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Synthesis and properties of *N*-substituted (1*R*,5*S*)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-2-ones

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Abstract—*N*-Substituted (1*R*,5*S*)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones were prepared in three steps from (1*R*)-(+)-camphor via coupling of (1*R*,4*E*,5*S*)-3-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one with primary amines. *N*,*N*′-Bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}benzene-1,2-diamine was used as the ligand in the preparation of the corresponding coordination compounds with palladium(II), copper(II) and nickel(II). 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 shift reagents in NMR spectroscopy.[1–4] For example, the reaction of 3-hydroxymethylidene camphor[5] with amines followed by a reduction of the exocyclic C=C double bond leads to 3-aminomethylidene camphor derivatives exhibiting local anesthetic and smooth muscle relaxant properties.[6–8] Pyridine and 2,2′-bipyridine thioethers and diols derived from (+)-camphor were used as N–S and N–O chiral ligands for asymmetric catalysis.[9,10] Recently, Fang and co-workers reported the synthesis and utilisation of bis(camphorylmethylene)benzene-1,2-diamine and *N*,*N*′-bis-(camphormethylene)-1,2-di(ethoxycarbonyl)ethylenediamine as chiral ligands[11] related to Jacobsen's ligand.[12–14]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates have been prepared as versatile reagents for the preparation of various heterocyclic systems.[15–19] 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 an α-amino acid, dipeptide, β-amino alcohol, α-hydroxy acid and propane-1,2-diol structural element.[15–20] Our studies on ex-chiral pool derived enaminones have recently been extended on the preparation and synthetic applications of (+)-camphor derived enaminones.[20,21] In connection with this, we have previously reported a stereoselective one-pot synthesis of (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]-azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones.[21] In continuation of our work in this field, we herein report a preparation of some novel chiral enaminones, *N*-substituted (1*R*,5*S*)-3-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **6a**–**y**, their properties, and utilisation of *N*,*N*′-bis-{(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]-methyl}benzene-1,2-diamine **6w** as the N–O ligand for the preparation of coordination compounds **7a**–**c** with Pd(II), Cu(II) and Ni(II).

2. Results and discussion

The starting compound, (1*R*,4*E*,5*S*)-3-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]-octan-3-one **4**, was prepared in two steps from (1*R*)-(+)-camphor **1**. First, **1** was transformed by a Baeyer–Villiger oxidation into a mixture of isomeric oxabicyclo[3.2.1]octanones **2** and **3**.[22] Treatment of this

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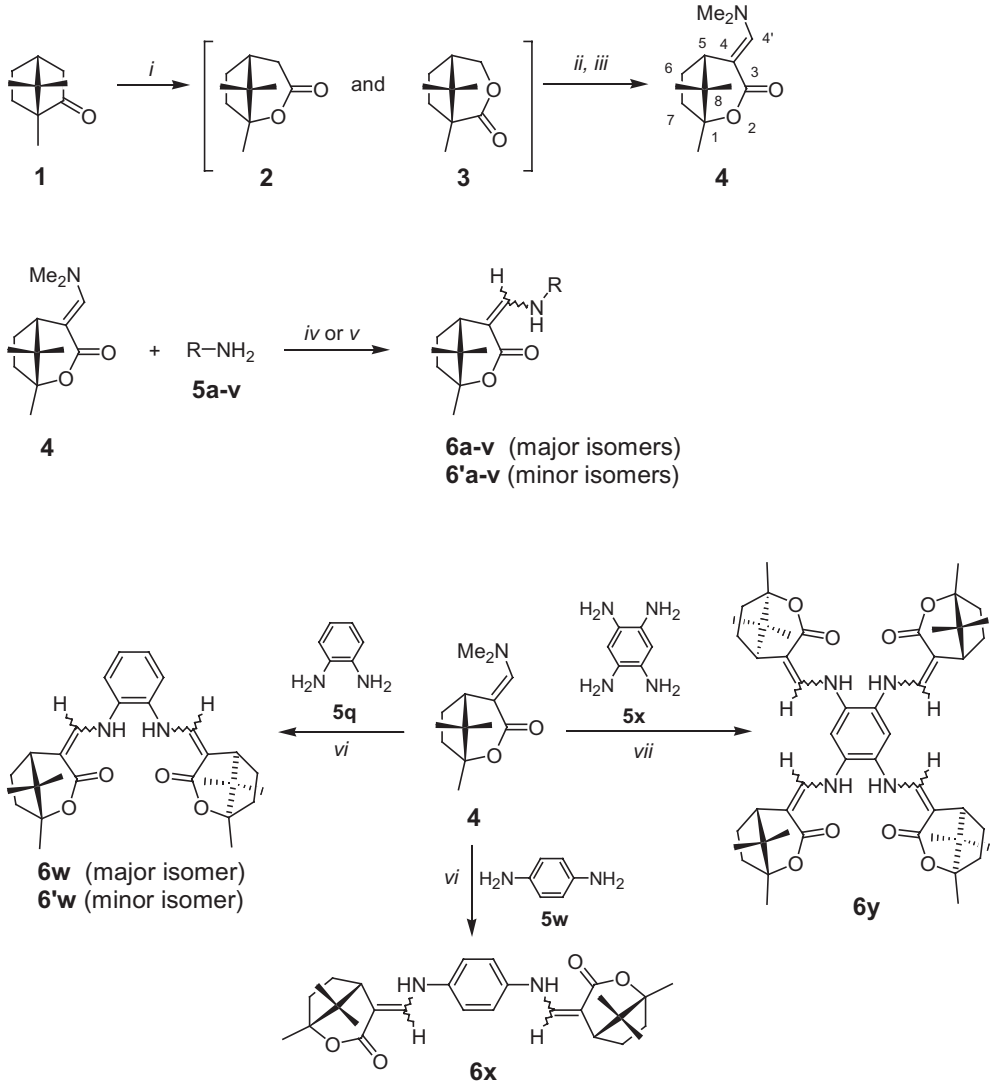
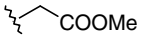
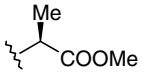
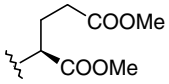
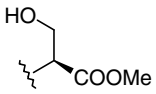
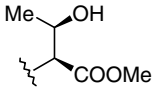
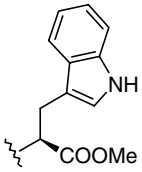
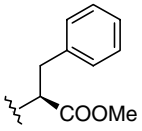
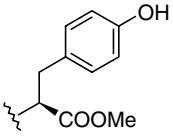
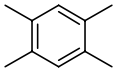
mixture of lactones **2** and **3** with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) in decalin under reflux, followed by chromatographic separation from the unreacted lactone **3**, furnished the enamino lactone **4** in 43% yield. Treatment of **4** with primary amines **5a**–**v** in anhydrous methanol or 1-propanol in the presence of an equimolar amount of hydrochloric or sulfuric acid at 20–100 °C afforded the corresponding dimethylamine substitution products, in most cases, as mixtures of the major isomers **6** and the minor isomers **6′**, with respect to the configuration around the exocyclic C=C double bond (Scheme 1, Table 1). Compounds **6d**,**k**,**m**–**o**,**r**–**v** were obtained as single isomers. In the reactions of **4** with amines **5a**–**c**,**e**–**j**,**l**,**p** and **q**, the corresponding substitution products were formed as mixtures of the major isomers **6a**–**c**,**e**–**j**,**l**,**p** and **q** and the minor isomers **6′a**–**c**,**e**–**j**,**l**,**p** and **q**. In the case of (*S*)-α-amino acid derived enamino lactones **6a**–**c**,**e**–**g**, chromatographic separation afforded both isomers in either pure forms (**6a**,**b**,**e**–**g** and **6′a**–**c**,**e**–**g**) or isomerically enriched forms (**6c** and **6′l**). Minor isomers **6′h**–**j**,**p** and **q** were not isolated and thus characterised only by ^{1}H NMR. When **4** was reacted with benzene-1,2-diamine **5q** and sulfuric acid in a molar ratio of 2:2:1, respectively, the monosubstitution products **6q** and **6′q** were formed. However, changing the molar ratio to **4**:**5q**:H_2SO_4 = 2:1:1, resulted in the formation of bis-substitution products **6w** and **6′w**, which could be separated by chromatography to give isomerically pure compounds **6w** and **6′w**. Similarly, reacting **4** with benzene-1,4-diamine **5w** and H_2SO_4 (2:1:1) afforded bis-substitution product **6x**, while from **4** and benzene-1,2,4,5-tetramine tetrahydrochloride (**5x**) in a molar ratio of 4:1, the tetra-substitution product **6y** was obtained (Scheme 1, Table 1).

Since compounds **6** and **6′** can be regarded as aza analogues of chiral β-keto esters and could be used as chiral



Scheme 1. Reagents and conditions: (i) AcOOH, AcOH, AcONa, rt, six weeks; (ii) *tert*-BuOCH(NMe_2)$_2$, decalin, reflux; (iii) chromatographic purification; (iv) R–NH_2 × HCl (**5a**–**j**,**m**,**n**,**r**, 1 equiv), MeOH or *n*-PrOH, rt–reflux; (v) R–NH_2 (**5k**,**l**,**o**,**p**,**q**,**s**–**v**, 1 equiv), MeOH or *n*-PrOH, H_2SO_4 (1 equiv), rt–reflux; (vi) benzenediamine (**5q** or **5w**, 0.5 equiv), MeOH, H_2SO_4 (1 equiv), reflux; (vii) benzene-1,2,4,5-tetramine tetrahydrochloride (**5x**, 0.25 equiv), MeOH, reflux.

Table 1. Amines **5** and (1*R*,5*S*)-4-[(substituted amino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **6**/**6′**

Compound	R	Major isomer **6**			Minor isomer **6′**		
		Yield [%]	*E* or *Z*	**6**:**6′**	Yield [%]	*E* or *Z*	**6**:**6′**
5a, **6a**, **6′a**		50	*Z*	100:0	26	*E*	0:100
5b, **6b**, **6′b**		35	*Z*	100:0	23	*E*	0:100
5c, **6c**, **6′c**		41	*Z*	84:16	12	*E*	0:100
5d, **6d**, **6′d**		77	*Z*	100:0			
5e, **6e**, **6′e**		55	*Z*	100:0	29	*E*	0:100
5f, **6f**, **6′f**		36	*Z*	100:0	17	*E*	0:100
5g, **6g**, **6′g**		43	*Z*	100:0	17	*E*	0:100
5h, **6h**, **6′h**		62	*Z*	92:8			
5i, **6i**, **6′i**	CH_2CN	34	*E*	92:8			
5j, **6j**, **6′j**	CH_2CH_2 COOEt	77	*Z*	77:23			
5k, **6k**, **6′k**	(1-Adamantyl)methyl	43	*E*	100:0			
5l, **6l**, **6′l**	Prop-1-yn-3-yl	46	*Z*	100:0	23	*E*	4:96
5m, **6m**, **6′m**	Ph	67	*E*	100:0			
5n, **6n**, **6′n**	4-Methylphenyl	41	*E*	100:0			
5o, **6o**, **6′o**	4-Methoxyphenyl	29	*E*	100:0			
5p, **6p**, **6′p**	4-Nitrophenyl	44	*E*	68:32			
5q, **6q**, **6′q**	2-Aminophenyl	63	*Z*	90:10			
5r, **6r**, **6′r**	4-Hydroxyphenyl	59	*Z*	100:0			
5s, **6s**, **6′s**	1*H*-Triazol-3-yl	52	*E*	100:0			
5t, **6t**, **6′t**	Pyrazinyl	41	*Z*	100:0			
5u, **6u**, **6′u**	1*H*-Indazol-3-yl	35	*Z*	100:0			
5v, **6v**, **6′v**	Quinolin-3-yl	69	*E*	100:0			
5q, **6w**, **6′w**	1,2-Phenylene	64	*Z*,*Z*	100:0	23	*E*,*Z*	0:100
5w, **6x**, **6′x**	1,4-Phenylene	86	[a]	[a]			
5x, **6y**, **6′y**		53	[a]	[a]			

[a] Due to extremely low solubility, ^{1}H NMR spectra could not be recorded. Consequently, the isomer ratio and configuration around the C=C double bond were not established.

ligands for coordination with transition metals, we carried out three reactions of **6w** with palladium(II), copper(II) and nickel(II) acetate. Treatment of (*Z*,*Z*)-*N*,*N*′-bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo-[3.2.1]oct-4-ylidene]methyl}benzene-1,2-diamine **6w** with $Pd(OAc)_2$ in a mixture of acetonitrile and dichloromethane at rt afforded *N*,*N*′-bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-hydroxy-2-oxabicyclo[3.2.1]oct-3-en-4-yl]methylidene}benzene-1,2-diaminatopalladium(II) **7a** in 71% yield. An identical product was also obtained when the minor (*E*,*Z*)-isomer **6′w** or a mixture of **6w** and **6′w** was used. Similarly, reactions of **6w** with $Cu(OAc)_2 \times H_2O$ and $Ni(OAc)_2 \times 4H_2O$ gave the corresponding coordination compounds, *N*,*N*′-bis-{[(1*R*,5*S*)-1,8,8-trimethyl-

3-hydroxy-2-oxabicyclo[3.2.1]oct-3-en-4-yl]methylidene}-benzene-1,2-diaminatocopper(II) **7b** and *N*,*N*′-bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-hydroxy-2-oxabicyclo[3.2.1]-oct-3-en–4-yl]methylidene}benzene-1,2-diaminatonickel (II) **7c** in 67% and 62% yields, respectively (Scheme 2).

3. Structure determination

The structures of starting compound **4**, substitution products **6** and **6′** and transition metal complexes **7** 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 **6c**,**h**–**j**,**l**,**p** and **q** were characterised as isomerically enriched mixtures of (*E*)- and (*Z*)-isomers. Compounds **6c**, **6x** and **7c** were not prepared in analytically pure form. The identity of **6c** was confirmed by ^{13}C NMR and EI-HRMS, while for compounds **6x** and **7c**, it was established by EI-HRMS. Due to insolubility, even in DMSO-d_6, ^{1}H NMR characterisation of compounds **6x** and **6y** was not possible.

