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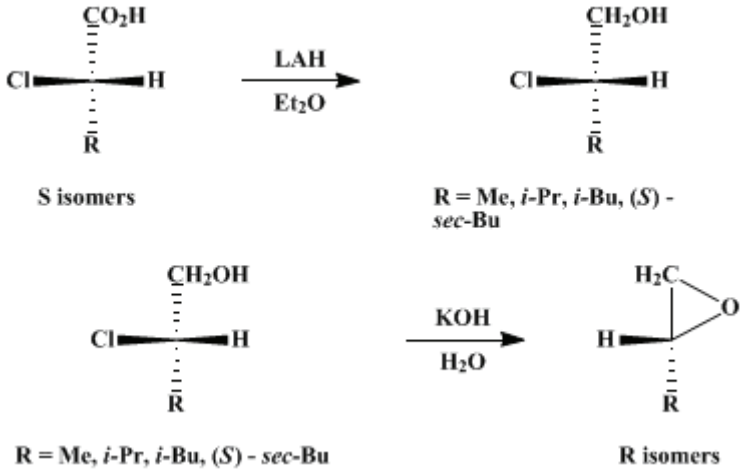
(*R*)-ALKYLOXIRANES OF HIGH ENANTIOMERIC PURITY FROM (*S*)-2-CHLOROALKANOIC ACIDS VIA (*S*)-2-CHLORO-1-ALKANOLS: (*R*)-METHYLOXIRANE

[Oxirane, methyl- (*R*)-]



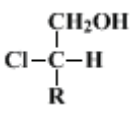
Submitted by Bernhard Koppenhoefer and Volker Schurig[1].
Checked by G. Nagabhushana Reddy and James D. White.

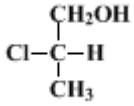
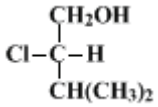
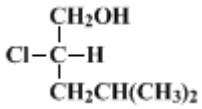
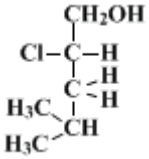
1. Procedure

Caution! Methyloxirane is a suspected carcinogen for humans.

A. *(S)-2-Chloropropan-1-ol.* Into a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a 250-mL dropping funnel, a stopper (Note 1), and an efficient reflux condenser fitted with a calcium chloride drying tube is placed 9.1 g (0.24 mol) of lithium aluminum hydride; 400 mL of dry diethyl ether is added with caution. The slurry is cooled in an ice bath and a solution of 21.7 g (0.20 mol) of (*S*)-2-chloropropanoic acid (Note 2) in 150 mL of dry diethyl ether is added carefully with vigorous stirring over a 10-min period so that refluxing of the solvent is kept under control. After a total reaction time of 15 min (Note 3), the drying tube is removed and 20 mL of water is added drop by drop *(Caution: Vigorous evolution of hydrogen!)* with efficient stirring and cooling (Note 4). The precipitate is dissolved (Note 5) by addition of 0.6 L of 2 *N* sulfuric acid (Note 6). The layers are separated, and the aqueous layer is extracted with two 200-mL portions of diethyl ether. The combined ether layers are washed with 50 mL of water, 50 mL of sodium carbonate solution (Note 4), and 50 mL of sodium bicarbonate solution, each aqueous layer being reextracted with two 50-mL portions of diethyl ether (Note 7). The combined ethereal layers are concentrated with a rotary evaporator at atmospheric pressure (bath temperature 40–50°C) to approximately 300 mL, dried over sodium sulfate, and concentrated to give an oily residue. Fractional distillation at reduced pressure (Note 8) affords 10.6–11.0 g (56–58%) of a colorless oil. This procedure can be applied to chlorohydrins with other alkyl residues (see (Note 3) and (Note 8), Table I).

