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One-Pot Conversion of Carbohydrates into Pyrrole-2-carbaldehydes as Sustainable Platform Chemicals

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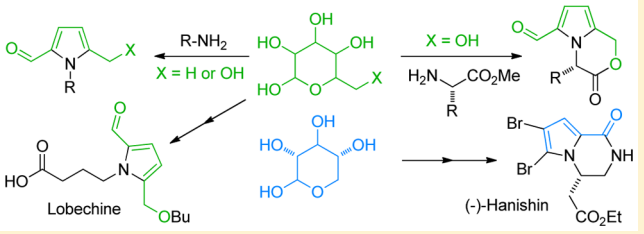
Supporting Information

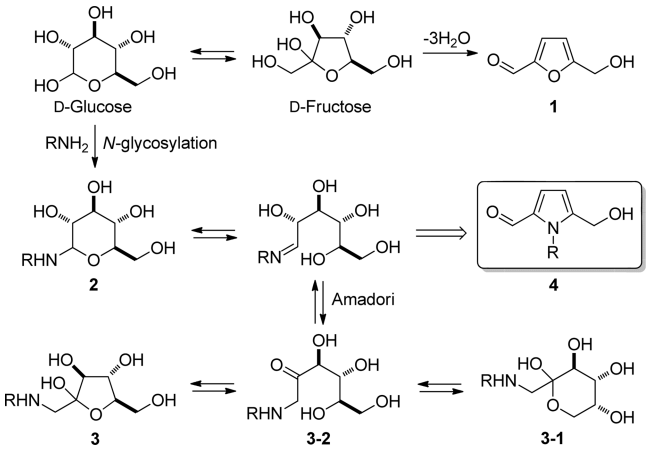
ABSTRACT: A practical conversion method of carbohydrates into *N*-substituted 5-(hydroxymethyl)pyrrole-2-carbaldehydes (pyrralines) was developed by the reaction with primary amines and oxalic acid in DMSO at 90 °C. Further cyclization of the highly functionalized pyrralines afforded the pyrrole-fused poly-heterocyclic compounds as potential intermediates for drugs, food flavors, and functional materials. The mild Maillard variant of carbohydrates and amino esters in heated DMSO with oxalic acid expeditiously produced the pyrrole-2-carbaldehyde skeleton, which can be concisely transformed into the pyrrole alkaloid natural products, 2-benzyl- and 2-methylpyrrolo[1,4]oxazin-3-ones **8** and **9**, lobechine **10**, and (−)-hanishin **11** in 23−32% overall yields from each carbohydrate.



INTRODUCTION

Searching for an efficient transformation method of biomass into platform chemicals is an imperative and timely task for securing sustainable chemical and energy materials. The conversion of carbohydrates into 5-(hydroxymethyl)-2-furfural (**1**, 5-HMF) has been extensively studied in this sense (Scheme 1) because this highly important platform chemical can be transformed into biofuels and useful commodity chemicals.[1] Fructose is most efficiently converted into 5-HMF among all the naturally occurring carbohydrates because it is the furanoid form that is directly transformed into 5-HMF upon removal of three water molecules. Glucose should be converted into fructose first by the acid- or base-catalyzed process known as the Lobry de Bruyn−Alberda van Ekenstein transformation.[2] Because the next dehydration step is catalyzed by acids, one-pot conversion of D-glucose into 5-HMF has been practiced under acidic conditions utilizing metal chloride Lewis acids,[3] Brönsted acids,[4] solid acids,[5] and acidic ionic liquids.[6] However, these conversion methods generally suffered from low yields due to the strongly acidic conditions required for the aldose−ketose transformation. It was envisioned that the carbohydrate conversion would be facilitated or at least diversified by the presence of a nitrogen substituent at the anomeric carbon (see glycosylamine **2**). Amadori and Maillard reactions are well-known carbohydrate conversion reactions with amines. However, Amadori rearrangement of glycosylamine **2** produced the equilibrium mixture of furanose **3**, pyranose **3-1**, and the open chain isomer **3-2** in solution.[7] Furthermore, the Maillard reaction, browning of sugars with amines (or amino acids) at 200 °C or higher, is impractical, producing a complex mixture of poorly characterized molecules presumably due to the equilibrium among the various reaction pathways and extensive decomposition of the intermediate compounds.[8]

Scheme 1. Conversion of D-Glucose into 5-HMF 1, *N*-glycosylamine 2, Amadori Products 3, and Pyrraline 4



We carefully investigated the reaction of D-glucose with *N*-benzylamine for the synthetic purpose of stable platform chemicals and found that 1-benzyl-5-(hydroxymethyl)pyrrole-2-carbaldehyde **4a**, named benzylpyrraline (R = benzyl in **4**), was a reproducible product under the mild nonaqueous acidic variant of the Maillard reaction. Identification and detection of pyrralines **4**, which are formed as the advanced *N*-glycosylation end products in vivo, had been studied to understand the correlations with aging, diabetes, lipid peroxidation, and Alzheimer's disease.[9] A couple of chemical syntheses of

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butylpyrraline **4b** from D-glucose had been reported, but the yield never exceeded 3.4%.[9a,10] We were able to develop a practical conversion method of carbohydrates into diverse alkyl- and aryl-substituted pyrrole-2-carbaldehydes **4** as platform chemicals, which may lead to various important drugs, food flavors, and functional materials. Detailed studies on the one-pot conversion of carbohydrates into pyrrole-2-carbaldehydes **4**, its mechanism, and application to the total syntheses of several pyrrole alkaloid natural products are herein disclosed.

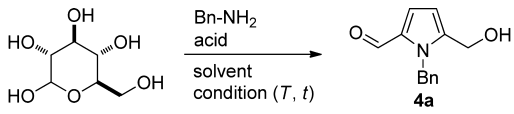
RESULT AND DISCUSSION

The variables of acid, solvent, reaction temperature, and time were screened to maximize the formation of benzylpyrraline **4a** (Table 1). First, polar aprotic solvent, DMSO was utilized with oxalic acid considering its dehydrating efficacy and the polarity of glucose.[11] The reaction of D-glucose and *N*-benzylamine was carried out in the presence of 1.5 equiv of oxalic acid in DMSO at 80 °C for 1 h to produce **4a** in 19% yield (entry 1). An improved yield (27%) was observed at 100 °C (entry 2), the effective temperature for glucose dehydration,[3a,b] but a significant amount of humins was also observed to give a viscous reaction mixture. A further increase of the yield of **4a** up to 40% was attained by decreasing the amount of oxalic acid to 1 equiv and reducing the reaction time and temperature to 0.5 h at 90 °C, respectively (entry 3–6). Further decreasing the amount of oxalic acid (0.5 equiv) and changing the solvent (DMF) were not effective in improving the yield of **4a** (entries 7 and 8).

It seems that oxalic acid (pK_a 1.25) provides the optimal acidity for dehydration in the presence of the basic amino functional groups. Other Brönsted acids tested were not as effective as oxalic acid: acetic acid (pK_a 4.7) allowed the formation of **4a** in 8% yield, sulfuric acid (pK_a −3.0) in 16% yield, and trifluoroacetic acid (pK_a 0.23) in 28% yield all in DMSO at 90 °C for 0.5 h (entries 9–11). Even though Lewis acid $CrCl_2$ in imidazolium ionic liquid was reported to be an excellent condition for glucose dehydration,[3a] only 5% yield of **4a** was obtained in this condition (entry 12). Additional use of *N*-heterocyclic carbene ligand to $CrCl_2$ improved the yield,[3b] but not higher than 24% (entry 13).

This reaction was clean (except for some humins), and the organic extract exhibited one major spot in TLC. Simple filtration through silica gel produced the pure pyrraline. We proved the efficiency of this one-pot conversion by a practical-scale reaction: heating a solution of 7.21 g (40 mmol) of D-glucose and 4.29 g (40 mmol) of *N*-benzylamine with 3.60 g of oxalic acid (40 mmol) in DMSO (30 mL) at 90 °C for 0.5 h produced 3.32 g (15.4 mmol) of **4a** in 39% yield after purification.

