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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones

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Abstract—(1*R*,3*R*,4*R*)-3-(1,2,4-Triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones were prepared in 68–94% d.e. in three steps from (1*R*)-(+)-camphor via coupling of (1*R*,4*R*)-3-[(*E*)-(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one with hydrazinoazines followed by oxidative cyclisation of the intermediate hydrazones with methanolic bromine. The structures were determined by 2D NMR techniques and NOESY spectroscopy as well as by X-ray diffraction.

1. Introduction

(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one ((+)-camphor) **1** and its derivatives certainly belong among the most frequently used types of chiral compounds. They have been employed as chiral building blocks, chiral ligands for various asymmetric reagents and/or catalysts, resolving agents, and shift reagents in NMR spectroscopy.[1,2] For example, chiral pyridine and 2,2′-bipyridine thioethers and diols derived from (+)-camphor were used as *N*–*S* and *N*–*O* ligands for asymmetric catalysis.[3,4] Similarly, reaction of 3-hydroxymethylidenecamphor[5] with amines followed by reduction of the exocyclic C=C double bond leads to 3-aminomethylidenecamphor derivatives exhibiting local anaesthetic and smooth muscle relaxant properties.[6–8]

On the other hand, the 1,2,4-triazolo[4,3-*x*]azine moiety is a constituent of several biologically active compounds, such as trazodone and 3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine.[9,10] A common synthetic approach towards 1,2,4-triazolo[4,3-*x*]azines consists of treatment of a hydrazinoazine with an aldehyde to give the corresponding hydrazone, which is then oxidatively cyclised into the corresponding 1,2,4-triazolo[4,3-*x*]azine.[11–13] In this manner, 1,2,4-triazolo[4,3-*x*]azin-3-yl substituted alanines[14,15] and polyols[16,17] have also been prepared from suitable chiral aldehydes.

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates have been prepared and were found to be versatile reagents for the preparation of various heterocyclic systems. In connection with this, their chiral cyclic analogs have been employed in the synthesis of heteroaryl substituted α-amino- and α-hydroxy acids and their analogs via 'ring switching' transformations, 1,3-dipolar cycloadditions, and aminations.[18,19] In continuation of our work in this field, we now report a one-pot preparation of the novel (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones **6a**–**g**.

2. Results and discussion

The starting material, (1*R*,4*R*)-3-[(*E*)-(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one **2**,[20] was prepared in 43% yield by treatment of (1*R*)-(+)-camphor **1** with bis(dimethylamino)-*tert*-butoxymethane (*Bredereck's* reagent) in DMF under reflux. Treatment of **2** with hydrazinoazines **3a**–**g**, having the hydrazine group attached at the position adjacent to the ring nitrogen atom, in methanol in the presence of an equimolar amount of hydrochloric acid at room temperature followed by oxidative cyclisation with methanolic bromine in the presence of sodium acetate afforded the corresponding (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ones **6a**–**g** in 37–79% yields and in 68–94% d.e. Compounds **6a**–**g** were obtained and char-

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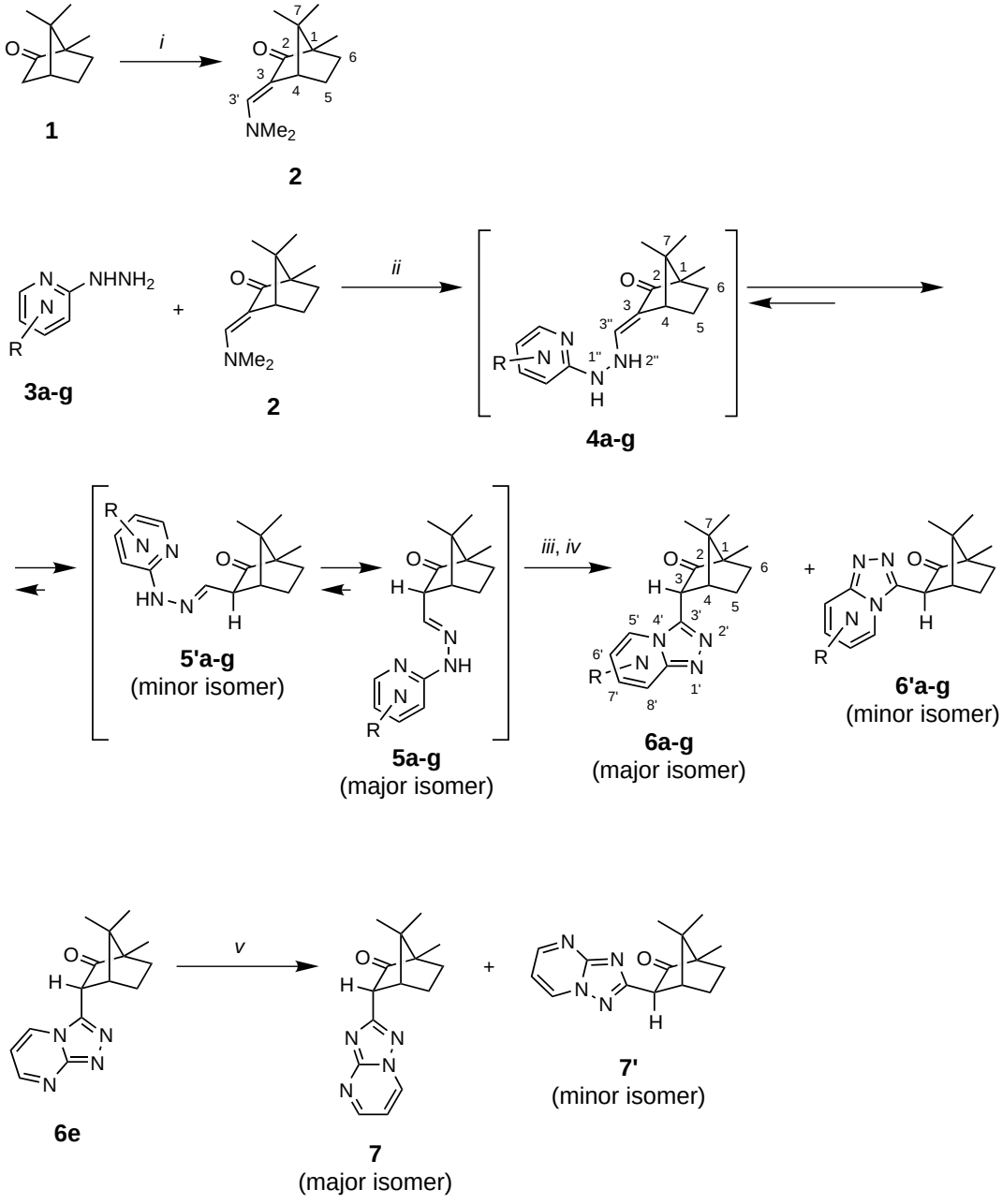
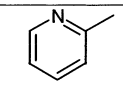
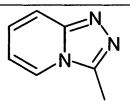
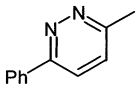
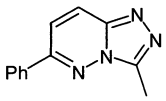
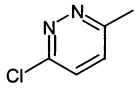
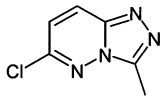
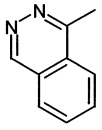
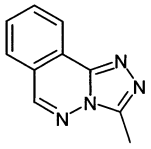
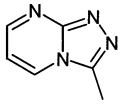
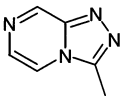
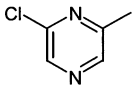
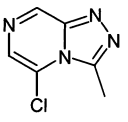
acterised as mixtures of the major *endo*-isomers **6a**–**g** and the minor *exo*-isomers **6′a**–**g**. Upon repeated crystallisation, compounds **6c**–**g** were obtained in diastereomerically pure form, while compounds **6a** and **6b** were obtained in 98 and 92% d.e., respectively. Treatment of diastereomerically pure **6e** with sodium methoxide in methanol under reflux resulted in the Dimroth rearrangement of the 1,2,4-triazolo[4,3-*a*]pyrimidine system to give (1*R*,3*R*,4*R*) - 3 - (1,2,4 - triazolo[1,5 - *a*]pyrimidin - 2 - yl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one **7** in 92% d.e. and in 55% yield. According to previous observations for 3-(dimethylamino)propenoates and 1,2,4-triazolo[4,3-*x*]azines, the reaction mechanism could be explained by the initial substitution of the dimethylamino group of **2** with the hydrazino group of **3** to give the enehydrazine **4**, which tautomerises into the hydrazone form **5**. Further oxidation of **5** with bromine leads to 1,2,4-triazolo[4,3-*x*]azine derivative **6**. This proposed reaction mechanism is supported by the isolation of the hydrazone intermediates **5b** and **5c**, which were obtained in 78 and 22% d.e., respectively. Compounds **5b**,**c** and **7** were obtained and characterised as mixtures of the major *endo*-isomers **5b**,**c** and **7** and the minor *exo*-isomers **5′b**,**c** and **7′**. (Scheme 1, Table 1).



