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Analogues of insulin secretagogue (2*S*,3*R*,4*S*)-4-hydroxyisoleucine: synthesis by 1,3-dipolar cycloaddition reactions of chiral nitrones to alkenes

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Abstract—(2*S*,3*R*,4*S*)-4-Hydroxyisoleucine, found in fenugreek, is an insulin secretagogue molecule. Non-natural analogues of (2*S*,3*R*,4*R*)- and (2*R*,3*S*,4*S*)-4-hydroxyisoleucine were efficiently prepared by 1,3-dipolar cycloaddition reactions of chiral nitrones derived from either (−)- or (+)-menthone to alkenes. The cycloadducts, obtained via the *exo*-approach of the alkenes to the nitrone's less hindered face, led after a reductive step and cleavage of the chiral auxiliary, to enantiopure non-natural amino acids in good overall yield.

1. Introduction

There are two major forms of diabetes, type 1 and type 2. The hallmark of type 1 diabetes is the destruction of insulin producing β-cells in the pancreas, primarily due to immune response. Type 1 diabetes is manifested with absolute insulin deficiency. In contrast, type 2 diabetes is characterized by two defects: insulin deficiency and insulin resistance. Type 2 diabetes which accounts for 90–95% of the incidence of diabetes is a multi-organ disease, the etiology of which is largely unknown. Its worldwide prevalence has increased substantially in recent decades. Therefore, new therapies are currently being explored based in particular on pharmacological approaches.[1] Our contribution to this field concerns the synthesis and evaluation of inhibitors of glycogen phosphorylase of the following type: *N*-acyl-*N*-glucopyranosyl-ureas,[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 offers examples of plants and herbs used traditionally as hypoglycemic remedies, the effectiveness of which has been conclusively established in some cases, by identifying the active molecule (*from the plant*), such as galegine (*Galega officinalis*), casuarine (*Casuarinas 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 coll. 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 hyperglycemia and glucose-intolerance.[12b]

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Other beneficial properties have been claimed for 4-OH-Ile,[13,14] which therefore appears as a promising molecule of dietetic and cosmetic interest.

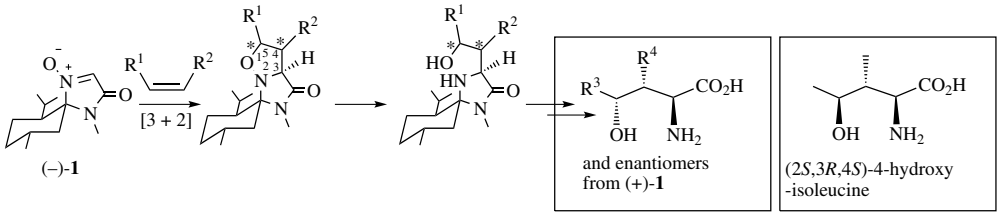
In this context, because of the limitations in the extraction procedure from natural sources (w/w extraction yield: 0.56%),[9] several stereocontrolled synthetic routes to 4-OH-Ile or the corresponding lactones[10,11] have been investigated in recent years (Scheme 1). For example, the opening of (2*R*,3*R*)-epoxybutane by a chiral glycine anion equivalent was claimed to mainly afford the (3*R*,4*R*,5*R*)-lactone,[15] but this structure was later suspected to be (3*S*,4*R*,5*R*) based on the comparison with (2*R*,3*R*,4*R*) and (2*S*,3*R*,4*R*) 4-OH-Ile synthesized from benzyl 2,3-anhydro-4-*O*-(*tert*-butyl-dimethyl-silyl)-β-L-ribopyranoside, and studied by crystal analysis.[16] Deprotonation of an oxazinone derived from (1*R*,2*R*,5*R*)-(+)-2-hydroxypinan-3-one furnished a glycine anion equivalent which by reaction with butan-2,3-dione and dehydration afforded a didehydroamino acid derivative. Two reductive steps led to the (3*R*,4*R*,5*R*)-lactone, precursor of (2*R*,3*R*,4*R*)-4-OH-Ile.[17] The same group reported a six-step synthesis of (2*S*,3*R*,4*S*)-4-OH-Ile, with as the key step an enzymatic resolution by hydrolysis using immobilized penicillin acylase.[18] In an attempt to design a synthesis of (2*S*,3*R*,4*S*)-4-OH-Ile that can be applied to large-scale production, a process involving a biotransformation with *Geotrichum candidum* and an asymmetric Strecker synthesis was published and patented.[19] In another approach, ethyl (*R*)-hydroxybutanoate was elaborated into an unsaturated trichloroacetimidate suitable for a palladium(II)-catalyzed 3,3-sigmatropic rearrangement. Conditions could be optimized so as to obtain (2*S*,3*S*,4*R*)-4-OH-Ile as the major product.[20] Lately, short syntheses of isoxazole-3-carboxylic acid and imino-oxopentanoic acid as achiral precursors[21a] of 4-OH-Ile have been reported, as well as the amino acid-catalyzed synthesis of amino-oxopentanoic acid derivatives.[21b–d] Our recently reported access[22] to enantiopure dihydroxylated amino acids upon the cycloaddition of chiral nitrones[23] derived from (+)- or (−)-menthone[24] to substituted alkenes exploited the potential of such chiral nitrones as glycine equivalents for the stereocontrolled synthesis of amino acids. After developing routes to (2*S*,3*R*,4*R*) 4-OH-Ile,[25] we herein report on the synthesis of related derivatives.

