39. Absolute Configuration of 3-Substituted 1-Azabicyclo[2.2.1]heptanes

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Dedicated to Professor Dr. *Vladimir Prelog* on the occasion of his 85th birthday

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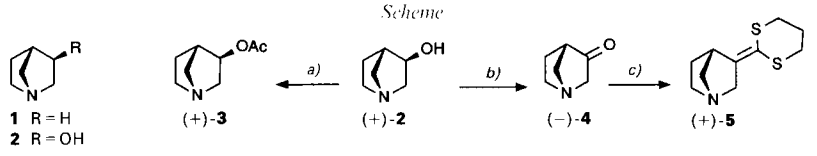
The 1-azabicyclo[2.2.1]heptan-3-*exo*-ol (**2**) was resolved by fractional crystallisation of its hydrogen tartrate salts. The enantiomers (+)- and (−)-**2** were oxidised to the ketones (−)-**4** and (+)-**4**, respectively (*Scheme*). CD spectroscopy suggested that (−)-**4** possesses the (1*R*,4*S*)-configuration. This absolute configuration was confirmed by single-crystal X-ray diffraction of the derivative (+)-(1*R*,4*R*)-3-(1,3-dithian-2-ylidene)-1-azabicyclo[2.2.1]-heptane ((+)-**5**).

Introduction. – The 1-azabicyclo[2.2.1]heptane (**1**) was first prepared by *Prelog* and *Clemo* [1] in 1936. In the last few years, there has been great interest in this skeleton for preparing rigid structural analogues of biogenic amines (for acetylcholine analogues, see [2a–k]; for serotonine analogues, see [2l–n]). In derivatives of **1** in which the 3-position is substituted with an ester isostere, the *gauche* conformation of acetylcholine is mimicked. The 3-*exo*-(1,2,4-oxadiazolyl) derivatives of 1-azabicyclo[2.2.1]heptane were claimed to be among the most potent muscarinic agonists known [3]. When we started our work in this area, all chiral compounds in this series had been reported as racemates [2]. Very recently, methods for resolving 1-azabicyclo[2.2.1]heptane-3-carboxylates as their diastereoisomeric amides [4] were disclosed, as well as the synthesis of (+)-(3*S*,4*R*)-ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate [5]. For a suitable comparison of the biological activity of these and similar compounds with that of other muscarinic agonists in our models [6], we needed the compounds in enantiomerically pure form and knowledge of their absolute configuration.

We, therefore, synthesised both enantiomers of 3-(1,3-dithian-2-ylidene)-1-azabicyclo[2.2.1]heptane ((+)- and (−)-**5**), a key intermediate in the synthesis of a large number of cholinergic agonists [2a], and determined their absolute configurations both using CD spectroscopy and X-ray crystallography.

Results and Discussion. – Racemic 1-azabicyclo[2.2.1]heptan-3-*exo*-ol (**2**) was synthesised previously by several groups [7] [2b] [2l]. We prepared racemic **2** using the method described in [2l] and resolved the alcohol by fractional crystallisation of its hydrogen tartrate salt. The enantiomer (+)-**2** crystallised preferentially using (+)-L-tartaric acid and (−)-**2** with (−)-D-tartaric acid. The corresponding hydrogen tartrates of alcohols (+)- and (−)-**2** were obtained in 36 and 33% yield, respectively. After 3 recrystallisations, the

Scheme



a) AcCl, Et_3N, 2 h. *b*) DMSO/$(COCl)_2$, Et_3N, −60°, 5 h). *c*) 2-(Trimethylsilyl)-1,3-dithiane, BuLi, THF, −35°.

optical rotations of the isolates did not increase. The enantiomers (+)- and (−)-**2** were converted to their acetates (+)- and (−)-**3**, respectively, by treatment with acetyl chloride and Et_3N (*Scheme*).

Oxidation of 1-azabicyclo[2.2.1]heptan-3-ol using *Jones* reagent was reported [7]. We compared the results of the *Jones* oxidation with the *Corey-Kim* [8] and *Swern* oxidation and found that the *Swern* procedure provided the highest yields. Thus, oxidation of alcohol (+)-**2** under *Swern* conditions gave ketone (−)-**4** which was isolated as its (+)-hydrochloride in 76% yield (*Scheme*). Treatment of (−)-**4** with the lithium salt of 2-(trimethylsilyl)-1,3-dithiane [2a] gave the corresponding ketene thioacetal (+)-**5** in 73% yield. The enantiomer (−)-**5** was synthesised in analogous fashion from alcohol (−)-**2**.

