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Preparation of highly substituted 7-oxa-1-azabicyclo[2.2.1]heptanes from 4-nitro-1-butene derivatives. Route to polysubstituted piperidines

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Abstract—4-Nitro-1-butene derivatives **2** readily available from the palladium(0)-catalyzed *C*-allylation of nitroalkanes were converted into highly substituted 7-oxa-1-azabicyclo[2.2.1]heptane derivatives **6** in three steps including an intramolecular 1,3-dipolar cycloaddition reaction. Catalytic hydrogenolysis of the N–O bond in **6** afforded polysubstituted 4-hydroxypiperidines.

1. Introduction

N-(3-alkenyl)nitrones readily undergo intramolecular 1,3-dipolar cycloaddition to give 7-oxa-1-azabicyclo[2.2.1]heptane derivatives in high yield and stereoselectivity.[1–12] Since these adducts are smoothly converted into piperidine derivatives via reductive cleavage of the N–O bond, access to the *N*-(3-alkenyl)nitrones or hydroxylamines opens the route to piperidine derivatives.[1,4–6,8,10] There are a few useful methods for preparation of these unsaturated nitrones. Usually nitrones are obtained from *N*-substituted hydroxylamines and carbonyl derivatives. However, the key problem in the application of this approach for preparation of the unsaturated nitrones is the synthesis of the corresponding *N*-homoallylhydroxylamines, which may be prepared from a sodium cyanoborohydride reduction of oximes of β,γ-unsaturated aldehydes[2,3] which are not readily available, or from the addition of allylic boronates to aldoximes.[4–6] Some *N*-(3-alkenyl)nitrones may be obtained from *N*-homoallylation of salts of *Z*-aldoximes[1,9,11] and Michael addition of oximes to 1,3-butadienes substituted at the 2 and 3 positions with electron-withdrawing groups.[7–10] Allylation of the salts of acidic nitrones has also been used for preparation of *N*-(3-alkenyl)nitrones.[12]

Tufariello and Trybulski have shown that *N*-homoallylhydroxylamines may be prepared from the unsaturated nitro derivatives, in which the 4-nitrobut-1-ene moiety may be found. These authors reduced 7,7-dimethoxy-4-nitrohept-1-ene to 7,7-dimethoxyhept-1-en-4-hydroxylamine, which was converted into pseudotropine via the cyclic unsaturated nitrone followed by tricyclic isoxazolidine.[13] The idea of applying 4-nitrobut-1-enes for the synthesis of piperidine derivatives seemed to be very attractive due to its simplicity and the fact that these nitro compounds, aside from Tufariello's approach,[13] could be conveniently prepared with vast structural diversity from palladium(0)-catalyzed *C*-allylation of nitroalkanes.[15–20] In a preliminary communication we reported the utility of this strategy for the synthesis of highly substituted piperidine derivatives, e.g. *cis*-2,2-bis(hydroxymethyl)-4-hydroxy-2-phenylpiperidine.[21] Herein we describe details of this methodology. Polyhydroxylated piperidines are potent inhibitors of various glycosidases,[22] and in order to obtain structurally similar compounds we utilized 5-allylic derivatives of 5-nitro-1,3-dioxane as the basic starting materials.

2. Results and discussion

The allylation of sodium salt of 5-nitro-2,2-pentamethylene-1,3-dioxane[23] **1** and 2-nitropropane was carried out in the presence of palladium(0) catalyst, generated in situ from bis(triphenylphosphine)palladium(II) chloride and triphenylphosphine [15] (Scheme 1, Table 1) or 1,2-bis-(diphenylphosphino)ethane. The latter phosphine only appeared to be better than the former for the preparation of **3c**, giving more pure product. Allyl acetate was used for the preparation of **3a** and **3e** while to obtain derivatives **3b**–**3d**, substituted at the double bond, the corresponding commercial allylic chlorides were employed.[17] For cinnamylation of **1**, both cinnamyl chloride and acetate were used, furnishing **3d** in 52 and 76% yield, respectively. Crotylation of **1** with crotyl chloride (mixture of *E*/*Z* isomers) afforded **3b** as the inseparable *E*/*Z* mixture in an 85:15 ratio.

Keywords: nitrocompounds; nitrones; cycloaddition; piperidines.

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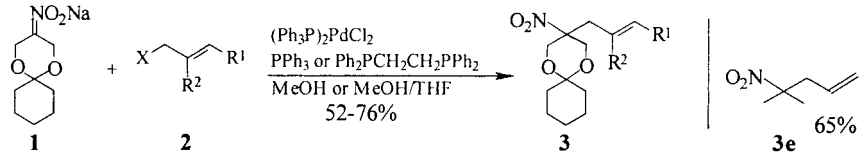


Scheme 1.

Table 1. Yields of allylic derivatives **3**

Entry	Allylating agent	**3**	R^1	R^2	Yield (%)
1	Allyl acetate	**a**	H	H	75
2	Crotyl chloride[a]	**b**	Me	H	75[b]
3	Methallyl chloride	**c**	H	Me	65[c]
4	Cinnamyl acetate	**d**	Ph	H	52
5	Cinnamyl chloride	**d**	Ph	H	76

[a] Mixture of *E* and *Z* isomers.
[b] (*E*)-**3b** and (*Z*)-**3b** in ratio 85:15, respectively.
[c] Obtained in the presence of 1,2-bis(diphenylphosphino)ethane.

Initially, we reduced **3a** using the zinc–acetic acid system in methanol, and crude **4a** was converted to the corresponding nitrone **5**, which without any purification was transformed into the bicyclic adduct **6** by heating in boiling toluene.[21] However, we later discovered that the yields of **6** were not reproducible and the reduction of **3** was responsible for these results. In addition, the zinc reduction failed to give **4d**. All reduction problems disappeared when we employed aluminum amalgam in wet THF[24] for the preparation of **4**. Next we examined whether isolation of the nitrone **5** was necessary. In order to test this, we prepared **6ab** in two ways. Firstly, crude **4a** was heated with benzaldehyde in boiling toluene to afford **6ab** in 61% (for comparison the best yield of **6ab** was 43% when zinc was utilized for the reduction). After that, **6ab** was prepared from the nitrone **5ab**, which was obtained as single isomer, presumably *Z*, in 75% yield calculated on **3a**. Heating of **5ab** in boiling toluene furnished **6ab** in 85% yield (overall yield was 62%). Since both procedures gave **6ab** in almost identical yields (calculated on **3a**), we therefore used the simpler one-pot protocol to prepare **6** throughout this work.

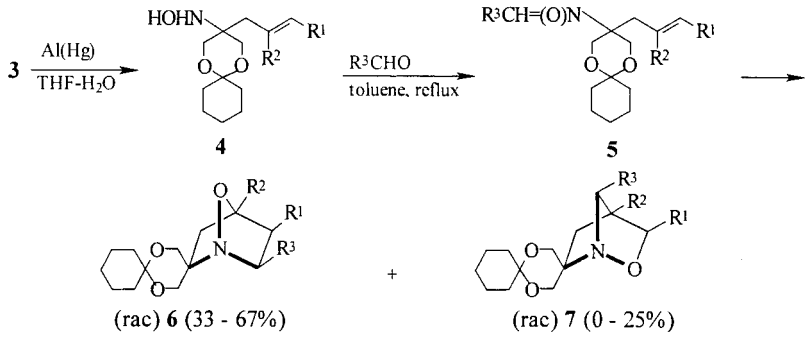
Thus, heating of crude **4** with various aldehydes[†] (0.8 equiv. with respect to **3**) in boiling toluene usually gave the bicyclic isoxazolidines **6** and very occasionally the **6/7** mixtures in satisfactory yields (Scheme 2, Tables 2 and 3). The reaction of **4a–c** and **4e** afforded only 7-oxa-1-azabicyclo [2.2.1]heptanes **6**, in which R^3 occupied the *exo* position.[‡] This new procedure appeared to be beneficial for the preparation of **6aa** (Table 2, entry 1), which could not be obtained when zinc was used for the reduction of **3a**. We reasoned that in this case the pollution of crude **5aa** with acetic acid might be responsible for this failure. Indeed, the reaction of **4a**, obtained from the aluminum reduction, with formaldehyde, conducted in the presence of acetic acid, afforded a mixture of products. The yields of **6bb** and **6cb** (Table 3, entries 1 and 2), compared to the yield of **6ab**, were somewhat lower. However, in the case of **6bb** the decrease in yield might be partially caused by the contamination of (*E*)-**3b** with the *Z* isomer. In contrast to other compounds **4**, the reaction of **4d** with benzaldehyde and paraformaldehyde gave the mixture of regioisomers **6d** and **7d** in a 3:1 ratio (Table 3, entries 3 and 4).[§] However, heating **4d** with formaldehyde (obtained from the triethylamine-catalyzed depolymerization of paraformaldehyde) in boiling *n*-propanol furnished the **6da/7da** mixture in a 1:1 ratio. This result showed that the selectivity of the cycloaddition depends upon the substitution type of double bond but not of the nitrone part. Oppolzer and co-workers also reported a decrease in the selectivity of the intramolecular cycloaddition of *N*-(4-phenyl-3-butenyl)nitrone, which heated in boiling toluene gave a 7:1 mixture of the less substituted analogues of **6da** and **7da**, respectively.[2,3]

The structures of the cycloadducts **6** and **7** were derived from their ^{1}H NMR spectra, which are generally similar to the spectra of 7-oxa- and 2-oxa-1-azabicyclo[2.2.1]heptane derivatives, respectively, described in literature.[1,3,5,8] Thus all **6a** (R^1=R^2=H), as well as 5-substituted derivatives (**6bb**, **6da** and **6db**), display the H-4 proton as a 'triplet' and doublet, respectively, at δ=4.80–4.95 ppm. All **6a** (R^1=R^2=H) and **6cb** show long range coupling (ca. 2.5 Hz) between H-3ex and H-5ex, being in the planar 'W' arrangement. In contrast, both **7da** and **7db** show a singlet for H-3 at low field. All these findings indicate that R^1 substituents occupy the *exo* position in **6** as well as **7**. The *exo* position of R^3 in all **6a** is evident from the fact that the coupling constant $J_{6,5ex}$ (4.0–4.8 Hz) is smaller than $J_{6,5en}$ (7.6–8.4 Hz). For both **6bb** and **6db** the coupling constants between protons H-6 and H-5 ($J_{6,5}$=8.2 Hz) fall in the range of values characteristic for an *endo–endo* interaction, therefore both R^1 and R^3 occupy the *exo* position.

