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Stereoselective additions to the exocyclic C=C bond of some α-alkylidene-(+)-camphor derivatives

Uroš Grošelj, David Bevk, Renata Jakše, Anton Meden, Branko Stanovnik and Jurij Svete*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, PO Box 537, 1000 Ljubljana, Slovenia

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Abstract—Stereoselective additions to the exocyclic C=C double bond of some (1*R*,3*E*,4*S*)-3-alkylidene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones and (1*R*,4*E*,5*S*)-4-alkylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones were studied. All additions took place predominantly from the less hindered *endo*-face of the methylidene compounds to give the corresponding *exo*-adducts as the major isomers. Thus, catalytic hydrogenations afforded the α-alkylated (1*R*,3*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones and (1*R*,4*R*,5*R*)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones in 28–100% de. Similarly, 1,3-dipolar cycloadditions of 2,4,6-trisubstituted benzonitrile oxides gave the corresponding spiro cycloadducts in 66–100% de. The structures were determined by 2D NMR techniques, NOESY spectroscopy and X–ray diffraction.

1. Introduction

(+)-Camphor **1** and its derivatives are among the most frequently employed types of ex-chiral pool starting materials, building blocks, ligands in various asymmetric reagents and/or catalysts, resolving agents and as shift reagents in NMR spectroscopy.[1–4] In addition, many camphor derivatives are biologically active. For example, the reaction of 3-hydroxymethylidenecamphor[5] with amines, followed by reduction of the exocyclic C=C double bond, leads to 3-aminomethylcamphor derivatives exhibiting local anesthetic and smooth muscle relaxant properties.[6–8]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)prop-2-enoates and alkyl 3-cyanoprop-2-enoates have been prepared as versatile reagents for the preparation of various heterocyclic systems.[9–19] Chiral cyclic enamino lactams and lactones, derived from α-amino acids, have been employed in the synthesis of functionalised heterocycles, such as heteroarylalanines and their analogues and other related heterocyclic systems containing either an α-amino acid, dipeptide, β-amino alcohol, α-hydroxy acid or propane-1,2-diol structural element.[9–12,18,19] Our studies on ex-chiral pool derived enaminones have recently been extended to the preparation and synthetic applications of two (+)-camphor derived enaminones, (1*R*,3*E*,4*S*)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one[21] and (1*R*,4*E*,5*S*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one.[22] These two reagents were used in various synthetic applications, such as the stereoselective synthesis of α-([1,2,4]triazolo[4,3-*x*]azin-3-yl) substituted camphors[21] and analogous compounds,[23,24] in the synthesis of terpene-functionalised pyrazoles,[25] in coupling reactions with amines[22] and Grignard reagents,[26] and 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.[27] In a continuation of our work in this field, we herein report catalytic hydrogenations and 1,3-dipolar cycloadditions of stable benzonitrile oxides to (+)-camphor derived α-alkylidene compounds **4**–**8** and **11**.

2. Results and discussion

Starting enaminones **2**[21] and **3**,[22] and α-alkylidene compounds **4b**,**c**,**h** and **5**[26] were prepared from (1*R*)-(+)-camphor **1** according to literature procedures. Treatment of **2** with KCN and 2-methyl-1*H*-indole under acidic conditions afforded the corresponding dimethylamine substitution products, (*E*)-3-[(1*R*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptan-3-ylidene]acetonitrile **6**[28] and (1*R*,3*E*,4*S*)-1,7,7-trimethyl-3-[(2-methyl-1*H*-indol-3-yl)methylidene]-bicyclo[2.2.1]heptan-2-one **7** in 14% and 84% yield, respectively. According to the previously described reactions of

* Corresponding author. Tel.: +386 1 2419 100; fax: +386 1 2419 220; e-mail: jurij.svete@fkkt.uni-lj.si

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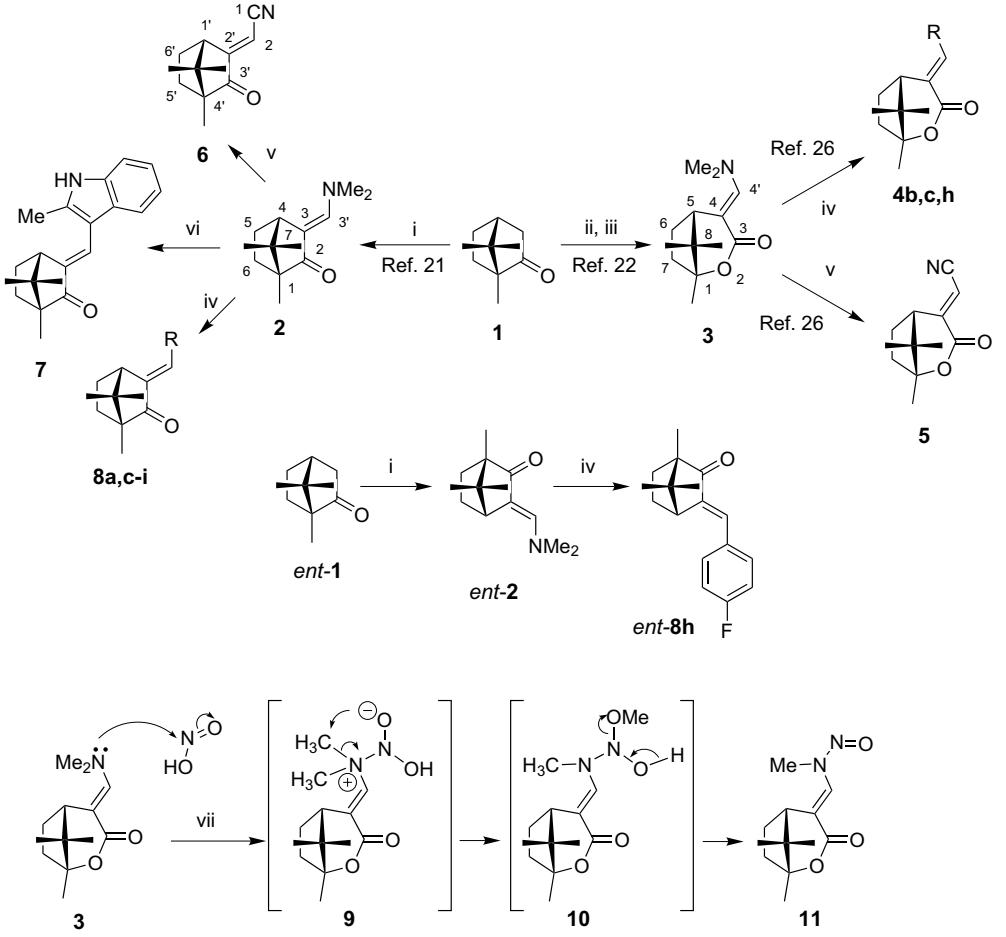
the enamino lactone **3**,[26] treatment of enamino ketone **2** with Grignard reagents also resulted in the stereoselective substitution of the dimethylamino group to give (*E*)-α-alkylidene-(+)-camphors **8a**,**c**–**i** in 51–95% yields. α-Benzylidene-(+)-camphors **8e**–**i** were formed as pure (*E*)-isomers, while their α-alkylidene analogues **8a**,**c**,**d** were formed as mixtures of the major (*E*)-isomers **8a**,**c**,**d** and the minor (*Z*)-isomers **8′a**,**c**,**d**. Upon chromatographic purification over silica gel, the (*E*)-isomers **8a**,**c**,**d** were obtained. In the same manner, compound *ent*-**8h** was prepared in two steps from (−)-camphor *ent*-**1** via (1*S*,3*E*,4*R*)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one *ent*-**2**. It is noteworthy that the carbonyl group did not react, despite the presence of excess Grignard reagent. In contrast to the previously reported nitrosation of enamino lactone **3** with aqueous sodium nitrite in the presence of hydrochloric acid,[27] reaction of **3** with *tert*-butyl nitrite in anhydrous dichloromethane in the presence of CF_3COOH took place at the dimethylamino group and not at the exocyclic C=C double bond to give *N*-methyl-*N*-{[(1*R*,4*E*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]octan-4-ylidene]methyl}nitrous amide **11** in 50% yield. Although we do not have a firm mechanistic explanation for this, rather unusual, nitroso-demethylation reaction, the reaction mechanism might involve migration of a methyl group from the nitrogen to the oxygen atom via a Stevens-type rearrangement. Presumably, the dimethylamino group undergoes addition to the in situ formed nitrous acid to give zwitterionic adduct **9**, followed by *N*→*O* migration of a methyl group to form intermediate **10**, from which elimination of methanol takes place to furnish *N*-methyl-*N*-nitrosoamino compound **11** (Scheme 1 and Table 1).

Next, catalytic hydrogenations of α-methylidene compounds **3**, **4b**, **7** and **11** in the presence of Pd–C under 50 bar of hydrogen were carried out. Hydrogenation of **3** in *n*-propanol at 60 °C gave (1*R*,4*R*,5*R*)-1,4,8,8-tetramethyl-2-oxabicyclo[3.2.1]octan-3-one **13** in 83% yield and 28% de. Formation of compound **13** could be explained by initial hydrogenolytic removal of the dimethylamino group to give the α-methylidene intermediate **12**, followed by addition of hydrogen to the exocyclic C=C double bond. This proposed reaction mechanism is supported by a related transformation of ethyl 2-benzoyl-3-(dimethylamino)prop-2-enoate with sodium cyanoboro-



Scheme 1. Reagents and conditions: (i) bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent), DMF, reflux; (ii) AcOOH, AcOH, AcONa, rt; (iii) bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent), decalin, reflux; (iv) RMgX, THF, −78 °C → rt; (v) KCN, AcOH, rt; (vi) 2-methyl-1*H*-indole, EtOH, HCl (1 equiv), reflux; (vii) *tert*-butyl nitrite, CH_2Cl_2, CF_3COOH, rt.

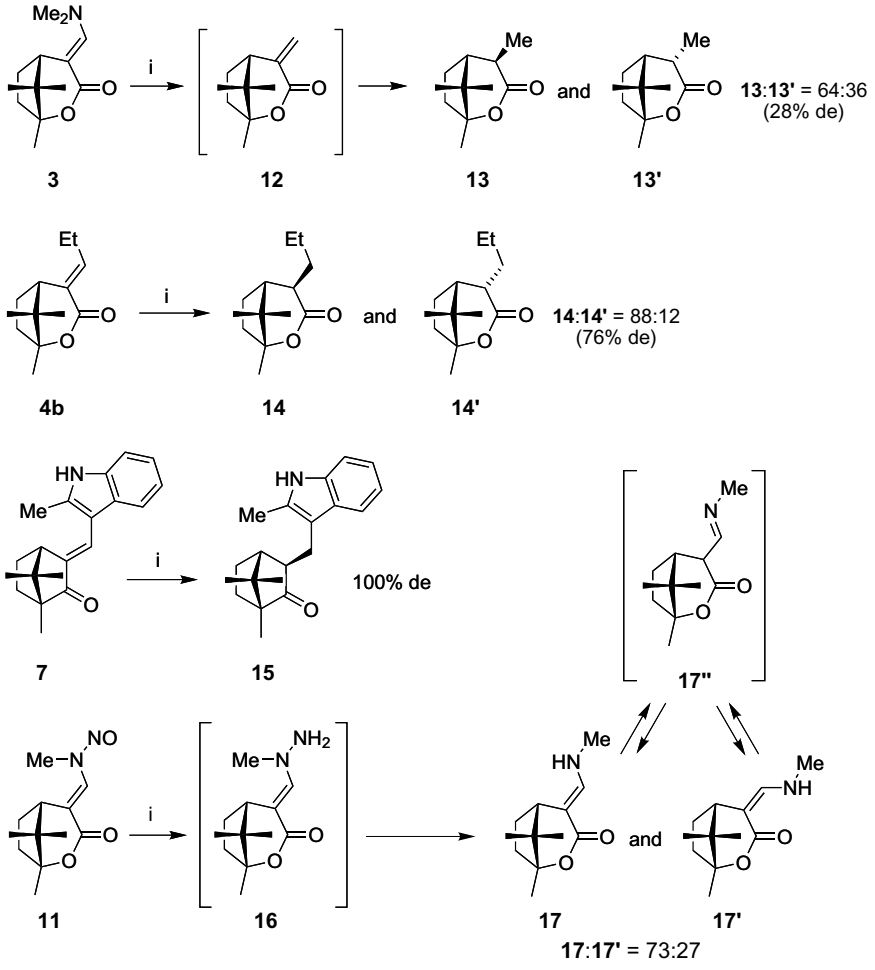
Table 1. Experimental data for alkylidene compounds **4**–**8**, **11** and **17**

Compound	R	*E*:*Z*	Yield (%)
4b	Et	100:0[a]	83[a]
4c	*n*-Bu	100:0[a]	68[a]
4h	4-Fluorophenyl	100:0[a]	64[a]
5	—	100:0[a]	49[a]
6	—	100:0	14
7	—	100:0	84
8/8′a	Me	98:2[b]	93[c]
8/8′c	*n*-Bu	95:5[b]	95[c]
8/8′d	Cyclopentyl	85:15[b]	51[c]
8e	Ph	100:0	91
8f	2-Methylphenyl	100:0	90
8g	4-Methylphenyl	100:0	93
8h	4-Fluorophenyl	100:0	91
ent-**8h**	4-Fluorophenyl	100:0	96
8i	3,5-Bis(trifluoromethyl)phenyl	100:0	70
11	—	100:0	50
17/17′	—	73:27[d]	97

[a] Ref. 26.
[b] *E*:*Z* ratio of the crude product. CC afforded pure (*E*)-isomer.
[c] Yield of the pure (*E*)-isomer.
[d] Upon crystallisation, the *E*:*Z* ratio changed to 95:5.

hydride into ethyl 2-benzoylpropanoate, reported previously.[29] Nevertheless, the loss of dimethylamino group was somewhat surprising, since the literature reported hydrogenation of the enamino ketone **2** resulted only in saturation of the C=C double bond.[7,30] Hydrogenation of compound **4b** in ethanol at 50 °C yielded (1*R*,4*R*,5*R*)-1,8,8-trimethyl-4-propyl-2-oxabicyclo[3.2.1]octan-3-one **14** in 98% yield and 76% de. Crystallisation of this mixture of isomers **14** and **14′** furnished isomerically pure compound **14**. On the other hand, hydrogenation of **7** in ethanol at 50 °C was highly stereoselective and gave isomerically pure (1*R*,3*R*,4*R*)-3-[(2-methyl-1*H*-indol-3-yl)-methyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **15** in 86% yield. Compound **15** turned out to be quite unstable and slowly decomposed, even when kept under argon and in the absence of light (Scheme 2 and Table 2).

Hydrogenation of compound **11** in *n*-propanol at 35 °C afforded a mixture of the major (1*R*,4*E*,5*S*)-1,8,8-trimethyl-4-[(methylamino)methylidene]-2-oxabicyclo[3.2.1]-octan-3-one **17** and its minor (1*R*,4*Z*,5*S*)-isomer **17′** in a ratio of 73:27 and in 97% yield. Subsequent crystallisation furnished a mixture of **17** and **17′** in a ratio of 95:5. Formation of **17** and **17′** may be due to initial reduction of the nitroso group to give the enehydrazine intermediate **16**, followed by N–N bond fission, and partial *E*/*Z*-isomerisation of **17**[22] via the imino tautomeric form **17″**. To our



Scheme 2. Reagents and conditions: (i) H_2 (50 bar), 10% Pd–C, EtOH or *n*-PrOH, 35–60 °C, 24–120 h.