Scheme 1. (i) *tert*-BuOCH(NMe$_2$)$_2$, DMF, reflux, then crystallisation; (ii) MeOH, HCl, rt; (iii) Br$_2$, MeOH, AcONa, rt; (iv) chromatographic purification; (v) MeONa, MeOH, reflux.

Table 1. Hydrazinoazines **3a–g**, enehydrazines **4a–g**, hydrazones **5a–g**, and camphor derivatives **6a–g**

Compound	Heteroaryl Residue		Yield [%]		*endo/exo*		D.e. [%]	
	3–5	**6**	**5/5'**	**6**	**5:5'**	**6:6'**	**5**	**6**
3a–6a			-	37	-	84:16	-	68
3b–6b			51	79	89:11	92:8	78	84
3c–6c			48	71	61:39	97:3	22	94
3d–6d			-	61	-	96:4	-	92
3e–6e			-	42	-	92:8	-	84
3f–6f			-	59	-	86:14	-	72
3g–6g			-	60	-	97:3	-	94

3. Structure determination

The structures of starting compound **2**, hydrazones **5b**,**c**, and camphor derivatives **6a–g**, **7** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, 2D NMR, NOESY spectroscopy, MS) and by elemental analyses for C, H, and N. Compounds **5b**,**c**, **6a–g**, and **7** were characterised as mixtures of diastereomers. Specific rotation angles for compounds **6a–g** were measured with the diastereomerically pure samples **6c–g** and diastereomerically enriched samples **6a**,**b**, obtained upon repeated crystallisation of mixtures of diastereomers. Total assignment of ^{13}C signals for compound **6a** was achieved by means of HMQC, HMBC and NOESY. Spectroscopic data of compounds **2**, **5–7** were in agreement with the data for related 1,2,4-triazolo[4,3-*x*]azines, 1,2,4-triazolo[1,5-*a*]pyrimidines, and camphor derivatives.[9,10,21–26]

3.1. Structure of enaminone 2, hydrazones 5b,c, and camphor derivatives 6a–g, 7

The configuration about the exocyclic C=C double bond in **2** was determined by NMR on the basis of long-range coupling constants ($^{3}J_{C\text{-}H}$) between the methylidene proton (*H*–C(3′)) and the carbonyl carbon (O=*C*(2)), measured from the antiphase splitting of cross peaks in the HMBC spectrum. Generally, the magnitude of the coupling constants $^{3}J_{C\text{-}H}$ for nuclei with *cis*-configuration about the C=C double bond are smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz).[27,28] The magnitude of coupling constant ($^{3}J_{C\text{-}H}=4.8$ Hz) showed the (*E*)-configuration around the exocyclic C=C double bond in compound **2**. The (3*R*)-configuration (*endo*-configuration) of compounds **5–7** was determined on the basis of the magnitude of the coupling constant, $J_{H3\text{-}H4}$.[25,26] In the major *endo*-isomers **5b**,**c**, **6a–g**, and **7**, coupling constant $J_{H3\text{-}H4}=$ 4.3–5.3 Hz, while in the minor *exo*-isomers **5′b**,**c**, **6′a–g**, and **7′**, no coupling between these two protons ($J_{H3\text{-}H4}$ ~0 Hz) was observed. The (3*R*)-configuration of **6a** was also established on the basis of the NOE effect between the C(5′) proton of the heteroaryl residue and the C(3) and C(4) protons of the camphor residue (Fig. 1).

The structures of compounds **2**, **5c**, **6b**,**c**,**e** and **7** were also determined by X-ray diffraction (Figs. 2–7)

4. Stereoselectivity

It has been reported previously, that 3-formylcamphor and its derivatives exist in solution as mixtures of

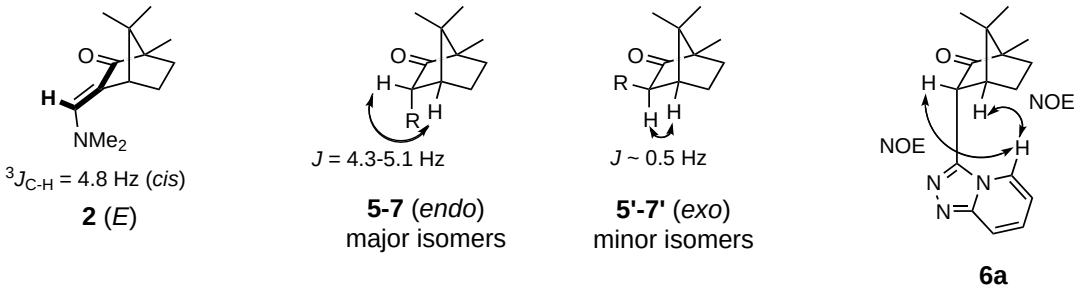


Figure 1.

(*Z*/*E*)-3-hydroxymethylidenecamphor and *exo*/*endo*-3-formylcamphor where the ratio between the various possible isomers depends on the solvent employed.[21,23,24] Although the crystal structure of the 2-formylcamphor derived enaminone **2** was determined by X-ray diffraction, compound **2** might still isomerise in solution. However, the single set of signals in the ^{1}H NMR spectrum of **2**, taken in $CDCl_3$, indicates that compound **2** exists (in $CDCl_3$ solution) as a single (1*R*,4*R*)-isomer with (*E*)-configuration about the exocyclic double bond.

On the other hand, the ^{1}H NMR spectra of isolated hydrazones **5b**,**c**, taken in $CDCl_3$ solution, showed that these exist as mixtures of the *endo*-isomers **5b**,**c** and the *exo*-isomers **5′b**,**c** in a ratio of 89:11 and 61:39, respectively. In DMSO-d_6 solution, **5b**/**5′b** isomerised into a mixture of **4b**, **5b**, and **5′b** in a ratio of 16:70:14 and **5c**/**5′c** isomerised into a mixture of **4c**, **5c**, and **5′c** in a ratio of 15:48:37. Similarly, upon standing in DMSO-d_6 solution at room temperature for 4 days, diastereomerically pure compound **6c** isomerised to a mixture of the *endo*-isomer **6c** and the *exo*-isomers **6′c** in a ratio of 97.5:2.5. Furthermore, heating a solution of diastereomerically pure compound **6e** in methanol for 10 h afforded a mixture of **6e**, **6′e**, **7**, and **7′** in a ratio of 71:3:25:1, respectively. Therefore, both types of compounds, the intermediate hydrazones as well as 1,2,4-triazolo[4,3-*x*]azines as the final products, exist in solution predominantly in the *endo*-isomeric forms **5** and **6** (Scheme 2).

Stereoselective formation of compounds **5** and **6** might be predominantly due to equilibrium between the less strained *endo*-isomers **5** and **6** and the more strained *exo*-isomers **5′** and **6′**. The products **6** could initially be formed as mixtures of the *endo*-isomers **6** and the *exo*-isomers **6′**, which can equilibrate via the enol form **6″** into the more thermodynamically stable *endo*-isomers **6**. Thermodynamic control in the stereoselective formation of the less strained *endo*-isomers **6** is supported by the fact that the Dimroth rearrangement of **6e** into **7**, carried out with sodium methoxide in methanol under reflux, took place with almost no epimerisation at the C(3) centre. On the other hand, kinetically controlled stereoselective formation of the *endo*-isomers **6** still cannot be excluded on the basis of these studies (Scheme 3).