The structures of compounds **4**, **6b**, **6′e**, **6g** and **6o** were determined by X-ray diffraction (Figs. 1–5). The configuration around the exocyclic C=C double bond in compounds **4**, **6e** and **6′e** was determined by NMR on the basis of long-range coupling constants ($^{3}J_{C-H}$) between the methylidene proton (*H*–C(4′)) and the carbonyl carbon atom (O=*C*(3)), measured from the anti-phase splitting of cross peaks in the HMBC spectrum. Generally, the magnitude of coupling constant, $^{3}J_{C-H}$ for nuclei with *cis*-configuration around the C=C double bond are smaller (2–6 Hz) than that for the *trans*-oriented nuclei (8–12 Hz).[19,23–33] In compound **4**, the magnitude of the coupling constant ($^{3}J_{C-H} = 5$ Hz) showed an (*E*)-configuration around the exocyclic C=C double bond. Similarly, the (*Z*)-configuration was established

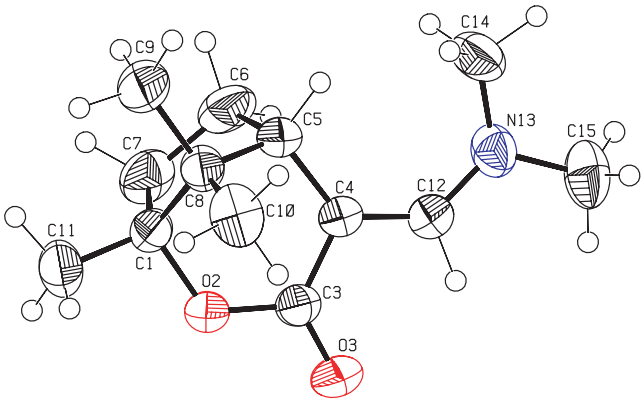
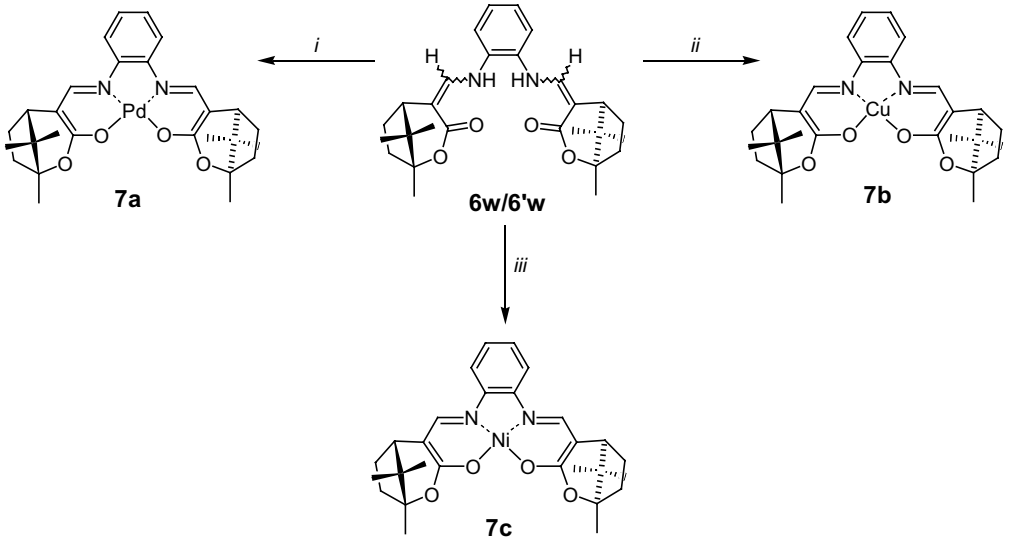


Figure 1. The asymmetric unit of compound **4**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

for compound **6d** ($^{3}J_{C-H} = 11$ Hz) and the (*E*)-configuration for its minor isomer **6′d** ($^{3}J_{C-H} = 4$ Hz) (Fig. 6).

The configuration around the exocyclic C=C double bond in the major isomers **6b**,**c**,**i**,**k**,**m**–**w** and the minor isomers **6′b**,**c**,**p** and **w** was determined by NOESY spectroscopy. In compounds **6i**,**k**,**m**–**p**,**s** and **v** and **6′b** and **c**, the (*E*)-configuration was established on the basis of NOE between N–*H* and *H*–C(5). On the other hand, NOE between *H*–C(5) and *H*–C(4′) indicated a (*Z*)-configuration in compounds **6b**,**c**,**q**,**r**,**t** and **u** and **6′p**. Accordingly, the (*Z*,*Z*)-configuration for compound **6w** and the (*E*,*Z*)-configuration for compound **6′w** were determined (Fig. 6).

In compounds **6/6′a**–**l**, obtained from **4** and aliphatic amines **5a**–**l**, the configurations around the exocyclic C=C double bond were correlated with the chemical shifts δ for *H*–C(4′) and N*H*. In the case of the (*Z*)-isomers, signals for *H*–C(4′) appeared at higher field (6.00–6.50 ppm) than in the case of the (*E*)-isomers



Scheme 2. Reagents and conditions: (i) $Pd(OAc)_2$, acetonitrile–dichloromethane, rt; (ii) $Cu(OAc)_2 \times H_2O$, acetonitrile, dichloromethane, rt; (iii) $Ni(OAc)_2 \times 4H_2O$, acetonitrile, reflux.

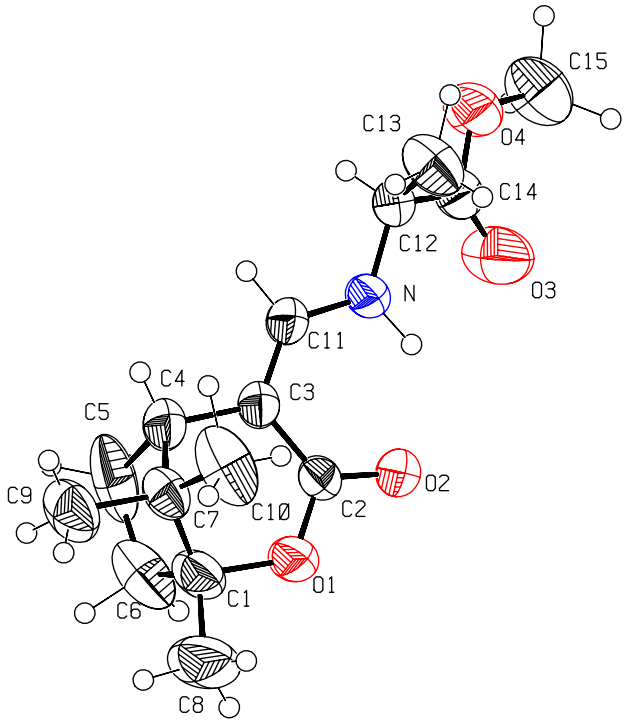


Figure 2. The asymmetric unit of compound **6b**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

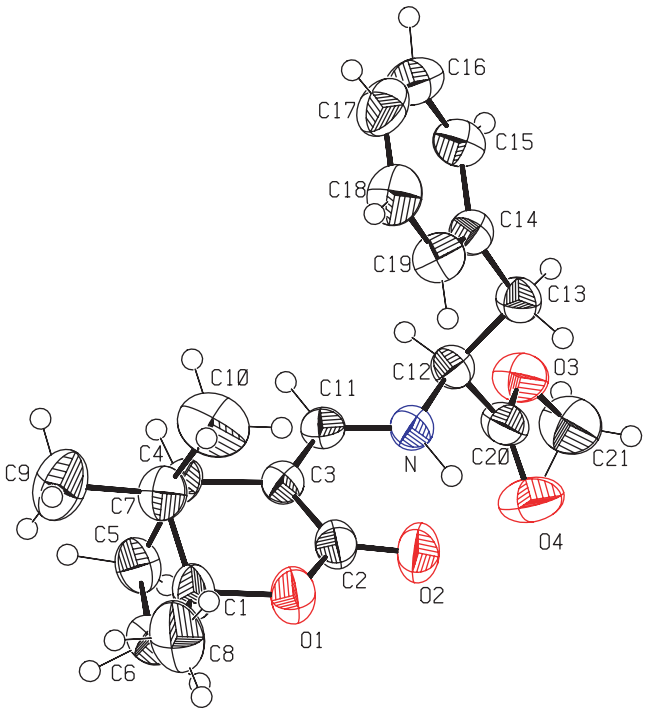


Figure 4. The asymmetric unit of compound **6g**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

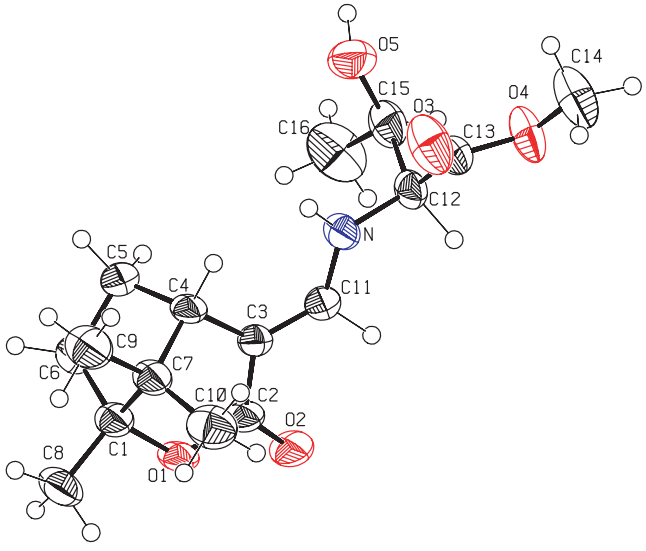


Figure 3. The asymmetric unit of compound **6′e**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

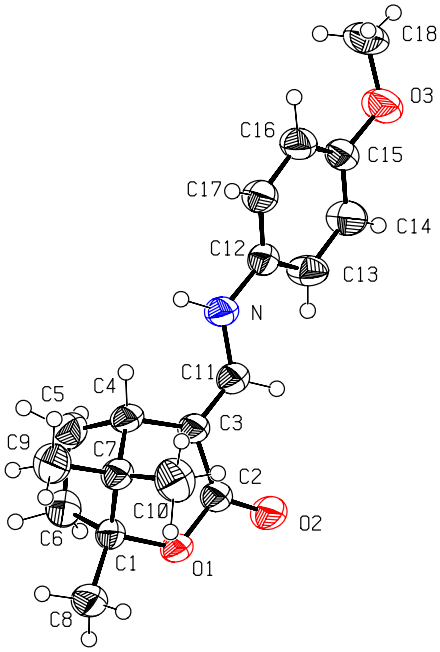


Figure 5. The asymmetric unit of compound **6o**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

(7.00–7.34 ppm). Signals for N*H* exhibited an even stronger dependence of chemical shift on the configuration. Typically, chemical shifts for the N*H* protons of the (*Z*)-isomers were 7.97–8.29 ppm and, in the case of the (*E*)-isomers, 4.24–6.92 ppm. In this manner, the configurations of compounds **6a**,**d**,**f**,**h**,**j** and **l** and **6′a**,**f**–**j** and **l** were determined. The downfield shift of the N*H* proton in the (*Z*)-isomers can be rationalised by the intramolecular hydrogen bond, N–H···O=C(3). Similarly, the downfield shift of *H*–C(4′) signal in the case of the (*E*)-isomers, can be attributed to the effect of the ring carbonyl group (Table 2).

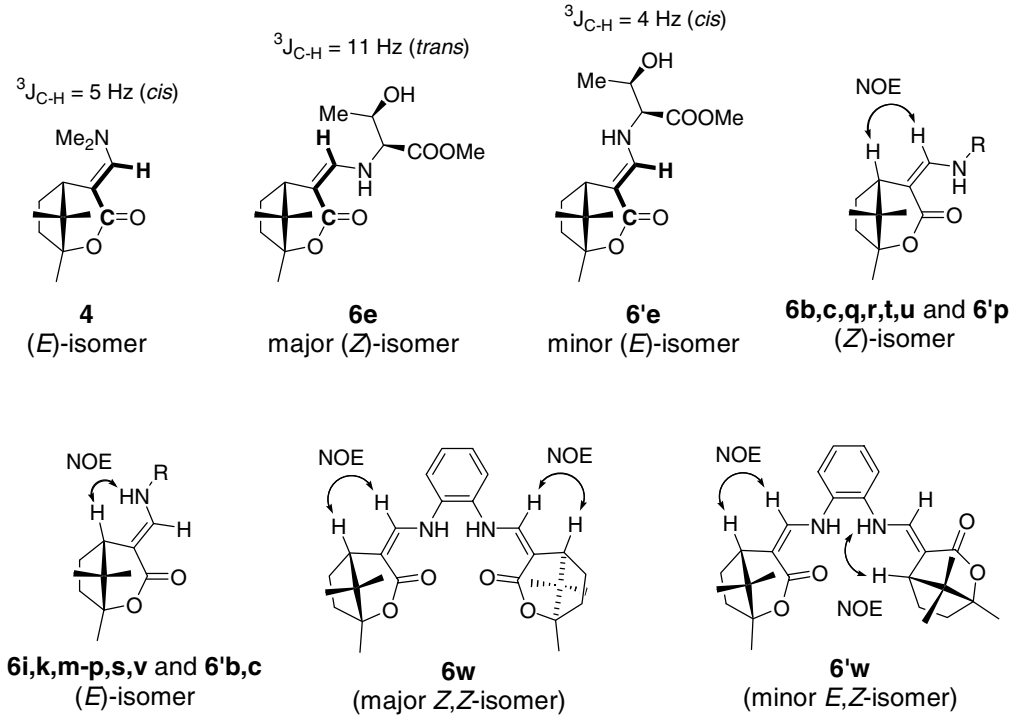


Figure 6. Determination of configuration around the exocyclic C=C double bond by NMR.

