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Tetrabromoepifenchone: a convenient precursor for the synthesis of chiral bicyclo[2.2.1]heptane and bicyclo[2.1.1]hexane derivatives

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ABSTRACT

The regiospecific reduction and Favorskii rearrangement of enantiopure tetrabromoepifenchone, which could be easily obtained by bromination of camphor, have been investigated. The selective formation of new functionalized chiral bicyclo[2.2.1]heptane and bicyclo[2.1.1]hexane derivatives in good yield has been demonstrated. Our approach provides a simple pathway for the large-scale synthesis of a wide range of novel functionalized bicyclic terpenoids starting from easily available camphor.

1. Introduction

Naturally occurring bicyclic terpenoids have attracted the attention of many chemists. Among many other compounds, special attention has been paid to camphor derivatives, which are widely used in the construction of complex chiral molecules;[1–10] the framework for chiral auxiliaries in synthesis and catalysis,[11–16] and drugs and cosmetics.[17–22] These compounds have many applications due to their unique possibility of forming regio- and diastereoselective derivatives at almost all positions of the camphor skeleton. Camphor is an inexhaustible natural source for the synthesis of various chiral structures since its enantiomers are readily available.

Electrophilic bromination is a very important approach for the preparation of bromo-functionalized terpenoid derivatives, which are popular as intermediates in organic synthesis due to the ease of further modifications via nucleophilic substitutions or various skeletal rearrangements and cyclizations.[23–27]

Despite the large number of studies on bicyclic terpenoids, only a few epifenchone (3,3,4-trimethylbicyclo[2.2.1]heptan-2-one) derivatives are known. The reported chemical properties of epifenchone are limited to the reaction of the carbonyl group; the formation of a semicarbazone[28] and the reduction to a mixture of the corresponding *exo*- and *endo*-alcohols.[29]

Herein we report our investigation into the chemical reactivity of tetrabromoepifenchone **1**, a compound that can be obtained in high yield by the direct bromination of camphor, with the aim to explore potential synthetic pathways to a range of novel chiral scaffolds.[30]

2. Results and discussion

The synthesis of (1*S*,4*R*,7*R*)-1,7-dibromo-4-(dibromomethyl)-3,3-dimethylbicyclo[2.2.1]heptan-2-one **1** was performed in two steps starting from commercially available (*R*)-(+)-camphor. Since **1** is a tetrabromoketone, it is, in principle, possible to modify this compound in several ways. We decided to focus on the selective reduction and rearrangement reactions to obtain new functionalized chiral bicyclo[2.2.1]heptane and bicyclo[2.1.1]hexane derivatives.

We have demonstrated that the selective substitution of one, two, and three bromine atoms can be achieved by careful choice of the reduction conditions with three different products **2**–**4** obtained in good yields (Scheme 1). When a mixture of **1** and zinc dust in acetic acid was stirred for 2 h at 23 °C, the formation of tribromoketone **2** was observed due to the selective reduction of one bromine atom of the dibromomethyl group. Under harsher reaction conditions (60–65 °C, 4 h), the reduction of the dibromomethyl group to a methyl group was possible and led to the formation of dibromoketone **3**. In both cases, the formation of small amounts of symmetric alkene **5** was observed. The third bridge bromine atom could also be reduced to yield monobromoketone **4** when the reaction mixture was refluxed for 50 h (bromine atom in the bridgehead position remained unchanged). The use of zinc in acetic acid for the reduction of *gem*-dibromide into its monobromide;[31,32] a bromomethyl group into methyl group;[33,34] a bridge bromide to a methylene group[35] was previously reported. These reactions usually proceed via the formation of carbanionic intermediates (Scheme 2).

