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Abstract—The absolute configuration of bicyclo[2.2.1]heptan-2-one has not been correlated with a crystal structure of a chemical precursor. The only chemical correlation available had an ambiguity, which could have reversed the assignment. Herein, we report the resolution of 2-chlorobicyclo[2.2.1]hept-5-en-2-exo-carboxamide on a cellulose triacetate column and the crystal structures of the enantiomerically pure and racemic a-chloroamide. We found the absolute configuration (1R,2R,4R) for the (+)-enantiomer of the a-chloroamide. This compound was converted to (+)-bicyclo[2.2.1]hept-5-en-2-one by base hydrolysis, and the 5,6-unsaturated compounds converted to the saturated congeners. This is the first unambiguous experimental determination of the absolute configuration of bicyclo[2.2.1]heptan-2-one and of bicyclo[2.2.1]hept-5-en-2-one. The three crystal structures of 2-chlorobicyclo[2.2.1]hept-5-en-2-exo-carboxamide reported herein reveal H-bonded dimers, with two distinct orientations of the bicyclic portion relative to the carboxamide dimer. In the racemic crystal, each dimer is composed of two enantiomers, and the bicyclic portions have their bridge carbon atom (C-7) on opposite sides of the H-bonded carboxamide dimer moiety. In the enantiomerically pure crystals, the major dimer had both C-7 atoms on the same side of the carboxamide dimer moiety while the minor dimer had the C-7 atoms on opposite sides. The dimers are present in solution, and can be easily monitored.

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1. Introduction

Bicyclo[2.2.1]heptane systems are a structural motif in many naturally and artificially produced compounds. For example, the motif occurs in complex natural products such as dolabellane, 1 echinosporin 2 and the sesquiterpene pheromone from a stink bug, 3 as well as in synthetic materials, such as norbornyl-containing peptides where the norbornane group templates the folding of the peptide in a well-defined manner. 4 Bicyclo[2.2.1]heptan-2-one (norcamphor) 1, bicyclo[2.2.1]-hept-5-en-2-one (5,6-dehydronorcamphor) 2 and their substituted analogues have been used as starting points or key intermediates for the synthesis of many chiral compounds with highly substituted cyclopentyl moieties, such as prostaglandins, 5–9 some terpenes, 10–12 some iridoids, 13, 14 methyl epi-jasmonate, 15 11-fluorojasmonate, 16 carbocyclic sugars, 17, 18 and cyclopentane-containing polymers. 19 We intend to use the framework of bicyclo[2.2.1]hept-5-en-2-one 2 as a starting point for the synthesis of conformationally constrained pheromone analogues. For all these studies, knowing the absolute configuration of the enantiomers of bicyclic compounds 1 and 2 is essential.

There has been one attempt to correlate the absolute configuration of (+)-bicyclo[2.2.1]heptan-2-one (++)-1 to (−)-fenchone (−)-G, by a six-step chemical conversion (Scheme 1A). 20 The problems associated with that attempt were (1) a moderate ee of the starting (+)-1

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(A) Chemical correlations of configuration at C-4 of (+)-bicyclo[2.2.1]heptan-2-one (+)-1, Berson et al. 1961

(B) Correlation of (+)-fenchone, (+)-G, with (+)-(2S)-isopropyl butanedioic acid, (+)-J

(C) Correlation of 2-alkyl, thio and hydroxy butanedioic acids by quasi-racemates

Scheme 1. (A) Summary of routes used for the correlation of the absolute configuration of (+)-I to (-)-fenchone, (-)-G,20 (B) of (+)-G to (+)-(2S)-isopropyl butanedioic acid, (+)-J31–24 and (C) of (+)-J to (+)-(2R)-hydroxybutanedioic acid, (+)-M.24,25 Pairs of compounds, for which the configuration at C-2 was correlated by the quasi-racemate method are labelled I–III.24,25

