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Development of a new class of (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-oxazoline ligands and their application in asymmetric transfer hydrogenation

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Abstract—New 2-aza-norbornane-oxazoline compounds were synthesized and evaluated as ligands in the transfer hydrogenation of acetophenone. The best catalyst prepared in situ from $[IrCl_2(COD)]_2$ and a ligand afforded 1-(*S*)-phenylethanol in good yields and 79% ee.

1. Introduction

The development of new chiral ligands for catalytic asymmetric transformations is one of the most important issues in the research of asymmetric synthesis.[1] Among the nitrogen ligands[1c] oxazoline compounds have been used for a long time in different asymmetric catalytic reactions.[2] Chelating atoms could, in addition to the nitrogen in the oxazoline ring, be phosphorus, amino nitrogen, aromatic nitrogen or sulfur atoms present in the molecule.[3] Bis(oxazolines) are widely employed as ligands[4] as well.

Enantioselective transfer hydrogenation represents a very useful method for the preparation of optically active alcohols.[5] Recently Noyori and co-workers[6] showed that the NH function within the ligand molecule is crucial for the asymmetric transformation of prochiral ketones into chiral alcohols. Several C_2 symmetric chiral bis(oxazolinylmethyl)amine ligands[7a] were found to be efficient in the Ru(II) catalyzed asymmetric transfer hydrogenation. Recently the use of ruthenium and iridium complexes with bis(oxazoline) ligands in this asymmetric process was also reported.[7b] However, there are few reports on the use of C_1 symmetric amine-oxazoline ligands in transfer hydrogenation of prochiral ketones. The only example described is the application of chiral 1,2,3,4-tetrahyroquinolinyl-oxazoline ligands in complexes with Ru(II)[7b] (conversion 40–78%, ee 12–83%).

Previously 2-aza-norbornan-3-ylmethanol has been used by our research group[8] as an efficient ligand in Ru(arene)-catalyzed asymmetric transfer hydrogenation. Herein we describe the synthesis of a new class of 2-aza-norbornane-oxazoline ligands. We also show the importance of the bulky aza-bicyclic group in the ligand molecule for asymmetric transfer hydrogenation of acetophenone by comparison of the results obtained using acyclic chiral amine-oxazoline ligand complexes and initial results from a series of aza-bicycle-oxazoline ligand complexes.

2. Results and discussion

The syntheses of bicyclic amine-oxazoline ligands using a Cbz-protecting group for cyclic secondary nitrogen are shown in Scheme 1. The (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]-heptane-3-carboxylic acid (**1**) is easily available from a stereoselective aza-Diels Alder reaction.[9] The protection of the amine was performed using benzyl chloroformate[10] to give **2** in 72% yield. The amide coupling[11,12] of **2** with appropriate L- and D-aminoalcohols lead to hydroxylamines **3a**, **3b**, **4a**, **4b**, **5a** and **5b** (yield 64–94%). These compounds were converted into protected oxazolines **6a**, **6b**, **7a**, **7b**, **8a** and **8b** by treatment with mesyl chloride under basic conditions[11] in 65–95% yield after purification. The cleavage of the benzyloxycarbonyl group from the amine was accomplished by hydrogenolysis using palladium on carbon as a catalyst[13] to yield the ligands **9a**, **9b**, **10a**, **10b**, **11a** and **11b** in 55–74%.

The syntheses of bicyclic amine-oxazoline ligands using *p*-nitrobenzyloxycarbonyl protecting group are shown in Scheme 2. First, the compounds having the secondary amine protected by benzyloxycarbonyl were synthesized. It turned out that the deprotection of these oxazolines by

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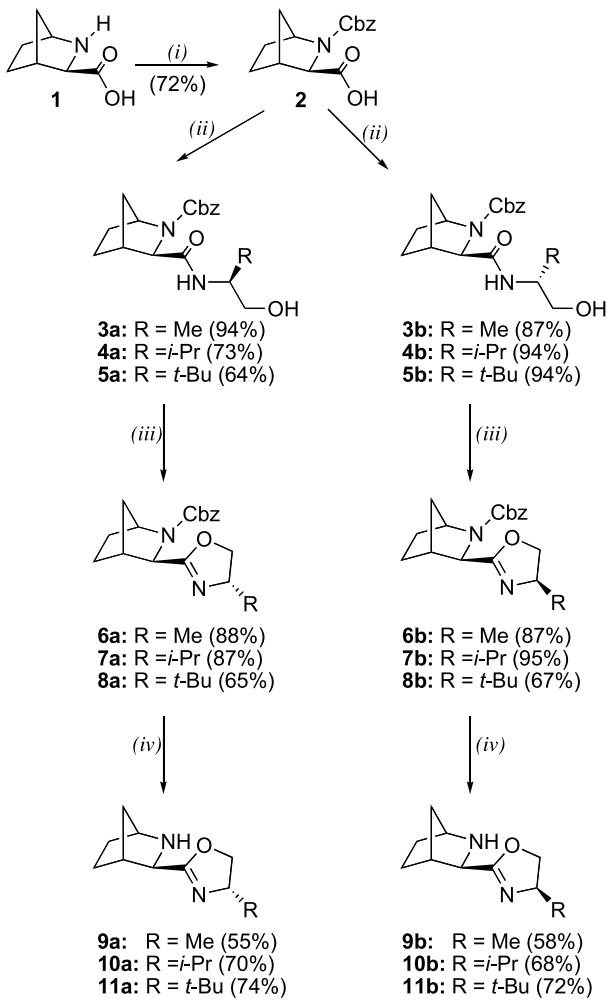


Scheme 1. Synthesis of ligands **9a**, **9b**, **10a**, **10b**, **11a** and **11b**. Conditions and reagents: (i) CbzCl, sat. $NaHCO_3$ in H_2O, rt, 3 h; (ii) EDC, HOBt, aminoalcohol, CH_2Cl_2, rt, overnight; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, overnight; (iv) Pd/C (10 wt%), H_2 (1 atm.), EtOH, rt, overnight.

hydrogenolysis using Pd/C as a catalyst resulted in decomposition of the oxazoline ring. We then started a search for a new protecting group, which could be removed under basic conditions (oxazolines are highly unstable under acidic conditions) or is more readily cleaved by catalytic hydrogenation. It was found that a recently reported method[14] for the preparation of oxazolines using a base-labile Fmoc protecting group did not work in the case of bicyclic amine-oxazoline molecules. It was not possible to cleave the Fmoc group by treatment of these compounds with piperidine, diethyl amine or *t*-butyl ammonium fluoride.[15] Instead, *p*-nitrobenzyloxycarbonyl was chosen because of its higher lability under mild catalytic hydrogenation conditions as compared to benzyloxycarbonyl. Alternatively, the deprotection can also be accomplished by treatment of the substrate with sodium dithionite,[16] but it was found, that the oxazolines were not stable under these conditions, even in the presence of a base.

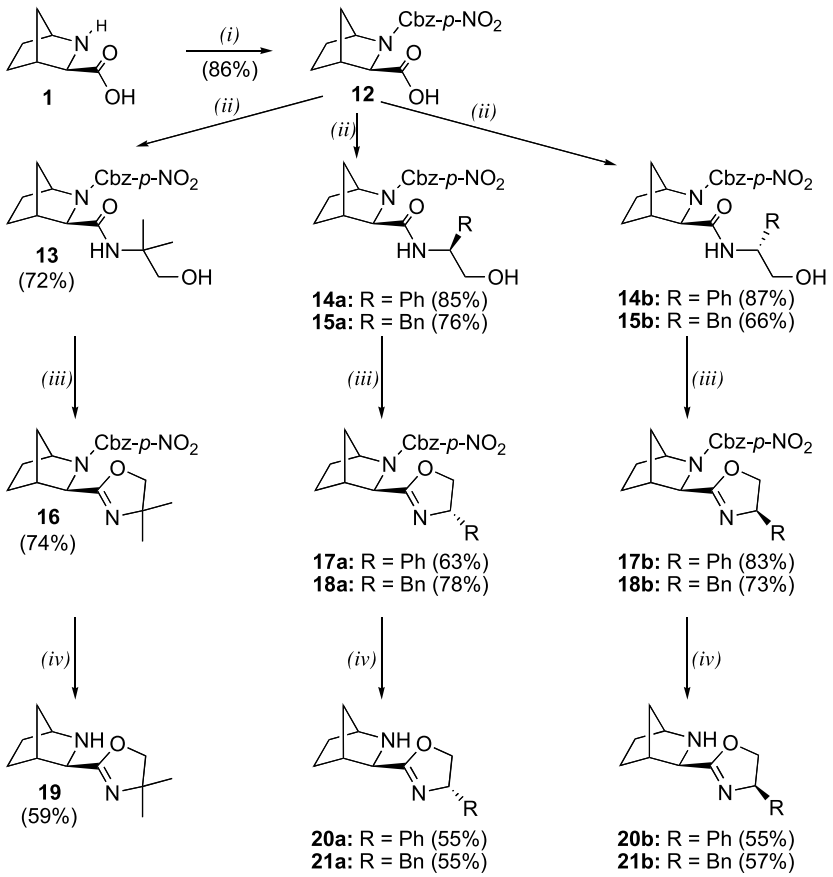
The *p*-nitrobenzyl ester protected amino acid[17] **12** was coupled[11,12] with the appropriate L- and D-aminoalcohols to produce hydroxylamines **13**, **14a**, **14b**, **15a** and **15b** in 66–87% yield. These compounds were cyclized by treatment with mesyl chloride under basic conditions[11] to give protected oxazolines **16**, **17a**, **17b**, **18a** and **18b** in 63–83% yield. The *p*-nitrobenzyloxycarbonyl group was readily cleaved by hydrogenolysis using palladium on carbon as a catalyst[16b] to yield the ligands **19**, **20a**, **20b**, **21a** and **21b** in 55–59% yield. No considerable amounts of oxazoline decomposition products were observed in the ^1H NMR spectra of the crude materials after deprotection.

