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Synthesis and biological evaluation of ether bridged bicyclic iminosugar derivatives

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ABSTRACT

Bicyclic iminosugar derivatives with an ether bridge bearing different substituents on C-2 and the nitrogen atom have been synthesized from a C-glycoside bearing an isopropylidene acetal. The activities of these compounds were investigated against several glycosidase enzymes and showed moderate inhibition and activation.

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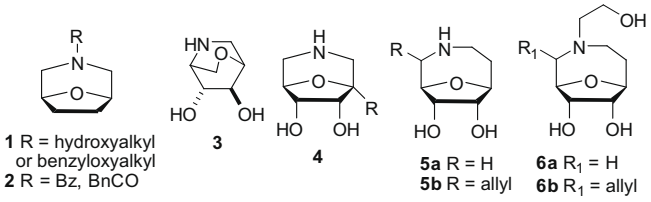
1. Introduction

N-Alkylated iminosugars have been clinically applied as potent glycosidase inhibitors for the treatment of diabetes and glycosidase-deficiency diseases.[1] For example, *N*-hydroxyethyl 1-deoxynojirimycin (Miglitol)[2] and *N*-butyl 1-deoxynojirimycin (Miglustat)[3] have been used in the treatment of type II diabetes and type I Gaucher's disease, respectively. Previous studies suggest that even better selectivity of inhibition may be achieved by modification of the iminosugars, including alteration of the alkyl chain length, saturation, hydroxylation, and ring hydroxyl residues.[4,5] Recently, researchers have focused considerable effort on the preparation of bicyclic iminosugars[6–8] and bridge bicyclic iminosugar derivatives[9,10] for glycosidase inhibition.

The N-substituted derivatives of 8-oxa-3-azabicyclo-[3,2,1]octanes **1** and **2** are types of an ether bridged bicycle azasugar, and they exhibit analgesic and anti-inflammatory activities in mice and rats.[11–14] In addition, [2,2,2]-bicyclic iminosugar analogue **3,** which lacks both the 2- and 6-hydroxyl groups, shows weak inhibition of several glycosidase enzymes.[15] Fuentes and co-workers synthesized related derivatives of ether bridged bicyclic iminosugars **4**,[16] prompting us to synthesize other ether bridged bicyclic iminosugar analogues for the current study. Recently, we described the preparation of N-alkylated iminosugar derivatives.[17] Now, we report the syntheses of various ether bridged bicyclic iminosugars (**5a**, **5b, 6a, 6b,** and **22**) and their biological evaluation.



2. Results and discussion

The synthetic route to the ether bridged bicyclic iminosugars **5a** and **5b** started with the conversion of C-glycoside **7**[8] to azido-C-glycoside **8** by mesylation and azido substitution (Scheme 1).[18] Compound **8** was further converted to an amine by hydrogenation and subsequently treated with base to promote intramolecular amidation between the amino group and the ester. This process produced ether bridged bicyclic iminosugar **9** (63%) as a major product, together with aza-C-glycoside **10**[17] (35%). An allyl functionality was introduced by treatment of **7** with *O*-iodoxybenzoic acid (IBX) to afford an aldehyde intermediate. The aldehyde was in turn subjected to $BF_3{\cdot}OEt_2$-induced allylation at a low temperature,[19] leading to a diastereomeric mixture of allyl alcohol in a ~1:1 ratio. Subsequent mesylation and azido substitution

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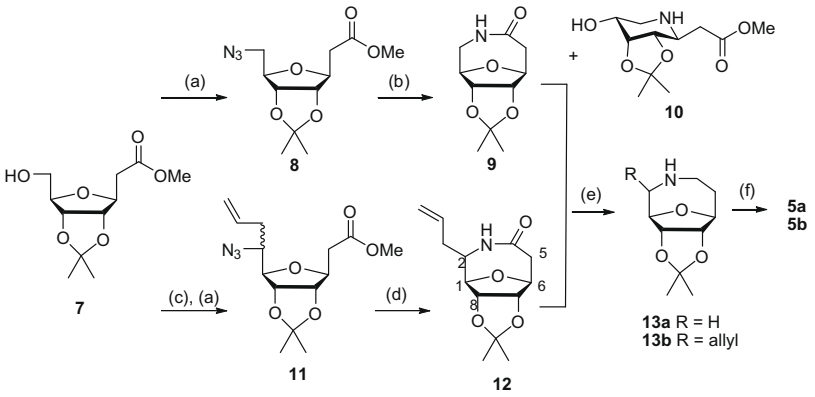


Scheme 1. Synthesis of ether bridged bicyclic iminosugars **5a** and **5b**. Reagents and conditions: (a) MsCl, TEA, CH_2Cl_2; NaN_3, DMF; (b) H_2/Pd/C, MeOH; NaOMe, MeOH; (c) IBX, CH_3CN; allylTMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (d) PPh_3, CH_3CN; NaOMe, MeOH; (e) BH_3/THF or LAH/THF; (f) 80% HOAc.

converted this allyl alcohol to the corresponding desired diastereomeric mixture, allyl-azido-C-glycoside **11** in a ~1:1 ratio. Reduction of **11** with triphenylphosphine (PPh_3) in CH_3CN afforded the corresponding amine (92%) as a diastereomeric mixture in a ratio of ~2:1.

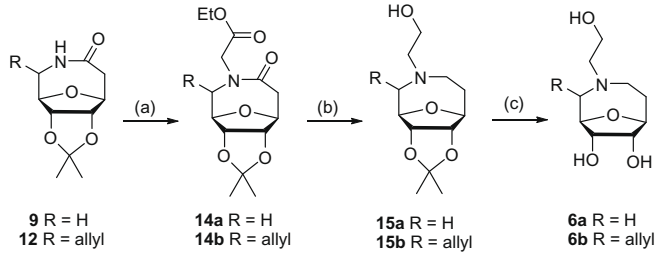
The intramolecular amidation of the amine and ester was examined under basic conditions (2% $NaOCH_3$ in CH_3OH) and was totally stereoselective, producing a lactam **12** (73%) as a single diastereomer with the *S*-configuration at C-2 as indicated by NMR analysis. The higher conversion of **12** compared with **9** is probably due to the presence of an allyl group in the lactam ring. Next, **9** was reduced with $BH_3{\cdot}THF$[20,21] and **12** was reduced with lithium aluminum hydride (LAH) to afford isopropylidenenated amines **13a** (96%) and **13b** (81%), respectively. Finally, the reaction of **13a** and **13b** with 80% acetic acid at 100 °C produced the O-unprotected target compounds **5a** (67%) and **5b** (59%), respectively. The products were obtained as ammonium acetates after filtration and removal of acetic acid and were fairly pure. Free amines were obtained by dissolving the ammonium salt in organic solvent followed by washing with $NaHCO_3$.