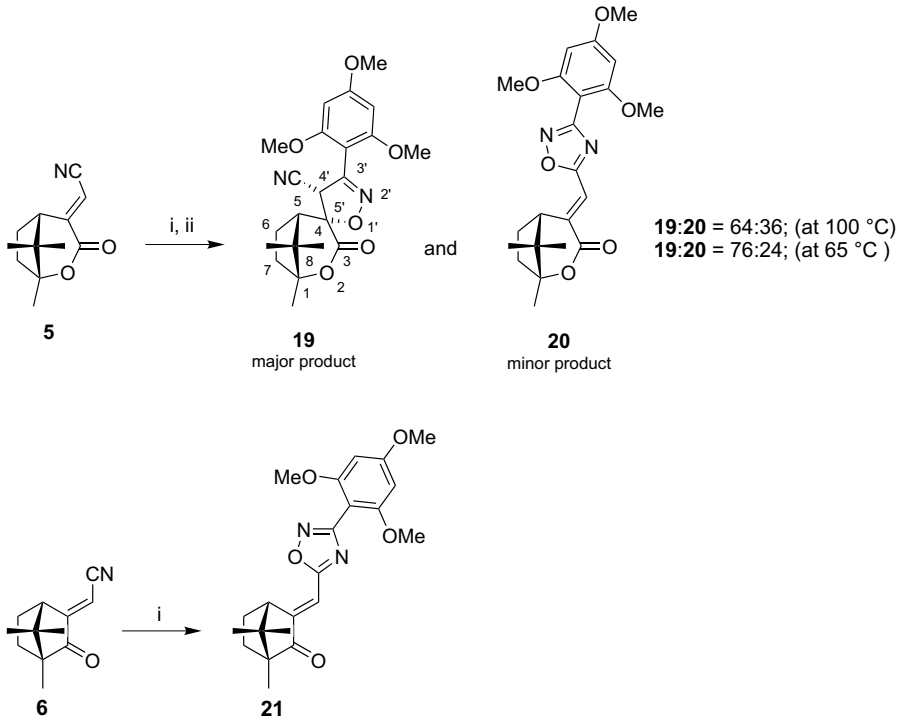
Table 2. Selected experimental data of (cyclo)addition products **13**–**15** and **19**–**24**

Reaction	R	Reaction conditions	Yield (%)	De (%)[a]
3 → **13**/**13′**	—	H_2 (50 bar), Pd–C, *n*-PrOH, 60 °C, 120 h	83	28
4b → **14**/**14′**	—	H_2 (50 bar), Pd–C, EtOH, 50 °C, 24 h	98	76
7 → **15**	—	H_2 (50 bar), Pd–C, EtOH, 50 °C, 24 h	86	100
5 + **18a** → **19** + **20**	—	Toluene, reflux, 4 h	46[b]	100[c]
5 + **18a** → **19** + **20**	—	Toluene, 65 °C, 36 h	42[d]	100[c]
6 + **18a** → **21**	—	Toluene, reflux, 5 h	40	—
4b + **18a** → **22b**	Et	Decalin, reflux, 6 h	8	100
4c + **18a** → **22c**	*n*-Bu	Decalin, reflux, 6 h	10	100
4h+**18a** → **22h**	4-Fluorophenyl	Decalin, reflux, 6 h	49	76
8a + **18a** → **23a**	Me	Anisole, 215 °C, MW, 3 h	27	84[e]
8c + **18a** → **23c**	*n*-Bu	Anisole, 215 °C, MW, 3 h	11	100[e]
8e + **18a** → **23e**	Ph	Anisole, 215 °C, MW, 3 h	30	89
8f + **18a** → **23f**	2-Methylphenyl	Anisole, 215 °C, MW, 3 h	38	66
8g + **18a** → **23g**	4-Methylphenyl	Anisole, 215 °C, MW, 3 h	23	90
8h + **18a** → **23h**	4-Fluorophenyl	Anisole, 215 °C, MW, 3 h	28	88
ent-**8h** + **18a** → *ent*-**23h**	4-Fluorophenyl	Anisole, 215 °C, MW, 3 h	29	92
8i + **18a** → **23i**	3,5-Bis(trifluoromethyl)phenyl	Anisole, 215 °C, MW, 3 h	60	88
8f + **18b** → **24f**	2-Methylphenyl	Anisole, 215 °C, MW, 3 h	9	92
8h + **18b** → **24h**	4-Fluorophenyl	Anisole, 215 °C, MW, 3 h	4	86
8i + **18b** → **24i**	3,5-Bis(trifluoromethyl)phenyl	Anisole, 215 °C, MW, 3 h	17[f]	86

[a] Determined by ^{1}H NMR of the crude reaction mixture.
[b] **19**:**20** = 64:36.
[c] De of compound **20**.
[d] **19**:**20** = 76:24.
[e] De was determined by ^{1}H NMR of partially purified product (upon CC and MPLC).
[f] Yield of the purified **24i** (100% de). According to ^{1}H NMR of the crude reaction mixture, the conversion was ~23%.

surprise, hydrogenation did not take place at the exocyclic C=C double bond (Scheme 2 and Table 1).

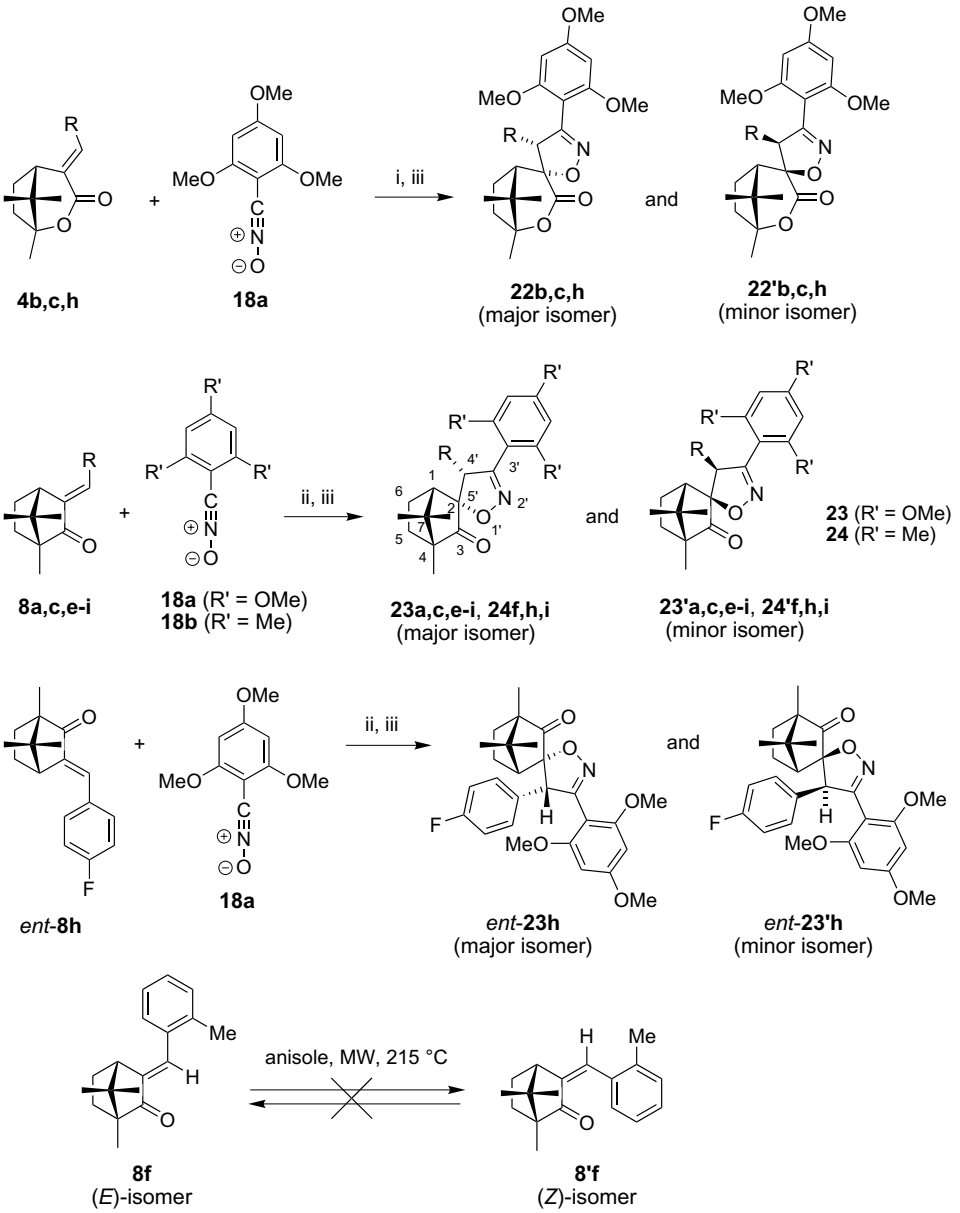
1,3-Dipolar cycloadditions of 2,4,6-trimethoxybenzonitrile oxide **18a** to the unsaturated nitriles **5** and **6** were carried out. In contrast to the previously reported cycloadditions to α-cyanomethylidene substituted γ-lactams[17–19] and γ-lactones,[20] 1,3-dipolar cycloaddition of nitrile oxide **18a** to the dipolarophile **5** gave a mixture of spiro compound **19** and the 1,2,4-oxadiazole **20** in a ratio of 64:36, respec-



Scheme 3. Reagents and conditions: (i) 2,4,6-trimethoxybenzonitrile oxide (**18a**) (1 equiv), toluene, reflux; (ii) chromatographic purification (CC and MPLC).

tively, and in a combined yield of 46%. When the reaction was carried out at 65 °C, the ratio of products changed in favour of the spiro compound **19** (**19**:**20** = 76:24). Further chromatographic separation of this product mixture afforded the pure spiro product **19**. Furthermore, reaction of **18a** with the dipolarophile **6** furnished the 1,2,4-oxadiazole **21**, exclusively. Formation of 1,2,4-oxadiazoles **20** and **21** might be attributed to steric factors, since the exocyclic C=C bond is sterically more hindered by the terpene residue than the C≡N bond (Scheme 3 and Table 2).

Finally, 1,3-dipolar cycloadditions of **18a** and 2,4,6-trimethylbenzonitrile oxide **18b** to α-alkylidene lactones **4b**,**c**,**h** and α-alkylidene ketones **8a**,**c**–**i** and *ent*-**8h** were studied. Since the C=C double bonds of the dipolarophiles **4** and **8** are less activated for 1,3-dipolar cycloadditions to nitrile oxides, the reactions had to be performed at higher temperatures. Thus, within the lactone **4b**,**c**,**h** series, reactions were carried out with **18a** in refluxing decalin and furnished the expected spiro cycloadducts **22b**,**c**,**h** in 8–49% yield. Compounds **22b** and **22c** were obtained in isomerically pure forms, while cycloadduct **22h** was isolated in 76% de. Further chromatographic separation of **22**/**22′h** afforded isomerically enriched major isomer **22h** in 35% yield and 94% de and isomerically pure minor isomer **22′h** in 1% yield. On the other hand, the above mentioned reaction conditions were not applicable for the cycloadditions of benzonitrile oxides **18a**,**b** to α-alkylidene ketones **8a**,**c**–**i** and *ent*-**8h**, due to low conversions and formation of various by-products. However, when cycloadditions were carried out in anisole under microwave irradiation at 215 °C, a series of cycloadducts **23a**,**c**,**e**–**i**, *ent*-**23h** and



Scheme 4. Reagents and conditions: (i) decalin, reflux; (ii) anisole, 215 °C (MW irradiation, 300 W, 3–5 bar); (iii) chromatographic purification (CC and/or MPLC).

24f,**h**,**i** was synthesised in 4–60% yields and in 66–100% de. An exception was (1*R*,3*E*,4*S*)-3-(cyclopentylmethylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one **8d**, which did not react with nitrile oxide **18a** (Scheme 4 and Table 2).

Reductions and other transformations of camphor at the 3-position often afford initial kinetically controlled *exo*-products, as a result of an attack of a reagent from the less hindered *endo*-face of the bicyclic system. Epimerisation of the *exo*-isomers, either in situ or as isolated products, can afford thermodynamically more stable *endo*-isomers, which are sterically less hindered.[1,7,30–34] The literature data for the reductions of α-methylidene camphor derivatives into the corresponding methylene products usually report moderate *exo*-selectivitiy, ranging from 34% de to 100% de.[1,33–36] Moderate *endo*-selectivity, which has been reported in the catalytic hydrogenation of 3-[(dimethylamino)methylidene]camphor **2**,[7,30] can be explained by partial in situ base-promoted epimerisation of the less stable *exo*-epimer into the more stable *endo*-isomer.[31–34] In our case, hydrogenations of the exocyclic C=C bond in compounds **3**, **4b** and **7** proceeded selectively from the sterically less hindered *endo*-face and led to the corresponding *exo*-products **13**–**15** as the major isomers. Similarly, 1,3-dipolar cycloadditions of benzonitrile oxides **18a** and **b** to the dipolarophiles **4b**,**c**,**h**, **5** and **8a**,**c**,**e**–**i** took place preferentially from the less hindered *endo*-face (Fig. 1).

High temperatures, employed in the above mentioned 1,3-dipolar cycloadditions of nitrile oxides **18**, could cause partial in situ *E*/*Z*-isomerisation of dipolarophiles **4** and **8**. Consequently, minor isomers **19′** and **22′**–**24′** would not be formed by attack of nitrile oxide **18** from the more hindered *exo*-face of the (*Z*)-dipolarophiles **4** and **8** (cf. Fig. 1) but rather by attack from the less hindered *endo*-face of the (*E*)-dipolarophiles **4′** and **8′**. In order to clarify this issue, the dipolarophile **8f** was heated in anisole at 215 °C under microwave irradiation for 3 h, followed by evaporation of the solvent. The ^{1}H NMR spectrum of the residue was identical to the spectrum of the starting compound **8f**, thus

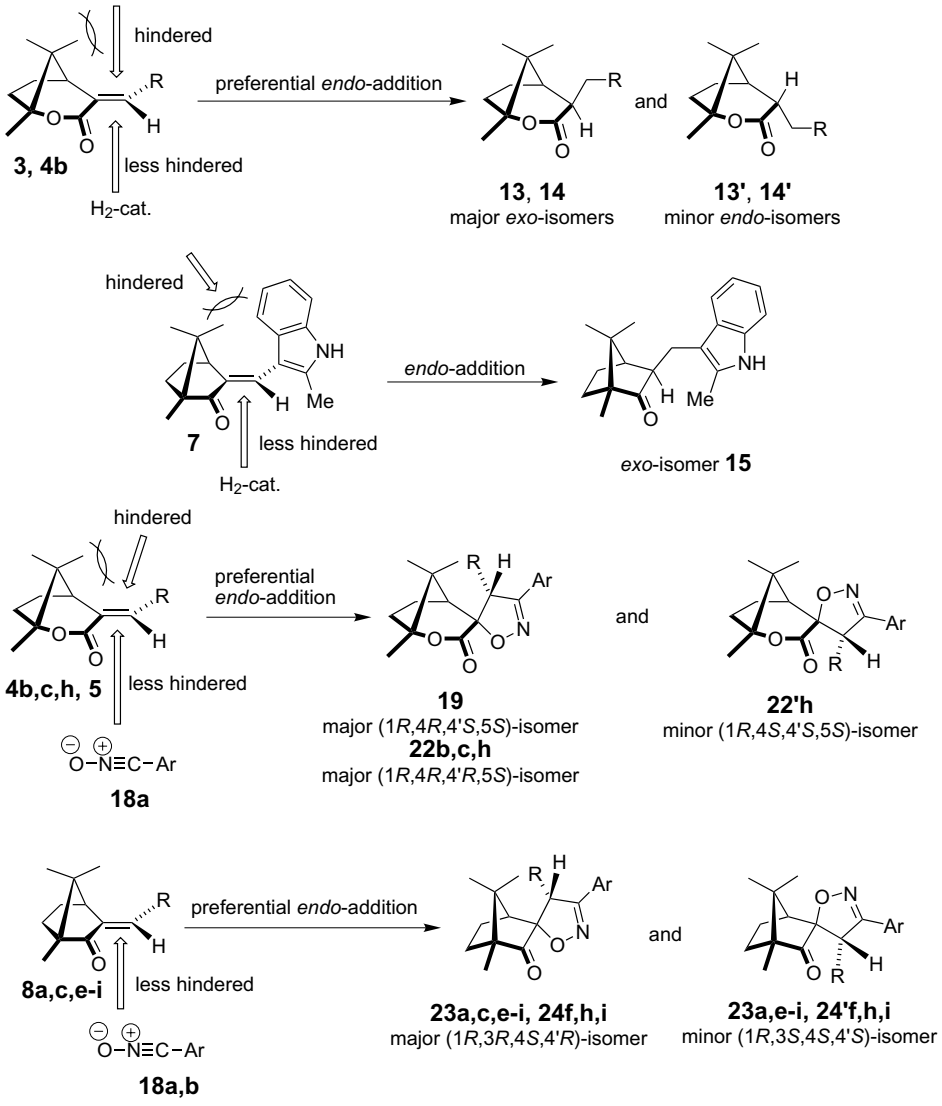


Figure 1. Stereoselectivity of additions to the exocyclic C=C double bond.

revealing that no *E*/*Z*-isomerisation took place. This experiment supported formation of two isomeric cycloadducts via facial differentiation and not via (otherwise possible) *Z*/*E*-isomerisation of the dipolarophile (Scheme 4, see also Fig. 1).

3. Structure determination

The structures of compounds **6**, **7**, **8a**,**c**–**i**, **11**, **13**/**13′**, **14**/**14′**, **15**, **17**/**17′**, **19**–**21**, **22b**,**c**, **22**/**22′h**, **23**/**23′a**,**c**,**e**–**i**, **23c**, *ent*-**23**/**23′h** and **24**/**24′f**,**h**,**i** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, 2D NMR, NOESY spectroscopy, MS) and by elemental analyses for C, H and N. Compounds **6**, **7**, **8a**,**c**–**i**, **11**, **14**, **15**, **19**, **21**, **22a**,**b**, **22′h**, **23a**,**c**,**e**,**g**–**i**, *ent*-**23h** and **24f**,**h**,**i** were prepared in isomerically pure form. Compounds **13**/**13′**, **17**/**17′**, **22**/**22′h** and **23**/**23′f** were characterised as mixtures of the major isomers **13**, **17**, **22h** and **23f** and the minor isomers **8′a**,**c**,**d**, **13′**, **17′**, **22′h** and **23′f**. The minor isomer **22′h** was characterised by mp, ^{1}H NMR, EI-MS and HRMS, while the other minor isomers **13′**, **14′**, **17′**, **23′a**,**e**–**i** and **24f**,**h**,**i** were only characterised by ^{1}H NMR. Compound **20** could not be separated from a mixture of isomeric products **19** and **20** and was characterised by ^{1}H NMR and by elemental analysis as a mixture of isomeric compounds **19** and **20**. Compounds *ent*-**2**, **8a**,**c**–**g**, **11**, **13**, **15**, **23a**,**c**,**e**–**i** and *ent*-**23h** were not prepared in analytically pure form; their identities were confirmed by ^{13}C NMR and EI–HRMS.

