DOI: 10.1002/ejoc.200800744

Multi-Step Synthesis and Biological Evaluation of Analogues of Insulin Secretagogue (2*S*,3*R*,4*S*)-4-Hydroxyisoleucine

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Keywords: Carbohydrates / Lactones / Nucleophilic substitution / Amino acids / Biological activity

A series of stereochemically defined analogues of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine and related α-hydroxy acids have been prepared by multi-step routes from D-glucose, whereas ketolization between TBDMS-protected hydroxypropanone and ethyl isocyanoacetate led to racemic analogues. Bioassays showed that of eight newly synthesized compounds, two of them presented an interesting statistical trend to increase glucose-induced insulin secretion when tested in isolated rat pancreatic islets in the presence of 8.3 mM glucose and at a concentration of 200 μM, which has previously been shown to be effective for (2*S*,3*R*,4*S*)-4-hydroxyisoleucine.

Introduction

There are two major forms of diabetes, type 1 and type 2. The hallmark of type 1 diabetes is the autoimmune-mediated destruction of insulin-producing β-cells in the pancreas, which results in absolute insulin deficiency. In contrast, type 2 diabetes is characterized by two defects: relative insulin deficiency and liver and peripheral insulin resistance. Type 2 diabetes, which accounts for 90–95% of the incidence of diabetes, is a multi-factorial disease of largely unknown etiology involving both genetic and environmental factors. Its worldwide prevalence has increased substantially in recent decades. Therefore, new therapies are being widely researched, in particular those based on pharmacological approaches.[1] In this context, we are interested in the synthesis and evaluation of inhibitors of glycogen phosphorylase of the following type: *N*-Acyl-*N*-glucopyranosylureas,[2,3] 5-substituted 3-*C*-glucopyranosyl-1,2,4-oxadiazoles,[4] and isomeric 3-substituted 5-*C*-glucopyranosyl-1,2,4-oxadiazoles,[5] as well as 2-(*C*-β-D-glucopyranosyl)hydro-, and -benzoquinones,[6] some of them being among the most effective glucose-derived inhibitors.[7] However, the pharmacopoeia from different areas offer examples of plants and herbs used traditionally as hypoglycaemic remedies; the effectiveness of these remedies has been conclusively established in some cases by identifying the active molecule (from the plant), for example, galegine (*Galega officinalis*), casuarine (*Casuarina equisetifolia*, *Eugenia jambolana*, *Eugenia jambolona*), salacinol (*Salacia reticulata*),[8] and (2*S*,3*R*,4*S*)-4-hydroxyisoleucine (*Trigonella foenum-graecum*).[9]

T. foenum-graecum (Leguminosae family), an annual herbaceous plant commonly known as fenugreek, is widely distributed across the Mediterranean area and Asia. After several groups found 4-hydroxyisoleucine (4-OH-Ile) in particular in *Amanita phalloides*[10] and the seeds of *T. foenum-graecum*,[11] Sauvaire and co-workers demonstrated the insulinotropic properties of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine[9,12] Interestingly, this effect is glucose-dependent and occurs only in the presence of moderate (8.3 mM) or high (16.7 mM) glucose concentrations.[9] In addition, 4-OH-Ile partly corrects hyperglycaemia and glucose intolerance in a rat model of type 2 diabetes.[12b] These two beneficial therapeutic effects result not only from an increase in insulin secretion, but also from an insulin-sensitizing effect. Indeed, more recently, Broca et al.[12c] demonstrated that 4-hydroxyisoleucine is able to increase the peripheral glucose utilization rate and to decrease hepatic glucose production. Other interesting properties have been claimed for 4-OH-Ile,[13,14] which has made it a promising molecule for dietetic and cosmetic applications. In this context, because of limitations in the extraction procedure from natural sources

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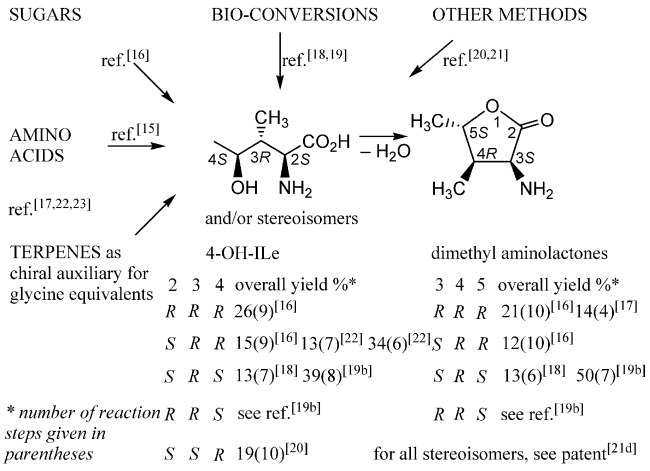
(w/w extraction yield: 0.56%),[9] several stereocontrolled synthetic routes to 4-OH-Ile or the corresponding lactones[10,11] have been investigated in recent years (Scheme 1).



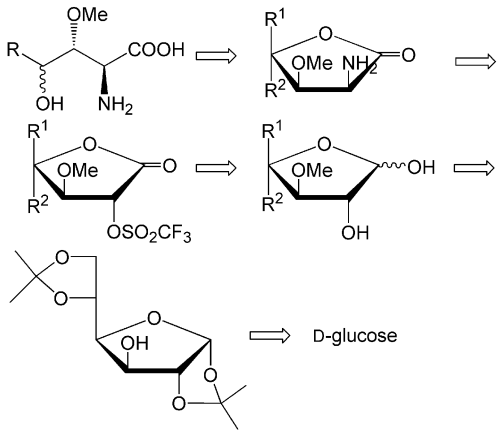
Scheme 1. Synthetic routes to stereoisomers of 4-hydroxyisoleucine.

Therefore, in the quest for possible new therapeutic treatments of type 2 diabetes, (2*S*,3*R*,4*S*)-4-hydroxyisoleucine has attracted our interest, and we have investigated unprecedented routes based on the 1,3-dipolar cycloaddition of chiral nitrones [as a glycine equivalent; derived from (+)- or (–)-menthone] to suitable alkenes. This approach was found to be efficient for the synthesis of enantiopure dihydroxy amino acids, (2*S*,3*R*,4*R*)-4-hydroxyisoleucine,[22] and its (2*S*,3*R*,4*R*)- or (2*R*,3*S*,4*S*)-configured analogues.[23] In fact, after we became aware of the antidiabetic properties of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine, our first plan was to synthesize analogues by the modification of precursors from the chiral pool. We herein describe the synthesis of analogues of 4-hydroxyisoleucine from D-glucose[24] and by ketolization.

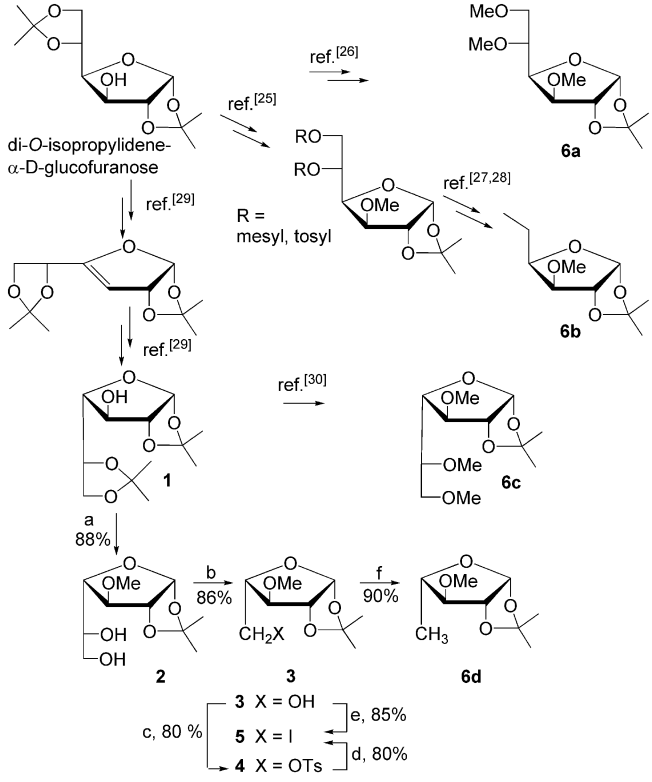
Results and Discussion

Synthetic Results

As outlined in Scheme 2, the final step of our synthetic strategy towards 4-hydroxy amino acids involves the base-catalyzed hydrolysis of aminolactone precursors, as reported for the preparation of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine.[18,19b] The precursors of such aminolactones are azido derivatives, themselves prepared by nucleophilic displacement by using sugar lactones with leaving groups at C-2. Such hydroxylactones can be obtained from 1,2-*O*-isopropylidenefuranoses by acid-catalyzed hydrolysis followed by regioselective oxidation of the hemiacetalic hydroxy group, which leaves the 2-OH group available for activation. As depicted in Scheme 3, the 1,2-*O*-isopropylidene-protected furanose derivatives can have the D-*gluco* configuration of the initial substrate or a D-*galacto* configuration, as established by known procedures. It was assumed that this strategy would deliver hydroxy amino acids with controlled configurations at C-2, C-3, and C-4, because nucleophilic displacement at C-2 by azide was expected to occur by a stereospecific S_N2 process, with the configuration at C-3 remaining unchanged from the precursors to the products in contrast to that at C-4, which depends on the D-*gluco*- or D-*galacto* configuration of the intermediates (note that the numbering is the same for the sugar-derived precursors and the final amino acids). These sequences would deliver analogues of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine with a methoxy



Scheme 2. Synthetic strategy for the synthesis of 4-hydroxy amino acids.