The observed regio- and stereoselectivity of the 1,3-dipolar cycloadditions of *N*-(3-alkenyl)-nitrones **5** are consistent with literature findings.[3,8] Thus, for the intramolecular 1,3-dipolar cycloaddition of **5**, two transition states **TS-A** and **TS-B** (Scheme 3) leading to regioisomers **6** and **7**, respectively, are feasible.

It has been shown that due to angle strain **TS-B** is much higher in energy than **TS-A**, therefore 7-oxa-1-azabicyclo-[2.2.1]heptane derivatives are formed as the sole or the major products.[3,8] Deviations from complete selectivity are fortunately rare and have been observed only by the Oppolzer group and by us for the reaction of the nitrones of the type **5d**. We assume that the decrease of selectivity

[†] Ketones did not react with **4a**.[21]
[‡] In one experiment the reaction of 'aluminum'-**4a** with 2-thiophenecarboxaldehyde gave mixture of *exo*/*endo* stereoisomers of **6ak** (R^3=2-thienyl). Our attempts to repeat this result failed and in all other experiments only *exo* **6ak** was isolated.
[§] The **6db/7db** mixture was inseparable by chromatography.



Scheme 2.

Table 2. Yields of 7-oxa-1-azabicylo[2.2.1]heptanes **6a** (R^1=R^2=H)

Entry	R^3	No	Yield[a] (%)
1	H	**6aa**	56[b]
2	C_6H_5	**6ab**	61
3	*p*-FC_6H_4	**6ac**	36
4	*p*-$CF_3C_6H_4$	**6ad**	56
5	2-$CH_3OC_6H_4$	**6ae**	33
6	3,4-$(CH_3O)_2C_6H_3$	**6af**	35
7	(*E*)-C_6H_5CH=CH	**6ag**	55
8	$C_6H_5CH_2$	**6ah**	42
9	3-Pyridyl	**6ai**	51
10	2-Pyridyl	**6aj**	63
11	2-Thienyl	**6ak**	67

[a] Calculated on **3a**.
[b] The reaction was carried out in *n*-propanol.

Table 3. Yields of isoxazolidines **6** and **7** (R^1≠R^2)

Entry	No	R^1	R^2	R^3	Yield (%)
1	**6bb**	CH_3	H	C_6H_5	42
2	**6cb**	H	CH_3	C_6H_5	49
3	**6da**	C_6H_5	H	H	44[a]
	7da				15[a]
4	**6db**	C_6H_5	H	C_6H_5	50[b]
	7db				17[b]

[a] The **6da/7da** ratio was 1:1 for the reaction carried out in propanol.
[b] Ratio **6/7** determined from ^{1}H NMR spectra.

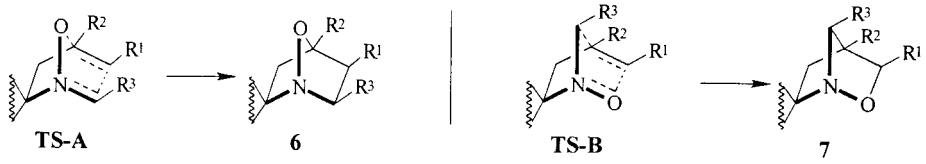
for **5da** and **5db** is caused by unfavorable substitution pattern of the double bond. In both **5da** and **5db** the dipolarophile part might be regarded as a 1-alkyl-2-phenylethylene, where the dipolarophile–dipole connection is considered as an alkyl substituent. This type of alkene undergoes the intramolecular 1,3-dipolar cycloaddition to nitrones, to afford 4-alkyl-5-phenylisoxazolidines as the major product.[25] So, the substitution effect favoring, in contrast to the strain factor, the formation of **7da** and **7db**, possessing the 4-alkyl-5-phenylisoxazolidine subunit, lowers the selectivity of the cycloaddition. Luckily for other nitrones **5** (except **5bb**)[‖] the substitution[26] and strain effect cooperate and only derivatives **6** arise. In the case of **5bb** the substitution effect are 'neutral' from the selectivity point of view and strain factor means that also only **6bb** is formed. The formation of **6** having *exo* R^3 as well as **7db** possessing the structure shown in Scheme 2 is consistent with the fact that only the (*Z*)-nitrones undergo the cycloaddition.[3] The *exo* position of the R^1group in both cycloadducts **6** and **7** is a consequence of *E*-configuration of double bond.

Having secured access to the bicyclic isoxazolidines **6** we examined their conversion into piperidine derivatives (Scheme 4, Table 4). Since the N–O bond in 7-oxa-1-azabicyclo[2.2.1]heptanes **6** is in a more crowded environment than the N–O bond in the analogous compounds described in literature, transformation of **6** into piperidines appeared to be more difficult than we might have expected based on reported data. We have already discovered[21] that the N–O bond could not be cleaved by zinc in an acidic medium[4–6] or by molybdenum hexacarbonyl.[27] Thus the best method of converting **6** into piperidine derivatives was catalytic hydrogenolysis carried out in the presence of 10% palladium on charcoal [1,4–6,8] or Raney nickel. The latter catalyst was used when the palladium-catalyzed reduction was very slow or failed.

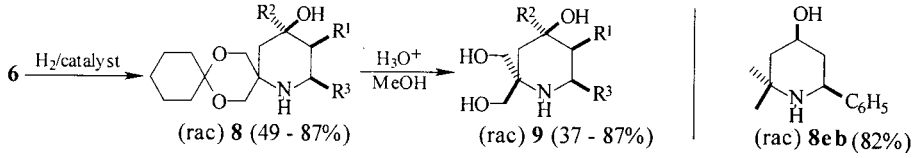
The 6-alkyl derivatives **6** underwent the N–O bond cleavage slower than the corresponding 6-aryl derivatives. However, for 6-phenyl derivatives **6** the hydrogenolysis of the N–O bond competes with the benzylic cleavage of the N–C bond. The benzylic cleavage problem was overcome by the addition of sodium borohydride to the palladium-catalyzed hydrogenation.[¶] In this way all the 6-phenyl derivatives **8** were obtained. The isoxazolidine **6ag** (R^3=2-phenylethenyl) could be transformed only into piperidine **8ag** (R^3=2-phenylethyl) since the hydrogenation of the double bond was much easier than the N–O cleavage. Thus, to obtain **8ag** the reduction of **6ag** was carried out in the presence of Raney nickel at elevated temperature and under 8 bar pressure. We also failed to split the N–O bond in **6ag** by lithium aluminum hydride in boiling THF. The derivative **6aj** underwent reduction sluggishly and the piperidine **9aj** was obtained, after deprotection (see below), in only 37%

[‖] The dipolarophile-dipole bridge in nitrones **5a**, **5bb** and **5cb** is also treated as an alkyl substituent.

[¶] We discovered the influence of sodium borohydride on the selectivity of hydrogenolysis of **6ab** by accident. Inspired by referee we performed additional experiments to explain how sodium borohydride acts. So based on literature data[28] we assumed that sodium borohydride might work just as a base, increasing pH of the reaction mixture. Indeed, the hdrogenolysis of **6ab** carried out in the presence of 10% palladium on charcoal in methanol is also selective if pH of the reaction mixture was increased up to 9 with the addition of sodium hydroxide. In addition we found out that the rise of the pH to 10 impedes both N–O and the benzylic hydrogenolysis.



Scheme 3.



Scheme 4.

Table 4. Yield of the piperidines **8** and **9**

Entry	No	R^1	R^2	R^3	Catalyst	Yield (%)[a]
1	**9aa**	H	H	H	10% Pd–C	87
2	**9ab**	H	H	Ph	10% Pd–C–$NaBH_4$	74[b]
3	**8ag**	H	H	$PhCH_2CH_2$	Raney-Ni	87
4	**9ah**	H	H	$PhCH_2$	10% Pd–C	81
5	**9aj**	H	H	2-Pyridyl	10% Pd–C	37[c]
6	**8ak**	H	H	2-Thienyl	Raney-Ni–DMSO	73
7	**9bb**	CH_3	H	Ph	10% Pd–C–$NaBH_4$	73
8	**9cb**	H	CH_3	Ph	10% Pd–$NaBH_4$	87

[a] Based on **6**.
[b] Yield of intermediate **8ab** was 85%.
[c] Yield of intermediate **8aj** was 49%.

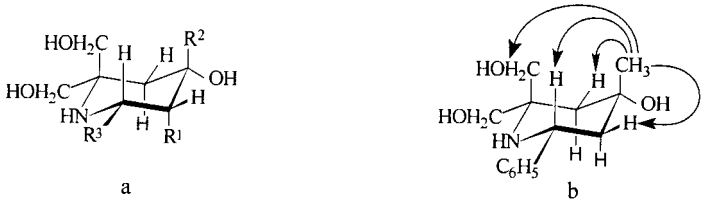


Figure 1.

overall yield (Table 4, entry 5). To convert 2-thienyl derivative **6ak** into the piperidine **8ak** it was necessary to use Raney nickel. The reaction conditions depended on the quality of the catalyst used; when old catalyst was employed for the reduction of **6ak** the piperidine **8ak** was obtained selectively at room temperature and under 8–9 bar pressure. Freshly prepared catalyst (W2) was so active, however, that to obtain **8ak**, its activity had to be moderated by the addition of DMSO.

Hydroxymethyl groups were readily deprotected by 5% hydrochloric acid in methanol to afford the derivatives of 2,2-bis(hydroxymethyl)-4-hydroxypiperidine **9**.

