Solid acid-catalysed isomerization of *R*(+)-limonene diepoxides

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The isomerization of diastereomeric *R*(+)-limonene diepoxides on solid catalysts, such as clays, zeolites, and solid superacids, results in the formation of bicyclic and tricyclic oxygen-containing compounds.

Epoxides (oxiranes) are versatile intermediates in organic synthesis. Chemical reactions of terpene epoxide compounds are of considerable interest because various products can be prepared on this basis.[1] The use of zeolites, clays, and solid superacids as catalysts in intramolecular and intermolecular reactions of terpenes and their oxygen-containing derivatives provides an opportunity not only to lower the activation barriers of well-known reactions but also to change the reaction paths, as compared with homogeneous chemical reactions.[2] For example, previously,[3] we found that the isomerization of citral and citronellal 6,7-epoxides on solid acid catalysts resulted in the formation of bicyclic ethers, which are structural analogues of well-known pheromones, whereas these products were not formed under conditions of homogeneous acid catalysis. In the context of the biological importance of oxygen-containing *p*-menthane derivatives,[4] we studied the reactions of the diepoxy derivatives of *R*(+)-limonene, which is a widespread naturally occurring compound. Note that terpene diepoxides are a poorly studied class of organic compounds. Diepoxides **1a**,**b**† as a mixture of diastereomers with respect to the C(8) atom were prepared by the action of bromosuccinimide on limonene in an aqueous dioxane solution followed by dibromohydrin decomposition.[5]

We found that the isomerization of diastereomeric diepoxides **1a**,**b** on either synthetic K-10 clay or natural ascanite-bentonite clay resulted in compounds **2**, **4**, **5** and **6a**,**b** in a ratio of ~4:3:7:2, respectively (GLC data).‡ With the use of wide-pore zeolite β or a TiO_2/SO_4^{2-} solid superacid as a catalyst, the qualitative and quantitative composition of the reaction mixture was changed: compounds **2**, **3** and **5** were formed in a ratio of ~2:2:5 or ~3:1:2,§ respectively (GLC data).

We proposed a mechanism for the formation of these compounds. Initially, an epoxide ring is opened to form cations **A** or **B**. Next, cation **A** reacts *via* the following two alternative paths: (*a*) the narrowing of a six-membered ring to a five-membered ring due to the migration of a C–C bond followed by the reaction of the resulting aldehyde group with a second epoxide ring to form compound **2**; (*b*) proton detachment occurs with the formation of a double bond followed by the opening of an 8,9-epoxide ring with the nucleophilic participation of a hydroxyl group to form compounds **3** or **4**. Cation **B** also reacts *via* two paths. One of the reaction paths of this rearrangement consists in the intermediate formation of an aldehyde group by hydride shift followed by the interaction of this group with the epoxide ring to form two isomeric compounds **6a**,**b**. The other reaction path, the stabilization of a cation due to the interaction with the 1,2-epoxide ring, leads to two bicyclic ions **C** and **D**, which are formed by rotation about the C(4)–C(8) bond in cation **B**. Next, cation **C** is converted into compound **4** as a result of proton detachment and the formation of a double bond, whereas cation

† Limonene diepoxides **1a**,**b** in a 3:2 ratio between isomers were obtained from *R*(+)-limonene (Aldrich, 98% *ee*), yield 31%.

Limonene diepoxide **1a**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 1.01 (dddd, H^{4a}, $J_{4a,3a}$ 12 Hz, $J_{4a,5a}$ 12 Hz, $J_{4a,3e}$ 6.5 Hz, $J_{4a,5e}$ 3 Hz), 1.14 (s, 3H^{10}), 1.23 (s, 3H^{7}), 1.26 (m, H^{5a}), 1.44 (dm, H^{5e}, $J_{5e,5a}$ 15 Hz), 1.55 (dd, H^{3a}, $J_{3a,3e}$ 15.5 Hz, J 12 Hz), 1.57 (ddd, H^{6a}, $J_{6a,6e}$ 15.5 Hz, $J_{6a,5a}$ 12 Hz, $J_{6a,5e}$ 5 Hz), 1.86 (dddd, H^{3e}, J 15.5 Hz, J 6.5 Hz, $J_{3e,2e}$ 5 Hz, $J_{3e,5e}$ 2 Hz), 1.97 (dm, H^{6e}, J 15.5 Hz), 2.37–2.47 (m, 2H^{9}), 2.85 (br. d, H^{2e}, $J_{2e,3e}$ 5 Hz). ^{13}C NMR, δ: 57.17 (s, C-1), 58.08 (d, C-2), 26.59 (t, C-3), 39.97 (d, C-4), 21.36 (t, C-5), 30.21 (t, C-6), 22.95 (q, C-7), 58.29 (s, C-8), 52.79 (t, C-9), 17.48 (q, C-10).