2.1. Evaluation of the new oxazoline ligands in transfer hydrogenation

As a starting point of our investigation, we screened a number of different metal complexes as precatalysts for transfer hydrogenation using isopropanol as a hydrogen source and *i*-PrOK as a base. The following metal complexes were tested together with ligand **10a**: $[RuCl_2(benzene)]_2$, $RuCl_2(PPh_3)_3$, $[IrCl(COD)]_2$, $RhCl(PPh_3)_3$, $[Rh(COD)Cl]_2$ and $RuCl_2(DMSO)_4$. The results are shown in Table 1. Surprisingly, in our study we found that with the complexes $[RuCl_2(benzene)]_2$, $RuCl_2(PPh_3)_3$ and $RuCl_2(DMSO)_4$, no 1-phenylethanol formation was observed at all.[7] Rh(I) complexes $RhCl(PPh_3)_3$ and $[Rh(COD)Cl]_2$ were also able to catalyze this asymmetric transformation, but the catalyst was not as efficient as the one formed from $[IrCl_2(COD)]_2$ and produced the 1-phenylethanol with lower enantiomeric excess.

The presence of the bulky 2-aza-norbornanyl group in the ligand molecule was found to be crucial. The acyclic amine-oxazoline ligands **22a** and **22b**[18] (Scheme 3) were tested in transfer hydrogenation of acetophenone with $[IrCl_2(COD)]_2$ as the catalyst precursor. These catalysts turned out to be unselective and produced racemic 1-phenylethanol with low conversion (10%).

Next, the influence of the size and configuration of the substituent on the oxazoline part of the ligand was studied (Table 2). First, the Ir-complex was prepared from compound **19**, which has two methyl groups in the oxazoline (entry 1). When we employed this catalyst, acetophenone was reduced to 1-(*R*)-phenylethanol in 73% conversion and moderate ee (53%). To investigate how the configuration of the methyl substituent influences the stereoselectivity, oxazolines **9a** and **9b** were tested. These ligands gave 1-(*R*)-phenylethanol in 41% ee (20% conversion) and 33% ee (40% conversion) respectively (entries 2 and 3). These results show that in the case of ligands with a methyl substituent on the oxazoline ring the configuration of the bicycle is mainly responsible for the stereoselectivity. The diastereomeric pair of ligands **10a** and **10b** (entries 4 and 5) having a larger substituent on the oxazoline ring had higher selectivity. Use of ligand **10a** lead to the formation of 1-(*R*)-phenylethanol with 79% ee (32% conversion), while ligand **10b** resulted in formation of 1-(*S*)-phenylethanol (27% ee, 58% conv.). A further increase of the substituent steric size (*t*-butyl group) made the reaction more sluggish and also decreased the ee significantly (ligands **11a** and **11b**, entries 6 and 7). The ligands **20a** and **20b** prepared from L- and D-phenylglycinol also formed less selective catalysts with $[IrCl_2(COD)]_2$ (entries 8 and 9). This is in accordance with the hypothesis that the steric bulk of the substituent is crucial for asymmetric induction. The best conversion of acetophenone to 1-(*R*)-phenylethanol (83%) was observed

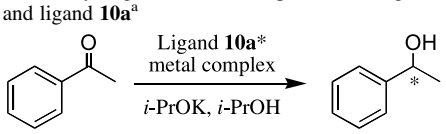


Scheme 2. Synthesis of ligands **19**, **20a**, **20b**, **21a** and **21b**. Conditions and reagents: (i) *p*-NO_2-CbzCl, 2.0 M NaOH in dioxane/H_2O, rt, overnight; (ii) EDC, HOBt, aminoalcohol, CH_2Cl_2, rt, overnight; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, overnight; (iv) Pd/C (10 wt%), H_2 (1 atm.), EtOH, rt, overnight.

when ligand **21a** (entry 10) was employed, but in this case the selectivity was low (28%). The diastereomeric ligand **21b** (entry 11) also afforded 1-(*R*)-phenylethanol (35% ee) but with lower conversion (15%).

These results show that in diastereomeric ligand pairs the configuration of product strongly depends on the configuration of a substituent on the oxazoline ring, except the molecules where steric bulk is missing (ligands **9a**, **9b**, **21a** and **21b**). Use of ligands produced from L-aminoalcohol leads to 1-(*R*)-phenylethanol formation. 1-(*S*)-Phenylethanol is obtained employing the Ir-complex with an oxazoline synthesized from a D-aminoalcohol. It was also noticed, that the rate of the reaction with ligands prepared from D-aminoalcohol is usually higher, but the ee of the product is lower.

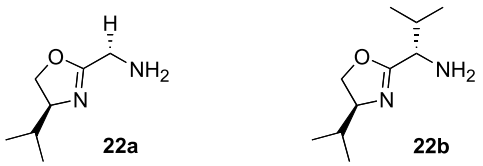
Table 1. Transfer hydrogenation of acetophenone using different metal complexes and ligand **10a**[a]



Entry	Metal complex[b]	Conv., 16 h (%)[c]	ee (%)[c]	Conf. of product
1	$RhCl(PPh_3)_3$	3	25	*R*
2	$[RhCl(COD)]_2$	18	71	*R*
3	$[IrCl(COD)]_2$	32	79	*R*
4	$[RuCl_2(benzene)]_2$	—	—	—
5	$RuCl_2(PPh)_3$	—	—	—
6	$RuCl_2(DMSO)_4$	—	—	—

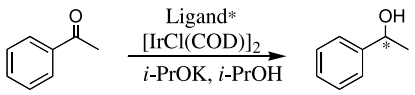
[a] See Section 4.1 for procedure.
[b] Substrate/metal/ligand/base=200:1:2:5.
[c] Determined by chiral GC.

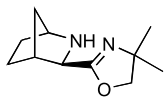
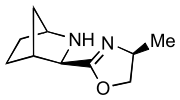
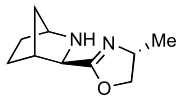
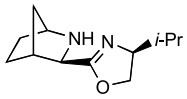
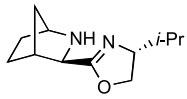
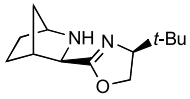
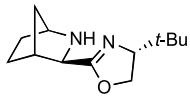
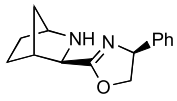
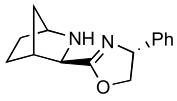
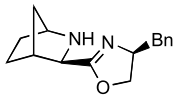
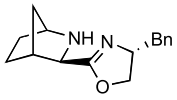
Interestingly, it was found that the enantioselectivity changes during the reaction time (Table 3). For example the Ir-complex prepared from ligand **10a** produced 1-(*R*)-phenylethanol in 38% ee after 1 h. When the product was analyzed after 16 h of reaction time its enantiomeric excess unexpectedly increased up to 79% (entry 1). Compound **10b** gave 1-(*S*)-phenylethanol in 16% ee after 1 h and 27% ee after 16 h (entry 2). Similar behaviour was recorded for the Ir-complex of compound **20b**. Using this ligand acetophenone was reduced to 1-(*S*)-phenylethanol in 14% ee in 1 h and in 24% ee after 16 h (entry 3). In reaction with oxazoline **21b** the enantiomeric excess of 1-(*R*)-phenylethanol significantly decreased during the reaction time (42% ee in 1 h and 28% ee in 16 h, entry 4). In a recently published computational study the mechanisms for transfer hydrogenation reactions of ketones catalyzed by Ru- and Ir-amino alcohol complexes were compared.[19] The calculation suggests that the Ru-catalysis proceeds via a concerted



Scheme 3. Structure of ligands **22a** and **22b**.

