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Reductions 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 and their analogues

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Abstract—Reductions 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 and their lactone analogues, prepared from (1*R*)-(+)-camphor, were studied. Catalytic hydrogenation selectively led to partial saturation of the [1,2,4]triazolo[4,3-*x*]azine residue, while in reactions with borane–methylsulfide coordination of borane to the 1-position of [1,2,4]triazolo[4,3-*x*]azine system took place. On the other hand, activation of the carbonyl group in (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 with boron trifluoride etherate followed by reaction with borane–methylsulfide furnished the corresponding isoborneols, stereoselectively. The structures of all representative compounds were confirmed by X-ray diffraction.

1. Introduction

In organic synthesis, especially in asymmetric applications, (+)-camphor and its derivatives represent one of the most important groups of enantiopure chiral pool starting materials, building blocks, ligands, reagents and resolving agents, including shift reagents in NMR spectroscopy.[1–4]

On the other hand, the [1,2,4]triazolo[4,3-*x*]azine system is a constituent of several biologically active compounds.[5,6] Most frequently, [1,2,4]triazolo[4,3-*x*]azines are prepared by the treatment of a hydrazinoazine with an aldehyde to give the intermediate hydrazone, followed by oxidative cyclisation into the corresponding [1,2,4]triazolo[4,3-*x*]azine. Usually, bromine and lead tetraacetate are employed for the oxidation of (*N*-azin-yl)aldohydrazones into [1,2,4]triazolo[4,3-*x*]azines.[7–12] Recently, this synthetic approach has also been extended towards the preparation of functionalised [1,2,4]triazolo[4,3-*x*]azines, utilising functionalised aldehydes and their enamino analogues,[13–16] derived from α-amino acids,[17,18] sugars[19–21] and (+)-camphor.[22,23] Within this context, we have previously reported a one-pot 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 **1a**–**1g**[22] and (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*x*]azin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **2a** and **2b**.[23]

Previous studies on the reductions of [1,2,4]triazolo[4,3-*b*]-pyridazines showed that the saturation of the pyridazine part of the bicyclic system takes place upon either catalytic hydrogenation[24] or treatment with sodium borohydride.[25–27] Additionally, we studied the reductions of compounds **1** and **2** by catalytic hydrogenation and by treatment with borane–methylsulfide (BMS). We herein report results, which show, that catalytic hydrogenation takes place at the azine part of the [1,2,4]triazolo[4,3-*x*]azine system, while treatment with BMS leads, depending on the reaction conditions, either to stable complexes with borane, or to stereoselective reduction of the keto group.

2. Results and discussion

Starting compounds, **1a**–**1g**[22] and **2a** and **2b**,[23] were prepared from (1*R*)-(+)-camphor according to the

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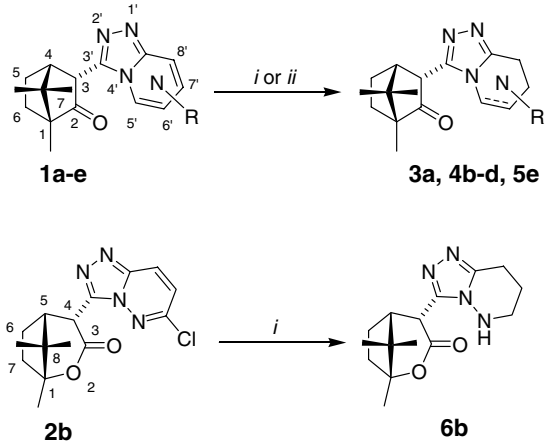
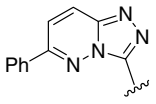
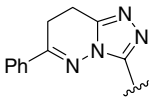
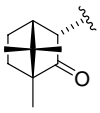
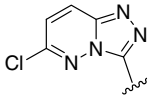
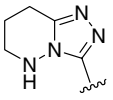
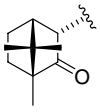
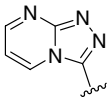
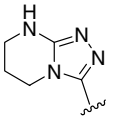
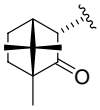
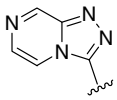
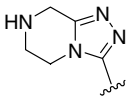
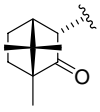
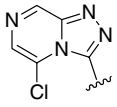
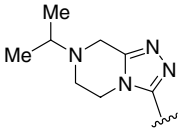
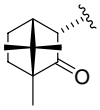
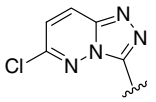
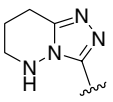
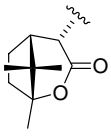
previously published procedures. It has been observed previously that even isomerically pure compounds **1** and **2** partially epimerise in solution[22] and, for this reason, some of them, for example, **1a** and **1f**[22] and **2a**,[23] could not be prepared in isomerically pure form. Furthermore, purification of compounds **1b**–**1e**,**1g** and **2b** by repeated crystallisation was accompanied by substantial loss of material.[22,23] Therefore, starting compounds **1a**–**1g** and **2a** and **2b** were not prepared in isomerically pure form and were used for further transformations as mixtures of the major *endo*-isomers **1a**–**1g** and **2a** and **2b** (68–94% de) and the minor *exo*-isomers **1′a**–**1′g** and **2′a** and **2′b**.

First, the catalytic hydrogenations of **1a**–**1e** and **2b** were carried out under 50 bar of H_2 in the presence of 10% Pd–C in ethanol. Under these conditions, hydrogenation of **1a** afforded 7,8-dihydro analogue **3a**, which was isolated in 20% yield and 100% de, whilst hydrogenations of **1b**–**1d** and **2b** gave the corresponding 5,6,7,8-tetrahydro analogues **4b**–**4d** and **6b** in 68–93% yields and 68–92% de. Hydrogenation of **1e** under identical conditions in a mixture of ethanol and acetone afforded 7-isopropyl-5,6,7,8-tetrahydro derivative **5e** as a product of additional reductive alkylation at the 7′-position, which was isolated in 22% yield and 56% de. In the catalytic hydrogenations of the chlorinated substrates **1b**, **1e** and **2b**, dechlorination also took place. Unfortunately, all attempts to prepare isomerically pure compounds **4b**–**4d**, **5e** and **6b** by crystallisation or chromatographic purification failed. Nevertheless, upon crystallisation of compound **4b** from *n*-heptane–chloroform, a few crystals of **4b** with the same isomer composition were obtained. These crystals were used for X-ray structure analysis (Scheme 1, Table 1).



Scheme 1. Reagents and conditions: (i) H_2 (50 bar), 10% Pd–C, EtOH, 50 °C; (ii) H_2 (50 bar), 10% Pd–C, EtOH–acetone, 50 °C.

Table 1. Experimental data for compounds **3a**, **4b**–**4d**, **5e** and **6b**

Reaction	Heteroaryl residue		Terpene residue	Method	Yield (%)	de (%)	
	1, **2**	**3**–**5**				**1**, **2**[a]	**3**–**6**[b]
1a→3a				A	20	84	100
1b→4b				A	73	94	92
1c→4c				A	93	84	70
1d→4d				A	89	72	68
1e→5e				B	22	94	56
2b→6b				A	68	90	84

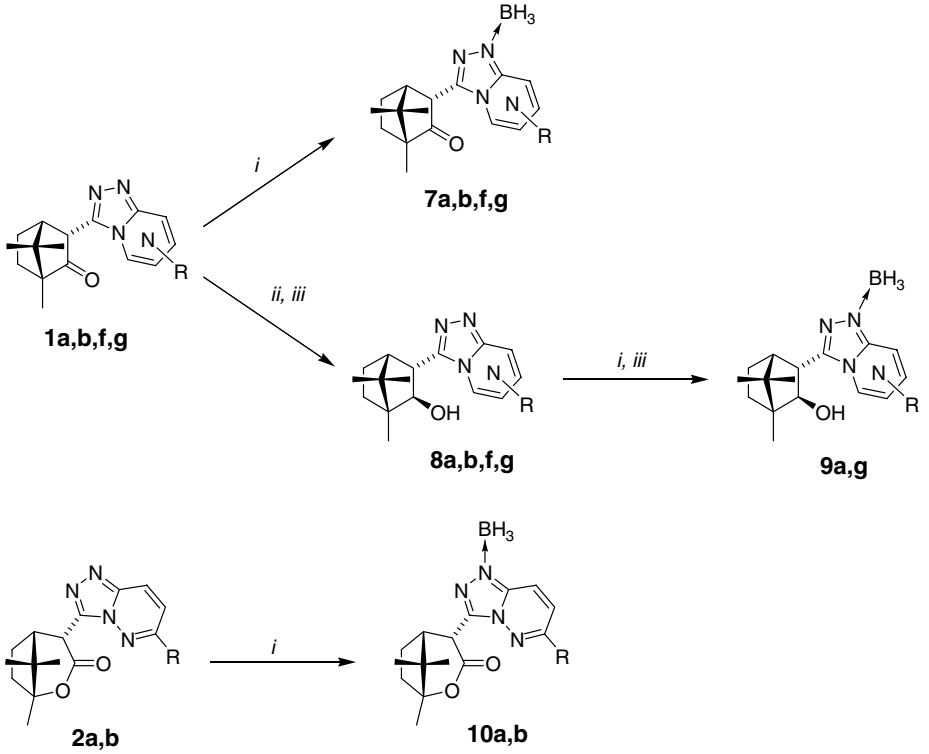
[a] De of the starting compound.
[b] De of the isolated compound.