5. Conclusion

(1*R*,3*R*,4*R*)-3-(1,2,4-Triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones can be prepared stereoselectively from *o*-hydrazinoazines and (+)-camphor by a three-step synthesis. The synthesis proceeds by transformation of (+)-camphor with Bredereck's reagent into (1*R*,4*R*)-3-[(*E*)-(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one followed by dimethylamine substitution with hydrazinoazines to give the corresponding hydrazones which are then oxidatively cyclised with methanolic bromine to give (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones in fair yields and high d.e. The structures of products were determined by ^{1}H NMR, 2D HMBC correlation techniques, NOESY spectroscopy, and X-ray analysis. Although diastereoselective formation of (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ones could be due to kinetic as well as thermodynamic

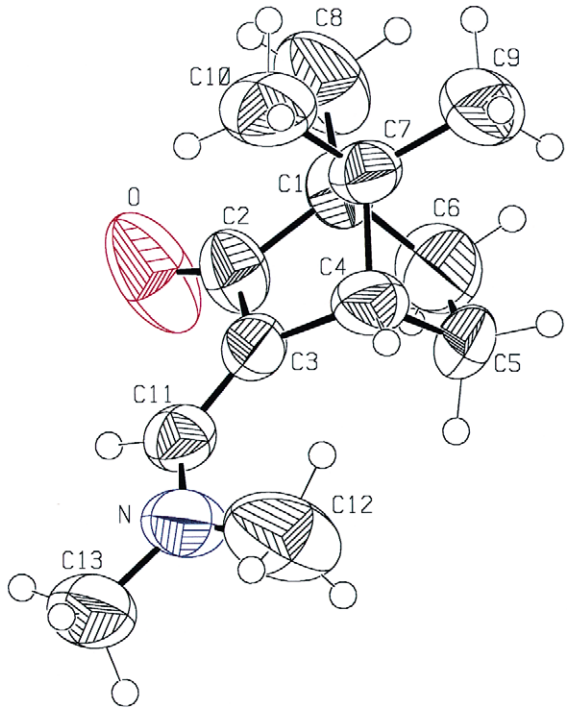


Figure 2. The asymmetric unit of compound **2**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

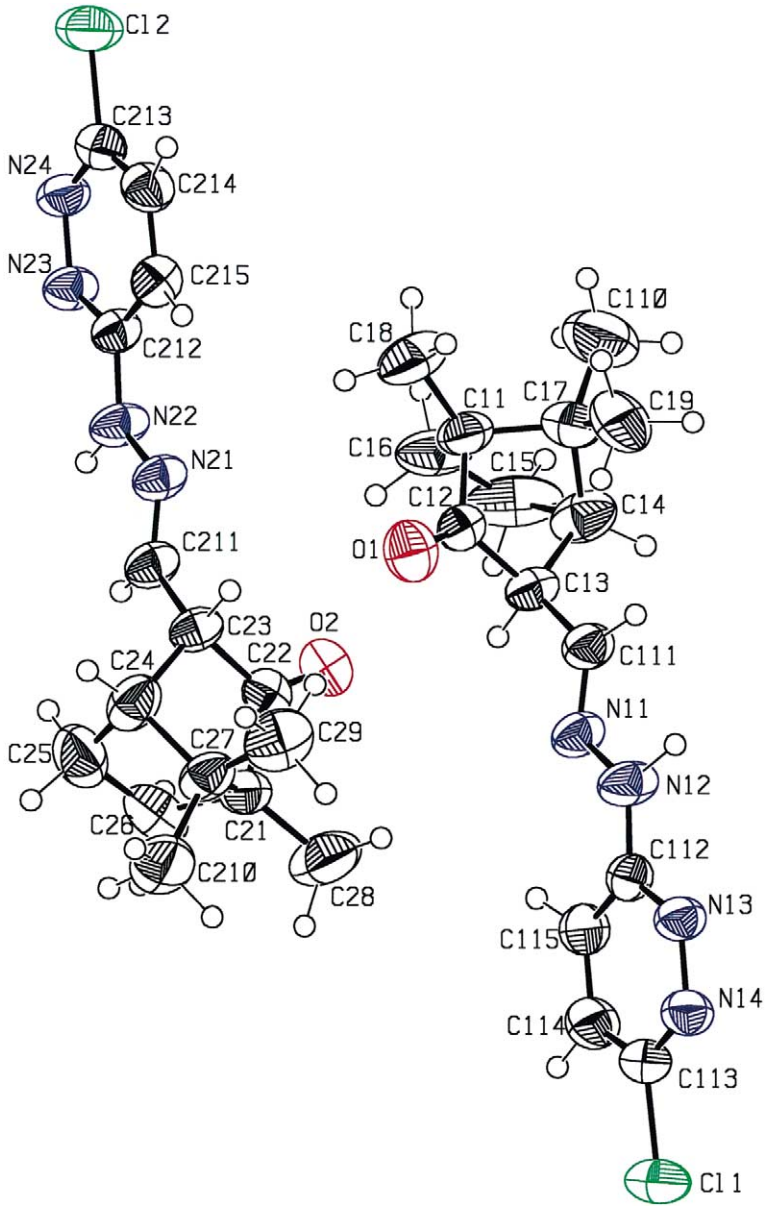


Figure 3. The asymmetric unit of compound **5c**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

factors, the experimental evidence indicates that thermodynamic control predominates in formation of the *endo*-isomers.

6. Experimental

6.1. General methods

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$, with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). Medium-pressure liquid chromatography (MPLC) was performed with a Büchi isocratic system with detection[†] on silica gel (Merck, silica gel 40, 0.015–0.035 mm); column dimensions (dry filled): 15×460 mm; backpressure: 10–15 bar; detection: UV 254 nm; sample amount: 100–150 mg of isomeric mixture per each run. The d.e. of the isolated and the diastereomerically enriched compounds **5**–**7** were determined by ^{1}H NMR.

[†] Donation of Alexander von Humboldt Foundation, Germany.

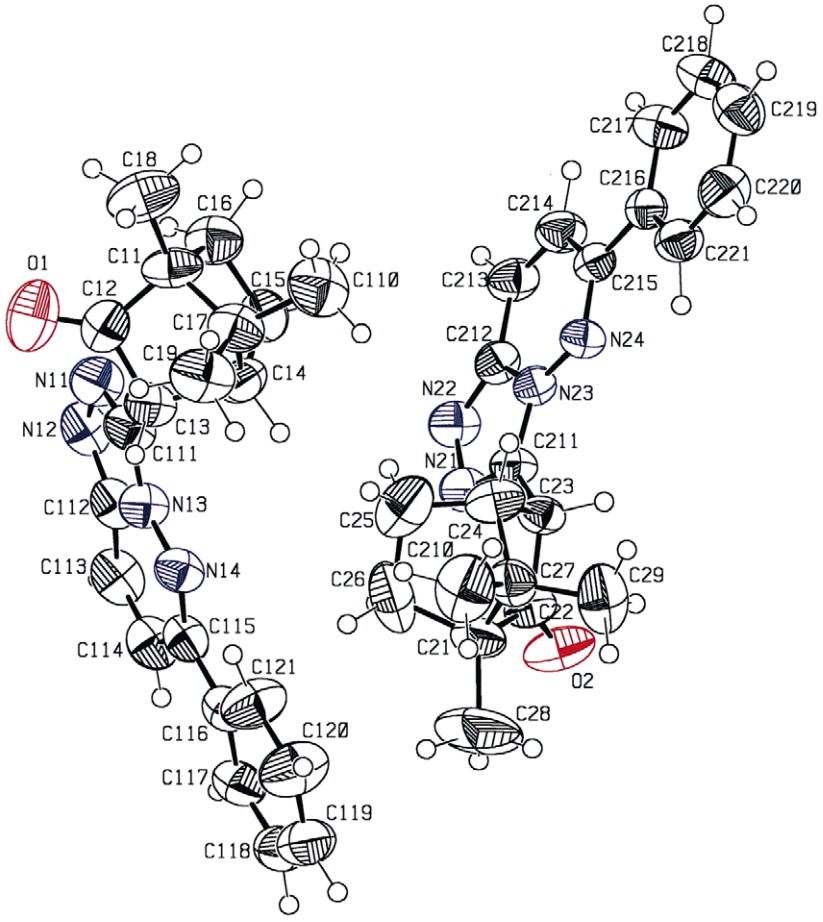


Figure 4. The asymmetric unit of compound **6b**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