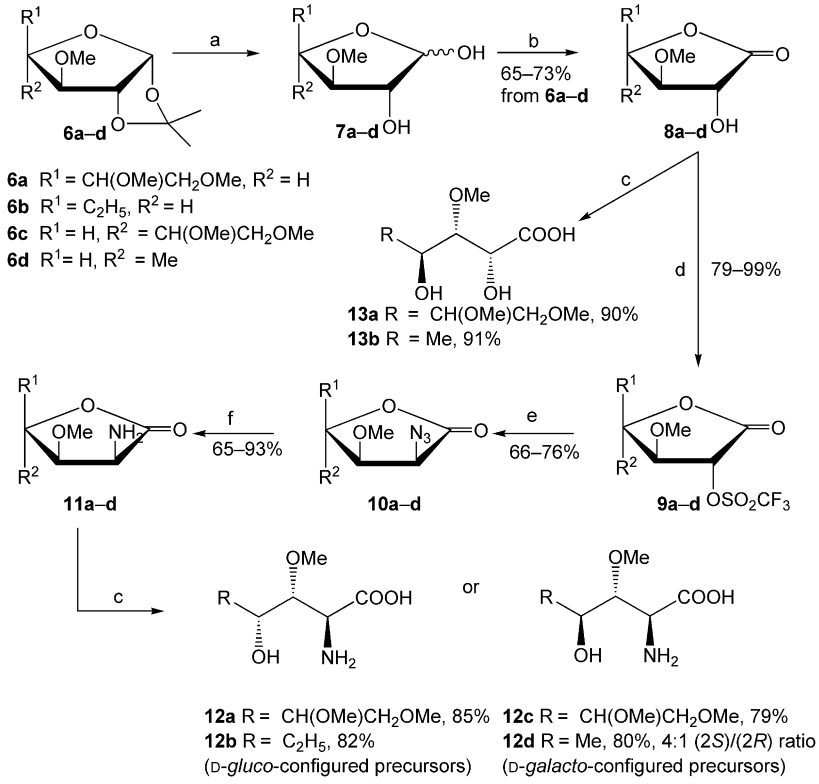


Scheme 3. Reagents and conditions: (a) (i) CH_3I, KOH, $Bu_4N^+Br^-$, acetone, (ii) AcOH/H_2O; (b) (i) $NaIO_4$, H_2O, room temp., (ii) $NaBH_4$, H_2O, room temp.; (c) TsCl, pyridine, room temp.; (d) NaI, acetone, 56 °C; (e) PPh_3, I_2, imidazole, toluene, 110 °C; (f) H_2, 10% Pd/C, K_2CO_3, MeOH, room temp.

group at C-3 (instead of methyl) and a similar stereochemistry at C-2, C-3, and C-4 when using D-*galacto*-configured precursors. The choice of D-*gluco*-configured precursors leads to amino acids analogous to (2*S*,3*R*,4*R*)-4-hydroxyisoleucine. In addition, hydrolysis of the intermediate D-*galacto*-configured hydroxylactones to dihydroxy acids appeared worthy of consideration for biological tests of analogues related to (2*R*,3*R*,4*S*)-4-hydroxyisoleucine and SAR studies. Finally, the addition by ketolization of ethyl isocyanoacetate to a ketone was explored as a route to racemic analogues and our results for this reaction are also disclosed in this paper (see Scheme 5).

The common starting material for the planned syntheses was 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone glucose), a cheap and commercially available substrate amenable to appropriate modifications, such as methylation of the 3-OH group and regioselective acid-catalyzed hydrolysis of the 5,6-*O*-isopropylidene acetal.[25] Permethylation of 1,2-*O*-isopropylidene-α-D-glucofuranose afforded 1,2-*O*-isopropylidene-3,5,6-tri-*O*-methyl-α-D-glucofuranose (**6a**).[26] The synthesis of the ethyl derivative **6b** was also straightforward, based on the known conversion of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[25] into the corresponding disulfonates [dimesylate (85%) or ditosylate (60%)] followed by 1,2-elimination[27] (NaI, Zn, refluxing DMF, 78 and 76% yields, respectively) and quantitative reduction (H_2, 10% Pd/C, MeOH).[28] The conversion of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose into its D-*galacto*-configured analogue **1**[29] with inversion of the configuration at C-4 was achieved in three high-yielding steps (trifluoromethylsulfonylation of the 3-OH, DBU-induced 1,2-elimination, and regio- and stereoselective hydroboration from the less hindered side). Compound **1** was regioselectively hydrolyzed[29] and then subjected to trimethylation to afford **6c**.[30] These procedures were then applied to compound **1**, which was methylated, then regioselectively hydrolyzed[29] to afford **2** as a diol. Its oxidative cleavage in the presence of sodium periodate delivered **3** (86% yield) as a pentose, which was converted by two routes into the corresponding iodide **5**. The one-step Garegg method gave good results (85% yield) compared with the two-step tosylation and displacement procedure (64% overall yield). A final reductive step delivered **6d** in 90% yield.

The 1,2-*O*-isopropylidene-α-D-furanoses **6a**–**d** were subjected to similar modifications at the 1- and 2-positions. Acid-catalyzed hydrolysis of the isopropylidene acetal and regioselective oxidation of the hemiacetal by bromine[31] afforded fairly stable γ-lactones **8a**–**d** with a free 2-OH group (Scheme 4). Sulfonylation was considered to afford activated molecules amenable to displacement by azide ions with inversion of configuration. However, published data indicated that 2-bromo sugar lactones can undergo configurational changes,[32] whereas 1,4-, and 1,5-sugar-derived lactones sulfonylated at C-2 may undergo displacement by azide with a changing stereoselectivity, not predicted simply by invoking an S_N2 reaction,[33] and in fact such a displacement has been shown to occur with retention of the configuration at C-2.[33–35] Monitoring of the reaction showed

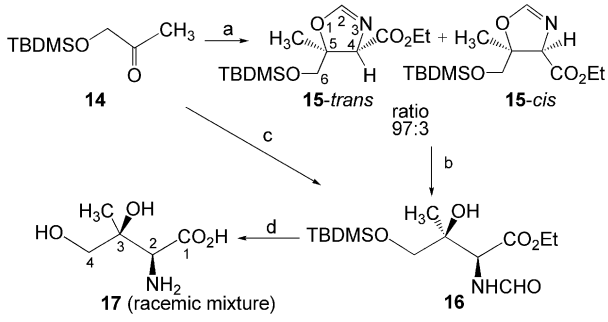


Scheme 4. Reagents and conditions: (a) 0.5 N HCl, 70 °C; (b) dioxane/H_2O, $BaCO_3$, Br_2, room temp.; (c) $LiOH·H_2O$, H_2O, AcOH, room temp.; (d) CH_2Cl_2, pyridine, Tf_2O, –50 °C; (e) NaN_3, DMSO, room temp.; (f) H_2, 10% Pd/C, EtOH, room temp.

that the azido compounds initially formed under kinetic conditions arise from an S_N2 reaction, whereas more stable products predominate under thermodynamic control.[33,36] Indeed, experiments with deuterium oxide showed deuterium incorporation at C-2, which indicates the possibility of deprotonation at this position and subsequent epimerization.[33] Substitution of tosylate groups by NaN_3 required 5 d at room temp. and led to epimeric mixtures due to long reaction times.[37,38] More reactive triflate groups[35,39] were preferred to investigate the selectivity outcome of the substitution, which depended on both the epimerization rate of the triflate used[33,36] and on the conditions applied.[36]

On the basis on these reports, hydroxy lactones **8a**–**d** were converted at –48 °C into the corresponding triflates **9a**–**d** obtained in high yield as reactive molecules that were purified by flash chromatography and used without delay. Upon treatment with NaN_3 in DMSO at room temp., the D-*gluco*-configured triflates **9a** and **9b** underwent substitution within 2.5 h, whereas the D-*galacto*-configured analogues **9c** and **9d** reacted within 15 min to afford the corresponding azido derivatives exclusively by an S_N2 reaction. Catalytic reduction to the corresponding amino lactones **11a**–**d** followed by base-catalyzed hydrolysis afforded the desired acyclic products **12a**–**d**. Because of its lability, amino lactone **11c** was not purified. Epimerization was observed only when opening amino lactone **11d**, compound **12d** being obtained as a (2*S*)/(2*R*) = 4:1 epimeric mixture, as shown by ^1H NMR spectroscopy. Thus, the amino acids prepared were obtained by multi-step syntheses (8–15 steps) in 12–26% overall yields. Finally, base-catalyzed hydrolysis of sugar-derived lactones **8c** and **8d** afforded in good yields dihydroxy acids **13a** and **13b**.

