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Stereoselective [4+2] cycloadditions of tetrazines to 3-oxo- and 3-arylimino-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furans]

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Abstract—Stereoselective inverse-demand [4+2] cycloadditions of 3,6-bis(pyridin-2-yl)-1,2,4,5-tetrazine and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate to 4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furans] and 4′-methylene-1′-(4-nitrophenyl)spiro[bicyclo-[2.2.1]heptane-3,2′-pyrrolidine] were studied. Cycloadditions took place stereoselectively at the exocyclic C=C double bonds to give novel 11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadecane and 11:14-isopropylidene-11-methyl-2,3,8-triazadispiro-[5.1.5.2]pentadecane derivatives in 50–98% de. The structures of the novel dispiro compounds were determined by NMR techniques, NOESY spectroscopy and X-ray diffraction.

1. Introduction

Camphor and its derivatives are amongst the most frequently employed types of chiral pool starting materials, building blocks, resolving agents, shift reagents in NMR spectroscopy and ligands in various asymmetric reagents and/or catalysts.[1–4]

Within the fully unsaturated six-membered nitrogen heterocycles, 1,2,4,5-tetrazines represent an important group of heterocycles, which have found use in various applications. For example, 1,2,4,5-tetrazines can act as reactive electron-poor dienes in inverse-demand [4+2] cycloadditions to various electron-rich dienophiles. Generally, reactions with alkynes require higher temperatures and prolonged reaction times than reactions with alkenes. Cycloadditions of 1,2,4,5-tetrazines to alkynes proceed via initially formed 2,3,5,6-tetraazabicyclo[2.2.2]octa-2,5,7-trienes, which immediately decompose with the extrusion of nitrogen to form pyridazine derivatives. In the reactions of tetrazines with bicyclo[2.2.1]hept-2-ene, bicyclo[2.2.2]octa-2,5-diene and related systems, the initially formed fused dihydropyridazines may undergo a cycloreversion reaction via elimination of the pyridazine derivative to give the corresponding cyclopentadienes, benzenes and related systems.[5–7] However, despite the widely elaborated [4+2] cycloaddition chemistry of 1,2,4,5-tetrazines, only a few examples of cycloadditions to the exocyclic C=C double bonds leading to spirodihydropyridazines have been reported (Fig. 1).[8,9]

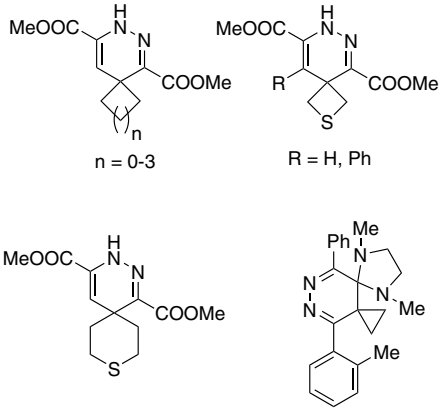

Figure 1. Known examples of spiro-1,4-dihydropyridazines and spiro-4,5-dihydropyridazines obtained by [4+2] cycloaddition of tetrazines to exocyclic C=C double bonds.

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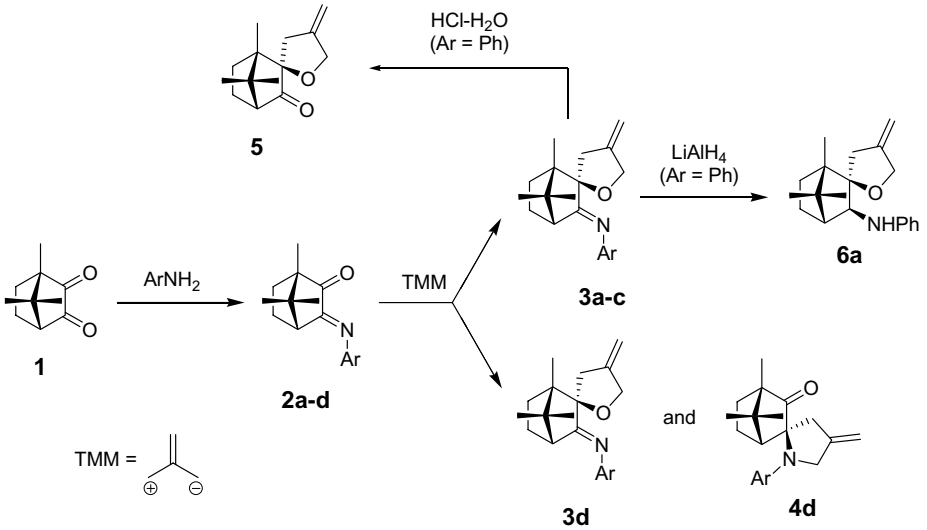
Recently, a series of 3-(dimethylamino)prop-2-enoates and related enaminones have been prepared as versatile reagents in the synthesis of functionalised heterocycles and natural product analogues.[10] Within this context, (+)-camphor derived enaminones have been used in coupling reactions with amines[11] and Grignard reagents,[12] and in the synthesis of (1*R*,4*S*,5*S*)-4-dialkylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones[13] and various terpene-functionalised heterocycles.[14] Recently, we reported the highly stereoselective [3+2] cycloadditions of trimethylenemethane (TMM) to 3-arylimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones **2** leading to 4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furans] **3**, **5** and 4′-methylene-1′-(nitrophenyl)spiro[bicyclo[2.2.1]heptane-3,2′-pyrrolidines] **4** and further reductions of these cycloadducts into novel non-racemic amines, diamines and aminoalcohols.[15] In continuation of this study, we herein report [4+2] cycloadditions of 3,6-disubstituted 1,2,4,5-tetrazines **7a** and **7b** to 4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]-heptane-2,2′-furans] **3a–d**, **5**, **6a** and 4′-methylene-1′-(4-nitrophenyl)spiro[bicyclo[2.2.1]heptane-3,2′-pyrrolidine] **4d**, which afforded novel dispiro compounds, 11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dienes **8a**,**b**, **9a–e** and **11** and 11:14-isopropylidene-11-methyl-2,3,8-triazadispiro[5.1.5.2]pentadeca-1,4-diene **10**.

2. Results and discussion

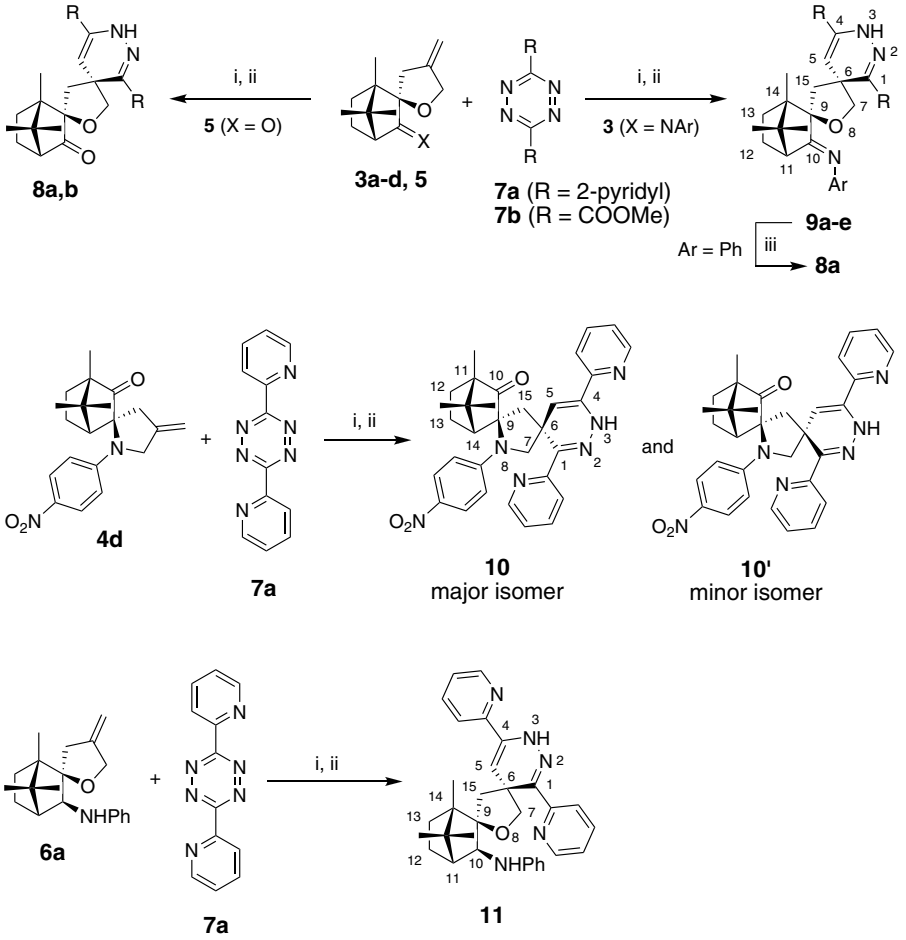
The starting imines **2a–d** were prepared from (1*S*)-(+)-camphorquinone **1** according to a literature procedure. Next, the desired spiro dienophiles **3a–d** and **4d** were prepared by the [3+2] cycloadditions of trimethylenemethane (TMM) to 3-arylimino-(1*S*)-(+)-camphorquinones **2a–d** following the previously reported general procedure. Finally, hydrolysis of imine **3a** gave furan **5**, while reduction of imine **3a** with $LiAlH_4$ gave secondary amine **6a** (Scheme 1).[15]