TABLE I
(2*S*)-2-CHLOROALKAN-1-OLS (CHLOROHYDRINS)



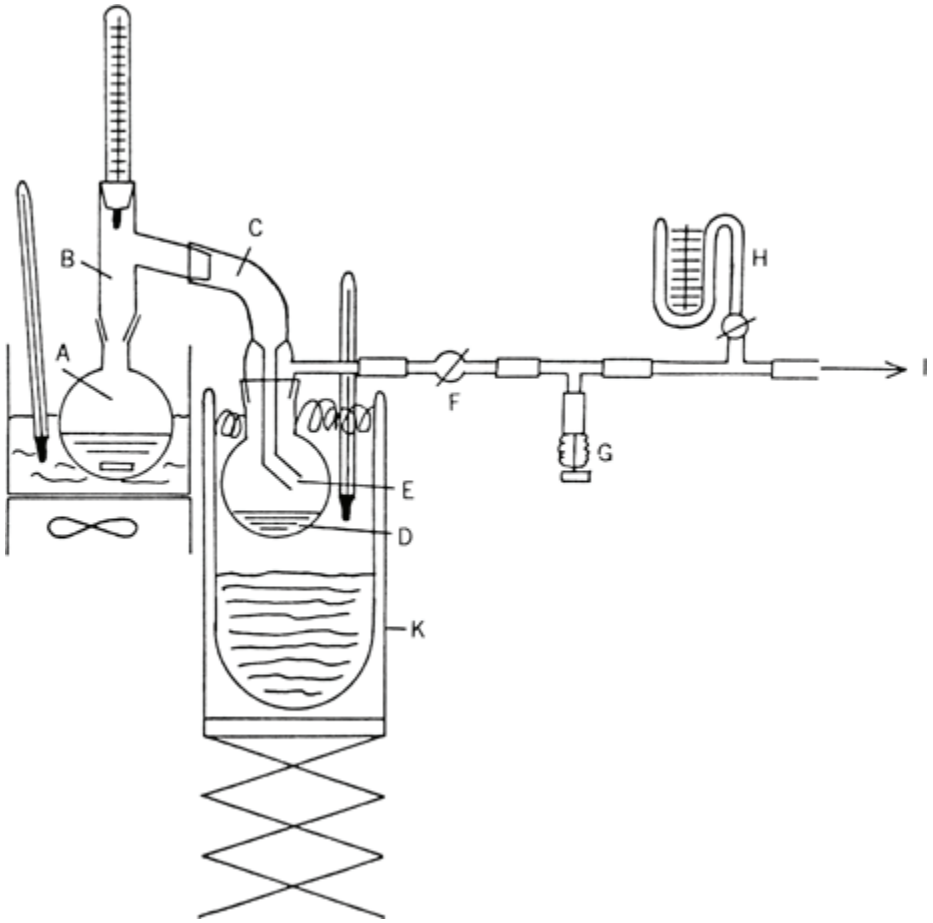
Substituent R	Yield (%)	bp (°C/mm)	d_4 (g/cm^3)	$[\alpha]_D$ (°)[a]
 -CH_3	56	131/725	1.110_1	+17.8
 -$CH(CH_3)_2$	70	91/50	1.044_2	+3.6
 -$CH_2CH(CH_3)_2$	64	92/30	1.005_3	−48.8
 (*S*)-$CH(CH_3)CH_2CH_3$	56	75/10	1.028_6	−7.6

[a] Rotations were measured on the neat liquids.

B. *(R)-Methyloxirane* (Note 9). The reaction is conveniently carried out in a special apparatus (see Fig. 1) in order to prevent loss of the volatile oxirane. A 50-mL, narrow-necked vessel (A) is equipped with a magnetic stirrer and a small Claisen stillhead (B), fitted with a thermometer and connected to a small receiver adapter with vacuum connection (C). A 25-mL or 50-mL flask (D) serves as a trap for the oxirane. To prevent clogging of the inlet pipe (E) by solidified reaction product, an appropriate flask (D) is chosen so that the distance between the inlet pipe (E) and the flask (D) is approximately 5–10 mm. The vacuum end of the adapter (C) is connected via a stopcock (F), a T-piece carrying a needle valve (G), and a manometer (H) to a water aspirator (I). The reaction vessel (A) is equipped with an ice bath, a thermometer, and a combined heater and magnetic stirrer that is placed on a jack. After the entire apparatus is connected (F closed), the trap (D) is air-cooled in a Dewar (K) that is partially filled with liquid nitrogen and heat-insulated at the top with cotton. A low-temperature thermometer (L) is placed at the same height near trap (D). The temperature of the trap (D) is controlled by moving the jack to the appropriate height to approximately −80°C. The pressure is adjusted by a needle valve (G) to 100 mm (F remains closed). A solution of 12.3 g (0.22 mol) of potassium hydroxide pellets in 12 mL of water is placed in the vessel (A) and cooled to 0°C. Neat (*S*)-2-chloropropan-1-ol, 11.8 g (0.125 mol), is poured at once into the alkaline solution (Note 10), and the reaction vessel is immediately fitted with a stillhead (B) and stirred vigorously with efficient cooling. The stopcock (F) is opened occasionally for a short period until the pressure in the closed system is reduced to 100 mm (Note 11). The ice bath is replaced by a water bath at 20°C. As the cyclization reaction proceeds, a white precipitate of potassium chloride is formed. After 10 min, the bath temperature is raised slowly to 30°C. Gentle boiling of the oxirane is maintained by cautiously opening the stopcock (F) from time to time, with attention paid to the reaction vessel. After a total reaction time of 40 min (Note 12), air is allowed to enter the closed system at the top of the stillhead, and the trap (D) is allowed to warm (Note 13) until two liquid phases are formed. The lower phase containing water is transferred via a Pasteur pipette into a small flask (Note 14). The flask (D) containing 5.9 g (81%) of crude (*R*)-methyloxirane is used in position (A) of the clean, dry apparatus (see Fig. 1) for redistillation of the oxirane from calcium hydride. At atmospheric pressure