The configuration around the exocyclic C=C double bond in compounds **6**, **8f**,**h**,**i** and **21** was determined by NMR on

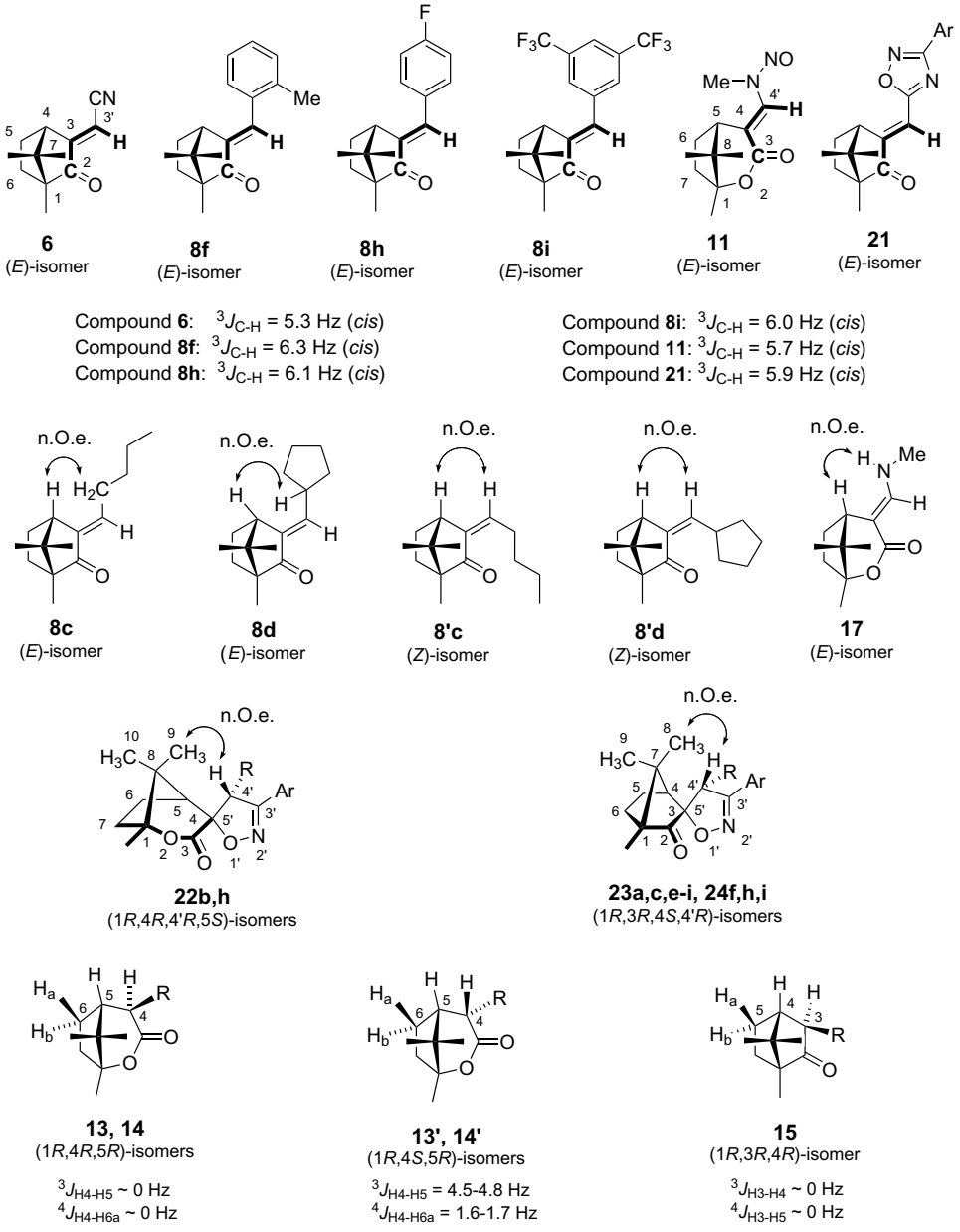


Figure 2. Structure determination by ^{1}H NMR, HMBC and NOESY spectroscopy.

Table 3. Selected ^{1}H NMR data for compounds **6**–**8**, **13**–**15**, **20** and **22**–**24**

	Solvent	δ (ppm)	
		H–C(3′)	H–C(4)
(1R,3E,4S)-Isomers **6**–**8**			
6	$CDCl_3$	6.20	2.98
7	$CDCl_3$	7.44	3.04
8a	$CDCl_3$	6.42	2.71
8c	$CDCl_3$	6.36	2.69
8d	$CDCl_3$	6.29	2.71
8e	$CDCl_3$	7.24	3.11
8f	$CDCl_3$	7.41	2.93
8g	$CDCl_3$	7.18	3.10
8h	$CDCl_3$	7.19	3.05
8i	$CDCl_3$	7.24	3.00
(1R,3Z,4S)-Isomers **8′**			
8′a	$CDCl_3$	5.83	2.39
8′c	$CDCl_3$	5.75	2.39
8′d	$CDCl_3$	5.65	2.37

		δ (ppm)	J_{H-H} (Hz)	
		H–C(4)	4–5	4–6
(1R,4R,5R)-Isomers **13**, **14**				
13	$CDCl_3$	2.49	0	0
14	$CDCl_3$	2.27	0	0
(1R,4S,5R)-Isomers **13′**, **14′**				
13′	$CDCl_3$	2.87	4.8	1.7
14′	$CDCl_3$	2.66	4.5	1.6

		δ (ppm)	J_{H-H} (Hz)	
		H–C(3)	3–4	3–5
(1*R*,3*R*,4*R*)-Isomer **15**	$CDCl_3$	2.21	0	0

		δ (ppm)	
		H–C(4′)	H–C(5)
(1R,4R,4′S,5S)-Isomer **19** *and (1R,4R,4′R,5S)-isomers* **22**			
19	$CDCl_3$	5.19	~2.8[a]
22b	$CDCl_3$	3.87	~2.5[a]
22c	$CDCl_3$	3.86	~2.5[a]
22h	$CDCl_3$	5.20	~2.2[a]
(1*R*,4*S*,4′*S*,5*S*)-Isomer **22′h**	$CDCl_3$	5.36	2.08
		H–C(4′)	H–C(4)
(1R,3R,4S,4′R)-Isomers **23**, **24**			
23a	$CDCl_3$	3.57	2.39
23c	$CDCl_3$	3.60	2.43
23e	$CDCl_3$	4.80	2.02
23f	$CDCl_3$	5.14	~2.36[a]
23g	$CDCl_3$	4.78	2.01
23h and *ent*-**23h**	$CDCl_3$	4.79	1.99
23i	$CDCl_3$	4.94	~1.78[a]
24f	$CDCl_3$	4.79	2.49
24h	$CDCl_3$	4.47	2.20
24i	$CDCl_3$	4.63	~1.82[a]
		H–C(4′)	H–C(4)
(1R,3S,4S,4′S)-Isomers **23′**, **24′**			
23a	$CDCl_3$	3.43	[a]
23e	$CDCl_3$	4.61	
23f	$CDCl_3$	5.03	[a]
23g	$CDCl_3$	4.59	[a]
23h and *ent*-**23h**	$CDCl_3$	4.59	[a]
23i	$CDCl_3$	4.72	[a]
24f	$CDCl_3$	4.66	[a]
24h	$CDCl_3$	4.34	[a]
24i	$CDCl_3$	4.49	[a]

[a] Overlapped by other signals.

the basis of long-range coupling constants, $^3J_{C(2)-H(3')}$, between the methylidene proton (*H*–C(3′)) and the carbonyl carbon atom (O=*C*(2)), measured from the antiphase splitting of cross peaks in the HMBC spectrum. Generally, the magnitude of coupling constants, $^3J_{C-H}$, for nuclei with *cis*-configuration around the C=C double bond are smaller (2–6 Hz) than that for *trans*-oriented nuclei (8–12 Hz).[13,37–47] The magnitude of the coupling constant in compounds **6**, **8f**,**h**,**i** and **21** ($^3J_{C-H} = 5.3–6.3$ Hz) was in agreement with the (*E*)-configuration. In the same manner, the (*E*)-configuration of compound **11** was established on the basis of the magnitude of coupling constant, $^3J_{C(3)-H(4')} = 5.7$ Hz, between the carbonyl carbon atom (O=*C*(3)) and the methylidene proton (*H*–C(4′)) (Fig. 2).

Additionally, the configuration around the exocyclic C=C double bond in isomeric compounds **8c**,**d** and **8′c**,**d** was established by NOESY spectroscopy. The NOE between the allylic proton(s) and *H*–C(4) indicated the (*E*)-configuration of **8c**,**d**, while the NOE between *H*–(3′) and *H*–C(4) in the minor isomers **8′c**,**d** was in agreement with the (*Z*)-configuration. Similarly, the NOE between N–*H* and *H*–C(5) suggested the (*E*)-configuration of compound **17**. The *E*/*Z*-configuration of compounds **17** and **17′** was also established by correlation of chemical shifts δ for *H*–C(4′) and N*H* with typical values, reported previously for a series of closely related (1*R*,5*S*)-4-alkylaminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones.[22] In the spiro cycloadduct series, the NOE between *H*–C(4′) and the bridge methyl group in compounds **22b**,**h**, **23a**,**c**,**e**–**i**, *ent*-**23h** and **24f**,**h**,**i** supported the proposed configuration at the newly formed stereogenic centres (Fig. 2).

The configuration at the 4-position in compounds **13**, **13′**, **14** and **14′**, as well as at the 3-position in compound **15**, was determined by NMR on the basis of vicinal coupling constants, $^3J_{H(3)-H(4)}$ and $^3J_{H(4)-H(5)}$. The dihedral angles between *H*–C(4) and *H*–C(5) in the major *exo*-isomers **13** and **14** and between *H*–C(3) and *H*–C(4) in the *exo*-isomer **15** are close to 90° and, following the Karplus equation,[48] no appreciable coupling between these protons would be expected. Accordingly, negligible coupling constants, $^3J_{H3-H4} \sim 0$ Hz and $^3J_{H4-H5} \sim 0$ Hz, were observed in the ^{1}H NMR spectra of the *exo*-isomers **13**–**15**. On the other hand, a coupling constant, $^3J_{H4-H5} = 4.5–4.8$ Hz was characteristic for the minor *endo*-isomers **13′** and **14′**, due to a smaller dihedral angle (~30°) between *H*–C(4) and *H*–C(5). Furthermore, a long-range coupling, $J_{H4-H6a} = 1.6–1.7$ Hz, between *H*–C(4) and H_a–C(6), by the virtue of the 'W' configuration,[49] was observed in minor *endo*-isomers **13′** and **14′**. Similar patterns of multiplicities for *H*–C(4) and magnitudes of coupling constants, J_{H4-H5} and J_{H4-H6a}, were also reported in the literature for analogous compounds (Fig. 2 and Table 3).[21,23,24,27,50,51]

The structures of compounds **8h**, **19**, **22b**, **23a**, **23f**, **23g**, *ent*-**23h** and **24h** were determined by X-ray diffraction (Figs. 3–10).

Data for the known compounds **6**,[28] **8a**,[54] **8c**,[55] **8e**,[54,56] **8g**[31] and **8h**[57] were consistent with the literature data.

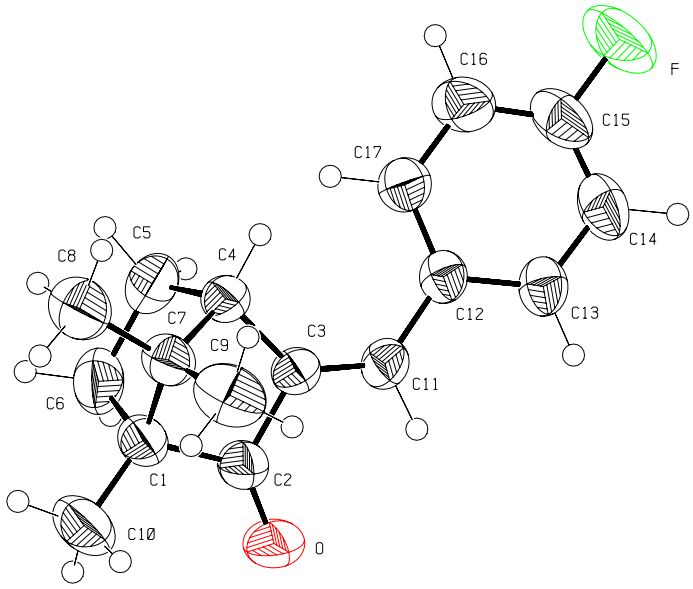


Figure 3. The asymmetric unit of compound **8h**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

4. Conclusion

Catalytic hydrogenation of α-alkylidene compounds **3**, **4b** and **7** proceeded stereoselectively from the sterically less hindered *endo*-face to afford the major *exo*-isomers of hydrogenation products **13**–**15** in 28–100% de. On the other hand, catalytic hydrogenation of compound **11** took place only at the nitroso group to furnish a mixture of isomers **17** and **17′**. 1,3-Dipolar cycloadditions of stable benzonitrile oxides **18a**,**b** to the dipolarophiles **4b**,**c**,**h**, **5**, **6** and **8a**,**c**,**e**–**i** led to two types of products. In the case of the unsaturated nitrile **6**, 1,2,4-oxadiazole **21** was the only product, while in the case of the lactone analogue **5**, cycloaddition took place at the exocyclic C=C bond, as well as at the cyano group to give a mixture of spiro compound **19** and 1,2,4-oxadiazole **20**. The ratio between products **19** and **20** was temperature dependent. On the other hand, 1,3-dipolar cycloadditions of **18a**,**b** to α-alkylidene lactones **4b**,**c**,**h** and α-alkylidene camphors **8a**,**c**,**e**–**i** were diastereoselective and afforded the corresponding spirolactones **22b**,**c**,**h** and spirocamphors **23a**,**c**,**e**–**i** and **24f**,**h**,**i** in low to moderate yields and in 66–100% de. The *exo*-selectivity of the additions to the exocyclic C=C bond is in agreement with the literature data and seems to be dependent on the substituent attached to the methylidene carbon atom, as well as on the type of the terpene residue. Spiro compounds

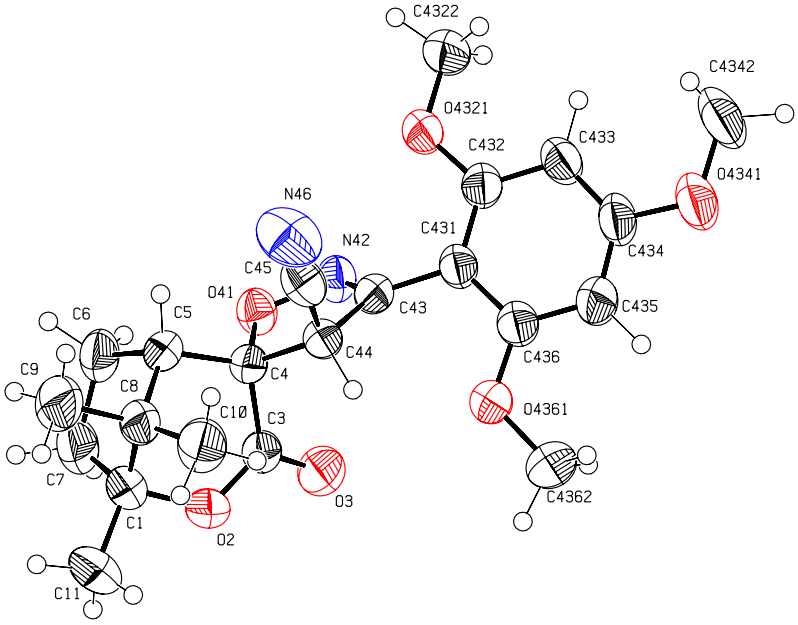


Figure 4. The asymmetric unit of compound **19**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

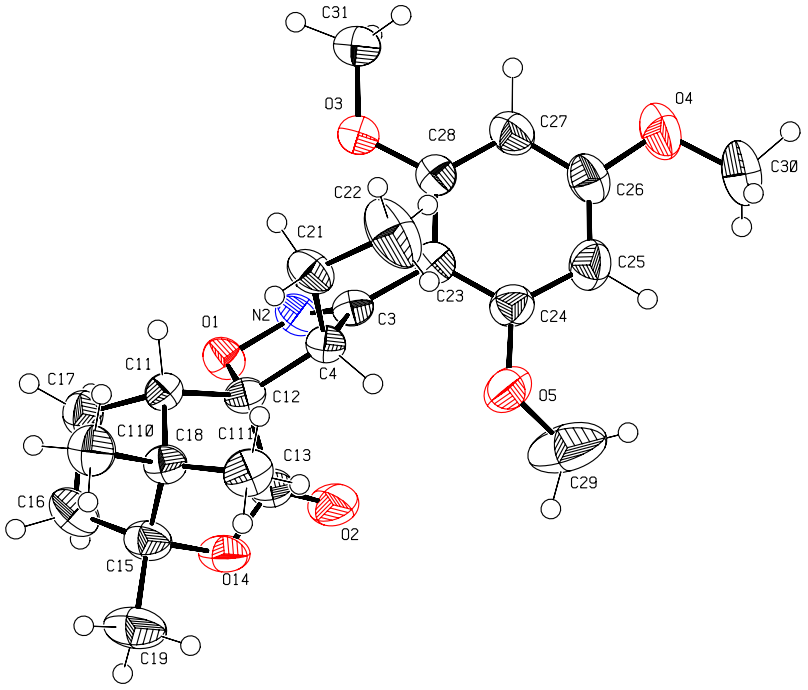


Figure 5. The asymmetric unit of compound **22b**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

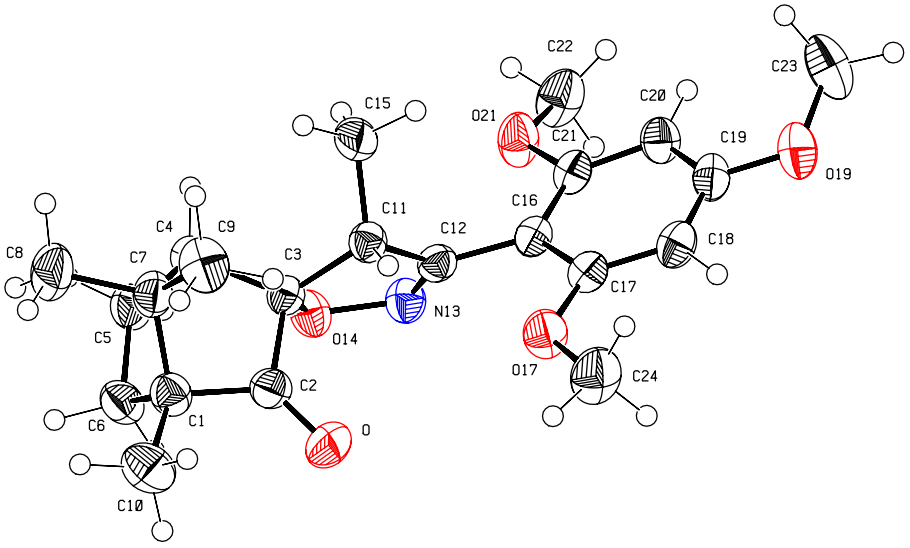


Figure 6. The asymmetric unit of compound **23a**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

19 and **22**–**24** might be useful intermediates for further reductive transformations into novel nonracemic camphor derived γ-amino alcohols.