Of the analogues tested, two of them (**16** and **17**) were prepared by another approach (Scheme 5) involving nucleophilic attack of a carbonyl group by an anion derived from alkyl isocyanoacetate.[40] This reaction has been applied to aldehydes and ketones, in some cases with chiral centers,[41] and to sugar lactones as a route to *C*-glycosyl amino acids.[42] To improve its selectivity, the reaction has also been conducted in the presence of transition-metal salts (CuCl, $AgClO_4$)[43] or chiral ligands.[44] In our hands, silyl-protected hydroxy ketone **14** and ethyl isocyanoacetate reacted in the presence of Cu_2O in toluene at room temp. to afford, after purification by flash chromatography, a *cis*/*trans* = 3:97 mixture of oxazolines **15** in 73% yield. The selectivity observed is in accordance with the mechanism proposed for the reaction.[45] It is assumed that nucleophilic attack of the carbonyl group of the ketone by the anion led first to a chelated copper alcoholate that cyclized to a copper-bound oxazoline. In a final step, this intermediate was transformed into the oxazoline by proton transfer from ethyl isocyanoacetate, which can react further. It is reasonable to assume that oxazoline intermediates with *trans*-disposed substituents are favored because of minimized steric hindrance in the transition state. Oxazoline **15** appeared to be sensitive to hydrolysis, which occurred during standard column chromatography to afford acyclic hydroxy formamide **16**. When *t*BuOK was used as the base, compound **15** was not observed (TLC), and **16** was isolated in 81% yield. Hydrolysis of the formamide and silyl groups in **16** occurred under acidic conditions to provide **17**.



Scheme 5. Reagents and conditions: (a) $CNCH_2CO_2C_2H_5$, Cu_2O, toluene, room temp., 73%; (b) hydrolysis during column chromatography; (c) $CNCH_2CO_2C_2H_5$, *t*BuOK, THF, –78 °C, 81%; (d) 6 N HCl, 60 °C, 50%.

Structure determination of the products obtained was based mainly on NMR spectroscopy. In particular, the chemical shifts of the 2-H protons were found in the following ranges: δ = 4.35–4.48 (**8b**–**d**), 5.26–5.59 (**9a**–**d**), 3.98–4.30 (**10a**–**d**), 3.67–3.69 ppm (**11a**–**d**), which indicates, as expected, a deshielding of the 2-H protons of the azido and amino lactones relative to the 2-H protons of **8b**–**d**. The $J_{2,3}$ coupling constants were in the range 6.0–8.0 (for **8b**,**c** and **9a**–**d** with 2-H and 3-H in a *trans* relationship) and 4.5–

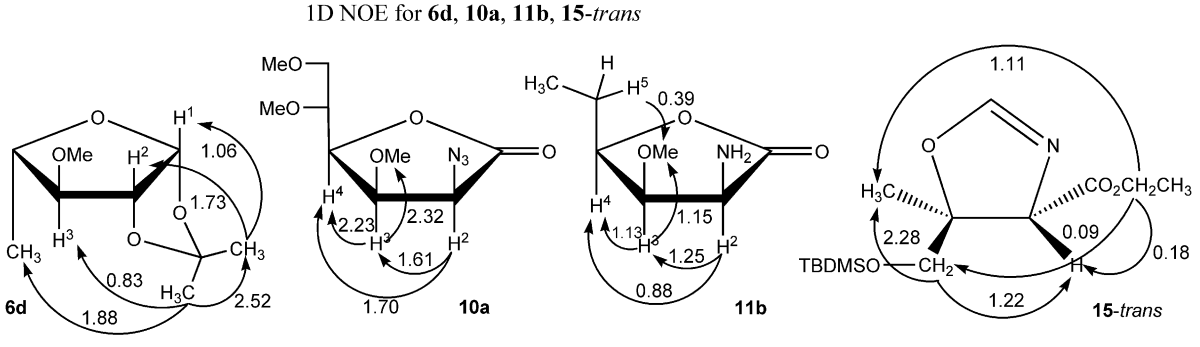
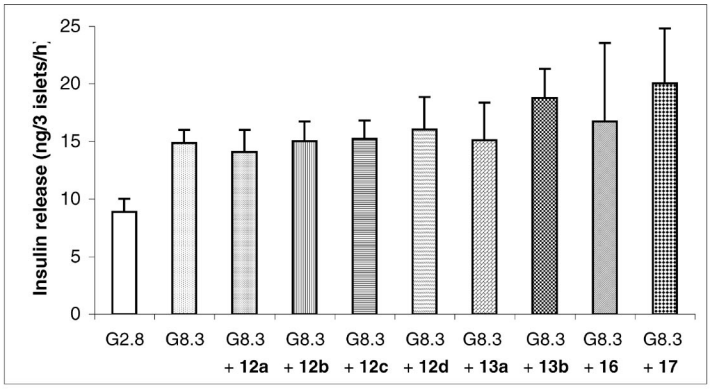


Figure 1. 1D NOE enhancements measured for **6d**, **10a**, **11b**, and **15**-*trans*.



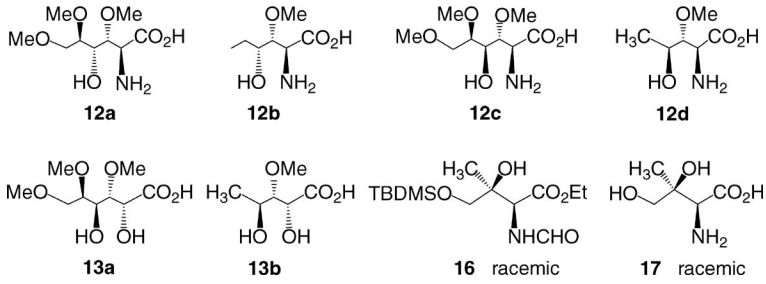


Figure 2. Insulin release (ng/3 islets/h) in control batches with concentrations of 2.8 and 8.3 mM glucose and for compounds **12a**–**d**, **13a**,**b**, **16**, and **17** (200 μM) in the presence of glucose (8.3 mM).

5.7 Hz (for **10a**,**c**,**d** and **11a**,**b**,**d** with 2-H and 3-H in a *cis* relationship). 1D NOE experiments provided further data in support of the proposed structures (Figure 1).

Evaluation of the Prepared Compounds as Insulin Secretagogues

To evaluate the possible insulinotropic effects of the different compounds prepared, secretory tests were performed in vitro in isolated rat islets of Langerhans,[46] and the insulin concentrations in the different aliquots obtained were determined by a radioimmunological method[47] (see Exp. Sect.). Control experiments were performed with preparations containing glucose (G) at a low 2.8 mM and moderately stimulating 8.3 mM concentration, as used to study the 4-hydroxyisoleucine insulinotropic effect.[12c] For the assays, the preparations contained glucose and one of the synthetic compounds at concentrations of 8.3 mM and 200 μM, respectively. Values of insulin release from isolated islets, expressed in ng/3 islets/h, are shown in Figure 2 plotted as means ± SEM (standard error of the mean). From our control batches (Figure 2, left) it appeared that an increase in glucose concentration from 2.8 to 8.3 mM provoked, as expected, a 70% increase in insulin release, reaching 14.96 ± 1.1 ng/3 islets/h. Of the eight different compounds tested, two of them, **13b** (p = 0.09) and **17** (p = 0.16), presented a statistical trend for the stimulation of insulin secretion, reaching 18.8 ± 2.5 and 20.0 ± 4.7 ng/3 islets/h, respectively. As for the other six compounds, insulin secretion ranged between 14.1 ± 1.9 (**12a**) and 16.7 ± 6.8 ng/3 islets/h (**16**). Note that the 26 and 34% increases in insulin secretion observed upon addition of compounds **13b** and **17**, respectively, were lower than the significant 50% increase previously recorded with (2*S*,3*R*,4*S*)-4-hydroxyisoleucine at the same 200 μM concentration and in the presence of 8.3 mM glucose.[12c] Unexpectedly, the best responses were obtained with compounds structurally rather different to (2*S*,3*R*,4*S*)-4-hydroxyisoleucine: **17** is a dihydroxy amino acid obtained as a racemic mixture, and **13b** is a dihydroxy acid with an MeO substituent at C-3 replacing the Me group found in the natural product. In this respect, it is noteworthy that the threshold concentrations of the classical structurally related amino acids required to potentiate glucose-induced insulin secretion were 5 mM for L-leucine (2*S*) and 3 mM for L-isoleucine (2*S*,3*S*) and L-alloisoleucine (2*S*,3*R*). More interestingly, monomethylated analogues such as (2*S*,4*R*)- and (2*S*,4*S*)-γ-hydroxynorvalines, as well as (2*S*,3*S*)- and (2*S*,3*R*)-γ-hydroxyvalines, were found to stimulate insulin secretion at a concentration of 0.5 mM in isolated rat pancreatic islets.[12c] Therefore, structures such as **13b** and **17** are worthy of consideration in the future search for new 4-hydroxyisoleucine-related insulinotropic compounds.

Conclusions

A series of stereochemically defined analogues of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine and related α-hydroxy acids have been prepared by multi-step routes from D-glucose and ketolization between TBDMS-protected hydroxypropanone and ethyl isocyanoacetate led to racemic analogues. Bioassays showed that of the eight newly synthesized compounds, two of them, dihydroxy acid **13b** and racemic dihydroxy amino acid **17**, presented an interesting trend to increase

glucose-induced insulin secretion when tested in isolated rat pancreatic islets in the presence of 8.3 mM glucose and at a concentration (200 μM) previously shown to be effective for (2*S*,3*R*,4*S*)-4-hydroxyisoleucine. However, based on the observed increases in insulin secretion (26 and 34%, respectively), they appear to have lower insulinotropic effects than (2*S*,3*R*,4*S*)-4-hydroxyisoleucine (50% increase).