The symmetric alkene **5** is particularly interesting in the light of the chemical rearrangement discussed herein since it could basically undergo selective reduction of bromine atoms, Favorskii

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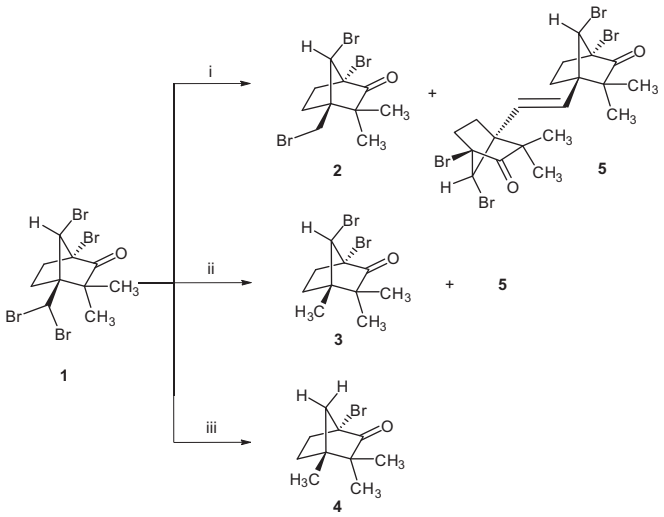


Scheme 1. Selective reduction of tetrabromoepifenchone **1**. Reagents and conditions: (i) Zn, AcOH, 23 °C, 2 h, 81% (**2**) and 10% (**5**); (ii) Zn, AcOH, 60–65 °C, 4 h, 82% (**3**) and 10% (**5**); (iii) Zn, AcOH, reflux, 50 h, 85% (**4**).

rearrangement (if attacked by a nucleophile at the carbonyl groups) or oxidative cleavage of the double bond with the formation of simpler scaffolds, which were carboxy-functionalized at the bridgehead position. It should be noted that this alkene, which is practically insoluble in alcohol or dichloromethane, can be easily separated.

A possible mechanism for the formation of **5** could involve the formation of radical **6** stabilized by the presence of the bromine atom at the α-position,[36] which dimerizes to the dibromoderivative **7**, which could further give the corresponding alkene via vicinal reductive elimination of two bromine atoms.

We obtained a crystal structure of **5** using single-crystal X-ray diffraction in order to provide evidence of its structure and a

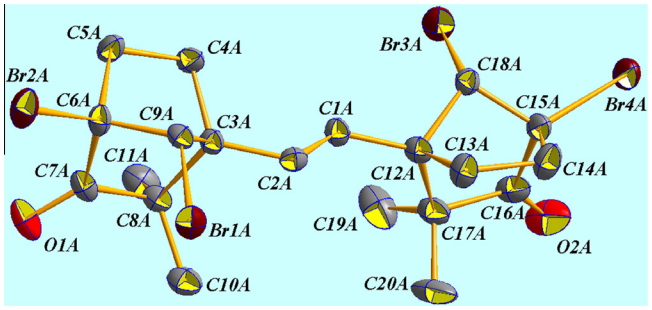


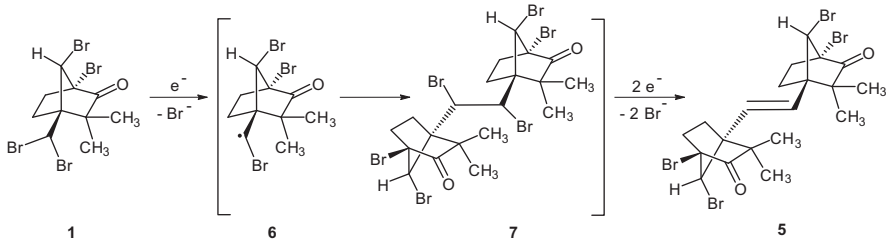
Figure 1. X-ray crystal structure of **5**, showing 30% probability displacement ellipsoids.

clear-cut answer regarding the double bond configuration (Fig. 1). The selective formation of the *trans*-alkene could be explained by considerable steric repulsion of the bulky bicyclic substituents during the final step of the transformation of **7** into **5**.