5. Experimental

5.1. General methods

Melting points were determined on a Kofler microhot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. Microwave irradiations were performed on a CEM Discover laboratory microwave oven.

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; detection: UV 254 nm; sample amount: 100–150 mg of iso-

[†] Donation of Alexander von Humboldt Foundation.

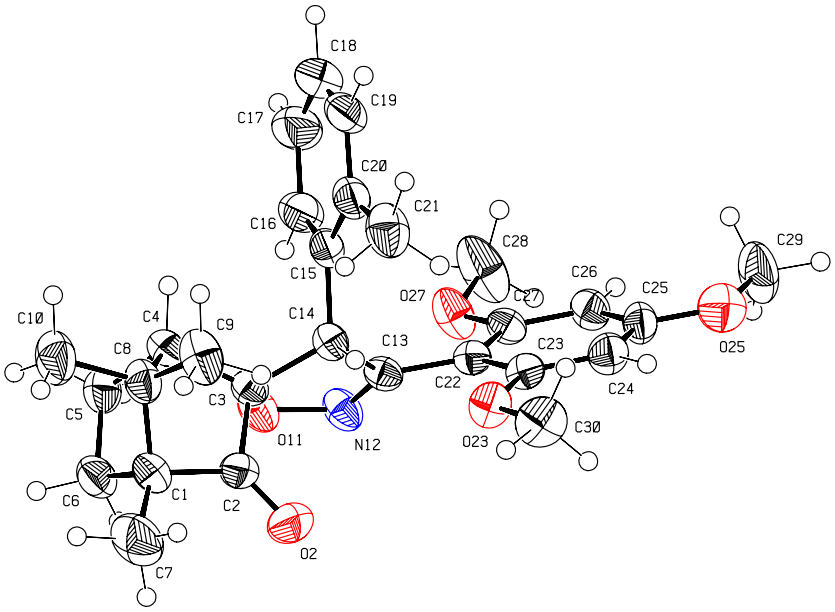


Figure 7. The asymmetric unit of compound **23f**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

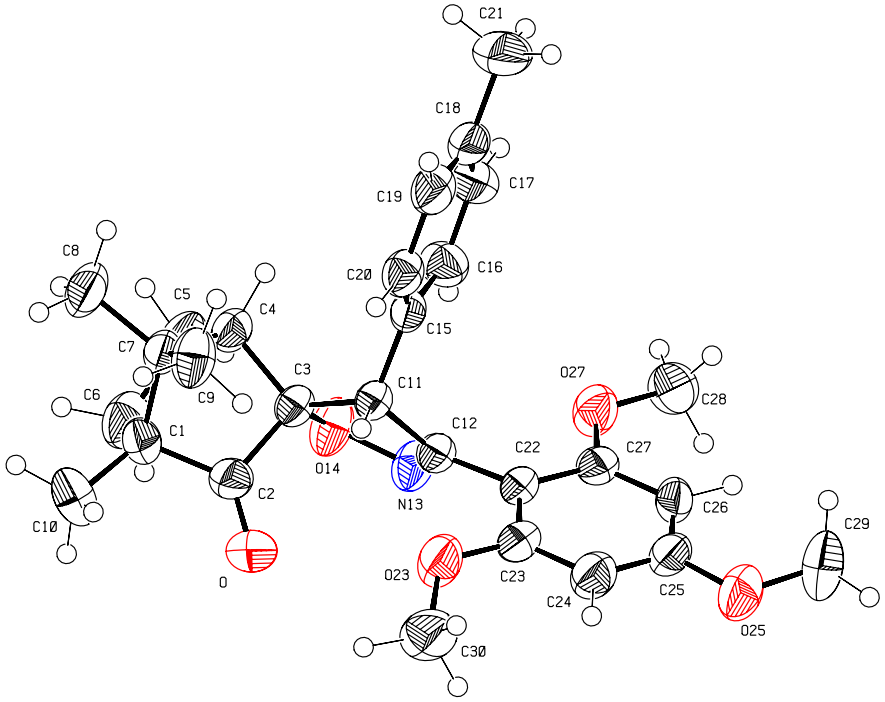


Figure 8. The asymmetric unit of compound **23g**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

meric mixture per each run. MPLC column characteristics: (a) dry filled column: 15 × 460 mm, Merck, silica gel 60, 15–035 μm, backpressure ~12 bar; (b) wet filled column: 15 × 460 mm, Merck, LiChrospher®, 12 μm, backpressure ~26 bar. Ratio of isomers and de were determined by ^{1}H NMR.

PhMgBr (1 M in THF), 4-Me–C_6H_4MgBr (1 M in Et_2O), 2-Me–C_6H_4MgCl (1 M in THF), 4-F–C_6H_4MgBr (2 M in Et_2O), [3,5-bis(trifluoromethyl)phenyl]magnesium bromide (0.5 M in THF), MeMgCl (3 M in THF), *n*-BuMgCl (2 M in THF), cyclopentylmagnesium chloride (2 M in Et_2O), potassium cyanide, 2-methyl-1*H*-indole and *tert*-butyl nitrite are commercially available (Fluka AG). (1*R*,3*E*,4*S*)-3-[(Dimethylamino)methylidene]-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one **2**,[21] (1*R*,4*E*,5*S*)-4-[(dimethylamino) methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **3**,[22] (1*R*,4*E*,5*S*)-1,8,8-trimethyl-4-propylidene-2-oxabi-

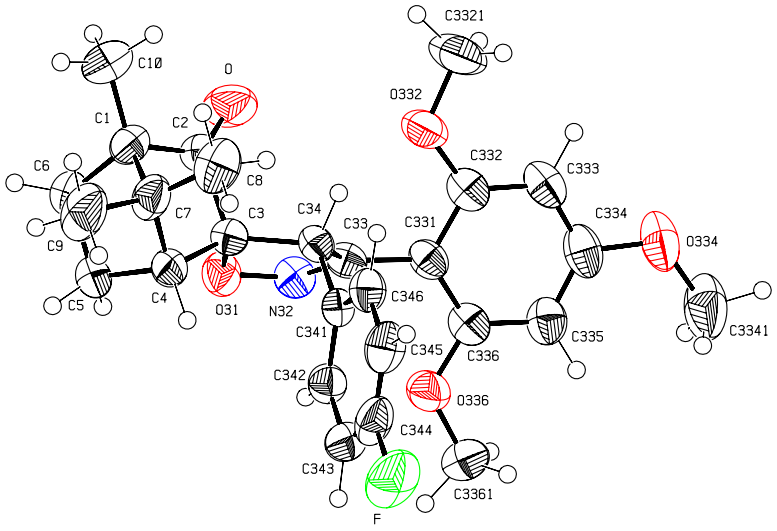


Figure 9. The asymmetric unit of compound *ent*-**23h**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

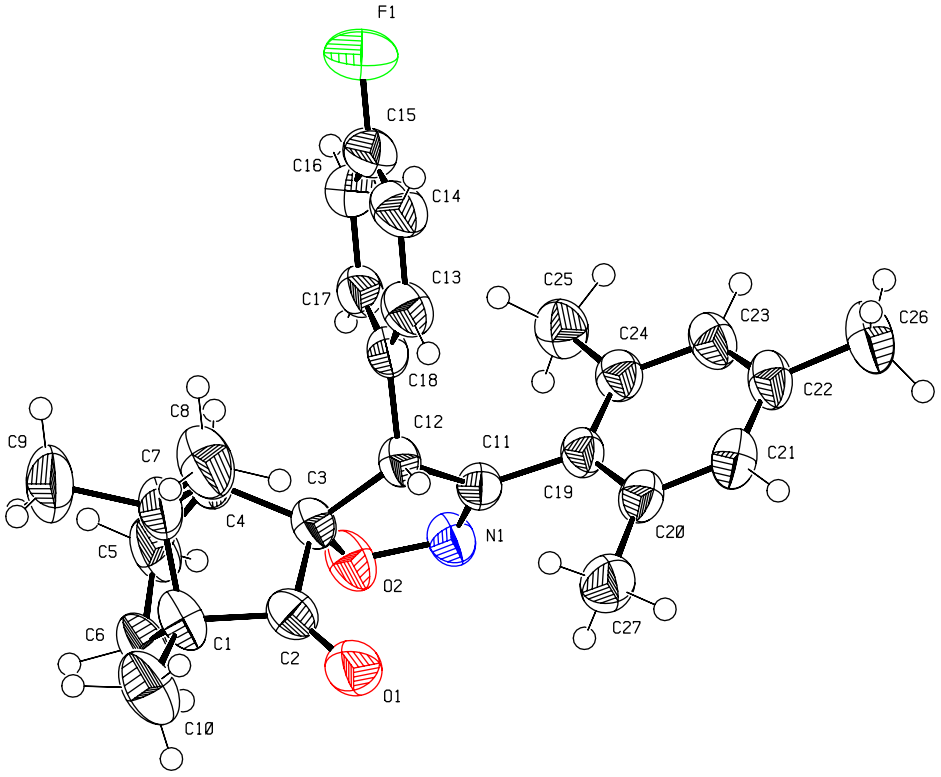


Figure 10. The asymmetric unit of compound **24h**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

cyclo[3.2.1]octan-3-one **4b**, (1*R*,4*E*,5*S*)-1,8,8-trimethyl-4-pentylidene-2-oxabicyclo[3.2.1]octan-3-one **4c**, (1*R*,4*E*,5*S*)-4-(4-fluorobenzylidene)-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one **4h** and (1*R*,4*E*,5*S*)-4-(cyanomethylidene)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **5**,[26] 2,4,6-trimethoxybenzonitrile oxide **18a** and 2,4,6-trimethylbenzonitrile oxide **18b**[52,53] were prepared according to the literature procedures.

Sources of chirality: (a) (+)-camphor (**1**) (Fluka AG), product number 21,300, purum, natural, ⩾97.0% (GC, sum of enantiomers), $[\alpha]^{20}_{546} = +54.5 \pm 2.5$ (*c* 10, EtOH), $[\alpha]^{20}_{D} = +42.5 \pm 2.5$ (*c* 10, EtOH), mp 176–180 °C, ee not specified; (b) (−)-camphor (*ent*-**1**) (Fluka AG), product number 21,295, purum, natural, ⩾95.0% (GC, sum of enantiomers), $[\alpha]^{20}_{D} = -43 \pm 2$ (*c* 10, EtOH), mp and ee not specified.

5.2. (1*S*,3*E*,4*R*)-3-[(Dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one *ent*-2

This compound was prepared from (1*S*)-(−)-camphor *ent*-**1** (5 g, 33 mmol) and *Bredereck's* reagent (8.9 ml, 43 mmol) in refluxing DMF (40 ml) according to the literature procedure for the preparation of its (1*R*,2*E*,4*S*)-enantiomer **2**.[21] Yield: 2.183 g (32%) of a dirty white solid; mp 60–63 °C, lit.[21] mp 59–62 °C; $[\alpha]_D^{21} = -455.7$ (*c* 0.19, CH_2Cl_2). *m*/*z* (EI) = 207 (M^+); *m*/*z* (HRMS) found: 207.162650 (M^+); $C_{13}H_{21}NO$ requires: *m*/*z* = 207.162314 (Found: C, 75.28; H, 10.50; N, 7.85. $C_{13}H_{21}NO$ requires: 75.32; H, 10.21; N, 6.76.) ^{1}H NMR and IR data for *ent*-**2** were identical to the literature data for its (1*R*,3*E*,4*S*)-enantiomer **2**.[21]

5.3. (*E*)-3-[(1*R*,4*S*)-1,7,7-Trimethyl-2-oxobicyclo[2.2.1]-heptan-3-ylidene]acetonitrile 6

KCN (0.130 g, 2 mmol) was added to a solution of **2** (0.207 g, 1 mmol) in acetic acid (100%, 3 ml) and the mixture was stirred at rt for 120 h. Volatile components were evaporated in vacuo and the residue suspended in CH_2Cl_2 (50 ml). The so formed suspension was filtered, the undissolved material washed with CH_2Cl_2 (50 ml) and the filtrate evaporated in vacuo. The residue was purified by CC (Et_2O) and MPLC (dry filled column, EtOAc–hexanes, 1:10). Fractions containing the product were combined and evaporated in vacuo to give **6**. Yield: 27 mg (14%) of a white solid; mp 40–45 °C, lit.[28] mp 46–47 °C; $[\alpha]_D^{23} = +183.7$ (*c* 0.40, CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ 0.75, 0.93, 0.99 (9H, 3s, 1:1:1, 3 × Me); 1.34–1.44, 1.78–1.85 and 2.11–2.20 (4H, 3m, 2:1:1, 2 × CH_2); 2.98 (1H, d, $J = 4.1$ Hz, H–C(4)); 6.20 (1H, d, $J = 0.8$ Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.4, 18.2, 21.2, 26.4, 30.2, 46.2, 51.4, 58.5, 95.6, 116.4, 162.7, 204.2 (Found: C, 75.90; H, 8.24; N, 7.13. $C_{12}H_{15}NO$ requires: 76.16; H, 7.99; N, 7.40.) ν_{max} (KBr) 2962, 2222 (C≡N), 1740 (C=O), 1645, 1450, 1375, 1323, 1257, 1107, 1065 cm^{-1}.

5.4. (1*R*,3*E*,4*S*)-1,7,7-Trimethyl-3-[(2-methyl-1*H*-indol-3-yl)-methylidene]bicyclo[2.2.1]heptan-2-one 7

Hydrochloric acid (37%, 0.10 ml, ~1 mmol) was added to a solution of **2** (0.207 g, 1 mmol) and 2-methyl-1*H*-indole (0.131 g, 1 mmol) in anhydrous ethanol (3 ml) and the mixture was heated under reflux for 5 h. Volatile components were evaporated in vacuo and the residue was purified by CC (EtOAc–hexanes, 1:3). Fractions containing the product were combined and evaporated in vacuo to give **7**. Yield: 247 mg (84%) of a yellow solid; mp 175–182 °C (diethyl ether–*n*-hexane); $[\alpha]_D^{22} = +261.9$ (*c* 0.26, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.85, 0.98, 1.04 (9H, 3s, 1:1:1, 3 × Me); 1.50–1.59, 1.67–1.82 and 2.15–2.26 (4H, 3m, 1:2:1, 2 × CH_2); 2.48 (3H, s, Me); 3.04 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.11–7.20 and 7.28–7.32 (3H, 2m, 2:1, 3H of indole); 7.44 (1H, s, H–C(3′)); 7.67–7.70 (1H, m, 1H of indole); 8.30 (1H, s, NH). ^{13}C NMR ($CDCl_3$): δ 9.9, 13.1, 18.9, 21.0, 27.6, 31.0, 47.0, 50.5, 58.0, 110.0, 111.2, 120.4, 120.7, 121.7, 122.3, 127.3 136.1, 138.3, 139.1, 208.9 (Found: C, 82.10; H, 8.00; N, 4.50. $C_{20}H_{23}NO$ requires: 81.87; H, 7.90; N, 4.77.); ν_{max} (KBr) 3242, 2957, 1700 (C=O), 1612, 1492, 1459, 1388, 1328, 1250, 1159, 1067 cm^{-1}.

5.5. General procedure for the preparation of (1*R*,3*E*,4*S*)-3-alkylidene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones 8a,c–i and (1*S*,3*E*,4*R*)-3-(4-fluorobenzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one *ent*-8h

A solution of **2** or its enantiomer *ent*-**2** (1.037 g, 5 mmol) in anhydrous THF (15 ml) was cooled to −78 °C under argon and a solution of Grignard reagent in THF or Et_2O (15 mmol) then added slowly over a period of 5 min. The mixture was stirred at −78 °C for 1 h, warmed up to rt, and stirred at rt for an additional 24 h. Then saturated aq NH_4Cl (30 ml) was added, the mixture was stirred at rt for 1 h, poured into brine (70 ml) and the product extracted with CH_2Cl_2 (3 × 70 ml). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated in vacuo to give the crude **8**/**8**′ and *ent*-**8**/**8**′**h**.[‡] The residue was purified by column chromatography (CC). Fractions containing the product were combined and evaporated in vacuo to give **8a**,**c**–**i** and *ent*-**8h**. The following compounds were prepared in this manner.

5.5.1. (1*R*,3*E*,4*S*)-3-Ethylidene-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one 8a and its (1*R*,3*Z*,4*S*)-isomer 8′a. Prepared from **2** and MeMgCl (3 M in THF); **8a**:**8**′**a** = 98:2. CC (EtOAc–hexanes, 1:30) afforded isomerically pure **8a**.