Experimental Section

General Methods: Thin-layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60 F_{254} (Merck). TLC plates were inspected under UV light and developed by charring after spraying with 5% H_2SO_4 in EtOH. Preparative C_{18} reversed-phase chromatography (RP-18) was performed by using a 15×15 mm column of fully endcapped silica gel 100 C_{18} (>400 mesh; Fluka). ^1H and ^{13}C NMR spectra were recorded with Bruker AC200 and DRX300 spectrometers with residual solvent as the internal standard.[48] Chemical shifts are expressed on the δ scale in parts per million (ppm). ^{19}F NMR spectra were recorded with a Bruker AC200 spectrometer at 188 MHz (with $CFCl_3$ as reference). The following abbreviations have been used to explain the observed multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quadruplet; quint, quintuplet; m, multiplet; br., broad. Coupling constants have been assigned and listed without duplication in the ^1H NMR description of the synthesized compounds, as generally accepted in the field of sugar chemistry. NMR solvents were purchased from Eurisotop (91194 Saint Aubin, France). HRMS (LSIMS) data were recorded in the positive mode (unless stated otherwise) with a Thermo Finnigan Mat 95 XL spectrometer. MS (ESI) data were recorded in the positive mode with a Thermo Finnigan LCQ spectrometer. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter in a 1 dm cell. Melting points were measured with a Büchi apparatus (values are uncorrected). IR spectra (KBr pellets or films) were recorded with a Perkin-Elmer spectrophotometer model 681. Structure elucidation was performed by 1D and 2D NMR spectroscopy, which allowed signal assignment based on NOE effects and COSY and HSQC correlations. Elemental analyses were performed by the Laboratoire Central d'Analyses du CNRS (Vernaison, France).

1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-galactofuranose (2): 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**1**)[29] by an improved procedure,[29d] and this compound was methylated under standard conditions.[25] 1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-α-D-galactofuranose (3.58 g, 13.1 mmol), dissolved in a mixture of AcOH (37 mL) and H_2O (16 mL), was transformed into a more polar product (TLC) upon stirring at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/petroleum ether, 3:1) to give compound **2** as a colorless oil (3.35 g, 88%). R_f = 0.39 (EtOAc/petroleum ether, 3:1). $[\alpha]_D^{27}$ = –23 (*c* = 1.0, CH_2Cl_2) {ref.[49] $[\alpha]_D$ = –31 (*c* = 0.9, $CHCl_3$)}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.34, 1.53 [2 s, 6 H, $C(CH_3)_2$], 2.59 (s, 2 H, OH), 3.41 (s, 3 H, OCH_3), 3.69 (m, 2 H, 6a-H, 6b-H), 3.75 (m, 1 H, 5-H), 3.80 (dd, $J_{3,2}$ = 0.8, $J_{3,4}$ = 3.6 Hz, 1 H, 3-H), 3.92 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ = 6.5 Hz, 1 H, 4-H), 4.58 (dd, $J_{2,3}$ = 0.8, $J_{2,1}$ = 4.2 Hz, 1 H, 2-H), 5.87 (d, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4, 27.1 [$C(CH_3)_2$], 57.6 (OCH_3), 63.8 (C-6), 71.0 (C-5), 84.7 (C-2), 85.1 (C-4), 85.5 (C-3), 105.5 (C-1), 113.2 [$C(CH_3)_2$] ppm. MS (CI, isobutane): *m*/*z* (%) = 235 (24) $[MH]^+$, 177 (72) $[MH - CH_3COCH_3]^+$.

1,2-*O*-Isopropylidene-3-*O*-methyl-β-L-arabinofuranose (3): 1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-galactofuranose (**2**) (454 mg, 1.94 mmol) was dissolved in water (13 mL) and treated with $NaIO_4$ (416.3 mg, 1.94 mmol) at room temperature for 1 h. The solution was concentrated to dryness, and the residue was extracted with CH_2Cl_2 (3×13 mL). The extract was concentrated again to dryness. The resulting syrup was dissolved in water (4 mL), and $NaBH_4$ (182 mg, 4.78 mmol) was added at room temperature. After being kept at room temperature for 2 h, AcOH was added carefully until neutralization, and the solution was concentrated to dryness. Boric acid was removed by evaporation of MeOH (5×2 mL) from the residue, which was then purified by flash chromatography (EtOAc/petroleum ether, 3:7) to give compound **3** as a colorless syrup (341 mg, 86%). R_f = 0.38 (EtOAc/petroleum ether, 1:1). $[\alpha]_D^{22}$ = –26 (*c* = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3410 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34, 1.53 [2 s, 6 H, $C(CH_3)_2$], 2.17 (br. s, 1 H, OH), 3.38 (s, 3 H, OCH_3), 3.76 (m, 3 H, 3-H, 5a-H, 5b-H), 4.11 (ddd, $J_{3,4}$ = 3.2, $J_{4,5a}$ = 5.3, $J_{4,5b}$ = 8.8 Hz, 1 H, 4-H), 4.60 (d, $J_{2,1}$ = 4.0 Hz, 1 H, 2-H), 5.88 (d, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.3, 27.1 [$C(CH_3)_2$], 57.5 (OCH_3), 62.7 (C-5), 84.6 (C-2), 85.0 (C-4), 85.5 (C-3), 105.6 (C-1), 112.8 [$C(CH_3)_2$] ppm. $C_9H_{16}O_5$ (204.099): calcd. C 52.93, H 7.90, O 39.17; found C 53.25, H 7.91, O 39.46.

1,2-*O*-Isopropylidene-3-*O*-methyl-5-*O*-tosyl-β-L-arabinofuranose (4): 1,2-*O*-Isopropylidene-3-*O*-methyl-β-L-arabinofuranose (**3**) (861 mg, 4.22 mmol) was dissolved in pyridine (8.6 mL) and treated with *p*-toluenesulfonyl chloride (1.72 g, 9.05 mmol). After stirring the mixture at room temperature for 24 h, TLC showed the formation of a less polar product. Removal of pyridine by co-evaporation with toluene and purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:1) gave compound **4** as a white solid (1.19 g, 80%). M.p. 88–90 °C (Et_2O). R_f = 0.78 (EtOAc/petroleum ether, 1:1). $[\alpha]_D^{22}$ = –25 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28, 1.37 [2 s, 6 H, $C(CH_3)_2$], 2.45 (s, 3 H, CH_3), 3.36 (s, 3 H, OCH_3), 3.75 (d, $J_{3,4}$ = 1.5 Hz, 1 H, 3-H), 4.16 (m, 3 H, 4-H, 5a-H, 5b-H), 4.53 (d, $J_{2,1}$ = 3.8 Hz, 1 H, 2-H), 5.82 (d, 1 H, 1-H), 7.35 (d, *J* = 7.9 Hz, 2 H, H_{Ar}), 7.80 (d, 2 H, H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 25.9, 26.6 [$C(CH_3)_2$], 57.5 (OCH_3), 68.5 (C-5), 81.8, 83.8, 84.5 (C-2, C-3, C-4), 105.9 (C-1), 112.6 [$C(CH_3)_2$], 128.0, 129.9 (CH_{Ar}), 132.6, 145.0 (C_{Ar}) ppm. HRMS (ESI): calcd. for $C_{16}H_{22}NaO_7S$ $[MNa]^+$ 381.0984; found 381.0986.

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-arabinofuranose (5). Method 1: NaI (126 mg, 0.84 mmol) was added to a solution of **4** (100 mg, 0.28 mmol) in acetone (10 mL) at room temperature under argon, and the reaction mixture was heated at reflux for 3 d. After completion of the reaction (TLC) and the formation of a less polar compound, the mixture was cooled, poured into H_2O (6 mL), and extracted with Et_2O (3×6 mL). The combined ethereal extracts were washed with saturated $Na_2S_2O_3$ and brine, and dried (Na_2SO_4). Evaporation of the volatiles followed by flash chromatography of the resulting residue afforded **5** as a colorless oil (70 mg, 80%). **Method 2:** 1,2-*O*-Isopropylidene-3-*O*-methyl-β-L-arabinofuranose (**3**) (720 mg, 3.5 mmol) was dissolved in toluene (15 mL). Iodine (1.77 g, 7 mmol), triphenylphosphane (2.75 g, 10.5 mmol), and then imidazole (720 mg, 10.5 mmol) were added, and the mixture was stirred at 110 °C for 6 h. The mixture was filtered through Celite, concentrated, and purified by flash chromatography (EtOAc/petroleum ether, 2:8) to give compound **5** as a colorless oil (942 mg, 85%). R_f = 0.6 (EtOAc/petroleum ether,