Next, reactions of **1** and **2** with borane–methylsulfide (BMS) were studied. When compounds **1a**,**1b**,**1f**,**1g** and **2a** and **2b** were treated with BMS in dichloromethane, no reduction of the carbonyl group occurred and stable complexes with borane **7a**,**7b**,**7f**,**7g** and **10a** and **10b** were obtained in 29–73% yields. Complexes **7b**,**7f**,**7g** and **10a** and **10b** were obtained in isomerically pure form, whilst compound **7a** was isolated in 82% de. Repeated crystallisation furnished isomerically enriched compound **7a** in 1.5% yield and 96% de. In order to achieve reduction of the keto group, compounds **1a**,**1b**,**1f** and **1g** were first activated with boron trifluoride etherate and then treated with BMS. Upon thorough chromatographic purification (CC followed by MPLC), the corresponding isoborneols **8a**,**8b**,**8f** and **8g** were isolated in 39–62% yields and 100% de. Treatment of isoborneols **8a** and **8g** with BMS in dichloromethane afforded complexes with boranes **9a** and **9g** in 23% and 27% yield, respectively. In contrast to the previously reported reductions of [1,2,4]triazolo[4,3-*b*]pyridazines with sodium borohydride,[25–27] no reduction of [1,2,4]triazolo[4,3-*x*]azine system was observed upon treatment of **1a**,**1b**,**1f**,**1g** with BMS (Scheme 2, Table 2).

The isomeric purities of the hydrogenation products **4**–**6** were lower than the isomeric purities of the corresponding starting compounds **1** and **2** (cf. Table 1). This was expected, since the hydrogenations were carried out in polar solvents at slightly elevated temperatures, which both promote epimerisation at the α-position with respect to the carbonyl group. Similarly, the formation of borane complex **7a** was accompanied by a slight decrease of de, while other boranes **7b**,**7f** and **7g** were isolated in isomerically pure form. In these cases, isolation of pure *endo*-isomers **7b**,**7f** and **7g** was due to crystallisation from dichloromethane–methanol during the isolation procedure.

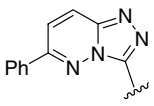
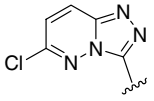
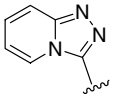
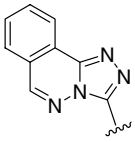
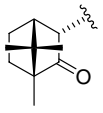
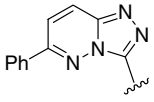
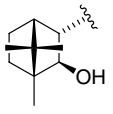
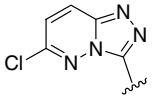
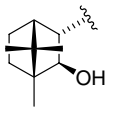
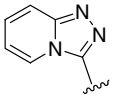
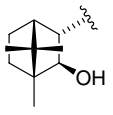
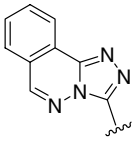
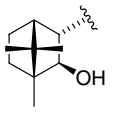
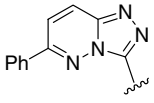
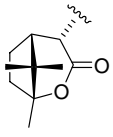
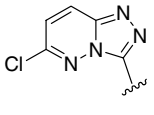
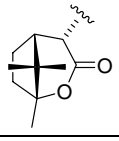
On the other hand, only the (1*R*,2*R*,3*R*,4*R*)-isomers of isoborneols **8a**,**8b**,**8f** and **8g** were isolated upon treatment of **1a**,**1b**,**1f** and **1g** with BF_3–Et_2O followed by reduction with BMS. These results were very surprising, since the formation of detectable, or even isolable amounts of minor stereoisomer(s) would be expected. Unfortunately, we were unable to establish the stereoselectivity of reduction of the C=O group in compounds **1** by ^1H NMR, due to the presence of impurities in the crude products **8**. However, stereoselective formation of the (1*R*,2*R*,3*R*,4*R*)-isomers **8a**,**8b**,**8f** and **8g** was supported by experimental evidence. Due to [1,2,4]triazolo[4,3-*x*]-azine residue,[5–12] the starting compounds **1**, as well as the products **8** are highly fluorescent and can be easily distinguished among impurities. In the case of reduction of camphors **1** with BMS, the products **8** were always detected as single fluorescent spots by TLC. During the chromatographic workup (CC then MPLC), all fluorescent fractions were combined and evaporated to give (1*R*,2*R*,3*R*,4*R*)-isomers **8a**,**8b**,**8f** and **8g**. This experimental evidence supports the preferential formation of the (1*R*,2*R*,3*R*,4*R*)-isomers **8** (see Experimental).

The observed *endo*-facial selectivity in the formation of isoborneols **8a**,**8b**,**8f** and **8g** is in agreement with previous reductions of the carbonyl group in the camphor series[28] and isolation of isomerically pure isoborneols **8a**,**8b**,**8f** and **8g** could be explained by the stereospecific



Scheme 2. Reagents and conditions: (i) $BH_3 \times Me_2S$, CH_2Cl_2, rt or reflux; (ii) $BF_3 \times Et_2O$, CH_2Cl_2, 0 °C, 1 h, then BH_3–Me_2S, CH_2Cl_2, 0 °C, 1 h, then rt, 24 h; (iii) chromatographic separation (CC and/or MPLC).

Table 2. Experimental data for compounds **7a**,**7b**,**7f**,**7g**, **8a**,**8b**,**8f**,**8g**, **9a**,**g** and **10a** and **10b**

Compound	Heteroaryl residue	Terpene residue	Yield (%)[a]			
			7	8	9	10
1a, **7a**			58			
1b, **7b**			29			
1f, **7f**			58			
1g, **7g**			34			
1a, **8a**, **9a**				62	23	
1b, **8b**				57		
1f, **8f**				58		
1g, **8g**, **9g**				39	27	
2a, **10a**						73
2b, **10b**						53

[a] With exception of **7a** (82% de), all other compounds **7**–**10** were isolated in isomerically pure form.

attack of the hydride from the less hindered *endo*-face of **1a**,**1b**,**1f** and **1g**. However, this explanation is not very appropriate, since a complete loss of facial selectivity was previously observed during bromination of **1a**.[23] Furthermore, the *endo*-face in compounds **1** is also quite hindered by the bulky [1,2,4]triazolo[4,3-*x*]azinyl substituent at the 3-position. It seems more probable that high *endo*-facial selectivity could be attributed to [1,2,4]triazolo[4,3-*x*]azinyl residue as a ligand (or tether), which is involved in the reduction mechanism. It might also be presumed that in the presence of a Lewis acid, such as BF_3–Et_2O, isomerisation of the minor *exo*-isomer **1′** into the thermodynamically more stable *endo*-isomer **1** takes place. Consequently, activation of a mixture of **1** and **1′** with BF_3–Et_2O followed by the addition of BMS leads to intermediate **11** with an activated C=O bond and borane attached at the 1′-position. Migration of borane to the 2′-position gives intermediate **12**, which then undergoes intramolecular reduction of the C=O bond from the *endo*-face, exclusively (Scheme 3).

3. Structure determination

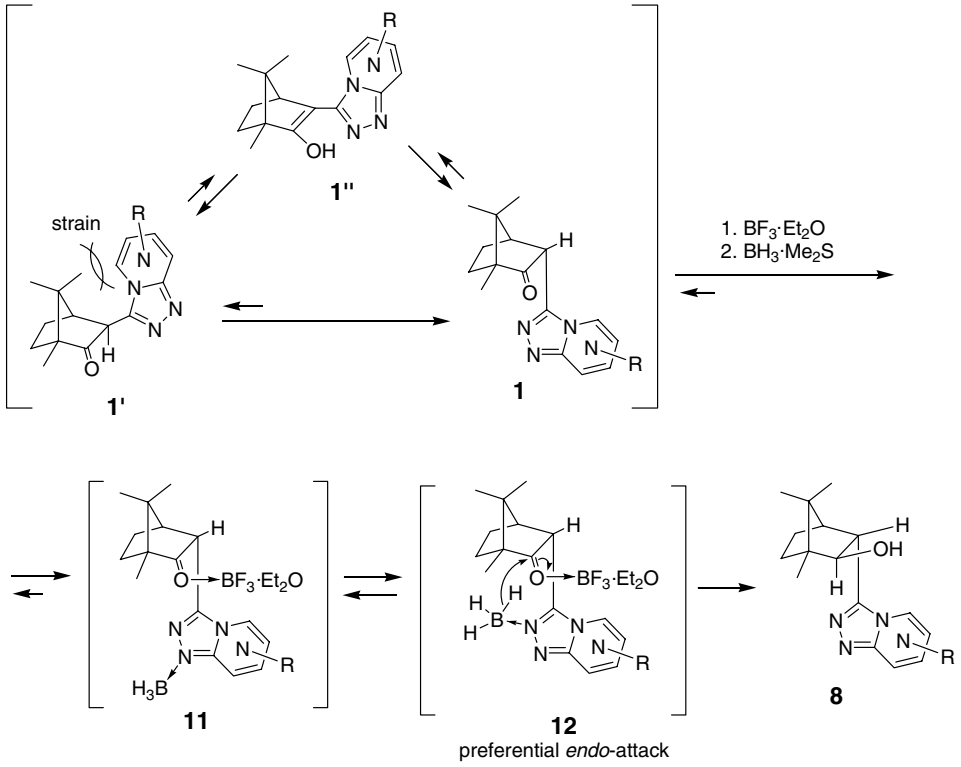
The structures of all novel compounds **3a**, **4b**–**4d**, **5e**, **6b**, **7a**,**7b**,**7f**,**7g**, **8a**,**8b**,**8f**,**8g**, **9a**,**9g** and **10a** and **10b** were determined by spectroscopic methods (IR, ^1H and ^{13}C NMR, MS) and by elemental analyses for C, H and N. Compounds **3a**, **7b**,**7f**,**7g**, **8a**,**8b**,**8f**,**8g**, **9a**,**9g** and **10a** and **10b** were prepared in isomerically pure form, while compounds **4b**–**4d**, **5e**, **6b** and **7a** were prepared and characterised as a mixture of the major *endo*-isomers **4b**–**4d**, **5e**, **6b** and **7a** and the minor *exo*-isomers **4′b**–**4d**, **5′e**, **6′b** and **7′a**. Compounds **4d**, **8a** and **10a** were not prepared in analytically pure form. The identities of **4d** and **8a** were confirmed by ^{13}C NMR and EI-HRMS, while identity of **10a** was established by ^{13}C NMR.