5.5.1.1. Data for the major (1*R*,3*E*,4*S*)-isomer 8a. Yield: 0.829 g (93%) of a colourless oil, lit.[54] mp 28–29 °C; **8a**:**8**′**a** = 100:0; $[\alpha]_D^{21} = +185.1$ (*c* 1.51, $CHCl_3$), lit.[54] $[\alpha]_D^{20} = +178.6$ (C_6H_6). *m*/*z* (EI) = 178 (M^+); *m*/*z* (HRMS) found: 178.136120 (M^+); $C_{12}H_{18}O$ requires: *m*/*z* = 178.135765. ^{1}H NMR ($CDCl_3$): δ 0.78, 0.96 (9H, 2s, 1:2, 3 × Me); 1.29–1.44 (2H, m, 2H of CH_2); 1.61–1.73 (1H, m, 1H of CH_2); 1.77 (3H, d, $J = 7.2$ Hz, Me); 1.95–2.07 (1H, m, 1H of CH_2); 2.71 (1H, d, $J = 4.1$ Hz, H–C(4)); 6.42 (1H, dq, $J = 0.7$, 7.2 Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.6, 14.5, 18.7, 20.8, 26.6, 30.8, 46.4, 47.6, 58.2, 125.7, 144.1, 207.4. ν_{max} (NaCl) 2959, 1730 (C=O), 1667 (C=O), 1445, 1390, 1372, 1323, 1255, 1170, 1105, 1068, 933, 874, 795 cm^{-1}.

5.5.1.2. NMR data for the minor (1*R*,3*Z*,4*S*)-isomer 8′a. ^{1}H NMR ($CDCl_3$): δ 2.39 (1H, d, $J = 4.1$ Hz, H–C(4)); 5.83 (1H, q, $J = 7.2$ Hz, H–C(3′)).

5.5.2. (1*R*,3*E*,4*S*)-3-Pentylidene-1,7,7-trimethyl-bicyclo[2.2.1]-heptan-2-one 8c and its (1*R*,3*Z*,4*S*)-isomer 8′c. Prepared from **2** and *n*-BuMgCl (2 M in THF); **8c**:**8**′**c** = 95:5. CC (EtOAc–hexanes, 1:30) afforded isomerically pure **8c**.

5.5.2.1. Data for the major (1*R*,3*E*,4*S*)-isomer 8c. Yield: 1.047 g (95%) of a colourless oil, lit.[55] bp 139–141 °C/12 Torr; **8c**:**8**′**c** = 100:0; $[\alpha]_D^{21} = +158.9$ (*c* 0.53, $CHCl_3$), lit.[55] $[\alpha]_D^{20} = +116.5$ (neat). *m*/*z* (EI) = 220 (M^+); *m*/*z* (HRMS) found: 220.183450 (M^+); $C_{15}H_{24}O$ requires: *m*/*z* = 220.182716. ^{1}H NMR ($CDCl_3$): δ 0.78 (3H, s, Me);

[‡] ^{1}H NMR of the residue was taken in order to establish the isomer composition. NMR data for the minor isomers **8**′**a**,**c**,**d** were acquired from these spectra.

0.90 (3H, t, $J = 7.2$ Hz, $CH_2CH_2CH_2CH_3$); 0.96, 0.97 (6H, 2s, 1:1, 2 × Me); 1.26–1.47 (6H, m, 6H of CH_2); 1.64–1.73 (1H, m, 1H of CH_2); 1.95–2.05 (1H, m, 1H of CH_2); 2.13 (2H, deg q, $J = 7.2$, 7.5 Hz, $CH_2CH_2CH_2CH_3$); 2.69 (1H, d, $J = 3.8$ Hz, H–C(4)); 6.36 (1H, dq, $J = 0.7$; 7.7 Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.5, 14.2, 18.6, 20.8, 22.7, 26.8, 28.7, 30.7, 31.3, 46.3, 47.9, 58.1, 130.8, 143.2, 207.5. ν_{max} (NaCl) 2959, 1732 (C=O), 1666, 1453, 1389, 1371, 1324, 1255, 1106, 1069, 1010, 940 cm^{-1}.

5.5.2.2. NMR data for the minor (1*R*,3*Z*,4*S*)-isomer 8′c. ^{1}H NMR ($CDCl_3$): δ 0.81, 0.91, 0.93 (9H, 3s, 1:1:1, 3 × Me); 2.39 (1H, d, $J = 4.1$ Hz, H–C(4)); 2.50–2.77 (2H, m, $CH_2CH_2CH_2CH_3$); 5.75 (1H, t, $J = 7.9$ Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.7, 14.3, 18.9, 20.8, 22.7, 27.7, 28.0, 30.3, 31.9, 46.5, 53.0, 59.7, 136.8, 141.8, 209.2.

5.5.3. (1*R*,3*E*,4*S*)-3-Cyclopentylmethylidene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 8d and its (1*R*,3*Z*,4*S*)-isomer 8′d. Prepared from **2** and cyclopentylmagnesium chloride (2 M in Et_2O); **8d**:**8′d** = 85:15. CC (EtOAc–hexanes, 1:40) afforded isomerically pure **8d**.

5.5.3.1. Data for the major (1*R*,3*E*,4*S*)-isomer 8d. Yield: 0.593 g (51%) of a colourless oil; **8d**:**8′d** = 100:0; $[\alpha]_D^{21} = +162.6$ (*c* 0.83, $CHCl_3$). *m*/*z* (EI) = 232 (M^+); *m*/*z* (HRMS) found: 232.183450 (M^+); $C_{16}H_{24}O$ requires: *m*/*z* = 232.182716. ^{1}H NMR ($CDCl_3$): δ 0.78, 0.95, 0.96 (9H, 3s, 1:1:1, 3 × Me); 1.25–1.45 (4H, m, 4H of CH_2); 1.52–1.87 (7H, m, 7H of CH_2); 1.95–2.08 (1H, m, 1H of CH_2); 2.54–2.68 (1H, m, H–C(1) of cyclopentyl); 2.71 (1H, d, $J = 4.1$ Hz, H–C(4)); 6.29 (1H, d, $J = 9.4$ Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.6, 18.7, 20.9, 25.8, 25.9, 27.1, 30.8, 33.6, 33.7, 40.0, 46.4, 48.2, 58.2, 135.8, 141.8, 208.1. ν_{max} (NaCl) 2958, 1731 (C=O), 1664 (C=O), 1474, 1451, 1390, 1370, 1327, 1254, 1107, 1064, 1012, 950, 800 cm^{-1}.

5.5.3.2. Data for the minor (1*R*,3*Z*,4*S*)-isomer 8′d. ^{1}H NMR ($CDCl_3$): δ 0.81, 0.91, 0.93 (9H, 3s, 1:1:1, 3Me); 2.37 (1H, d, $J = 3.8$ Hz, H–C(4)); 3.71–3.85 (1H, m, H–C(4′)); 5.65 (1H, d, $J = 9.8$ Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.7, 18.9, 20.9, 25.8, 25.9, 27.7, 30.3, 33.8, 33.9, 38.6, 46.4, 52.9, 59.6, 140.4, 141.6, 209.0.

5.5.4. (1*R*,3*E*,4*S*)-3-Benzylidene-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one 8e. Prepared from **2** and phenylmagnesium bromide (1 M in THF); **8e**:**8′e** = 100:0; CC (EtOAc–hexanes, 1:15). Yield: 1.094 g (91%) of a white solid; mp 74–75 °C (from *n*-heptane at −20 °C), lit.[56] mp 71–73 °C; $[\alpha]_D^{21} = +446.6$ (*c* 0.30, $CHCl_3$), lit.[56] $[\alpha]_D^{20} = +418$ (EtOH), lit.[54] $[\alpha]_D^{20} = +426.6$ (C_6H_6). *m*/*z* (EI) = 240 (M^+); *m*/*z* (HRMS) found: 240.151950 (M^+); $C_{17}H_{20}O$ requires: *m*/*z* = 240.151415. ^{1}H NMR ($CDCl_3$): δ 0.81, 1.00, 1.03 (9H, 3s, 1:1:1, 3 × Me); 1.48–1.64 (2H, m, 2H of CH_2); 1.74–1.82 (1H, m, 1H of CH_2); 2.10–2.24 (1H, m, 1H of CH_2); 3.11 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.24 (1H, s, H–C(3′)); 7.30–7.42 (3H, m, 3H of Ph); 7.45–7.50 (2H, m, 2H of Ph). ^{13}C NMR ($CDCl_3$): δ 9.7, 18.7, 21.0, 26.4, 31.1, 47.1, 49.6, 57.5, 127.9, 129.0, 129.1, 130.2, 136.1, 142.5, 208.5 (Found: C, 84.40; H, 8.35. $C_{17}H_{20}O$ requires: C, 84.96; H, 8.39.) ν_{max} (KBr) 2959, 1726 (C=O), 1643, 1493, 1447, 1388, 1367, 1325, 1257, 1059, 1017, 926, 748, 693 cm^{-1}.

5.5.5. (1*R*,3*E*,4*S*)-3-(2-Methylbenzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 8f. Prepared from **2** and 2-methylphenylmagnesium chloride (1 M in THF); **8f**:**8′f** = 100:0; CC (EtOAc–hexanes, 1:30). Yield: 1.145 g (90%) of a white solid; mp 77–78 °C (from *n*-heptane at −20 °C); $[\alpha]_D^{21} = +397.1$ (*c* 0.24, $CHCl_3$). *m*/*z* (EI) = 254 (M^+); *m*/*z* (HRMS) found: 254.168110 (M^+); $C_{18}H_{22}O$ requires: *m*/*z* = 254.167066. ^{1}H NMR ($CDCl_3$): δ 0.81, 0.98, 1.03 (9H, 3s, 1:1:1, 3 × Me); 1.49–1.64 (2H, m, 2H of CH_2); 1.74–1.85 (1H, m, 1H of CH_2); 2.08–2.22 (1H, m, 1H of CH_2); 2.35 (3H, s, Me); 2.93 (1H, d, $J = 4.5$ Hz, H–C(4)); 7.17–7.24 (3H, m, 3H of Ar); 7.29–7.34 (1H, m, 1H of Ar); 7.41 (1H, s, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.72, 18.7, 20.4, 21.0, 26.7, 31.0, 46.9, 49.2, 57.9, 126.0, 126.2, 128.9, 130.8, 135.1, 138.5, 143.2, 208.4 (Found: C, 84.41; H, 8.60. $C_{18}H_{22}O$ requires: C, 84.99; H, 8.72.) ν_{max} (KBr) 2957, 1723 (C=O), 1638, 1473, 1440, 1400, 1390, 1323, 1288, 1257, 1154, 1105, 1067, 1015, 961, 914, 805, 747, 720 cm^{-1}.

5.5.6. (1*R*,3*E*,4*S*)-3-(4-Methylbenzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 8g. Prepared from **2** and 4-methylphenylmagnesium bromide (1 M in Et_2O); **8g**:**8′g** = 100:0; CC (EtOAc–hexanes, 1:20). Yield: 1.182 g (93%) of a white solid; mp 94–98 °C (from *n*-heptane at −20 °C), lit.[31] mp 98.5–99.5 °C; $[\alpha]_D^{21} = +458.1$ (*c* 0.28, $CHCl_3$), lit.[31] $[\alpha]_D^{24} = +412$ (*c* 1.35, C_6H_6). *m*/*z* (EI) = 254 (M^+); *m*/*z* (HRMS) found: 254.167550 (M^+); $C_{18}H_{22}O$ requires: *m*/*z* = 254.167066. ^{1}H NMR ($CDCl_3$): δ 0.80, 0.99, 1.03 (9H, 3s, 1:1:1, 3 × Me); 1.46–1.62 (2H, m, 2H of CH_2); 1.73–1.84 (1H, m, 1H of CH_2); 2.12–2.22 (1H, m, 1H of CH_2); 2.37 (3H, s, Me); 3.10 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.18 (1H, s, H–C(3′)); 7.19–7.21 (2H, m, 2H of Ar); 7.36–7.40 (2H, m, 2H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.7, 18.8, 21.0, 21.8, 26.4, 31.2, 47.1, 49.7, 57.5, 128.0, 129.8, 130.2, 133.3, 139.3, 141.7, 208.6 (Found: C, 84.42; H, 8.86. $C_{18}H_{22}O$ requires: C, 84.99; H, 8.72.) ν_{max} (KBr) 2961, 1721 (C=O), 1642, 1608, 1511, 1444, 1324, 1254, 1152, 1106, 1064, 1015, 959, 919, 814 cm^{-1}.

5.5.7. (1*R*,3*E*,4*S*)-3-(4-Fluorobenzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 8h. Prepared from **2** and 4-fluorophenylmagnesium bromide (2 M in Et_2O); **8h**:**8′h** = 100:0; CC (EtOAc–hexanes, 1:30). Yield: 1.176 g (91%) of a white solid; mp 97–99 °C (from *n*-heptane at −20 °C), lit.[57] mp 97 °C; $[\alpha]_D^{21} = +413.4$ (*c* 0.19, $CHCl_3$), lit.[57] $[\alpha]_D^{20} = +387.5$ (dioxane). *m*/*z* (EI) = 258 (M^+). ^{1}H NMR ($CDCl_3$): δ 0.80, 1.00, 1.03 (9H, 3s, 1:1:1, 3 × Me); 1.47–1.61 (2H, m, 2H of CH_2); 1.75–1.85 (1H, m, 1H of CH_2); 2.11–2.23 (1H, m, 1H of CH_2); 3.05 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.04–7.11 (2H, m, 2H of Ar); 7.19 (1H, s, H–C(3′)); 7.42–7.48 (2H, m, 2H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.6, 18.7, 20.9, 26.3, 31.1, 47.1, 49.5, 57.5, 116.1 (d, $J = 86.9$ Hz), 126.7, 131.9 (d, $J = 32.0$ Hz), 132.2 (d, $J = 11.4$ Hz), 142.2 (d, $J = 9.2$ Hz), 163.2 (d, $J = 994.2$ Hz), 208.3 (Found: C, 78.72; H, 7.37. $C_{17}H_{19}FO$ requires: C, 79.04; H, 7.41.) ν_{max} (KBr) 2963, 1712 (C=O), 1641, 1601, 1508, 1369, 1325, 1228, 1163, 1104, 1065, 1016, 963, 914, 868, 841, 820 cm^{-1}.

5.5.8. (1*S*,3*E*,4*R*)-3-(4-Fluorobenzylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one *ent*-8h. Prepared from *ent*-**2** and 4-fluorophenylmagnesium bromide (2 M in Et_2O); *ent*-**8h**:*ent*-**8′h** = 100:0; CC (EtOAc–hexanes, 1:30). Yield: 1.240 g (96%) of a white solid; $[\alpha]_D^{21} = -399.4$ (*c* 0.34, $CHCl_3$). *m*/*z* (EI) = 258 (M^+); *m*/*z* (HRMS) found: 258.142440 (M^+); $C_{17}H_{19}FO$ requires: *m*/*z* = 258.141994 (Found: C, 79.26; H, 7.62. $C_{17}H_{19}FO$ requires: C, 79.04; H, 7.41.). ^1H NMR and IR spectral data were identical to those given above for its enantiomer **8h** (see Section 5.5.7).

5.5.9. (1*R*,3*E*,4*S*)-3-[3,5-Bis(trifluoromethyl)benzylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 8i. Prepared from **2** and 3,5-bis(trifluoromethyl)phenyl]magnesium bromide (0.5 M in THF); **8i**:**8′i** = 100:0; CC (EtOAc–hexanes, 1:15). Yield: 1.318 g (70%) of a dirty white solid; mp 85–87 °C (from *n*-heptane at −20 °C); $[\alpha]_D^{21} = +242.0$ (*c* 0.27, $CHCl_3$). *m*/*z* (EI) = 376 (M^+); *m*/*z* (HRMS) found: 376.127320 (M^+); $C_{19}H_{18}F_6O$ requires: *m*/*z* = 376.126185. ^1H NMR ($CDCl_3$): δ 0.82, 1.04, 1.05 (9H, 3s, 1:1:1, 3 × Me); 1.51–1.64 (2H, m, 2H of CH_2); 1.79–1.90 (1H, m, 1H of CH_2); 2.18–2.30 (1H, m, 1H of CH_2); 3.00 (1H, d, $J = 4.1$ Hz, H–C(4)); 7.24 (1H, s, H–C(3′)); 7.82–7.85 (3H, m, 3H of Ar). ^{13}C NMR ($CDCl_3$): δ 9.4, 18.4, 20.9, 26.1, 30.8, 47.0, 49.5, 57.5, 122.1–122.3 (m), 123.5 (q, $J = 1084.5$ Hz), 124.2, 129.3–129.5 (m), 132.5 (q, $J = 133.7$ Hz), 138.3, 145.9, 207.3 (Found: C, 60.81; H, 4.89. $C_{19}H_{18}F_6O$ requires: C, 60.64; H, 4.82.) ν_{max} (KBr) 2965, 1732 (C=O), 1652, 1617, 1468, 1450, 1386, 1350, 1327, 1280, 1210, 1136, 1107, 1065, 1019, 982, 949, 899, 847, 706, 679 cm^{-1}.

5.6. *N*-Methyl-*N*-{[(1*R*,4*E*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]octan-4-ylidene]methyl}nitrous amide 11

tert-Butyl nitrite (92%, 0.2 ml, ~1.5 mmol) was added to a solution of **3** (0.223 g, 1 mmol) in anhydrous dichloromethane (4 ml), followed by the addition of trifluoroacetic acid (0.5 ml, ~6.5 mmol) and the mixture was stirred at rt for 24 h. Volatile components were evaporated in vacuo and the residue purified by CC (EtOAc–hexanes, 1:4). Fractions containing the product were combined and evaporated in vacuo to give **11**. Yield: 119 mg (50%) of a yellow oil; $[\alpha]_D^{22} = +462.3$ (*c* 0.22, CH_2Cl_2). *m*/*z* (EI) = 209 (M^+); *m*/*z* (FAB) = 239 (MH^+). ^1H NMR ($CDCl_3$): δ 1.01, 1.03, 1.36 (9H, 3s, 1:1:1, 3 × Me); 1.65–1.76 and 2.04–2.30 (4H, 2m, 1:3, 2 × CH_2); 3.15 (1H, d, $J = 6.0$ Hz, H–C(5)); 3.24 (3H, s, NMe); 7.95 (1H, s, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.6, 18.9, 23.7, 28.5, 34.6, 37.1, 44.7, 47.9, 93.6, 122.8, 136.0, 167.2 (Found: C, 59.96; H, 7.51; N, 13.10. $C_{12}H_{18}N_2O_3$ requires: 60.49; H, 7.61; N, 11.76.) ν_{max} (NaCl) 2974, 1713 (C=O), 1634, 1470, 1274, 1204, 1147, 1067, 1019, 972, 944, 904 cm^{-1}.

