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Synthesis and Transformations of Some N-Substituted (1*R*,4*S*)-3-Aminomethylidene-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ones†

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Abstract

Acid-catalysed reactions of (1*R*,3*E*,4*S*)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**2**) with amino acid derivatives **3a–d** and pyrazolidin-3-ones **5a–e** gave the substitution products **4/4'a–d** and **6a–e**, respectively, in 40–83% yields. Compound **4a** was transformed with Bredereck's reagent into the 3-(dimethylamino)propenoate **7/7'**. Treatment of 1-{[(1*R*,3*Z*,4*S*)-1,7,7-trimethyl-2-oxobicyclo-[2.2.1]hept-3-ylidene]methyl}pyrazolidin-3-ones **6a** and **6b** with dimethyl acetylenedicarboxylate in refluxing anisole furnished the corresponding cycloadducts as mixtures of four diastereomers, the major *endo*-isomers **10/11a,b** and the minor *exo*-isomers **12/13a,b** with moderate *endo*-selectivity. Chromatographic separation of **10/11/12/13a,b** afforded the *endo*/*exo*-pairs of diastereomers, **10/13a,b** and **11/12a,b**. The structures of compounds **4/4'**, **6**, **7/7'**, and **10/11/12/13** were determined by NMR and by X-ray diffraction.

Keywords: camphor, enaminones, condensations, pyrazolidin-3-ones, pyrazolo[1,2–*a*]pyrazoles

1. Introduction

(+)-Camphor (**1**) and its derivatives belong to the most frequently employed types of ex-chiral pool starting materials, building blocks, ligands, reagents and/or catalysts, resolving agents in various asymmetric applications, and as shift reagents in NMR spectroscopy.[1] For example, reaction of 3-hydroxymethylidenecamphor[2] 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.[3–5]

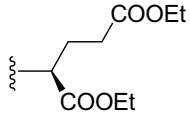
On the other hand, 2-aminopyrazolo[1,2–*a*]-pyrazole-7-carboxylate moiety belongs to a family of conformationally constrained peptide mimetics.[6] It is a constituent of biologically active compounds, such as Eli-Lilly's γ-lactam antibiotics LY 186826, LY 193239, and LY 255262.[7–11] In this context, we have previously reported preparation and synthetic utilisation of various 3-pyrazolidinone-1-azomethine imines including their regioselective and stereoselective 1,3-dipolar cycloadditions leading to polysubstituted pyrazolo-[1,2–*a*]pyrazoles.[12–27]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates and analogous enaminones have been prepared as versatile reagents for the preparation of various heterocyclic systems.[12,18,28] Chiral non-racemic 3-(dimethylamino)propenoate analogues, derived from α-amino acids, have been employed in the synthesis of heterocycles, functionalised with an α-amino acid, dipeptide, β-amino alcohol, and related structural elements.[12,14,18,28,29] Recently, our studies on ex-chiral pool derived enaminones have been extended towards the preparation and synthetic utilisation of (+)-camphor (**1**) derived enaminones.[30–37] In the present work, we now report reactions of (1*R*,3*E*,4*S*)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**2**) with amino acid derivatives **3** and pyrazolidin-3-ones **5**, and some further transformations of the substitution products **4** and **6** with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) and dimethyl acetylenedicarboxylate (DMAD).

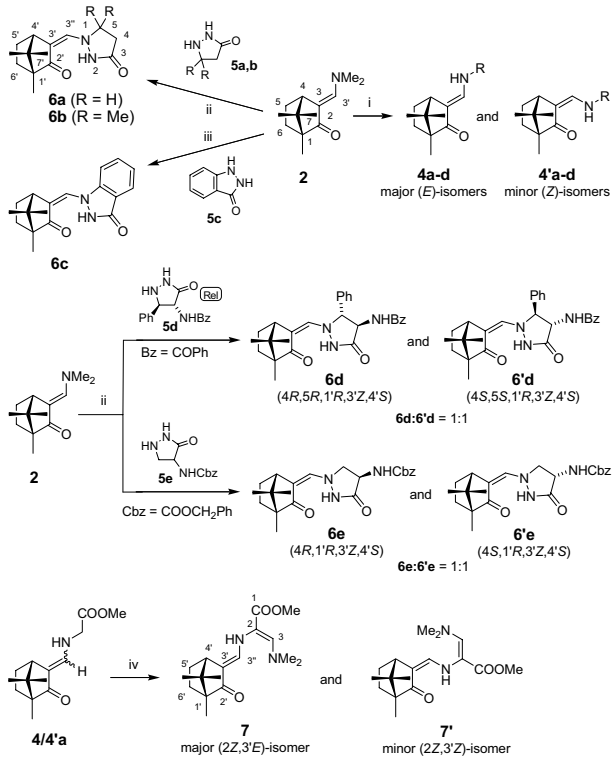
2. Results and Discussion

The starting compound **2** was prepared from (+)-camphor (**1**) in one step according to the literature procedure.[30] Treatment of enaminone **2** with amino acid derivatives **3a–d** in ethanol under reflux afforded the corresponding substitution products, in all cases as mixtures of the major (*E*)-isomers **4a–d** and the minor (*Z*)-isomers **4'a–d** in 54–83% yields. Similarly, acid-catalysed reactions of **2** with pyrazolidin-3-ones **5a–e** in acetic acid or in ethanol in the presence of equimolar amount of hydrochloric acid at room temperature or under reflux gave the corresponding substitution products **6a–e** in 40–80% yields. In contrast to the amino acid derivatives **4a–d**, compounds **6a–e** were obtained as the (*Z*)-isomers, exclusively. Crystallisation of a mixture of **4a** and **4'a** in a ratio of 68:32, respectively, gave isomerically pure compound **4a**. Similarly, chromatographic separation of **4b** and **4'b** in a ratio of 80:20, respectively, yielded pure (*E*)-isomer **4b** and isomerically enriched (*Z*)-isomer **4'b** (*Z*:*E* = 96:4). On the other hand, attempted chromatographic separation of a 70:30 mixture of **4d** and **4'd** failed, most probably due to the fast *E*/*Z*-isomerisation.[29c,31] Reactions of **2** with chiral racemic pyrazolidin-3-ones **5d** and **5e** gave mixtures of two diastereoisomeric substitution products **6**/**6'd** and **6**/**6'e** in a ratio of 1:1, respectively. Unfortunately, these diastereomers could not be separated, neither by crystallization, nor by chromatographic techniques (CC and/or MPLC). Reaction of **4**/**4'a** with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) in toluene under reflux furnished a mixture of isomeric enamino esters **7** and **7'** in a ratio of 59:41 and in 48% yield (Scheme 1, Table 1).

Table 1. Selected Experimental Data for Compounds **4**, **4'**, **6**, and **7**/**7'**.

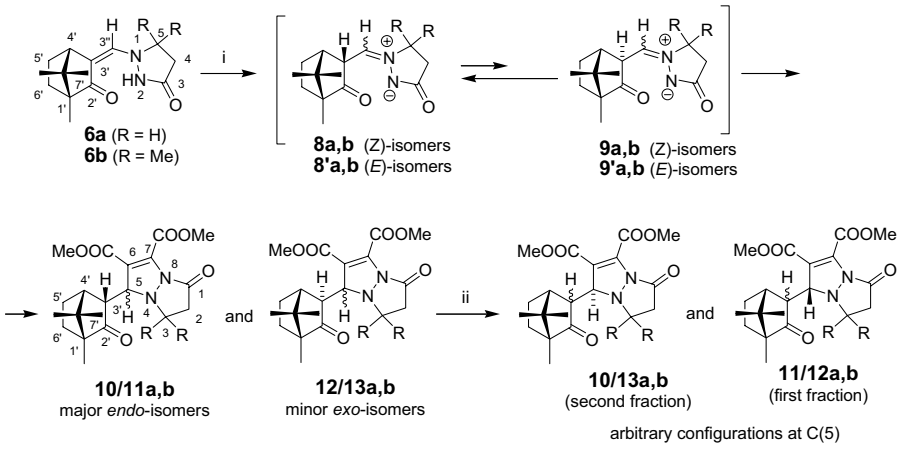
Compound	R	Yield (%)	*E*:*Z*
4/4'a	CH_2COOMe	76	68:32[a]
4/4'b	CH_2CN	81	80:20[b]
4/4'c	CH_2CH_2COOEt	54	97:3
4/4'd		83	70:30
6a	H	46	0:100
6b	Me	80	0:100
6c	-	40	0:100
6d	-	46	0:100
6e	-	48	0:100
7/7'	-	48	59:41

[a]Pure (*E*)-isomer **4a** was obtained upon crystallization.
[b]Pure (*E*)-isomer **4b** and almost pure (*Z*)-isomer **4'b** (*Z*:*E* = 96:4) were obtained upon MPLC.



