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2-Chlorobicyclo[2.2.1]hept-5-ene-2-carboxamide and 2-chlorobicyclo[2.2.1]heptane-2-carboxamide as precursors of bicyclo[2.2.1]hept-5-en-2-one and bicyclo[2.2.1]heptan-2-one: resolution, absolute configuration and hydrogen-bonding properties

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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 α-chloroamide. We found the absolute configuration (1*R*,2*R*,4*R*) for the (+)-enantiomer of the α-chloroamide. This compound was converted to (+)-bicyclo[2.2.1]hept-5-ene-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-ene-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.

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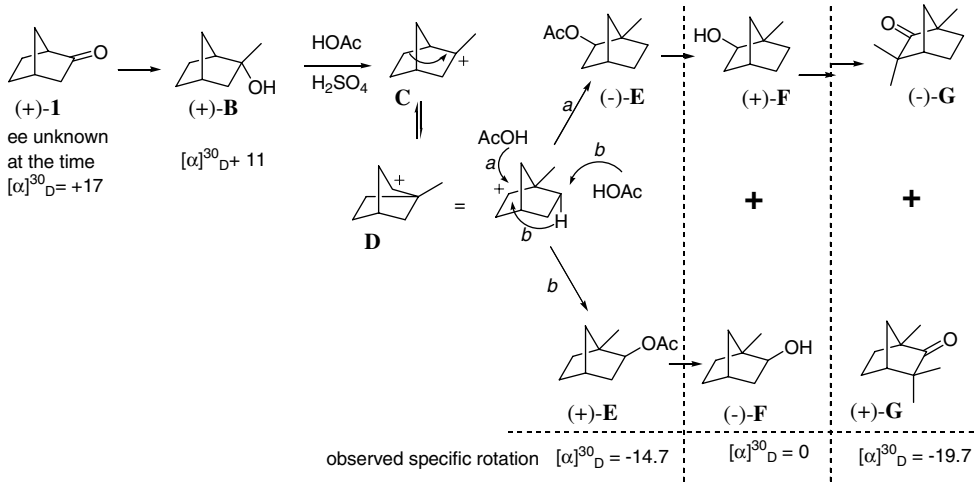
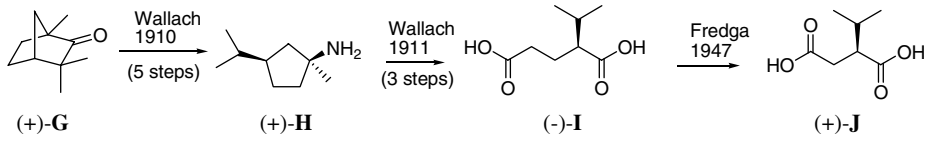
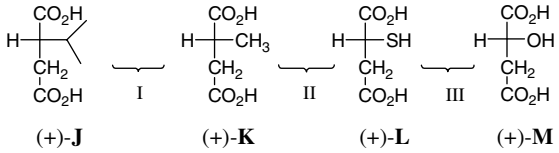
(A) Chemical correlations of configuration at C-4 of (+)-bicyclo[2.2.1]heptan 2-one (+)-1, Berson et.al. 1961



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



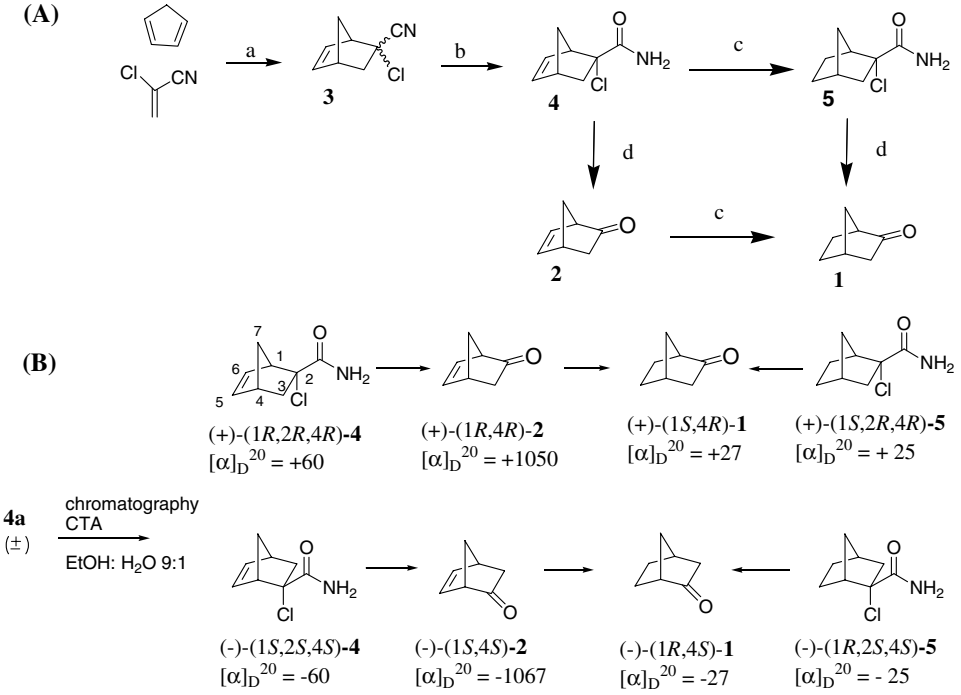
(C) Correlation of 2-alkyl, thio and hydroxy butanedioic acids by quasi-racemates