Crystals of (+)-**5** were obtained by slow evaporation from Et_2O and their structure was determined (*Fig. 1*). Enantiomer (+)-**5** was shown to have the absolute configuration

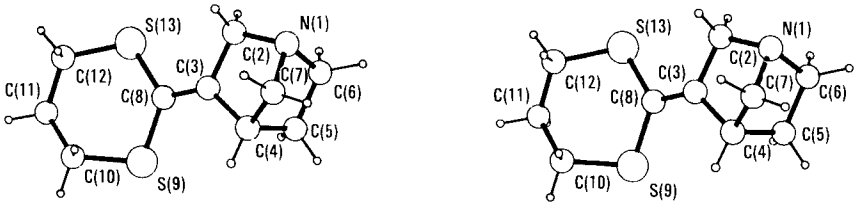


Fig. 1. *Stereoscopic projection of the crystal structure of (+)-***5**

(1*R*,4*R*). All bond lengths, bond angles, and torsion angles of (+)-**5** lie within the expected ranges. Fractional atomic coordinates and anisotropic temperature factors of the non-H-atoms were deposited and are available on request from the Director of the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

A simple but effective procedure was used to determine the absolute configuration of (+)-**5**. The difference between $|F_h|$ and $|F_{-h}|$ will be greatest when the contributions to the structure factor from the anomalous atoms are as near as possible 90° out-of-phase with that of all the atoms and is as large as possible. In terms of the contributions of all atoms (T) and anomalous (H) atoms, these conditions may be met by maximising $\sin^2(\phi_T - \phi_H)$ and $|F_H|^2$. The required values may be obtained using SHELX-76 [9] by carrying out first a normal structure-factor calculation and listing the values of $A_T = |F_T|\cos\phi_T$ and $B_T = |F_T|\sin\phi_T$ for each reflection. A second calculation is then done allowing only the anomalous atoms to contribute, thus obtaining A_H and B_H. Since $\sin(\phi_T - \phi_H) = \sin\phi_T\cos\phi_H - \cos\phi_T\sin\phi_H$, the first term of the discriminator may be expressed as $(B_TA_H - A_TB_H)^2/F_T^2F_H^2$. The overall discriminator is, therefore,

$$(B_TA_H - A_TB_H)^2/F_T^2 \qquad (1)$$

Eqn. 1 gives the maximum possible difference of $2|F''_H|$ between $F_T(h)$ and $F_T(-h)$. As a selection criterion, two additional conditions are required[1]), $|F''_H| \leq |F_T|$ and $|F''_H| > n\sigma(F_T)$. For organic structures with weak anomalous scatterers, the condition $|F''_H| \leqslant |F_T|$ is usually met, because reflections with $|F''_H| \gtrsim |F_T|$ tend to be too weak to be measured. This may not be true for structures with strong anomalous scatterers. The condition $|F''_H| > n\sigma(F_T)$ is also usually fulfilled because, apart from the maximum condition(s) on $|F_H|^2\sin^2(\phi_T - \phi_H)$, least-squares and structure-factor calculations include only those reflections for which $|F_T| \geqslant n\sigma(F_T)$.

In practice, the denominator is replaced by the similar term $|F_O||F_C|$ for the total structure. The two structure-factor lists are then used to calculate those fifty reflections with the largest discriminators. These selected reflections can then be used to calculate a conventional R factor for the structure in both enantiomorphs (in this case, in the two enantiomorphic space groups $P4_32_12$ and $P4_12_12$). It is also worth pointing out that this procedure does not necessarily require measurement of *Friedel* pairs.

The conventional R factor using all data for $P4_32_12$ is 0.047 compared to $R = 0.056$ for the enantiomeric structure in $P4_12_12$. The difference in R factor between the enantiomorphs using the 50 selected reflections is markedly larger, with $R = 0.0336$ in $P4_32_12$ compared to $R = 0.0702$ for $P4_12_12$.