Table 2. Correlation between the chemical shifts δ of *H*–C(4′) and *H*–N protons, specific rotations $[\alpha]_D$ and configuration around the exocyclic C=C double bond in compounds **6a**–**w** and **6′**-**w**

Major isomers **6a**–**w**						Minor isomers **6′a**–**c**,**e**–**l**,**p**,**q**,**w**					
	Solvent	δ [ppm]		$[\alpha]_D$	*Z* or *E*		Solvent	δ [ppm]		$[\alpha]_D$	*Z* or *E*
		H–C(4′)	*H*–N					*H*–C(4′)	*H*–N		
6a,	$CDCl_3$	6.33	8.09	+2.9	*Z*						
6b	$CDCl_3$	6.39	8.10	+38.1	*Z*[a,c]	**6′b**	$CDCl_3$	7.29	4.70	+131.4	*E*[c]
6c	$CDCl_3$	6.35	8.09	−19.6	*Z*[c,f]	**6′c**	$CDCl_3$	7.21	4.68	+81.1	*E*[c]
6d	$CDCl_3$	6.41	8.22	+3.0	*Z*						
6e	$CDCl_3$	6.38	8.25	−5.1	*Z*[b]	**6′e**	$CDCl_3$	7.24	4.93	+92.2	*E*[a,b]
6f	$CDCl_3$	6.10	8.29	−120.2	*Z*	**6′f**	$CDCl_3$	7.28	4.71	+109.0	*E*
6g	$CDCl_3$	6.00	8.25	−153.4	*Z*[a]	**6′g**	$CDCl_3$	~7.25[d]	4.57	+129.5	*E*
6h	DMSO-d_6	6.47	8.00	−97.6	*Z*[f]	**6′h**	DMSO-d_6	[d]	[d]	[e]	*E*
6i	DMSO-d_6	7.15	6.92	+120.5	*E*[c,f]	**6′i**	DMSO-d_6	6.66	7.90	[e]	*Z*
6j	$CDCl_3$	6.43	8.00	+18.0	*Z*[f]	**6′j**	$CDCl_3$	7.32	4.77	[e]	*E*
6k	DMSO-d_6	7.00	~6.5[d]	+30.8	*E*[c]						
6l	$CDCl_3$	6.50	7.97	0	*Z*	**6′l**	$CDCl_3$	7.33	4.24	+130.6	*E*[f]
6m	DMSO-d_6	7.70	8.82	+188.2	*E*[c]						
6n	DMSO-d_6	7.66	8.75	+183.5	*E*[c]						
6o	DMSO-d_6	7.61	8.70	+193.6	*E*[a,c]						
6p	DMSO-d_6	7.74	9.46	+142.0	*E*[c,f]	**6′p**	DMSO-d_6	7.59	10.35	[e]	*Z*[c]
6q	$CDCl_3$	~6.9[d]	9.83	−5.9	*Z*[c,f]	**6′q**	$CDCl_3$	[d]	9.95	[e]	*E*
6r	$CDCl_3$	6.93	9.94	−12.8	*Z*[c]						
6s	DMSO-d_6	7.88	9.59	+125.6	*E*[c]						
6t	DMSO-d_6	7.71	10.36	+12.9	*Z*[c]						
6u	DMSO-d_6	7.56	10.29	+3.7	*Z*[c]						
6v	DMSO-d_6	7.84	9.19	+175.3	*E*[c]						
6w	$CDCl_3$	6.84	9.95	+23.0	*Z*,*Z*[c]	**6′w**	$CDCl_3$	6.95 7.80	6.10 9.99	+129.6	*E*,*Z*[c]

[a] Determined by X-ray diffraction.
[b] Determined by HMBC spectroscopy.
[c] Determined by NOESY spectroscopy.
[d] Overlapped by other signals.
[e] Not isolated.
[f] Not isomerically pure—the *E*/*Z*-ratio of isomers is given in Table 1.

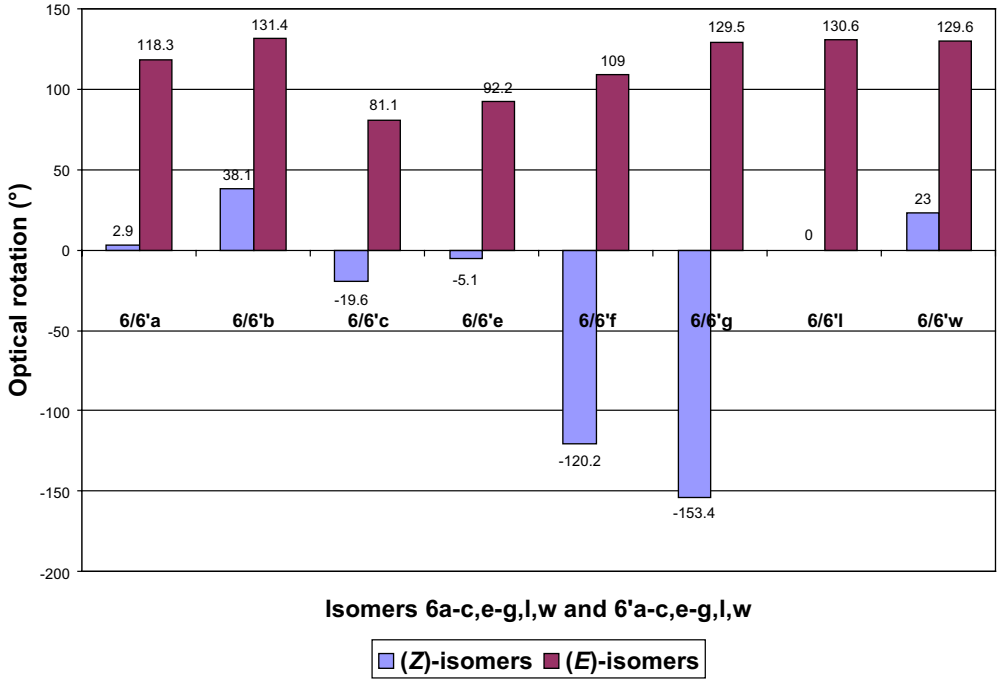
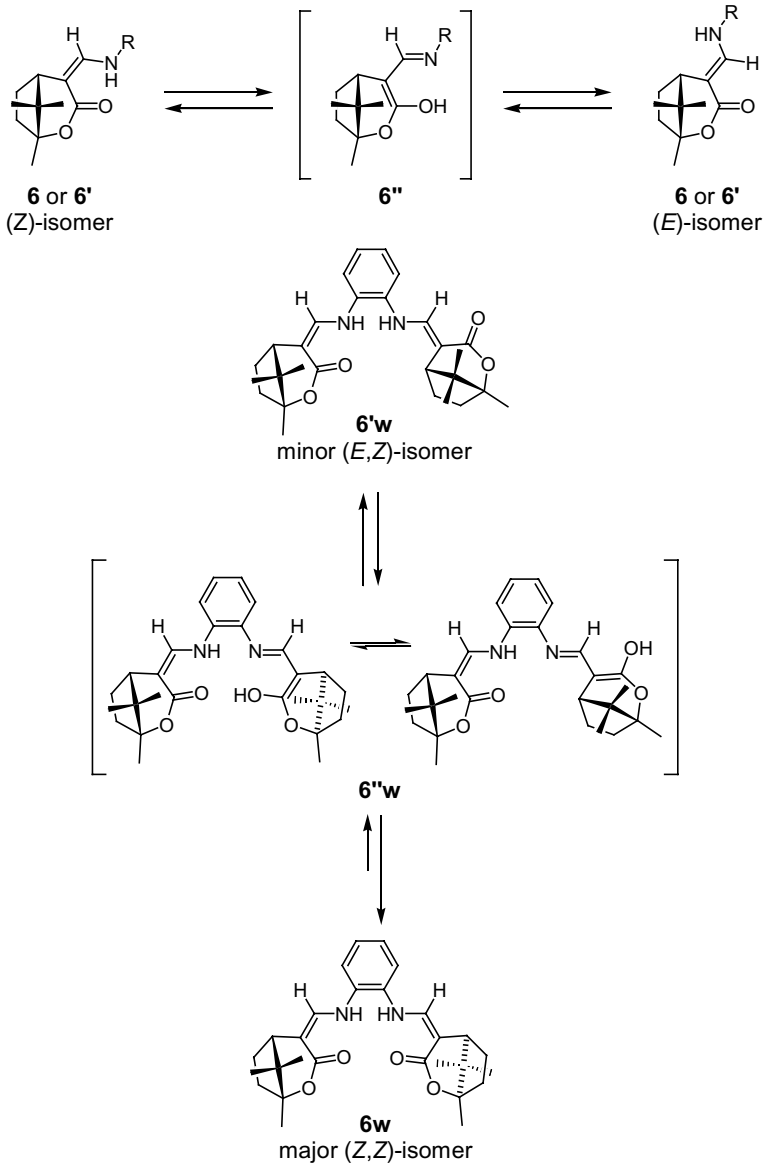


Figure 7. Correlation between specific rotation and (*Z*)- or (*E*)-configuration in isomeric compounds **6a**–**c**,**e**–**g**,**l** and **w** and **6′a**–**c**,**e**–**g**,**l** and **w**. The *E*/*Z*-ratios of isomerically impure compounds **6c**,**h**–**j**,**p**,**q** and **6′l** are given in Table 1.

Furthermore, correlation between the specific rotation data of compounds **6** and **6′** and the configuration around the C=C double bond showed, that the (*E*)- and the (*Z*)-isomers can be differentiated on the basis of specific rotation values. The (*Z*)-isomers exhibited specific rotations between −153.4 and +38.1 whereas with the (*E*)-isomers, specific rotations ranged from +81.1 to +131.4, with differences between the specific rotations of the (*E*)- and the (*Z*)-isomers exceeding 100. Thus, the configuration around the C=C double bond in *N*-substituted (1*R*,5*S*)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-2-ones **6** can be determined on the basis of specific rotation data (Table 2, Fig. 7).

Since compounds **7a**–**c** with the (*Z*)-configuration around both exocyclic C=C double bonds were obtained from both isomers of the ligand, the (*Z*,*Z*)-isomer **6w** and the (*E*,*Z*)-isomer **6′w**, coordination of **6′w** with transition metal ions must have included isomerisation of the (*E*,*Z*)-isomer **6′w** into the (*Z*,*Z*)-isomer **6w**. Similarly, *Z*/*E*-isomerisation of enamino lactones **6** and **6′** in solution, especially in the case of alkylamino derivatives **6/6′a**–**l**, was observed. Most probably, *Z*/*E*-isomerisation of compounds **6** takes place via the enol intermediate **6″**. This explanation is supported by IR data of coordination compounds **7a**–**c**, where the absence of the carbonyl absorption supports the enol tautomeric form. On the other hand, spectra of *N*,*N*-dimethylenaminone **4** and the substitution products **6a**–**w** exhibit absorption at $\nu = 1660$–$1690\,\mathrm{cm}^{-1}$, typical for the conjugate lactone carbonyl group (Scheme 3).

The *E*/*Z*-isomerisation of the isomerically pure isomers **6a** and **6′a** in $CDCl_3$ solution was monitored by ^{1}H NMR for three weeks at 23 °C. In the case of the (*Z*)-isomer **6a**, the equilibrium between **6a** and **6′a** in a ratio *Z*:*E* = 88:12 was reached after one week and then remained unchanged for the next two weeks. On the other hand, after three weeks, the 99% pure (*E*)-isomer **6′a** isomerised into a mixture of **6a** and **6′a** in a ratio *Z*:*E* = 84:16. From the equilibrium ratio of isomers, *Z*:*E* = 88:12, the free energy between the isomers, $\Delta G^0_{296} = 4.9\,\mathrm{kJ\,mol}^{-1}$, was calculated (Fig. 8). These measurements confirm, that the (*Z*)-isomer **6a** is thermodynamically more stable than the (*E*)-isomer **6′a**. However, the *Z*/*E*-equilibrium in solution may vary with solvent and temperature. For example, the (*Z*)-isomer **6a** and the (*E*)-isomer **6′a** were isolated in comparable yields (**6a**:**6′a** = 66:34) upon reaction of **4** with methyl glycinate hydrochloride **5a** in methanol under reflux; these reaction conditions should favour the thermodynamically more stable (*Z*)-isomer **6a**. In order to confirm the dependence of the *Z*/*E*-equilibrium on the solvent and temperature, the more stable (*Z*)-isomer **6a** was heated in methanol under reflux for 5 h after which the methanol was evaporated in vacuo. ^{1}H NMR of the residue, taken in $CDCl_3$, showed that an isomeric mixture of **6a** and **6′a** in a ratio of *Z*:*E* = 64:36 was formed. Upon standing of this sample at 23 °C in $CDCl_3$ for 48 h, the equilibrium ratio was shifted back to *Z*:*E* = 89:11. Increasing the temperature facilitated *E*/*Z*-isomerisation, while at room temperature the equilibrium ratio shifted in favour of the more stable (Z)-isomer **6a**. These experiments also support broad melting point intervals of enaminones **6** (4–9 °C), which indicate *E*/*Z*-isomerisation at elevated temperatures. Broad melting point intervals were also often observed in related enamino compounds.[15–20]



Scheme 3.