Limonene diepoxide **1b**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 1.15 (d, 3H^{10}, $J_{10,9}$ 0.8 Hz), 1.23 (s, 3H^{7}), 1.06–1.32 (m, H^{4}, 2H^{5}), 1.49–1.61 (m, H^{6}), 1.66 (dd, H^{3a}, $J_{3a,3e}$ 15.5 Hz, $J_{3a,4a}$ 11.5 Hz), 1.94 (m, H$^{6'}$), 2.01 (m, H^{3e}), 2.37–2.47 (m, 2H^{9}), 2.88 (br. d, H^{2e}, $J_{2e,3e}$ 5 Hz). ^{13}C NMR, δ: 57.21 (s, C-1), 58.20 (d, C-2), 26.46 (t, C-3), 39.39 (d, C-4), 21.24 (t, C-5), 30.33 (t, C-6), 22.93 (q, C-7), 58.61 (s, C-8), 52.41 (t, C-9), 18.06 (q, C-10).

Limonene diepoxides **1a**,**b** in a 3:2 ratio between isomers: MS, *m*/*z*: 168 [M$^+$]. $[\alpha]_{580}^{20}$ +35.5 (*c* 3.5, $CHCl_3$).

‡ Limonene diepoxide **1a**,**b** (0.5 g, 3 mmol) was added to a suspension of K-10 clay (1 g, calcined for 3 h at 100 °C) and CH_2Cl_2 (20 ml, dried). The reaction mixture was stirred at room temperature for 20 min and filtered. The crude product (0.46 g) was chromatographed (SiO_2, a hexane/hexane–80% diethyl ether eluent was used) to give 0.05 g (10%) of compound **2**, 0.07 g (14%) of compound **4**, 0.085 g (17%) of compound **5** and 0.01 g (2%) of compounds **6a**,**b**.

(1S,2S,5S,6R)-1,5-Dimethyl-3,10-dioxatricyclo[4.2.1.1^{2,5}]decane **2**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 0.95 (s, 3H^{11}), 1.158 (ddd, H^{9an}, $J_{an,syn}$ 11.5 Hz, $J_{9an,6}$ 4 Hz, $J_{9an,2}$ 1.5 Hz), 1.161 (ddd, H^{8ex}, $J_{8ex,8en}$ 11.5 Hz, $J_{8ex,7ex}$ 11.5 Hz, $J_{8ex,7en}$ 4 Hz), 1.22 (s, 3H^{12}), 1.61 (dddd, H^{7ex}, $J_{7ex,7en}$ 11.5 Hz , $J_{7ex,8ex}$ 11.5 Hz, $J_{7ex,6}$ 5.5 Hz, $J_{7ex,8en}$ 2.5 Hz), 1.80–1.95 (m, H^{8en}, H^{6}, H^{7en}), 2.00 (ddd, H^{9syn}, J 11.5 Hz, $J_{9syn,6}$ 2.5 Hz, $J_{9syn,7en}$ 2.5 Hz), 3.33 (d, H^{4}, $J_{4,4'}$ 7 Hz), 4.05 (d, H$^{4'}$, J 7 Hz), 4.82 (d, H^{2}, $J_{2,9an}$ 1.5 Hz). ^{13}C NMR, δ: 46.21 (s, C-1), 108.84 (d, C-2), 74.55 (t, C-4), 82.01 (s, C-5), 44.09 (d, C-6), 27.75 (t, C-7), 34.13 (t, C-8), 38.91 (t, C-9), 20.04 (q, C-11), 19.27 (q, C-12). MS, *m*/*z*: 168 [M$^+$]. $[\alpha]_{580}^{20}$ +29.4 (*c* 1.36, $CHCl_3$).

{(1R,5R,7R)-4,7-Dimethyl-6-oxabicyclo[3.2.1]oct-3-en-7-yl}methanol **4**.[6] $[\alpha]_{580}^{20}$ +154.0 (*c* 0.91, $CHCl_3$).