N-Alkyl bicyclic iminosugar derivatives **6a** and **6b** were easily prepared using isopropylidene lactams **9** and **12** as key intermediates (Scheme 2), and the following reaction sequences: (a) treatment of **9** and **12** with ethyl bromoacetate[22] produces **14a** (68%) and **14b** (83%), respectively; (b) subsequent reduction of **14a/b** with LAH afforded alcohols **15a** (92%) and **15b** (95%), respectively; (c) deprotection of **15a/b** with 80% acetic acid at 100 °C gave the products **6a** and **6b**. After filtration and removal of the solvent, the acetate salts **6a** and **6b** were washed with $NaHCO_3$ to afford the respective free amines **6a** (63%) and **6b** (53%) as single products.

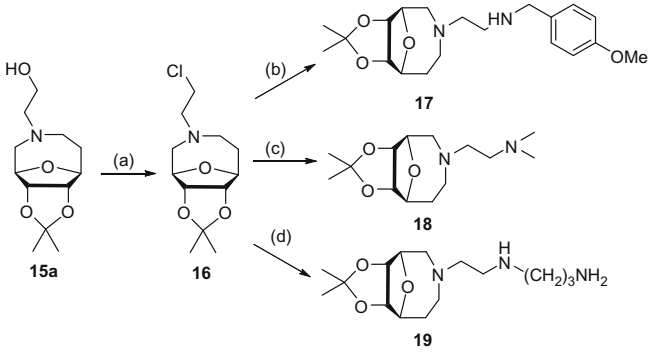
N-Alkyl bicyclic iminosugar derivatives **17**, **18,** and **19** were then prepared from **15a** by standard mesylation in the presence of triethylamine or pyridine. This process produced an unexpected chloride derivative **16** (62%) instead of the mesyl derivative. The direct substitution of the chloride derivative **16** was carried out with 4-methyloxylbenzylamine in DMF to afford **17** (36%). Treating chloride derivative **16** with 1,3-diaminopropane in DMF did not yield the product **19**, but instead produced dimethylamine-substituted **18** (42%) (see Scheme 3). This implies that dimethylformamide is not stable in the presence of 1,3-diaminopropane, but hydrolyzes to formic acid and dimethylamine. This 'in situ' reaction produces dimethylamine, which can further act as a nucleophile in an S_N2 reaction. Dimethylamine is a colorless gas produced by the catalytic reaction of CH_3OH and ammonia at elevated temperatures and high pressure.[23] Thus, using 1,3-diaminopropane in DMF is a good approach to synthesize dimethylamine derivatives. Nevertheless, the desired product **19** (68%) was obtained when **16** was reacted under nitrogen with a large excess of 1,3-diaminopropane.

In addition to N-alkylated derivatives, we attempted to introduce a sugar triazole to the bicyclic iminosugar via a Click reaction[24,25] (Scheme 4). Compound **13a** served as the starting material for the synthesis of **22.** Compound **13a** underwent alkylation by treatment with propargyl bromide to afford alkyne **20** (71%). Compound **20** was treated with a copper(I) catalyst and azido-C-glycoside **8** in ethanol under refluxing conditions,[26] producing sugar triazole bicyclic iminosugar **21** (55%) with 1,4-regioselectivity. Further deprotection of **21** with 80% acetic acid at 100 °C produced **22** (58%). All products were characterized by ^1H, ^{13}C, and COSY NMR spectroscopies, as well as mass spectrometry.

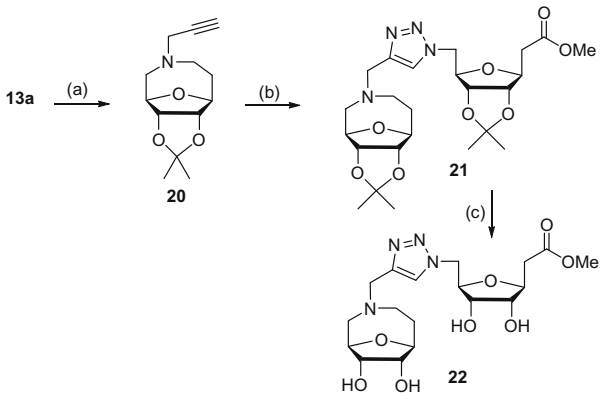
Due to the low yields of **16**, **17, 18**, and **19**, we did not evaluate their biological activities. The compounds **5a**, **5b**, **6a**, **6b,** and **22**



Scheme 2. Synthesis of ether bridged bicyclic iminosugars **6a** and **6b**. Reagents and conditions: (a) $BrCH_2CO_2Et$, KO*t*Bu, THF; (b) LAH, THF; (c) 80% HOAc.



Scheme 3. Synthesis of ether bridged bicyclic iminosugar derivatives **17**–**19**. Reagents and conditions: (a) MsCl, TEA; (b) 4-methyloxylbenzylamine, Et_3N, DMF; (c) 1,3-diaminopropane, Et_3N, DMF; (d) 1,3-diaminopropane, Et_3N.



Scheme 4. Synthesis of ether bridged bicyclic iminosugar derivative **22**. Reagents and conditions: (a) propagyl bromide, Et_3N, CH_3CN, reflux; (b) **8**, Cu(0), $CuSO_4$, EtOH, reflux; (c) 80% HOAc.

were assayed[27,28]29 for their inhibitory activity toward 10 commercially available glycosidases (see Table 1). None of these compounds showed significant inhibitory activity against α-mannosidase (jack bean), α-glucosidase (baker's yeast), β-glucosidase (almonds), α-galactosidase (coffee bean and guar seed), and β-galactosidase (*Escherichia coli*) at a concentration of 1 mM. When screened against β-galactosidase from *Aspergillus oryzae*, only **6a** (41%) and **22** (36%) show moderate inhibitory activity. On the other hand, **6a** (48%) showed moderate inhibitory activity toward bovine liver β-galactosidase. Interestingly, compounds **5b** (+26%) and **6b** (+47%), which both contain an allyl group in the bridge ring, showed moderate activation activity of α-galactosidase (*Aspergillus niger*). These results show that structural variations in these compounds, such as the absence or presence of the *N*-ethylenehydroxyl group and the C-2 allyl substituent group of ether bridge bicyclic iminosugars, can affect the activities (inhibition or activation) of glycosidase enzymes.