The configuration at the 3-position in camphors **3**–**5**, **7** and isoborneols **8**, **9** was determined by NMR on the basis of vicinal coupling constants, $^3J_{H3-H4}$. Coupling constant, $^3J_{H3-H4} = 3.7$–4.5 Hz was observed in the case of the major *endo*-isomers **3**–**5** and **7**–**9**, while the coupling constant, $^3J_{H3-H4} \sim 0$ Hz, was characteristic for the minor *exo*-isomers **3′**–**5′** and **7′**. In the same manner, the configuration at the 4-position in camphorlactones **6**, **6′** and **10** was determined on the basis of vicinal coupling constants, $^3J_{H4-H5} = 4.1$–4.5 Hz. These two characteristic values of coupling constants, $^3J_{H3-H4}$ and $^3J_{H4-H5}$, are also in agreement with the values reported in the literature for analogous compounds (Fig. 1).[22,23]

The structures of compounds **4b**, **7a**, **8b**, **9a** and **10a** were determined by X-ray diffraction (Figs. 2–6).

4. Conclusion

The catalytic hydrogenation 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 **1a**–**1e** and their lactone analogue **2b** took place at the six-membered ring of the [1,2,4]triazolo-[4,3-*x*]azinyl residue and led to the partially saturated analogues **3**–**6**. In the case of **1a**, hydrogenation only took place at the C(7′)=C(8′) double bond to give 7,8-dihydro derivative **3a**, while with other substrates, 5,6,7,8-tetrahydro derivatives **4**–**6** were formed. Reactions of **1**, **2** and **8** with borane–methylsulfide in dichloromethane afforded stable complexes with boranes **7**, **10** and **9**, respectively. Coordination of borane at the



Scheme 3.

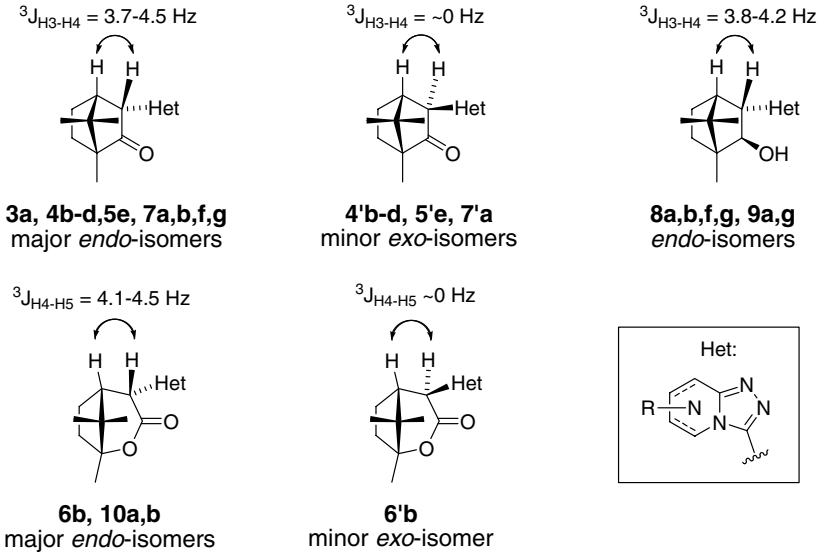


Figure 1. Determination of *exo*/*endo*-configuration in compounds **3**–**10** and **4′**–**7′** by ^{1}H NMR.

1′-position was established by X-ray diffraction. The stereoselective reduction of camphors **1a**,**1b**,**1f** and **1g** into isoborneols **8a**,**8b**,**8f** and **8g** was achieved by activation of the C=O bond with boron trifluoride, followed by reduction with borane–methylsulfide. Under these conditions, reduction proceeded selectively at the carbonyl group without affecting [1,2,4]triazolo[4,3-*x*]azine system. The high selectivity of these reductions can be explained by Lewis acid promoted isomerisation of **1**/**1′** into the thermodynamically more stable *endo*-isomer **1**, followed by complexation of borane to [1,2,4]-triazolo[4,3-*x*]azinyl residue, followed by *endo*-attack of the hydride to the carbonyl group. The novel compounds **3**–**10** might be useful substrates, reagents or ligands in asymmetric applications.

5. Experimental

5.1. General

Melting points were determined on a Kofler micro hot stage. ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for

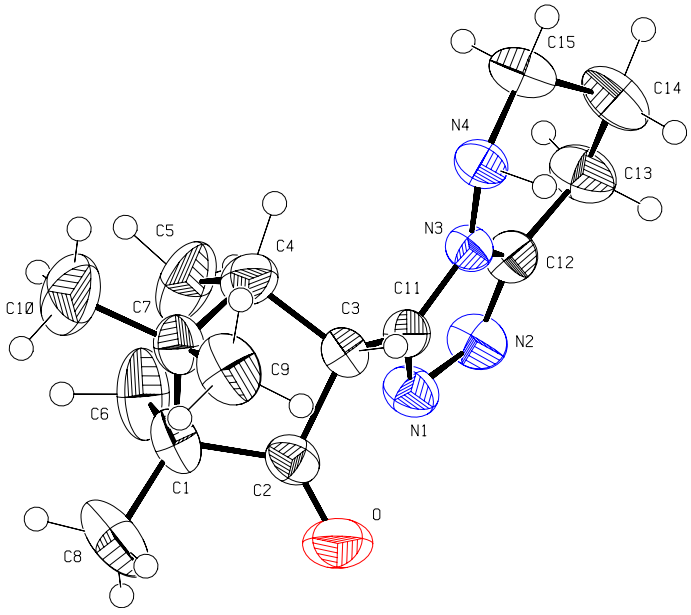


Figure 2. The asymmetric unit of compound **4b**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

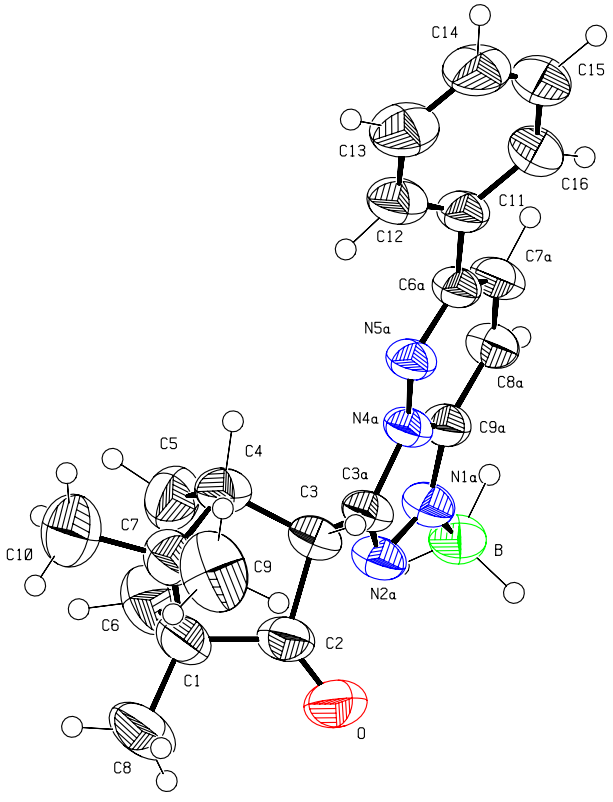


Figure 3. The asymmetric unit of compound **7a**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