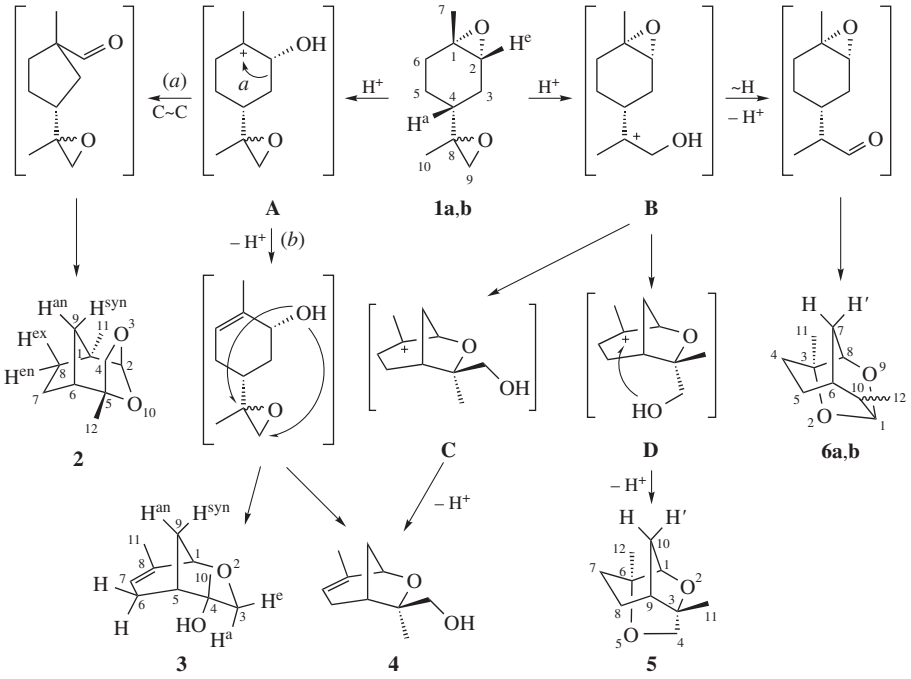
(1R,3S,6S,9R)-3,6-Dimethyl-2,5-dioxatricyclo[4.4.0.0^{3,9}]decane **5**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 1.17 (s, 3H^{12}), 1.24 (s, 3H^{11}), 1.52 (m, H^{7}), 1.55 (br. d, H^{10}, $J_{10,10'}$ 11 Hz), 1.62–1.72 (m, H$^{7'}$, H^{8}, H$^{10'}$), 1.82 (m, H$^{8'}$, $J_{8',8}$ 14 Hz, $J_{8',7}$ 9 Hz , $J_{8',7'}$ 9 Hz, $J_{8',10'}$ 2 Hz , $J_{8',9}$ 1.5 Hz), 2.20 (dddd, H^{9}, $J_{9,10'}$ 6.5 Hz, $J_{9,8}$ 5 Hz, $J_{9,1}$ 2 Hz, $J_{9,8'}$ 1.5 Hz), 3.47 (dd, H^{4}, $J_{4,4'}$ 9.5 Hz, $J_{4,10}$ 1 Hz), 3.94 (d, H$^{4'}$, J 9.5 Hz), 4.03 (dd, H^{1}, $J_{1,10'}$ 3 Hz, $J_{1,9}$ 2 Hz). ^{13}C NMR, δ: 81.80 (d, C-1), 78.21 (s, C-3), 70.01 (t, C-4), 72.41 (s, C-6), 32.17 (t, C-7), 25.02 (t, C-8), 41.40 (d, C-9), 33.01 (t, C-10), 23.32 (q, C-11), 27.91 (q, C-12). MS, *m*/*z*: 168 [M$^+$]. $[\alpha]_{580}^{20}$ +3.9 (*c* 7.7, $CHCl_3$).