1:4). $[\alpha]_D^{22}$ = +8 (*c* = 0.8, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28, 1.50 [2 s, 6 H, $C(CH_3)_2$], 3.35 (m, 2 H, 5a-H, 5b-H), 3.39 (s, 3 H, OCH_3), 3.88 (d, 1 H, 3-H), 4.23 (ddd, $J_{4,3}$ = 1.2, $J_{4,5a}$ = 6.6, $J_{4,5b}$ = 9.0 Hz, 1 H, 4-H), 4.57 (d, $J_{2,1}$ = 3.9 Hz, 1 H, 2-H), 5.89 (d, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.2 (C-5), 25.8, 26.9 [$C(CH_3)_2$], 57.2 (OCH_3), 84.0, 85.1, 85.9 (C-2, C-3, C-4), 106.3 (C-1), 112.4 [$C(CH_3)_2$] ppm. $C_9H_{15}IO_4$ (314.001): calcd. C 34.41, H 4.81, O 20.37, I 40.40; found C 34.11, H 5.02, O 20.54, I 39.98.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-arabinofuranose (6d): 5-Deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-arabinofuranose (**5**) (276 mg, 0.87 mmol) was dissolved in MeOH (10 mL). K_2CO_3 (122 mg, 0.87 mmol) and then 10% Pd/C (97 mg) were added, whereupon **5** was transformed upon stirring at room temperature under H_2 (1 atm) within 1 h into a more polar compound. The mixture was filtered through Celite, concentrated, and purified by flash chromatography (EtOAc/petroleum ether, 2:8) to afford compound **6d** as a colorless syrup (149 mg, 90%). R_f = 0.5 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{22}$ = –25 (*c* = 1.0, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 [s, 3 H, $C(CH_3)_2$], 1.41 (d, $J_{5,4}$ = 6.7 Hz, 3 H, 5-H), 1.55 [s, 3 H, $C(CH_3)_2$], 3.41 (s, 3 H, OCH_3), 3.54 (dd, $J_{3,2}$ = 0.8, $J_{3,4}$ = 3.5 Hz, 1 H, 3-H), 4.07 (dq, 1 H, 4-H), 4.55 (d, $J_{2,1}$ = 4.1 Hz, 1 H, 2-H), 5.82 (d, 1 H, 1-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.1 (C-5), 26.5, 27.2 [$C(CH_3)_2$], 57.6 (OCH_3), 80.4, 85.0, 89.6 (C-2, C-3, C-4), 105.4 (C-1), 112.9 [$C(CH_3)_2$] ppm. HRMS (CI, isobutane): calcd. for $C_9H_{17}O_4$ $[MH]^+$ 189.1127; found 189.1129.

5,6-Dideoxy-3-*O*-methyl-D-*xylo*-hexono-1,4-lactone (8b): A solution of **6b** (879 mg, 4.34 mmol) in HCl (0.5 N, 32 mL) was stirred at 70 °C for 1.5 h. The mixture was cooled to room temperature and neutralized by the addition of saturated aqueous $NaHCO_3$ (12 mL). After concentrated to dryness, the residue was washed with hot EtOAc (3 × 20 mL). The organic solution was concentrated, and the residue was dissolved in a mixture of dioxane and water (2:1, 32 mL). Bromine (503.46 μL, 9.66 mmol) and then $BaCO_3$ (833.6 mg, 4.25 mmol) were added to the solution, which was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$, and the resulting mixture was extracted with EtOAc (3 × 25 mL). The ethyl acetate extracts were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated to give a crude residue. Purification by flash chromatography (CH_2Cl_2) afforded the lactone **8b** as a colorless syrup (477 mg, 68% overall yield). R_f = 0.46 (EtOAc/petroleum ether, 3:1). $[\alpha]_D^{21}$ = +48 (*c* = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3412, 1770 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.01 (t, $J_{6,5a}$ = $J_{6,5b}$ = 7.4 Hz, 3 H, CH_3), 1.56 (ddd, $J_{5a,6}$ = 7.4, $J_{5a,4}$ = 9.4, $J_{5a,5b}$ = 12.0 Hz, 1 H, 5a-H), 1.83 (ddd, $J_{5b,4}$ = 4.2, $J_{5b,6}$ = 7.4 Hz, 1 H, 5b-H), 3.48 (s, 3 H, OCH_3), 3.88 (br. s, 1 H, OH), 4.04 (t, $J_{2,3}$ = $J_{3,4}$ = 7.1 Hz, 1 H, 3-H), 4.44 (d, 1 H, 2-H), 4.54 (m, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.0 (CH_3), 22.7 (CH_2), 58.3 (OCH_3), 71.4, 81.5, 82.4 (C-2, C-3, C-4), 175.6 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_7H_{13}O_4$ $[MH]^+$ 161.0814; found 161.0817.

3,5,6-Tri-*O*-methyl-D-galactono-1,4-lactone (8c): Prepared, as described for **8b**, from **6c** (300 mg) to afford **8c** (164 mg, 65% overall yield) as a white solid. M.p. 50–51 °C (Et_2O). R_f = 0.65 (EtOAc/petroleum ether, 1:3). $[\alpha]_D^{22}$ = –46 (*c* = 0.7, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3400, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.38, 3.52, 3.53 (3 s, 9 H, 3 OCH_3), 3.53 (br. s, 1 H, OH), 3.57 (m, 2 H, 5-H, 6a-H), 3.63 (m, 1 H, 6b-H), 4.06 (t, 1 H, 3-H), 4.35 (dd, $J_{2,OH}$ = 2.5, $J_{2,3}$ = 6.6 Hz, 1 H, 2-H), 4.43 (dd, $J_{4,5}$ = 4.8, $J_{3,4}$ = 6.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 58.1, 59.2, 59.2 (3 OCH_3), 70.5 (C-6), 73.9 (C-4), 77.8 (C-5), 79.7 (C-2), 82.2 (C-3), 174.6 (C-1) ppm. $C_9H_{16}O_6$ (220.094): calcd. C 49.09, H 7.32, O 43.59; found C 49.31, H 7.32, O 43.78.

5-Deoxy-3-*O*-methyl-L-arabinono-1,4-lactone (8d): Prepared, as described for **8b**, from **6d** (200 mg, 1.06 mmol) to afford **8d** (112.6 mg, 73% overall yield) as a white solid. M.p. 84–85 °C (Et_2O). R_f = 0.64 (EtOAc/petroleum ether, 1:3). $[\alpha]_D^{21}$ = –27 (*c* = 1.0, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3410, 1760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50 (d, $J_{5,4}$ = 6.3 Hz, 3 H, 5-H), 3.40 (d, $J_{OH,2}$ = 3.3 Hz, 1 H, OH), 3.56 (s, 3 H, OCH_3), 3.67 (t, $J_{2,3}$ = $J_{3,4}$ = 8.0 Hz, 1 H, 3-H), 4.27 (dq, 1 H, 4-H), 4.48 (dd, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.8 (C-5), 58.6 (OCH_3), 74.6, 76.5, 87.9 (C-2, C-3, C-4), 175.1 (C-1) ppm. HRMS (ESI): calcd. for $C_6H_{10}O_4$ $[M]^+$ 146.0579; found 146.0577. $C_6H_{10}O_4$ (146.057): calcd. C 49.31, H 6.90, O 43.79; found C 49.25, H 6.98, O 43.43.

3,5,6-Tri-*O*-methyl-2-*O*-trifluoromethylsulfonyl-D-glucono-1,4-lactone (9a): 3,5,6-Tri-*O*-methyl-D-glucono-1,4-lactone (**8a**) (500 mg, 2.27 mmol) and dry pyridine (634.3 μL) were stirred under nitrogen in dry CH_2Cl_2 (10 mL) at –50 °C. Trifluoromethanesulfonic anhydride (634.3 μL, 3.77 mmol) was added, and the mixture was stirred at –50 °C for 3 h; CH_2Cl_2 (58 mL) was added, and the organic solution was washed with 1 N HCl (1 × 20 mL) and then with brine (1 × 20 mL). After drying (Na_2SO_4) and concentration, the crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:9) to give compound **9a** (632 mg, 79%) as a colorless syrup. R_f = 0.37 (EtOAc/petroleum ether, 1:3). $[\alpha]_D^{22}$ = +22 (*c* = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1800, 1420, 1210, 1340, 1140, 1051, 995 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.36, 3.45, 3.53 (3 s, 9 H, 3 OCH_3), 3.67 (m, 3 H, 5-H, 6a-H, 6b-H), 4.35 (t, 1 H, 3-H), 4.78 (dd, $J_{4,5}$ = 3.8, $J_{3,4}$ = 7.0 Hz, 1 H, 4-H), 5.59 (d, $J_{2,3}$ = 7.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 59.2, 59.3, 59.5 (3 OCH_3), 70.5 (C-6), 77.5 (C-5), 79.5, 81.2, 81.4 (C-2, C-3, C-4), 118.0 (q, $J_{C,F}$ = 317.7 Hz, CF_3), 166.5 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_{10}H_{15}F_3O_8S$ $[MH]^+$ 353.0518; found 353.0516.

