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Synthesis of spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-amines via stereoselective cycloadditions of trimethylenemethane to (1*S*,3*EZ*,4*R*)-3-arylimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones

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Abstract—Stereoselective [3+2] cycloadditions of trimethylenemethane (TMM) to the exocyclic C=O and C=N double bonds of (1*S*,3*EZ*,4*R*)-3-arylimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones gave the corresponding spiro[bicyclo[2.2.1]heptane-2,2′-furan] and spiro[bicyclo[2.2.1]heptane-3,2′-pyrrolidine] derivatives. Further stereoselective reductions of the C=N or C=O bond in these cycloadducts furnished new chiral amines, diamines, and a new aminoalcohol. All cycloadditions and reductions of the C=N double bonds took place from the less hindered *endo*-face of the (1*S*,3*EZ*,4*R*)-3-arylimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones, exclusively, thus giving the corresponding products in 100% de. The structures were determined by NMR, NOESY spectroscopy, and by X-ray diffraction.

1. Introduction

Camphor and its derivatives belong among 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] For example, Noyori's (−)-3-*exo*-dimethylaminoisoborneol [(−)-DAIB][5] and its morpholino-modified analogue[6] are highly enantioselective ligands for the dialkylzinc addition to aldehydes. Similarly, (1*R*,2*R*)-*N*,*N*′-bis{[(1*S*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]-heptan-1-yl]methylsulfonyl}cyclohexane-1,2-diamine was used in the asymmetric addition of diphenylzinc to ketones,[7] whereas various camphor based P,N-ligands[8,9] and P,P-ligands[10] were used in asymmetric hydrogenations (Fig. 1).

Recently, a series of 3-(dimethylamino)prop-2-enoates and related enaminones have been prepared as versatile reagents in the synthesis of heterocyclic systems, including functionalized heterocycles and natural product analogues.[11–22] Within this context, (+)-camphor derived enaminones were used in the stereoselective synthesis of

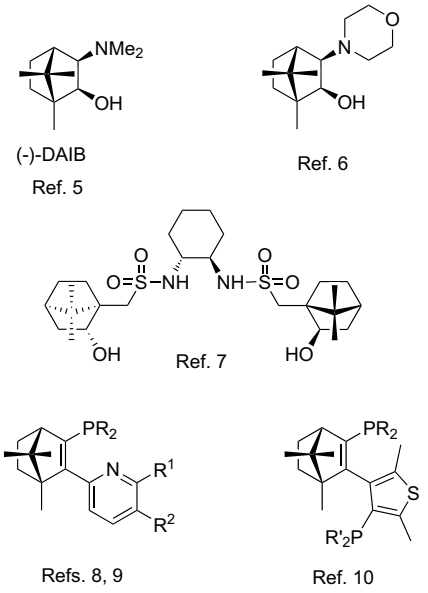

Figure 1. Some examples of (+)-camphor derived chiral ligands.

3-([1,2,4]triazolo[4,3-*x*]azin-3-yl)-(+)-camphors and their analogues;[23–25] the synthesis of terpene functionalized pyrazoles;[26] coupling reactions with amines[27] and

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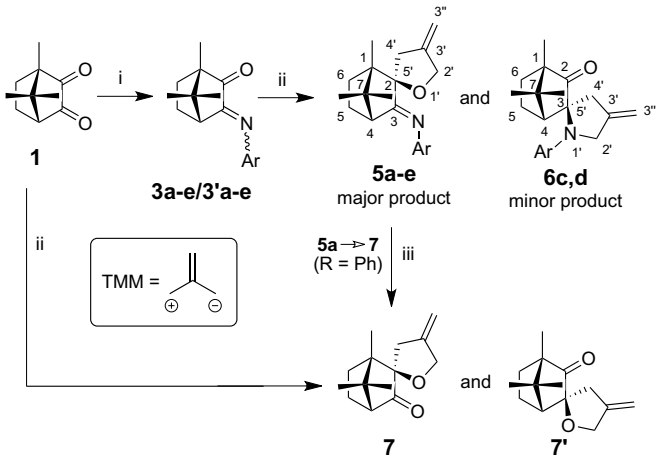
Grignard reagents,[28] in the preparation and reductions of (1*R*,4*E*,5*S*)-4-oximino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one;[29] in 1,3-dipolar cycloaddition reactions of α-alkylidene-(+)-camphors and analogues[30] and (+)-camphor derived pyrazolidin-3-ones;[31] and in the preparation of β-campholenolactone derivatives.[32] In continuation of this work, we herein report the acid-catalyzed transformations of (1*S*)-(+)-camphorquinone **1** with anilines **2a**–**e** into 3-iminocamphor derivatives **3a**–**e**, stereoselective 1,3-dipolar cycloadditions of trimethylenemethane **4** to dipolarophiles **3a**–**e**, and further reductions of the so formed spiro cycloadducts **5** and **6** into novel non-racemic amines **8a**,**b**; diamines **8c**,**d**, **9d**, **10d**; and aminoalcohol **11d**.

2. Results and discussion

The starting compounds, (1*S*,3*EZ*,4*R*)-3-arylimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones **3a**–**e**/**3′a**–**e**, were prepared as mixtures of the major (3*E*)-isomers **3a**–**e** and the minor (3*Z*)-isomers **3′a**–**e** by condensation of (1*S*)-(+)-camphorquinone **1** with anilines **2a**–**e** in the presence of catalytic amounts of *p*-toluenesulfonic acid according to a slightly modified literature procedure.[33] Carbocyclic 1,3-dipolar cycloadditions of trimethylenemethane (TMM), formed in situ from the [2-(acetoxymethyl)allyl]-trimethylsilane **4**, $Pd(OAc)_2$, and $(i\text{-PrO})_3P$,[34,35] to 3-iminocamphors **3a**–**e**/**3′a**–**e** were *endo*-selective and proceeded predominantly at the C=O double bond giving the corresponding spiro[bicyclo[2.2.1]heptane-2,2′-furans] **5a**–**e** as the major products and spiro[bicyclo[2.2.1]heptane-3,2′-pyrrolidines] **6d**,**e** as the minor products. Cycloadditions to imines **3a**–**c**/**3′a**–**c** gave spirofurans **5a**–**c** as the only products, whilst the reactions of TMM with **3d**,**e**/**3′d**,**e** gave mixtures of the major spirofurans **5d**,**e** and the minor spiropyrrolidines **6d**,**e**. Further chromatographic separation of a mixture of **5d** and **6d** furnished pure compounds **5d** and **6d**, whilst a mixture of compounds **5e** and **6e** could not be separated, either by crystallization, or by using chromatographic techniques. Chemoselectivity depended on the electronic and steric properties of the aryl group. The electron-rich phenylimines **3a**/**3′a** and naphthylimines **3b**/**3′b** and the electron-deficient *ortho*-nitrophenylimines **3c**/**3′c** reacted at the C=O group exclusively, while electron-deficient *para*- and *meta*-nitrophenylimines **3d**/**3′d** and **3e**/**3′e** also reacted at the C=N double bond. The position of the electron withdrawing nitro group markedly influenced the chemoselectivity of the additions, ranging from **5d**:**6d** = 56:44 (*para*) to **5e**:**6e** = 86:14 (*meta*) and **5c**:**6c** 100:0 (*ortho*). The formation of **5c** as the sole product could be rationalized by the steric hindrance imposed by the *ortho*-nitro group in imines **3c**/**3′c**, which efficiently disables the addition to the C=N double bond. Finally, cycloaddition of TMM to (1*S*)-(+)-camphorquinone **1** was carried out. It proceeded *endo*-selectively, yet without any regioselectivity, giving products **7** and **7′** in a ratio of 1:1. The formation of **7** was additionally confirmed by acid-catalyzed hydrolysis of imine **5a** (Scheme 1, Table 1).

Next, reductions of spirofurans **5** and spiropyrrolidines **6** were studied in order to prepare new chiral non-racemic amines, diamines, and amino alcohols. $LiAlH_4$ proved to be the reagent of choice for this purpose. Thus, the reduction of imines **5a** and **5b** gave the corresponding secondary amines **8a** and **8b** in 77% and 94% yield, respectively. Similarly, treatment of 2-nitrophenylimine **5c** with excess $LiAlH_4$ yielded the corresponding diamine **8c** in 63% yield. On the other hand, the reduction of 4-nitrophenylimine **5d** afforded a mixture of diamine **8d**, azo compound **9d**, and azoxy compound **10d** in a ratio of 77:17:6, respectively. Subsequent chromatographic separation afforded products **8d**, **9d**, and **10d** in 51%, 3%, and 5% yield, respectively. Reduction of spiropyrrolidine **6d** with $LiAlH_4$ gave an inseparable mixture of products. However, sequential reduction of **6d** with $Na_2S_2O_4$ and $LiAlH_4$ followed by chromatographic workup gave aminoalcohols **11d** and **11′d** in a ratio of 88:12 and in 20% yield (Scheme 2, Table 1).



Scheme 1. Reagents and conditions: (i) R–NH_2, **2a**–**e** (1 equiv), *p*-TsOH, toluene, reflux; (ii) [2-(acetoxymethyl)allyl]-trimethylsilane **4** (1.4 equiv), $Pd(OAc)_2$, $(i\text{-PrO})_3P$, toluene, reflux; (iii) HCl, MeOH, H_2O, 0 °C→rt.