The absolute configuration of (+)-bicyclo[2.2.1]heptan-2-one (+)-1 has not been assigned by correlation to a crystal structure of a chemically related compound. Herein, we report the chromatographic resolution (on a column of microcrystalline cellulose triacetate, MCTA) of the enantiomers of 2-chloro bicyclo[2.2.1]-hept-5-ene-2-exo-carboxamide 4 and the absolute configuration of both, the (+)- and the (-)-enantiomers. The crystal structures, we present, are the first report and in addition to enabling us to determine the absolute
configuration of 4, the structures reveal H-bonded dimers. For the pure enantiomers, the H-bonded dimers appeared in two orientations in the crystal, and for the racemic material, the H-bonded dimers were racemic, present in one orientation. The two forms of the enantiomerically pure dimers differed by the orientation of the bridge carbon (C-7) relative to the H-bonded carboxamide unit. To correlate the configuration of (+)- and (−)-2-chloro bicyclo[2.2.1]hept-5-ene-2-carboxamide, (+)-4 and (−)-4, to the configuration of (+)- and (−)-bicyclo[2.2.1]hept-5-ene-2-one, (+)-2 and (−)-2, we converted (+)-4 and (−)-4 to (+)-2 and (−)-2, respectively, in one step. These four compounds were converted to their saturated congeners (Scheme 2), to correlate the configuration of (+)- and (−)-2-chloro bicyclo[2.2.1]heptane-2-carboxamide (+)-5 and (−)-5 and to (+)- and (−)-bicyclo[2.2.1]heptan-2-one (+)-1 and (−)-1.

2. Results and discussion

2.1. Preparation of the x-chloroamide 4

The Diels–Alder adduct 3 was obtained by the reaction of freshly distilled cyclopentadiene with 2-chloroacrylonitrile, in 92% yield and a 4:1 exolendo chloronitrile selectivity. This compared well with the literature values.26–28 The use of ZnI2 or in situ generated Cu(I) as catalysts gave similar yields and the same exolendo selectivity, consistent with previous studies.30,6

When the chloronitrile 3 exolendo mixture was subjected to aqueous basic conditions, the endo-CN isomer of 3 reacted more quickly to afford the corresponding endo x-chloro amide than did the exo-CN isomer. The x-chloro amides reacted further to afford ketone 2,30 while the endo-amide reacted faster than the exo-isomer. Ketone 2 is volatile whereas the exo- and endo x-chloro amides are not. If the reaction is carried out at 50–60 °C, until the exo- and endo-chloronitriles have reacted, then the major product is the exo-amide 4, while the minor product (~10%) is the endo-amide isomer of 4. Both the x-chloro exo- and endo-amides 4 can be converted to ketone 2 by re-subjecting them to basic conditions.

2.2. Resolution of chloroamide enantiomers 4, crystallization and absolute configuration

Amide 4 was separated from traces of the endo-carboxamide by column chromatography. The enantiomers of pure 4 were resolved on a medium pressure column packed with microcrystalline cellulose triacetate (MCTA). Nearly baseline separation was obtained at room temperature, using ethanol–H2O 9:1 as the mobile phase (Fig. 1). Crystals of both pure enantiomers were obtained. Initially, the late-eluting (+)-enantiomer of 4 was used successfully to obtain a crystal diffraction pattern. In a later experiment, the early-eluting (−)-enantiomer was used to obtain crystals and a diffraction pattern. Because of the anomalous dispersion of the chlorine atom, it was possible to assign the (1R,2R,4R)-configuration to the late-eluting (+)-enantiomer. (Fig. 2, Table 1). The early-eluting (−)-enantiomer was (1S,2S,4S). We then subjected (+)-4 to base hydrolysis and obtained (+)-2. Similarly, (−)-4 afforded (−)-2 upon base hydrolysis (Scheme 2). The corresponding saturated congeners 5 and 1 were obtained by
The specific rotations for (+)-4 and (-)-4, and for (+)-5 and (-)-5 (Scheme 2B) have not been reported previously; the specific rotations for (+)-1 and (-)-1, and for (+)-2 and (-)-2 are in agreement with those reported previously (Table 3).

(+)-Bicyclo[2.2.1]heptan-2-one (+)-1 was obtained from (+)-2, thus allowing the configuration of these two compounds to be correlated. In a previous work, compound (+)-2 had been prepared from endo-(+)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid via a four-step procedure. The maximal rotations for endo- and exo-bicyclo[2.2.1]hept-5-ene-2-carboxylic acids and their saturated congeners have been determined, and the configuration has been correlated among these four compounds and their methyl esters. The configuration of (−)-exo-bicyclo[2.2.1]heptane-2-carboxylic acid was correlated with (−)-exo-2-acetyl bicyclo[2.2.1]heptane. Similarly, (+)-2 has been prepared from (+)-exo-bicyclo[2.2.1]hept-5-en-2-ol while the configuration of both compounds was correlated with the configuration of the corresponding hydrogenated products. Attempts were also made to predict the chirooptical behavior of exo-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid and (+)-2. Finally, (+)-2 (83% ee) was prepared from exo-2-bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde, which in turn was generated by an asymmetric Diels–Alder reaction of cyclopentadiene and 2-bromoacrolein. The relative orientation of the two reactants during the catalyzed Diels–Alder reaction was predicted and correlated to the configuration of the product. All these correlations of configuration form a consistent set, but despite an extensive literature search, we found no direct correlation of the configuration of (+)-1 or (+)-2 with a close synthetic precursor or derivative, for which the absolute configuration has been determined by X-ray crystallography.