^{1}H NMR spectra of the piperidines **8** and **9** were very similar to the spectra described in literature for related piperidine derivatives[5–7] and the structures derived from these spectra were consistent with the structures of the corresponding **6**. Thus **8** and **9** of the series '**a**' (R^1=R^2=H) have the *cis* configuration and in the chair conformation both the 4-OH group and R^3 occupy equatorial positions (Fig. 1a). Indeed, the signal of the H-4 proton is nearly a regular 'triplet of triplets' with a large axial–axial coupling constant (J=11.1–12.0 Hz) and a smaller one (J=4.2–4.5 Hz) for the axial–equatorial couplings. Proton H-6 is coupled with protons H-5e and H-5a by 2.2–2.8 and 11.5–12.3 Hz, respectively. In addition, the H-3e and H-5e protons being in a planar 'W' arrangement are coupled by ^4J=2.0–2.5 Hz. The all-*cis* configuration of the piperidine **9bb** requires that in the chair conformation the methyl group has an axial orientation. The ^{1}H NMR spectrum confirms this fact; the H-4 signal is doublet of triplets with coupling constant J_{43a}=12.3 Hz (doublet) and $J_{4-3e}\approx J_{4-5e}$=4.5–4.8 Hz, respectively, while the resonance for H-6 is a doublet with a coupling constant characteristic (J_{6-5e}=2.5 Hz) of the axial–equatorial interaction. Long range coupling between H-3e and H-5e is not observed for this derivative. The ^{1}H NMR spectrum of **9cb** suggests that also this compound exists in a chair conformation. Indeed, values of vicinal coupling constants J_{6-5a}=12.1 Hz and J_{6-5e}=2.2 Hz are characteristic for such a conformation. However, the determination of the **9cb** conformation was based only on two vicinal coupling constants. So it is possible that **9cb** might exist in a twist-boat conformation.[**] In order to clarify this ambiguity we measured NOE-diff spectra of **9cb** (Fig. 1b). Irradiation of the methyl group resulted in an enhancement of the intensities of signals H-6 (1.8%), one hydroxymethyl group (1.6%) and H-3e and H-5e protons (2.2%). Such a NOE-diff spectrum is only possible when the chair conformation is the dominating one.

In conclusion, we have demonstrated that 4-nitrobut-1-ene derivatives prepared from the palladium(0) catalyzed *C*-allylation of nitroalkanes are useful starting materials

[**] Molecular modeling of **9cb** by MM^+ and AM1 calculation showed that such twist-boat conformation is quite probable.

for the preparation of highly substituted piperidines via intramolecular 1,3-dipolar cycloaddition reaction of *N*-(3-alkenyl)nitrones.

3. Experimental

^{1}H NMR spectra were measured with a Varian GEMINI 2000 or with a Bruker AMX-500 spectrometers. ^{13}C NMR spectra were recorded only on the former apparatus at 50 MHz. In APT spectra resonances corresponding to CH and CH_3 are indicated by '-'. TMS and DSS were used as internal standards for $CDCl_3$ and D_2O solution, respectively. Coupling constants (J) are in Hz and chemical shifts (δ) in ppm. IR spectra were recorded with a Specord M80 (Carl-Ziess Jena) spectrometer. Mass spectra (electron impact or LSIMS) were obtained from an AMD 604 instrument. Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used for TLC and column chromatography was performed on Marchery Nagel MN-Kieselgel 60 (200–300 mesh).

3.1. General procedure for a preparation of the allylic 5-nitro-1,3-dioxanes 3

Nitro derivative (**1** or 2-nitropropane, 0.019 mol) and a solution of sodium methoxide, prepared from Na (0.625 g, 0.025 mol) and MeOH (15 mL), were stirred for 0.5 h under argon. To this mixture, PPh_3 (0.5 g, 1.9 mmol) or 1,2-bis(diphenylphosphino)ethane (0.38 g, 0.95 mmol; for preparation of **3c**) followed by bis(triphenylphosphine)dichloropalladium (0.67 g, 0.95 mmol) was added. After 0.5 h, allylating reagent (0.025 mol) was introduced dropwise with stirring. Additionally, THF (30 mL) was added to the reaction in which allylic chlorides were used. The reaction with allyl acetate was carried out at 50–55°C for ca.15 h and with allylic chlorides at room temperature for 20–25 h. The reaction was followed by TLC (except the preparation of **3e**) with hexane–ethyl acetate (3:1, v/v) mixture as eluent. At the end of the reaction, black palladium separated frequently. The reaction mixture was passed through a short pad of Celite® and the filtrate was diluted with cold water and the resulting mixture was extracted three times with CH_2Cl_2. The organic solution was successively washed with 20% aqueous sodium hydroxide, then water until washings were neutral, and finally with brine. After drying over anhydrous magnesium sulfate the solvent was removed under reduced pressure and the residue was dissolved in methylene chloride and passed through short pad of silica gel and then purified by column chromatography on silica gel (10–25% of ethyl acetate in hexane) and/or by crystallization from hexane (**3a** and **3c**) or methanol (**3d**). The yields of **3a**–**3d** are listed in Table 1. ^{1}H (200 MHz) and ^{13}C NMR spectra of **3** were measured in $CDCl_3$ solution.

3.1.1. 2,2-Pentamethylene-5-nitro-5-(2-propenyl)-1,3-dioxane (3a). Yield 75%, white crystals; mp 37–39°C (hexane). δ_H 1.35–1.80 (m, 10H, C_6H_{10}), 2.55 (bd, J=7.3 Hz, 2H, CH_2), 3.92 (d, J=12.9 Hz, 2×CH-O), 4.43 (d, J=12.9 Hz, 2H, 2×CH-O), 5.21–5.23 (m, 2H, CH_2=), 5.60 (ddt, J=16.6, 10.4, 7.3 Hz, 1H, CH=). δ_C (APT) 22.39, 22.52, 25.41, 29.76, 34.49, 38.45, 62.87, 85.99, 99.14, 121.44, 128.52 (−). IR (neat): 3084, 2940, 1640, 1548, 1360, 1160, 1136 cm^{-1}; Anal. calcd for $C_{12}H_{19}NO_4$: C 59.73, H 7.94, N 5.81; found: C 59.90, H 7.90, N 5.72.

3.1.2. 2,2-Pentamethylene-5-(2-butenyl)-5-nitro-1,3-dioxane (3b). Yield 75%, oil, the *E*/*Z* mixture in 85:15 ratio, respectively. (*E*)-**3b**: δ_H 1.41–1.81 (m, 10H, C_6H_{10}), 1.66 (bd, J=6.5 Hz, 3H, CH_3), 2.47 (bd, J=7.4 Hz, 2H, CH_2), 3.93 (d, J=12.9 Hz, 2H, 2×CH-O), 4.43 (d, J=12.9 Hz, 2H, 2×CH-O), 5.22 (dtq, J=15.1, 7.4, 1.6 Hz, 1H, =C*H*CH_2), 5.57 (dqt, J=15.1, 1.2, 6.5 Hz, 1H, =C*H*CH_3). δ_C (APT) 17.93 (−), 22.37, 22.51, 25.40, 29.52, 34.71, 37.42, 62.89, 86.28, 99.01, 120.85 (−), 132.33 (−). IR (neat): 2940, 1644, 1546, 1148 cm^{-1}. HRMS (EI) m/z calcd for $C_{13}H_{21}NO_4$ (M^+) 255.1471, found 255.1479.

3.1.3. 2,2-Pentamethylene-5-(2-methyl-2-propenyl)-5-nitro-1,3-dioxane (3c). Yield 65%, white crystals after chromatography, mp 87–88°C (hexane). δ_H 1.35–1.85 (m, 10H, C_6H_{10}), 1.68 (dd, J=1.0, 1.4 Hz, 3H, CH_3), 2.52 (bs, 2H, CH_2), 3.97 (d, J=12.8 Hz, 2×CH-O), 4.47 (d, J=12.8 Hz, 2×CH-O), 4.74 (p, J=1.5 Hz, 1H, C*H*=) 4.94 (m, 1H, C*H*=). δ_C (APT) 22.37, 22.52, 23.30 (−), 25.41, 29.46, 34.81, 42.06, 63.35, 85.83, 99.01, 117.37, 137.37: IR (KBr): 3076, 2924, 1638, 1548, 1460, 1292, 1156 cm^{-1}. Anal. calcd for $C_{13}H_{21}NO_4$: C 61.16, H 8.29, N 5.48; found C 61.30, H 8.38, N 5.51.

3.1.4. 2,2-Pentamethylene-5-nitro-5-(3-phenyl-2-propenyl)-1,3-dioxane (3d). White crystals, mp 106–107°C (methanol). δ_H 1.35–1.85 (m, 10H, C_6H_{10}), 2.74 (dd, J=7.6, 1.2 Hz, 2H, CH_2), 4.01 (d, J=12.9 Hz, 2H, 2×CH-O), 4.49 (d, J=12.9 Hz, 2H, 2×CH-O), 5.94 (dd, J=15.6, 7.6 Hz, 1H, CH_2C*H*=), 6.48 (dt, J=15.6, 1.2 Hz, 1H, PhC*H*=), 7.30 (m, 5H, C_6H_5). δ_C (APT) 22.37, 22.52, 25.38, 30.05, 34.14, 37.70, 62.89, 86.11, 99.18, 119.50 (−), 126.41 (−), 128.01 (−), 128.59 (−), 136.03 (−), 136.11. IR (KBr): 3032, 2948, 1664, 1542, 1272, 1140 cm^{-1}. Anal. calcd for $C_{18}H_{24}NO_4$: C 68.12, H 7.30, N 4.41; found C 68.28, H 7.29, N 4.42.

3.1.5. 5-Methyl-5-nitropent-1-ene (3e). Colorless liquid, bp 60°C/16 mmHg (lit.[14] bp 73°C/30 mmHg).

3.2. General procedure for preparation of 6 and 7 (the one-pot procedure)

Aluminum foil cut in small pieces (0.55 g, 20.0 mmol) was added to a solution of mercury(II) chloride (0.2 g, 0.75 mmol) in THF (30 mL) and water (1.0 mL). The resulting mixture was stirred at room temperature for 10 min, then **3** (10 mmol) in THF (15 mL) was added dropwise. When TLC (ethyl acetate–hexane 3:1 v/v) showed that the reaction was complete (usually after 3 h; reduction to 1–5 mmol scale required shorter reaction time) the mixture was passed through short pad of Celite and washed with THF. The solvent was distilled off under reduced pressure and crude **4** was combined with aldehyde (8.5 mmol) and toluene (30 mL) unless otherwise stated. The mixture was refluxed under argon for 10–20 h until TLC (10–20% ethyl acetate in hexane) showed that the reaction was complete. Toluene was removed under reduced pressure and the residue was

taken into methylene chloride and the solution was passed through a short column of silica gel. The solvent was distilled off and the residue was purified by chromatography and/or by crystallization as it is specified for each **6**. ^{1}H (500 MHz) and ^{13}C NMR spectra of **6** and **7** were measured for $CDCl_3$ solution.