The mechanism of the formation of pyrralines **4** was proposed in Scheme 2. The Maillard reaction of D-glucose in aqueous solution was proposed to proceed through 3-deoxyglucosone.[9a,12] It would be reasonable to propose the imine derivative **C** of 3-deoxyglucosone as a key intermediate for this mild, nonaqueous version of the Maillard reaction. The reaction is undoubtedly initiated from *N*-glycosylation of amine to form **2**. The ring-opened enamine tautomer **B** from **A** pushes electrons to remove the protonated 3-hydroxyl group, thereby producing the key intermediate **C**. The enamine **D** formed by the addition of another amine may undergo cyclization to **E**, in which nitrogen pushes electrons to facilitate the removal of the protonated 4-hydroxyl group and the aromatization to pyrrole. Hydrolysis of the 2-iminyl group produces pyrraline **4** and regenerates amine.



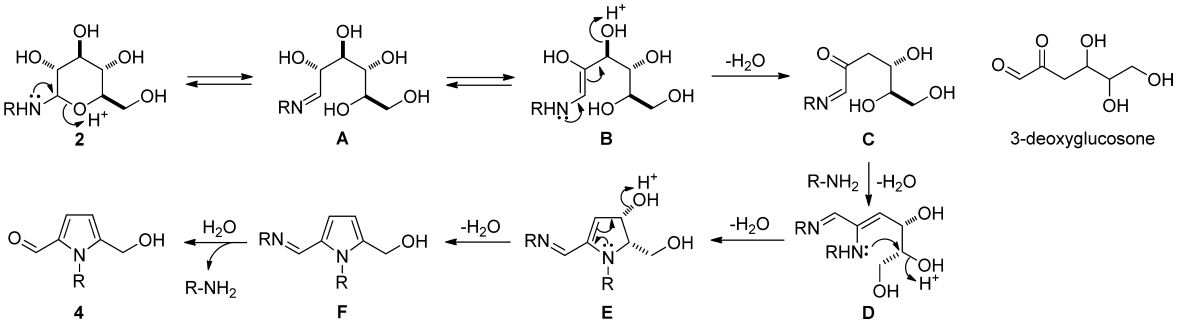
(7.2 g, 40 mmol) condition of entry 5 (3.32 g, 15.4 mmol, 39%)

Table 1. Study on the Conversion of D-Glucose into Benzylpyrraline 4a

entry[a]	acid (equiv)	solvent	T (°C)	time (h)	yield[b] (%)
1	$(COOH)_2$ (1.5)	DMSO	80	1	19
2	$(COOH)_2$ (1.5)	DMSO	100	1	27
3	$(COOH)_2$ (1.0)	DMSO	100	1	32
4	$(COOH)_2$ (1.0)	DMSO	100	0.5	35
5	$(COOH)_2$ (1.0)	DMSO	90	0.5	40
6	$(COOH)_2$ (1.0)	DMSO	90	1	39
7	$(COOH)_2$ (0.5)	DMSO	90	1	25
8	$(COOH)_2$ (1.0)	DMF	90	1	14
9	AcOH (1.0)	DMSO	90	0.5	8
10	CF_3CO_2H (1.0)	DMSO	90	0.5	28
11	H_2SO_4 (1.0)	DMSO	90	0.5	16
12	$CrCl_2$ (1.0)	EMIMCl[c]	90	0.5	5
13	NHC/Cr (1.0)[d]	BMIMCl[e]	90	0.5	24

[a]All reactions were performed with 0.72 g (4.0 mmol) of D-glucose and 0.44 mL (4.0 mmol) of benzylamine in 1.3 M solution of the designated dry solvent (3 mL) unless otherwise stated. [b]Isolated yield of 1-benzyl-5-(hydroxymethyl)-1*H*-pyrrole-2-carbaldehyde (**4a**) after column chromatographic purification. [c]1-Ethyl-3-methylimidazolium chloride (2.0 g). [d]Prepared in situ by the reaction of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (1.0 equiv), *t*-BuOK (1.0 equiv), and $CrCl_2$ (1.0 equiv). [e]1-Butyl-3-methylimidazolium chloride (2.0 g).

Scheme 2. Proposed Mechanism of the Formation of Pyrraline 4 from Glycosylamine 2



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The configuration of the hydroxyl groups is not important for dehydration due to the participation of the lone pair electrons on nitrogen (**B** and **E**). D-Galactose and D-mannose also produced benzylpyrraline **4a** in 37% and 39% yield, respectively, under the above-optimized condition (entry 5, Table 1). Similar yields of pyrrole **14** were obtained from D-ribose and D-xylose (vide infra). It is not necessary to rigorously dry the solvent. The original Maillard conditions (at 200 °C or higher) were too harsh to give pyrralines in practical yields, and the equilibrium for the dehydration of carbohydrates in aqueous conditions was not favorable. On the other hand, the oxalic acid-promoted dehydration of carbohydrates was successful in the presence of the amine functional groups, especially in DMSO at 90 °C.

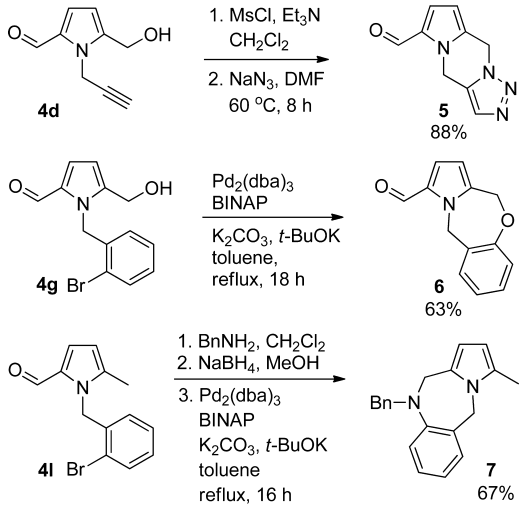
The generality of the carbohydrate conversion into pyrrole-2-carbaldehydes **4** was demonstrated by the reaction of D-glucose and L-rhamnose with various primary amines under the above-optimized conditions of using 1 equiv of oxalic acid in DMSO at 90 °C for 30 min (Table 2). Aliphatic amines such as *n*-butyl-, allyl-, propargyl-, 3-hydroxypropyl-, and phenethylamines reacted with D-glucose to produce the corresponding *N*-substituted 5-(hydroxymethyl)pyrrole-2-carbaldehydes **4b–f** in 21–48% yield (entries 1–5). 3-Hydroxypropylamine gave the lowest yield for **4e** (21%), which contained terminal hydroxyl groups susceptible to further reactions (entry 4). Anilines, regardless of the electronic nature of the substituent, produced the corresponding *N*-phenyl-5-hydroxymethylpyrrole-2-carbaldehydes **4h–j** in a relatively low 21–27% yield range (entries 7–9). L-Rhamnose also reacted with *n*-butylamine to give the corresponding pyrrole-2-carbaldehyde **4k** in 35% yield (entry 10). The highest yields of pyrrole-2-carbaldehydes **4g** (51%) and **4l** (53%) from each carbohydrate were obtained for *o*-bromobenzylamine, an aliphatic amine with the stabilized electron-deficient aromatic group (entries 6 and 11).

Table 2. Conversion of Carbohydrates into Diversely *N*-Substituted Pyrrole-2-carbaldehydes 4

entry	carbohydrate (X)	amines (*R*)-NH_2		yield of **4** (%)
1	D-glucose (OH)	**b**	Bu	36
2		**c**	allyl	29
3		**d**	propargyl	48
4		**e**	$HO(CH_2)_3$	21
5		**f**	$C_6H_5(CH_2)_2$	33
6		**g**	*o*-$BrC_6H_4CH_2$	51
7		**h**	Ph	21
8		**i**	*p*-MeC_6H_4	25
9		**j**	*p*-CNC_6H_4	27
10	L-rhamnose (H)	**k**	Bu	35
11		**l**	*o*-$BrC_6H_4CH_2$	53

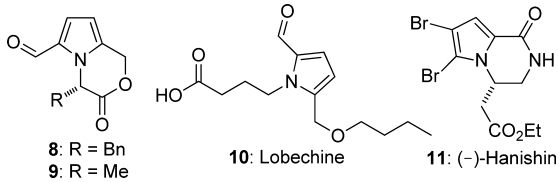
We further demonstrated the utility of pyrrole-2-carbaldehydes **4** as platform chemicals by subsequent cyclization to poly-heterocyclic compounds (Scheme 3). Activation of the 5-hydroxymethyl group of **4d** by a methanesulfonyl (Ms) group and then nucleophilic substitution by sodium azide in DMF at 60 °C induced the intramolecular azide cycloaddition to form pyrrolotriazolopiperazine **5** in 88% yield.[13,14] Application of the modified Buchwald's condition for the palladium-catalyzed amination of aryl halides [$Pd_2(dba)_3$, BINAP, *t*-BuOK, K_2CO_3, toluene][15] to **4g** produced pyrrolo[1,4]oxazepine **6** in 63% yield through the intramolecular etherification. Reductive benzyl amination of the 2-formyl group of **4l** (78% yield), followed by the intramolecular Buchwald's amination with aryl bromide (86% yield), produced pyrrolo[1,4]diazepine **7**. Pyrrole-fused six- and seven-membered poly-heterocyclic compounds were efficiently prepared in this way.