Since amide 4 converts to the corresponding ketone, and the conversion proceeds without rearrangement of the bicyclo[2.2.1]heptane framework, the crystal structures determined herein establish the absolute configuration of (+)-2. The specific rotations observed for the enantiomers of 2 and of 1 are in the range of the previously reported values (Table 2). As (+)-1 was readily obtained by hydrogenation, this work also establishes the configuration of (+)-1. This confirms that the previous work led to the correct assignment of (+)-1, despite the ambiguous step.

![Figure 1](image1.png)

**Figure 1.** Separation of (−)- and (+)-2-chlorobicyclo[2.2.1]hept-5-ene-exo-2-carboxamide 4 on a column of microcrystalline cellulose triacetate (MCTA), with ethanol–water 9:1 (see methods). This chromatogram shows results from a run, in which racemic 4 loaded on the column.

![Figure 2](image2.png)

**Figure 2.** Structures obtained by X-ray crystallography for 2-chlorobicyclo[2.2.1]hept-5-ene-exo-2-carboxamide 4: (A) racemic, (B) the early-eluting (−)-(1S,2S,4S) enantiomer, and (C) the late-eluting (+)-(1R,2R,4R) enantiomer. Graphics were generated with ORTEP-3, (A)–(C) 50% probability ellipsoids for all non-hydrogen atoms.
that one of the amide Hs (Hb, Fig. 3A) is influenced
by the temperature decrease or the concentration of amide increases or as the temperature decreases. The signal assigned to Hα, on the other hand becomes increasingly deshielded relative to that of Hb (Fig. 3A) as the temperature decreases or the concentration increases (Table 4). The data are consistent with Hα being involved in the amide dimer, since H-bonding is known to cause deshielding of hydrogen atoms involved as H-bond donors.38 The spectra represent the time average for the monomeric and dimeric forms, H-bonding interaction. Such an interaction is expected to cause deshielding of the Hα signal relative to Hb. Experiments with racemic chloroamide 5 reveal that the chemical shift of Hα does not change significantly as the concentration of amide increases or as the temperature decreases. The signal assigned to Hα, on the other hand becomes increasingly deshielded relative to that of Hb (Fig. 3A) as the temperature decreases or the concentration increases (Table 4). The data are consistent with Hα being involved in the amide dimer, since H-bonding is known to cause deshielding of hydrogen atoms involved as H-bond donors.38 The spectra represent the time average for the monomeric and dimeric forms.
(+)–2 Enantioselective cycloaddition of a ketene equivalent to cyclopentadiene

Not given

(+)(+)$\alpha$-Chloroamide increases and/or the temperature decreases, a higher proportion of dimers was expected to form. In the dimer, the rotation around the C-2-carboxamide bond should be more restricted than in the monomer, and H-7A and H-3exo are more likely to be in the shielding cone of the amide. The behavior of the amide hydrogens in the NMR and the observation that dimers were obtained in crystals grown under different conditions suggests that the dimers can readily form in solution, and in organic and aqueous solvent.

Data from the temperature and concentration study of racemic $\alpha$-chloroamide 5 (Table 4, Fig. 3) were used to estimate enthalpy and entropy parameters, $\Delta H$ and $\Delta S$, for the dimerization. Two assumptions were made. First, the spectrum obtained for a 0.1 M solution at 4 °C was assumed to represent 100% dimeric species. This is reasonable, since these conditions are at the solubility limit and the crystals contain 100% dimers. Second, the spectrum obtained for a 0.01 M solution at 55 °C was assumed to represent 100% monomeric species. This is reasonable, because the chemical shift difference between H_a and H_b of 5, for the spectra obtained with 0.01 M solutions leveled off at 35 °C (Table 4). The values obtained (Fig. 3B) suggest $\Delta H$ for dimerization of amide 5 of $-11$ kcal/mol and a $\Delta S$ of $-36$ cal/mol. This gives a $\Delta G$ at 22 °C of $-0.6$ kcal/mol. Such easily monitored H-bonding properties could be very useful in the assembly of new materials from solutions of H-bonded