Inverse-demand [4+2] cycloadditions of tetrazines **7a**[16] and **7b**[17,18] to dienophiles **3–6** were studied in order to prepare novel dispiroheterocyclic systems possessing interesting structural features. All inverse-demand [4+2] cycloadditions of tetrazines **7a** and **7b** to dienophiles **3–6** were carried out under argon in refluxing toluene. Reactions of tetrazines **7a** and **7b** with spirofuranone **5** and spirofuranone imines **3a–d** proceeded with excellent selectivities to give the corresponding cycloadducts **8a** and **8b** and **9a–e** as the major isomers in 84–98% de. Further chromatographic purification furnished isomerically pure (6*R*,9*R*,11*R*,14*S*)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dien-10-ones **8a** and **8b** and their arylimines **9a–e** in 45–81% yields. Acid-catalysed hydrolysis of imine **9a** gave a mixture of ketone **8a** and aniline in a ratio of 2:1, respectively. In contrast to highly stereoselective [4+2] cycloadditions of tetrazines **7a** and **7b** to spirofuranone imines **3** and spirofuranone **5**, the cycloaddition of tetrazine **7a** to spiropyrrolidinone **4d** proceeded with moderate selectivity and furnished a mixture of (6*R*,9*S*,11*S*,14*R*)-1,4-bis(pyridin-2-yl)-11:14-isopropylidene-11-methyl-8-(4-nitrophenyl)-2,3,8-triazadispiro[5.1.5.2]pentadeca-1,4-dien-10-one **10** and its (6*S*,9*S*,11*S*,14*R*)-epimer **10′** in a ratio of 75:25, respectively, in



Compound	Ar
2a, **3a**, **6a**	phenyl
2b, **3b**	1-naphthyl
2c, **3c**	2-nitrophenyl
2d, **3d**, **4d**	4-nitrophenyl

Scheme 1. Synthesis of dienophiles **3–6**.[15]



Scheme 2. Reagents and conditions: (i) Toluene, reflux; (ii) chromatographic purification; (iii) HCl, MeOH, H_2O, 0 °C→rt.

54% yield. The ratio of isomers, **10**:**10′** = 75:25, remained unchanged upon attempted chromatographic separation. Similarly, reaction of **7a** with 3-anilino-4′-methylene-dihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan] **6a** afforded a mixture of epimeric cycloadducts **11** and **11′** in a ratio of 81:19. Further chromatographic purification furnished isomerically pure compound **11** in 45% yield (Scheme 2, Table 1).

Inverse-demand [4+2] cycloadditions of 3,6-disubstituted 1,2,4,5-tetrazines **7a** and **7b** proceeded predominantly from the *Re*-face of the exocyclic C=C double bond of spirofurans **3a**–**d**, **5** and **6a** and from the *Si*-face of the C=C double bond in the spiropyrrolidine **4d** due to the steric hindrance imposed by an α-imino, or α-keto or α-amino group. Surprisingly, cycloadditions to dienophiles **4d** and **6a** with an *exo*-anilino group were substantially less selective (50% and 62% de, respectively) than cycloadditions to dienophiles **3a**–**d** and **5** (84–98% de). Steric arguments seem quite weak here and a better explanation for the high facial selectivity of cycloadditions to spirofurans **3a**–**d** and **5** might be due to the electronic interaction (repulsion) between the furan oxygen and the carbonyl (or imino) group, which forces the furan ring to adopt conformation **3″** (or **5″**) with the exposed *Re*-face of the exocyclic C=C double bond. On the other hand, the strongly electron withdrawing group on the pyrrolidine nitrogen in **4d** and the absence of the imino group in compound **6a** both diminish the interaction discussed above and, consequently, lead to a reduction of facial selectivity (Fig. 2).

Table 1. Selected experimental data for compounds **8a**,**b**, **9a**–**e**, **10**/**10′** and **11**

Reaction	Ar	Ratio of isomers[a]	de (%)[a]	Yield (%)[b]
5 + **7a**→**8a**	—	98:2	96	81
5 + **7b**→**8b**	—	92:8	84	77
3a + **7a**→**9a**	Phenyl	97:3	94	45
3b + **7a**→**9b**	Naphth-1-yl	98:2	96	55
3c + **7a**→**9c**	2-Nitrophenyl	99:1	98	74
3d + **7a**→**9d**	4-Nitrophenyl	97:3	94	55
3d + **7b**→**9e**	4-Nitrophenyl	97:3	94	80
4d + **7a**→**10** + **10′**	4-Nitrophenyl	75:25	50	54[d]
6a + **7a**→**11**	Phenyl	81:19	62	45
9a→**8a**	—	100:0	100	[c]

[a] Determined by ^{1}H NMR of the crude reaction mixture or after FC.
[b] Isolated yield of the isomerically pure compound (unless otherwise stated).
[c] Isolated as a mixture of compound **8a** and aniline in a ratio of 2:1, respectively.
[d] Isolated as a mixture of isomers **10** and **10′** in a ratio of 75:25, respectively.

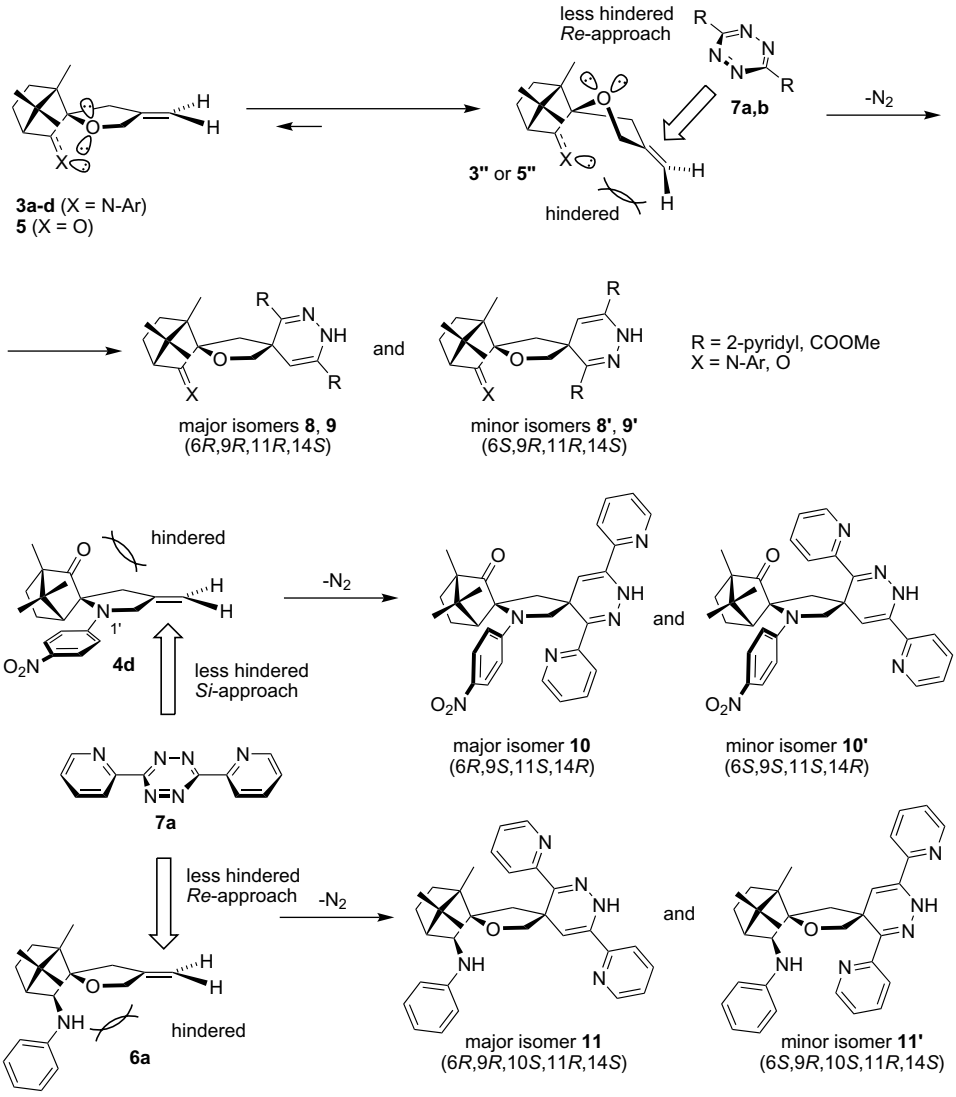


Figure 2. Stereoselectivity of [4+2] cycloadditions of 1,2,4,5-tetrazines **7a** and **7b** to the exocyclic C=C double bonds of dienophiles **3**–**6**.