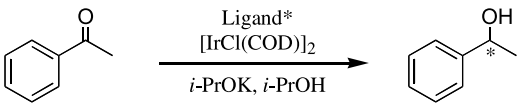
Table 2. Transfer hydrogenation of acetophenone using ligands **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **19**, **20a**, **20b**, **21a** and **21b**[a]

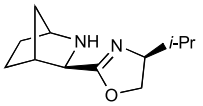
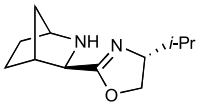
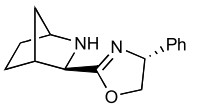
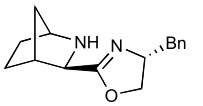


Entry	Ligand[b]	Conv., 16 h (%)[c]	ee (%)[c]	Conv. of product
1	 **19**	73	53	*R*
2	 **9a**	20	41	*R*
3	 **9b**	40	33	*R*
4	 **10a**	32	79	*R*
5	 **10b**	58	27	*S*
6	 **11a**	10	18	*R*
7	 **11b**	43	23	*S*
8	 **20a**	16	48	*R*
9	 **20b**	48	24	*S*
10	 **21a**	15	35	*R*
11	 **21b**	83	28	*R*

[a] See Section 4 for procedure.
[b] Substrate/metal/ligand/base=200:1:2:5.
[c] Determined by chiral GC.

Table 3. Transfer hydrogenation of acetophenone using ligands **10a**, **10b**, **20b** and **21b**[a]



Entry	Ligand[b]	Time (h)	Conv. (%)[c]	ee (%)[c]	Conv. of product
1	 **10a**	1 16	3 32	38 79	*R*
2	 **10b**	1 16	9 58	16 27	*S*
3	 **20b**	1 16	14 48	14 24	*R*
4	 **21b**	1 16	13 83	42 28	*R*

[a] See Section 4 for procedure.
[b] Substrate/metal/ligand/base=200:1:2:5.
[c] Determined by chiral GC.

mechanism while the Ir-catalyzed reaction proceeds via direct hydrogen transfer between simultaneously coordinated ketone and alcohol. This difference in reaction mechanisms might explain the change of the enantiomeric excess in Ir-catalyzed transfer hydrogenation.

3. Conclusions

The synthesis of a new class of (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-oxazoline ligands has been developed. This route can be used to prepare various derivatives of these new ligands in enantiomerically pure forms from commercially available starting materials.

The compounds were evaluated in the asymmetric transfer hydrogenation of acetophenone. It was found that $[IrCl_2(COD)]_2$ was the best catalyst precursor and use of the oxazoline **10a** as a ligand gave rise to a catalyst of good selectivity, 79% ee. These C_1 symmetric oxazolinyl azabicyclic amine ligands are currently under investigation and will be also tested in other asymmetric transformations.

4. Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 399.95/100.57 MHz. The chemical shifts are reported using the residual signal of $CDCl_3$ as the internal reference. Optical rotations were recorded on a thermostated polarimeter using a 1.0 dm cell. GC analysis was performed using

the chiral column CP-Chiralsil-Dex CB with N_2 as the carrier gas at 15 psi and using a FID detector. Flash chromatography was performed on silica gel (37–70 μm). The TLCs were performed on 0.25 mm precoated plates, silica gel 60 UV_{254} and spots were visualized using UV light and ethanolic phosphomolybdic acid followed by heating. The chiral starting materials, amines, acids and other reagents were used as received from commercial suppliers. Dichloromethane and isopropanol were dried over CaH_2 and distilled under nitrogen prior to use.

4.1. General procedure for transfer hydrogenation of acetophenone

$[IrCl(COD)]_2$ (3.35 mg, 5.0 μmol), ligand (20.0 μmol) and *i*-PrOH (2 mL) were added to a dry 50 mL Schlenk flask under argon. The solution was stirred for 1 h at 80 °C and then cooled down to room temperature. *i*-PrOH (18 mL) was added followed by acetophenone (235 μL, 2.0 mmol) and 1.0 M *i*-PrOK in *i*-PrOH (50 μL, 50.0 μmol). The reaction mixture was stirred for 16 h at room temperature and quenched by addition of two drops of 1.0 M HCl. Evaporation of solvent and flash chromatography (diethyl ether/pentane) gave the pure 1-phenylethanol. The enantiomeric excess was determined by chiral GC analysis.

4.1.1. (1*S*,3*R*,4*R*)-2-Aza-bicyclo-[2.2.1]-heptane-2,3-dicarboxylic acid 2-benzyl ester (2). Compound **1** (7.0 g, 47.6 mmol) was dissolved in 476 mL of H_2O (10 mL/mmol). A solid $NaHCO_3$ (10.0 g, 119.0 mmol) was added and the mixture was stirred until a clear solution was obtained. Benzyl chloroformate (7.5 mL, 52.4 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. The water solution was extracted with diethyl ether (2×200 mL), the phases were separated and the aqueous phase was acidified with conc. HCl to pH~4. (A milky white suspension was formed.) The suspension was extracted with diethyl ether (2×300 mL), the organic phase was dried over $MgSO_4$ and evaporated to yield compound **2** (9.4 g, 34.3 mmol, yield 72%) as a colorless oil, which was used in later steps without further purification. (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 10.24 (brs, 1H); 7.39–7.26 (m, 5H); 5.23–5.08 (m, 2H); 4.44–4.34 (m, 1H); 3.96–3.90 (m, 1H); 2.90–2.79 (m, 1H); 2.00–1.30 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 175.1, 174.0, 155.5, 153.8, 136.2, 136.0, 128.2, 128.1, 127.8, 127.6, 127.5, 127.1, 67.2, 66.6, 64.45, 63.8, 57.4, 56.9, 42.35, 41.0, 35.4, 34.4, 30.2, 29.8, 27.5, 27.0 ppm; IR (neat) ν_{max} 2952, 1750, 1705, 1666, 1426, 1359, 1130, 1109 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 276 (M^++1, 40%), 232 (20), 186 (34), 158 (48), 141 (52), 112 (28), 92 (100), 68 (44); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{18}NO_4$: 276.1236. Found: 276.1247.

4.1.2. (1*S*,3*R*,4*R*)-2-Aza-bicyclo-[2.2.1]-heptane-2,3-dicarboxylic acid 2-*p*-nitrobenzyl ester (12). Compound **1** (4.1 g, 29.0 mmol) was dissolved in mixture of dioxane (96 mL) and water (68 mL) followed by addition of 2.0 M NaOH (16.6 mL). The solution was stirred for 5 min. Then *p*-nitrobenzylchloroformate (8.1 g, 37.7 mmol) in dioxane (58 mL) and 2.0 M NaOH (19.9 mL) were added simultaneously. The reaction was stirred at room temperature overnight. Water (280 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2×500 mL). The water phase was acidified with conc. HCl and extracted with EtOAc (2×500 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using 0–5%MeOH/CH_2Cl_2 as the eluent to give after evaporation the title compound **12** as pale yellow crystals (8.0 g, 24.9 mmol, yield 86%) mp=198–199 °C. (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.32–8.07 (m, 2H), 7.62–7.38 (m, 2H), 5.43–4.18 (m, 2H), 4.52–4.30 (m, 1H), 4.00–3.86 (m, 1H), 2.98–2.76 (m, 1H), 2.00–1.10 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 176.1, 174.1, 155.3, 153.2, 147.7, 147.4, 144.0, 143.6, 66.05, 65.4, 64.8, 64.0, 57.8, 57.35, 42.7, 41.1, 35.9, 34.7, 30.5, 30.1, 27.8, 27.15 ppm; IR (neat) ν_{max} 3444, 2955, 1700, 1607, 1520, 1436, 1407, 1130, 859, 737 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 321 (M^+, 1%), 275 (20), 203 (69), 160 (20), 154 (47), 137 (100), 107 (90); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{17}N_2O_6$: 321.1087. Found: 321.1084.

4.2. General procedure for preparation of hydroxylamides 3a, 3b, 4a, 4b, 5a, 5b, 13, 14a, 14b, 15a and 15b

A mixture of protected acid **2** or **12** (1 equiv.), EDC (2 equiv.) and HOBt (2 equiv.) was stirred in dry CH_2Cl_2 (4 mL/mmol of acid) at 0 °C for 5 min. The appropriate aminoalcohol (1.5 equiv.) was dissolved in dry CH_2Cl_2 (2 mL/mmol) and added to the reaction mixture. The resulting clear solution was warmed up to room temperature and stirred overnight. The reaction mixture was washed with 1.0 M HCl (aq.) and saturated $NaHCO_3$ (aq.). The organic phase was dried over $MgSO_4$ and evaporated to give the crude hydroxylamide, which was purified by column chromatography using 0–2%MeOH/CH_2Cl_2 as the eluent to yield pure compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **13**, **14a**, **14b**, **15a** and **15b** after removal of solvents.