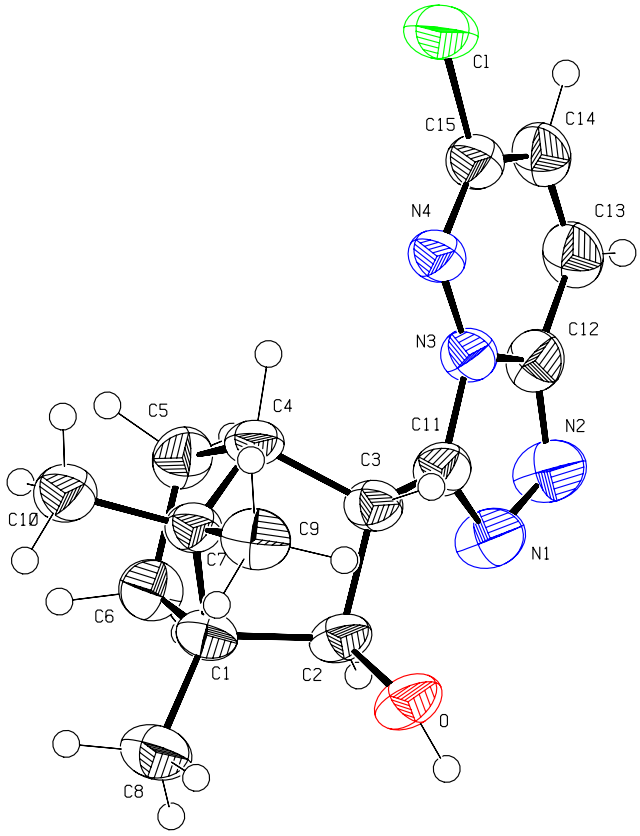


Figure 4. The asymmetric unit of a salt of compound **8b**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

^{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) and on aluminium oxide (Fluka, type 507 C neutral, 0.05–0.15 mm, pH 7.0 ± 0.5). Medium pressure liquid chromatography (MPLC) was per-

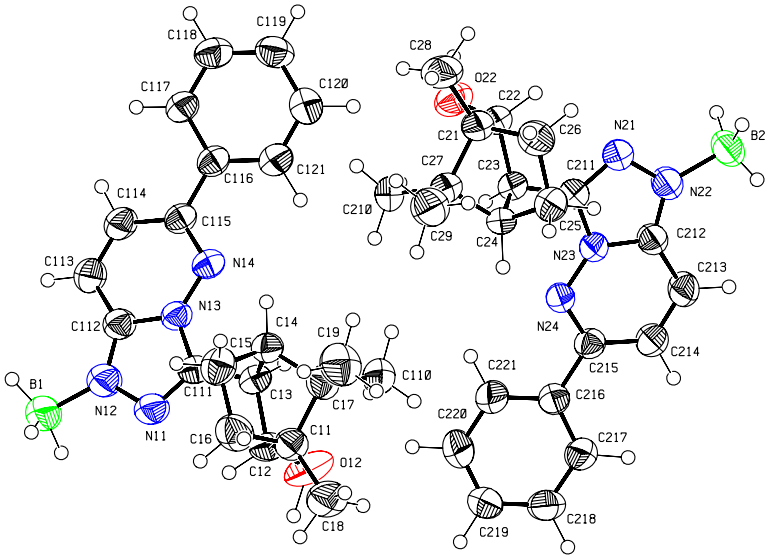


Figure 5. The asymmetric unit of compound **9a**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

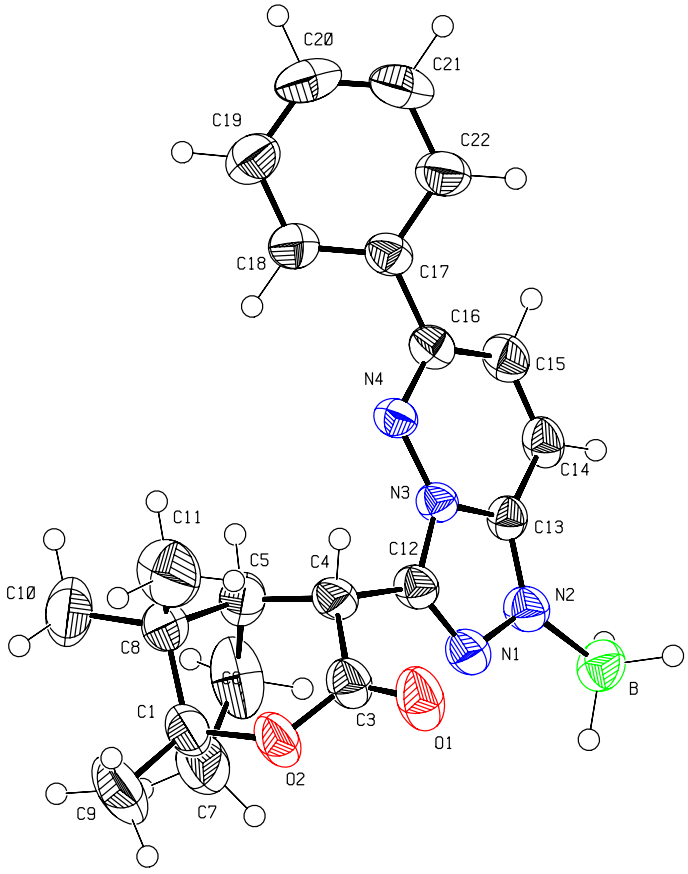


Figure 6. The asymmetric unit of compound **10a**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

formed with a Büchi isocratic system with detection[†] on silica gel (Merck, silica gel 60, 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 ratio of isomers and de were determined by ^{1}H NMR.

Borane–methylsulfide (BMS) and boron trifluoride ethyl etherate are commercially available (Fluka AG). (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 **1a**–**1g**,[22] and (1*R*,4*R*,5*R*)-

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

4-([1,2,4]triazolo[4,3-*x*]azin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **2a**,**2b**[23] were prepared in 68–94% de from (1*R*)-(+)-camphor according to procedures described in the literature.

Source of chirality: (i) (+)-Camphor (Fluka AG), product number 21300, purum, natural, ⩾97.0% (GC, sum of enantiomers), $[\alpha]_{546}^{20} = +54.5 \pm 2.5$ (*c* 10, EtOH), $[\alpha]_{D}^{20} = +42.5 \pm 2.5$ (*c* 10, EtOH), mp 176–180 °C, ee not specified.

5.2. (1*R*,3*R*,4*R*)-3-(7,8-Dihydro-6-phenyl[1,2,4]triazolo-[4,3-*b*]pyridazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one 3a

A mixture of **1a** (346 mg, 1 mmol, ~84% de), ethanol (15 ml) and 10% Pd–C (100 mg) was hydrogenated in an autoclave (50 bar of H_2, 40 °C) for 72 h. The reaction mixture was filtered through a short pad of Celite®, washed with ethanol (15 ml) and the filtrate evaporated in vacuo. The residue was purified by CC ($CHCl_3$–MeOH, 30:1). Fractions containing the product were combined and evaporated in vacuo to give compound **3a**. Yield: 70 mg (20%) of a white solid; mp 122–126 °C; $[\alpha]_{D}^{21} = +80.2$ (*c* 0.26, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.03, 1.06, 1.08 (9H, 3s, 1:1:1, 3Me); 1.66–1.93 (4H, m, 4H of CH_2); 2.45 (1H, t, $J = 3.8$ Hz, H–C(4)); 3.07–3.13 and 3.22–3.28 (4H, 2m, 1:1, $2 \times CH_2$); 4.17 (1H, dd, $J = 0.8$; 4.5 Hz, H–C(3)); 7.45–7.54 and 7.83–7.86 (5H, 2m, 3:2, Ph). EI-MS: $m/z = 348$ (M^+). (Found: C, 72.41; H, 7.11; N, 16.08. $C_{21}H_{24}N_4O$ requires C, 72.39; H, 6.94; N, 16.08.) ν_{max} (KBr) 2958, 1743 (C=O), 1548, 1519, 1445, 1414, 1355, 1288, 1092, 1008 cm^{-1}.

5.3. General procedure for the preparation of (1*R*,3*R*,4*R*)-3-(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones 4b–4d, their (1*R*,3*S*,4*R*)-epimers 4′b–4d, (1*R*,4*R*,5*R*)-4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6b and their (1*R*,4*S*,5*R*)-epimer 6′b

A mixture of **1b**–**1d** or **2b** (1 mmol), ethanol (15 ml) and 10% Pd–C (100 mg) was hydrogenated in an autoclave (50 bar of H_2, 50 °C) for 24 h. The reaction mixture was filtered through a short pad of Celite®, washed with ethanol (15 ml) and the filtrate evaporated in vacuo to give compounds **4b**–**4d** and **6b**. Compounds **4b** and **6b** were additionally purified in the following manner. The residue was dissolved in dichloromethane (70 ml), the solution washed with saturated aqueous $NaHCO_3$ (30 ml), dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated in vacuo. The residue was purified by CC ($CHCl_3$–MeOH, 20:1). Fractions containing the product were combined and evaporated in vacuo to give compounds **4b** and **6b**.

5.3.1. (1*R*,3*R*,4*R*)-3-(5,6,7,8-Tetrahydro[1,2,4]triazolo-[4,3-*b*]pyridazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 4b and its (1*R*,3*S*,4*R*)-isomer 4′b.