The CD spectra of enantiomers (+)- and (−)-**4** and (+)- and (−)-**5** are given in *Fig. 2*. The free base (−)-**4** presents a CD spectrum with a negative minimum $\Delta\varepsilon = -2.00$ (309) and a positive tail absorption below 220 nm (*Fig. 2d*). Free base (+)-**4** presents the opposite *Cotton* effect ($\Delta\varepsilon = 1.98$ (309); *Fig. 2b*), as expected. Studying a series of α-amino-ketones, *Hudec* proposed that the observed CD spectra are the result of the coupling of the $n - \pi^*$ and $\pi - \pi^*$ transitions and are closely dependent on the relative geometry of the lone pair on the N-atom and the C(α)–CO bond [10]. This coupling is removed by protonation of the N lone pair. One may, therefore, consider the hydrochlorides of aminoketones (+)- and (−)-**4** as analogues of norcamphor, albeit perturbed by an asymmetric charge. Indeed, (+)- and (−)-**4**·HCl in MeOH present bisigmate CD spectra analogous to those of norcamphor [11]. (+)-Norcamphor is known to have (1*S*,4*R*)-con-

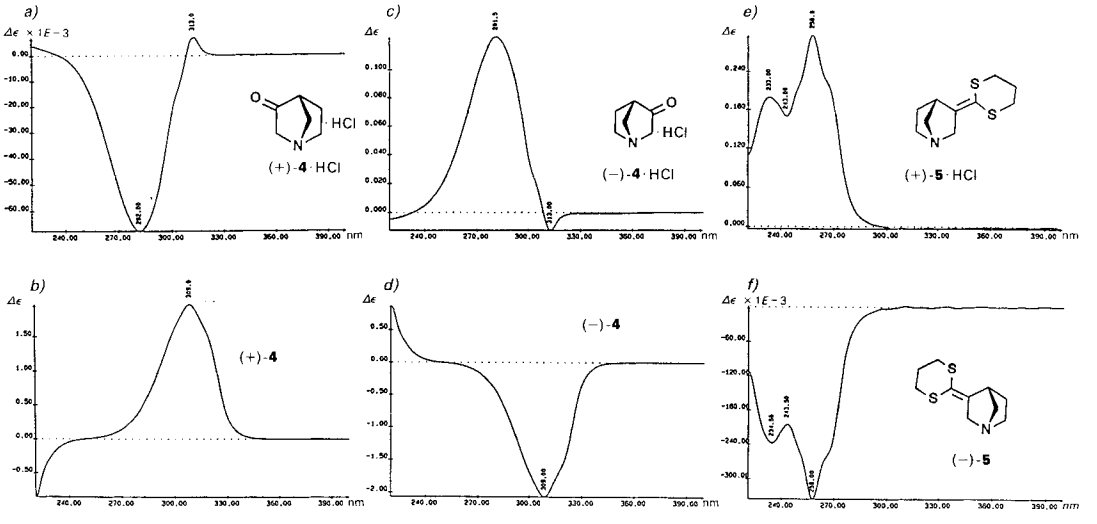


Fig. 2. *CD Spectra of* a) *hydrochloride of (+)*-**4**, b) *free base (+)*-**4**, c) *hydrochloride of (−)*-**4**, d) *free base (−)*-**4**, e) *free base (+)*-**5**, f) *and free base (−)*-**5**. All spectra were measured in MeOH; the ordinate represents $\Delta\varepsilon$.

[1]) The authors thank an anonymous referee for bringing this point to their attention.

figuration [12] and a CD with $\Delta\varepsilon = -0.25$ (305), + 0.15 (280) [13]. The CD spectrum of (−)-**4**·HCl shows $\Delta\varepsilon = -0.012$ (313), and +0.12 (281.5) (see *Fig. 2c*). Although the longer-wavelength band in the norcamphor spectrum is much stronger than in that of (−)-**4**·HCl, assuming that similar structural parameters are present, then (−)-**4**·HCl should have the same absolute configuration as (+)-(1*S*,4*R*)-norcamphor. Similarly, (+)-**4**·HCl should correlate with (−)-(1*R*,4*S*)-norcamphor. The absolute configuration of (+)-**5**, determined as (1*R*,4*R*) by X-ray crystallography, shows that this is indeed the case.

The CD spectra of ketene thioacetals (+)- and (−)-**5** (*Fig. 2, e* and *f*) show two distinct but partially overlapping *Cotton* effects, with maxima at 234 and 258 nm; both are positive in the case of the (1*R*,4*R*)-enantiomer (+)-**5**, the converse being the case for the enantiomer (−)-**5**.