4.3. General procedure for preparation of protected oxazolines 6a, 6b, 7a, 7b, 8a, 8b, 16, 17a, 17b, 18a and 18b

The hydroxylamide (1 equiv.) was dissolved in CH_2Cl_2/Et_3N (3/1, v/v, 9 mL/mmol) under nitrogen atmosphere and the solution was cooled to 0 °C. To this solution MsCl (2 equiv.) was slowly added and the reaction mixture was stirred at room temperature overnight. It was washed with water; the organic phase was dried over $MgSO_4$ and evaporated to afford crude protected oxazoline. Purification by column chromatography with 0–2%MeOH/CH_2Cl_2 as the eluent and evaporation of solvents gave protected oxazolines **6a**, **6b**, **7a**, **7b**, **8a**, **8b**, **16**, **17a**, **17b**, **18a** and **18b** as clear colorless oils.

4.4. General deprotection procedure for preparation of oxazolines 9a, 9b, 10a, 10b, 11a, 11b, 19, 20a, 20b, 21a and 21b

The protected oxazoline was dissolved in dry EtOH (10 mL/mmol) and a solution of activated Pd/C in dry EtOH (10 wt% of Pd/C related to oxazoline) was added. The mixture was connected to the H_2 source (1 atm.) and stirred at room temperature overnight. The Pd/C was filtered off

and the solvent was evaporated to give crude deprotected oxazoline. The crude compounds were purified on a deactivated silica gel column. The deactivation was done as follows: the column was packed with a suspension of silica gel in 20%Et_3N/CH_2Cl_2 and the silica was washed with 1%Et_3N/CH_2Cl_2. The chromatography was performed using 0–2%MeOH/1%Et_3N/CH_2Cl_2 as the eluent to afford oxazolines **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **19**, **20a**, **20b**, **21a** and **21b** after evaporation of solvents under reduced pressure.

4.4.1. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-methyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-carboxylic acid 2-benzyl ester (3a). (0.92 g, 2.86 mmol, yield 94%) (white crystals) mp=92–95 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.45–7.22 (m, 5H); 6.82–6.68 (m, 0.55H); 6.28–6.18 (m, 0.45H); 5.30–4.93 (m, 2H); 4.34–4.19 (m, 1H); 4.08–3.90 (m, 1H); 3.81–3.72 (m, 1H); 3.64–3.37 (m, 2H); 3.19–2.78 (m, 2H); 1.91–0.86 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.1, 156.5, 155.7, 136.1, 135.9, 128.4, 128.1, 127.8, 67.3, 67.0, 66.9, 47.8, 47.5, 42.1, 40.3, 35.9, 34.55, 30.05, 29.0, 27.2, 26.6, 16.6, 16.5 ppm; IR (neat) ν_{max} 3408, 3325, 2947, 2871, 1702, 1650, 1530, 1411, 1352, 1101, 1050 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 333 (M^++1, 22%), 302 (24), 230 (32), 186 (84), 158 (82), 92 (100), 65 (20); HRMS (FAB^+) (M+H^+): calcd for $C_{18}H_{25}N_2O_4$: 333.1814. Found: 333.1817.

4.4.2. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-methyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (3b). (0.96 g, 2.98 mmol, yield 87%) (white crystals) mp=143–145 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.38–7.23 (m, 5H); 6.73–6.63 (m, 0.6H); 6.38–6.31 (m, 0.4H); 5.27–4.93 (m, 2H); 4.30–4.19 (m, 1H); 4.04–3.89 (m, 1H); 3.81–3.73 (m, 1H); 3.68–3.16 (m, 2.6H); 2.94–2.63 (m, 1.4H); 1.82–0.98 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.6, 156.5, 155.0, 136.0, 128.4, 128.05, 127.8, 67.3, 66.9, 66.2, 66.05, 57.9, 47.4, 47.1, 42.0, 40.2, 35.9, 34.5, 29.9, 29.0, 27.2, 26.7, 16.7 ppm; IR (neat) ν_{max} 3408, 3330, 2952, 2874, 1691, 1661, 1536, 1414, 1354, 1167, 1102, 1050 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 333 (M^++1, 42%), 302 (14), 230 (30), 186 (90), 158 (80), 92 (100), 65 (16); HRMS (FAB^+) (M+H^+): calcd for $C_{18}H_{25}N_2O_4$: 333.1814. Found: 333.1820.

4.4.3. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-isopropyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (4a). (1.10 g, 3.32 mmol, yield 73%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.38–7.23 (m, 5H); 6.80–6.71 (m, 0.55H); 6.42–6.34 (m, 0.45H); 5.20–5.02 (m, 2H); 4.30–4.14 (m, 1H); 3.80–3.20 (m, 5H); 2.94–2.72 (m, 1H); 1.92–1.09 (m, 7H); 0.98–0.59 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.0, 170.8, 156.2, 155.3, 136.0, 135.8, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 67.1, 67.0, 66.7, 63.3, 62.8, 57.8, 56.8, 56.4, 42.0, 40.4, 35.6, 34.3, 29.9, 28.9, 28.5, 28.2, 27.0, 26.6, 19.4, 19.2, 18.3, 18.0 ppm; IR (neat) ν_{max} 3411, 2959, 2875, 1700, 1530, 1409, 1354, 1299, 1168, 1101, 1049, 912 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 361 (M^++1, 18%), 344 (6), 159 (11), 92 (100); HRMS (FAB^+) (M+H^+): calcd for $C_{20}H_{29}N_2O_4$: 361.2127. Found: 361.2125.

4.4.4. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-isopropyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (4b). (1.68 g, 4.69 mmol, yield 94%) (white crystals) mp=129–132 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.41–7.26 (m, 5H); 6.77–6.65 (m, 0.6H); 6.33–6.23 (m, 0.4H); 5.30–4.97 (m, 2H); 4.34–4.25 (m, 1H); 3.86–3.35 (m, 4H); 2.96–2.81 (m, 1H); 1.79–1.30 (m, 7H); 0.94–0.78 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.1, 171.0, 156.7, 155.6, 136.1, 136.0, 128.4, 128.15, 127.8, 67.4, 67.2, 63.7, 63.3, 58.0, 57.3, 56.7, 42.05, 40.1, 36.1, 34.7, 30.0, 28.8, 28.7, 27.3, 26.7, 19.4, 18.6, 18.5 ppm; IR (neat) ν_{max} 3408, 2960, 2873, 1687, 1530, 1414, 1353, 1301, 1167, 1100 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 361 (M^++1, 40%), 329 (33), 275 (20), 230 (26), 186 (100), 158 (70), 92 (88), 65 (18); HRMS (FAB^+) (M+H^+): calcd for $C_{20}H_{29}N_2O_4$: 361.2127. Found: 361.2125.

4.4.5. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-*tert*-butyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (5a). (0.68 g, 1.87 mmol, yield 64%) (white crystals) mp=120–122 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.42–7.20 (m, 5H); 6.98–6.78 (m, 0.6H); 6.36–6.19 (m, 0.4H); 5.27–5.02 (m, 2H); 4.39–4.09 (m, 1H); 3.93–3.65 (m, 3H); 3.35–3.52 (m, 1H); 3.01–2.81 (m, 1H); 2.72–2.57 (m, 0.6H); 2.21–2.38 (m, 0.4H); 1.93–1.18 (m, 6H); 0.53–1.01 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.8, 170.9, 156.65, 156.62, 136.4, 136.3, 128.4, 128.1, 127.8, 67.3, 66.9, 63.3, 62.7, 60.1, 59.3, 58.0, 42.3, 40.2, 36.1, 34.55, 33.2, 30.1, 29.0, 27.1, 26.6 ppm; IR (neat) ν_{max} 3412, 3331, 2959, 2871, 1704, 1653, 1528, 1399, 1352, 1300, 1167, 1097, 1050 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 375 (M^++1, 5%), 343 (50), 255 (20), 230 (22), 186 (82), 158 (62), 91 (100), 65 (20); HRMS (FAB^+) (M+H^+): calcd for $C_{21}H_{31}N_2O_4$: 375.2284. Found: 375.2282.

4.4.6. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-*tert*-butyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (5b). (1.55 g, 4.15 mmol, yield 94%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.41–7.25 (m, 5H); 6.78–6.65 (m, 0.7H); 6.38–6.27 (m, 0.3H); 5.30–4.97 (m, 2H); 4.37–4.18 (m, 1H); 3.86–3.27 (m, 4H); 3.02–2.77 (m, 1.7H); 2.53–1.98 (m, 0.3H); 1.88–1.23 (m, 6H); 0.83 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.1, 156.6, 155.3, 136.05, 135.9, 128.4, 128.0, 127.7, 67.3, 67.1, 62.4, 59.7, 58.9, 57.9, 42.0, 39.9, 36.2, 34.7, 33.0, 29.9, 28.95, 26.6 ppm; IR (neat) ν_{max} 3332, 2960, 2874, 1685, 1540, 1414, 1355, 1302, 1169, 1100, 1050 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 375 (M^++1, 9%), 186 (24), 158 (22), 91 (100), 68 (19); HRMS (FAB^+) (M+H^+): calcd for $C_{21}H_{31}N_2O_4$: 375.2284. Found: 375.2279.

