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A novel free C-12 higher carbon sugar: asymmetric synthesis and reactivity with nucleophiles

Hong-Min Liu,* Feng-Wu Liu, Xiao-Ping Song, Jing-Yu Zhang and Lin Yan

New Drug Research and Development Center, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450052, PR China

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Abstract—A novel C-12 higher carbon sugar, (1*R*)-(1,4:3,6-dianhydro-D-mannitol-2-yl)-1,4:3,6-dianhydro-D-fructose, was firstly synthesized via a convenient aldol reaction of 1,4:3,6-dianhydro-D-fructose without any protection and activation of functional groups. The reactivity of the novel higher sugar with nucleophiles was also studied, through which a series of oxazolidines and other derivatives of the higher sugar were available. The study showed that the higher sugar possesses a highly reactive carbonyl group and a good stereo controlling ability in the reaction.

1. Introduction

Higher carbon sugars have been attracting the increasing attention of organic chemists in the past decades due to the fact that they can be used as non-metabolized analogues of di- and oligosaccharides and are components of some antibiotics[1] and also that they are carbohydrate precursors for higher carbon amino sugars. This class of compounds, therefore, is interesting targets for developing new synthetic methodologies. Several approaches toward higher carbon sugars, including the Wittig reaction,[2] Horner–Emmons procedure,[3] aldol condensation,[4] radical addition,[5] hetero-Diels–Alder reaction,[6] and enzymatic aldolization,[7] have been well documented. However most of these approaches were limited by being complicated and having multi-steps, or requiring separation of the product stereoisomers, or activation of the starting monosaccharide, and in particular, requiring protection of functional groups. Accordingly, development of simple, convenient, and protecting group free synthetic methodology is a real challenge for organic chemists.

Thus, we are interested in designing a convenient approach to new and special higher carbon sugars and the corresponding amino derivatives that may have desired biological activity. Following success in the stereoselective synthesis of a C-10 higher sugar starting from D-xylose,[8] we reported, in our previous paper,[9] the synthesis of novel tetrahydroquinoline derivatives **1** via reaction of 1,4:3,6-dianhydro-D-fructose **2**, a useful building block, with anilines in the presence of *p*-TsOH. From the structure of compound **1**, we noticed that the C-12 higher carbon sugar skeleton was constructed through a simple dimerization of the Schiff base derived from 1,4:3,6-dianhydro-D-fructose. Thus, we pondered whether the free C-12 higher carbon sugar **3** (as shown in Fig. 1) could be synthesized directly from 1,4:3,6-dianhydro-D-fructose via a concise route. Our interest in the synthesis of the target sugar molecule and its derivatives stemmed from the potent bioactivity and pharmaceutical application of 1,4:3,6-dianhydrohexitol derivatives and the wide utilization of the special V-shaped skeleton in asymmetric synthesis.[10]

Herein, we report a simple and convenient methodology for asymmetric synthesis of the C-12 higher carbon sugar and an investigation into its asymmetric reactivity with different nucleophiles. To our knowledge, this kind of higher carbon sugar has not been reported in the literature.

2. Results and discussion

In accordance with the literature[11] and our previous experimental data, the carbonyl group of keto-sugar **2** gave a hydrated carbonyl signal in the ^{13}C NMR spectrum in D_2O (102.2 ppm) compared to the free carbonyl group (213.3 ppm) in acetonitrile-d_3, indicating that the carbonyl group possesses a high reactivity toward nucleophiles. Moreover, a methylene group α to a carbonyl group would

* Corresponding author. E-mail: liuhm@zzu.edu.cn

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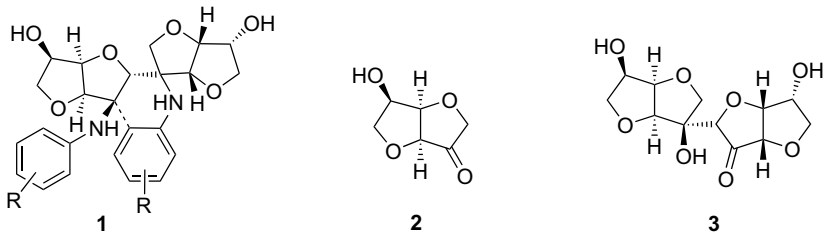
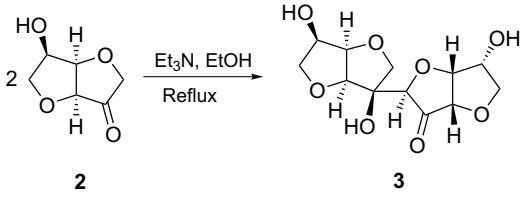


Figure 1.

be reactive due to the influence of the neighboring oxygen atom and carbonyl group. Therefore, we attempted to use different reagents and different reaction conditions to construct the above-mentioned free C-12 sugar **3**. When a solution of **2** in EtOH was treated with Et_3N at reflux, a white precipitate was formed. Structural analysis by HRMS, ^1H, ^{13}C, and 2D NMR spectra confirmed that the precipitate is the desired sugar product. The following single-crystal X-ray analysis established the absolute configuration as depicted in Figure 2. From examination of the structure and configuration we noted that, due to the stereo control of the sugar rings, the 'back to back' aldol reaction between the carbonyl group in one molecule and the methylene in another molecule of 1,4:3,6-dianhydro-D-fructose afforded the *exo–exo* combined product (Scheme 1).