3.2.1. 7-Oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6aa). Paraformaldehyde (0.132 g, 4.4 mmol), triethylamine (48 μL) and *n*-propanol (24 mL) were refluxed to obtain a clear solution, then **4a** (prepared from 1 mmol of **3a**) was added and heating was continued for 1.5 h. Propanol was removed and crystallization from hexane afforded 0.132 g (56%) of **6aa** (white crystals); mp 80–81°C. δ_H (COSY) 1.37 (d, J=11.9 Hz, 1H, H-3en), 1.41 (m, 2H, C_6H_{10}), 1.45–1.56 (m, 5H, H-5en, 4H of C_6H_{10}), 1.67–1.85 (m, 4H, C_6H_{10}), 1.90 (ddd, J=11.9, 5.3, 2.6 Hz, 1H, H-3ex), 1.96 (m, 1H, H-5ex), 2.99 (ddd, J=12.3, 10.7, 5.6 Hz, 1H, 6-ex), 3.07 (ddd, J=12.3, 8.3, 3.9 Hz, 1H, H-6en), 3.53 (dd, J=11.5, 1.3 Hz, CH-O), 3.66 (dd, J=11.6, 1.3 Hz, 1H, CH-O), 3.90 (d, J=11.6 Hz, 1H, CH-O), 3.94 (d, J=11.5 Hz, 1H, CH-O), 4.86 (t, J=5.3 Hz, 1H, H-4). δ_C (APT) 22.48, 22.62, 25.57, 30.95, 32.61, 33.61, 42.57, 49.11, 63.73, 65.47, 67.70, 80.00 (−), 98.03. IR (KBr): 2940, 1288, 1276, 1118 cm^{-1}. Anal. calcd for $C_{13}H_{21}NO_3$: C 65.24, H 8.84, N 5.85; found C 64.93, H 8.77, N 5.88.

3.2.2. 6-*exo*-Phenyl-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ab). Yield 61%, white crystals, mp 114–115°C (hexane). δ_H (COSY) 1.38–1.60 (m, 6H, C_6H_{10}), 1.45 (d, J=11.9 Hz, 1H, H-3en), 1.63–1.87 (m, 4H, C_6H_{10}), 2.08 (dddd, J=12.0, 4.9, 5.0, 2.5 Hz, 1H, H-5ex), 2.12 (dd, J=12.0, 8.0 Hz, 1H, H-5en), 2.14 (ddd, J=12.0, 5.0, 2.5 Hz, 1H, H-3ex), 3.59 (dd, J=11.4, 1.9 Hz, CH-O), 3.74 (dd, J=11.2, 1.9 Hz, 1H, CH-O), 4.04 (d, J=11.4 Hz, 1H, CH-O), 4.08 (d, J=11.2 Hz, 1H, CH-O), 4.11 (dd, J=8.0, 4.9 Hz, 1H, H-6), 4.98 (t, J=5.0 Hz, 1H, H-4), 7.30 (m, 5H, C_6H_5). δ_C (APT) 22.52, 22.73, 25.62, 28.92, 35.80, 42.39, 42.61, 62.35 (−), 64.04, 65.24, 68.06, 80.71 (−), 98.12, 127.08 (−), 128.45 (−), 143.52. IR (KBr): 2940, 1456, 1274, 1252, 1118 cm^{-1}. Anal. calcd for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; found C 72.50, H 8.00, N 4.33.

3.2.3. The preparation of 6ab from 5ab. The mixture of crude **4a**, prepared from **3a** (1 mmol), THF (3 mL), benzaldehyde (0.091 mL, 0.9 mmol) and acetic acid (0.057 mL) was stirred overnight under argon at room temperature then heated at 60°C for 6 h. THF was removed under reduced pressure and the residue was dissolved in methylene chloride and successively washed with water, aqueous sodium bicarbonate, water, brine and dried with anhydrous magnesium sulfate. The residue was purified by chromatography (10–20% of ethyl acetate in hexane) to give 0.24 g (75%) of **5ab** as pale yellow syrup. δ_H (200 MHz, $CDCl_3$) 1.49 (m, 10H, C_6H_{10}), 2.58 (d, J=7.3 Hz, 2H, CH_2), 4.01 (d, J=12.9 Hz, 2H, 2×CH-O), 4.34 (d, J=12.9 Hz, 2H, 2×CH-O), 5.11 (m, 2H, =CH_2), 5.62 (m, 1H, =CH), 7.40 (m, 3H, C_6H_5), 7.74 (s, 1H, N=CH), 8.32 (m, 2H, C_6H_5). δ_C ($CDCl_3$) 22.33, 22.42, 25.41, 28.57, 35.95, 37.26, 63.51, 70.27, 98.86, 119.94, 128.29, 129.18, 130.28, 130.61, 134.77. IR (KBr): 3080, 2936, 1640, 1584, 1160, 1118 cm^{-1}. HRMS (EI) m/z calcd for $C_{19}H_{25}NO_3$ (M^+) 315.1834, found 315.1832. **5ab** (0.235 g, 0.745 mmol) was refluxed in toluene (5 mL) under argon for 18 h to afford after chromatographic purification (15% ethyl acetate in hexane) 0.20 g (85%) of **6ab**, mp 113–115°C.

3.2.4. 6-*exo*-(4-Fluorophenyl)-7-oxa-1-azabicyclo[2.2.1]-heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ac). Yield 36%, white crystals, mp 80–81°C (hexane). δ_H 1.38–1.58 (m, 6H, C_6H_{10}), 1.56 (d, J=12.0 Hz, 1H, H-3en), 1.64–1.86 (m, 4H, C_6H_{10}), 2.04 (dddd, J=11.8, 5.2, 4.5, 2.5 Hz, 1H, H-5ex), 2.12 (ddd, J=12.0, 5.2, 2.5 Hz, 1H, H-3ex), 2.12 (dd, J=11.8, 8.2 Hz, 1H, H-5en), 3.58 (dd, J=11.4, 1.8 Hz, CH-O), 3.74 (dd, J=11.1, 1.8 Hz, 1H, CH-O), 4.02 (d, J=11.4 Hz, 1H, CH-O), 4.08 (d, J=11.1 Hz, 1H, CH-O), 4.10 (dd, J=8.2, 4.5 Hz, 1H, H-6), 4.98 (t, J=5.2 Hz, 1H, H-4), 6.98 (m, 2H of C_6H_4), 7.35 (m, 2H of C_6H_4). δ_C (APT) 22.50, 22.69, 25.59, 29.21, 35.45, 42.25, 42.66, 61.76 (−), 63.93, 65.27, 67.96, 80.65 (−), 98.14, 115.12 (−) (d, J_{C-F}=21.1 Hz), 128.51 (−) (d, J_{C-F}=1.8 Hz), 139.36 (d, J_{C-F}=2.8 Hz), 161.8 (d, J_{C-F}=243.7 Hz). IR (KBr): 2952, 1450, 1254, 1224, 1114 cm^{-1}. Anal. calcd for $C_{19}H_{24}NFO_3$: C 68.45, H 7.26, N 4.20; found C 68.68, H 7.26, N 4.13.

3.2.5. 6-*exo*-(4-Trifluoromethylphenyl)-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ad). Yield 56%, white crystals, mp 125–126°C (hexane). δ_H 1.39–1.58 (m, 6H, C_6H_{10}), 1.57 (d, J=12.1 Hz, 1H, H-3en), 1.65–1.86 (m, 4H, C_6H_{10}), 2.03 (dddd, J=11.7, 5.1, 4.6, 2.5 Hz, 1H, H-5ex), 2.11 (ddd, J=12.1, 5.3, 2.5 Hz, 1H, H-3ex), 2.16 (dd, J=11.7, 8.3 Hz, 1H, H-5en), 3.60 (dd, J=11.4, 1.7 Hz, 1H, CH-O), 3.76 (dd, J=11.1, 1.7 Hz, 1H, CH-O), 4.03 (d, J=11.4 Hz, CH-O), 4.08 (d, J=11.1 Hz, 1H, CH-O), 4.19 (dd, J=8.3, 4.6 Hz, 1H, H-6), 4.99 (dd, J=5.3, 5.1 Hz, 1H, H-4), 7.52 (m, 2H of C_6H_4), 7.55 (m, 2H of C_6H_4). δ_C (APT) 22.51, 22.69, 25.58, 29.43, 35.20, 42.22, 42.57, 61.90 (−), 63.88, 65.35, 67.90, 80.71 (−), 98.21, 125.35 (−) (q, J_{C-F}=3.8 Hz), 127.20 (−), 147.48. IR (KBr): 2944, 1448, 1288, 1256, 1112 cm^{-1}. HRMS (EI) m/z calcd for $C_{20}H_{24}NF_3O_3$ (M^+) 383.1708, found 383.1696.

3.2.6. 6-*exo*-(2-Methoxyphenyl)-7-oxa-1-azabicyclo[2.2.1]-heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ae). Yield 33%, yellowish oil after chromatography (hexane–ethyl acetate, 5:1, v/v). δ_H 1.39–1.60 (m, 6H, C_6H_{10}), 1.60 (d, J=12.0 Hz, 1H, H-3en), 1.62–1.86 (m, 4H, C_6H_{10}), 1.86 (dddd, J=11.9, 5.2, 4.6, 2.6 Hz, 1H, H-5ex), 2.12 (dd, J=11.9, 8.2 Hz, 1H, H-5en), 2.13 (ddd, J=12.0, 5.2, 2.6 Hz, 1H, H-3ex), 3.59 (dd, J=11.4, 1.9 Hz, CH-O), 3.76 (dd, J=11.1, 1.9 Hz, 1H, CH-O), 3.80 (s, 3H, OCH_3), 4.04 (d, J=11.4 Hz, 1H, CH-O), 4.09 (d, J=11.1 Hz, 1H, CH-O), 4.47 (dd, J=8.2, 4.6 Hz, 1H, H-6), 4.91 (t, J=5.2 Hz, 1H, H-4), 6.81 (m, 1H, C_6H_4), 6.93 (m, 1H, C_6H_4), 7.18 (m, 1H, C_6H_4), 7.61 (m, 1H, C_6H_4). δ_C (APT) 22.47, 22.68, 25.58, 28.72, 35.90, 42.24, 42.60, 55.22 (−), 56.18 (−), 63.93, 65.19, 68.12, 80.57 (−), 97.96, 109.83 (−), 120.58 (−), 126.98 (−), 127.58 (−), 131.73, 155.94. IR (KBr): 2948, 1464, 1268, 1244, 1100 cm^{-1}. HRMS (EI) m/z calcd for $C_{20}H_{27}NO_4$ (M^+) 345.1940, found 345.1935.