2. Results and discussion

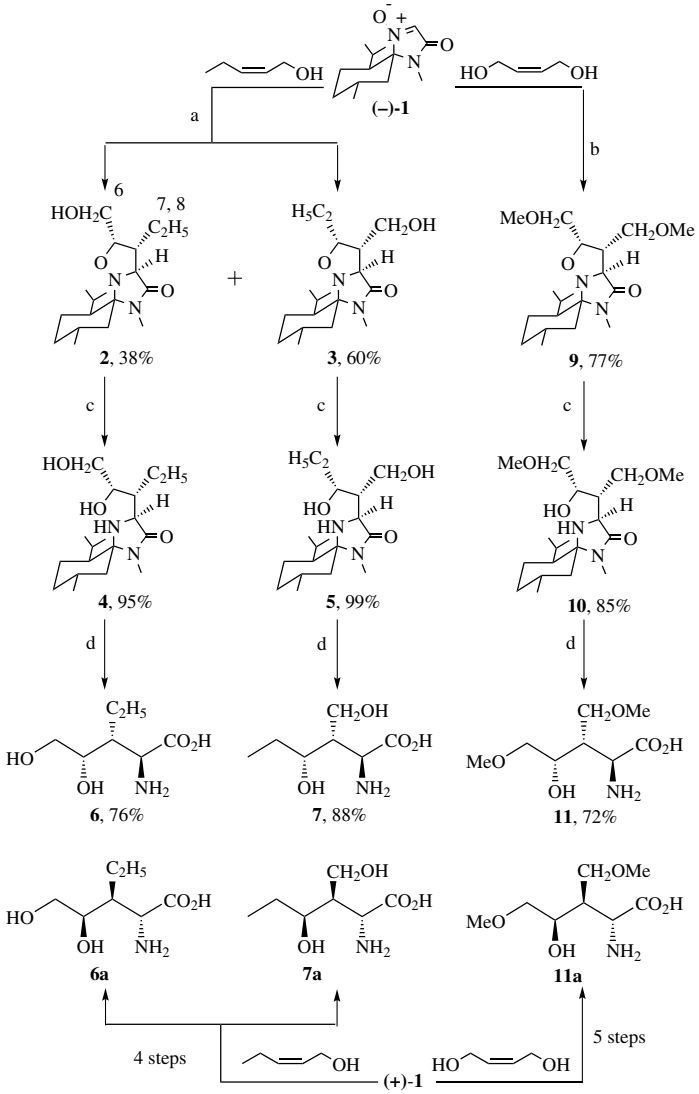
While the cycloaddition of nitrone (−)-**1** to (*Z*)-but-2-en-1,4-diol (3 equiv) proceeded in refluxing toluene within 48 h to produce a single cycloadduct,[25] the reaction carried out under similar conditions with (*Z*)-pent-2-en-1-ol (~3 equiv) occurred within 24 h to deliver regioisomers **2** and **3** in 38% and 60% yield, respectively (Scheme 2). Why compound **3** predominated was questionable,[26] but electronic reasons can account for the regioselectivity observed, since it was resembling (although much less pronounced) that observed for the cycloaddition to crotonaldehyde,[25] in which the electron-rich oxygen atom of the nitrone reacted with the electron-depleted carbon of the enone. The reductive cleavage of the isoxazolidine ring in **2**, **3**, and **9** (obtained after methylation of the cycloadduct formed with (*Z*)-but-2-en-1,4-diol), led to **4**, **5**, and **10** in excellent yields. Cleavage of the chiral auxiliary proceeded smoothly by successive acid-, then basic-catalyzed hydrolysis (Scheme 2). Purification of the products was achieved by reverse-phase flash chromatography (C18) as reported, to afford the products in good yields as colorless oils **6** and **11** or white solid **7**. The use of (+)-**1** to achieve analogous cycloadditions with the same alkenes led to the corresponding cycloadducts, imidazolidinones, and amino acid derivatives, as enantiomers, for example, **6a**, **7a**, and **11a**. This route proved to be quite efficient for preparing six analogues of 4-OH-Ile, with either the (2*S*,3*R*,4*R*) or (2*R*,3*S*,4*S*) configuration, in good overall yields (**6**: 27%, **7**: 52%, **11**: 47%).