The transformation of camphor at the 3-position often afforded initial kinetically controlled *exo*-products as a result of the attack of a reagent from the less hindered *endo*-face of the bicyclic system. Epimerization of the *exo*-isomers can afford thermodynamically more stable *endo*-products, which are sterically less hindered.[1–4,36–40] Accordingly, [3+2] cycloadditions of TMM (cf. Scheme 1) as well as $LiAlH_4$ reductions of the C=N and C=O bonds (cf. Scheme 2) proceeded from the less hindered *endo*-face of substrates to afford the corresponding *exo*-products. Epimerization at the newly formed stereogenic center did not take place, since cycloadducts **5**–**7** are not epimerizable because of the low acidity of the α-position in amines **8**–**10** and alcohol **11d**. The *endo*-stereocontrol in (cyclo)addition reactions at the C=N and C=O bonds in compounds **1**, **3**, **5**, and **6** was also in agreement with that reported for 1,3-dipolar cycloadditions of benzonitrile oxides to α-alkylidene-(+)-camphor derivatives (Fig. 2).[30]

3. Structure determination

The structures of compounds **3a**–**e**/**3′a**–**e**, **5a**–**e**, **6d**,**e**, **7**, **7′**, **8a**–**d**, **9d**, **10d**, and **11d**/**11′d** were determined by spectro-

Table 1. Selected experimental data for compounds **3a–e/3′a–e**, **5a–e**, **6d,e**, **7/7′**, **8a–d**, and **9d–11d**

Reaction	Ar	Ratio of isomers[a]	Yield[b] (%)
1+2a→3a/3′a	Phenyl	96:4[c]	66 (**3a**:**3′a** = 96:4)[c]
1+2b→3b/3′b	1-Naphthyl	97:3[c]	19 (**3b**:**3′b** = 97:3)[c]
1+2c→3c/3′c	2-Nitrophenyl	75:25[c]	45 (**3c**:**3′c** = 75:25)[c]
1+2d→3d/3′d	4-Nitrophenyl	90:10[c]	54 (**3d**:**3′d** = 90:10)[c]
1+2e→3e/3′e	3-Nitrophenyl	89:11[c]	64 (**3e**:**3′e** = 89:11)[c]
3a+4→5a	Phenyl	100:0	91
3b+4→5b	1-Naphthyl	100:0	35
3c+4→5c	2-Nitrophenyl	100:0	77
3d+4→5d+6d	4-Nitrophenyl	**5d**:**6d** = 56:44	43 (**5d**), 34 (**6d**)
3e+4→5e+6e	3-Nitrophenyl	**5e**:**6e** = 87:13	58 (**5e**:**6e** = 86:14)[e]
1+4→7/7′	—	**7**:**7′** = 1:1	95 (**7**:**7′** = 1:1)
5a→7	—	**7**:**7′** = 100:0	61
5a→8a	Phenyl	100:0	77
5b→8b	1-Naphthyl	100:0	94
5c→8c	2-Aminophenyl[d]	100:0	63
5d→8d/9d/10d	4-Aminophenyl[d]	**8d**:**9d**:**10d** = 77:17:6	51 (**8d**), 3 (**9d**), 5 (**10d**)
6d→11d/11′d	4-Aminophenyl[d]	**11d**:**11′d** = 86:14	20 (**11d**:**11′d** = 88:12)[e]

[a] Determined by ^{1}H NMR of the crude reaction mixture or after FC (unless otherwise stated).
[b] Isolated yield of the isomerically pure compound (unless otherwise stated).
[c] After crystallization from EtOH.
[d] Obtained by concomitant reduction of the nitro group.
[e] After purification by column chromatography.

scopic methods (IR, ^{1}H and ^{13}C NMR, NOESY spectroscopy, MS) and by elemental analyses for C, H, and N. Compounds **5a–d**, **6d**, **7**, **8a–d**, **9d**, and **10d** were prepared in isomerically pure form. Compounds **5e/6e** and **11d/11′d** were isolated and characterized as mixtures of the major isomers **5e** and **11d** and the minor isomers **6e** and **11′d**, respectively. Similarly, compounds **3a–e/3′a–e** were isolated and characterized as mixtures of the major isomers **3a–e** and the minor isomers **3′a–e**, respectively. Compound **7′** could not be separated from a mixture of isomeric products **7** and **7′** and was characterized by ^{1}H NMR, ^{13}C NMR and by EI-HRMS as a 1:1 mixture of isomeric compounds **7** and **7′**. Compounds **5a–c,e**, **6e**, **7/7′**, **8a–c,d**, **9d**, and **11d** were not prepared in analytically pure forms; their identities were confirmed by ^{13}C NMR and EI-HRMS.

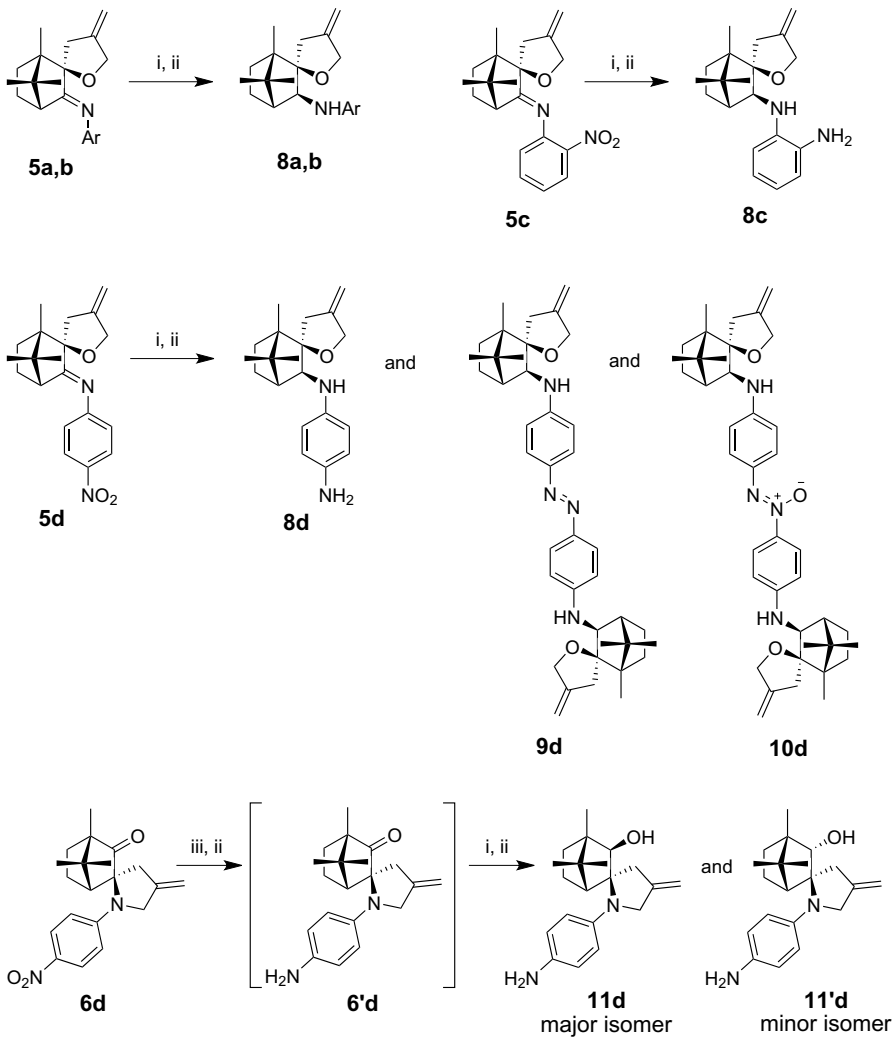
The configurations of compounds **6d**, **8a–c**, and **8d–11d** were determined by NOESY spectroscopy. In spiropyrrolidine **6d**, the NOE between the *ortho*-protons of the 4-nitrophenyl group and the bridge methyl group supports the (1*S*,3*S*,4*R*)-configuration. Next, the NOE between *H*–C(2) and *H*a–C(4′) and the NOE between the hydroxy group and the bridge methyl group in compound **11d** suggest an *exo*-orientation at the C(2) and C(3) positions, that is, the (1*R*,2*S*,3*R*,4*S*)-configuration. Similarly, the (*S*)-configuration at the 3-position in secondary amines **8a–d**, **9d**, and **10d** was confirmed by NOE between *H*–C(3) and *H*a–C(4′). Additionally, the NOE between *H*–N group and the bridge methyl group reconfirmed the (*S*)-configuration at the 3-position in secondary amines **8a–c** and **9d** (Fig. 3).

The configuration at the 3-position in secondary amines **8a–d**, **9d**, and **10d** was determined by ^{1}H NMR on the basis of vicinal coupling constants ($^3J_{H(3)–H(4)}$) and multiplicities for proton *H*–C(3).[23–25,29–31,41,42] The dihedral angles between *H*–C(3) and *H*–C(4) in the secondary *exo*-amines **8a–d**, **9d**, and **10d** are close to 90° and, following the Karplus equation,[43] no appreciable coupling between these protons would be expected. Accordingly, negligible coupling constants, $^3J_{H(3)–H(4)} \sim 0$ Hz, were observed in ^{1}H NMR spectra of the secondary *exo*-amines **8a–d**, **9d**, and **10d**. Finally, the configuration of compounds **5a–e**, **6d,e**, **7**, **7′**, **8a–d**, **9d**, and **10d** was confirmed by correlation of the chemical shifts and vicinal coupling constants, $^3J_{H–H}$ (Fig. 3, Table 2).

The (*E*)-configuration around the exocyclic C=N double bond in compounds **3d** and **3e** was determined by X-ray diffraction (Figs. 4 and 5). On the basis of these results and because the (*E*)-configuration imposes a lesser steric strain than the (*Z*)-configuration around the exocyclic C=N double bond, it seems reasonable to assume the (*E*)-configuration in imines **3a–e** and **5a–e**.

4. Conclusion

[3+2] Cycloadditions of trimethylenemethane (TMM) **4** to the exocyclic C=N and C=O double bonds of 3-iminocamphors **3a–e/3′a–e** took place preferentially at the C=O double bond to give the corresponding spirofurans **5a–e** as the major products. In the case of imino camphors **3d,e/3′d,e**, the reaction also took place at the C=N double bond to give the spiropyrrolidines **6d,e** as the minor products. A lower reactivity of the C=N bond was not surprising, since it is sterically shielded by the aryl group, whilst the C=O double bond is not. Electron-rich imines **3a,b/3′a,b** and sterically hindered electron poor *ortho*-nitrophenylimine **3c/3′c** gave the corresponding furan derivatives **5a–c**, exclusively, whereas the less-hindered electron poor *para*-nitrophenylimine **3d/3′d** and *m*-nitrophenylimine **3e/3′e** furnished mixtures of spirofurans and spiropyrrolidines **5d/6d** and **5e/6e**, respectively. To our surprise, the



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, Et_2O/THF, 55 °C; (ii) chromatographic purification; (iii) $Na_2S_2O_4$, K_2CO_3, EtOH/H_2O, reflux.

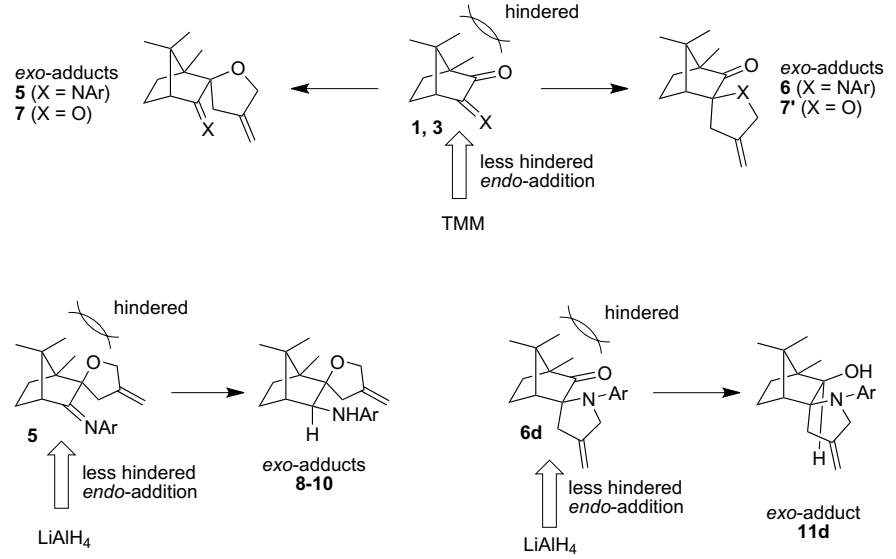


Figure 2. Stereoselectivity of [3+2] cycloadditions of trimethylenemethane (TMM) **4** and reductions with $LiAlH_4$ to/of exocyclic C=N and C=O double bonds.

