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Synthesis and absolute stereochemistry of marine nor-sesquiterpene austrodoric acid

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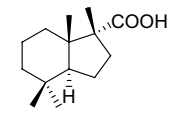
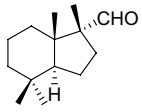
Abstract—An enantiospecific synthesis of the nor-sesquiterpene austrodoric acid **1**, recently isolated from an Antarctic marine mollusk, has been achieved. The synthetic strategy was based on the ring contraction of a suitable homo-drimanic epoxide **3**, easily obtained from commercial (+)-sclareolide **4**. The absolute configuration of natural austrodoric acid, not determined previously, has been now established by analyzing the CD profile of synthetic **1**, which was the same as the natural compound.

1. Introduction

Austrodoric acid **1** and austrodoral **2** are two related nor-sesquiterpenes recently isolated from the skin extract of Antarctic dorid nudibranch *Austrodoris kerguelenensis*.[1] They possess a bicyclic structure with the unprecedented carbon backbone, which could biogenetically arise from a drimanic-like framework by a ring contraction process. The relative stereochemistry of natural nor-sesquiterpenes **1** and **2** was established on the basis of spectral data, whereas their absolute stereochemistry remained undetermined. A role of stress metabolites was suggested for these molecules that were detected in high levels in some selected specimens of *A. kerguelenensis*, which were kept in captivity in aquarium.[1] However, the biological activities of both compounds could not be evaluated due to their degradation during work-up. With the aim at both obtaining larger amounts of such molecules to test their biological potential and determining their absolute stereochemistry, a synthetic study towards this rearranged skeleton has been carried out.



austrodoric acid **1**



austrodoral **2**

2. Results and discussion

As shown in Scheme 1, in our retrosynthetic analysis the key step is the ring contraction of the homo-drimanic epoxide **3** followed by the cleavage of the side chain to give the desired final product. The key intermediate **3** could be easily obtained from commercial (+)-sclareolide **4**, via the acetate **5**.

Preparation of compound **3** was carried out as shown in Scheme 2, starting from compound **5**, which was obtained from commercial (+)-sclareolide **4** according to the literature procedure.[2,3] Selective dehydration of acetate **5** to the corresponding tetra-substituted olefin **6** was performed with iodine in refluxing benzene. As has been reported,[4] the direction of this kind of dehydration strongly depends on the refluxing temperature conditions. So, we have investigated this reaction using an oil heating bath adjusted at different temperatures: from 85 °C (minimum refluxing rate) to 127 °C (the maximum refluxing rate). As expected, at the minimum refluxing rate a mixture of isomeric dehydrated compounds was

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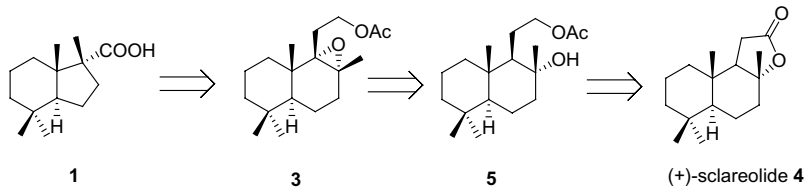
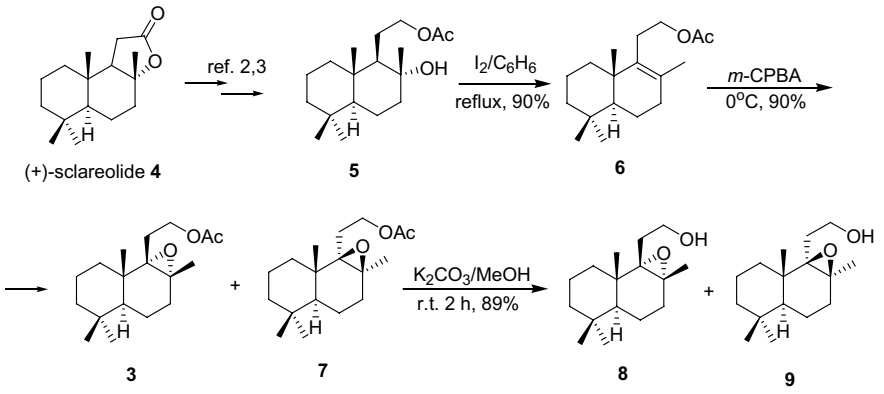


Scheme 1. Retrosynthetic analysis of austrodoric acid.