3. Structure determination

The structures of compounds **8/8′a**,**b**, **9/9′a**–**e**, **10/10′** and **11/11′** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, NOESY spectroscopy and MS) and by elemental analyses for C, H and N. Compounds **8a** and **8b**, **9a**–**e** and **11** were prepared in isomerically pure form. Compounds **10/10′** were characterised as a mixture of major isomer **10** and minor isomer **10′**. The minor isomers **8′a**,**b**, **9′a**–**e** and **11′** were characterised only by ^{1}H NMR. Compounds **8a**,**b**, **9a**–**c**, and **10/10′** were not prepared in analytically pure form; their identities were confirmed by ^{13}C NMR and EI-HRMS.

The configuration at position 10 in the isomeric secondary amines **11** and **11′** was determined by ^{1}H NMR on the basis of vicinal coupling constants ($^{3}J_{H(10)-H(11)}$) and multiplicity of the proton *H*–C(10).[14,15,19,20] In the secondary *exo*-amines **11** and **11′**, the dihedral angle between *H*–C(10) and *H*–C(11) is close to 90° and, following the Karplus equation,[21] no appreciable coupling between these protons would be expected. Accordingly, negligible coupling constants, $^{3}J_{H(10)-H(11)} \sim 0$ Hz, were observed in the ^{1}H NMR spectra of epimeric compounds **11** and **11′**. The configuration at position 10 in the secondary amine **11′** was additionally confirmed by NOESY spectroscopy on

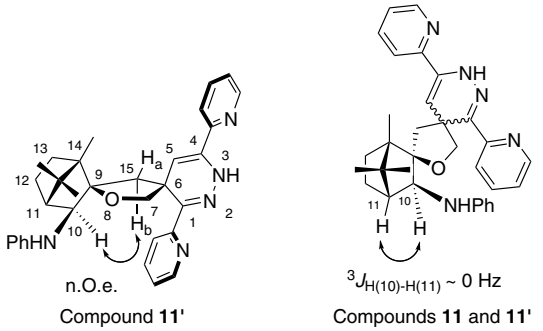


Figure 3. Structure determination of compounds **11/11′** by ^{1}H NMR and NOESY spectroscopy.

Table 2. Selected ^{1}H NMR (300.13 MHz, $CDCl_3$) data for compounds **8/8′a,b**, **9/9′a–e**, **10/10′** and **11/11′**

	δ (ppm)							
	H–C(5)	*H*a–C(7)	*H*b–C(7)	*H*–C(10)	*H*–C(11)[a]	*H*a–C(15)	*H*b–C(15)	*H*–N(3)
Major isomers **8a,b**, **9a–e**, **10**, **11**								
8a	6.31	3.94	4.68	—	2.19	1.87	3.31	9.13
8b	6.63	3.94	4.36	—	2.19	1.76	2.78	8.29
9a	6.74	4.10	4.69	—	2.46	2.11	3.34	9.11
9b	6.79	4.24	4.75	—	2.43	2.29	3.40	9.18
9c	6.40	4.11	4.68	—	2.35	2.28	3.30	9.13
9d[b]	6.53	4.04	4.74	—	2.32	2.12	3.40	9.14
9e[b]	6.94	4.09	4.43	—	2.37	2.00	2.87	8.17
10	6.00	4.25	4.37	—	3.15	1.96	3.08	9.24
11[b]	5.40	3.91	4.80	3.27	1.82	2.03	3.40	9.14
Minor isomers **8′a,b**, **9′a–e**, **10′**, **11′**								
8′a	[c]	[c]	[c]	—	[c]	[c]	[c]	9.41
8′b	[c]	[c]	[c]	—	[c]	[c]	[c]	8.33
9′a	[c]	[c]	[c]	—	[c]	[c]	[c]	9.40
9′b	[c]	[c]	[c]	—	[c]	[c]	[c]	9.42
9′c	[c]	[c]	[c]	—	[c]	[c]	[c]	9.36
9′d	[c]	[c]	[c]	—	[c]	[c]	[c]	9.38
9′e	[c]	[c]	[c]	—	2.28	[c]	2.67	8.38
10′	5.37	3.55	4.62	—	2.48	2.35	3.06	9.30
11′[d]	5.59	3.83	4.81	3.36	1.86	2.41	3.11	9.10

[a] Signal *H*–C(14) in the case of compounds **10** and **10′**.
[b] The structure was determined by X-ray diffraction.
[c] Overlapped by other signals.
[d] The structure was determined by NOESY spectroscopy.

the basis of NOE between *H*–C(10) and *H*b–C(15), which was in agreement with the *exo*-configuration of the secondary amine. Finally, the configurations of compounds **8/8′a,b**, **9/9′a–e**, **10/10′** and **11/11′** were confirmed by correlation of the chemical shifts (Fig. 3, Table 2).

The structures of compounds **9d**, **9e** and **11** were determined by X-ray diffraction (Figs. 4–6). These data also offer an additional and unambiguous proof for the structures of starting dienophiles **3a–d**, **5** and **6a**.[15] The structure of compound **8a** was confirmed by acid-catalysed hydrolysis of compound **9a** (cf. Scheme 2).

On the basis of X-ray diffraction analysis data for compounds **9d** and **9e** (Figs. 4 and 5) and taking into account that the (*E*)-configuration imposes less steric strain than the (*Z*)-configuration around the exocyclic C=N double bond, it is safe to assume the (*E*)-configuration in all imines **9a–e** and **9′a–e**.

4. Conclusion

Stereoselective [4+2] cycloadditions of 3,6-disubstituted 1,2,4,5-tetrazines **7a,b** to the exocyclic C=C double bonds of 3-arylimino and 3-oxo substituted spirofurans **3a–d** and **5** gave the corresponding dispirofurans **9a–e** and **8a** and **8b** as the major isomers in 84–98% de. On the other hand, cycloadditions of **7a** to spiropyrrolidine **4d** and to 3-anilino substituted spirofuran **6** were less stereoselective and furnished the corresponding cycloadducts **10** and **11** in 62% and 50% de, respectively. A significant difference in stereodirecting effect of the imino or keto group in dienophiles **3** and **5** versus the *exo*-amino group in dienophiles **4d** and **6a** in cycloaddition reactions with 1,2,4,5-tetrazines **7a** and **7b** was observed. The structures of 11:14-isopropylidene-14-methyl-10-oxo-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-diene derivatives **9d**, **9e** and **11** were determined by X-ray diffraction. Thus, the [4+2] cycloaddition reactions of 1,2,4,5-tetrazines to spirofurans and spiropyrrolidines provided access to 2,3-diaza-8-oxadispiropentadeca-1,4-dienes and 2,3,8-triazadispiropentadeca-1,4-dienes, respectively, as novel chiral dispiro heterocyclic systems.

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. All NMR experiments were carried out at 302 K. Optical rotations were measured on a Perkin–Elmer 241MC Polarimeter. 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

[†] Donation of Alexander von Humboldt Foundation.

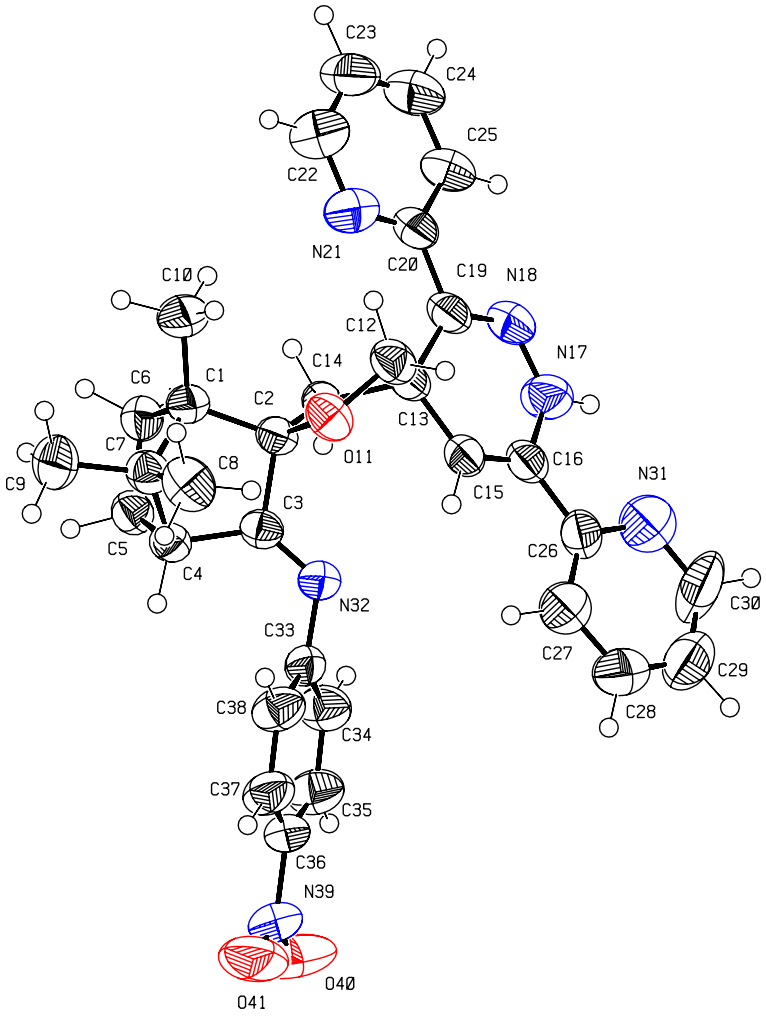


Figure 4. The asymmetric unit of compound **9d**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

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. Ratio of isomers and de were determined by ^{1}H NMR. Dienophiles **3a**–**d**, **4**, **5** and **6**,[15] 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **7a**,[16] and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **7b**[17,18] were prepared according to the literature procedures. Source of chirality: (1*S*)-(+)-camphorquinone (**1**), 99%, (Fluka AG), product number 27,207-8, $[\alpha]_D^{20} = +100$ (*c* 1.9, toluene), mp 200–202 °C.