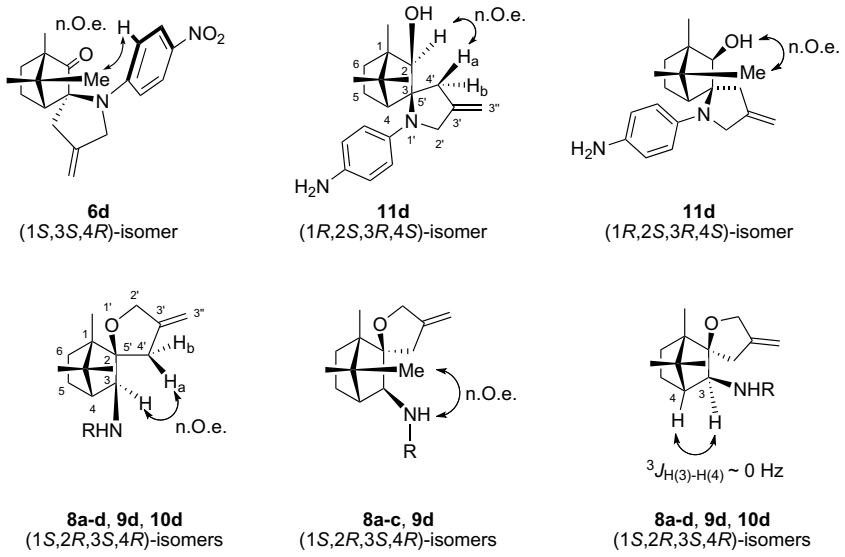


Figure 3. Structure determination by ^{1}H NMR and NOESY spectroscopy.

Table 2. Selected ^{1}H NMR data for the prepared compounds **5a**–**e**, **6d**,**e**, **7**, **7′**, **8a**–**d**, **9d**, **10d**, and **11d**[a]

Compound	δ (ppm)						$^3J_{H-H}$ (Hz)		
	3-H	4-H	2′-CH_2	4′-CH_2	3″-CH_2	NH	3-4	4–5	HC(3)–NH
5a		2.38	4.47/4.87	2.65/2.78	4.92/5.02			4.9	
5b		2.32	4.58/5.03	2.79/2.88	4.95/5.09			4.5	
5c		2.27	4.46/4.73	2.79/2.79	4.88/5.02			4.1	
5d		2.26	4.48/4.79	2.62/2.80	4.93/5.03			4.9	
5e		2.31	4.49/4.83	2.64/2.81	4.94/5.04			4.9	
6d[d]		2.49	3.69/4.77	2.54/2.87	5.01/5.11			4.5	
6e		2.20	3.55/4.74	2.55/2.92	5.02/5.15			4.5	
7		2.18	4.44/4.67	2.41/2.65	4.93/5.02			5.3	
7′		2.01	[b]	2.50/2.70	[b]			4.1	
8a[c,d]	3.09	~1.7[b]	4.40/4.40	2.49/2.81	4.80/4.93	4.78	0	[b]	7.2
8b[c,d]	3.33	1.86	~4.50[b]	2.60/2.91	4.81/4.95	5.33	0	4.5	6.0
8c[c,d]	3.10	~1.7[b]	4.40/4.53	2.51/2.83	4.80/4.94	4.21	0	[b]	6.8
8d[c,d]	3.00	~1.6[b]	4.38/4.38	2.46/2.79	4.79/4.92	4.00	0	[b]	6.6
9d[d]	3.20	1.90	4.37/4.49	2.44/2.91	4.82/4.95	4.74	0	4.9	6.6
10d[d]	3.17/3.20	1.88	4.36/4.49	2.43/2.91	4.82/4.95	4.76/4.81	0	5.1	6.9/7.0
	2-H	4-H	2′-CH_2	4′-CH_2	3″-CH_2	OH		4–5	CH–OH
11d[c,d]	2.85	1.77	3.41/3.91	2.36/3.02	4.88/5.03	4.31		3.9	4.9
11′d[c]	[b]	1.65	[b]	[b]	4.80/4.94	4.60		4.2	6.1

[a] Unless otherwise stated, the spectra were taken in $CDCl_3$.
[b] Overlapped by other signals or the position of the desired signal could not be unambiguously determined.
[c] The spectrum was taken in DMSO-d_6.
[d] Determined by NOESY spectroscopy.

stereoselectivity of cycloadditions was very high—the approach of trimethylenemethane **4** took place exclusively from the less hindered *endo*-face of the dipolarophile **3** to furnish cycloadducts **5** and **6** as single diastereomers. Similarly, reductions of imines **5a**–**d** with $LiAlH_4$ took place from the less hindered *endo*-face of the bicyclic system, exclusively, thus giving diastereomerically pure *exo*-amines **8a**–**d**. In the reduction of *para*-nitrophenylimine **5d**, azo compound **9d** and azoxy compound **10d** were also formed as by-products. Upon sequential reduction of spiropyrrolidine **6d** with $Na_2S_2O_4$/$LiAlH_4$, β-amino alcohol **11d** was isolated in 76% de.

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 except for compound **3c** where NMR experiments were carried out also at 358 K. Optical rotations were measured on a Perkin–Elmer 241MC

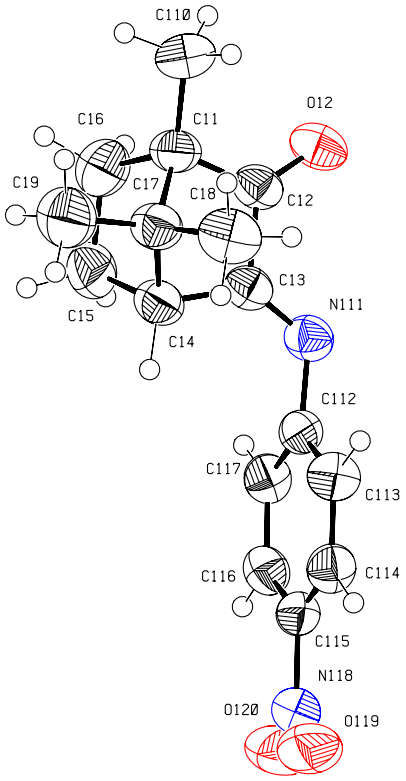


Figure 4. The asymmetric unit of compound **3d**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

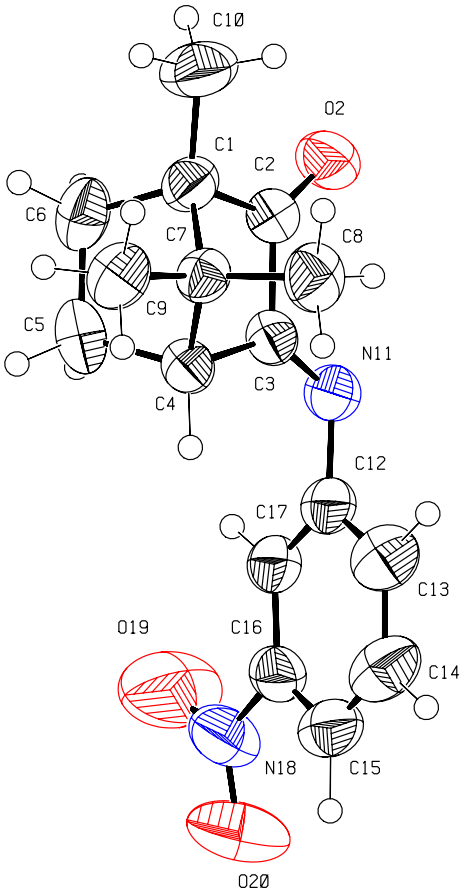


Figure 5. The asymmetric unit of compound **3e**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

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 40, 0.015–0.035 mm); column dimensions (dry filled): 15 × 460 mm; backpressure: 10–15 bar; detection: UV 254 nm; sample amount: 100–150 mg of isomeric mixture per run. Ratio of isomers and de were determined by ^{1}H NMR.

(1*S*)-(+)-Camphorquinone **1**, anilines **2a**–**e**, 4-toluenesulfonic acid monohydrate, [2-(acetoxymethyl)allyl]trimethylsilane (TMM) **4**, $Pd(OAc)_2$, $(i\text{-}PrO)_3P$ and $LiAlH_4$ are commercially available (Sigma–Aldrich).

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 the preparation of (1*S*,3*E*,4*R*)-3-(arylimino)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ones 3a–e and their (1*S*,3*Z*,4*R*)-isomers 3′a–e

Compounds **3a**–**e**/**3′a**–**e** were prepared according to the modified literature procedure.[33] A mixture of (1*S*)-(+)-camphorquinone **1** (3 mmol, 499 mg), anilines **2a**–**e** (3 mmol), 4-toluenesulfonic acid monohydrate (0.3 mmol, 58 mg), and anhydrous toluene (35 mL) was heated at reflux for 6 h. A Dean–Stark water trap was used to remove water during the reaction. The reaction mixture was cooled to 5 °C, poured into a cooled saturated aq $NaHCO_3$ (150 mL, 5 °C) and the product extracted with EtOAc (2 × 100 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated in vacuo, and the residue crystallized from ethanol. Compounds **3a**–**e**/**3′a**–**e** were prepared in this manner.