As reported recently, the 1,3-dipolar cycloaddition of chiral nitrone (−)-**1** to (*Z*)-but-2-en-1,4-diol took place via an *exo*-approach mode of the alkene on the opposite side of the bulky isopropyl group to afford **9** as a single cycloadduct.[25] We also measured previously the vicinal coupling constants for the isoxazolidine protons, found as follows: $J_{3,4}$ (*syn*) = 8–9 Hz and $J_{3,4}$ (*anti*) < 2 Hz.[22,25]

Structure elucidation for regioisomers **2** and **3** was achieved in part, with the aid of 1D NOE and 2D NMR techniques (COSY, HMBC, and HSQC) which allowed clear assignments of the observed resonances (see Section 4). Nevertheless, regioisomer **2** was subjected to crystal analysis (Fig. 1), which clearly showed the hydrogen atom at C13 pointing to the rear (numbering of the crystal structure),[27] while those at C14, and C15 are pointing to the opposite direction, as expected for a cycloadduct formed via an *exo*-approach mode from the less hindered side. Crystallization of **3** occurred upon storage in a cool place for long time, but the obtained crystals were not suitable for diffractometry. HSQC and HMBC correlations recorded for **3** afforded additional structural informations, among them, the observed HMBC correlations between H-3 (δ_H 4.03) and



Scheme 1.



Scheme 2. Reagents and conditions: (a) (*Z*)-pent-2-en-1-ol, toluene, 110 °C, 24 h; (b) 1-(*Z*)-but-2-en-1,4-diol, toluene, 110 °C, 48 h; 2-MeI, KOH, acetone, $Bu_4N^+Br^-$, 18 h; (c) H_2 (1 atm), $Pd(OH)_2$, MeOH, rt, 4 days; (d) 1-HCl 3 N, 80 °C, 2h; 2-LiOH·H_2O, H_2O, rt, 2 h.

C-7 (δ_C 60.0), on the one hand, and Me-8 (δ_H 0.97) and C-5 (δ_C 80.8) on the other hand were of particular significance to determine the position of the isoxazolidine substituents (see Fig. 2 for numbering). In 1D NOE experiments with a $CDCl_3$ solution of **3a** [the enantiomer of **3** produced from (+)-**1**], selective irradiation of 3-H enhanced the following signals (%): vicinal 4-H proton (2.32), C*H*$(CH_3)_2$ (3.22), CH(C*H*$_3)_2$ (3.71), 5-H/7-H (2.01) (Fig. 2). In addition, selective irradiation of 4-H gave rise to a positive NOE effects (%) on 5-H/7-H (7.43), 3-H (2.12), 7-H (1.29), whereas the irradiation of the 5-H/7-H protons enhanced 4-H (4.33), 6-H (3.16), and a cyclohexyl proton (2.27). These results clearly showed that the C-3-H bond in **3** pointed toward the isopropyl group and concluded to an *anti*-relationship between 3-H and 4-H and a *syn*-relationship between 4-H and 5-H, as found for **9**[25] and **2** (Fig. 1) and as also true for **2a**, **3a**, and **9a**. As a consequence of the similarity of the absolute configuration of the newly created asymmetric carbons of cycloadducts (Scheme 2), the vicinal couplings $J_{3,4}$ (*anti*) were found to be small (**2**: 3.9 Hz, **3**, **9**: 0 Hz). The relationship of the 4-H and 5-H protons was anticipated to be *syn* based on the preferred *exo*-approach of (*Z*)-alkenes in the transition state, as confirmed by the crystal structure of **2** and the NOE observed in **3a**.