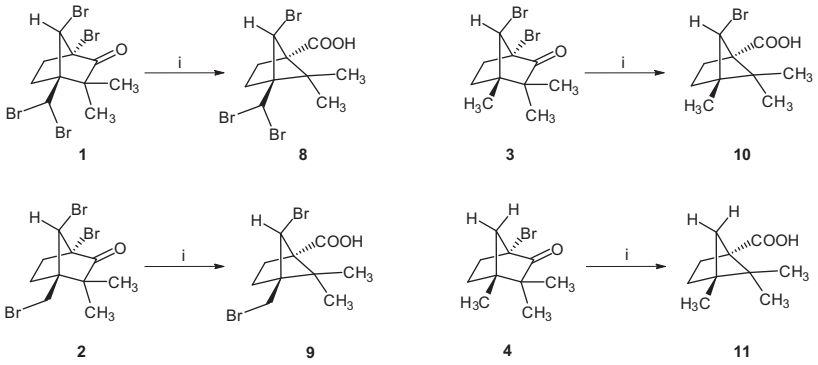
Compounds **1**–**4**, which have a bridgehead bromine atom at the α-position to the carbonyl group, undergo Favorskii rearrangement, to form bicyclo[2.1.1]hexane carboxylic acids in good yields; this was previously reported for the transformation of **1** into **8** (Scheme 3).[37]

Compounds **1** and **2**, which contain dibromomethyl and bromomethyl groups, form the corresponding carboxylic acids **8** and **9** without nucleophilic substitutions of bromine atoms under basic reaction conditions (sodium 2-propoxide in 2-propanol, reflux 2 h). These results prove the hypothesis that the formation of symmetric alkene **5** via carbanionic intermediates is unlikely due to the exceptionally low reactivity of neopentyl-type dibromomethyl and bromomethyl groups in the reactions of nucleophilic substitution.

Hypothetically, acids **9**, **10**, and **11** can be prepared by the stepwise reduction of bromine atoms in **8**. However, our attempts to prepare **9** in this way always led to a mixture of **9** and **10** under



Scheme 2. Proposed mechanism of formation of alkene **5**.



Scheme 3. Formation of bicyclo[2.1.1]hexane carboxylic acids via Favorskii rearrangement. Reagents and conditions: (i) *i*-PrONa/*i*-PrOH, reflux 1 h; then H_2O, reflux 1 h; HCl.

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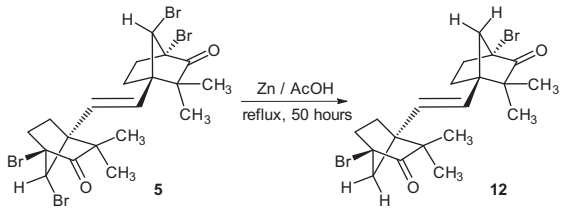
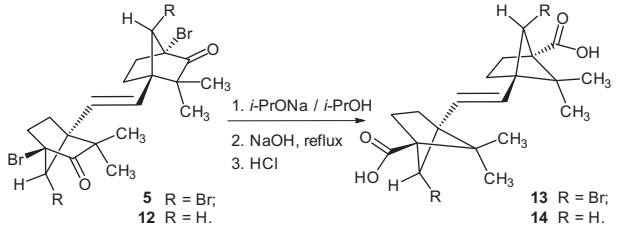
all of the tested reaction conditions. Carboxylic acids **10** and **11** can be obtained from **8** in preparative yields. As a result of treatment of the alkene **5** with zinc powder in acetic acid it was converted into compound **12** (Scheme 4).



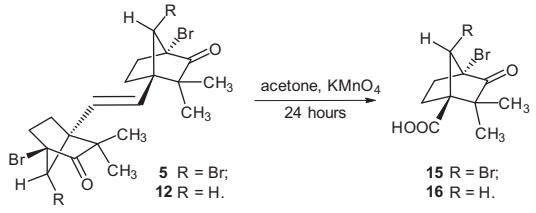
Scheme 4. Selective reduction of alkene **5**.

Since both compound **5** and **12** have a bridgehead bromine atom, we decided to examine the possibility of obtaining the corresponding acid derivatives of alkenes using the same rearrangement conditions as in the case of compounds **8**–**11** discussed above. Dicarboxylic acids **13** and **14** were prepared successfully in high yields (Scheme 5).



Scheme 5. Formation of bicyclo[2.1.1]hexane dicarboxylic acids via a Favorskii rearrangement.

The double C=C bonds in **5** and its reduced analog **12** can be easily oxidized into carboxyl groups by using potassium permanganate in acetone solution, to give bicyclo[2.2.1]heptane carboxylic acids **15** and **16**, respectively (Scheme 6).



Scheme 6. Formation of bicyclo[2.2.1]heptane carboxylic acids.

The orthogonality of the functional groups in the obtained compounds enables easy further modification, thus making them convenient starting materials for the construction of more complicated chiral molecules.

