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Synthesis of (1*R*,4*E*,5*S*)-4-{[(*E*)-(azinyl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones 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

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Abstract—4-[(Heteroaryldiazenyl)methylidene] and 4-([1,2,4]triazolo[4,3-*x*]azin-3-yl) substituted (1*R*,5*R*)-4-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **6**/**6′** and **7**/**7′** were obtained in a one-pot transformation of the enamino lactone **2** with hydrazinoazines **3a**–**g** followed by oxidation of the intermediate mixture of isomeric enehydrazines **4**/**4′** and hydrazones **5**/**5′** with lead tetraacetate. The oxidation selectivity was dependent on the ratio of isomeric intermediates **4**/**4′** and **5**/**5′**. Treatment of **7b** with lead tetraacetate led to α-acetoxylated compound **11**, while bromination of **9b** afforded a 1:1 mixture of α-bromination products **12** and **12′**, which were separated by medium pressure liquid chromatography (MPLC). The structures of intermediates and products were confirmed by NMR and X-ray diffraction.

1. Introduction

(+)-Camphor and its derivatives have found widespread use in organic synthesis, especially in asymmetric applications. They belong amongst the most frequently used chiral pool starting materials for building blocks, chiral ligands and 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] Usually, [1,2,4]triazolo[4,3-*x*]azines are prepared by treatment of a hydrazinoazine with an aldehyde to give the intermediate hydrazone, which is then oxidatively cyclised into the corresponding [1,2,4]triazolo[4,3-*x*]azine. Bromine and lead tetraacetate are most frequently employed for the oxidation of (*N*-azinyl)aldohydrazones into [1,2,4]triazolo[4,3-*x*]-azines.[7–9] 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, derived from α-amino acids,[10,11] sugars[12–14] and (+)-camphor[15] as starting materials.[16–18]

Azo compounds (diazenes) also represent an important group of organic compounds, which found versatile applications, for example, as azo dyes, as reagents in organic synthesis, in the complexation of metal ions and in biological applications.[19–23]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates and their analogues have been prepared and used as versatile reagents in the synthesis of various heterocyclic systems and functionalised heterocycles, such as heterocyclic compounds containing α-amino acid, dipeptide, β-amino alcohol, α-hydroxy acid, (+)-camphor and related structural elements.[16–18,24–27] Within this context, we have previously reported the preparation and synthetic utilisation of two (+)-camphor derived enaminones, (1*R*,3*E*,4*S*)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **1**[15,28] and (1*R*,4*E*,5*S*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one

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2.[28–31] With respect to this, a one-pot stereoselective synthesis of [1,2,4]triazolo[4,3-*x*]azin-3yl substituted (+)-camphors was developed, starting from **1** and α-hydrazinoazines **3** followed by oxidative ring closure of the intermediate hydrazones with methanolic bromine.[15] In continuation of this work, we studied the formation, isomerisation and oxidation of enehydrazines **4**/**4′** and hydrazones **5**/**5′**, formed upon treatment of the enamino lactone **2** with α-hydrazinoazines **3**. Herein, we report the results of this study, which showed, that selectivity is controlled mostly by the equilibrium between the enehydrazine and the hydrazone tautomeric form of the intermediates.

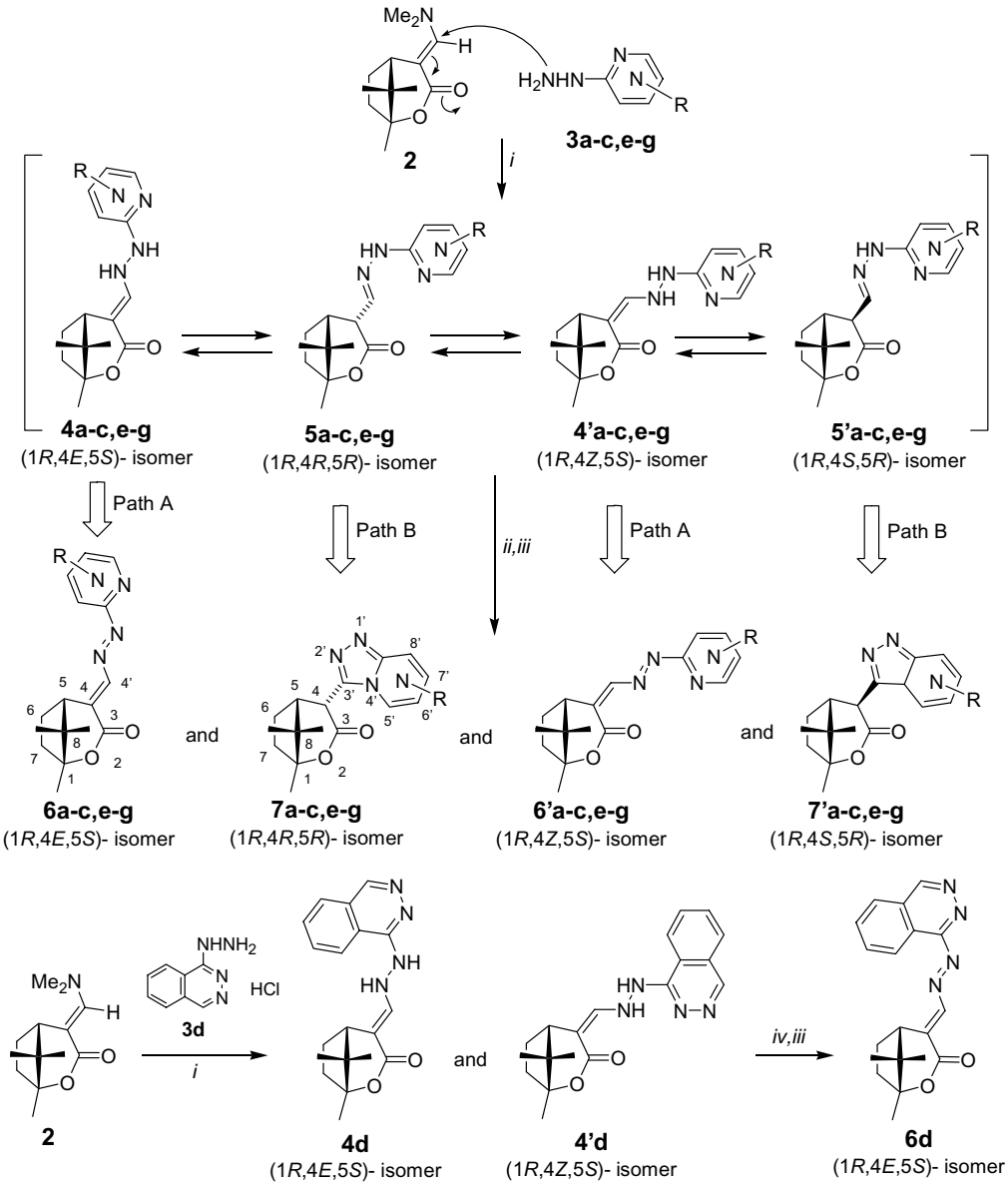
2. Results and discussion

The starting compound **2** was prepared in two steps from (1*R*)-(+)-camphor.[29,32] Acid-catalysed treatment of **2** with α-hydrazinoazines **3a**–**c**,**e**–**g**, having the hydrazino group attached at the position adjacent to the ring nitrogen atom, in methanol at rt followed by oxidation of intermediates **4**/**4′a**–**c**,**e**–**g** and **5**/**5′a**–**c**,**e**–**g** with lead tetraacetate afforded two types of products, (1*R*,4*E*,5*S*)-4-{[(azinyl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **6a**–**c**,**e**–**g** in 10–54% yields 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 **7a**–**c**,**f**,**g** in 4–52% yields and in 54–92% de. Similarly, treatment of **2** with 1-hydrazinophthalazine **3d** afforded a mixture of isomeric enehydrazines **4d** and **4′d** in 73% yield. Further oxidation of **4**/**4′d** with lead tetraacetate in dichloromethane gave, selectively, diazene **6d** in 84% yield. The reaction mechanism can be explained according to: (a) the general reactivity of 3-(dimethylamino)propenoates with amines and hydrazines,[7–9] (b) the literaturely known oxidations of nitrogen compounds with $Pb(OAc)_4$[33,34] and (c) the previously observed formation of [1,2,4]triazolo[4,3-*x*]-azines from *N*-azinylhydrazones.[6–9] Substitution of the dimethylamino group in enamino lactone **2** with hydrazinoazine **3** gives a mixture of isomeric enehydrazines **4** and **4′**, which, in solution, are in equilibrium with hydrazones **5** and **5′**. Subsequent oxidation of the intermediates **4**, **4′**, **5** and **5′** can take place in two different ways, depending on the tautomeric form of the intermediate: (a) the enehydrazines **4** and **4′** are oxidised into diazenes **6** and **6′** (Path A), whilst (b) hydrazones **5** and **5′** are oxidised into [1,2,4]triazolo[4,3-*x*]azines **7** and **7′** (Path B). This proposed reaction mechanism is supported by the isolation of the intermediates, obtained as mixtures of isomeric compounds **4a**–**d**,**f**, **4′a**–**d**,**f**, **5a**–**d**,**f** and **5′a**–**d**,**f** (Scheme 1).

Unlike previously published selective transformations of enamino ketone **1**,[15] the transformations of analogous enamino lactone **2** were not selective. Lead tetraacetate was used as the oxidizing agent instead of bromine, since initially attempted oxidations with bromine afforded complex mixtures of inseparable products. Generally, diazenes **6** were obtained as the major products, while [1,2,4]triazolo[4,3-*x*]azines **7** were obtained as the minor products. Only in the reactions of **2** with hydrazinopyridazines **3b**,**c** followed by oxidation, did the predominant formation of **7b**,**c** take place. The ratios between the enehydrazine **4**/**4′a**–**d**,**f** and the hydrazone tautomeric forms **5**/**5′a**–**d**,**f** were of the same values as the ratios between the products, diazenes **6**/**6′a**–**d**,**f** and [1,2,4]triazolo[4,3-*x*]azines **7**/**7′a**–**d**,**f**, respectively. For example, in the reactions of **2** with hydrazines **3a**,**d**,**f**, where the enehydrazines **4**/**4′a**,**d**,**f** were the major intermediates, subsequent oxidation gave diazenes **6a**,**d**,**f** as the major products. Conversely, in the reaction of **2** with hydrazinopyridazines **3b**,**c**, where hydrazones **5b**,**c** were the predominant intermediates, oxidation led to the corresponding [1,2,4]triazolo[4,3-*b*]pyridazines **7b**,**c** as the major products. Diazenes **6a**,**c**–**g** were isolated as pure (*E*)-isomers, while diazene **6b** was obtained as a mixture of the major (*E*)-isomer **6b** and the minor (*Z*)-isomer **6′b** in a ratio of 64:36, respectively. On the other hand, all [1,2,4]triazolo[4,3-*x*]azines **7**/**7′a**–**c**,**f**,**g** were obtained as mixtures of the major (1*R*,4*R*,5*R*)-isomers **7a**–**c**,**f**,**g** and the minor (1*R*,4*S*,5*R*)-isomers **7′a**–**c**,**f**,**g**. Crystallisation of isomeric mixtures **6**/**6′b** and **7**/**7′c**,**g** afforded isomerically pure compounds **6b**, **7c** and **7g** (Scheme 1, Table 1).

These results prompted us to reinvestigate the previously reported oxidation of hydrazones **8b**,**c** and **8′b**,**c**, derived from enamino ketone **1** and hydrazinopyridazines **3b**,**c**. The previously reported oxidations of **8**/**8′b**,**c** were carried out with bromine in methanol and furnished compounds **9**/**9′b**,**c** along with several by-products, which could not be isolated and were removed during isolation, that is by chromatographic purification.[15] Since we were interested in the influence of oxidising agent (Br_2 and $Pb(OAc)_4$) on the outcome of the reaction, oxidations of the previously reported hydrazones **8**/**8′b**,**c**[15] were repeated with lead tetraacetate in dichloromethane. These two experiments afforded compounds **9b**,**c** as the major products in almost identical yields and de as previously described oxidations with bromine.[15] However, since much less by-products were formed, we were also able to isolate and characterise diazenes **10**/**10′** as the minor products. Compounds **10**/**10′b** and **10**/**10′c** were isolated as ~3:7 mixtures of the major (3*Z*)-isomers **10′b**,**c** and the minor (3*E*)-isomers **10b**,**c** in 6% and 9% yield, respectively (Scheme 2).

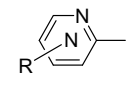
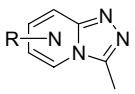
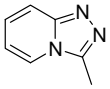
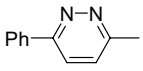
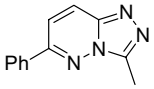
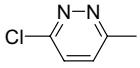
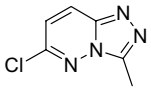
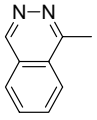
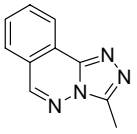
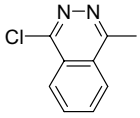
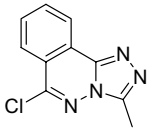
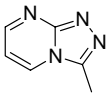
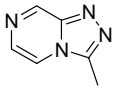
The oxidation of a mixture of hydrazones **5b** and **5′b** and the (*Z*)-enehydrazine **4′b** in dichloromethane at rt, followed by chromatographic separation, afforded **7**/**7′b** in 54% yield and 88% de, **6′b** in 13% yield and (1*R*,4*R*,5*S*)-3-oxo-4-(6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]oct-4-yl acetate **11** in 6% yield. Compound **11** was a product of oxidation of **7**/**7′b** with lead tetraacetate. This was confirmed by another experiment, where compound **7b** was treated with one equivalent of lead tetraacetate in dichloromethane at rt to give a mixture of isomeric α-acetoxylated compounds **11** and **11′** in a ratio of 73:27 in 87% yield. Similarly, bromination of **9b** afforded a 1:1 mixture of α-bromination products **12** and **12′**, which were separated by medium pressure liquid chromatography (MPLC) (Scheme 3).



Scheme 1. Reagents and conditions: (i) MeOH, H_2SO_4 (1 equiv), rt or reflux; (ii) $Pb(OAc)_4$, MeOH, rt; (iii) chromatographic separation; (iv) $Pb(OAc)_4$, CH_2Cl_2, rt.