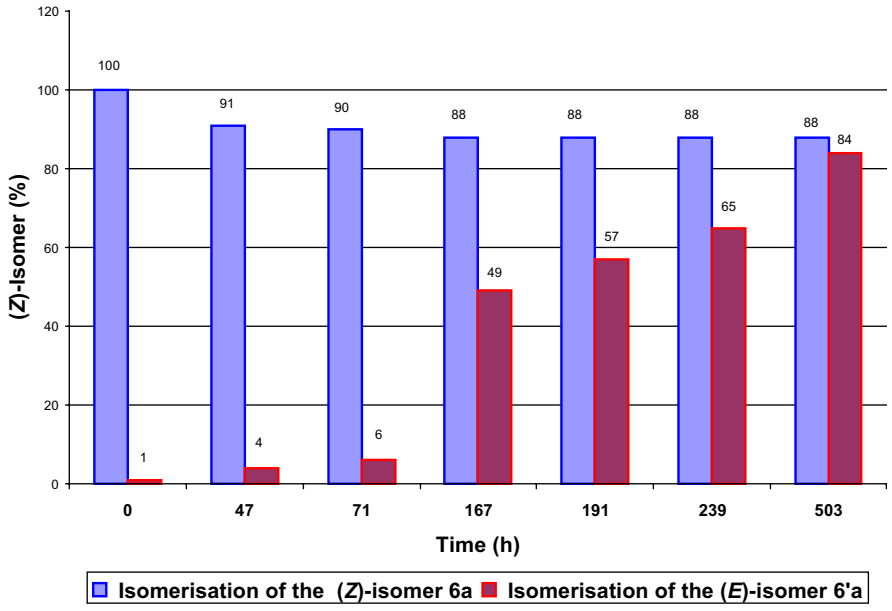
4. Conclusion

Various *N*-substituted (1*R*,5*S*)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **6** and **6′** were prepared in three steps from (1*R*)-(+)-camphor via coupling of (1*R*,4*E*,5*S*)-3-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **4** with aliphatic and (hetero)aromatic primary amines **5**, including optically active α-amino acid esters **5a**–**h**. Most dimethylamine substitution reactions proceeded stereoselectively. The configurations around the exocyclic C=C double bond were dependent on the type of amine **5**. Reactions of **4** with α-amino acid esters **5a**–**h** favoured the formation of the major (*Z*)-isomers **6a**–**h**, while with other amines **5i**–**x**, no specific preference was observed. The structures were determined by NMR and X-ray diffraction. Correlation of configurations around the exocyclic C=C double bond with specific optical rotation angles showed a clear dependence, which means that a specific rotation could be used as quite reliable criterion for determining an (*E*)- and/or (*Z*)-configuration of *N*-substituted (1*R*,5*S*)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones. Structurally, enaminones **6** and **6′** (especially *N*,*N*′-bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}-benzene-1,2-diamine **6w**), are structurally analogous to Jacobsen's and related Salen-ligands, which are used in asymmetric synthesis. From **6w** and palladium(II), copper(II) and nickel(II) acetate, the corresponding coordination compounds **7a**–**c** were prepared.

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



Exp. Nr.	Time (h)	*E*:*Z*	
		From (*Z*)-Isomer **6a**	From (*E*)-Isomer **6'a**
1	0	0:100	99:1
2	47	9:91	96:4
3	71	10:90	94:6
4	167	12:88	51:49
5	191	12:88	43:57
6	239	12:88	35:65
7	503	12:88	16:84

Figure 8. *E*/*Z*-isomerisation of isomers **6a** and **6′a** in $CDCl_3$ solution.

Avance DPX 300 at 300 MHz for ^1H 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 and 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 each run. The *Z*/*E*-ratio of isomers were determined by ^1H NMR.

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

tert-Butoxy-bis(dimethylamino)methane, (+)-camphor **1**, primary amines **5a**–**x**, $Pd(OAc)_2$, $Cu(OAc)_2\times H_2O$ and $Ni(OAc)_2\times 4H_2O$ are commercially available (Fluka AG). A mixture of (1*R*,5*R*)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **2** and (1*R*,5*S*)-1,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one **3** was prepared according to the procedure described.[22]

Sources of chirality: (i) (+)-Camphor **1** (Fluka AG), product number 21300, purum, natural, ⩾97.0% (GC, sum of enantiomers), $[\alpha]_{546}^{20} = +54.5 \pm 2.5$ (*c* 10, EtOH), $[\alpha]_{D}^{20} = +42.5 \pm 2.5$ (*c* 10, EtOH), mp 176–180 °C, ee not specified; (ii) L-alanine methyl ester hydrochloride **5b** (Fluka AG), product number 05200, puriss., ⩾99.0% (AT, dried material), $[\alpha]_{546}^{20} = +9.3 \pm 0.5$ (*c* 2, MeOH), $[\alpha]_{D}^{20} = +7.5 \pm 0.5$ (*c* 2, MeOH), mp 107–110 °C, ee not specified; (iii) L-glutamic acid dimethyl ester hydrochloride **5c** (Fluka AG), product number 49560, puriss., ⩾99.0% (AT, dried material), $[\alpha]_{546}^{20} = +30.5 \pm 1$ (*c* 5, H_2O), $[\alpha]_{D}^{20} = +26.0 \pm 1$ (*c* 5, H_2O), mp ~179 °C (dec.),

ee not specified; (iv) L-serine methyl ester hydrochloride **5d** (Fluka AG), product number 85000, purum, $\geqslant 99.0\%$ (AT), $[\alpha]_{546}^{20} = +6 \pm 0.5$ (*c* 2, MeOH), $[\alpha]_{D}^{20} = +5 \pm 0.5$ (*c* 2, MeOH), mp ~165 °C, ee $\geqslant 98.0$; (v) L-threonine methyl ester hydrochloride **5e** (Fluka AG), product number 89210, purum, $\geqslant 97.0\%$ (AT), $[\alpha]_{546}^{20} = -19 \pm 2$ (*c* 5, 5 M HCl), $[\alpha]_{D}^{20} = -16 \pm 2$ (*c* 5, 5 M HCl), mp and ee not specified; (vi) L-tryptophan methyl ester hydrochloride **5f** (Fluka AG), product number 93730, puriss., $\geqslant 99.0\%$ (AT), $[\alpha]_{546}^{20} = +22 \pm 1$ (*c* 3, MeOH), $[\alpha]_{D}^{20} = +18 \pm 1$ (*c* 3, MeOH), mp ~220 °C (dec.), ee not specified; (vii) L-phenylalanine methyl ester hydrochloride **5g** (Fluka AG), product number 78090, puriss., $\geqslant 99.0\%$ (AT), $[\alpha]_{546}^{20} = +45 \pm 1$ (*c* 2, EtOH), $[\alpha]_{D}^{20} = +38 \pm 1$ (*c* 2, EtOH), mp 158–160 °C, ee not specified; (viii) L-tyrosine methyl ester hydrochloride **5h** (Fluka AG), product number 93930, puriss., $\geqslant 99.0\%$ (AT), $[\alpha]_{546}^{20} = +91 \pm 2$ (*c* 3, pyridine), $[\alpha]_{D}^{20} = +76 \pm 2$ (*c* 3, pyridine), mp ~190 °C (dec.), ee not specified.

5.2. (1*R*,4*E*,5*S*)-3-[(Dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 4

A mixture of compounds **2** (~2350 mg, ~14 mmol) and **3**[22] was dissolved in decalin (40 mL). *tert*-Butoxybis(dimethylamino)methane (5.8 mL, 28 mmol) was added to the solution and the mixture heated under reflux for 13 h. Volatile components were evaporated in vacuo and the residue purified by CC. Elution with CH_2Cl_2 afforded unreacted lactone **3**. This was followed by elution with EtOAc/hexane (2:1) to afford product **4**. Fractions containing the product were combined and evaporated in vacuo to give **4**. Yield: 1340 mg (43%); mp 110–114 °C of a white solid; $[\alpha]_{D}^{21} = +372.9$ (*c* 0.262, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.98, 1.00, 1.27 (9H, 3s, 1:1:1, 3Me); 1.63–1.71 (1H, m, 1H of CH_2); 1.92–2.01 (1H, m, 1H of CH_2); 2.04–2.27 (2H, m, CH_2); 2.87 (1H, br d, $J = 5.3$ Hz, H–C(5)); 3.02 (6H, s, NMe_2); 7.36 (1H, s, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.8, 19.2, 24.0, 31.4, 37.8, 43.7, 43.8, 45.9, 90.3, 99.8, 149.0, 171.1. *m*/*z* (EI) = 223 (M^+); *m*/*z* (HRMS) = 223.157750. (Found: C, 69.83; H, 9.26; N, 6.61. $C_{13}H_{21}NO_2$ requires: C, 69.92; H, 9.48; N, 6.27.); ν_{max} (KBr) 2963, 1682 (C=O), 1589, 1437, 1304, 1246, 1223, 1170, 1099, 1056.

5.3. General procedures for the preparation of *N*-substituted (1*R*,5*S*)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-2-ones 6a–v

Procedure A. Amine hydrochloride **5** (1 mmol) was added to a solution of compound **4** (223 mg, 1 mmol) in either anhydrous methanol (3 mL) or 1-propanol (3 mL) and the mixture stirred at rt–reflux for 5–36 h. In the cases of the reactions with amines **5h**,**i**,**m** and **n**, the precipitate was collected by filtration to give **6h**,**i**,**m** and **n**. In the cases of reactions with amines **5a**–**g**,**j** and **r**, the volatile components were evaporated in vacuo and the residue purified by chromatography (CC, MPLC). Fractions containing the product were combined and evaporated in vacuo to give **6a**–**g**,**j** and **r**.

Procedure B. Compound **4** (223 mg, 1 mmol) was added to a solution of amine **5** (1 mmol) in a mixture of anhydrous methanol (3 mL) or 1-propanol (3 mL) and sulfuric acid (97%, 0.027 mL, 0.5 mmol) and the mixture stirred at rt–reflux for 5–36 h. In the cases of the reactions with amines **5k**,**o**,**p**,**t** and **v**, the precipitate was collected by filtration to give **6k**,**o**,**p**,**t** and **v**. In the cases of the reactions with amines **5l**,**q**,**s** and **u**, the volatile components were evaporated in vacuo and the residue purified by chromatography (CC, MPLC). Fractions containing the product were combined and evaporated in vacuo to give **6l**,**q**,**s** and **u**.

5.3.1. Methyl ({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}amino)acetate 6a and its (*E*)-isomer 6′a.

Prepared from compound **4** and methyl glycinate hydrochloride **5a** in methanol; reflux for 8 h; Procedure A; purification and separation of isomers by CC (EtOAc/hexane, 1:2).

Data for major (Z)-isomer **6a**. 134 mg (50%) of a white solid; mp 105–110 °C; $[\alpha]_{D}^{20} = +2.9$ (*c* 0.456, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.97, 0.98, 1.28 (9H, 3s, 1:1:1, 3Me); 1.56–1.64 (1H, m, 1H of CH_2); 1.89–2.22 (4H, m, 3H of CH_2 and H–C(5)); 3.75 (3H, s, COOMe); 3.87 (2H, d, $J = 6.0$ Hz, CH_2NH); 6.33 (1H, d, $J = 12.4$ Hz, H–C(4′)); 8.09 (1H, br m, NH). ^{13}C NMR ($CDCl_3$): δ 18.8, 18.9, 23.8, 31.9, 38.0, 43.7, 49.5, 50.4, 52.6, 91.5, 100.2, 148.9, 170.1, 170.9. *m*/*z* (EI) 267 (M^+); *m*/*z* (HRMS): 267.147750. (Found: C, 62.92; H, 7.98; N, 5.43. $C_{14}H_{21}NO_4$ requires: C, 62.90; H, 7.92; N, 5.24.); ν_{max} (KBr) 3304, 2961, 1751 (C=O), 1676 (C=O), 1597, 1347, 1206, 1138, 1067 cm^{-1}.

Data for minor (4E)-isomer **6′a**. 69 mg (26%) of a white solid; mp 136–142 °C; $[\alpha]_{D}^{20} = +118.3$ (*c* 0.240, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.99, 1.01, 1.29 (9H, 3s, 1:1:1, 3Me); 1.54–1.61 (1H, m, 1H of CH_2); 1.96–2.21 (1H, m, 3H of CH_2); 2.37 (1H, d, $J = 4.9$ Hz, H–C(5)); 3.78 (3H, s, COOMe); 3.95 (2H, d, $J = 5.7$ Hz, CH_2NH); 4.52 (1H, br m, NH); 7.23 (1H, d, $J = 13.9$ Hz, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.5, 19.2, 23.8, 29.3, 37.5, 43.9, 44.9, 49.2, 52.8, 90.8, 103.9, 145.0, 169.3, 171.0. (Found: C, 62.74; H, 8.09; N, 5.24. $C_{14}H_{21}NO_4$ requires: C, 62.90; H, 7.92; N, 5.24.); ν_{max} (KBr) 3301, 2982, 1746, 1729 (C=O), 1690 (C=O), 1578, 1299, 1264, 1220, 1172, 1136, 1055 cm^{-1}.

5.3.2. Methyl (2*S*)-2-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}-amino)propanoate 6b and its (*E*)-isomer 6′b.

Prepared from compound **4** and methyl L-alaninate hydrochloride **5b** in methanol; reflux for 7 h; Procedure A; purification and separation of isomers by CC (EtOAc/hexane, 1:3).

Data for major (Z)-isomer **6b**. 102 mg (36%) of a white solid; mp 140–145 °C; $[\alpha]_{D}^{22} = +38.1$ (*c* 0.210, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.95, 0.98, 1.27 (9H, 3s, 1:1:1, 3Me); 1.46 (3H, d, $J = 7.2$ Hz, Me); 1.55–1.63 (1H, m, 1H of CH_2); 1.88–2.22 (4H, m, 3H of CH_2 and H–C(5)); 3.74 (3H, s, COOMe); 3.83–3.93 (1H, dq, $J = 7.2$,

14.3 Hz, C*H*COOMe); 6.39 (1H, d, $J = 12.4$ Hz, H–C(4′)); 8.10 (1H, br dd, $J = 9.1$, 10.2 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.8, 18.9, 19.3, 23.8, 32.0, 38.0, 43.7, 50.5, 52.8, 56.1, 91.4, 99.9, 147.1, 170.0, 173.3. m/z (EI) 281 (M^+); m/z (HRMS): 281.163550. (Found: C, 64.02; H, 8.44; N, 5.03. $C_{15}H_{23}NO_4$ requires: C, 64.03; H, 8.24; N, 4.98.); ν_{max} (KBr) 3315, 2976, 1745 (C=O), 1674 (C=O), 1595, 1389, 1316, 1211, 1134 cm^{-1}.

