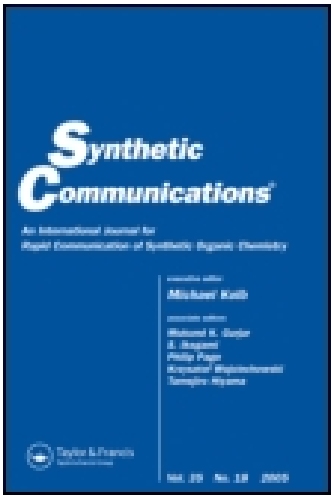

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Synthesis of Novel Pyran β-Amino Acid and 5,6-Dihydro-2H-pyran β-aminoxy Acid from Carbohydrate Derivatives

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SYNTHESIS OF NOVEL PYRAN β-AMINO ACID AND 5,6-DIHYDRO-2H-PYRAN β-AMINOXY ACID FROM CARBOHYDRATE DERIVATIVES

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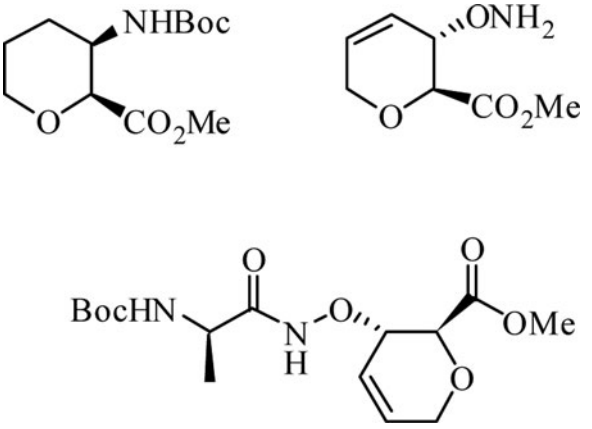
GRAPHICAL ABSTRACT



Abstract *Synthesis of two new amino acids, containing pyran rings, is reported from carbohydrate derivatives. The* cis*-3-amino-pyran-2-carboxylic acid (*cis*-APyC) was prepared from (*R*)-glyceraldehyde derivative, using nucleophilic substitution reaction for pyran ring formation. Similarly, the* trans*-3-aminoxy-5,6-dihydro-2H-pyran-2-carboxylic acid (*trans*-AmPyC) was prepared from diacetone glucose (DAG), using ring closing metathesis (RCM) reaction for the ring formation.*

Keywords *cis*-3-Amino-pyran-2-carboxylic acid (*cis*-APyC); diacetone glucose; nucleophilic substitution; RCM; (*R*)-glyceraldehyde derivative; *trans*-3-aminoxy-5,6-dihydro-2H-pyran-2-carboxylic acid (AmPyC)

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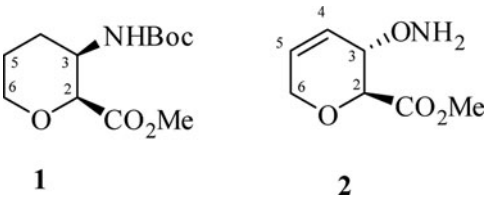


1 2

Figure 1. Structures of the amino acids **1** and **2**.