In conclusion, we have synthesized different substituted ether bridge bicyclic iminosugars from C-glycoside **7** and have evaluated them against a variety of glycosidases derived from different sources. Although the compounds displayed weak to moderate effects (inhibition or activation), further modification may lead to more potent glycosidase inhibitors or activators.

3. Experimental

3.1. General methods

All reagents were obtained from commercial suppliers and were used without further purification. DCM was distilled over CaH_2. CH_3OH was distilled over magnesium and iodine. Analytical thin-layer chromatography was performed using Silica Gel 60 F254 plates (Merck). The ^1H and ^{13}C NMR spectra were recorded with Bruker AM 300 (300 MHz) spectrometers. Chemical shifts are expressed in ppm with residual $CHCl_3$ or CD_3OD as reference. Low- and high-resolution mass spectra were recorded under fast atom bombardment (FAB) or electron spray interface (ESI) conditions.

3.2. Enzyme assays

The enzyme assays were performed with a procedure previously reported in the literature.[27,28] Briefly, the glycosidases and the compounds we synthesized (**5a**, **5b**, **6a**, **6b,** and **22**) were pre-incubated at room temperature for 5 min before the addition of the appropriate *p*-nitrophenyl glycosides substrates at the optimum pH for each enzyme. The microtiter plate was incubated at 37 °C for 10 min, and the reaction was terminated by addition of 0.5 M Na_2CO_3. The released *p*-nitrophenol was measured spectrophotometrically at 400 nm using a microtiter plate reader.

3.3. (1*R*,6*S*,7*S*,8*S*)-7,8-Isopropylidene-7-methyl-9-oxa-3-azabicyclo[4.2.1]nonan-4-one (9)

A mixture of **8** (1.72 g, 6.35 mmol) and 10% Pd–C (0.17 g) in CH_3OH (20 mL) was stirred under H_2 atmosphere (balloon pressure) for 40 min when the starting material was completely consumed. The reaction mixture was filtered and the filtrate was concentrated. Purification by chromatography (DCM–CH_3OH, 10:1) gave amine (1.44 g, 92%) as a yellow oil. The solution of amine (1.44 g, 5.85 mmol) in 2% $NaOCH_3$–CH_3OH (10 mL) was stirred overnight and then neutralized by the addition of Dowex 50WX8 (H^+) resin. The filtrate was concentrated to a residue. Purification by chromatography (hexanes–EtOAc 12:1) gave tricyclic lactams **9** (0.79 g, 63%) and **10** (0.50 g, 35%) as a yellow oil. For **9**, ^1H NMR ($CDCl_3$) δ: 6.43 (s, 1H, NH), 4.79 (d, J = 5.7 Hz, 1H, H-8), 4.63 (d, J = 6.0 Hz, 1H, H-7), 4.35 (d, J = 3.6 Hz, 1H, H-1), 4.26 (q, J = 2.4 Hz, 1H, H-6), 3.55 (d, J = 15.0 Hz,1H, H-2a), 3.17–3.08 (m, 1H, H-2b), 2.83 (dd, J = 16.2, 2.4 Hz, 1H, H-5a), 2.70–2.62 (m, 1H, H-5b), 1.47 (s, 3H, $C(CH_3)_3$), 1.25 (s, 3H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 176.0 (C=O), 112.0 ($C(CH_3)_2$), 83.9 (C-7), 82.9 (C-8), 82.4 (C-1), 79.2 (C-6), 46.3 (C-2), 43.7 (C-5), 26.0 ($C(CH_3)_2$), 24.3 ($C(CH_3)_2$); ESIMS: calcd for $C_{10}H_{15}NO_4$ $[M]^+$, m/z 213.1001; found m/z 213.1005.

3.4. Methyl 2-*C*-(5-azido-5-allyl-2,3-di-*O*-isopropylidene-5-deoxy-β-D-ribofuranosyl)acetate (11)

To a solution of **7** (0.4 g, 1.63 mmol) in CH_3CN (150 mL) was added IBX (1.37 g, 3 equiv), and the mixture was stirred at 80 °C

Table 1
Activity of glycosidases against compounds **5a**, **5b**, **6a**, **6b,** and **22**

Enzyme	Origin	5a	5b	6a	6b	22
α-Galactosidase	Coffee bean	–	–	–	–	–
	A. niger	–	+26%	25%	+47%	–
	Guar seed	–	–	–	–	–
β-Galactosidase	*A. oryzae*	–	–	41%	–	36%
	E. coli	–	–	–	–	–
	Bovine liver	20%	35%	48%	34%	–
	K. lactis	15%	–	–	–	–
α-Mannosidase	Jack bean	–	–	–	–	–
α-Glucosidase	Baker's yeast	–	–	–	–	–
β-Glucosidase	Almonds	–	–	–	–	–

Percentage inhibition or activation (+) at 1 mM concentration. (–) = no inhibition at 1 mM concentration.

for 1.5 h. Upon cooling to room temperature the reaction mixture was diluted by the addition of benzene (40 mL) and then the solvent was removed to afford the crude aldehyde. Without further purification, to a solution of the above crude aldehyde (0.276 g, 1.13 mmol) in CH_2Cl_2 (10 mL) at −78 °C under nitrogen were added allyltrimethylsilane (0.22 mL, 1.2 equiv) and $BF_3{\cdot}OEt_2$ (0.07 mL, 0.5 equiv) and the temperature was raised to −20 °C and was further stirred overnight. The reaction mixture was added to H_2O and extracted with EtOAc. The organic layers were combined, washed with brine, and dried with $MgSO_4$. Purification by chromatography (hexanes–EtOAc 4:1) gave allyl alcohol (0.39 g, 83%) as a yellow oil. The allyl alcohol underwent mesylation, azido substitution[7], and was purified by chromatography (hexanes–EtOAc 1:6) to obtain compound **11** (1:1 mixture of anomers) in 86% yield; ^{1}H NMR ($CDCl_3$) δ: 5.86–5.72 (m, 1H, CH=), 5.21–5.06 (m, 2H, $=CH_2$), 4.65–4.43 (m, 2H), 4.26–4.20 (m, 1H), 3.95–3.90 (m, 1H), 3.67 (s, 3H, CO_2 CH_3), 2.68–2.60 (m, 2H), 2.41 (t, J = 6.0 Hz, 1H), 1.50 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.8 (C=O), 133.3 (C-7), 133.2 (C-7), 118.63 (C-8), 118.60 (C-8), 114.8 ($C(CH_3)_2$), 85.7 (C-4), 85.5 (C-4), 84.0 (2C-3), 82.4 (C-2), 80.7 (2C-1), 80.4 (C-2), 62.6 (C-5), 62.0 (C-5), 51.8 (CO_2CH_3), 51.7 (CO_2CH_3), 38.0 (C-1′), 37.9 (C-1′), 35.2 (C-6), 34.5 (C-6), 27.4 (2 $C(CH_3)_2$), 25.5 (2 $C(CH_3)_2$).