Prepared from **1b** (305 mg, 1 mmol, 94% de); yield: 200 mg (73%) of a white solid; **4b**:**4′b** = 96:4 (92% de); mp 255–260 °C; $[\alpha]_{D}^{22} = -85.8$ (*c* 0.23, $CHCl_3$). (Found: C, 65.54; H, 8.20; N, 20.62. $C_{15}H_{22}N_4O$ requires C, 65.67; H, 8.08; N, 20.42.) ν_{max} (KBr) 3469, 3164, 2957, 1744 (C=O), 1523, 1482, 1450, 1395, 1370, 1188, 1101 cm^{-1}.

5.3.1.1. NMR data for the major (1*R*,3*R*,4*R*)-isomer 4b. ^{1}H NMR ($CDCl_3$): δ 0.97, 1.01, 1.07 (9H, 3s, 1:1:1, 3Me); 1.55–1.65, 1.69–1.79, 1.80–2.05, 2.24–2.33 (6H, 4m, 1:1:3:1, $3 \times CH_2$); 2.51 (1H, t, $J = 4.1$ Hz, H–C(4)); 2.93–3.22, 3.30–3.39 (4H, 2m, 3:1, $2 \times CH_2$); 3.91 (1H, dd, $J = 1.5$; 4.1 Hz, H–C(3)); 5.30 (1H, dd, $J = 6.0$; 9.0 Hz, H–N(5′)). ^{13}C NMR ($CDCl_3$): δ 9.7, 19.1, 19.7, 20.5, 20.9, 21.6, 30.6, 45.4, 46.3, 46.8, 47.3, 59.0, 146.8, 148.4, 216.3.

5.3.1.2. NMR data for the minor (1*R*,3*R*,4*R*)-isomer 4′b. ^{1}H NMR ($CDCl_3$): δ 0.86, 0.93, 1.04 (9H, 3s, 1:1:1, 3Me); 6.01 (1H, dd, $J = 3.8$; 10.9 Hz, H–N(5′)).

5.3.2. (1*R*,3*R*,4*R*)-3-(5,6,7,8-Tetrahydro[1,2,4]triazolo-[4,3-*a*]pyrimidin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 4c and its (1*R*,3*S*,4*R*)-isomer 4′c.

Prepared from **1c** (270 mg, 1 mmol, 84% de); yield: 255 mg (93%) of a white solid; **4c**:**4′c** = 85:15 (70% de); mp 227–232 °C; $[\alpha]_{D}^{21} = +98.4$ (*c* 0.25, CH_2Cl_2). EI-MS: $m/z = 274$ (M^+). *m*/*z* (HRMS) Found: 274.180260 (M^+); $C_{15}H_{22}N_4O$ requires: 274.179362. (Found: C, 65.53; H, 7.84; N, 20.19. $C_{15}H_{22}N_4O$ requires C, 65.67; H, 8.08; N, 20.42.) ν_{max} (KBr) 3375, 3249, 2962, 1747 (C=O), 1610, 1535, 1442, 1394, 1327, 1277, 1032 cm^{-1}.

5.3.2.1. NMR data for the major (1*R*,3*R*,4*R*)-isomer 4c. ^{1}H NMR ($CDCl_3$): δ 0.98, 0.99, 1.06 (9H, 3s, 1:1:1, 3Me); 1.67–1.85 and 1.94–2.15 (6H, 2m, 1:1, $3 \times CH_2$); 2.36 (1H, t, $J = 4.1$ Hz, H–C(4)); 3.36–3.44 (2H, m; CH_2); 3.55 (1H, dd, $J = 1.1$; 4.1 Hz, H–C(3)); 3.71–3.79 and 3.97–4.06 (2H, 2m, 1:1, CH_2); 5.42 (1H, dd, $J = 6.0$; 9.0 Hz, H–N(8′)). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.7, 19.9, 21.8, 21.9, 30.1, 39.5, 41.2, 46.4, 47.0, 47.7, 58.8, 146.3, 154.1, 214.0.

5.3.2.2. NMR data for the minor (1*R*,3*S*,4*R*)-isomer 4′c. ^{1}H NMR ($CDCl_3$): δ 0.90, 0.94, 1.02 (9H, 3s, 1:1:1, 3Me); 3.05 (1H, s, H–C(3)); 3.81–3.87 and 4.44–4.52 (2H, 2m, 1:1, CH_2); 5.18 (1H, br s, H–N(8′)).

5.3.3. (1*R*,3*R*,4*R*)-3-(5,6,7,8-Tetrahydro[1,2,4]triazolo-[4,3-*a*]pyrazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 4d and its (1*R*,3*S*,4*R*)-isomer 4′d.

Prepared from **1d** (270 mg, 1 mmol, 72% de); yield: 244 mg (89%) of a white solid; **4d**:**4′d** = 84:16 (68% de); mp 71–81 °C; $[\alpha]_{D}^{21} = +81.4$ (*c* 0.27, CH_2Cl_2). EI-MS: $m/z = 274$ (M^+). *m*/*z* (HRMS) Found: 274.180020 (M^+); $C_{15}H_{22}N_4O$ requires: 274.179362. (Found: C, 64.71; H, 8.30; N, 20.69. $C_{15}H_{22}N_4O$ requires C, 65.67; H, 8.08; N, 20.42.) ν_{max} (KBr) 2413, 3278, 2962, 1747 (C=O), 1514, 1482, 1448, 1393, 1341, 1128, 1040 cm^{-1}.

5.3.3.1. NMR data for the major (1*R*,3*R*,4*R*)-isomer 4d. ^{1}H NMR (DMSO-d_6): δ 0.88, 0.93, 1.01 (9H, 3s, 1:1:1, 3Me); 1.38–1.74 (4H, m, $2 \times CH_2$); 2.33–2.36

(1H, br t, $J = 3.9$ Hz, H–C(4)); 2.73 (1H, br s, H–N(7′)); 2.92–3.09 (2H, m; 1H of CH_2 and H–C(3)); 3.70 (1H, ddd, $J = 4.9$, 7.0, 11.9 Hz, 1H of CH_2); 3.85–4.01 (4H, m, $2 \times CH_2$). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.7, 19.8, 21.9, 30.0, 42.6, 43.1, 43.2, 46.5, 46.6, 47.6, 58.8, 149.8, 150.7, 214.3.

5.3.3.2. NMR data for the minor (1*R*,3*S*,4*R*)-isomer 4′d. ^1H NMR (DMSO-d_6): δ 0.80, 0.84, 1.00 (9H, 3s, 1:1:1, 3Me); 2.70 (1H, d, $J = 3.8$ Hz, H–C(4)); 3.57 (1H, s, H–C(3)), 4.09–4.18 (1H, m, 1H of CH_2).

5.3.4. (1*R*,4*R*,5*R*)-4-(5,6,7,8-Tetrahydro[1,2,4]triazolo-[4,3-*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 6b and its (1*R*,4*S*,5*R*)-isomer 6′b. Prepared from **2b** (321 mg, 1 mmol, 90% de); yield: 197 mg (68%) of a white solid; **6b**:**6′b** = 92:8 (84% de); mp 210–235 °C; $[\alpha]_D^{28} = -114.2$ (*c* 0.25, $CHCl_3$). EI-MS: $m/z = 290$ (M^+). *m/z* (HRMS) Found: 290.175320 (M^+); $C_{15}H_{22}N_4O_2$ requires: 290.174276. (Found: C, 62.09; H, 7.80; N, 19.13 $C_{15}H_{22}N_4O_2$ requires C, 62.05; H, 7.64; N, 19.30.) ν_{max} (KBr) 3164, 2971, 1730 (C=O), 1519, 1447, 1381, 1338, 1266, 1227, 1144, 1101 cm^{-1}.

5.3.4.1. NMR data for the major (1*R*,4*R*,4*R*)-isomer 6b. ^1H NMR (DMSO-d_6): δ 1.02, 1.12, 1.26 (9H, 3s, 1:1:1, 3Me); 1.69–1.78 (1H, m, 1H of CH_2); 1.80–1.91 (2H, m, CH_2); 2.02–2.10 (3H, m, 3H of CH_2); 2.13 (1H, dd, $J = 4.5$, 6.4 Hz, H–C(5)); 2.92 (2H, t, $J = 6.8$ Hz, CH_2), 3.00–3.19 (2H, m, CH_2); 4.30 (1H, dd, $J = 1.9$; 4.5 Hz, H–C(4)); 6.16 (1H, dd, $J = 7.9$; 6.8 Hz, H–N(5′)). ^{13}C NMR ($CDCl_3$): δ 18.1, 18.4, 20.8, 21.2, 23.0, 23.4, 24.2, 37.1, 43.3, 45.0, 45.6, 47.4, 96.0, 162.7, 170.7.

5.3.4.2. NMR data for the minor (1*R*,4*S*,4*R*)-isomer 6′b. ^1H NMR (DMSO-d_6): δ 0.97, 1.09 (6H, 2s, 1:1, 2Me); 3.95 (1H, s, H–C(4)).