Scheme 3. Transformation of Selected Pyrrole-2-carbaldehydes into Poly-heterocyclic Compounds



We then applied this mild variant of the Maillard reaction to the concise total syntheses of the pyrrole alkaloid natural products, pyrrolo[1,4]oxazin-3-ones **8** (R = Bn) and **9** (R = Me), lobechine **10**, and (−)-hanishin **11**. Pyrrole alkaloid natural products exhibit various biological effects such as sedative, anti-inflammatory, pain-relieving, hepatoprotective, and immunostimulatory activities, which leads to their hosting plants being used as substances of traditional folk medicines.[16] Pyrrolo[1,4]oxazin-3-ones **8** (R = Bn) and **9** (R = Me) and lobechine **10** were isolated from the plants of *Celastrus orbiculatus*,[16a] *Capparis spinosa*,[17] and *Lobelia chinese*,[18] respectively (Scheme 4). (−)-Hanishin **11**, the brominated pyrrole alkaloid, was isolated from the marine sponge *Acanthella carteri* and shows cytotoxicity against NSCLC-N6 human non-small-cell-lung carcinoma.[19]

Scheme 4. Pyrrole Alkaloid Natural Products: Pyrrolo[1,4]oxazin-3-ones 8 (2-benzyl) and 9 (2-methyl), Lobechine 10, and (−)-Hanishin 11



These pyrrole alkaloids have interesting structural features in common, namely a carbonyl group at the 2-position and the integrated amino acid portion. It was thus conceived that these pyrrole natural products might be the enzymatic glycosylation end products of amino acids and that those would be chemically synthesized by the reaction between carbohydrates

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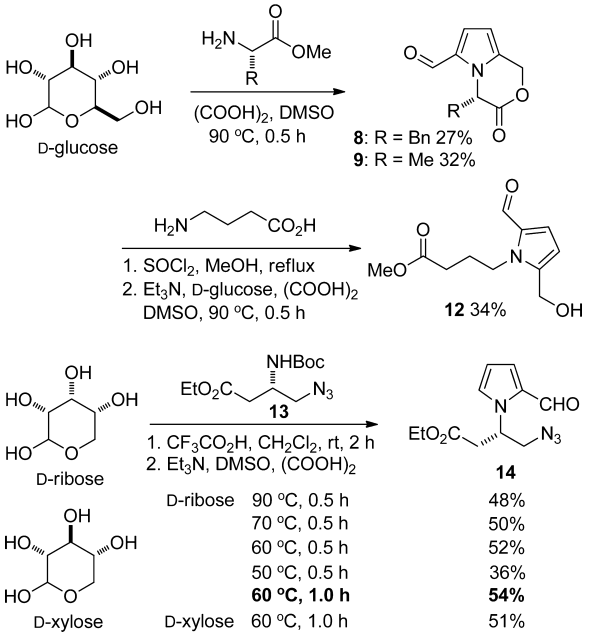
and amino acids. The utility and general applicability of the above practical preparative variant of the Maillard reaction was demonstrated for the synthesis of various pyrrole-2-carbonyl compounds (Scheme 5), which were further applied to the concise total syntheses of the pyrrole alkaloid natural products **8**–**11**.

Scheme 5. Maillard Reaction of Carbohydrates and Various Amino Esters to Pyrrole-2-carbaldehydes

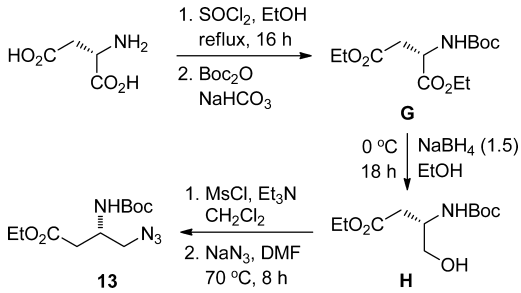


The reaction of D-glucose with α-amino acid methyl esters under the above-optimized conditions (1 equiv of oxalic acid in DMSO at 90 °C for 0.5 h) directly produced the pyrrolo-[1,4]oxazin-3-one skeleton, in which the 5-(hydroxymethyl)-pyrrole-2-carbaldehydes underwent intramolecular lactonization with the amino ester part. Even though roasting D-glucose with α-amino acid at 200–250 °C had been reported to produce the above compound, it came together with various kinds of aroma products, and it is impractical to obtain pyrrolo[1,4]oxazin-3-ones by the conventional Maillard reaction (maximum 0.5% yield).[20] The natural product **8** possessing sedative and anti-inflammatory activities was synthesized from D-glucose in 27% yield when L-phenylalanine methyl ester was used under the above-optimized condition. The methyl ester of L-alanine efficiently promoted one-pot conversion of D-glucose into **9** in 32% yield, whereas the total synthesis of **9** has been reported in six steps with overall 17% yield.[16b]

γ-Aminobutyric acid (GABA) methyl ester, which was generated in situ by the reaction of GABA and thionyl chloride in refluxing MeOH,[16c] followed by neutralization with Et_3N, efficiently produced the corresponding pyrraline **12** in 34% yield by the reaction with D-glucose under the above conditions (1 equiv of oxalic acid in DMSO at 90 °C for 0.5 h). D-Ribose also reacted with the amino ester, derived from *N*-Boc-protected β-amino ester **13** under the above conditions, to give the corresponding pyrrole-2-carbaldehyde **14** in 48% yield. Tuning the reaction conditions allowed the highest 54% yield at 60 °C for 1 h. D-Xylose was also effective in producing **14** in 51% yield under these Maillard conditions. The configuration of the 3-hydroxyl group is not important for dehydration as described in the above mechanism (Scheme 2). It is worth mentioning that an azido group in **14** and its precursors are compatible in these Maillard conditions, which may undergo further useful transformations by click chemistry.

The required chiral β-amino ester **13** for pyrrole-2-carbaldehyde **14** was prepared from L-aspartic acid in five steps, 25% overall yield, by the modification of the reported procedure (Scheme 6).[21] Compound **G**,[21a] which was routinely

Scheme 6. Preparation of Chiral β-Aminoester 13 from L-Aspartic Acid for (−)-Hanishin Synthesis

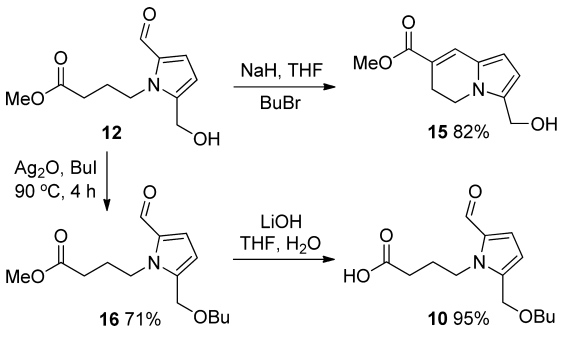


prepared by esterification ($SOCl_2$ in EtOH) and Boc-protection of L-aspartic acid, underwent the regioselective reduction of α-amino ester by $NaBH_4$ (1.5 equiv) at 0 °C for 18 h.[21b] The monoalcohol **H** was directly protected with a methanesulfonyl group to avoid the lactone formation,[21b] which was then replaced by azide in DMF at 70 °C to produce the β-amino ester **13**.