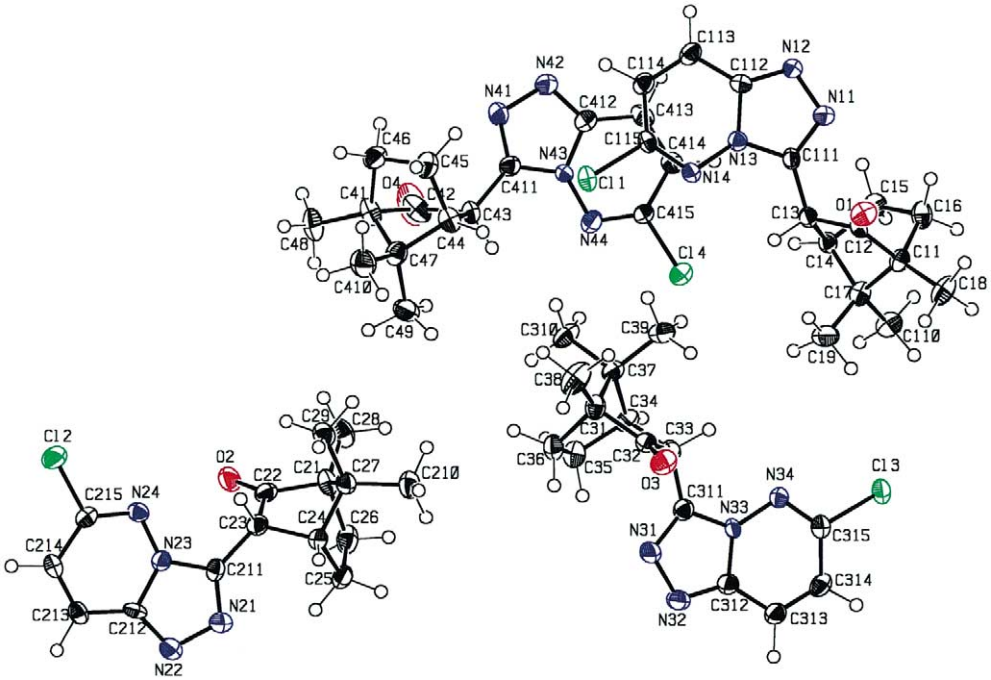


Figure 5. The asymmetric unit of compound **6c**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

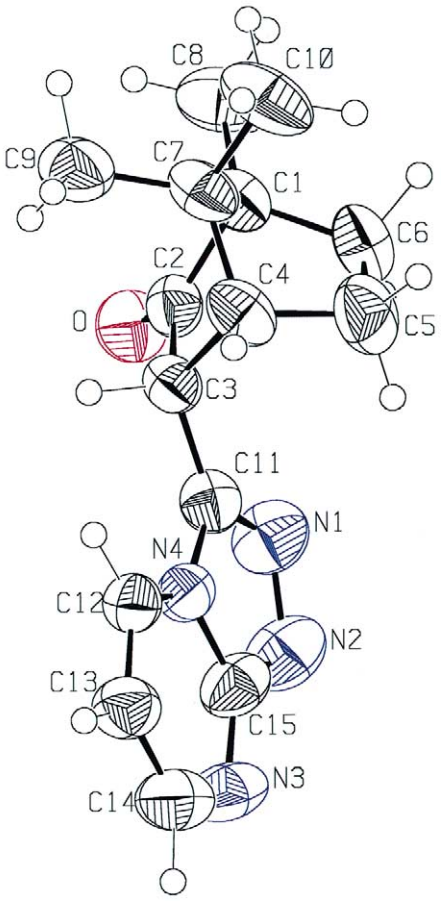


Figure 6. The asymmetric unit of compound **6e**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

The minor isomers **5′**–**7′** were not isolated and were characterised only by ^{1}H NMR.

tert-Butoxy-bis(dimethylamino)methane, (+)-camphor **1**, 2-hydrazinopyridine **3a** and 1-hydrazinophthalazine **3d** are commercially available (Fluka AG). 3-Hydrazino-6-phenylpyridazine **3b**,[29] 6-chloro-3-hydrazinopyridazine **3c**,[30] 2-hydrazinopyrimidine **3e**,[31] 2-hydrazinopyrazine **3f**,[32] and 6-chloro-2-hydrazinopyrazine **6g**[33] were prepared according to the procedures described in the literature. Compound **2** has previously been prepared from **1** via formylation followed by treatment with dimethylamine.[20]

Source of chirality: (+)-camphor **1** (Fluka AG), product number 21300, purum, natural, ≥97.0% (GC, sum of enantiomers), $[\alpha]^{20}_{546}$ = +54.5±2.5 (*c* 10, EtOH), $[\alpha]^{20}_{D}$ = +42.5±2.5 (*c* 10, EtOH), mp 176–180°C. The e.e. of (+)-camphor **1** is not specified by the producer (Fluka AG).

6.2. (1*R*,4*R*)-3-[(*E*)-(Dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 2

A mixture of compound **1** (4567 mg, 30 mmol), DMF (50 mL), and *tert*-butoxy-bis(dimethylamino)methane (10 mL, 48.4 mmol) was heated under reflux for 7 h. Volatile components were evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (70 mL) and washed with water (2×60 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in petroleum ether (40 mL), cooled (−20°C), and the precipitate was collected by filtration to give **2** (2670 mg, 43%), which was characterised by spectral (IR, ^{1}H NMR, and ^{13}C NMR) and elemental analyses.; mp 59–62°C (petroleum ether), lit.[20] mp 63–64°C (petroleum ether); $[\alpha]^{20}_{D}$ = +484.8 (*c* 0.506, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.84, 0.89, 0.94 (9H, 3s, 1:1:1, 3Me), 1.30–1.46 (2H, m, CH_2), 1.52–1.64 (1H, m, 1H of CH_2), 1.92–2.04 (1H, m, 1H of CH_2), 2.90 (1H, br d, J = 3.8 Hz, H–C(4)), 2.98 (6H, s, NMe_2), 7.00 (1H, d, J = 0.76 Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.4, 21.1, 28.8, 30.7, 42.6, 48.4, 48.6, 56.8, 111.4, 141.5, 207.7. Found: C, 75.28; H, 10.43; N, 6.57. $C_{13}H_{21}NO$ requires: C, 75.32; H, 10.21; N, 6.76%; ν_{max} (KBr) 1690 cm^{-1} (C=O).

6.3. General procedure for the preparation of mixtures of (1*R*,3*R*,4*R*)-3-{[*N*-(6-substituted pyridazin-3-yl)-hydrazono]methyl}-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones 5b,c and their (1*R*,3*S*,4*R*)-epimers 5′b,c

Hydrochloric acid (37%, 0.05 mL, ∼0.5 mmol) was added to a stirred suspension of compound **2** (104 mg, 0.5 mmol) and hydrazine **3b**,**c** (0.5 mmol) in methanol (1.5 mL) and the mixture was stirred at rt for 3 h. The precipitate was collected by filtration and washed with cold (0°C) methanol (∼10 mL) to give a white solid, which was characterised by spectral (IR and ^{1}H NMR) and elemental analyses. Isomeric mixtures **5b**/**5′b** and **5c**/**5′c** were prepared in this manner.

In DMSO-d_6 solution, the mixtures **5b**/**5′b** and **5c**/**5′c** isomerised into the mixtures **4b**/**5b**/**5′b** and **4c**/**5c**/**5′c**, respectively. The isomers **4b**,**c** were characterised by ^{1}H NMR.

6.3.1. (1*R*,3*R*,4*R*)-3-[(6-Phenylpyridazin-3-yl)hydrazonomethyl]-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one 5b and its (1*R*,3*S*,4*R*)-epimer 5′b

Prepared from compound **2** and 3-hydrazino-6-phenylpyridazine **3b**; 89 mg (51%) of a white solid; **5b**:**5′b** = 89:11; mp 224–228°C; $[\alpha]^{20}_{D}$ = −39.3 (*c* 0.293, CH_2Cl_2). (Found: C, 72.51; H, 7.28; N, 16.27. $C_{21}H_{24}N_4O$ requires: C, 72.39; H, 6.94; N, 16.08.); ν_{max} (KBr) 1740 cm^{-1} (C=O).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 5b: ^{1}H NMR ($CDCl_3$): δ 0.96, 0.98, 1.03 (9H, 3s, 1:1:1, 3Me), 1.40–1.88 (4H, m, $2CH_2$), 2.30–2.37 (1H, m, H–C(4)), 3.43 (1H, t, J = 5.5 Hz, H–C(3)), 7.37–7.52 (3H, m, 3H of Ph), 7.59 (1H, br d, J = 9.4 Hz, H–C(4′)), 7.73 (1H, br d, J = 9.4 Hz, H–C(5′)), 7.74 (1H, d, J = 6.0 Hz, H–C(3″)), 7.92–7.99 (2H, m, 2H of Ph), 11.72 (1H, br s, H–N(1″)).

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 5′b: ^{1}H NMR ($CDCl_3$): δ 0.78 (3H, s, Me), 2.61 (1H, d, J = 4.1 Hz, H–C(4)), 2.96 (1H, d, J = 3.8 Hz, H–C(3)), 7.78 (1H, d, J = 4.1 Hz, H–C(3″)). In DMSO-d_6 solution, a mixture of **5b** and **5′b** isomerised into a mixture of **4b**, **5b**, and **5′b**.