Oxidations of enehydrazines **4/4′a**,**c**,**e**–**g** in methanol, as well as the oxidation of enehydrazines **4/4′d** in dichloromethane were stereoselective and afforded the (4*E*)-diazenes **6a**,**c**–**g**, exclusively, regardless of the ratio between the isomeric (4*E*)-enehydrazines **4a**,**c**–**g** and (4*Z*)-enehydrazine **4′a**,**c**–**g**. Similarly, oxidation of enehydrazines **4/4′b** in methanol was selective, leading to a mixture of major (4*E*)-diazene **6b** and minor (4*Z*)-diazene **6′b** in a ratio of 64:36, respectively (Table 1). However, the (3*Z*)-diazenes **10′b**,**c** were formed as the major isomers in the oxidation of **8/8′b**,**c** in dichloromethane (cf. Scheme 2). Furthermore, only the (4*Z*)-diazene **6′b** was isolated upon oxidation of a mixture of **4′b**, **5b** and **5′b** in dichloromethane (cf. Scheme 3). It could be presumed that the configuration around the exocyclic C(4)=C(4′) double bond in diazenes **6** and **6′** depends on the equilibrium ratio between the intermediate enehydrazines **4** and **4′**, and the *E*/*Z*-isomerisation of diazenes **6**/**6′** in solution. However, since no *E*/*Z*-isomerisation was observed for compounds **6** and/or **6′** upon standing at rt for 7 days in $CDCl_3$ or DMSO-d_6 solution, it could be concluded, that the ratio between the isomeric diazenes **6** and **6′** is mostly dependent on the equilibrium ratio between the intermediate enehydrazines **4** and **4′**. The *E*/*Z*-isomerisation of enehydrazines **4** and **4′** in solution was observed by NMR. For example, the ratio between isomers **4a**:**4′a** was 5:95 in $CDCl_3$ solution and 63:37 in DMSO-d_6 solution. Similar solvent-dependent isomer composition was observed in the case of isomeric enehydrazines **4f** and **4′f** (**4f**:**4′f** = 9:91 in $CDCl_3$ and **4f**:**4′f** = 41:59 in DMSO-d_6). The favourisation of the (*Z*)-isomers in $CDCl_3$ can be explained by the intramolecular (3)C=*O*···*H*–N hydrogen bond, which stabilises sterically less favourable (4*Z*)-isomer **4′** in aprotic non-polar solvents, such as $CDCl_3$ and CH_2Cl_2. In DMSO-d_6, however, solvation and competitive

Table 1. Compounds **3**, **4/4′–7/7′**

Compound			Yield (%)			Ratio of isomers			de (%)[a]
	3–6	**7**	**4/4′/5/5′**	**6/6′**	**7/7′**	**4:4′:5:5′**	**6:6′**	**7:7′**	
3a–7a			91	50	11	3:59:31:7[b] 45:26:23:6[c]	100:0	84:16	68
3b–7b			63	10	52	0:17:71:12[b]	64:36	96:4	92
3c–7c			80	29	46	5:19:53:23[b]	100:0	95:5	90
3d–6d			73	84	0	87:13:0:0[c]	100:0	—	—
3e–6e			—	42	0	—	100:0	—	—
3f–7f			90	54	4	7:74:16:3[b] 41:59:0:0[c]	100:0	77:23	54
3g–7g			—	42	6	—	100:0	85:15	70

[a] De of **7** with respect to the minor isomer **7′**.
[b] In $CDCl_3$.
[c] In DMSO-d_6.

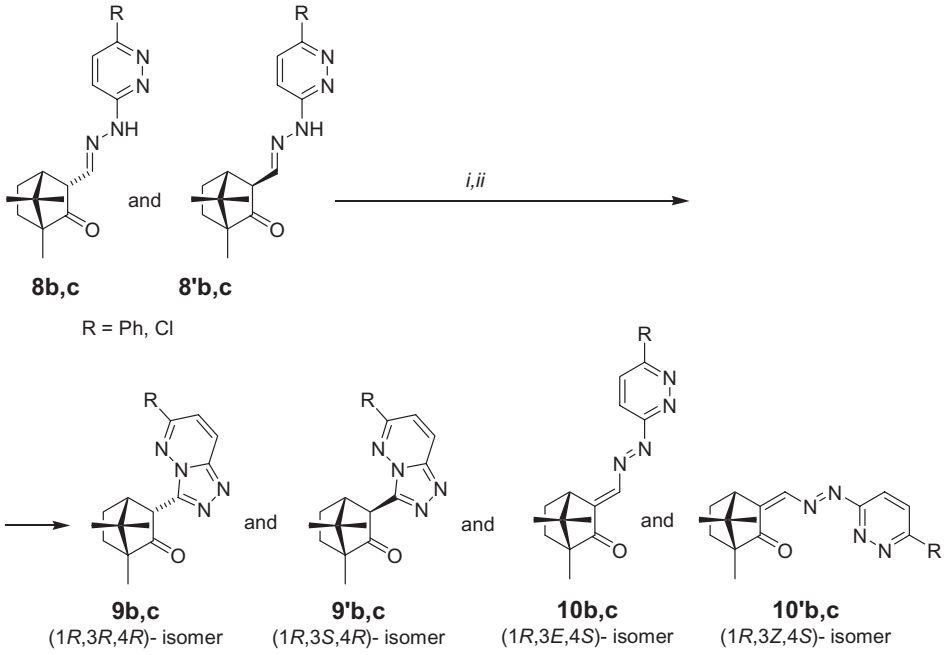
intermolecular $Me_2S{=}O\cdots H$–N hydrogen bond formation allows the isomerisation into sterically more favourable (4*E*)-isomer **4** (Scheme 4, Table 1).

The stereoselective formation of [1,2,4]triazolo[4,3-*x*]azines **7** can be explained according to the previously proposed explanation for stereoselective formation of their close analogues **14**.[15] In solution, epimers **7** and **7′** can equilibrate via the enol form **7″** and, consequently, the equilibrium would be shifted towards the less strained *endo*-isomers **7** (Scheme 4).

The stereoselectivity of the acetoxylation of **7b** was low, most probably due to the steric hindrance from both faces of the camphorolactone residue. The predominant formation of *endo*-isomer **11**, might be due to the preferential attack from the less hindered *endo*-face. Thus, intramolecular acetate transfer[35–37] is less hindered in the enol-lead triacetate intermediate **13** than in the conformer **13′**, where the acetate transfer is more hindered by the methyl group at position 8. On the other hand, bromination of **9b** exhibited no facial selectivity. Since facial differentiation in the (+)-camphor and related norbornane series is quite well documented in the literature,[38] the loss of selectivity in the case of the bromination of **9b** should be attributed to a very bulky 6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl residue at position 3, which equally hinders the approach of the bromine to the enol C=C double bond from the *exo*- and the *endo*-face of **9b** (Scheme 5).

3. Structure determination

The structures of all novel compounds **4/4′/5/5′a–d,f**, **6a,c–g**, **6/6′b**, **7/7′a–c,f,g**, **10/10′b,c**, **11/11′**, **12** and **12′** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, MS) and by elemental analyses for C, H and N. Compounds **6a–g**, **6′b**, **7c,g**, **11**, **12** and **12′** were isolated and characterised in isomerically pure forms. Intermediates **4/4′/5/5′a–d,f** were characterised as mixtures of isomeric (1*R*,4*E*,5*S*)-enehydrazines **4**, (1*R*,4*Z*,5*S*)-enehydrazines **4′**, (1*R*,4*R*,5*R*)-hydrazones **5** and (1*R*,4*S*,5*R*)-hydrazones **5′**. [1,2,4]Triazolo[4,3-*x*]azine derivatives **7a,b,f** were characterised as mixtures of diastereomers. Diazenes **10/10′b,c** were characterised as the *E*/*Z*-mixtures of isomers. Compounds **4/4′/5/**



Compound	R	Yield (%)		Ratio of isomers[a]		de (%)[b]
		9/9'	**10/10'**	**9:9'**	**10:10'**	**9**
8b–10b	Ph	59	6	93:7	30:70	86
8c–10c	Cl	62	9	96:4	31:69	92

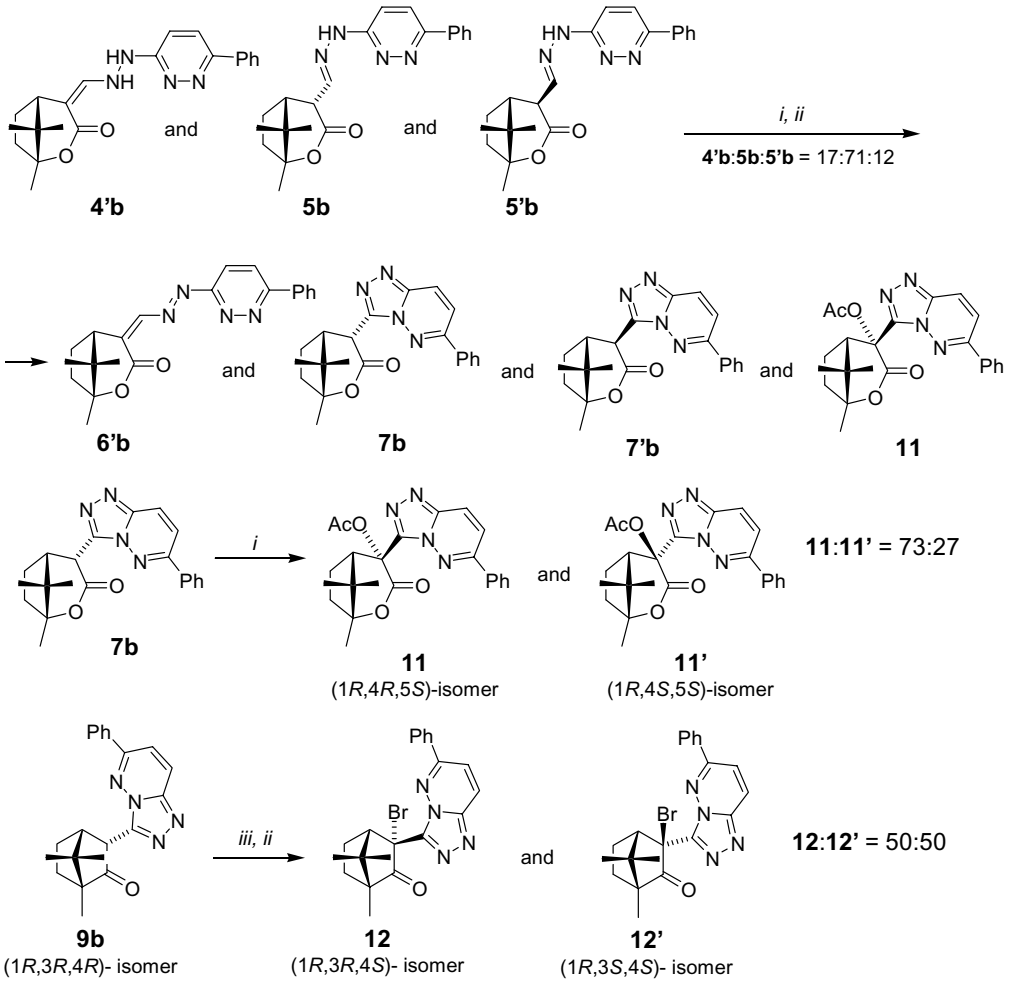
[a] In $CDCl_3$.
[b] de of **9** with respect to the minor isomer **9'**.

Scheme 2. Reagents and conditions: (i) $Pb(OAc)_4$, CH_2Cl_2, rt; (ii) chromatographic separation.

5′a,**f**, **7**/**7′b** and **10**/**10′b** were not prepared in analytically pure form. The identity of **7b** was confirmed by ^{13}C NMR and EI-HRMS, while the identities of **4**/**4′**/**5**/**5′a**,**f** and **10**/**10′b** were established by EI-HRMS.

The configuration around the exocyclic C=C double bond in compounds **4d**, **4′d** and **4′f** was determined by NMR on the basis of long-range coupling constants ($^3J_{C-H}$) between the methylidene proton (*H*–C(4′)) and the carbonyl carbon atom (O=*C*(3)), measured from the antiphase splitting of cross peaks in the HMBC spectrum. Generally, the magnitude of the coupling constant, $^3J_{C-H}$, for nuclei with a *cis*-configuration around the C=C double bond are smaller (2–6 Hz) than those for *trans*-oriented nuclei (8–12 Hz).[27,39–49] In compound **4d**, the magnitude of the coupling constant ($^3J_{C-H}$ = 5.0 Hz) meant there was an (*E*)-configuration around the exocyclic C=C double bond. Similarly, a (*Z*)-configuration was established for compound **4′d** ($^3J_{C-H}$ = 11.5 Hz) and compound **4′f** ($^3J_{C-H}$ = 12.0 Hz) (Fig. 1). Unfortunately, attempts to establish a configuration around the exocyclic C=C double bond in enehydrazines **4**/**4′a**–**d**,**f** by NOESY spectroscopy failed. Consequently, the configurations at position 4 in compounds **4**/**4′a**, **4′b**, **4**/**4′c** and **4f** were established by a correlation of chemical shifts δ for *H*–C(4′), and *H*–N–C(4′) in the ^1H NMR spectra taken in DMSO-d_6. Signals for *H*–C(4′) of the (*Z*)-isomers **4′a**,**d**,**f** appeared at higher fields (6.69–7.08 ppm) than signals of the corresponding (*E*)-isomers **4a**,**d**,**f** (7.02–7.51 ppm). On the other hand, signals for *H*–N–C(4′) of the (*Z*)-isomers **4′a**,**d**,**f** appeared at lower fields (8.95–10.01 ppm) than those for the (*E*)-isomers **4a**,**d**,**f** (7.34–8.70 ppm). The downfield shift of the N*H* proton in the (*Z*)-isomers **4′a**,**d**,**f** could be rationalised by the intramolecular hydrogen bond, N–H···O=C(3). Similarly, the downfield shift of the *H*–C(4′) signal in the case of the (*E*)-isomers **4a**,**d**,**f** might be explained by the effect of the ring carbonyl group. These characteristic chemical shifts are also in agreement with the reported values for analogous compounds (Fig. 1, Table 2).[29,30]

The configuration around the exocyclic C=C double bond in azo compounds **6′b** and **10′b**,**c** was established by NOESY spectroscopy. NOE between *H*–C(5) and *H*–C(4′) in compound **6′b** and **10′b**,**c** was in agreement with the (*Z*)-configuration, while absence of NOE between these two protons in isomers **6b** and **10b**,**c**



Scheme 3. Reagents and conditions: (i) $Pb(OAc)_4$, CH_2Cl_2, rt; (ii) chromatographic separation; (iii) Br_2 (2 equiv), CH_2Cl_2, reflux.