INTRODUCTION

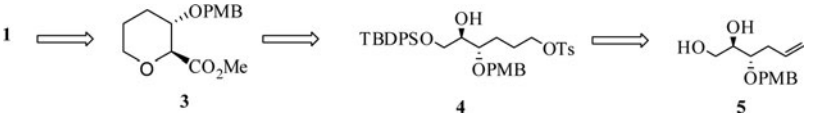
A variety of β-amino acids[1] are found in nature and many of them are present as part of the structures of several natural products.[2] The first reports on the use of β-amino acids for the synthesis of β-peptides, with novel 14-helical structures were reported[3] in 1996 by Gellman and Seebach. Gellman *et al.*[4] utilized *trans*-2-amino-cyclopentane-carboxylic acid (ACPC) for the synthesis of α/β-peptides.[5,6] The earlier results by Gellman *et al.*[4a] on the use of *trans*-2-amino-cyclohexane-carboxylic acid (ACHC) for the synthesis of α/β-peptides prompted us to undertake the synthesis of *trans*-3-amino-pyran-2-carboxylic acid (*trans*-APyC) and its peptides.[7] The oxygen atom in the pyran ring, by its participation in electrostatic interaction in the α/β-peptides,[7] supported the stabilization of the 9/11-helix.[6a] In a further study, enantiomeric APyCs were prepared and utilized for the synthesis of enantiomeric peptides.[7b] In continuation of our studies on the synthesis of synthetic amino acids with carbohydrate side chains[8] and their use[9] for the synthesis of "foldamers"[10] herein, we report the synthesis of two new β-amino acids, *cis*-3-amino-pyran-2-carboxylic acid (*cis*-APyC) **1** and *trans*-3-aminoxy-5,6-dihydro-2H-pyran-2-carboxylic acid (*trans*-AmPyC) **2** (Fig. 1), from (*R*)-glyceraldehyde derivative and diacetone glucose (DAG) respectively.

RESULTS AND DISCUSSION

Synthesis of (2*S*,3*R*)-Methyl 3-(*tert*-Butoxycarbonylamino) tetrahydro-2H-pyran-2-carboxylate (1)

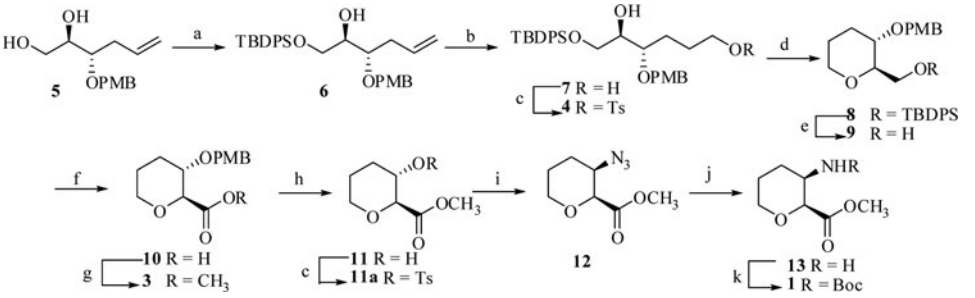
The retro-analysis of **1** revealed that it could be prepared from ester **3** by the introduction of amino group through inversion, while the pyran system could be realized from tosylate **4** by nucleophilic cyclization reaction. The tosylate **4** in turn could be obtained from the diol **5** (Scheme 1).

The known diol[11] **5**, prepared from 2,3-*O*-isopropylidine-(*R*)-glyceraldehyde, on reaction with TBDPSCl and imidazole in CH_2Cl_2 afforded ether **6** in 85% yield (Scheme 2). Olefin **6** on hydroboration with $BH_3 \cdot DMS$ in tetrahydrofuran (THF) gave the alcohol **7** in 78% yield. Alcohol **7** on reaction with *p*-TsCl and Et_3N in



3 4 5

Scheme 1. Retro-analysis of amino acid **1**.



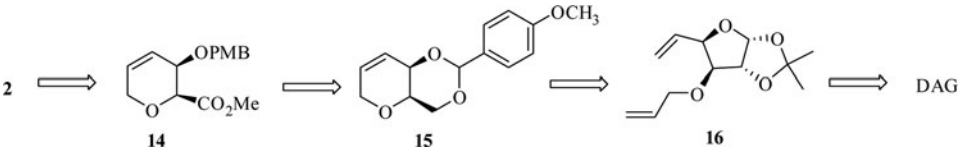
Scheme 2 Synthesis of amino acid **1.** Reagents and conditions: (a) TBDPSCl, imidazole, n-Bu_2SnO, CH_2Cl_2, 0 °C–rt, 2 h; (b) BH_3-DMS, cyclohexene, THF, 10% NaOH, 30% aq H_2O_2, 0 °C–rt, 7 h; (c) p-TsCl, Et_3N, CH_2Cl_2, 0 °C–rt, 2 h; (d) K_2CO_3, MeOH, 0 °C–rt, 2 h; (e) TBAF, THF, 0 °C–rt, 2 h; (f) TEMPO, BAIB, CH_2Cl_2:H_2O (1:1), 0 °C–rt, 2 h; (g) CH_2N_2, Et_2O, 0 °C–rt, 30 min; (h) DDQ, CH_2Cl_2:H_2O (19:1), 0 °C–rt, 2 h; (i) NaN_3, DMF, 70 °C, 3 h; (j) 10% Pd-C, H_2, MeOH, rt, 4 h; (k) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C–rt, 5 h.