5.2.1. (1*S*,3*E*,4*R*)-1,7,7-Trimethyl-3-(phenylimino)bicyclo-[2.2.1]heptan-2-one 3a and its (1*S*,3*Z*,4*R*)-isomer 3′a. Prepared from aniline **2a** (280 mg, 3 mmol); **3a**:**3′a** = 96:4. Yield: 0.478 g (66%) of a yellow solid; mp 104–106 °C (from ethanol at −20 °C), lit.[44] mp 107–108 °C; $[\alpha]_D^{23} = -652.1$ (*c* 0.14, $CHCl_3$), lit.[44] $[\alpha]_{589}^{35} = -659.8$ (*c* 0.50, $CHCl_3$). *m*/*z* (EI) = 241 (M^+); *m*/*z* (HRMS) Found: 241.147350 (M^+); $C_{16}H_{19}NO$ requires: *m*/*z* = 241.146664. (Found: C, 79.84; H, 8.13; N, 5.70. $C_{16}H_{19}NO$ requires: C, 79.63; H, 7.94; N, 5.80.) ν_{max} (KBr) 2955, 1744 (C=O), 1664, 1652, 1589, 1485, 1448, 1397, 1373, 1325, 1259, 1106, 1060, 1015, 969, 795, 779, 699 cm^{-1}.

[†] Donation of Alexander von Humboldt Foundation.

5.2.1.1. Data for major (1*S*,3*E*,4*R*)-isomer 3a. ^{1}H NMR ($CDCl_3$): δ 0.92, 0.99, and 1.11 (9H, 3s, 1:1:1, 3 × Me); 1.59–1.73, (2H, m, CH_2); 1.80–1.92 and 2.04–2.16 (2H, 2m, 1:1, CH_2); 2.82 (1H, d, $J = 4.5$ Hz, H–C(4)); 6.90–6.94, 7.15–7.20, and 7.34–7.39 (5H, 3m, 2:1:2, Ph). ^{13}C NMR ($CDCl_3$): δ 9.1, 17.6, 21.0, 24.5, 30.2, 44.6, 50.2, 58.2, 120.4, 125.3, 129.0, 149.7, 171.9, 206.4.

5.2.1.2. Data for minor (1*S*,3*Z*,4*R*)-isomer 3′a. ^{1}H NMR ($CDCl_3$): δ 0.96, 1.02, and 1.05 (9H, 3s, 1:1:1, 3 × Me); 2.75 (1H, d, $J = 4.5$ Hz, H–C(4)); 6.77–6.81 (1H, m, 1H of Ph).

5.2.2. (1*S*,3*E*,4*R*)-1,7,7-Trimethyl-3-[(1-naphthyl)imino]-bicyclo[2.2.1]heptan-2-one 3b and its (1*S*,3*Z*,4*R*)-isomer 3′b. Prepared from 1-naphthylamine **2b** (430 mg, 3 mmol); **3b**:**3′b** = 97:3. Yield: 0.167 g (19%) of a yellow solid; mp 146–148 °C (from ethanol); $[\alpha]_D^{23} = -620.8$ (*c* 0.11, $CHCl_3$). *m*/*z* (EI) = 291 (M^+); *m*/*z* (HRMS) Found: 291.163130 (M^+); $C_{20}H_{21}NO$ requires: *m*/*z* = 291.162314. (Found: C, 82.48; H, 7.40; N, 4.76. $C_{20}H_{21}NO$ requires: C, 82.44; H, 7.26; N, 4.81.) ν_{max} (KBr) 2965, 1753 (C=O), 1669, 1585, 1571, 1505, 1448, 1389, 1373, 1323, 1265, 1226, 1166, 1077, 1059, 1046, 1013, 999, 966, 807, 779 cm^{-1}.

5.2.2.1. Data for major (1*S*,3*E*,4*R*)-isomer 3b. ^{1}H NMR ($CDCl_3$): δ 0.95, 0.96, and 1.15 (9H, 3s, 1:1:1, 3 × Me); 1.58–1.66, 1.69–1.78, 1.83–1.93, and 1.98–2.10 (4H, 4m, 1:1:1:1, 2 × CH_2); 2.68 (1H, d, $J = 4.9$ Hz, H–C(4)); 6.75 (1H, dd, $J = 0.8$; 7.2 Hz, 1H of Ar); 7.41–7.54 (3H, m, 3H of Ar); 7.67 (1H, d, $J = 8.3$ Hz, 1H of Ar); 7.83–7.88 (2H, m, 2H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.2, 17.6, 21.2, 24.7, 30.3, 44.5, 50.4, 58.5, 113.3, 123.8, 125.2, 125.6, 125.9, 126.6, 126.7, 127.9, 134.1, 146.7, 173.1, 206.1.

5.2.2.2. Data for minor (1*S*,3*Z*,4*R*)-isomer 3′b. ^{1}H NMR ($CDCl_3$): δ 2.94 (1H, d, $J = 4.7$ Hz, H–C(4)).

5.2.3. (1*S*,3*E*,4*R*)-1,7,7-Trimethyl-3-[(2-nitrophenyl)imino]-bicyclo[2.2.1]heptan-2-one 3c and its (1*S*,3*Z*,4*R*)-isomer 3′c. Prepared from 2-nitroaniline **2c** (415 mg, 3 mmol); **3c**:**3′c** = 75:25. Repeated crystallization from ethanol gave isomerically pure compound **3c**. Yield: 0.387 g (45%) of a yellow solid; mp 133–141 °C (from ethanol); $[\alpha]_D^{23} = -94.6$ (*c* 0.11, $CHCl_3$). *m*/*z* (EI) = 286 (M^+); *m*/*z* (HRMS) Found: 286.130950 (M^+); $C_{16}H_{18}N_2O_3$ requires: *m*/*z* = 286.131743. (Found: C, 67.10; H, 6.37; N, 9.74. $C_{16}H_{18}N_2O_3$ requires: C, 67.12; H, 6.34; N, 9.78.) ν_{max} (KBr) 2959, 1749 (C=O), 1678, 1605, 1575, 1533, 1476, 1447, 1393, 1362, 1159, 1014, 970, 861, 779, 770 cm^{-1}.

5.2.3.1. Data for major (1*S*,3*E*,4*R*)-isomer 3c. ^{1}H NMR (DMSO-d_6, 302 K): δ 0.91, 0.96, 1.00 (9H, 3br s, 1:1:1, 3 × Me); 1.47–1.77, 1.84–1.94, and 1.97–2.24 (4H, 3m, 2:1:1, 2 × CH_2); 2.62 (1H, br s, H–C(4)); 6.89–7.08, 7.21–7.46, 7.56–7.82 (3H, 3m, 1:1:1, 3H of C_6H_4); 8.08 (1H, br d, $J = 7.9$ Hz, 1H of C_6H_4). ^{1}H NMR (DMSO-d_6, 358 K): δ 0.92, 0.97, 0.98 (9H, 3s, 1:1:1, 3 × Me); 1.50–1.59, 1.62–1.71, 1.84–1.93, and 2.04–2.14 (4H, 4m, 1:1:1:1, 2 × CH_2); 2.68 (1H, d, $J = 4.1$ Hz, H–C(4)); 6.94 (1H, d, $J = 7.9$ Hz, 1H of C_6H_4); 7.33 (1H, t, $J = 7.7$ Hz, 1H of C_6H_4); 7.67 (1H, t, $J = 7.5$ Hz, 1H of C_6H_4); 8.03 (1H, d, $J = 8.3$ Hz, 1H of C_6H_4). ^{13}C NMR (DMSO-d_6, 358 K): δ 8.1, 16.7, 20.0, 22.9, 29.1, 43.6, 51.4, 57.7, 120.3, 124.2, 124.3, 133.9, 139.1, 144.3.

5.2.3.2. Data for minor (1*S*,3*Z*,4*R*)-isomer 3′c. ^{1}H NMR (DMSO-d_6, 302 K): δ 2.83 (1H, br s, H–C(4)).

5.2.4. (1*S*,3*E*,4*R*)-1,7,7-Trimethyl-3-[(4-nitrophenyl)imino]-bicyclo[2.2.1]heptan-2-one 3d and its (1*R*,3*Z*,4*S*)-isomer 3′d. Prepared from 4-nitroaniline (**2d**) (415 mg, 3 mmol); **3d**:**3′d** = 90:10. Yield: 0.464 g (54%) of a yellow solid; mp 128–130 °C (from ethanol); $[\alpha]_D^{23} = -358.2$ (*c* 0.17, $CHCl_3$). *m*/*z* (EI) = 286 (M^+); *m*/*z* (HRMS) Found: 286.132530 (M^+); $C_{16}H_{18}N_2O_3$ requires: *m*/*z* = 286.131743. (Found: C, 67.41; H, 6.47; N, 9.79. $C_{16}H_{18}N_2O_3$ requires: C, 67.12; H, 6.34; N, 9.78.) ν_{max} (KBr) 2956, 1755 (C=O), 1692, 1587, 1512, 1482, 1342, 1262, 1221, 1198, 1166, 1105, 1015, 869, 857 cm^{-1}.

5.2.4.1. Data for major (1*S*,3*E*,4*R*)-isomer 3d. ^{1}H NMR ($CDCl_3$): δ 0.95, 1.01, and 1.13 (9H, 3s, 1:1:1, 3 × Me); 1.54–1.62, 1.66–1.75, 1.86–1.96, and 2.05–2.17 (4H, 4m, 1:1:1:1, 2 × CH_2); 2.68 (1H, d, $J = 4.9$ Hz, H–C(4)); 6.97 and 8.26 (4H, 2d, 1:1, $J = 8.7$ Hz, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 9.0, 17.4, 21.1, 24.4, 30.0, 44.5, 50.4, 58.3, 120.1, 125.1, 145.0, 155.8, 173.6, 205.3.

5.2.4.2. Data for minor (1*S*,3*Z*,4*R*)-isomer 3′d. 1.08 (3H, s, Me); 2.78 (1H, br s, H–C(4)); 6.82 (1H, br d, $J = 8.0$ Hz, 2H of Ar); 8.16 (1H, br d, $J = 8.0$ Hz, 2H of Ar).

5.2.5. (1*S*,3*E*,4*R*)-1,7,7-Trimethyl-3-[(3-nitrophenyl)imino]-bicyclo[2.2.1]heptan-2-one 3e and its (1*S*,3*Z*,4*R*)-isomer 3′e. Prepared from 3-nitroaniline **2e** (415 mg, 3 mmol); **3e**:**3′e** = 89:11. Yield: 0.550 g (64%) of a yellow solid; mp 121–123 °C (from ethanol); $[\alpha]_D^{23} = -377.3$ (*c* 0.11, $CHCl_3$). *m*/*z* (EI) = 286 (M^+); *m*/*z* (HRMS) Found: 286.132520 (M^+); $C_{16}H_{18}N_2O_3$ requires: *m*/*z* = 286.131743. (Found: C, 67.41; H, 6.41; N, 9.78. $C_{16}H_{18}N_2O_3$ requires: C, 67.12; H, 6.34; N, 9.78.) ν_{max} (KBr) 2960, 1754 (C=O), 1686, 1612, 1525, 1450, 1393, 1375, 1349, 1308, 1278, 1202, 1016, 985, 804 cm^{-1}.