Data for minor (E)-isomer **6′b**. 66 mg (23%) of a white solid; mp 109–117 °C; $[\alpha]_D^{28} = +131.4$ (c 0.172, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.99, 1.01, 1.29 (9H, 3s, 1:1:1, 3Me); 1.46 (3H, d, $J = 7.2$ Hz, Me); 1.51–1.57 (1H, m, 1H of CH_2); 1.95–2.20 (3H, m, 3H of CH_2); 2.37 (1H, d, $J = 4.5$ Hz, H–C(5)); 3.77 (3H, s, COOMe); 3.93–4.03 (1H, dq, $J = 7.2$, 14.3 Hz, C*H*COOMe); 4.70 (1H, dd, $J = 7.5$, 13.2 Hz, NH); 7.29 (1H, d, $J = 13.9$ Hz, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.5, 19.2, 20.4, 23.8, 29.2, 37.5, 43.9, 44.9, 53.0, 55.6, 90.8, 103.8, 143.3, 169.3, 173.9. (Found: C, 64.16; H, 8.52; N, 5.13. $C_{15}H_{23}NO_4$ requires: C, 64.03; H, 8.24; N, 4.98.); ν_{max} (KBr) 3289, 2982, 1753, 1733 (C=O), 1690 (C=O), 1578, 1383, 1258, 1168, 1142, 1064 cm^{-1}.

5.3.3. Dimethyl (2*S*)-2-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}-amino)pentane-1,5-dioate 6c and its (*E*)-isomer 6′c. Prepared from compound **4** and dimethyl L-glutamate hydrochloride **5c** in methanol; reflux for 7 h; Procedure A; purification and separation of isomers by CC (EtOAC/hexane, 1:2) followed by purification of **6c** and **6′c** by MPLC [EtOAc/hexane, 1:3 (**6c**), 1:0 (**6′c**)].

Data for major (Z)-isomer **6c**. 145 mg (45%) of a colourless oil; $[\alpha]_D^{25} = -19.6$ (c 0.260, $CHCl_3$); **6c**:**6′c** = 84:16. ^{1}H NMR ($CDCl_3$): δ 0.95, 0.98, 1.27 (9H, 3s, 1:1:1, 3Me); 1.54–1.62 (1H, m, 1H of CH_2); 1.89–2.25 (6H, m, 5H of CH_2 and H–C(5)); 2.41 (2H, t, $J = 7.2$ Hz, CH_2); 3.68 and 3.75 (6H, 2s, 1:1, 2×COOMe); 3.85 (1H, ddd, $J = 5.7$, 8.7, 14.3 Hz, C*H*COOMe); 6.35 (1H, d, $J = 12.4$ Hz, H–C(4′)); 8.09 (1H, br dd, $J = 9.0$, 11.7 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.9, 23.8, 28.7, 30.2, 31.9, 38.0, 43.7, 50.4, 52.2, 52.8, 60.2, 91.5, 100.4, 147.2, 170.0, 172.2, 173.2. m/z (EI) 353 (M^+); m/z (HRMS): 353.184950. (Found: C, 60.42; H, 7.93; N, 4.20. $C_{18}H_{27}NO_6$ requires: C, 61.17; H, 7.70; N, 3.96.); ν_{max} (KBr) 3302, 2955, 1738 (C=O), 1674 (C=O), 1607, 1438, 1378, 1213, 1134 cm^{-1}.

Data for minor (E)-isomer **6′c**. 42 mg (12%) of a white solid; mp 115–120 °C; $[\alpha]_D^{25} = +81.1$ (c 0.106, $CHCl_3$); **6′c**:**6c** = 100:0. ^{1}H NMR ($CDCl_3$): δ 0.98, 1.01, 1.29 (9H, 3s, 1:1:1, 3Me); 1.49–1.55 (1H, m, 1H of CH_2); 1.97–2.24 (5H, m, 5H of CH_2); 2.32–2.50 (3H, m, CH_2 and H–C(5)); 3.69 and 3.77 (6H, 2s, 1:1, 2×COOMe); 3.94 (1H, ddd, $J = 5.3$, 8.3, 14.6 Hz, C*H*COOMe); 4.68 (1H, dd, $J = 8.3$, 13.6 Hz, NH); 7.21 (1H, d, $J = 13.6$ Hz, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.5, 19.2, 23.8, 28.8, 29.2, 30.1, 37.5, 44.0, 45.0, 52.3, 53.1, 59.9, 90.9, 104.5, 143.7, 169.2, 172.9, 173.4. (Found: C, 61.44; H, 8.00; N, 3.87. $C_{18}H_{27}NO_6$ requires: C, 61.17; H, 7.70; N, 3.96.); ν_{max} (KBr) 3277, 2982, 1751 (C=O), 1730 (C=O), 1687 (C=O), 1579, 1331, 1272, 1246, 1227, 1199, 1169, 1132, 1054 cm^{-1}.

5.3.4. Methyl (2*S*)-3-hydroxy-2-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}-amino)propanoate 6d. Prepared from compound **4** and methyl L-serinate hydrochloride **5d** in methanol; reflux for 7 h; Procedure A; purification and separation of isomers by CC (EtOAc) followed by MPLC (EtOAc/hexane, 3:1); 229 mg (77%) of a white solid; mp 170–174 °C; $[\alpha]_D^{21} = +3.0$ (c 0.164, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.95, 0.98, 1.28 (9H, 3s, 1:1:1, 3Me); 1.55–1.65 (1H, m, 1H of CH_2); 1.90–2.22 (4H, m, 3H of CH_2 and H–C(5)); 2.40–2.44 (1H, m, OH); 3.78 (3H, s, COOMe); 3.84–3.95 (3H, m, C*H*C*H*$_2$OH); 6.41 (1H, d, $J = 12.1$ Hz, H–C(4′)); 8.15–8.28 (1H, m, NH). ^{13}C NMR ($CDCl_3$): δ 18.8, 18.9, 23.8, 32.0, 38.0, 43.7, 54.4, 52.9, 63.0, 63.8, 91.6, 100.3, 148.0, 170.2, 171.3. m/z (EI) 297 (M^+); m/z (HRMS): 297.158510. (Found: C, 60.53; H, 8.03; N, 5.09. $C_{15}H_{23}NO_5$ requires: C, 60.59; H, 7.80; N, 4.71.); ν_{max} (KBr) 3512, 3329, 2972, 2940, 1732 (C=O), 1676 (C=O), 1596, 1456, 1391, 1322, 1217, 1166, 1136, 1067 cm^{-1}.

5.3.5. Methyl (2*S*,3*R*)-3-hydroxy-2-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}-amino)butanoate 6e and its (*E*)-isomer 6′e. Prepared from compound **4** and methyl L-threoninate hydrochloride **5e** in methanol; reflux for 7 h; Procedure A; purification and separation of isomers by CC [EtOAc/hexane, 1:1 (**6e**), 2:1 (**6′e**)].

Data for major (Z)-isomer **6e**. 172 mg (55%) of a white solid; mp 139–144 °C; $[\alpha]_D^{22} = -5.1$ (c 0.214, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.95 and 0.98 (6H, 2s, 1:1, 2Me); 1.22 (3H, d, $J = 6.0$ Hz, CHC*H*$_3$); 1.28 (3H, s, Me); 1.55–1.63 (1H, m, 1H of CH_2); 1.89–2.22 (4H, m, 3H of CH_2 and H–C(5)); 2.47 (1H, d, $J = 5.3$ Hz, OH); 3.61 (1H, dd, $J = 4.5$, 9.4 Hz, C*H*COOMe); 3.78 (3H, s, COOMe); 4.11–4.21 (1H, m, C*H*OH); 6.38 (1H, d, $J = 12.4$ Hz, H–C(4′)); 8.25 (1H, br t, $J = 10.6$, 11.3 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.9, 19.7, 23.8, 31.8, 38.0, 43.7, 50.4, 52.9, 67.3, 68.8, 91.6, 100.2, 148.3, 170.1, 171.4. m/z (EI) 311 (M^+); m/z (HRMS): 311.174450. (Found: C, 61.56; H, 8.25; N, 4.68. $C_{16}H_{25}NO_5$ requires: C, 61.72; H, 8.09; N, 4.50.); ν_{max} (KBr) 3469, 3352, 2974, 1737 (C=O), 1676 (C=O), 1567, 1393, 1264, 1219, 1138, 1069 cm^{-1}.

Data for minor (E)-isomer **6′e**. 92 mg (29%) of a white solid; mp 110–115 °C; $[\alpha]_D^{22} = +92.2$ (c 0.370, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.99, 1.01 (6H, 2s, 1:1, 2Me); 1.26 (3H, d, $J = 6.4$ Hz, CHC*H*$_3$); 1.29 (3H, s, Me); 1.52–1.58 (1H, m, 1H of CH_2); 1.95–2.21 (3H, m, 3H of CH_2); 2.38 (1H, d, $J = 4.9$ Hz, OH); 2.43 (1H, d, $J = 4.9$ Hz, H–C(5)); 3.75 (1H, dd, $J = 2.6$, 9.4 Hz, C*H*COOMe); 3.79 (3H, s, COOMe); 4.24–4.33 (1H, m, C*H*OH); 4.93 (1H, dd, $J = 9.4$, 13.9 Hz, NH); 7.24 (1H, d, $J = 14.3$ Hz, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.5, 19.1, 20.2, 23.7, 29.4, 37.5, 43.8, 44.7, 52.9, 66.5, 68.5, 91.1, 103.2, 146.0, 170.0, 172.1. m/z (EI) = 311 (M^+); m/z (HRMS) =

311.174140. (Found: 62.07; H, 7.93; N, 4.38. $C_{16}H_{25}NO_5$ requires: C, 61.72; H, 8.09; N, 4.50.); ν_{max} (KBr) 3406, 3290, 2985, 1753 (C=O), 1682 (C=O), 1570, 1272, 1196, 1169, 1142, 1101, 1092, 1057, 1011 cm^{-1}.

5.3.6. Methyl (2*S*)-3-(1*H*-indol-3-yl)-2-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]-methyl}amino)propanoate 6f and its (*E*)-isomer 6′f. Prepared from compound **4** and methyl L-tryptophanate hydrochloride **5f** in 1-propanol; reflux for 5 h; Procedure A; purification and separation of isomers by CC (EtOAc/hexane, 1:2).

Data for major (Z)-isomer **6f**. 142 mg (36%) of a white solid; mp 66–73 °C; $[\alpha]_D^{22} = -120.2$ (*c* 0.252, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 0.85, 0.92, 1.25 (9H, 3s, 1:1:1, 3Me); 1.47–1.54 (1H, m, 1H of CH_2); 1.84–2.16 (4H, m, 3H of CH_2 and H–C(5)); 3.15 (1H, dd, $J = 8.3$, 14.3 Hz, 1H of CH_2); 3.35 (1H, dd, $J = 4.5$, 14.3 Hz, 1H of CH_2); 3.71 (3H, s, COOMe); 4.01–4.08 (1H, ddd, $J = 4.9$, 8.3, 13.2 Hz, C*H*COOMe); 6.10 (1H, d, $J = 12.4$ Hz, H–C(4′)); 7.05–7.21 (3H, m, 3H of Ar); 7.36 (1H, d, $J = 7.9$ Hz, 1H of Ar); 7.57 (1H, d, $J = 7.9$ Hz, 1H of Ar); 8.26 (1H, s, NH); 8.29 (1H, dd, $J = 9.4$, 11.7 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.7, 18.9, 23.8, 30.4, 31.9, 38.0, 43.5, 50.3, 52.8, 61.8, 91.4, 99.2, 110.0, 111.8, 118.7, 119.9, 122.4, 124.3, 127.4, 136.7, 147.8, 170.1, 172.5. *m/z* (EI) 396 (M^+); *m/z* (HRMS): 396.206150. (Found: C, 69.42; H, 7.28; N, 7.19. $C_{23}H_{28}N_2O_4$ requires: C, 69.67; H, 7.12; N, 7.07.); ν_{max} (KBr) 3389, 2956, 1745 (C=O), 1669 (C=O), 1598, 1379, 1218, 1134, 1067, 742 cm^{-1}.

Data for minor (E)-isomer **6′f**. 68 mg (17%) of a white solid; mp 75–80 °C; $[\alpha]_D^{28} = +109.0$ (*c* 0.122, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.93, 1.26 (9H, 2s, 2:1, 2Me); 1.36–1.43 (1H, m, 1H of CH_2); 1.88–2.20 (4H, m, 3H of CH_2 and H–C(5)); 3.30 (1H, d, $J = 5.7$ Hz, 1H of CH_2); 3.71 (3H, s, COOMe); 4.20–4.26 (1H, ddd, $J = 5.3$, 8.3, 10.9 Hz, C*H*COOMe); 4.71 (1H, dd, $J = 8.7$, 13.6 Hz, NH); 6.96 (1H, d, $J = 2.6$ Hz, 1H of Ar); 7.08–7.22 (2H, m, 2H of Ar); 7.28 (1H, d, $J = 13.3$ Hz, H–C(4′)); 7.35–7.38 (1H, m, 1H of Ar); 7.51 (1H, d, $J = 7.9$ Hz, 1H of Ar); 8.15 (1H, s, NH). ^{13}C NMR ($CDCl_3$): δ 18.5, 19.2, 23.6, 29.3, 30.1, 37.6, 43.9, 44.7, 52.9, 61.4, 90.9, 103.2, 109.5, 111.9, 118.8, 120.0, 122.6, 123.5, 127.9, 136.6, 144.0, 169.6, 172.7. (Found: C, 69.59; H, 7.40; N, 6.86. $C_{23}H_{28}N_2O_4$ requires: C, 69.67; H, 7.12; N, 7.07.); ν_{max} (KBr) 3409, 2959, 1740 (C=O), 1683 (C=O), 1600, 1458, 1383, 1272, 1199, 1167, 1133, 1055 cm^{-1}.

