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Synthesis and reductions of (1*R*,4*E*,5*S*)-4-oximino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one

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Abstract—(1*R*,4*E*,5*S*)-4-Oximino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **9** was prepared in three steps from (1*R*)-(+)-camphor **1** via nitrosation of (1*R*,4*E*,5*S*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **8**. Catalytic hydrogenation of **9** under various reaction conditions afforded (1*R*,4*S*,5*S*)-4-amino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one derivatives **11**, **13**, and **15b**. On the other hand, reduction of **9** with Grignard reagents led to two types of products, (1*R*,4*S*,5*S*)-4-dialkylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **15b** and **15c** and/or 2-substituted (1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]ethane-1,2-dione 1-oximes **16a**,**b** and **15d**–**f**. The structures of compounds **9**, **10′**, **15b**, and **16b** were determined by X-ray diffraction.

1. Introduction

(+)-Camphor **1** and its derivatives are among the most frequently employed types of chiral pool starting materials and building blocks, chiral ligands in various asymmetric reagents and/or catalysts, resolving agents, and as shift reagents in NMR spectroscopy.[1–4] For example, (+)-camphor derived compounds **2**–**5**,[5–8] as well as their ring opened analogues, (+)-camphoric acid **6**[9] and 1,3-diamino-1,2,2-trimethylcyclopentane **7** derivatives,[10–12] were used as chiral ligands for asymmetric catalysis (Fig. 1).

Unnatural α-amino acids represent an important group of compounds, not only due to pharmaceutical and biological applications, but also because of their utilization in organic synthesis and asymmetric transformations.[13–16]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates and their analogues have been prepared as versatile reagents for the preparation of various heterocyclic systems and in the synthesis of functionalized heterocycles, such as heterocyclic compounds containing α-amino acid, dipeptide, β-amino alcohol, α-hydroxy acid, and related structural elements.[17–22] Within this context, we have previously reported a stereoselective α-amination of lactams and lactones, which is based on the nitrosation of chiral α-enamino lactams and lactones into the corresponding α-oximino derivatives, followed by catalytic hydrogenation to furnish 5-substituted (3*S*,5*S*)-3-acetylamino-2-pyrrolidinones and (3*S*,5*S*)-3-acetylaminotetrahydrofuran-2-ones.[23] Our studies on chiral enaminones have recently been extended to the preparation and synthetic applications of (+)-camphor **1** derived enaminones, such as (1*R*,3*E*,4*R*)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one[22,24,25] and (1*R*,4*E*,5*S*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **8**.[22,25–27] In continuation of our work in this field, we herein report the preparation of (1*R*,4*E*,5*S*)-4-oximino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one **9** and its reductions into *N*,*N*-disubstituted (1*R*,4*S*,5*S*)-4-amino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-ones **11**, **13**, and **15** and 2-substituted (1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]ethane-1,2-dione 1-oximes **16**.

2. Results and discussion

Starting compound, (1*R*,4*E*,5*S*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **8**,

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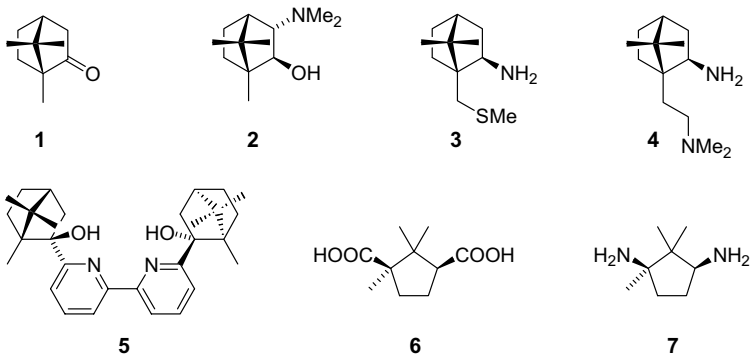
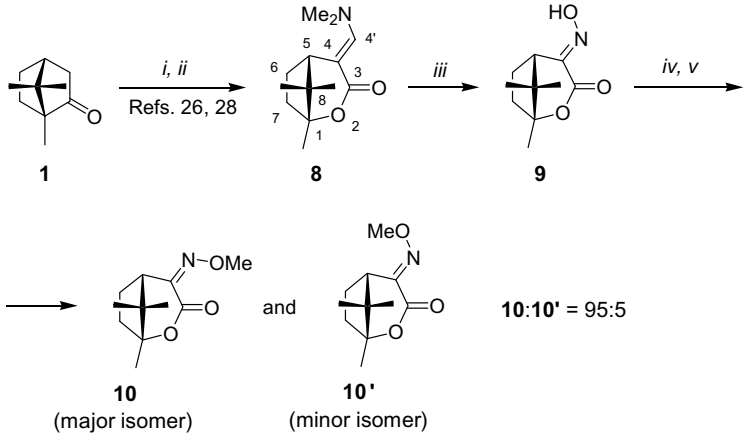


Figure 1. (+)-Camphor **1** and some examples of (+)-camphor **1** derived chiral ligands **2**–**7**.

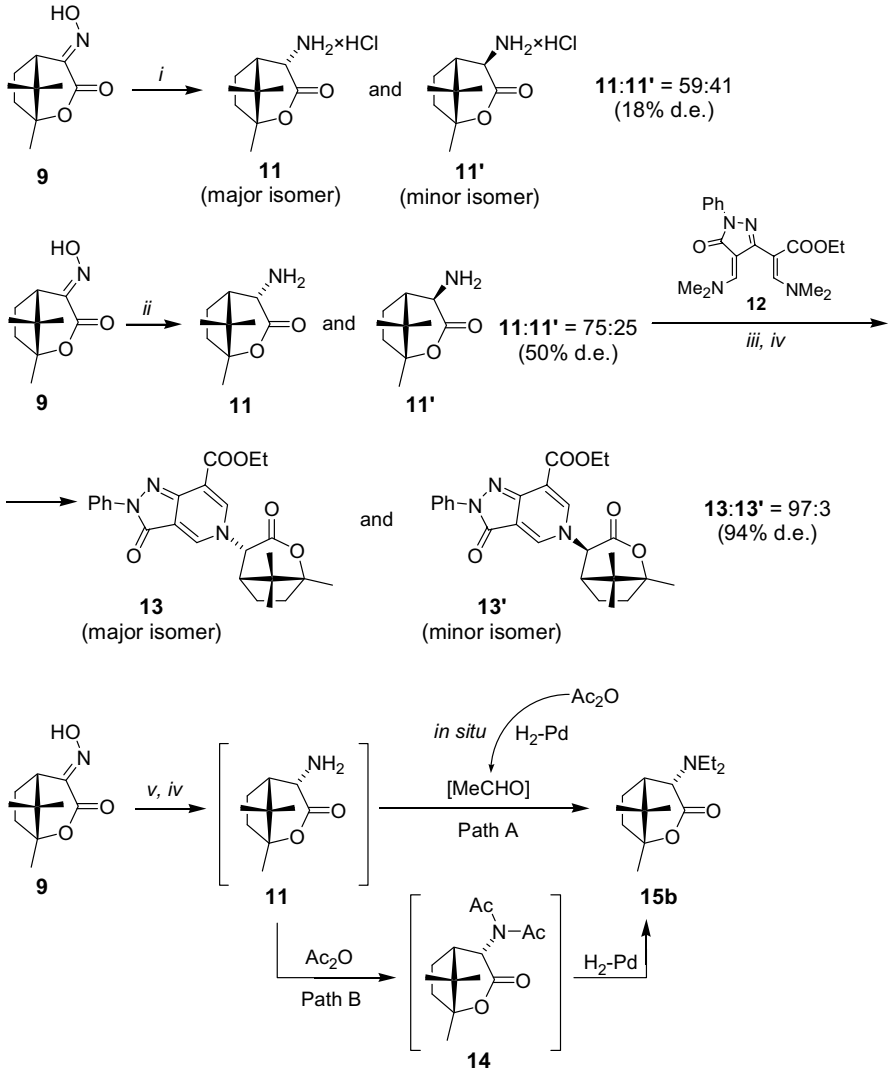
was prepared in two steps from (1*R*)-(+)-camphor **1**.[26,28] Treatment of **8** with aqueous sodium nitrite in diluted hydrochloric acid at rt afforded (1*R*,4*E*,5*S*)-4-oximino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**9**) in 43% yield. Reaction of oxime **9** with excess diazomethane in ether afforded the isomeric *O*-methyl derivatives **10** and **10′** in a ratio of 95:5. Upon chromatographic separation, the major (*Z*)-isomer **10** and the minor (*E*)-isomer **10′** were obtained in 90% and 5% yield, respectively (Scheme 1).