3. Conclusion

1,3-Dipolar cycloaddition reactions of chiral nitrones derived from (−)- or (+)-menthone to (*Z*)-pent-2-en-1-ol and (*Z*)-but-2-en-1,4-diol occurred via *exo*-approach and with simultaneous creation of three stereogenic centers to afford isoxazolidines as precursors of non-natural α-amino acids. Considering the fact that the chiral auxiliary can be recovered, this route proved to be quite efficient for preparing analogues of (2*S*,3*R*,4*R*)- and (2*R*,3*S*,4*S*)-4-hydroxyisoleucine.

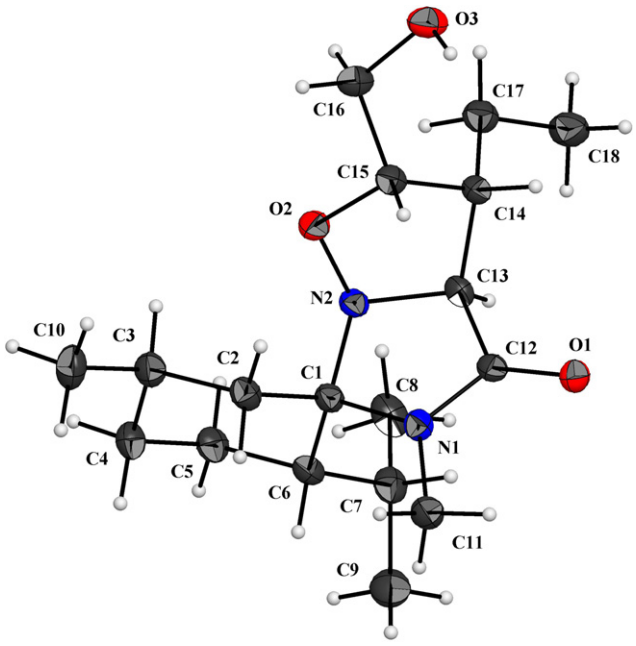


Figure 1. ORTEP representation of the crystal structure of **2**.

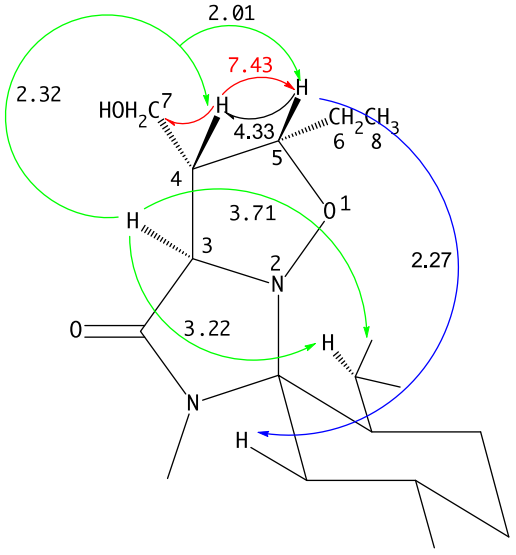


Figure 2. 1D NOE measured for **3a** (7.43% is the enhancement measured for both 5-H and 7-H).

Compounds **7** and **7a** were evaluated as insulin secretagogue by Dr. René Gross (University of Montpellier1, France).[28] Preliminary tests revealed no significant activity.

4. Experimental

4.1. General methods

(*Z*)-Pent-2-en-1-ol and (*Z*)-but-2-en-1,4-diol were used as purchased from Lancaster and Aldrich, respectively. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (Merck). The plates were visualized under UV light, or by gentle heating, or by ninhydrin spray, followed by heating, for amines. Preparative C_{18}-reversed phase chromatography (RP-18) was performed using a 15 × 15 mm column of fully endcapped Silica Gel 100 C_{18} (>400 mesh, Fluka). Optical rotations were determined with a Perkin–Elmer model 241 polarimeter in a 1 dm cell. Melting points were measured with a Büchi apparatus (values were uncorrected). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX300 spectrometer. Chemical shifts are quoted in parts per million, referenced to the residual solvent peak.[29] The following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quadruplet; quin, quintuplet; m, multiplet; br, broad. Coupling constants are reported in Hertz (Hz). HRMS (LSIMS) data were recorded in the positive mode (unless stated otherwise) using a Thermo Finnigan Mat 95 XL spectrometer. MS (ESI) data were recorded in the positive mode using a Thermo Finnigan LCQ spectrometer.