All of the reactions of carbohydrates and amino esters under the modified Maillard conditions (stoichiometric oxalic acid in heated DMSO) proceeded smoothly to give the corresponding pyrrole-2-carbaldehydes in acceptable yields with easy purification. The *S*-configuration of the amino ester was maintained during the reaction, which was evidenced by the almost identical optical rotation value (−4.7) of (−)-Hanishin synthesized from **14** (vide infra) to the reported one (−4.3).[22] The same sign but even higher optical rotation value (−86.0) was observed in the case of 2-methylpyrrolo[1,4]oxazin-3-one **9**, compared to the previously reported one (−33.3).[17]

The concise total syntheses of lobechine **10** and (−)-hanishin **11** were completed from the above pyrrole-2-carbaldehydes **12** and **14**, respectively.[22,23] Deprotonation of pyrraline **12** by NaH and reaction with butyl bromide preferentially produced the intramolecular aldol condensation product **15** of the ester instead of the desired *O*-alkylation (Scheme 7). This problem was overcome by using silver(I) oxide as a base and alkylation with butyl iodide at 90 °C

Scheme 7. Synthesis of Lobechine 10 from Pyrraline 12



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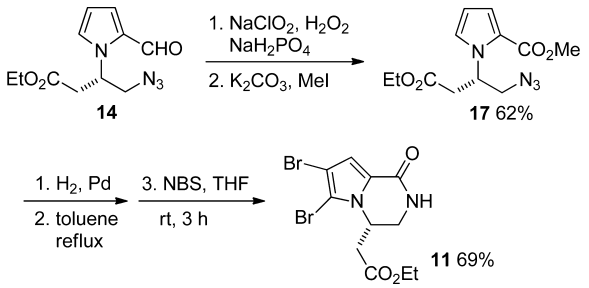
without any solvent (71% yield).[16d] Hydrolysis (95% yield) of the methyl ester by LiOH in aqueous THF produced lobechine **10** in 67% yield from pyrraline **12** (23% overall yield from D-glucose). Oxidation of pyrrole-2-carbaldehyde **14** to the corresponding carboxylic acid by sodium chlorite and hydrogen peroxide in phosphate buffer solution, followed by esterification (K_2CO_3, MeI), produced methyl pyrrole-2-carboxylate **17** in 62% yield (Scheme 8). The azide reduction by catalytic

Scheme 8. Synthesis of (−)-Hanishin 11 from Pyrrole-2-carbaldehyde 14



hydrogenation, intramolecular amidation in refluxing toluene, and the known bromination using NBS (2.0 equiv)[22,24] finally produced (−)-hanishin **11** in 69% yield (23% overall yield from D-ribose).

CONCLUSION

We developed a practical, one-pot conversion method of carbohydrates and primary amines with a stoichiometric oxalic acid in DMSO at 90 °C for 30 min, in which *N*-substituted pyrrole-2-carbaldehydes **4** were obtained in 21−53% yields. These sustainable platform chemicals from carbohydrates are highly functionalized and easily converted to the polyheterocyclic compounds such as piperazine, oxazepine, and diazepine as potential intermediates for drugs, food flavors, and functional materials. Sedative and anti-inflammatory 2-benzyl- and 2-methylpyrrolo[1,4]oxazin-3-one natural products **8** and **9** were synthesized in 27% and 32% yields by the mild variant of Maillard reaction of D-glucose with methyl esters of L-phenylalanine and L-alanine, respectively. The Maillard product of D-glucose and amino ester derived from GABA was smoothly transformed into hepatoprotective lobechine **10**; on the other hand, that of D-ribose and the *β*-amino ester derived from L-aspartic acid was efficiently converted into cytotoxic (−)-hanishin **11**.

EXPERIMENTAL SECTION

General Experimental Methods. Reactions were performed in a well-dried flask under argon atmosphere unless noted otherwise. Solvents used as reaction media were dried over predried molecular sieves (4 Å) in a microwave oven. Solvents for extraction and chromatography were reagent grade and used as received. Column chromatography was performed with silica gel 60 (70−230 mesh) using a mixture of EtOAc/hexane as eluent. ^{1}H and ^{13}C NMR spectra were, respectively, recorded on a 400 and 100 MHz NMR spectrometer in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference. High-resolution mass spectroscopy was performed using a magnetic sector analyzer. All of the new compounds were identified by ^{1}H and ^{13}C NMR, IR, and high-resolution mass spectroscopy. The identity of the known compounds was established by the comparison of their ^{1}H and ^{13}C NMR peaks with the authentic values. The NMR spectra of all the numbered compounds synthesized are included in the Supporting Information.

General Procedure for the Modified Maillard Reaction of Carbohydrate and Amine (Amino Acid). To a stirred mixture of D-glucose (0.72 g, 4.0 mmol) or L-rhamnose monohydrate (0.73 g, 4.0 mmol) and appropriate amines or L-amino acid methyl esters (4.0 mmol) in dry DMSO (3.0 mL) was added oxalic acid (0.36 g, 4.0 mmol). The mixture was heated at 90 °C for 0.5 h and cooled to room temperature. The viscous reaction mixture was diluted with water (10 mL), and the solution was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude products, which were purified by silica gel flash column chromatography (eluent 1:3 EtOAc/hexane) to give pure pyrrole-2-carbaldehydes.

1-Benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde ***(4a):*** clear thick oil, yield 40% (0.34 g, 1.60 mmol); ^{1}H NMR δ = 1.52 (br s, 1H), 4.57 (s, 2H), 5.76 (s, 2H), 6.31 (d, J = 4.0 Hz, 1H), 6.96 (d, J = 4.0 Hz, 1H), 6.97−7.02 (m, 2H), 7.20−7.32 (m, 3H), 9.57 (s, 1H) ppm; ^{13}C NMR δ = 48.5, 56.5, 110.7, 124.3, 126.1, 127.3, 128.7, 132.7, 137.7, 142.0, 179.7 ppm; IR (neat) 3328, 1637, 1484, 1408, 1374, 1295 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_{14}NO_2$ (M + H)$^+$ 216.1025, found. 216.1028.

1-Butyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde ***(4b):***[10] brown foamy solid, yield 36% (0.26 g, 1.44 mmol); mp 48−49 °C; ^{1}H NMR δ = 0.95 (t, J = 7.2 Hz, 3H), 1.33−1.44 (m, 2H), 1.57 (br s, 1H), 1.67−1.76 (m, 2H), 4.36 (t, J = 7.6 Hz, 2H), 4.68 (s, 2H), 6.22 (d, J = 4.0 Hz, 1H), 6.87 (d, J = 4.0 Hz, 1H), 9.52 (s, 1H) ppm; ^{13}C NMR δ = 13.7, 19.9, 33.5, 45.6, 56.4, 110.0, 124.3, 132.3, 141.6, 179.3 ppm; IR (neat) 3391, 1647, 1469, 1415, 1376, 1191 cm^{-1}; HRMS (CI$^+$) calcd for $C_{10}H_{16}NO_2$ (M + H)$^+$ 182.1181, found 182.1178.

1-Allyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde ***(4c):*** clear thick oil, yield 29% (0.19 g, 1.16 mmol); ^{1}H NMR δ = 1.64 (t, J = 6.0 Hz, 1H), 4.65 (d, J = 6.0 Hz, 2H), 4.83 (d, J = 16.8 Hz, 1H), 5.09−5.15 (m, 3H), 6.01 (dddd, J = 16.8, 10.0, 5.2, 4.8 Hz, 1H), 6.27 (d, J = 4.0 Hz, 1H), 6.90 (d, J = 4.0 Hz, 1H), 9.53 (s, 1H) ppm; ^{13}C NMR δ = 47.4, 56.2, 110.3, 115.7, 124.2, 132.2, 134.3, 141.9, 179.5 ppm; IR (neat) 3316, 1643, 1484, 1447, 1293 cm^{-1}; HRMS (CI$^+$) calcd for $C_9H_{12}NO_2$ (M + H)$^+$ 166.0868, found 166.0872.