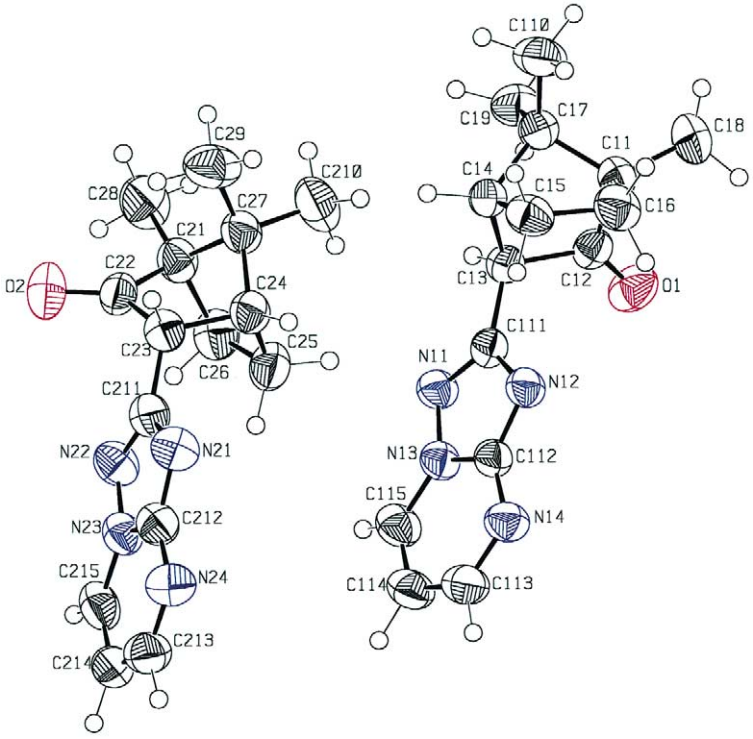


Figure 7. The asymmetric unit of compound **7**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

NMR data for the (1*R*,4*R*)-isomer 4b: ^{1}H NMR (DMSO-d_6): δ 2.81 (1H, d, J=3.4 Hz, H–C(3)), 6.90 (1H, d, J=7.5 Hz, H–C(3″), 6.98 (1H, d, J=9.4 Hz, H–C(4′)), 7.58 (1H, d, J=9.4 Hz, H–C(5′)), 8.48 (1H, br d, J=7.5 Hz, H–N(2″), 9.23 (1H, s, H–N(1″)); **4b**:**5b**:**5′b**=16:70:14.

6.3.2. (1*R*,3*R*,4*R*)-3-[(6-Chloropyridazin-3-yl)hydrazonomethyl]-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one 5c and its (1*R*,3*S*,4*R*)-epimer 5′c

Prepared from compound **2** and 6-chloro-3-hydrazinopyridazine **3c**; 74 mg (48%) of a white solid; ratio **5b**:**5′b**=61:39 (in $CDCl_3$); mp 208–214°C; $[\alpha]_D^{23}=-9.3$ (c 0.484, CH_2Cl_2). Found: C, 58.94; H, 6.49; N, 18.40. $C_{15}H_{19}ClN_4O$ requires: C, 58.72; H, 6.24; N, 18.26%; ν_{max} (KBr) 1746 cm^{-1} (C=O).

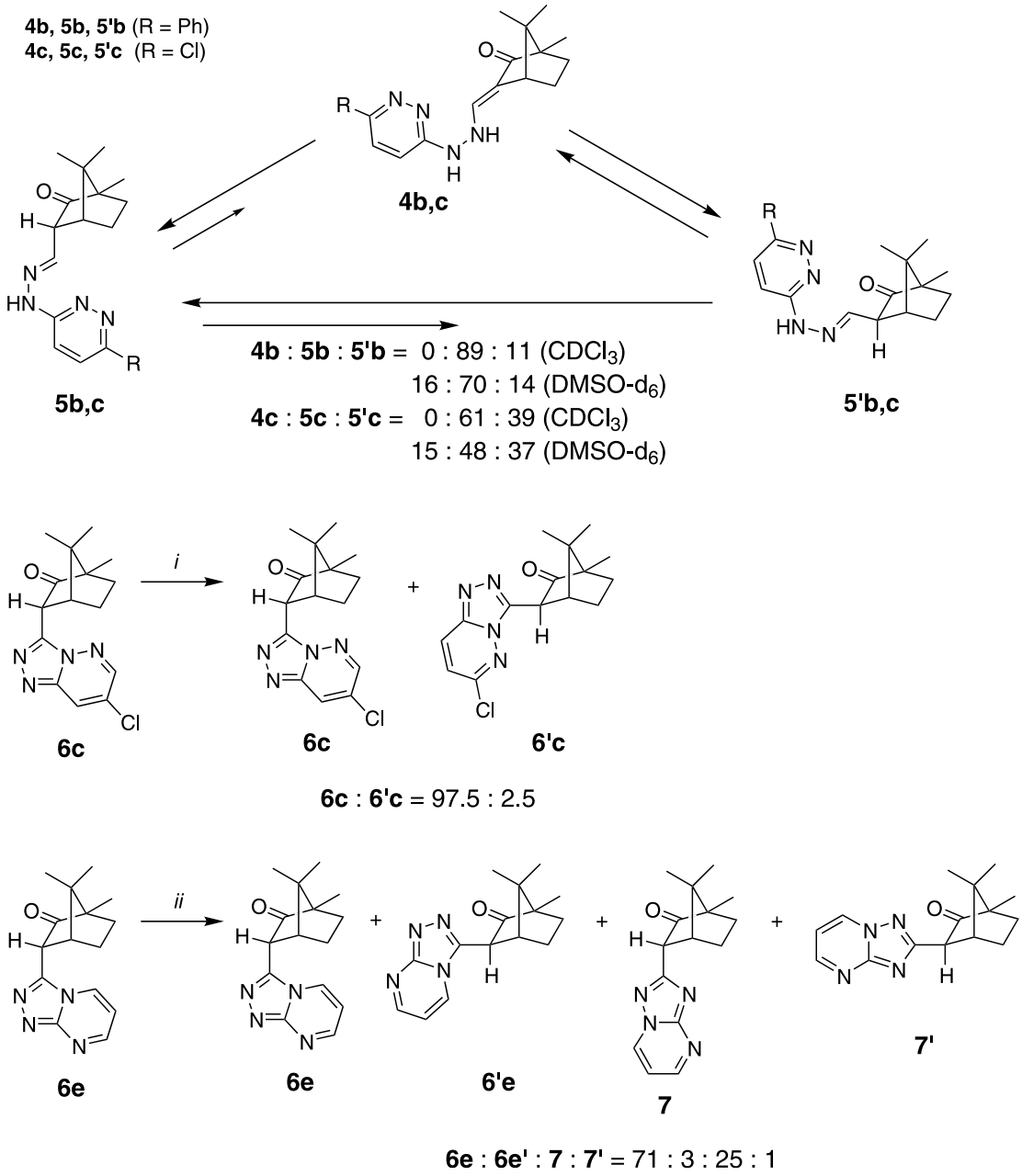
NMR data for the major (1*R*,3*R*,4*R*)-isomer 5c: ^{1}H NMR ($CDCl_3$): δ 0.94, 0.98, 1.05 (9H, 3s, 1:1:1, 3Me), 1.44–1.95 (4H, m, $2CH_2$), 2.28–2.35 (1H, m, H–C(4)), 3.36 (1H, dd, J=5.1, 6.2 Hz, H–C(3)), 7.29 (1H, d, J=9.4 Hz, H–C(4′)), 7.50 (1H, d, J=9.4 Hz, H–C(5′)), 7.62 (1H, d, J=6.4 Hz, H–C(3″)), 11.53 (1H, br s, H–N(1″).

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 5′c: ^{1}H NMR ($CDCl_3$): δ 0.90, 0.96, 1.01 (9H, 3s, 1:1:1, 3Me), 2.09 (1H, tt, J=4.0, 11.7 Hz, 1H of CH_2), 2.48 (1H, d, J=4.1 Hz, H–C(4)), 2.92 (1H, d, J=4.9 Hz, H–C(3)), 7.30 (1H, d, J=9.4 Hz, H–C(4′)), 7.51 (1H, d, J=9.4 Hz, H–C(5′)), 7.59 (1H, d, J=4.9 Hz, H–C(3″)), 10.93 (1H, br s, H–N(1″). In DMSO-d_6 solution, a mixture of **5c** and **5′c** isomerised into a mixture of **4c**, **5c**, and **5′c**.