Scheme 1. (A) Summary of routes used for the correlation of the absolute configuration of (+)-**1** to (−)-fenchone, (−)-**G**,[20] (B) of (+)-**G** to (+)-(2*S*) isopropyl butanedioic acid, (+)-**J**[21–24] and (C) of (+)-**J** to (+)-(2*R*) 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]

(∼41%) and (2) an ambiguity in a rearrangement step (**C** to **D**, Scheme 1A). The rearranged cation **D** could be trapped by an acetate via routes *a* or *b*, which gave enantiomeric products, (+)-**E** and (−)-**E**. Given that the relative ratio of the two trapping modes was unknown, this step could have easily reversed the final result. The (+)-**1** enantiomer for that study was prepared from (+)-*endo*-bicyclo[2.2.1]heptan-2-ol, which in turn was prepared by resolution of the corresponding phthalate ester.[20] However, a correlation with the terpene series and, from there, with the hydroxy diacid/carbohydrate series was required, in order to correlate the absolute configuration of (+)-**1** to that of D-glyceraldehyde (Scheme 1B and C). Compound (+)-**1** was correlated with (−)-**G**, which connects to earlier work, in which the configuration at C-4 of (+)-**G** had been established to be the same as that of (+)-limonene.[21] Compound (+)-**G** was converted to (−)-2-isopropyl pentanedioic acid, (−)-**I** (Scheme 1B).[22,23] Furthermore, in an effort to compare the configuration of the terpenes to the configuration of the sugar series, Fredga devised a scheme to selectively chain-shorten (−)-2-isopropyl pentanedioic acid (−)-**I** to (+)-2-isopropyl butanedioic acid (+)-**J** (Scheme 1B).[24] The configuration of this compound was related, by the quasi-racemate method,[25] with (+)-2-methyl butanedioic acid (+)-**K**, which had been related with (+)-2-hydroxy butanedioic acid (+)-**M** (Scheme 1C).[25] These compounds were represented as having an (*S*)-configuration. Working back, (+)-**G** was denoted as (1*S*,4*R*). This, in turn would imply that (+)-bicyclo-[2.2.1]heptan-2-one (+)-**1** is the (1*S*,4*R*)-enantiomer.

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



Scheme 2. Preparation of the α-chloro amides and ketones and specific rotation data (in $CHCl_3$; see experimental section for concentrations). Conditions: (a) catalytic ZnI_2 or $CuSO_4$/hydroquinone, rt; (b) DMSO, 0.5 M aq NaOH, 50 °C; (c) H_2, Pd/C; (d) DMSO, 2.5 M NaOH, 70 °C.

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-*exo*-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-*exo*-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 α-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 *exo*/*endo* chloronitrile selectivity. This compared well with the literature values.[26–28] The use of ZnI_2[29] or in situ generated Cu(I) as catalysts gave similar yields and the same *exo*/*endo* selectivity, consistent with previous studies.[30,6]

When the chloronitrile **3** *exo*/*endo* mixture was subjected to aqueous basic conditions, the *endo*-CN isomer of **3** reacted more quickly to afford the corresponding *endo* α-chloro amide than did the *exo*-CN isomer. The α-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* α-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 α-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–H_2O 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 (1*R*,2*R*,4*R*)-configuration to the late-eluting (+)-enantiomer. (Fig. 2, Table 1). The early-eluting (−)- enantiomer was (1*S*,2*S*,4*S*). 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