5.4. (1*R*,3*R*,4*R*)-3-(7-Isopropyl-5,6,7,8-tetrahydro[1,2,4]-triazolo[4,3-*a*]pyrazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one 5e and its minor (1*R*,3*S*,4*R*)-epimer 5′e

A mixture of **1e** (305 mg, 1 mmol, 94% de), ethanol (15 ml), acetone (4 ml) and 10% Pd–C (100 mg) was hydrogenated in an autoclave (50 bar of H_2, 50 °C) for 24 h. The reaction mixture was filtered through a short pad of Celite®, washed with ethanol (15 ml) and the filtrate evaporated in vacuo. The residue was dissolved in dichloromethane (70 ml), the solution was washed with saturated aqueous $NaHCO_3$ (30 ml), dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated in vacuo. The residue was purified by CC ($CHCl_3$–MeOH, 20:1). Fractions containing the product were combined and evaporated in vacuo to give compound **5e**. Yield: 70 mg (22%) of a white solid; **5e**:**5′e** = 78:22 (56% de); mp 145–165 °C; $[\alpha]_D^{21} = +86.7$ (*c* 0.31, CH_2Cl_2). *m/z* (EI) = 316 (M^+). *m/z* (FAB) = 317 (MH^+). (Found: C, 68.40; H, 9.20; N, 17.56. $C_{18}H_{28}N_4O$ requires: C, 68.32; H, 8.92; N, 17.71.) ν_{max} (KBr) 3430, 3197, 2965, 1748 (C=O), 1512, 1449, 1395, 1324, 1175, 1039 cm^{-1}.

5.4.1. NMR data for the major (1*R*,3*R*,4*R*)-isomer 5e. ^1H NMR ($CDCl_3$): δ 0.99, 1.00, 1.07 (9H, 3s, 1:1:1, 3Me); 1.13 (6H, d, $J = 6.4$ Hz, Me_2CH); 1.59–1.92 (4H, m, $2 \times CH_2$); 2.36 (1H, t, $J = 3.7$ Hz, H–C(4)); 2.80–3.01 (3H, m, $1 \times CH_2$ and Me_2CH); 3.63 (1H, dd, $J = 1.1$; 4.4 Hz, H–C(3)); 3.76–3.87 and 3.87–4.09 (4H, 2m, 1:1, $2 \times CH_2$). ^{13}C NMR ($CDCl_3$): δ 9.7, 18.5, 19.3, 19.6, 19.8, 21.6, 29.8, 42.7, 45.4, 35.6, 46.2, 46.4, 47.4, 54.0, 149.8, 150.2, 213.3.

5.4.2. NMR data for the minor (1*R*,3*S*,4*R*)-isomer 5′e. ^1H NMR ($CDCl_3$): δ 0.88, 0.94, 1.04 (9H, 3s, 1:1:1, 3Me); 1.12 (6H, d, $J = 6.4$ Hz, Me_2CH); 3.12 (H, s, H–C(3)); 4.60–4.67 (1H, m, 1H of CH_2).

5.5. Reactions of 1a,1b,1f,1g and 2a,2b with borane–methylsulfide. General procedure for the preparation 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-one-1′-boranes 7a,7b,7f and 7g and (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one-1′-boranes 10a and 10b

Under argon, borane–methylsulfide (BMS, 0.095 ml, 1 mmol) was added to a solution of compound **1a**,**1b**, **1f**,**1g** or **2a** and **2b** (1 mmol) in anhydrous dichloromethane (10 ml). The mixture was heated and stirred at reflux for 3 h, and then cooled to rt. Volatile components were evaporated in vacuo to 0.25 of the initial volume (~2–3 ml), methanol (6 ml) was added and the mixture cooled to 0 °C. The precipitate was collected by filtration to give compounds **7a**,**7b**,**7f**,**7g** and **10a** and **10b**. In the case of compounds **7a** and **g**, the filtrate was evaporated in vacuo and the residue purified by CC on silica gel. Fractions containing the product were combined and evaporated in vacuo to give the second portion of **7a** and **7g**. Both portions of **7a** and **7g** were combined. The following compounds were prepared in this manner.

5.5.1. (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-1′-borane 7a and its minor (1*R*,3*S*,4*R*)-isomer 7′a. Prepared from **1a** (346 mg, 1 mmol, 84% de); CC (EtOAc); 209 mg (58%) of a white solid; **7a**:**7′a** = 91:9 (82% de); mp 208–222 °C; $[\alpha]_D^{21} = +44.2$ (*c* 0.33, $CHCl_3$). (Found: 70.00; H, 7.15; N, 15.57. $C_{21}H_{25}BN_4O$ requires: C, 70.01; H, 6.99; N, 15.55.) ν_{max} (KBr) 2961, 2379 (B–H), 2270 (B–H), 1747 (C=O), 1533, 1485, 1445, 1364, 1170, 1153, 1104 cm^{-1}. Repeated crystallisation of **7/7′a** from *n*-heptane–CH_2Cl_2, afforded 5 mg (1.4%) of diastereomerically enriched compound **7a** as white crystals with the following physical data: **7a**:**7′a** = 98:2 (96% de); mp 197–208 °C; $[\alpha]_D^{21} = +24.0$ (*c* 0.10, $CHCl_3$).

5.5.1.1. NMR data for the major (1*R*,3*R*,4*R*)-isomer 7a. Yield: 5 mg (1.4%) of white crystals; ^1H NMR ($CDCl_3$): δ 1.07, 1.12, 1.13 (9H, 3s, 1:1:1, $3 \times Me$); 1.69–2.04 (4H, m, $2 \times CH_2$); 2.10–3.10 (3H, s, BH_3); 2.59 (1H, t, $J = 3.8$ Hz, H–C(4)); 4.54 (1H, dd, $J = 1.1$; 4.5 Hz, H–C(3)); 7.56–7.63 (3H, m, 3H of Ph);

7.86 (1H, d, $J = 9.8$ Hz, H–C(7′)); 7.93–7.96 (2H, m, 2H of Ph); 8.50 (1H, d, $J = 9.8$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.6, 20.2, 22.4, 30.3, 46.4, 46.9, 48.4, 59.3, 123.7, 123.9, 128.0, 129.9, 132.3, 133.4, 140.4, 146.8, 155.8, 211.7.

5.5.1.2. NMR data for the major (1*R*,3*S*,4*R*)-isomer 7′a. ^{1}H NMR ($CDCl_3$): δ 1.01, 1.05, 1.09 (9H, 3s, 1:1:1, 3 × Me); 3.03 (1H, d, $J = 3.8$ Hz, H–C(4)); 4.03 (1H, s, H–C(3)); 7.84 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.00-8.03 (2H, m, 2H of Ph); 8.45 (1H, d, $J = 9.8$ Hz, H–C(8′)).

5.5.2. (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-1′-borane 7b. Prepared from **1b** (304 mg, 1 mmol, 94% de); 92 mg (29%) of a white solid; mp >350 °C; $[\alpha]_D^{22} = +27.0$ (c 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.05, 1.11, 1.12 (9H, 3s, 1:1:1, 3 × Me); 1.67–1.97 (4H, m, 2 × CH_2); 2.03–3.10 (3H, s, BH_3); 2.54–2.56 (1H, m, H–C(4)); 4.39 (1H, dd, $J = 1.1$; 4.5 Hz, H–C(3)); 7.42 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.43 (1H, d, $J = 9.8$ Hz, H–C(8′)). ^{13}C NMR (DMSO-d_6): δ 10.4, 19.8, 20.0, 22.4, 46.1, 46.8, 47.5, 59.0, 80.0, 125.6, 128.2, 141.2, 146.3, 151.6, 211.7. (Found: C, 56.84; H, 6.47; N, 17.41. $C_{15}H_{20}BClN_4O$ requires: C, 56.55; H, 6.33; N, 17.58.) ν_{max} (KBr) 2969, 2378 (B–H), 2275 (B–H), 1745 (C═O), 1526, 1482, 1353, 1155, 1090, 828 cm^{-1}.

5.5.3. (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-1′-borane 7f. Prepared from **1f** (269 mg, 1 mmol, 68% de); 164 mg (58%) of a white solid; mp 210–215 °C; $[\alpha]_D^{22} = -150$ (c 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.03, 1.09, 1.13 (9H, 3s, 1:1:1, 3 × Me); 1.57–1.67, 1.77–1.87, 1.91–2.03 (3H, 3m, 1:1:1, 3H of CH_2); 2.10–3.15 (3H, br s, BH_3); 2.25–2.34 (1H, m, 1H of CH_2); 2.69 (1H, t, $J = 4.1$ Hz, H–C(3)); 4.07 (1H, dd, $J = 1.5$; 4.1 Hz, H–C(4)); 7.10 (1H, dt, $J = 1.1$; 6.8 Hz, H–C(6′)); 7.59 (1H, ddd, $J = 1.1$; 6.8; 9.4 Hz, H–C(7′)); 8.07 (1H, td, $J = 1.1$; 9.4 Hz, H–C(8′)); 8.44 (1H, td, $J = 1.1$; 6.8 Hz, H–C(5′)). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.4, 20.2, 22.2, 30.6, 46.8, 47.1, 47.5, 59.4, 115.1, 115.9, 124.3, 131.8, 142.8, 145.7, 213.0. (Found: C, 68.09; H, 8.08; N, 15.12. $C_{16}H_{22}BN_3O$ requires: C, 67.86; H, 7.83; N, 14.84.) ν_{max} (KBr) 2935, 2374 (B–H), 2271 (B–H), 1752 (C═O), 1641, 1530, 1506, 1391, 1151, 1099 cm^{-1}.