The percentage of the dimer was estimated, on the assumption that the dimerization reaction has $D$ and dimers in the solution. Two other signals change consistent with the rapid exchange between monomers and dimers in the solution. Two other signals change very slightly with increasing concentration or decreasing temperature (H-3exo and H-7A). Both of these signals became more shielded with lower temperature and/or higher concentration (Table 4). The slight shielding of H-7A and H-3exo is more difficult to explain. In the crystal structures, we have obtained H-7A and H-3exo both placed in the shielding cone of the carboxamide group. As the concentration of $\alpha$-chloroamide increases and/or the temperature decreases, a higher proportion of dimers was expected to form. In the dimer, the rotation around the C-2-carboxamide bond should be more restricted than in the monomer, and H-7A and H-3exo are more likely to be in the shielding cone of the amide.

The behavior of the amide hydrogens in the NMR and the observation that dimers were obtained in crystals grown under different conditions suggests that the dimers can readily form in solution, and in organic and aqueous solvent.

Table 3. Specific rotation reported previously for enantiomers of compounds 1 and 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Synthetic precursor or approach</th>
<th>Specific rotation of the enantiomer of 2 or 1 prepared</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-2</td>
<td></td>
<td>[:36]^D = +1186 (c 0.7, CHCl_3)</td>
<td>18</td>
</tr>
<tr>
<td>(+)-2</td>
<td></td>
<td>[:36]^D = +1033 (c 10.1 CHCl_3)</td>
<td>31</td>
</tr>
<tr>
<td>(+)-2</td>
<td></td>
<td>[:36]^D = +1088 (c 1.7, CHCl_3)</td>
<td>55, 31</td>
</tr>
<tr>
<td>(+)-2</td>
<td>Enantioselective cycloaddition</td>
<td>[:36]^D = +1032 (c 0.025, acetone)</td>
<td>57</td>
</tr>
<tr>
<td>(+)-2</td>
<td></td>
<td>[:36]^D = +980 (c 0.3, CHCl_3)</td>
<td>36</td>
</tr>
<tr>
<td>(-)-2</td>
<td>Enantioselective cycloaddition</td>
<td>[:36]^D = -1051 (c 0.030, acetone)</td>
<td>57</td>
</tr>
<tr>
<td>(-)-2</td>
<td>Kinetic enzymatic resolution of the racemic endo alcohol</td>
<td>[:36]^D = -930 (c 1.1, CHCl_3) ee by GC: 82%</td>
<td>58, 59</td>
</tr>
<tr>
<td>(+)-1</td>
<td>Jones oxidation of endo bicyclo[2.2.1]heptan-2-ol</td>
<td>[:36]^D = +17 (c 4.4, CHCl_3)</td>
<td>20</td>
</tr>
<tr>
<td>(+)-1</td>
<td>From bicyclo[2.2.1]heptan-2-ol by resolution of phthalate</td>
<td>[:36]^D = +29.1 (c 1.5, CHCl_3)</td>
<td>60</td>
</tr>
<tr>
<td>(-)-1</td>
<td>From bicyclo[2.2.1]heptan-2-ol by resolution of phthalate</td>
<td>[:36]^D = -28.7 (c 2.2, CHCl_3)</td>
<td>60</td>
</tr>
<tr>
<td>(-)-1</td>
<td>From nortricyclanone using L-proline perchlorate</td>
<td>[:36]^D = -4.7 (c not given, CHCl_3)</td>
<td>61</td>
</tr>
</tbody>
</table>

Very slightly with increasing concentration or decreasing temperature (H-3exo and H-7A). Both of these signals became more shielded with lower temperature and/or higher concentration (Table 4). The slight shielding of H-7A and H-3exo is more difficult to explain. In the crystal structures, we have obtained H-7A and H-3exo both placed in the shielding cone of the carboxamide group. As the concentration of $\alpha$-chloroamide increases and/or the temperature decreases, a higher proportion of dimers was expected to form. In the dimer, the rotation around the C-2-carboxamide bond should be more restricted than in the monomer, and H-7A and H-3exo are more likely to be in the shielding cone of the amide. The behavior of the amide hydrogens in the NMR and the observation that dimers were obtained in crystals grown under different conditions suggests that the dimers can readily form in solution, and in organic and aqueous solvent.