Scheme 1. The highly stereoselective Aldol reaction of **2**.

After the novel 12-carbon sugar **3** was synthesized successfully, we intended to investigate its reactivity with nucleophiles and the stereoselectivity of nucleophilic addition reactions. Because chiral oxazolidines are important intermediates used in numerous asymmetric transformations, our first attempt was to treat **3** with 2-aminoethanol at ambient temperature under catalyst-free conditions. Six hours later, when the reaction was complete by TLC detection, the mixture was worked up to give product **4** in a yield of 90%. HRMS and spectroscopic data suggested that compound **4** is an oxazolidine derivative. The stereochemistry for the newly formed stereogenic center at C-8 was established as being of (*R*)-configuration by X-ray crystallographic analysis. The generality of this nucleophilic addition was examined by replacement of 2-aminoethanol with other vicinal amino alcohol analogues (VAA) in the reaction. The results are outlined in Scheme 2 and Table 1.

The same absolute configurations at C-8 for the oxazolidines **5** and **6** were also confirmed by X-ray crystallographic analysis. Therefore we deduced that the formation of the five-membered oxazolidine ring was highly stereoselective. From entries 1 to 3, amino ethanol (VAA-1), 1-amino-3-phenoxyl-isopropanol (VAA-2), and methyl L-threoninate (VAA-3) were used in the reaction in sequence. With the primary amine being changed to a secondary one, the increase of steric hindrance of the substituent (R_1) at the α carbon resulted in a decrease of the reaction rate and yield. Another reason for the poor yield of entries 3 and 4 could also be explained by the diminished nucleophilicity of the amino group due to the electron-drawing effect of methoxycarbonylmethenylmethyl group at the α carbon. When the reaction was catalyzed with *p*-TsOH and heated at reflux, the yield was improved (entry 4). In comparison with R_1, the steric hindrance of the substituent (R_2) at the β carbon gave slightly less influence on the reaction, which could be observed from the good yields for entries 1, 2, 5, and 6. The two amino alcohols (VAA-4 and 5[12]) with bulky cyclic groups, smoothly furnished the corresponding oxazolidines (entries 5 and 6).

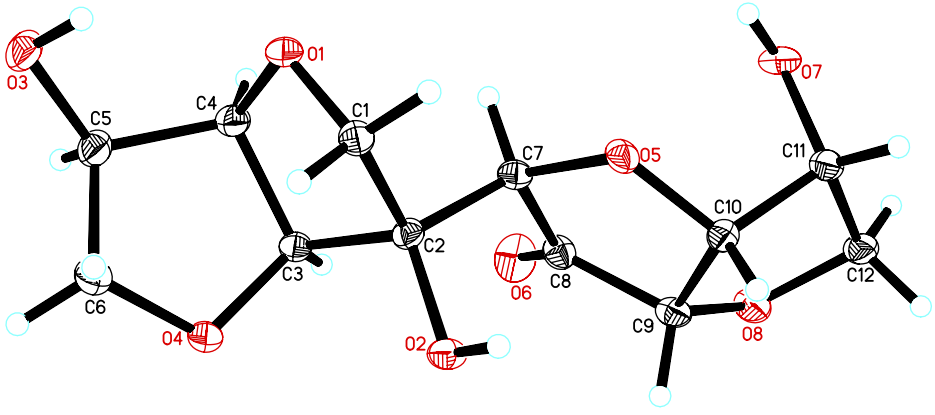
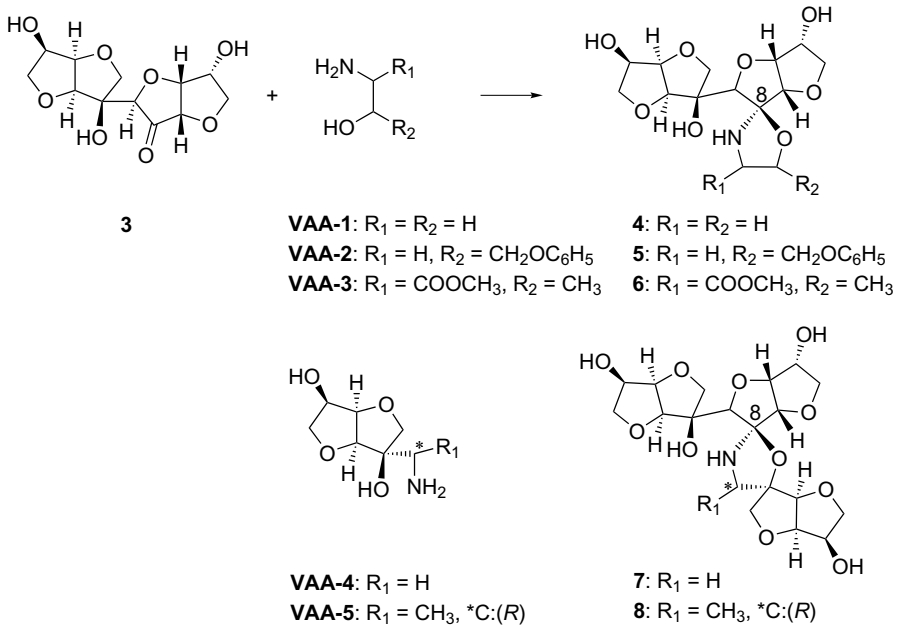


Figure 2. ORTEP diagram of compound **3**.