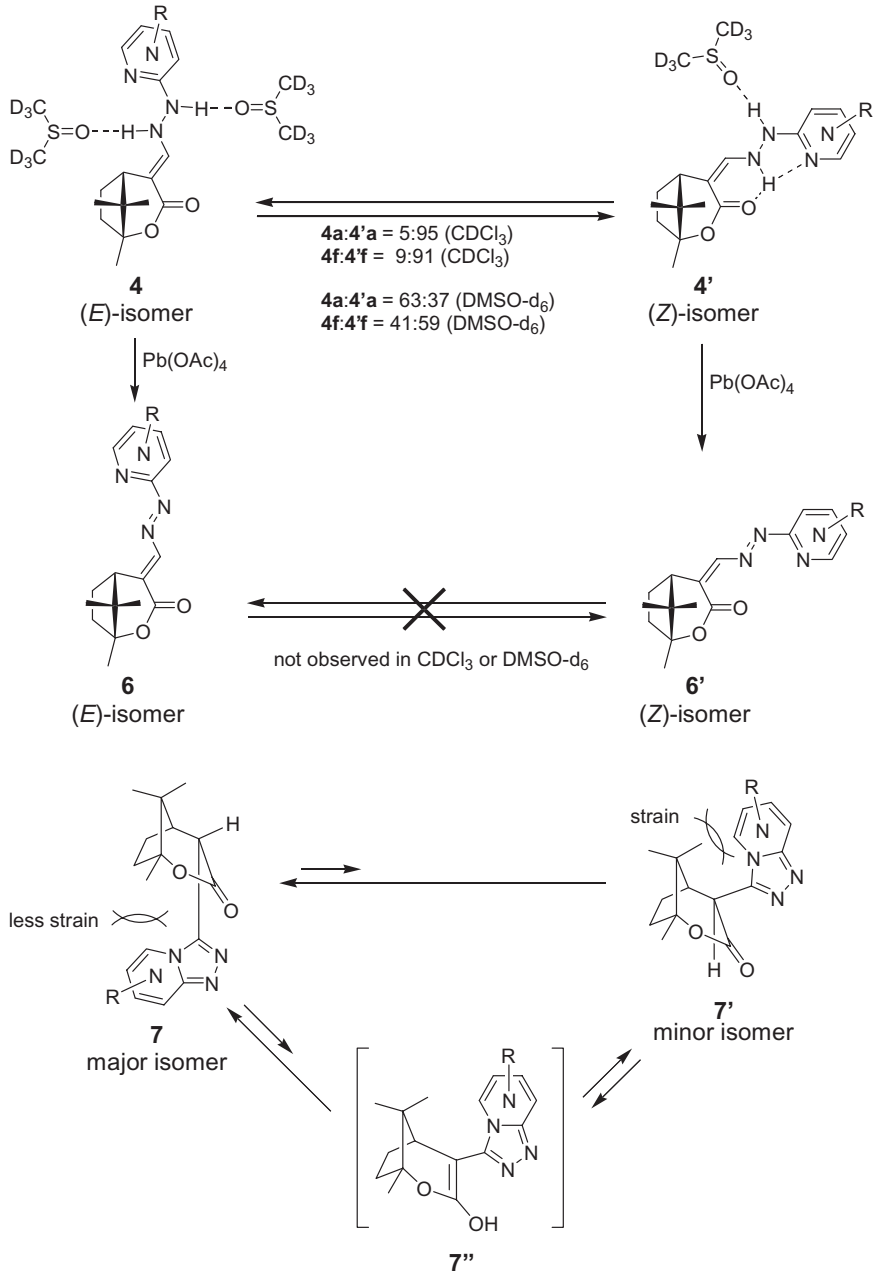
supported the (*E*)-configuration. The configuration around the exocyclic C=C double bond in compounds **6a**,**c**–**g** was established by a correlation of the chemical shifts for *H*–C(5) and *H*–C(4′). In the case of the (4*E*)-isomers **6a**–**g**, signals for *H*–C(5) appeared at lower field (3.98–4.27 ppm) than in the case of the (4*Z*)-isomer **6′b** (2.84 ppm). Similarly, signals for *H*–C(4′) of the (4*E*)-isomers **6a**–**g** appeared at lower field (8.09–8.18 ppm) than that of the (4*Z*)-isomer **6′b** (7.50 ppm) (Fig. 1, Table 2).

The configuration at position 4 in compounds **5a**–**c**,**f**, **5′a**–**c**,**f**, **7a**–**c**,**f**,**g** and **7′a**–**c**,**f**,**g** was determined by NMR on the basis of vicinal coupling constants, $^3J_{H4-H5}$. The coupling constant, $^3J_{H4-H5} = 3.4$–4.8 Hz, was observed in the case of the major *endo*-isomers **5a**–**c**,**f** and **7a**–**c**,**f**,**g**, while the coupling constant, $^3J_{H4-H5} \sim 0$ Hz, was characteristic for the minor *exo*-isomers **5′a**–**c**,**f** and **7′a**–**c**,**f**,**g**. Furthermore, a long-range coupling constant, $^3J_{H4-H6} \sim 2$ Hz, was observed in the case of the *endo*-isomers **7a**–**c**,**f**,**g**, while no such coupling between *H*–C(4) and *H*–C(6) was found for the *exo*-isomers **7′a**–**c**,**f**,**g**. These characteristic coupling constants are also in agreement with the values reported for analogous compounds (Fig. 1, Table 2).[15,31]

The structures of compounds **6c**, **11**, **12** and **12′** were determined by X-ray diffraction (Figs. 2–5).

4. Conclusion

In contrast to the previously reported selective one-pot 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,[15] analogous treatment of the enaminone **2** with hydrazinoazines **3a**–**f** followed by oxidation led to two types of products, diazenes **6** and [1,2,4]triazolo[4,3-*x*]azines **7**. The selectivity of oxidations was dependent on the ratio of isomeric intermediates **4**/**4′**:**5**/**5′**. Oxidations of intermediates with predominant enehydrazine form **4a**,**d**–**f** led to diazenes **6a**,**d**–**f**, while oxidations of intermediates with predominant hydrazone form **4b**,**c** led to [1,2,4]triazolo[4,3-*x*]azines **7b**,**c** as the major products. In addition, upon repeated oxidation of the closely analogous hydrazones **8**/**8′b**,**c**[15] with lead tetraacetate, small amounts of diazenes **10**/**10′b**,**c** were also formed and isolated. α-Acetoxylation of **7b** gave, selectively, the *endo*-isomer **11** in 46% de, while α-bromination of **9b** was not selective and furnished a 1:1 mixture of the α-bromination products **12** and **12′**, which were separated



Scheme 4.

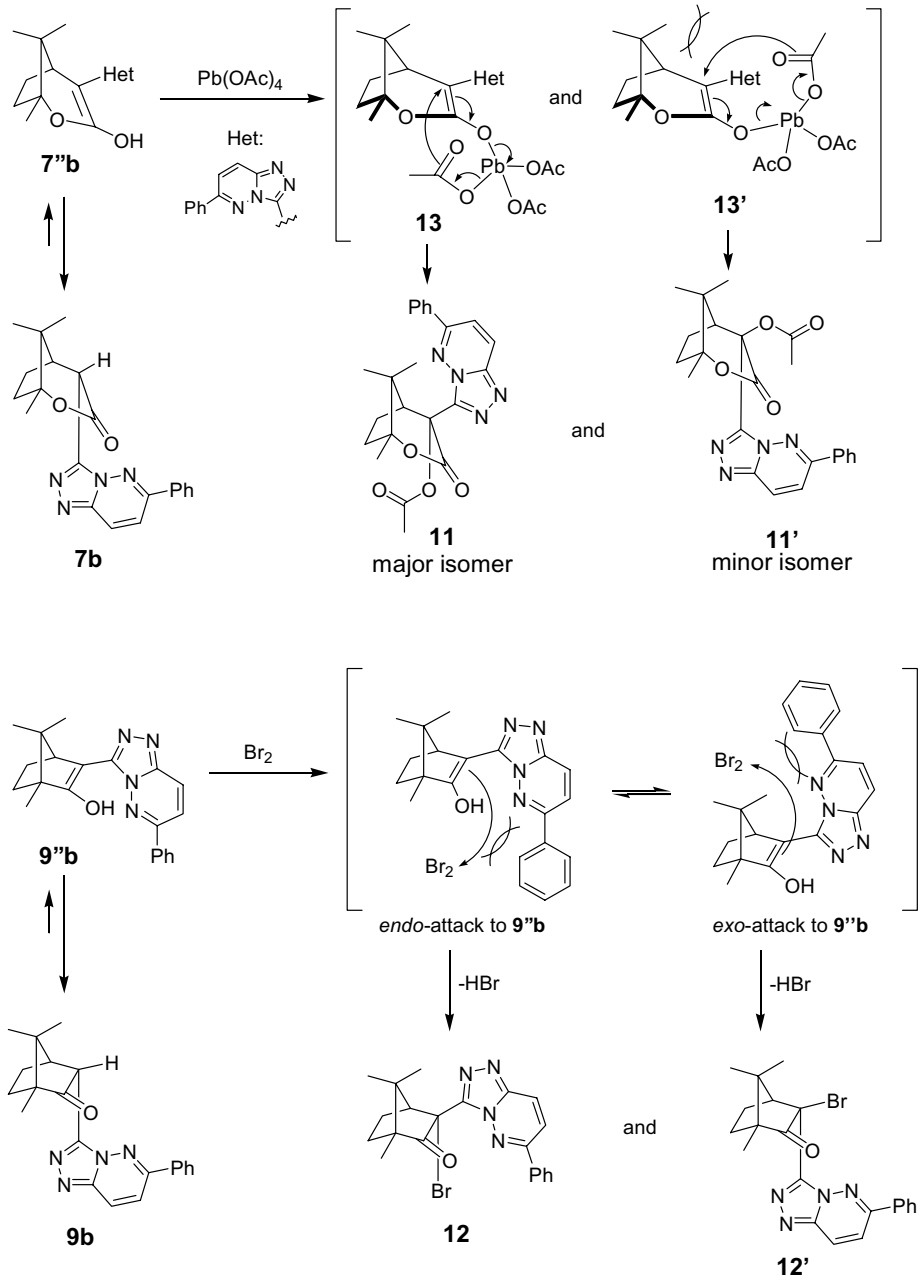
by MPLC. Poor selectivity of both α-substitution reactions indicate, that facial selectivity, which is typical for transformations of (+)-camphor related compounds, can be substantially diminished by a bulky substituent attached to the α-position with respect to the ring carbonyl group.

5. Experimental

5.1. 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 60, 0.015–0.035 mm); column dimensions (dry filled):

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



Scheme 5.

15×460 mm; backpressure: 10–15 bar; detection: UV 254 nm; sample amount: 100–150 mg of isomeric mixture per each run. The *Z*/*E*-ratio of isomers and de were determined by ^{1}H NMR.

Lead tetraacetate, 2-hydrazinopyridine **3a** and 1-hydrazinophthalazine **3d** hydrochloride are commercially available (Fluka AG). (1*R*,3*E*,4*S*)-3-[(Dimethylamino)-methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **1**,[15] and (1*R*,4*E*,5*S*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **2**,[29] 3-hydrazino-6-phenylpyridazine **3b**,[50] 6-chloro-3-hydrazinopyridazine **3c**,[51] 1-chloro-4-hydrazinophthalazine **3e**,[52] 2-hydrazinopyrimidine **3f**,[53] hydrazinopyrazine **3g**,[54] a mixture of (1*R*,3*R*,4*R*)-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptan-3-carbaldehyde (6-phenylpyridazin-3-yl)hydrazone **8b** and its (1*R*,3*S*,4*R*)-isomer **8′b** and a mixture of (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 **8c** and its (1*R*,3*S*,4*R*)-isomer **8′c**[15] were prepared according to the procedures described in the literature.

Source of chirality: (i) (+)-Camphor **1** (Fluka AG), product number 21300, purum, natural, $\geqslant$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.

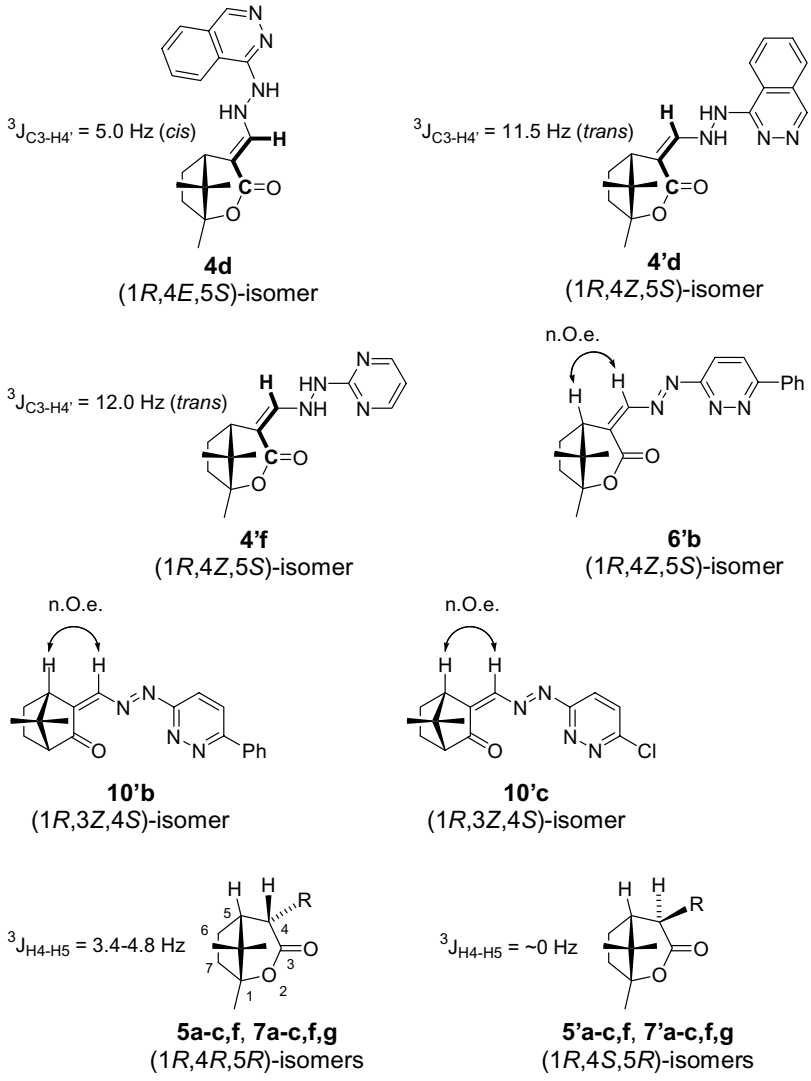


Figure 1.