Catalytic hydrogenation (Pd–C, 50 bar of H_2, 35 °C, 48 h) of **9** in ethanol in the presence of 1.3 equiv of hydrochloric acid did not go to completion and afforded a mixture of the unreacted starting oxime **9** and two isomeric products, (1*R*,4*S*,5*S*)-4-amino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **11** hydrochloride and its (1*R*,4*R*,5*S*)-epimer **11′** in a ratio of 65:20:15, respectively. Upon crystallization, a mixture of hydrochlorides of **11** and **11′** in a ratio of 59:41 was obtained in 25% yield. On the other hand, when hydrogenation of **9** was carried out in ethanol at 50 °C, a 75:25 mixture of the free α-amino lactones **11** and **11′** was formed. Further acid-catalyzed treatment of **11**/**11′** with ethyl 3-dimethylamino-2-{4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl}propenoate **12** in ethanol under reflux furnished a mixture of ethyl 3,5-dihydro-3-oxo-2-phenyl-5-[(1*R*,4*S*,5*S*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]oct-4-yl]-2*H*-pyrazolo[4,3-*c*]pyridin-7-carboxylate **13** and its (1′*R*,4′*R*,5′*S*)-epimer **13′** in a ratio of 97:3. Upon chromatographic separation, isomerically pure compounds **13** and **13′** were obtained in 54% and 2% yield, respectively. Finally, hydrogenation of **9** was carried out in a mixture of acetic acid and acetic anhydride under 55 bar of hydrogen at 60 °C to give, surprisingly, isomerically pure (1*R*,4*S*,5*S*)-4-diethylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **15b** in 39% yield. The formation of **15b** can be explained by the initial formation of **11** as the primary intermediate, which undergoes reductive bis-alkylation with in situ formed acetaldehyde (Path A).[29–31] Alternatively, amine **11** is bis-acetylated into **14**, followed by reduction of both acetyl groups to give compound **15b** (Path B) (Scheme 2).[32]

In continuation, we studied reactions of oxime **9** with Grignard reagents. Since we expected that these reactions would proceed by the addition of a Grignard reagent to the C=O and/or C=N bond, we were very surprised by the outcome of the first experiment, where reaction of **9** with excess of ethylmagnesium bromide furnished two products: (1*R*,4*S*,5*S*)-4-diethylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **15b** was obtained as the major product in 39% yield and



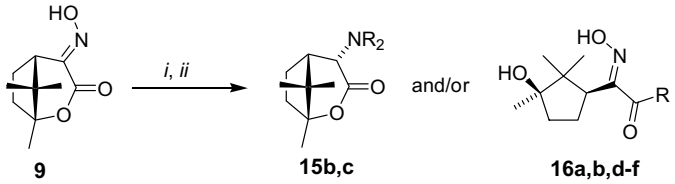
Scheme 1. Reagents and conditions: (i) AcOOH–AcOH, AcONa, rt (Ref. 27); (ii) bis(dimethylamino)-*tert*-butoxymethane, decaline, reflux (Ref. 25); (iii) $NaNO_2$, HCl, H_2O, rt; (iv) ~0.33 M CH_2N_2–Et_2O (3 equiv), dichloromethane, rt; (v) chromatographic separation.



Scheme 2. Reagents and conditions: (i) H_2 (50 bar), 10% Pd–C, EtOH, 37% aq HCl (1.3 equiv), 35 °C, 48 h, then crystallization; (ii) H_2 (50 bar), 10% Pd–C, EtOH, 50 °C, 48 h; (iii) ethyl 3-dimethylamino-2-{4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl}propenoate **12** (1 equiv), EtOH, 37% aq HCl (2 equiv), reflux; (iv) chromatographic separation; (v) H_2 (55 bar), 10% Pd–C, AcOH–Ac_2O (1:1), 60 °C, 48 h.

(1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]-butane-1,2-dione 1-oxime **16b** as the minor product in 8% yield. Further experiments showed that chemoselectivity was dependent on the type of Grignard reagent. Thus, reactions of **9** with excess methyl- and arylmagnesium halides led, selectively, to 2-substituted (1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]ethane-1,2-dione 1-oximes **16a** and **16d–f**, which were obtained in 53–66% yields. However, treatment of **9** with excess *n*-butylmagnesium chloride afforded (1*R*,4*S*,5*S*)-4-di(*n*-butyl)amino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **15c** in 46% yield, while inseparable mixtures of products were formed upon reactions of **9** with *iso*-propyl-, *iso*-butyl, *sec*-butyl, and *tert*-butylmagnesium halides (Scheme 3).

Two reactions took place upon treatment of **9** with excess Grignard reagents (a) stereoselective reduction into α-dialkylaminolactones **15** and (b) reductive ring-opening into α-keto oximes **16**, with the chemoselectivity depending on the type of organomagnesium halide employed. To the best of our knowledge, there is no example in the literature where a related reduction of an oxime with Grignard reagent into a *N*,*N*-disubstituted amine has been reported. Therefore, we do not have a firm explanation for the mechanism of formation of compounds **15b** and **15c**. The proposed mechanism is based on presumption that in solution oxime **9** might be in equilibrium with the minor nitroso tautomer **9′**. The reaction of **9** and **9′** with excess Grignard reagent starts by deprotonation of the hydroxy group to give intermediates **17** and **17′**. In the case of intermediate **17**, the organomagnesium halide underwent addition to the carbonyl group leading to stable chelate **18** as the primary reduction product. Upon hydrolysis, ring opening takes place to furnish the α-keto oxime **16**. Similar selective reductions of carboxylic acid derivatives into ketones are also known in the literature, for example, reactions of Weinreb amides with organometallic reagents.[33,34] Presumably, addition to the carbonyl group in lactone **9** is the preferential reaction, however, due to steric



9 **15b,c** **16a,b,d-f**

Reaction	R	Yield [%]	
		15	**16**
9 + MeMgBr → **16a**	Me	0	63
9 + EtMgBr → **15b** + **16b**	Et	39	8
9 + *n*-BuMgBr → **15c**	*n*-Bu	46	0
9 + PhMgBr → **16d**	Ph	0	66
9 + 4-F-C_6H_4MgBr → **16e**	4-fluorophenyl	0	53
9 + 4-Me-C_6H_4MgBr → **16f**	4-methylphenyl	0	56

Scheme 3. Reagents and conditions: (i) RMgX (12 equiv), THF, −78 °C → rt, then aq NH_4Cl, rt; (ii) chromatographic separation.