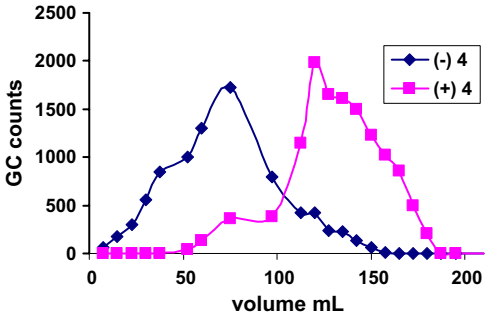


Figure 1. Separation of (−)- and (+)-2-chlorobicyclo[2.2.1]hept-5-ene-exo-2-carboxamide **4** on a column of microcrystalline cellulose triacetate (MCTA), with ethanol–water 9:1 (see methods). This chromatogram shows results from a run, in which racemic **4** loaded on the column.

hydrogenation (Scheme 2). 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.[18,31] 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.[32] The configuration of (−)-*exo*-bicyclo[2.2.1]heptane-2-carboxylic acid was correlated with (−)-*exo*-2-acetyl bicyclo[2.2.1]heptane.[33] 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.[34] Attempts were also made to predict the chirooptical behavior of *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid[20] and (+)-**2**.[34,35] Finally, (+)-**2** (~83% ee) was prepared from *exo*-2-bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde,[36] which in turn was generated by an asymmetric Diels–Alder reaction of cyclopentadiene and 2-bromoacrolein.[36,37] 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,[30] 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.[20]

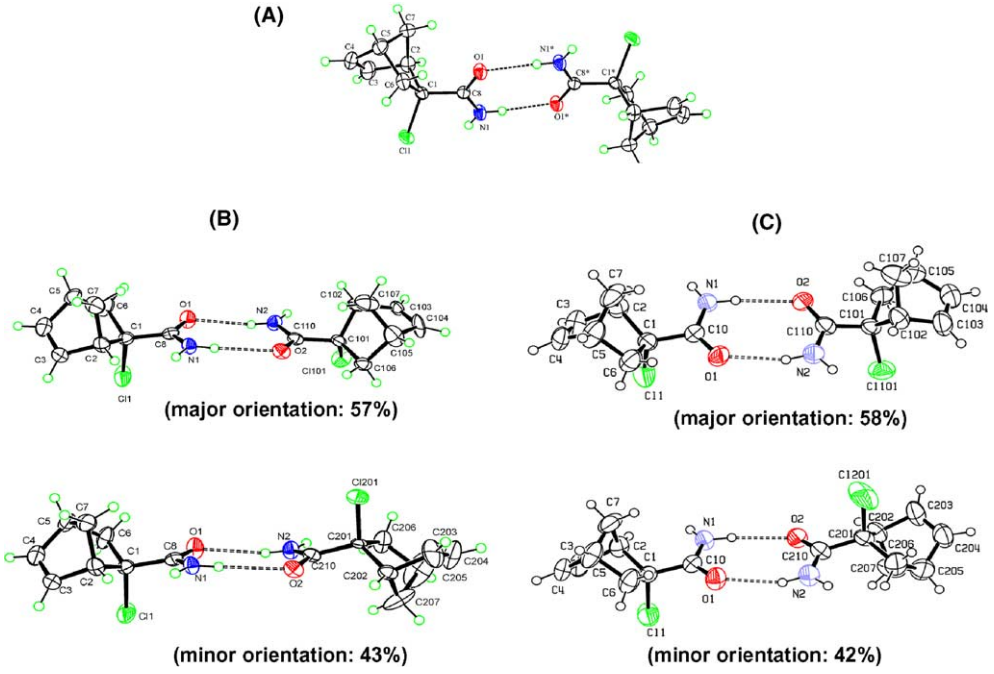
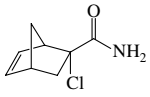
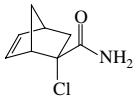


Figure 2. Structures obtained by X-ray crystallography for 2-chlorobicyclo[2.2.1]hept-5-ene-exo-2-carboxamide **4**: (A) racemic, (B) the early-eluting (−)-(1*S*,2*S*,4*S*) enantiomer, and (C) the late-eluting (+)- (1*R*,2*R*,4*R*) enantiomer. Graphics were generated with ORTEP-3, (A)–(C) 50% probability elipsoids for all non-hydrogen atoms.