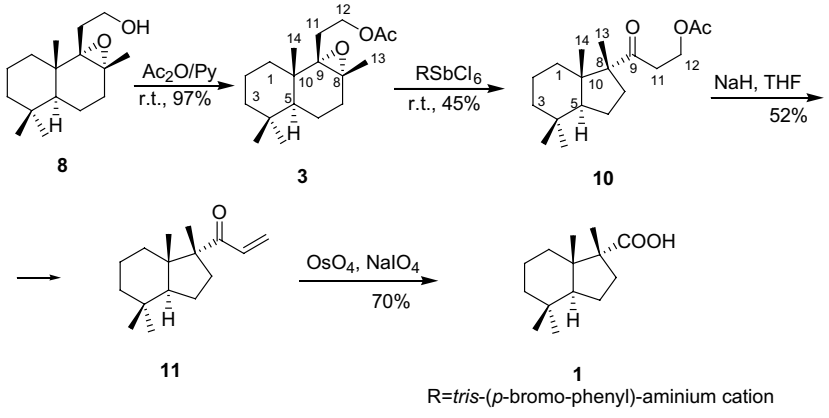


Scheme 2.

obtained, while dehydration performed at the maximum refluxing rate (heating bath temperature 127 °C) gave the thermodynamically more favored isomer **6** almost exclusively (90% yield). Treatment of compound **6** with *m*-CPBA at 0 °C for 2 h gave a mixture of the corresponding epoxides **3** and **7** (ratio 3:1 by ^{1}H NMR). Unfortunately, the separation of this mixture proved impossible by flash chromatography. So we decided to hydrolyze the mixture and separate the corresponding epoxyalcohols **8** and **9** by silica-gel column chromatography (ethyl acetate/light petroleum ether gradient).

Acetylation of the individual epoxyalcohols **8** and **9** provided pure epoxyacetates **3** (97% yield) and **7** (97% yield). Epoxide **3** was considered as the precursor for the subsequent steps, as shown in Scheme 3. The ring contraction reaction that has been reported to occur with different reagents[5–7] was in this case performed by using a complex Lewis acid, tris-(*p*-bromo-phenyl)-aminium-hexachloro-antimonate, which has efficiently promoted this kind of isomerization in related epoxides.[8] Treatment of epoxide **3** with a catalytic amount of *tris*-(*p*-bromo-phenyl)-aminium-hexachloro-antimonate in DCM at room temperature provided a mixture of isomerization products that was subjected to chromatography on a silica-gel column. Pure rearranged acetoxy-ketone **10** was obtained by elution with 3% ethylacetate in benzene.

The next objective was the cleavage of the side chain of the acetoxy-ketone **10**. The formation of the silyl enolether derivative of **10**, which could be submitted to a subsequent oxidative degradation, was examined.[9] But the treatment of **10** with *tert*-butyldimethylsilyl chloride



Scheme 3.

in the presence of sodium hydride (6 equiv) did not give the expected silyl enolether, the α,β-unsaturated ketone **11** being the predominating reaction product. The explanation for this reaction course can most probably be found on examining the steric hindrance around the oxygen atom of the ketone functionality. Under these circumstances, the formation of a bulky TBDMS enolether did not occur. On the contrary, the anion formed under the action of sodium hydride was stabilized by the elimination of the acetate group.