4.4.7. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (6a). (0.45 g, 1.42 mmol, yield 88%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.35–7.25 (m, 5H); 5.24 (d, *J*=12.7 Hz, 0.45H); 5.21 (d, *J*=12.7 Hz, 0.55H); 5.01 (d, *J*=13.1 Hz, 0.55H); 4.98 (d, *J*=13.1 Hz, 0.45H); 4.39–3.99 (m, 4H); 3.81–3.79 (m, 0.55H); 3.62–3.57 (m, 0.45H); 2.70–2.62 (m, 1H); 2.08–2.03 (m, 1H); 1.80–1.42

(m, 4H); 1.33–1.10 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.8, 165.6, 155.0, 153.9, 136.7, 136.6, 129.3, 128.15, 127.75, 127.73, 127.5, 127.3, 74.2, 74.05, 66.8, 66.3, 61.35, 61.30, 60.6, 60.3, 57.4, 56.9, 42.9, 41.6, 35.3, 34.7, 30.4, 29.9, 27.5, 27.1, 21.3, 21.05 ppm; IR (neat) ν_{max} 3330, 2966, 2871, 1705, 1670, 1415, 1355, 1190, 1166, 1101 cm^{-1}; MS (EI) *m/z* (rel. intensity) 314 (M^+, 16%), 208 (18), 179 (30), 164 (16), 91 (100), 65 (24); HRMS (FAB^+) ($M+H^+$): calcd for $C_{18}H_{23}N_2O_3$: 315.1709. Found: 315.1711.

4.4.8. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (6b). (0.82 g, 2.61 mmol, yield 87%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.37–7.26 (m, 5H); 5.25 (d, *J*=12.6 Hz, 0.45H); 5.20 (d, *J*=12.6 Hz, 0.55H); 5.06 (d, *J*=12.6 Hz, 0.55H); 4.97 (d, *J*=12.6 Hz, 0.45H); 4.40–3.96 (m, 4H); 3.85–3.69 (m, 1H); 2.68–2.62 (m, 1H); 2.08–2.02 (m, 1H); 1.82–1.45 (m, 4H); 1.33–1.11 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.5, 165.4, 156.7, 155.6, 136.8, 136.6, 128.3, 128.2, 127.77, 127.75, 127.5, 127.3, 74.2, 74.1, 66.8, 66.3, 61.3, 61.2, 60.7, 60.3, 57.4, 56.9, 42.7, 41.9, 35.5, 34.7, 30.5, 29.9, 27.5, 27.2, 21.3, 21.2 ppm; IR (neat) ν_{max} 3336, 2967, 1705, 1671, 1416, 1356, 1190, 1164, 1101 cm^{-1}; MS (EI) *m/z* (rel. intensity) 315 (M^++1, 90%), 230 (12), 208 (24), 186 (50), 158 (44), 112 (18), 93 (100), 65 (18); HRMS (FAB^+) ($M+H^+$): calcd for $C_{18}H_{23}N_2O_3$: 315.1709. Found: 315.1709.

4.4.9. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (7a). (0.99 g, 2.89 mmol, yield 87%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.36–7.25 (m, 5H); 5.21 (d, *J*=12.6 Hz, 0.55H); 5.19 (d, *J*=12.6 Hz, 0.45H); 5.04 (d, *J*=12.4 Hz, 0.55H); 5.02 (d, *J*=12.4 Hz, 0.44H); 4.40–4.22 (m, 2H); 4.08–3.97 (m, 2H); 3.87–3.77 (m, 1H); 2.65–2.59 (m, 1H); 2.17–2.08 (m, 1H); 1.90–1.45 (m, 5H); 1.38–1.28 (m, 1H); 0.93–0.76 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.7, 165.4, 154.85, 153.9, 136.7, 136.6, 128.4, 128.25, 128.1, 127.9, 127.7, 127.5, 127.3, 71.9, 71.6, 70.0, 69.6, 60.6, 60.3, 57.35, 56.9, 43.2, 42.0, 35.4, 34.8, 32.2, 31.9, 30.4, 29.9, 27.5, 27.2, 18.63, 18.59, 17.8, 17.2 ppm; IR (neat) ν_{max} 3350, 2959, 2871, 1703, 1661, 1414, 1354, 1300, 1166, 1102 cm^{-1}; MS (EI) *m/z* (rel. intensity) 343 (M^++1, 22%), 275 (15), 230 (30), 207 (16), 186 (96), 158 (72), 92 (100), 68 (20); HRMS (FAB^+) ($M+H^+$): calcd for $C_{20}H_{27}N_2O_3$: 343.2022. Found: 343.2018.

4.4.10. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (7b). (1.36 g, 3.97 mmol, yield 95%) (light-yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5H); 5.22–4.99 (m, 2H); 4.40–3.81 (m, 5H); 2.71–2.61 (m, 1H); 2.07–1.99 (m, 1H); 1.90–1.45 (m, 5H); 1.34–1.23 (m, 1H); 0.94–0.73 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.5, 165.3, 154.7, 153.9, 136.71, 136.66, 128.2, 128.1, 127.6, 127.5, 127.3, 71.5, 71.4, 69.7, 69.5, 66.6, 66.2, 60.6, 60.4, 57.4, 57.0, 43.1, 42.1, 35.5, 34.7, 32.0, 31.9, 30.4, 29.9, 27.4, 27.1, 18.34, 18.28, 17.4, 17.1 ppm; IR (neat) ν_{max} 3411, 3331, 3012, 2961, 2875, 1700, 1416, 1356, 1191, 1103 cm^{-1}; MS (EI) *m/z* (rel. intensity) 342 (M^+, 100%), 255 (30), 236 (52), 208 (58), 192 (32), 158 (30); HRMS (FAB^+) ($M+H^+$): calcd for $C_{20}H_{27}N_2O_3$: 343.2022. Found: 343.2025.

4.4.11. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (8a). (0.43 g, 1.22 mmol, yield 65%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.37–7.26 (m, 5H); 5.21–5.04 (m, 2H); 4.38–3.76 (m, 5H); 2.63–2.59 (m, 1H); 2.21–2.13 (m, 1H); 1.76–1.25 (m, 5H); 0.90–0.73 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.7, 165.4, 154.1, 154.0, 136.8, 136.7, 128.3, 128.15, 127.72, 127.70, 127.5, 127.3, 75.63, 75.54, 68.73, 68.68, 60.6, 60.3, 57.3, 57.0, 43.3, 42.3, 35.5, 34.8, 33.7, 33.4, 30.5, 29.9, 27.5, 27.3, 25.7, 25.6 ppm; IR (neat) ν_{max} 2952, 1707, 1414, 1356, 1190, 1102 cm^{-1}; MS (EI) *m/z* (rel. intensity) 357 (M^++1, 32%), 255 (30), 186 (16), 158 (18), 91 (100), 65 (26); HRMS (FAB^+) ($M+H^+$): calcd for $C_{21}H_{29}N_2O_3$: 357.2178. Found: 357.2175.

4.4.12. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid benzyl ester (8b). (0.46 g, 1.25 mmol, yield 67%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 7.37–7.24 (m, 5H); 5.20–4.98 (m, 2H); 4.38–4.30 (m, 1H); 4.18–3.7 (m, 4H); 2.70–2.60 (m, 1H); 2.01–1.96 (m, 1H); 1.78–1.21 (m, 5H); 0.93–0.73 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.5, 165.2, 154.6, 153.9, 136.6, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 75.2, 68.7, 68.5, 66.5, 66.2, 60.6, 60.4, 57.3, 56.9, 43.2, 42.2, 35.5, 34.7, 33.6, 33.4, 30.4, 29.8, 27.3, 27.0, 25.4, 25.3 ppm; IR (neat) ν_{max} 2953, 2871, 1706, 1415, 1357, 1305, 1190, 1164, 1128, 1102, 1050, 998 cm^{-1}; MS (EI) *m/z* (rel. intensity) 357 (M^++1, 100%), 255 (25), 91 (70); HRMS (FAB^+) ($M+H^+$): calcd for $C_{21}H_{29}N_2O_3$: 357.2178. Found: 357.2179.

4.4.13. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (9a). (140 mg, 0.78 mmol, yield 55%) (yellow oil) $[\alpha]_D^{23}$=−63 (*c*=0.55 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.37 (dd, *J*=8.0, 9.4 Hz, 1H); 4.17–4.11 (m, 1H); 3.82–3.78 (m, 1H); 3.56–3.49 (m, 1H); 3.41–3.36 (m, 1H); 2.60–2.53 (m, 1H); 1.82 (brs, 1H); 1.65–1.57 (m, 3H); 1.48–1.43 (m, 2H); 1.45–1.23 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.55, 74.4, 60.95, 58.8, 55.9, 40.9, 35.4, 31.4, 28.2, 21.3 ppm; IR (neat) ν_{max} 3304, 2968, 2871, 1665, 1360, 1203, 1055, 1033, 1002, 853 cm^{-1}; MS (EI) *m/z* (rel. intensity) 181 (M^++1, 100%), 151 (26), 94 (22); HRMS (FAB^+) ($M+H^+$): calcd for $C_{10}H_{17}N_2O$: 181.1341. Found: 181.1343.