4.2. (1*S*,2*S*,2′*S*,3′*R*,3′a*S*,5*R*)-3′-Ethyl-2′-(hydroxymethyl)-2-isopropyl-5,5′-dimethyl-3′,3′a-dihydro-2′*H*-spiro[cyclohexane-1,6′-imidazo[1,5-*b*]isoxazol]-4′(5′*H*)-one 2 and (1*S*,2*S*,2′*R*,3′*S*,3′a*S*,5*R*)-2′-ethyl-3′-(hydroxymethyl)-2-isopropyl-5,5′-dimethyl-3′,3′a-dihydro-2′*H*-spiro[cyclohexane-1,6′-imidazo[1,5-*b*]isoxazol]-4′(5′*H*)-one 3

Nitrone (−)-**1** (1.68 mmol, 400 mg) and *Z*-pent-2-en-1-ol (4.92 mmol, 423.5 mg) were dissolved in toluene (15 mL) and heated at reflux for 24 h. TLC showed the complete conversion of the nitrone. The solution was concentrated and the residue was purified by flash chromatography ($CHCl_3$–isopropanol 98:2) to afford compounds **2** (190 mg, 35%) and **3** (326 mg, 60%).

4.2.1. Compound 2. Colorless needles; mp 94–95 °C (Et_2O); R_f 0.33 ($CHCl_3$–isopropanol 98:2); $[\alpha]_D^{22} = +62$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.78 (d, 3H, $J = 6.6$ Hz, $CH(CH_3)_2$), 0.85 (d, 3H, $J = 6.9$ Hz, $CH(CH_3)_2$), 0.93 (d, 3H, $J = 6.6$ Hz, CH_3), 0.93 (m, 1H), 1.06 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.24 (t, $J = 12.6$ Hz, 1H), 1.37 (m, 1H), 1.44 (m, 1H, $CH(CH_3)_2$), 1.64 (m, 4H, $2CH_2$), 1.82 (m, 1H), 1.98 (m, 1H), 2.16 (dt, $J = 2.4$ Hz, $J = 2.4$ Hz, $J = 12.9$ Hz, 1H), 2.71 (dddd, 1H, $J_{3,4} = 3.9$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz, $J = 10.8$ Hz, 4-H), 2.73 (s, 3H, NCH_3), 2.80 (br s, 1H, OH), 3.59 (d, 1H, $J_{3,4} = 3.9$ Hz, 3-H), 3.75 (m, 2H, CH_2), 4.06 (ddd, 1H, $J = 4.5$ Hz, $J = 6.9$ Hz, $J = 9.0$ Hz, 5-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.9 (C-8), 18.4 ($CH(CH_3)_2$), 21.6 (C-7), 22.2 (CH_3), 22.4 (CH_2), 24.0 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$), 25.8 (NCH_3), 29.5 (CH), 34.5 (CH_2), 40.3 (CH_2), 47.9 (CH), 49.7 (C-4), 62.1 (C-6), 70.1 (C-3), 79.2 (C-5), 88.0 (C^{IV}), 172.9 (C=O). HRMS, (ESI) calcd for $C_{18}H_{33}N_2O_3$ $(MH)^+$ 325.2491, found: 325.2492.

4.2.2. Compound 3. Colorless crystals; mp 111–113 °C (Et_2O); R_f 0.26 ($CHCl_3$–isopropanol 98:2); $[\alpha]_D^{22} = +29$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (d, 3H, $J = 6.6$ Hz, $CH(CH_3)_2$), 0.86 (d, 3H, $J = 6.6$ Hz, $CH(CH_3)_2$), 0.91 (d, 3H, $J = 6.6$ Hz, CH_3), 0.91 (m, 1H), 0.97 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.27 (t, $J = 12.3$ Hz, 1H), 1.33 (dd, $J = 2.7$ Hz, $J = 12.1$ Hz, 1H), 1.40 (m, 1H,