5.2. Reactions of 2 with hydrazinoazines 3a–d,f. General procedure for the preparation of enehydrazines 4/4′a–d,f and hydrazones 5/5′a–c,f

Sulfuric acid (1 M in MeOH, 0.5 ml, 0.5 mmol) was added[‡] to a stirred suspension of compound **2** (223 mg, 1 mmol) and hydrazinoazine **3a**–**f** (1 mmol) in anhydrous methanol (5 ml) and the mixture stirred at 20–70 °C for 6–72 h. The products, which precipitated from the reaction mixtures, were collected by filtration and washed with cold (0 °C) methanol (2 ml) to give enehydrazines **4**/**4′** and hydrazones **5**/**5′**. Compounds **4c**,**d**, **4′b**–**d**, **5b**,**c** and **5′b**,**c** were prepared in this manner. Compounds **4a**,**f**, **4′a**,**f**, **5a**,**f** and **5′a**,**f** did not precipitate from the reaction mixture. Volatile components were evaporated in vacuo and the residue purified by column chromatography (CC). Fractions containing the products were combined and evaporated in vacuo to give compounds **4a**,**f**, **4′a**,**f**, **5a**,**f** and **5′a**,**f**.

[‡] In the case of reaction of **2** with 1-hydrazinophthalazine **3d** hydrochloride, no sulfuric acid was added.

5.2.1. (1*R*,4*E*,5*S*)-4-{[2-(Pyridin-2-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 4a, its (1*R*,4*Z*,5*S*)-isomer 4′a, (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (pyridin-2-yl)hydrazone 5a and its (1*R*,4*S*,5*R*)-isomer 5′a. Prepared from **2** and 2-hydrazinopyridine **3a**; stirring at rt for 72 h; CC (ethyl acetate). Yield: 262 mg (91%) of greyish crystals; **4a**:**4′a**:**5a**:**5′a** = 3:59:31:7 (in $CDCl_3$), **4a**:**4′a**:**5a**:**5′a** = 45:26:23:6 (in DMSO-d_6); mp 62–75 °C; $[\alpha]_D^{24} = +25.4$ (c 0.122, $CHCl_3$). m/z (EI) 287 (M^+); m/z (HRMS) Found: 287.164050 (M^+), $C_{16}H_{21}N_3O_2$ requires: 287.163377. (Found: C, 67.01; H, 7.80; N, 14.12. $C_{16}H_{21}N_3O_2$ requires: C, 66.88; H, 7.37; N, 14.62); ν_{max} (KBr) 3415, 3229, 2971, 1728 (C=O), 1674 (C=O), 1600, 1445, 1250, 1214, 1165, 1143, 1069 cm^{-1}.

5.2.1.1. NMR data for (1*R*,4*E*,5*S*)-4-{[2-(pyridin-2-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 4a. ^1H NMR ($CDCl_3$): δ 2.51 (1H, d, $J = 6.0$ Hz, H–C(5)). ^1H NMR (DMSO-d_6): δ 6.72 (1H, d, $J = 10.6$ Hz, H–C(4′)); 8.59 (1H, br s, CHNHN*H*); 8.95 (1H, d, $J = 10.7$ Hz, CHN*H*NH).

Table 2. Characteristic ^{1}H NMR data for compounds **4**–**7** and **4′**–**7′**

	Solvent	δ (ppm)	
		H–C(4′)	*H*–N–C(4′)
(1R,4E,5R)-Isomers **4a**–**d**,**f**			
4a	$CDCl_3$	—[a]	—[a]
4c	$CDCl_3$	—[a]	—[a]
4f	$CDCl_3$	—[a]	—[a]
4a	DMSO-d_6	7.06	8.48
4d[b]	DMSO-d_6	7.51	8.70
4f	DMSO-d_6	7.02	8.46
(1R,4Z,5R)-Isomers **4′a**–**d**,**f**			
4′a	$CDCl_3$	6.60	9.04
4′b	$CDCl_3$	6.34	9.12
4′c	$CDCl_3$	6.55	9.07
4′f[b]	$CDCl_3$	6.56	9.09
4′a	DMSO-d_6	6.72	8.95
4′d[b]	DMSO-d_6	7.08	10.01
4′f	DMSO-d_6	6.69	8.98

	Solvent	δ (ppm)		J_{H-H} (Hz)
		H–C(4)	*H*–N–C(4)	4–5
(1R,4R,5R)-Isomers **5a**–**c**,**f**				
5a	$CDCl_3$	3.73	2.39	4.7
5a	DMSO-d_6	3.68	2.2[a]	4.7
5b	$CDCl_3$	3.77	2.35	4.7
5c	$CDCl_3$	3.73	2.3[a]	4.8
5f	$CDCl_3$	3.88	2.45	4.6
(1R,4S,5R)-Isomers **5′a**–**c**,**f**				
5′a	$CDCl_3$	3.42	2.78	0
5′a	DMSO-d_6	3.53	—[a]	0
5′b	$CDCl_3$	3.50	2.70	0
5′c	$CDCl_3$	3.44	2.52	0
5′f	$CDCl_3$	3.56	2.71	0

	Solvent	δ (ppm)	
		H–C(4′)	H–C(5)
(1R,4E,5R)-Isomers **6a**–**g**			
6a	$CDCl_3$	8.09	4.05
6b	$CDCl_3$	~8.2[a]	4.05
6c[d]	$CDCl_3$	8.18	3.98
6d	$CDCl_3$	8.18	4.27
6e	$CDCl_3$	8.17	4.24
6f	$CDCl_3$	8.13	4.11
6g	$CDCl_3$	8.11	4.06
(1R,4Z,5R)-Isomer **6′b**			
6′b[c]	$CDCl_3$	7.50	2.84

	Solvent	δ (ppm)		J_{H-H} (Hz)
		H–C(4)	H–C(5)	4–5
(1R,4R,5R)-Isomers **7a**–**c**,**f**,**g**				
7a	$CDCl_3$	4.51	2.62	3.4
7b	$CDCl_3$	5.07	~2.5[a]	4.2
7c	$CDCl_3$	4.93	2.36	4.2
7f	$CDCl_3$	4.45	2.76	3.4
7g	$CDCl_3$	4.51	2.70	3.4
(1R,4S,5R)-Isomers **7′a**–**c**,**f**,**g**				
7′a	$CDCl_3$	4.03	3.24	0
7′b	$CDCl_3$	4.64	2.70	0
7′c	$CDCl_3$	4.49	2.66	0
7′f	$CDCl_3$	4.05	3.35	0
7′g	$CDCl_3$	4.07	3.29	0

[a] Overlapped by other signals or exchanged.
[b] Determined by HMBC spectroscopy.
[c] Determined by NOESY spectroscopy.
[d] Determined by X-ray diffraction.

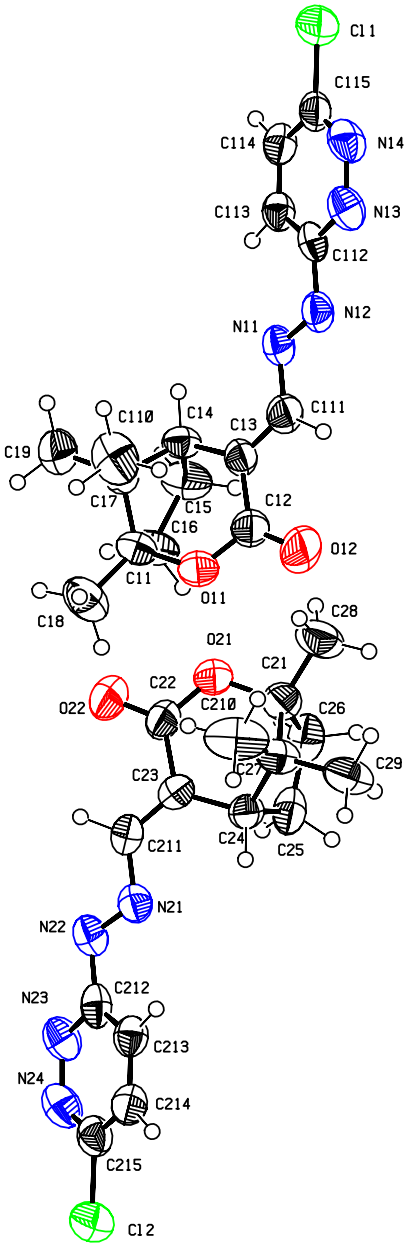


Figure 2. The asymmetric unit of compound **6c**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

5.2.1.2. NMR data for (1*R*,4*Z*,5*S*)-4-{[2-(pyridin-2-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 4′a. ^{1}H NMR ($CDCl_3$): δ 1.00, 1.01, 1.31 (9H, 3s, 1:1:1, 3Me); 1.59–1.67 (1H, m, 1H of CH_2); 1.82–2.26 (4H, m, 3H of CH_2; H–C(5)); 6.60 (1H, d, $J = 10.3$ Hz, H–C(4′)); 6.70 (1H, br s, CHNHN*H*); 6.72–6.81 (1H, m, H–C(5″)); 7.31–7.41 (1H, m, H–C(3″)); 7.52–7.59 (1H, m, H–C(4″)); 8.13–8.15 (1H, m, H–C(6″)); 9.04 (1H, d, $J = 10.3$ Hz, CHN*H*NH). ^{1}H NMR (DMSO-d_6): δ 7.06 (1H, d, $J = 10.8$ Hz, H–C(4′)); 8.48 (1H, d, $J = 10.8$ Hz, CHN*H*NH); 8.58 (1H, br s, CHNHN*H*).

5.2.1.3. NMR data for (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (pyridin-2-yl)hydrazone 5a. ^{1}H NMR ($CDCl_3$): δ 1.08, 1.17, 1.33 (9H, 3s, 1:1:1, 3Me); 2.39 (1H, m, H–C(5)); 3.73 (1H, br deg t, $J = 4.7$ Hz, H–C(4)); 7.14–7.18 (1H, m, H–C(3″)); 8.08–8.11 (H–C(6″)); 8.42 (1H, br s, NH). ^{1}H NMR (DMSO-d_6): δ 2.22–2.27 (1H, m, 5–H); 3.68 (1H, deg dt, $J = 1.5$, 4.7 Hz, H–C(4)); 7.50 (1H, d, $J = 5.0$ Hz, H–C(4′)); 10.52 (1H, br s, NH).

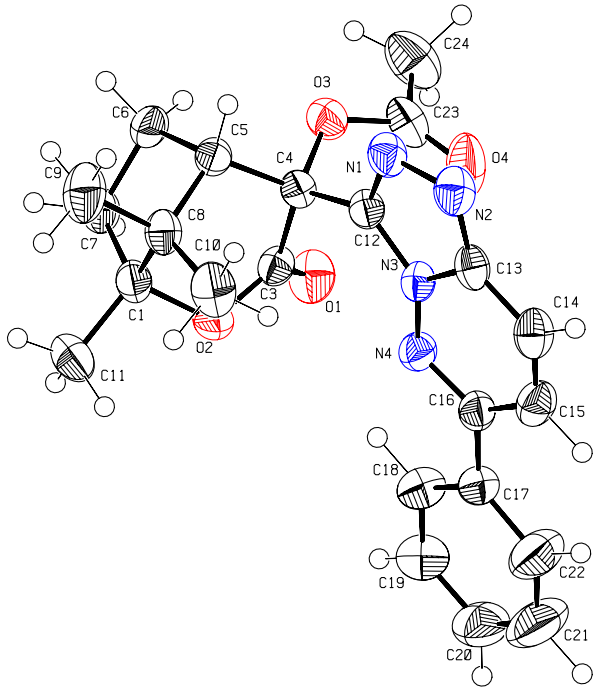


Figure 3. The asymmetric unit of compound **11**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

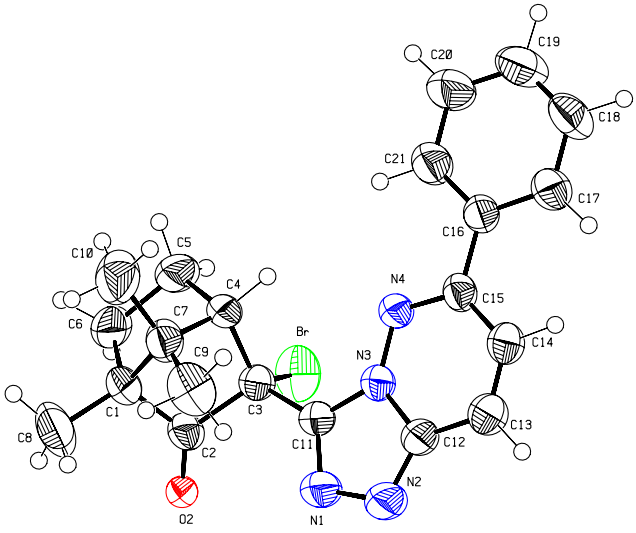


Figure 4. The asymmetric unit of compound **12**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

5.2.1.4. NMR data for (1*R*,4*S*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (pyridin-2-yl)hydrazone 5′a. ^{1}H NMR ($CDCl_3$): δ 0.96, 1.04 (6H, 2s, 1:1, 2Me); 2.78 (1H, d, $J = 6.4$ Hz, H–C(5)); 3.42 (1H, d, $J = 3.4$ Hz, H–C(4)). ^{1}H NMR

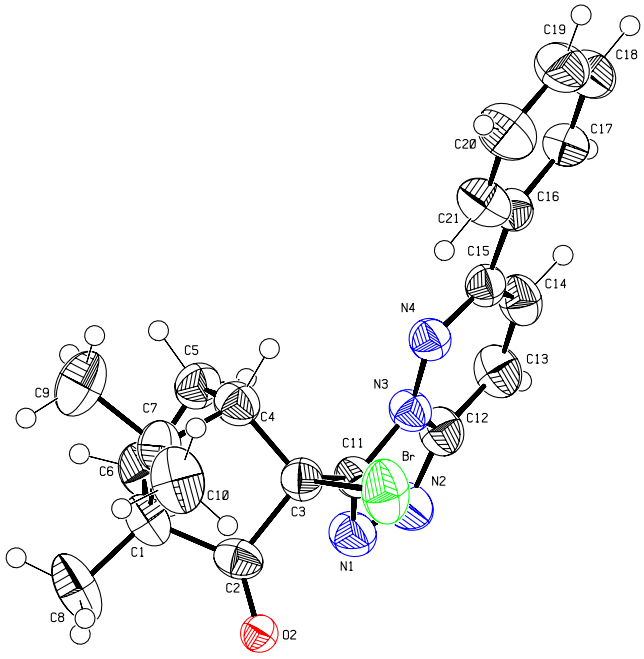


Figure 5. The asymmetric unit of compound **12′**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

(DMSO-d_6): δ 3.53 (1H, d, $J = 4.3$ Hz, H–C(4)); 7.47 (1H, d, $J = 4.0$ Hz, H–C(4′)); 10.46 (1H, br s, NH).