5.7. General procedure for catalytic hydrogenation of alkylidene compounds 3, 4b, 7 and 11

A mixture of methylidene compound **3**, **4b**, **7** or **11** (1 mmol) and 10% Pd–C (60–100 mg) in anhydrous *n*-propanol or ethanol (15 ml) was hydrogenated in an autoclave (50 bar of H_2, 35–60 °C) for 24–120 h. The reaction mixture was filtered through a short pad of Celite®, washed with ethanol (50 ml) and the filtrate evaporated in vacuo. The residue was purified by CC or/and crystallisation. Fractions containing the product were combined and evaporated in vacuo to give **13**/**13′**, **14**/**14′**, **15** and **17**/**17′**. The following compounds were prepared in this manner.

5.7.1. (1*R*,4*R*,5*R*)-1,4,8,8-Tetramethyl-2-oxabicyclo[3.2.1]-octan-3-one 13 and its (1*R*,4*S*,5*R*)-isomer 13′. Prepared from compound **3** (0.223 g, 1 mmol) in *n*-propanol; 10% Pd–C (90 mg); 60 °C, 120 h; CC (EtOAc–hexanes, 1:7). Yield: 151 mg (83%) of a colourless oil; **13**:**13′** = 64:36 (28% de); $[\alpha]_D^{19} = -31.4$ (*c* 0.17, $CHCl_3$). *m*/*z* (EI) = 182 (M^+); *m*/*z* (HRMS) found: 182.131020 (M^+); $C_{11}H_{18}O_2$ requires: *m*/*z* = 182.130680. ^{13}C NMR ($CDCl_3$): δ 14.3, 17.4, 17.8, 18.5, 19.6, 20.2, 24.0, 24.1, 30.4, 36.3, 38.6, 43.9, 44.3, 45.4, 48.3, 48.7, 92.5, 93.2, 175.0, 175.5 (Found: C, 70.34; H, 9.70; N, 4.40. $C_{11}H_{18}O_2$ requires: C, 72.49; H, 9.95; N, 0.00.) ν_{max} (NaCl) 2980, 1725 (C=O), 1472, 1395, 1377, 1343, 1252, 1223, 1148, 1060, 1012 cm^{-1}.

5.7.1.1. Data for the major (1*R*,4*R*,5*R*)-isomer 13. ^1H NMR ($CDCl_3$): δ 0.97, 1.06, 1.30 (9H, 3s, 1:1:1, 3 × Me); 1.38 (3H, d, $J = 7.5$ Hz, Me); 1.47–1.56 (1H, m, 1H of CH_2); 1.80 (1H, d, $J = 5.3$ Hz, H–C(5)); 1.91–2.20 (3H, m, 3H of CH_2); 2.49 (1H, q, $J = 7.5$ Hz, H–C(4)).

5.7.1.2. Data for the minor (1*R*,4*S*,5*R*)-isomer 13′. ^1H NMR ($CDCl_3$): δ 1.02, 1.09 (6H, 2s, 1:1, 2 × Me); 1.23 (3H, d, $J = 7.2$ Hz, Me); 1.27 (3H, s, Me); 2.87 (1H, ddq, $J = 1.7$, 4.8, 7.2 Hz, H–C(4)).

5.7.2. (1*R*,4*R*,5*R*)-4-Propyl-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 14 and its (1*R*,4*S*,5*R*)-isomer 14′. Prepared from compound **4b** (0.208 g, 1 mmol) in ethanol; 10% Pd–C (60 mg); 50 °C, 24 h. Yield: 206 mg (98%) of a white solid; **14**:**14′** = 88:12 (76% de). Crystallisation from a mixture of diethyl ether and *n*-heptane afforded isomerically pure **14**.

5.7.2.1. Data for the major (1*R*,4*R*,5*R*)-isomer 14. Yield: 112 mg (53%) of a white solid; **14**:**14′** = 100:0; mp 92–95 °C (Et_2O–*n*-heptane); $[\alpha]_D^{23} = -11.9$ (*c* 0.19, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.93 (3H, t, $J = 7.2$ Hz, $CH_2CH_2CH_3$); 0.97, 1.04, 1.29 (9H, 3s, 1:1:1, 3 × Me); 1.36–1.57 (4H, m, $CH_2CH_2CH_3$); 1.90–2.20 (5H, m, 2 × CH_2, H–C(5)); 2.27 (1H, dd, $J = 4.1$, 8.7 Hz, H–C(4)). ^{13}C NMR ($CDCl_3$): δ 14.2, 19.0, 19.1, 22.1, 24.7, 31.0, 36.6, 37.0, 44.3, 46.5, 51.5, 92.7, 175.9 (Found: C, 73.96; H, 10.83; N, 0.00. $C_{13}H_{22}O_2$ requires: C, 74.24; H, 10.54; N, 0.00.) ν_{max} (KBr) 2985, 1715 (C=O), 1467, 1450, 1394, 1382, 1335, 1265, 1239, 1222, 1205, 1153, 1072, 1020 cm^{-1}.

5.7.2.2. Data for the minor (1*R*,4*S*,5*R*)-isomer 14′. ^1H NMR ($CDCl_3$): δ 1.03, 1.07, 1.27 (9H, 3s, 1:1:1, 3 × Me); 2.66 (1H, ddt, $J = 1.6$, 4.5, 5.8 Hz, H–C(4)).

5.7.3. (1*R*,3*R*,4*R*)-3-[(2-Methyl-1*H*-indol-3-yl)methyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 15. Prepared from compound **7** (0.293 g, 1 mmol) in ethanol; 10% Pd–C (100 mg); 50 °C, 24 h; CC (EtOAc–hexanes, 1:2). Yield:

254 mg (86%) of a colourless oil; $[\alpha]_D^{23} = +12.1$ (*c* 0.78, $CHCl_3$). *m/z* (EI) = 295 (M^+); *m/z* (HRMS) found: 295.194260 (M^+); $C_{20}H_{25}NO$ requires: *m/z* = 295.193615. ^1H NMR ($CDCl_3$): δ 0.92, 0.95, 1.05 (9H, 3s, 1:1:1, 3 × Me); 1.09–1.17, 1.38–1.49, 1.54–1.64 and 1.78–1.89 (4H, 4m, 1:1:1:1, 2 × CH_2); 1.93 (1H, d, $J = 4.1$ Hz, H–C(4)); 2.21 (1H, dd, $J = 9.8$; 3.8 Hz, H–C(3)); 2.36 (3H, s, Me); 2.66 (1H, dd, $J = 14.7$; 9.8 Hz, H_a–C(3′)); 3.25 (1H, dd, $J = 14.7$; 3.8 Hz, H_b–C(3′)); 7.04–7.12, 7.21–7.24 and 7.50–7.53 (4H, 3m, 2:1:1, 4H of indole); 7.88 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 9.9, 12.2, 21.0, 22.4, 26.4, 29.7, 29.8, 47.3, 47.6, 56.9, 58.2, 110.7, 111.5, 118.4, 119.6, 121.4, 128.9, 131.6, 135.8, 221.9. ν_{max} (NaCl) 3403, 2959, 1729 (C=O), 1462, 1445, 1385, 1301, 1239, 1101, 1074, 1018 cm^{-1}.

5.7.4. (1*R*,4*E*,5*S*)-4-[(Methylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 17 and its (1*R*,4*Z*,5*S*)-isomer 17′. Prepared from compound **11** (0.238 g, 1 mmol) in *n*-propanol; 10% Pd–C (80 mg); 35 °C, 48 h; CC (EtOAc). Yield: 203 mg (97%), **17**:**17′** = 77:23. Crystallisation from CH_2Cl_2–*n*-hexane gave isomerically enriched **17**. Yield: 172 mg (82%) of a white solid; **17**:**17′** = 95:5; mp 140–150 °C; $[\alpha]_D^{20} = +155.9$ (*c* 0.26, CH_2Cl_2) (Found: C, 69.00; H, 8.83; N, 6.55. $C_{12}H_{19}NO_2$ requires: C, 68.87; H, 9.15; N, 6.69.) ν_{max} (KBr) 3304, 2985, 1683 (C=O), 1579, 1430, 1277, 1171, 1133, 1060, 1007, 970 cm^{-1}.

5.7.4.1. Data for the major (1*R*,4*E*,5*S*)-isomer 17. ^1H NMR ($CDCl_3$): δ 0.99, 1.28 (9H, 2s, 2:1, 3 × Me); 1.46–1.61 and 1.89–2.21 (4H, 2m, 1:3, 2 × CH_2); 2.25 (1H, d, $J = 4.9$ Hz, H–C(5)); 2.97 (3H, d, $J = 4.5$ Hz, *Me*NH); 4.15 (1H, br s, NH); 7.33 (1H, d, $J = 14.3$ Hz, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.8, 19.0, 23.8, 32.4, 35.1, 38.1, 43.5, 50.3, 91.0, 97.2, 151.1, 170.3.

5.7.4.2. Data for the minor (1*R*,4*Z*,5*S*)-isomer 17′. ^1H NMR ($CDCl_3$): δ 0.96, 0.98, 1.27 (9H, 3s, 1:1:1, 3 × Me); 2.93 (1H, d, $J = 4.9$ Hz, *Me*NH); 6.38 (1H, d, $J = 12.8$ Hz, H–C(4′)); 7.79 (1H, br s, NH).

5.8. General procedure for 1,3-dipolar cycloadditions of 2,4,6-trimethoxybenzonitrile oxide 18a to alkylidene compounds 4b,c,h, 5 and 6

A mixture of alkylidene compound **4b**,**c**,**h**, **5** or **6** (1 mmol) and 2,4,6-trimethoxybenzonitrile oxide **18a** (0.209 g, 1 mmol) in anhydrous toluene (6 ml) or decalin (4 ml) was heated at 65 °C or at reflux for 4–36 h. Volatile components were evaporated in vacuo and the residue[§] purified by CC and MPLC (dry filled column). Fractions containing the product were combined and evaporated in vacuo to give **19**–**22**. The following compounds were prepared in this manner.

[§] ^1H NMR spectra of the crude reaction mixtures before chromatographic separation were taken in order to establish the de as accurately as possible. In the case of very complex spectra, the de were determined after the chromatographic purification.

5.8.1. (1*R*,4*R*,4′*S*,5*S*)-3′-(2,4,6-Trimethoxyphenyl)-1,8,8-trimethyl-3-oxo-4′*H*-2-oxaspiro[bicyclo[3.2.1]octane-4,5′-isoxazole]-4′-carbonitrile 19 and (1*R*,4*E*,5*S*)-4-{[3-(2,4,6-trimethoxyphenyl)-1,2,4-oxadiazol-5-yl]mehyilidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 20. Prepared from compound **5** (0.205 g, 1 mmol) in toluene; reflux for 4 h; **19**:**20** = 64:36; CC (EtOAc–hexanes, 1:2). Yield: 191 mg (46%) of a greyish solid (Found: C, 63.97; H, 6.46; N, 6.52. $C_{22}H_{26}N_2O_6$ requires: 63.76; H, 6.32; N, 6.76.) Further purification by MPLC (EtOAc–hexanes, 1:2) afforded pure compound **19**.

5.8.1.1. Data for the major compound 19. Yield: 50 mg (12%) of a white solid; mp 183–185 °C; $[\alpha]_D^{22} = -338.3$ (*c* 0.09, $CHCl_3$). *m/z* (EI) = 414 (M^+); *m/z* (FAB) = 415 (MH^+); *m/z* (HRMS) found: 414.180250 (M^+); $C_{22}H_{26}N_2O_6$ requires: *m/z* = 414.179087. ^1H NMR ($CDCl_3$): δ 1.11, 1.19, 1.36 (9H, 3s, 1:1:1, 3Me); 1.99–2.29 and 2.46–2.61 (4H, 2m, 3:1, 2 × CH_2); 2.77–2.82 (1H, m, H–C(5)); 3.84 (9H, s, 3 × OMe); 5.19 (1H, s, H–C(4′)); 6.15 (2H, s, C_6H_2) (Found: C, 63.83; H, 6.42; N, 6.67. $C_{22}H_{26}N_2O_6$ requires: 63.76; H, 6.32; N, 6.76.) ν_{max} (KBr) 2965, 2242 (C≡N), 1737 (C=O), 1608, 1587, 1471, 1459, 1416, 1343, 1261, 1237, 1212, 1193, 1161, 1130, 1067 cm^{-1}.

5.8.1.2. NMR data for the minor compound 20. ^1H NMR ($CDCl_3$): δ 1.03, 1.07, 1.38 (9H, 3s, 1:1:1, 3 × Me); 1.62–1.71 and 2.03–2.43 (4H, 2m, 1:3, 2 × CH_2); 3.79 and 3.88 (9H, 2s, 2:1, 3 × OMe); 4.03 (1H, br d, $J = 6.4$ Hz, H–C(5)); 6.21 (2H, s, C_6H_2); 7.55 (1H, s, H–C(4′)).

5.8.2. (1*R*,3*E*,4*S*)-3-{[3-(2,4,6-Trimethoxyphenyl)-1,2,4-oxadiazol-5-yl]methylidene}-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one 21. Prepared from compound **6** (0.189 g, 1 mmol) in toluene; reflux for 5 h; CC (EtOAc–hexanes, 1:3) and MPLC (EtOAc–hexanes, 1:4). Yield: 159 mg (40%) of a greyish solid; mp 90–95 °C (Et_2O); $[\alpha]_D^{21} = -346.6$ (*c* 0.32, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 0.86, 1.04, 1.05 (9H, 3s, 1:1:1, 3 × Me); 1.47–1.60, 1.76–1.84 and 2.17–2.25 (4H, 3m, 2:1:1, 2 × CH_2); 3.69 (1H, d, $J = 4.1$ Hz, H–C(4)); 3.78 and 3.86 (9H, 2s, 2:1, 3 × OMe); 6.20 (2H, s, C_6H_2); 7.09 (1H, d, $J = 0.8$ Hz, H–C(3′)). ^{13}C NMR ($CDCl_3$): δ 9.6, 18.4, 21.4, 26.4, 30.7, 46.3, 50.8, 55.9, 56.5, 58.0, 91.3, 108.8, 153.8, 160.6, 163.8, 165.3, 174.1, 207.0 (Found: C, 66.60; H, 6.80; N, 6.93. $C_{22}H_{26}N_2O_5$ requires: 66.32; H, 6.58; N, 7.03.) ν_{max} (KBr) 2969, 1753 (C=O), 1608, 1470, 1416, 1340, 1232, 1207, 1159, 1130 cm^{-1}.

5.8.3. (1*R*,4*R*,4′*R*,5*S*)-4′-Ethyl-3′-(2,4,6-trimethoxyphenyl)-1,8,8-trimethyl-4′*H*-2-oxaspiro[bicyclo-[3.2.1]octane-4,5′-isoxazol]-3-one 22b. Prepared from compound **4b** (0.208 g, 1 mmol) in decalin; reflux for 6 h; CC (EtOAc–hexanes, 1:1) then MPLC (EtOAc–hexanes, 1:2). Yield: 33 mg (8%) of a white solid; **22b**:**22′b** = 100:0 (100% de); mp 145–152 °C; $[\alpha]_D^{23} = -402.2$ (*c* 0.09, $CHCl_3$). *m/z* (EI) = 417 (M^+). ^1H NMR ($CDCl_3$): δ 0.71 (3H, t, $J = 7.5$ Hz, CH_2CH_3); 1.05, 1.10, 1.31 (9H, 3s, 1:1:1, 3 × Me); 1.36–1.68 and 1.90–2.05 (4H, 2m, 1:1, 2 × CH_2); 2.12–2.27 (1H, m, 1H of CH_2); 2.48–2.57 (2H, m, 1H of CH_2, H–C(5)); 3.81 and 3.83 (9H, 2s, 2:1, 3 × OMe); 3.87 (1H, dd,

$J = 3.4$; 8.7 Hz, H–C(4′)); 6.14 (2H, s, C_6H_2) (Found: C, 65.91; H, 7.68; N, 3.57. $C_{23}H_{31}NO_6$ requires: 66.17; H, 7.48; N, 3.35.) ν_{max} (KBr) 2978, 1733 (C=O), 1624, 1605, 1584, 1465, 1416, 1228, 1205, 1155, 1126 cm^{-1}.