Data from the temperature and concentration study of racemic $\alpha$-chloroamide 5 (Table 4, Fig. 3) were used to estimate enthalpy and entropy parameters, $\Delta H$ and $\Delta S$, for the dimerization. Two assumptions were made. First, the spectrum obtained for a 0.1 M solution at 4 °C was assumed to represent 100% dimeric species. This is reasonable, since these conditions are at the solubility limit and the crystals contain 100% dimers. Second, the spectrum obtained for a 0.01 M solution at 55 °C was assumed to represent 100% monomeric species. This is reasonable, because the chemical shift difference between H_a and H_b of 5, for the spectra obtained with 0.01 M solutions leveled off at 35 °C (Table 4). The values obtained (Fig. 3B) suggest $\Delta H$ for dimerization of amide 5 of $-11$ kcal/mol and a $\Delta S$ of $-36$ cal/mol. This gives a $\Delta G$ at 22 °C of $-0.6$ kcal/mol. Such easily monitored H-bonding properties could be very useful in the assembly of new materials from solutions of H-bonded
α-chloroamide units. The dimerization may also explain the low volatility of the α-chloroamides 4 and 5. This property makes compound 4 a more practical precursor for synthesis than volatile ketone 2.

3. Conclusions

We have determined the absolute configuration of the enantiomers of 2-chlorobicyclo[2.2.1]hept-5-ene-2-carboxamide 4 by X-ray crystallography. Through 1-step chemical conversions, we have correlated (+) 2-chlorobicyclo[2.2.1]hept-5-ene-2-carboxamide (+)-4 with (+)-bicyclo[2.2.1]hept-5-en-2-one (+)-2 and (+)-bicyclo[2.2.1]heptan-2-one (+)-1. Amides 4 and 2-chloro bicyclo[2.2.1]heptane-2-carboxamide 5 form hydrogen-bonded dimers in the crystals. The racemic dimers adopted one orientation in the crystal, while the dimers comprised of a single enantiomer adopting two orientations in the crystal.

4. Experimental

4.1. General

Melting points were determined using a Fisher–Johns melting point apparatus and are uncorrected. GC were run on a Hewlett Packard 5890 using a SPB-5 column (Supelco, 30 m, 0.25 mm i.d., 0.25 μm film), programmed 50 °C (5 min), 5°C/min, 100°C (4 min), 50°C/min, 250°C (20 min). To enable cross-referencing of retention times between our GC and GC–MS instruments, retention indices (RI) were calculated for the SPB-5 column data, with reference to hydrocarbon standards (Sigma). Enantiomer compositions were analyzed on a Varian 3400 gas chromatograph, equipped with a CycloSil B column (J & W, 30 m, 0.25 mm i.d., 0.25 μm film), programmed isothermally at 140 °C and 25 psi head pressure. Since GC retention times of the α-chloroamide enantiomers did not differ much (16.3 and 16.8 min), analysis was repeated on a Waters 625 HPLC with a 486 absorbance detector, fitted with a Chiralcel OJ-RH analytical column (2.1 mm i.d., Chiral Tech. Inc., Exton, PA) and programmed isocratically at 0.06 mL/min with hexane–2-propanol 3:1. The eluent was monitored at 245 nm. Here, the baseline resolution was obtained (13.5 and 16.4 min). Large-scale low-pressure chromatography (up to 300 mg/run) was performed on a Varian 5000 LC, equipped with a 3 cm inner diameter × 110 cm packed jacketed column. The column temperature was controlled by a Haake recirculating water pump. Separations with the column at 50°C and a flow rate of 0.2 mL/min gave nearly baseline separation (Fig. 1). Mass spectra were recorded on a Varian Saturn 2000 MS coupled to a CP 300 GC, equipped with a SPB-5 GC column (same type as above). Both EI (70 eV) and CI (isobutane) modes of ionization were used. IR was recorded on a Nexus 670 FT-IR. NMR spectra were recorded using a Varian 500 MHz instrument. Optical rotations were obtained using the sodium line at 20°C in a Perkin–Elmer polarimeter 340. Solvents were distilled under nitrogen before use.

4.2. Preparation of 4 and derivatives

4.2.1. 2-Chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile, 3.