Sheme 1. Reagents and conditions: (i) R–NH_2×HCl (**3a-d**), EtOH, reflux; (ii) EtOH, HCl, r.t. or reflux (iii) AcOH, reflux; (iv) *t*-BuOCH(NMe_2)$_2$, toluene, reflux.

Treatment of 1-{[(1*S*,3*Z*,4*R*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]methyl}pyrazolidin-3-one (**6a**) with dimethyl acetylenedicarboxylate (DMAD) in refluxing anisole afforded (5*RS*)-2,3-dihydro-1-oxo-5-[(1*R*,3*RS*,4*R*)-2-oxo-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl]-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylate in 77% yield as a mixture of four diastereomers **10a**, **11a**, **12a**, and **13a**, in a molar ratio of 44:36:12:8, respectively. Similarly, reaction of the 5,5-dimethyl analogue **6b** with DMAD furnished a mixture of four diastereomeric cycloadducts **10b**, **11b**, **12b**, and **13b**, in a molar ratio of 51:31:9:9, respectively, in 83% yield. Both mixtures of isomers, **10**/**11**/**12**/**13a** and **10**/**11**/**12**/**13b**, consisted of the major pair of the *endo*-isomers **10**/**11** and the minor pair of the *exo*-isomers **12**/**13**. Separation of **10**/**11**/**12**/**13a** by medium pressure liquid chromatography (MPLC) was only partial and furnished two *endo*/*exo*-mixtures of isomers: (a) a mixture of the *endo*-isomer **10a** and the *exo*-isomer **13a** (**10a**:**13a** = 84:16) in 15% yield and (b) a mixture of the *endo*-isomer **11a** and the *exo*-isomer **12a** (**11a**:**12a** = 79:21) in 22% yield. In the same manner, MPLC separation of **10**/**11**/**12**/**13b** furnished two *endo*/*exo*-mixtures, **10b**:**13b** = 77:23 and **11b**:**12b** = 84:16, in 40% and 22% yield, respectively. In all isomeric cycloadducts **10a,b–13a,b** the *endo*/*exo*-configurations at C(3') were unambigously determined by NMR, while



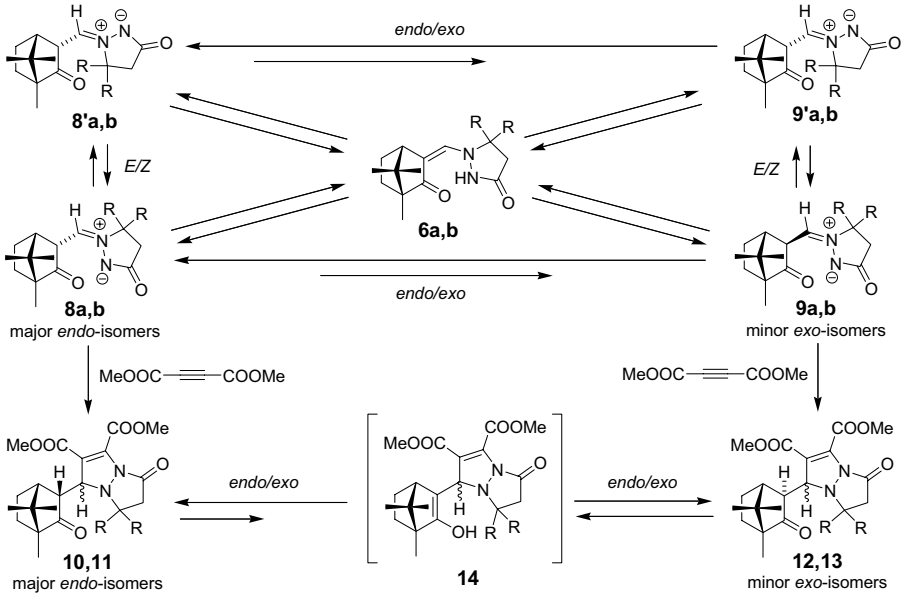
Sheme 2

configurations at C(5) could not be established (for details see Structure Determination). Consequently, the configurations at C(5) in the isomeric pairs **10**/**13** and **11**/**12**, as drawn in the Scheme 2, are arbitrary. They to do not necessarily correspond to the actual configurations (Scheme 2).

Compound	R	Yield (%)	Ratio of Isomers
10a/11a/12a/13a	H	77	44:36:12:8
10b/11b/12b/13b	Me	83	51:31:9:9
10a/13a	H	15	84:16
11a/12a	H	22	79:21
10b/13b	Me	40	77:23
11b/12b	Me	22	84:16

Reagents and conditions: (i) dimethyl acetylenedicarboxylate (DMAD), anisole, reflux; (ii) chromatographic separation (MPLC).

Low stereoselectivity of cycloadditions of **6a,b** to DMAD could be explained by initial thermal isomerisation of the enaminone **6** into a mixture of four isomeric azomethine imines **8**, **8'**, **9**, and **9'** as a consequence of fast *E*/*Z*-isomerisation and *endo*/*exo*-isomerisation. Consequently, 1,3-dipolar cycloaddition of DMAD to a mixture of four isomeric dipoles **8**, **8'**, **9**, and **9'** leads to four isomeric cycloadducts **10–13** with variable configurations at positions 5 and 3'. Besides, the *exo*/*endo*-equilibration is also feasible in cycloadducts **10–13** *via* the enol **14**. Predominant formation of the *endo*-isomers **10**/**11** is in agreement with the literature data for related α-substituted camphor derivatives, which exist predominantly in the thermodynamically more stable *endo*-form because of steric repulsions between the *exo*-substituent and the *Me*–C(7) group.[1,38] In contrast to the moderate *endo*/*exo*-selectivity (position 3' in the cycloadducts),



Sheme 3

the facial selectivity of cycloadditions (position 5 in the cycloadducts) was almost neglible according to the ratio of epimers within the *endo*-pair of isomers (**10**:**11** ~ 3:2) and the *exo*-pair of isomers (**12**:**13** ~ 1:1). In addition to the above mentioned explanation by fast *E*/*Z*-isomerisation around the exocyclic C=N double bond of the intermediate azomethine imines **8** and **9**, low facial selectivity might also be due to weak stereodirecting effect of the (+)-camphor residue, because of rotation around the C(3')–C(3'') single bond (Scheme 3).

3. Structure Determination

Structures of compounds **4a–d**/**4'a–d**, **6a–e**, **6'd,e**, **7**/**7'**, **10**/**11**/**12**/**13a**, and **10**/**11**/**12**/**13b** were determined by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR, 2D NMR NOESY spectroscopy, MS) and by elemental analyses for C, H, and N. Compounds **4a**, **4b**, and **6a–d** were prepared in isomerically pure form. Compounds **4c**, **4d**, and **7** were characterised as isomerically enriched mixtures of major (*E*)-isomers and the minor (*Z*)-isomers, whereas compounds **10**/**11**/**12**/**13** were characterized as mixtures of isomers. Compound **4d** was not prepared in analytically pure form. Identity of **4b** was confirmed by ^{13}C NMR and EI-HRMS.

The configuration around the C=C double bonds in isomers **7** and **7'** were determined by NMR on the basis of long-range coupling constants, $^{3}J_{C–H}$, between the corresponding methylidene protons and the carbonyl carbon atoms, measured from the antiphase 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 *trans*-oriented nuclei (8–12 Hz).[39–49] The magnitude of coupling constant, $^{3}J_{C(1)–H(3)}$ = 2.8 Hz, in the isomer **7** indicated the (2*Z*)-configuration. In the isomer **7'**, coupling constants, $^{3}J_{C(2')–H(3'')}$ = 8.3 Hz and $^{3}J_{C(1)–H(3)}$ = 2.8 Hz, showed the (2*Z*,3*Z*)-configuration (Figure 1).