NMR data for the (1*R*,4*R*)-isomer 4c: ^{1}H NMR (DMSO-d_6): δ 2.76 (1H, d, J=3.8 Hz, H–C(3)), 6.84 (1H, d, J=7.9 Hz, H–C(3″), 6.99 (1H, d, J=9.4 Hz, H–C(4′)), 7.58 (1H, d, J=9.0 Hz, H–C(5′)), 8.45 (1H, br d, J=7.5 Hz, H–N(2″), 9.34 (1H, s, H–N(1″)); **4c**:**5c**:**5′c**=15:48:37.

6.4. General procedure for the preparation of mixtures of (1*R*,3*R*,4*R*)-3-[1,2,4-triazolo[4,3-*x*]azin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones 6a–g and their (1*R*,3*S*,4*R*)-epimers 6′a–g

Hydrochloric acid (37%, 0.10 mL, ~1 mmol) was added to a stirred mixture of compound **2** (207 mg, 1 mmol), hydrazine **3a**–**g** (1 mmol), and methanol (5 mL) and the resulting mixture was stirred at rt for 5–7 h. The reaction mixture was cooled to 0–5°C (ice-bath), sodium acetate (246 mg, 3 mmol) was added and, with vigorous stirring, a solution of bromine (0.051 mL, ~1 mmol) in methanol (3 mL) was added dropwise over a period of 5–10 min. The mixture was stirred at 0–5°C (ice-bath) for 2–6 h. Volatile components were evaporated in vacuo, dichloromethane (40 mL) was added to the residue and the mixture was washed with saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulphate, filtered, and the filtrate was evaporated in vacuo. The residue was purified by CC. Fractions containing the product were combined and evaporated in vacuo. Compounds **6c**–**f** were additionally purified by MPLC. Fractions containing the product were combined and evaporated in vacuo to give a white solid, which was characterised by spectral



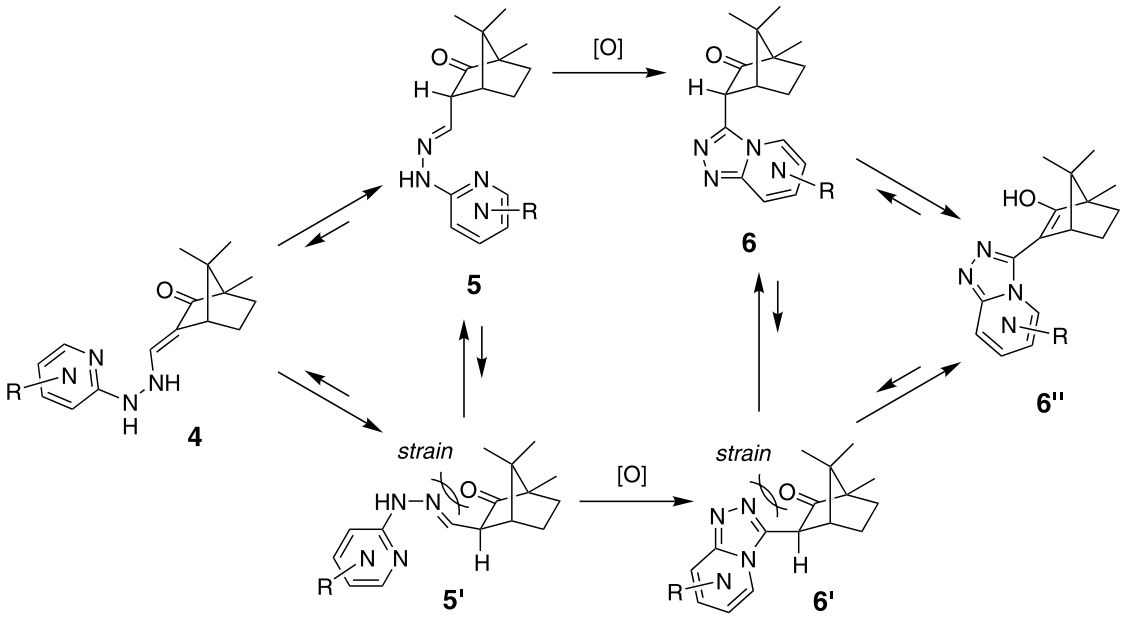
Scheme 2. Isomerisation of compounds **5b**,**c** and **6c**,**e** in solution: (i) DMSO-d_6, rt, 4 days; (ii) MeOH, reflux.

(IR, ^{1}H NMR, ^{13}C NMR, and MS) and elemental analyses. Isomeric mixtures **6a**–**g**/**6′a**–**g** were prepared in this manner.

Repeated crystallisation of isomeric mixtures **6a**–**g**/**6′a**–**g** from a mixture of chloroform and *n*-heptane furnished diastereomerically enriched compounds **6a** (98% d.e.) and **6b** (92% d.e.) and diastereomerically pure compounds **6c**–**g** (100% d.e.), which were characterised by melting point and measurement of the specific rotation. Diastereomerically enriched mixtures **6a**/**6′a**, **6b**/**6′b** and diastereomerically pure compounds **6c**–**g** were prepared in this manner.

6.4.1. (1*R*,3*R*,4*R*)-3-[1,2,4-Triazolo[4,3-*a*]pyridin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6a and its (1*R*,3*S*,4*R*)-epimer 6′a. Prepared from compound **2** and 2-hydrazinopyridine (**3a**), 6 h, CC (EtOAc); 100 mg (37%) of a white solid; mp 186–190°C; **6a**:**6′a** = 84:16. Found: C, 71.60; H, 7.24; N, 15.65. $C_{16}H_{19}N_3O$ requires: 71.35; H, 7.11; N, 15.60%; ν_{max} (KBr) 1749 cm^{-1} (C=O).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 6a: ^{1}H NMR ($CDCl_3$): δ 1.06, 1.10, 1.12 (9H, 3s, 1:1:1, 3Me); 1.76–1.92 (4H, m, $2CH_2$), 2.59–2.61 (1H, m, H–C(4)), 4.05 (1H, d, J = 4.5 Hz, H–C(3)), 6.83 (1H, dt, J = 1.1,



Scheme 3. Stereoselective formation of the *endo*-isomers of compounds **5** and **6**.

6.8 Hz, H–C(6′)); 7.24 (1H, ddd, $J=1.1$, 6.8, 9.4 Hz, H–C(7′)); 7.76 (1H, dt, $J=1.1$, 9.4 Hz, H–C(8′)), 8.11 (1H, dt, $J=1.1$, 7.2 Hz, H–C(5′)). ^{13}C NMR ($CDCl_3$): δ 10.1 (*Me*–C(1)), 19.6 (*Me*–C(7)), 20.1 (*Me*–C(7)), 22.3 (C(5)), 30.3 (C(6)), 46.6 (C(7)), 47.1 (C(3)), 47.6 (C(4)), 59.0 (C(1)), 114.0 (C(6′)), 116.9 (C(8′)), 122.8 (C(5′)), 127.3 (C(7′)), 144.1 (C(3′)), 150.4 (C(8a)), 213.6 (C(2)).

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 6′a: ^{1}H NMR ($CDCl_3$): δ 0.87, 0.96, 1.09 (9H, 3s, 1:1:1, 3Me), 3.36 (1H, d, $J=4.1$ Hz, H–C(4)), 3.57 (1H, s, H–C(3)), 7.67 (1H, dt, $J=1.1$, 9.4 Hz, H–C(8′)), 8.59 (1H, dt, $J=1.1$, 7.2 Hz H–C(5′)). Upon repeated crystallisation of **6a**/**6′a** from a mixture of chloroform and *n*-heptane, diastereomerically enriched mixture of isomers **6a** and **6′a** with the following physical data was obtained: **6a**:**6′a** = 99:1; mp 178–182°C; $[\alpha]_D^{26} = -9.5$ ($c=0.474$, $CHCl_3$).

6.4.2. (1*R*,3*R*,4*R*)-3-[6-Phenyl-1,2,4-triazolo[4,3-*b*]-pyridazin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6b and its (1*R*,3*S*,4*R*)-epimer 6′b. Prepared from compound **2** and 3-hydrazino-6-phenylpyridazine (**3b**), 2 h, CC (EtOAc); 274 mg (79%) of a white solid; mp 248–256°C; **6b**:**6′b** = 92:8. Found: C, 72.51; H, 6.56; N, 16.10. $C_{21}H_{22}N_4O$ requires: C, 72.81; H, 6.40; N, 16.17%; ν_{max} (KBr) 1744 cm^{-1} (C=O); m/z (EI) 346 (M^+); (m/z (HRMS): 346.180050. $C_{21}H_{22}N_4O$ requires: 346.179362.).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 6b: ^{1}H NMR ($CDCl_3$): δ 1.09, 1.12, 1.14 (9H, 3s, 1:1:1, 3Me); 1.50–1.60 (1H, m, 1H of CH_2), 1.71–1.87 (2H, m, 2H of CH_2), 1.91–2.06 (1H, m, 1H of CH_2), 2.57–2.63 (1H, m, H–C(4)), 4.52 (1H, dd, $J=1.1$, 4.5 Hz, H–C(3)), 7.52–7.59 (4H, m, 3H of Ph and H–C(7′)), 7.90–7.97 (2H, m, 2H of Ph), 8.17 (1H, d, $J=9.4$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 10.2, 19.7, 20.1, 22.5, 30.3, 46.78, 46.81, 48.2, 59.2, 119.8, 125.5, 127.7, 129.6, 131.3, 134.7, 143.8, 148.0, 153.9, 213.6.