5.2.5.1. Data for major (1*S*,3*E*,4*R*)-isomer 3e. ^{1}H NMR ($CDCl_3$): δ 0.95, 1.02, and 1.14 (9H, 3s, 1:1:1, 3 × Me); 1.59–1.76 (2H, m, CH_2); 1.87–1.96 and 2.08–2.19 (2H, 2m, 1:1, CH_2); 2.75 (1H, d, $J = 4.9$ Hz, H–C(4)); 7.22–7.26 (1H, m, 1H of C_6H_4); 7.55 (1H, t, $J = 7.9$ Hz, 1H of C_6H_4); 7.74 (1H, t, $J = 1.9$ Hz, 1H of C_6H_4); 8.03–8.06 (1H, m, 1H of C_6H_4). ^{13}C NMR ($CDCl_3$): δ 9.1, 17.5, 21.2, 24.4, 30.1, 44.7, 50.3, 58.3, 115.0, 120.0, 126.5, 130.1, 148.9, 150.9, 174.1, 205.5.

5.2.5.2. Data for minor (1*S*,3*Z*,4*R*)-isomer 3′e. 0.97, 1.03, and 1.08 (9H, 3s, 1:1:1, 3 × Me); 2.79 (1H, d, $J = 4.6$ Hz, H–C(4)); 7.05–7.09 (1H, m, 1H of Ar); 7.42 (1H, t, $J = 8.1$ Hz, 1H of Ar); 7.61 (1H, t, $J = 2.1$ Hz, 1H of Ar); 7.91–7.98 (1H, m, 1H of Ar).

5.3. General procedure for 1,3-dipolar cycloadditions of trimethylenemethane to (1*S*)-(+)-camphorquinone 1 and 3-iminocamphors 3a–e/3′a–e

(1*S*)-(+)-Camphorquinone **1** (1 mmol, 166 mg) or 3-iminocamphors **3a–e/3′a–e** (1 mmol) and [2-(acetoxymethyl)-allyl]trimethylsilane (TMM) **4** (1.4 mmol, 261 mg) were dissolved in anhydrous toluene (3 mL) and heated under argon at reflux. Then, a solution of $Pd(OAc)_2$ (23 mg, 0.1 mmol) and $(i\text{-PrO})_3P$ (0.139 mL, $d_4^{20} = 0.905$ g/l, 0.6 mmol) in anhydrous THF (1 mL) was added and the reaction mixture was heated at reflux for 3 h. Volatile components were evaporated in vacuo and the residue was purified by CC and/or MPLC. Fractions containing the product were combined and evaporated in vacuo. Compounds **5a–e**, **6d,e**, and **7/7′** were prepared in this manner.

5.3.1. *N*-{(1*S*,2*R*,3*E*,4*R*)-1,7,7-Trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-ylidene}aniline 5a.

Prepared from compound **3a/3′a** (241 mg, 1 mmol); CC (EtOAc–hexanes, 1:10); 0.269 g (91%) of a colorless oil; $[\alpha]_D^{26} = -18.0$ (*c* 0.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.84, 0.94, and 1.13 (9H, 3s, 1:1:1, 3 × Me); 1.26–1.35, 1.49–1.68, and 1.72–1.83 (4H, 3m, 1:2:1, 2 × CH_2); 2.38 (1H, d, $J = 4.9$ Hz, H–C(4)); 2.65 (1H, br d, $J = 15.8$ Hz, Ha–C(4′)); 2.73–2.82 (1H, m, Hb–C(4′)); 4.47 (1H, br d, $J = 12.4$ Hz, Ha–C(2′)); 4.84–4.90 (1H, m, Hb–C(2′)); 4.90–4.93 (1H, m, Ha–C(3″)); 5.00–5.03 (1H, m, Hb–C(3″)); 6.71–6.74, 6.99–7.05, and 7.24–7.29 (5H, 3m, 2:1:2, Ph). ^{13}C NMR ($CDCl_3$): δ 9.6, 19.0, 22.4, 24.2, 31.7, 39.5, 47.6, 51.7, 52.2, 72.6, 90.1, 103.7, 120.0, 123.2, 128.8, 147.9, 151.8, 185.9. *m/z* (EI) = 295 (M^+); *m/z* (HRMS) Found: 295.194350 (M^+); $C_{20}H_{25}NO$ requires: *m/z* = 295.193615. (Found: C, 79.67; H, 8.35; N, 7.05. $C_{20}H_{25}NO$ requires: C, 81.31; H, 8.53; N, 4.74.) ν_{max} (NaCl) 2957, 2875, 1687, 1595, 1485, 1454, 1392, 1373, 1215, 1193, 1160, 1067, 1018, 878, 776, 697 cm^{-1}.

5.3.2. *N*-{(1*S*,2*R*,3*E*,4*R*)-1,7,7-Trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-ylidene}naphthalen-1-amine 5b.

Prepared from compound **3b/3′b** (291 mg, 1 mmol); CC (EtOAc–hexanes, 1:10); 0.121 g (35%) of a colorless oil; $[\alpha]_D^{26} = -36.8$ (*c* 0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.82, 0.99, and 1.17 (9H, 3s, 1:1:1, 3 × Me); 1.28–1.37 and 1.56–1.80 (4H, 2m, 1:3, 2 × CH_2); 2.32 (1H, d, $J = 4.5$ Hz, H–C(4)); 2.79 (1H, br d, $J = 15.8$ Hz, Ha–C(4′)); 2.84–2.92 (1H, m, Hb–C(4′)); 4.58 (1H, br d, $J = 12.8$ Hz, Ha–C(2′)); 4.93–4.97 (1H, m, Ha–C(3″)); 5.00–5.07 (1H, m, Hb–C(2′)); 5.08–5.11 (1H, m, Hb–C(3″)); 6.67 (1H, dd, $J = 0.8$; 7.2 Hz, 1H of Ar); 7.34–7.49 (3H, m, 3H of Ar); 7.54 (1H, d, $J = 8.3$ Hz, 1H of Ar); 7.78–7.88 (2H, m, 2H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.5, 18.9, 22.4, 24.4, 31.7, 39.7, 47.6, 51.7, 52.2, 72.7, 90.2, 103.8, 113.5, 123.3, 123.8, 125.3, 125.8, 126.1, 127.0, 127.8, 134.1, 147.8, 147.9, 186.8. *m/z* (EI) = 345 (M^+); *m/z* (HRMS) Found: 345.210150 (M^+); $C_{24}H_{27}NO$ requires: *m/z* = 345.209265. (Found: C, 82.96; H, 8.23; N, 3.74. $C_{24}H_{27}NO$ requires: C, 83.44; H, 7.88; N, 4.05.) ν_{max} (NaCl) 2956, 2876, 1687, 1682, 1588, 1574, 1505, 1483, 1455, 1391, 1373, 1283, 1269, 1226, 1192, 1065, 1035, 1014, 877, 799, 776 cm^{-1}.

5.3.3. 2-Nitro-*N*-{(1*S*,2*R*,3*E*,4*R*)-1,7,7-trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-ylidene}aniline 5c.

Prepared from compound **3c/3′c** (286 mg, 1 mmol); CC (EtOAc–hexanes, 1:10); 0.262 g (77%) of a yellow oil; $[\alpha]_D^{23} = +133.9$ (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.88, 0.96, and 1.21 (9H, 3s, 1:1:1, 3 × Me); 1.40–1.47 and 1.52–1.75 (4H, 2m, 1:3, 2 × CH_2); 2.27 (1H, d, $J = 4.1$ Hz, H–C(4)); 2.71–2.87 (2H, m, Ha–C(4′), Hb–C(4)); 4.46 (1H, br d, $J = 12.8$ Hz, Ha–C(2′)); 4.73 (1H, br d, $J = 12.8$ Hz, Hb–C(2′)); 4.86–4.90 (1H, m, Ha–C(3″)); 5.00–5.04 (1H, m, Hb–C(3″)); 6.77 (1H, dd, $J = 1.5$; 8.3 Hz, 1H of Ar); 7.10–7.15 (1H, m, 1H of Ar); 7.46–7.52 (1H, m, 1H of Ar); 8.00 (1H, dd, $J = 1.1$; 8.3 Hz, 1H of Ar); 7.78–7.88 (2H, m, 2H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.4, 19.0, 22.5, 22.6, 31.5, 38.8, 47.9, 52.4, 52.7, 72.5, 89.9, 104.0, 122.0, 123.3, 125.2, 134.0, 140.3, 146.5, 147.4, 186.2. *m/z* (EI) = 340 (M^+); *m/z* (HRMS) Found: 340.179750 (M^+); $C_{20}H_{24}N_2O_3$ requires: *m/z* = 340.178693. (Found: C, 70.28; H, 7.26; N, 9.23. $C_{20}H_{24}N_2O_3$ requires: C, 70.56; H, 7.11; N, 8.23.) ν_{max} (NaCl) 2958, 2869, 1694, 1603, 1572, 1519, 1472, 1456, 1392, 1374, 1344, 1310, 1266, 1218, 1191, 1142, 1067, 1017, 874, 771 cm^{-1}.

5.3.4. 4-Nitro-*N*-{(1*S*,2*R*,3*E*,4*R*)-1,7,7-trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-ylidene}aniline 5d and (1*S*,3*S*,4*R*)-1,7,7-trimethyl-4′-methylene-1′-(4-nitrophenyl)spiro[bicyclo[2.2.1]heptane-3,2′-pyrrolidin]-2-one 6d.

Prepared from compound **3d/3′d** (286 mg, 1 mmol); CC (EtOAc–hexanes, 1:1); **5d**:**6d** = 56:44. Subsequent separation of **5d/6d** by MPLC (EtOAc–hexanes, 1:10) furnished pure compounds **5d** and **6d**.