The (*E*)-configuration around the exocyclic C=C double bond in compounds **4a–c** was determined by NOESY spectroscopy on the basis of n.O.e. between N*H* and *H*–C(4). On the other hand, n.O.e. between *H*–C(3'') and *H*–C(4) in compounds **4'a**, **6a–e,** and **7'** were in agreement with the (3'*Z*)-configuration (Figure 1).

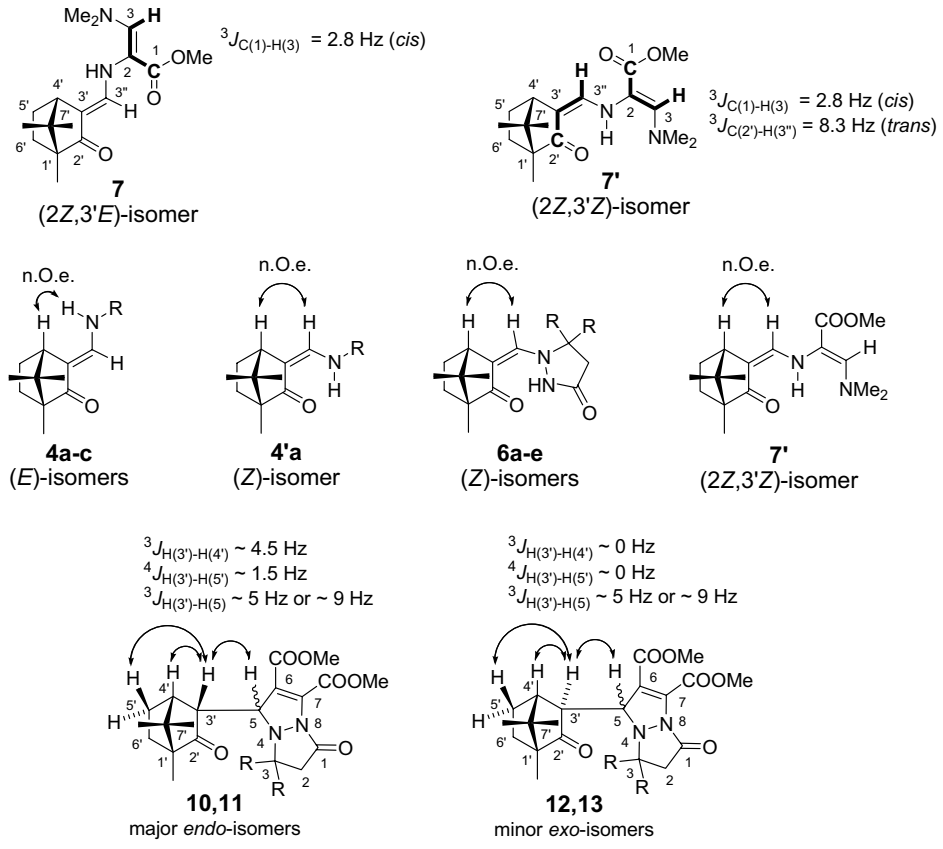


Figure 1. Structure Determination by NMR Methods.

The configuration at position 3' in compounds **10–13** was determined by NMR on the basis of multiplicity of coupling of proton H–C(3'). Following the Karplus equation[50] and the possibility of a long-range coupling between *H*–C(3') and *Ha*–C(5') by the virtue of the "W" configuration,[51] the *H*–C(3') proton in major *endo*-isomers **9**/**10a,b** coupled with *H*–C(4'), *Ha*–C(5'), and *H*–C(5), therefore appearing as a doublet of a doublet of a doublet (or a multiplet) with typical coupling constants, $^{3}J_{H(3')-H(4')}$ = 4.5 Hz, $^{4}J_{H(3')-H(5')}$ = 1.5 Hz, and $^{3}J_{H(3')-H(5)}$ = 5.3–8.3 Hz. On the other hand, the *H*–C(3') proton in the minor *ex*o-isomers **12**/**13a,b** coupled only with *H*–C(5), therefore appearing as doublet ($^{3}J_{H(3')-H(5)}$ = 7.2–9.1 Hz). Similar patterns of multiplicities and values of coupling constants were also reported in the literature for analogous compounds.[34–36,52,53] Unfortunately, the configuration at position 5 in compounds **10–13** could not be determined on the basis of the NMR data (Figure 1, Table 2).

In compounds **4**/**4'a–d** and **7**/**7'**, the configurations around the exocyclic C(3')=C(3'') double bond were correlated with chemical shifts δ for *H*–C(3'') and N*H*. In the case of the (*Z*)-isomers **4'a–d** and **7'**, signals for *H*–C(3'') appeared at higher field (6.23–6.44 ppm) than in the case of the (*E*)-isomers **4a–d** and **7** (6.82–6.96 ppm). Signals for N*H* exhibited even stronger dependence of chemical shift on the configuration. Typical chemical shifts for the N*H* proton of the (*Z*)-isomers **4'a–d** and **7'** were 7.53–8.19 ppm, while chemical shifts for N*H* protons of the (*E*)-isomers **4a–d** and **7** were 4.13–6.58 ppm. The downfield shift of the NH proton in the (*Z*)-isomers **4'a–d** and **7'** could be rationalised by intramolecular hydrogen bond, N–H···O=C(2'). Similarly, the downfield shift of *H*–C(3'') signals of the (*E*)-isomers **4a–d** and **7** might be attributed to the effect of the ring carbonyl group. These typical NMR data were in agreement with the previously published typical data of related α-alkylidene substituted (1*R*,4*S*)-1,7,7-trimethyl-2-oxabicyclo[2.2.1]heptan-2-ones and (1*R*,5*S*)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones (Table 2).[31]

Table 2. Correlation between NMR data and configuration of compounds **4/4'**, **7/7'**, **10/11**, and **12/13**.

*Major Isomers **4** and **7***				
Compound	Solvent	δ [ppm]		*Z* or *E*
		3''–H	NH	
4a	DMSO-d_6	6.82	6.58	*E*[a]
4b	$CDCl_3$	6.85	4.13	*E*[a,b]
4c	$CDCl_3$	6.96	4.49	*E*[a]
4b	$CDCl_3$	6.88	4.46	*E*
7	$CDCl_3$	6.90	4.80	*E*,*Z*[c]
*Minor Isomers **4'** and **7'***				
Compound	Solvent	δ [ppm]		*Z* or *E*
		3''–*H*	N*H*	
4'a	DMSO-d_6	6.44	7.55	*Z*[a]
4'd	$CDCl_3$	6.23	7.53	*Z*
4'c	$CDCl_3$	6.33	7.66	*Z*
4'b	$CDCl_3$	6.26	7.74	*Z*
7'	$CDCl_3$	6.24	8.19	*Z*,*Z*[a,c]
Major endo-*Isomers **10** and **11***				
Compound	Solvent	δ [ppm]		$^{3}J_{H-H}$ [Hz]
		3'–H	5–H	3'–4' 3'–5' 3'–5
10a	$CDCl_3$	2.81	4.44	[d] [d] 6.4
11a	$CDCl_3$	3.19	4.94	4.7 1.3 5.3
10b	$CDCl_3$	2.55	4.66	4.5 1.5 8.3
11b	$CDCl_3$	2.92	4.98	4.7 1.0 5.3
Minor exo-*Isomers **12** and **13***				
Compound	Solvent	δ [ppm]		$^{3}J_{H-H}$ [Hz]
		3'–H	5–H	3'–4' 3'–5' 3'–5
12a	$CDCl_3$	2.44	4.49	0 0 9.1
13a	$CDCl_3$	2.49	4.64	0 0 7.2
12b	$CDCl_3$	2.26	4.58	0 0 9.1
13b	$CDCl_3$	2.17	4.59	0 0 8.9

[a] Determined by NOESY spectroscopy.
[b] Determined by X-ray diffraction.
[c] Determined by HMBC spectroscopy.
[d] H–C(3') appeared as multiplet.

The structure of compound **4b** was also determined by X-ray diffraction (Figure 2).