Table 1. Summary of crystals of α-chloroamide **4** and their properties

Peak on MCTA	Late-eluting	Early-eluting	Racemic
Specific rotation	$[\alpha]_D^{20} = +60$ (c 0.4, $CHCl_3$)	$[\alpha]_D^{20} = -60$ (c 0.6, $CHCl_3$)	N/A
Enantiomer	 (1*R*,2*R*,4*R*)-**4**	 (1*S*,2*S*,4*S*)-**4**	N/A
Flack parameter[a]	$x = -0.01$ (16)	$x = -0.02$ (8)	N/A
Parameters and notes	Temperature = 25 °C	Temperature = −100 °C	Temperature = −100 °C
	Two forms of a H-bonded dimer:	Two forms of a H-bonded dimer:	One form of H-bonded racemic dimer
	Form 1: 58%	Form 1: 57%	
	Form 2: 42%	Form 2: 43%	
	Crystal system: monoclinic	Crystal system: monoclinic	Crystal system: monoclinic
	Space group: $P2_1$ (#4)	Space group: $P2_1$ (#4)	Space group: $P2_1/c$ (#14)
	$a = 10.1628$ (13), $b = 6.8521$ (11), $c = 11.9639$ (14) Å	$a = 10.066$ (1), $b = 6.8038$ (8), $c = 11.921$ (1) Å	$a = 12.987$ (3), $b = 5.917$ (1), $c = 10.524$ (3) Å
	$\alpha = 90°$, $\beta = 98.923$ (10)°, $\gamma = 90°$	$\alpha = 90°$, $\beta = 98.930$ (4)°, $\gamma = 90°$	$\alpha = 90.0°$, $\beta = 104.006$ (9)°, $\gamma = 90.0°$
	$V = 823$ Å^3	$V = 806.5$ (1) Å^3	$V = 784.7$ (3) Å^3
	$Z = 4$	$Z = 4$	$Z = 4$
	D_{calc} 1.385 g cm^{-3}	D_{calc} 1.413 g cm^{-3}	D_{calc} 1.453 g cm^{-3}
	μ = (MoKα) 4.01 cm^{-1}	μ = (MoKα) 4.11 cm^{-1}	μ = (MoKα) 4.22 cm^{-1}
	F(000) 360	F(000) 360	F(000) 360
	$R_F = 0.0411$[b]	$R_1 = 0.041$[d]	$R_1 = 0.032$[d]
	$R_wF = 0.0423$[c]	$wR_2 = 0.098$[e,f]	$wR_2 = 0.079$[e,g]
	No. obs. 1444 ($I_o \geqslant 2.5\sigma(I_o)$)	No. obs. 2327 ($I_o > 2.0\sigma(I_o)$)	No. obs. 1134 ($I_o > 2.0\sigma(I_o)$)

[a] x is the refined Flack enantiopole parameter, as in the expression: $F_o^2 = (1-x)F(h)^2 + xF(-h)^2$.
[b] $R_F = \Sigma||F_o| - |F_c||/\Sigma|F_o$.
[c] $R_{wF} = [\Sigma(w(|F_o| - |F_c|)^2)/\Sigma(wF_o^2)]^{1/2}$, where $w = [\sigma(F_o)^2 + 0.0001F_o^2]^{-1}$.
[d] $R_1 = R_F$.
[e] $R_2 = [\Sigma(w(F_o^2 - F_c^2)^2)/\Sigma(wF_o^2)^2]^{1/2}$.
[f] $w = [\sigma^2(F_o^2) + (0.0661(F_o^2 + 2F_c^2)/3)^2]^{-1}$.
[g] $w = [\sigma^2(F_o^2) + (0.0396(F_o^2 + 2F_c^2)/3)^2 + 0.5393(F_o^2 + 2F_c^2)/3]^{-1}$.

2.3. H-bonding of compounds 4 and 5

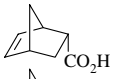
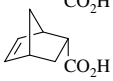
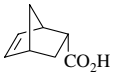
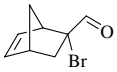
The crystal structures reveal that in all cases, the amide crystallized as H-bonded dimers, regardless of the crystallization conditions (see experimental section). In the racemic crystal, each dimer was a racemate, and the hydrogen-bonded dimers were present in a single orientation, with bridge C-7 carbons on opposite sides of the carboxamide H-bonded moiety (Fig. 2A). In the first crystal grown from enantiomerically purified material, two orientations were detected. These dimers differed in the orientation of C-7 atoms relative to the H-bonded moiety (Fig. 2B). More quantitatively, the N–C–C2–C1 and the N–C–C2–C1 dihedral angles of the second amide unit in the dimer differed significantly between the two forms (Table 2). The second enantiomerically pure crystal gave the same distribution of the two H-bonded dimers, even though that the crystal was grown under very different conditions (water as opposed to ethyl acetate–hexane) and collected at −100 °C (as opposed to room temperature). This suggests that the H-bonding is robust and that the two forms in the enantiomerically pure crystals are a result of the molecular asymmetry and not of the experimental conditions used for crystal growth and diffraction.