5.2. General procedure for cycloadditions of 1,2,4,5-tetrazines 7a,b to methylene compounds 3–6

A mixture of dienophiles **3**–**6** (0.5 mmol), tetrazine **7a** (118 mg, 0.5 mmol) or **7b** (99 mg, 0.5 mmol) and anhydrous toluene (6 mL) under argon was heated at reflux for either 30 h or 3 h, respectively. Volatile components were evaporated in vacuo and the residue was purified by CC to give **8a**,**b**, **9a**–**e**, **10** and **11** in 50–98% de. Further chromatographic purification by CC and/or MPLC afforded isomerically pure compounds **8a**,**b**, **9a**–**e** and **11**. Compounds **8a**,**b**, **9a**–**e**, **10**/**10′** and **11** were prepared in this manner.

5.2.1. (6*R*,9*R*,11*R*,14*S*)-1,4-Bis(pyridin-2-yl)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dien-10-one 8a and its (6*S*,9*R*,11*R*,14*S*)-isomer 8′a.

Prepared from tetrazine **7a** and compound **5** (110 mg, 0.5 mmol), reflux for 30 h; CC: first (EtOAc, **8a**:**8′a** = 98:2), then (EtOAc–hexanes, 1:3; **8a**:**8′a** = 100:0).

5.2.1.1. Data for major (6*R*,9*R*,11*R*,14*S*)-isomer 8a. 0.090 g (81%) of a yellowish solid; mp 104–145 °C; $[\alpha]_{589}^{25} = +64.0$ (*c* 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.97, 1.15 (9H, 3s, 1:2, 3Me); 1.35–1.45 (1H, m, 1H of CH_2); 1.48–1.57 (1H, m, 1H of CH_2); 1.62–1.72 (1H, m, 1H of CH_2); 1.87 (1H, d, $J = 12.8$ Hz, Ha–C(15)); 1.84–1.93 (1H, m, 1H of CH_2); 2.19 (1H, d, $J = 5.3$ Hz, H–C(11)); 3.31 (1H, d, $J = 12.8$ Hz, Hb–C(15)); 3.94 (1H, d, $J = 7.9$ Hz, Ha–C(7)); 4.68 (1H, d, $J = 8.3$ Hz, Hb–C(7)); 6.31 (1H, d, $J = 1.9$ Hz, H–C(5)); 7.16–7.24 (2H, m, 2H of Ar); 7.63–7.78 (3H, m, 3H of Ar); 7.90 (1H, d, $J = 7.9$ Hz, 1H of Ar); 8.50–8.54 (2H, m, 2H of Ar); 9.13 (1H, s, NH). ^{13}C NMR ($CDCl_3$): δ 9.1, 18.9, 21.9, 22.1, 30.8, 44.4, 45.9, 46.5, 53.4, 60.3, 80.2, 90.5, 104.8, 119.4, 122.5, 122.7, 122.8, 132.8, 136.3, 136.6, 139.9, 147.6, 148.2, 150.5, 156.4, 220.3. *m*/*z* (EI) = 428 (M^+); *m*/*z* (HRMS) found: 428.222060 (M^+); $C_{26}H_{28}N_4O_2$ requires:

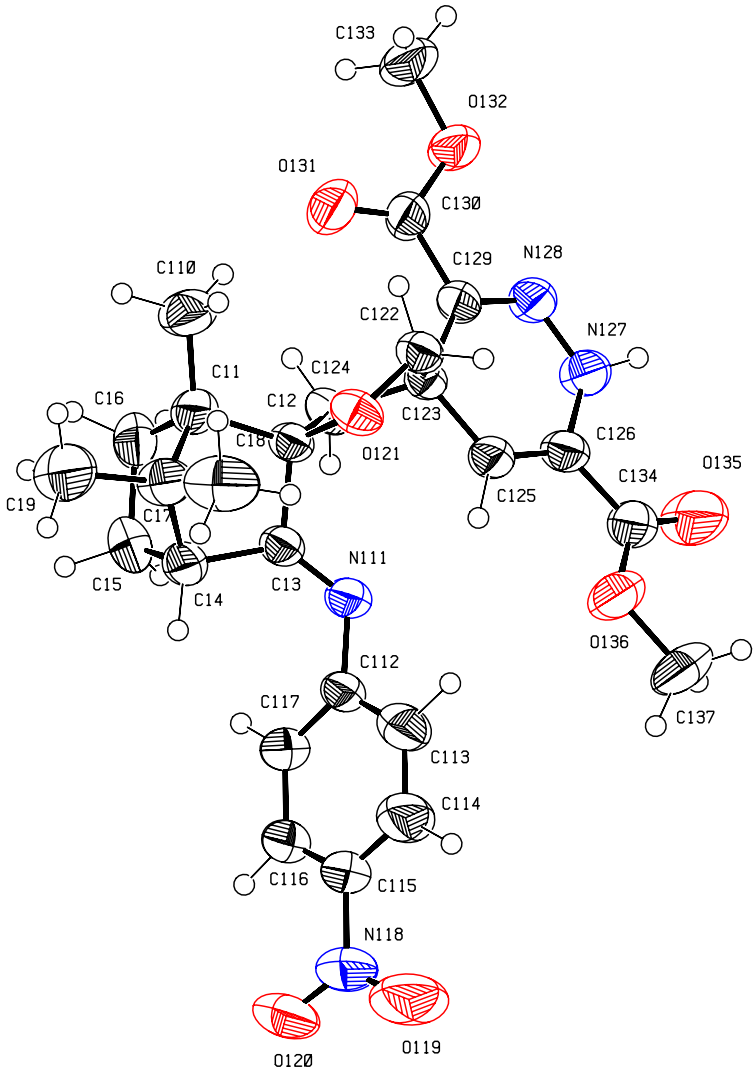


Figure 5. The asymmetric unit of compound **9e**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

$m/z = 428.221226$ (found: C, 71.44; H, 6.76; N, 12.05. $C_{26}H_{28}N_4O_2$ requires: C, 72.87; H, 6.59; N, 13.07.); ν_{max} (KBr) 3414, 2962, 1743 (C=O), 1590, 1565, 1467, 1457, 1424, 1393, 1373, 1284, 1245, 1177, 1155, 1095, 1054, 1024, 994, 780, 745 cm^{-1}.

5.2.1.2. Data for minor (6*S*,9*R*,11*R*,14*S*)-isomer 8′a. ^1H NMR ($CDCl_3$): δ 9.41 (1H, br s, NH).

5.2.2. Dimethyl (6*R*,9*R*,11*R*,14*S*)-11:14-isopropylidene-14-methyl-10-oxo-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-diene-1,4-dicarboxylate 8b and its (6*S*,9*R*,11*R*,14*S*)-isomer 8′b. Prepared from tetrazine **7b** and compound **5** (110 mg, 0.5 mmol), reflux for 3 h; **8b**:**8′b** = 92:8 (crude reaction mixture); CC (EtOAc–hexanes, 1:3; **8b**:**8′b** = 100:0).

5.2.2.1. Data for major (6*R*,9*R*,11*R*,14*S*)-isomer 8b. 0.151 g (77%) of a white solid; mp 227–228 °C; $[\alpha]_{589}^{25} = +144.9$ (*c* 0.18, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.96, 1.08, 1.11 (9H, 3s, 1:1:1, 3Me); 1.34–1.53 (2H, m, 2H of CH_2); 1.65–1.75 (1H, m, 1H of CH_2); 1.76 (1H, d, $J = 13.2$ Hz, Ha–C(15)); 1.85–1.97 (1H, m, 1H of CH_2); 2.19 (1H, d, $J = 4.9$ Hz, H–C(11)); 2.78 (1H, d, $J = 13.2$ Hz, Hb–C(15)); 3.82 (3H, s, COOMe); 3.86 (3H, s, COOMe); 3.94 (1H, d, $J = 9.0$ Hz, Ha–C(7)); 4.36 (1H, d, $J = 9.1$ Hz, Hb–C(7)); 6.63 (1H, d, $J = 2.3$ Hz, H–C(5)); 8.29 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 9.1, 18.8, 22.0, 22.1, 30.9, 42.4, 46.6, 47.8, 52.3, 52.7, 53.0, 60.1, 81.7, 90.7, 115.7, 124.9, 131.4, 162.1, 164.2, 219.9. m/z (EI) = 390 (M^+); m/z (HRMS) found: 390.180050 (M^+); $C_{20}H_{26}N_2O_6$ requires: $m/z = 390.179087$ (found: C, 61.08; H, 6.75; N, 8.05. $C_{20}H_{26}N_2O_6$ requires: C, 61.53; H, 6.71; N, 7.18.); ν_{max} (KBr) 3437, 3081, 2961, 2856, 1743 (C=O), 1719 (C=O), 1665, 1573, 1460, 1437, 1399, 1379, 1356, 1344, 1296, 1283, 1249, 1205, 1154, 1115, 1099, 1053, 1018, 953, 817, 765 cm^{-1}.