3.2.7. 6-*exo*-(3,4-Dimethoxyphenyl)-7-oxa-1-azabicyclo-[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6af). Yield 35%, yellowish oil after chromatography (hexane–ethyl acetate, 4:1, v/v). δ_H 1.40–1.57 (m, 6H, C_6H_{10}), 1.58 (d, J=12.0 Hz, 1H, H-3en), 1.64–1.87 (m, 4, C_6H_{10}), 2.06 (dddd, J=11.9, 4.8, 5.0, 2.4 Hz, 1H, H-5ex), 2.10 (dd, J=11.9, 8.1 Hz, 1H, H-5en), 2.15 (ddd, J=12.0, 5.3, 2.4 Hz, 1H, H-3ex), 3.59 (dd, J=11.4, 2.0 Hz, CH-O), 3.73 (dd, J=11.0, 2.0 Hz, 1H, CH-O), 3.85 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.04 (d, J=11.4 Hz, 1H, CH-O), 4.04 (dd, J=8.1, 5.0 Hz, 1H, H-6), 4.11 (d, J=11.0 Hz, 1H, CH-O), 4.99 (dd, J=5.3, 4.8 Hz, 1H, H-4), 6.79 (d, J=8.3 Hz, 1H of C_6H_3), 6.87 (dd, J=8.3, 2.0 Hz, 1H of C_6H_3), 6.97 (d, J=2.0 Hz, 1H of C_6H_3). δ_C (APT) 22.45, 22.65, 25.48, 28.73, 35.87, 42.26, 42.72, 55.82 (−), 62.15 (−), 63.97, 65.12, 68.00, 80.54 (−), 98.02, 110.14 (−), 110.88 (−), 119.09 (−), 136.27, 148.00, 148.96. IR (KBr): 2936, 1464, 1252, 1236, 1110 cm^{-1}. HRMS (EI) m/z calcd for $C_{21}H_{29}NO5$ (M^+) 375.2046, found 375.2047.

3.2.8. 6-*exo*-[(*E*)-2-Phenylethenyl)]-7-oxa-1-azabicyclo-[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ag). Yield 55%, white needles, mp 129–130°C (hexane). δ_H 1.41 (m, 2H, C_6H_{10}), 1.49 (d, J=12.0 Hz, 1H, H-3en), 1.50–1.68 (m, 6H, C_6H_{10}), 1.85 (m, 3H, 2H of C_6H_{10}, H-5ex), 1.89 (dd, J=11.7, 7.8 Hz, 1H, H-5en), 2.04 (ddd, J=12.0, 5.3, 2.3 Hz, 1H, H-3ex), 3.56 (dd, J=11.4, 1.5 Hz, CH-O), 3.70 (dd, J=11.3, 1.5 Hz, 1H, CH-O), 3.76 (ddd, J=7.8, 7.5, 4.2 Hz, 1H, H-6), 4.00 (d, J=11.4 Hz, 1H, CH-O), 4.06 (d, J=11.3 Hz, 1H, CH-O), 4.92 (dd, J=5.3, 4.7 Hz, 1H, H-4), 6.21 (dd, J=16.0, 7.5 Hz, 1H, CH=), 6.44 (d, J=16.0 Hz, 1H, PhCH=), 7.18–7.36 (m, 5H, C_6H_5). δ_C (APT) 22.52, 22.70, 25.61, 29.52, 35,16, 40.69, 42.38, 61.70 (−), 63.87, 65.24, 67.90, 80.57 (−), 98.16, 126.39 (−), 127.45 (−), 128.42 (−), 130.09 (−), 131.40 (−), 136.71. IR (KBr): 2936, 1660, 1448, 1288,1256,1110 cm^{-1}. Anal. calcd for $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10; found C 73.63, H 8.0, N 4.14.

3.2.9. 6-*exo*-(Phenylmethyl)-7-oxa-1-azabicyclo[2.2.1]-heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ah). Yield 42%, yellow oil after chromatography (hexane–ethyl acetate, 6:1, v/v). δ_H (COSY) 1.34 (d, J=12.0 Hz, 1H, H-3en), 1.39–1.56 (m, 6H, C_6H_{10}), 1.55 (dd, J=12.0, 7.6 Hz, 1H, H-5en), 1,62–1.72 (m, 3H, H-5ex, 2H, C_6H_{10}), 1.81 (m, 2H, C_6H_{10}), 1.93 (ddd, J=12.0, 5.3, 2.5 Hz, 1H, H-3ex), 2.54 (dd, J=13.9, 8.1 Hz, 1H, C*H*Ph), 3.11 (dd, J=13.9, 6.4 Hz, 1H, C*H*Ph), 3.35 (dddd, J=8.1, 7.6, 6.4, 4.0 Hz, 1H, H-6), 3.54 (dd, J=11.4, 1.4 Hz, CH-O), 3.65 (dd, J=11.4, 1.4 Hz, 1H, CH-O), 3.92 (d, J=11.4 Hz, 1H, CH-O), 3.95 (d, J=11.4 Hz, 1H, CH-O), 4.85 (dd, J=5.3, 5.0 Hz, 1H, H-4), 7.25 (m, 5H, C_6H_5). δ_C (APT) 22.49, 22.63, 25.57, 30.34, 34.25, 39.08, 41.82, 42.13, 60.73 (−), 63.71, 65.22, 67.80, 80.66 (−), 98.01, 126.11 (−), 128.27 (−), 129.19 (−), 138.86. IR (KBr): 2936, 1448, 1286, 1264, 1108 cm^{-1}. HRMS (EI) m/z calcd for $C_{20}H_{27}NO_3$ (M^+) 329.1991, found 329.1983.

3.2.10. 6-*exo*-(3-Pyridyl)-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ai). Yield 51%, yellow oil (solidifying during standing in a refrigerator) after chromatography (5% methanol in chloroform). δ_H 1.40–1.56 (m, 6H, C_6H_{10}), 1.56 (d, J=12.1 Hz, 1H, H-3en), 1.66–1.85 (m, 4H, C_6H_{10}), 2.05 (dddd, J=11.7, 5.0, 4.3, 2.5 Hz, 1H, H-5ex), 2.08 (ddd, J=12.1, 5.3, 2.5 Hz, 1H, H-3ex), 2.17 (dd, J=11.7, 8.3 Hz, 1H, H-5en), 3.59 (dd, J=11.5, 1.5 Hz, CH-O), 3.79 (dd, J=11.3, 1.5 Hz, 1H, CH-O), 4.01 (d, J=11.5 Hz, 1H, CH-O), 4.08 (d, J=11.3 Hz, 1H, CH-O), 4.20 (dd, J=8.3, 4.3 Hz, 1H, H-6), 5.00 (dd, tl, J=5.3, 5.0 Hz, 1H, H-4), 7.25 (dd, J=7.9, 4.8 Hz, 1H, H-5pyr), 7.83 (dt, J=7.9, 1.8 Hz, 1H, H-4pyr.), 8.47 (dd, J=4.8, 1.2 Hz, 1H, H-6pyr.), 8.56 (d, J=1.8 Hz, 1H, H-2pyr). δ_C (APT) 22.51, 22.68, 25.57, 29.74, 34.90, 42.15, 42,37, 60.32 (−), 63.82, 65.55, 67.63, 80.69 (−), 98.26, 123.58 (−), 135.01 (−), 139.23, 148.03 (−), −148.43 (−). IR (KBr): 2940, 1576, 1456, 1288, 1258, 1110 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{24}N_2O_3$ (M^+) 316.1787, found 316.1795.

3.2.11. 6-*exo*-(2-Pyridyl)-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6aj). Yield 63%, light brown powder; analytical sample was purified by chromatography (ethyl acetate–hexane, 5:1,v/v), crystals, mp 106–108°C. δ_H 1.4–1.59 (m, 6H, C_6H_{10}), 1.61 (d, J=12.1 Hz, 1H, H-3en), 1.67–1.86 (m, 4H, C_6H_{10}), 2.10 (ddd, J=12.1, 5.3, 2.6 Hz, 1H, H-3ex), 2.18 (dd, J=11.9, 8.5 Hz, 1H, H-5en), 2.26 (dddd, J=11.9, 5.0, 4.4, 2.6 Hz, 1H, H-5ex), 3.62 (dd, J=11.4, 1.8 Hz, CH-O), 3.78 (dd, J=11.3, 1.8 Hz, 1H, CH-O), 4.06 (d, J=11.4 Hz, 1H, CH-O), 4.09 (d, J=11.3 Hz, 1H, CH-O), 4.34 (dd, J=8.5, 4.4 Hz, 1H, H-6), 4.96 (dd, tl, J=5.3, 5.0 Hz, 1H, H-4), 7.13 (m, 1H, pyr), 7.66 (m, 1H, pyr), 7.73 (m, 1H, pyr), 8.49 (m, 1H, pyr). δ_C (APT) 22.52, 22.71, 25.61, 29.53, 35.18, 40.90, 42.45, 63.89 (−), 63.96, 65.29, 67.99, 80.80 (−), 98.18, 121.23 (−), 121.89 (−), 136.80 (−), 148.67 (−), 162.33. IR (KBr):2956, 1592, 1468, 1284, 1258, 1106 cm^{-1}. HRMS (EI) m/z calcd for $C_{18}H_{24}N_2O_3$ (M^+) 316.1787, found 316.1795.