The crystal structures and the NMR data also suggest that one of the amide Hs (H_b, Fig. 3A) is influenced by the α-chloro substituent, perhaps through a weak H-bonding interaction. Such an interaction is expected to cause deshielding of the H_b signal relative to H_a. Experiments with racemic chloroamide **5** reveal that the chemical shift of H_b does not change significantly as the concentration of amide increases or as the temperature decreases. The signal assigned to H_a, on the other hand becomes increasingly deshielded relative to that of H_b (Fig. 3) as the temperature decreases or the concentration increases (Table 4). The data are consistent with H_a 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,

Table 2. Amide dimer conformers observed by X-ray crystallography

Crystal	Form	Dihedral angle	Unit 1 (°)	Unit 2 (°)
(+)-**4**	Major (58%)	N–C–C2–C1	97.0	53.0
		N–C–C2–C1	−24.6	−70.4
	Minor (42%)	N–C–C2–C1	97.0	−97.5
		N–C–C2–C1	−24.6	141.5
(−)-**4**	Major (57%)	N–C–C2–C1	−98.3	67.8
		N–C–C2–C1	22.9	−54.0
	Minor (43%)	N–C–C2–C1	−98.3	101.7
		N–C–C2–C1	22.9	−139.8
Racemic **4**	One form	N–C–C2–C1	32.8	−32.8
		N–C–C2–C1	−88.7	88.7

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

Compound	Synthetic precursor or approach	Specific rotation of the enantiomer of **2** or **1** prepared	Reference
(+)-**2**		$[\alpha]_D^{23} = +1186$ (*c* 0.7, $CHCl_3$)	18
(+)-**2**		$[\alpha]_D^{23} = +1033$ (*c* 10.1 $CHCl_3$)	31
(+)-**2**		$[\alpha]_D^{23} = +1088$ (*c* 1.7, $CHCl_3$)	55, 31
(+)-**2**	Enantioselective cycloaddition of a ketene equivalent to cyclopentadiene	Not given	56
(+)-**2**	Enantioselective cycloaddition	$[\alpha]_D^{25} = +1032$ (*c* 0.025, acetone)	57
(+)-**2**		$[\alpha]_D^{23} = +980$ (*c* 0.3, $CHCl_3$)	36
(−)-**2**	Enantioselective cycloaddition	$[\alpha]_D^{25} = -1051$ (*c* 0.030, acetone)	57
(−)-**2**	Kinetic enzymatic resolution of the racemic *endo* alcohol	$[\alpha]_D^{25} = -930$ (*c* 1.1, $CHCl_3$) ee by GC: 82%	58, 59
(+)-**1**	Jones oxidation of *endo* bicyclo[2.2.1]heptan-2-ol	$[\alpha]_D^{30} = +17$ (*c* 4.4, $CHCl_3$)	20
(+)-**1**	From bicyclo[2.2.1]heptan-2-ol by resolution of phthalate	$[\alpha]_D^{25} = +29.1$ (*c* 1.5, $CHCl_3$)	60
(−)-**1**	From bicyclo[2.2.1]heptan-2-ol by resolution of phthalate	$[\alpha]_D^{25} = -28.7$ (*c* 2.2, $CHCl_3$)	60
(−)-**1**	From nortricyclanone using L-proline perchlorate	$[\alpha]_D^{25} = -4.7$ (*c* not given, $CHCl_3$)	61