3.5. (1*R*,6*S*,7*S*,8*S*)-2-Allyl-7,8-isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonan-4-one (12)

To a solution of **11** (0.15 g, 0.48 mmol) in CH_3CN (50 mL) was added PPh_3 (0.139 g, 1.1 equiv), and the mixture was stirred at 80 °C for 12 h. The solvent was removed under reduced pressure affording the crude residue. Purification by column chromatography (hexanes–EtOAc 1:1) gave amine (0.125 g, 92%) as a yellow oil. The solution of amine (0.125 g, 0.44 mmol) in 2% $NaOCH_3$–CH_3OH (10 mL) was stirred overnight and then neutralized by the addition of Dowex 50WX8(H^+) resin. The filtrate was concentrated to a residue. Purification by chromatography (hexanes–EtOAc 2:1) obtained **12** (88.7 mg, 73%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.29 (d, J = 5.4 Hz, 1H, NH), 5.77–5.68 (m, 1H, CH=), 5.17–5.11 (m, 2H, $=CH_2$), 4.75 (d, J = 5.7 Hz, 1H, H-8), 4.60 (d, J = 6.0 Hz, 1H, H-7), 4.35 (d, J = 2.7 Hz, 1H, H-1), 4.28 (t, J = 3.6 Hz, 1H, H-6), 3.08–3.05 (m, 1H, H-2), 2.85 (dd, J = 16.3, 3 Hz, 1H, H-5a), 2.66 (dd, J = 27.0, 3.3 Hz, 1H, H-5b), 2.50–2.42 (m, 2H, CH_2CH=), 1.47 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 174.62 (C=O), 133.27 (CH), 119.09 ($=CH_2$), 112.12 ($C(CH_3)_2$), 84.43 (C-1), 83.94 (C-8), 83.43 (C-7) 79.57 (C-6), 55.83 (C-2) 43.16 (C-5), 37.01 (CH_2CH=), 26.00 ($C(CH_3)_2$), 24.29 ($C(CH_3)_2$); FABMS: calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$, m/z 254.1392; found m/z 254.1402.

3.6. (1*R*,6*S*,7*S*,8*S*)-7,8-Isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonane (13a)

To a solution of **9** (1.61 g, 7.55 mmol) in distilled THF (40 mL) was added $BH_3{\cdot}$THF (1.5 M in THF, 25.0 mL, 22.65 mmol), and the mixture was stirred at 65 °C overnight. A few drops of EtOH were added after cooling the solution, then the solvent was removed, and the residue diluted with EtOH (40 mL) and heated at reflux for 48 h. After evaporation, the residue was partitioned between CH_2Cl_2–NaOH (1 M in H_2O). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes–EtOAc 4:1) afforded **13a** (1.45 g, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.56 (s, 2H, H-7, H-8), 4.34 (d, J = 8.4 Hz, 1H, H-6), 4.27 (t, J = 2.4 Hz, 1H, H-1), 2.98–2.84 (m, 2H, H-4a, H-2a), 2.69–2.55 (m, 2H, H-2b, H-4b), 1.95–1.85 (m, 1H, H-5a), 1.74–1.64 (m, 1H, H-5b), 1.43 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 111.1 ($C(CH_3)_2$), 89.2 (C-7), 86.2 (C-8), 84.8 (C-1), 84.3 (C-6), 55.0 (C-2), 46.8 (C-4), 34.7 (C-5), 26.4 ($C(CH_3)_2$), 24.7 ($C(CH_3)_2$); ESIMS: calcd for $C_{10}H_{17}NO_3$ $[M]^+$, m/z 199.1208; found m/z 199.1205.

3.7. (1*R*,6*S*,7*S*,8*S*)-2-Allyl-7,8-isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonane (13b)

To a solution of LAH (60 mg, 1.58 mmol) in dry THF (10 mL) under N_2 at 0 °C was added **12** (0.2 g, 0.79 mmol) and stirred for 2 h, and then acidified with aq ammonium chloride. The resulting precipitate was filtered through a Celite pad and the filtrate was extracted with CH_2Cl_2. Purification by column chromatography (hexanes–EtOAc 4:1) afforded **13b** (0.153 g, 81%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 5.76–5.65 (m, 1H, CH=), 5.10–5.04 (m, 2H, $=CH_2$), 4.61 (d, J = 6.3 Hz, 1H), 4.55 (d, J = 6.0 Hz, 1H, H-8), 4.41 (d, J = 7.2 Hz, 1H, H-7), 4.13 (s, 1H, H-1), 3.01–2.92 (m, 1H, H-4a), 2.80 (t, J = 7.5 Hz, 1H, H-2), 2.47–2.35 (m, 2H, H-4b, CH_2CH=), 2.26–2.17 (m, 1H, CH_2CH=), 1.88–1.82 (m, 1H, H-5a), 1.73–1.64 (m, 1H, H-5b), 1.46 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 135.0 (CH=), 117.8 ($=CH_2$), 111.5 ($C(CH_3)_2$), 88.7 (C-1), 87.7 (C-7), 87.0 (C-6), 84.4 (C-8), 59.4 (C-2), 39.6 (C-4), 36.4 (CH_2CH=), 35.3 (C-5), 26.4 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$); FABMS: calcd for $C_{13}H_{22}NO_3$ $[M+H]^+$, m/z 240.1600; found m/z 240.1596.