4.4.14. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-methyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (9b). (272 mg, 1.51 mmol, yield 58%) (yellow oil) $[\alpha]_D^{23}$=+48 (*c*=0.62 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.36 (dd, *J*=8.0, 9.3 Hz, 1H); 4.18–4.10 (m, 1H); 3.84–3.80 (m, 1H); 3.53–3.48 (m, 1H); 3.40–3.35 (m, 1H); 2.57–2.52 (m, 1H); 1.90 (brs, 1H); 1.63–1.58 (m, 3H); 1.47–1.42 (m, 2H); 1.26–1.21 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.5, 74.3, 60.9, 58.8, 55.8, 40.95, 35.4, 31.3, 28.2, 21.2 ppm; IR (neat) ν_{max} 3305, 2968, 1664, 1357, 1199, 1054, 1033, 1002 cm^{-1}; MS (EI) *m/z* (rel. intensity) 181

(M^++1, 100%), 151 (52), 94 (38); HRMS (FAB^+) (M+H^+): calcd for $C_{10}H_{17}N_2O$: 181.1341. Found: 181.1343.

4.4.15. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (10a). (420 mg, 2.02 mmol, yield 70%) (oily white crystals, melts at rt) $[\alpha]_D^{23}=-61$ (c=1.00 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.23 (dd, J=8.15, 9.6 Hz, 1H); 3.99–3.95 (m, 1H); 3.92–3.85 (m, 1H); 3.51–3.49 (m, 1H); 3.38–3.34 (m, 1H); 2.53–2.49 (m, 1H); 2.24 (brs, 1H); 1.79–1.69 (m, 1H); 1.61–1.55 (m, 3H); 1.47–1.39 (m, 2H); 1.23–1.20 (m, 1H); 0.90 (d, J=6.75 Hz, 3H); 0.84 (d, J=6.75 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.55, 71.3, 70.2, 58.9, 55.9, 41.15, 35.5, 32.2, 31.3, 28.3, 18.5, 17.7 ppm; IR (neat) ν_{max} 3306, 2963, 2872, 1667, 1468, 1363, 1208, 1146, 1055, 1032, 945, 854 cm^{-1}; MS (EI) m/z (rel. intensity) 208 (M^+, 24%), 179 (100), 94 (22), 68 (20); HRMS (FAB^+) (M+H^+): calcd for $C_{12}H_{21}N_2O$: 209.1654. Found: 209.1651.

4.4.16. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-isopropyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (10b). (562 mg, 2.70 mmol, yield 68%) (yellow oil) $[\alpha]_D^{23}=+42$ (c=1.07 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.23 (dd, J=9.9, 8.5 Hz, 1H); 3.99 (dd, J=7.5, 8.5 Hz, 1H); 3.89–3.83 (m, 1H); 3.51–3.47 (m, 1H); 3.40–3.36 (m, 1H); 2.56–2.51 (m, 1H); 2.26 (brs, 1H); 1.78–1.65 (m, 1H); 1.62–1.53 (m, 3H); 1.50–1.39 (m, 2H); 1.24–1.21 (m, 1H); 0.91 (d, J=6.75 Hz, 3H); 0.83 (d, J=6.35 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.4, 71.3, 70.4, 58.95, 55.9, 41.1, 35.5, 32.3, 31.2, 28.3, 18.4, 17.7 ppm; IR (neat) ν_{max} 3387, 2961, 2872, 1666, 1471, 1361, 1203, 1055, 1033, 946, 853 cm^{-1}; MS (EI) m/z (rel. intensity) 209 (M^++1, 100%), 179 (94), 96 (38), 68 (55); HRMS (FAB^+) (M+H^+): calcd for $C_{12}H_{21}N_2O$: 209.1654. Found: 209.1650.

4.4.17. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (11a). (200 mg, 0.90 mmol, yield 74%) (white crystals) mp=105–108 °C; $[\alpha]_D^{23}=-54$ (c=0.61 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.21 (dd, J=8.75, 10.05 Hz, 1H); 4.08 (dd, J=7.7, 8.75 Hz, 1H); 3.83 (ddd, J=1.65, 7.7, 10.05 Hz, 1H); 3.55–3.48 (m, 1H); 3.41–3.33 (m, 1H); 2.55–2.47 (m, 1H); 2.09 (brs, 1H); 1.66–1.42 (m, 5H); 1.30–1.23 (m, 1H); 0.88 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.5, 75.2, 69.15, 59.1, 55.95, 41.3, 35.6, 33.5, 31.2, 28.4, 25.7 ppm; IR (neat) ν_{max} 3256, 2954, 2900, 2869, 1656, 1361, 1346, 1248, 1218, 985 cm^{-1}; MS (EI) m/z (rel. intensity) 223 (M^++1, 100%), 193 (40), 100 (26), 68 (16); HRMS (FAB^+) (M+H^+): calcd for $C_{13}H_{23}N_2O$: 223.1810. Found: 223.1805.

4.4.18. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-*tert*-butyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (11b). (200 mg, 0.90 mmol, yield 72%) (white crystals) mp=45–47 °C; $[\alpha]_D^{23}=+45$ (c=1.03 in $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.17 (dd, J=10.0, 8.7 Hz, 1H); 4.09 (dd, J=7.6, 8.7 Hz, 1H); 3.78 (ddd, J=0.9, 7.6, 10.0 Hz, 1H); 3.52–3.47 (m, 1H); 3.42–3.37 (m, 1H); 2.58–2.52 (m, 1H); 2.31 (brs, 1H); 1.62–1.52 (m, 3H); 1.48–1.40 (m, 2H); 1.25–1.20 (m, 1H); 0.85 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.35, 75.0, 69.15, 59.05, 55.9, 41.2, 35.6, 33.5, 31.2, 28.3, 25.5 ppm; IR (neat) ν_{max} 3306, 2955, 2904, 2870, 1669, 1479, 1359, 1199, 1055, 1027, 1004, 945, 853 cm^{-1}; MS (EI) m/z (rel. intensity) 223 (M^++1, 100%); HRMS (FAB^+) (M+H^+): calcd for $C_{13}H_{23}N_2O$: 223.1810. Found: 223.1803.

4.4.19. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′,1′-dimethyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (13). (0.62 g, 2.25 mmol, yield 72%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.21–8.08 (m, 2H), 7.49–7.38 (m, 2H), 6.69 and 6.15 (2 brs, 1H) 5.34–5.14 and 5.10–4.98 (m, 2H), 4.69–4.38 (m, 1H), 4.28–4.18 (m, 1H), 3.69 (*s*, 1H) 3.55–3.39 (m, 1H), 2.88–2.69 (m, 1H), 1.86–1.05 (m, 12H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.7, 155.9, 147.5, 143.5, 128.0, 123.6, 69.8, 67.2, 65.8, 65.6, 65.5, 59.2, 58.0, 55.7, 53.3, 42.4, 40.2, 39.0, 36.0, 34.5, 30.1, 29.5, 29.0, 27.4, 26.6, 24.3, 24.1, 22.8 ppm; IR (neat) ν_{max} 3383, 2973, 2872, 1707, 1607, 1522, 1403, 1344, 1165, 1107, 857, 736, 668 cm^{-1}; MS (EI) m/z (rel. intensity) 392 (M^++1, 5%), 360 (30), 275 (79), 203 (100), 140 (32), 136 (36), 106 (32), 89 (42), 78 (78), 68 (40); HRMS (FAB^+) (M+H^+): calcd for $C_{19}H_{26}N_3O_6$: 392.1822. Found: 392.1821.

4.4.20. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-phenyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (14a). (0.82 g, 2.66 mmol, yield 85%) (pale yellow semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.30–8.06 (m, 2H), 7.58–7.40 (m, 2H), 7.39–7.12 (m, 5H), 6.80 (brs, 1H), 5.40–4.96 (m, 3H), 4.38–4.16 (m, 1H), 4.00–3.66 (m, 3H), 3.06–2.22 (m, 1H), 1.89–1.18 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.5, 143.4, 138.7, 128.8, 128.2, 127.8, 127.7, 126.6, 123.8, 67.2, 66.3, 66.0, 65.8, 58.3, 55.7, 40.2, 36.3, 30.2, 29.6, 26.7 ppm; IR (neat) ν_{max} 3401, 2952, 1703, 1606, 1521, 1400, 1106, 458, 700 cm^{-1}; MS (EI) m/z (rel. intensity) 441 (M^++1, 5%), 408 (50), 276 (61), 259 (100), 203 (40), 91(47), 77 (53), 68 (44); HRMS (FAB^+) (M+H^+): calcd for $C_{23}H_{26}N_3O_6$: 440.1822. Found: 440.1819.