Conclusion. – The classical resolution of **2** provides ready access to an important starting material in the synthesis of conformationally restricted, enantiomerically pure analogues of biogenic amines. With the determination of the absolute configuration of (−)-**4** and (+)-**5**, it is now possible to correlate the configuration of their derivatives. Previous workers described conditions for alcoholysis of the racemic ketene thioacetals to the corresponding esters, which were converted to a variety of acyclic and heterocyclic acetate isosteres [2]. The ketene thioacetals (+)- and (−)-**5** were used to prepare the pure enantiomers of several muscarinic agents. Their syntheses and biological activities will be the subject of a separate publication.

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Experimental Part

General. M.p.: *Büchi-510* melting-point apparatus; in open capillaries; uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter; 1-ml micro-cuvette (10 cm). CD-Spectra (λ,$\Delta\varepsilon$): *Jobin Yvon CD-6*. IR (cm^{-1}): *Bruker IFS-66 FT-IR*. ^{1}H-NMR (δ in ppm, *J* in Hz): *Bruker WH-360* (360 MHz). MS (*m/z*, (%)): *AEI MS 30* and *Varian MAT 212* (EI: 70 eV).

Resolution of rac-*Azabicyclo[2.2.1]heptan-3-ol* (**2**). A soln. of **2** (47.5 g, 0.42 mmol) in CH_2Cl_2 (200 ml) was added dropwise to a well stirred soln. of (−)-D-tartaric acid (63.04 g, 0.42 mmol) in 80% EtOH/H_2O. The resulting crystalline precipitate was filtered off, dried (111.8 g), and recrystallised from boiling 70% EtOH/H_2O (800 ml). The crystals thus obtained (60.3 g) were recrystallised two further times, to give (−)-1-azabicyclo[2.2.1]heptan-3-*exo*-ol hydrogen (−)-D-tartrate (40.6 g, 36.3%). M.p. 210° (dec.). $[\alpha]_D^{20} = -5.4$ (*c* = 1.0, MeOH). Anal. calc. for $C_{10}H_{17}NO_7$: C 45.6, H 6.5, N 5.3, O 42.5; found: C 45.6, H 6.5, N 5.3, O 42.4.

Free base (−)-**2**: M.p. 122–123°. $[\alpha]_D^{20} = -15.0$ (*c* = 0.5, CH_2Cl_2).

The mother liquors were evaporated. The residue was taken up in H_2O, the soln. made alkaline by addition of Na_2CO_3 and extraeted with CH_2Cl_2 (6 × 50 ml), the org. extract dried (Na_2CO_3) and evaporated, and the resulting oil treated with (+)-L-tartaric acid as described above. After 3 recrystallisations, (+)-1-azabicyclo[2.2.1]heptan-3-*exo*-ol hydrogen (+)-L-tartrate was obtained (36.9 g, 33.0%). M.p. 210° (dec.). $[\alpha]_D^{20} = +5.8$ (*c* = 1.0, MeOH). Anal. calc. for $C_{10}H_{17}NO_7$: C 45.6, H 6.5, N 5.3, O 42.5; found: C 45.1, H 6.4, N 5.2, O 42.5.

Free base (+)-**2**: M.p. 130–131° ([7]: 128–129° for racemate). $[\alpha]_D^{20} = +14.8$ (*c* = 0.5, CH_2Cl_2).

(+)-(1R,3R,4S)-1-Azabicyclo[2.2.1]hept-3-yl Acetate ((+)-**3**). AcCl (1.04 g, 13.26 mmol) was added dropwise over 2 h to a cooled (0°) soln. of (+)-**2** (1.0 g, 8.84 mmol) in THF (120 ml). Et_3N (1.33 g, 13.26 mmol) was then added dropwise, and the milky mixture was stirred for further 2 h, and evaporated. The residue was chromatographed (alox III, AcOEt): (+)-**3** as a yellow oil, $[\alpha]_D^{20} = +49.7$ (*c* = 0.38, CH_2Cl_2). The oil was then crystallised (i-PrOH/H_2O) as the hydrogen (+)-L-tartrate (0.74 g, 27.5%). M.p. 108–109°. $[\alpha]_D^{20} = +23.5$ (*c* = 0.34, MeOH).