However, having the keto-olefin **11** in our hands, we decided to carry out the double bond hydroxylation followed by an oxidative degradation of diol derivative. This was achieved in a one-pot procedure, employing a catalytic amount of osmium tetraoxide for double bond hydroxylation together with an excess of sodium periodate as both co-oxidant and reagent for oxidative cleavage of the arising hydroxyketone. The reaction mixture was stirred for 12 h in *tert*-butanol at 45 °C, at the end of this period the initial keto-olefin **11** was consumed. Usual work-up followed by flash chromatography of crude reaction mixture provided pure austrodoric acid **1**. Spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) of synthetic product were identical with those of natural sample isolated from the nudibranch *A. kerguelenensis*, whereas the specific rotation value was slightly different: $[\alpha]_D$ synth. −2 (*c* 0.15, $CHCl_3$); $[\alpha]_D$ nat. −16 (*c* 0.1, $CHCl_3$).[10] However, the absolute stereochemistry of natural austrodoric acid was definitively established as that reported by comparing the CD curve with that of synthetic product. Identical profiles[11] were obtained for both natural and synthetic samples.

In summary, a stereospecific synthesis of austrodoric acid **1**, a marine nor-sesquiterpene exhibiting an unprecedented carbon backbone, has been accomplished in seven steps from commercial homodrimane (+)-sclareolide **4**. Natural austrodoric acid **1**, the absolute stereochemistry of which has also been determined here, could be obtained by the mollusc in an analogous process from a drimane precursor. Further biosynthetic studies are necessary to demonstrate this hypothesis.

3. Experimental

3.1. General

Melting points were measured on a Kofler apparatus and are uncorrected. IR spectra were taken on a Bio-Rad FTS 7 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker WM 500, Bruker AM 400 and Bruker WM 300 spectrometers; chemical shifts are reported in ppm and are referred to $CHCl_3$ as internal standard (δ 7.26 for proton and δ 77.0 for carbon). Optical rotations were measured in $CHCl_3$ on a Jasco DIP 370 polarimeter, using a 10-cm cell. EIMS spectra were recorded on a Carlo Erba TRIO 2000 spectrometer, coupled with an INTEL computer. Commercial Merck Si gel 60 (70–230 mesh ASTM) was used for flash chromatography (FC), and Merck precoated Si gel plates were used for TLC. The chromatograms were sprayed with 0.1% $Ce(SO_4)_2$ in 2 N H_2SO_4 and heated at 80 °C for 5 min to detect the spots. All air and water sensitive reactions were performed in flasks flame dried and cooled under a positive flow of argon and conducted under an atmosphere of argon. Benzene was dried on refluxing with sodium and distillation. Dichloromethane was refluxed over P_2O_5 and distilled. All the reagents were purchased from Aldrich and used such as received.