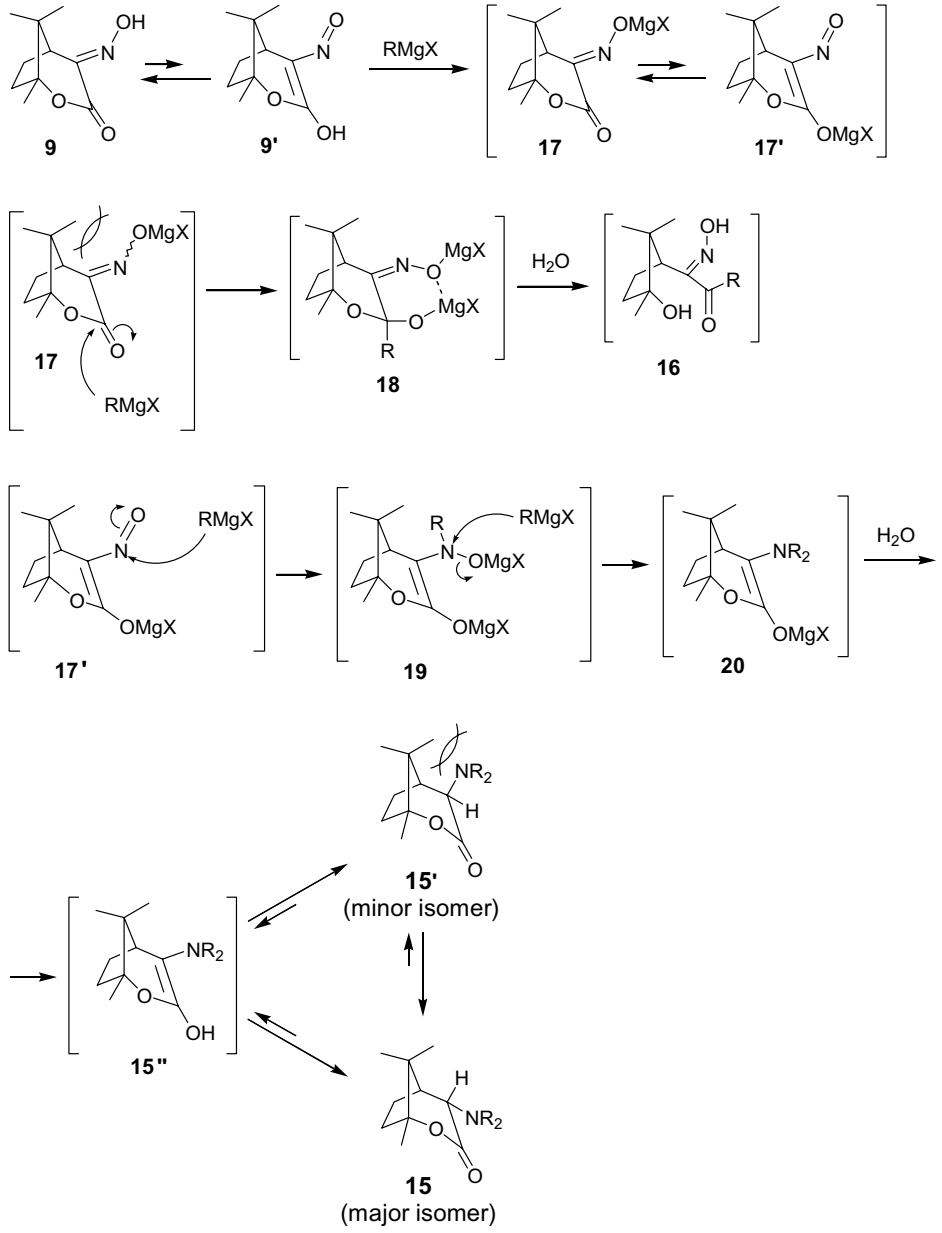
hindrance, especially forms the *exo*-face of **17**, only sterically less demanding methyl- and arylmagnesium halides can approach the carbonyl group. In the cases of the sterically more demanding ethylmagnesium bromide and *n*-butylmagnesium chloride, addition takes place predominantly at the unhindered nitroso group in the minor intermediate **17′** to form the *N*-alkyl-*N*-hydroxyamino intermediate **19**. This is then followed by reductive cleavage of the N–O bond with a second equivalent of alkylmagnesium halide to furnish enolate **20**. Upon hydrolysis, the so formed enol **15″** tautomerizes into the *endo*-isomer **15** as the major product. In the case of sterically most demanding *iso*-propyl-, *iso*-butyl-, *sec*-butyl-, and *tert*-butylmagnesium halides, no selective reaction took place and complex mixtures of products were formed (Scheme 4).

The stereoselectivity in the hydrogenation of oxime **9** into amine **11** was poor, when reaction was carried out under acidic conditions (18% de of **11**) and low, when performed under neutral conditions (50% de of **11**). On the other hand, hydrogenation of **9** in the presence of acetic anhydride and reductions of **9** with ethylmagnesium bromide and *n*-butylmagnesium chloride led to the isolation of isomerically pure compounds **15c** and **15d**. Unfortunately, stereoselectivity determination for these reactions was not possible, due to the presence of several by-products and impurities in the crude reaction mixtures, which prevented us from establishing the amount of the minor *exo*-isomers **15′b** and **15c**. Although isomerically pure *endo*-dialkylaminolactones **15b** and **15c** were isolated in all cases, it cannot be concluded that these reductions proceeded stereospecifically. Taking into account the diastereomeric enrichment, which was observed in the transformation of free amine **11** (50% de) into its derivative **13** (94% de) (cf. Scheme 2), it seems more likely that the stereoselective formation of compounds **15** is thermodynamically controlled. Thus, due to steric repulsion between the dialkylamino group at position 4 and the methyl group at position 8 in the *exo*-isomer **15′**, equilibration between **15** and **15′** via the enol **15″** would result in *endo*-isomer **15** as the predominant isomer (Scheme 4). Similarly, preferential formation of the *endo*-isomers was observed in the (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*b*]azin-3yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one series.[24]

3. Structure determination

The structures of all novel compounds **9**, **10**, **10′**, **11**, **11′**, **13**, **13′**, **15b**,**c**, and **16a**,**b**,**d**–**f** were determined by spectroscopic methods (IR, ^1H, and ^{13}C NMR, MS) and by elemental analyses for C, H, and N. Compounds **9**, **10**, **10′**, **13**, **13′**, **15b**,**c**, and **16a**,**b**,**d**–**f** were prepared in isomerically pure form, while compounds **11** and **11′** were prepared and characterized as mixture of the major (4*S*)-isomer **11** and the minor (4*R*)-isomer **11′**. Compounds **10**, **11/11′**, **15b**, and **15c** were not prepared in analytically pure form. The identities of **10**, **15b**, and **15c** were confirmed by ^{13}C NMR and EI-HRMS, while the identity of **11/11′** was established by EI-MS.

The configuration at position 4 in compounds **11**, **11′**, **13**, **13′**, **15b**, and **15c** was determined by NMR on the basis of vicinal coupling constants, $^3J_{H4–H5}$. Coupling constant, $^3J_{H4–H5}$ = 4.1–5.3 Hz, was observed in the case of the *endo*-isomers **11**, **13**, **15b**, and **15c**, while the coupling constant, $^3J_{H4–H5} \sim 0$ Hz, was characteristic for the minor *exo*-isomers **11′** and **13′**. These two characteristic values of coupling constants, $^3J_{H4–H5}$, are also in agreement with the values reported in the literature for analogous compounds (Fig. 2).[24]



Scheme 4.

