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Synthesis of (*R*)- and (*S*)-Allyloxiranes *via* Enantioselective Allylboration of Bromoacetaldehyde. Transformation of (*R*)-Allyloxirane into (−)-(*R*)-GABOB (GABOB = γ-amino-β-hydroxybutyric acid)

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Enantioselective allylboration of bromoacetaldehyde with allyl(diisopinocampheyl)borane **2** or allyl(diisocaranyl)borane **3** has been used as a key step in the first synthesis of (+)-(*R*)-**6** [89% enantiomeric excess (e.e.)] and (−)-(*S*)-allyloxirane **7** (92% e.e.), respectively; in two steps, oxirane **6** was converted into (−)-GABOB [(*R*)-4-amino-3-hydroxybutyric acid] **9** (89% e.e.), which is both a neuromodulator of the mammalian central nervous system and a drug.

Allyloxiranes **A** with a terminal double bond are highly functionalized five-carbon building blocks and they are useful starting materials for the preparation of many types of organic compounds. However, they have rarely been used in synthesis owing to a lack of general methods for their preparation.[1,2] Three routes to **A** from allyl-[2,3] and vinyl-magnesium bromides[3] as well as *via* the allylboration reaction[4,5] have been developed recently. The preferred route to the parent (±)-allylepoxide **A** ($R^1 = R^1 = H$) consists of an allylboration reaction of bromoacetaldehyde diethyl acetal in acidic aqueous medium (10% HCl) (*in situ* generation of $BrCH_2CHO$)[6] followed by alkaline work up[3,4] of the 5-bromo-4-hydroxypent-1-ene obtained. It is clear that optically active (*R*)- and (*S*)-allyloxiranes **6** and **7** are the most promising substances of this type as chiral precursors for the preparation of various organic compounds, including natural products.

In this communication, we wish to report the first synthesis of **6** and **7** *via* enantioselective allylboration of bromoacetaldehyde **1**† with allyl(diisopinocampheyl)borane **2** and allyl(diisocaranyl)borane **3**, prepared[7,8] from (−)-α-pinene and (+)-3-carene,‡ respectively, and having opposite enantioselectivities (Scheme 1).

† The monomeric bromoacetaldehyde was prepared by bromination of acetaldehyde in dry ether in the presence of 4 mol.% of 1,4-dioxane at 0–3 °C, according to ref. 9, followed by neutralisation of the reaction mixture with $NaHCO_3$ powder at the same temperature. Drying of the decanted ethereal solution with $MgSO_4$ followed by distillation led to pure **1** (b.p. 52–54 °C at 96 mmHg) with a reproducible yield of 70%. As **1** is readily polymerized, it was depolymerized before introduction into the reaction by distillation (100 mmHg) into cold ether (−30 °C).

‡ Allylic borane **2** was synthesized[7,8] from (−)-α-pinene (93% e.e., $[\alpha]_D^{23}$ −47.8°, b.p. 52–53 °C at 16 mmHg), which was prepared by double crystallization of (−)-α-pinene (80% e.e.) from pentane at −130 °C[16] and distillation over $LiAlH_4$. Borane **3** was obtained from (+)-3-carene (100% e.e., $[\alpha]_D^{23}$ +17.7°, b.p. 45–46 °C at 9 mmHg) which was purified[17] similarly (four crystallisations at −130 °C).

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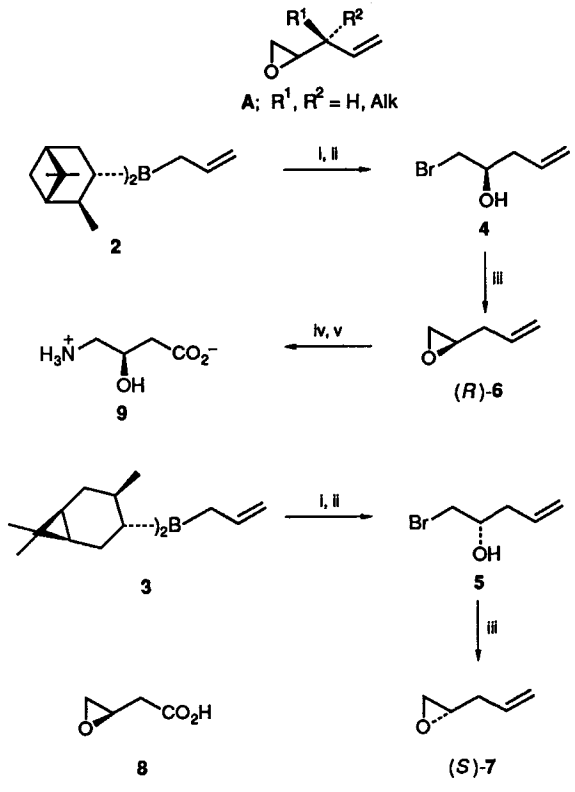
Table 1 Optical rotation and enantiomeric excess of **4–7** and **9**