5,6-Dideoxy-3-*O*-methyl-2-*O*-trifluoromethylsulfonyl-D-*xylo*-hexono-1,4-lactone (9b): Prepared, as described for **9a**, from **8b** (675 mg) to afford **9b** (1.22 g, 99%) as a colorless syrup. R_f = 0.76 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{21}$ = +71 (*c* = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1800, 1420, 1330, 1210, 1140, 1050, 995 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.05 (t, $J_{5a,6}$ = $J_{5b,6}$ = 7.4 Hz, 3 H, CH_3), 1.65 (ddd, $J_{5a,6}$ = 7.4, $J_{5a,4}$ = 9.3, $J_{5a,5b}$ = 12.0 Hz, 1 H, 5a-H), 1.85 (ddd, $J_{5b,4}$ = 4.5, $J_{5b,6}$ = 7.5 Hz, 1 H, 5b-H), 3.50 (s, 3 H, OCH_3), 4.27 (t, $J_{2,3}$ = $J_{3,4}$ = 6.6 Hz, 1 H, 3-H), 4.63 (m, 1 H, 4-H), 5.26 (d, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.7 (C-6), 22.5 (C-5), 58.8 (OCH_3), 80.1, 81.1, 81.7 (C-2, C-3, C-4), 118.4 (q, $J_{C,F}$ = 317.8 Hz, CF_3), 166.4 (C-1) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –74.7 (s, 3 F, CF_3) ppm. MS (CI, isobutane): *m*/*z* (%) = 293 (100) $[MH]^+$.

3,5,6-Tri-*O*-methyl-2-*O*-trifluoromethylsulfonyl-D-galactono-1,4-lactone (9c): Prepared, as described for **9a**, from **8c** (200 mg) to afford **9c** (276 mg, 86%) as a colorless syrup. R_f = 0.53 (EtOAc/petroleum ether, 4:1). $[\alpha]_D^{21}$ = –19 (*c* = 0.6, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.35, 3.50, 3.55 (3 s, 9 H, 3 OCH_3), 3.59 (m, 3 H, 5-H, 6a-H, 6b-H), 4.48 (m, 2 H, 3-H, 4-H), 5.40 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 58.8, 59.0 (3 OCH_3), 69.7 (C-6), 77.0 (C-5), 79.9 (C-3, C-4), 83.1 (C-2), 118.3 (q, $J_{C,F}$ = 317.5 Hz, CF_3), 166.1 (C-1) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –74.84 (s, 3 F, CF_3) ppm. HRMS (CI, isobutane): calcd. for $C_{10}H_{15}F_3O_8S$ $[MH]^+$ 353.0518; found 353.0516.

5-Deoxy-3-*O*-methyl-2-*O*-trifluoromethylsulfonyl-L-arabinono-1,4-lactone (9d): Prepared, as described for **9a**, from **8d** (200 mg, 1.36 mmol) to afford **9d** (325 mg, 85%) as a colorless syrup. R_f =

0.61 (EtOAc/petroleum ether, 4:1). $[a]_D^{21} = -8$ (c = 1.0, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1810, 1420, 1210, 1140, 1110, 1080, 1010 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.56 (d, $J_{5,4}$ = 6.3 Hz, 3 H, 5-H), 3.56 (s, 3 H, OCH_3), 3.94 (t, $J_{3,2} = J_{3,4}$ = 7.9 Hz, 1 H, 3-H), 4.39 (dq, 1 H, 4-H). 5.40 (d, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.8 (C-5), 59.4 (OCH_3), 76.8, 83.2, 85.6 (C-2, C-3, C-4), 118.4 (q, $^1J_{C,F}$ = 317.5 Hz, CF_3), 165.9 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_7H_{10}F_3O_6S$ $[MH]^+$ 279.0150; found 279.0151.

2-Azido-2-deoxy-3,5,6-tri-*O*-methyl-D-mannono-1,4-lactone (10a): A solution of 3,5,6-tri-*O*-methyl-2-*O*-trifluoromethylsulfonyl-D-glucono-1,4-lactone (**9a**) (100 mg, 0.28 mmol) in DMSO (1 mL) was added slowly to a solution of NaN_3 (18.26 mg, 0.28 mmol) in DMSO (1 mL) at room temperature. The reaction mixture was stirred for 2.5 h, and then water (3 mL) was added. The aqueous phase was extracted with Et_2O (4 × 2 mL), and the combined organic phases were washed with water. After drying (Na_2SO_4) and concentration, the crude product was purified by flash chromatography (Et_2O/petroleum ether, 2:1) to give compound **10a** (47 mg, 68%) as a white solid. M.p. 80–81 °C (Et_2O). R_f = 0.42 (Et_2O/petroleum ether, 2:1). $[a]_D^{20} = -17$ (c = 0.7, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2100, 1800 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.40, 3.45, 3.62 (3 s, 9 H, 3 OCH_3), 3.52 (m, 1 H, 6a-H), 3.67 (m, 1 H, 5-H), 3.81 (dd, $J_{5,6b}$ = 1.7, $J_{6a,6b}$ = 11.0 Hz, 1 H, 6b-H), 3.98 (d, $J_{2,3}$ = 4.5 Hz, 1 H, 2-H), 4.16 (dd, 1 H, 3-H), 4.45 (dd, $J_{4,3}$ = 3.0, $J_{4,5}$ = 9.4 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 57.3 (C-2), 59.5, 60.5, 61.4 (3 OCH_3), 69.0 (C-6), 75.8 (C-5), 77.6, 79.6 (C-3, C-4), 170.5 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_9H_{16}N_3O_5$ $[MH]^+$ 246.1090; found 246.1091.

2-Azido-2,5,6-trideoxy-3-*O*-methyl-D-*lyxo*-hexono-1,4-lactone (10b): Prepared, as described for **10a**, from **9b** (144 mg) to afford, after 2.5 h of reaction, **10b** (101 mg, 70%) as a yellow syrup. R_f = 0.4 (Et_2O/petroleum ether, 2:1). $[a]_D^{22} = -30$ (c = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2100, 1775 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.03 (t, $J_{5,6}$ = 7.5 Hz, 3 H, CH_3), 1.85 (m, 2 H, CH_2), 3.60 (s, 3 H, OCH_3), 4.02 (m, 2 H, 2-H, 3-H), 4.29 (m, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.5 (CH_3), 21.7 (C-5), 60.7 (OCH_3), 61.7 (C-2), 80.3, 83.1 (C-3, C-4), 171.0 (C-1) ppm. MS (CI, isobutane): m/z (%) = 186 (100) $[MH]^+$, 114 (86) $[MH - N_2 - CO_2]^{2+}$.

2-Azido-2-deoxy-3,5,6-tri-*O*-methyl-D-talono-1,4-lactone (10c): Prepared, as described for **10a**, from **9c** (150 mg) to afford, after 15 min of reaction, **10c** (69 mg, 66%) as a colorless syrup. $[a]_D^{20}$ = +15 (c = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2100, 1800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.38, 3.43, 3.52 (3 s, 9 H, 3 OCH_3), 3.49 (m, 2 H, 5-H, 6a-H), 3.60 (dd, $J_{6b,5}$ = 8.4, $J_{6b,6a}$ = 12.6 Hz, 1 H, 6b-H), 4.02 (dd, $J_{3,4}$ = 0.6, $J_{3,2}$ = 5.7 Hz, 1 H, 3-H), 4.30 (d, 1 H, 2-H), 4.65 (d, $J_{4,5}$ = 1.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 58.4, 58.7, 59.3 (3 OCH_3), 59.4 (C-2), 69.8 (C-6), 79.1 (C-5), 80.2 (C-3), 82.4 (C-4), 171.7 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_9H_{16}N_3O_5$ $[MH]^+$ 246.1090; found 246.1085.

2-Azido-2,5-dideoxy-3-*O*-methyl-L-ribono-1,4-lactone (10d): Prepared, as described for **10a**, from **9d** (130 mg, 0.46 mmol) to afford, after 15 min of reaction, **10d** (52 mg, 76%) as a colorless syrup. R_f = 0.20 (EtOAc/petroleum ether, 1:4). $[a]_D^{21}$ = +11 (c = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 2100, 1775 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 (d, $J_{5,4}$ = 6.8 Hz, 3 H, CH_3), 3.53 (s, 3 H, OCH_3), 3.79 (dd, $J_{3,4}$ = 1.6, $J_{3,2}$ = 5.3 Hz, 1 H, 3-H), 4.11 (d, 1 H, 2-H), 4.66 (dq, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.4 (CH_3), 58.4 (C-2), 58.7 (OCH_3), 78.9, 82.5 (C-3, C-4), 170.5 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_6H_{10}N_3O_3$ $[MH]^+$ 172.0722; found 172.0726.

2-Amino-2-deoxy-3,5,6-tri-*O*-methyl-D-mannono-1,4-lactone (11a): A suspension of 2-azido-2-deoxy-3,5,6-tri-*O*-methyl-D-mannono-1,4-lactone (**10a**) (120 mg, 0.49 mmol) and Pd/C (10%, 26.43 mg) was stirred in MeOH (15 mL) at room temperature under H_2 (1 atm) for 12 h. The mixture was filtered through Celite, concentrated, and purified by flash chromatography (EtOAc/MeOH, 4:1) to afford the desired amino lactone **11a** as a white solid (100 mg, 93%). M.p. 111–112 °C (Et_2O). R_f = 0.37 (EtOAc/MeOH, 3:1). $[a]_D^{20}$ = +8 (c = 0.6, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.03 (br. s, 2 H, NH_2), 3.41, 3.46, 3.59 (3 s, 9 H, 3 OCH_3), 3.54 (m, 2 H, 5-H, 6a-H), 3.67 (d, $J_{2,3}$ = 4.9 Hz, 1 H, 2-H), 3.84 (dd, $J_{6b,5}$ = 1.8, $J_{6b,6a}$ = 10.9 Hz, 1 H, 6b-H), 4.09 (dd, 1 H, 3-H), 4.43 (dd, $J_{4,3}$ = 3.1, $J_{4,5}$ = 9.4 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, DMSO): δ = 57.3 (C-2), 59.5, 60.5, 61.4 (3 OCH_3), 69.0 (C-6), 75.8 (C-5), 77.6, 79.6 (C-3, C-4), 170.5 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_9H_{17}NO_5$ $[MH]^+$ 220.1185; found 220.1182.