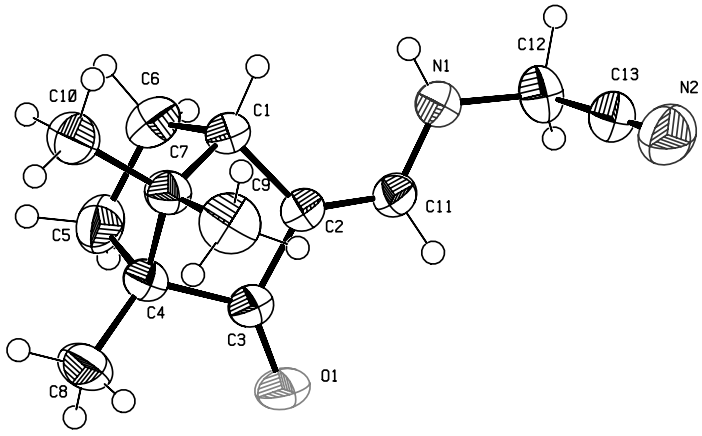


Figure 2. The asymmetric unit of compound **4b**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

4. Experimental

4.1. General Procedures.

Melting points were determined on a Kofler micro hot stage. The 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 $CDCl_3$ as solvents and TMS as the internal standard. 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, 40–60 μm). Medium pressure liquid chromatography (MPLC) was performed with a Büchi isocratic system with detection on silica gel (Merck, silica gel 60, 15–35 μm); 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. Ratio of isomers and d.e. were determined by ^{1}H NMR.

tert-Butoxy-bis(dimethylamino)methane (Bredereck's reagent), amino acid derivatives **3a–d**, 1,2-dihydro-3*H*-indazol-3-one (**5c**), and dimethyl acetylenedicarboxylate (DMAD) 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**),[30] pyrazolidin-3-one hydrochloride (**5a**),[54,55] 5,5-dimethylpyrazolidin-3-one (**5b**),[56,57] *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenylpyrazolidin-3-one (**5d**),[22] and (*RS*)-4-(benzyloxycarbonylamino)-pyrazolidin-3-one (**5e**)[58,59] were prepared according to the literature procedures.

Source of chirality: (i) (+)-Camphor (**1**) (Fluka AG), product number 21300, purum, natural, ≥ 97.0% (GC, sum of enantiomers), $[\alpha]_{546}^{20}$ +54.5 ± 2.5 (c = 10, EtOH), $[\alpha]_D^{20}$ +42.5 ± 2.5 (c = 10, EtOH), mp 176–180 °C, e.e. not specified; (ii) (*S*)-glutamic acid diethyl ester hydrochloride (**3d**) (Fluka AG), product number 49550, puriss., ≥ 99.0% (AT, dried material), $[\alpha]_D^{20}$ +22 ± 1 (c = 5, EtOH), mp 113–115 °C, e.e. not specified; (iii) *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenylpyrazolidin-3-one (**5d**), racemic compound obtained by diastereoselective synthesis;[22] (iv) (*RS*)-4-(benzyloxycarbonylamino)pyra zolidin-3-one (**5e**), racemic compound obtained from (*S*)-serine.[58]

4.2. General Procedure for the Preparation of N-substituted (1*R*,4*S*)-3-(aminomethylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones 4a–c.

Amine hydrochloride **3a–c** (1 mmol) was added to a solution of compound **2** (207 mg, 1 mmol) in anhydrous ethanol (3 ml), the mixture was stirred under reflux for 3–5 h, and the volatile components were evaporated *in vacuo*. The oily residue was triturated with water (10 ml) and kept at 5 °C for 24 h. The precipitate was collected by filtration to give **4a–c**.

The following compounds were prepared in this manner:

4.2.1. Methyl {([(1*R*,3*E*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]methyl}glycinate (4a) and its (1*R*,3*Z*,4*S*)-isomer 4'a. Prepared from **2** and methyl glicinate hydrochloride (**3a**) (126 mg, 1 mmol); reflux for 5 h. Yield: 191 mg (76%) of a white solid; **4a**:**4'a** = 68:32; mp 81–91 °C. (Found: C, 66.83; H, 8.73; N, 5.78. $C_{14}H_{21}NO_3$ requires: C, 66.91; H, 8.42; N, 5.57.); IR, ν_{max} (KBr): 3242, 2950, 1749 (C=O), 1697 (C=O), 1616, 1411, 1318, 1236, 1200, 1104, 1075 cm^{-1}. Crystallization from a mixture of acetone and water (1:1) afforded pure compound **4a**.

4.2.1.1. Data for the major (1*R*,3*E*,4*S*)-isomer 4a. Yield: 48 mg (19%) of a white solid; **4a**:**4'a** = 100:0; mp 107–112 °C (from acetone–water); $[\alpha]_D^{21}$ +242.5 (c = 0.31, CH_2Cl_2); ^{1}H NMR (DMSO-d_6): δ 0.72, 0.79, 0.86 (9H, 3s, 1:1:1, 3×CH_3); 1.12–1.26, 1.51–1.62, and 1.82–1.94 (4H, 3m, 2:1:1, CH_2CH_2); 2.66 (1H, d, J = 3.4 Hz, H–C(4')); 3.64 (3H, s, OCH_3); 3.93 (2H, d, *J* = 6.0 Hz, C*H*$_2$NH); 6.54–6.62 (1H, m, NH); 6.82 (1H, d, J = 12.0 Hz, H–C(3'')).

4.2.1.2. Data for the minor (1*R*,3*Z*,4*S*)-isomer 4'a. ^{1}H NMR (DMSO-d_6): δ 0.74, 0.81, 0.83 (9H, 3s, 1:1:1, 3×CH_3); 2.31 (1H, d, *J* = 3.4 Hz, H–C(4')); 3.64 (3H, s, OCH_3); 3.96 (2H, d, J = 6.4 Hz, C*H*$_2$NH); 6.44 (1H, d, J = 12.4 Hz, H–C(3')); 7.50–7.60 (1H, m, NH).

4.2.2. ({[(1*R*,3*E*,4*S*)-1,7,7-Trimethyl-2-oxobicyclo-[2.2.1]hept-3-ylidene]methyl}amino)acetonitrile (4b) and its minor (1*R*,3*Z*,4*S*)-isomer 4'b.

Prepared from **2** and aminoacetonitrile hydrochloride (**3b**) (93 mg, 1 mmol); reflux for 3 h. Yield: 177 mg (81%) of a white solid; **4b**:**4'b** = 80:20; mp 100–137 °C. (Found: C, 71.71; H, 8.48; N, 13.04. $C_{13}H_{18}N_2O$ requires: C, 71.53; H, 8.31; N, 12.83.). MPLC (EtOAc–hexanes, 1:2) afforded pure compound **4b** (second fraction) and isomerically enriched **4'b** (first fraction, **4b'**:**4b** = 96:4).

4.2.2.1. Data for the major (1*R*,3*E*,4*S*)-isomer 4b. Yield: 103 mg (47%) of a white solid; **4b**:**4'b** = 100:0; mp 130–136 °C; $[\alpha]_D^{20}$ +262.5 (c = 0.28, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): *δ* 0.83, 0.94, 0.95 (9H, 3s, 1:1:1, 3×CH_3); 1.31–1.46, 1.61–1.71, 1.93–2.05 (4H, 3m, 2:1:1, C*H*$_2$C*H*$_2$); 2.51 (1H, d, *J* = 3.8 Hz, H–C(4')); 4.06 (2H, d, *J* = 6.4 Hz, C*H*$_2$NH); 4.13 (1H, br s, NH); 6.85 (1H, d, *J* = 11.3 Hz, H–C(3'')). ^{13}C NMR (DMSO-d_6): *δ* 9.7, 19.1, 20.7, 27.2, 31.5, 36.0, 46.7, 48.1, 58.0, 117.0, 117.9, 134.6,

207.4. (Found: C, 71.80; H, 8.39; N, 12.55. $C_{13}H_{18}N_2O$ requires: C, 71.53; H, 8.31; N, 12.83.); IR, ν_{max} (KBr): 3338, 2959, 2249 (C≡N), 1699 (C=O), 1613, 1451, 1423, 1311, 1237, 1221, 1202, 1173, 1070, 1019, 945 cm^{-1}.

4.2.2.2. Data for the minor (1*R*,3*Z*,4*S*)-isomer 4'b. Yield: 18 mg (8%) of a white solid; **4b**:**4'b** = 4:96; mp 95–101 °C; $[\alpha]_D^{20}$ +228.5 (c = 0.46, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.81, 0.90, 0.94 (9H, 3s, 1:1:1, 3×CH_3); 1.31–1.41, 1.61–1.71, 1.95–2.08 (4H, 3m, 2:1:1, CH_2CH_2); 2.37 (1H, d, J = 3.8 Hz, H–C(4')); 4.00 (2H, d, J = 6.0 Hz, CH_2NH); 6.23 (1H, d, J = 11.7 Hz, H–C(3'')); 7.53 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ 9.2, 19.1, 20.6, 28.4, 30.3, 35.9, 49.1, 49.7, 116.2, 116.5, 138.5, 209.2. (Found: C, 71.58; H, 8.58; N, 12.73. $C_{13}H_{18}N_2O$ requires: C, 71.53; H, 8.31; N, 12.83.); IR, ν_{max} (KBr): 3318, 2965, 2250 (C≡N), 1682 (C=O), 1623, 1467, 1416, 1370, 1279, 1225, 1161, 1107, 1068, 1030, 940 cm^{-1}.