5.3.4.1. Data for compound 5d. Yield: 0.147 g (43%) of a brownish-yellow solid; mp 123–135 °C; $[\alpha]_D^{23} = +32.8$ (*c* 0.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.87, 0.95, and 1.14 (9H, 3s, 1:1:1, 3 × Me); 1.23–1.36, 1.51–1.60, 1.62–1.72, and 1.76–1.87 (4H, 4m, 1,:1:1:1, 2 × CH_2); 2.26 (1H, d, $J = 4.9$ Hz, H–C(4)); 2.62 (1H, br d, $J = 15.8$ Hz, Ha–C(4′)); 2.76–2.85 (1H, m, Hb–C(4′)); 4.48 (1H, br d, $J = 12.8$ Hz, Ha–C(2′)); 4.79 (1H, br d, $J = 12.8$ Hz, Ha–C(2′)); 4.93 (1H, br s, Hb–C(3″)); 5.03 (1H, br s, Hb–C(3″)); 6.79–6.83 and 8.14–8.19 (4H, 2m, 1:1, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 9.3, 18.8, 22.3, 24.0, 31.3, 39.3, 47.7, 52.2, 72.4, 89.8, 104.0, 120.1, 124.9, 143.7, 147.2, 157.7, 187.5. *m/z* (EI) = 340 (M^+); *m/z* (HRMS) Found: 340.179520 (M^+); $C_{20}H_{24}N_2O_3$ requires: *m/z* = 340.178693. (Found: C, 70.79; H, 7.28; N, 8.17. $C_{20}H_{24}N_2O_3$ requires: C, 70.56; H, 7.11; N, 8.23.) ν_{max} (KBr) 2998, 2954, 2931, 2866, 1683, 1598, 1586, 1508, 1481, 1450, 1390, 1375, 1339, 1313, 1296, 1285, 1265, 1220, 1191, 1160, 1102, 1066, 1017, 883, 866, 741, 703, 647 cm^{-1}.

5.3.4.2. Data for compound 6d. Yield: 0.116 g (34%) of a brownish-yellow solid; mp 65–80 °C; $[\alpha]_D^{23} = -237.5$ (*c* 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.90, 0.93, and 1.00 (9H, 3s, 1:1:1, 3 × Me); 1.45–1.53, 1.59–1.75, and 1.91–2.02 (4H, 3m, 1:2:1, 2 × CH_2); 2.49 (1H, d, $J = 4.5$ Hz, H–C(4)); 2.54 (1H, dt, $J = 1.5$; 16.2 Hz, Ha–C(4′)); 2.87 (1H, ddd, $J = 2.3$; 4.5; 16.2 Hz, Hb–C(4′)); 3.65–3.73

(1H, m, Ha–C(2′)); 4.73–4.81 (1H, m, Hb–C(2′)); 4.99–5.03 (1H, m, Ha–C(3″)); 5.09–5.13 (1H, m, Hb–C(3″)); 7.04–7.10 and 8.09–8.14 (4H, 2m, 1:1, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 9.8, 20.0, 22.4, 24.2, 31.0, 41.2, 46.6, 49.7, 59.5, 61.8, 75.3, 106.7, 124.6, 125.2, 143.0, 145.2, 157.4, 218.5. m/z (EI) = 340 (M^+); m/z (HRMS) Found: 340.179550 (M^+); $C_{20}H_{24}N_2O_3$ requires: m/z = 340.178693. (Found: C, 70.79; H, 7.22; N, 8.20. $C_{20}H_{24}N_2O_3$ requires: C, 70.56; H, 7.11; N, 8.23.) ν_{max} (KBr) 2990, 2957, 2929, 2878, 1737 (C=O), 1586, 1507, 1488, 1458, 1392, 1339, 1318, 1247, 1177, 1111, 1024, 1000, 975, 956, 943, 895 cm^{-1}.

5.3.5. 3-Nitro-*N*-{(1*S*,2*R*,3*E*,4*R*)-1,7,7-trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-ylidene}aniline 5e and (1*S*,3*S*,4*R*)-1,7,7-trimethyl-4′-methylene-1′-(3-nitrophenyl)spiro[bicyclo[2.2.1]heptane-3,2′-pyrrolidin]-2-one 6e. Prepared from compound **3e**/**3′e** (286 mg, 1 mmol); CC (EtOAc–hexanes, 1:1); **5e**:**6e** = 87:13; CC (EtOAc–hexanes, 1:25); **5e**:**6e** = 86:14; 0.198 g (58%) of a yellow oil; $[\alpha]_D^{23} = 0$ (c 0.45, $CHCl_3$). m/z (EI) = 340 (M^+); m/z (HRMS) Found: 340.179350 (M^+); $C_{20}H_{24}N_2O_3$ requires: m/z = 340.178693. (Found: C, 68.45; H, 7.27; N, 7.59. $C_{20}H_{24}N_2O_3$ requires: C, 70.56; H, 7.11; N, 8.23.) ν_{max} (NaCl) 2959, 2929, 2871, 1744 (C=O), 1682, 1612, 1575, 1526, 1472, 1455, 1392, 1372, 1348, 1308, 1284, 1217, 1192, 1161, 1067, 1017, 887, 806, 738, 696 cm^{-1}.

5.3.5.1. Data for compound 5e. ^{1}H NMR ($CDCl_3$): δ 0.87, 0.96, and 1.14 (9H, 3s, 1:1:1, 3 × Me); 1.28–1.37, 1.51–1.72, and 1.77–1.88 (4H, 3m, 1:2:1, 2 × CH_2); 2.31 (1H, d, J = 4.9 Hz, H–C(4)); 2.64 (1H, br d, J = 15.8 Hz, Ha–C(4′)); 2.76-2.85 (1H, m, Hb–C(4′)); 4.49 (1H, br d, J = 12.8 Hz, Ha–C(2′)); 4.79–4.86 (1H, m, Hb–C(2′)); 4.91–4.96 (1H, m, Ha–C(3″)); 5.02–5.07 (1H, m, Hb–C(3″)); 7.03–7.06 (1H, m, 1H of Ar); 7.43 (1H, t, J = 8.1 Hz, 1H of Ar); 7.58 (1H, t, J = 2.1 Hz, 1H of Ar); 7.88–7.92 (1H, m, 1H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.3, 18.9, 22.4, 24.1, 31.5, 39.4, 47.8, 51.9, 52.2, 72.5, 90.0, 104.0, 115.0, 118.2, 126.3, 129.7, 147.4, 148.8, 152.7, 188.5.

5.3.5.2. Data for compound 6e. ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, s, Me); 1.90–1.97 (1H, m, 1H of CH_2); 2.20 (1H, d, J = 4.5 Hz, H–C(4)); 2.51–2.59 (1H, m, Ha–C(4′)); 2.92 (1H, ddd, J = 2.6; 4.9; 16.9 Hz, Hb–C(4′)); 3.52–3.59 (1H, m, Ha–C(2′)); 4.70–4.78 (1H, m, Hb–C(2′)); 5.00–5.03 (1H, m, Ha–C(3″)); 5.13–5.16 (1H, m, Hb–C(3″)); 7.34–7.38 (1H, m, 1H of Ar); 7.95–7.99 (1H, m, 1H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.7, 19.8, 22.5, 24.2, 31.1, 40.5, 46.7, 49.4, 59.4, 62.8, 75.4, 106.7, 119.6, 122.1, 129.6, 133.8, 146.1, 148.6, 153.0, 218.9.

5.3.6. (1*S*,2*R*,4*R*)-1,7,7-Trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-one 7 and (1*S*,3*S*,4*R*)-1,7,7-trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclotane-3,2′-furan]-2-one 7′. Prepared from (1*S*)-(+)-camphorquinone **1** (166 mg, 1 mmol); CC (EtOAc–hexanes, 1:1); **7**:**7′** = 1:1; CC (EtOAc–hexanes, 1:15) 7:7′ = 1:1. Yield: 0.210 g (95%) of a colorless oil. ^{13}C NMR ($CDCl_3$): δ 8.9, 9.2, 18.5, 19.6, 21.87, 21.88, 22.0, 23.3, 30.0, 31.3, 37.4, 39.3, 46.1, 46.3, 51.5, 52.3, 58.4, 59.8, 71.7, 72.2, 87.4, 88.6, 104.13, 104.14, 146.2, 146.3, 219.1, 219.6. m/z (EI) = 220 (M^+); m/z (HRMS) Found: 220.147100 (M^+); $C_{14}H_{20}O_2$ requires: m/z = 220.146330. (Found: C, 73.23; H, 7.44; N, 3.92. $C_{14}H_{20}O_2$ requires: C, 76.33; H, 9.15; N, 0.00.) ν_{max} (NaCl) 2960, 2872, 1748 (C=O), 1671, 1485, 1456, 1426, 1393, 1374, 1325, 1310, 1239, 1156, 1105, 1068, 1025, 1015, 1002, 985, 939, 883, 852 cm^{-1}.

5.3.6.1. Data for compound 7. ^{1}H NMR ($CDCl_3$): δ 0.94, 0.95, 1.11 (9H, 3s, 1:1:1, 3 × Me); 1.36–1.55, 1.67–1.77, and 1.86–1.98 (4H, 3m, 2:1:1, 2 × CH_2); 2.18 (1H, d, J = 5.3 Hz, H–C(4)); 2.38–2.45 (1H, m, Ha–C(4′)); 2.60–2.69 (1H, m, Hb–C(4′)); 4.40–4.48 (1H, m, Ha–C(2′)); 4.62–4.71 (1H, m, Hb–C(2′)); 4.91–4.95 (1H, m, Ha–C(3″)); 5.00–5.04 (1H, m, Hb–C(3″)).

5.3.6.2. Data for compound 7′. ^{1}H NMR ($CDCl_3$): δ 0.91, 0.97, 1.08 (9H, 3s, 1:1:1, 3 × Me); 2.01 (1H, d, J = 4.1 Hz, H–C(4)); 2.50 (1H, br d, J = 15.8 Hz, Ha–C(4′)); 2.66–2.75 (1H, m, Hb–C(4′)).

5.4. Synthesis of (1*S*,2*R*,4*R*)-1,7,7-trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-one 7 by hydrolysis of imine 5a

Hydrochloric acid (37%, 0.38 mL, ~2.5 mmol) was added to a cooled solution (0 °C) of **5a** (1 mmol, 295 mg) in a mixture of MeOH and H_2O (3:1, 20 mL). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. Methanol was evaporated in vacuo, the aqueous residue was poured into EtOAc (100 mL), and the organic phase was washed subsequently with saturated aq $NaHSO_4$ (100 mL) and water (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated in vacuo. The residue was purified by CC (EtOAc–hexanes, 1:10). Fractions containing the product were combined and evaporated in vacuo to give **7**. Yield: 0.135 g (61%) of a colorless oil; $[\alpha]_D^{27} = +122.8$ (c 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.94, 0.95, 1.11 (9H, 3s, 1:1:1, 3 × Me); 1.36–1.54, 1.67–1.77, 1.86–1.98 (4H, 3m, 2:1:1, 2 × CH_2); 2.18 (1H, d, J = 5.3 Hz, H–C(4)); 2.37-2.45 (1H, m, Ha–C(4′)); 2.60-2.69 (1H, m, Hb–C(4′)); 4.41–4.47 (1H, m, Ha–C(2′)); 4.63–4.70 (1H, m, Hb–C(2′)); 4.91–4.95 (1H, m, Ha–C(3″)); 5.00–5.03 (1H, m, Hb–C(3″)). ^{13}C NMR ($CDCl_3$): δ 9.2, 18.8, 22.1, 22.2, 31.5, 37.6, 46.5, 51.8, 60.0, 72.4, 88.9, 104.4, 146.5, 219.6. m/z (EI) = 220 (M^+); m/z (HRMS) Found: 220.147020 (M^+); $C_{14}H_{20}O_2$ requires: m/z = 220.146330. (Found: C, 73.36; H, 9.14; N, 0.00. $C_{14}H_{20}O_2$ requires: C, 76.33; H, 9.15; N, 0.00.) ν_{max} (NaCl) 2961, 2872, 1748 (C=O), 1672, 1484, 1456, 1425, 1393, 1374, 1326, 1281, 1240, 1156, 1107, 1071, 1014, 883 cm^{-1}.