CH_2Cl_2 furnished the tosylate **4**, which on ring closure with K_2CO_3 in MeOH gave **8** in 67% yield. Desilylation of **8** with tetrabutylammonium fluoride (TBAF) and oxidation of alcohol **9** with TEMPO and BAIB in aqueous CH_2Cl_2(1:1) furnished the acid **10** (76%). Reaction of **10** with CH_2N_2 at 0 °C afforded the ester **3** in 89% yield (Scheme 2).

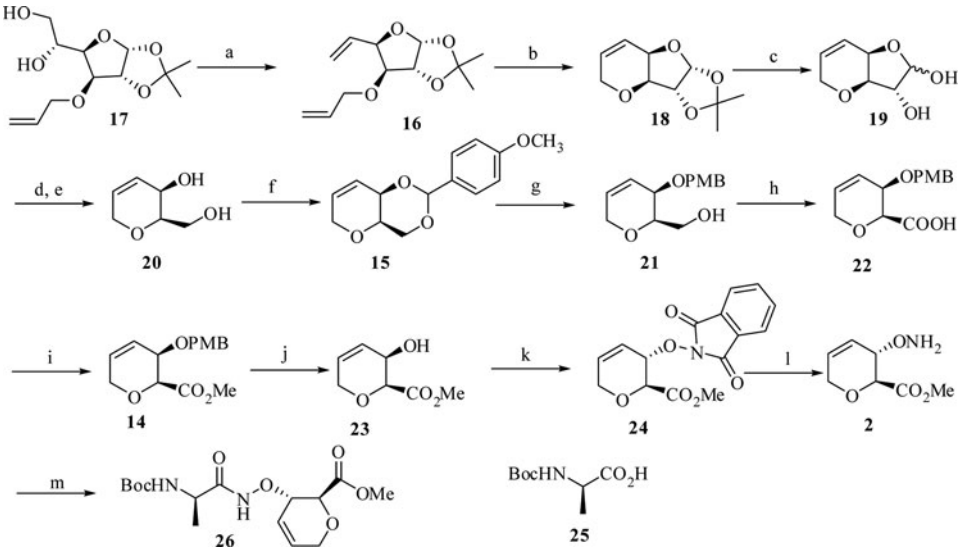
Having prepared the pyran ring and introduced the ester group, next we aimed at the introduction of amino group by inversion. Accordingly, oxidative removal of the PMB group in **3** with DDQ in aqueous CH_2Cl_2 (19:1) gave alcohol **11** (86%), which on tosylation in CH_2Cl_2 afforded **11a** (Scheme 2). Treatment of **11a** with NaN_3 in dimethylformamide (DMF) at 70 °C afforded the azide **12** (85%) through S_N2 mode. Finally, reduction of azide **12** with 10% Pd-C in methanol under a hydrogen atmosphere gave the amine **13**, which on reaction with $(Boc)_2O$ and Et_3N in CH_2Cl_2 furnished **1** in 85% yield (Scheme 2).

Synthesis of (2*S*,3*S*)-Methyl 3-(Aminoxy)-3,6-dihydro-2H-pyran-2-carboxylate (2)

From the retrosynthetic analysis of **2**, it was envisaged that **2** could be prepared from ester **14** (Scheme 3), which in turn could be obtained from **15**. Further, **15** could be realized from **16**, which in turn could come from DAG. The C3 stereocenter of DAG will be retained as pyran ring oxygen, while C4 would assist in the introduction of aminoxy group and the C1/C2 would result in the ester moiety. Thus, for the synthesis of **2**, ring closing metathesis (RCM) would result in the 5,6-dihydro-2H-pyran ring and Mitsunobu reaction efficiently would introduce the aminoxy group.