4.2.3. Ethyl 3-({[(1*R*,3*E*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]methyl}amino)-propanoate (4c) and its minor (1*R*,3*Z*,4*S*)-isomer 4'c. Prepared from (**2**) and ethyl β-alaninate hydrochloride (**3c**) (154 mg, 1 mmol); reflux for 5 h. Yield: 151 mg (54%) of a white solid; **4c:4'c** = 93:7; mp 83–90 °C; $[\alpha]_D^{20}$ +245.4 (c = 0.39, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 9.5, 9.8, 14.6, 19.3, 19.6, 20.6, 20.7, 27.1, 29.0, 30.6, 31.9, 36.1, 36.7, 44.0, 44.6, 46.5, 48.3, 49.3, 50.3, 57.9, 61.1, 61.2, 111.7, 114.0, 137.5, 142.6, 171.7, 172.3, 206.8, 207.9. (Found: C, 68.73; H, 9.18; N, 5.29. $C_{16}H_{25}NO_3$ requires: C, 68.79; H, 9.02; N, 5.01.); IR, ν_{max} (KBr): 3283, 2956, 1721 (C=O), 1692 (C=O), 1619, 1580, 1452, 1369, 1318, 1260, 1196, 1169, 1086, 1072 cm^{-1}.

4.2.3.1. Data for the major (1*R*,3*E*,4*S*)-isomer 4c. ^{1}H NMR ($CDCl_3$): δ 0.81, 0.90, 0.93 (9H, 3s, 1:1:1, 3×CH_3); 1.23–1.42 (2H, m, CH_2CH_2); 1.27 (3H, t, J = 7.2 Hz, CH_2CH_3); 1.58–1.67 (1H, m, 1H of CH_2); 1.88–1.98 (2H, 2m, 1:1, CH_2CH_2); 2.42 (1H, d, J = 3.8 Hz, H–C(4')); 2.54 (2H, t, J = 6.4 Hz, CH_2COOEt); 3.42 (2H, q, J = 6.4 Hz, CH_2NH); 4.17 (2H, q, J = 7.2 Hz, CH_2CH_3); 4.40–4.57 (1H, m, NH); 6.96 (1H, d, J = 13.6 Hz, H–C(3'')).

4.2.3.2. Data for the minor (1*R*,3*Z*,4*S*)-isomer 4'c. ^{1}H NMR ($CDCl_3$): δ 0.79, 0.86, 0.92 (9H, 3s, 1:1:1, 3×CH_3); 2.29 (1H, d, J = 3.8 Hz, H–C(4')); 6.33 (1H, d, J = 12.4 Hz, H–C(3'')); 7.66 (1H, br s, NH).

4.3. Diethyl (2*S*)-2-({[(1*R*,3*E*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptan-3-ylidene]methyl}-amino)pentanedioate (4d) and its minor (2*S*,1'*R*,3'*Z*,4'*S*)-isomer 4'd.

Diethyl (*S*)-glutaminate hydrochloride (**3d**) (240 mg, 1 mmol) was added to a solution of compound **2** (207 mg, 1 mmol) in anhydrous ethanol (3 ml), the mixture was stirred under reflux for 6 h, and the volatile components were evaporated *in vacuo*. The oily residue was purified by CC (EtOAc–hexanes, 2:1). Fractions containing the product were combined and evaporated *in vacuo* to give **4d**. Yield: 303 mg (83%) of a colorless oil; **4d:4'd** = 70:30; $[\alpha]_D^{20}$ +134.5 (c = 0.39, CH_2Cl_2, **4d:4'd** = 48:52). EI-MS (*m*/*z*): 365 (M^+); EI-HRMS (*m*/*z*): Found: 365.221050 (M^+); $C_{20}H_{31}NO_5$ requires: 365.220223 (M^+); (Found: C, 65.16; H, 8.56; N, 4.16. $C_{20}H_{31}NO_5$ requires: C, 65.73; H, 8.55; N, 3.83.); IR, ν_{max} (NaCl): 3308, 2957, 1738 (C=O), 1689 (C=O), 1615, 1472, 1447, 1373, 1325, 1253, 1183, 1161, 1107, 1073, 1027 cm^{-1}.

4.3.1. Data for the major (2*S*,1'*R*,3'*E*,4'*S*)-isomer 4d. ^{1}H NMR ($CDCl_3$): δ 0.81, 0.92, 0.94 (9H, 3s, 1:1:1, 3×CH_3); 1.22–1.44 (8H, m, 2×CH_2CH_3 and CH_2CH_2); 1.54–1.69 (1H, m, 1H of CH_2CH_2); 1.91–2.22 (3H, m, 1H of CH_2CH_2 and CH_2CH_2COOEt); 2.31–2.51 (3H, m, CH_2COOEt and H–C(4')); 3.84–3.92 (1H, m, CH_2CHNH); 4.09–4.24 (4H, m, 2×OCH_2CH_3); 4.46 (1H, dd, J = 8.7, 13.2 Hz, NH); 6.88 (1H, d, J = 13.2 Hz, H–C(3'')). ^{13}C NMR ($CDCl_3$): δ 9.4, 14.5, 14.5, 19.5, 20.7, 28.7, 30.3, 30.5, 49.3, 50.2, 58.8, 60.1, 61.0, 61.8, 62.1, 113.5, 140.2, 171.9, 172.9, 208.4.

4.3.2. Data for the minor (2*S*,1'*R*,3'*Z*,4'*S*)-isomer 4'd. ^{1}H NMR ($CDCl_3$): δ 0.81, 0.88 (6H, 2s, 1:1, 2×CH_3); 3.75–3.83 (1H, m, CH_2CHNH); 6.26 (1H, d, J = 12.1 Hz, H–C(3'')); 7.74 (1H, br t, J = 10.4 Hz, NH).

4.4. 1-{[(1*R*,3*Z*,4*S*)-1,7,7-Trimethyl-2-oxobicyclo-[2.2.1]hept-3-ylidene]methyl}pyrazolidin-3-one (6a).

Pyrazolidin-3-one hydrochloride (**3a**) (123 mg, 1 mmol) was added to a solution of compound **2** (207 mg, 1 mmol) in anhydrous ethanol (6 ml) and the mixture was stirred under reflux for 2 h. Volatile components were evaporated *in vacuo* and the oily residue was purified by CC (EtOAc). Fractions containing the product were combined and evaporated *in vacuo* to give **6a**. Yield: 114 mg (46%) of a yellow solid; mp 140–145 °C; $[\alpha]_{588}^{20}$ = +260.8 (c = 0.291, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 0.87, 0.93 (9H, 2s, 2:1, 3×CH_3); 1.26–1.42, 1.57–1.70, 1.96–2.04 (4H, 3m, 2:1:1, CH_2CH_2 of camphor); 2.31 (1H, d, J = 3.4 Hz, H–C(4')); 2.72 (2H, t, J = 8.7 Hz, 4–CH_2); 3.95 (2H, t, J = 8.7 Hz, 5–CH_2); 5.99 (1H, s, H–C(3'')); 13.15 (1H, s, H–N(2)). ^{13}C NMR ($CDCl_3$): δ 10.0, 19.5, 20.6, 29.1, 30.5, 31.6, 49.5, 50.0, 52.2, 59.3, 108.9, 132.1, 169.3, 205.4. (Found: C, 67.80; H, 8.32; N, 11.24. $C_{14}H_{20}N_2O_2$ requires: C, 67.71; H, 8.12; N, 11.28.); IR, ν_{max} (KBr): 2959, 1704 (C=O), 1656 (C=O), 1557, 1466, 1397, 1369, 1277, 1223, 1030 cm^{-1}.

4.5. General Procedure for the Preparation of 1-{[(1*R*,3*Z*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]methyl}pyrazolidin-3-ones 6b,d,e.