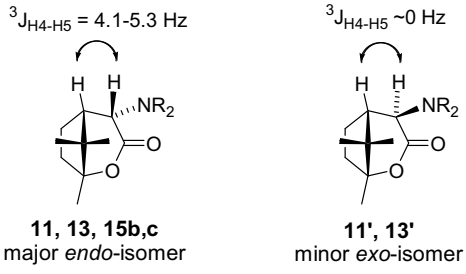


Figure 2. Determination of configuration at C(4) in compounds **11**, **11′**, **13**, **13′**, **15b**, and **15c**.

The structures of compounds **9**, **10′**, a salt of **15b** with D-(+)-camphor-10-sulfonic acid, and **16b** were determined by X-ray diffraction (Figs. 3–6).

4. Conclusion

(1*R*,4*E*,5*S*)-4-Oximino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one **9** is available in three steps from (+)-camphor **1**, via nitrosation of (1*R*,4*E*,5*S*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **8**. Catalytic hydrogenation of oxime **9** led, stereoselectively, to *N*,*N*-disubstituted (1*R*,4*S*,5*S*)-4-amino-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-ones **11**, **13**, and **15**. Unusual transformations took place in the reactions of **9** with Grignard reagents. α-Dialkylamino lactones **15b** and **15c** were formed in the reaction of **9** with ethylmagnesium bromide and *n*-butylmagnesium chloride, while reactions with methyl- and arylmagnesium halides proceeded by opening of the lactone ring of **9** to give α-keto oximes **16**. Thus, compound **9** is a suitable precursor for the preparation of

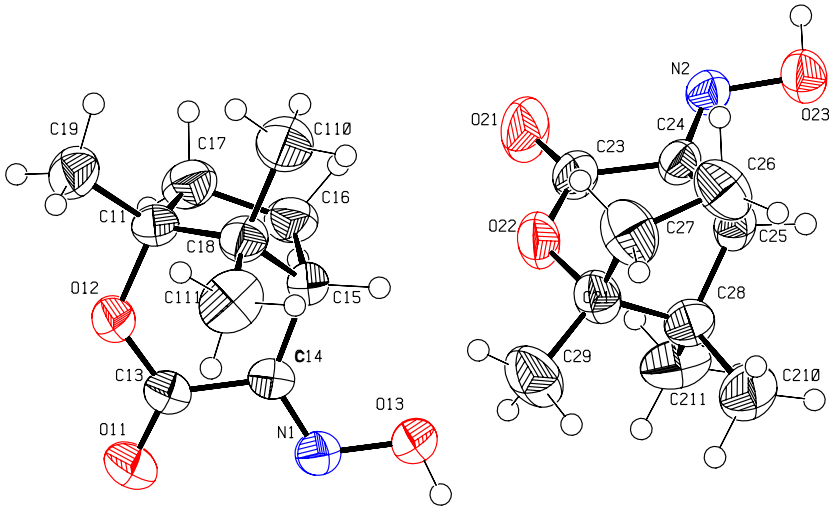


Figure 3. The asymmetric unit of compound **9**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

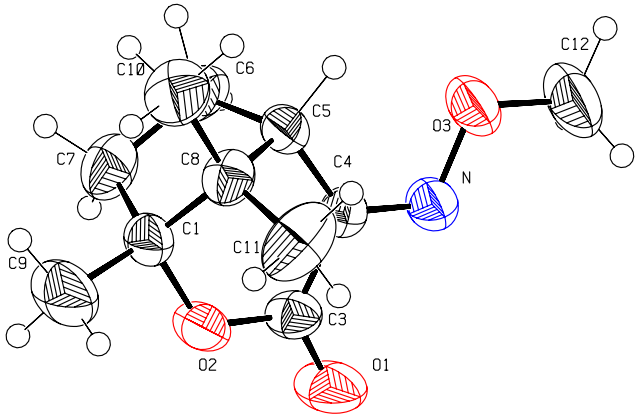


Figure 4. The asymmetric unit of compound **10′**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

N,*N*-disubstituted (1*R*,4*S*,5*S*)-4-amino-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one derivatives **11**, **13**, and **15** as a novel nonproteinogenic α-amino acid derivative, as well as for the preparation of 2-substituted (1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]ethane-1,2-dione 1-oximes **16**.

In order to gain better insight into the unusual transformation of α-oximino lactone **9** into α-dialkylamino lactones **15**, our attention is now focused on the reactions of related α-oximino lactones and lactams with Grignard reagents.

5. Experimental

5.1. General methods

Melting points were determined on a Kofler micro-hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). Medium pressure liquid chromatography

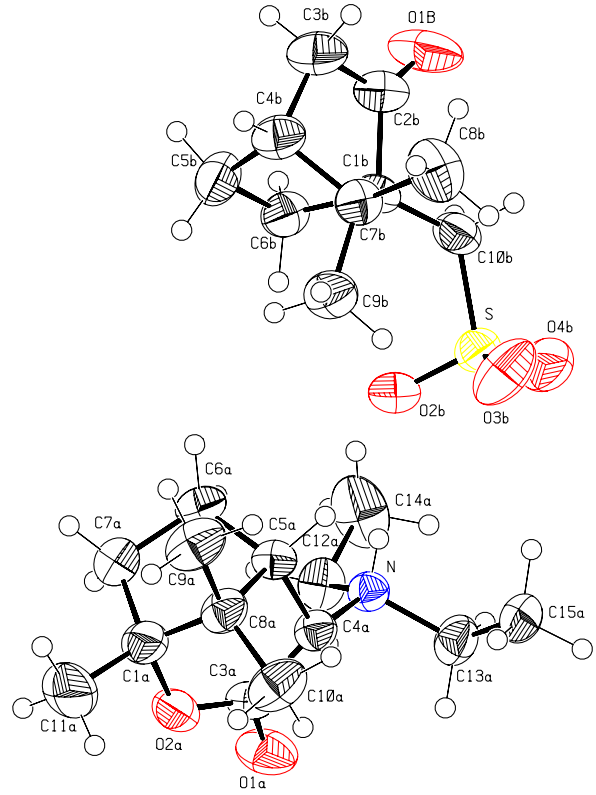


Figure 5. The asymmetric unit of a salt of compound **15b** with D-(+)-camphor-10-sulfonic acid. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

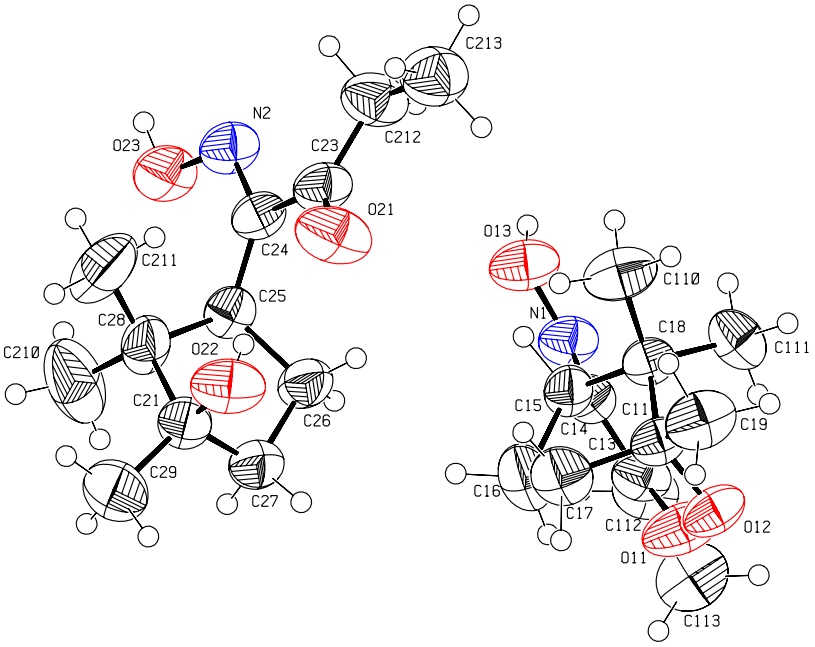


Figure 6. The asymmetric unit of compound **16b**. Ellipsoids are plotted at 50% probability level. H atoms are drawn as circles of arbitrary radii.