3.8. (1*R*,6*S*,7*S*,8*S*)-9-Oxa-3-azabicyclo[4.2.1]nonane-7,8-diol (5a)

Compound **13a** (95 mg, 0.48 mmol) was dissolved in AcOH–H_2O (9.0 mL:3.0 mL) and stirred at 100 °C for 6 h. After removal of the solvents under reduced pressure, the solid residue was coevaporated with CH_3OH–toluene (1:1 v/v, 10 mL) to yield the crude diol (salt form of **5a**). The amine form was obtained by dissolving the salt in dichloromethane followed by washing with aqueous sodium bicarbonate. The organic phase was dried and concentrated to give syrup. Purification by chromatography (EtOAc–CH_3OH, 8:1) gave **5a** (51 mg, 67%) as a white oil. $[\alpha]_D$ +16.3 (c 1.0, CH_3OH); ^{1}H NMR (CD_3OD) δ: 4.13–4.02 (m, 4H), 2.88–2.80 (m, 2H), 2.76–2.67 (m, 2H), 1.95–1.85 (m, 1H), 1.62–1.52 (m, 1H); ^{13}C NMR (CD_3OD) δ: 88.0, 85.5, 79.4, 75.5, 53.1, 46.4, 34.7; FABMS: calcd for $C_7H_{14}NO_3$ $[M+H]^+$, m/z 160.0974; found m/z 160.0980.

3.9. (1*R*,6*S*,7*S*,8*S*)-2-Allyl-9-oxa-3-azabicyclo[4.2.1]nonane-7,8-diol (5b)

The same procedures as described above were used to obtain **5b** (59%) as a yellow oil. $[\alpha]_D$ +20.5 (c 1.0. $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 5.78–5.66 (m, 1H, CH=), 5.13–5.08 (m, 2H, $=CH_2$), 4.32 (d, J = 5.7 Hz, 1H, H-8), 4.28 (d, J = 7.5 Hz, 1H, H-7), 4.09 (d, J = 5.4 Hz, 1H, H-6), 3.92 (s, 1H, H-1), 3.09–−3.00 (m, 1H, H-4a), 2.91 (t, J = 6.6 Hz, 1H, H-2), 2.61–2.53 (m, 1H, H-4b), 2.47–2.38 (m, 1H, CH_2CH=), 2.31–2.24 (m, 1H, CH_2CH=), 2.00–1.89 (m, 1H, H-5a), 1.71–1.56 (m, 1H, H-5b); FABMS: calcd for $C_{10}H_{18}NO_3$ (M+H), m/z 200.1287; found m/z 200.1288.

3.10. Ethyl 2-((1*R*,6*S*,7*S*,8*S*)-7,8-isopropylidene-4-oxo-9-oxa-3-azabicyclo-[4.2.1]nonan-3-yl)acetate (14a)

To a solution of **9** (0.27 g, 1.27 mmol) in dry THF (20 mL) was added potassium *tert*-butoxide (0.29 g, 2 equiv) and ethyl bromoacetate (0.18 mL, 1.7 mmol). The reaction mixture was stirred at room temperature for 4 h. After removal of the solvent under reduced pressure, the residue was dissolved in ether, washed with aq $NaHCO_3$, and dried over $MgSO_4$. Purification by chromatography (hexanes–EtOAc 8:1) led to **14a** as an orange syrup (0.26 g, 68%). ^{1}H NMR ($CDCl_3$) δ: 4.93 (d, J = 5.7 Hz, 1H, H-8), 4.54 (d, J = 5.7 Hz,1H, H-7), 4.29 (d, J = 4.5 Hz, 1H, H-1), 4.21 (t, J = 3.3 Hz,

1H, H-6), 4.10 (q, J = 7.2 Hz, 2H, OCH_2), 3.99 (d, J = 7.5 Hz, 2H, N–CH_2), 3.81 (d, J = 7.5 Hz, 1H, H-2a), 3.13 (dd, J = 15.3, 4.8 Hz, 1H, H-2b), 2.77 (dd, J = 3.6, 0.6 Hz, 2H, H-5a, H-5b), 1.40 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 1.19 (t, J = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 173.0 (C=O), 168.7 (C=O), 111.7 ($C(CH_3)_2$), 83.4 (C-7), 82.4 (C-8), 81.5 (C-1), 78.6 (C-6), 61.2 (OCH_2), 54.6 (C-2), 51.5 (NCH_2), 43.8 (C-5), 25.8 ($C(CH_3)_2$), 24.2 ($C(CH_3)_2$), 14.0 (OCH_2CH_3); FABMS: calcd for $C_{14}H_{22}NO_6$ $[M+H]^+$, m/z 300.1447; found m/z 300.1454.

3.11. Ethyl 2-((1*R*,6*S*,7*S*,8*S*)-2-Allyl-7,8-7,8-isopropylidene-4-oxo-9-oxa-3-azabicyclo[4.2.1]nonan-3-yl)acetate (14b)

The same procedures as described above were used to obtained **14b** (83%) as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ: 5.74–5.69 (m, 1H, CH=), 5.27 (d, J = 6.0 Hz, 1H, H-8), 5.19–5.12 (m, 2H, $=CH_2$), 4.63 (d, J = 6.0 Hz, 1H, H-7), 4.54 (d, J = 17.1 Hz, 1H, N–CH_2'), 4.37 (d, J = 3.6 Hz, 1H, H-1), 4.29 (dd, J = 4.2, 2.7 Hz, 1H, H-6), 4.18 (q, J = 6.9 Hz, 2H, CO_2CH_2), 3.46 (d, J = 17.1 Hz, 1H, N–CH_2), 3.23–3.16 (m, 1H, H-2), 2.92–2.75 (m, 2H, H-5a, H-5b), 2.57–2.40 (m, 2H, CH_2CH=), 1.48 (s, 3H, $C(CH_3)_2$), 1.32 (s, 3H, $C(CH_3)_2$), 1.28 (t, J = 6.9 Hz, 2H, OCH_2); ^{13}C NMR ($CDCl_3$) δ: 171.8 (C=O), 169.1 (C=O), 133.2 (=CH), 119.4 (CH_2=), 111.9 ($C(CH_3)_2$), 83.6 (C-1), 83.1 (C-8), 83.0 (C-7), 79.1 (C-6), 64.6 (C-2), 61.3 (CO_2CH_2), 52.1 (NCH_2), 43.4 (C-5), 35.2 (CH_2CH=), 26.0 ($C(CH_3)_2$), 24.5 ($C(CH_3)_2$), 14.2 (CH_3); FABMS: calcd for $C_{17}H_{26}NO_6$ (M+H), m/z 340.1760; found m/z 340.1766.