5.2.2. (1*R*,4*Z*,5*S*)-4-{[2-(6-Phenylpyridazin-3-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]-octan-3-one 4′b, (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (6-phenylpyridazin-3-yl)hydrazone 5b and its (1*R*,4*S*,5*R*)-isomer 5′b. Prepared from **2** and 3-hydrazino-6-phenylpyridazine **3b**; reflux for 6 h. Yield: 230 mg (63%) of greyish crystals; **4′b**:**5b**:**5′b** = 17:71:12 (in $CDCl_3$); mp 196–201 °C; $[\alpha]_D^{24} = +13.0$ (c 0.316, CH_2Cl_2). (Found: C, 68.92; H, 6.90; N, 15.46. $C_{21}H_{24}N_4O_2$ requires: C, 69.21; H, 6.64; N, 15.37); ν_{max} (KBr) 3208, 2972, 1728 (C=O), 1603, 1545, 1452, 1412, 1379, 1271, 1142, 1108 cm^{-1}.

5.2.2.1. NMR data for (1*R*,4*Z*,5*S*)-4-{[2-(6-phenylpyridazin-3-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 4′b. ^{1}H NMR ($CDCl_3$): δ 1.01, 1.02, 1.32 (9H, 3s, 1:1:1, 3Me); 6.34 (1H, d, $J = 10.2$ Hz, H–C(4′)); 7.13 (1H, d, $J = 9.4$ Hz, H–C(4″)); 9.12 (1H, d, $J = 9.8$ Hz, CHN*H*NH-Het).

5.2.2.2. NMR data for (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (6-phenylpyridazin-3-yl)hydrazone 5b. ^{1}H NMR ($CDCl_3$): δ 1.07, 1.19, 1.34 (9H, 3s, 1:1:1, 3Me); 1.55–1.73 (1H, m, 1H of CH_2); 1.90–2.29 (3H, m, 3H of CH_2); 2.31–2.38 (1H, m, H–C(5)); 3.77 (1H, br deg t; $J = 4.7$ Hz, H–C(4)); 7.39–7.52 (3H, m, 3H of Ph); 7.55 (1H, d, $J = 9.4$ Hz, H–C(4″)); 7.74 (1H, d, $J = 9.4$ Hz, H–C(5″)); 7.98 (1H, d, $J = 5.3$ Hz, H–C(4′)); 7.98–8.04 (2H, m, 2H of Ph); 11.36 (1H, br s, NH).

5.2.2.3. NMR data for (1*R*,4*S*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (6-phenylpyridazin-3-yl)hydrazone 5′b. ^{1}H NMR ($CDCl_3$): δ 0.99 (3H, s, Me); 2.70 (1H, br d, $J = 6.0$ Hz, H–C(5)); 3.50 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.89 (1H, d, $J = 4.1$ Hz, H–C(4′)).

5.2.3. (1*R*,4*E*,5*S*)-4-{[2-(6-Chloropyridazin-3-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]-octan-3-one 4c, its (1*R*,4*Z*,5*S*)-isomer 4′c, (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (6-chloropyridazin-3-yl)hydrazone 5c and its (1*R*,4*S*,5*R*)-isomer 5′c. Prepared from **2** and 6-chloro-3-hydrazinopyridazine **3c**; stirring at rt for 24 h. Yield: 258 mg (80%) of greyish crystals; **4c**:**4′c**:**5c**:**5′c** = 5:19:53:23 (in $CDCl_3$); mp 217–223 °C; $[\alpha]_D^{24} = +12.5$ (c 0.160, CH_2Cl_2). (Found: C, 55.78; H, 5.99; N, 17.60. $C_{15}H_{19}ClN_4O_2$ requires: C, 55.81; H, 5.93; N, 17.36); ν_{max} (KBr) 2974, 1719 (C=O), 1680 (C=O), 1607, 1528, 1411, 1280, 1140, 1066, 1014 cm^{-1}.

5.2.3.1. NMR data for (1*R*,4*E*,5*S*)-4-{[2-(6-chloropyridazin-3-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 4c. ^{1}H NMR ($CDCl_3$): δ 1.02, 1.30 (6H, 2s, 1:1, 2Me); 2.54 (1H, d, $J = 5.7$ Hz, H–C(5)); 7.03 (1H, d, $J = 9.0$ Hz, H–C(4″)).

5.2.3.2. NMR data for (1*R*,4*Z*,5*S*)-4-{[2-(6-chloropyridazin-3-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 4′c. ^{1}H NMR ($CDCl_3$): δ 1.00, 1.01, 1.32 (9H, 3s, 1:1:1, 3Me); 6.55 (1H, d, $J = 10.1$ Hz, H–C(4′)); 7.07 (1H, d, $J = 9.3$ Hz, H–C(4″)); 7.35 (1H, d, $J = 9.3$ Hz, H–C(5″)); 9.07 (1H, d, $J = 10.1$ Hz, CHN*H*NH).

5.2.3.3. NMR data for (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (6-chloropyridazin-3-yl)hydrazone 5c. ^{1}H NMR ($CDCl_3$): δ 1.07, 1.17, 1.34 (9H, 3s, 1:1:1, 3Me); 1.59–1.69 (1H, m, 1H of CH_2); 1.94–2.29 (4H, m, 3H of CH_2; H–C(5)); 3.73 (1H, br deg t, $J = 4.8$ Hz, H–C(4)); 7.31 (1H, d, $J = 9.3$ Hz, H–C(4″)); 7.47 (1H, d, $J = 9.3$ Hz, H–C(5″)); 7.71 (1H, d, $J = 5.4$ Hz, H–C(4′)); 10.5 (1H, br s, NH).

5.2.3.4. NMR data for (1*R*,4*S*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (6-chloropyridazin-3-yl)hydrazone 5′c. ^{1}H NMR ($CDCl_3$): δ 1.04, 1.09, 1.34 (9H, 3s, 1:1:1, 3Me); 2.52 (1H, d, $J = 5.7$ Hz, H–C(5)); 3.44 (1H, d, $J = 4.4$ Hz, H–C(4)); 7.32 (1H, d, $J = 9.3$ Hz, H–C(4″)); 7.48 (1H, d, $J = 9.3$ Hz, H–C(5″)); 7.66 (1H, d, $J = 4.8$ Hz, H–C(4′)).

5.2.4. (1*R*,4*E*,5*S*)-4-{[2-(Phthalazin-1-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 4d and its (1*R*,4*Z*,5*S*)-isomer 4′d. Prepared from **2** and 1-hydrazinophthalazine **3d** hydrochloride; stirring at 45 °C for 7 h. Yield: 247 mg (73%) of yellow crystals; **4d**:**4′d** = 87:13 (in DMSO-d_6); mp 193–196 °C; $[\alpha]_D^{25} = -68.4$ (c 0.234, CH_2Cl_2). m/z (EI) 338 (M^+); m/z (HRMS) Found: 338.175530 (M^+), $C_{19}H_{22}N_4O_2$ requires: 338.174276. (Found: C, 67.29; H, 6.71; N, 16.63. $C_{19}H_{22}N_4O_2$ requires: C, 67.44; H, 6.55; N, 16.56); ν_{max}

(KBr) 3278, 1675 (C=O), 1560, 1487, 1466, 1272, 1172, 1129, 1064 cm^{-1}.

5.2.4.1. NMR data for (1*R*,4*E*,5*S*)-4-{[2-(phthalazin-1-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 4d. ^1H NMR (DMSO-d_6): δ 0.91, 1.00, 1.19 (9H, 3s, 1:1:1, 3Me); 1.47–1.53 (1H, m, 1H of CH_2); 1.92–2.14 (3H, m, 3H of CH_2); 2.88 (1H, br s, H–C(5)); 7.51 (1H, d, $J = 10.2$ Hz, H–C(4′)); 7.55–7.62 (3H, m, 3H of phthalazine); 7.85 (1H, s, 1H of phthalazine); 7.97–8.01 (1H, m, 1H of phthalazine); 8.70 (1H, d, $J = 10.6$ Hz, CHN*H*NH); 11.31 (1H, s, CHNHN*H*). ^{13}C NMR (DMSO-d_6): δ 18.9, 19.6, 23.9, 30.2, 35.1, 37.8, 43.6, 45.1, 90.5, 101.3, 123.4, 126.5, 127.2, 127.9, 131.7, 132.7, 137.9, 168.0.

5.2.4.2. NMR data for (1*R*,4*Z*,5*S*)-4-{[2-(phthalazin-1-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 4′d. ^1H NMR (DMSO-d_6): δ 0.97, 1.21 (6H, 2s, 1:1, 2Me); 2.34 (1H, d, $J = 5.3$ Hz, H–C(5)); 7.08 (1H, d, $J = 10.6$ Hz, H–C(4′)); 10.01 (1H, d, $J = 10.9$ Hz, CHN*H*NH); 11.55 (1H, br s, CHNHN*H*).

5.2.5. (1*R*,4*E*,5*S*)-4-{[2-(Pyrimidin-2-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 4f, its (1*R*,4*Z*,5*S*)-isomer 4′f, (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (pyrimidin-2-yl)hydrazone 5f and its (1*R*,4*S*,5*R*)-isomer 5′f. Prepared from **2** and 2-hydrazinopyrimidine **3f**; stirring at rt for 24 h; CC ($CHCl_3$–MeOH, 40:1). Yield: 260 mg (90%) of greyish crystals; **4f**:**4′f**: **5f**:**5′f** = 7:74:16:3 (in $CDCl_3$), **4f**:**4′f**:**5f**:**5′f** = 41:59:0:0 (in DMSO-d_6); mp 75–84 °C; $[\alpha]_D^{24} = +22.5$ (c 0.138, $CHCl_3$). m/z (EI) 288 (M^+); m/z (HRMS) Found: 288.159550 (M^+), $C_{15}H_{20}N_4O_2$ requires: 288.158626. (Found: C, 62.01; H, 7.33; N, 18.00. $C_{15}H_{20}N_4O_2$ requires: C, 62.48; H, 6.99; N, 19.43); ν_{max} (KBr) 3419, 2967, 1727 (C=O), 1676 (C=O), 1584, 1450, 1413, 1383, 1253, 1222, 1203, 1165, 1144, 1070, 1052 cm^{-1}.

5.2.5.1. NMR data for (1*R*,4*E*,5*S*)-4-{[2-(pyrimidin-2-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 4f. ^1H NMR ($CDCl_3$): δ 2.54 (1H, d, $J = 5.3$ Hz, H–C(5)). ^1H NMR (DMSO-d_6): δ 0.89, 0.94, 1.17 (9H, 3s, 1:1:1, 3Me); 2.72–2.75 (1H, m, H–C(5)); 6.79 (1H, t, $J = 4.8$ Hz, H–C(5″)); 7.02 (1H, d, $J = 10.6$ Hz, H–C(4′)); 8.40 (2H, d, $J = 4.8$ Hz, H–C(4″) and H–C(6″)); 8.46 (1H, d, $J = 10.6$ Hz, CHN*H*NH); 9.24 (1H, s, CHNHN*H*).

5.2.5.2. NMR data for (1*R*,4*Z*,5*S*)-4-{[2-(pyrimidin-2-yl)hydrazino]methylidene}-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 4′f. ^1H NMR ($CDCl_3$): δ 0.99, 1.01, 1.29 (9H, 3s, 1:1:1, 3Me); 1.65–1.80 (1H, m, 1H of CH_2); 1.92–2.25 (4H, m, 3H of CH_2; H–C(5)); 6.56 (1H, d, $J = 10.6$ Hz, H–C(4′)); 6.74 (1H, t, $J = 4.8$ Hz, H–C(5″)); 7.12 (1H, br s, CHNHN*H*); 8.39 (2H, dd, $J = 0.8$, 4.8 Hz, H–C(4″) and H–C(6″)); 9.09 (1H, d, $J = 10.2$ Hz, CHN*H*NH). ^1H NMR (DMSO-d_6): δ 0.90, 0.95, 1.19 (9H, 3s, 1:1:1, 3Me); 1.44–1.52 (1H, m, 1H of CH_2); 1.92–2.08 (3H, m, 3H of CH_2); 2.27 (1H, br d, $J = 5.3$ Hz, H–C(5)); 6.69 (1H, d, $J = 10.6$ Hz, H–C(4′)); 6.80 (1H, t, $J = 4.8$ Hz, H–C(5″)); 8.39 (2H, d, $J = 4.8$ Hz, H–C(4″) and H–C(6″)); 8.98 (1H, d, $J = 10.6$ Hz, CHN*H*NH); 9.31 (1H, s, CHNHN*H*).