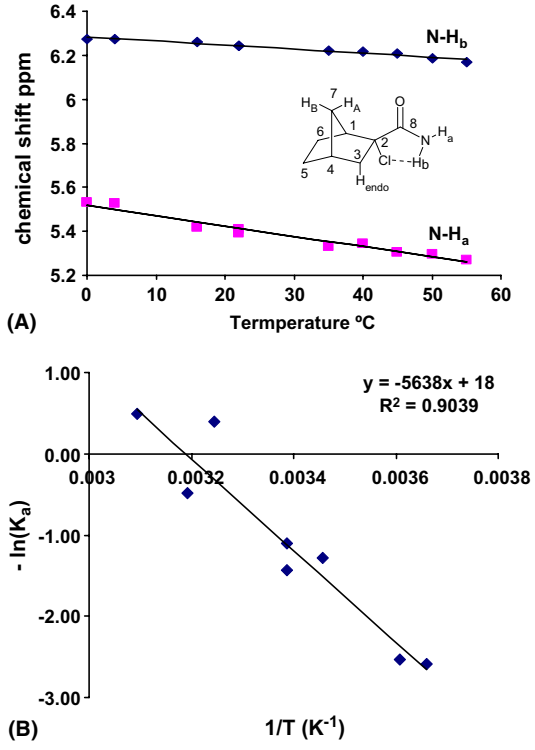


Figure 3. (A) Chemical shift of the NH protons of amide **5** at different temperatures in $CDCl_3$. (B) Using the chemical shift difference (see Table 4) to estimate the percentage of the dimer in solution, the dimerization reaction has $\Delta H = -11$ kcal/mol, $\Delta S = -36$ cal/mol. The percentage of the dimer was estimated, on the assumption that the chemical shift difference for the 0.1 M amide solution at 4 °C corresponds to 100% dimer and that chemical shift difference of the 0.01 M solution at 55 °C corresponds to 100% monomer.

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-3_{exo} and H-7_A). Both of these signals became more shielded with lower temperature and/or higher concentration (Table 4). The slight shielding of H-7_A and H-3_{exo} is more difficult to explain. In the crystal structures, we have obtained H-7_A and H-3_{exo} both placed in the shielding cone of the carboxamide group. As the concentration of α-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-7_A and H-3_{exo} 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 α-chloroamide **5** (Table 4, Fig. 3) were used to estimate enthalpy and entropy parameters, ΔH and ΔS, 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 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 a ΔH for dimerization of amide **5** of −11 kcal/mol and a ΔS of −36 cal/mol. This gives a ΔG 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

Table 4. Temperature and concentration dependence of hydrogen chemical shifts in α-chloroamide **5**, in $CDCl_3$

Compound (conc. M)	Temperature (°C)	δNH_b	δNH_a	$\Delta\delta$	δH-3$_{endo}$	δH-7$_A$
5 (0.01)	0	6.28	5.53	0.74	2.82	1.76
	4	6.27	5.53	0.75	2.83	1.76
	16	6.26	5.42	0.84	2.83	1.78
	22	6.25	5.41	0.84	2.83	1.78
		6.25	5.39	0.85	2.83	1.78
	35	6.22	5.33	0.89	2.83	1.80
	40	6.22	5.34	0.87	2.83	1.80
	45	6.21	5.31	0.90	2.84	1.80
	50	6.19	5.30	0.89	2.83	1.80
	55	6.17	5.29	0.90	2.84	1.81
5 (0.1)	4	6.29	6.20	0.10	2.79	1.72
	22	6.28	5.97	0.30	2.80	1.75
	50	6.27	5.97	0.30	2.80	1.75
D_2–5 (0.01)	22	6.24	5.33	0.92	2.83	1.78

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-chloro bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxamide **4** by X-ray crystallography. Through 1-step chemical conversions, we have correlated (+) 2-chloro bicyclo[2.2.1]hept-5-ene-2-*exo*-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-*exo*-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°/min, 100° (4 min), 50°/min, 250° (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).[39] Enantiomer compositions were analyzed on a Varian 3400 gas chromatograph, equipped with a Cyclo-Sil 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-chloro amide 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 Chiracel 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), $CuSO_4$ (7 mg, 0.04 mmol) and hydroquinone (5 mg, 0.04 mmol) with gently stirring. The mixture was maintained at room temperature for about 7 h, 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 Na_2SO_4, 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 R_t (SPB 5) 17.8 and 18.1 (4:1 intensity ratio) (RI 1146 and 1153, respectively). ^{1}H NMR ($CDCl_3$, *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-3$_{exo}$), 1.75–1.83 (m, 2H, H-7), 1.71 (dd, $J = 3.7$, 13.2 Hz, 1H, H-3$_{endo}$); (*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-3_{exo}), 2.24 (dd, $J = 2.7$, 13.2 Hz, 1H, H-3_{endo}), 1.92–1.96 (br d $J = 9.7$, 2H, H-7); ^{13}C NMR ($CDCl_3$) 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 ^{1}H NMR matches the literature spectrum;[26] IR (KBr) 3071, 2990, 2946, 2869, 2235, 1712, 1336, 1269, 766, 725 cm^{-1}; MS (EI): *m/z* (rel. intensity) 154 ($M^{+\cdot}$ 11%), 117 ($M^{+\cdot}$-HCl, 4%), 91 ($M^{+\cdot}$-HClCN, 15%), 66 (retro Diels–Alder, 100%).

