*)-**5c**.

$C_6H_{12}O$	calc.	C 71.95	H 12.07
(100.2)	found	71.36	11.93

(*S*)-3-Methylpentanol [(*S*)-6c]; Typical Procedure:

A solution of (2*S*,3*S*)-2-chloro-3-methylpentanoic acid [(2*S*,3*S*)-**3c**; 111.5 g, 0.74 mol) in dry ether (1000 ml) is gradually added to a stirred slurry of lithium alanate (60.8 g, 1.6 mol) in dry ether (2000 ml) *(caution!)*. The mixture is refluxed for 3 days and then worked up as described for **4c**; yield of **6c**: 50.6 g (67%). Repeated distillation using a "Spaltrohr HMS 300" column[19] (~50 theoretical plates) affords the alcohol in 99% purity (G.L.C.); yield: 43.0 g (57%); b.p. 152°C/740 torr (Ref.[17], b.p. 152°C). Optical rotation measured with a fraction of 99.9% (G.L.C.) purity dried by percolation over active alumina; $[\alpha]_D^{20}$:

Table. ^{13}C-N.M.R. Data (20 MHz; $CDCl_3$ as solvent and internal standard) of Compounds **3–6**; δ [ppm]

Compound	C-1	C-2	C-3	C-4	C-5	C-6
(*S*)-**3a**	176.0	52.0	20.9			
(*S*)-**3b**	175.4	63.8	32.4	19.4[a]	17.7[a]	
(2*S*,3*S*)-**3c**	175.7	62.5	38.8	24.8	10.8	15.8
(*S*)-**4a**	67.7	58.8	20.7			
(*S*)-**4b**	71.0	65.0	30.9	19.7[a]	17.4[a]	
(2*S*,3*S*)-**4c**	70.5	64.7	38.1	25.3	11.1	15.8
(*R*)-**5a**	47.2[b]	48.0	17.0			
(*R*)-**5b**	45.3[b]	56.9	30.4	18.5[a]	17.6[a]	
(2*R*,3*S*)-**5c**	46.3[b]	56.3	37.5	26.0	11.1	16.2
(2*S*,3*S*)-**5c**	45.0[b]	56.3	37.3	26.9	10.8	14.6
(*S*)-**6c**	60.6	39.8	31.0	29.4	11.0	18.9

[a] The diastereotopic atoms C-4/C-5 are not assigned.
[b] The terminal C-atom of the oxiranes is denoted as C-1.

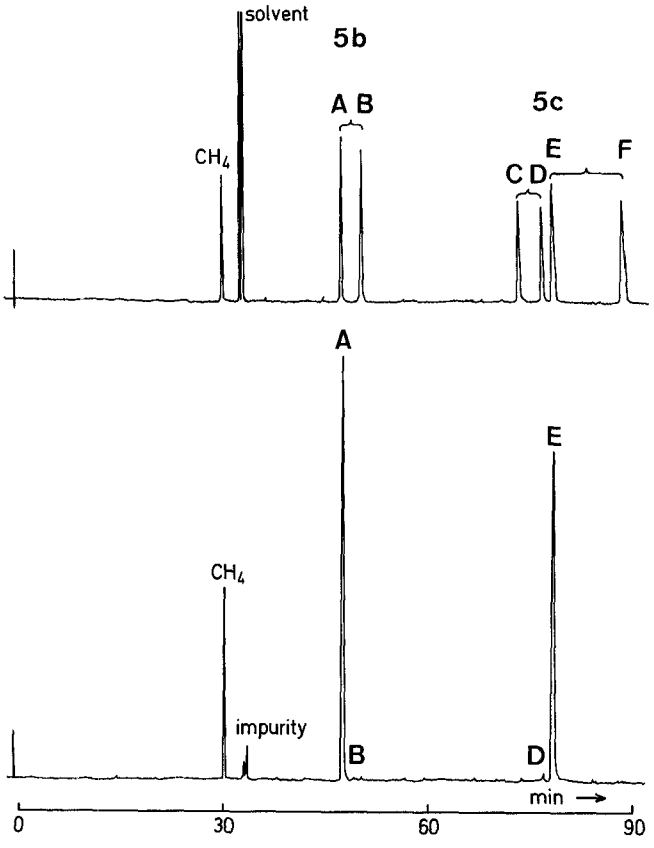

Figure. Complexation Gas Chromatography of Products **5b** and **5c**. Conditions: 160 m × 0.4 mm stainless-steel capillary column coated with manganese(II) bis[3-heptafluorobutanoyl-(1*R*)-camphorate] (0.05 molal) in squalane[13]; carrier gas: 1.5 ml/min N_2, split ratio 1:50, oven temperature: 60°C, injector temperature: 200°C.

Upper Chromatogram: Quantitative resolution of the enantiomers of **5b** (**A** = *R*, **B** = *S*) and of the four configurational isomers of **5c** (**C** = 2*R*,3*R*; **D** = 2*S*,3*S*; **E** = 2*R*,3*S*; **F** = 2*S*,3*R*).

Lower Chromatogram: Determination of the enantiomeric purity of (*R*)-**5b** and of the epimeric and enantiomeric purity of (2*R*,3*S*)-**5c**.

6.75°; $[\alpha]_D^{20}$ 8.18° (neat) [d^{20}: 0.8262[18]; $[\alpha]_D^{19}$: 8.24° (neat)[17]]. Note that the value of the optical rotation is significantly increased by traces of water. Assuming no racemization at the chiral center during hydrogenolysis, the enantiomeric purity of the alcohol would be >99.8% as judged from the composition of the oxirane **5c** [i.e., <0.1% (2*R*,3*R*)-**5c**, see Figure, lower chromatogram].

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