Scheme 3 Retro-analysis of aminoxy acid **2**.



Scheme 4 Synthesis of aminoxy acid **2.** Reagents and conditions: (a) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C–rt, 4 h; (b) Grubbs-I catalyst, toulene, reflux, 3 h; (c) 60% acetic acid, reflux, 3 h; (d) $NaIO_4$, acetone/H_2O (5:1), 0 °C–rt, 30 min; (e) $NaBH_4$, CH_3OH, 0 °C–rt, 1 h; (f) CH_3O-PhCH$(OMe)_2$, CH_2Cl_2, PTSA, 0 °C–rt, 3 h; (g) DIBAL-H, CH_2Cl_2, 0 °C–rt, 1 h; (h) TEMPO, BAIB, CH_2Cl_2:H_2O (1:1), 0 °C–rt, 1 h; (i) CH_2N_2, Et_2O, 0 °C–rt, 30 min; (j) DDQ, CH_2Cl_2/H_2O, (19:1), 0 °C–rt, 2 h; (k) Ph_3P, N-hydroxy phthalimide, DIAD, THF, 0 °C–rt, 6 h; (l) $N_2H_4.H_2O$, CH_2Cl_2/CH_3OH, (4:1), 0 °C–rt, 30 min; (m) 25, EDCI, HOBT, DIPEA, CH_2Cl_2, 0 °C–rt.

Accordingly, known diol[12] **17** on treatment with Ph_3P, imidazole, and I_2 afforded the bis-olefin **16** in 63% yield (Scheme 4). Subsequently, ring closure of **16** with Grubbs-I catalyst[13] for 4 h furnished the tricyclic system **18** (89%), which on acid hydrolysis afforded the lactol **19** in 65% yield. Oxidative cleavage of the lactol **19** and reduction of the resultant product with $NaBH_4$ gave the diol **20** in 60% yield (for two steps). Treatment of **20** with anisaldehyde dimethylacetal and *p*-toluenesulfonic acid (PTSA) in CH_2Cl_2 gave the acetal **15** (90%), which on reaction with diisobutylaluminiumhydride (DIBAL-H) in CH_2Cl_2 afforded the ether **21** in 91% yield. Oxidation of alcohol **21** with TEMPO and BAIB furnished acid **22** (60%), which on reaction with CH_2N_2 afforded the ester **14** in 60% yield (Scheme 4).

For the preparation of aminoxy ester **2**,[14] ether **14** was subjected to reaction with DDQ in aqueous CH_2Cl_2 to give alcohol **23** (72%), which on treatment with Ph_3P, DIAD, and N-hydroxy phthalimide in THF under Mitsunobu reaction conditions[15] afforded **24** in 70% yield. Further, reaction of **24** with hydrazine hydrate[16] in methanol gave the respective aminoxy ester **2**, which on coupling with acid **25** in the presence of EDCI, HOBT, and DIPEA in CH_2Cl_2[17] afforded dipeptide **26** in 52% yield (Scheme 4).

EXPERIMENTAL

Solvents were dried over standard drying agents and freshly distilled prior to use. All commercially available chemicals were used without further purification.

All reactions were performed under nitrogen. ^{1}H NMR and ^{13}C NMR spectra were measured with Varian Gemini FT 200-MHz, Bruker Avance 300-MHz, Unity 400-MHz, and Inova 500-MHz instruments with tetramethylsilane (TMS) as internal standard for solutions in $CDCl_3$. *J* values are given in hertz (Hz). Chemical shifts were reported in parts per million (ppm) relative to the solvent signal. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. IR spectra were recorded on FT IR (Perkin-Elmer IR-683) spectrophotometer with NaCl optics. A Jasco DIP 300 digital polarimeter was used for measurement of optical rotations at 25 °C. Mass spectra were recorded on direct inlet system or liquid chromatography (LC) by MSD trap SL (Agilent Technologies), and the high-resolution mass spectrometric (HRMS) data were obtained using Q-TOF mass spectrometry.

tert-Butyl(((2*R*,3*S*)-3-(4-methoxybenzyloxy)tetrahydro-2H-pyran-2-yl)-methoxy)diphenylsilane (8)

Et_3N (6 mL, 43.3 mmol) and *p*-TsCl (4.11 g, 21.6 mmol) were added to a solution of **7** (11.0 g, 21.6 mmol) in CH_2Cl_2 (165 mL) at 0 °C and stirred at room temperature for 2 h. The reaction mixture was washed with water (80 mL) and brine (80 mL) and dried (Na_2SO_4). Evaporation of solvent furnished **4** as a colorless oil, which was immediately used for the next reaction without further purification.