(MPLC) was performed with a Büchi isocratic system with detection[†] on silica gel (Merck, silica gel 60, 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. Ratio of isomers and de were determined by ^{1}H NMR.

D-(+)-Camphor-10-sulfonic acid, methylmagnesium bromide (3 M in Et_2O), ethylmagnesium bromide (1 M in THF), *n*-butylmagnesium chloride (2 M in THF), phenylmagnesium bromide (1 M in THF), 4-fluorophenylmagnesium bromide (2 M in Et_2O), and 4-methylmagnesium bromide (1 M in Et_2O) are commercially available (Fluka AG). (1*R*,4*E*,5*S*)-4-[(Dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]-octan-3-one **8**,[26] a solution of diazomethane in diethyl ether,[35] and ethyl 3-dimethylamino-2-{4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl}propenoate **12**[36] were prepared according to the procedures described in the literature.

Source of chirality: (i) (+)-Camphor **1** (Fluka AG), product number 21,300, purum, natural, ⩾97.0% (GC, sum of enantiomers), $[\alpha]^{20}_{546} = +54.5 \pm 2.5$ (*c* 10, EtOH), $[\alpha]^{20}_{D} = +42.5 \pm 2.5$ (*c* 10, EtOH), mp 176–180 °C, ee not specified.

5.2. (1*R*,4*E*,5*S*)-4-Oximino-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 9

Hydrochloric acid (1 M, 9 mL, 9 mmol) was added slowly to a stirred suspension of compound **8** (2230 mg, 10 mmol) in aqueous $NaNO_2$ (0.3 M, 50 mL, 15 mmol), stirred at rt for 2 h, and then poured into brine (300 mL). The product was extracted with chloroform (2 × 300 mL), after which the organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated in vacuo. The residue was purified by CC. First, the nonpolar impurities were eluted with EtOAc–hexanes (1:2) followed by elution of the product **9** with EtOAc–hexanes (2:1). Fractions containing the product were combined and evaporated in vacuo to give **9**. Yield: 850 mg (43%); mp 202–208 °C of a white solid; $[\alpha]^{22}_{D} = +59.8$ (*c* 0.39, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.03, 1.04, 1.37 (9H, 3s, 1:1:1, 3Me); 1.57–1.68 (1H, m, 1H of CH_2); 2.06–2.26 (3H, m, 3H of CH_2); 3.53 (1H, m, H–C(5)); 9.72 (1H, br s, OH). ^{13}C NMR ($CDCl_3$): δ 18.4, 18.8, 23.4, 25.3, 36.7, 45.0, 45.1, 94.6, 152.6, 162.3. MS: *m*/*z* = 198 (MH^+); HRMS: *m*/*z* = 197.1055 (M^+); $C_{10}H_{15}NO_3$ requires: *m*/*z* = 197.1051 (M^+). (Found: C, 60.76; H, 7.56; N, 7.18. $C_{10}H_{15}NO_3$ requires: C, 60.90; H, 7.67; N, 7.10.) ν_{max} (KBr) 3206, 2973, 1736 (C=O), 1646, 1394, 1306, 1211, 1163, 1146, 997 cm^{-1}.

5.3. (1*R*,4*Z*,5*S*)-1,8,8-Trimethyl-2-oxabicyclo[3.2.1]octan-3,4-dione 4-(*O*-methyloxime) 10 and its (1*R*,4*E*,5*S*)-isomer 10′

A solution of diazomethane in Et_2O[35] (~0.3 M, 7 mL, ~2.1 mmol) was added to a solution of oxime **9** (197 mg, 1 mmol) in dichloromethane (7 mL) and the mixture was left to stand at rt for 24 h. Volatile components were evaporated in vacuo, and the residue purified by CC (EtOAc–hexanes, 1:2). Fractions containing the products were combined and evaporated in vacuo to give **10** and **10′**.

5.3.1. Data for (1*R*,4*Z*,5*S*)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3,4-dione 4-(*O*-methyloxime) 10. Yield: 190 mg (90%) of a colorless oil; $[\alpha]^{21}_{D} = +142.5$ (*c* 0.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.01, 1.04, 1.36 (9H, 3s,

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

1:1:1, 3Me); 1.58–1.66 (1H, m, 1H of CH_2); 2.08–2.26 (3H, m, 3H of CH_2); 3.65 (1H, d, J = 6.0 Hz, H–C(5)); 4.26 (3H, s, OMe). ^{13}C NMR ($CDCl_3$): δ 18.3, 18.6, 23.3, 25.7, 36.5, 44.6, 47.4, 54.5, 94.9, 141.9, 161.0. m/z (EI) = 211 (M^+); m/z (HRMS) Found: 211.1210 (M^+); $C_{11}H_{17}NO_3$ requires: 211.1208. (Found: C, 56.89; H, 7.64; N, 8.88. $C_{11}H_{17}NO_3$ requires: C, 62.54; H, 8.11; N, 6.63.) ν_{max} (NaCl) 2973, 1710 (C=O), 1530, 1467, 1449, 1395, 1382, 1347, 1314, 1282, 1201, 1162, 1135, 1100, 1064 cm^{-1}.

5.3.2. Data for (1*R*,4*E*,5*S*)-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3,4-dione 4-(*O*-methyloxime) 10′. Yield: 11 mg (5%) of a white solid; mp 140–145 °C; $[\alpha]_D^{21} = +61.4$ (c 0.09, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.02, 1.36 (9H, 2s, 2:1, 3Me); 1.57–1.64 (1H, m, 1H of CH_2); 2.08–2.22 (3H, m, 3H of CH_2); 3.41 (1H, d, J = 6.0 Hz, H–C(5)); 4.08 (3H, s, OMe). m/z (EI) = 211 (M^+); m/z (HRMS) Found: 211.1199 (M^+); $C_{11}H_{17}NO_3$ requires: 211.1208. (Found: C, 62.43; H, 8.31; N, 6.88. $C_{11}H_{17}NO_3$ requires: C, 62.54; H, 8.11; N, 6.63.) ν_{max} (NaCl) 2969, 1732 (C=O), 1600, 1383, 1319, 1299, 1209, 1163, 1148, 1069, 1043 cm^{-1}.

5.4. (1*R*,4*S*,5*S*)-4-Amino-1,8,8-trimethyl-2-oxabicyclo-[3.2.1]octan-3-one 11 hydrochloride and its (1*R*,4*R*,5*S*)-isomer 11′

A mixture of oxime **9** (197 mg, 1 mmol), ethanol (15 mL), hydrochloric acid (37%, 0.13 mL, ~1.3 mmol), and 10% Pd–C (100 mg) was hydrogenated in an autoclave (50 bar of H_2, 35 °C) for 48 h. The reaction mixture was filtered through a short pad of Celite®, washed with ethanol (15 mL), and the filtrate evaporated in vacuo. The residue was crystallized from ethyl acetate and the precipitate collected by filtration to give a mixture of **11** and **11′**. Yield: 55 mg (25%) of a white solid; **11**:**11′** = 59:41; mp 195–210 °C; $[\alpha]_D^{22} = -21.6$ (c 0.12, DMSO). MS: m/z = 184 (MH^+). (Found: C, 50.42; H, 7.97; N, 5.80. $C_{10}H_{18}ClNO_2{\cdot}H_2O$ requires: C, 50.52; H, 8.48; N, 5.89.) ν_{max} (KBr) 3418, 2910, 1745 (C=O), 1585, 1517, 1385, 1269, 1177, 1159, 1060 cm^{-1}.