Scheme 2. The reaction of **3** with various vicinal amino alcohols.

Table 1. Results for the reaction of **3** with 2-amino alcohols[a]

Entry	VAA	Mol ratio (**3**:VAA)	Time (h)	Temperature (°C)	Product	Isolated yield (%)
1	VAA-1	1:1.2	6	rt	**4**	90
2	VAA-2[b]	1:2.4	12	rt	**5**	78
3	VAA-3	1:1.2	48	rt	**6**	31
4	VAA-3[c]	1:1.2	12	Reflux	**6**	43
5	VAA-4[c]	1:1.2	12	Reflux	**7**	86
6	VAA-5[c]	1:1.2	12	Reflux	**8**	75

[a] In MeOH.
[b] Racemate was used.
[c] In the presence of catalytic amount of *p*-TsOH.

The high stereoselectivity in the reaction could be explained as follows. The amino group of the 2-amino alcohol condensed with the carbonyl group of the sugar to give an imine intermediate. Then, an immediate five-membered ring closure involving a nucleophilic attack of a hydroxyl group to an imine double bond afforded the oxazolidine derivative. The OH group attacked different diastereotopic faces of the imine double bond and gave rise to the two different configurations of the oxazolidine. Because of the larger steric hindrance from the *endo* face than the *exo* face with respect to the V-shaped molecule, the OH group preferred to attack from the less hindered *exo* face, which resulted in the (*R*)-isomer of oxazolidine. From the X-ray crystallographical analysis of compounds **4**, **5**, and **6**, we noted that the intramolecular H-bond between N–H and O(2) existed in each of them. Therefore, we could conclude that both the stereocontrol of the V-shaped molecule and the induction of an intramolecular H-bond should be crucial to the highly stereoselective ring closure. Based on the speciality of the reaction and in consideration of the bulky tertiary hydroxyl groups in VAA-4 and 5, we could deduce that compounds **7** and **8** have the same stereochemistry as **4**, **5**, and **6**. This deduction was confirmed by the NOE effect observed between protons H-9 and H-3′ in the NOESY spectrum of oxazolidine **7**.

From the examination of the oxazolidine **5**, we note that the amino alcohol moiety in the molecule is the (*R*)-isomer, which indicated that when the racemic VAA-2 was treated with C-12 higher carbon sugar **3**, only the (*R*)-isomer could react with **3** to furnish the corresponding oxazolidine derivative **5**. Based upon the characteristics of the reaction, the racemic amino alcohol (VAA-2) was resolved with a sufficient higher carbon sugar. The extension of this method to the resolution of other synthetic chiral amino alcohols and amino acids would be meaningful in organic synthesis and drug development.

Being interested in the special biological property of amino derivatives of higher carbon sugars,[1d] we attempted to synthesize this class of derivatives via a Henry reaction. At first, the reaction was conducted with compound **3** and nitromethane in the presence of Et_3N at reflux temperature, (1*S*)-(1,4:3,6-dianhydro-D-mannitol-2-yl)-2-nitromethyl-1,4:3,6-dianhydro-D-glucitol **9** being obtained in high yield. Product **9** was confirmed by HRMS, ^1H

NMR, and ^{13}C NMR spectral analysis. The correlation between the two protons of CH_2NO_2 and H-7 in the NOESY spectrum reveals that the CH_2NO_2 and H-7 are on the same side of the C(7)–C(8)–C(9) plane, which indicates that C-8 possess the (*R*)-configuration. The solution of compound **9** in CH_3OH was hydrogenated in the presence of Pd–C catalyst at 50 °C, leading to a novel amino alcohol: (1*S*)-(1,4:3,6-dianhydro-D-mannitol-2-yl)-2-aminomethyl-1,4:3,6-dianhydro-D-glucitol **10**, as shown in Scheme 3. However, the Henry reaction did not take place when nitroethane was used in the reaction, which could be due to the larger hindrance of nitroethane than nitromethane.

Subsequently, dimethyl malonate, another nucleophile, was allowed to react with the C-12 higher carbon sugar and NaOMe, affording a new lactone derivative **11**. The structure was deduced from the $[M+Na]^+$ peak at *m*/*z* 411.0885 in the HRMS spectrum and that only one methyl signal was observed in the ^1H NMR spectrum. It is obvious that the nucleophilic addition first occurred and then was followed by an intramolecular ester-exchange reaction. From ^1H NMR, ^{13}C NMR, and DEPT-135 spectra we note that only seven CH groups are present in the molecule. A strong absorption at 1688 cm^{-1} in the IR spectrum reveals the presence of one conjugated ester carbonyl group in the lactone. In consideration of all the above experimental data and the stereoselective feature of the nucleophilic addition of this sugar, we can conclude that the carbonyl group in the lactone ring exists in enolic form. This reaction is designated in Scheme 4.