3.2.12. 6-*exo*-(2-Thienyl)-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6ak). Yield 67%, white crystals, mp 149.5–150°C (hexane). δ_H 1.40–1.56 (m, 6H, C_6H_{10}), 1.57 (d, J=12.0 Hz, 1H, H-3en), 1.62–188 (m, 4H, C_6H_{10}), 2.11 (dd, J=11.7, 8.0 Hz, 1H, H-5en) 2.11–2.19 (m, 2H, H-3ex, H-5ex), 3.58 (dd, J=11.4, 2.0 Hz, CH-O), 3.69 (dd, J=11.0, 2.0 Hz, 1H, CH-O), 4.03 (d, J=11.4 Hz, 1H, CH-O), 4.11 (d, J=11.0 Hz, 1H, CH-O), 4.39 (dd, J=8.0, 4.2 Hz, 1H, H-6), 5.02 (t, J=5.2 Hz, 1H, H-4), 6.91 (m, 2H, C_4H_3S), 7.19 (m, 1H, C_4H_3S). δ_C (APT) 22.50, 22.68, 25.59, 28.79, 35.87, 42.22, 43.11, 59.26 (−), 63.93, 65.02, 67.96, 80.73 (−), 98.12, 124.04 (−), 125.05 (−), 126.28 (−), 147.31. IR (KBr): 2936, 1444, 1270, 1252, 1120 cm^{-1}. Anal. calcd for $C_{17}H_{23}NO_3S$: C 63.52, H 7.21, N 4.36; found C 63.79, H 7.27, N 4.37.

3.2.13. 6-*exo*-2,2-Dimethyl-6-phenyl-7-oxa-1-azabicyclo-[2.2.1]heptane (6eb). Yield 58%, white crystals, mp 38–39°C (hexane). δ_H 1.31 (s, 3H, CH_3), 1.35, (d, J=11.3 Hz, 1H H-3en), 1.36 (s, 3H, CH_3), 1.84 (ddd, J=11.3, 5.4, 2.3 Hz, 1H, H-3ex), 2.00 (dddd, J=11.5, 5.0, 4.6, 2.3 Hz, 1H, H-5ex), 2.05 (dd, J=11.5, 8.3 Hz, 1H, H-5en), 4.44 (dd, J=8.3, 4.6 Hz, 1H, H-6), 4.90 (dd, J=5.4, 5.0 Hz, 1H, H-4), 7.177.42 (m, 5H, C_6H_5). δ_C 24.62, 31.48, 42.24, 46.59, 62.71, 65.70, 81.34, 126.60, 127.02, 128.35, 144.58. IR

(KBr): 2964, 1456, 1282, 1260 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{13}H_{17}NO$ (M^+) 203.1310, found 203.1302.

3.2.14. 5-*exo*-Methyl-6-*exo*-phenyl-7-oxa-1-azabicyclo-[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6bb). Yield 42%, white crystals, mp 123–124°C (hexane). δ_H 0.55 (d, *J*=7.2 Hz, 3H, CH_3), 1.38–1.64 (m, 8H, C_6H_{10}), 1.69 (d, *J*=12.2 Hz, 1H, H-3en), 1.83 (m, 2H, C_6H_{10}), 2.22 (dd, *J*=12.2 Hz, 5.4, H-3ex), 2.35 (qd, *J*=7.2, 8.2 Hz, 1H, H-5en), 3.62 (dd, *J*=11.3, 2.0 Hz, 1H, CH-O), 3.71 (dd, *J*=11.0, 2.0 Hz, 1H, CH-O), 4.06 (d, *J*=11.3 Hz, CH-O), 4.08 (d, *J*=11.0 Hz, 1H, CH-O), 4.17 (d, *J*=8.2 Hz, 1H, H-6), 4.48 (d, *J*=5.4 Hz, 1H, H-4), 7.17–7.34 (m, 5H, C_6H_5). δ_C (APT) 16.52 (−), 22.48, 22.73, 25.60, 28.36, 36.30, 42.76, 46.06 (−), 64.01, 65.01, 66.27 (−), 68.09, 86.72 (−), 98.08, 126.61 (−), 127.83 (−), 128.04 (−), 138.96. IR (KBr): 2936, 1452, 1286, 1256, 1112 cm^{-1}. Anal. calcd for $C_{20}H_{27}NO_3$: C 72.92, H 8.26, N 4.25; found C 72.69, H 8.33, N 4.21.

3.2.15. 4-Methyl-6-*exo*-phenyl-7-oxa-1-azabicyclo[2.2.1]-heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6cb). Yield 49%, white crystals, after chromatography (hexane–ethyl acetate, 6:1, v/v) followed by crystallization, mp 85–86°C (hexane). δ_H (COSY) 1.38–1.51 (m, 4H, C_6H_{10}), 1.56 (m, 2H, C_6H_{10}), 1.60 (s, 3H, CH_3), 1.64 (m, 2H, C_6H_{10}), 1.77 (d, *J*=12.1 Hz, 1H, H-3en), 1.87 (m, 3H, H-5ex, 2H, C_6H_{10}), 1.98 (dd, *J*=12.1, 2.9 Hz, H-3ex), 2.26 (dd, *J*=11.7, 8.4 Hz, 1H, H-5en), 3.65 (dd, *J*=11.4, 2.0 Hz, 1H, CH-O), 3.74 (dd, *J*=11.0, 2.0 Hz, 1H, CH-O), 4.06 (d, *J*=11.4 Hz, 1H, CH-O), 4.07 (d, *J*=11.0 Hz, 1H, CH-O), 4.15 (dd, *J*=8.4, 4.7 Hz, 1H, H-6), 7.19–7.40 (m, 5H, C_6H_5). δ_C 18.24, 22.50, 22.72, 25.61, 28.47, 36.24, 48.03, 48.14, 64.05, 64.20 66.42, 68.19, 89.91, 98.07, 126.89, 128.43, 143.76. IR (KBr): 2944, 1452, 1288, 1258, 1108 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{20}H_{27}NO_3$ (M^+) 329.1991, found 329.1986.

3.2.16. 5-*exo*-Phenyl-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (6da) and 3-*exo*-phenyl-2-oxa-1-azabicyclo[2.2.1]heptane-6-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (7da). *Method (a) The one-pot procedure.* **4d** and paraformaldehyde was heated in boiling toluene as described in general procedure for preparation of **6**. The mixture of **6da** and **7da** was separated by column chromatography (15–20% ethyl acetate in hexane). **6da** was obtained in 44% yield as white crystals, mp 156–157°C); δ_H 1.42 (m, 2H, C_6H_{10}), 1.54 (d, *J*=12.2 Hz, 1H, H-3en), 1.49–1.87 1.97 (dd, *J*=12.2, 5.3 Hz, 1H, H-3ex), 2.89 (dd, *J*=8.1, 5.6 Hz, 1H, H-5en), 3.04 (dd, *J*=12.7, 5.6 Hz, 1H, H-6ex), 3.59 (m, 2H, H-6en, CH-O), 3.75 (dd, *J*=11.8, 1.4 Hz, 1H, CH-0), 3.97 (d, *J*=11.2 Hz, 1H, CH-O), 3.99 (d, *J*=11.2 Hz, 1H, CH-O), 4.73 (d, *J*=5.3 Hz, 1H, H-4), 7.19–7.30 (m, 5H, C_6H_5). δ_C 22.52, 22.65, 25.59, 31.09, 33.53, 42.46, 51.70, 59.85, 63.54, 65.42, 67.63, 86.99, 98.18, 126.78, 127.25, 128.61, 143.53. IR (KBr): 2988, 1456, 1284, 1220, 1120 cm^{-1}. Anal. calcd for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; found C 71.79, H 7.98, N 4.25. **7da** was obtained in 15% as white crystals, mp 142–143°C. δ_H (COSY) 1.41–1.57 (m, 6H, C_6H_{10}), 1.58 (dd, *J*=12.6, 2.0 Hz, 1H, H-5en), 1.70 (m, 2H, C_6H_{10}), 1.74 (dd, *J*=12.6, 4.1 Hz, 1H, H-5ex), 1.87 (m, 2H, C_6H_{10}), 2.66 (dd, *J*=10.8, ca. 1 Hz, 1H, H-7), 2.92 (bd, *J*=4.1 Hz, 1H, H-4), 2.96 (bdd, *J*=10.8, 2.0 Hz, 1H, H-7), 3.39 (dd, *J*=11.7, 1.4 Hz, 1H, CH-O), 3.74 (dd, *J*=11.9, 1.4 Hz, 1H, CH-O), 3.82 (d, *J*=11.7 Hz, 1H, CH-O), 4.25 (d, *J*=11.9 Hz, 1H, CH-O), 4.55 (bs, 1H, H-3), 7.22–7.35 (m, 5H, C_6H_5). δ_C 22.56, 22.70, 25.62, 30.56, 34.12, 37.99, 48.09, 55.47, 64.69, 66.75, 67.14, 83.21, 98.16, 125.52, 127.35, 128.26, 140.93. IR (KBr): 2940, 1436, 1272, 1224, 1102 cm^{-1}. Anal. calcd for $C_{19}H_{25}NO_3$: C 72.35, H 7.99, N 4.44; found C 72.39, H 7.99, N 4.45.

Method (b) From formaldehyde. Hydroxylamine **4d** (obtained from 1 mol of **3d**) was added to solution of formaldehyde (prepared from paraformaldehyde (0.033 g, 1.1 mmol), propanol (5 mL) and NEt_3 (4 μL) as described for compound **6aa**) and resulting mixture was refluxed under argon for 1 h. The product was separated as described in general procedure for preparation of **6**. Chromatography separation afforded **6da** (0.08 g, 25.5%, mp 156–157°C) and **7da** (0.08 g, 25.5%, mp 142–145°C).