5.2.2.2. Data for minor (6*S*,9*R*,11*R*,14*S*)-isomer 8′b. ^1H NMR ($CDCl_3$): δ 8.33 (1H, br s, NH).

5.2.3. *N*-[(6*R*,9*R*,10*E*,11*R*,14*S*)-1,4-Bis(pyridin-2-yl)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dien-10-ylidene]aniline 9a and its (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′a. Prepared from tetrazine **7a** and com-

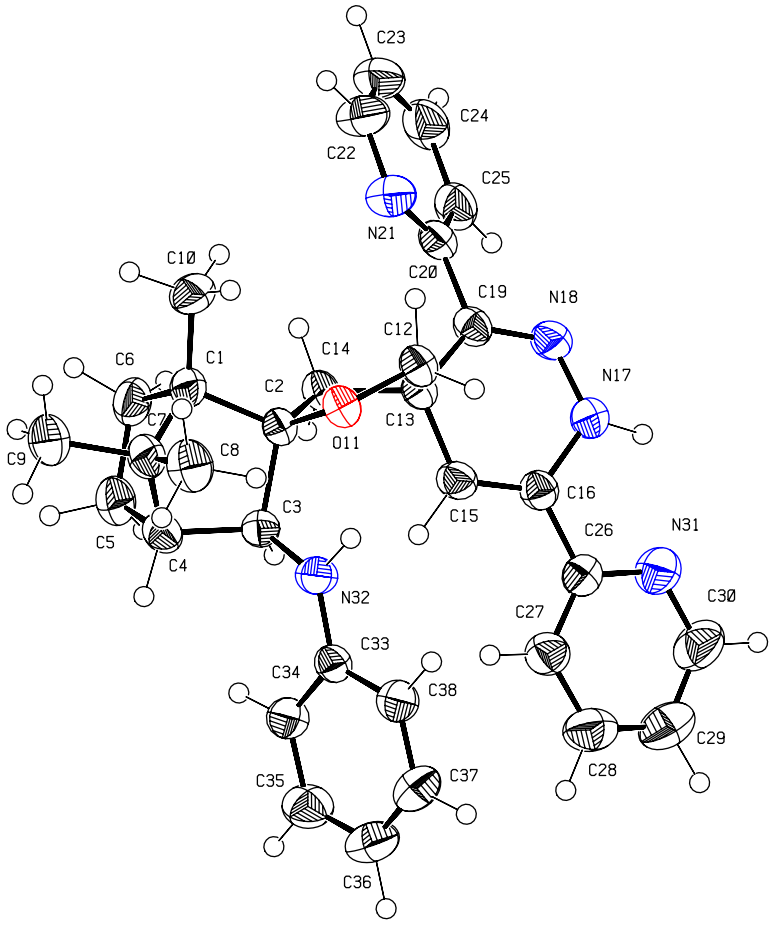


Figure 6. The asymmetric unit of compound **11**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

pound **3a** (148 mg, 0.5 mmol), reflux for 30 h, CC: first (EtOAc, **9a**:**9′a** = 97:3) then (EtOAc–hexanes, 1:3; **9a**:**9′a** = 100:0).

5.2.3.1. Data for major (6*R*,9*R*,10*E*,11*R*,14*S*)-isomer 9a. Yield: 0.114 g (45%) of a brownish-yellow solid; mp 69–78 °C; $[\alpha]_D^{26} = +38.8$ (*c* 0.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.87, 1.15, 1.18 (9H, 3s, 1:1:1, 3 × Me); 1.21–1.30, 1.53–1.581.66–1.77 (4H, 3m, 1:2:1, 2 × CH_2); 2.11 (1H, d, $J = 12.4$ Hz, Ha–C(15)); 2.46 (1H, d, $J = 4.9$ Hz, H–C(11)); 3.34 (1H, d, $J = 12.4$ Hz, Hb–C(15)); 4.10 (1H, d, $J = 7.9$ Hz, Ha–C(7)); 4.69 (1H, d, $J = 8.3$ Hz, Hb–C(7)); 6.74 (1H, d, $J = 2.2$ Hz, H–C(5)); 6.79–6.84 (2H, m, 2H of Ar); 7.04–7.15 (2H, m, 2H of Ar); 7.17–7.22 (1H, m, 1H of Ar); 7.29–7.35 (2H, m, 2H of Ar); 7.47–7.53 (1H, m, 1H of Ar); 7.64–7.70 (2H, m, 2H of Ar); 7.73–7.78 (1H, m, 1H of Ar); 8.48–8.56 (2H, m, 2H of Ar); 9.11 (1H, br d, $J = 1.8$ Hz, H–N(3)). ^{13}C NMR ($CDCl_3$): δ 9.5, 19.1, 22.4, 23.9, 31.0, 44.6, 47.5, 47.9, 51.4, 53.8, 80.0, 91.8, 106.6, 119.4, 119.8, 122.60, 122.62, 123.0, 123.2, 129.0, 132.6, 136.4, 136.6, 141.0, 147.9, 148.2, 150.9, 152.1, 156.7, 186.3. *m*/*z* (EI) = 503 (M^+); *m*/*z* (HRMS) found: 503.269950 (M^+); $C_{32}H_{33}N_5O$ requires: *m*/*z* = 503.268511 (found: C, 75.33; H, 6.99; N, 12.67. $C_{32}H_{33}N_5O$ requires: C, 76.31; H, 6.60; N, 13.91.); ν_{max} (KBr) 3396, 2957, 2929, 2877, 1684, 1592, 1564, 1485, 1468, 1459, 1424, 1394, 1283, 1095, 1073, 1058, 1027, 995, 782, 744, 697 cm^{-1}.

5.2.3.2. Data for minor (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′a. ^{1}H NMR ($CDCl_3$): δ 9.40 (1H, br d, $J = 1.9$ Hz, NH).

5.2.4. *N*-[(6*R*,9*R*,10*E*,11*R*,14*S*)-1,4-Bis(pyridin-2-yl)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dien-10-ylidene]-*N*-(naphth-1-yl)amine 9b and its (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′b. Prepared from tetrazine **7a** and compound **3b** (173 mg, 0.5 mmol), reflux for 30 h; CC: first (EtOAc, **9b**:**9′b** = 98:2), then (EtOAc–hexanes, 1:3; **9b**:**9′b** = 100:0).

5.2.4.1. Data for major (6*R*,9*R*,10*E*,11*R*,14*S*)-isomer 9b. 0.153 g (55%) of a brownish-yellow solid; mp96–103 °C; $[\alpha]_D^{23} = 0$ (*c* 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.84, 1.19, 1.25 (9H, 3s, 1:1:1, 3Me); 1.22–1.28 (1H, m, 1H of CH_2); 1.55–1.71 (3H, m, 3H of CH_2); 2.29 (1H, d, $J = 12.8$ Hz, Ha–C(15)); 2.43 (1H, d, $J = 4.5$ Hz, H–C(11)); 3.40 (1H, d, $J = 12.8$ Hz, Hb–C(15)); 4.24 (1H, d, $J = 8.3$ Hz, Ha–C(7)); 4.75 (1H, d, $J = 8.3$ Hz, Hb–C(7)); 6.72–6.76 (1H, m, 1H of Ar); 6.79 (1H, d, $J = 2.2$ Hz, H–C(5)); 6.99–7.03 (1H, m, 1H of Ar); 7.10–7.16 (1H, m, 1H of Ar); 7.18–7.27 (2H, m, 2H of Ar); 7.40–7.47 (3H, m, 3H of Ar); 7.59 (1H, br d, $J = 8.3$ Hz, 1H of Ar); 7.65–7.71 (1H, m, 1H of Ar); 7.77–7.85 (2H, m, 2H of Ar); 7.95 (1H, br d, $J = 8.3$ Hz, 1H of Ar); 8.43–8.46 (1H, m, 1H of Ar); 8.56–8.58 (1H, m, 1H of Ar); 9.18 (1H, br d, $J = 2.1$ Hz, NH). ^{13}C NMR ($CDCl_3$): δ 9.5, 19.1, 22.6, 24.1, 31.1, 44.4,

47.5, 48.8, 51.4, 53.8, 80.5, 92.0, 106.3, 113.3, 119.5, 122.56, 122.62, 123.0, 123.2, 123.9, 125.5, 126.0, 126.2, 127.1, 127.9, 132.9, 134.2, 136.3, 141.4, 147.9, 148.1, 148.2, 150.5, 156.6, 187.4. *m*/*z* (EI) = 553 (M^+); *m*/*z* (HRMS) found: 553.286020 (M^+); $C_{36}H_{35}N_5O$ requires: *m*/*z* = 553.284161 (found: C, 77.04; H, 6.39; N, 12.30. $C_{36}H_{35}N_5O$ requires: C, 78.09; H, 6.37; N, 12.65); ν_{max} (KBr) 3398, 2959, 1683, 1590, 1565, 1468, 1457, 1423, 1390, 1283, 1153, 1094, 1035, 777 cm^{-1}.