3. Conclusions

A range of new functionalized bicyclic building blocks with a sterically crowded chiral environment were obtained starting from readily available tetrabromoepifenchone. Regiospecific reduction of bromine atoms, along with Favorskii rearrangement allowed the preparation of bridgehead bicyclo[2.2.1]heptane and bicyclo[2.1.1]hexane carboxylic acids in high yields. Such scaffolds can be used as convenient and effective chiral auxiliaries in enantioselective synthesis.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on 'Mercury 400' Varian and Bruker AM 400 (400 MHz) spectrometers. Tetramethylsilane was used as the internal standard. IR spectra were obtained on a Perkin Elmer BX II spectrometer. λ_{max} (cm^{-1}) values in IR spectra are given for the main absorption bands. HRMS were recorded on a LTQ Orbitrap equipped with electrospray ion source. Optical rotations were measured with a Perkin Elmer P 241 polarimeter in a 10 cm cell with the solvent indicated.

Suitable X-ray quality crystals of **5** were grown in nitromethane. Intensities of reflections were measured on an automatic Xcalibur 3 diffractometer (Oxford Diffraction, Abingdon, UK; graphite monochromated $Mo_{K\alpha}$ radiation, CCD detector x scanning). All structures were solved by a direct method using the SHELX97 package.[38] The positions of the hydrogen atoms were located from electron density difference maps and refined by a riding model with $U_{iso} = nU_{eq}$ of the carrier non-hydrogen atom ($n = 1.5$ for methyl-group and $n = 1.2$ for other hydrogen atoms). Nonhydrogen atoms were refined by a full-matrix least-squares method against F^2 within the anisotropic approximation. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (12 Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). The CCDC dep. number for **5** is 1030932. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/products/csd/request/.

4.1.1. Materials

All starting materials were purchased from Acros, Merck, Aldrich and Fluka chemicals. All solvents were distilled before use.

4.2. (1*S*,4*S*,7*R*)-1,7-Dibromo-4-(bromomethyl)-3,3-dimethylbicyclo[2.2.1]heptan-2-one 2 and (1*S*,4*R*,7*R*,1′*S*,4′*R*,7′*R*)-4,4′-(*E*)-ethene-1,2-diylbis(1,7-dibromo-3,3-dimethylbicyclo[2.2.1]heptan-2-one) 5

Zinc powder 5.00 g (0.077 mol) was added slowly to a stirred solution of compound **1** 10.00 g (21.4 mmol) in glacial acetic acid (350 mL) to maintain the solution at 23 °C. Upon completion of the addition, the resulting mixture was stirred for a further 2 h. Insoluble zinc salts and an excess of zinc powder were filtered off and washed by warm acetic acid three times. The resulting solution was evaporated under reduced pressure, after which distilled water (100 mL) and CH_2Cl_2 (50 mL) were added to the residue and the insoluble precipitate was filtered off to give alkene **5** with yield 0.66 g (10%). Mp: 290–293 °C. $[\alpha]_D^{20} = +68.3$ (c 0.95, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.92$ (s, 2H), 4.97 (s, 2H), 2.28–2.41 (m, 2H), 2.14–2.26 (m, 4H), 1.86–1.98 (m, 2H), 1.31 (s, 6H), 1.05 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 209.9$, 129.2, 72.6, 63.2, 52.3, 47.9, 32.3, 29.7, 24.4, 24.1. IR (KBr, cm^{-1}): 2993, 2973, 2933, 1760, 1458, 1259, 983, 842, 805. HRMS calcd for $C_{20}H_{25}Br_4O_2$ $[M+H]^+$: 612.8583; found: 612.8578.

The obtained CH_2Cl_2 solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give yellow crystals of **2** (81%). The product could be crystallized from a mixture of *i*-PrOH/hexane (5:1) 35 mL at −15 °C. Mp: 116–118 °C.

$[\alpha]_D^{20}$ = −41.0 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.33 (s, 1H), 3.65 (s, 2H), 2.26–2.41 (m, 1H), 2.01–2.23 (m, 3H), 1.47 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 70.4, 62.0, 50.9, 48.5, 33.1, 32.9, 28.5, 25.5, 23.9. IR (KBr, cm^{-1}): 2975, 2932, 2873, 1755, 983, 808, 788, 729, 669. HRMS calcd for $C_{10}H_{14}Br_3O$ $[M+H]^+$: 386.8589; found: 386.8585.