3.12. (1*R*,6*S*,7*S*,8*S*)-3-(2-Hydroxyethyl)-7,8-isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonane (15a)

To a solution of **14a** (1.74 g, 5.82 mmol) in dry CH_2Cl_2 (20 mL) was added a 1 M solution of DIBAL (18.3 mL, 3 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h. CH_3OH (1.8 mL) was added at 0 °C and the temperature was raised to room temperature. Saturated NaCl (3.6 mL) was added and the mixture was diluted with Et_2O (89 mL). $MgSO_4$ (9.4 g) was added, and the mixture was stirred for 1 h and then filtered through a Celite pad. The solvent was removed and the crude mixture was purified by column chromatography (hexanes–EtOAc 4:1) to give **15a** (1.30 g, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.58 (d, J = 6.0 Hz, 1H, H-8), 4.53 (d, J = 6.0 Hz, 1H, H-7), 4.38 (d, J = 8.7 Hz, 1H, H-6), 4.30 (t, J = 2.1 Hz, 1H, H-1), 3.60–3.48 (m, 2H, CH_2OH), 2.75–2.49 (m, 6H, H-2a, H-2b, H-4a, H-4b, N–CH_2), 2.02–1.92 (m, 1H, H-5a), 1.76–1.65 (m, 1H, H-5b), 1.47 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 111.6 ($C(CH_3)_2$), 89.2 (C-7), 85.0 (C-1), 84.5 (C-8), 83.9 (C-6), 61.7 (C-2), 61.1 (N–CH_2), 59.0 (CH_2OH), 53.6 (C-4), 33.3 (C-5), 26.4 ($C(CH_3)_2$), 24.7 ($C(CH_3)_2$); ESIMS: calcd for $C_{12}H_{21}NO_4$ $[M]^+$, m/z 243.1471; found m/z 243.1476.

3.13. (1*R*,6*S*,7*S*,8*S*)-2-Allyl-3-(2-hydroxyethyl)-7,8-isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonane (15b)

To a solution of LAH (46 mg, 1.2 mmol) in dry THF (4 mL) under N_2 at 0 °C was added **14b** (0.2 g, 0.59 mmol). The solution was stirred at 0 °C for 2 h, and then acidified with aq ammonium chloride. The precipitate was filtered through a Celite pad and the filtrate was extracted with CH_2Cl_2. The solvent was removed and the crude mixture was purified by column chromatography (hexanes–EtOAc 4:1) to afford **15b** (0.16 g, 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 5.82–5.69 (m, 1H, =CH), 5.08 (m, 2H, $=CH_2$), 4.61 (d, J = 6.0, 1H, H-8), 4.54 (d, J = 6.3, 1H, H-7), 4.40 (d, J = 9.0 Hz, 1H, H-6), 4.24 (s, 1H, H-1), 3.54–3.50 (m, 2H, CH_2OH), 3.03–2.93 (m, 1H, H-4a), 2.71 (t, J = 6.0 Hz, 2H, N–CH_2), 2.73–2.44 (m, 2H, H-2, $=CH_2$), 2.37–2.26 (m, 2H, H-4b, $=CH_2$), 1.99–1.90 (m, 1H, H-5a), 1.73–1.62 (m, 1H, H-5b), 1.47 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 135.46 (CH=), 117.95 ($=CH_2$), 111.67 ($C(CH_3)_2$), 89.35 (C-1), 86.67 (C-6), 85.67 (C-7), 84.00 (C-8), 66.03 (C-2), 59.29 (CH_2OH), 59.01 (N–CH_2), 44.22 (C-4), 33.93 (C-5), 29.40 (CH_2CH=), 26.47 ($C(CH_3)_2$), 24.73 ($C(CH_3)_2$); FABMS: calcd for $C_{15}H_{26}NO_4$ $[M+H]^+$, m/z 284.1862; found m/z 284.1869.

3.14. (1*R*,6*S*,7*S*,8*S*)-3-(2-Hydroxyethyl)-9-oxa-3-azabicyclo[4.2.1]nonane-7,8-diol (6a)

Compound **15a** (0.11 g, 0.45 mmol) was dissolved in AcOH–H_2O (5.4 mL/1.8 mL) and reacted at 100 °C for 6 h. After removal of the solvents under reduced pressure, the solid residue was coevaporated with CH_3OH–toluene (1:1 v/v, 5 mL) to yield the crude diol. Purification by chromatography (CH_2Cl_2–CH_3OH 2:1) gave **6a** (58 mg, 63%) as a colorless syrup. $[\alpha]_D$ +51.4 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 4.28–4.19 (m, 3H), 3.62–3.49 (m, 2H), 2.79–2.48 (m, 7H), 2.06–1.96 (m, 1H), 1.76–1.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 86.3, 84.2, 79.6, 74.5, 61.0, 60.8, 59.1, 53.3, 33.3; FABMS: calcd for $C_9H_{18}NO_4$ $[M+H]^+$, m/z 204.1236; found m/z 204.1228.

3.15. (1*R*,6*S*,7*S*,8*S*)-2-Allyl-3-(2-hydroxyethyl)-9-oxa-3-azabicyclo[4.2.1]nonane-7,8-diol (6b)

The same procedures as described above were used to obtained **6b** (53%) as a yellow syrup. $[\alpha]_D$ +1.9 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 5.82–5.68 (m, 1H, =CH), 5.14–5.04 (m, 2H, CH_2=), 4.32 (dd, J = 5.7, 6.0 Hz, 1H, H-8), 4.25 (d, J = 8.7 Hz, 1H, H-6), 4.12 (d, J = 5.1 Hz, 1H, H-7), 3.75 (br s, 1H, OH), 4.06 (s, 1H, H-1), 3.54–3.50 (m, 2H, CH_2OH), 3.03–2.93 (m, 1H, H-4), 2.77–2.62 (m, 3H, NCH_2, H-2), 2.51–2.22 (m, 5H, CH_2CH=, H-4b, 2OH), 1.99–1.89 (m, 1H, H-5a), 1.63–1.52 (m, 1H, H-5b); ^{13}C NMR ($CDCl_3$) δ: 135.7 (CH=), 117.7 ($=CH_2$), 87.3 (C-1), 83.9 (C-6), 79.2 (C-7), 74.9 (C-8), 65.0 (C-2), 59.6 (CH_2OH), 58.5 (NCH_2), 44.3 (C-4), 33.5 (C-5), 29.5 (CH_2CH=); FABMS: calcd for $C_{12}H_{22}NO_4$ $[M+H]^+$, m/z 244.1549; found m/z 244.1541.