3.2. (5*S*,10*S*)-Bicyclo-homofarnes-8(9)-en-12-yl acetate 6

Oxyacetate **5** (130 mg, 0.44 mmol), obtained from sclareolide **4** according to the literature procedure,[2,3] was dissolved in dry benzene (24 mL) and I_2 (89 mg, 0.35 mmol) was added in one portion. The reaction mixture was heated at reflux on an oil bath (bath temperature 127 °C) for 2 h. Then, the reaction mixture was poured into an ice-cooled solution of $Na_2S_2O_3$ (5%, 50 mL). Separation of the organic phase and extraction of the water phase with Et_2O (3 × 15 mL), provided the combined organic phase, which was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product (117 mg), which was subjected to flash chromatography (FC) on a short SiO_2 column. Elution with EtOAc/light petroleum ether mixture (3:97) gave pure **6** (110 mg, 90%): R_f (10% EtOAc in light petroleum ether) 0.61; $[\alpha]_D^{25}$ +117.1 (*c* 1.4, $CHCl_3$); IR (liquid film, cm^{-1}) 1742; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00 (m, 2H, H_2-12), 2.40 (m, 1H, H-11a), 2.25 (m, 1H, H-11b), 2.04 (OAc), 2.03 (m, 1H, H-7a), 1.95 (m, 1H, H-7b), 1.85 (m, 1H, H-1a), 1.65 (m, 2H, H-2a and H-6a), 1.62 (s, 3H, H_3-13), 1.40 (m, 3H, H-2b, H-3a and H-6b), 1.13 (m, 1H, H-3b), 1.10 (m, 2H, H-1b and H-5), 0.93 (s, 3H, H_3-14), 0.88 (s, 3H, H_3-15), 0.83 (s, 3H, H_3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.1 (*C*OCH_3), 135.6 (s, C-9), 128.9 (s, C-8), 64.1 (t, C-12), 51.7 (d, C-5), 41.7 (t, C-3), 38.6 (s, C-10), 37.0 (t, C-1), 33.7 (t, C-7), 33.3 (s, C-4), 33.3 (q, C-15), 27.1 (t, C-11), 21.7 (q, C-16), 21.0 (CO*C*H_3), 19.9 (q, C-14), 19.7 (q, C-13), 18.9 (t, C-2), 18.7 (t, C-6); EIMS (*m*/*z*) 278 (M^+, 3%), 218 (71), 203 (100), 189 (18), 175 (18), 147 (31), 133 (24), 107 (27); HREIMS: found 278.2249, $C_{18}H_{30}O_2$ requires 278.2246.

3.3. Epoxidation of compound 6

The tetrasubstituted acetate **6** (47 mg, 0.17 mmol) was dissolved in dry dichloromethane (0.5 mL) and treated at 0 °C with *m*-CPBA (0.22 mmol, 58 mg containing ca. 65% of *m*-CPBA) in 0.5 mL of dichloromethane. After stirring for 1 h at 0 °C, the reaction mixture was diluted with diethyl ether (3 mL) and treated with 5 mL of an aqueous solution of $Na_2S_2O_3$ (5%). Separation of phases, extraction of the aqueous phase with diethyl ether (3 × 10 mL) gave the crude ether extract, which was washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude

product (57 mg), which was subjected to FC on a short SiO_2 column. Elution with EtOAc/petroleum ether mixture (3:97) gave a one-spot mixture of epoxides **3** and **7** (45 mg, 90%): R_f (10% EtOAc in light petroleum ether) 0.42; ratio **3/7**, 3:1 by ^1H NMR spectrum of the mixture (integration of H_2-12 signal: triplet at δ 4.06 in **3** and multiplet at δ 4.19 in **7**).

3.4. Hydrolysis of epoxide mixture

The mixture of epoxides **3** and **7** (62 mg, 0.21 mmol) was dissolved in methanol (1.5 mL) and treated with K_2CO_3 (58 mg, 0.42 mmol). After 2 h of stirring at room temperature, methanol was distilled off and the residuum was partitioned between brine (10 mL) and diethyl ether (10 mL). Separation of the ether part and extraction of the aqueous phase with diethyl ether (3×10 mL) gave the crude ether extract, which was washed with brine to neutral and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a crude product (52.0 mg), which was subjected to FC on a short SiO_2 column. Elution with 10% EtOAc/light petroleum ether gave pure epoxyalcohols **8** (32 mg, 60%) and **9** (15 mg, 29%).