4.3. (1*S*,4*S*,7*R*)-1,7-Dibromo-3,3,4-trimethylbicyclo[2.2.1]heptan-2-one 3

Zinc powder 1.40 g (0.021 mol) was added slowly to a stirred solution of compound **1** 1.00 g (2.14 mmol) in glacial acetic acid (40 mL) to maintain the solution at 60–65 °C. Upon completion of the addition, the resulting mixture was stirred for a further 4 h. The insoluble zinc salts and an excess of zinc powder were filtered off. Acetic acid was evaporated under reduced pressure, after which distilled water (20 mL) and CH_2Cl_2 (25 mL) were added to the remaining solution and the insoluble precipitate was filtered off to give alkene **5** with 10% yield.

The obtained CH_2Cl_2 solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Yield 0.544 g (82%). An analytical sample could be prepared by crystallization from ethanol. Spectroscopic data of compound are identical to those reported earlier.[39]

4.4. (1*R*,4*R*)-1-Bromo-3,3,4-trimethylbicyclo[2.2.1]heptan-2-one 4

Zinc powder 42.0 g (0.63 mol) was added slowly to the stirred solution of compound **1** 10.00 g (21.4 mmol) in glacial acetic acid (300 mL), after which the mixture was refluxed for 50 h. Insoluble zinc salts and an excess of zinc powder were then filtered off. Acetic acid was evaporated under reduced pressure, after which distilled water (100 mL) was added to the remaining solution and the organic phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Distillation provided pure **4**, bp: 65–67 °C at 1.00 mmHg. Yield 4.2 g (85%). Spectroscopic data of compound are identical to those reported earlier.[33]

4.5. General procedure for synthesis of bicyclo[2.2.1]heptan carboxylic acids 8-11

Compound **1**–**4** (0.01 mol) was added to a stirred solution of sodium isopropoxide in 2-propanol, made by the addition of sodium (1.60 g, 0.069 mol) to 50 mL of dry 2-propanol. The resulting mixture was refluxed until the disappearance of the starting ketone (monitored by TLC, ca. 1 h). The mixture was then cooled to room temperature and water (270 mg, 15 mmol) was added before restarting the reflux until full hydrolysis of the intermediate isopropyl ester (monitored by TLC, ca. 45 min). Distilled water (15 mL) was added to the cooled mixture, and then the solvent was removed from the mixture under reduced pressure. Distilled water (100 mL) was added to the residue, then filtered and acidified using 1 M HCl to pH = 3. The resultant precipitate was filtered off and crystallized using 2-propanol.

4.5.1. (1*R*,4*R*,6*S*)-6-Bromo-4-(dibromomethyl)-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid 8

Yield 3.2 g (81%). White solid. Mp: 220–222 °C. $[\alpha]_D^{20}$ = −1.2 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.68 (s, 1H), 6.28 (s, 1H), 4.17 (s, 1H), 1.95–2.15 (m, 4H), 1.47 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.9, 59.6, 58.0, 54.3, 51.1, 46.8, 28.8, 26.0, 22.8, 18.5. IR (KBr, cm^{-1}): 3030, 2933, 2992, 2896, 1696, 1430, 1288, 757, 723, 701, 659, 647. HRMS calcd for $C_{10}H_{12}Br_3O_2$ $[M-H]^-$: 400.8382; found: 400.8388.

4.5.2. (1*R*,4*S*,6*S*)-6-Bromo-4-(bromomethyl)-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid 9

Yield 2.18 g (67%). White solid. Mp: 188–190 °C. $[\alpha]_D^{20}$ = +33.2 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.57 (s, 1H), 4.11 (s, 1H), 3.66 (d, *J* = 10.4 Hz, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 2.0–2.1 (m, 1H), 1.91–2.0 (m, 1H), 1.77–1.89 (m, 2H), 1.55 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 59.3, 55.8, 52.9, 49.9, 31.9, 29.6, 27.8, 22.4, 19.0. IR (KBr, cm^{-1}): 3042, 3004, 2955, 2902, 1693, 1426, 1289, 1271, 750, 668, 645. HRMS calcd for $C_{10}H_{13}Br_2O_2$ $[M-H]^-$: 322.9277; found: 322.9281.