A solution of **4** (9.0 g, 13.60 mmol) in MeOH (45 mL) was treated with K_2CO_3 (5.62 g, 40.72 mmol) and stirred at room temperature for 2 h. MeOH was evaporated under reduced pressure and the residue was extracted with EtOAc (3 × 70 mL). The organic layer was washed with water (70 mL) and brine (70 mL). The solvent was dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (silica gel 60–120 mesh, 8% ethyl acetate in petroleum ether) to furnish **8** (4.5 g, 67%) as a colorless liquid. $[\alpha]^{20}_D = +39.84$, (*c* 1.2, $CHCl_3$); IR (neat): ν 3021, 1730, 1374, 1247, 1045, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75–7.70 (m, 4H, ArH), 7.42–7.31 (m, 6H, ArH), 7.12 (d, 2H, $J = 8.5$ Hz, ArH), 6.8 (d, 2H, $J = 8.5$ Hz, ArH), 4.52 (d, 1H, $J = 10.9$ Hz, benzylic), 4.35 (d, 1H, $J = 10.9$ Hz, benzylic), 3.91 (d, 2H, $J = 2.6$ Hz, OCH_2), 3.77 (s, 3H, OCH_3), 3.54–3.43 (m, 1H, OCH), 3.37–3.20 (m, 2H, OCH_2), 2.28–2.23 (m, 1H, OCH), 1.68–1.60 (m, 2H, CH_2), 1.49–1.36 (m, 2H, CH_2), 1.06 (s, 9H, 3 × CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.0, 135.8, 135.7, 129.5, 129.2, 127.6, 127.5, 113.7, 81.8, 73.0, 70.6, 67.5, 64.0, 55.3, 29.7, 29.4, 26.9, 19.4; HRMS (ESI): *m*/*z* calculated for $C_{30}H_{38}O_4SiNa$ $[M+Na]^+$ 513.2435, found 513.2431.

(2*S*,3*R*)-Methyl 3-Azidotetrahydro-2H-pyran-2-carboxylate (12)

Et_3N (0.25 mL, 1.90 mmol) and *p*-TsCl (0.18 g, 0.95 mmol) were added to a solution of **11** (0.15 g, 0.94 mmol) in CH_2Cl_2 (10 mL) at 0 °C and stirred at room temperature for 2 h. Workup as described for **4** furnished **11a** as a colorless oil, which was used for the next reaction without further purification.

To a solution of **11a** in DMF (5 mL), NaN_3 (0.12 g, 1.91 mmol) was added and stirred at 70 °C for 3 h. The reaction mixture was cooled to room temperature,

treated with water (8 mL), and extracted with ether (2 × 10 mL). Organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue purified by column chromatography (60- to 120-mesh silica gel, 10% ethyl acetate in petroleum ether) to give **12** (0.10 g, 85%) as a colorless liquid. $[\alpha]^{20}_D = -132.11$ (*c* 1.2, $CHCl_3$); IR (KBr): ν 2971, 2945, 2105, 1736, 1437, 1370, 1272, 1085, 976, 868, 751, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.08 (d, 1H, $J = 11$ Hz, OCH), 4.01 (m, 1H, OCH), 3.77 (s, 3H, OCH_3), 3.50 (t, 1H, $J = 11.4$ Hz, OCH), 1.98–1.83 (m, 3H, CH_2), 1.71–1.55 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 80.3, 68.2, 53.1, 52.0, 27.9, 24.1; HRMS (ESI): *m/z* calculated for $C_7H_{11}N_3O_2Na$ $[M+Na]^+$ 208.0613, found 208.0616.