5.2.5.3. NMR data for (1*R*,4*R*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (pyrimidin-2-yl)hydrazone 5f. ^1H NMR ($CDCl_3$): δ 1.04, 1.15, 1.32 (9H, 3s, 1:1:1, 3Me); 2.43–2.47 (1H, m, H–C(5)); 3.88 (1H, br deg t, $J = 4.6$ Hz, H–C(4)); 6.75 (1H, t, $J = 4.8$ Hz, H–C(5″)); 7.49 (1H, d, $J = 5.7$ Hz, H–C(4′)); 8.44 (2H, dd, $J = 0.8$, 4.8 Hz, H–C(4″) and H–C(6″)); 8.70 (1H, br s, NH).

5.2.5.4. NMR data for (1*R*,4*S*,5*R*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octane-4-carbaldehyde (pyrimidin-2-yl)hydrazone 5′f. ^1H NMR ($CDCl_3$): δ 2.71 (1H, d, $J = 5.2$ Hz, H–C(5)); 3.56 (1H, d, $J = 4.5$ Hz, H–C(4)); 7.44 (1H, d, $J = 4.0$ Hz, H–C(4′)); 8.48 (2H, d, $J = 5.0$ Hz, H–C(4″) and H–C(6″)).

5.3. One-pot reactions of 2 with hydrazinoazines 3a–g followed by oxidation with lead tetraacetate. General one-pot procedure for the preparation of (1*R*,4*E*,5*S*)-4-{[(*E*)-(azinyl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones 6a–g and their (1*R*,4*Z*,5*S*)-isomers 6′a–g 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 7a–g and their (1*R*,4*S*,5*R*)-isomers 7′a–g

Sulfuric acid (1 M in MeOH, 0.5 ml, 0.5 mmol) was added[‡] to a stirred suspension of compound **2** (223 mg, 1 mmol) and hydrazinoazine **3a**–**f** (1 mmol) in anhydrous methanol (6 ml) and the mixture stirred at rt for 24–72 h. Then lead tetraacetate (85%, 521 mg, 1 mmol) was added and the mixture stirred at rt for 1 h. Volatile components were evaporated in vacuo and the residue was purified by CC. Deep red coloured compounds **6** and **6′** were eluted first with ethyl acetate–hexanes, followed by elution of colourless compounds **7** and **7′** with chloroform–methanol. Fractions containing the products were combined and evaporated in vacuo. Compounds **6a**,**c**–**g** and **6**/**6′b** were crystallised from ethyl acetate–*n*-hexane to give isomerically and analytically pure compounds **6a**–**g**. Compounds **7**/**7′a**–**g** were additionally purified by MPLC. Fractions containing the products were combined and evaporated in vacuo to give analytically pure compounds **7**/**7′a**–**g**. The following compounds were prepared in this manner.

5.3.1. (1*R*,4*E*,5*S*)-4-{[(*E*)-(Pyridin-2-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 6a, (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 7a and its (1*R*,4*S*,5*R*)-isomer 7′a. Prepared from compound **2** and 2-hydrazinopyridine **3a**; stirring at rt for 24 h; CC (EtOAc–hexanes, 2:1; then $CHCl_3$–MeOH, 20:1); MPLC (EtOAc).

5.3.1.1. Data for (1*R*,4*E*,5*S*)-4-{[(*E*)-(pyridin-2-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-ocan-3-one 6a. Yield: 143 mg (50%) of deep red crystals; mp 150–151 °C (from EtOAc–*n*-hexane); $[\alpha]_D^{21} = -17.4$ (c 0.132, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ

1.09, 1.12, 1.41 (9H, 3s, 1:1:1, 3Me); 1.71–1.81 (1H, m, 1H of CH_2); 2.09–2.44 (3H, m, 3H of CH_2); 4.05 (1H, d, $J = 6.4$ Hz, H–C(5)); 7.43 (1H, ddd, $J = 0.8$, 4.5, 7.2 Hz, H–C(5″)); 7.72–7.75 (1H, m, H–C(3″)); 7.90 (1H, dt, $J = 1.9$, 7.9 Hz, H–C(4″)); 8.09 (1H, s, H–C(4′)); 8.75–8.77 (1H, m, H–C(6″)). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.8, 23.8, 28.0, 37.1, 45.4, 47.1, 94.5, 115.6, 126.3, 138.6, 144.4, 149.7, 150.2, 163.6, 166.4. (Found: C, 67.22; H, 6.75; N, 14.86. $C_{16}H_{19}N_3O_2$ requires: C, 67.35; H, 6.71; N, 14.73); ν_{max} (KBr) 2974, 1708 (C=O), 1577, 1466, 1304, 1275, 1262, 1204, 1176, 1146, 1052 cm^{-1}.

5.3.1.2. Data for (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*a*]-pyridin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 7a and its (1*R*,4*S*,5*R*)-isomer 7′a. Yield: 31 mg (11%) of a light yellow solid; **7a**:**7′a** = 84:16; mp 70–80 °C; $[\alpha]_D^{22} = -81.8$ (*c* 0.088, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.15, 1.30, 1.41 (9H, 3s, 1:1:1, 3Me); 2.03–2.39 (3H, m, 3H of CH_2); 2.50–2.58 (1H, m, 1H of CH_2); 2.62 (1H, dd, $J = 3.8$, 6.4 Hz, H–C(5)); 4.51 (1H, dd, $J = 1.9$, 3.4 Hz, H–C(4)); 6.82–6.87 (1H, m, H–C(6′)); 7.23–7.29 (1H, m, H–C(7′)); 7.74–7.78 (1H, m, H–C(8′)); 8.06–8.09 (1H, m, H–C(5′)). *m*/*z* (EI) = 285 (M^+); *m*/*z* (HRMS) Found: 285.148220 (M^+), $C_{16}H_{19}N_3O_2$ requires: 285.147727. (Found: C, 67.29; H, 7.01; N, 14.48. $C_{16}H_{19}N_3O_2$ requires: C, 67.35; H, 6.71; N, 14.73); ν_{max} (KBr) 2973, 1725 (C=O), 1637, 1507, 1391, 1339, 1273, 1223, 1142, 1059, 957 cm^{-1}.

5.3.1.3. NMR data for the minor (1*R*,4*S*,5*R*)-isomer 7′a. ^{1}H NMR ($CDCl_3$): δ 1.15, 1.28 (6H, s, 1:1, 2Me); 3.24 (1H, d, $J = 6.0$ Hz, H–C(5)); 4.03 (1H, s, H–C(4)); 8.37–8.41 (1H, m, H–C(5′)).

5.3.2. (1*R*,4*E*,5*S*)-4-{[(*E*)-(6-Phenylpyridazin-3-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6b and its (1*R*,4*Z*,5*S*)-isomer 6′b and (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[3.2.1]octan-3-one 7b and its (1*R*,4*S*,5*R*)-isomer 7′b. Prepared from compound **2** and 3-hydrazino-6-phenylpyridazine **3b**; stirring at rt for 48 h; CC (EtOAc–hexanes, 1:1; then EtOAc); MPLC (EtOAc).

5.3.2.1. Data for (1*R*,4*E*,5*S*)-4-{[(*E*)-(6-phenylpyridazin-3-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6b and its (1*R*,4*Z*,5*S*)-isomer 6′b. Yield: 36 mg (10%) of deep red crystals; **6b**:**6′b** = 64:36. Crystallisation from EtOAc–*n*-hexane afforded isomerically pure compound **6b**.

5.3.2.2. Data for (1*R*,4*E*,5*S*)-4-{[(*E*)-(6-phenylpyridazin-3-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxa-bicyclo[3.2.1]octan-3-one 6b. Mp 185–190 °C (from EtOAc–*n*-hexane); $[\alpha]_D^{21} = +24.2$ (*c* 0.124, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.10, 1.14, 1.43 (9H, 3s, 1:1:1, 3Me); 1.72–1.88 (1H, m, 1H of CH_2); 2.12–2.46 (3H, m, 3H of CH_2); 4.05 (1H, d, $J = 6.4$ Hz, H–C(5)); 7.54–7.59 (3H, m, 3H of Ph); 7.90 (1H, d, $J = 9.0$ Hz, H–C(4″)); 8.03 (1H, d, $J = 9.0$ Hz, H–C(5″)); 8.18–8.21 (3H, m, 2H of Ph; H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.8, 18.9, 23.9, 27.9, 37.1, 45.5, 47.3, 94.7, 118.3, 125.9, 127.9, 129.6, 131.3, 135.8, 145.9, 149.5, 160.8, 165.5, 166.0. (Found: C, 69.29; H, 6.02; N, 15.47. $C_{21}H_{22}N_4O_2$ requires: C, 69.59; H, 6.12; N, 15.46); ν_{max} (KBr) 2972, 1710 (C=O), 1572, 1415, 1299, 1269, 1203, 1181, 1145, 1054 cm^{-1}.

5.3.2.3. NMR data for the minor (1*R*,4*Z*,5*S*)-isomer 6′b. ^{1}H NMR ($CDCl_3$): δ 1.13, 1.41 (9H, 2s, 2:1, 3Me); 1.78–1.88 (1H, m, 1H of CH_2); 2.11–2.22 (1H, m, 1H of CH_2); 2.27–2.43 (2H, m, 2H of CH_2); 2.84 (1H, d, $J = 6.4$ Hz, H–C(5)); 7.50 (1H, s, H–C(4′)); 7.53–7.58 (3H, m, 3H of Ph); 8.00 (1H, d, $J = 9.0$ Hz, H–C(4″)); 8.06 (1H, d, $J = 9.0$ Hz, H–C(5″)); 8.18–8.22 (2H, m, 2H of Ph).

5.3.2.4. Data for (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-[3.2.1]-octan-3-one 7b and its (1*R*,4*S*,5*R*)-isomer 7′b. Yield: 188 mg (52%) of a white solid; **7b**:**7′b** = 96:4; mp 228–235 °C; $[\alpha]_D^{22} = -18.7$ (*c* 0.214, CH_2Cl_2). *m*/*z* (EI) = 362 (M^+); *m*/*z* (HRMS) Found: 362.175030 (M^+), $C_{21}H_{22}N_4O_2$ requires: 362.174276. (Found: C, 68.80; H, 6.09; N, 15.62. $C_{21}H_{22}N_4O_2$ requires: C, 69.59; H, 6.12; N, 15.46); ν_{max} (KBr) 2976, 1737 (C=O), 1545, 1473, 1437, 1335, 1266, 1166, 1144, 1062, 1014, 962, 778 cm^{-1}.

5.3.2.5. NMR data for the major (1*R*,4*R*,5*R*)-isomer 7b. ^{1}H NMR ($CDCl_3$): δ 1.11, 1.36, 1.42 (9H, 3s, 1:1:1, 3Me); 1.78–1.92 (1H, m, 1H of CH_2); 2.01–2.20 (2H, m, 2H of CH_2); 2.40–2.52 (2H, m, 1H of CH_2; H–C(5)); 5.07 (1H, dd, $J = 1.9$, 4.2 Hz, H–C(4)); 7.53–7.58 (3H, m, 3H of Ph); 7.58 (1H, d, $J = 9.4$ Hz, H–C(7′)); 7.93–7.98 (2H, m, 2H of Ph); 8.18 (1H, d, $J = 9.8$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 18.2, 18.7, 23.5, 24.3, 37.3, 43.7, 45.4, 48.6, 95.0, 119.9, 125.6, 127.8, 129.7, 131.4, 134.6, 143.9, 147.9, 153.9, 168.7.

5.3.2.6. NMR data for the minor (1*R*,4*S*,5*R*)-isomer 7′b. ^{1}H NMR ($CDCl_3$): δ 2.70 (1H, d, $J = 5.7$ Hz, H–C(5)); 4.64 (1H, s, H–C(4)).

5.3.3. (1*R*,4*E*,5*S*)-4-{[(*E*)-(6-Chloropyridazin-3- yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6c (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[3.2.1]octan-3-one 7c and its (1*R*,4*S*,5*R*)-isomer 7′c. Prepared from compound **2** and 6-chloro-3-hydrazinopyridazine **3c**; stirring at rt for 24 h; CC (EtOAc–hexanes, 2:1; then $CHCl_3$–MeOH, 20:1); MPLC (EtOAc).

5.3.3.1. Data for (1*R*,4*E*,5*S*)-4-{[(*E*)-(6-chloropyridazin-3-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6c. Yield: 93 mg (29%) of deep red crystals; mp 183–188 °C (from EtOAc–*n*-hexane); $[\alpha]_D^{21} = -6.6$ (*c* 0.198, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.09, 1.13, 1.43 (9H, 3s, 1:1:1, 3Me); 1.70–1.80 (1H, m, 1H of CH_2); 2.10–2.45 (3H, m, 3H of CH_2); 3.98 (1H, d, $J = 6.4$ Hz, H–C(5)); 7.68 (1H, d, $J = 9.0$ Hz, H–C(4″)); 7.82 (1H, d, $J = 9.0$ Hz, H–C(5″)); 8.18 (1H, s, H–C(4′)). *m*/*z* (FAB) = 321 (MH^+). (Found: C, 56.38; H, 5.59; N, 17.65. $C_{15}H_{17}ClN_4O_2$ requires: C, 56.16;

H, 5.34; N, 17.47); ν_{max} (KBr) 2965, 1709 (C=O), 1398, 1300, 1271, 1206, 1180, 1139, 1077, 1049 cm^{-1}.

5.3.3.2. Data for (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[3.2.1]-octan-3-one 7c and its (1*R*,4*S*,5*R*)-isomer 7′c. Yield: 148 mg (46%) of a white solid; **7c**:**7′c** = 95:5; mp 183–188 °C. *m*/*z* (EI) = 320 (M^+); *m*/*z* (HRMS) Found: 320.105350 (M^+), $C_{15}H_{17}ClN_4O_2$ requires: 320.104004. (Found: C, 56.21; H, 5.46; N, 17.42. $C_{15}H_{17}ClN_4O_2$ requires: C, 56.16; H, 5.34; N, 17.47); ν_{max} (KBr) 2976, 1727 (C=O), 1466, 1329, 1272, 1167, 1142, 1084, 1052, 955, 908 cm^{-1}. Repeated crystallisation from $CHCl_3$–*n*-hexane afforded isomarically pure **7c**.