4.5.3. (1*R*,4*S*,6*R*)-6-Bromo-4,5,5-trimethylbicyclo[2.1.1]hexane-1-carboxylic acid 10

Yield 1.87 g (76%). White solid. Mp: 180–182 °C. $[\alpha]_D^{20}$ = −99.8 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.44 (s, 1H), 4.01 (s, 1H), 2.11–2.24 (m, 1H), 1.95–2.08 (m, 1H), 1.74–1.88 (m, 1H), 1.6 (m, 4H), 1.04 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 60.7, 56.7, 51.2, 49.7, 31.1, 30.7, 21.5, 19.0, 11.5. IR (KBr, cm^{-1}): 2997, 2896, 2959, 2925, 1701, 1431, 1292, 1267, 947, 758, 663. HRMS calcd for $C_{10}H_{14}BrO_2$ $[M-H]^-$: 245.0172; found: 245.0179.

4.5.4. (1*R*,4*R*,)-4,5,5-Trimethylbicyclo[2.1.1]hexane-1-carboxylic acid 11

Yield 1.34 g (80%). White solid. Mp: 119–122 °C. $[\alpha]_D^{20}$ = −7.2 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.11 (s, 1H), 2.04–2.08 (m, 1H), 1.97–2.03 (m, 1H), 1.82–1.88 (m, 1H), 1.48–1.64 (m, 2H), 1.23 (d, *J* = 7.2 Hz, 1H), 1.22 (s, 3H), 0.96 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4, 54.2, 50.2, 48.4, 42.4, 32.5, 29.9, 17.7, 17.4, 13.5. IR (KBr, cm^{-1}): 2985, 2958, 2924, 2890, 1691, 1425, 1273, 954, 753. HRMS calcd for $C_{10}H_{17}O_2$ $[M+H]^+$: 169.1223; found: 169.1221.

4.6. (1*R*,4*R*,1′*R*,4′*R*)-4,4′-(*E*)-Ethene-1,2-diylbis(1-bromo-3,3-dimethylbicyclo[2.2.1]heptan-2-one) 12

Zinc powder 23.50 g (0.36 mol) was added slowly to a stirred solution of 2.80 g (4.54 mmol) of alkene **5** in glacial acetic acid (250 mL), and the mixture was refluxed for 50 h. Insoluble zinc salts and an excess of zinc powder were filtered off. Acetic acid was evaporated under reduced pressure, after which distilled water (100 mL) was added to the remaining solution and the organic phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was crystallized using chloroform. Yield 1.73 g (83%). White solid. Mp: 215–217 °C. $[\alpha]_D^{20}$ = +33.6 (*c* 0.654, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.7 (s, 2H), 2.33–2.45 (m, 2H), 2.1–2.2 (m, 4H), 1.86–2.06 (m, 4H), 1.7–1.84 (m, 2H), 1.01 (s, 6H), 0.94 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 212.0, 129.2, 66.6, 52.0, 49.2, 46.5, 35.0, 30.9, 22.0, 19.7. IR (KBr, cm^{-1}): 2976, 2934, 2877, 1752, 1460, 972, 806, 745. HRMS calcd for $C_{20}H_{27}O_2Br_2$ $[M+H]^+$: 457.0372; found: 457.0368.

4.7. (1*R*,4*R*,6*R*,1′*R*,4′*R*,6′*R*)-4,4′-(*E*)-Ethene-1,2-diylbis(6-bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid) 13

Using the procedure for the preparation of acids **8**–**11**, carboxylic acid **13** was obtained from alkene **5** in 58% yield. White solid. Mp: 290 °C (dec.). $[\alpha]_D^{20}$ = −21.6 (*c* 0.95, EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.49 (s, 2H), 5.63 (s, 2H), 4.23 (s, 2H), 1.69–2.12 (m, 8H), 1.55 (s, 6H), 0.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.1, 128.3, 61.2, 57.2, 54.4, 51.3, 29.9, 28.4, 22.2, 19.9. IR (KBr, cm^{-1}): 3030, 2997, 2966, 2929, 2896, 1701, 1438, 1264, 1099, 971, 759. HRMS calcd for $C_{20}H_{25}O_4Br_2$ $[M-H]^-$: 487.0114; found: 487.0123.