5.2.4.2. Data for minor (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′b. ^1H NMR ($CDCl_3$): δ 9.42 (1H, br d, *J* = 1.5 Hz, NH).

5.2.5. 2-Nitro-*N*-[(6*R*,9*R*,10*E*,11*R*,14*S*)-1,4-bis(pyridin-2-yl)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]-pentadeca-1,4-dien-10-ylidene]aniline 9c and its (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′c. Prepared from tetrazine **7a** and compound **3c** (171 mg, 0.5 mmol), reflux for 30 h; CC: first (EtOAc, **9c**:**9′c** = 99:1), then (EtOAc–hexanes, 1:3; **9c**:**9′c** = 100:0).

5.2.5.1. Data for major (6*R*,9*R*,10*E*,11*R*,14*S*)-isomer 9c. 0.203 g (74%) of a brownish-yellow oil; $[\alpha]_{589}^{27} = +25.0$ (*c* 0.24, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.89, 1.14, 1.26 (9H, 3s, 1:1:1, 3Me); 1.35–1.43 (1H, m, 1H of CH_2); 1.53–1.69 (3H, m, 3H of CH_2); 2.28 (1H, d, *J* = 12.8 Hz, Ha–C(15)); 2.35 (1H, d, *J* = 4.5 Hz, H–C(11)); 3.30 (1H, d, *J* = 12.8 Hz, Hb–C(15)); 4.11 (1H, d, *J* = 8.3 Hz, Ha–C(7)); 4.68 (1H, d, *J* = 8.3 Hz, Hb–C(7)); 6.40 (1H, d, *J* = 2.3 Hz, H–C(5)); 6.85 (1H, dd, *J* = 1.1; 7.9 Hz, 1H of Ar); 7.09–7.21 (3H, m, 3H of Ar); 7.43–7.57 (3H, m, 3H of Ar); 7.63–7.69 (1H, m, 1H of Ar); 7.75 (1H, br d, *J* = 7.9 Hz, 1H of Ar); 8.01 (1H, dd, *J* = 1.1; 8.3 Hz, 1H of Ar); 8.46–8.55 (2H, m, 2H of Ar); 9.13 (1H, br d, *J* = 1.5 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 9.4, 19.0, 22.3, 22.6, 30.9, 44.3, 47.3, 47.7, 52.4, 53.9, 80.8, 91.6, 105.7, 119.1, 121.9, 122.5, 122.6, 123.1, 123.4, 125.1, 132.8, 134.0, 136.3, 136.4, 140.5, 140.9, 146.5, 147.8, 148.1, 150.7, 156.6, 187.4. *m*/*z* (EI) = 548 (M^+); *m*/*z* (HRMS) found: 548.254540 (M^+); $C_{32}H_{32}N_6O_3$ requires: *m*/*z* = 548.253589 (found: C, 64.58; H, 5.74; N, 13.25. $C_{32}H_{32}N_6O_3$ requires: C, 70.05; H, 5.88; N, 15.32); ν_{max} (NaCl) 3399, 2962, 1693, 1602, 1592, 1567, 1519, 1469, 1424, 1392, 1344, 1304, 1285, 1256, 1154, 1142, 1094, 1057, 1035, 994, 910, 866, 780, 732 cm^{-1}.

5.2.5.2. Data for minor (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′c. ^1H NMR ($CDCl_3$): δ 9.36 (1H, br s, NH).

5.2.6. 4-Nitro-*N*-[(6*R*,9*R*,10*E*,11*R*,14*S*)-1,4-bis(pyridin-2-yl)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]-pentadeca-1,4-dien-10-ylidene]aniline 9d and its (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′d. Prepared from tetrazine **7a** and compound **3d** (171 mg, 0.5 mmol), reflux for 30 h; CC: first (EtOAc, **9d**:**9′d** = 97:3), then (EtOAc–hexanes; 1:3; **9d**:**9′d** = 100:0).

5.2.6.1. Data for major (6*R*,9*R*,10*E*,11*R*,14*S*)-isomer 9d. 0.153 g (55%) of a yellow solid; mp 214–220 °C; $[\alpha]_D^{23} = +116.2$ (*c* 0.15, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.89, 1.17, 1.19 (9H, 3s, 1:1:1, 3Me); 1.22–1.29 (1H, m, 1H of CH_2); 1.56–1.62 (2H, m, 2H of CH_2); 1.70–1.82 (1H, m, 1H of CH_2); 2.12 (1H, d, *J* = 12.8 Hz, Ha–C(15)); 2.32 (1H, d, *J* = 4.9 Hz, H–C(11)); 3.40 (1H, d, *J* = 12.4 Hz, Hb–C(15)); 4.04 (1H, d, *J* = 7.9 Hz, Ha–C(7)); 4.74 (1H, d, *J* = 7.9 Hz, Hb–C(7)); 6.53 (1H, d, *J* = 2.3 Hz, H–C(5)); 6.86–6.91 (2H, m, 2H of Ar); 7.13–7.23 (2H, m, 2H of Ar); 7.48–7.58 (2H, m, 2H of Ar); 7.65–7.78 (2H, m, 2H of Ar); 8.19–8.24 (2H, m, 2H of Ar); 8.50–8.55 (2H, m, 2H of Ar); 9.14 (1H, br d, *J* = 1.1 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 9.3, 19.0, 22.4, 23.7, 30.7, 44.6, 47.65, 47.70, 52.1, 53.9, 79.9, 91.5, 105.8, 118.9, 119.8, 122.6, 122.7, 122.9, 125.2, 132.8, 136.4, 136.5, 140.4, 143.8. 147.7, 148.3, 150.6, 156.5, 158.1, 188.3. *m*/*z* (EI) = 548 (M^+); *m*/*z* (HRMS) found: 548.256230 (M^+); $C_{32}H_{32}N_6O_3$ requires: *m*/*z* = 548.253589 (found: C, 70.29; H, 5.94; N, 15.16. $C_{32}H_{32}N_6O_3$ requires: C, 70.05; H, 5.88; N, 15.32); ν_{max} (KBr) 3405, 2957, 2951, 2895, 1686, 1589, 1564, 1510, 1482, 1459, 1424, 1390, 1338, 1284, 1246, 1220, 1195, 1185, 1155, 1111, 1100, 1052, 1038, 1020, 995, 862, 779 cm^{-1}.

5.2.6.2. Data for minor (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′d. ^1H NMR ($CDCl_3$): δ 9.38 (1H, br d, *J* = 1.9 Hz, NH).

5.2.7. 4-Nitro-*N*-[(6*R*,9*R*,10*E*,11*R*,14*S*)-1,4-bis(methoxycarbonyl)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dien-10-ylidene]aniline 9e and its (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′e. Prepared from tetrazine **7b** and compound **3d** (171 mg, 0.5 mmol), reflux for 3 h; CC (EtOAc–hexanes, 2:3; **9e**:**9′e** = 97:3). Crystallisation from CH_2Cl_2/*n*-heptane gave isomerically pure compound **9e**.

5.2.7.1. Data for major (6*R*,9*R*,10*E*,11*R*,14*S*)-isomer 9e. 0.205 g (80%) of a white solid; mp 183–187 °C; $[\alpha]_{589}^{21} = +214.7$ (*c* 0.03, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.89, 1.10, 1.16 (9H, 3s, 1:1:1, 3Me); 1.20–1.31 (1H, m, 1H of CH_2); 1.47–1.56 (1H, m, 1H of CH_2); 1.59–1.70 (1H, m, 1H of CH_2); 1.73–1.84 (1H, m, 1H of CH_2); 2.00 (1H, d, *J* = 12.8 Hz, Ha–C(15)); 2.37 (1H, d, *J* = 4.9 Hz, H–C(11)); 2.87 (1H, d, *J* = 13.2 Hz, Hb–C(15)); 3.74 (3H, s, COOMe); 3.85 (3H, s, COOMe); 4.09 (1H, d, *J* = 9.1 Hz, Ha–C(7)); 4.43 (1H, d, *J* = 8.7 Hz, Hb–C(7)); 6.85–6.90 (2H, m, 2H of Ar); 6.94 (1H, d, *J* = 2.3 Hz, H–C(5)); 8.17 (1H, br s, NH); 8.19–8.24 (2H, m, 2H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.4, 18.9, 22.4, 23.9, 31.0, 42.5, 47.9, 50.0, 51.9, 52.5, 52.7, 53.4, 81.8, 92.1, 117.1, 120.0, 124.9, 125.2, 132.0, 144.1, 157.2, 162.0, 164.3, 188.0. *m*/*z* (EI) = 510 (M^+); *m*/*z* (HRMS) found: 510.212660 (M^+); $C_{26}H_{30}N_4O_7$ requires: *m*/*z* = 510.211450 (found: C, 61.35; H, 6.19; N, 10.80. $C_{26}H_{30}N_4O_7$ requires: C, 61.17; H, 5.92; N, 10.97); ν_{max} (KBr) 3379, 2981, 2959, 1715 (C═O), 1692 (C═O), 1588, 1573, 1520, 1514, 1484, 1440, 1395, 1345, 1298, 1280, 1202, 1156, 1097, 960, 866, 771 cm^{-1}.