C*H*(CH_3)$_2$), 1.58 (m, 3H, 6-H), 1.72 (dq, $J = 3.3$ Hz, $J = 12.9$ Hz, 1H), 1.81 (br d, $J = 12.7$ Hz, 1H), 1.95 (dt, $J = 2.7$ Hz, $J = 2.7$ Hz, $J = 12.9$ Hz, 1H), 2.07 (m, 1H), 2.74 (s, 3H, NCH_3), 2.89 (m, 1H, 4-H), 3.18 (br s, 1H, OH), 3.71 (m, 2H, 5-H, 7-H), 3.84 (dd, 1H, $J = 4.8$ Hz, $J = 6.3$ Hz, 7-H), 4.03 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.2 (C-8), 17.9 (CH_2), 18.2 (CH(*C*H_3)$_2$), 21.2 (C-6), 22.1 (CH_2), 22.2 (CH_3), 24.0 (CH(*C*H_3)$_2$), 24.3 (*C*H(CH_3)$_2$), 26.0 (NCH_3), 29.6 (CH), 34.4 (CH_2), 40.2 (CH_2), 47.9 (CH), 51.0 (C-4), 60.0 (CH_2OH), 68.9 (C-3), 80.8 (C-5), 90.0 (C^{IV}), 173.0 (C=O). HRMS, (ESI) calcd for $C_{18}H_{33}N_2O_3$ (MH)$^+$325.2491, found: 325.2486.

4.3. (1*R*,2*R*,2′*R*,3′*S*,3′a*R*,5*S*)-3′-Ethyl-2′-(hydroxymethyl)-2-isopropyl-5,5′-dimethyl-3′,3′a-dihydro-2′*H*-spiro[cyclohexane-1,6′-imidazo[1,5-*b*]isoxazol]-4′(5′*H*)-one 2a and (1*R*,2*R*,2′*S*,3′*R*,3′a*R*,5*S*)-2′-Ethyl-3′-(hydroxymethyl)-2-isopropyl-5,5′-dimethyl-3′,3′a-dihydro-2′*H*-spiro[cyclohexane-1,6′-imidazo [1,5-*b*]isoxazol]-4′(5′*H*)-one 3a

The previous procedure was applied to (+)-**1** (463 mg, 1.94 mmol) and (*Z*)-pent-2-en-1-ol (4.93 mmol, 425 mg) afforded **2a** (115 mg, 19%) and **3a** (345 mg, 55%).

4.3.1. Compound 2a. White crystals; mp 94–95 °C (Et_2O); R_f 0.28 ($CHCl_3$–*i*PrOH 98:2); $[\alpha]_D^{22} = -61$ (*c* 1.0, CH_2Cl_2). HRMS, (CI, isobutane) calcd for $C_{18}H_{33}N_2O_3$ (MH)$^+$ 325.2491, found: 325.2491.

4.3.2. Compound 3a. White crystals; mp 111–113 °C (Et_2O); R_f 0.21 ($CHCl_3$–*i*PrOH 98:2); $[\alpha]_D^{22} = -27$ (*c* 1.0, CH_2Cl_2). HRMS, (CI, isobutane) calcd for $C_{18}H_{33}N_2O_3$ (MH)$^+$ 325.2491, found: 325.2490.

4.4. (3*S*,5*R*,6*S*,9*R*)-3-[(1*R*,2*S*)-1-Ethyl-2,3-dihydroxypropyl]-6-isopropyl-1,9-dimethyl-1,4-diazaspiro[4.5]decan-2-one 4