(stopcock F open), flask (A) is cooled to 0°C, whereas the trap (D) is kept at room temperature. Calcium hydride is added in small portions over a period of 1–2 hr until evolution of hydrogen ceases. The stopcock (F) is closed, the trap (D) is cooled, and the oxirane is distilled as described. Reduced pressure is applied with great care to avoid too vigorous boiling; 4.7–5.0 g (65–70%) of anhydrous oxirane is obtained as a clear liquid. This procedure can be employed for other oxiranes with slight modifications (see (Note 12) and (Note 14) and Table II).

Figure 1. Apparatus for the preparation of (*R*)-methyloxirane.



2. Notes

1. As a safeguard it is recommended that the reaction be performed under nitrogen using a gas inlet instead of the stopper. The flask should be dry and free of faults.
2. (*S*)-2-Chloroalkanoic acids are prepared according to the procedure described.[2]
3. A total reaction time of 30 min is needed for more sterically hindered (*S*)-2-chloroalkanoic acids. Prolonged reaction times should be avoided to prevent hydrogenolysis of the chlorine-carbon bond.
4. Prolonged exposure to alkaline conditions should be avoided to prevent oxirane formation at this step.
5. The aqueous phase is allowed to remain opalescent to avoid unnecessarily low pH-values.
6. Concentrated sulfuric acid, 60 g, is added to a beaker charged with 540 g of crushed ice. Precooled 2 *N* sulfuric acid is added to the reaction mixture.
7. Less than 5% of the chloroalkanoic acid is reisolated after acidification of the sodium carbonate phase and extraction with diethyl ether.
8. (*S*)-2-Chloropropan-1-ol is carefully distilled at atmospheric pressure using a 20-cm Vigreux column. (*S*)-2-Chloro-3-methylbutan-1-ol, (*S*)-2-chloro-4-methyl-pentan-1-ol, and (2*S*,3*S*)-2-chloro-3-methylpentan-1-ol are distilled under reduced pressure with a spinning-band column or a "Spaltrohr-column" (approximately 50 theoretical plates, supplier: W. G. Fischer, D-5309 Meckenheim, FRG); see Table I. The main fractions are >99% pure by GLC (OV 17 on Chromosorb P AW-DMCS). Because of