5.2.7.2. Data for minor (6*S*,9*R*,10*E*,11*R*,14*S*)-isomer 9′e. ^1H NMR ($CDCl_3$): δ 0.87, 0.99 (6H, 2s, 1:1, 2Me); 2.28 (1H, d, *J* = 5.7 Hz, H–C(11)); 2.67 (1H, d, *J* = 13.6 Hz, Hb–C(15)); 8.38 (1H, br s, NH).

5.2.8. (6*R*,9*S*,11*S*,14*R*)-1,4-Bis(pyridin-2-yl)-11:14-isopropylidene-11-methyl-8-(4-nitrophenyl)-2,3,8-triazadispiro-[5.1.5.2]pentadeca-1,4-dien-10-one 10 and its (6*S*,9*S*,11*S*,14*R*)-isomer 10′. Prepared from tetrazine **7a** and compound **4d** (171 mg, 0.5 mmol), reflux for 30 h; CC: first (EtOAc, **10**:**10**′ = 75:25), then (EtOAc–hexanes, 1:2; **10**:**10**′ = 75:25). Yield: 0.149 g (54%) of a brownish-yellow solid; mp 102–117 °C; $[\alpha]_D^{23} = -327.9$ (*c* 0.14, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 9.8, 10.5, 19.8, 21.3, 22.53, 22.55, 22.57, 24.0, 24.8, 29.9, 31.4, 40.6, 42.0, 46.3, 46.6, 49.2, 50.5, 52.3, 54.3, 59.4, 59.7, 68.1, 69.5, 75.4, 78.2, 103.4, 105.0, 118.1, 118.6, 119.2, 121.5, 122.5, 122.6, 123.1, 123.4, 123.5, 124.3, 125.0, 134.4, 135.3, 136.2, 136.7, 136.8, 138.6, 139.4, 141.7, 143.1, 147.6, 147.8, 148.5, 148.8, 150.0, 150.3, 155.0, 156.1, 156.4, 157.3, 218.1, 220.3. *m*/*z* (EI) = 549 (MH^+); *m*/*z* (HRMS) found: 549.262890 (MH^+); $C_{32}H_{33}N_6O_3$ requires: *m*/*z* = 549.261414 (found: C, 66.60; H, 6.33; N, 14.22. $C_{32}H_{32}N_6O_3$ requires: C, 70.05; H, 5.88; N, 15.32); ν_{max} (KBr) 3387, 2960, 2929, 2871, 1739 (C=O), 1588, 1566, 1495, 1467, 1424, 1394, 1373, 1317, 1238, 1202, 1178, 1154, 1113, 1039, 1019, 991, 969, 851, 837, 778, 754 cm^{-1}.

5.2.8.1. Data for major (6*R*,9*S*,11*S*,14*R*)-isomer 10. ^1H NMR ($CDCl_3$): δ 0.68, 0.92, 0.94 (9H, 3s, 1:1:1, 3Me); 1.46–1.56 (1H, m, 1H of CH_2); 1.62–1.82 (2H, m, 2H of CH_2); 1.96 (1H, d, *J* = 12.8 Hz, Ha–C(15)); 1.96–2.10 (1H, m, 1H of CH_2); 3.08 (1H, d, *J* = 13.2 Hz, Hb–C(15)); 3.15 (1H, d, *J* = 4.2 Hz, H–C(14)); 4.25 (1H, d, *J* = 10.9 Hz, Ha–C(7)); 4.37 (1H, d, *J* = 11.3 Hz, Hb–C(7)); 6.00 (1H, d, *J* = 2.3 Hz, H–C(5)); 6.83–6.88 (2H, m, 2H of Ar); 6.93–7.01 (2H, m, 2H of Ar); 7.47–7.62 (2H, m, 2H of Ar); 7.72–7.77 (2H, m, 2H of Ar); 7.85–7.88 (1H, m, 1H of Ar); 7.95–7.99 (2H, m, 2H of Ar); 8.53–8.56 (1H, m, 1H of Ar); 9.24 (1H, br d, *J* = 1.9 Hz, NH).

5.2.8.2. Data for minor (6*S*,9*S*,11*S*,14*R*)-isomer 10′. ^1H NMR ($CDCl_3$): δ 0.86, 0.99, 1.03 (9H, 3s, 1:1:1, 3Me); 1.31–1.39 (1H, m, 1H of CH_2); 2.35 (1H, d, *J* = 12.8 Hz, Ha–C(15)); 2.48 (1H, d, *J* = 3.8 Hz, H–C(14)); 3.06 (1H, d, *J* = 13.2 Hz, Hb–C(15)); 3.55 (1H, d, *J* = 11.7 Hz, Ha–C(7)); 4.62 (1H, d, *J* = 11.3 Hz, Hb–C(7)); 5.37 (1H, d, *J* = 2.3 Hz, H–C(5)); 7.69–7.71 (1H, m, 1H of Ar); 7.79–7.80 (1H, m, 1H of Ar); 7.99–8.05 (2H, m, 2H of Ar); 8.56–8.59 (1H, m, 1H of Ar); 9.30 (1H, br d, *J* = 1.5 Hz, NH).

5.2.9. (6*R*,9*R*,10*S*,11*R*,14*S*)-10-Anilino-1,4-bis(pyridin-2-yl)-11:14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]-pentadeca-1,4-diene 11 and its (6*S*,9*R*,10*S*,11*R*,14*S*)-isomer 11′. Prepared from tetrazine **7a** and compound **6a** (149 mg, 0.5 mmol), reflux for 30 h; CC (EtOAc–hexanes, 1:1; **11**:**11**′ = 81:19); MPLC (EtOAc–hexanes, 1:6; **11**:**11**′ = 100:0).

5.2.9.1. Data for major (6*R*,9*R*,10*S*,11*R*,14*S*)-isomer 11. 0.114 g (45%) of a yellow solid; mp 206–209 °C; $[\alpha]_{589}^{23} = +189.4$ (*c* 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.85, 1.04, 1.18 (9H, 3s, 1:1:1, 3Me); 1.15–1.26 (1H, m, 1H of CH_2); 1.32–1.49 (2H, m, 2H of CH_2); 1.69–1.80 (1H, m, 1H of CH_2); 1.82 (1H, d, *J* = 4.5 Hz, H–C(11)); 2.03 (1H, d, *J* = 12.4 Hz, Ha–C(15)); 3.27 (1H, d, *J* = 5.7 Hz, H–C(10)); 3.40 (1H, d, *J* = 12.4 Hz, Hb–C(15)); 3.91 (1H, d, *J* = 7.9 Hz, Ha–C(7)); 4.80 (1H, d, *J* = 7.9 Hz, Hb–C(7)); 4.94 (1H, d, *J* = 5.3 Hz, H–N(10′)); 5.40 (1H, d, *J* = 2.3 Hz, H–C(5)); 6.44–6.48 (1H, m, 1H of Ar); 6.57–6.63 (2H, m, 2H of Ar); 6.69–6.76 (1H, m, 1H of Ar); 7.02–7.07 (1H, m, 1H of Ar); 7.16–7.24 (4H, m, 4H of Ar); 7.63–7.72 (2H, m, 2H of Ar); 8.40–8.42 (1H, m, 1H of Ar); 8.52–8.55 (1H, m, 1H of Ar); 9.14 (1H, br d, *J* = 1.5 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 9.8, 21.6, 22.3, 25.9, 31.3, 44.3, 49.0, 49.8, 50.1, 53.1, 69.5, 80.3, 93.4, 102.9, 112.5, 116.1, 119.2, 122.7, 122.8, 122.9, 129.8, 134.4, 136.4, 136.9, 140.6, 147.92, 147.97, 148.03, 149.8, 156.3. *m*/*z* (EI) = 505 (M^+); *m*/*z* (HRMS) found: 505.284161 (M^+); $C_{32}H_{35}N_5O$ requires: *m*/*z* = 505.285500 (found: C, 76.26; H, 7.24; N, 13.45. $C_{32}H_{35}N_5O$ requires: C, 76.01; H, 6.98; N, 13.85); ν_{max} (KBr) 3378, 3349, 2992, 2958, 2931, 2878, 1601, 1575, 1564, 1503, 1466, 1427, 1388, 1328, 1311, 1283, 1178, 1151, 1122, 1097, 1083, 1022, 999, 989, 784, 762, 751, 696 cm^{-1}.