Hydrochloric acid (37%, 0.1 ml, ~1 mmol) was added to a solution of **2** (207 mg, 1 mmol) and pirazolidin-3-one **5b,d,e** (1 mmol) in anhydrous ethanol (6 ml) and the mixture was stirred at r.t. or under reflux for 1.5–7 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC. Fractions containing the product were combined and evaporated *in vacuo* to give **6b,d,e**.

The following compounds were prepared in this manner:

4.5.1. 5,5-Dimethyl-1-{[(1*R*,3*Z*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]methyl}-pyrazolidin-3-one (6b). Prepared from **2** and 5,5-dimethylpyrazolidin-3-one (**5b**) (114 mg, 1 mmol); r.t. for 7 h; CC: EtOAc–hexanes, 1:1. Yield: 221 mg (80%) of a yellow solid; mp 173–178 °C; $[\alpha]_D^{20}$ = +250.4 (c = 0.48, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 0.86, 0.87, 0.93 (9H, 3s, 1:1:1, 3×CH_3); 1.26–1.40 (2H, m, CH_2CH$_2$ of camphor); 1.48 (6H, s, 2×CH_3); 1.56–1.68, 1.93–2.07 (2H, 2m, 1:1, CH_2CH_2 of camphor); 2.31 (1H, d, J = 3.8 Hz, H–C(4')); 2.55 (2H, s, 4–CH_2); 6.00 (1H, s, H–C(3'')); 13.63 (1H, s, H–N(2)). ^{13}C NMR ($CDCl_3$): δ 10.1, 19.6, 20.6, 27.5, 27.6, 29.2, 30.5, 45.7, 49.5, 52.6, 59.4, 64.1, 108.1, 127.0, 167.1, 204.9. (Found: C, 69.27; H, 9.00; N, 10.33. $C_{16}H_{24}N_2O_2$ requires: C, 69.53; H, 8.75; N, 10.14.); IR, ν_{max} (KBr): 2963, 1702 (C=O), 1651 (C=O), 1553, 1386, 1371, 1286, 1200, 1108, 1026 cm^{-1}.

4.5.2. (4*R,5*R**)-4-Benzoylamino-5-phenyl-1-{[(1*R*,3*Z*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]methyl}pyrazolidin-3-one (6/6'd).** Prepared from **2** and (4*R**,5*R**)-4-benzoylamino-5-phenylpyrazolidin-3-one (**5d**) (282 mg, 1 mmol); r.t. for 4 h; CC ($CHCl_3$–MeOH, 40:1). Yield: 204 mg (46%) of a yellow solid; **6d:6d'** = 1:1; mp 123–128 °C. EI-MS (*m*/*z*): 443 (M^+); EI-HRMS (*m*/*z*): Found: 443.221760 (M^+); $C_{27}H_{29}N_3O_3$ requires: 443.220892. (Found: C, 72.88; H, 6.70; N, 9.56. $C_{27}H_{29}N_3O_3$ requires: C, 73.11; H, 6.59; N, 9.47.); IR, ν_{max} (KBr): 2958, 1724 (C=O), 1657 (C=O), 1538, 1490, 1374, 1340, 1167, 1072, 1020 cm^{-1}.

4.5.2.1. NMR data for the first isomer. ^{1}H NMR ($CDCl_3$): δ 0.85, 0.89, 0.96 (9H, 3s, 1:1:1, 3×CH_3); 1.22–1.44, 1.58–1.68, 1.88–1.99 (4H, 3m, 2:1:1, CH_2CH_2); 2.21 (1H, br d, J = 3.4 Hz, H–C(4')); 4.94 (1H, dd, J = 6.8, 9.0 Hz, H–C(4)); 5.09 (1H, d, J = 9.0 Hz, H–C(5)); 5.76 (1H, s, H–C(3'')); 7.28–7.33 and 7.39–7.46 (8H, 2m, 2:6, 8H of Ph); 7.54 (1H, br d, J = 6.4 Hz, N*H*CH); 7.67–7.72 (2H, m, 2H of Ph); 14.19 (1H, br s, H–N(2)).

4.5.2.2. NMR data for the second isomer. ^{1}H NMR ($CDCl_3$): δ 0.85, 0.89, 0.96 (9H, 3s, 1:1:1, 3×CH_3); 1.22–1.44, 1.58–1.68, 1.88–1.99 (4H, 3m, 2:1:1, CH_2CH_2); 2.21 (1H, br d, J = 3.4 Hz, H–C(4')); 4.77 (1H, dd, J = 6.8, 8.3 Hz, H–C(4)); 5.14 (1H, d, J = 8.3 Hz, H–C(5)); 5.79 (1H, s, H–C(3'')); 7.28–7.33 and 7.39–7.46 (8H, 2m, 2:6, 8H of Ph); 7.50 (1H, br d, J = 6.8 Hz, H–N(4)); 7.67–7.72 (2H, m, 2H of Ph); 14.16 (1H, s, H–N(2)).

4.5.3.(4*R)-4-Benzyloxycarbonylamino-1-{[(1*R*,3*Z*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]-methyl}pyrazolidin-3-one (6/6'e).** Prepared from **2** and (4*RS*)-4-benzyloxycarbonyl-aminopyrazolidin-3-one (**5e**) (236 mg, 1 mmol); reflux for 1.5 h; CC ($CHCl_3$–MeOH, 40:1). Yield: 191 mg (48%) of a yellow solid; **6e**:**6'e** = 1:1; mp 60–70 °C; EI-MS (*m*/*z*) = 397 (M^+); EI-HRMS (*m*/*z*): Found: 397.201250 (M^+); $C_{22}H_{27}N_3O_4$ requires: 397.200157. (Found: C, 66.19; H, 7.10; N, 10.48. $C_{22}H_{27}N_3O_4$ requires: C, 66.48; H, 6.85; N, 10.57.); IR, ν_{max} (KBr): 2958, 1717 (C=O), 1657 (C=O), 1619, 1536, 1455, 1388, 1258, 1071, 1026 cm^{-1}.

4.5.3.1. NMR data for the first isomer. ^{1}H NMR ($CDCl_3$): δ 0.88, 0.94 (9H, 2s, 2:1, 3×CH_3); 1.32–1.45, 1.61–1.68, and 1.95–2.05 (4H, 3m, 2:1:1, CH_2CH_2); 2.35 (1H, d, J = 3.8 Hz, H–C(4')); 3.68–3.76 (1H, m, Ha–C(5)); 4.32–4.40 (1H, m, H–C(4)); 4.49–4.57 (1H, m, Hb-C(5)); 5.11 (2H, s, OCH_2Ph); 5.67 (1H, br s, N*H*CH); 6.04 (1H, s, H–C(3'')); 7.27–7.41 (5H, m, Ph); 13.67 (1H, s, H–N(2)).

4.5.3.2. NMR Data for the second isomer. ^{1}H NMR ($CDCl_3$): δ 0.84, 0.93, 0.94 (9H, 3s, 1:1:1, 3×CH_3); 1.32–1.45, 1.61–1.68, and 1.95–2.05 (4H, 3m, 2:1:1, CH_2CH_2); 2.33 (1H, d, J = 3.4 Hz, H–C(4')); 3.68–3.76 (1H, m, Ha–C(5)); 4.32–4.40 (1H, m, H–C(4)); 4.49–4.57 (1H, m, Hb-C(5)); 5.11 (2H, s, OCH_2Ph); 5.67 (1H, br s, N*H*CH); 6.04 (1H, s, H–C(3'')); 7.27–7.41 (5H, m, Ph); 13.61 (1H, s, H–N(2)).

4.6. 1-{[(1*R*,3*Z*,4*S*)-1,7,7-Trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]methyl}-1,2-dihydro-3*H*-indazol-3-one (6c).