Major diastereoisomer (5*S*,8*R*,9*S*,10*S*)-8,9-epoxy-bicyclo-homofarnes-12-ol **8**: R_f (30% EtOAc/light petroleum ether) 0.26; $[\alpha]_D^{25}$ +29.1 (*c* 0.5, $CHCl_3$); IR (liquid film, cm^{-1}) 3431, 1461, 1381; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.81 (m, 1H, H-12a), 3.66 (m, 1H, H-12b), 2.55 (br s, –OH), 2.00 (m, 1H, H-11a), 1.90 (m, 2H, H-7a and H-11b), 1.80 (m, 1H, H-7b), 1.70 (m, 1H, H-1a), 1.52 (m, 2H, H_2-2), 1.48 (m, 1H, H-5), 1.35 (m, 3H, H-1b), 1.30 (s, 3H, H_3-13), 1.20 (m, 1H, H-6b), 1.18 (m, 1H, H-3b), 0.98 (s, 3H, H_3-14), 0.84 (s, 3H, H_3-15), 0.81 (s, 3H, H_3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 72.4 (s, C-9), 63.0 (s, C-8), 61.8 (t, C-12), 42.2 (d, C-5), 41.4 (t, C-3), 38.4 (s, C-10), 34.8 (t, C-1), 33.5 (q, C-15), 32.9 (s, C-4), 29.0 (t, C-7), 27.7 (t, C-11), 21.8 (q, C-13), 21.5 (q, C-16), 18.3 (t, C-2), 17.2 (t, C-6), 17.1 (q, C-14); EIMS (*m*/*z*) 252 (M^+, 5%), 237 (20), 219 (21), 207 (43), 189 (34), 167 (77), 149 (52), 138 (59), 123 (100), 95 (87), 81 (59).

Minor diastereoisomer (5*S*,8*S*,9*R*,10*S*)-8,9-epoxy-bicyclo-homofarnes-12-ol **9**: R_f (30% EtOAc/light petroleum ether) 0.18; $[\alpha]_D^{25}$ +17.6 (*c* 0.6, $CHCl_3$); IR (liquid film, cm^{-1}) 3414, 1465, 1379; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (m, 1H, H-12a), 3.75 (m, 1H, H-12b), 2.44 (br s, –OH), 2.09 (m, 1H, H-7a), 2.08 (m, 1H, H-11a), 1.82 (m, 1H, H-11b), 1.76 (m, 1H, H-1a), 1.71 (m, 1H, H-2a), 1.66 (m, 1H, H-7b), 1.54 (m, 1H, H-2b), 1.42 (m, 1H, H-3a), 1.33 (s, 3H, H_3-13), 1.32 (m, 1H, H-6), 1.30 (m, 1H, H-1b), 1.20 (m, 1H, H-6b), 1.15 (m, 1H, H-3b), 1.11 (s, 3H, H_3-14), 0.83 (s, 3H, H_3-15), 0.77 (m, 1H, H-5), 0.78 (s, 3H, H_3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 72.3 (s, C-9), 64.4 (s, C-8), 61.7 (t, C-12), 53.6 (d, C-5), 41.3 (t, C-3), 38.5 (s, C-10), 38.0 (t, C-1), 35.6 (t, C-7), 33.9 (s, C-4), 33.2 (q, C-15), 31.3 (t, C-11), 21.9 (q, C-16), 21.2 (q, C-13), 19.8 (t, C-2), 17.1 (q, C-14), 16.9 (t, C-6); EIMS (*m*/*z*) 252 (M^+, 2%), 234 (6), 207 (22), 179 (18), 167 (50), 123 (67), 95 (100), 69 (84), 55 (62).