^{1}H-NMR ((D$_6$)DMSO): 1.43 (br. *s*, 1 H, H–C(5)); 1.75 (br. *s*, 1 H, H–C(5)); 2.0 (*s*, CH$_3$); 2.70 (br. *s*, CH$_2$(7), H–C(4)); 3.4 (br. *s*, 3 H, CH$_2$(6), H–C(2)); 3.21 (br. *s*, 1 H, H–C(2)); 4.09 (*s*, 2 H, tartrate-H), 4.58 (br. *s*, H–C(3)); 5.5–6.5 (br. *s*, 4 H, exchangeable). EI-MS: 155 (15, M^+), 112 (100), 96 (70), 84 (48). Anal. calc. for C$_{12}$H$_{19}$NO$_8$ · 2.1 H$_2$O: C 42.0, H 6.8, N 4.1, O 47.0; found: C 42.1, H 6.8, N 4.1, O 47.0 (H$_2$O-content (*Karl Fischer*), 1.7%).

(–)-(1S,3S,4R)-Azabicyclo[2.2.1]hept-3-yl Acetate ((–)-**3**). Prepared as described for (+)-**3**. Light yellow oil. $[\alpha]_D^{20} = -50.2$ (*c* = 0.7, CH$_2$Cl$_2$). Hydrogen (–)-D-tartrate: M.p. 106–107. $[\alpha]_D^{20} = -22.8$ (*c* = 0.68, MeOH). Anal. calc. for C$_{12}$H$_{19}$NO$_8$ · 2.1 H$_2$O: C 42.0, H 6.8, N 4.1, O 47.1; found: C 42.1, H 6.9, N 4.1, O 46.9.

(+)-(1S,4R)-1-Azabicyclo[2.2.1]heptan-3-one ((+)-**4**). A soln. of DMSO (1.96 ml, 2.16 g, 27.6 mmol) in CH$_2$Cl$_2$ (5 ml) was added dropwise over 5 min to a cooled (–60°) soln. of oxalyl chloride (1.08 ml, 1.60 g, 12.57 mmol) in CH$_2$Cl$_2$ (20 ml), and the mixture was stirred for 1 h at –60°. To this was added a soln. of (–)-**2** (1.53 g, 11.44 mmol) in CH$_2$Cl$_2$ (20 ml) over 20 min. The resulting milky suspension was stirred vigorously for 2 h at –60°, after which Et$_3$N (3.19 ml, 2.32 g, 12.57 mmol) was added dropwise over 5 min. The mixture was then allowed to warm up to r.t. After 2 h at r.t. the mixture was diluted with CH$_2$Cl$_2$ (40 ml) and aq. sat. Na$_2$CO$_3$ soln. (20 ml). The aq. phase was extracted with CH$_2$Cl$_2$ (3 × 20 ml), the combined org. extract dried (MgSO$_4$) and evaporated, and the yellow oil treated with HCl/EtOH. The crude (+)-**4** · HCl was recrystallised from acetone/Et$_2$O to give colourless crystals (1.28 g, 75.7%). M.p. 231° (dec.). $[\alpha]_D^{20} = -4.2$ (*c* = 0.5, MeOH). CD (*c* = 0.014M, MeOH): 313 (0.0073), 282 (–0.067). IR (KBr): 3022, 2976, 2860, 2766, 2711, 2577, 1744, 1463, 1172, 950.

The soln. of (+)-**4** · HCl in sat. aq. Na$_2$CO$_3$ soln. was extracted with CH$_2$Cl$_2$ to give the free base (+)-**4** as an oil which crystallised on standing. Colourless crystals. M.p. 26–28° [3b]: (25–27° for racemate). R_f (alumina, AcOEt) 0.25. $[\alpha]_D^{20} = +153$ (*c* = 0.58, CH$_2$Cl$_2$). CD (*c* = 0.012M, MeOH): 309 (+1.98). IR (CH$_2$Cl$_2$): 2971, 2899, 1753, 1456, 1416, 1173, 1062, 990, 909. ^{1}H-NMR (CDCl$_3$): 1.75 (*m*, 1 H, 1 H–C(5)); 2.1 (*m*, 1 H, 1 H–C(5)); 2.65–2.8 (overlapping *m*'s, 4 H); 2.95–3.15 (overlapping *m*'s, 3 H). EI-MS: 111 (0.75, $M^{+\cdot}$), 83 (79), 55 (26), 42 (100).

(–)-(1R,4S)-1-Azabicyclo[2.2.1]heptan-3-one ((–)-**4**). Prepared as described for (+)-**4**. $[\alpha]_D^{20} = -153$ (*c* = 0.58, CH$_2$Cl$_2$). CD (*c* = 0.012M, MeOH): 309 (–2.07). R_f, IR, ^{1}H-NMR, and MS: identical to those of (+)-**4**. (–)-**4** · HCl: m.p. 231° (dec.). $[\alpha]_D^{20} = +4.5$ (*c* = 4.85 in MeOH). CD (*c* = 0.028M, MeOH): 313 (–0.012), 281.5 (+0.123).