A solution of **2** (207 mg, 1 mmol) and 1,2-dihydro-3*H*-indazol-3-one (**5c**) (134 mg, 1 mmol) in acetic acid (6 ml) was stirred under reflux for 2.5 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc–hexanes, 1:1). Fractions containing the product were combined and evaporated *in vacuo* to give **6c**. Yield: 119 mg (40%) of a yellow solid; mp 173–177 °C; $[\alpha]_D^{21}$ = +350.6 (c = 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.92, 0.97, 1.02 (9H, 3s, 1:1:1, 3×CH_3); 1.42–1.58, 1.72–1.82, and 2.09–2.18 (4H, 3m, 2:1:1, CH_2CH_2); 2.58 (1H, d, J = 3.8 Hz, H–C(4')); 6.75 (1H, s, H–C(3'')); 7.23–7.29 (1H, m,

1H of Ar); 7.33 (1H, d, J = 8.3 Hz, 1H of Ar); 7.59 and 7.91–7.94 (2H, 2m, 2H of Ar); 13.62 (1H, s, H–N(2)). ^{13}C NMR ($CDCl_3$): δ 9.9, 19.2, 20.9, 28.5, 30.3, 48.6, 52.5, 59.9, 109.3, 117.3, 118.8, 120.9, 123.7, 124.9, 132.9, 140.4, 160.4, 207.5. (Found: C, 72.88; H, 6.87; N, 9.70. $C_{18}H_{20}N_2O_2$ requires: C, 72.95; H, 6.80; N, 9.45.); IR, ν_{max} (KBr): 2961, 1691 (C=O), 1659 (CO), 1577, 1464, 1374, 1332, 1068, 1018, 993 cm^{-1}.

4.7. Methyl (2*Z*)-3-(dimethylamino)-2-({[(1*R*,3*E*,4*S*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]hept-3-ylidene]-methyl}amino)propenoate (7) and its (2*Z*,1'*R*,3'*Z*,4'*S*)-isomer 7'.

Bis(dimethylamino)-*tert*-butoxy-methane (0.31 ml, 1.5 mmol) was added to a mixture of **4**/**4'a** (251 mg, 1 mmol, **4a**:**4'a** = 68:32) and anhydrous toluene (5 ml) and the solution was stirred under reflux for 1 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc–hexanes, 1:1). Fractions containing the product were combined and evaporated *in vacuo* to give **7**/**7'**. 147 mg (48%) of a yellow solid; **7**:**7'** = 59:41; mp 136–144 °C (from *n*-hexane–CH_2Cl_2); $[\alpha]_D^{20}$ +247.1 (c = 0.31, CH_2Cl_2); ^{13}C NMR ($CDCl_3$): δ 9.5, 9.7, 19.2, 19.5, 20.6, 20.7, 27.4, 28.9, 30.6, 31.6, 38.9, 42.7, 42.8, 46.6, 48.2, 49.3, 50.1, 51.5, 57.7, 58.7, 100.1, 101.0, 112.5, 115.1, 139.1, 144.1, 144.9, 145.7, 168.9, 170.0, 207.3, 208.0. EI-MS (*m*/*z*): 306 (M^+); EI-HRMS (*m*/*z*): Found: 306.195650 (M^+); $C_{17}H_{26}N_2O_3$ requires: 306.194343 (M^+). (Found: C, 66.37; H, 8.81; N, 9.36. $C_{17}H_{26}N_2O_3$ requires: C, 66.64; H, 8.55; N, 9.14.); IR, ν_{max} (KBr): 3298, 2953, 1693 (C=O), 1622, 1607, 1580, 1432, 1378, 1299, 1281, 1252, 1217, 1179, 1128, 1086, 948 cm^{-1}.

4.7.1. NMR Data for the major (2*Z*,1'*R*,3'*E*,4'*S*)-isomer 7: ^{1}H NMR ($CDCl_3$): δ 0.83, 0.91, 0.94 (9H, 3s, 1:1:1, 3×CH_3); 1.24–1.45, 1.55–1.68, and 1.91–2.04 (4H, 3m, 2:1:1, CH_2CH_2); 2.58 (1H, d, J = 3.4 Hz, H–C(4')); 3.02 (6H, s, NMe_2); 3.66 (3H, s, COOMe); 4.80 (1H, d, J = 11.3 Hz, NH); 6.90 (1H, d, J = 11.7 Hz, H–C(3'')); 7.19 (1H, s, H–C(3)).

4.7.2. NMR Data for the minor (2*Z*,1'*R*,3'*Z*,4'*S*)-isomer 7': ^{1}H NMR ($CDCl_3$): δ 0.84, 0.88, 0.93 (9H, 3s, 1:1:1, 3×CH_3); 2.33 (1H, d, J = 3.4 Hz, H–C(4')); 3.00 (6H, s, NMe_2); 6.24 (1H, d, J = 12.1 Hz, H–C(3'')); 7.16 (1H, s, H–C(3)); 8.19 (1H, d, J = 12.4 Hz, NH).

4.8. General Procedure for the Preparation of Dimethyl 2,3-dihydro-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates 10/11/12/13.

A mixture of **6a** (276 mg, 1 mmol) or **6b** (248 mg, 1 mmol) and DMAD (142 mg, 1 mmol) in anisole (5 ml) was stirred under reflux for 4 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc–hexanes, 1:2). Fractions containing the product were combined and evaporated *in vacuo* to give a mixture of four isomeric cycloadducts **10**/**11**/**12**/**13**.

The following compounds were prepared in this manner:

4.8.1. Dimethyl (5*R)-2,3-dihydro-1-oxo-5-[(1*R*,3*R*,4*R*)-1,7,7-trimethyl-2-oxobicyclo[2.2.1]-hept-3-yl]-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-6,7-dicarboxylates 10/11a and their (5*R**,1'*R*,3'*S*,4'*R*)-isomers 12/13a.** Prepared from **6a**; CC (EtOAc–hexanes, 1:2). Yield: 301 mg (77%) of a yellow solid; **10a:11a:12a:13a** = 44:36:12:8. Further chromatographic separation by MPLC (EtOAc–hexanes, 1:2) afforded a mixture of **11a** and **12a** (first fraction) and a mixture of **10a** and **13a** (second fraction).

4.8.1.1. Data for a mixture of 10a and 13a (second fraction). Yield: 59 mg (15%) of a yellow solid; **10a:13a** = 84:16; mp 51–63 °C. (Found: C, 61.65; H, 6.94; N, 7.39. $C_{20}H_{26}N_2O_6$ requires: C, 61.53; H, 6.71; N, 7.18.); IR, ν_{max} (KBr): 2958, 1741 (C=O), 1709 (C=O), 1635, 1438, 1394, 1361, 1251, 1199, 1166, 1121, 1094, 1030 cm^{-1}.

4.8.1.1.1. NMR data for the major *endo*-isomer 10a. ^{1}H NMR ($CDCl_3$): δ 0.88, 0.91, 0.99 (9H, 3s, 1:1:1, 3×CH_3); 1.35–1.55 and 1.61–1.91 (4H, 2m, 1:3, CH_2CH_2); 2.07–2.11 (1H, m, H–C(4')); 2.51–2.56 (1H, m, Ha–C(2)); 2.79–2.83 (1H, m, H–C(3')); 2.85–3.18 (2H, m, Hb–C(2) and Ha–C(3)); 3.73 (3H, s, 6–COOMe); 3.93–4.00 (1H, m, Hb–C(3)); 3.95 (3H, s, 7–COOMe); 4.44 (1H, d, J = 6.4 Hz, H–C(5)).

4.8.1.1.2. NMR data for the minor *exo*-isomer 13a. ^{1}H NMR ($CDCl_3$): δ 0.96, 1.02 (6H, 2s, 1:1, 2×CH_3); 2.49 (1H, d, J = 7.2 Hz, H–C(3')); 3.57–3.63 (1H, m, Hb–C(3)); 3.74 (3H, s, 6–COOMe); 3.94 (3H, s, 7–COOMe); 4.64 (1H, d, J = 7.2 Hz, H–C(5)).

4.8.1.2. Data for a mixture of 11a and 12a (first fraction). Yield: 86 mg (22%) of a yellow solid; **11a:12a** = 79:21; mp 53–61 °C. (Found: C, 61.71; H, 6.96; N, 7.47. $C_{20}H_{26}N_2O_6$ requires: C, 61.53; H, 6.71; N, 7.18.); IR, ν_{max} (KBr): 2958, 1757 (C=O), 1738 (C=O), 1707 (C=O), 1627, 1439, 1392, 1368, 1345, 1255, 1202, 1170, 1092, 1033 cm^{-1}.