3.5. Acetylation of compound 8

Pure epoxyalcohol **8** (28 mg, 0.11 mmol) was dissolved in 0.5 mL of dry pyridine and treated with 0.2 mL of acetic anhydride at room temperature. The reaction mixture was left overnight. Then it was poured into ice water (10 mL) and extracted with diethyl ether (3×10 mL). The ether extracts were washed successively with a 10% aqueous solution of sulfuric acid (5 mL), brine (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product (34 mg), which was subjected to FC on a short SiO_2 column. Elution with EtOAc/light petroleum ether mixture (3:97) gave pure (5*S*,8*R*,9*S*,10*S*)-8,9-epoxy-bicyclohomofarnes-12-yl acetate **3** (32 mg, 97%): R_f (10% EtOAc/light petroleum ether) 0.42; $[\alpha]_D^{25}$ +50.3 (*c* 0.7, $CHCl_3$); IR (liquid film, cm^{-1}) 1743, 1460, 1237; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.06 (t, 2H, H_2-12), 2.08 (m, 1H, H-11a), 2.02 (–OAc), 1.90 (m, 1H, H-7a), 1.89 (m, 1H, H-11b), 1.80 (m, 1H, H-7b), 1.72 (m, 1H, H-1a), 1.52 (m, 2H, H_2-2), 1.50 (m, 1H, H-5), 1.36 (m, 1H, H-3a), 1.35 (m, 2H, H-1b and H-6a), 1.22 (s, 3H, H_3-13), 1.20 (m, 1H, H-6b), 1.15 (m, 1H, H-3b), 0.98 (s, 3H, H_3-14), 0.82 (s, 3H, H_3-15), 0.80 (s, 3H, H_3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.0 (*C*OCH$_3$), 69.7 (s, C-9), 62.3 (t, C-12), 61.9 (s, C-8), 42.3 (d, C-5), 41.4 (t, C-3), 38.2 (s, C-10), 34.4 (t, C-1), 33.5 (q, C-15), 32.9 (s, C-4), 29.0 (t, C-7), 25.4 (t, C-11), 21.7 (q, C-13), 21.4 (q, C-16), 21.0 (CO*C*H$_3$), 18.4 (t, C-2), 17.1 (t, C-6), 16.9 (q, C-14); EIMS (*m*/*z*) 294 (M^+, 1.6%), 276 (5), 234 (16), 219 (28), 191 (23), 163 (100), 133 (29), 119 (46), 97 (49); HRE-IMS: found 294.2191, $C_{18}H_{30}O_3$ requires 294.2195.

3.6. Acetylation of compound 9

Pure epoxyalcohol **9** (10 mg, 0.04 mmol) was dissolved in 0.5 mL of dry pyridine and treated with 0.2 mL of acetic anhydride at room temperature. The reaction mixture was left overnight. Then it was poured into ice water (10 mL) and extracted with ether (3×10 mL). The ether extracts were washed successively with a 10% aqueous solution of sulfuric acid (5 mL), brine (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product (14 mg), which was subjected to FC on a short SiO_2 column. Elution with EtOAc/light petroleum ether mixture (3:97) gave pure (5*S*,8*S*,9*R*,10*S*)-8,9-epoxy-bicyclo-homofarnes-12-yl acetate **7** (11 mg, 97%): R_f (10% EtOAc/light petroleum ether) 0.42; $[\alpha]_D^{25}$ +30.6 (*c* 0.6, $CHCl_3$); IR (liquid film, cm^{-1}) 1743, 1465, 1234; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.19 (m, 2H, H_2-12), 2.05 (m, 1H, H-2a), 2.04 (–OAc), 2.03 (m, 1H, H-11a), 1.89 (m, 1H, H-11b), 1.81 (m, 1H, H-1a), 1.70 (m, 1H, H-2a), 1.65 (m, 1H, H-7b), 1.58 (m, 1H, H-2b), 1.39 (m, 1H, H-3a), 1.36 (m, 1H, H-1b), 1.31 (s, 3H, H_3-13), 1.30 (m, 1H, H-6a), 1.20 (m, 1H, H-6b), 1.14 (m, 1H, H-3b), 1.02 (s, 3H, H_3-14), 0.83 (s, 3H, H_3-15), 0.77 (s, 3H, H_3-16), 0.76 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.0 (*C*OCH$_3$), 70.6 (s, C-9), 64.5 (s, C-8), 62.3 (t, C-12), 53.7 (d, C-5), 41.3 (t, C-3), 38.4 (s, C-10), 37.4 (t, C-1), 35.6 (t, C-7), 33.8 (s, C-4), 33.1

(q, C-15), 30.1 (t, C-11), 21.9 (q, C-16), 21.0 (q, C-13), 21.0 (CO*CH*$_3$) 19.7 (t, C-2), 16.8 (t, C-6), 16.6 (q, C-14); EIMS (*m*/*z*) 294 (M^+, 3%), 276 (6), 234 (28), 219 (34), 191 (24), 163 (100), 133 (31), 119 (54).