4.2.2. 2-Chlorobicyclo[2.2.1]hept-5-ene-*exo*-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 EtOAc (3×10 mL) and dried over Na_2SO_4. Concentration in vacuo gave a light yellow solid. Purification by column chromatography on silica gel with hexane–EtOAc (gradient, starting at 6:1 and ending at 2:1) gave **4** (192 mg, 71% yield, white crystalline, 1:9 *endo*/*exo* carboxamide). The *exo*-amide diastereomer was purified further by column chromatography. Found; Mp 112–114 °C (lit. 114–115 °C),[26] GC R_t (SPB 5) 22.2 min (RI 1354); UV–vis ($\lambda_{max} = 204$ nm, $\varepsilon_{max} = 6000$ M^{-1} cm^{-1}, EtOH 95%); ^{1}H NMR δ 6.46 (br, 1H, NH), 6.40 (dd, $J = 3.0$, 5.6 Hz; 1H, H-6), 6.22 (dd, $J = 3.0$, 5.6 Hz; 1H, H-5), 5.54 (br, 1H, NH), 3.24 (m, 1H, H-1), 2.98 (m, 1H, H-4), 2.86 (dd, J 3.7, 12.9 Hz; 1H, H-3_{endo}), 1.89 (br d, $J = 9.1$ Hz, 1H, H-7_A), 1.57 (br d, $J = 8.9$ Hz, 1H, H-7_B), 1.50 (dd, $J = 3.6$, 12.9 Hz; 1H, H-3_{exo}); ^{13}C NMR δ 175.3 (C-amide), 139.4 (C-5), 134.9 (C-6), 74.7 (C-2), 54.3 (C-1), 48.4 (C-4), 42.7 (C-3), 42.3 (C-7); IR (KBr) 3413, 3282, 3188, 2977, 1662, 1604, 1383; MS (EI) 172 ($M^{+\cdot}$+1, 40%), 136 ($M^{+\cdot}$-Cl, 9%), 106 (79%), 91 (53%), 66 (100%). Anal. Calcd for $C_8H_{10}OCl$: C, 55.8; H, 5.81; N, 8.14. Found: C, 56.1; H, 5.90; N, 8.01.

Pure 2-chlorobicyclo[2.2.1]hept-5-ene-exo-2-carboxamide **4** was then subjected to chromatographic resolution on a medium-pressure liquid chromatograph equipped with an MCTA column. This gave the (−) (1*S*,2*S*,4*S*)-enantiomer first; $[\alpha]_D^{20} = -60$ (*c* 0.6, $CHCl_3$) R_t (Cyclosil B) 16.3 min, (Chiracel) 13.5 min, followed by the (+) (1*R*,2*R*,4*R*)-enantiomer; $[\alpha]_D^{20} = +60$ (*c* 0.4, $CHCl_3$) R_t (Cyclosyl B) 16.8 min, (Chiracel) 16.4 min. A typical separation profile for a large-scale MCTA separation is shown in Figure 1.

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 screw-cap and a rubber septum. The vial was sealed, pressurized with hydrogen, and the reaction mixture stirred for ca. for 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-*exo*-2-carboxamide 5. Hydrogenation of 2-chlorobicyclo[2.2.1]hept-5-ene-exo-2-carboxamide **4** 98% yield. ^{1}H NMR δ 6.24 (br s, 1H, NH), 5.40 (br s, 1H, NH), 2.82 (ddd, $J = 2.8$, 4.5, 13.6 Hz, 1H, H-3_{endo}), 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-6_{endo}), 1.78 (br d, $J = 10.2$ Hz, 1H, H-7_A), 1.62 (m, $J \sim 4$ and 8-8.7, 12.3 Hz, 1H, H-6_{exo}), 1.53 (br d, $J = 13.5$ Hz, 1H, H-5_{exo}), 1.49 (m, 1H, H-3_{exo}), 1.38 (m, $J = 3.4$, 10.2, 1H, H-7_B), 1.34 (m, $J = 2.3$, 8.9, 11.3, 1H, H-5_{endo}). ^{13}C 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, 1386, 769, 589 cm^{-1}; MS 174 ($M^{+\cdot}$, 31%), 138 ($M^{+\cdot}$−Cl, 30%), 129 (18%), 106 (100%), 93 (38%), 67 (30%). For the chiral amide $[\alpha]_D^{20} = -25$ (*c* 1.0, $CHCl_3$); R_t (Cyclosil B) 19.3 min, and $[\alpha]_D^{20} = +25$ (*c* 0.9, $CHCl_3$); R_t (CycloSil B) 18.9 min.