5.4.1. NMR data for the major (1*R*,4*S*,5*S*)-isomer 11. ^{1}H NMR (DMSO-d_6): δ 1.01, 1.06, 1.24 (9H, 3s, 1:1:1, 3Me); 1.66–2.11 (4H, m, 2 × CH_2); 2.31–2.36 (1H, m, H–C(5)); 4.25 (1H, dd, J = 1.5, 4.1 Hz, H–C(4)); 8.71 (3H, br s, NH_3^+).

5.4.2. NMR data for the minor (1*R*,4*R*,5*S*)-isomer 11′. ^{1}H NMR (DMSO-d_6): δ 0.93, 1.00, 1.26 (9H, 3s, 1:1:1, 3Me); 4.00 (1H, s, H–C(4)).

5.5. Ethyl 3,5-dihydro-3-oxo-2-phenyl-5-[(1*R*,4*S*,5*S*)-3-oxo-1,8,8-trimethyl-2-oxabicyclo[3.2.1]oct-4-yl]-2*H*-pyrazolo[4,3-*c*]pyridin-7-carboxylate 13 and its (1*R*,4*R*,5*S*)-isomer 13′

A mixture of oxime **9** (197 mg, 1 mmol), ethanol (20 mL), and 10% Pd–C (100 mg) was hydrogenated in an autoclave (50 bar of H_2, 50 °C) for 48 h. The reaction mixture was filtered through a short pad of Celite®, washed with ethanol (15 mL), and the filtrate evaporated in vacuo to give a mixture of isomeric free amines **11** and **11′** in a ratio of 75:25, respectively. This mixture of isomers **11** and **11′** was dissolved in ethanol (10 mL), ethyl 3-dimethylamino-2-{4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl}propenoate **12**[36] (356 mg, 1 mmol), and hydrochloric acid (37%, 0.2 mL, ~2 mmol) were added, and the mixture refluxed for 5 h. Volatile components were evaporated in vacuo and the residue purified by CC (EtOAc–hexanes, 1:1) followed by MPLC (EtOAc–hexanes, 2:1). Fractions containing the isomeric products were combined and evaporated in vacuo to give compounds **13** and **13′**.

5.5.1. Data for major-(1*R*,4*S*,5*S*)-isomer 13. A red solid (243 mg (54%)), solvate with 0.2 *n*-heptane; mp 95–130 °C (from CH_2Cl_2–*n*-heptane); $[\alpha]_D^{23} = +12.5$ (c 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.86 (1.2H, t, J = 6.8 Hz, 2 × Me of *n*-heptane); 1.14, 1.28, 1.41 (9H, 3s, 1:1:1, 3Me); 1.24–1.30 (2H, m, 5 × CH_2 of *n*-heptane); 1.47 (3H, t, J = 7.2 Hz, CH_2CH_3); 1.58–1.67 (1H, m, 1H of CH_2); 1.89–2.04 (1H, m, 1H of CH_2); 2.12–2.23 (1H, m, 1H of CH_2); 2.28–2.42 (2H, m, 1H of CH_2 and H–C(5′)); 4.48 (2H, q, J = 7.2 Hz, CH_2CH_3); 5.09 (1H, dd, J = 1.9; 4.5 Hz, H–C(4′)); 7.17–7.23 (1H, m, Ph); 7.40–7.46 (2H, m, 2H of Ph); 7.83 and 8.11 (2H, 2d, 1:1, J = 1.9 Hz, H–C(4) and H–C(6)); 8.18–8.22 (2H, m, 2H of Ph). ^{13}C NMR ($CDCl_3$): δ 14.2, 17.3, 17.8, 20.6, 24.1, 36.4, 46.3, 49.9, 61.9, 68.7, 96.1, 113.1, 118.0, 120.4, 125.3, 128.7, 138.6, 139.1, 139.6, 140.4, 160.4, 163.5, 165.8. m/z (EI) 449 (M^+); m/z (HRMS) Found: 449.1965 (M^+); $C_{25}H_{27}N_3O_5$ requires: m/z = 449.1950. (Found: C, 67.16; H, 6.81; N, 8.88. $C_{25}H_{27}N_3O_5 \times 0.2$ *n*-C_7H_{16} requires: C, 67.53; H, 6.48; N, 8.95.) ν_{max} (KBr) 2976, 1735 (C=O), 1668 (C=O), 1648 (C=O), 1595, 1537, 1487, 1383, 1344, 1299, 1262, 1187, 1136 cm^{-1}.

5.5.2. Data for minor-(1*R*,4*R*,5*S*)-isomer 13′. A red solid (10 mg (2%)); mp 193–207 °C (from CH_2Cl_2–*n*-heptane); $[\alpha]_D^{23} = +74.3$ (c 0.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.07, 1.15, 1.42 (9H, 3s, 1:1:1, 3Me); 1.46 (3H, t, J = 7.2 Hz, CH_2CH_3); 1.79–1.88 (1H, m, 1H of CH_2); 2.04–2.43 (3H, m, 3H of CH_2); 2.59 (1H, d, J = 6.4 Hz, H–C(5′)); 4.47 (2H, q, J = 7.2 Hz, CH_2CH_3); 4.74 (1H, s, H–C(4′)); 7.17–7.23 (1H, m, Ph); 7.38–7.45 (2H, m, 2H of Ph); 8.03 and 8.32 (2H, 2d, 1:1, J = 1.5 Hz, H–C(4) and H–C(6)); 8.18–8.21 (2H, m, 2H of Ph). m/z (EI) 449 (M^+); m/z (HRMS) Found: 449.1965 (M^+); $C_{25}H_{27}N_3O_5$ requires: m/z = 449.1950. (Found: C, 66.48; H, 6.11; N, 9.07. $C_{25}H_{27}N_3O_5$ requires: C, 66.80; H, 6.05; N, 9.35.) ν_{max} (KBr) 2977, 1730 (C=O), 1649 (C=O), 1595, 1536, 1489, 1384, 1339, 1295, 1188, 1165, 1134 cm^{-1}.