3.7. Ring contraction reaction

Epoxyacetate **3** (300 mg, 1.02 mmol) was dissolved in dichloromethane (5 mL) and tris-(*p*-bromophenyl)-aminium hexachloroantimonate ($RSbCl_6$) (17 mg, 0.02 mmol) was added. The solution was left under stirring for 1 h at room temperature. After this period, the solvent was evaporated off and the crude material was subjected to FC on a silica gel column. Elution with Et_2O/benzene mixture (1:99) gave pure (5*S*,8*R*,10*S*)-9-(2-acetoxy-ethyl)-austrodor-9-one **10** (135 mg, 45%): R_f (5% EtOAc/benzene) 0.43; $[\alpha]_D^{25}$ −2.4 (*c* 1.6, $CHCl_3$); CD (*n*-hexane), θ_{241} +700, θ_{293} −1850; IR (liquid film, cm^{-1}) 1734, 1695; ^1H NMR ($CDCl_3$, 400 MHz, numbering is given as shown in formula to make clear the comparison with the precursor) δ 4.33 (dd, $J = 6.8$, 6.1 Hz, 2H, H_2-12), 2.81 (dt, $J = 17.6$, 6.8 Hz, 1H, H-11a), 2.70 (dt, $J = 17.6$, 6.1 Hz, 1H, H-11b), 2.23 (m, 1H, H-7a), 2.01 (–OAc), 1.68 (m, 1H, H-6a), 1.60 (m, 1H, H-1a), 1.56 (m, 1H, H-2a), 1.48 (m, 1H, H-2b), 1.40 (m, 1H, H-6b), 1.38 (m, 2H, H-3a and H-5), 1.22 (m, 1H, H-7b), 1.18 (s, 3H, H_3-13), 0.93 (m, 1H, H-3b), 0.91 (m, 1H, H-1b), 0.883 (s, 3H, H_3-14), 0.877 (s, 3H, H_3-16), 0.86 (s, 3H, H_3-15); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 214.1 (s, C-9), 170.9 (*CO*CH_3), 61.3 (s, C-8), 60.0 (t, C-12), 52.4 (d, C-5), 47.2 (s, C-10), 41.1 (t, C-3), 39.8 (t, C-11), 35.4 (t, C-1), 33.7 (q, C-15), 33.2 (s, C-4), 32.7 (t, C-7), 21.7 (t, C-6), 21.5 (q, C-16), 20.9 (CO*CH*$_3$), 20.1 (q, C-13), 20.0 (t, C-2), 16.0 (q, C-14); EIMS (*m*/*z*) 234 (M^+−Ac, 10%), 219 (20), 191 (20), 177 (47), 163 (80), 138 (57), 123 (100), 97 (70), 81 (47).