(1R,3S,6R,8R,10S)-3,10-Dimethyl-2,9-dioxatricyclo[4.3.1.0^{3,8}]decane **6a**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 1.01 (d, 3H^{12}, $J_{12,10}$ 7 Hz), 1.214 (s, 3H^{11}), 1.31 (dm, H^{7}, $J_{7,7'}$ 13.5 Hz, $J_{7,8}$ 3 Hz), 1.55 (br. q, H^{10}, $J_{10,12}$ 7 Hz), 1.98 (dm, H$^{7'}$, J 13.5 Hz, $J_{7',6}$ 4 Hz, $J_{7',5'}$ 2 Hz, $J_{7',8}$ 2 Hz), 3.82 (m, H^{8}, $J_{8,7}$ 3 Hz, $J_{8,7'}$ 2 Hz, $J_{8,6}$ 1.5 Hz), 5.01 (br. s, H^{1}), 1.37–1.55 and 1.65–1.93 (m, H^{6}, 2H^{5}, 2H^{4}). ^{13}C NMR, δ: 105.04 (d, C-1), 78.17 (s, C-3), 29.70 (t, C-4), 27.79 (t, C-5), 31.57 (d, C-6), 26.10 (t, C-7), 78.58 (d, C-8), 43.41 (d, C-10), 27.07 (q, C-11), 15.76 (q, C-12).

(1R,3S,6R,8R,10R)-3,10-Dimethyl-2,9-dioxatricyclo[4.3.1.0^{3,8}]decane **6b**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 0.85 (d, 3H^{12}, $J_{12,10}$ 7 Hz), 1.211 (s, 3H^{11}), 1.88 (m, H^{10}), 3.86 (m, H^{8}), 4.94 (m, H^{1}). ^{13}C NMR, δ: 104.96 (d, C-1), 79.34 (s, C-3), 29.18 (t, C-4), 19.49 (t, C-5), 31.02 (d, C-6), 30.95 (t, C-7), 77.73 (d, C-8), 40.07 (d, C-10), 26.98 (q, C-11), 14.60 (q, C-12).

Compounds **6a**,**b** in a ratio of ~1:1 between isomers: MS, *m*/*z*: 168 [M$^+$]. $[\alpha]_{580}^{20}$ +0.35 (*c* 0.45, $CHCl_3$).

Limonene diepoxide **1a**,**b** (0.01 g, 0.06 mmol) was added to a suspension of ascanite-bentonite clay (0.02 g, calcined for 3 h at 100 °C) and CH_2Cl_2 (2 ml, dried). The reaction mixture was stirred at room temperature for 5 min and filtered. Analysis by gas-liquid chromatography showed that the reaction mixture contained compounds **2**, **4**, **5** and **6a**,**b**.



Scheme 1

D results in compound **5** by the interaction of the hydroxyl group with the cationic centre.

With the use of column chromatography, individual compounds **2**–**5** were isolated, and compounds **6a**,**b** were separated as isomer mixtures in a ~1:1 ratio. The structures of compounds **1**–**6** were found by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Spectroscopic data for compound **4** are consistent with published data.[6]

Let us consider in more detail the structural characterization of the compounds obtained. In the structure of **3**, the occurrence of the long-range spin–spin coupling constant $^4J_{10,3a}$ 1 Hz of the $C^{10}H_3$ group suggests its axial orientation. According to Dreiding models, the spin–spin coupling constant between H-2 and H-9an protons ($^4J_{2,9an}$ 1.5 Hz) observed in the ^{1}H NMR spectrum of compound **2** is consistent with a structure in which the pyran ring exhibits a chair rather than boat shape. Signals due to methyl groups in the ^{1}H NMR spectra of compound **5** were attributed based on LRJMD spectra. Thus, on the suppression of the signal due to a methyl group at 1.24 ppm, a singlet at 78.21 ppm, a triplet at 70.01 ppm, and a doublet at 41.40 ppm appeared in the LRJMD spectra, which were attributed to the C-3, C-4 and C-9 atoms, respectively, whereas another set of signals appeared in the LRJMD spectrum on the suppression of the signal of another methyl group at 1.17 ppm: a doublet at 81.80 ppm (C-1), a singlet at 72.41 ppm (C-6) and a triplet at 31.12 ppm (C-7). Hence it follows that signals at 1.24 and 1.17 ppm in the ^{1}H NMR spectrum belong to the $C^{11}H_3$ and $C^{12}H_3$ groups, respectively. The signals of methyl groups in the ^{13}C NMR spectrum were attributed based on a two-dimensional ^{13}C–^{1}H correlation spectrum. The isomerism of compounds **6a**,**b** is likely due to different orientations of the methyl group at the C-10 atom; it is believed that this group occurs in the β- or α-position in isomer **6a** or **6b**, respectively. This is suggested by the chemical shifts of C-10, C-5 and C-7 atoms, which are most sensitive to changes in the position of a substituent at the C-10 atom.[8]