3.16. (1*R*,6*S*,7*S*,8*S*)-3-(2-Chloroethyl)-7,8-isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonane (16)

To a solution of **15a** (1.38 g, 5.68 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under argon atmosphere were added dry triethylamine (1.58 mL, 11.34 mmol) and methanesulfonyl chloride (0.57 mL, 7.37 mmol). The solution was stirred at room temperature for 4 h, and then neutralized by the addition of aq $NaHCO_3$. The mixture was diluted with water and extracted with CH_2Cl_2 (3×10 mL). The organic phase was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a residue, which upon column chromatography (hexanes–EtOAc 10:1), yielded **16** (0.92 g, 62%) as an oil. ^{1}H NMR ($CDCl_3$) δ: 4.66 (d, J = 11.1 Hz, 1H, H-8), 4.61 (d, J = 2.4 Hz, 1H, H-7), 4.35 (d, J = 8.4 Hz, 1H, H-6), 4.27 (t, J = 2.1 Hz, 1H, H-1), 3.46 (t, J = 6.3 Hz, 2H, CH_2Cl), 2.80–2.52 (m, 6H, N–CH_2, H-2a, H-2b, H-4a, H-4b), 1.95–1.85 (m, 1H, H-5a), 1.78–1.67(m, 1H, H-5b), 1.46 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 111.4 ($C(CH_3)_2$), 89.1 (C-7), 85.2 (C-1), 84.8 (C-8), 84.3 (C-6), 61.7 (C-2), 61.1 (N–CH_2), 53.9 (C-4), 42.4 (CH_2Cl), 33.5 (C-5), 26.5 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$); ESIMS: calcd for $C_{12}H_{20}ClNO_3$ $[M]^+$, m/z 261.1132; found m/z 261.1133.

3.17. (1*R*,6*S*,7*S*,8*S*)-3-(2-(4-Methoxybenzylamino)ethyl)-7,8-isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonane (17)

To a solution of **16** (50 mg, 0.19 mmol) in DMF (5 mL) was added 4-methyloxylbenzylamine (0.03 mL, 0.25 mmol) and triethylamine (0.08 mL, 0.57 mmol) and the reaction mixture was heated at reflux overnight. After cooling, the solvent was removed under

reduced pressure and the crude mixture was purified by column chromatography (hexanes–EtOAc 1:3) to give **17** (25 mg, 36%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.17 (d, J = 8.4 Hz, 2H, Ph), 6.83 (d, J = 8.7 Hz, 2H, Ph), 5.00 (s, 1H, NH), 4.55 (s, 2H, H-7, H-8), 4.34–4.25 (m, 4H, H-6, H-1, $PhCH_2$), 4.14–4.06 (m, 2H, N–CH_2), 3.76 (s, 3H, OCH_3), 2.73–2.47 (m, 6H, NCH_2CH_2, H-2a, H-2b, H-4a, H-4b), 1.92–1.83 (m, 1H, H-5a), 1.76–1.65 (m, 1H, H-5b), 1.46 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 159.0 (Ph), 156.3 (Ph), 130.4 (Ph), 128.9 (Ph), 114.0 (2Ph), 111.3 ($C(CH_3)_2$), 89.1 (C-8), 85.1 (C-7), 84.7 (C-1), 84.2 (C-6), 62.9 (N–CH_2), 62.1 (C-2), 58.6 (NCH_2CH_2), 55.2 (OCH_3), 54.1 (C-4), 44.6 ($PhCH_2$), 33.4 (C-5), 26.5 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$); ESIMS: calcd for $C_{20}H_{30}N_2O_4$ $[M]^+$, m/z 362.2206; found m/z 326.2214.

3.18. (1*R*,6*S*,7*S*,8*S*)-3-(2-(Dimethylamino)ethyl)-7,8-isopropylidene-9-oxa-3-azabicyclo[4.2.1]nonane (18)

To a solution of **16** (42 mg, 0.16 mmol) in DMF (5 mL) was added triethylamine (0.07 mL, 0.48 mmol) and 1,3-diaminopropane (0.02 mL, 0.21 mmol) and the reaction mixture was heated at reflux overnight. After cooling, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (EtOAc–CH_3OH, 14:1) to give **18** (18 mg, 42%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 4.58 (d, J = 6.0 Hz, 1H, H-8), 4.56 (d, J = 3.6 Hz, 1H, H-7), 4.33 (d, J = 8.7 Hz, 1H, H-6), 4.26 (bt, J = 1.8 Hz, 1H, H-1), 2.71–2.29 (m, 8H, H-2a, H-2b, H-4a, H-4b, NCH_2CH_2), 2.20 (s, 6H, $2NCH_3$), 1.94–1.85 (m, 1H, H-5a), 1.74–1.63 (m, 1H, H-5b), 1.46 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 111.3 ($C(CH_3)_2$), 89.1 (C-7), 85.2 (C-1), 84.8 (C-8), 84.2 (C-6), 62.1 (C-2), 58.2 (NCH_2CH_2), 57.9 (NCH_2CH_2), 54.2 (C-4), 45.9 ($2NCH_3$), 33.5 (C-5), 26.5 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$); ESIMS: calcd for $C_{14}H_{26}N_2O_3$ $[M]^+$, m/z 270.1943; found m/z 270.1952.

3.19. (1*R*,6*S*,7*S*,8*S*)-3-(2-(Dimethylamino)ethyl)-7,8-isopropylidene-7-methyl-9-oxa-3-azabicyclo[4.2.1]nonane (19)

A solution of **16** (0.20 g, 0.77 mmol) in 1,3-diaminopropane (15 mL) was heated at reflux overnight. After cooling, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (EtOAc–CH_3OH, 1:1) to give **19** (0.16 g, 68%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 4.51 (s, 2H, H-7, H-8), 4.31 (d, J = 8.4 Hz, 1H, H-6), 4.25 (t, J = 1.8 Hz, H-1), 2.77–2.53 (m, 12H), 2.06 (s, 3H, 3NH), 1.93–1.85 (m, 1H, H-5), 1.64–1.59 (m, 3H, H-5, H-4), 1.43 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 111.4 ($C(CH_3)_2$), 89.2 (C-8), 85.1 (C-1), 84.7 (C-7), 84.0 (C-6), 62.0 (C-2), 59.1, 53.7, 48.0, 47.7, 40.5, 33.5 (C-5), 33.1 (C-4), 26.4 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$).