Freshly distilled cyclopentadiene (2.41 g, 36.5 mmol) was added to a solution of 2-chloroacrylonitrile (3.21 g, 36.7 mmol), CuSO4 (7 mg, 0.04 mmol) and hydroquinone (5 mg, 0.04 mmol) with gently stirring. The mixture was then quenched with water and extracted with EtOAc (3 × 10 mL). The organic extract was washed with water (2 × 5 mL) then with 10 mL brine, dried over Na2SO4, and concentrated in vacuo to give 2-chloro-2-cyano bicyclo[2.2.1]hept-5-ene 3 (5.17 g, 92% yield), as a colorless solid (1:4 endo/exo selectivity). Alternatively, the reaction was performed with a catalytic amount of zinc iodide and found to give comparable yields and selectivity. Mp 38–39°C (lit. 39°C[26] and 42–43°C[30]), GC Rf (SPB 5) 17.8 and 18.1 (4:1 intensity ratio) (RI 1146 and 1153, respectively). 1H NMR (CDCl3, major diastereomer) δ 6.42 (dd, J = 3.1, 5.7 Hz, 1H, H-6), 6.12 (dd, J = 3.05, 5.7 Hz, 1H, H-5), 3.51 (br, 1H, H-1), 3.09 (br, 1H, H-4), 2.72 (dd, J = 3.7, 13.2 Hz, 1H, H-3exo), 1.75–1.83 (m, 2H, H-7), 1.71 (dd, J = 3.7, 13.2 Hz, 1H, H-3endo); (minor diastereomer) δ 6.46 (dd,
J = 3.0, 5.7 Hz, 1H, H-6), 6.22 (dd, J = 3.0, 5.8 Hz, 1H, H-5), 3.35 (br, 1H, H-1), 3.09 (br, 1H, H-4, H-4 of major diastereomer), 2.36 (dd, J = 3.4, 13.2 Hz, 1H, H-3exo), 2.24 (dd, J = 2.7, 13.2 Hz, 1H, H-3endo), 1.92–1.96 (br d, J = 9.7, 2H, H-7); 13C NMR (CDCl3) δ (major diastereomer) 140 (C-6), 132 (C-5), 122 (CN), 55.6 (C-1), 48.8 (C-4), 45.9 (C-7), 43.1 (C-3), 22.8 (C-2) (minor diastereomer) 142 (C-6), 133 (C-5), 121 (CN), 56.3 (C-1), 47.2 (C-4), 47.1 (C-7), 42.8 (C-3), 24.8 (C-2). The 1H NMR matches the literature spectrum;26 IR (KBr) 3071, 2990, 2946, 2869, 2235, 1712, 1326, 1269, 766, 725 cm−1; MS (rel. intensity) 154 (M+ 11%), 117 (M′-HCl, 4%), 91 (M′′-HCIN, 15%), 66 (retro Diels-Alder, 100%).

4.2.2. 2-Chlorobicyclo[2.2.1]hept-5-ene-endo-2-carboxamide 4. A solution of 3 (240 mg, 1.56 mmol) in DMSO (10 mL) and 3 equiv of 0.5 M aqueous NaOH was stirred at 50°C for 4 h. The reaction mixture was diluted with water (10 mL) and neutralized with concentrated HCl. The product was extracted into freshly distilled ether (3 × 10 mL) and dried over Na2SO4. Concentration in vacuo gave a reduced compound. This was passed through a short silica gel column and concentrated in vacuo to give a reduced compound.

4.2.3. Typical hydrogenation of the bicyclo[2.2.1]hept-5-ene compounds 4 or 2. A solution of the compound in hexane and a catalytic amount of palladium on charcoal were placed in a 6 mL vial, fitted with a stirbar, a screwcap and a rubber septum. The vial was sealed, pressurized with hydrogen, and the reaction mixture stirred for ca. 4 h. The crude product was passed through a short silica gel column and concentrated in vacuo to give a reduced compound.