5.5.4. (1*R*,3*R*,4*R*)-3-([1,2,4]Triazolo[3,4-*a*]phthalazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one-1′-borane 7g. Prepared from **1g** (320 mg, 1 mmol, 92% de); CC ($CHCl_3$–MeOH, 80:1); 114 mg (34%) of a white solid; mp 200–208 °C; $[\alpha]_D^{22} = +29.8$ (c 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.06, 1.12, 1.12 (9H, 3s, 1:1:1, 3 × Me); 1.75–2.03 (4H, m, 2 × CH_2); 2.40–3.30 (3H, s, BH_3); 2.56 (1H, t, $J = 3.8$ Hz, H–C(4)); 4.49 (1H, dd, $J = 1.1$; 4.5 Hz, H–C(3)); 7.96–8.17 (3H, m, H–C(7′), H–C(8′), H–C(9′)); 8.78 (1H, s, H–C(6′)); 9.68 (1H, d, $J = 8.3$ Hz, H–C(10′)). ^{13}C NMR (DMSO-d_6): δ 10.4, 19.8, 20.0, 22.3, 30.0, 46.3, 46.8, 47.8, 59.1, 121.2, 125.6, 127.1, 130.2, 133.6, 135.3, 140.1, 146.8, 151.1, 212.2. (Found: 67.99; H, 7.11; N, 17.00. $C_{19}H_{23}BN_4O$ requires: C, 68.28; H, 6.94; N, 16.76.) ν_{max} (KBr) 2963, 2417 (B–H), 2352 (B–H), 2300 (B–H), 2256 (B–H), 1754 (C═O), 1531, 1459, 1164 cm^{-1}.

5.5.5. (1*R*,4*R*,5*R*)-4-(6-Phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[2.2.1]octan-3-one-1′-borane 10a. Prepared from **2a** (362 mg, 1 mmol, 92% de); 275 mg (73%) of a white solid; mp 191–195 °C; $[\alpha]_D^{22} = -38.2$ (c 0.22, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.12, 1.34, 1.42 (9H, 3s, 1:1:1, 3 × Me); 1.88–2.00, 2.04–2.16 (3H, 2m, 1:2, 3H of CH_2); 2.63 (3H, br s, BH_3); 2.37–2.47 (2H, m, 1H of CH_2, H–C(5)); 5.04 (1H, dd, $J = 1.9$; 4.1 Hz, H–C(4)); 7.55–7.63 (3H, m, 3H of Ph); 7.89 (1H, d, $J = 9.8$ Hz, H–C(7′)); 7.94–7.98 (2H, m, 2H of Ph); 8.50 (1H, d, $J = 9.8$ Hz, H–C(8′)). ^{13}C NMR (DMSO-d_6): δ 18.2, 18.9, 23.3, 24.3, 37.3, 43.2, 45.3, 95.6, 123.8, 125.5, 128.5, 130.3, 132.6, 133.8, 141.3, 146.8, 155.3, 162.7, 167.7. (Found: C, 65.02; H, 6.65; N, 14.58. $C_{21}H_{25}BN_4O_2$ requires: C, 67.03; H, 6.70; N, 14.89.) ν_{max} (KBr) 3106, 2974, 2383 (B–H), 2267 (B–H), 1732 (C═O), 1530, 1481, 1445, 1385, 1364, 1341, 1267, 1221, 1149, 1092, 1060 cm^{-1}.

5.5.6. (1*R*,4*R*,5*R*)-4-(6-Chloro[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[2.2.1]octan-3-one-1′-borane 10b. Prepared from **2b** (320 mg, 1 mmol, 90% de); 178 mg (53%) of a white solid; mp 208–222 °C; $[\alpha]_D^{22} = -44.6$ (c 0.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.13, 1.32, 1.41 (9H, 3s, 1:1:1, 3 × Me); 2.50 (3H, br s, BH_3); 1.93–2.49 (5H, m, 4H of CH_2; H–C(5)); 4.92 (1H, dd, $J = 1.9$; 4.1 Hz, H–C(4)); 7.45 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.44 (1H, d, $J = 9.4$ Hz, H–C(8′)). ^{13}C NMR (DMSO-d_6): δ 18.1, 18.8, 23.2, 24.2, 37.2, 42.9, 45.3, 47.2, 95.6, 125.7, 128.5, 141.1, 146.3, 151.8, 167.3. (Found: C, 53.89; H, 6.01; N, 16.59. $C_{15}H_{20}BClN_4O_2$ requires: C, 53.84; H, 6.02; N, 16.74.) ν_{max} (KBr) 3084, 2973, 2379 (B–H), 2268 (B–H), 1731 (C═O), 1523, 1481, 1384, 1345, 1276, 1242, 1222, 1145, 1091, 1060, 1015, 958 cm^{-1}.

5.6. Reductions of 1a,1b,1f and 1g. General procedure for the preparation of (1*R*,2*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-ols 8a,8b,8f and 8g

Under argon, BF_3–Et_2O (0.251 ml, 2 mmol) was added to a cooled (0 °C) solution of compounds **1a**,**1b**,**1f** and **1g** (1 mmol) in anhydrous dichloromethane (10 ml) and the mixture stirred at 0 °C for 1 h. Then BH_3–Me_2S (0.095 ml, 1 mmol) was added and the mixture stirred at 0 °C for 1 h and at rt for 24 h. Methanol (3 ml) was added and the reaction mixture stirred at rt for 1 h. Volatile components were evaporated in vacuo, and the residue purified by CC on neutral alumina ($CHCl_3$–MeOH, 40:1). Fractions containing the product were combined and evaporated in vacuo. The residue was purified by MPLC on silica gel ($CHCl_3$–MeOH, 20:1). Fractions containing the product were combined and evaporated in vacuo to give compounds **8a**,**8b**,**8f** and **8g**. The following compounds were prepared in this manner:

5.6.1. (1*R*,2*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-ol 8a. Prepared from **1a** (346 mg, 1 mmol, 84% de); 216 mg (62%) of a white solid; mp 100–107 °C; $[\alpha]_D^{21} = +71.8$ (*c* 0.30, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 0.90, 0.93 (6H, 2s, 1:1, 2 × Me); 1.13–1.21 (2H, m, CH_2); 1.26 (3H, s, Me); 1.34–1.42, 1.49–1.59 (2H, 2m, 1:1, CH_2); 2.22 (1H, t, $J = 4.1$ Hz, H–C(4)); 3.86 (1H, dt, $J = 1.9$; 4.1 Hz, H–C(3)); 4.46 (1H, t, $J = 4.5$ Hz, H–C(2)); 5.21 (1H, d, $J = 4.9$ Hz, OH); 7.60–7.64 (3H, m, 3H of Ph); 7.92 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.09–8.12 (2H, m, 2H of Ph); 8.41 (1H, d, $J = 9.8$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 11.9, 20.3, 21.0, 22.4, 34.6, 47.5, 48.5, 48.7, 49.9, 81.8, 119.6, 125.5, 127.6, 129.7, 131.3, 134.9, 144.3, 151.9, 153.8. *m*/*z* (EI) = 348 (M^+). *m*/*z* (HRMS) Found: 348.196003 (M^+); $C_{21}H_{24}N_4O$ requires: 348.195012. (Found: C, 71.44; H, 7.14; N, 15.80. $C_{21}H_{24}N_4O$ requires: C, 72.93; H, 6.94; N, 16.08.) ν_{max} (KBr) 3392, 2953, 1546, 1476, 1440, 1390, 1341, 1186, 1072, 1002, 770 cm^{-1}.

5.6.2. (1*R*,2*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-ol 8b. Prepared from **1b** (304 mg, 1 mmol, 94% de); 175 mg (57%) of a white solid; mp 215–223 °C; $[\alpha]_D^{21} = +120.5$ (*c* 0.22, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 0.78–0.85 (1H, m, 1H of CH_2); 0.88, 0.91 (6H, 2s, 1:1, 2 × Me); 1.10–1.23 (1H, m, 1H of CH_2); 1.21 (3H, s, Me); 1.32–1.41, 1.48–1.57 (2H, 2m, 1:1, CH_2); 2.11 (1H, t, $J = 4.1$ Hz, H–C(4)); 3.68 (1H, dt, $J = 1.9$; 4.1 Hz, H–C(3)); 4.38 (1H, t, $J = 4.5$ Hz, H–C(2)); 5.22 (1H, d, $J = 4.5$ Hz, OH); 7.46 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.42 (1H, d, $J = 9.8$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 11.9, 20.2, 21.0, 22.3, 34.3, 47.1, 48.3, 48.9, 49.9, 81.6, 122.2, 126.7, 143.5, 149.3, 151.8. *m*/*z* (EI) = 306 (M^+). *m*/*z* (HRMS) Found: 306.125230 (M^+); $C_{15}H_{19}ClN_4O$ requires: 306.124739. (Found: C, 58.53; H, 6.38; N, 18.39. $C_{15}H_{19}ClN_4O$ requires: C, 58.72; H, 6.24; N, 18.26.) ν_{max} (KBr) 3262, 2961, 1529, 1502, 1466, 1395, 1332, 1147, 1080, 1068, 1002 cm^{-1}.