A suspension of **2** (0.31 mmol, 100 mg) and $Pd(OH)_2$/C (20%, 86 mg) was stirred in MeOH (10 mL) at rt under H_2 (1 atm) for 4 days. The mixture was filtered over Celite, evaporated, and purified by flash chromatography ($CHCl_3$–isopropanol 98:2) to afford compound **4** (99.6 mg, 99%) as a white solid. Mp 125–128 °C (Et_2O); R_f 0.16 ($CHCl_3$–*i*PrOH 98:2); $[\alpha]^{22} = +8$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (d, 3H, $J = 6.6$ Hz, CH(CH_3)$_2$), 0.87 (m, 1H), 0.88 (d, 3H, $J = 6.9$ Hz, CH(CH_3)$_2$), 0.94 (d, 3H, $J = 6.6$ Hz, CH_3), 0.97 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.33 (m, 1H), 1.48 (m, 3H), 1.60 (m, 3H), 1.74 (m, 4H), 2.55 (s, 2H, 2OH), 2.78 (s, 3H, NCH_3), 3.53 (dd, 1H, $J = 4.5$ Hz, $J = 11.1$ Hz), 3.67 (dd, 1H, $J = 7.8$ Hz, $J = 11.1$ Hz), 3.85 (m, 2H), 4.67 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.4 (CH_3), 17.9 (CH_2), 18.5 (CH_3), 22.1 (CH_3), 22.3 (CH_2), 23.9 (CH_3), 24.4 (CH), 25.2 (NCH_3), 28.8 (CH), 34.3 (CH_2), 42.9 (CH), 46.7 (CH), 47.6 (CH_2), 60.8 (CH), 64.8 (CH_2OH), 72.8 (CHOH), 80.6 (C^{IV}), 173.1 (C=O). HRMS, (CI, isobutane) calcd for $C_{18}H_{35}N_2O_3$ (MH)$^+$ 327.2648, found: 327.2650.

4.5. (3*R*,5*S*,6*R*,9*S*)-3-[(1*S*,2*R*)-1-Ethyl-2,3-dihydroxypropyl]-6-isopropyl-1,9-dimethyl-1,4-diazaspiro[4.5]decan-2-one 4a

The previous procedure was applied to **2a** (0.31 mmol, 100 mg) afforded compound **4a** (89.5 mg, 89%) as a white solid. Mp 125–128 °C (Et_2O); R_f 0.16 ($CHCl_3$–*i*PrOH 98:2); $[\alpha]_D^{22} = -9$ (*c* 1.0, CH_2Cl_2). HRMS, (CI, isobutane) calcd for $C_{18}H_{35}N_2O_3$ (MH)$^+$: 327.2648, found: 327.2644.

4.6. (3*S*,5*R*,6*S*,9*R*)-3-[(1*S*,2*R*)-2-Hydroxy-1-(hydroxymethyl)butyl]-6-isopropyl-1,9-dimethyl-1,4-diazaspiro[4.5]-decan-2-one 5

Prepared, as described for **4**, from **3** (0.31 mmol, 100 mg) to afford **5** (95 mg, 95%) as a colorless syrup. R_f 0.48 ($CHCl_3$–*i*PrOH 98:2); $[\alpha]_D^{22} = +10$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (d, 3H, $J = 6.6$ Hz, CH(CH_3)$_2$), 0.89 (d, 3H, $J = 6.9$ Hz, CH(CH_3)$_2$), 0.90 (m, 1H), 0.93 (d, 3H, $J = 6.3$ Hz, CH_3), 0.96 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.31 (m, 1H), 1.50 (m, 4H), 1.70 (m, 5H), 1.97 (m, 1H), 2.80 (s, 3H, NCH_3), 3.08 (br s, 2H, 2OH), 3.80 (m, 2H), 4.02 (d, 1H, $J = 3.0$ Hz), 4.06 (dd, 1H, $J = 5.4$ Hz, $J = 11.7$ Hz), 5.44 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.6 (CH_3), 18.7 (CH_3), 22.0 (CH_3), 22.4 (CH_2), 23.9 (CH_3), 24.5 (CH), 25.3 (NCH_3), 27.7 (CH_2), 28.8 (CH), 34.3 (CH_2), 44.8 (CH), 46.7 (CH), 47.9 (CH_2), 61.5 (CH_2OH), 62.3 (CH), 74.5 (CHOH), 80.7 (C^{IV}), 173.0 (C=O). HRMS, (ESI) calcd for $C_{18}H_{35}N_2O_3$ (MH)$^+$ 327.2648, found: 327.2647.

4.7. (3*R*,5*S*,6*R*,9*S*)-3-[(1*R*,2*S*)-2-Hydroxy-1-(hydroxymethyl)butyl]-6-isopropyl-1,9-dimethyl-1,4-diazaspiro[4.5]-decan-2-one 5a

The previous procedure applied to **3a** (0.31 mmol, 100 mg) afforded compound **5a** (96.5 mg, 96%) as a colorless syrup. R_f 0.48 ($CHCl_3$–*i*PrOH 98:2); $[\alpha]_D^{22} = -10$ (*c* 1.0, CH_2Cl_2). HRMS, (ESI) calcd for $C_{18}H_{35}N_2O_3$ (MH)$^+$ 327.2648, found: 327.2647.