To facilitate the assignment of the ^{1}H NMR spectrum of **5**, racemic **4** (28.7 mg, 0.17 mmol) was deuterated as described above to give 5,6-$\mathbf{D_2}$-**5** 27.2 mg (93%); ^{1}H NMR δ 6.21 (br, 1H, NH), 5.30 (br, 1H, NH), 2.83 (ddd, $J < 2$, $J = 4.5$, 13.6 Hz), 2.60 (br, 1H, H-1), 2.31 (br, 1H, H-4), 2.15 (dm, 1H, H-6_{endo}), 1.77 (br d, $J = 10.2$ Hz, 1H, H-7_A), 1.50 (ddd, $J = 2.1$, 3.3, 13.6 Hz, 1H, H-3_{exo}), 1.36 (br d, $J = 10.2$, 1H, H-7_B), 1.33 (br d, $J = 8.9$, 1H, H-5_{endo}); IR (KBr) 3423, 3181, 2967, 2926, 2161 (C-D str.), 1648, 1373, 779, 588 cm^{-1}. MS 176 ($M^{+\cdot}$, 100%), 140 ($M^{+\cdot}$-Cl, 28%), 131 (12%), 108 (16%), 106 (50%), 95 (17%), 93 (16%), 67 (13%). Additions of electrophiles and nucleophiles, halogens 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-5_{exo} and H-6_{exo} in compound **5** disappeared in the spectrum of compound 5,6 $\mathbf{D_2}$–**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 Na_2SO_4. 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-*exo*-2-carboxamide **4** was converted to (±)-**2** in 83% yield. ^{1}H 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). ^{13}C NMR δ 216 (C-2), 143 (C-6), 131 (C-5), 56 (C-1), 51 (C-4), 40, 37; IR 3477 (∼twice C=O stretch), 3067, 2970, 2936, 1749, 1326, 1125, 709 cm^{-1}; GC R_t (SPB 5) 10.2 min (RI 931); MS *m/z* 108 ($M^{+\cdot}$ 48%), 91 ($M^{+\cdot}$-OH, 3.8%), 77 (5%), 66 (100%).

4.2.6. (+)-Bicyclo[2.2.1]hept-5-en-2-one (+)-2 from (+)-2-chlorobicyclo[2.2.1]hept-5-ene-*exo*-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**. $[\alpha]_D^{20} = +1050$ (*c* 0.2, $CHCl_3$) lit. Table 2; R_t (Cyclosyl B) 7.0 min. Similarly, (−)-**2** was prepared in 48% yield from (−)-**4**. $[\alpha]_D^{20} = -1067$ (*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 **2**, to give bicyclo[2.2.1]heptan-2-one **1** (3.6 mg, quantitative, colorless oil); ^{1}H NMR δ 2.66 (br m, 1H, H-1), 2.59 (br d, J 3.5 Hz, 1H, H-4), 2.02–2.09 (br dd, $J = 4.8$, 17.8 Hz, 1H, H-3$_{exo}$), 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$_{exo}$), 1.50–1.53 (m, 2H, H-5), 1.40–1.46 (m, 1H, H-6$_{endo}$). ^{13}C NMR δ 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 ($M^{+\cdot}$ 66%), 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**. $[\alpha]_D^{22} = +27.2$ (*c* 1.8 $CHCl_3$); R_t (Cyclosyl B) 7.1 min. Lit. Table 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**, $[\alpha]_D^{20} = -25$ (*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). $[\alpha]_D^{20} = -27$ (*c* 1.1 $CHCl_3$); $\mathbf{R_t}$ (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-Kα radiation at room temperature. The data collection process was controlled with the program Difrac.[42] Data reduction was performed using programs from the NRCVAX Crystal Structure System.[43] The structure was refined using CRYSTALS.[44] Diagrams were produced using ORTEP-3.[45] Data for the other structures were obtained using a Bruker X8 APEX diffractometer with graphite monochromated Mo-Kα radiation. The data were collected at −100.0 °C to a maximum of 2θ value of 50.2° in a series of ϕ and ω scans in 0.50° oscillations with 30.0 s exposures. The crystal-to-detector distance was 38.00 mm. The data collection process was controlled with the Brucker SAINT software.[46] Data reduction was performed with Brucker SADABS software.[47] The structures were refined using the SHELXL software package of Brucker-AXS.[48–53] The absolute configuration was determined on the basis of the Flack enantiopole parameter.[54] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC: 274933, 274934 and 274935.

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