4.2.4. 2-Chlorobicyclo[2.2.1]heptane-endo-2-carboxamide 5. Hydrogenation of 2-chlorobicyclo[2.2.1]hept-5-ene-endo-2-carboxamide 4 98% yield. 1H NMR δ 6.24 (br s, 1H, H-5), 5.40 (br s, 1H, H-4), 2.82 (dd, J = 2.8, 4.5, 13.6 Hz, 1H, H-3endo), 2.60 (br d, J = 4.0 Hz 1H, H-1), 2.31 (br t, J = 4.4 Hz, 1H, H-4), 2.13 (m, J = 3.0, 9.2, 12.4 Hz, 1H, H-5exo). 1.78 (br d, J = 10.2 Hz, 1H, H-7A), 1.62 (m, J = 4–8.8, 12.3 Hz, 1H, H-6exo), 1.53 (br d, J = 13.5 Hz, 1H, H-5exo). 1.49 (m, 1H, H-3exo), 1.38 (m, J = 3.4, 10.2, 1H, H-7b). 1.34 (m, J = 2.3, 8.9, 11.3, 1H, H-5endo). 13C NMR δ 174.9 (C-amide), 75.7 (C-2), 49.0 (C-1), 44.8 (C-4), 38.2, 36.8, 28.3, 25.2. IR (KBr) 3406, 3295, 3181, 2957, 2873, 1662, 1608, 1368, 769, 589 cm−1; MS (M+ 1, 40%), 136 (M + Cl, 31%), 138 (M′′-Cl, 30%), 129 (18%), 106 (100%), 93 (38%), 67 (30%).

To facilitate the assignment of the 1H NMR spectrum of 5, racemic 4 (28.7 mg, 0.17 mmol) was deuterated as described above to give 5-0.6-D-5 27.2 mg (93%); 1H NMR δ 6.21 (br, 1H, NH), 5.30 (br, 1H, NH), 2.83 (dd, J = 2.8, 13.6 Hz), 2.60 (br, 1H, H-1), 2.31 (br, 1H, H-4), 2.15 (dm, 1H, H-6endo), 1.77 (brd, J = 10.2 Hz, 1H, H-7A), 1.50 (dd, J = 2.1, 3.3, 13.6 Hz, 1H, H-3exo), 1.36 (br d, J = 10.2, 1H, H-7b). 1.33 (br d, J = 8.9, 1H, H-5endo). IR (KBr) 3423, 3181, 2967, 2926, 2161 (C-D str.), 1648, 1373, 779, 588 cm−1. MS 176 (M′+, 100%), 140 (M′′-Cl, 28%), 131 (12%), 108 (16%), 106 (50%), 95 (17%), 93 (16%), 67 (13%).

Additions of electrophiles and nucleophiles, halogen or hydrogen to the bicyclo[2.2.1]hept-5-ene system are known to proceed exclusively from the exo face.40,41 In this case, the signals corresponding to H-5exo and H-6exo in compound 5 disappeared in the spectrum of compound 5.6 D2-5, which facilitated assignment of the spectrum of 5.

4.2.5. (±)-Bicyclo[2.2.1]hept-5-ene-2-one 2. α-Chloronitrile 3 (0.93 g, 6.0 mmol) was placed in a round-bottom flask, fitted with a condenser, dissolved in a minimum volume of ether, DMSO (15 mL) and 2.5 M NaOH (10 mL). The mixture was maintained at 70°C ca. 4 h. The product was extracted into freshly distilled ether (2 × 15 mL), washed with brine (15 mL), and dried over Na2SO4. The solvent was removed by fractional distillation to give bicyclo[2.2.1]hept-5-ene-2-one 2 (0.286 g, 44% yield). Similarly, 2-chlorobicyclo[2.2.1]hept-5-ene-endo-2-carboxamide 4 was converted to (±)-2 in 83% yield. 1H NMR δ 6.52 (dd, J = 2.8, 5.6 Hz, 1H, H-6), 6.06 (m, 1H, H-5), 3.14 (br s, 1H, H-1), 2.95 (m, 1H, H-4), 2.15 (m, J = 9.2 Hz, 1H, H-7), 1.96–1.88 (m, J = 9.2, 16.5 Hz, 2H, H-7 and H-3), 1.79 (dd, J = 4.5, 16.5 Hz, 1H, H-3). 13C NMR δ 216 (C-2), 143 (C-6), 131 (C-5), 56 (C-1), 51 (C-4), 40, 37; IR 3477 (K-C=O stretch), 3067, 2970, 2936, 1749, 1326, 1125, 709 cm−1; IR (KBr) 5.20 (S-CH3) 108 (M′+ 48%), 91 (M′′-OH, 38%), 77 (5%), 66 (100%).