5.6.3. (1*R*,2*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-ol 8f. Prepared from **1f** (269 mg, 1 mmol, 68% de); 157 mg (58%) of a white solid; mp 277–282 °C; $[\alpha]_D^{21} = +126.5$ (*c* 0.16, $CHCl_3$–MeOH, 1:5). ^{1}H NMR (DMSO-d_6): δ 0.77–0.94 (1H, m, 1H of CH_2); 0.88, 0.90 (6H, 2s, 1:1, 2 × Me); 1.07–1.15 (1H, m, 1H of CH_2); 1.24 (3H, s, Me);1.31–1.39, 1.45–1.54 (2H, 2m, 1:1, CH_2); 2.14 (1H, t, $J = 4.1$ Hz, H–C(4)); 3.61 (1H, dt, $J = 1.9$; 4.1 Hz, H–C(3)); 4.38 (1H, t, $J = 4.5$ Hz, H–C(2)); 5.25 (1H, d, $J = 4.5$ Hz, OH); 6.93 (1H, dt, $J = 1.1$; 6.8 Hz, H–C(6′)); 7.33 (1H, ddd, $J = 1.1$; 6.8; 9.4 Hz, H–C(7′)); 7.69–7.74 (1H, m, H–C(8′)); 8.44–8.48 (1H, m, H–C(5′)). ^{13}C NMR (DMSO-d_6): δ 12.7, 20.6, 21.7, 22.2, 34.3, 47.0, 48.0, 49.0, 49.8, 80.7, 114.0, 116.2, 124.6, 128.1, 150.4. *m*/*z* (EI) = 271 (M^+). *m*/*z* (HRMS) Found: 271.169350 (M^+); $C_{16}H_{21}N_3O$ requires: 271.168463. (Found: C, 71.14; H, 7.80; N, 15.30. $C_{16}H_{21}N_3O$ requires: C, 70.82; H, 7.80; N, 15.49.) ν_{max} (KBr) 3246, 2955, 1636, 1512, 1495, 1388, 1367, 1342, 1185, 1077, 1060 cm^{-1}.

5.6.4. (1*R*,2*R*,3*R*,4*R*)-3-([1,2,4]Triazolo[3,4-*a*]phthalazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 8g. Prepared from **1g** (320 mg, 1 mmol, 92% de); 126 mg (39%) of a white solid; mp 260–290 °C; $[\alpha]_D^{21} = +110.0$ (*c* 0.16, $CHCl_3$–MeOH, 1:5). ^{1}H NMR (DMSO-d_6): δ 0.89, 0.92 (6H, 2s, 1:1, 2 × Me); 1.13–1.24 (2H, m, CH_2); 1.23 (3H, s, Me); 1.32–1.41, 1.48–1.56 (2H, 2m, 1:1, CH_2); 2.16 (1H, t, $J = 4.1$ Hz, H–C(4)); 3.78 (1H, dt, $J = 1.9$; 4.1 Hz, H–C(3)); 4.43 (1H, t, $J = 4.5$ Hz, H–C(2)); 5.22 (1H, d, $J = 4.5$ Hz, OH); 7.90–7.95, 8.03–8.08 (2H, 2m, 1:1, H–C(8′), H–C(9′)); 8.21 (1H, d, $J = 7.5$ Hz, H–C(10′)); 8.49 (1H, dd, $J = 0.7$; 7.9 Hz, H–C(7′)); 9.04 (1H, s, H–C(6′)). *m*/*z* (EI) = 322 (M^+). *m*/*z* (HRMS) Found: 322.180250 (M^+); $C_{19}H_{22}N_4O$ requires: 322.179362. (Found: C, 70.93; H, 7.07; N, 17.37. $C_{19}H_{22}N_4O$ requires: C, 70.78; H, 6.88; N, 17.38.) ν_{max} (KBr) 3256, 2957, 1625, 1527, 1456, 1390, 1355, 1264, 1229, 1187, 1075 cm^{-1}.

5.7. Reactions of isoborneols 8a,8g with borane–methylsulfide. General procedure for the preparation of (1*R*,2*R*,3*R*,4*R*)-3-([1,2,4]triazolo[4,3-*x*]pyridazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol-1′-boranes 9a,9g

Under argon, borane–methylsulfide (BMS, 0.095 ml, 1 mmol) was added to a solution of compound **8a** and **g** (1 mmol) in anhydrous dichloromethane (7 ml) and the mixture was stirred at rt or at reflux for 2–24 h. Volatile components were evaporated in vacuo and the residue purified by CC on silica gel. Fractions containing the product were combined and evaporated in vacuo to give **9a** and **9g**. The following compounds were prepared in this manner.

5.7.1. (1*R*,2*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-ol-1′-borane 9a. Prepared from **8a** (348 mg, 1 mmol); reflux for 2 h; CC (EtOAc–hexanes, 1:1). Yield: 84 mg (23%) of a white solid; mp 231–235 °C; $[\alpha]_D^{19} = +115.4$ (*c* 0.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.97, 1.02 (6H, 2s, 1:1, 2 × Me); 1.04–1.12, 1.26–1.34 (2H, 2m, 1:1, CH_2); 1.31 (3H, s, Me); 1.49–1.67 (2H, m, CH_2); 2.37 (1H, d, $J = 4.2$ Hz, OH); 2.42 (1H, t, $J = 3.8$ Hz, H–C(4)); 2.05–3.15 (3H, br s, BH_3); 4.00 (1H, dt, $J = 1.9$; 4.2 Hz, H–C(3)); 4.57 (1H, t, $J = 4.2$ Hz, H–C(2)); 7.57–7.64 (3H, m, 3H of Ph); 7.85 (1H, d, $J = 9.8$ Hz, H–C(7′)); 7.95–7.99 (2H, m, 2H of Ph); 8.48 (1H, d, $J = 9.8$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 11.8, 20.2, 21.0, 22.3, 34.1, 47.1, 48.5, 49.0, 49.9, 81.1, 123.3, 123.8, 127.9, 129.9, 132.2, 133.5, 140.8, 151.0, 155.5. (Found: C, 69.40; H, 7.61; N, 15.53. $C_{21}H_{27}BN_4O$ requires: C, 69.62; H, 7.51; N, 15.47.) ν_{max} (KBr) 3515, 2952, 2372 (B–H), 2269 (B–H), 1561, 1529, 1485, 1444, 1390, 1365, 1168, 1107, 1071, 1001 cm^{-1}.

5.7.2. (1*R*,3*R*,4*R*)-3-([1,2,4]Triazolo[3,4-*a*]phthalazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol-1′-borane 9g. Prepared from **8g** (322 mg, 1 mmol); stirring at rt for 24 h; CC ($CHCl_3$–MeOH, 80:1). Ninety-one milligrammes (27%) of a white solid; mp 205–225 °C; $[\alpha]_D^{19} = +103.3$ (*c* 0.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.96, 1.02 (6H, 2s, 1:1, 2 × Me); 1.05–1.12, 1.26–1.34 (2H, 2m, 1:1, CH_2); 1.30 (3H, s, Me); 1.47–1.66 (2H,

m, CH_2); 2.39 (1H, t, $J = 3.8$ Hz, H–C(4)); 2.51 (1H, d, $J = 3.0$ Hz, OH); 2.30–3.30 (3H, br s, BH_3); 3.95 (1H, dt, $J = 1.9$; 4.1 Hz, H–C(3)); 4.57 (1H, br t, $J = 3.0$ Hz, H–C(2)); 7.95–8.13 (3H, m, H–C(7′), H–C(8′), H–C(9′)); 8.79 (1H, s, H–C(6′)); 9.61 (1H, br d, $J = 8.3$ Hz, H–C(10′)). (Found: C, 68.16; H, 7.75; N, 16.49. $C_{19}H_{25}BN_4O$ requires: C, 67.87; H, 7.49; N, 16.66.) ν_{max} (KBr) 3483, 2951, 2373 (B–H), 2346 (B–H), 1534, 1459, 1400, 1320, 1159, 1072 cm^{-1}.

5.8. X-ray structure analysis for compounds 4b, 7a, 8b, 9a and 10a

Single crystal X-ray diffraction data of compounds **4b**, **7a**, **8b**, **9a** and **10a** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[29] DENZO and SCALEPACK[30] were used for indexing and scaling of the data. The structure was solved by means of SIR97.[31] Refinement was done using Xtal3.4[32] program package and the crystallographic plot was prepared by ORTEP III.[33] Crystal structure was refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[34] weighting scheme was used.

The crystallographic data for compounds **4b**, **7a**, **8b**, **9a** and **10a** have been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: CCDC 286428–286432. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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