5-(Hydroxymethyl)-1-prop-2-ynyl-1H-pyrrole-2-carbaldehyde ***(4d):*** white foamy solid, yield 48% (0.31 g, 1.92 mmol); mp 70−71 °C; ^{1}H NMR δ = 1.76 (br t, J = 4.8 Hz, 1H), 2.33 (t, J = 2.4 Hz, 1H), 4.79 (d, J = 4.8 Hz, 2H), 5.39 (d, J = 2.4 Hz, 2H), 6.27 (d, J = 4.0 Hz, 1H), 6.90 (d, J = 4.0 Hz, 1H), 9.56 (s, 1H) ppm; ^{13}C NMR δ = 34.6, 56.4, 72.6, 78.5, 110.9, 124.4, 131.9, 141.4, 179.9 ppm; IR (neat) 3280, 1632, 1462, 1350, 1187 cm^{-1}; HRMS (CI$^+$) calcd for $C_9H_{10}NO_2$ (M + H)$^+$ 164.0712, found. 164.0712.

5-(Hydroxymethyl)-1-(3-hydroxy-propyl)-1H-pyrrole-2-carbaldehyde ***(4e):*** brown oil, yield 21% (0.15 g, 0.84 mmol); ^{1}H NMR δ = 2.03−2.10 (m, 2H), 2.66 (br s, 2H), 3.55 (t, J = 5.6 Hz, 2H), 4.50 (t, J = 6.4 Hz, 2H), 4.69 (s, 1H), 6.27 (d, J = 4.0 Hz, 1H), 6.93 (d, J = 4.0 Hz, 1H), 9.49 (s, 1H) ppm; ^{13}C NMR δ = 33.6, 41.9, 56.0, 58.6, 111.0, 125.3, 132.5, 142.3, 179.7 ppm; IR (neat) 3221, 1627, 1470, 1402, 1363, 1293 cm^{-1}; HRMS (EI$^+$) calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0897.

5-(Hydroxymethyl)-1-phenethyl-1H-pyrrole-2-carbaldehyde ***(4f):*** clear oil, yield 33% (0.30 g, 1.32 mmol); ^{1}H NMR δ = 1. 58 (br s, 1H), 3.05 (t, J = 7.2 Hz, 2H), 4.29 (s, 2H), 4.55 (t, J = 7.2 Hz, 2H), 6.17 (d, J = 4.0 Hz, 1H), 6.93 (d, J = 4.0 Hz, 1H), 7.07−7.13 (m, 2H), 7.20−7.30 (m, 3H), 9.58 (s, 1H) ppm; ^{13}C NMR δ = 37.6, 47.5, 56.1, 110.0, 124.8, 126.6, 128.5, 129.0, 132.0, 138.3, 142.0, 179.4 ppm; IR (neat) 3333, 1646, 1497, 1409, 1376, 1185 cm^{-1}; HRMS (CI$^+$) calcd for $C_{14}H_{16}NO_2$ (M + H)$^+$ 230.1181, found. 230.1181.

1-(2-Bromobenzyl)-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde ***(4g):*** light yellow oil, yield 51% (0.60 g, 2.04 mmol); ^{1}H NMR δ = 1.56 (br s, 1H), 4.55 (s, 2H), 5.77 (s, 2H), 6.25 (d, J = 7.6 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 7.00 (d, J = 4.0 Hz, 1H), 7.08−7.16 (m, 2H), 7.57 (dd, J = 7.6, 1.6 Hz, 1H), 9.56 (s, 1H) ppm; ^{13}C NMR δ = 49.1, 56.4, 110.8, 121.6, 124.2, 126.1, 127.8, 128.6, 132.6, 132.7, 137.2, 141.9, 179.6 ppm; IR (neat) 3381, 1657, 1463, 1406, 1370, 1218 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_{13}BrNO_2$ (M + H)$^+$ 294.0130, found 294.0125.

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*5-(Hydroxymethyl)-1-phenyl-1H-pyrrole-2-carbaldehyde (**4h**):* brown oil, yield 21% (0.17 g, 0.84 mmol); ^{1}H NMR δ = 1.58 (br s, 1H), 4.45 (s, 2H), 6.44 (d, J = 4.0 Hz, 1H), 7.09 (d, J = 4.0 Hz, 1H), 7.32−7.38 (m, 2H), 7.48−7.54 (m, 3H), 9.41 (s, 1H) ppm; ^{13}C NMR δ = 56.1, 110.6, 120.3, 127.8, 129.0, 129.1, 134.1, 136.5, 141.8, 179.2 ppm; IR (neat) 3340, 1650, 1472, 1409, 1378, 1293, 1183 cm^{-1}; HRMS (CI$^+$) calcd for $C_{12}H_{12}NO_2$ (M + H)$^+$ 202.0868, found 202.0867.

*5-(Hydroxymethyl)-1-p-tolyl-1H-pyrrole-2-carbaldehyde (**4i**):* brown gummy oil, yield 25% (0.22 g, 1.0 mmol); ^{1}H NMR δ = 1.59 (br s, 1H), 2.44 (s, 3H), 4.44 (s, 2H), 6.42 (d, J = 4.0 Hz, 1H), 7.08 (d, J = 4.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 9.40 (s, 1H) ppm; ^{13}C NMR δ = 21.1, 56.0, 110.4, 120.0, 127.5, 129.7, 133.8, 134.0, 139.0, 142.0, 179.3 ppm; IR (neat) 3306, 1647, 1409, 1184, 1034 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_{14}NO_2$ (M + H)$^+$ 216.1025, found 216.1029.

*4-[2-Formyl-5-(hydroxymethyl)-pyrrol-1-yl]benzonitrile (**4j**):* colorless gummy oil, yield 27% (0.25 g, 1.08 mmol); ^{1}H NMR δ = 1.56 (br s, 1H), 4.43 (s, 2H), 6.48 (d, J = 4.0 Hz, 1H), 7.09 (d, J = 4.0 Hz, 1H), 7.49 (dd, J = 6.8, 1.6 Hz, 2H), 7.79 (dd, J = 6.8, 1.6 Hz, 2H), 9.50 (s, 1H) ppm; ^{13}C NMR δ = 55.7, 111.6, 112.6, 117.9, 123.6, 128.7, 132.8, 133.6, 141.2, 142.0, 178.7 ppm; IR (neat) 3311, 1645, 1490, 1407, 1374, 1180, 1045 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_{11}N_2O_2$ (M + H)$^+$ 227.0821, found. 227.0819.

*1-Butyl-5-methyl-1H-pyrrole-2-carbaldehyde (**4k**):*[10] clear oil, yield 35% (0.23 g, 1.40 mmol); ^{1}H NMR δ = 0.94 (t, J = 7.6 Hz, 3H), 1.31−1.41 (m, 2H), 1.62−1.71 (m, 2H), 2.29 (s, 3H), 4.26 (t, J = 7.6 Hz, 2H), 6.01 (d, J = 4.0 Hz, 1H), 6.84 (d, J = 4.0 Hz, 1H), 9.40 (s, 1H) ppm; ^{13}C NMR δ = 12.0, 13.7, 19.8, 33.0, 45.0, 109.7, 124.9, 131.3, 139.9, 178.0 ppm; IR (neat) 1642, 1462, 1411, 1177, 1022 cm^{-1}; HRMS (CI$^+$) calcd for $C_{10}H_{16}NO$ (M + H)$^+$ 166.1232, found 166.1228.

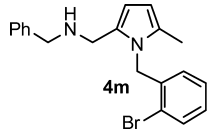
*1-(2-Bromobenzyl)-5-methyl-1H-pyrrole-2-carbaldehyde (**4l**):* light yellow crystal, yield 53% (0.59 g, 2.12 mmol); mp 89−90 °C; ^{1}H NMR δ = 2.15 (s, 3H), 5.66 (s, 2H), 6.15 (d, J = 4.0 Hz, 1H), 6.25 (dd, J = 8.0, 2.0 Hz, 1H), 6.97 (d, J = 4.0 Hz, 1H), 7.07−7.18 (m, 2H), 7.56 (dd, J = 7.6, 1.6 Hz, 1H), 9.46 (s, 1H) ppm; ^{13}C NMR δ = 11.8, 48.7, 110.4, 121.7, 125.0, 126.4, 127.8, 128.6, 131.8, 132.6, 136.9, 140.7, 178.5 ppm; IR (neat) 1653, 1487, 1435, 1369, 1257, 1038 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_{13}BrNO$ (M + H)$^+$ 278.0181, found 278.0176.