(+)-(1R,4R)-3-(1,3-Dithian-2-ylidene)-1-azabicyclo[2.2.1]heptane ((+)-**5**). BuLi (1.6M in hexane, 34.2 ml, 1.2 equiv.) was added dropwise over 4 min to a soln. of 2-(trimethylsilyl)-1,3-dithiane (10.36 ml, 10.79 g, 1.2 equiv.) in THF (200 ml) cooled to –35°. The resulting light yellow soln. was further stirred for 2 h at –35°, and then a soln. of (–)-**4** (5.2 g, 46.8 mmol) in THF (80 ml) was added over 20 min. The deep yellow mixture was then allowed to warm up to r.t. over 2.5 h, and stirred at r.t. for 1.5 h, after which it was diluted with H$_2$O (100 ml) and concentrated to ½ of its volume. The mixture was then extracted with CH$_2$Cl$_2$ (3 × 150 ml), the org. extract dried (Na$_2$CO$_3$) and evaporated, and the thick yellow oil scratched under hexane to give (+)-**5** as light yellow crystals (5.03 g, 50.4%). M.p. 89–91°. $[\alpha]_D^{20} = 111.7$ (*c* = 0.75, CH$_2$Cl$_2$). Slow recrystallisation from Et$_2$O gave colourless crystals (m.p. 94–95°) which were suitable for X-ray structure determination. $[\alpha]_D^{20} = +113.7$ (*c* = 0.175, CH$_2$Cl$_2$). R_f (alox, AcOEt) 0.56. CD (*c* = 0.8 mM, MeOH): 258 (979), 243.5 (565), 232.5 (658). IR (KBr): 2954, 2939, 2876, 1419, 1278, 1271, 1167, 1068, 982, 910, 813, 782. ^{1}H-NMR (CDCl$_3$): 1.4 (*m*, 1 H, H–C(5)); 1.8 (*m*, 1 H, H–C(5)); 2.15 (*m*, 2 H); 2.43 (*ddd*, *J* = 9.6, 3.0, 0.8, 1 H, H–C(7)); 2.50 (*m*, 1 H); 2.60 (*ddt*, *J* = 9.6, 1.1, 1 H, H–C(7)); 2.75–2.95 (overlapping *m*, 6 H); 3.02 (*dd*, *J* = 16.5, 3.1, 1 H, H–C(2)); 3.42 (*dm*, *J* = 16.5, 1 H, H–C(2)). EI-MS: 213 (96, $M^{+\cdot}$), 185 (20), 172 (19), 171 (100), 139 (25), 138 (20), 111 (21), 97 (47).

*Crystal-Structure Determination of (+)-***5**. Crystal data: C$_{10}$H$_{15}$NS$_2$; *M* 213.36; space group $P4_32_12$; *a* = *b* = 8.262(2), *c* = 31.105(15) Å; *V* = 2122.7 Å^3; d_{calc} = 1.335 g/cm^3; *Z* = 8; μ = 40.97 cm^{-1}; crystal dimensions 0.3 × 0.4 × 0.4 mm. Intensities were measured on an *Enraf-Nonius-CAD-4* diffractometer, using monochromated CuK_α radiation to $\Theta < 70°$; counting time, 90 s. Decay correction factors were in the range 0.9555 to 1.058. Empirical absorption correction factors from 0.87 to 1.13, based on a 360° ψ scan. Of the measured 2012 reflections, 1914 had $I > 2.5\,\sigma(I)$ and were considered observed. The structure was solved by direct methods, using SHELX-86 [14]. All H-atoms were located from a difference *Fourier* map and were refined. The final *R* factor was 0.0421.

(–)-(1S,4S)-3-(1,3-Dithian-2-ylidene)-1-azabicyclo[2.2.1]heptane ((–)-**5**) was prepared as described for (+)-**5**. M.p. 94–96°. $[\alpha]_D^{20} = -106.1$ (*c* = 0.58, CH$_2$Cl$_2$). CD (*c* = 0.7 mM, MeOH): 257.5 (–1109), 244 (678), 234 (799). R_f, IR, ^{1}H-NMR, and MS: identical to those of (+)-**5**.

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