5.3.3.3. Data for (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-[3.2.1]octan-3-one 7c. Mp 185–189 °C; $[\alpha]_D^{22} = -19.0$ (*c* 0.252, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.12, 1.34, 1.41 (9H, 3s, 1:1:1, 3Me); 1.82–1.95 (1H, m, 1H of CH_2); 2.04–2.15 (1H, m, 1H of CH_2); 2.19–2.28 (1H, m, 1H of CH_2); 2.36 (1H, dd, $J = 4.5$, 6.4 Hz, H–C(5)); 2.42–2.52 (1H, m, 1H of CH_2); 4.93 (1H, dd, $J = 1.9$, 4.2 Hz, H–C(4)); 7.13 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.09 (1H, d, $J = 9.4$ Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 18.1, 18.6, 23.2, 24.3, 37.1, 43.1, 45.3, 47.8, 95.2, 122.9, 126.9, 143.1, 147.6, 149.8, 168.3.

5.3.3.4. NMR data for the minor (1*R*,4*S*,5*R*)-isomer 7′c. ^1H NMR ($CDCl_3$): δ 1.08, 1.26, 1.38 (9H, 3s, 1:1:1, 3Me); 2.66 (1H, d, $J = 4.9$ Hz, H–C(5)); 4.49 (1H, s, H–C(4)); 8.08 (1H, d, $J = 9.8$ Hz, H–C(8′)).

5.3.4. (1*R*,4*E*,5*S*)-4-{[(*E*)-(4-Chlorophthalazin-1-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6e. Prepared from compound **2** and 4-chloro-1-hydrazinophthalazine **3e**; stirring at rt for 72 h; CC (EtOAc–hexanes, 1:1; then EtOAc–hexanes, 2:1), followed by crystallisation from CH_2Cl_2–*n*-hexane. Yield: 156 mg (42%) of deep red crystals; mp 193–195 °C (from CH_2Cl_2–*n*-hexane); $[\alpha]_D^{21} = -215.9$ (*c* 0.063, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.12, 1.43 (9H, 2s, 2:1, 3Me); 1.75–1.84 (1H, m, 1H of CH_2); 2.12–2.48 (3H, m, 3H of CH_2); 4.24 (1H, d, $J = 6.4$ Hz, H–C(5)); 8.05–8.12 (2H, m, 2H of phthalazine); 8.17 (1H, s, H–C(4′)); 8.36–8.43 (1H, m, 1H of phthalazine); 8.51–8.57 (1H, m, 1H of phthalazine). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.8, 23.7, 27.9, 37.1, 45.6, 47.1, 95.2, 125.2, 125.7, 125.9, 127.8, 134.4, 134.5, 147.6, 149.8, 156.3, 160.4, 166.3. (Found: C, 61.29; H, 5.33; N, 14.82. $C_{19}H_{19}ClN_4O_2$ requires: C, 61.54; H, 5.16; N, 15.11); ν_{max} (KBr) 2971, 1715 (C=O), 1626, 1567, 1387, 1295, 1273, 1205, 1174, 1144, 1053, 980 cm^{-1}.

5.3.5. (1*R*,4*E*,5*S*)-4-{[(*E*)-(Pyrimidin-2-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 6f, (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*a*]pyrimidin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 7f and its (1*R*,4*S*,5*R*)-isomer 7′f. Prepared from compound **2** and 2-hydrazinopyrimidine **3f**; stirring at rt for 24 h; CC (EtOAc–hexanes, 2:1; then $CHCl_3$–MeOH, 20:1); MPLC ($CHCl_3$–MeOH, 20:1).

5.3.5.1. Data for (1*R*,4*E*,5*S*)-4-{[(*E*)-(pyrimidin-2-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 6f. Yield: 155 mg (54%) of deep red crystals; mp 186–191 °C (from EtOAc–*n*-heptane); $[\alpha]_D^{21} = -28.2$ (*c* 0.142, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.09, 1.10, 1.41 (9H, 3s, 1:1:1, 3Me); 1.71–1.81 (1H, m, 1H of CH_2); 2.09–2.46 (3H, m, 3H of CH_2); 4.11 (1H, d, $J = 6.0$ Hz, H–C(5)); 7.40 (1H, t, $J = 4.9$ Hz, H–C(5″)); 8.13 (1H, s, H–C(4′)); 8.98 (2H, d, $J = 4.5$ Hz, H–C(4″) and H–C(6″)). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.8, 23.7, 27.9, 37.1, 45.6, 47.0, 94.9, 121.6, 146.8, 149.9, 159.4, 166.1, 167.4. (Found: C, 63.17; H, 6.55; N, 19.77. $C_{15}H_{18}N_4O_2$ requires: C, 62.92; H, 6.34; N, 19.57); ν_{max} (KBr) 2964, 1714 (C=O), 1626, 1566, 1385, 1304, 1251, 1200, 1167, 1144, 1048 cm^{-1}.

5.3.5.2. Data for (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*a*]-pyrimidin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 7f and its (1*R*,4*S*,5*R*)-isomer 7′f. Yield: 11 mg (4%) of a white solid; **7f**:**7′f** = 77:23; mp 80–90 °C; $[\alpha]_D^{22} = -79.2$ (*c* 0.130, CH_2Cl_2). (Found: C, 63.16; H, 6.20; N, 19.84. $C_{15}H_{18}N_4O_2$ requires: C, 62.92; H, 6.34; N, 19.57); ν_{max} (KBr) 2972, 1731 (C=O), 1622, 1508, 1383, 1275, 1220, 1142, 1013, 957, 770 cm^{-1}.

5.3.5.3. NMR data for the major (1*R*,4*R*,5*R*)-isomer 7f. ^1H NMR ($CDCl_3$): δ 1.17, 1.28, 1.41 (9H, 3s, 1:1:1, 3Me); 2.03–2.40 (3H, m, 3H of CH_2); 2.53–2.63 (1H, m, 1H of CH_2); 2.76 (1H, dd, $J = 3.4$, 6.4 Hz, H–C(5)); 4.45 (1H, dd, $J = 1.9$, 3.4 Hz, H–C(4)); 6.90 (1H, dd, $J = 3.8$, 7.2 Hz, H–C(6′)); 8.58 (1H, dd, $J = 1.9$, 7.2 Hz, H–C(7′)); 8.68 (1H, dd, $J = 1.9$, 3.8 Hz, H–C(5′)).

5.3.5.4. NMR data for the minor (1*R*,4*S*,5*R*)-isomer 7′f. ^1H NMR ($CDCl_3$): δ 1.22 (3H, s, Me); 3.35 (1H, d, $J = 6.0$ Hz, H–C(5)); 4.05 (1H, s, H–C(4)); 8.85 (1H, dd, $J = 1.9$, 7.2 Hz, H–C(7′)).

5.3.6. (1*R*,4*E*,5*S*)-4-{[(*E*)-(Pyrazinyl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6g, (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 7g and its (1*R*,4*S*,5*R*)-isomer 7′g. Prepared from compound **2** and hydrazinopyrazine **3g**; stirring at rt for 24 h; CC (EtOAc–hexanes, 1:1; then EtOAc); MPLC (EtOAc).

5.3.6.1. Data for (1*R*,4*E*,5*S*)-4-{[(*E*)-(pyrazinyl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6g. Yield: 120 mg (42%) of deep red crystals; mp 179–186 °C (from EtOAc–*n*-heptane); $[\alpha]_D^{21} = -35.7$ (*c* 0.140, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.10, 1.13, 1.42 (9H, 3s, 1:1:1, 3Me); 1.71–1.81 (1H, m, 1H of CH_2); 2.10–2.47 (3H, m, 3H of CH_2); 4.06 (1H, d, $J = 6.4$ Hz, H–C(5)); 8.11 (1H, s, H–C(4′)); 8.71 (2H, s, H–C(3″), H–C(5″)); 8.99 (1H, s, H–C(6″)). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.8, 23.8, 27.9, 37.1, 45.5, 47.2, 94.8, 138.2, 144.4, 146.2, 146.9, 149.6, 158.2, 166.1. (Found: C, 63.08; H, 6.51; N, 19.31. $C_{15}H_{18}N_4O_2$ requires: C, 62.92; H, 6.34; N, 19.57); ν_{max} (KBr) 2982, 1715 (C=O), 1387, 1304, 1270, 1204, 1145, 1048, 1016 cm^{-1}.

5.3.6.2. Data for (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*a*]-pyrazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 7g and its (1*R*,4*S*,5*R*)-isomer 7′g. Yield: 17 mg (6%) of a white solid; **7g**:**7′g** = 85:15; mp 198–204 °C. (Found: C, 63.05; H, 6.26; N, 19.80. $C_{15}H_{18}N_4O_2$ requires: C, 62.92; H, 6.34; N, 19.57); ν_{max} (KBr) 2980, 1735 (C=O), 1474, 1396, 1268, 1255, 1165, 1142, 1060, 1014 cm^{-1}. Crystallisation from chloroform–*n*-heptane afforded isomerically pure **7g**.

5.3.6.3. Data for (1*R*,4*R*,5*R*)-4-([1,2,4]triazolo[4,3-*a*]-pyrazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 7g. Mp 200–205 °C (from chloroform–*n*-heptane); $[\alpha]_D^{22} = -175.0$ (*c* 0.112, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.17, 1.30, 1.42 (9H, 3s, 1:1:1, 3Me); 2.04–2.16 (1H, m, 1H of CH_2); 2.21–2.36 (2H, m, 2H of CH_2); 2.45–2.55 (1H, m, 1H of CH_2); 2.70 (1H, dd, $J = 3.4$, 6.4 Hz, H–C(5)); 4.51 (1H, dd, $J = 2.3$, 3.4 Hz, H–C(4)); 7.90 (1H, d, $J = 4.9$ Hz, H–C(8′)); 8.08 (1H, dd, $J = 1.5$, 4.9 Hz, H–C(6′)); 9.35 (1H, d, $J = 1.9$ Hz, H–C(5′)).

5.3.6.4. NMR data for the minor (1*R*,4*S*,5*R*)-isomer 7′g. ^1H NMR ($CDCl_3$): δ 1.24 (3H, s, Me); 3.29 (1H, d, $J = 6.0$ Hz, H–C(5)); 4.07 (1H, s, H–C(4)); 8.38 (1H, dd, $J = 1.5$, 4.9 Hz, H–C(6′)); 9.32 (1H, d, $J = 1.5$ Hz, H–C(5′)).

5.4. (1*R*,4*E*,5*S*)-4-{[(*E*)-(Phthalazin-1-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 6d

Lead tetraacetate (85%, 521 mg, 1 mmol) was added to a solution of **4d** and **4′d** (338 mg, 1 mmol, **4d**:**4′d** = 87:13, see Section 5.2.4.) in dichloromethane (8 ml) and the mixture stirred at rt for 3 h. Volatile components were evaporated in vacuo and the residue purified by CC (EtOAc). Fractions containing the product were combined and evaporated in vacuo and the residue crystallised from EtOAc–*n*-hexane to give **6d**. Yield: 282 mg (84%) of deep red crystals; mp 180–182 °C (from CH_2Cl_2–*n*-hexane–EtOAc); $[\alpha]_D^{21} = -106.3$ (*c* 0.025, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.11, 1.12, 1.43 (9H, 3s, 1:1:1, 3Me); 1.76–1.85 (1H, m, 1H of CH_2); 2.11–2.48 (3H, m, 3H of CH_2); 4.27 (1H, d, $J = 6.4$ Hz, H–C(5)); 7.99–8.10 (3H, m, 3H of phthalazine); 8.18 (1H, d, $J = 0.8$ Hz, H–C(4′)); 8.49–8.52 (1H, m, 1H of phthalazine); 9.58 (1H, d, $J = 1.1$ Hz, H–C(1′)). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.8, 23.7, 28.0, 37.1, 45.6, 47.0, 95.1, 124.4, 124.6, 126.7, 128.9, 133.5, 133.8, 147.0, 149.9, 153.1, 160.5, 166.4. (Found: C, 67.89; H, 6.18; N, 16.61. $C_{19}H_{20}N_4O_2$ requires: C, 67.84; H, 5.99; N, 16.66); ν_{max} (KBr) 2962, 1713 (C=O), 1624, 1408, 1396, 1298, 1271, 1203, 1172, 1143, 1048 cm^{-1}.

5.5. General procedure for oxidation of mixtures of hydrazones 8/8′b,c with lead tetraacetate in dichloromethane. Preparation of compounds 9/9′b,c and 10/10′b,c

Lead tetraacetate (85%, 521 mg, 1 mmol) was added to a solution of hydrazones **8/8′b**,**c**[23] dichloromethane (10 ml) and the mixture stirred at rt for 2 h. Volatile components were evaporated in vacuo and the residue purified by CC. The non-polar impurities were eluted first (EtOAc–hexanes, 1:5), followed by the elution of compounds **9/9′b**,**c** (EtOAc–hexanes, 1:2), followed by the elution of compounds **10/10′b**,**c** (EtOAc). Fractions containing the products were combined and evaporated in vacuo to give **9/9′b**,**c** and **10/10′b**,**c**. 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 9b, its (1*R*,3*S*,4*R*)-isomer 9′b, (1*R*,3*E*,4*S*)-3-{[(*E*)-(6-phenylpyridazin-3-yl)diazenyl]methylidene}-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one 10b, its (1*R*,3*Z*,4*S*)-isomer 10′b. Prepared from **1** and hydrazones **8/8′b** (**8b**:**8′b** = 89:11, 348 mg, 1 mmol).