5.8.4. (1*R*,4*R*,4′*R*,5*S*)-4′-Butyl-3′-(2,4,6-trimethoxyphenyl)-1,8,8-trimethyl-4′*H*-2-oxaspiro[bicyclo-[3.2.1]octane-4,5′-isoxazol]-3-one 22c. Prepared from compound **4c** (0.236 g, 1 mmol) in decalin; reflux for 6 h; CC ($CHCl_3$–MeOH, 100:1 → 20:1) and MPLC (EtOAc–hexanes, 1:2). Yield: 45 mg (10%) of a white solid; **22c**:**22′c** = 100:0 (100% de); mp 145–151 °C; $[\alpha]_D^{23} = -358.7$ (*c* 0.14, $CHCl_3$). *m*/*z* (EI) = 445 (M^+); *m*/*z* (HRMS) found: 445.247500 (M^+); $C_{25}H_{35}NO_6$ requires: *m*/*z* = 445.246438. ^1H NMR ($CDCl_3$): δ 0.72 (3H, t, $J = 7.2$ Hz, $CH_2CH_2CH_2CH_3$); 0.96–1.20 (4H, m, 2 × CH_2); 1.05, 1.09, 1.31 (9H, 3s, 1:1:1, 3Me); 1.36–1.54 and 1.89–2.05 (4H, 2m, 1:1, 2 × CH_2); 2.11–2.26 (1H, m, 1H of CH_2); 2.49–2.56 (2H, m, 1H of CH_2, H–C(5)); 3.80 and 3.83 (9H, 2s, 2:1, 3 × OMe); 3.86 (1H, dd, $J = 3.0$; 8.7 Hz, H–C(4′)); 6.13 (2H, s, C_6H_2) (Found: C, 67.66; H, 8.12; N, 3.13. $C_{25}H_{35}NO_6$ requires: 67.39; H, 7.92; N, 3.14.) ν_{max} (KBr) 2959, 1737 (C=O), 1606, 1585, 1464, 1415, 1383, 1228, 1206, 1158, 1130 cm^{-1}.

5.8.5. (1*R*,4*R*,4′*R*,5*S*)-4′-(4-Fluorophenyl)-3′-(2,4,6-trimethoxyphenyl)-1,8,8-trimethyl-4′*H*-2-oxaspiro[bicyclo[3.2.1]octane-4,5′-isoxazol]-3-one 22h and (1*R*,4*S*,4′*S*,5*S*)-isomer 22′h. Prepared from compound **4h** (0.274 g, 1 mmol), in decalin; reflux for 6 h; **22h**:**22′h** = 88:12 (76% de); CC (EtOAc–hexanes, 1:2). Yield: 237 mg (49%) of a white solid; **22h**:**22′h** = 88:12 (76% de). Further purification by MPLC (EtOAc–hexanes, 1:3) afforded isomerically enriched **22h** (first fraction) and isomerically pure **22′h** (second fraction).

5.8.5.1. Data for the major (1*R*,4*R*,4′*R*,5*S*)-isomer 22h. Yield: 169 mg (35%) of a white solid; **22h**:**22′h** = 97:3 (94% de); mp 95–105 °C; $[\alpha]_D^{21} = -352.9$ (*c* 0.14, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 0.73, 0.89, 1.28 (9H, 3s, 1:1:1, 3Me); 1.77–1.98 (2H, m, 2H of CH_2); 2.15–2.27 (2H, m, 1H of CH_2, H–C(5)); 2.48–2.56 (1H, m, 1H of CH_2); 3.73 and 3.75 (9H, 2s, 1:2, 3 × OMe); 5.20 (1H, s, H–C(4′)); 5.98 (2H, s, C_6H_2); 6.85–7.23 (4H, m, C_6H_4) (Found: C, 67.11; H, 6.22; N, 2.96. $C_{27}H_{30}FNO_6$ requires: 67.07; H, 6.25; N, 2.90.) ν_{max} (KBr) 3416, 2980, 1738 (C=O), 1607, 1509, 1460, 1384, 1227, 1202, 1155, 1132 cm^{-1}.

5.8.5.2. Data for the minor (1*R*,4*S*,4′*S*,5*S*)-isomer 22′h. Yield: 6 mg (1%) of a white solid; **22h**:**22′h** = 0:100 (100% de); mp 103–107 °C. *m*/*z* (EI) = 483 (M^+); *m*/*z* (HRMS) found: 483.206950 (M^+); $C_{27}H_{30}FNO_6$ requires: *m*/*z* = 483.205716. ^1H NMR ($CDCl_3$): δ 0.87 (3H, s, Me); 0.88–0.95 (1H, m, 1H of CH_2); 1.32 and 1.33 (6H, 2s, 1:1, 2 × Me); 1.45–1.54, 1.72–1.83 and 1.91–2.01 (3H, 3m, 1:1:1, 3H of CH_2); 2.08 (1H, d, $J = 7.5$ Hz, H–C(5)); 3.74 and 3.78 (9H, 2s, 1:2, 3 × OMe); 5.36 (1H, s, H–C(4′)); 6.00 (2H, s, C_6H_2); 6.88–6.94 (2H, m, 2H of C_6H_4); 7.05–7.24 (2H, m, 2H of C_6H_4). ν_{max} (KBr) 3417, 2936, 1734 (C=O), 1606, 1509, 1466, 1383, 1229, 1206, 1160, 1131 cm^{-1}.

5.9. General procedure for 1,3-dipolar cycloadditions of 2,4,6-trisubstituted benzonitrile oxides 18a,b to α-alkylidene camphors 8a,c,e–i and *ent*-8h

A mixture of alkylidene compound **8a**,**c**,**e**–**i** or *ent*-**8h** (1 mmol) and 2,4,6-trimethoxybenzonitrile oxide **18a** (0.251 g, 1.2 mmol) or 2,4,6-trimethylbenzonitrile oxide **18b** (0.194 g, 1.2 mmol) in anhydrous anisole (5 ml) under argon was irradiated in a laboratory microwave oven ($P = 300$ W, $T = 215$ °C, $P = 3$–5 bar) for 3 h. Volatile components were evaporated in vacuo and the residue[§] purified by CC and MPLC (wet filled column). Fractions containing the product were combined and evaporated in vacuo to give diastereomerically pure compounds **23c** and **24i** and isomeric mixtures **23**/**23′a**,**e**–**i**, *ent*-**23**/**23′h** and **24**/**24′f**,**h**. Repeated crystallisation of isomeric mixtures afforded diastereomerically enriched compound **23**/**23′f** (90% de) and diastereomerically pure compounds **23a**,**e**,**g**–**i**, *ent*-**23h** and **24f**,**h**. The following compounds were prepared in this manner.

5.9.1. (1*R*,3*R*,4*S*,4′*R*)-1,4′,7,7-Tetramethyl-3′-(2,4,6-trimethoxyphenyl)-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one 23a and its (1*R*,3*S*,4*S*,4′*S*)-isomer 23′a. Prepared from **8a** (0.178 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); CC and MPLC (EtOAc–hexanes, 1:3). Yield: 105 mg (27%) of a white solid; **23a**:**23′a** = 92:8 (84% de). Upon repeated crystallisation from EtOAc–*n*-heptane, diastereomerically pure compound **23a** was obtained.

5.9.1.1. Data for major (1*R*,3*R*,4*S*,4′*R*)-isomer 23a. Yield: 0.023 g (6%) of a white solid; mp 169–173 °C; **23a**:**23′a** = 100:0 (100% de); $[\alpha]_D^{19} = -421.3$ (*c* 0.15, $CHCl_3$). *m*/*z* (EI) = 387 (M^+); *m*/*z* (HRMS) found: 387.205540 (M^+); $C_{22}H_{29}NO_5$ requires: *m*/*z* = 387.204573. ^1H NMR ($CDCl_3$): δ 0.86, 0.95 (6H, 2s, 1:1, 2 × Me); 1.02 (3H, d, $J = 7.5$ Hz, Me); 1.04 (3H, s, Me); 1.64–1.88 (3H, m, 3H of CH_2); 2.26–2.35 (1H, m, 1H of CH_2); 2.39 (1H, d, $J = 3.8$ Hz, H–C(4)); 3.57 (1H, q, $J = 7.5$ Hz, H–C(4′)); 3.81, 3.82 (9H, 2s, 2:1, 3 × OMe); 6.13 (2H, s, C_6H_2). ^{13}C NMR ($CDCl_3$): δ 10.0, 14.4, 19.3, 21.6, 21.7, 31.3, 43.9, 48.9, 50.0, 55.8, 56.6, 57.9, 90.2, 91.5, 100.7, 157.6, 160.6, 162.8, 215.7 (Found: C, 67.85; H, 7.62; N, 4.45. $C_{22}H_{29}NO_5$ requires: C, 68.20; H, 7.54; N, 3.61.) ν_{max} (KBr) 2966, 1754 (C=O), 1604, 1586, 1456, 1412, 1343, 1225, 1205, 1157, 1126, 1007, 948, 884, 812, 746 cm^{-1}.

5.9.1.2. Data for minor (1*R*,3*S*,4*S*,4′*S*)-isomer 23′a. ^1H NMR ($CDCl_3$): δ 0.97 (3H, s, Me); 1.12 (3H, d, $J = 7.2$ Hz, Me); 1.20 (3H, s, Me); 3.43 (1H, q, $J = 7.2$ Hz, H–C(4′)).

5.9.2. (1*R*,3*R*,4*S*,4′*R*)-4′-Butyl-3′-(2,4,6-trimethoxyphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one 23c. Prepared from **8c** (0.220 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); CC and MPLC (EtOAc–hexanes, 1:3). Yield: 48 mg (11%) of a colourless oil; **23c**:**23′c** = 100:0 (100% de); $[\alpha]_D^{19} = -470.5$ (*c* 0.42, $CHCl_3$). *m*/*z* (EI) = 429 (M^+); *m*/*z* (HRMS) found: 429.252750 (M^+); $C_{25}H_{35}NO_5$ requires: *m*/*z* = 429.251524. ^1H NMR ($CDCl_3$): δ 0.73 (3H, deg t, $J = 6.8$, 7.2 Hz, $CH_2CH_2CH_2CH_3$); 0.84, 0.94,

1.04 (9H, 3s, 1:1:1, 3 × Me); 1.02–1.21 (4H, m, 4H of CH_2); 1.43–1.50 (2H, m, 2H of CH_2); 1.63–1.88 (3H, m, 3H of CH_2); 2.25–2.34 (1H, m, 1H of CH_2); 2.43 (1H, d, $J = 3.8$ Hz, H-C(4)); 3.60 (1H, deg t, $J = 6.0$, 5.7 Hz, H–C(4′)); 3.81, 3.82 (9H, 2s, 2:1, 3 × OMe); 6.13 (2H, s, C_6H_2). ^{13}C NMR ($CDCl_3$): δ 10.0, 14.2, 19.3, 21.7, 21.8, 23.2, 28.5, 29.1, 31.3, 44.0, 48.7, 53.7, 55.7, 56.6, 57.8. 90.4, 91.6, 101.9, 157.0, 160.5, 162.7, 215.5. ν_{max} (KBr) 2960, 1751 (C=O), 1606, 1586, 1458, 1415, 1340, 1228, 1206, 1159, 1130, 1065, 1038, 1019, 944, 893, 814 cm^{-1}.

5.9.3. (1*R*,3*R*,4*S*,4′*R*)-4′-Phenyl-3′-(2,4,6-trimethoxyphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one 23e and its (1*R*,3*S*,4*S*,4′*S*)-isomer 23′e. Prepared from compound **8e** (0.240 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); **23e**:**23′e** = 94.5:5.5 (89% de); CC and MPLC (EtOAc–hexanes, 1:2). Yield: 138 mg (30%) of a white solid; **23e**:**23′e** = 95:5 (90% de). Repeated crystallisation of **23**/**23′e** from EtOAc–*n*-hexane furnished diastereomerically pure compound **23e**.

5.9.3.1. Data for major (1*R*,3*R*,4*S*,4′*R*)-isomer 23e. 0.050 g (11%) of a white solid; mp 222–225 °C; **23e**:**23′e** = 100:0 (100% de); $[\alpha]_D^{21} = -508.9$ (*c* 0.09, $CHCl_3$). *m*/*z* (EI) = 449 (M^+); *m*/*z* (HRMS) found: 449.221820 (M^+); $C_{27}H_{31}NO_5$ requires: *m*/*z* = 449.220223. ^{1}H NMR ($CDCl_3$): δ 0.70, 0.82, 0.95 (9H, 3s, 1:1:1, 3 × Me); 1.63–1.88 (3H, m, 3H of CH_2); 2.02 (1H, d, $J = 3.4$ Hz, H–C(4)); 2.24–2.35 (1H, m, 1H of CH_2); 3.72, 3.74 (9H, 2s, 1:2, 3 × OMe); 4.80 (1H, s, H–C(4′)); 5.97 (2H, s, Ar); 7.04–7.25 (5H, m, C_6H_2). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.0, 21.7, 22.5, 31.5, 44.0, 49.7, 55.6, 56.6, 58.6, 61.8, 91.1, 91.5, 101.0, 127.8, 128.2, 130.7, 136.1, 156.2, 160.4, 162.6, 215.3 (Found: C, 72.18; H, 6.97; N, 3.83. $C_{27}H_{31}NO_5$ requires: C, 72.14; H, 6.95; N, 3.12.) ν_{max} (KBr) 2966, 1752 (C=O), 1606, 1455, 1415, 1340, 1234, 1209, 1163, 1129, 1071, 1031, 819, 707 cm^{-1}.

5.9.3.2. Data for minor (1*R*,3*S*,4*S*,4′*S*)-isomer 23′e. ^{1}H NMR ($CDCl_3$): δ 0.92, 0.99, 1.22 (9H, 3s, 1:1:1, 3 × Me); 3.67, 3.72 (9H, 2s, 2:1, 3 × OMe); 4.61 (1H, s, H–C(4′)).

5.9.4. (1*R*,3*R*,4*S*,4′*R*)-4′-(2-Methylphenyl)-3′-(2,4,6-trimethoxyphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one 23f and its (1*R*,3*S*,4*S*,4′*S*)-isomer 23′f. Prepared from **8f** (0.254 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); **23f**:**23′f** = 83:17 (66% de); CC and MPLC (EtOAc–hexanes, 2:3). Yield: 177 mg (38%) of a white solid; **23f**:**23′f** = 90:10 (80% de). Repeated crystallisation of **23**/**23′f** from EtOAc–*n*-hexane furnished diastereomerically enriched compound **23f**. Yield: 0.047 g (10%) of a white solid; **23f**:**23′f** = 95:5 (90% de); mp 249–252 °C; $[\alpha]_D^{21} = -533.6$ (*c* 0.12, $CHCl_3$). *m*/*z* (EI) = 463 (M^+); *m*/*z* (HRMS) found: 463.236980 (M^+); $C_{28}H_{33}NO_5$ requires: *m*/*z* = 463.235874 (Found: C, 71.90; H, 7.05; N, 4.75. $C_{28}H_{33}NO_5$ requires: C, 72.55; H, 7.18; N, 3.02.) ν_{max} (KBr) 2966, 1746 (C=O), 1604, 1581, 1456, 1417, 1340, 1234, 1209, 1162, 1128, 1072, 900, 876, 820, 764 cm^{-1}.

5.9.4.1. NMR data for the major (1*R*,3*R*,4*S*,4′*R*)-isomer 23f. ^{1}H NMR ($CDCl_3$): δ 0.61, 0.84, 0.96 (9H, 3s, 1:1:1, 3 × Me); 1.63–1.92 (3H, m, 3H of CH_2); 2.08 (3H, s, Me); 2.31–2.41 (2H, m, 1H of CH_2, H–C(4)); 3.68, 3.73 (9H, 2s, 2:1, 3 × OMe); 5.14 (1H, s, H–C(4′)); 5.95 (2H, s, C_6H_2); 6.92–6.96, 7.00–7.06, 7.09–7.14 and 7.22–7.25 (4H, 4m, 1:1:1:1, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.1, 19.5, 21.7, 21.8, 31.7, 44.0, 50.0, 55.6, 56.5, 56.6, 58.6, 91.2, 91.3, 100.9, 125.5, 127.5, 130.4, 132.1, 134.4, 136.2, 156.5, 160.3, 162.6, 215.6.

5.9.4.2. NMR data for the minor (1*R*,3*S*,4*S*,4′*S*)-isomer 23′f. ^{1}H NMR ($CDCl_3$): δ 0.57, 0.83 (6H, 2s, 1:1, 2 × Me); 3.75 (6H, s, 2 × OMe); 5.03 (1H, s, H–C(4′)); 5.99 (2H, s, C_6H); 6.84–6.87 (1H, m, 1H of C_6H_4).

5.9.5. (1*R*,3*R*,4*S*,4′*R*)-4′-(4-Methylphenyl)-3′-(2,4,6-trimethoxyphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]-heptane-3,5′-isoxazol]-2-one 23g and its (1*R*,3*S*,4*S*,4′*S*)-isomer 23′g. Prepared from **8g** (0.254 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); **23g**:**23′g** = 95:5 (90% de); CC (EtOAc–hexanes, 1:2) and MPLC (EtOAc–hexanes, 1:3). Yield: 107 mg (23%) of a white solid; **23g**:**23′g** = 95:5 (90% de). Repeated crystallisation from $CHCl_3$–*n*-heptane furnished diastereomerically pure compound **23g**.

5.9.5.1. Data for major (1*R*,3*R*,4*S*,4′*R*)-isomer 23g. Yield: 0.033 g (7%) of a white solid; mp 205–208 °C; **23g**:**23′g** = 100:0 (100% de); $[\alpha]_D^{19} = -496.4$ (*c* 0.14, $CHCl_3$). *m*/*z* (EI) = 463 (M^+); *m*/*z* (HRMS) found: 463.237020 (M^+); $C_{28}H_{33}NO_5$ requires: *m*/*z* = 463.235874. ^{1}H NMR ($CDCl_3$): δ 0.70, 0.83, 0.95 (9H, 3s, 1:1:1, 3 × Me); 1.62–1.87 (3H, m, 3H of CH_2); 2.01 (1H, d, $J = 3.4$ Hz, H–C(4)); 2.23–2.33 (1H, m, 1H of CH_2); 2.26 (3H, s, Me); 3.72, 3.74 (9H, 2s, 1:2, 3 × OMe); 4.78 (1H, s, H–C(4′)); 5.98 (2H, s, C_6H_2); 6.90–7.05 (4H, m, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.0, 21.5, 21.7, 22.5, 31.5, 44.0, 49.7, 55.6, 56.6, 58.6, 61.4, 91.0, 91.6, 101.2, 129.0, 130.5, 133.0, 137.3, 156.3, 160.4, 162.5, 215.5 (Found: C, 72.07; H, 7.18; N, 4.10. $C_{28}H_{33}NO_5$ requires: C, 72.55; H, 7.18; N, 3.02.) ν_{max} (KBr) 2954, 1751 (C=O), 1608, 1583, 1455, 1405, 1340, 1322, 1220, 1203, 1180, 1155, 1130, 1022, 908, 876, 838, 811, 782 cm^{-1}.