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 6′b: ^{1}H NMR ($CDCl_3$): δ 1.03, 1.08, 1.10 (9H, 3s, 1:1:1, 3Me); 2.96 (1H, d, $J=4.2$ Hz, H–C(4)), 4.02 (1H, s, H–C(3)), 7.97–8.01 (2H, m, 2H of Ph), 8.13 (1H, d, $J=9.4$ Hz, H–C(8′)). Upon repeated crystallisation of **6b**/**6′b** from a mixture of chloroform and *n*-heptane, diastereomerically enriched mixture of isomers **6b** and **6′b** with the following physical data was obtained: **6b**:**6′b** = 96:4; mp 255–261°C; $[\alpha]_D^{25} = +107.5$ (c 0.400, $CHCl_3$).

6.4.3. (1*R*,3*R*,4*R*)-3-[6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6c and its (1*R*,3*S*,4*R*)-epimer 6′c. Prepared from compound **2** and 6-chloro-3-hydrazinopyridazine (**3c**), 3 h, CC and MPLC (EtOAc); 216 mg (71%) of a white solid; mp 178–183°C; **6c**:**6′c** = 97:3. Found: C, 59.11; H, 5.83; N, 18.30. $C_{15}H_{17}ClN_4O$ requires: C, 59.11; H, 5.62; N, 18.38%; ν_{max} (KBr) 1743 cm^{-1} (C=O).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 6c: ^{1}H NMR ($CDCl_3$): δ 1.07, 1.11 (9H, 2s, 1:2, 3Me); 1.49–1.58 (1H, m, 1H of CH_2), 1.70–1.87 (2H, m, 2H of CH_2), 1.88–2.02 (1H, m, 1H of CH_2), 2.53–2.59 (1H, m, H–C(4)), 4.37 (1H, dd, $J=1.5$, 4.5 Hz, H–C(3)), 7.10 (1H, d, $J=9.4$ Hz, H–C(7′)), 8.08 (1H, d, $J=9.8$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.7, 20.1, 22.4, 30.3, 46.5, 46.8, 48.0, 59.2, 122.5, 126.9, 143.1, 147.9, 149.7, 213.1.

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 6′c: ^{1}H NMR ($CDCl_3$): δ 1.01, 1.07 (6H, 2s, 1:1, 2Me); 2.89 (1H, d, $J=3.8$ Hz, H–C(4)), 3.90 (1H, s, H–C(3)), 7.10 (1H, d, $J=9.4$ Hz, H–C(7′)), 8.04 (1H, d, $J=9.8$ Hz, H–C(8′)). Upon repeated crystallisation of **6c**/**6′c** from a mixture of chloroform and *n*-heptane, diastereomerically pure isomer **6c** with the following physical data was obtained: **6c**:**6′c** = 100:0; mp 180–184°C; $[\alpha]_D^{25} = +97.0$ (c 0.400, $CHCl_3$).

6.4.4. (1*R*,3*R*,4*R*)-3-[1,2,4-Triazolo[4,3-*b*]phthalazin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6d and its (1*R*,3*S*,4*R*)-epimer 6′d. Prepared from compound **2** and 3-hydrazinophthalazine (**3d**), 2 h, CC (EtOAc) and MPLC (ethyl acetate/petroleum ether, 1:1); 195 mg (61%) of a white solid; mp 223–227°C; **6d**:**6′d** = 96:4. Found: C, 71.20; H, 6.31; N, 17.20. $C_{19}H_{20}N_4O$ requires: C, 71.23; H, 6.29; N, 17.49%; ν_{max} (KBr) 1747 cm^{-1} (C=O); *m*/*z* (EI) 320 (M^+); (*m*/*z* (HRMS): 320.164950. $C_{19}H_{20}N_4O$ requires: 320.163711.).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 6d: ^{1}H NMR ($CDCl_3$): δ 1.07, 1.11, 1.12 (9H, 3s, 1:1:1, 3Me); 1.59–1.87 (3H, m, 3H of CH_2), 1.93–2.05 (1H, m, 1H of CH_2), 2.53–2.59 (1H, m, H–C(4)), 4.45 (1H, dd, J = 1.1, 4.9 Hz, H–C(3)), 7.76–7.83 (1H, m, 1H of Ar), 7.89–7.98 (2H, m, 2H of Ar), 8.59 (1H, s, H–C(6′)), 8.64–8.69 (1H, m, 1H of Ar). ^{13}C NMR ($CDCl_3$): δ 10.2, 19.7, 20.11; 22.3, 30.3, 46.8, 46.8, 48.3, 59.2, 123.5, 123.6, 124.0, 128.4, 131.1, 134.3, 143.0, 147.7, 148.6, 213.7.

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 6′d: ^{1}H NMR ($CDCl_3$): δ 3.88 (1H, d, J = 4.5 Hz, H–C(4)), 3.97 (1H, s, H–C(3)). Upon repeated crystallisation of **6d**/**6′d** from a mixture of chloroform and *n*-heptane, diastereomerically pure isomer **6d** with the following physical data was obtained: **6d**:**6′d** = 100:0; mp 227–231°C; $[\alpha]_D^{25}$ = +66.0 (*c* 0.444, $CHCl_3$).

6.4.5. (1*R*,3*R*,4*R*)-3-[1,2,4-Triazolo[4,3-*a*]pyrimidin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6e and its (1*R*,3*S*,4*R*)-epimer 6′e. Prepared from compound **2** and 2-hydrazinopyrimidine (**3e**), 3 h, CC and MPLC ($CHCl_3$/MeOH, 20:1); 114 mg (42%) of a white solid; mp 253–258°C; **6e**:**6′e** = 92:8. Found: C, 66.86; H, 6.75; N, 21.02. $C_{15}H_{18}N_4O$ requires: C, 66.64; H, 6.71; N, 20.73%; ν_{max} (KBr) 1753 cm^{-1} (C=O).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 6e: ^{1}H NMR ($CDCl_3$): δ 1.03, 1.09, 1.14 (9H, 3s, 1:1:1, 3Me); 1.54–1.67 (1H, m, 1H of CH_2), 1.75–1.87 (1H, m, 1H of CH_2), 1.89–2.04 (1H, m, 1H of CH_2), 2.25–2.36 (1H, m, 1H of CH_2), 2.73 (1H, t, J = 4.3 Hz, H–C(4)), 4.06 (1H, dd, J = 1.5, 4.5 Hz, H–C(3)), 6.88 (1H, dd, J = 3.8, 7.2 Hz, H–C(6′)), 8.65 (1H, dd, J = 1.9, 3.8 Hz, H–C(7′)), 8.74 (1H, dd, J = 1.9, 7.2 Hz, H–C(5′)). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.5, 20.2, 22.3, 30.6, 46.7, 47.5, 47.6, 59.3, 109.8, 132.2, 143.3, 154.2, 154.4, 214.2.

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 6′e: ^{1}H NMR ($CDCl_3$): δ 0.81, 0.97, 1.10 (9H, 3s, 1:1:1, 3Me); 3.44 (1H, d, J = 4.2 Hz, H–C(4)), 3.57 (1H, s, H–C(3)), 8.62 (1H, dd, J = 1.9, 3.8 Hz, H–C(7′)), 9.01 (1H, dd, J = 1.9, 7.2 Hz, H–C(5′)). Upon repeated crystallisation of **6e**/**6′e** from a mixture of chloroform and *n*-heptane, diastereomerically pure isomer **6e** with the following physical data was obtained: **6e**:**6′e** = 100:0; mp 255–258°C; $[\alpha]_D^{25}$ = −147.6 (*c* 0.245, $CHCl_3$).