4.8.1.2.1. NMR data for the major *endo*-isomer 11a. ^{1}H NMR ($CDCl_3$): δ 0.87, 0.92, 0.99 (9H, 3s, 1:1:1, 3×CH_3); 1.48–1.82 (3H, m, 3H of CH_2); 1.95–2.05 (2H, m, 1H of CH_2 and H–C(4')); 2.52–2.60 (1H, m, Ha–C(2)); 2.75–2.88 (1H, m, Hb–C(2)); 3.01–3.11 (1H, m, Ha–C(3)); 3.19 (1H, br deg dt, J = 1.3, 5.0 Hz, H–C(3')); 3.62–3.68 (1H, m, Hb–C(3)); 3.75 (3H, s, 6–COOMe); 3.94 (3H, s, 7–COOMe); 4.94 (1H, d, J = 5.3 Hz, H–C(5)).

4.8.1.2.2. NMR data for the minor *exo*-isomer 12a. ^{1}H NMR ($CDCl_3$): δ 0.93, 0.94 (6H, 2s, 1:1, 2×CH_3); 2.17 (1H, d, J = 4.1 Hz, H–C(4')); 2.44 (1H, d, J = 9.1 Hz, H–C(3')); 3.76 (3H, s, 6–COOMe); 3.93 (3H, s, 7–COOMe); 4.49 (1H, d, J = 9.1 Hz, H–C(5)).

4.8.2. Dimethyl (5*R)-2,3-dihydro-5,5-dimethyl-1-oxo-3-[(1*R*,3*R*,4*R*)-1,7,7-trimethyl-2-oxo-bicyclo[2.2.1]hept-3-yl]-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylates 10/11b and their (5*R**,1'*R*,3'*S*,4'*R*)-isomers 12/13b.** Prepared from **6b**; CC (EtOAc–hexanes, 1:2). Yield: 347 mg (83%) of a yellow solid; **10b:11b:12b:13b** = 51:31:9:9. Further chromatographic separation by MPLC (EtOAc–hexanes, 1:4) afforded a mixture of **11b** and **12b** (first fraction) and a mixture of **10b** and **13b** (second fraction).

4.8.2.1. Data for a mixture of 10b and 13b (second fraction). Yield: 167 mg (40%) of a yellow solid; **10b:13b** = 77:23; mp 51–56 °C. (Found: C, 63.48; H, 7.44; N, 6.70. $C_{22}H_{30}N_2O_6$ requires: C, 63.14; H, 7.23; N, 6.69.); IR, ν_{max} (KBr): 2961, 1744 (C=O), 1712 (C=O), 1630, 1438, 1374, 1346, 1292, 1272, 1231, 1199, 1167, 1115, 1034 cm^{-1}.

4.8.2.1.1. NMR Data for major *endo*-isomer 10b. ^{1}H NMR ($CDCl_3$): δ 0.86, 0.90, 0.97, 1.04, 1.37 (15H, 5s, 1:1:1:1:1, 5×CH_3); 1.25–1.48, 1.62–1.87, and 1.93–2.04 (5H, 3m, 1:2:2, CH_2CH_2 and H–C(4')); 2.25 (1H, d, J = 15.5 Hz, Ha–C(2)); 2.55 (1H, ddd, J = 1.5; 4.5; 8.3 Hz, H–C(3')); 2.87 (1H, d, J = 15.5 Hz, Hb–C(2)); 3.72 (3H, s, 6–COOMe); 3.94 (3H, s, 7–COOMe); 4.66 (1H, d, J = 8.3 Hz, H–C(5)).

4.8.2.1.2. NMR data for minor *exo*-isomer 13b. ^{1}H NMR ($CDCl_3$): δ 0.89, 0.96, 1.01, 1.07, 1.36 (15H, 5s, 1:1:1:1:1, 5×CH_3); 2.17 (1H, d, J = 8.9 Hz, H–C(3')); 2.22 (1H, d, J = 15.4 Hz, Ha–C(2)); 2.74 (1H, d, J = 15.8 Hz, Hb–C(2)); 3.74 (3H, s, 6–COOMe); 3.93 (3H, s, 7–COOMe); 4.59 (1H, d, J = 8.8 Hz, H–C(5)).

4.8.2.2. Data for a mixture of 11b and 12b (first fraction). Yield: 92 mg (22%) of a yellow solid; **11b:12b** = 84:16; mp 46–51 °C. (Found: C, 63.23; H, 7.51; N, 6.74. $C_{22}H_{30}N_2O_6$ requires: C, 63.14; H, 7.23; N, 6.69.); IR, ν_{max} (KBr): 2961, 1758 (C=O), 1744 (C=O), 1707 (C=O), 1634, 1439, 1371, 1358, 1340, 1292, 1258, 1232, 1200, 1169, 1118, 1038 cm^{-1}.

4.8.2.2.1. NMR data for major *endo*-isomer 11b. ^{1}H NMR ($CDCl_3$): δ 0.84, 0.90, 0.99, 1.10, 1.27 (15H, 5s, 1:1:1:1:1, 5×CH_3); 1.45–1.53, 1.57–1.83, and 1.96–2.08 (5H, 3m, 1:2:2, CH_2CH_2 and H–C(4')); 2.25 (1H, d, J = 15.5 Hz, Ha–C(2)); 2.67 (1H, d, J = 15.5 Hz, Hb–C(2)); 2.92 (1H, br deg dt, J = 1.0, 5.0 Hz, H–C(3')); 3.73 (3H, s, 6–COOMe); 3.94 (3H, s, 7–COOMe); 4.98 (1H, d, J = 5.3 Hz, H–C(5)).

4.8.2.2.2. NMR data for minor *exo*-isomer 12b. ^{1}H NMR ($CDCl_3$): δ 0.91, 0.92, 0.98, 1.26, 1.43 (15H, 5s, 1:1:1:1:1, 5×CH_3); 2.23 (1H, d, J = 15.8 Hz, Ha–C(2)); 2.26 (1H, d, J = 9.1 Hz, H–C(3')); 2.84 (1H, d, J = 15.8 Hz, Hb–C(2)); 3.76 (3H, s, 6–COOMe); 3.94 (3H, s, 7–COOMe); 4.58 (1H, d, J = 9.1 Hz, H–C(5)).

4.9. X-Ray Structure Determination.

Single crystal X-ray diffraction data of compound **4b** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[60] DENZO and SCALEPACK[61] were used for indexing and scaling of the data. The structure was solved by means of SIR97.[62] Refinement was done using Xtal3.4[63] program package and the crystallographic plot was prepared by ORTEP III.[64] Crystal structure was refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[65] weighting scheme was used.

The crystallographic data for compound **4b** have been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: CCDC 604181. These data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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Povzetek

Pri kislinsko kataliziranih reakcijah (1*R*,3*E*,4*S*)-3-[(dimetilamino)metiliden]-1,7,7-trimetilbiciklo-[2.2.1]heptan-2-ona (**2**) z α-aminokislinskimi derivati **3a–d** in pirazolidin-3-oni **5a–e** poteče izmenjava dimetilaminske skupine, ki vodi do nastanka ustreznih N-substituiranih (1*R*,4*S*)-3-aminometiliden-1,7,7-trimetilbiciklo[2.2.1]heptan-2-onov **4/4'a–d** in **6a–e**. Izmenjave dimetilaminske skupine z α-aminokislinskimi derivati **3a–d** so vodile do zmesi večinskih (*3E*)-izomerov **4a–d** in manjšinskih (*3Z*)-izomerov **4'a–d**, medtem ko so bile pretvorbe enaminona **2** s pirazolidinoni **5a–e** stereoselektivne saj so nastali izključno ustrezni (3*Z*)-izomeri **6a–e**. Pretvorba spojine **4a** z bis(dimetilamino)-*terc*-butoksimetanom (Bredereckovim reagentom) je vodila do 3-(dimetilamino)propenoata **7/7'**.
Izvedli smo tudi pretvorbi 1-{[(1*R*,3*Z*,4*S*)-1,7,7-trimetil-2-oksobiciklo[2.2.1]hept-3-iliden]metil}pirazolidin-3-onov **6a** and **6b** z dimetil acetilendikarboksilatom (DMAD). V obeh primerih sta nastali ustrezni zmesi štirih diastereomernih spojin, **10/11/12/13a** in **10/11/12/13b**, z večinskima *endo*-izomeroma **10** in **11** ter manjšinskima *ekso*-izomeroma **12** in **13**. S preparativno tekočinsko kromatografijo (MPLC) smo zmesi štirih izomerov **10/11/12/13** uspeli ločiti na dva *endo*/*ekso*-para izomerov, **10/13** in **11/12**. Strukture produktov so bile potrjene z NMR spektroskopijo in z rentgensko strukturno analizo.