*4-Benzyl-3-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-6-carbaldehyde (**8**):*[16a] yellow solid, yield 27% (0.28 g, 1.08 mmol); mp 106−108 °C (lit. mp =112−114 °C);[16a] $[\alpha]^{23}_D$ = 186.6 (c 0.96, MeOH); ^{1}H NMR δ = 3.45 (dd, J = 14.0, 4.8 Hz, 1H), 3.48 (d, J = 14.8 Hz, 1H), 3.54 (dd, J = 14.0, 3.6 Hz, 1H), 4.84 (d, J = 14.8 Hz, 1H), 5.98 (d, J = 4.0 Hz, 1H), 6.04 (dd, J = 4.8, 3.6 Hz, 1H), 6.76−6.82 (m, 2H), 7.06 (d, J = 4.0 Hz, 1H), 7.17−7.23 (m, 2H), 7.24−7.31 (m, 1H), 9.62 (s, 1H) ppm; ^{13}C NMR δ = 40.2, 59.1, 63.3, 105.4, 125.5, 128.0, 128.8, 129.5, 130.3, 132.1, 134.4, 167.3, 179.0 ppm; IR (neat) 1749, 1660, 1505, 1467, 1395, 1244 cm^{-1}; HRMS (EI$^+$) calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0891.

*(S)-4-Methyl-3-oxo-3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazine-6-carbaldehyde (**9**):*[20,16b,17] yellow oil, yield 32% (0.23 g, 1.28 mmol); $[\alpha]^{23}_D$ = −86.0 (c 1.24, MeOH) {literature $[\alpha]_D^{25}$ = −33.3 (c 0.42, MeOH)};[17] ^{1}H NMR δ = 1.72 (d, J = 7.2 Hz, 3H), 5.39 (d, J = 15.2 Hz, 1H), 5.47 (d, J = 15.2 Hz, 1H), 5.85 (q, J = 7.2 Hz, 1H), 6.21 (d, J = 4.0 Hz, 1H), 6.98 (d, J = 4.0 Hz, 1H), 9.54 (s, 1H) ppm; ^{13}C NMR δ = 19.0, 53.7, 63.2, 106.5, 124.5, 130.3, 130.7, 168.1, 179.2 ppm.

*4,9-Dihydropyrrolo[1,2-a][1,2,3]triazolo[1,5-d]pyrazine-6-carbaldehyde (**5**).* To stirred solution of *N*-propargylic pyrrole **4d** (0.60 g, 3.68 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (1.02 mL, 7.36 mmol) and MsCl (0.34 mL, 4.42 mmol). The reaction mixture was stirred at that temperature for 30 min and allowed to warm to room temperature. After being stirred for 30 min, the mixture was poured onto crushed ice and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude mesylation product as sticky oil. Without further purification, the crude product was dissolved in dry DMF (10 mL), and NaN_3 (0.72 g, 11.04 mmol) was added. The mixture was heated at 60 °C for 8 h, cooled to room temperature, diluted with H_2O (15 mL), and extracted with EtOAc (3 × 10 mL). The organic layer was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent 2:1 EtOAc/hexane) to give pyrrolotriazolopiperazine **5** (0.61 g, 3.23 mmol) in 88% yield as white solid. Data for **5**: mp 184 °C; ^{1}H NMR δ = 5.71 (s, 2H), 5.80 (s, 2H), 6.36 (d, J = 4.0 Hz, 1H), 7.09 (d, J = 4.0 Hz, 1H), 7.74 (s, 1H), 9.61 (s, 1H) ppm; ^{13}C NMR δ = 41.6, 43.8, 107.4, 125.0, 128.6, 129.7, 130.9, 131.2, 179.4 ppm; IR (neat) 1648, 1486, 1327, 1174, 1035 cm^{-1}; HRMS (CI$^+$) calcd for $C_9H_9N_4O$ (M + H)$^+$ 189.0776, found 189.0778.

Reductive Amination of 4l with Benzylamine: Benzyl[1-(2-bromobenzyl)-5-methyl-1*H*-pyrrol-2-ylmethyl]amine (4m). *N*-(2-Bromobenzyl)pyrrole **4l** (0.55 g, 2.0 mmol) was dissolved in dry CH_2Cl_2 (5 mL). The resulting solution was treated with $MgSO_4$ and then with benzylamine (0.26 g, 2.4 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h under argon atmosphere and then filtered. The filtrate was concentrated under reduced pressure, and the crude product was dissolved in dry MeOH (10 mL). Small portions of $NaBH_4$ (151 mg, 4.0 mmol) were added over a period of 1 h at 0 °C. Stirring was continued for another 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel (eluent 1:9 EtOAc/hexane) afforded amine **4m** (0.58 g, 1.56 mmol) in 78% yield as clear thick oil. Data for **4m**: ^{1}H NMR δ = 2.09 (s, 3H), 3.60 (s, 2H), 3.73 (s, 2H), 5.20 (s, 2H), 5.90 (dd, J = 3.6, 0.8 Hz, 1H), 6.04 (d, J = 3.6 Hz, 1H), 6.21 (dd, J = 7.6, 1.6 Hz, 1H), 7.06−7.29 (m, 7H), 7.55 (dd, J = 7.6, 1.2 Hz, 1H) ppm; ^{13}C NMR δ = 12.0, 45.3, 47.4, 53.1, 105.7, 107.6, 121.4, 126.7, 126.8, 127.9, 127.9, 128.3, 128.4, 129.5, 130.3, 132.3, 138.2, 140.3 ppm; IR (neat) 3332, 1449, 1360, 1310, 1225, 1035 cm^{-1}; HRMS (EI$^+$) calcd for $C_{20}H_{21}BrN_2$ 368.0888, found 368.0891.



General Procedure for Palladium Catalyzed Cyclization. To a stirred solution of alcohol **4g** or amine **4m** (1.0 mmol) in dry toluene (10 mL) were added *t*-BuOK (224 mg, 2.0 equiv), K_2CO_3 (276 mg, 2.0 equiv), $Pd_2(dba)_3$ (5 mol % for **4g**, 3 mol % for **4m**), and (+)-BINAP (10 mol % for **4g**, 6 mol % for **4m**). The reaction mixtures were heated at reflux (18 h for **4g**, 16 h for **4m**) under argon atmosphere. After completion of the reaction (monitored by TLC), the crude mixtures were passed through a bed of silica gel. The solvents were evaporated, and the residues were extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by flash column chromatography over silica gel (eluent 1:19 EtOAc/hexane) to furnish the corresponding cyclized product **6** or **7** in a pure form.

*5,11-Dihydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine-3-carbaldehyde (**6**):* brown foamy solid, yield 63% (0.13 g, 0.63 mmol); mp 110 °C; ^{1}H NMR δ = 5.28 (s, 2H), 5.97 (s, 2H), 6.28 (d, J = 4.0 Hz, 1H), 6.86 (d, J = 4.0 Hz, 1H), 6.88−6.94 (m, 2H), 7.18−7.25 (m, 2H) 9.56 (s, 1H) ppm; ^{13}C NMR δ = 47.2, 62.7, 109.8, 120.0, 121.8, 121.9, 123.7, 129.7, 130.5, 131.6, 138.7, 156.9, 180.3 ppm; IR (neat) 1662, 1485, 1452, 1211, 1036 cm^{-1}; HRMS (CI$^+$) calcd for $C_{13}H_{12}NO_2$ (M + H)$^+$ 214.0868, found 214.0864.

*10-Benzyl-3-methyl-10,11-dihydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine (**7**):* colorless gummy oil, yield 86% (0.25 g, 0.86 mmol); ^{1}H NMR δ = 2.31 (s, 3H), 4.37 (s, 2H), 4.45 (s, 2H), 5.14 (s, 2H), 5.78 (d, J = 2.8 Hz, 1H), 5.88 (d, J = 2.8 Hz, 1H), 6.71 (t, J = 7.2 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 7.04−7.12 (m, 2H), 7.26−7.32 (m, 2H), 7.33−7.38 (m, 3H) ppm; ^{13}C NMR δ = 12.1, 47.8, 48.1, 58.8, 105.0, 105.2, 118.8, 118.8, 124.3, 127.0, 127.6, 127.8, 128.1, 128.6,

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129.0, 129.5, 139.0, 149.9 ppm; IR (neat) 1661, 1607 cm^{-1}; HRMS (EI^+) calcd for $C_{20}H_{20}N_2$ 288.1626, found 288.1629.