5.6. Hydrogenation of 9 in the presence of acetic anhydride. Preparation of (1*R*,4*S*,5*S*)-4-diethylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 15b

A mixture of oxime **9** (197 mg, 1 mmol), acetic acid (10 mL), acetic anhydride (10 mL), and 10% Pd–C (110 mg) was hydrogenated in an autoclave (55 bar of

H_2, 60 °C) for 48 h. The reaction mixture was filtered through a glass-fritted funnel and the filtrate evaporated in vacuo. The residue was dissolved in ethanol (20 mL), filtered through a short pad of Celite®, washed with ethanol (15 mL), and the filtrate evaporated in vacuo. The residue was dissolved in ethanol (30 mL) and the solution set aside for 24 h. Volatile components were evaporated in vacuo, and the residue purified by CC (EtOAc–hexanes, 1:3). Fractions containing the product were combined and evaporated in vacuo to give compound **15b**. Yield: 93 mg (39%) of a colorless oil; $[\alpha]_D^{21} = -117.6$ (*c* 0.31, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, s, Me); 1.06 (6H, t, $J = 7.2$ Hz, $2 \times CH_2CH_3$); 1.09, 1.26 (6H, 2s, 1:1, 2Me); 1.77–2.11 (5H, m, 4H of CH_2; H–C(5)); 2.41–2.53 (2H, m, 2–C$H_{2(a)}$CH$_3$); 2.79–2.90 (2H, m, 2–C$H_{2(b)}$CH$_3$); 3.70 (1H, dd, $J = 1.5$, 4.9 Hz, H–C(4)). ^{13}C NMR ($CDCl_3$): δ 14.5, 17.7, 18.7, 21.4, 24.5, 37.0, 46.0, 48.2, 51.5, 64.0, 92.9, 172.0. *m*/*z* (EI) 239 (M^+); *m*/*z* (FAB): 240 (MH^+); *m*/*z* (HRMS) Found: 239.1892 (M^+); $C_{14}H_{25}NO_2$ requires: *m*/*z* = 239.1885. (Found: C, 69.74; H, 10.62; N, 6.66. $C_{14}H_{25}NO_2$ requires: C, 70.25; H, 10.53; N, 5.85.) ν_{max} (NaCl) 2969, 1730 (C=O), 1465, 1449, 1381, 1258, 1207, 1158, 1139, 1049, 1012 cm^{-1}.

5.6.1. Preparation a salt of (1*R*,4*S*,5*S*)-4-diethylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 15b with D-(+)-camphor-10-sulfonic acid. In a small beaker, a mixture of **15b** (20 mg, 0.084 mmol) and D-(+)-camphor-10-sulfonic acid (19.5 mg, 0.084 mmol) was dissolved in a minimum amount of ethyl acetate. *n*-Heptane was added dropwise slowly while stirring, until the solution became slightly turbid. Then, ethyl acetate was added slowly and dropwise until the solution became clear again. This solution was then set aside in an open beaker at rt for 2–3 days, and volatile components allowed to evaporate. The so-formed crystals were collected by filtration, washed with hexanes, and used for X-ray structure determination of **15b** D-(+)-camphor-10-sulfonate. Yield: 20 mg (51%) of colorless crystals. ^{1}H NMR (DMSO-d_6): δ 0.74 (3H, s); 1.04–1.31 (21H, m); 1.72–2.15 (7H, m); 2.19–2.27 (1H, m); 2.35 (1H, d, $J = 14.7$ Hz); 2.71 (1H, br t, $J = 10.6$ Hz); 2.86 (1H, d, $J = 14.7$ Hz); 3.05–3.25 (2H, m); 3.37–3.47 (1H, m); 3.60–3.72 (1H, m); 4.30 (1H, m); 9.67 (1H, br s). ν_{max} (NaCl) 2651, 2587, 2496, 1738 (C=O), 1456, 1386, 1261, 1235, 1206, 1152, 1101, 1037 cm^{-1}.

5.7. Reduction of 9 with Grignard reagents. General procedure for the preparation of (1*R*,4*S*,5*S*)-4-dialkylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones 15b and 15c and 2-substituted (1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]ethane-1,2-dione 1-oximes 16a,b,d–f

A solution of compound **9** (197 mg, 1 mmol) in anhydrous THF was cooled under argon to −78 °C. Grignard reagent (12 mmol) was added slowly and the reaction mixture stirred at −78 °C for 1 h and then at rt for 5–24 h. Saturated aqueous ammonium chloride (20 mL) was added, the mixture stirred at rt for 1 h, transferred to a separatory funnel, aqueous sodium chloride (20 mL) then added, and the products extracted with dichloromethane (3×70 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate evaporated in vacuo. Dichloromethane (10 mL) was added to the residue and the mixture set aside for 24 h. Volatile components were evaporated in vacuo and the residue purified by CC and/or MPLC. Fractions containing the products were combined and evaporated in vacuo to give compounds **15** and/or **16**. The following compounds were prepared in this manner.

5.7.1. (1*E*)-1-[(1*S*,3*R*)-3-Hydroxy-2,2,3-trimethylcyclopentyl]propane-1,2-dione 1-oxime 16a. Prepared from compound **9** and methylmagnesium bromide (3 M in Et_2O); stirring at rt for 18 h; purification by CC (EtOAc–hexanes, 1:3); 134 mg (63%) of a white solid; mp 144–153 °C (from $CHCl_3$–EtOAc–*n*-heptane); $[\alpha]_D^{21} = -44.2$ (*c* 0.16, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.76, 1.07, 1.18 (9H, 3s, 1:1:1, 3Me); 1.64–1.74 (1H, m, 1H of CH_2); 1.80–1.98 (2H, m, 2H of CH_2); 2.12–2.26 (1H, m, 1H of CH_2); 2.39 (3H, s, MeCO); 3.60 (1H, t, $J = 9.8$ Hz, H–C(5)); 4.67 (1H, s, OH); 9.20 (1H, s, =N–OH). ^{13}C NMR (DMSO-d_6): δ 20.8, 22.5, 23.5, 27.5, 28.5, 39.4, 43.8, 48.9, 81.3, 159.7, 200.1. (Found: C, 62.10; H, 8.83; N, 6.82. $C_{11}H_{19}NO_3$ requires: C, 61.95; H, 8.98; N, 6.57.) ν_{max} (KBr) 3112, 2974, 1669 (C=O), 1470, 1446, 1373, 1288, 1145, 1077, 993, 925 cm^{-1}.

5.7.2. (1*R*,4*S*,5*S*)-4-Diethylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 15b and (1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]butane-1,2-dione 1-oxime 16b. Prepared from compound **2** and ethylmagnesium bromide (1 M in THF); stirring at rt for 5 h; purification and separation of **15b** and **16b** by CC (EtOAc–hexanes, 1:4, **15b** elutes first followed by elution of **16b**).

5.7.2.1. Data for (1*R*,4*S*,5*S*)-4-diethylamino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 15b. A colorless oil (93 mg, 39%) with physical, analytical, and spectral data identical to those given in Section 5.6.

5.7.2.2. Data for (1*E*)-1-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]butane-1,2-dione 1-oxime 16b. A white solid (18 mg, 8%); mp 148–155 °C (from $CHCl_3$–*n*-heptane); $[\alpha]_D^{21} = -32.9$ (*c* 0.08, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.76, 1.08 (6H, 2s, 1:1, 2Me); 1.08 (3H, t, $J = 7.2$ Hz, CH_2CH_3); 1.19 (3H, s, Me); 1.66–1.74 (1H, m, 1H of CH_2); 1.80–1.98 (2H, m, 2H of CH_2); 2.05–2.22 (1H, m, 1H of CH_2); 2.65–2.79 (1H, m, C$H_{2(a)}$CH$_3$); 2.87–3.00 (1H, m, C$H_{2(b)}$CH$_3$); 3.60 (1H, t, $J = 9.8$ Hz, H–C(1′)); 4.91 (1H, s, OH); 9.43 (1H, s, =N–OH). *m*/*z* (EI) = 227 (M^+); *m*/*z* (FAB) = 228 (MH^+). (Found: C, 63.10; H, 9.06; N, 6.47. $C_{12}H_{21}NO_3$ requires: C, 63.41; H, 9.31; N, 6.16.) ν_{max} (NaCl) 3331, 2987, 1672 (C=O), 1474, 1446, 1408, 1385, 1268, 1136, 1099, 1081, 1016, 922 cm^{-1}.