Compound	Boiling point, t/°C, p/mmHg	$[\alpha]_D^{23}$ (c/mol dm^{-3}, Et_2O)	E.e. (%)	Configuration
4	69, 10	+9.3 (5.77)	89	*R*
5	69, 10	−9.6 (5.50)	92	*S*
6	91, 745	+8.9 (7.06)	89	*R*
7	91, 745	−9.2 (7.20)	92	*S*
9	M.p. 208–210°C	−18.5 (c 1.47, H_2O)	89	*R*



Scheme 1 *Reagents and conditions*: i, $BrCH_2CHO$ (**1**), Et_2O, −110°C, 15 min, → 20°C; ii, butane-1,4-diol, 100°C, 2 Torr; iii, KOH powder, distillation; iv, 4.5 equiv. $NaIO_4$, 2.5 mol.% $RuCl_3 \cdot H_2O$, H_2O–MeCN–CCl_4, 0°C, 3 h; v, conc. aq. NH_3, 20°C, 24 h

Reactions of **1** with boranes **2** and **3** (liberated from magnesium salts[7]) were carried out on a 0.03 mole scale in ether at −110 to −100°C (liq. N_2–pentane bath) for 15 min, followed by slow heating of the reaction mixture to room temperature.§ Then 5 equivalents of MeOH and 0.033 mol of butane-1,4-diol were added consecutively (reesterification) and the corresponding bromohydrin **4** or **5** was distilled off *in vacuo* (2 mmHg) into a cooled receiver (−70°C). Bromohydrins **4** and **5** were isolated in a pure state by column chromatography on silica gel (eluent diethyl ether–pentane, 1:4) and distillation (*ca.* 50% yields, Table 1). The transformation of **4** and **5** into (*R*)- and (*S*)-epoxides **6** and **7** was performed by treatment with KOH powder and instantaneous distillation[3] (*ca.* 70% yield).

Both pairs of bromohydrin–oxirane obtained had the same optical purity (89% for **4** and **6** and 92% for **5** and **7**; Table 1). This was determined for each compound by ^{1}H NMR spectroscopy in the presence of a chiral paramagnetic shift reagent, tris (heptafluorobutyrylcamphorato)europium(III) [Eu(hfbc)$_3$].¶

Some decrease in the enantioselectivity of allylboration of **1** with **2** and **3** in comparison with MeCHO (89–92% e.e. and 99% e.e.)[8] can be explained in terms of the effect of the bromine atom. Similar results were observed in the reactions of allylboronic diisopropyltartrate with α- and γ-benzyl- and silyloxyaldehydes.[10]

In order to determine the absolute configuration of **6** and **7** and also to demonstrate one of their synthetic applications, we have accomplished the synthesis of the (−)-(*R*)-enantiomer **9** of the naturally occurring γ-amino-β-hydroxybutyric acid (GABOB). Compound **9** is both a neuromodulator of the mammalian central nervous system[11] and a drug and it exhibits a greater biological activity than the (*S*)-enantiomer.[12]

Oxidative cleavage of the double bond[13] in **6** led to oxiranyl acetic acid **8** which was treated[14] (without purification) with conc. aq. NH_3 at room temperature. Amino acid **9**[15] was obtained in 34% yield by crystallization from ethanol–water and was found to have $[\alpha]_D^{23}$ −18.5° (c 1.47, H_2O), corresponding to 89% e.e. and an (*R*)-configuration of the starting oxirane **6**.

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§ Deboration of the reaction mixture by the usual method, using hydrogen peroxide (30%) and an excess of 3 mol dm^{-3} NaOH, gave epoxides **6** and **7** at once. However, they are very volatile compounds and it is difficult to separate them quantitatively from diethyl ether.

¶ ^{1}H NMR spectra were recorded on a Bruker AC-200P instrument in $CDCl_3$ (internal standard $SiMe_4$). Optical rotations were measured on DIP-360 (JASCO, Japan) in Et_2O or H_2O (**9**). Compounds **4–7** were obtained in a chromatographically pure form and had spectroscopic data consistent with those reported.[3]

Spectroscopic data for **4** and **5**: δ_H[0.33 mol dm^{-3} in $CDCl_3$, 9 mol.% Eu(hfbc)$_3$] **4**: 4.77; **5**: 4.95 (dd, 1H, J 10.5, 3.8 Hz, CHBr).

6 and **7**: δ_H [0.71 mol dm^{-3} in $CDCl_3$, 5.5 mol.% Eu(hfbc)$_3$] **6**: 4.00; **7**: 4.10 (t, 1H, J 4.5 Hz, CH_2O).

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