5.3.7. Methyl (2*S*)-3-phenyl-2-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}amino)propanoate 6g and its (*E*)-isomer 6′g. Prepared from compound **4** and methyl L-3-phenylalaninate hydrochloride (**5g**) in methanol; reflux for 7 h; Procedure A; purification and separation of isomers by CC (EtOAc/hexane, 1:4).

Data for major (Z)-isomer **6g**. 153 mg (43%) of a white solid; mp 100–109 °C; $[\alpha]_D^{21} = -153.4$ (*c* 0.088, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 0.86, 0.92, 1.25 (9H, 3s, 1:1:1, 3Me); 1.48–1.55 (1H, m, 1H of CH_2); 1.84–2.16 (4H, m, 3H of CH_2 and H–C(5)); 2.94 (1H, dd, $J = 9.0$, 13.6 Hz, 1H of CH_2); 3.16 (1H, dd, $J = 5.3$, 13.9 Hz, 1H of CH_2); 3.74 (3H, s, COOMe); 3.87–3.95 (1H, ddd, $J = 4.9$, 9.01, 13.9 Hz, C*H*COOMe); 6.00 (1H, d, $J = 12.4$ Hz, H–C(4′)); 7.14–7.30 (5H, m, Ph); 8.25 (1H, br dd, $J = 9.8$, 11.7 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.9, 18.9, 23.8, 31.8, 38.0, 40.7, 43.6, 50.3, 52.8, 63.4, 91.3, 99.5, 127.4, 129.0, 129.9, 136.7, 147.3, 170.0, 172.0. *m/z* (EI) 357 (M^+); *m/z* (HRMS): 357.195250. (Found: C, C, 70.60; H, 7.74; N, 4.15. $C_{21}H_{27}NO_4$ requires: C, 70.56; H, 7.61; N, 3.92.); ν_{max} (KBr) 3283, 2974, 1732 (C=O), 1676 (C=O), 1611, 1389, 1219, 1135, 1065 cm^{-1}.

Data for minor (E)-isomer **6′g**. 61 mg (17%) of a white solid; mp 122–128 °C; $[\alpha]_D^{28} = +129.5$ (*c* 0.156, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.95, 0.98, 1.28 (9H, 3s, 1:1:1, 3Me); 1.41–1.50 (1H, m, 1H of CH_2); 1.94–2.20 (3H, m, 3H of CH_2); 2.27 (1H, d, $J = 4.9$ Hz, H–C(5)); 3.03–3.15 (2H, m, CH_2); 3.75 (3H, s, COOMe); 4.18 (1H, ddd, $J = 5.7$, 8.3, 11.7 Hz, H–C(6′)); 4.57 (1H, br dd, $J = 8.30$, 13.6 Hz, NH); 7.05–7.08 (2H, m, 2H of Ph); 7.20–7.32 (4H, m, 3H of Ph and H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.5, 19.2, 23.7, 29.2, 37.5, 40.5, 43.9, 44.8, 52.8, 61.3, 90.8, 103.8, 127.7, 129.0, 129.7, 135.5, 143.4, 169.2, 172.3. *m/z* (EI) = 357 (M^+); *m/z* (HRMS) = 357.195240. (Found: C, 70.83; H, 7.76; N, 3.92. $C_{23}H_{28}N_2O_4$ requires: C, 70.56; H, 7.61; N, 3.92.); ν_{max} (KBr) 3267, 2982, 1742 (C=O), 1687 (C=O), 1567, 1385, 1255, 1171, 1133, 1054 cm^{-1}.

5.3.8. Methyl (2*S*)-3-(4-hydroxyphenyl)-2-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]-methyl}amino)propanoate 6h and its (*E*)-isomer 6′h. Prepared from compound **4** and methyl L-tyrosinate hydrochloride (**5h**) in 1-propanol; reflux for 5 h; Procedure A; 231 mg (62%) of a white solid; **6h**:**6′h** = 92:8; mp 218–223 °C; $[\alpha]_D^{22} = -97.6$ (*c* 0.332, DMSO). *m/z* (EI) 373 (M^+); *m/z* (HRMS): 373.190020. (Found: C, 67.26; H, 7.43; N, 3.74. $C_{21}H_{27}NO_5$ requires: C, 67.54; H, 7.29; N, 3.75.); ν_{max} (KBr) 3443, 3128, 2972, 1732 (C=O), 1660 (C=O), 1571, 1458, 1389, 1326, 1278, 1228, 1142, 1067 cm^{-1}.

NMR data for major (Z)-isomer **6h**. ^1H NMR ($CDCl_3$): δ 0.81, 0.91, 1.16 (9H, 3s, 1:1:1, 3Me); 1.36–1.42 (1H, m, 1H of CH_2); 1.90–2.04 (4H, m, 3H of CH_2, 1H of H–C(5)); 2.83 (1H, dd, $J = 7.2$, 13.6 Hz, 1H of CH_2); 2.94 (1H, dd, $J = 5.3$, 13.6 Hz, 1H of CH_2); 3.66 (3H, s, COOMe); 4.20–4.27 (1H, m, C*H*COOMe); 6.47 (1H, d, $J = 12.8$ Hz, H–C(4′)); 6.60–6.66 (2H, m, 2H of Ar); 6.85–6.91 (2H, m, 2H of Ar); 8.00 (1H, dd, $J = 9.0$, 12.4 Hz, NH); 9.22 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 19.0, 19.3, 23.8, 32.3, 38.1, 39.4, 43.4, 49.9, 52.9, 61.8, 90.7, 98.7, 115.9, 126.9, 131.2, 148.6, 157.0, 169.1, 172.6.

NMR data for minor (E)-isomer **6′h**. ^1H NMR ($CDCl_3$): δ 0.84, 0.94, 1.14 (9H, 3s, 1:1:1, 3Me); 3.64 (3H, s, COOMe); 6.97–7.02 (2H, m, 2H of Ar); 9.19 (1H, s, OH).

5.3.9. 2-({(*E*)-[(1*R*,5*S*)-1,8,8-Trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}amino)acetonitrile 6i and its (*Z*)-isomer 6′i. Prepared from compound **4** and aminoacetonitrile hydrochloride **5i** in methanol; stirring at rt for 36 h; Procedure A; 79 mg (34%) of a white solid; **6i**:**6′i** = 92:8; mp 195–201 °C (from MeOH); $[\alpha]_D^{22} = +120.5$ (*c* 0.224, CH_2Cl_2). (Found: C, 66.90; H, 7.83; N, 12.10. $C_{13}H_{18}N_2O_2$ requires: C, 66.64; H, 7.74; N, 11.96.); ν_{max} (KBr) 3269, 2974, 2245 (C≡N), 1692 (C=O), 1586, 1302, 1219, 1171, 1135, 1001, 1052 cm^{-1}.

NMR data for major (E)-isomer **6i**. ^{1}H NMR (DMSO-d_6): δ 0.85, 0.95, 1.17 (9H, 3s, 1:1:1, 3Me); 1.30–1.44 (1H, m, 1H of CH_2); 1.85–2.09 (3H, m, 3H of CH_2); 2.56 (1H, br s, H–C(5)); 4.30 (2H, d, $J = 5.7$ Hz, CH_2CN); 6.88–6.96 (1H, m, NH); 7.15 (1H, d, $J = 13.6$ Hz, H–C(4′)). ^{13}C NMR (DMSO-d_6): δ 18.8, 19.5, 23.8, 29.9, 36.0, 37.7, 43.6, 44.5, 90.4, 104.3, 119.3, 145.4, 167.9.

NMR data for minor (Z)-isomer **6′i**. ^{1}H NMR (DMSO-d_6): δ 2.21 (1H, d, $J = 5.3$ Hz, H–C(5)); 4.23 (2H, d, $J = 6.0$ Hz, CH_2CN); 6.66 (1H, d, $J = 12.4$ Hz, H–C(4′)); 7.84–7.95 (1H, m, NH).

5.3.10. Ethyl 3-({(*Z*)-[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}amino)propanoate 6j and its (*E*)-isomer 6′j. Prepared from compound **4** and ethyl β-alaninate hydrochloride **5j** in 1-propanol; reflux for 6 h; Procedure A; purification by CC (EtOAc/hexane, 1:3); 228 mg (77%) of a colourless oil; **6j**:**6′j** = 77:23; $[\alpha]_D^{25} = +18.0$ (*c* 0.538, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 14.5, 18.5, 18.7, 18.9, 19.2, 23.7, 23.8, 29.4, 32.2, 36.1, 36.7, 37.5, 38.0, 43.5, 43.7, 44.4, 44.5, 44.7, 50.3, 61.1, 61.2, 90.4, 91.1, 98.0, 101.7, 146.1, 149.7, 169.5, 170.2, 171.7, 172.3. $m/z = 295$ (M^+); m/z (HRMS) = 295.179260. (Found: C, 64.99; H, 8.81; N, 4.52. $C_{16}H_{25}NO_4$ requires: C, 65.06; H, 8.53; N, 4.74.); ν_{max} (KBr) 3310, 2979, 1732 (C=O), 1673 (C=O), 1607, 1446, 1376, 1198, 1132 cm^{-1}.

NMR data for major (Z)-isomer **6j**. ^{1} H NMR ($CDCl_3$): δ 0.94, 0.97, 1.26 (9H, 3s, 1:1:1, 3Me); 1.27 (3H, t, $J = 7.2$ Hz, CH_2CH_3); 1.52–1.59 (1H, m, 1H of CH_2); 1.87–2.20 (4H, m, 3H of CH_2 and H–C(5)); 2.53 (2H, t, $J = 6.6$ Hz, CH_2); 3.43 (2H, deg q, $J = 6.6$ Hz, CH_2); 4.15 (2H, q, $J = 7.2$ Hz, CH_2CH$_3$); 6.43 (1H, d, $J = 12.4$ Hz, H–C(4′)); 8.00 (1H, br m, NH).

NMR data for minor (E)-isomer **6′j**. ^{1}H NMR ($CDCl_3$): δ 4.77 (1H, br m, NH); 7.32 (1H, d, $J = 12.3$ Hz, H–C(4′)).

5.3.11. (1*R*,4*E*,5*S*)-4-({[(1-Adamantyl)methyl]amino}-methylidene)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6k. Prepared from compound **4** and (1-adamantyl)methylamine hydrogensulfate **5k** in methanol; reflux for 7 h; Procedure B; 148 mg (43%) of a white solid; mp 170–180 °C; $[\alpha]_D^{19} = +30.8$ (*c* 0.013, DMSO). ^{1}H NMR (DMSO-d_6): δ 0.85, 0.94, 1.14 (9H, 3s, 1:1:1, 3Me); 1.35–1.45 (7H, m, 1H of CH_2 and 6H of adamantane); 1.50–1.72 (6H, m, 6H of adamantane); 1.88–2.06 (6H, m, 3H of CH_2 and 3H of adamantane); 2.62–2.67 (1H, m, H–C(5)); 2.73 (2H, d, $J = 6.4$ Hz, CH_2); 6.47–6.61 (1H, m, NH); 7.00 (1H, d, $J = 13.9$ Hz, H–C(4′)). $m/z = 343$ (M^+); m/z (HRMS) = 343.252550. (Found: C, 76.53; H, 9.93; N, 4.16. $C_{22}H_{33}NO_2$ requires: C, 76.92; H, 9.68; N, 4.08.); ν_{max} (KBr) 3299, 2898, 1687 (C=O), 1580, 1439, 1271, 1207, 1169, 1127, 1076, 1053 cm^{-1}.

5.3.12. (1*R*,4*Z*,5*S*)-4-{[(Prop-1-yn-3-yl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6l and its (*E*)-isomer 6′l. Prepared from compound **4** and 3-aminoprop-1-yne hydrogensulfate **5l** in methanol; reflux for 4 h; Procedure B; purification and separation of isomers by CC [EtOAc/hexane, 1:3 (**6l**), 2:1 (**6′l**)].

Data for major (Z)-isomer **6l**. 107 mg (46%) of a white solid; mp 110–115 °C; $[\alpha]_D^{21} = 0$ (*c* 0.158, CH_2Cl_2); **6l**:**6′l** = 100:0. ^{1}H NMR ($CDCl_3$): δ 0.96, 0.98, 1.28 (9H, 3s, 1:1:1, 3Me); 1.55–1.63 (1H, m, 1H of CH_2); 1.90–2.22 (4H, m, 3H of CH_2 and H–C(5)); 2.32 (1H, t, $J = 2.6$ Hz, *H*–C≡C); 3.91 (2H, dd, $J = 2.3$, 5.3 Hz, C≡C–CH_2); 6.50 (1H, d, $J = 12.4$ Hz, H–C(4′)); 7.97 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 18.3, 18.5, 23.3, 31.6, 36.7, 37.5, 43.1, 49.9, 72.8, 79.4, 91.0, 99.5, 147.4, 169.7. (Found: C, 71.84; H, 8.43; N, 6.05. $C_{14}H_{19}NO_2$ requires: C, 72.07; H, 8.21; N, 6.00). m/z (EI) = 233 (M^+); m/z (HRMS) = 233.142210. ν_{max} (KBr) 3235, 2974, 2114 (C≡C),1670 (C=O), 1596, 1384, 1213, 1161, 1137, 1063 cm^{-1}.

Data for minor (E)-isomer **6′l**. 54 mg (23%) of a white solid; mp 165–175 °C (sublimation at $T > 140$ °C); $[\alpha]_D^{21} = +130.6$ (*c* 0.170, CH_2Cl_2); **6l**:**6′l** = 4:96. ^{1}H NMR ($CDCl_3$): δ 0.99, 1.00, 1.29 (9H, 3s, 1:1:1, 3Me); 1.52–1.58 (1H, m, 1H of CH_2); 1.95–2.21 (3H, m, 3H of CH_2); 2.30 (1H, d, $J = 4.9$ Hz, H–C(5)); 2.34 (1H, t, $J = 2.6$ Hz, *H*–C≡C); 3.94 (2H, dd, $J = 2.3$, 5.3 Hz, C≡C–CH_2); 4.24 (1H, br s, NH); 7.33 (1H, d, $J = 14.3$ Hz, H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.2, 18.7, 23.4, 28.9, 37.1, 37.2, 43.5, 44.5, 72.9, 79.5, 90.3, 103.4, 144.4, 168.8. (Found: C, 72.03; H, 8.49; N, 5.96. $C_{14}H_{19}NO_2$ requires: C, 72.07; H, 8.21; N, 6.00). ν_{max} (KBr) 3228, 2962, 2113 (C≡C), 1687 (C=O), 1563, 1302, 1216, 1171, 1132, 1081 cm^{-1}.