4.4.21. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-phenyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (14b). (0.85 g, 2.72 mmol, yield 87%) (pale yellow semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.25–7.98 (m, 2H), 7.57–7.47 (m, 1H), 7.39–7.10 (m, 6H), 6.70 (brs, 1H), 5.40–4.96 (m, 4H), 4.40–4.22 (m, 1H), 3.94–3.68 (m, 3H), 3.03–2.87 (m, 1H), 2.39–2.08 (m, 1H), 2.00–1.16 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.6, 165.2, 154.9, 147.6, 143.6, 143.0, 138.5, 128.8, 128.1, 127.8, 126.5, 123.8, 67.4, 67.1, 66.5, 66.3, 66.0, 58.2, 55.6, 55.4, 55.3, 42.5, 40.4, 36.2, 34.8, 30.3, 29.7, 29.2, 27.5, 26.7 ppm; IR (neat) ν_{max} 3372, 2943, 1692, 1519, 1402, 1344, 1106, 747, 668 cm^{-1}; MS (EI) m/z (rel. intensity) 441 (M^++1, 3%), 408 (47), 275 (72), 259 (100), 203 (60), 91(41), 77 (50), 68 (45); HRMS (FAB^+) (M+H^+): calcd for $C_{23}H_{26}N_3O_6$: 440.1822. Found: 440.1835.

4.4.22. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*S*)-benzyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (15a). (0.75 g, 2.38 mmol, yield 76%) (yellow foam) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.29–8.17 (m, 2H), 7.59–7.43 (m, 2H), 7.34–7.11 (m, 5H), 6.63 (brs, 0.6H), 6.20 (brs, 0.4H), 5.31–5.05 (m, 2H), 4.26–4.11 (m, 1H), 3.81–3.44 (m, 2H), 2.98–2.30 (m, 5H), 1.82–1.06 (m,

7H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.3, 170.1, 155.6, 154.4, 147.2, 143.4, 137.5, 132.1, 131.8, 131.7, 131.6, 131.1, 128.8, 128.3, 128.2, 128.0, 127.8, 127.6, 126.1, 123.4, 66.8, 65.6, 65.3, 63.2, 63.0, 58.8, 57.8, 57.6, 53.3, 52.1, 52.0, 42.1, 40.3, 36.6, 35.4, 33.9, 29.9, 29.3, 29.0, 27.1, 26.5 ppm; IR (neat) ν_{max} 3396, 2952, 1703, 1656, 1606, 1521, 1401, 1344, 1107, 756, 747 cm^{-1}; MS (EI) *m/z* (rel. intensity) 454 (M^+, 5%), 362 (10), 273 (100), 203 (34), 91 (29), 78 (19), 68 (12); HRMS (FAB^+) ($M+H^+$): calcd for $C_{24}H_{28}N_3O_6$: 454.1978. Found: 454.1972.

4.4.23. (1*S*,3*R*,4*R*)-3-(2′-Hydroxy-1′(*R*)-benzyl-ethyl-carbomoyl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (15b). (0.63 g, 2.07 mmol, yield 66%) (pale yellow crystals) mp=57–60 °C; (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.16–8.01 (m, 1H), 7.60–7.53 (m, 1H), 7.51–7.33 (m, 2H), 7.20–7.05 (m, 5H), 6.75 (brs, 0.7H), 6.66 (brs, 0.3H), 5.24–4.95 (m, 2H), 4.27–4.08 (m, 2H), 4.00–3.68 (m, 2H), 3.64–3.42 (m, 2H), 2.92–2.65 (m, 1H), 2.58 (brs, 1H), 1.73–1.00 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.5, 170.2, 155.8, 154.5, 147.3, 143.4, 137.5, 128.9, 128.1, 127.9, 127.7, 126.2, 123.5, 66.9, 65.7, 65.4, 63.4, 57.9, 57.7, 52.2, 42.1, 40.3, 36.6, 35.4, 34.0, 30.0, 29.3, 29.0, 27.1, 26.5 ppm; IR (neat) ν_{max} 3366, 2943, 1700, 1651, 1521, 1400, 1344, 1106, 756, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 274 (M^+-p-Cbz-NO_2, 19%), 273 (100), 203 (46), 91 (42), 78 (20), 68 (12); HRMS (FAB^+) ($M+H^+$): calcd for $C_{24}H_{28}N_3O_6$: 454.1978. Found: 454.1990.

4.4.24. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′,5′-dimethyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (16). (0.41 g, 1.09 mmol, yield 74%) (yellow oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.27–8.09 (m, 2H), 7.56–7.43 (m, 2H), 5.42–4.48 (m, 2H), 4.42–4.30 (m, 1H), 4.03–3.80 (m, 3H), 2.71–2.62 (m, 1H), 2.14–2.01 (m, 1H), 1.87–1.09 (m, 11H) ppm; ^{13}C NMR ($CDCl_3$) δ 164.4, 164.2, 154.6, 153.9, 147.6, 144.7, 144.6, 138.4, 127.8, 124.0, 123.8, 79.64, 79.61, 67.5, 65.7, 65.3, 61.1, 60.9, 58.0, 57.6, 43.1, 42.1, 35.7, 35.0, 30.9, 30.1, 28.5, 28.4, 27.8, 27.5 ppm; IR (neat) ν_{max} 2969, 1709, 1667, 1522, 1402, 1345, 1103, 736, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 374 (M^+, 24%), 373 (36), 344 (25), 305 (27), 203 (18), 178 (100), 150 (26), 136 (25), 89 (38), 78 (68); HRMS (FAB^+) ($M+H^+$): calcd for $C_{19}H_{24}N_3O_5$: 374.1716. Found: 374.1720.

4.4.25. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (17a). (0.45 g, 1.08 mmol, yield 63%) (white semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.14–7.95 (m, 2H), 7.50–7.32 (m, 2H), 7.30–7.03 (m, 5H), 5.34–4.97 (m, 3H), 4.63–4.51 (m, 1H), 4.37–4.27 (m, 1H), 4.14–3.90 (m, 2H), 2.77–2.65 (m, 1H), 3.20–2.05 (m, 1H), 1.86–1.13 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.6, 166.3, 153.9, 153.1, 147.1, 146.9, 144.0, 143.9, 141.9, 141.5, 128.2, 128.1, 127.7, 127.2, 127.1, 126.2, 126.0, 123.3, 123.1, 74.9, 74.7, 69.3, 69.21, 69.20, 65.1, 54.8, 60.5, 60.2, 57.3, 57.0, 42.8, 41.6, 35.2, 34.6, 30.4, 29.7, 27.2, 27.0 ppm; IR (neat) ν_{max} 3400, 2952, 1708, 1519, 1402, 1344, 1104, 755 cm^{-1}; MS (EI) *m/z* (rel. intensity) 286 (M^+-p-NO_2-C_7H_7, 2%), 285 (90), 275 (23), 241 (28), 226 (66), 225 (89), 203 (36), 106 (49), 91 (72), 78 (100); HRMS (FAB^+) ($M+H^+$): calcd for $C_{23}H_{24}N_3O_5$: 422.1716. Found: 422.1720.

4.4.26. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (17b). (0.48 g, 1.13 mmol, yield 83%) (white semicrystals) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.21–7.98 (m, 2H), 7.54–7.36 (m, 2H), 7.34–6.70 (m, 5H), 5.36–5.06 (m, 3H), 4.65–4.51 (m, 1H), 4.42–4.35 (m, 1H), 4.17–4.06 (m, 2H), 2.81–2.72 (m, 1H), 2.27–2.04 (m, 1H), 1.89–1.16 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.6, 166.5, 153.8, 153.3, 147.1, 156.9, 144.0, 144.0, 142.0, 141.7, 128.3, 128.2, 127.7, 127.3, 127.8, 127.0, 126.3, 126.2, 126.0, 123.3, 123.2, 69.2, 65.1, 64.8, 60.4, 60.3, 57.3, 57.1, 42.6, 41.7, 35.3, 34.5, 30.5, 29.3, 27.3, 27.1 ppm; IR (neat) ν_{max} 3305, 2947, 1708, 1666, 1519, 1403, 1344, 1103, 747, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 423 (M^++1, 5%), 421 (23), 285 (83), 226 (60), 225 (24), 106 (26), 104 (48), 91 (58), 78 (100); HRMS (FAB^+) ($M+H^+$): calcd for $C_{23}H_{24}N_3O_5$: 422.1716. Found: 422.1714.