Compounds **2**, **5** and **6a**,**b** were not described previously, whereas compound **3** was isolated from the essential oil of *Haplopappus multifolius*,[7] and (+)-bottrospicatol **4** is the product of the action of *Streptomyces bottropensis* on (–)-*cis*-carveol.[6] The oxirane ring is a structural unit of many synthetic and natural biologically active compounds. Diepoxides can be formed in nature as a result of the enzymatic oxidation or autoxidation of terpene double bonds; therefore, studies of the reactions of diepoxides in acidic media are of importance for modelling reactions that occur under natural conditions and for supporting various biogenetic schemes.

Thus, we examined the reactions of limonene diepoxides under conditions of heterogeneous acid catalysis. Along with known compounds, a number of bicyclic and tricyclic oxygen-containing products, which were not described previously, were obtained.

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§ Limonene diepoxide **1a**,**b** (0.1 g, 0.6 mmol) was added to a suspension of zeolite β (0.2 g, calcined for 3 h at 500 °C) and CH_2Cl_2 (10 ml, dried). The reaction mixture was stirred for 20 min at room temperature and filtered. The crude product (0.08 g) was chromatographed (SiO_2, a hexane/hexane–80% diethyl ether eluent was used) to give 0.002 g (2%) of compound **2**, 0.01 g (10%) of compound **3** and 0.02 g (20%) of compound **5**.

(1R,4R,5R)-4,8-Dimethyl-2-oxabicyclo[3.3.1]non-7-en-4-ol **3**. ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 1.38 (d, 3H^{10}, $J_{10,3a}$ 1 Hz), 1.58 (dddd, H^{9an}, $J_{9an,9syn}$ 13 Hz, $J_{9an,5}$ 3.5 Hz, $J_{9an,1}$ 2 Hz, $J_{9an,3e}$ 1 Hz), 1.67 (m, 3H^{11}, $J_{11,6}$ 2.5 Hz, $J_{11,6'}$ 1.5 Hz, $J_{11,7}$ 1.5 Hz), 1.79 (m, H^5), 2.03 (dddd, H^{9syn}, J 13 Hz, $J_{9syn,5}$ 3.5 Hz, $J_{9syn,1}$ 3.5 Hz, $J_{9syn,6'}$ 1.5 Hz), 2.05 (m, H^6), 2.42 (dm, H$^{6'}$, $J_{6',6}$ 19 Hz, $J_{6',7}$ 4.5 Hz, $J_{6',5}$ 1.5 Hz, $J_{6',9syn}$ 1.5 Hz, $J_{6',11}$ 1.5 Hz), 3.16 (ddd, H^{3e}, $J_{3e,3a}$ 11 Hz, $J_{3e,5}$ 1.2 Hz, $J_{3e,9an}$ 1 Hz), 3.33 (dq, H^{3a}, J 11 and 1 Hz), 3.86 (m, H^1, $J_{1,9syn}$ 3.5 Hz, $J_{1,9an}$ 2 Hz), 5.67 (m, H^7, $J_{7,6'}$ 4.5 Hz, $J_{7,6}$ 3 Hz, $J_{7,11}$ 1.5 Hz). ^{13}C NMR, δ: 69.46 (d, C-1), 67.46 (t, C-3), 69.52 (s, C-4), 36.37 (d, C-5), 26.10 (t, C-6), 126.49 (d, C-7), 130.02 (s, C-8), 29.58 (t, C-9), 27.55 (q, C-10), 21.48 (q, C-11). MS, *m*/*z*: 168 [M$^+$]. $[\alpha]_{580}^{20}$ +50 (*c* 0.2, $CHCl_3$).

Limonene diepoxide **1a**,**b** (0.01 g, 0.06 mmol) was added to a suspension of a TiO_2/SO_4^{2-} solid superacid (0.02 g, calcined for 3 h at 400 °C) and CH_2Cl_2 (2 ml, dried). The reaction mixture was stirred for 5 min at room temperature and filtered. Analysis by gas–liquid chromatography showed that the reaction mixture contained compounds **2**, **3** and **5**.

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