5.2.9.2. Data for minor (6*S*,9*R*,10*S*,11*R*,14*S*)-isomer 11′. ^1H NMR ($CDCl_3$): δ 0.85, 1.04, 1.20 (9H, 3s, 1:1:1, 3Me); 1.86 (1H, d, *J* = 4.5 Hz, H–C(11)); 2.41 (1H, d, *J* = 13.6 Hz, Ha–C(15)); 3.11 (1H, d, *J* = 13.6 Hz, Hb–C(15)); 3.36 (1H, d, *J* = 4.9 Hz, H–C(10)); 3.83 (1H, d, *J* = 8.3 Hz, Ha–C(7)); 4.48 (1 H, d, *J* = 4.9 Hz, H–N(10′)); 4.81 (1H, d, *J* = 7.9 Hz, Hb–C(7)); 5.59 (1H, d, *J* = 2.3 Hz, H–C(5)); 6.48 (2H, d, *J* = 7.5 Hz, 2H of Ar); 6.62–6.67 (1H, m, 1H of Ar); 6.82–6.84 (1H, m, 1H of Ar); 7.13–7.24 (3H, m, 3H of Ar); 7.41–7.47 (1H, m, 1H of Ar); 7.51–7.54 (1H, m, 1H of Ar); 7.61–7.66 (2H, m, 2H of Ar); 7.69–7.75 (1H, m, 1H of Ar); 8.54–8.56 (1H, m, 1H of Ar); 9.10 (1H, br s, NH).

5.3. Synthesis of compound 8a by acid-catalysed hydrolysis of imine 9a

Hydrochloric acid (37%, 0.15 mL, ~1 mmol) was added to a cooled solution (0 °C) of **9a** (0.1 mmol, 51 mg) in an $EtOH/H_2O$ mixture (3 mL/1 mL). The reaction mixture was stirred at 0 °C for 1 h and further 48 h at room temperature. EtOH was evaporated in vacuo and the residue was poured into saturated aq $NaHCO_3$ (50 mL) and the product was extracted with $CHCl_3$ (2 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated in vacuo. The residue was purified by CC (EtOAc–hexanes, 1:2). Fractions containing the product were combined and evaporated in vacuo to give a mixture of **8a** and aniline in a ratio of 2:1.

5.4. NMR data for the mixture of 8a and aniline

^1H NMR ($CDCl_3$): δ 0.97, 1.15 (9H, 2s, 1:2, 3Me); 1.35–1.44 (1H, m, 1H of CH_2); 1.48–1.57 (1H, m, 1H of CH_2); 1.63–1.72 (1H, m, 1H of CH_2); 1.84–1.95 (1H, m, 1H of CH_2); 1.86 (1H, d, *J* = 12.8 Hz, Ha–C(15)); 2.19 (1H, d, *J* = 5.3 Hz, H–C(11)); 3.30 (1H, d, *J* = 13.2 Hz, Hb–C(15)); 3.64 (2H, br s, NH_2 of aniline); 3.95 (1H, d, *J* = 7.9 Hz, Ha–C(7)); 4.68 (1H, d, *J* = 7.9 Hz, Hb–C(7)); 6.31 (1H, d, *J* = 2.3 Hz, H–C(5)); 6.66–6.78 (3H, m, 3H of aniline); 7.12–7.23 (4H, m, 2H of Ar, 2H of aniline);

7.63–7.78 (3H, m, 3H of Ar); 7.88–7.91 (1H, m, 1H of Ar); 8.49–8.54 (2H, m, 2H of Ar); 9.13 (1H, s, NH).

5.5. X-ray structure analysis for compounds 9d, 9e and 11

Single crystal X-ray diffraction data of compounds **9d**, **9e** and **11** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[22] DENZO and SCALEPACK[23] were used for indexing and scaling of the data and the structures were solved by means of SIR97.[24] Refinement was done using an Xtal3.4[25] program package and the crystallographic plots were prepared by ORTEP III.[26] Crystal structures were refined on *F* values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases, while 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[27] weighting scheme was used in all cases.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 649420–649422. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

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References

1. Money, T. *Nat. Prod. Rep.* **1985**, 253–289.
2. Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004.
3. Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241–1250.
4. Money, T. In *Remote Functionalization of Camphor: Application to Natural Product Synthesis in Organic Synthesis: Theory and Applications*; JAI Press, 1996; Vol. 3, pp 1–83.
5. Neunhoeffer, H. In *Tetrazines and Pentazines in Comprehensive Heterocyclic Chemistry I*; Katritzky, A. R., Rees, C. W., Eds.; Elsevier, 1984; Vol. 3, Chapter 2.21, pp 531–572.
6. Sauer, J. In *1,2,4,5-Tetrazines in Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier, 1995; Vol. 6,, Chapter 6.21, pp 901–955.
7. Grošelj, U.; Svete, J.; Stanovnik, B. In *1,2,4,5*-Tetrazines in *Comprehensive Heterocyclic Chemistry III*; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: 2008; Vol. 8, Chapter 8.12, in press.
8. Seitz, G.; Kämpchen, Th. *Arch. Pharm. (Weinheim)* **1975**, *308*, 237–239.
9. Hartmann, K.-P.; Heuschmann, M. *Tetrahedron* **2000**, *56*, 4213–4218.
10. For reviews and recent publications see: (a) Stanovnik, B.; Svete, J. *Targets Heterocycl. Syst.* **2000**, *4*, 105–137; (b) Stanovnik, B.; Svete, J. *Synlett* **2000**, 1077–1091; (c) Svete, J. *J. Heterocycl. Chem.* **2002**, *39*, 437–454; (d) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433–2480, and references cited therein; (e) Svete, J. *Monatsh. Chem.* **2004**, *135*, 629–647; (f) Stanovnik, B.; Svete, J. *Mini-Rev. Org. Chem.* **2005**, *2*, 211–224; (g) Pirc, S.; Bevk, D.; Jakše, R.; Rečnik, S.; Golič, L.; Golobič, A.; Meden, A.; Stanovnik, B.; Svete, J. *Synthesis* **2005**, 2969–2988; (h) Pirc, S.; Bevk, D.; Golobič, A.; Stanovnik, B.; Svete, J. *Helv. Chim. Acta* **2006**, *89*, 30–44; (i) Jakše, R.; Bevk, D.; Golobič, A.; Svete, J.; Stanovnik, B. *Z. Naturforsch.* **2006**, *61b*, 1–7; (j) Časar, Z.; Bevk, D.; Svete, J.; Stanovnik, B. *Tetrahedron* **2005**, *61*, 7508–7519; (k) Wagger, J.; Bevk, D.; Meden, A.; Svete, J.; Stanovnik, B. *Helv. Chim. Acta* **2006**, *89*, 240–248; (l) Wagger, J.; Golič Grdadolnik, S.; Grošelj, U.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2007**, *18*, 464–475.
11. Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Pirc, S.; Rečnik, S.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2004**, *15*, 2367–2383.
12. Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Rečnik, S.; Stanovnik, B.; Svete, J. *Synthesis* **2005**, 1087–1094.
13. Grošelj, U.; Bevk, D.; Jakše, R.; Pirc, S.; Stanovnik, B.; Svete, J.; Meden, A. *Tetrahedron: Asymmetry* **2005**, *16*, 2187–2197.
14. (a) Grošelj, U.; Rečnik, S.; Svete, J.; Meden, A.; Stanovnik, B. *Tetrahedron: Asymmetry* **2002**, *13*, 821–833; (b) Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2006**, *17*, 79–91; (c) Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2927–2945; (d) Grošelj, U.; Bevk, D.; Jakše, R.; Rečnik, S.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron* **2005**, *61*, 3991–3998; (e) Grošelj, U.; Rečnik, S.; Meden, A.; Stanovnik, B.; Svete, J. *Acta Chim. Slov.* **2006**, *53*, 245–256; (f) Grošelj, U.; Tavčar, G.; Bevk, D.; Meden, A.; Žemva, B.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1715–1727; (g) Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1217–1237.
15. Grošelj, U.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2007**, *18*, 2365–2376.
16. Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318–319.
17. Boger, D. L.; Panek, J. S.; Patel, M. *Org. Synth.* **1992**, *70*, 79–92.
18. Boger, D. L.; Coleman, R. S.; Panek, J. S.; Huber, F. X.; Sauer, J. *J. Org. Chem.* **1985**, *50*, 5377–5379.
19. Abraham, R. J.; Fisher, J. *Magn. Reson. Chem.* **1985**, *23*, 862–871.
20. Abraham, R. J.; Fisher, J. *Magn. Reson. Chem.* **1986**, *24*, 451–459.
21. Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.
22. Collect Software. Nonius, BV, Delft, The Netherlands, **1998**.
23. Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307–326.

24. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
25. Hall, S. R.; King, G. S. D.; Stewart, J. M. *The Xtal3.4 User's Manual*, University of Western Australia, Lamb, Perth, 1995.
26. Burnett, M. N.; Johnson, C. K. In ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL-6895, 1996.
27. Wang, H.; Robertson, B. E. In *Structure and Statistics in Crystallography*; Wilson, A. J. C., Ed.; Adenine Press: New York, 1985.