5.5. General procedure for reduction of compounds 5a–d with $LiAlH_4$

To a solution of compounds **5a**–**d** (0.5 mmol) in anhydrous Et_2O (15 mL) under argon was added a solution of $LiAlH_4$ (5 mL, 1 M in THF) and the reaction mixture was heated at 55 °C for 2–5 h. The reaction mixture was cooled to 0 °C and the unreacted $LiAlH_4$ was quenched carefully

with saturated aq Na_2SO_4 (just enough to quench all $LiAlH_4$). The reaction mixture was filtered through a short column ($d = 1$ cm) consisting of Celite® (bottom layer, $h = 3$ cm) and anhydrous Na_2SO_4 (top layer, $h = 3$ cm) in dichloromethane and washed with dichloromethane (200 mL). The combined filtrates were evaporated in vacuo and the residue was purified by CC. Fractions containing the products were combined and evaporated in vacuo. Compounds **8a–d**, **9d**, and **10d** were prepared in this manner.

5.5.1. (1*S*,2*R*,3*S*,4*R*)-1,7,7-Trimethyl-4′-methylene-*N*-phenyldihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-amine 8a. Prepared from compound **5a** (148 mg, 0.5 mmol); $t = 2$ h; CC (EtOAc–hexanes, 1:40); 0.115 g (77%) of a colorless oil; $[\alpha]_{589}^{27} = +141.5$ (c 0.27, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 0.78, 0.85, and 1.10 (9H, 3s, 1:1:1, 3 × Me); 1.17–1.47 (3H, m, 3H of CH_2); 1.60–1.72 (2H, m, 1H of CH_2, H–C(4)); 2.49 (1H, Ha–C(4′)); 2.81 (1H, br d, $J = 15.5$ Hz, Hb–C(4′)); 3.09 (1H, d, $J = 7.2$ Hz, H–C(3)); 4.40 (2H, br s, Ha–C(2′), Hb–C(2′)); 4.78 (1H, br d, $J = 7.2$ Hz, NH); 4.80 (1H, br s, Ha–C(3″)); 4.93 (1H, br s, Hb–C(3″)); 6.45–6.54 and 7.00–7.06 (5H, 2m, 3:2, Ph). ^{13}C NMR ($CDCl_3$): δ 10.0, 21.6, 22.4, 26.0, 31.7, 43.0, 48.8, 49.2, 52.3, 68.9, 73.1, 93.9, 104.5, 112.7, 116.0, 129.2, 146.5, 147.4. m/z (EI) = 297 (M^+); m/z (HRMS) Found: 297.210500 (M^+); $C_{20}H_{27}NO$ requires: $m/z = 297.209265$. ν_{max} (NaCl) 3434, 3048, 2953, 2886, 1672, 1600, 1504, 1485, 1427, 1389, 1371, 1323, 1312, 1263, 1194, 1179, 1153, 1074, 1045, 1028, 992, 885, 746, 692 cm^{-1}.

5.5.2. (1*S*,2*R*,3*S*,4*R*)-1,7,7-Trimethyl-4′-methylene-*N*-(naphthalen-1-yl)dihydro-3′*H*-spiro[bicyclo-[2.2.1]heptane-2,2′-furan]-3-amine 8b. Prepared from compound **5b** (173 mg, 0.5 mmol); $t = 2$ h; CC (EtOAc–hexanes, 1:20); 0.164 g (94%) of a colorless oil; $[\alpha]_{589}^{25} = +211.6$ (c 0.07, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 0.80, 0.92, 1.16 (9H, 3s, 1:1:1, 3 × Me); 1.30–1.54 (3H, m, 3H of CH_2); 1.68–1.78 (1H, m, 1H of CH_2); 1.86 (1H, d, $J = 4.5$ Hz, H–C(4)); 2.60 (1H, d, $J = 15.5$ Hz, Ha–C(4′)); 2.91 (1H, br d, $J = 15.1$ Hz, Hb–C(4′)); 3.33 (1H, d, $J = 6.0$ Hz, H–C(3)); 4.44–4.55 (2H, m, Ha–C(2′), Hb–C(2′)); 4.81 (1H, br s, Ha–C(3″)); 4.95 (1H, br s, Hb–C(3″)); 5.33 (1H, d, $J = 6.0$ Hz, NH); 6.34 (1H, d, $J = 7.5$ Hz, 1H of Ar); 7.10 (1H, d, $J = 8.3$ Hz, 1H of Ar); 7.29 (1H, t, $J = 7.9$ Hz, 1H of Ar); 7.41–7.48 (2H, m, 2H of Ar); 7.71–7.81 (2H, m, 1H of Ar). ^{13}C NMR ($CDCl_3$): δ 10.1, 21.9, 22.4, 26.0, 31.8, 43.2, 48.4, 49.3, 52.5, 68.5, 73.5, 94.4, 103.6, 104.9, 115.5, 119.9, 123.3, 124.6, 125.7, 127.0, 128.8, 134.7, 142.4, 146.4. m/z (EI) = 347 (M^+); m/z (HRMS) Found: 347.225450 (M^+); $C_{24}H_{29}NO$ requires: $m/z = 347.224915$. (Found: C, 78.31; H, 8.05; N, 5.55. $C_{24}H_{29}NO$ requires: C, 82.95; H, 8.41; N, 4.03.) ν_{max} (NaCl) 3457, 3058, 2952, 2885, 1582, 1524, 1476, 1456, 1410, 1389, 1371, 1339, 1313, 1278, 1252, 1148, 1072, 1050, 1036, 886, 782, 765 cm^{-1}.

5.5.3. N^1-{(1*S*,2*R*,3*S*,4*R*)-1,7,7-Trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-yl}benzene-1,2-diamine 8c. Prepared from compound **5c** (170 mg, 0.5 mmol); $t = 5$ h; CC (EtOAc–hexanes, 1:10); 0.099 g (63%) of a black solid; mp 95–103 °C; $[\alpha]_{589}^{25} = +150.0$ (c 0.09, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 0.78, 0.85, and 1.14 (9H, 3s, 1:1:1, 3 × Me); 1.19–1.28 and 1.32–1.48 (3H, 2m, 1:2, 3H of CH_2); 1.61–1.74 (2H, m, 1H of CH_2, H–C(4)); 2.51 (1H, Ha–C(4′)); 2.83 (1H, br d, $J = 15.5$ Hz, Hb–C(4′)); 3.10 (1H, d, $J = 6.8$ Hz, H–C(3)); 4.11 (2H, br s, NH_2); 4.21 (1H, d, $J = 6.8$ Hz, NH); 4.40 (1H, br d, $J = 12.8$ Hz, Ha–C(2′)); 4.53 (1H, br dd, $J = 1.9$; 13.2 Hz, Hb–C(2′)); 4.80 (1H, br s, Ha–C(3″)); 4.94 (1H, br s, Hb–C(3″)); 6.24 (1H, dd, $J = 0.75$; 7.9 Hz, 1H of Ar); 6.38 (1H, dt, $J = 1.1$; 7.5 Hz, 1H of Ar); 6.55 (1H, dt, $J = 1.5$; 7.5 Hz, 1H of Ar); 6.63 (1H, dd, $J = 1.5$; 7.5 Hz; 1H of Ar). ^{13}C NMR ($CDCl_3$): δ 10.1, 21.8, 22.4, 26.1, 31.7, 43.1, 48.9, 49.3, 52.4, 69.1, 73.4, 94.2, 104.6, 111.4, 116.9, 117.0, 121.0, 133.5, 137.6, 146.8. m/z (EI) = 312 (M^+); m/z (HRMS) Found: 312.220850 (M^+); $C_{20}H_{28}N_2O$ requires: $m/z = 312.220164$. (Found: C, 75.72; H, 9.12; N, 10.39. $C_{20}H_{28}N_2O$ requires: C, 76.88; H, 9.03; N, 8.97.) ν_{max} (KBr) 3405, 2992, 2939, 2865, 1623, 1598, 1517, 1426, 1401, 1386, 1312, 1271, 1073, 1039, 1026, 884, 777, 759, 738, 720 cm^{-1}.

5.5.4. N^1-{(1*S*,2*R*,3*S*,4*R*)-1,7,7-Trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-yl}benzene-1,4-diamine 8d, (*E*)-1,2-bis(4-{(1*S*,2*R*,3*S*,4*R*)-1,7,7-trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-ylamino}phenyl)diazene 9d and (*E*)-1,2-bis(4-{(1*S*,2*R*,3*S*,4*R*)-1,7,7-trimethyl-4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furan]-3-ylamino}phenyl)-diazene-1-oxide 10d. Prepared from compound **5d** (170 mg, 0.5 mmol); $t = 3$ h; **8d**:**9d**:**10d** = 77:17:6 (crude reaction mixture); CC (first EtOAc–hexanes, 1:3, **9d/10d**, the first fraction; then EtOAc–hexanes, 1:1, **8d**, the second fraction). The mixture of compounds **9d** and **10d** was separated by MPLC (EtOAc–hexanes, 1:10). Fractions containing the products were combined and evaporated in vacuo to give pure compounds **9d** and **10d**.