All these reactions of the higher carbon sugar **3** as described above reveal that both the nucleophilic addition and hydrogenation are highly stereoselective due to the fixed stereochemistry of the sugar. Undoubtedly, the higher sugar is an ideal chiral building block in asymmetric organic chemistry. The compounds obtained, except for **11**, are amino sugars and are also chiral α,β- or α,γ-amino alcohol derivatives, which should be precursors to other biobased amino compounds and could be applied in organic synthesis and asymmetric catalysis.

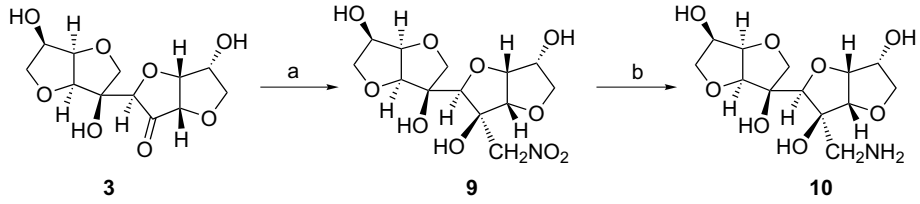
3. Conclusions

In summary, we have developed a simple and convenient approach to a free C-12 higher carbon sugar and its amino alcohol and lactone derivatives from a simple C-6 ketosugar. The notable features of the methodology are mild reaction conditions, high stereoselectivity, high yields, and operational simplicity. The addition reactions of the novel higher sugar with the various nucleophiles show the high stereocontrol effect and high reactivity of the sugar. The selective reaction with (*R*)-amino alcohol provides a new method for the resolution of racemic amino alcohols and amino acids. The evaluation of the bioactivity and further study on the applications of the novel compounds in asymmetric synthesis are in progress.

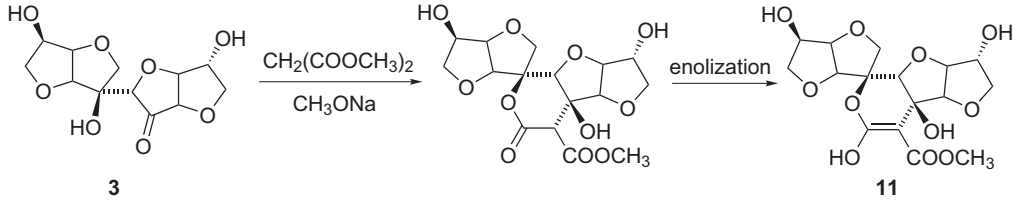
4. Experimental

4.1. General experimental methods

^1H and ^{13}C NMR spectra were acquired on Bruker AVANCE DPX-400 spectrometer with chemical shift (δ) given in parts per million relative to tetramethylsilane as an internal standard (δ = 0.00 ppm). All assignments were based upon the two-dimension NMR spectra. X-ray diffraction experiment was made on a Rigaku RAXIS-IV imaging plate with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). All data were collected at a temperature of 291(2) K or 293(2) K and corrected for Lorentz-polarization effects. Melting points were determined on WC-1 melting-point apparatus and are uncorrected. Infrared spectra were recorded on Nicolet IR200 instrument using KBr disks in the 400–4000 cm^{-1} regions. Optical rotation was detected on Perkin–Elmer 341 Polari-



Scheme 3. Conversion of **3** to amino derivative **10**. Reagents and conditions: (a) CH_3NO_2, Et_3N, reflux; (b) CH_3OH, H_2, Pd–C, 50 °C.



Scheme 4. Preparation of lactone derivative **11**.

meter. HRMS (high-resolution mass spectra) were taken with a Q-Tof Micromass spectrometer.

4.2. (1*R*)-(1,4:3,6-Dianhydro-D-mannitol-2-yl)-1,4:3,6-dianhydro-D-fructose 3

A catalytic amount of Et_3N was added to a solution of **2** (1.44 g, 10 mmol) in EtOH (20 mL) with stirring. The mixture was heated and kept at refluxing temperature for 6 h, followed by concentration under vacuumed pressure to dryness. Recrystallization of the residue with absolute EtOH furnished product **3** as a white solid (1.15 g, 80%). Mp 190–191 °C, $[\alpha]_D^{20} = +173.4$ (*c* 1.10, CH_3OH). IR (KBr): 3381, 1771 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.87 (dd, 1H, $J = 4.8$, 6.8 Hz, H-10), 4.39–4.41 (m, 2H, H-3, H-4), 4.26 (d, 1H, $J = 6.8$ Hz, H-9), 4.10–4.15 (m, 2H, H-5, H-11), 3.92 (s, 1H, H-7), 3.95 (d, 1H, $J = 8.8$ Hz, H-1a), 3.82 (dd, 1H, $J = 4.8$, 8.8 Hz, H-12a), 3.79 (m, 1H, H-6a), 3.54 (dd, 1H, $J = 4.8$, 8.8 Hz, H-12b), 3.42 (d, 1H, $J = 8.8$ Hz, H-1b), 3.38 (m, 1H, H-6b); ^{13}C NMR (100 MHz, DMSO-d_6): δ 212.8 (C-8), 83.2 (C-2), 81.4 (C-4), 81.0 (C-7), 80.3 (C-10), 79.7 (C-3), 78.4 (C-9), 72.5 (C-12), 72.3 (C-1), 72.2 (C-5), 71.8 (C-6), 71.3 (C-11). HRMS: calcd for $C_{12}H_{16}O_8$: 288.0845. Found: 289.0901 $[M+H]^+$.