Methyl 4-[2-Formyl-5-(hydroxymethyl)pyrrol-1-yl]butyrate (12).[16d,e] The mixture of γ-aminobutyric acid methyl ester, hydrochloride salt (0.61 g, 4.0 mmol), Et_3N (0.40 g, 4.0 mmol), D-glucose (0.72 g, 4.0 mmol), and oxalic acid (0.36 g, 4.0 mmol) in dry DMSO (3.0 mL) was heated at 90 °C for 0.5 h. The resulting black viscous reaction mixture was cooled to room temperature and quenched with water (10 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined extract was washed with brine and water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by SiO_2 flash column chromatography (EtOAc/hexane 1:2) to give **12** (0.31 g, 1.36 mmol) in 34% yield as a colorless, thick oil. Data for **12**: ^1H NMR δ = 2.10 (heptet, J = 7.2 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.69 (br s, 1H), 3.68 (s, 3H), 4.41 (t, J = 7.2 Hz, 2H), 4.69 (s, 2H), 6.24 (d, J = 3.6 Hz, 1H), 6.88 (d, J = 3.6 Hz, 1H), 9.50 (s, 1H) ppm; ^{13}C NMR δ = 25.9, 30.5, 44.6, 51.8, 56.0, 110.6, 124.5, 132.3, 141.9, 174.1, 179.4 ppm; IR (neat) 3423, 1740, 1657, 1373, 1178, 1026 cm^{-1}; HRMS (EI^+) calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.0998.

Methyl 3-(Hydroxymethyl)-5,6-dihydroindolizine-7-carboxylate (15). To a stirred solution of **12** (0.40 g, 1.78 mmol) in dry THF (10 mL) at 0 °C was added 60% NaH (0.085g, 2.14 mmol, 1.2 equiv) in several portions. The mixture was stirred for 5 min, and 1-bromobutane (0.29 g, 2.14 mmol) was added dropwise. The mixture was then stirred at room temperature for 3 h and cooled to 0 °C again. Excess NaH was discharged by a dropwise addition of saturated $NaHCO_3$ solution in H_2O. The resulting mixture was evaporated to dryness under reduced pressure and extracted with EtOAc (5 × 3 mL). The combined organic extract was washed with water, dried over anhydrous Na_2SO_4, filtered, and evaporated to give crude **15**, which was purified by SiO_2 flash column chromatography (EtOAc/hexane 1:4) as a colorless viscous liquid in 82% yield (0.30 g, 1.46 mmol). Data for **15**: ^1H NMR δ = 1.46 (br s, 1H), 2.81 (dt. J_d = 1.2, J_t = 7.2 Hz, 2H), 3.80 (s, 3H), 4.07 (t, J = 7.2 Hz, 2H), 4.63 (d, J = 3.6 Hz, 2H), 6.17 (d, J = 3.6 Hz, 1H), 6.28 (d, J = 3.6 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H) ppm; ^{13}C NMR δ = 23.3, 41.0, 51.7, 56.5, 110.2, 111.2, 119.3, 128.2, 129.5, 134.7, 167.5 ppm; IR (neat) 3464, 1705, 1614, 1440, 1187, 1031 cm^{-1}; HRMS (CI^+) calcd for $C_{11}H_{14}NO_3$ $(M + H)^+$ 208.0974, found 208.0969.

Methyl 4-[2-(Butoxymethyl)-5-formyl-pyrrol-1-yl]butyrate (16).[16c] A mixture of **12** (0.23 g, 1.0 mmol), Ag_2O (0.35 g, 1.5 mmol), and 1-iodobutane (1.84 g, 10 mmol) was heated at 90 °C for 4 h. The mixture was then cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and filtered through a short pad of Celite. The solvent was evaporated under reduced pressure, and the remaining mass was subjected to SiO_2 flash column chromatography (EtOAc/hexane 1:6) to give **16** (0.20 g, 0.71 mmol) in 71% yield as colorless oil. Data for **16**: ^1H NMR δ = 0.91 (t, J = 7.2 Hz, 3H), 1.36 (sextet, J = 7.2 Hz, 2H), 1.57 (quintet, J = 7.2 Hz, 2H), 2.06 (quintet, J = 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 3.67 (s, 3H), 4.39 (t, J = 7.6 Hz, 2H), 4.48 (s, 2H), 6.22 (d, J = 4.0 Hz, 1H), 6.87 (d, J = 4.0 Hz, 1H), 9.50 (s, 1H) ppm; ^{13}C NMR δ = 13.8, 19.3, 26.3, 30.9, 31.6, 44.8, 51.6, 63.9, 70.4, 111.4, 124.2, 132.5, 139.3, 173.3, 179.3 ppm; IR (neat) 1742, 1662, 1370, 1189, 1105 cm^{-1}; HRMS (EI^+) calcd for $C_{15}H_{23}NO_4$ 281.1627, found 281.1621.

Lobechine 10.[16c] To a stirred solution of the above methyl ester **16** (0.10 g, 0.36 mmol) in THF and H_2O (1:1 v/v, 10 mL) at 0 °C was added $LiOH·H_2O$ (0.045 g, 1.08 mmol). The mixture was warmed to room temperature, and stirring was continued for 2 h. The reaction mixture was then acidified with saturated $KHSO_4$ solution and extracted with EtOAc (5 × 3 mL). The combined organic extract was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give analytically pure lobechine **10** (0.091 g, 0.34 mmol) as colorless viscous oil in 95% yield. Data for lobechine **10**: ^1H NMR δ = 0.90 (t, J = 7.2 Hz, 3H), 1.36 (sextet, J = 7.2 Hz, 2H), 1.57 (quintet, J = 7.2 Hz, 2H), 2.08 (quintet, J = 7.2 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 3.46 (t, J = 6.4 Hz, 2H), 4.41 (t, J = 7.6 Hz, 2H), 4.48 (s, 2H), 6.23 (d, J = 4.0 Hz, 1H), 6.88 (d, J = 4.0 Hz, 1H), 9.49 (s, 1H) ppm; ^{13}C NMR δ = 13.8, 19.3, 26.1, 30.8, 31.6, 44.7, 63.9, 70.4, 111.6, 124.5, 132.4, 139.4, 178.4, 179.5 ppm.

Ethyl 4-Azido-3-[(tert-butoxycarbonyl)amino]butyrate (13). L-Aspartic acid (1.00 g, 7.51 mmol) was suspended in dry EtOH (10 mL), and $SOCl_2$ (0.6 mL) was added dropwise at 0 °C. The mixture was then heated at reflux for 16 h. After the mixture was cooled to room temperature, solvent was evaporated under reduced pressure, and the resulting solid was dissolved in saturated $NaHCO_3$ solution (10 mL) and 1,4-dioxane (10 mL). Boc_2O (1.639 g, 7.51 mmol) was added, and the mixture was stirred at room temperature for 12 h. The mixture was then extracted with EtOAc (10 × 3 mL). The combined organic extract was washed with brine and H_2O, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to give *N*-Boc diester **G** (1.79 g, 6.2 mmol crude).[21]

The crude *N*-Boc diester **G** (1.79 g, 6.2 mmol) was dissolved in absolute EtOH and treated with $NaBH_4$ (0.36 g, 9.5 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 18 h, after which it was concentrated and extracted with CH_2Cl_2 (10 × 3 mL). Combined organic extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to give monoalcohol **H** (0.60 g, 2.43 mmol crude).