5.3.13. (1*R*,4*E*,5*S*)-4-(Anilinomethylidene)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6m. Prepared from compound **4** and aniline hydrochloride **5m** in methanol; stirring at rt for 26 h; Procedure A; purification of the precipitate by CC (EtOAc/hexane, 1:1 → 2:1); 182 mg (67%) of a pale grey solid; mp 219–226 °C (MeOH); $[\alpha]_D^{22} = +188.2$ (*c* 0.068, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.91, 1.01, 1.21 (9H, 3s, 1:1:1, 3Me); 1.41–1.50 (1H, m, 1H of CH_2); 1.92–2.18 (3H, m, 3H of CH_2); 2.97 (1H, d, $J = 4.9$ Hz, H–C(5)); 6.89–6.95 (1H, m, 1H of Ph); 7.09–7.13 (2H, m, 2H of Ph); 7.24–7.30 (2H, m, 2H of Ph); 7.70 (1H, d, $J = 13.6$ Hz, H–C(4′)); 8.82 (1H, d, $J = 13.2$ Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.9, 19.5, 23.8, 29.9, 37.7, 43.8, 44.7, 90.9, 106.8, 115.8, 122.2, 130.3,

137.0, 142.8, 168.1. m/z (EI) = 271 (M^+); m/z (HRMS) = 271.158050. (Found: C, 74.98; H, 7.80; N, 5.43. $C_{17}H_{21}NO_2$ requires: C, 75.25; H, 7.80; N, 5.16.); ν_{max} (KBr) 3299, 3276, 1693 (C=O), 1602, 1576, 1497, 1256, 1201, 1059 cm^{-1}.

5.3.14. (1*R*,4*E*,5*S*)-4-{[(4-Methylphenyl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6n. Prepared from compound **4** and 4-methylaniline hydrochloride **5n** in methanol; stirring at rt for 26 h; Procedure A; 114 mg (41%) of a white solid; mp 225–229 °C (MeOH); $[\alpha]_D^{22} = +183.5$ (c 0.242, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.90, 1.00, 1.20 (9H, 3s, 1:1:1, 3Me); 1.40–1.49 (1H, m, 1H of CH_2); 1.91–2.17 (3H, m, 3H of CH_2); 2.22 (3H, s, Me); 2.94 (1H, d, J = 4.9 Hz, H–C(5)); 7.00 (2H, m, 2H of Ar); 7.08 (2H, m, 2H of Ar); 7.66 (1H, d, J = 13.6 Hz, H–C(4′)); 8.75 (1H, d, J = 13.2 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 19.0, 19.2, 21.1, 23.8, 32.1, 38.1, 43.7, 49.8, 91.7, 102.4, 115.9, 130.8, 131.5, 139.1, 140.9, 169.4. (Found: C, 75.87; H, 8.26; N, 4.55. $C_{18}H_{23}NO_2$ requires: C, 75.76; H, 8.12; N, 4.91.); ν_{max} (KBr) 3298, 3271, 1690 (C=O), 1602, 1572, 1255, 1171, 1124, 1057 cm^{-1}.

5.3.15. (1*R*,4*E*,5*S*)-4-{[(4-Methoxyphenyl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6o. Prepared from compound **4** and 4-methoxyaniline **5o** in methanol; stirring at rt for 26 h; Procedure B; 88 mg (29%) of a pale blue solid; mp 201–208 °C (MeOH); $[\alpha]_D^{22} = +193.6$ (c 0.202, DMF). ^{1}H NMR (DMSO-d_6): δ 0.90, 1.00, 1.20 (9H, 3s, 1:1:1, 3Me); 1.40–1.49 (1H, m, 1H of CH_2); 1.91–2.16 (3H, m, 3H of CH_2); 2.91 (1H, d, J = 4.5 Hz, H–C(5)); 3.07 (3H, s, OMe); 6.85–6.88 (2H, m, 2H of Ar); 7.02–7.06 (2H, m, 2H of Ar); 7.61 (1H, d, J = 13.6 Hz, H–C(4′)); 8.70 (1H, d, J = 13.6 Hz, NH). ^{13}C NMR (DMSO-d_6): δ 18.9, 19.5, 23.8, 30.0, 37.7, 43.7, 44.7, 56.1, 90.6, 105.3, 115.6, 117.2, 136.3, 138.1, 155.2, 168.2. (Found: C, 71.60; H, 7.66; N, 4.44. $C_{18}H_{23}NO_3$ requires: C, 71.73; H, 7.69; N, 4.65.); ν_{max} (KBr) 3300, 3277, 1692 (C=O), 1603, 1575, 1518, 1258, 1171, 1054 cm^{-1}.

5.3.16. (1*R*,4*E*,5*S*)-4-{[(4-Nitrophenyl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6p and its (*Z*)-isomer 6′p. Prepared from compound **4** and 4-nitroaniline **5p** in methanol; stirring at rt for 26 h; Procedure B; 140 mg (44%) of a yellow solid; mp 262–266 °C (MeOH); $[\alpha]_D^{22} = +142.0$ (c 0.150, MeOH); **6p**:**6′p** = 68:32. (Found: C, 64.79; H, 6.49; N, 8.56. $C_{17}H_{20}N_2O_4$ requires: C, 64.54; H, 6.37; N, 8.86.); ν_{max} (KBr) 2972, 1688 (C=O), 1618, 1582, 1381, 1331, 1258, 1198, 1165, 1059, 1055 cm^{-1}.

NMR data for major (E)-isomer **6p**. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.02, 1.23 (9H, 3s, 1:1:1, 3Me); 1.41–1.59 (1H, m, 1H iz CH_2); 1.94–2.20 (3H, m, 3H of CH_2); 3.06 (1H, d, J = 4.9 Hz, H–C(5)); 7.29–7.32 (2H, m, 2H of Ar); 7.74 (1H, s, H–C(4′)); 8.13–8.17 (2H, m, 2H of Ar); 9.46 (1H, s, NH).

NMR data for minor (Z)-isomer **6′p**. ^{1}H NMR (DMSO-d_6): δ 0.91, 1.00, 1.25 (9H, 3s, 1:1:1, 3Me); 1.41–1.59 (1H, m, 1H of CH_2); 1.94–2.20 (3H, m, 3H of CH_2); 2.54 (1H, d, J = 5.7 Hz, H–C(5)); 7.36–7.39 (2H, m, 2H of Ar); 7.59 (1H, d, J = 12.1 Hz, H–C(4′)); 8.13–8.17 (2H, m, 2H of Ar); 10.35 (1H, d, J = 12.1 Hz, NH).

5.3.17. (1*R*,4*Z*,5*S*)-4-{[(2-Aminophenyl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6q and its (*E*)-isomer 6′q. Prepared from compound **4** and 2-aminoaniline **5q** in methanol; reflux for 4 h; Procedure B; purification of by CC (EtOAc/hexane, 1:2); 182 mg (63%) of a yellow solid; mp 45–52 °C; $[\alpha]_D^{22} = -5.9$ (c 0.288, CH_2Cl_2); **6q**:**6′q** = 90:10. m/z = 286 (M^+); m/z (HRMS) = 286.169250. (Found: C, 71.20; H, 7.63; N, 10.00. $C_{17}H_{22}N_2O_2$ requires: C, 71.30; H, 7.74; N, 9.78.); ν_{max} (KBr) 3351, 2963, 1669 (C=O), 1607, 1363, 1248, 1219, 1161, 1137, 1067 cm^{-1}.

NMR data for major (Z)-isomer **6q**. ^{1}H NMR ($CDCl_3$): δ 1.00, 1.02, 1.31 (9H, 3s, 1:1:1, 3Me); 1.61–1.70 (1H, m, 1H of CH_2); 1.92–2.30 (4H, m, 3H of CH_2 and H–C(5)); 3.61 (2H, s, NH_2); 6.74–6.81 (2H, m, 2H of Ar); 6.86–7.00 (3H, m, 2H of Ar and H–C(4′)); 9.83 (1H, d, J = 11.7 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.9, 18.9, 23.8, 31.9, 38.0, 43.9, 50.5, 91.9, 102.6, 117.2, 117.5, 120.2, 124.3, 129.7, 137.1, 142.3, 170.4.

NMR data for minor (E)-isomer **6′q**. ^{1}H NMR ($CDCl_3$): δ 1.29 (1H, s, Me); 9.95 (1H, d, J = 10.6 Hz, NH).

5.3.18. (1*R*,4*Z*,5*S*)-4-{[(4-Hydroxyphenyl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6r. Prepared from compound **4** and 4-hydroxyaniline hydrochloride **5r** in methanol; reflux for 5 h; Procedure A; purification by CC (EtOAc/hexane, 1:1); 169 mg (59%) of a yellow solid; mp 184–187 °C; $[\alpha]_D^{22} = -12.8$ (c 0.196, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.99, 1.02, 1.31 (9H, 3s, 1:1:1, 3Me); 1.60–1.69 (1H, m, 1H of CH_2); 1.94–2.28 (4H, m, 3H of CH_2 and H–C(5)); 4.94 (1H, s, OH); 6.77–6.81 (2H, m, 2H of Ar); 6.83–6.87 (2H, m, 2H of Ar); 6.93 (1H, d, J = 12.4 Hz, H–C(4′)); 9.94 (1H, d, J = 12.4 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 14.5, 18.9, 23.8, 32.0, 38.1, 43.8, 50.5, 92.2, 100.8, 116.9, 117.5, 134.4, 141.9, 152.4, 170.7. (Found: C, 70.82; H, 7.45; N, 4.97. $C_{17}H_{21}N_2O_3$ requires: C, 71.06; H, 7.37; N, 4.87.); ν_{max} (KBr) 3286, 2964, 1663 (C=O), 1613, 1584, 1520, 1465, 1365, 1219, 1163, 1138 cm^{-1}.

5.3.19. (1*R*,4*E*,5*S*)-4-{[(1*H*-[1,2,4]Triazol-3-yl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6s. Prepared from compound **4** and 3-amino-1*H*-[1,2,4]triazole **5s** in methanol; reflux for 7 h; Procedure B; purification by CC (EtOAc); 138 mg (52%) of a white solid; mp 136–142 °C; $[\alpha]_D^{22} = +125.6$ (c 0.133, MeOH). ^{1}H NMR (DMSO-d_6): δ 0.87, 0.97, 1.20 (9H, 3s, 1:1:1, 3Me); 1.36–1.44 (1H, m, 1H of CH_2); 1.91–2.10 (3H, m, 3H of CH_2); 3.03 (1H, d, J = 3.8 Hz, H–C(5)); 7.88 (1H, s, H–C(4′)); 8.26 (1H, br s, H–C(5″)); 9.59 (1H, br s, NH); 13.40 (1H, br s, H–N(1″)). ^{13}C NMR (DMSO-d_6):

δ 14.8, 18.8, 19.4, 22.9, 23.8, 29.7, 31.8, 37.6, 43.7, 44.5, 91.2, 168.0. *m/z* (EI) = 262 (M^+); *m/z* (HRMS) = 262.143850. (Found: C, 59.44; H, 7.03; N, 21.38. $C_{13}H_{18}N_4O_2$ requires: C, 59.53; H, 6.92; N, 21.36.); ν_{max} (KBr) 3210, 2964, 1693 (C=O), 1603, 1545, 1301, 1246, 1200, 1169, 1129, 1061 cm^{-1}.

5.3.20. (1*R*,4*Z*,5*S*)-4-{[(Pyrazinyl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6t. Prepared from compound **4** and aminopyrazine **5t** in 1-propanol; reflux for 5 h then standing at −20 °C for 12 h; Procedure B; 112 mg (41%) of a white solid; mp 222–225 °C; $[\alpha]_D^{22} = +12.9$ (*c* 0.294, CH_2Cl_2). ^1H NMR (DMSO-d_6): δ 0.90, 0.99, 1.24 (9H, 3s, 1:1:1, 3Me); 1.50–1.56 (1H, m, 1H of CH_2); 1.99–2.18 (3H, m, 3H of CH_2); 2.53 (1H, d, *J* = 5.3 Hz, 1H iz H–C(5)); 7.71 (1H, d, *J* = 11.7 Hz, H–C(4′)); 8.13 (1H, d, *J* = 2.6 Hz, 1H of pyrazine); 8.20–8.22 (1H, m, 1H of pyrazine); 8.56 (1H, d, *J* = 1.5 Hz, 1H of pyrazine); 10.36 (1H, d, *J* = 11.7 Hz, NH). (Found: C, 65.80; H, 7.23; N, 15.59. $C_{15}H_{19}N_3O_2$ requires: C, 65.91; H, 7.01; N, 15.37.); ν_{max} (KBr) 3242, 2972, 1690 (C=O), 1622, 1602, 1533, 1505, 1476, 1389, 1273, 1229, 1167, 1126, 1055, 1007 cm^{-1}.