5.5.4.1. Data for compound 8d. Yield: 0.080 g (51%) of a black solid; mp 70–77 °C; $[\alpha]_{589}^{25} = +417.2$ (c 0.06, $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ 0.76, 0.83, and 1.09 (9H, 3s, 1:1:1, 3 × Me); 1.13–1.24 and 1.29–1.45 (3H, 2m, 1:2, 3H of CH_2); 1.58–1.68 (2H, m, 1H of CH_2, H–C(4)); 2.46 (1H, Ha–C(4′)); 2.79 (1H, br d, $J = 15.1$ Hz, Hb–C(4′)); 3.00 (1H, br d, $J = 6.6$ Hz, H–C(3)); 4.00 (1H, br d, $J = 6.6$ Hz, NH); 4.23 (2H, br s, NH_2); 4.38 (2H, br s Ha–C(2′), Hb–C(2′)); 4.79 (1H, br s, Ha–C(3″)); 4.92 (1H, br s, Hb–C(3″)); 6.29 and 6.40 (2H, 2 br d, 1:1, $J = 8.3$ Hz, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 10.1, 21.7, 22.4, 26.2, 31.7, 43.1, 49.0, 49.2, 52.3, 70.2, 73.2, 94.0, 104.4, 114.1, 117.2, 136.5, 141.3, 146.8. m/z (EI) = 312 (M^+); m/z (HRMS) Found: 312.221030 (M^+); $C_{20}H_{28}N_2O$ requires: $m/z = 312.220164$. (Found: C, 75.69; H, 9.04; N, 10.29. $C_{20}H_{28}N_2O$ requires: C, 76.88; H, 9.03; N, 8.97.) ν_{max} (KBr) 3423, 3332, 2950, 2888, 1616, 1516, 1478, 1463, 1416, 1388, 1332, 1307, 1262, 1194, 1151, 1073, 1043, 1023, 900, 881, 817 cm^{-1}.

5.5.4.2. Data for compound 9d. Yield: 0.010 g (3%) of a yellow solid; mp 207–212 °C; $[\alpha]_{589}^{25} = +100.0$ (c 0.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.83, 0.90, and 1.14 (18H, 3s, 1:1:1, 6 × Me); 1.16–1.26, 1.34–1.51, and 1.73–1.84

(8H, 3m, 1:2:1, 4 × CH_2); 1.90 (2H, d, $J = 4.9$ Hz, 2 × H–C(4)); 2.44 (2H, d, $J = 15.1$ Hz, 2 × Ha–C(4′)); 2.91 (2H, br d, $J = 15.4$ Hz, 2 × Hb–C(4′)); 3.20 (2H, d, $J = 6.6$ Hz, 2 × H–C(3)); 4.34–4.41 (2H, m, 2 × Ha–C(2′)); 4.49 (2H, br d, $J = 12.8$ Hz, 2 × Hb–C(2′)); 4.74 (2H, br d, $J = 6.6$ Hz, 2 × NH); 4.82 (2H, br s, 2 × Ha–C(3″)); 4.95 (2H, br s, 2 × Hb–C(3″)); 6.48–6.53 and 7.68–7.73 (8H, 2m, 1:1, 2 × C_6H_4). ^{13}C NMR ($CDCl_3$): δ 10.1, 21.8, 22.4, 26.1, 31.7, 43.1, 49.2, 49.4, 52.5, 68.7, 73.2, 93.9, 105.0, 112.5, 124.4, 144.6, 146.2, 148.8. m/z (EI) = 620 (M^+); m/z (HRMS) Found: 620.411520 (M^+); $C_{40}H_{52}N_4O_2$ requires: $m/z = 620.409027$. (Found: C, 74.29; H, 8.22; N, 9.30. $C_{40}H_{52}N_4O_2$ requires: C, 77.38; H, 8.44; N, 9.02.) ν_{max} (KBr) 3429, 2953, 1597, 1512, 1474, 1460, 1427, 1400, 1389, 1332, 1312, 1194, 1145, 1071, 1044, 1024, 888, 827 cm^{-1}.

5.5.4.3. Data for compound 10d. Yield: 0.016 g (5%) of a yellow solid; mp 219–224 °C; $[\alpha]_{589}^{25} = +85.3$ (c 0.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.83, 0.90, and 1.13 (18H, 3s, 1:1:1, 6 × Me); 1.34–1.60 and 1.73–1.84 (8H, 2m, 3:1, 4 × CH_2); 1.88 (2H, t, $J = 5.1$ Hz, 2 × H–C(4)); 2.43 (2H, d, $J = 15.1$ Hz, 2 × Ha–C(4′)); 2.91 (2H, br d, $J = 15.1$ Hz, 2 × Hb–C(4′)); 3.17 (1H, d, $J = 6.9$ Hz, H–C(3)); 3.20 (1H, d, $J = 7.0$ Hz, H–C(3)); 4.33–4.40 (2H, m, 2 × Ha–C(2′)); 4.49 (2H, br d, $J = 12.8$ Hz, 2 × Hb–C(2′)); 4.76 (1H, br d, $J = 6.4$ Hz, NH); 4.81 (1H, NH); 4.82 (2H, br s, 2 × Ha–C(3″)); 4.95 (2H, br s, 2 × Hb–C(3″)); 6.42–6.51, 8.03–8.09, and 8.17–8.23 (8H, 3m, 2:1:1, 2 × C_6H_4). ^{13}C NMR ($CDCl_3$): δ 10.0, 21.74, 21.76, 22.3, 26.1, 31.65, 31.67, 43.0, 49.1, 49.3, 49.39, 49.40, 52.5, 68.5, 68.7, 73.2, 77.4, 93.9, 105.02, 105.05, 111.6, 112.0, 123.6, 128.2, 135.1, 146.13, 146.17, 148.0, 149.1. m/z (EI) = 636 (M^+); m/z (HRMS) Found: 636.406200 (M^+); $C_{40}H_{52}N_4O_3$ requires: $m/z = 636.403942$. (Found: C, 75.13; H, 8.32; N, 9.03. $C_{40}H_{52}N_4O_3$ requires: C, 75.44; H, 8.23; N, 8.80.) ν_{max} (KBr) 3408, 2951, 1599, 1510, 1481, 1459, 1442, 1403, 1387, 1331, 1314, 1261, 1159, 1072, 1045, 1023, 887, 880, 826 cm^{-1}.

5.6. Synthesis of (1*R*,2*S*,3*R*,4*S*)-1′-(4-aminophenyl)-4,7,7-trimethyl-4′-methylenespiro[bicyclo[2.2.1]heptane-2,2′-pyrrolidin]-3-ol 11d and its (1*R*,2*R*,3*R*,4*S*)-isomer 11′d

A mixture of compound **6d** (340 mg, 1 mmol), $Na_2S_2O_4$ (1740 mg, 10 mmol), K_2CO_3 (414 mg, 3 mmol), ethanol (50 mL), and water (1 mL) was heated at reflux for 3 h. Volatile components were evaporated in vacuo, the residue was suspended in CH_2Cl_2 (200 mL), and the organic phase was washed with water (100 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, 3:1). Fractions containing the product were combined and evaporated in vacuo to give the crude amine **6′d**, which was dissolved in anhydrous Et_2O (15 mL). Then, a solution of $LiAlH_4$ (6 mL, 1 M in THF) was added and the reaction mixture was heated under argon at 55 °C for 2 h. The reaction mixture was cooled to 0 °C and the unreacted $LiAlH_4$ was carefully quenched with saturated aq Na_2SO_4 (just enough to quench all $LiAlH_4$). The reaction mixture was filtered through a short column ($d = 1$ cm) consisting of Celite® (bottom layer, $h = 3$ cm) and anhydrous Na_2SO_4 (top layer, $h = 3$ cm) in dichloromethane and washed with dichloromethane (200 mL). The combined filtrates were evaporated in vacuo to give the crude aminoalcohols **11d** and **11′d** in a ratio of 86:14. The raw product **11d/11′d** was purified by CC (EtOAc–hexanes, 1:1). Fractions containing the products were combined and evaporated in vacuo to give amino alcohols **11d** and **11′d** in a ratio of 88:12. Yield: 0.063 g (20%) of a brownish solid; mp 155–170 °C; $[\alpha]_{589}^{26} = -80.2$ (c 0.17, $CHCl_3$). m/z (EI) = 312 (M^+); m/z (HRMS) Found: 312.220650 (M^+); $C_{20}H_{28}N_2O$ requires: $m/z = 312.220164$. (Found: C, 75.91; H, 9.50; N, 8.54. $C_{20}H_{28}N_2O$ requires: C, 76.88; H, 9.03; N, 8.97.) ν_{max} (KBr) 3436, 3331, 2968, 2946, 1629, 1513, 1463, 1436, 1399, 1389, 1368, 1279, 1256, 1181, 1093, 1071, 1052, 1028, 1015, 884, 840 cm^{-1}.

5.6.1. Data for major (1*R*,2*S*,3*R*,4*S*)-isomer 11d. ^{1}H NMR (DMSO-d_6): δ 0.60, 0.80, and 1.00 (9H, 3s, 1:1:1, 3 × Me); 1.04–1.11, 1.31–1.42, and 1.46–1.56 (4H, 3m, 1:2:1, 2 × CH_2); 1.77 (1H, d, $J = 3.9$ Hz, H–C(4)); 2.36 (1H, d, $J = 15.9$ Hz, Ha–C(4′)); 2.85 (1H, br d, $J = 4.9$ Hz, H–C(2)); 2.99–3.06 (1H, m, Hb–C(4′)); 3.41 (1H, d, $J = 16.2$ Hz, Ha–C(2′)); 3.88–3.95 (1H, m, Hb–C(2′)); 4.31 (1H, br d, $J = 4.9$ Hz, OH); 4.88 (3H, s, Ha–C(3″), NH_2); 5.03 (1H, s, Hb–C(3″)); 6.43–6.48 and 6.80–6.85 (4H, 2m, 1:1, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 12.1, 22.1, 23.3, 24.7, 33.1, 47.1, 49.2, 51.07, 51.12, 65.1, 77.4, 87.7, 105.7, 115.3, 129.9, 143.2, 144.0, 147.5.

5.6.2. Data for minor (1*R*,2*R*,3*R*,4*S*)-isomer 11′d. ^{1}H NMR (DMSO-d_6): δ 0.71, 0.75, and 1.28 (9H, 3s, 1:1:1, 3 × Me); 1.65 (1H, d, $J = 4.2$ Hz, H–C(4)); 2.69 (1H, br d, $J = 16.8$ Hz); 3.69–3.72 (1H, m); 3.82 (1H, br d, $J = 16.5$ Hz); 4.60 (1H, d, $J = 6.1$ Hz, OH); 4.74 (2H, br s, NH_2); 4.80 (1H, s, Ha–C(3″)); 4.94 (1H, s, Hb–C(3″)); 6.39–6.43 and 6.72–6.76 (4H, 2m, 1:1, C_6H_4).

5.7. X-ray structure analysis for compounds 3d and 3e

Single crystal X-ray diffraction data of compounds **3d** and **3e** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[45] DENZO and SCALEPACK[46] were used for indexing and scaling of the data and the structures were solved by means of SIR97.[47] Refinement was done using Xtal3.4[48] program package and the crystallographic plots were prepared by ORTEP III.[49] 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[50] 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 649283 and 649284. 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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Crystallographic data were collected on the Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Science and Technology, Republic of Slovenia through grant Packet X-2000 and PS-511-102, which thus made the purchase of the apparatus possible.

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