(2*S*,3*R*)-Methyl 3-(*tert*-Butoxycarbonylamino)tetrahydro-2H-pyran-2-carboxylate (1)

A mixture of **12** (0.08 g, 0.43 mmol) and 10% Pd-C (cat.) in MeOH (1.5 mL) was stirred at room temperature under hydrogen atmosphere for 4 h. It was filtered and washed with EtOAc (10 mL). The filtrate was evaporated under reduced pressure to furnish amine **13**, which was used for the next reaction without further purification.

To a solution of amine **13** in CH_2Cl_2 (10 mL), Et_3N (0.15 mL, 0.99 mmol) and $(Boc)_2O$ (0.17 mL, 0.75 mmol) were added at 0 °C and stirred for 5 h. The reaction mixture was treated with water (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was washed with brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60- to 120-mesh silica gel, 12% ethyl acetate in petroleum ether) to furnish **1** (0.11 g, 85%) as a colorless syrup; $[\alpha]^{20}_D = -103.94$, (*c* 1.2, $CHCl_3$); IR (KBr): ν 3290, 2975, 2936, 1754, 1705, 1540, 1446, 1370, 1290, 1209, 1175, 1115, 1094, 1066, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (4.64 (brs, 1H, NH), 4.10–3.95 (m, 2H, OCH), 3.76 (s, 3H, $COOCH_3$), 3.50–3.39 (m, 2H, OCH), 2.13–2.0 (m, 2H, OCH), 1.78–1.68 (m, 2H, CH_2), 1.42 (s, 9H, Boc);^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 155.1, 80.1, 79.6, 66.7, 52.4, 48.2, 29.3, 28.3, 23.9; HRMS (ESI): *m/z* calculated for $C_{12}H_{21}NO_5Na$ $[M+Na]^+$ 282.1350, found 282.1352.

(3*R*,5*R*,6*S*,6*R*)(Allyloxy)2,2dimethylvinyltetrahydrofuro[2,3d][1,3] dioxole (18)

Grubbs I catalyst (10 mol%) was added to a stirred solution of **16** (12.3 g, 54.42 mmol) in dry toluene (50 mL) and stirred at reflux for 3 h. The reaction mixture was stirred for an additional 1 h at room temperature in open air. It was filtered through celite and washed with toluene (2 × 20 mL), and the solvent was evaporated. The residue on purification by column chromatography (60- to 120-mesh silica gel, 10% ethyl acetate in petroleum ether) afforded **18** (9.6 g, 90%) as a brown syrup; $[\alpha]^{20}_D = -22.7$ (*c* 0.1, $CHCl_3$); IR ($CHCl_3$): ν 2987, 2937, 1737, 1645, 1449, 1288, 1163, 954, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.0 (s, 2H, olefinic), 5.89 (d, 1H, $J = 3.7$ Hz, C_1H), 4.52 (d, 1H, $J = 3.7$ Hz, C_4H), 4.31 (m, 1H, C_2H), 4.12 (m, 2H, OCH), 3.88 (d, 1H, $J = 2.6$ Hz, C_3H), 1.48 (s, 3H, Me), 1.31(s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 121.4, 111.1, 104.9, 84.1, 78.5, 70.6, 64.3, 26.5, 25.9; HRMS (ESI): *m/z* calculated for $C_{10}H_{15}O_4[M+H]^+$ 199.0964, found 199.0963.

Methyl-2-((2*S*,3*S*)-3-(1,3-dioxoisoindolin-2-yloxy)-3,6-dihydro-2H-pyran-2-yl)-2-oxo Acetate (24)