5.3.21. (1*R*,4*Z*,5*S*)-4-{[(1*H*-Indazol-3-yl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6u. Prepared from compound **4** and 3-amino-1*H*-indazole **5u** in methanol; reflux for 7 h; Procedure B; purification by CC (EtOAc/hexane, 1:1); 109 mg (35%) of a white solid; mp 179–183 °C (EtOAc/hexane); $[\alpha]_D^{22} = +3.7$ (*c* 0.162, CH_2Cl_2). ^1H NMR (DMSO-d_6): δ 0.93, 1.00, 1.24 (9H, 3s, 1:1:1, 3Me); 1.52–1.60 (1H, m, 1H of CH_2); 1.99–2.19 (3H, m, 3H of CH_2); 2.52 (1H, d, *J* = 3.8 Hz, H–C(5)); 7.05–7.11 (1H, m, 1H of indazole); 7.33–7.43 (2H, m, 2H of indazole); 7.56 (1H, d, *J* = 12.1 Hz, H–C(4′)); 7.69 (1H, d, *J* = 7.9 Hz, 1H of indazole); 10.29 (1H, d, *J* = 12.1 Hz, NH); 12.39 (1H, s, NH). (Found: C, 69.45; H, 6.91; N, 13.56. $C_{18}H_{21}N_3O_2$ requires: C, 69.43; H, 6.80; N, 13.49.); ν_{max} (KBr) 3260, 2963, 1672 (C=O), 1620, 1540, 1379, 1214, 1138, 1065 cm^{-1}.

5.3.22. (1*R*,4*E*,5*S*)-4-{[(Quinolin-3-yl)amino]methylidene}-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 6v. Prepared from compound **4** and 3-aminoquinoline **5v** in 1-propanol; reflux for 5 h; Procedure B; 222 mg (69%) of a white solid; mp 255–262 °C; $[\alpha]_D^{22} = +175.3$ (*c* 0.178, DMF). ^1H NMR (DMSO-d_6): δ 0.93, 1.04, 1.24 (9H, 3s, 1:1:1, 3Me); 1.49–1.56 (1H, m, 1H of CH_2); 1.95–2.21 (3H, m, 3H of CH_2); 3.05 (1H, d, *J* = 5.3 Hz, H–C(5)); 7.51–7.56 (2H, m, 2H of quinoline); 7.84 (1H, d, *J* = 13.2 Hz, H–C(4′)); 7.89–7.92 (2H, m, 2H of quinoline,); 7.95 (1H, d, *J* = 2.6 Hz, 2H of quinoline); 8.86 (1H, d, *J* = 2.6 Hz, 1H of quinoline); 9.19 (1H, d, *J* = 13.2 Hz, NH). ^{13}C NMR (DMSO-d_6): δ 18.9, 19.5, 23.8, 29.7, 37.6, 44.0, 44.9, 91.3, 109.4, 115.4, 127.5, 127.9, 128.0, 129.4, 136.2, 136.7, 144.2, 144.3, 167.8. (Found: C, 74.24; H, 7.09; N, 8.94. $C_{18}H_{21}N_3O_2$ requires: C, 74.51; H, 6.88; N, 8.69.); ν_{max} (KBr) 3273, 3250, 2972, 1687 (C=O), 1581, 1468, 1386, 1335, 1273, 1251, 1173, 1057 cm^{-1}.

5.3.23. (*Z*,*Z*)-*N*,*N*′-Bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}-benzene-1,2-diamine 6w and its (*E*,*Z*)-isomer 6′w. Compound **4** (223 mg, 1 mmol) was added to a solution of benzene-1,2-diamine **5q** (54 mg, 0.5 mmol) in a mixture of anhydrous methanol (5 mL) and sulfuric acid (97%, 0.027 mL, 0.5 mmol) and the mixture heated under reflux for 8 h. Volatile components were evaporated in vacuo and the residue purified by CC [EtOAc/hexane, 1:3 (**6w**), 2:1 (**6′w**)]. Fractions containing the products were combined and evaporated in vacuo to give **6w** and **6′w**.

Data for major (Z,Z)-isomer **6w**. 148 mg (64%) of a pale yellow-brown solid; mp 189–192 °C; $[\alpha]_D^{21} = +23.0$ (*c* 0.178, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.01, 1.29 (18H, 2s, 2:1, 6Me); 1.63–1.72 (2H, m, 2H of CH_2); 1.92–2.25 (6H, m, 6H of CH_2); 2.28 (2H, d, *J* = 5.3 Hz, 2H–C(5)); 6.84 (2H, d, *J* = 11.7 Hz, 2H–C(4′)); 7.00 (4H, s, Ar); 9.95 (2H, d, *J* = 12.1 Hz, 2NH). ^{13}C NMR ($CDCl_3$): δ 18.4, 23.4, 31.0, 37.4, 43.5, 50.2, 91.3, 103.8, 118.3, 123.7, 132.4, 140.9, 169.2. (Found: C, 72.08; H, 8.05; N, 5.96. $C_{28}H_{36}N_2O_4$ requires: C, 72.39; H, 7.81; N, 6.03); ν_{max} (KBr) 3461, 2978, 1669 (C=O), 1634, 1589, 1374, 1252, 1211, 1135, 1068 cm^{-1}.

Data for minor (E,Z)-isomer **6′w**. 54 mg (23%) of a white solid; mp 207–212 °C; $[\alpha]_D^{21} = +129.6$ (*c* 0.142, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.01, 1.03, 1.04, 1.05, 1.32, 1.33 (18H, 6s, 1:1:1:1:1:1, 6Me); 1.62–1.74 (2H, m, 2H of CH_2); 1.96–2.28 (6H, m, 2H of CH_2); 2.33 (1H, d, *J* = 5.3 Hz, H–C(5), (*Z*)); 2.59 (1H, d, *J* = 4.9 Hz, H–C(5) (*E*)); 6.10 (1H, d, *J* = 13.2, NH, (*E*)); 6.95 (1H, d, *J* = 11.7 Hz, H-C(4′), (*Z*)); 7.00–7.08 (3H, m, 3H of Ar); 7.15–7.18 (1H, m, 1H of Ar); 7.80 (1H, d, *J* = 13.6 Hz, H–C(4′), (*E*)); 9.99 (1H, d, *J* = 11.7 Hz, NH, (*Z*)). ^{13}C NMR ($CDCl_3$): δ 18.1, 18.4, 18.7, 23.3, 23.4, 28.6, 31.2, 37.1, 37.5, 43.5, 43.8, 44.7, 50.0, 90.8, 91.9, 104.0, 107.7, 116.7, 118.4, 123.9, 124.0, 131.4, 131.5, 137.9, 140.6, 168.5, 169.8. (Found: C, 72.19; H, 7.93; N, 5.94. $C_{28}H_{36}N_2O_4$ requires: C, 72.39; H, 7.81; N, 6.03.); ν_{max} (KBr) 3461, 2964, 1695 (C=O), 1678 (C=O), 1629, 1580, 1376, 1261, 1217, 1201, 1167, 1135, 1058 cm^{-1}.

5.3.24. *N*,*N*′-Bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}benzene-1,4-diamine 6x. Compound **4** (223 mg, 1 mmol) was added to a solution of benzene-1,4-diamine **5w** (54 mg, 0.5 mmol) in a mixture of anhydrous methanol (5 mL) and sulfuric acid (97%, 0.027 mL, 0.5 mmol) and the mixture heated under reflux for 5 h. The precipitate was collected by filtration and washed with methanol to give **6x**. Yield: 200 mg (86%) of a yellow-brownish solid; mp 330–350 °C (decomp.). (Found: C, 71.76; H, 8.06; N, 6.08. $C_{28}H_{36}N_2O_4$ requires: C, 72.39; H, 7.81; N, 6.03.); *m/z* = 464 (M^+); HRMS: *m/z* (MI) = 464.268950. ν_{max} (KBr) 3453, 2980, 1687 (C=O), 1548, 1506, 1253, 1223, 1173, 1150, 1128, 1059 cm^{-1}. NMR characterisation and

determination of specific rotation was not possible due to the insolubility of **6x**.

5.3.25. *N*,*N*′,*N*″,*N*‴-Tetrakis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-4-ylidene]methyl}benzene-1,2,4,5-tetramine 6y. A mixture of compound **4** (223 mg, 1 mmol), benzene-1,2,4,5-tetramine tetrahydrochloride **5x** (71 mg, 0.25 mmol) and anhydrous methanol (15 mL) was heated under reflux for 6 h. The precipitate was collected by filtration and washed with methanol to give **6y**. Yield: 455 mg (53%) of a yellow-brownish solid; mp 315–320 °C (decomp.). (Found: C, 70.47; H, 8.06; N, 6.82. $C_{50}H_{66}N_4O_8$ requires: C, 70.56; H, 7.82; N, 6.58.); $m/z = 850$ (M^+). ν_{max} (KBr) 3417, 3271, 2976, 1690 (C═O), 1580, 1447, 1375, 1250, 1218, 1201, 1168, 1152, 1128, 1057 cm^{-1}. NMR characterisation and determination of specific rotation was not possible due to the insolubility of **6y**.

5.4. *N*,*N*′-Bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-hydroxy-2-oxabicyclo[3.2.1]oct-3-en-4-yl]methylidene}-benzene-1,2-diaminatopalladium(II) 7a

A solution of compound **6w** or **6′w** (465 mg, 1 mmol) in a mixture of acetonitrile (24 mL) and dichloromethane (9 mL) was added to a solution of palladium(II) acetate (225 mg, 1 mmol) in acetonitrile (15 mL). The mixture was allowed to stand at rt for 7 days. The precipitate, consisting of **7a** and Pd(0), was collected by filtration. The crude product was suspended in chloroform (15 mL), the suspension filtered through a pad of Celite® and the filtrate evaporated in vacuo to give pure **7a**. Yield: 404 mg (71%) of an orange-red solid; mp 325–335 °C; $[\alpha]_D^{21} = -210.0$ (c 0.013, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.96, 1.03, 1.28 (18H, 3s, 1:1:1, 6×Me); 1.67–1.74, 1.90–2.00, 2.07–2.25 (8H, 3m, 1:1:2, 4×CH_2); 2.38 (2H, d, $J = 4.9$ Hz, 2×H–C(5)); 6.86–6.92, 7.35–7.40 (4H, 2m, 1:1, Ar); 7.49 (2H, s, 2×H–C(4′)). ^{13}C NMR ($CDCl_3$): δ 18.7, 23.7, 33.1, 38.5, 42.9, 50.6, 93.4, 97.6, 113.3, 122.9, 143.8, 146.4, 168.1. EIMS: $m/z = 566$, 567, 568, 570, 572 (M^+). (Found: C, 59.35; H, 6.11; N, 4.77. $C_{28}H_{34}N_2O_4Pd$ requires: C, 59.10; H, 6.02; N, 4.92.); ν_{max} (KBr) 2980, 2937, 1608, 1450, 1356, 1342, 1306, 1273, 1211, 1168, 1142, 1076, 970 cm^{-1}.

5.5. *N*,*N*′-Bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-hydroxy-2-oxabicyclo[3.2.1]oct-3-en-4-yl]methylidene}-benzene-1,2-diaminatocopper(II) 7b

A solution of compound **6w** or **6′w** (465 mg, 1 mmol) in a mixture of acetonitrile (24 mL) and dichloromethane (9 mL) was added to a solution of copper(II) acetate monohydrate (200 mg, 1 mmol) in acetonitrile (15 mL). The mixture was allowed to stand at rt for 7 days. The precipitate was collected by filtration to give pure **7b**. Yield: 353 mg (67%) of deep blue solid; mp >350 °C; $[\alpha]_D^{21} = -237.5$ (c 0.024, $CHCl_3$). EIMS: $m/z = 525$, 527 (M^+). (Found: C, 64.26; H, 6.73; N, 5.41. $C_{28}H_{34}CuN_2O_4$ requires: C, 63.92; H, 6.51; N, 5.32.); ν_{max} (KBr) 2980, 2958, 2937, 1611, 1464, 1429, 1349, 1326, 1269, 1223, 1206, 1165, 1141, 1075, 967 cm^{-1}.

5.6. *N*,*N*′-Bis-{[(1*R*,5*S*)-1,8,8-trimethyl-3-hydroxy-2-oxabicyclo[3.2.1]oct-3-en-4-yl]methylidene}-benzene-1,2-diaminatonickel(II) 7c

Compound **6w** or **6′w** (465 mg, 1 mmol) was added to a solution of nickel(II) acetate tetrahydrate (249 mg, 1 mmol) in acetonitrile (20 mL). The mixture was heated under reflux for 3 h, cooled to rt and the precipitate collected by filtration and washed with acetonitrile (3 mL) to give **7c**. Yield: 323 mg (62%) of dark brown solid; mp >350 °C; $[\alpha]_D^{21} = -158.3$ (c 0.024, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.93, 1.00, 1.22 (18H, 3br s, 1:1:1, 6×Me); 1.64 (2H, br s, 2H of CH_2); 1.80–2.50 (8H, m, 6H of CH_2 and 2×H–C(5)); 6.79 (2H, br s, 2H–C(4′)); 7.23 (4H, br s, Ar). EI-MS: $m/z = 520$, 522 (M^+); EI-HRMS: $m/z = 520.189550$. (Found: C, 64.84; H, 7.03; N, 4.06. $C_{28}H_{34}N_2NiO_4$ requires: C, 64.51; H, 6.57; N, 5.37.); ν_{max} (KBr) 2978, 1615, 1463, 1434, 1337, 1313, 1277, 1209,1167, 1143, 1076, 967 cm^{-1}.

5.7. X-ray structure analysis for compounds 4, 6b, 6′e, 6g and 6o

Single crystal X-ray diffraction data of compounds **4**, **6b**, **6′e**, **6g** and **6o** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[34] DENZO and SCALEPACK[35] were used for indexing and scaling the data and the structures solved by means of SIR97.[36] Refinement and plotting were carried out by using a Xtal3.4[37] program package. 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[38] weighting scheme was used in all cases.

All studied compounds crystallize in non-centrosymmetric space groups and contain only one optical isomer of the chiral molecule in the asymmetric unit. Even the crystal packing is similar (orthorhombic space group $P2_12_12_1$ in four cases and monoclinic $P2_1$ in the case of **6o**). The crystal quality was good in all cases so that there were no special issues encountered during the structure analysis. The plots of final refined contents of the asymmetric units of compounds **4**, **6b**, **6′e**, **6g** and **6o** are presented in Figures 1–5.

Crystallographic data (excluding structure factors) for the structures herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 238071–238075. 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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