4.4.27. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-benzyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (18a). (0.45 g, 1.03 mmol, yield 78%) (colorless oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.22–8.03 (m, 2H), 7.51–7.38 (m, 2H), 7.28–7.03 (m, 5H), 5.37–4.93 (m, 2H), 4.47–4.25 (m, 2H), 4.23–4.08 (m, 1H), 4.05–3.80 (m, 2H), 3.12–2.87 (m, 1H), 2.69–2.47 (m, 2H), 2.14–2.02 (m, 1H), 1.82–1.14 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.9, 165.7, 154.1, 153.2, 147.2, 147.1, 144.3, 143.9, 137.4, 137.2, 129.0, 128.9, 128.4, 128.21, 128.2, 127.8, 127.2, 126.3, 126.2, 123.4, 123.3, 71.8, 71.7, 69.3, 66.99, 66.96, 65.2, 64.7, 60.5, 60.2, 57.4, 57.0, 53.3, 49.5, 42.6, 41.5, 41.2, 41.1, 35.3, 34.6, 30.4, 29.8, 29.4, 27.3, 27.0 ppm; IR (neat) ν_{max} 3400, 2952, 1707, 1606, 1521, 1404, 1345, 1188, 1105, 747, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 435 (M^+, 5%), 344 (82), 299 (19), 203 (32), 191 (100), 148 (30), 117 (25), 91 (80), 78 (49); HRMS (FAB^+) ($M+H^+$): calcd for $C_{24}H_{26}N_3O_5$: 436.1872. Found: 436.1869.

4.4.28. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-benzyl-1′,3′-oxazol-2′yl)-2-aza-bicyclo-[2.2.1]-heptane-2-*N*-carboxylic acid *p*-nitrobenzyl ester (18b). (0.42 g, 0.96 mmol, yield 73%) (colorless oil) (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR ($CDCl_3$) δ 8.21–8.05 (m, 2H), 7.54–7.41 (m, 2H), 7.29–7.05 (m, 5H), 5.35–5.00 (m, 2H), 4.45–4.25 (m, 2H), 4.17–3.89 (m, 3H), 3.11–2.94 (m, 1H), 2.69–2.41 (m, 2H), 2.03–1.90 (m, 1H), 1.85–1.15 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.0, 156.7, 154.0, 153.3, 147.3, 147.2, 144.2, 144.1, 137.5, 137.2, 129.1, 128.9, 128.3, 128.2, 127.8, 127.3, 126.3, 126.2, 123.5, 123.3, 71.7, 66.9, 65.2, 64.9, 60.7, 60.4, 57.5, 57.1, 42.7, 41.7, 41.3, 41.2, 35.4, 34.7, 30.5, 29.8, 29.4, 27.3, 27.1 ppm; IR (neat) ν_{max} 3400, 2923, 1708, 1605, 1521, 1403, 1345, 1106, 756, 668 cm^{-1}; MS (EI) *m/z* (rel. intensity) 436 (M^++1, 4%) 344 (52), 299 (6), 203 (23), 191 (63), 117 (19), 91 (100), 78 (64); HRMS (FAB^+) ($M+H^+$): calcd for $C_{24}H_{26}N_3O_5$: 436.1872. Found: 436.1881.

4.4.29. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′,5′-dimethyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (19). (32 mg, 0.17 mmol, yield 59%) (yellow oil) $[\alpha]_D^{20}=0$ (*c* 4.25 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.90 (d, *J*=8.1 Hz, 1H), 3.87 (d, *J*=8.1 Hz, 1H), 3.48–3.43 (m, 1H), 3.30–3.29 (m, 1H), 2.53–2.48 (m, 1H), 2.08 (brs, 1H), 1.61–1.50 (m, 3H), 1.42–1.34 (m, 2H), 1.24–1.14 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$) δ 167.2, 79.5, 66.6, 58.9, 55.9, 41.1, 35.4, 31.5, 28.31, 28.3, 28.1 ppm; IR (neat) ν_{max} 3305, 2968, 2926, 2872, 1663, 1191, 1004, 909, 732, 642 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 195 (M^++1, 98%), 194 (41), 165 (100), 94 (37), 72 (64), 68 (45); HRMS (FAB^+) ($M+H^+$): calcd for $C_{11}H_{19}N_2O$: 195.1497. Found: 195.1501.

4.4.30. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (20a). (64 mg, 0.26 mmol, yield 55%) (yellow oil) $[\alpha]_D^{20}=+2$ (*c*=5.0 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39–7.14 (m, 5H), 5.19–5.09 (m, 1H) 4.66 (dd, *J*=8.4, 1.7 Hz, 1H), 4.15–4.06 (m, 1H), 3.55–3.50 (m, 1H), 3.49–3.44 (m, 1H), 2.69–2.62 (m, 1H), 2.29 (brs, 1H), 1.73–1.57 (m, 3H), 1.54–1.40 (m, 2H), 1.33–1.11 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.2, 142.2, 128.6, 127.5, 126.5, 76.7, 75.4, 69.2, 59.1, 56.1, 41.3, 35.7, 31.4, 28.4 ppm; IR (neat) ν_{max} 3305, 2967, 1661, 1360, 1191, 1055, 1031, 755, 700 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 242 (M^+, 37%), 213 (70), 120 (100), 94 (52), 91 (23); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{19}N_2O$: 243.1497. Found: 243.1498.

4.4.31. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-phenyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (20b). (63 mg, 0.26 mmol, yield 55%) (yellow oil) $[\alpha]_D^{20}=-5$ (*c*=4.7 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39–7.18 (m, 5H), 5.23–5.12 (m, 1H), 4.66 (dd, *J*=8.3, 1.8 Hz, 1H), 4.19–4.10 (m, 1H), 3.57–3.50 (m, 2H), 2.68–2.63 (m, 1H), 2.26 (brs, 1H), 1.74–1.60 (m, 3H), 1.54–1.44 (m, 2H), 1.36–1.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.2, 142.1, 128.6, 127.5, 126.5, 69.1, 59.2, 56.1, 41.4, 35.7, 31.5, 28.5 ppm; IR (neat) ν_{max} 3304, 2967, 1661, 1453, 1358, 1189, 1054, 1033 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 242 (M^+ 40%), 213 (86), 120 (100), 94 (60), 91 (26); HRMS (FAB^+) ($M+H^+$): calcd for $C_{15}H_{19}N_2O$: 243.1497. Found: 243.1486.

4.4.32. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*S*)-benzyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (21a). (65 mg, 0.25 mmol, yield 55%) (yellow oil) $[\alpha]_D^{20}=-2$ (*c*=7.62 in $CDCl_3$); ^1H NMR ($CDCl_3$) δ 7.35–7.15 (m, 5H), 4.43–4.32 (m, 1H), 4.25–4.20 (m, 1H), 4.02 (dd, *J*=13.7, 7.3 Hz, 1H), 3.56–3.52 (m, 1H), 3.40–3.36 (m, 1H), 3.10 (dd, *J*=13.7, 5.1 Hz, 1H), 2.64 (dd, *J*=13.7, 8.5 Hz, 1H), 2.56–2.52 (m, 1H), 2.16 (brs, 1H), 1.68–1.59 (m, 3H), 1.51–1.40 (m, 2H), 1.30–1.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.3, 137.5, 129.2, 128.5, 126.5, 66.8, 58.9, 56.0, 41.6, 41.1, 35.6, 31.5, 29.6, 28.4 ppm; IR (neat) ν_{max} 3300, 2967, 2871, 1663, 1493, 1452, 1360, 1202, 1055, 1028, 946, 849, 757 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 256 (M^+ 30%), 227 (100), 117 (60), 94 (22), 91 (30), 68 (28); HRMS (FAB^+) ($M+H^+$): calcd for $C_{16}H_{21}N_2O$: 257.1654. Found: 257.1650.

4.4.33. (1*S*,3*R*,4*R*)-3-(4′,5′-Dihydro-5′(*R*)-benzyl-1′,3′-oxazol-2′-yl)-2-aza-bicyclo-[2.2.1]-heptane (21b). (67 mg, 0.26 mmol, yield 57%) (yellow oil) $[\alpha]_D^{20}=+1$ (*c*=7.66 in $CDCl_3$); ^1H NMR ($CDCl_3$) δ 7.34–7.17 (m, 5H), 4.43–4.32 (m, 1H), 4.22 (dd, *J*=9.3, 8.5 Hz, 1H), 4.01 (dd, *J*=9.4, 8.4 Hz, 1H), 3.55–3.51 (m, 1H), 3.40–3.37 (m, 1H), 3.08 (dd, *J*=8.4, 7.0 Hz, 1H), 2.65 (dd, *J*=13.6, 8.4 Hz, 1H), 2.57–2.53 (m, 1H), 2.15 (brs, 1H), 1.65–1.56 (m, 3H), 1.50–1.42 (m, 2H), 1.29–1.23 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.6, 137.7, 129.3, 128.5, 126.5, 66.8, 59.1, 56.0, 41.6, 41.2, 35.6, 31.5, 28.4 ppm; IR (neat) ν_{max} 3300, 2967, 2871, 1663, 1493, 1452, 1361, 1198, 1054, 1028, 946, 771, 701 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 257 (M^++1, 48%). 256 (44), 227 (100), 117 (49), 94 (22), 91 (12), 69 (27); HRMS (FAB^+) ($M+H^+$): calcd for $C_{16}H_{21}N_2O$: 257.1654. Found: 257.1658.

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