To a stirred solution of the above monoalcohol **H** (0.60 g, 2.43 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C were added Et_3N (0.61 g, 6.07 mmol) and MsCl (0.33 g, 2.92 mmol). The mixture was stirred at room temperature for 1 h, and crushed ice was added. The mixture was extracted with CH_2Cl_2 (10 × 3 mL). The combined organic extract was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the corresponding mesylate. The crude mesylate was dissolved in dry DMF (10 mL), and NaN_3 (0.47 g, 7.30 mmol) was added. The mixture was heated at 70 °C for 8 h and cooled to room temperature. The mixture was treated with H_2O (10 mL) and extracted with Et_2O (10 × 3 mL). The combined organic extract was washed with brine and H_2O, dried over anhydrous Na_2SO_4, filtered, concentrated, and SiO_2 column chromatographed (EtOAc/hexane 1:9) to produce the corresponding azide **13** (0.51 g, 1.88 mmol) as a colorless oil in overall 25% yield. Data for **13**: ^1H NMR δ = 1.27 (t, J = 7.2 Hz, 3H), 1.45 (s, 9H), 2.58 (d, J = 6 0.0 Hz, 2H), 3.46 (dd, J = 12.0, 5.6 Hz, 1H), 3.54 (dd, J = 12.0, 4.8 Hz, 1H), 4.10 (br s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 5.10 (br s, 1H) ppm; ^{13}C NMR δ = 14.1, 28.3, 36.2, 47.1, 53.6, 60.9, 79.9, 154.9, 171.0 ppm; IR (neat) 2112, 1714, 1505, 1376, 1166, 1037 cm^{-1}; HRMS (CI^+) calcd for $C_{11}H_{21}N_4O_4$ $(M + H)^+$ 273.1563, found 273.1565.

Ethyl 4-Azido-3-(2-formylpyrrol-1-yl)butyrate (14). To a stirred solution of **13** (1.52 g, 5.58 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C was slowly added trifluoroacetic acid (12 mL). Stirring was continued for 1 h at room temperature. The reaction mixture was evaporated to give the amine salt, which was neutralized with Et_3N (0.56 g, 5.58 mmol). The above mixture was then added to a solution of D-ribose (0.84 g, 5.58 mmol) and oxalic acid (0.50 g, 5.58 mmol) in dry DMSO (5 mL). The mixture was heated at 60 °C for 1 h and cooled to room temperature. The resulting black viscous mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined extract was washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude pyrrole **14**, which was purified by SiO_2 flash column chromatography (EtOAc/hexane 1:5) to give the pure product **14** (0.75 g, 3.01 mmol) in 54% yield as colorless oil. Data for **14**: ^1H NMR δ = 1.19 (t, J = 7.2 Hz, 3H), 2.94 (dd, J = 16.4, 6.4 Hz, 1H), 3.03 (dd, J = 16.4, 8.0 Hz, 1H), 3.66 (dd, J = 12.8, 4.8 Hz, 1H), 3.87 (dd, J = 12.8, 6.4 Hz, 1H), 4.03–4.16 (m, 2H), 5.53 (br s, 1H), 6.30 (dd, J = 4.0, 2.4 Hz, 1H), 7.02 (dd, J = 4.0, 1.6 Hz, 1H), 7.16 (dd, J = 2.4, 1.6 Hz, 1H), 9.52 (s, 1H) pm; ^{13}C NMR δ = 14.0, 36.5, 54.2, 54.4, 61.0, 110.4, 127.1, 130.1, 131.4, 169.8, 179.3 ppm; IR (neat) 2108, 1736, 1669, 1223, 1034 cm^{-1}; HRMS (CI^+) calcd for $C_{11}H_{15}N_4O_3$ $(M + H)^+$ 251.1144, found 251.1141.

Methyl 1-[2-Azido-1-[(ethoxycarbonyl)methyl]ethyl]-1H-pyrrole-2-carboxylate (17). To a stirred solution of **14** (0.56 g, 2.24 mmol) in CH_3CN (5 mL) at 0 °C were added 80% $NaClO_2$ (0.34 g, 2.97 mmol) in H_2O (2 mL), 96% NaH_2PO_4 (0.56 g, 4.48 mmol) in H_2O (2 mL), and 28% aqueous solution of H_2O_2 (0.63 g, 5.2 mmol). The

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reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated to half of the initial volume, and saturated $NaHCO_3$ solution (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The aqueous layer was acidified with saturated $KHSO_4$ solution and extracted with EtOAc (3 × 10 mL). The combined extract was washed with brine and H_2O and dried over anhydrous Na_2SO_4. Filtration and evaporation of the filtrate gave the crude pyrrolecarboxylic acid (0.43 g, 1.60 mmol).

To a solution of the above pyrrolecarboxylic acid in dry DMF (5 mL) were added K_2CO_3 (0.88 g, 6.4 mmol) and CH_3I (1.14 g, 8.0 mmol). The mixture was stirred at room temperature for 12 h and quenched with H_2O (10 mL). The resulting mixture was extracted with Et_2O (10 × 3 mL). The combined organic extract was washed with brine and H_2O, dried over anhydrous Na_2SO_4, filtered, concentrated, and SiO_2 column chromatographed (EtOAc/hexane 1:9) to give the azido methyl ester **17** (0.39 g, 1.39 mmol) as colorless oil in 62% overall yield. Data for **17**: ^{1}H NMR δ = 1.19 (t, J = 6.8 Hz, 3H), 2.95 (d, J = 7.2 Hz, 2H), 3.67 (dd, J = 12.4, 4.8 Hz, 1H), 3.80 (dd, J = 12.4, 6.4 Hz, 1H), 3.82 (s, 3H), 4.10 (q, J = 6.8 Hz, 2H), 5.82 (br s, 1H), 6.20 (br s, 1H), 7.01 (br s, 2H) ppm; ^{13}C NMR δ = 13.9, 37.0, 51.1, 52.9, 54.8, 60.9, 109.0, 119.0, 121.9, 125.9, 161.5, 169.7 ppm; IR (neat) 2116, 1734, 1702, 1228, 1114 cm^{-1}; HRMS (CI$^+$) calcd for $C_{12}H_{17}N_4O_4$ $(M + H)^+$ 281.1250, found 281.1253.

(−)-Hanishin (11).[19,22,25] To a stirred solution of azido methyl ester **17** (0.30 g, 1.07 mmol) in dry MeOH (20 mL) was added activated 10% Pd on carbon (0.053 g, 0.05 mmol Pd). The mixture was stirred under 1 atm of pressure of H_2 gas for 2 h. The mixture was then filtered through a short pad of Celite, and solvent was evaporated under reduced pressure. The concentrate was dissolved in dry toluene (10 mL), and the resulting solution was gently refluxed for 1 h. Solvent was removed under reduced pressure, and the solid mass was dissolved in dry THF (10 mL). To this solution was added NBS (0.38 g, 2.14 mmol), and the resulting mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, and the resulting mass was SiO_2 chromatographed (1:1 EtOAc/hexane) to produce (−)-hanishin (0.28 g, 0.74 mmol) as a white solid in 69% overall yield. Data for **11**: mp = 150 °C (lit.[25] mp = 148−150 °C); $[\alpha]^{23}_D$ = −4.7 (c 0.09, MeOH) [lit.[22] $[\alpha]^{20}_D$ = −4.3 (c 1, MeOH)]; ^{1}H NMR δ = 1.28 (t, J = 7.2 Hz, 3H), 2.58 (ddd, J = 16.4, 2.8, 1.2 Hz, 1H), 2.95 (dd, J = 16.4, 10.8 Hz, 1H), 3.69 (ddd, J = 13.2, 5.2, 1.2 Hz, 1H), 3.93 (ddd, J = 13.2, 4.0, 1.6 Hz, 1H), 4.19 (dq, J_d = 1.2, J_q = 7.2 Hz, 2H), 4.76 (m, 1H), 6.42 (br s, 1H), 7.00 (s, 1H) ppm; ^{13}C NMR δ = 14.1, 35.5, 43.1, 50.4, 61.3, 101.2, 106.5, 113.5, 116.2, 159.1, 169.7 ppm; HRMS (CI$^+$) calcd for $C_{11}H_{13}Br_2N_2O_3$ $(M + H)^+$ 378.9293, found 378.9286.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **4a−m**, **8**, **9**, **5−7**, **12**, **15**, **16**, **10**, **13**, **14**, **17**, and **11**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01349.

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Notes

The authors declare no competing financial interest.

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