5.5.1.1. Data for (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 9b and its (1*R*,3*S*,4*R*)-isomer 9′b. Yield: 204 mg (59%) of a white solid; **9b**:**9′b** = 93:7; with physical and spectral data identical to those reported in the literature.[15]

5.5.1.2. Data for (1*R*,3*E*,4*S*)-3-{[(*E*)-(6-phenylpyridazin-3-yl)diazenyl]methylidene}-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one 10b and its (1*R*,3*Z*,4*S*)-isomer 10′b. Yield: 21 mg (6%) of deep red crystals; **10b**:**10′b** = 30:70; mp 200–207 °C; $[\alpha]_D^{19} = +497.4$ (*c* 0.038, $CHCl_3$). *m*/*z* (EI) = 346 (M^+); *m*/*z* (HRMS) Found: 346.180440 (M^+), $C_{21}H_{22}N_4O$ requires: 346.179362. (Found: C, 71.69; H, 6.32; N, 16.20. $C_{21}H_{22}N_4O$ requires: C, 72.81; H, 6.40; N, 16.17); ν_{max} (KBr) 2958, 1726 (C=O), 1629, 1570, 1449, 1414, 1333, 1290, 1175, 1065, 1011 cm^{-1}.

5.5.1.3. NMR data for the minor (1*R*,3*E*,4*S*)-isomer 10b. ^1H NMR ($CDCl_3$): δ 0.95, 1.09 (9H, 2s, 1:2, 3Me); 3.70 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.91 (1H, d, $J = 9.0$ Hz, H–C(4″)); 7.93 (1H, d, $J = 0.8$ Hz, H–C(3′)); 8.01 (1H, d, $J = 9.0$ Hz, H–C(5″)).

5.5.1.4. NMR data for the major (1*R*,3*Z*,4*S*)-isomer 10′b. ^1H NMR ($CDCl_3$): δ 1.00, 1.08, 1.09 (9H, 3s, 1:1:1, 3Me); 1.61–1.71 (2H, m, 2H of CH_2); 1.81–1.91 (1H, m, 1H of CH_2); 2.19–2.31 (1H, m, 1H of CH_2); 2.90 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.51 (1H, s, H–C(3′)); 7.53–7.60 (3H, m, 3H of Ph); 7.98 (1H, d, $J = 9.0$ Hz, H–C(4″)); 8.06 (1H, d, $J = 9.1$ Hz, H–C(5″)); 8.17–8.21 (2H, m, 2H of Ph).

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 9c, its (1*R*,3*S*,4*R*)-isomer 9′c, (1*R*,3*E*,4*S*)-3-{[(*E*)-(6-chloropyridazin-3-yl)diazenyl]methylidene}-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one 10c and its (1*R*,3*Z*,4*S*)-isomer 10′c. Prepared from **1** and hydrazones **8/8′c** (**8c**:**8′c** = 61:39, 306 mg, 1 mmol).

5.5.2.1. Data for (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 9c and its (1*R*,3*S*,4*R*)-isomer 9′c. Yield: 189 mg (62%) of a white solid; **9c**:**9′c** = 96:4; with physical and spectral data identical to those reported in the literature.[15]

5.5.2.2. Data for (1*R*,3*E*,4*S*)-3-{[(*E*)-(6-chloropyridazin-3-yl)diazenyl]methylidene}-1,7,7-trimethylbicyclo-[2.2.1]-heptan-2-one 10c, its (1*R*,3*Z*,4*S*)-isomer 10′c. Yield: 27 mg (9%) of deep red crystals; **10c**:**10′c** = 31:69; mp 105–112 °C; $[\alpha]_D^{19} = -11.2$ (*c* 0.224, CH_2Cl_2). *m*/*z* (EI) = 304 (M^+); *m*/*z* (FAB) = 305 (MH^+); *m*/*z* (HRMS) Found: 304.110080 (M^+), $C_{15}H_{17}ClN_4O$ requires: 304.109089. (Found: C, 59.15; H, 5.82; N, 18.44. $C_{15}H_{17}ClN_4O$ requires: C, 59.11; H, 5.62; N, 18.38); ν_{max} (KBr) 2960, 1732 (C=O), 1634, 1555, 1394, 1372, 1176, 1133, 1075, 1064, 1009 cm^{-1}.

5.5.2.3. NMR data for the minor (1*R*,3*E*,4*S*)-isomer 10c. ^1H NMR ($CDCl_3$): δ 0.94, 1.09 (9H, 2s, 1:2, 3Me); 3.66 (1H, d, *J* = 4.1 Hz, H–C(4)); 7.66 (1H, d, *J* = 8.7 Hz, H–C(4″)); 7.83 (1H, d, *J* = 9.0 Hz, H–C(5″)); 7.90 (1H, d, *J* = 0.8 Hz, H–C(3′)).

5.5.2.4. NMR data for the major (1*R*,3*Z*,4*S*)-isomer 10′c. ^1H NMR ($CDCl_3$): δ 0.98, 1.07, 1.08 (9H, 3s, 1:1:1, 3Me); 1.59–1.70 (2H, m, 2H of CH_2); 1.81–1.91 (1H, m, 1H of CH_2); 2.19–2.31 (1H, m, 1H of CH_2); 2.91 (1H, d, *J* = 4.1 Hz, H–C(4)); 7.47 (1H, s, H–C(3′)); 7.63 (1H, d, *J* = 9.1 Hz, H–C(4″)); 7.98 (1H, d, *J* = 9.1 Hz, H–C(5″)).

5.6. Oxidation of a mixture of enehydrazine 4′b and hydrazones 5b and 5′b with lead tetraacetate in dichloromethane. Preparation of compounds 6′b, 7b, 7′b and 11

Lead tetraacetate (85%, 521 mg, 1 mmol) was added to a suspension of **4′/5/5′b** (**4′b**:**5b**:**5′b** = 17:71:12, 364 mg, 1 mmol) in dichloromethane (11 ml) and the mixture was stirred at rt for 1 h. Volatile components were evaporated in vacuo and the residue was purified by CC. Compound **6′b** was eluted first (EtOAc–hexanes, 1:1), followed by elution of compounds **7b**, **7′b** and **11** (EtOAc). Fractions containing the products were combined and evaporated in vacuo to give isomerically pure compound **6′b** and a mixture of **7b**, **7′b** and **11**, which were separated by MPLC (EtOAc). Fractions containing the products were combined and evaporated in vacuo to give isomerically pure compound **11** and a mixture of **7b** and **7′b**. Compounds **6′b**, **7/7′b** and **11** were prepared in this manner.

5.6.1. Data for (1*R*,4*Z*,5*S*)-4-{[(*E*)-(6-phenylpyridazin-3-yl)diazenyl]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one 6′b. Yield: 47 mg (13%) of deep red crystals; mp 154–155 °C (from EtOAc–*n*-heptane); $[\alpha]_D^{24} = +266.0$ (*c* 0.130, CH_2Cl_2). ^1H NMR are identical to those given in Section 5.3.2. ^{13}C NMR ($CDCl_3$): δ 18.5, 18.9, 24.0, 27.8, 37.1, 46.3, 53.5, 94.5, 117.2, 126.2, 128.0, 129.5, 131.2, 135.9, 141.0, 149.4, 160.9, 162.6, 166.2. (Found: C, 69.62; H, 6.18; N, 15.26. $C_{21}H_{22}N_4O_2$ requires: C, 69.59; H, 6.12; N, 15.46); ν_{max} (KBr) 2970, 1715 (C=O), 1611, 1572, 1454, 1414, 1165, 1138, 1063 cm^{-1}.

5.6.2. Data for (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-[3.2.1]octan-3-one 7b and its (1*R*,4*S*,5*R*)-isomer 7′b. Yield: 196 mg (54%) of a white solid, **7b**:**7′b** = 94:6, with physical and spectral data identical to those reported in Section 5.3.2.

5.6.3. Data for (1*R*,4*R*,5*S*)-3-oxo-4-(6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-oct-4-yl acetate 11. Yield: 25 mg (6%) of a white solid; mp 225–235 °C; $[\alpha]_D^{21} = -73.0$ (*c* 0.200, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 0.67, 1.08, 1.34 (9H, 3s, 1:1:1, 3Me); 2.00–2.34 (4H, m, 4H of CH_2); 2.04 (3H, s, OCOMe); 3.68 (1H, d, *J* = 5.7 Hz, H–C(5)); 7.52–7.55 (3H, m, 3H iz Ph); 7.62 (1H, d, *J* = 9.8 Hz, H–C(7′)); 8.00–8.03 (2H, m, 2H iz Ph); 8.14 (1H, d, *J* = 9.8 Hz, H–C(8′)). ^{13}C NMR ($CDCl_3$): δ 18.4, 18.9, 21.5, 22.1, 25.4, 35.7, 46.5, 53.7, 78.8, 97.5, 119.6, 125.3, 127.8, 129.6, 131.4, 134.5, 144.2, 148.1, 153.4, 166.8, 169.1. *m*/*z* (EI) = 420 (M^+); *m*/*z* (HRMS) Found: 420.180110 (M^+), $C_{23}H_{24}N_4O_4$ requires: 420.179756. (Found: C, 65.50; H, 5.83; N, 13.05. $C_{23}H_{24}N_4O_4$ requires: C, 65.70; H, 5.75; N, 13.33); ν_{max} (KBr) 2970, 1770 (C=O), 1752 (C=O), 1473, 1393, 1371, 1334, 1215, 1165, 1113, 1024 cm^{-1}.

5.7. (1*R*,4*R*,5*S*)-3-Oxo-4-(6-phenyl[1,2,4]triazolo[4,3-*b*]-pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]oct-4-yl acetate 11 and its (1*R*,4*S*,5*S*)-isomer 11′

Lead tetraacetate (85%, 42 mg, 0.08 mmol) was added to a solution of **7/7′b** (**7b**:**7′b** = 96:4, 29 mg, 0.08 mmol) in dichloromethane (2.5 ml) and the mixture was stirred at rt for 3 h. Volatile components were evaporated in vacuo and the residue was purified by CC ($CHCl_3$–MeOH, 20:1). Fractions containing the product were combined and evaporated in vacuo to give a mixture of **11** and its epimer **11′**, which was characterised by ^1H NMR. Yield: 29 mg (87%) of a white solid; **11**:**11′** = 73:27. ^1H NMR data for **11** were identical to those given above in Section 5.6.3.

5.7.1. NMR data for the minor (1*R*,4*S*,5*S*)-isomer 11′b. ^1H NMR ($CDCl_3$): δ 1.26, 1.38, 1.43 (9H, 3s, 1:1:1, 3Me); 2.10 (3H, s, OCOMe); 3.04 (1H, d, *J* = 6.8 Hz, H–C(5)); 7.61 (1H, d, *J* = 9.8 Hz, H–C(7′)); 7.92–7.97 (2H, m, 2H of Ph).

5.8. (1*R*,3*R*,4*S*)-3-Bromo-3-(6-phenyl[1,2,4]triazolo[4,3-*b*]-pyridazin-3-yl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one 12 and its (1*R*,3*S*,4*S*)-isomer 12′

Bromine (0.1 ml, 2 mmol) was added to a solution of **9** and **9′b** (**9b**:**9′b** = 92:8, 346 mg, 1 mmol) in dichloromethane (13 ml), the mixture was refluxed for 5 h and cooled to rt. Then dichloromethane (50 ml) was added and the solution washed with saturated aqueous $NaHCO_3$ (60 ml) and brine (60 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate evaporated in vacuo. The residue was purified by CC (EtOAc). Fractions containing the products were combined and evaporated in vacuo to give a 1:1 mixture of **12** and **12′**. Yield: 370 mg (87%) of a white solid. Isomeric compounds **12** and **12′** were separated by MPLC (EtOAc–hexanes, 2:1). Fractions containing the products were combined and evaporated in vacuo to give isomerically pure compounds **12** and **12′**.

5.8.1. Data for (1*R*,3*R*,4*S*)-3-bromo-3-(6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one 12. Yield: 180 mg (42%) of a white solid; mp 198–201 °C; $[\alpha]_D^{22} = +202.6$ (*c* 0.350, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.53, 1.03 (9H, 2br s, 1:2, 3Me); 1.54–1.63 (1H, m, 1H of CH_2); 1.84–1.93 (1H, m, 1H of CH_2); 2.23–2.44 (2H, m, 2H of CH_2); 3.65 (1H, br s, H–C(4)); 7.64–7.67 (3H, m, 3H of Ph); 8.10 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.16 (2H, br s, 2H of Ph); 8.54 (1H, br d, $J = 9.8$ Hz, H–C(8′)). (Found: C, 59.49; H, 5.07; N, 13.44. $C_{21}H_{21}BrN_4O$ requires: C, 59.30; H, 4.98; N, 13.17); ν_{max} (KBr) 2957, 1762 (C=O), 1545, 1471, 1436, 1373, 1331, 1006, 799, 781 cm^{-1}.

5.8.2. Data for (1*R*,3*S*,4*S*)-3-bromo-3-(6-phenyl[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one 12′. Yield: 178 mg (42%) of a white solid; mp 201–204 °C; $[\alpha]_D^{22} = -287.1$ (*c* 0.132, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.36–0.45 (1H, m, 1H of CH_2); 1.02, 1.07, 1.32 (9H, 3s, 1:1:1, 3Me); 1.35–1.44 (1H, m, 1H of CH_2); 1.57–1.66 (1H, m, 1H of CH_2); 1.78–1.90 (1H, m, 1H of CH_2); 3.38 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.63–7.67 (3H, m, 3H of Ph); 8.12 (1H, d, $J = 9.8$ Hz, H–C(7′)); 8.18–8.21 (2H, m, 2H of Ph); 8.54 (1H, d, $J = 9.8$ Hz, H–C(8′)). (Found: C, 59.38; H, 5.07; N 13.35. $C_{21}H_{21}BrN_4O$ requires: C, 59.30; H, 4.98; N, 13.17); ν_{max} (KBr) 2962, 1760 (C=O), 1546, 1474, 1436, 1398, 1334, 791, 780 cm^{-1}.

5.9. X-ray structure analysis for compounds 6c, 11, 12 and 12′

Single crystal X-ray diffraction data of compounds **6c**, **11**, **12** and **12′** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[55] DENZO and SCALEPACK[56] were used for indexing and scaling of the data. The structure was solved by means of SIR97.[57] Refinement was done using Xtal3.4[58] program package and the crystallographic plot was prepared by ORTEP III[59]. 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[60] weighting scheme was used.

The crystallographic data for compounds **6c**, **11**, **12** and **12′** have been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition numbers: CCDC 273752-273755. These data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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