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4.8. (1*R*,4*R*,1′*R*,4′*R*)-4,4′-(*E*)-Ethene-1,2-diylbis(5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid) 14

Using the procedure for the preparation of acids **8**–**11**, carboxylic acid **14** was obtained from alkene **12** in 52% yield. White solid. Mp: 280 °C (dec.). $[\alpha]_D^{20}$ = +15.0 (*c* 0.945, EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.04 (s, 2H), 5.43 (s, 2H), 2.11–2.19 (m, 2H), 1.81–1.91 (m, 2H), 1.67–1.78 (m, 4H), 1.46–1.56 (m, 2H), 1.13–1.22 (m, 2H), 0.99 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.4, 128.4, 53.0, 52.5, 50.1, 39.9, 29.6, 28.6, 17.5, 17.2. IR (KBr, cm^{-1}): 3014, 2961, 2885, 1694, 1426, 1269, 964, 751. HRMS calcd for $C_{20}H_{29}O_4$ [M+H]$^+$: 333.2060; found: 333.2058.

4.9. (1*S*,4*S*,7*R*)-4,7-Dibromo-2,2-dimethyl-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 15 and (1*S*,4*R*)-4-bromo-2,2-dimethyl-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 16 (general procedure)

Alkene **5** or **12** (1.62 mmol) was dissolved in acetone (30 mL), after which potassium permanganate 1.53 g (9.72 mmol) was added to the solution and left to stir for 24 h. Distilled water and potassium carbonate were then added and the mixture was evaporated under reduced pressure. Distilled water (10 mL) was added to the residue and manganese dioxide was filtered off. The filtrate was acidified using 1 M HCl. The resultant precipitate was filtered off.

4.9.1. Acid 15

Yield 0.71 g (65%). White solid. Mp: 230 °C (dec.). $[\alpha]_D^{20}$ = −11.2 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.15 (s, 1H), 4.92 (s, 1H), 2.28–2.41 (m, 1H), 2.11–2.26 (m, 3H), 1.40 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 209.0, 171.1, 71.9, 60.0, 56.2, 47.0, 31.9, 29.8, 25.2, 24.5. IR (KBr, cm^{-1}): 2977, 2938, 2879, 1766, 1735, 1705, 1443, 1426, 983, 841, 818, 735, 717. HRMS calcd for $C_{10}H_{11}O_3Br_2$ [M−H]$^-$: 336.9069; found: 336.9079.

4.9.2. Acid 16

Yield 0.52 g (62%). White solid. Mp: 172–176 °C. $[\alpha]_D^{20}$ = −0.4 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.68 (s, 1H), 2.33–2.46 (m, 2H), 2.18–2.3 (m, 1H), 2.02–2.16 (m, 2H), 1.9–2.01 (m, 1H), 1.17 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 210.6, 172.7, 65.2, 55.1, 48.8, 45.2, 34.4, 29.0, 21.9, 20.5. IR (KBr, cm^{-1}): 3233, 2981, 2929, 2873, 1750, 1733, 1456, 1200, 1081, 978, 811, 692. HRMS calcd for $C_{10}H_{13}BrNaO_3$ [M+Na]$^+$: 282.9940; found: 282.9938.

4.10. X-ray diffraction study

Crystal data for **5** at 293 K: $C_{20}H_{24}Br_4O_2$, M = 616.03, a = 13.699(1) Å, b = 23.565(1) Å, c = 26.951(1) Å, V = 8700.2(8) Å^3, space group $P2_12_12_1$, Z = 16, D_{calcd} = 1.881 g cm^{-3}, μ(Mo K_α) = 7.413 mm^{-1}, F(000) = 4800. 127,736 reflections measured up to $2\theta_{max}$ = 60°, 25296 unique (R_{int} = 0.090) which were used in all calculations. Refinement was converged at wR_2 = 0.087 (all data), R_1 = 0.050 (14,355 reflections with $I > 2\sigma(I)$), GoF = 0.95. The CCDC dep. number for **5** is 1030932. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/products/csd/request/.

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