5.7.3. (1*R*,4*S*,5*S*)-4-Di(*n*-butyl)amino-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one 15c. Prepared from compound **9** and *n*-butylmagnesium chloride (2 M in THF); stirring at rt for 24 h; purification by CC (EtOAc) followed by MPLC (EtOAc–hexanes, 1:6); 136 mg

(46%) of a colorless oil; $[\alpha]_D^{28} = -120.6$ (*c* 0.23, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.91 (6H, t, $J = 7.2$ Hz, $2 \times CH_2CH_2CH_2CH_3$); 0.99, 1.08, 1.26 (9H, 3s, 1:1:1, 3Me); 1.23–1.50 (8H, m, 8H of CH_2); 1.74–2.10 (5H, m, 4H of CH_2; H–C(5)); 2.32–2.41 (2H, m, $2 \times CH_{2(a)}CH_2CH_2CH_3$); 2.74–2.83 (2H, m, $2 \times CH_{2(b)}CH_2CH_2CH_3$); 3.66 (1H, dd, $J = 1.9$, 5.3 Hz, H–C(4)). ^{13}C NMR ($CDCl_3$): δ 14.1, 17.3, 18.3, 20.3, 21.0, 24.1, 31.6, 36.6, 45.7, 51.3, 54.9, 64.2, 92.4, 171.7. *m/z* (EI) 295 (M^+); *m/z* (HRMS) Found: 295.2515 (M^+); $C_{18}H_{33}NO_2$ requires: *m/z* = 295.2511. (Found: C, 72.96; H, 11.69; N, 6.17. $C_{18}H_{33}NO_2$ requires: C, 73.17; H, 11.26; N, 4.74.) ν_{max} (NaCl) 2957, 1730 (C=O), 1467, 1380, 1257, 1224, 1153, 1139, 1105, 1054, 1012 cm^{-1}.

5.7.4. (1*E*)-1-[(1*S*,3*R*)-3-Hydroxy-2,2,3-trimethylcyclopentyl]-2-phenylethane-1,2-dione 1-oxime 16d. Prepared from compound **9** and phenylmagnesium bromide (1 M in THF); stirring at rt for 5 h; purification by CC (EtOAc–hexanes, 1:4) followed by MPLC (EtOAc–hexanes, 1:3); 182 mg (66%) of a white solid; mp 163–167 °C (from EtOAc–*n*-heptane); $[\alpha]_D^{21} = -209.6$ (*c* 0.19, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 0.93, 1.15, 1.19 (9H, 3s, 1:1:1, 3Me); 1.71–2.04 (4H, m, 4H of CH_2); 3.63–3.69 (1H, m, H–C(5)); 4.73 (1H, s, OH); 7.41–7.46 (2H, m, 2H of Ph); 7.55–7.60 (1H, m, 1H of Ph); 7.91–7.94 (2H, m, 2H of Ph); 8.63 (1H, s, =N–OH). ^{13}C NMR (DMSO-d_6): δ 20.5, 23.1, 23.7, 28.1, 39.3, 45.9, 49.4, 81.2, 129.0, 131.0, 133.7, 138.3, 159.6, 194.4. *m/z* (EI) 275 (M^+); *m/z* (FAB) *m/z* = 276 (MH^+). (Found: C, 69.50; H, 7.72; N, 5.08. $C_{16}H_{21}NO_3$ requires: C, 69.79; H, 7.69; N, 5.09.) ν_{max} (KBr) 3387, 2972, 2784, 1656 (CO), 1451, 1385, 1271, 1214, 1136, 1087, 990, 956 cm^{-1}.

5.7.5. (1*E*)-1-[(1*S*,3*R*)-3-Hydroxy-2,2,3-trimethylcyclopentyl]-2-(4-fluorophenyl)ethane-1,2-dione 1-oxime 16e. Prepared from compound **9** and 4-fluorophenylmagnesium bromide (2 M in Et_2O); stirring at rt for 24 h; purification by CC (1. PhMe–Et_2O, 20:1; 2. PhMe–Et_2O, 7:1); 155 mg (53%) of a yellowish solid; mp 120–125 °C; $[\alpha]_D^{23} = -198.7$ (*c* 0.22, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.91, 1.15, 1.19 (9H, 3s, 1:1:1, 3Me); 1.68–2.05 (4H, m, 4H of CH_2); 3.63–3.69 (1H, m, H–C(5)); 4.91 (1H, s, OH); 7.05–7.12 (2H, m, 2H of Ar); 7.95–8.01 (2H, m, 2H of Ar); 9.24 (1H, s, =N–OH). ^{13}C NMR ($CDCl_3$): δ 19.2, 21.1, 23.7, 31.1, 39.4, 46.3, 49.7, 83.9, 115.5 ($J_{F-C3'} = 21.9$ Hz), 133.2 ($J_{F-C1'} = 2.9$ Hz), 134.2 ($J_{F-C2'} = 9.4$ Hz), 160.5, 166.4 ($J_{F-C4'} = 255.8$ Hz), 192.8. *m/z* (EI) 293 (M^+); *m/z* (HRMS) Found: 293.1435 (M^+); $C_{16}H_{20}FNO_3$ requires: 293.1427. (Found: C, 65.68; H, 6.90; N, 4.80. $C_{16}H_{20}FNO_3$ requires: C, 65.51; H, 6.87; N, 4.78.) ν_{max} (KBr) 3372, 3154, 2968, 1644 (C=O), 1599, 1506, 1472, 1298, 1234, 1180, 1157, 1082, 1020 cm^{-1}.

5.7.6. (1*E*)-1-[(1*S*,3*R*)-3-Hydroxy-2,2,3-trimethylcyclopentyl]-2-(4-methylphenyl)ethane-1,2-dione 1-oxime 16f. Prepared from compound **9** and 4-methylphenylmagnesium bromide (1 M in Et_2O); stirring at rt for 24 h; purification by CC (1. EtOAc–hexanes, 1:5; 2. EtOAc–hexanes, 1:2); 163 mg (56%) of a yellowish solid; mp 157–160 °C; $[\alpha]_D^{21} = -210.5$ (*c* 0.11, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.94, 1.15, 1.19 (9H, 3s, 1:1:1, 3Me); 1.72–1.99 (4H, m, 4H of CH_2); 2.41 (3H, s, Me); 3.62–3.68 (1H, m, H–C(5)); 4.74 (1H, s, OH); 7.23–7.26 (2H, m, 2H of Ar); 7.83–7.86 (2H, m, 2H of Ar); 8.30 (1H, s, =N–OH). ^{13}C NMR ($CDCl_3$): δ 18.8, 20.8, 21.7, 23.4, 30.7, 39.1, 46.1, 49.3, 83.0, 128.8, 131.1, 134.0, 144.4, 160.4, 193.4. (Found: C, 70.22; H, 8.25; N, 5.21. $C_{17}H_{23}NO_3$ requires: C, 70.56; H, 8.01; N, 4.84.) ν_{max} (KBr) 3378, 3223, 3150, 2968, 2882, 1636 (C=O), 1605, 1468, 1391, 1301, 1171, 1081, 1005, 916, 845, 756 cm^{-1}.

5.8. X-ray structure analysis for compounds 9, 10′, 15b, and 16b

Single crystal X-ray diffraction data of compounds **9**, **10′**, **15b**, and **16b** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[37] DENZO and SCALEPACK[38] were used for indexing and scaling of the data. The structure was solved by means of SIR97.[39] Refinement was done using Xtal3.4[40] program package and the crystallographic plot was prepared by ORTEP III.[41] Crystal structure was refined on *F* values using the full-matrix least-squares procedure. The nonhydrogen 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[42] weighting scheme was used.

The crystallographic data for compounds **9**, **10′**, **15b**, and **16b** have been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: CCDC 269439–269442. These data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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