3.8. (5*S*,8*R*,10*S*)-9-Vinyl-austrodor-9-one 11

The rearranged acetoxy-ketone **10** (29.3 mg, 0.10 mmol) was dissolved in dry THF (1 mL) and TBDSCl (20 mg, 0.13 mmol) was added. The resulting solution was cooled at −78 °C, while 9.6 mg (0.40 mmol) of NaH were added. After stirring the reaction mixture at room temperature for 4 h, it was diluted with diethyl ether and passed through a short silica gel pad. The crude product was subjected to FC. Elution with Et_2O/benzene mixture (1:99) gave 12 mg (52%) of α,β-unsaturated ketone **11**: R_f (5% EtOAc/benzene) 0.64; $[\alpha]_D^{25}$ −6.4 (*c* 0.3, $CHCl_3$); CD (*n*-hexane), θ_{234} −1014; IR (liquid film, cm^{-1}) 1687; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.66 (dd, $J = 16.9$, 10.2 Hz, 1H, H-11), 6.22 (dd, $J = 16.9$, 2.1 Hz, 1H, H-12a), 5.51 (dd, $J = 10.2$, 2.1 Hz, 1H, H-12b), 2.35 (ddd, $J = 16.1$, 9.9, 5.2 Hz, 1H, H-7a), 1.70 (m, 1H, H-6a), 1.60 (m, 1H, H-2a), 1.58 (m, 1H, H-1a), 1.46 (m, 1H, H-2b), 1.41 (m, 1H, H-6b), 1.38 (m, 1H, H-3a), 1.33 (m, 1H, H-5), 1.28 (m, 1H, H-7b), 1.18 (s, 3H, H_3-13), 0.98 (m, 1H, H-1b), 0.93 (m, 1H, H-3b), 0.91 (s, 3H, H_3-14), 0.88 (s, 3H, H_3-16), 0.84 (s, 3H, H_3-15); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 204.9 (s, C-9), 134.3 (d, C-11), 125.9 (t, C-12), 60.3 (s, C-8), 53.0 (d, C-5), 46.9 (s, C-10), 41.0 (t, C-3), 35.5 (t, C-1), 33.6 (q, C-15), 33.2 (s, C-4), 32.2 (t, C-7), 21.6 (t, C-6), 21.4 (q, C-16), 20.2 (q, C-13), 19.9 (t, C-2), 15.8 (q, C-14); EIMS (*m*/*z*) 234 (M^+, 11%), 219 (8), 201 (11), 191 (3), 179 (28), 150 (23), 138 (87), 123 (100), 97 (20); HREIMS: found 234.1980, $C_{16}H_{26}O$ requires 234.1983.

3.9. (5*S*,8*R*,10*S*)-Austrodoric acid 1

Ketone **11** (8 mg, 0.03 mmol) was dissolved in *tert*-butanol (0.5 mL) and water (0.1 mL) and $NaIO_4$ (37 mg, 0.17 mmol), along with a 2.5% solution of OsO_4 in *tert*-butanol (4.4 μL, 0.00035 mmol), was added to the resulting solution. The reaction mixture was stirred at 45 °C for 12 h. Then it was diluted with ether, filtrated and the filtrate was washed with brine. The crude material (11 mg) was subjected to FC. Elution with EtOAc/light petroleum ether mixture (3:97) gave 5 mg (70%) of pure compound **1**: R_f (20% EtOAc/light petroleum ether) 0.25; $[\alpha]_D^{25}$ −2.0 (*c* 0.15, $CHCl_3$); CD (*n*-hexane), θ_{214} −470; IR (liquid film, cm^{-1}) 1685; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.32 (m, 1H, H-7a), 1.68 (m, 1H, H-6a), 1.62 (m, 1H, H-5), 1.60 (m, 1H, H-2a), 1.58 (m, 1H, H-1a), 1.52 (m, 1H, H-2b), 1.45 (m, 1H, H-6b), 1.42 (m, 2H, H-3a, H-7b), 1.17 (s, 3H, H_3-10), 1.12 (ddd, $J = 13$, 13, 4 Hz, 1H, H-1b), 1.02 (ddd, $J = 13$, 13, 4 Hz, 1H, H-3b), 0.90 (s, 3H, H_3-14), 0.87 (s, 6H, H_3-12 and H_3-13); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 182.2 (s, C-11), 56.4 (s, C-9), 53.3 (d, C-5), 46.7 (s, C-8), 41.2 (t, C-3), 35.3 (t, C-1), 33.8 (q, C-13), 33.3 (s, C-4), 33.1 (t, C-7), 21.6 (t, C-6), 21.6 (q, C-14), 20.5 (q, C-10), 20.1 (t, C-2), 15.7 (q, C-12); EIMS (*m*/*z*) 224 (M^+, 3%), 209 (13), 191 (1.6), 163 (11), 138 (11), 123 (100), 95 (16).

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10. The $[\alpha]_D$ value of natural austrodoric acid has been erroneously reported with opposite sign in Ref. 1.
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