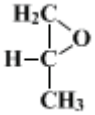
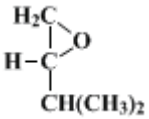
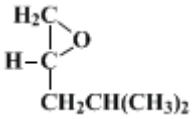
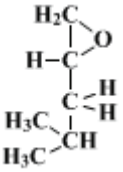
the low boiling points of the oxiranes, diethyl ether should be completely removed from the chlorohydrins.
9. The synthesis should be carried out in a well-ventilated hood. *Caution: Methyl-oxirane is a suspected carcinogen for humans.*
10. The amount of chlorohydrin used is determined from the weight remaining in the original flask (ca. 1 g).
11. During the course of the reaction, the stopcock (F) should remain closed except for short periods in order to avoid loss of the volatile oxirane. There is no danger of excess pressure in the closed system as long as the trap (D) is cooled efficiently.
12. The chlorohydrins show different rates of cyclization, reflecting the steric hindrance of residue R. The most vigorous reaction is observed in the case of (*S*)-2-chloropropan-1-ol (R = CH_3); only 30°C at 100 mm is required. For (*R*)-isopropyloxirane, the bath temperature is raised slowly to 50°C, and after 40 min to 60°C, while the pressure is reduced to 50 mm for an additional 5 min. For the higher-boiling oxiranes, such as (*R*)-isobutyloxirane and (*S*)-*sec*-butyl-(*R*)-oxirane [(2*R*,3*S*)-3-methyl-1,2-epoxybutane], the temperature is raised slowly to 60°C within 1 hr, while the pressure is reduced carefully to 30 mm.
13. Buildup of methyloxirane pressure is prevented by briefly opening the apparatus from time to time.
14. For methyloxirane, the binary system with water has been studied in detail.[3] By careful operation during the distillation, water is largely retained in the original flask (A). The racemate melts at −112°C, but the hydrate $C_3H_6O(H_2O)_{16}$ (mp −3°C) may solidify in the inlet tube (E). In the case of higher boiling oxiranes, substantial amounts of water are codistilled. After removal from the flask (D), the aqueous phase may be saturated with sodium chloride. Thereby a second portion of the oxirane (approximately 0.2 g) is separated and combined with the main portion in the flask (D).

3. Discussion

The method described here illustrates the transformation of optically active 2-chlorocarboxylic acids, which are readily available from 2-amino acids,[2] via 2-chloroalkan-1-ols to alkyloxiranes with inversion of configuration at the stereocenter. Thus (*R*)-methyloxirane is prepared from (*S*)-alanine, (*R*)-isopropyloxirane from (*S*)-valine, (*R*)-isobutyloxirane from (*S*)-leucine, and (*S*)-*sec*-butyl-(*R*)-oxirane from (2*S*,3*S*)-isoleucine, respectively. This useful three-step route complements the synthesis of (*S*)-alkyloxiranes from (*S*)-2-amino acids via (*S*)-2-hydroxy acids,[4,5] with retention of configuration at the stereocenter.

The stereoselective conversion of chlorohydrins into diols via oxiranes as intermediates in aqueous potassium hydroxide solution was originally described in Fickett et al.[6] In the present procedure, the oxiranes are distilled off as they are formed to prevent subsequent ring-opening. Among different reaction conditions investigated,[7] the procedure given here appears to be most convenient, and is accompanied by almost no racemization (Table II). The enantiomeric purities of the oxiranes are determined directly with high precision by complexation gas chromatography on optically active metal chelates [e.g., Ni(II) bis(2-heptafluorobutyryl-(*S*)-4-methylthujan-3-onate)[8] or Mn(II) bis(3-heptafluorobutyryl-(*R*)-camphorate),[7] respectively]. Depending on the chemical structure of the chloro acids used,[2] the degree of inversion of configuration is less than 0.5% for R = methyl, isopropyl, and (*S*)-sec-butyl, and approximately 1.5% for R = isobutyl. In the latter case, prolonged exposure of the oxirane to the reaction mixture leads to increased racemization. Both (*R*)- and (*S*)-methyloxirane have been synthesized with retention of configuration from (*R*)- and (*S*)-propane-1,2-diol, respectively, by cyclization of the bromoacetates,[9,10,11] which seems to be superior to the route via bromohydrins.[12] Starting from commercially available (*S*)-ethyl lactate,[9] other groups have employed different routes to (*S*)-methyloxirane[13,14] [$[\alpha]_D$ −12.5° (neat)][13] and to (*R*)-methyloxirane[15,16] [$[\alpha]_D^{24}$ + 13.9° (neat),[15] $[\alpha]_D^{20}$ + 13.4° (neat),[17] $[\alpha]_D^{22}$ + 13.0° (neat),[16] $[\alpha]_D^{25}$ + 11.97° (neat)[18]]. The apparent deviations of these specific rotations from the maximum optical rotation extrapolated for the pure enantiomer may be ascribed to lack of enantiomeric purity of the substances described, and to inappropriate optical rotation measurements (error in the density, chemical impurities). Enantiomeric impurities in the oxirane can also originate from the starting material since variable fractions of (*R*)-ethyl lactate (up to 5%) have been detected in commercial (*S*)-ethyl lactate by gas chromatography on D-Chirasil-Val.[19] The enantiomeric purity of the chiral starting material must be established with certainty in any "chiral pool" transformation.