3.2.17. 5,6-*exo*-Diphenyl-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane 6db and (±)(5*S,7*R**)-5,7-diphenyl-2-oxa-1-azabicyclo[2.2.1]heptane-6-spiro-5′-(1′,3′-dioxan)-2′-spiro-1″-cyclohexane (7db).** Yield 67%, the **6db/7db** mixture, white crystals, mp 135–144°C (hexane). The major isomer **6db** (75%) δ_H 1.40–1.73 (m, 2H, C_6H_{10}, **6db**+**7db**), 1.84 (d, *J*=12.4 Hz, 0.75H, H-3en), 2.32 (dd, *J*=12.4, 5.4 Hz, 0.75H, H-3ex), 3.48 (d, *J*=8.6 Hz, 0.75H, H-5en), 3.70 (dd, *J*=11.3, 2.0 Hz, 0.75H, CH-O), 3.83 (dd, *J*=11.0, 2.0 Hz, 0.75H, CH-O), 4.14 (d, *J*=11.3 Hz, 0.75H, CH-O), 4.15 (d, *J*=11.0, 2.0 Hz, 0.75H, CH-O), 4.63 (d, *J*=8.6 Hz, 0.75H, H-6), 4.98 (d, *J*=5.4 Hz, 0.75H, H-4), 6.74–7.17 (m, 10H, 2 C_6H_5, **6db**+**7db**) δ_C (APT) 22.53, 22.75, 25.63, 28.68, 36.08, 43.48, 58.55 (−), 64.07 65.34, 68.24, 68.34 (−), 87.26 (−), 98.21, 125.91 (−), 126.01 (−), 127.24 (−), 127.52 (−), 127.87 (−), 128.76 (−), 138.48, 139.65. **7db** (minor isomer, 25%) δ_H 1.84–1.90 (m, 0.25H, H-5en, 1.5H, C_6H_{10}, **6db**+**7db**), 1.94 (m, 0.5H, C_6H_{10}), 2.05 (dd, *J*=12.4, 3.8 Hz, 0.25H, H-5ex), 3.49 (dd, *J*=11.6, 1.8 Hz, 0.25H, CH-O), 3.59 (bd, *J*=3.8 Hz, 0.25H, H-4), 3.78 (dd, *J*=11.8, 1.8 Hz, 0.25H, CH-O), 4.04 (d, *J*=11.6 Hz, 0.25H, CH-O), 4.22 (bs, 0.25H, H-7), 4.37 (d, *J*=11.8 Hz, 0.25H, CH-O), 4.62 (s, 0.25H, H-3). δ_C (APT) 22.62, 29.56, 35,28, 40.96, 50.96 (−), 65.27, 67.54, 71.28 (−), 82.92 (−), 124.79 (−), 125.74 (−), 126.45 (−), 127.14 (−), 127.36 (−), 127.44 (−). IR (KBr): 2936, 1448, 1272, 1256, 1104 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{25}H_{29}NO_3$ (M^+) 391.2147, found 391.2142.

3.3. General procedure for preparation of 8 and 9

Compound **6** (1 mmol) in methanol (15–20 mL) was hydrogenated in the presence of catalyst and under conditions specified for each **6**. When TLC showed disappearance of **6** the catalyst was removed by filtration through a short pad of Celite® and the solvent was distilled off. The residue (**8**) was purified by chromatography or when crude **8** was chromatographically homogeneous it was deprotected without purification. (Only **8ab**, **8ag**, **8ak** and **8eb** were fully characterized.). **8** was treated with 5% HCl aq (5 mL) in boiling methanol (17 mL) for 1–3 h. The filtration rate

was neutralized by solid sodium bicarbonate then inorganic materials were filtered off. Methanol was removed and residue was taken into acetone or into a mixture of acetone and methanol. Residual inorganic material was filtered off then crude **9** was chromatographically purified (chloroform–methanol, 2:1,v/v). ^{1}H (500 MHz) and ^{13}C NMR spectra of **8** and **9** were recorded for $CDCl_3$ and D_2O solution, respectively.

3.3.1. *cis*-4-Hydroxy-6-phenylpiperidine-2-spiro-5′-(1′,3′-dioxan)-2′spiro-1″-cyclohexane (8ab). 6ab (0.41 g, 1.3 mmol) was hydrogenated in the presence of 10% Pd–C (0.117 g) and sodium borohydride (0.06 g) under ambient pressure for 3 h. Chromatographic purification (ethyl acetate–methanol, 9:1, v/v) afforded **8ab** (0.35 g, 85%) as a colorless glass. δ_H 1.15 (dd, J=12.4, 11.7 Hz, 1H, H-3a), 1.41 (m, 2H, C_6H_{10}), 1.46–1.55 (m, 5H, 4H of C_6H_{10}, H-5a), 1.60 (m, 2H, C_6H_{10}), 1.80 (ddd, J=12.4, 4.6, 1.9 Hz, 1H, H-3e), 1.86 (m, 2H, C_6H_{10}), 2.09 (dddd, J=11.9, 4.4, 2.4, 1.9 Hz, 1H, H-5e), 2.17 (bs, 2H, NH, OH), 3.49 (dd, J=11.3, 2.3 Hz, 1H, CH-O), 3.77 (d, J=11.9 Hz, 1H, CH-O), 3.79 (d, J=11.3 Hz, CH-O), 3.84 (dddd, J=11.7, 11.1, 4.4, 4.6 Hz, 1H, H-4), 3.92 (dd, J=11.6, 2.4 Hz, 1H, H-6), 4.00(dd, J=11.9, 2.3 Hz, 1H, CH-O), 7.24–7.44 (m, 5H, C_6H_5); δ_C 22.52, 25.61, 28.14, 36.50, 38.73, 44.71, 50.99, 53.57, 62.49, 65.81, 70.30, 77.20, 98.51, 126.87, 127.27, 128.38, 144.14. IR (KBr): 3332, 2936, 1448, 1108 cm^{-1}. HRMS (EI) m/z calcd for $C_{19}H_{27}NO_3$ (M^+) 317.1991, found 317.2012.

3.3.2. *cis*-4-Hydroxy-6-(2-phenylethyl)piperidine-2-spiro-5′-(1′,3′-dioxan)-2′spiro-1″-cyclohexane (8ag). 6ag (0.102 g, 0.3 mmol) was hydrogenated in the presence of Raney Nickel slurry (ca. 0.3 g under of 10 bar at 60°C for 3 h). Chromatographic purification (chloroform–methanol, 5:1, v/v) gave **8ag** (0.09 g, 87%) as colorless glass. δ_H (COSY) 1.06 (t, J=12.0 Hz, 1H, H-3a), 1.11 (q, J=11.5 Hz, 1H, H-5a), 1.41 (m, 2H, C_6H_{10}), 1.43 (m, 2H, C_6H_{10}), 1.58 (m, 2H, C_6H_{10}), 1.67 (m, 2H, C_6H_{10}), 1.71–1.78 (m, 3H, H-3e, CH_2CH$_2$Ph), 1.85 (m, 2H, C_6H_{10}), 1.98 (m, 1H, H-5e), 2.02 (bs, 2H, OH, NH), 2.69 (m, 2H, CH_2Ph), 2.79 (m, 1H, H-6), 3.46 (dd, J=11.3, 2.3 Hz, 1H, CH-O), 3.68 (d, J=11.8 Hz, 1H, CH-O), 3.70 (m, 1H, H-4 overlap with CH-O) 3.73 (d, J=11.3 Hz, 1H, CH-O), 3.83 (dd, J=11.8, 2.2 Hz, 1H, CH-O), 7.17–7.29 (m, 5H, C_6H_5). δ_C (APT) 22.52, 25.58, 28.15, 32.04, 36.56, 38.52, 38.98, 42.10, 48.00 (−), 50.88, 62.49, 65.43 (−), 70.01, 98.50, 125.82 (−), 128.35 (−), 128.40 (−), 141.702. IR (neat): 3332, 2936, 1664, 1448, 1156, 1108 cm^{-1}. HRMS (EI) m/z calcd for $C_{21}H_{21}NO_3$ (M^+) 345.2304, found 345.2292.

3.3.3. *cis*-4-Hydroxy-6-(2-thienyl)piperidine-2-spiro-5′-(1′,3′-dioxan)-2-′spiro-1″-cyclohexane (8ak). 6ak (0.115 g, 0.36 mmol) was hydrogenated in the presence of Raney Nickel (0.3 g) and DMSO (0.3 mL) under 10 bar for 29 h. at 90°C. **8ak** was purified as **8ag** to yield a colorless glass (0.085 g, 73%). δ_H 1.15 (dd, J=12.4, 11.4 Hz, 1H, H-3a), 1.40 (m, 2H, C_6H_{10}), 1.45–1.56 (m, 5H, H-5a, C_6H_{10}), 1.61 (m, 2H, C_6H_{10}), 1.79 (ddd, J=11.9, 4.6, 1.9 Hz, 1H, H-3e), 1.84 (m, 2H, C_6H_{10}), 2.19 (dddd, J=11.9, 4.5, 2.5, 1.9 Hz, 1H, H-5e), 2.38 (bs, 2H, NH, OH), 3.52 (dd, J=11.4, 2.3 Hz, 1H, CH-O), 3.75 (d, J=11.4 Hz, 1H, CH-O), 3.76 (d, J=11.9 Hz, 1H, CH-O), 3.81 (tt, J=11.5, 4.5 Hz, 1H, H-4), 3.94 (dd, J=1.9, 2.3 Hz, CH-O), 4.24 (dd, J=11.5, 2.5 Hz, 1H, H-6), 6.94 (dd, J=5.0, 3.5 Hz, 1H, C_4H_3S), 6.98, (bd, J=3 Hz, 1H of C_4H_3S), 7.19 (dd, J=5.0, 1.2 Hz, 1H of C_4H_3S). δ_C (APT) 22.42, 25.50, 28.20, 36.22, 38.55, 45.56, 49.46 (−), 51.18, 62.40, 65.27 (−), 69.86, 99,45, 123.03 (−), 123.68 (−), 126.17 (−), 148.42. IR (neat): 3412, 3324, 2936, 1664, 1448, 1156, 1108 cm^{-1}. HRMS (EI) m/z calcd for $C_{17}H_{25}NO_3S$ (M^+) 323.1555, found 323.1562.