3.20. (1*R*,6*S*,7*S*,8*S*)-7,8-Isopropylidene-3-(prop-2-ynyl)-9-oxa-3-azabicyclo[4.2.1]nonane (20)

To a solution of **13a** (93 mg, 0.46 mmol) in CH_3CN (10 mL) were added triethylamine (0.19 mL, 1.40 mmol) and propargyl bromide (0.06 mL, 0.70 mmol) and the reaction mixture was heated at reflux for 10 h. After removal of the solvent, the residue was dissolved in ether, washed with aq $NaHCO_3$, and dried over $MgSO_4$. Chromatographic separation (hexanes–EtOAc 12:1) led to **20** (77 mg, 71%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 4.56 (d, J = 6.0 Hz, 1H, H-8), 4.53 (d, J = 6.3 Hz, 1H, H-7), 4.32 (d, J = 8.4 Hz, 1H, H-6), 4.26 (t, J = 2.1 Hz, 1H, H-1), 3.25 (t, J = 2.7 Hz, 2H, N–CH_2), 2.70–2.61 (m, 2H, H-2a, H-2b), 2.55–2.45 (m, 2H, H-4a, H-4b), 2.17 (t, J = 2.4 Hz, 1H, ≡CH), 1.94–1.84 (m, 1H, H-5a), 1.74–1.63 (m, 1H, H-5b), 1.43 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 111.4 ($C(CH_3)_2$), 89.0 (C-7), 84.7 (C-1, C-8), 84.0 (C-6), 79.1 (C≡), 72.5 (≡CH), 60.7 (C-2), 53.1 (C-4), 49.0 (NCH_2), 32.8 (C-5), 26.4 ($C(CH_3)_2$), 24.8 ($C(CH_3)_2$); ESIMS: calcd for $C_{13}H_{19}NO_3$ $[M]^+$, m/z 237.1365; found m/z 237.1362.

3.21. Methyl 2-(5-((5-((7,8-dimethylmethylenedioxy-9-oxa-3-azabicyclo[4.2.1]nonan-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-3,4-isopropyliden-tetrahydrofuran-2-yl)acetate 21

To a solution of **20** (86 mg, 0.36 mmol) and **8** (0.10 g, 1.1 equiv) in 10 mL of EtOH were added copper turnings (8.6 mg) and saturated $Cu(SO_4)_2$ solution (0.18 mL, 1 M) and the reaction mixture was heated at reflux for 12 h. After completion of the reaction, the reaction mixture was filtered through Celite. The Celite pad was washed with $CHCl_3$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc 1:2) over silica gel to afford **21** (0.10 g, 55%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.47 (s, 1H, ArH), 4.61–4.47 (m, 4H, H-2, H-3, H-2′ H-3′), 4.34–4.15 (m, 6H, CH_2CO_2, H-4, H-4′ H-1 H-1′), 3.71 (s, 2H, N–CH_2), 3.66 (s, 3H, CO_2CH_3), 2.80–2.69 (m, 2H, H-5a, H-5b), 2.61 (dd, J = 15.7, 4.5 Hz, 1H, H-6a), 2.46–2.34 (m, 3H, H-6b, H-5′a, H-5′b), 1.93–1.84 (m, 1H, H-7a), 1.71–1.61 (m, 1H, H-7b), 1.47 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 1.26 (d, J = 2.1 Hz, 6H, $2C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ: 170.4 (C═O), 145.0 (Ar), 123.7 (ArH), 115.3 ($C(CH_3)_2$), 111.4 ($C(CH_3)_2$), 89.1, 84.9, 84.7, 84.0, 83.8, 82.3, 81.6, 80.7 (C-1, C-2, C-3, C-4, C-1′, C-2′ C-3′ C-4′), 61.2 (C-5), 54.8 (N–CH_2), 53.3 (C-5′), 51.8 (CO_2CH_3), 51.5 (CH_2CO_2), 37.9 (C-6), 33.1 (C-7), 27.3 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 25.4 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$); ESIMS: calcd for $C_{24}H_{36}N_4O_8$ $[M]^+$, m/z 508.2533; found m/z 508.2536.

3.22. Methyl 2-(5-((5-((7,8-Dihydroxy-9-oxa-3-azabicyclo[4.2.1]nonan-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)acetate 22

Compound **21** (0.10 g, 0.20 mmol) was dissolved in AcOH–H_2O (12.0 mL:4.0 mL) and heated at 100 °C for 6 h. After removal of the solvents under reduced pressure, the solid residue was coevaporated with CH_3OH–toluene (1:1 v/v, 10 mL) to yield the crude diol. The crude mixture was purified by column chromatography (EtOAc–CH_3OH, 4:1) to give **22** (50 mg, 58%) as a white solid. $[\alpha]_D$ +17.0 (c 1.0, CH_3OH); ^{1}H NMR (CD_3OD) δ: 7.78 (s, 1H), 4.65–4.43 (m, 2H), 4.20 (dd, J = 6.0, 1.8 Hz, 1H), 4.08–3.83 (m, 5H), 3.78 (t, J = 5.7 Hz, 1H), 3.65 (s, 2H), 3.59 (s, 3H), 3.42 (t, J = 5.4 Hz, 1H), 3.23–3.21 (m, 1H), 2.78–2.67 (m, 2H), 2.50 (dd, J = 15.6, 4.8 Hz, 1H), 2.42–2.23 (m, 2H), 1.88–1.78 (m, 1H), 1.68–1.57 (m, 1H); ^{13}C NMR (CD_3OD) δ: 172.9, 146.1, 126.3, 87.6, 85.7, 82.9, 81.3, 80.1, 75.4, 73.0, 61.3, 55.1, 54.0, 53.0, 52.3, 39.4, 34.1; FABMS: calcd for $C_{18}H_{29}N_4O_8$ $[M+H]^+$, m/z 429.1985; found m/z 429.1982.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.05.029.

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