TABLE II
(2*R*)-ALKYLOXIRANES (1,2-EPOXYALKANES)

Substituent R	Yield (%)[a]	bp (°C/mm)[b]	ee (%)	d_4^{20} (g/cm³)	$[\alpha]_D^{20}$ (°)[c]
 -CH_3	81/67	34/728	94.6 ± 0.4[d]	0.8309	+13.12
 -$CH(CH_3)_2$	93/87	82/730	97.4 ± 0.2[e]	0.8201	−4.46
 -$CH_2CH(CH_3)_2$	84/78	108/730	93.0 ± 0.4[e]	0.8241	+20.47
 (*S*)-$CH(CH_3)CH_2CH_3$	79/73	109/726	97.4 ± 0.2[d,f]	0.7598	+14.4

[a] First number: crude reaction product (organic layer). Second number: final yield after redistillation.
[b] Determined in a separate experiment.
[c] Rotations were determined on neat samples; specific rotations are for material of the indicated enantiomeric excess.
[d] Determined by complexation gas chromatography on Ni(II) bis(2-heptafluorobutyryl-(S)-4-methylthujan-3-onate) ([8]).
[e] Determined as Mn(II) bis(3-heptafluorobutyryl-(R)-camphorate) ([7]).
[f] Diastereomeric excess, referring to (2*S*,3*S*)-1,2-epoxy-3-methylpentane, (*S*)-*sec*-butyl-(*R*)-oxirane as impurity. Composition: 98.5 ± 0.1% 2*R*,3*S*; 1.3 ± 0.1% 2*S*,3*S*; 0.2 ± 0.1% 2*R*,3*R*, approximately 0% 2*S*,3*R*.

The "chiral pool" approach appears at present to be superior to other methods of access to optically active alkyl-substituted oxiranes, such as enzymatic,[20,21,22] and nonenzymatic[23] epoxidation of prochiral olefins, chromatographic resolution experiments,[11,24] and kinetic resolution methods.[8,25,26] Halohydrins and oxiranes of high enantiomeric purity have recently been obtained by diastereoselective synthesis.[27] As reviewed previously,[10] a variety of optically active compounds have been synthesized from (*R*)- and (*S*)-methyloxirane. Additional examples are macrolides,[28,29,30] alcohols,[31,32,33] amino alcohols,[20,34] 1-

chloro-2-alkanols,[35] and thiiranes.[17,36] The potential of higher, alkyl-substituted oxiranes as building blocks in chiral synthesis awaits its full exploitation. (*S*)-Ipsenol has been synthesized from (*S*)-isobutyloxirane,[37,38] which is also available from D-mannitol.[38,39] By stereoselective ring-opening reactions, optically active oligomers (crown ethers)[40] and polymers are conveniently prepared.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 119

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)- and (S)-methyloxirane

(S)-2-Chloroalkanoic acids

Ni(II) bis(2-heptafluorobutyryl-(S)-4-methylthujan-3-onate)

Mn(II) bis(3-heptafluorobutyryl-(R)-camphorate)

(R)- and (S)-propane-1,2-diol

S)-methyloxirane

R)-ethyl lactate

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

(S)-alanine (56-41-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

methyloxirane,
Methyl-oxirane (75-56-9)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

oxirane (75-21-8)

potassium chloride (7447-40-7)

lithium aluminum hydride (16853-85-3)

(2S,3S)-isoleucine (73-32-5)

(S)-Leucine (61-90-5)

(S)-valine (72-18-4)

calcium hydride (7789-78-8)

chlorine-carbon

D-mannitol (69-65-8)

(S)-ethyl lactate (97-64-3)

(R)-Methyloxirane,
Oxirane, methyl- (R)- (15448-47-2)

(S)-2-Chloropropanoic acid (29617-66-1)

(S)-2-Chloropropan-1-ol (19210-21-0)

(S)-2-Chloro-3-methylbutan-1-ol

(S)-2-chloro-4-methyl-pentan-1-ol

(2S,3S)-2-chloro-3-methylpentan-1-ol

(R)-isopropyloxirane,
(2R,3S)-3-methyl-1,2-epoxybutane

(R)-isobutyloxirane

(S)-sec-butyl-(R)-oxirane

(2S,3S)-1,2-epoxy-3-methylpentane

(S)-isobutyloxirane