4.3. General procedures for the synthesis of oxazolidines 4–8

To a solution of C-12 sugar **3** (1.44 g, 5 mmol) in ethanol (20 mL), vicinal amino alcohol (6–12 mmol) was added (a catalytic amount of *p*-TsOH was added as well if it was necessary as indicated in Table 1). The mixture was stirred at the indicated temperature and time, followed by concentration and purification by column chromatography on silica gel or by recrystallization from isopropanol, giving product oxazolidines as white solids (yields 31–90%).

4.3.1. (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*)-Spiro[6,3′,6′-trihydroxy-octahydro[2,3′]bi[furo[3,2-*b*]furan]-3,2″-[1″,3″-oxazolidine] 4. Recrystallization from isopropanol. Mp 97–98 °C, $[\alpha]_D^{20} = +105.7$ (*c* 1.06, CH_3OH); IR (KBr): 3385, 3295, 2981, 2872, 1651 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 4.62 (d, 1H, $J = 5.2$ Hz, H-3), 4.57 (t, 1H, $J = 4.4$ Hz, H-10), 4.33 (t, 1H, $J = 5.2$ Hz, H-4), 4.29 (m, 1H, H-11), 4.26 (d, 1H, $J = 4.4$ Hz, H-9), 4.25 (m, 1H, H-5), 3.96 (dd, 1H, $J = 6.4$, 8.4 Hz, H-6a), 3.95 (s, 1H, H-7), 3.91 (dd, 1H, $J = 2.0$, 8.8 Hz, H-12a), 3.90 (s, 2H, H-1), 3.76 (m, 2H, $HNCH_2CH_2O$), 3.57 (t, 1H, $J = 8.4$ Hz, H-6b), 3.47 (t, 1H, $J = 8.8$ Hz, H-12b), 3.15 (m, 1H, $HNCH_aH_bCH_2O$), 2.98 (m, 1H, $HNCH_aH_bCH_2O$); ^{13}C NMR (100 MHz, D_2O): δ 103.7 (C-8), 85.5 (C-3), 84.5 (C-9), 82.2 (C-7), 81.1 (C-2), 81.1 (C-4), 81.0 (C-10), 74.7 (C-1), 72.0 (C-11), 71.1 (C-6), 70.8 (C-12), 70.7 (C-5), 66.2 (OCH_2CH_2NH), 44.4 (OCH_2CH_2NH); HRMS: calcd for $C_{14}H_{21}NO_8$: 331.1267. Found: 332.1341 $[M+H]^+$, 354.1156 $[M+Na]^+$.

4.3.2. (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*,5″*R*)-Spiro[6,3′,6′-trihydroxy-octahydro[2,3′]bi[furo[3,2-*b*]furan]-3,2″-[5″-phenoxymethyl-1″,3″-oxazolidine] 5. Separation by chromatography with elution of chloroform/methanol (6/1). Mp 121–123 °C, $[\alpha]_D^{20} = +58.0$ (*c* 0.34, $CHCl_3$); IR (KBr): 3407, 3285, 2925, 2880, 1632, 1596, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 2H, H-3 and H-5, Ph), 6.98 (t, 1H, $J = 7.4$ Hz, H-4, Ph), 6.92 (d, 2H, $J = 8.4$ Hz, H-2 and H-6, Ph), 4.67 (t, 1H, $J = 4.4$ Hz, H-10), 4.65 (d, 1H, $J = 6.4$ Hz, H-3), 4.45 (t, 1H, $J = 6.0$ Hz, H-4), 4.39 (m, 1H, $CHCH_2OPh$), 4.31 (dd, 1H, $J = 6.0$, 11.6 Hz, H-11), 4.26 (d, 1H, $J = 4.4$ Hz, H-9), 4.18 (d, 1H, $J = 10.6$ Hz, H-1a), 4.14 (dd, 1H, $J = 5.2$, 9.6 Hz, H-5), 4.13 (d, 1H, $J = 10.6$ Hz, H-1b), 4.08 (dd, 1H, $J = 5.6$, 9.6 Hz, CH_aH_bO–Ph), 4.08 (s, 1H, H-7), 4.00 (dd, 1H, $J = 6.4$, 9.4 Hz, H-12a), 3.98 (dd, 1H, $J = 5.6$, 9.6 Hz, CH_aH_bO–Ph), 3.93 (dd, 1H, $J = 4.8$, 9.4 Hz, H-6b), 3.85 (dd, 1H, $J = 4.8$, 9.4 Hz, H-6a), 3.64 (dd, 1H, $J = 6.4$, 9.4 Hz, H-12b), 3.30 (dd, 1H, $J = 7.2$, 12.0 Hz, $HNCH_aH_bCH$), 3.22 (dd, 1H, $J = 4.0$, 12.0 Hz, $HNCH_aH_bCH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3 (C-1 Ph), 129.5 (C-3,5 Ph), 121.3 (C-4 Ph), 114.5 (C-2,6 Ph), 105.1 (C-8), 85.3 (C-9), 84.0 (C-3), 82.1 (C-7), 81.6 (C-4), 81.2 (C-10), 79.5 (C-2), 77.2 (C-1), 75.5 ($CHCH_2OPh$), 75.3 (C-12), 73.7 (C-6), 72.7 (C-5), 70.8 (C-11), 68.5 ($–CH_2OPh$), 47.3 ($CHCH_2NH$); HRMS: calcd for $C_{21}H_{27}NO_9$: 437.1686. Found: 438.1767 $[M+H]^+$.