S solution of **23** (1.02 g, 6.45 mmol) in dry THF (5 mL) was added to a solution of Ph_3P (2.53 g, 9.68 mmol) and N-hydroxy phthalimide (1.55 g, 9.68 mmol) in THF (5 mL) at 0 °C. DIAD (1.95 mL, 6.55 mmol) was added to the reaction mixture and stirred for 6 h. The solvent was evaporated and the residue was purified by column chromatography (60- to 120-mesh silica gel, 22% ethyl acetate in petroleum ether) to afford **24** (1.36 g, 70%) as yellow syrup; $[\alpha]^{20}_D = +74.19$, (*c* 0.09, $CHCl_3$); IR ($CHCl_3$): ν 3020, 2923, 2852, 2313, 1788, 1734, 1550, 1499, 1482, 1450, 1374, 1216, 1107, 1017, 979, 929, 87, 777, 667, 624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H, ArH), 7.78 (m, 2H, ArH), 6.14 (m, 2H, olefinic), 4.94 (m, 2H, OCH), 4.48 (m, 1H, OCH), 4.27 (m, 1H, OCH), 3.78 (s, 3H, $COOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 163.8, 134.5, 133.4, 128.7, 123.5, 119.5, 78.1, 74.3, 69.8, 52.3; HRMS (ESI): *m/z* calculated for $C_{15}H_{14}NO_6Na$ $[M+Na]^+$ 326.0640, found 326.0655.

Boc-(*R*)-β-AIA-(*S*)-AmA-OMe (26)

A solution of **24** (1.36 g, 4.48 mmol) and $N_2H_4.H_2O$ (0.61 mL, 13.46 mmol) in CH_3OH/CH_2Cl_2 (6.8 mL; 4:1) was stirred at room temperature. After 2 h, solvent was evaporated and CH_2Cl_2 was added to the residue. The organic layer was washed with 5% $NaHCO_3$ solution (10 mL) and brine (10 mL). It was dried (Na_2SO_4) and evaporated to afford (2S, 3S)-methyl 3-(aminoxy)-3,6-dihydro-2H-pyran-2-carboxylate, which was used directly in the next step.

A solution of acid **25** (0.37 g, 1.98 mmol), HOBT (0.26 g, 1.98 mmol), and EDCI (0.37 g, 1.98 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under N_2 atmosphere for 15 min and treated with a solution of **2** (0.22 g, 1.32 mmol) in CH_2Cl_2(1 mL) and DIPEA (0.34 mL, 1.5 mmol). The reaction mixture was stirred at room temperature for 5 h, quenched with saturated aqueous NH_4Cl solution (10 mL) at 0 °C, and diluted with $CHCl_3$ (10 mL). It was sequentially washed with 1 N HCl (10 mL), $NaHCO_3$(10 mL), water (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), evaporated, and purified the residue by column chromatography (60- to 120-mesh silica gel, 50% ethyl acetate in petroleum ether) to afford **26** (0.23 g, 52%) as a syrup; $[\alpha]^{20}_D = +83.46$ (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): ν 3328, 3301, 3270, 2960, 2922, 1746, 1682, 1514, 1367, 1169, 1073, 1019, 859, 717 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.85 (brs, 1H, NH-aminoxy), 6.02 (m, 2H, olefinic), 5.31 (d, 1H, $J = 7.9$ Hz, NH-amine), 4.58 (d, 1H, $J = 10.9$ Hz, OCH), 4.46 (d, 1H, $J = 17.3$ Hz, OCH), 4.22 (d, 1H, $J = 16.9$ Hz, OCH), 3.76 (s, 3H, $COOCH_3$), 1.43 (s, 9H, Boc), 1.34 (d, 3H, $J = 6.7$, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 169.9, 155.5, 132.2, 120.6, 80.3, 75.9, 73.4, 63.4, 63.3, 52.4, 47.4, 28.2, 17.6; HRMS (ESI): *m/z* calculated for $C_{15}H_{25}NO_7Na$ $[M+Na]^+$ 367.1481, found 367.1493.

CONCLUSION

In summary, new synthetic amino acid and aminoxy acid, based on pyran, are prepared from carbohydrate derivatives. Efficient nucleophilic substitution and RCM reactions were utilized for the ring formation, while the inversion of hydroxy

groups effectively introduced the amine and aminoxy groups in the respective amino acid **1** and aminoxy acid **2**. Utilization of such new amino acid and aminoxy acid in foldamer design with the possibility to participate in additional H-bonding through electrostatic interaction would help in the realization of novel skeletal and conformational diversity.

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SUPPLEMENTAL MATERIAL

Full experimental details, spectral data, and ^{1}H NMR and ^{13}C NMR of all the new products for this article can be accessed on the publisher's website.

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