4.2.6. (+)-Bicyclo[2.2.1]hept-5-ene-2-one (+)-2 from (+)-2-chlorobicyclo[2.2.1]hept-5-ene-endo-2-carboxamide (+)-4. Compound (+)-4 (10 mg, 0.059 mmol) was placed in a flask with a condenser. DMSO (1 mL) and
NaOH (2.5 M, 14 mL) were added, and the mixture heated at 50 °C for 4 h. The product was isolated as above to give (+)-2 (4 mg, 65% yield) as a light yellow liquid. GC–MS was identical to racemic 2. $|\alpha| = +1050$ (c 0.2, CHCl$_3$) lit. Table 2: R$_t$ (Cyclosyl B) 7.0 min. Similarly, (−)-2 was prepared in 48% yield from (−)-4. $|\alpha|_D = -1067$ (c 0.9, CHCl$_3$); R$_t$ (CycloSil B) 6.7 min.

4.2.7. (±)-Bicyclo[2.2.1]heptan-2-one 1. A solution of 5 (5.7 mg, 0.033 mmol) in 10 mL DMSO was placed in a flask with a condenser and mixed with NaOH (2.5 M, 6 mL). The mixture was heated to 70 °C and allowed to stir for 15 min. The product was isolated, as described above for bicyclo[2.2.1]hept-5-en-2-one to stir for 15 min. The product was isolated, as described above for bicyclo[2.2.1]hept-5-en-2-one to give bicyclo[2.2.1]heptan-2-one 1 (3.6 mg, quantitative, colorless oil). $^1$H NMR $\delta$ 2.66 (br m, 1H, H-1), 2.59 (br d, J 3.5 Hz, 1H, H-4), 2.02–2.09 (br dd, J = 4.3, 17.8 Hz, 1H, H-3$_{endo}$), 1.86 (d, J = 4.3 Hz, 1H, H-3$_{endo}$), 1.77–1.83 (m, 2H, H-7), 1.73 (dquin, J = 3.6, 10.3 Hz, 1H, H-6$_{endo}$), 1.50–1.53 (m, 2H, H-5), 1.40–1.46 (m, 1H, H-6$_{endo}$). $^1$C NMR $\delta$ 218.5 (C-2), 50.2 (C-1), 45.6 (C-4), 37.8, 35.4, 27.5, 24.0. GC $R_t$ (SPB 5) 12.25 min. (RI 983); IR (KBr) 2957, 2869, 1739, 1460, 1410 cm$^{-1}$. MS $m/z$ 110 (M$^+$), 95 (7%), 91 (9%), 81 (20%), 79 (12%), 67 (92%), 66 (100%).

4.2.8. (+)-Bicyclo[2.2.1]heptan-2-one (+)-1 from (+)-2. Compound (+)-2 was hydrogenated as described above to (+)-1 (100% yield). The GC–MS was identical to that of racemic 1. $|\alpha|_D = +27.2$ (c 1.8 CHCl$_3$); R$_t$ (Cyclosyl B) 7.1 min. Lit. Tab. 2.

4.2.9. (−)-Bicyclo[2.2.1]heptan-2-one (−)-1 from (−)-2-chlorobicyclo[2.2.1]heptane-exo-2-carboxamide (−)-5. The (−)-enantiomer of 4 was reduced to (−)-5 as described above (98% yield). The reduced enantiomer, (−)-5, $|\alpha|_D = -25$ (c 1.0 CHCl$_3$), (26 mg, 1.50 mmol) was placed in a reaction vial followed by NaOH (2.5 M, 5 mL). The mixture was heated to 70 °C and allowed to stir for 15 min. Product isolation was done as described above. This gave pure (−)-1 (7 mg, 39% yield). $|\alpha|_D = -27$ (c 1.1 CHCl$_3$); R$_t$ (CycloSil B) 7.4 min.

4.3. Crystallography

The crystals of (−)-4 were grown from hexane–ether (1:10) at 20 °C. The crystals of racemic 4 and of (−)-4 were obtained from water–ethanol (2:1) and water–2-propanol (2:1), respectively. The crystals were taken out of the mother liquor for inspection, and were briefly air-dried prior to mounting on a glass fiber. Data for the crystal structure of (−)-4 were collected on an Enraf Nonius CAD4 diffractometer, using graphite monochromated Mo-K$_\alpha$ radiation. The data were collected at −100.0 °C to a maximum of 20 value of 50.2° in a series of $\phi$ and $\omega$ scans with 30.0 s exposures. The crystal-to-detector distance was 38.00 mm. The data collection was controlled with the Brucker SADABS software. Data reduction was performed with Brucker SHELX software. The structures were refined using the SHELX software package of Brucker-AXS (operating) and STPGP 307515 (strategic) to E.P. and by Research Corporation (Research Innovation Award to E.P.)

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