4.3.3. (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*,4″*S*,5″*R*)-Spiro[6,3′,6′-trihydroxy-octahydro[2,3′]bi[furo[3,2-*b*]furan]-3,2″-[4″-methoxycarbonyl-5″-methyl-1″,3″-oxazolidine] 6. Separation by chromatography with elution of chloroform/methanol (7/1). Mp 98–100 °C, $[\alpha]_D^{20} = +77.0$ (*c* 0.266, CH_3OH); IR (KBr): 3503, 3390, 3275, 2972, 2932, 2874, 1742 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 4.62 (d, 1H, $J = 5.2$ Hz, H-3), 4.32 (t, 1H, $J = 4.0$ Hz, H-10), 4.13 (t, 1H, $J = 5.2$ Hz, H-4), 4.08 (m, 1H, H-11), 4.06 (d, 1H, $J = 4.0$ Hz, H-9), 4.00 (m, 1H, H-5), 3.88 (d, 1H, $J = 10.0$ Hz, H-1a), 3.81 (s, 1H, H-7), 3.77 (m, 1H, H-12a), 3.77 (d, 1H, $J = 8.0$ Hz, H-6a), 3.76 (m, 1H, CH_3CHO), 3.74 (d, 1H, $J = 10.0$ Hz, H-1b), 3.69 (s, 3H, CH_3O), 3.54 (t, 1H, $J = 8.0$ Hz, H-6b), 3.47 (dd, 1H, $J = 8.8$, 12.0 Hz, $NHCHCOO$), 3.31 (t, 1H, $J = 8.8$ Hz, H-12b), 1.27 (d, 1H, $J = 6.0$ Hz, CH_3CH); ^{13}C NMR (100 MHz, D_2O): δ 104.5 (C-8), 85.2 (C-9), 85.2 (C-3), 81.0 (C-10), 80.7 (C-2), 80.7 (C-4), 80.4 (C-7), 76.4 (CH_3CHO–), 74.9 (C-1), 72.6 (C-11), 72.0 (C-6), 71.2 (C-12), 71.2 (C-5), 65.2 ($NHCHCOO$), 52.4 (OCH_3), 19.6 ($CHCH_3$); HRMS: calcd for $C_{17}H_{25}NO_{10}$: 403.1478. Found: 404.1563 $[M+H]^+$ and 426.1392 $[M+Na]^+$, 442.1144 $[M+K]^+$.

4.3.4. (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*,5″*R*,6‴*R*,7‴*R*,8‴*S*)-Dispiro[6,3′,6′-trihydroxy-octahydro[2,3′]bi[furo[3,2-*b*]-furan]-3,2″-[1″,3″-oxazolidine]-5″,3‴-[6‴-hydroxy-tetrahydro-furo[3,2-*b*]furan] 7. Separation by chromatography with elution of chloroform/methanol (7/1). Mp 112–114 °C, $[\alpha]_D^{20} = +140.9$ (*c* 0.34, CH_3OH), IR (KBr): 3428, 2945, 2877, 1413 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 4.66 (t, 1H, $J = 4.6$ Hz, H-4), 4.59 (d, 1H, $J = 5.2$ Hz, H-9), 4.51 (t, 1H, $J = 4.5$ Hz, H-4′), 4.35 (m, 4H, H-3, H-5, H-10, H-5′), 4.25 (m, 1H, H-11), 4.25 (d, 1H, $J = 4.0$ Hz, H-3′), 4.0 (s, 1H, H-7), 3.98 (dd, 1H, $J = 6.2$, 8.4 Hz, H-6a), 3.97 (d, 1H, $J = 8.4$ Hz, H-1′a), 3.97 (d, 1H, $J = 10.7$ Hz, H-1a), 3.95 (t, 1H, $J = 8.4$ Hz, H-6b), 3.81 (d, 1H,

$J = 10.7$ Hz, H-1b), 3.76 (d, 1H, $J = 8.8$ Hz, H-12a), 3.73 (d, 1H, $J = 8.4$ Hz, H-1′b), 3.54 (t, 1H, $J = 8.8$ Hz, H-12b), 3.49 (t, 2H, $J = 8.4$ Hz, H-6′), 3.01 (d, 1H, $J = 12.3$ Hz, H-7′b), 2.98 (d, 1H, $J = 12.3$ Hz, H-7′a); ^{13}C NMR (100 MHz, D_2O): δ 104.7 (C-8), 88.3 (C-2′), 86.0 (C-9), 84.9 (C-3), 84.4 (C-3′), 82.4 (C-4), 81.7 (C-4′), 81.2 (C-10), 81.1 (C-7), 81.0 (C-2), 74.8 (C-1), 72.2 (C-1′), 72.1 (C-5), 71.9 (C-5′), 71.8 (C-6′), 70.9 (C-6), 70.9 (C-12), 70.8 (C-11), 51.9 (C-7′); HRMS: calcd for $C_{19}H_{27}NO_{11}$: 445.1584. Found: 446.1663 $[M+H]^+$ and 468.1465 $[M+Na]^+$.