6.4.6. (1*R*,3*R*,4*R*)-3-[1,2,4-Triazolo[4,3-*a*]pyrazin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6f and its (1*R*,3*S*,4*R*)-epimer 6′f. Prepared from compound **2** and 2-hydrazinopyrazine (**3f**), 3 h, CC ($CHCl_3$/MeOH, 20:1) and MPLC (EtOAc); 159 mg (59%) of a white solid; mp 250–258°C; **6f**:**6′f** = 86:14. (Found: C, 66.94; H, 6.70; N, 21.03. $C_{15}H_{18}N_4O$ requires: C, 66.64; H, 6.71; N, 20.73.); ν_{max} (KBr) 1754 cm^{-1} (C=O).

NMR data for the major (1*R*,3*E*,4*R*)-isomer 6f: ^{1}H NMR ($CDCl_3$): δ 1.06, 1.11, 1.14 (9H, 3s, 1:1:1, 3Me), 1.65–2.06 (4H, m, $2CH_2$), 2.67 (1H, t, J = 4.0 Hz, H–C(4)), 4.07 (1H, dd, J = 1.3, 4.3 Hz, H–C(3)), 7.88 (1H, d, J = 4.9 Hz, H–C(8′)), 8.18 (1H, dd, J = 1.9, 4.9 Hz, H–C(6′)), 9.34 (1H, d, J = 1.9 Hz, H–C(5′)). ^{13}C NMR ($CDCl_3$): δ 10.1 19.5, 20.2, 22.3, 30.5, 46.8, 47.2, 47.7, 59.2, 116.1, 130.0, 144.9, 145.0, 146.0, 213.4.

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 6′f: ^{1}H NMR ($CDCl_3$): δ 2.23–2.35 (1H, m, 1H of CH_2), 3.44 (1H, d, J = 4.1 Hz, H–C(4)), 3.61 (1H, s, H–C(3)), 8.60 (1H, dd, J = 1.5, 4.5 Hz, H–C(6′)), 9.30 (1H, d, J = 1.5 Hz, H–C(5′)). Upon repeated crystallisation of **6f**/**6′f** from a mixture of chloroform and *n*-heptane, diastereomerically pure isomer **6f** with the following physical data was obtained: **6f**:**6′f** = 100:0; mp 253–256°C; $[\alpha]_D^{25}$ = −83.0 (*c* 0.336, $CHCl_3$).

6.4.7. (1*R*,3*R*,4*R*)-3-[5-Chloro-1,2,4-triazolo[4,3-*a*]pyrazin-3-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6g and its (1*R*,3*S*,4*R*)-epimer 6′g. Prepared from compound **2** and 6-chloro-2-hydrazinopyrazine (**3g**), 3 h, CC (ethyl acetate/petroleum ether, 2:1); 182 mg (60%) of a white solid; mp 243–256; **6g**:**6′g** = 97:3. Found: C, 59.31; H, 5.51; N, 18.00. $C_{15}H_{17}ClN_4O$ requires: C, 59.11; H, 5.62; N, 18.38%; ν_{max} (KBr) 1748 cm^{-1} (C=O).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 6g: ^{1}H NMR ($CDCl_3$): δ 1.08, 1.12 (9H, 2s, 2:1, 3Me), 1.27–1.42 (1H, m, 1H of CH_2), 1.70–1.88 (2H, m, 2H of CH_2), 1.92–2.05 (1H, m, 1H of CH_2), 2.53 (1H, t, J = 4.0 Hz, H–C(4)), 4.72 (1H, dd, J = 1.1, 4.5 Hz, H–C(3)), 7.84 (1H, s, H–C(6′)), 9.24 (1H, s, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.8, 19.8, 21.7, 30.0, 46.7, 49.1, 50.67; 59.3, 121.5, 129.8, 143.5, 146.5, 147.5, 212.2.

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 6′g: ^{1}H NMR ($CDCl_3$): δ 3.07 (1H, d, J = 4.2 Hz, H–C(4)), 3.61 (1H, s, H–C(3)). Upon repeated crystallisation of **6g**/**6′g** from a mixture of chloroform and *n*-heptane, diastereomerically pure isomer **6g** with the following physical data was obtained: **6g**:**6′g** = 100:0; mp 245–251°C; $[\alpha]_D^{25}$ = +237.0 (*c* 0.430, CH_2Cl_2).

6.5. (1*R*,3*R*,4*R*)-3-[1,2,4-Triazolo[1,5-*a*]pyrimidin-2-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 7 and its (1*R*,3*S*,4*R*)-epimer 7′

A solution of sodium methoxide in methanol (0.82 M, 1 mL) was added to a solution of diastereomerically pure **6e** (200 mg, 0.74 mmol) in methanol (7 mL) and the mixture was refluxed for 20 min. A solution of sodium methoxide in methanol (0.82 M, 1 mL) was added and the reaction mixture was heated under reflux for 30 min. The reaction mixture was cooled, neutralised with a solution of acetic acid (100%, 1 mL) in

methanol (6 mL), and evaporated in vacuo. The residue was purified by CC (EtOAc). Fractions containing the product were combined and evaporated in vacuo to give a mixture of **7** and **7′**, which was characterised by spectral (IR, ^{1}H NMR, and ^{13}C NMR) and elemental analyses. Yield: 110 mg (55%) of a white solid; **7**:**7′** = 96:4; mp 190–200°C; $[\alpha]_D^{21} = +103.9$ (c 0.440, CH_2Cl_2). Found: C, 66.88; H, 6.64; N, 21.05. $C_{15}H_{18}N_4O$ requires: C, 66.64; H, 6.71; N, 20.73%; ν_{max} (KBr) 1744 cm^{-1} (C=O).

NMR data for the major (1*R*,3*R*,4*R*)-isomer 7: ^{1}H NMR ($DCCl_3$): δ 1.04, 1.08 (9H, 2s, 2:1, 3Me), 1.40–1.56 (1H, m, 1H of CH_2), 1.64–1.84 (3H, m, 3H of CH_2), 2.60 (1H, t, J = 4.0 Hz, H–C(4)), 4.12 (1H, dd, J = 1.1, 4.9 Hz, H–C(3)); 7.08 (1H, dd, J = 4.1, 6.8 Hz, H–C(6′)), 8.79 (1H, dd, J = 1.9, 4.1 Hz, H–C(8′)), 8.82 (1H, dd, J = 1.9, 6.8 Hz, H–C(5′)). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.6, 20.0, 22.2, 30.3, 46.5, 49.2, 51.3, 59.3, 110.3, 136.1, 154.8, 156.0, 167.2, 214.9.

NMR data for the minor (1*R*,3*S*,4*R*)-isomer 7′: ^{1}H NMR ($CDCl_3$): δ 3.11 (1H, d, J = 4.2 Hz, H–C(4)), 3.54 (1H, s, H–C(3)).

6.6. X-Ray structure analysis for compounds 2, 5c, 6b,c,e, 7

The crystal structures of compounds **2**, **5c**, **6b**, **6c**, **6e**, and **7** were determined. Single crystal X-ray diffraction data were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[34] Indexing and scaling of the data were performed using DENZO and SCALEPACK.[35] Structures were solved by means of SIR-92,[36] while the refinement and plotting were carried out using the Xtal3.4[37] program package. Refinement was carried out on F by a full-matrix least-squares procedure. In all cases the non-hydrogen atoms were refined anisotropically while the hydrogen atoms were geometrically restrained (riding) and their isotropic atomic displacement parameters (ADP) were not refined. These values were set to 1.5 times the isotropic ADP of methyl carbon atoms to which the H atoms were bound and to 1.2 times of the ADP of the 'carrying' atoms in other cases. Absorption correction was not performed. The weighting scheme in all cases was Regina.[38]

As expected, all six compounds crystallise in polar space groups and contain only one diastereomer of the chiral molecule (only one diastereomer was used in the synthesis). The crystal packing, however, is rather varied. In the six cases studied, the symmetry ranges from triclinic to trigonal and in four cases the asymmetric unit contains more than one molecule. The most outstanding example in this sense is the compound **6c**, which could be solved and even refined in the space group *C2* where only two instead of four molecules were present in the asymmetric unit. However, the R factors were rather high in *C2* and the atomic displacement parameters were unreasonably large in the camphor part of one of the molecules. This situation remained practically unchanged at low temperature (150 K). At low temperature it became obvious that the lattice is in fact primitive and there are indeed four molecules in the asymmetric unit. In the case of compound **5c** the presence of the centre of inversion was excluded by the argument stated above as well as by a final successful refinement in the space group *P1*, which clearly showed that the chiral parts of the two molecules are equal and can not be related by the centre of inversion. In other cases there were no special issues that would require comments. The plots of the final refined contents of the asymmetric units of compounds **2**, **5c**, **6b**, **6c**, **6e**, and **7** are presented in Figs. 2–7.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre.[39]

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