5.9.5.2. Data for minor (1*R*,3*S*,4*S*,4′*S*)-isomer 23′g. ^{1}H NMR ($CDCl_3$): δ 0.91, 0.98, 1.21 (9H, 3s, 1:1:1, 3 × Me); 3.69, 3.73 (9H, 2s, 2:1, 3 × OMe); 4.59 (1H, s, H–C(4′)); 7.06–7.10 (2H, m, 2H of C_6H_4).

5.9.6. (1*R*,3*R*,4*S*,4′*R*)-4′-(4-Fluorophenyl)-3′-(2,4,6-trimethoxyphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one 23h and its (1*R*,3*S*,4*S*,4′*S*)-isomer 23′h. Prepared from compound **8h** (0.258 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); **23h**:**23′h** = 94:6 (88% de); CC and MPLC (EtOAc–hexanes, 1:2). Yield: 131 mg (28%) of a white solid; **23h**:**23′h** = 96:4 (92% de). Repeated crystallisation from EtOAc–*n*-hexane furnished diastereomerically pure compound **23h**.

5.9.6.1. Data for major (1*R*,3*R*,4*S*,4′*R*)-isomer 23h. Yield: 56 mg (12%) of a white solid; mp 204–207 °C; **23h**:**23′h** = 100:0; $[\alpha]_D^{21} = -469.9$ (*c* 0.16, $CHCl_3$). *m*/*z* (EI) = 467 (M^+); *m*/*z* (HRMS) found: 467.211950 (M^+); $C_{27}H_{30}FNO_5$ requires: *m*/*z* = 467.210802. ^{1}H NMR ($CDCl_3$): δ 0.69, 0.84, 0.95 (9H, 3s, 1:1:1, 3 × Me); 1.64–

1.88 (3H, m, 3H of CH_2); 1.99 (1H, d, $J = 3.4$ Hz, H–C(4)); 2.24–2.34 (1H, m, 1H of CH_2); 3.74, 3.75 (9H, 2s, 1:2, 3 × OMe); 4.79 (1H, s, H–C(4′)); 5.98 (2H, s, C_6H_2); 6.86–6.94 (2H, m, 2H of C_6H_4); 7.06 (2H, br s, 2H of C_6H_4). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.0, 21.7, 22.5, 31.4, 44.0, 49.7, 55.6, 56.6, 58.6, 61.1, 90.9, 91.5, 100.7, 115.2 (d, $J = 84.5$ Hz), 132.0 (d, $J = 13.7$ Hz), 132.2 (d, $J = 32.0$ Hz), 156.1, 160.4, 162.5 (d, $J = 980.5$ Hz), 162.7, 215.1 (Found: C, 69.80; H, 6.67; N, 3.07. $C_{27}H_{30}FNO_5$ requires: C, 69.36; H, 6.47; N, 3.00.) ν_{max} (KBr) 2974, 1749 (C=O), 1603, 1586, 1508, 1458, 1410, 1346, 1231, 1220, 1207, 1158, 1132, 1021, 850, 810 cm^{-1}.

5.9.6.2. Data for minor (1*R*,3*S*,4*S*,4′*S*)-isomer 23′h. ^{1}H NMR ($CDCl_3$): δ 0.93, 0.99, 1.22 (9H, 3s, 1:1:1, 3 × Me); 4.59 (1H, s, H–C(4′)).

5.9.7. (1*S*,3*S*,4*R*,4′*S*)-4′-(4-Fluorophenyl)-3′-(2,4,6-trimethoxyphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one *ent*-23h and its (1*S*,3*R*,4*R*,4′*R*)-isomer *ent*-23′h. Prepared from compound *ent*-**8h** (0.258 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); *ent*-**23h**:*ent*-**23′h** = 96:4 (92% de); CC and MPLC (EtOAc–hexanes, 1:2). Yield: 136 mg (29%) of a white solid; *ent*-**23h**:*ent*-**23′h** = 97:3 (94% de). Repeated crystallisation from EtOAc–*n*-hexane furnished diastereomerically pure compound *ent*-**23h**.

5.9.7.1. Data for major (1*S*,3*S*,4*R*,4′*S*)-isomer *ent*-23h. Yield: 0.054 g (11%) of a white solid; mp 204–207 °C; *ent*-**23h**:*ent*-**23′h** = 100:0 (100% de); $[\alpha]_D^{21} = +498.9$ (*c* 0.09, $CHCl_3$). *m*/*z* (EI) = 467 (M^+); *m*/*z* (HRMS) found: 467.211500 (M^+); $C_{27}H_{30}FNO_5$ requires: *m*/*z* = 467.210802 (Found: C, 69.40; H, 6.56; N, 4.05. $C_{27}H_{30}FNO_5$ requires: C, 69.36; H, 6.47; N, 3.00.). ^{1}H NMR and IR spectral data for *ent*-**23h** were identical to the data for the (1*R*,3*R*,4*S*,4′*R*)-enantiomer **23h** (see Section 5.9.6.1).

5.9.7.2. NMR data for minor (1*S*,3*R*,4*R*,4′*R*)-isomer *ent*-23′h. ^{1}H NMR data for *ent*-**23′h** were identical to the data for the (1*R*,3*S*,4*S*,4′*S*)-enantiomer **23′h** (see Section 5.9.6.2).

5.9.8. (1*R*,3*R*,4*S*,4′*R*)-4′-[3,5-Bis(trifluoromethyl)phenyl]-3′-(2,4,6-trimethoxyphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo-[2.2.1]heptane-3,5′-isoxazol]-2-one 23i and its (1*R*,3*S*,4*S*,4′*S*)-isomer 23′i. Prepared from **8i** (0.376 g, 1 mmol) and **18a** (0.251 g, 1.2 mmol); first CC (EtOAc–hexanes, 1:2); **23i**:**23′i** = 94:6 (88% de); second CC ($CHCl_3$–MeOH, 100:1). Yield: 0.352 g (60%) of a greyish semisolid; **23i**:**23′i** = 93:7 (86% de); mp 64–70 °C; $[\alpha]_D^{21} = -309.3$ (*c* 0.162, $CHCl_3$). *m*/*z* (EI) = 585 (M^+); *m*/*z* (HRMS) found: 585.196520 (M^+); $C_{29}H_{29}F_6NO_5$ requires: *m*/*z* = 585.194993 (Found: C, 60.38; H, 5.48; N, 2.28. $C_{29}H_{29}F_6NO_5$ requires: C, 59.49; H, 4.99; N, 2.39.) ν_{max} (KBr) 2965, 1752 (C=O), 1605, 1585, 1468, 1458, 1416, 1376, 1341, 1278, 1230, 1207, 1131, 1034, 947, 911, 877, 831, 814, 710, 681 cm^{-1}.

5.9.8.1. NMR data for the major (1*R*,3*R*,4*S*,4′*R*)-isomer 23i. ^{1}H NMR ($CDCl_3$): δ 0.70, 0.86, 0.97 (9H, 3s, 1:1:1, 3 × Me); 1.66–1.90 (4H, m, 3H of CH_2, H–C(4)); 2.28–2.35 (1H, m, 1H of CH_2); 3.74 and 3.76 (9H, 2s, 1:2, 3 × OMe); 4.94 (1H, s, H–C(4′)); 5.99 (2H, s, C_6H_2); 7.57 (2H, br s, 2H of C_6H_3); 7.73 (1H, br s, 1H of C_6H_3). ^{13}C NMR ($CDCl_3$): δ 9.9, 18.9, 21.7, 22.6, 31.1, 44.2, 49.7, 55.6, 56.3, 58.7, 61.1, 91.0, 91.2, 99.4, 121.9–122.1 (m), 123.5 (q, J = 1085.7 Hz), 130.7 (br s), 131.7 (q, $J = 134.8$ Hz), 139.1, 155.2, 160.3, 163.1, 213.9.

5.9.8.2. NMR data for the minor (1*R*,3*S*,4*S*,4′*S*)-isomer 23′i. ^{1}H NMR ($CDCl_3$): δ 0.94, 1.01 (6H, 2s, 1:1, 2 × Me); 4.72 (1H, s, H–C(4′)).

5.9.9. (1*R*,3*R*,4*S*,4′*R*)-4′-(2-Methylphenyl)-1,7,7-trimethyl-3′-(2,4,6-trimethylphenyl)-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one 24f and its (1*R*,3*S*,4*S*,4′*S*)-isomer 24′f. Prepared from compound **8f** (0.254 g, 1 mmol) and **18b** (0.194 g, 1.2 mmol); **24f**:**24′f** = 96:4 (92% de); first CC ($CHCl_3$–MeOH, 300:1 → 100:1), second CC (EtOAc–hexanes, 1:10). Yield: 37 mg (9%) of a white solid; **24f**:**24′f** = 96:4 (92% de). Repeated crystallisation from $CHCl_3$–*n*-heptane furnished diastereomerically pure compound **24f**.

5.9.9.1. Data for major (1*R*,3*R*,4*S*,4′*R*)-isomer 24f. Yield: 0.015 g (3%) of a white solid; mp 223–226 °C; **24f**:**24′f** = 100:0 (100% de); $[\alpha]_D^{21} = -534.4$ (*c* 0.28, $CHCl_3$). *m*/*z* (EI) = 415 (M^+); *m*/*z* (HRMS) found: 415.252350 (M^+); $C_{28}H_{33}NO_2$ requires: *m*/*z* = 415.251130. ^{1}H NMR ($CDCl_3$): δ 0.66, 0.88, 0.97 (9H, 3s, 1:1:1, 3 × Me); 1.70–1.94 (3H, m, 3H of CH_2); 1.96, 2.18 (6H, 2s, 1:1, 2 × Me); 2.21 (6H, br s, 2 × Me); 2.32–2.43 (1H, m, 1H of CH_2); 2.49 (1H, d, $J = 3.8$ Hz, H–C(4)); 4.79 (1H, s, H–C(4′)); 6.71 (2H, s, C_6H_2); 6.96–6.99, 7.09–7.14, 7.17–7.22 and 7.34–7.37 (4H, 4m, 1:1:1:1, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.0, 19.8, 20.5, 21.4, 21.6, 21.8, 31.8, 44.0, 49.7, 57.5, 58.8, 91.8, 125.5, 126.0, 128.2, 128.9, 131.0, 131.9, 133.3, 136.3, 138.1, 138.9, 161.7, 216.0 (Found: C, 80.97; H, 8.08; N, 3.60. $C_{28}H_{33}NO_2$ requires: C, 80.93; H, 8.00; N, 3.37.) ν_{max} (KBr) 2962, 1744 (C=O), 1610, 1469, 1448, 1393, 1374, 1306, 1285, 1103, 1029, 903, 875, 856, 837, 757 cm^{-1}.

5.9.9.2. Data for minor (1*R*,3*S*,4*S*,4′*S*)-isomer 24′f. ^{1}H NMR ($CDCl_3$): δ 0.96, 1.01 (6H, 2s, 1:1, 2 × Me); 4.66 (1H, s, H–C(4′)); 7.56–7.60 (1H, m, 1H of C_6H_4).

5.9.10. (1*R*,3*R*,4*S*,4′*R*)-4′-(4-Fluorophenyl)-1,7,7-trimethyl-3′-(2,4,6-trimethylphenyl)-4′*H*-spiro[bicyclo[2.2.1]heptane-3,5′-isoxazol]-2-one 24h and its (1*R*,3*S*,4*S*,4′*S*)-isomer 24′h. Prepared from compound **8h** (0.258 g, 1 mmol) and **18b** (0.194 g, 1.2 mmol); **24h**:**24′h** = 93:7 (86% de); CC (EtOAc–hexanes, 1:15) and MPLC (EtOAc–hexanes, 1:13). Yield: 17 mg (4%) of a white solid; **24h**:**24′h** = 99:1 (98% de). Repeated crystallisation from $CHCl_3$–*n*-heptane furnished diastereomerically pure compound **24h**.

5.9.10.1. Data for major (1*R*,3*R*,4*S*,4′*R*)-isomer 24h. Yield: 0.007 g (1.5%) of a white solid; mp 196–208 °C; **24h**:**24′**h = 100:0 (100% de); $[\alpha]_D^{21} = -509.7$ (*c* 0.06, $CHCl_3$). *m*/*z* (EI) = 419 (M^+); *m*/*z* (HRMS) found: 419.227320 (M^+); $C_{27}H_{30}FNO_2$ requires: *m*/*z* =

419.226058. ^{1}H NMR ($CDCl_3$): δ 0.67, 0.87, 0.96 (9H, 3s, 1:1:1, 3 × Me); 1.69–1.92 (3H, m, 3H of CH_2); 2.18 (3H, s, Me); 2.20 (1H, d, $J = 3.8$ Hz, H–C(4)); 2.28–2.40 (1H, m, 1H of CH_2); 2.29 (6H, s, 2 × Me); 4.47 (1H, s, H × C(4′)); 6.74 (2H, s, C_6H_2); 6.92–6.98 (2H, m, 2H of C_6H_4); 7.02–7.10 (2H, m, 2H of C_6H_4). ^{13}C NMR ($CDCl_3$): δ 9.9, 19.0, 21.0, 21.3, 21.8, 22.1, 31.5, 44.1, 49.6, 58.8, 62.1, 91.5, 115.9 (d, $J = 86.9$ Hz), 125.2, 129.3, 130.9 (d, $J = 13.7$ Hz), 132.1 (d, $J = 32.0$ Hz), 138, 139.1, 161.2, 162.8 (d, $J = 985.1$ Hz), 215.5 (Found: C, 77.50; H, 7.24; N, 3.65. $C_{27}H_{30}FNO_2$ requires: C, 77.30; H, 7.21; N, 3.34.) ν_{max} (KBr) 2972, 1746 (C=O), 1604, 1509, 1455, 1396, 1374, 1309, 1224, 1163, 1101, 1024, 911, 844, 796 cm^{-1}.

5.9.10.2. Data for minor (1*R*,3*S*,4*S*,4′*S*)-isomer 24′h. ^{1}H NMR ($CDCl_3$): δ 4.34 (1H, s, H–C(4′)).

5.9.11. (1*R*,3*R*,4*S*,4′*R*)-4′-[3,5-Bis(trifluoromethyl)phenyl]-1,7,7-trimethyl-3′-(2,4,6-trimethyl-phenyl)-4′*H*-spiro[bicyclo-[2.2.1]heptane-3,5′-isoxazol]-2-one 24i and its (1*R*,3*S*,4*S*,4′*S*)-isomer 24′i. Prepared from compound **8i** (0.376 g, 1 mmol) and **18b** (0.194 g, 1.2 mmol); **24i**:**24′i** = 93:7 (86% de); CC and MPLC (EtOAc–hexanes, 1:30) afforded diastereomerically pure compound **24i**.

5.9.11.1. Data for major (1*R*,3*R*,4*S*,4′*R*)-isomer 24i. Yield: 92 mg (17%) of a white solid; mp 147–155 °C; **24i**:**24′i** = 100:0 (100% de); $[\alpha]_D^{21} = -401.1$ (*c* 0.09, $CHCl_3$). *m*/*z* (EI) = 537 (M^+); *m*/*z* (HRMS) found: 537.212020 (M^+); $C_{29}H_{29}F_6NO_2$ requires: *m*/*z* = 537.210249. ^{1}H NMR ($CDCl_3$): δ 0.67, 0.89, 0.98 (9H, 3s, 1:1:1, 3 × Me); 1.71–1.94 (4H, m, 3H of CH_2, H–C(4)); 2.19, 2.31 (9H, 2s, 1:2, 3 × Me); 2.29–2.43 (1H, m, 1H of CH_2); 4.63 (1H, s, H–C(4′)); 6.76 (2H, s, C_6H_2); 7.52 (2H, br s, 2H of C_6H_3); 7.79 (1H, s, 1H of C_6H_3). ^{13}C NMR ($CDCl_3$): δ 9.8, 18.9, 20.9, 21.3, 21.8, 22.2, 31.2, 44.3, 49.6, 58.9, 62.1, 91.6, 122.5–122.7 (m), 123.3 (q, $J = 1085.7$ Hz), 124.4, 129.6, 130.2–130.4 (m), 132.3 (q, $J = 132.6$ Hz), 137.8, 138.1, 139.6, 160.3, 214.3 (Found: C, 64.78; H, 5.40; N, 2.83. $C_{29}H_{29}F_6NO_2$ requires: C, 64.80; H, 5.44; N, 2.61.) ν_{max} (KBr) 2979, 1754 (C=O), 1613, 1455, 1395, 1374, 1276, 1179, 1133, 1107, 1032, 903, 874, 859, 830 cm^{-1}.

5.9.11.2. Data for minor (1*R*,3*S*,4*S*,4′*S*)-isomer 24′i. ^{1}H NMR ($CDCl_3$): δ 4.49 (1H, s, H–C(4′)).

5.10. X-ray structural analysis for compounds 8h, 19, 22b, 23a, 23f, 23g, *ent*-23h and 24h

Single crystal X-ray diffraction data of compounds **8h**, **19**, **22b**, **23a**, **23f**, **23g**, *ent*-**23h** and **24h** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[58] DENZO and SCALEPACK[59] were used for indexing and scaling of the data and the structures were solved by means of SIR97.[60] Refinement was done using Xtal3.4[61] program package and the crystallographic plots were prepared by ORTEP III.[62] 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 the hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters not refined. Absorption correction was not necessary. Regina[63] 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 289084, 289085 and 299415–299420. 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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