4.3.5. (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*,4″*R*,5″*R*,3‴a*S*,6‴*R*,6‴a*R*)-Dispiro[6,3′,6′-trihydroxy-octahydro[2,3′]bi[furo-[3,2-*b*]furan]-3,2″-[4″-methyl-1″,3″-oxazolidine]-5″,3‴-[6‴-hydroxy-tetrahydro-furo[3,2-*b*]furan] 8. Separation by chromatography with elution of chloroform/methanol (7/1). Mp 184–185 °C, $[\alpha]_D^{20} = +98.0$ (*c* 0.22, CH_3OH); IR (KBr): 3422, 2945, 2879, 1643 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 4.65 (m, 1H, H-4), 4.64 (d, 1H, $J = 5.2$ Hz, H-9), 4.51 (t, 1H, $J = 4.4$ Hz, H-4′), 4.39 (m, 1H, H-5′), 4.37 (m, 3H, H-3, H-5, H-10), 4.30 (m, 1H, H-11), 4.28 (d, 1H, $J = 4.0$ Hz, H-3′), 4.06 (d, 1H, $J = 10.8$ Hz, H-1a), 4.02 (s, 1H, H-7), 3.99 (d, 1H, $J = 8.4$ Hz, H-6′a), 3.98 (dd, 1H, $J = 6.8$, 8.8 Hz, H-12a), 3.96 (dd, 1H, $J = 6.8$, 8.8 Hz, H-6a), 3.91 (d, 1H, $J = 9.6$ Hz, H-1′a), 3.82 (d, 1H, $J = 10.8$ Hz, H-1b), 3.59 (d, 1H, $J = 9.6$ Hz, H-1′b), 3.57 (t, 1H, $J = 8.4$ Hz, H-6′b), 3.55 (t, 1H, $J = 8.8$ Hz, H-12b), 3.51 (t, 1H, $J = 8.8$ Hz, H-6b), 3.30 (q, 1H, $J = 6.4$ Hz, H-7′), 1.19 (d, 3H, $J = 6.8$ Hz, H-8′); ^{13}C NMR (100 MHz, D_2O): δ 103.1 (C-8), 89.8 (C-2′), 86.1 (C-9), 85.0 (C-3′), 84.0 (C-3), 81.2 (C-4), 80.8 (C-4′), 80.6 (C-10), 80.5 (C-7), 80.4 (C-2), 74.1 (C-1), 71.9 (C-5), 71.8 (C-5′), 71.2 (C-6′), 70.7 (C-12), 70.6 (C-6), 70.6 (C-11), 68.8 (C-1′), 57.2 (C-7′), 11.98 (C-8′); HRMS: calcd for $C_{20}H_{29}NO_{11}$: 459.1741. Found: 482.1638 $[M+Na]^+$.

4.4. (1*S*)-(1,4:3,6-Dianhydro-D-mannitol-2-yl)-2-nitromethyl-1,4:3,6-dianhydro-D-glucitol or (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*)-3,6,3′,6′-tetrahydroxy-3-nitromethyl-octahydro-[2,3′]bi[furo[3,2-*b*]furan] 9

A mixture of **3** (1.44 g, 5 mmol), nitromethane (0.5 mL), catalytic amount of Et_3N, and EtOH (20 mL) was heated at reflux temperature with stirring, After 1 h, the mixture was evaporated, and then crystallized with EtOH, to afford the compound **9** (1.66 g, 95%). Mp 160–162 °C, $[\alpha]_D^{20} = +92.9$ (*c* 1.06, CH_3OH); IR (KBr): 3405, 2942, 2849, 1554 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 4.95 (d, 1H, $J = 13.6$ Hz, CH_2NO_2), 4.85 (d, 1H, $J = 13.6$ Hz, CH_2NO_2), 4.60 (t, 1H, $J = 4.0$ Hz, H-10), 4.59 (d, 1H, $J = 5.4$ Hz, H-3), 4.48 (d, 1H, $J = 4.0$ Hz, H-9), 4.31 (m, 1H, H-11), 4.26 (t, 1H, $J = 5.4$ Hz, H-4), 4.17 (m, 1H, H-5), 3.91 (s, 2H, H-1), 3.89 (dd, 1H, $J = 6.4$, 8.8 Hz, H-6a), 3.86 (dd, 1H, $J = 6.8$, 8.8 Hz, H-12a), 3.78 (s, 1H, H-7), 3.50 (t, 1H, $J = 8.8$ Hz, H-6b), 3.45 (t, 1H, $J = 8.8$ Hz, H-12b); ^{13}C NMR (100 MHz, D_2O): δ 86.6 (C-9), 85.7 (C-3), 83.7 (C-7), 81.6 (C-8), 80.9 (C-10), 80.1 (C-4), 79.8 (C-2), 76.0 (CH_2NO_2), 74.1 (C-1), 71.6 (C-11), 71.1 (C-6), 70.5 (C-12), 70.1 (C-5). HRMS: calcd for $C_{13}H_{19}NO_{10}$: 349.1009. Found: 350.1099 $[M+H]^+$ and 372.0912 $[M+Na]^+$.