2-Amino-2,5,6-trideoxy-3-*O*-methyl-D-*lyxo*-hexono-1,4-lactone (11b): Prepared, as described for **11a**, from **10b** (136 mg) to afford **11b** (76 mg, 65%) as a white solid. M.p. 39–40 °C (Et_2O). R_f = 0.5 (EtOAc/MeOH, 4:1). $[a]_D^{25}$ = +4 (c = 0.3, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3390, 1775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, $J_{5,6}$ = 7.4 Hz, 3 H, CH_3), 1.86 (m, 2 H, 5a-H, 5b-H), 1.83 (br. s, 2 H, NH_2), 3.57 (s, 3 H, OCH_3), 3.67 (d, $J_{2,3}$ = 5.1 Hz, 1 H, 2-H), 3.92 (dd, 1 H, 3-H), 4.24 (ddd, $J_{4,3}$ = 3.0, $J_{4,5a}$ = 8.1, $J_{4,5b}$ = 6.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.3 (C-6), 21.2 (C-5), 56.8 (C-2), 61.5 (OCH_3), 80.8, 83.2 (C-3, C-4), 177.9 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_7H_{14}NO_3$ $[MH]^+$ 160.0974; found 160.0973.

2-Amino-2,5-dideoxy-3-*O*-methyl-L-ribono-1,4-lactone (11d): Prepared, as described for **11a**, from **10d** (130 mg, 0.76 mmol) to afford **11d** (77 mg, 70%) as a colorless syrup. R_f = 0.19 (EtOAc/MeOH, 9:1). $[a]_D^{21}$ –3.5 (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, $J_{5,4}$ = 6.9 Hz, 3 H, CH_3), 1.70 (br. s, 2 H, NH_2), 3.46 (s, 3 H, OCH_3), 3.69 (d, $J_{2,3}$ = 5.4 Hz, 1 H, 2-H), 3.71 (d, 1 H, 3-H), 4.62 (q, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.4 (CH_3), 52.8 (C-2), 57.7 (OCH_3), 77.4, 82.2 (C-3, C-4), 177.3 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_6H_{12}NO_3$ $[MH]^+$ 146.0817; found 146.0818.

(2*S*,3*R*,4*S*,5*R*)-2-Amino-4-hydroxy-3,5,6-trimethoxyhexanoic Acid (12a): A solution of amino lactone **11a** (100 mg, 0.45 mmol) in water (3 mL) was treated with $LiOH·H_2O$ (37.3 mg, 0.86 mmol) at room temperature for 24 h. AcOH (50 μL, 0.86 mmol) was then added to the reaction mixture, and the solvent was evaporated. The residue was then dissolved in water and treated with a Dowex 50WX8-200 ion-exchange resin (H^+ form). The mixture was filtered, and the resin was washed with 2 M NH_4OH. After drying and concentration, the crude product was purified by reversed-phase flash chromatography (C_{18}) to afford the desired amino acid **12a** (92 mg, 85%) as a white solid. M.p. 147–148 °C (dec.). $[a]_D^{20}$ = –22 (c = 0.4, H_2O). IR (KBr): $\tilde{\nu}$ = 3400, 3200, 1630 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 3.38, 3.44, 3.52 (3 s, 9 H, 3 OCH_3), 3.57 (m, 2 H, 5-H, 6a-H), 3.78 (m, 2 H, 4-H, 6b-H), 3.97 (dd, $J_{3,4}$ = 1.5, $J_{3,2}$ = 4.7 Hz, 1 H, 3-H), 4.35 (d, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 55.3 (C-2), 57.8, 58.1, 59.1 (3 OCH_3), 70.1 (C-6), 70.5 (C-4), 76.7 (C-3), 79.3 (C-5), 182.0 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_9H_{20}NO_6$ $[MH]^+$ 238.1291; found 238.1291.

(2*S*,3*R*,4*R*)-2-Amino-4-hydroxy-3-methoxyhexanoic Acid (12b): Prepared, as described for **12a**, from **11b** (76 mg) to afford **12b** (42 mg, 82%) as a yellow syrup. R_f = 0.36 (EtOAc/MeOH, 1:2). $[a]_D^{20}$ = +21 (c = 0.3, H_2O). IR (KBr): $\tilde{\nu}$ = 3400, 3200, 1620 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 0.93 (t, J = 7.5 Hz, 3 H, CH_3), 1.62 (quint, J = 7.5 Hz, 2 H, 5a-H, 5b-H), 3.54 (s, 3 H, OCH_3), 3.72 (m, 2 H,

3-H, 4-H), 4.27 (d, $J_{2,3}$ = 4.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 9.7 (C-6), 26.8 (C-5), 55.7 (C-2), 58.6 (OCH_3), 74.1, 79.3 (C-3, C-4), 172.9 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_7H_{16}NO_4$ $[MH]^+$ 178.1079; found 178.1077.

(2*S*,3*R*,4*R*,5*R*)-2-Amino-4-hydroxy-3,5,6-trimethoxyhexanoic Acid (12c): Prepared from **10c** (30 mg) in two steps (reduction, as described for the synthesis of **11a**, followed by hydrolysis, as described for the synthesis of **12a**) without purification of the labile amino lactone **11c**, to afford **12c** (23 mg, 79%) as a white solid. M.p. 153–155 °C (EtOH). R_f = 0.67 (H_2O/*i*PrOH, 5:5). $[\alpha]_D^{27}$ = –3 (*c* = 0.6, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 3.36, 3.44, 3.45 (3 s, 9 H, 3 OCH_3), 3.56 (m, 1 H, 5-H), 3.63 (m, 2 H, 6a-H, 6b-H), 3.80 (m, 2 H, 3-H, 4-H), 4.02 (d, $J_{2,3}$ = 1.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 55.4 (C-2), 58.3, 58.7, 58.9 (3 OCH_3), 70.3 (C-6), 71.5 (C-4), 79.0 (C-5), 80.0 (C-3), 173.2 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_9H_{20}NO_6$ $[MH]^+$ 238.1291; found 238.1298.

(2*S*,3*R*,4*S*)-2-Amino-4-hydroxy-3-methoxypentanoic Acid (12d): Prepared, as described for **12a**, from **11d** (20 mg, 0.14 mmol) to afford **12d** (18 mg, 80%) as a white solid. M.p. 133–135 °C (EtOH). R_f = 0.38 (H_2O/*i*PrOH, 2:8). $[\alpha]_D^{21}$ = +13 (*c* = 0.7, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.20 (d, $J_{5,4}$ = 6.9 Hz, 3 H, CH_3), 3.41 (s, 3 H, OCH_3), 3.54 (dd, $J_{3,2}$ = 3.3, $J_{3,4}$ = 6.0 Hz, 1 H, 3-H), 3.97 (dq, 1 H, 4-H), 4.03 (d, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 19.4 (CH_3), 55.1 (C-2), 58.4 (OCH_3), 67.4 (C-4), 83.2 (C-3), 172.3 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_6H_{14}NO_4$ $[MH]^+$ 164.0923; found 164.0923.

(2*R*,3*S*,4*S*,5*R*)-2,4-Dihydroxy-3,5,6-trimethoxyhexanoic Acid (13a): Prepared, as described for **12a**, from **8c** (50 mg) to afford **13a** (48 mg, 90%) as a white solid. M.p. 163–165 °C (dec.). R_f = 0.65 (EtOAc/MeOH, 1:2). $[\alpha]_D^{22}$ = –9 (*c* = 1.0, H_2O). IR (KBr): $\tilde{\nu}$ = 3300, 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.40, 3.51 (3 s, 9 H, 3 OCH_3), 3.66 (m, 4 H), 3.75 (d, $J_{3,4}$ = 9.3 Hz, 1 H, 3-H), 4.18 (d, $J_{2,1}$ = 0.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 58.8, 58.9, 59.5 (3 OCH_3), 69.6 (C-6), 70.3 (C-2), 72.4 (C-4), 78.2 (C-5), 81.7 (C-3), 180.1 (C-1) ppm. MS (CI, isobutane): *m*/*z* (%) = 193 (100) $[MH - HCO_2H]^+$, 221 (25) $[MH - H_2O]^+$.