3.3.4. *cis*-2,2-Dimethyl-4-hydroxy-6-phenylpiperidine (8eb). 6eb was hydrogenated for 24 h under conditions described for the reduction of **6ab**. Chromatographic purification afforded **8eb** in 82% yield as a colorless glass. δ_H 1.20 (s, 6H, 2×CH$_3$), 1.32 (dd, J=12.1, 11.3 Hz, 1H, H-3a), 1.33 (ddd, J=11.9, 11.2, 11.9 Hz, 1H, H-5a), 1.87 (ddd, J=12.1, 4.5, 2.0 Hz, 1H, H-3e), 2.12 (dddd, J=11.9, 4.5, 2.6, 2.0 Hz, 1H, H-5e), 3.89 (dd, J=11.8, 2.6 Hz, 1H, H-6), 3.97 (tt, J=11.2, 4.5 Hz, 1H, H-4), 7.22–27.37 (m, 5H, C_6H_5). δ_C (APT) 24.78 (−), 32.82 (−), 43.57, 46.66, 54.57 (−), 66.77 (−), 126.69 (−), 127.23 (−), 128.45 (−), 143.77. IR (neat); 3456, 2936, 1674, 1448, 1158 cm^{-1}. HRMS (EI) m/z calcd for $C_{13}H_{19}NO$ (M^+) 205.1467, found 205.1462.

3.3.5. 2,2-Bis(hydroxymethyl)-4-hydroxypiperidine (9aa). 6aa (0.25 g, 1 mmol) was hydrogenated in the presence of 10%-Pd–C (0.075 g) under ambient pressure for 20 h. Deprotection of crude **8aa** afforded after chromatographic purification **9aa** (0.14 g, 87%) as a colorless glass. δ_H 1.21 (dd, J=13.0, 10.9 Hz, 1H, H-3a), 1.34 (dddd, J=12.5, 12.3, 10.9, 4.5 Hz, 1H, H-5a), 1.88 (ddd, J=13.0, 4.5, 1.6 Hz, 1H, H-3e), 1.95 (m, 1H, H-5e), 2.78 (ddd, J=13.0, 12.3, 2.8 Hz, 1H, H-6a), 2.92 (dt, J=13.0, 3.9 Hz, 1H, H-6e), 3.48 (AB, Δ=0.07, J=11.3 Hz, 2H, CH_2OH), 3.62 (AB, Δ=0.05, J=11.9 Hz, CH_2OH), 3.92 (tt, J=10.9, 4.5 Hz, 1H, H-4). δ_C 36,09, 38.35, 40.73, 60.01, 62.32, 67.48, 68.88. IR (nujol): 3392, 2948, 1636, 1444, 1148 cm^{-1}. HRMS (LSIMS) m/z calcd for $C_7H_{16}NO_3$ (M+H$^+$) 162.1130, found 162.1127.

3.3.6. *cis*-2,2-Bis(hydroxymethyl)-4-hydroxy-6-phenylpiperidine (9ab). Deprotection of **8ab** (0.2 g, 0.63 mmol) gave **9ab** (0.13 g, 87%; the overall yield was 74%) as a colorless glass. δ_H 1.27 (dd, J=12.8, 11.8 Hz, 1H, H-3a), 1.51 (ddd, J=12.0, 12.1, 11.3 Hz, 1H, H-5a), 2.00 (ddd, J=12.8, 4.5, 1.7 Hz, 1H, H-3e), 2.16 (dddd, J=12.0, 4.5, 2.3, 1.7 Hz, 1H, H-5), 3.50 (AB, Δ=0.05, J=11.3 Hz, 2H, CH_2OH), 3.75 (AB, Δ=0.4, J=12.0 Hz, 2H, CH_2OH), 3.99 (dd, J=12.1, J=2.3 Hz, 1H, H-6), 4.09 (dddd, J=11.8, 11.3, 4.5, 4.5 Hz, 1H, H-4). δ_C (APT) 38.05, 43.22, 51.51 (−), 60.96, 62.15, 68.02 (−), 69.145, 129.47 (−), 130.45 (−), 131.48 (−), 144.70. IR (KBr): 3336, 2948, 1448, 1108 cm^{-1}. HRMS (LSIMS) m/z calcd for $C_{13}H_{20}NO_3$ (M+H$^+$) 238.1443, found 238.1445.

3.3.7. *cis*-2,2-Bis(hydroxymethyl)-4-hydroxy-6-(phenylmethyl)piperidine (9ah). 6ah (0.235 g, 0.71 mmol) was hydrogenated in the presence of 10% Pd–C (0.15 g) under 8 bar for 23 h. Deprotection of crude **8ah** yielded **9ah** (0.145 g, 81%) as a colorless glass. δ_H 1.08 (ddd, J=12.3, 11.5, 11.5 Hz, 1H, H-5a), 1.13 (dd, J=12.8, 11.5 Hz, 1H, H-3a), 1.89 (ddd, J=12.8, 4.65, 1.3 Hz, 1H, H-3e), 1.98 (m,

1H, H-5e), 2.72 (dd, J=13.4, 7.4 Hz, 1H, CH_2Ph), 2.76 (dd, J=13.4, 6.5 Hz, 1H, CH_2Ph), 3.10 (m, 1H, H-6), 3.40 (AB, Δ=0.02, J=11.3 Hz, CH_2OH), 3.56 (AB, Δ=0.02, J=11.9 Hz, CH_2OH), 3.92 (J=11.5, 4.6 Hz, 1H, H-4), 7.27–7.41 (m, 5H, C_6H_5). δ_C 38.60, 42.27, 44.51, 52.61, 60.03, 61.76, 67.80, 69.35, 129.34, 131.39, 132.03, 141.19. IR (KBr): 3416, 1632, 1496 cm^{-1}. HRMS (LSIMS) m/z calcd for $C_{14}H_{22}NO_3$ ($M+H^+$) 252.1600 found 252.1591.

3.3.8. *cis*-2,2-Bis(hydroxymethyl)-4-hydroxy-6-(2-pyridyl)piperidine (9aj). Crude **6aj** (0.316 g, 1 mmol) was hydrogenated in the presence of 10% Pd–C (0.15 g) under 9 bar for 21 h. Chromatographic purification (chloroform–methanol, 9:1,v/v) afforded 0.155 g (49%) of **8aj**. This (0.1 g, 0.31 mmol) was deprotected to give **9aj** (0.056 g, 76%; the summary yield 37%) as a as a colorless glass. δ_H 1.44 (dd, J=13.2, 11.5 Hz, 1H, H-3a), 1.58 (ql, J=12.1 Hz, 1H, H-5a), 2.07 (ddd, J=13.2, 4.5, ca. 1.5 Hz, 1H, H-3e), 2.36 (m, 1H, H-5e), 3.62 (bs, 2H, CH_2OH), 3.81 (AB, Δ=0.09, J=12.2 Hz, 2H, CH_2OH), 4.21 (tt, J=11.5, 4.5 Hz, 1H, H-4), 4.30 (bd, J=11.4 Hz, 1H, H-6), 7.42 (dd, J=7.0, 5.2 Hz, 1H, C_5H_4N), 7.51 (d, J=7.9 Hz, 1H, C_5H_4N), 7.91 (ddd J=7.9, 7.0, 1.4 Hz, 1H of C_5H_4N), 8.54 (db, J=4.6 Hz, 1H, C_5H_4N), δ_C 36.79, 40.49, 57.15, 61.44, 64.44, 66.13, 67.01, 124.88, 126.92, 141.32, 151.79, 158.27. IR (KBr): 3412, 1620, 1452, 1032 cm^{-1}. HRMS (LSIMS) m/z calcd for $C_{12}H_{18}N_2NaO_3$ ($M+Na^+$) 261.1215 found 261.1223.

3.3.9. (±)(4*S,5*S**,6*S**)-2,2-bis(hydroxymethyl)-4-hydroxy-5-methyl-6-phenylpiperidine (9bb).** The adduct **6bb** (0.33 g, 1 mmol) was hydrogenated for 20 h as it was described for **6ab**. Crude **8bb** was deprotected to give after chromatographic purification **9bb** (0.185 g, 73%) as a colorless glass. δ_H 0.60 (d, J=7.1 Hz, 3H, CH_3), 1.58 (dd, J=13.3, 12.3 Hz, 1H, H-3a), 1.68 (dd, J=13.3, 4.8 Hz, 1H, H-3e), 2.21 (m, 1H, H-5a), 3.59 (AB, Δ=0.04, J=11.3 Hz, 2H, CH_2OH), 3.68 (AB, Δ=0.03, J=12.0 Hz, CH_2OH), 4.19 (d, J=2.5 Hz, 1H, H-6), 4.27 (ddd, J=12.3, 4.8, 4.6 Hz, 1H, H-4), 7.31–7.44 (m, 5H, C_6H_5). δ_C 6.07, 30.89, 42.55, 58.59, 60.75, 62.98, 69.18, 70.94, 129.09, 129.66, 131.08, 143.90. IR (neat): 3352, 2940, 1656, 1452, 1152 cm^{-1}. HRMS (LSIMS) m/z calcd for $C_{14}H_{22}NO_3$ ($M+H^+$) 252.1600 found 252.1596.

3.3.10. (±)(4*S,6*S**)-2,2-bis(hydroxymethyl)-4-hydroxy-4-methyl-6-phenylpiperidine (9cb). 9cb** (87%) was obtained as a colorless glass in the way described for **9bb**. δ_H 1.46 (s, 3H, CH_3), 1.54 (d, J=13.9 Hz, 1H, H-3a), 1.72 (dd, J=12.8, 12.1 Hz, 1H, H-5a), 1.92 (dd, J=13.9, ca. 1 Hz, 1H, H-3e), 1.92 (ddd, J=12.8, 2.2, ca. 1 Hz, 1H, H-5e), 3.50 (AB, Δ=0.05, J=11.3 Hz, CH_2OH), 3.75 (s, 2H, CH_2OH), 3.95 (dd, J=12.1, 2.2 Hz, 1H, H-6), 7.35–7.45 (m, 5H, C_6H_5). δ_C 30.91, 42.21, 48.65, 55.31, 60.44, 63.06, 70.09, 72.92, 129.45, 130.40,131.53, 145.29. IR (KBr): 3392, 1630, 1436, 1132 cm^{-1}. HRMS (LSIMS) m/z calcd for $C_{14}H_{22}NO_3$ ($M+H^+$) 252.1600 found 252.1612.

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