4.5. (1*S*)-(1,4:3,6-Dianhydro-D-mannitol-2-yl)-2-amino-methyl-1,4:3,6-dianhydro-D-glucitol or (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*)-3-aminomethyl-3,6,3′,6′-tetrahydroxy-octahydro[2,3′]bi[furo[3,2-*b*]furan]) 10

Nitromethyl sugar **9** (1.05 g, 3 mmol) was dissolved in EtOH (120 mL), to which 10% Pd–C catalyst (0.105 g, 10%) was added. The mixture was hydrogenated under 50 psi at 50 °C with shaking for 8 h. Subsequent filtration and evaporation of the mixture gave allowed product **10** (0.85 g, 89%). Mp 76–78 °C, $[\alpha]_D^{20} = +86.5$ (*c* 0.32, CH_3OH); IR (KBr): 3367, 2946, 2872 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 4.66 (d, 1H, $J = 4.4$ Hz, H-3), 4.65 (t, 1H, $J = 4.4$ Hz, H-10), 4.32 (m, 1H, H-11), 4.31 (t, 1H, $J = 4.4$ Hz, H-4), 4.28 (d, 1H, $J = 4.4$ Hz, H-9), 4.24 (m, 1H, H-5), 3.95 (s, 2H, H-1), 3.94 (m, 1H, H-6a), 3.87 (s, 1H, H-7), 3.85 (dd, 1H, $J = 6.4$, 9.2 Hz, H-12a), 3.58 (t, 1H, $J = 8.4$ Hz, H-6b), 3.52 (dd, 1H, $J = 7.2$, 9.2 Hz, H-12b), 3.28 (s, 2H, CH_2NH_2); ^{13}C NMR (100 MHz, D_2O): δ 88.1 (C-9), 85.9 (C-3), 85.3 (C-7), 80.9 (C-10), 80.8 (C-6), 80.4 (C-8), 79.7 (C-2), 74.7 (C-1), 71.9 (C-11), 71.8 (C-6), 71.7 (C-12), 70.5 (C-5), 41.4 (CH_2NH_2). HRMS: calcd for $C_{13}H_{21}NO_8$: 319.1267. Found: 320.1341 $[M+H]^+$ and 342.1175 $[M+Na]^+$.

4.6. (2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*)-Spiro[6‴-hydroxy-tetrahydro-furo[3,2-*b*]furan]-3‴,2-[6,4′,4″-trihydroxy-5-methoxycarbonyl-furo[2″,3″:4′,5′]furo[2,3-*c*]pyran-5-ene] 11

C-12 Sugar **3** (118 mg, 0.41 mmol) was dissolved in MeOH (5 mL), to which dimethyl malonate (70 mg, 0.55 mmol) and 1 mL 0.55 M solution of NaOMe in methanol were added. The mixture was stirred at room temperature for 12 h, followed by filtration, giving compound **11** as a white solid (100 mg, 63%): mp 210–212 °C, $[\alpha]_D^{20} = +81.0$ (*c* 0.218, H_2O); IR (KBr): 3422, 2951, 2893, 1688, 1589, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.83 (d, 1H, $J = 4.8$ Hz, H-3), 4.27 (m, 1H, H-4), 4.26 (m, 1H, H-9), 4.07 (m, 1H, H-10), 4.03 (m, 2H, H-5, H-11), 4.00 (d, 1H, $J = 8.8$ Hz, H-1a), 3.80 (t, 1H, $J = 7.6$ Hz, H-12a), 3.69 (dd, 1H, $J = 7.2$, 8.0 Hz, H-6a), 3.60 (s, 1H, H-7), 3.56 (d, 1H, $J = 8.8$ Hz, H-1b), 3.43 (s, 3H, CH_3), 3.39 (m, 1H, H-12b), 3.35 (m, 1H, H-6b); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.1 (C-15, C=O), 164.7 (C-14), 88.1 (C-9), 83.3 (C-2), 82.0 (C-4), 81.0 (C-10), 80.5 (C-7), 79.4 (C-13), 79.3 (C-3), 73.7 (C-1), 73.1 (C-11), 72.7 (C-8), 72.4 (C-5), 71.5 (C-6), 71.1 (C-12), 49.0 (C-16, CH_3); HRMS: calcd for $C_{16}H_{20}O_{11}$: 388.1006. Found: 411.0885 $[M+Na]^+$, 427.0630 $[M+K]^+$.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-622930, 622931, 622932, and 622933. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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