(2*R*,3*S*,4*S*)-2,4-Dihydroxy-3-methoxypentanoic Acid (13b): Prepared, as described for **12a**, from **8d** (20 mg) to afford **13b** (20.7 mg, 91%) as a white solid. M.p. 198–200 °C (EtOH). $[\alpha]_D^{20}$ = +10 (*c* = 0.45, H_2O). IR (KBr): $\tilde{\nu}$ = 3380, 1600 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): δ = 1.14 (d, $J_{5,4}$ = 6.3 Hz, 3 H, CH_3), 3.27 (s, 3 H, OCH_3), 3.32 (dd, $J_{3,2}$ = 1.5, $J_{3,4}$ = 6.9 Hz, 1 H, 3-H), 3.74 (dq, 1 H, 4-H), 4.04 (d, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 18.9 (CH_3), 59.9 (OCH_3), 67.1 (C-4), 70.9 (C-2), 86.4 (C-3), 179.7 (C-1) ppm. HRMS (CI, isobutane): calcd. for $C_6H_{10}O_4$ $[MH - H_2O]^+$ 148.0736; found 148.0737.

Ethyl 5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-methyl-4,5-dihydrooxazole-4-carboxylate (15): Ethyl isocyanoacetate (0.53 mmol, 58 μL) was added at room temp. to a solution of 1-[(*tert*-butyldimethylsilyl)oxy]propan-2-one (**14**)[50] (0.53 mmol, 100 mg) in toluene (5 mL). The resulting mixture was then stirred at 0 °C and Cu_2O (0.53 mmol, 1.22 mg) was added. The solution was removed from the cold bath and stirred at room temp. After 2 h, the reaction was complete with the formation of a more polar compound [R_f = 0.51 (EtOAc/petroleum ether, 3:7)]. The mixture was filtered through Celite to remove the solids. Evaporation of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel; EtOAc/petroleum ether, 3:7) furnished compound **15** (73%, 117 mg) as a *cis*/*trans* = 3:97 mixture. This ratio was deduced from a comparison of the integrals of the ^{1}H NMR resonances of 4-H (δ = 4.81 ppm, integral = 0.03 for *cis*-**15**; δ = 4.57 ppm, integral = 1.00 for *trans*-**15**). (Attempts to achieve purification by standard column chromatography did not afford **15**, but the more polar acyclic formamide **16**.) Yellow syrup. R_f = 0.51 (EtOAc/petroleum ether, 3:7). ^{1}H NMR (300 MHz, CD_3COCD_3): *trans*-**15**: δ = 0.08 [2 s, 6 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 1.23 (s, 3 H, CH_3), 1.26 (t, *J* = 6.0 Hz, 3 H, CH_3), 3.64 (d, $J_{6a,6b}$ = 12.0 Hz, 1 H, 6a-H), 3.73 (d, $J_{6b,6a}$ = 12.0 Hz, 1 H, 6b-H), 4.17 (q, *J* = 6.0 Hz, 2 H, CH_2), 4.57 (d, $J_{4,2}$ = 3.0 Hz, 1 H, 4-H), 7.00 (d, $J_{2,4}$ = 3.0 Hz, 1 H, 2-H) ppm; *cis*-**15**: δ = 0.01, 0.02 [2 s, 6 H, $Si(CH_3)_2$], 0.83 [s, 9 H, $SiC(CH_3)_3$], 1.32 (t, *J* = 6.9 Hz, 3 H, CH_3), 3.91 (d, $J_{6a,6b}$ = 11.4 Hz, 1 H, 6a-H), 3.98 (d, $J_{6b,6a}$ = 11.4 Hz, 1 H, 6b-H), 4.31 (q, *J* = 6.0 Hz, 2 H, CH_2), 4.81 (d, $J_{4,2}$ = 2.7 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): *trans*-**15**: δ = –4.4 ($SiCH_3$), –4.3 ($SiCH_3$), 15.5 (CH_3), 19.2 (CH_3), 19.6 [$C(CH_3)_3$], 27.1 [$C(CH_3)_3$], 62.2 (CH_2), 69.5 (C-6), 72.8 (C-4), 88.0 (C-5), 157.3 (C-2), 171.8 (C=O) ppm. MS (ESI): *m*/*z* (%) = 301.9 (100) $[M + H]^+$, 603 (37) $[2 M + H]^+$, 624.9 (17) $[2 M + Na]^+$.

Ethyl 4-[(*tert*-Butyldimethylsilyl)oxy]-2-formamido-3-hydroxy-3-methylbutanoate (16): Ethyl isocyanoacetate (58 μL, 0.53 mmol) in THF (1 mL) was added dropwise at –78 °C to a solution of *t*BuOK (59.5 mg, 0.53 mmol) in THF (1 mL). After stirring at this temperature for 0.5 h, a solution of 1-[(*tert*-butyldimethylsilyl)oxy]propan-2-one[50] (100 mg, 0.53 mmol) in THF (3 mL) was added. The resulting mixture was stirred at –78 °C for 1 h and then at room temp. for 1 h. After 2 h, the reaction was complete with the formation of a more polar compound [R_f = 0.37 (EtOAc/petroleum ether, 5:5)]. The reaction was quenched with a solution of 1 N HCl (5 mL), the mixture extracted with CH_2Cl_2 (3 × 6 mL), and dried with Na_2SO_4. Concentration under reduced pressure led to a residue, which, after flash chromatography (silica gel; EtOAc/petroleum ether, 5:5), afforded formamide **16** as a white solid (81%, 83 mg). M.p. 76–77 °C (Et_2O). R_f = 0.37 (EtOAc/petroleum ether, 5:5). IR: $\tilde{\nu}$ = 3300 (ν_{OH}), 1880 ($\nu_{C=O}$), 1700 ($\nu_{C=O}$) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.90 [s, 9 H, $SiC(CH_3)_3$], 1.20 (s, 3 H, CH_3), 1.28 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.47 (d, $J_{4a,4b}$ = 9.9 Hz, 1 H, 4a-H), 3.55 (d, $J_{4b,4a}$ = 9.9 Hz, 1 H, 4b-H), 4.22 (q, *J* = 7.2 Hz, 2 H, CH_2), 4.75 (d, *J* = 8.4 Hz, 1 H, 2-H), 6.65 (d, *J* = 8.4 Hz, 1 H, NH), 8.22 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6 [$Si(CH_3)_2$], 14.1 (CH_3), 18.2 [$C(CH_3)_3$], 21.7 (CH_3), 25.8 [$C(CH_3)_3$], 55.5 (C-2), 61.8 (CH_2), 67.9 (CH_2), 73.3 (C-3), 160.9 (CHO), 170.5 (C=O) ppm. MS (ESI): *m*/*z* (%) = 320 (99) $[M + H]^+$, 302 (100) $[MH - H_2O]^+$, 342 (25) $[M + Na]^+$, 661 (33) $[2 M + Na]^+$.

2-Amino-3,4-dihydroxy-3-methylbutanoic Acid (17): Formamide **16** (0.13 mmol, 20 mg) was treated with 6 N HCl (2 mL) and stirred at 60 °C for 3 h. After completion of the reaction with the formation of a more polar compound (TLC), the reaction mixture was concentrated, and the residue was purified by chromatography on Sephadex G10 to afford the desired compound **17** as a white solid (50%, 4.7 mg). M.p. 192–195 °C (MeOH). R_f = 0.6 (H_2O/2-propanol, 1:4). ^{1}H NMR (500 MHz, D_2O): δ = 1.19 (s, 3 H, CH_3), 3.66 (d, $J_{4a,4b}$ = 7.2 Hz, 1 H, 4a-H), 3.77 (d, $J_{4b,4a}$ = 7.2 Hz, 1 H, 4b-H), 3.81 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 19.0 (CH_3), 59.8 (C-2), 67.8 (C-4), 72.1 (C-3), 172.1 (C=O) ppm. HRMS (CI, isobutane): calcd. for $C_5H_{12}NO_4$ $[M + H]^+$ 150.0766; found 150.0774.

Bioassays: To perform in vitro secretory tests with isolated rat islets of Langerhans, adult male albino rats weighing 300–330 g (Iffa-Credo, L'Arbresle, France) were fed ad libidum. Animals were sacrificed and their pancreata dissected out. Pancreatic islets were isolated by the collagenase method.[46] For each experiment, islets were first preincubated for 60 min in a Krebs Ringer Bicarbonate buffer with the following ionic composition (mM): NaCl (108),

$NaHCO_3$ (18), KCl (4.7), $CaCl_2$ (2.5), $MgSO_4 \cdot 7H_2O$ (1.2), KH_2PO_4 (1.2) and supplemented with 8.3 mM glucose and 2 g/L bovine serum albumin. The pH of the medium was adjusted to 7.4 by bubbling through a mixture of O_2/CO_2 (95:5). Batches of three islets were then incubated for 60 min in tubes containing 1 mL of the medium and the different compounds at a concentration of 200 μM, similar to that known to induce a significant stimulating effect for 4-hydroxyisoleucine. At the end of the incubation, 200 μL aliquots were immediately frozen until insulin assay. To determine insulin concentrations in the different samples, the radioimmunological method of Herbert et al.[47] with a guinea pig antiporcine insulin antibody (ICN, Paris, France) was used. Rat insulin (Novo, Copenhagen, Denmark) was used as the standard. The sensitivity of the assay was 0.1 ng/mL. The values of insulin release from isolated islets are expressed in ng/3 islets/h. The statistical significance between means was assessed by using Student's test for paired values.

Acknowledgments

Région Rhône-Alpes is thanked for a stipend (K. A.) and financial support (MIRA Recherche 2006). Other support from the CNRS and the University of Lyon is acknowledged.

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Received: July 26, 2008
Published Online: November 25, 2008