4.8. (2*S*,3*R*,4*S*)-2-Amino-3-ethyl-4,5-dihydroxy-pentanoic acid 6

A solution of **4** (0.24 mmol, 60 mg) and AcOH (19.5 mL) in aq HCl (3 N, 24 mL) was stirred at 80 °C for 2 h. The reaction mixture was then concentrated to dryness and LiOH·H_2O (160 mg) in THF–H_2O (1:1, 8 mL) was added. The resulting mixture was stirred at rt for 2 h, then evaporated to dryness, and purified by reverse-phase flash chromatography (C18) to afford the desired amino acid **6** (24 mg, 76%) as a colorless oil. R_f 0.52 (MeOH–H_2O 9:1); $[\alpha]_D^{22} = -7$ (*c* 1.0, H_2O); ^{1}H NMR (D_2O, 300 MHz): δ 1.00 (t, 3H, $J = 7.5$ Hz, CH_3), 1.43 (m, 1H, CH_2CH$_3$), 1.58 (m, 1H, CH_2CH$_3$), 1.98 (m, 1H, H-3), 3.58 (m, 2H, CH_2OH), 3.81 (d, 1H, $J_{2,3} = 3.9$ Hz, H-2), 3.89 (m, 1H, H-4); ^{13}C NMR (D_2O, 75 MHz): δ 11.7 (CH_3), 17.3 (CH_2), 42.9 (C-3), 57.0 (C-2), 64.1 (CH_2), 73.1 (C-4), 178.1 (C=O). HRMS, (CI, isobutane) calcd for $C_7H_{16}NO_4$ (MH)$^+$ 178.1079, found: 178.1083.

4.9. (2*R*,3*S*,4*R*)-2-Amino-3-ethyl-4,5-dihydroxy-pentanoic acid 6a

The previous procedure applied to **4a** (60 mg, 0.24 mmol) afforded compound **6a** (24.6 mg, 78%) as a colorless syrup. R_f 0.52 (MeOH–H_2O 9:1); $[\alpha]_D^{22} = +7$ (*c* 1.0, H_2O). HRMS, (CI, isobutane) calcd for $C_7H_{16}NO_4$ $(MH)^+$ 178.1079, found: 178.1082.

4.10. (2*S*,3*S*,4*R*)-2-Amino-4-hydroxy-3-(hydroxymethyl)-hexanoic acid 7

Prepared, as described for **6**, from **5** (0.30 mmol, 100 mg) to afford **7** (48 mg, 88%) as a white solid. Mp 125–130 °C (MeOH); R_f 0.52 (MeOH–H_2O 9:1); $[\alpha]_D^{22} = -31$ (*c* 0.4, H_2O); ^{1}H NMR (D_2O, 300 MHz): δ 0.86 (t, 3H, $J_{6,5} =$ 7.5 Hz, CH_3), 1.51 (quin, 2H, $J = 7.5$ Hz, CH_2), 2.17 (m, 1H, H-3), 3.71 (m, 2H), 3.89 (m, 2H); ^{13}C NMR (D_2O, 75 MHz): δ 10.0 (CH_3), 27.9 (CH_2), 45.1 (C-3), 56.7 (C-2), 58.4 (CH_2), 73.5 (C-4), 177.3 (C=O). HRMS, (CI, isobutane) calcd for $C_7H_{16}NO_4$ $(MH)^+$178.1079, found: 178.1078.

4.11. (2*R*,3*R*,4*S*)-2-Amino-4-hydroxy-3-(hydroxymethyl)-hexanoic acid 7a

The previous procedure applied to **5a** (0.36 mmol, 120 mg) afforded compound **7a** (60 mg, 92%) as a white solid. Mp 125–130 °C (MeOH); R_f 0.54 (MeOH–H_2O 9:1); $[\alpha]_D^{22} =$ +28 (*c* 1.0, H_2O). HRMS, (CI, isobutane) calcd for $C_7H_{16}NO_4$ $(MH)^+$ 178.1079, found: 178.1078.

4.12. (1*S*,2*S*,2′*S*,3′*S*,3′a*S*,5*R*)-2′,3′-Bis(methoxymethyl)-2-isopropyl-5,5′-dimethyl-3′,3′a-dihydro-2′*H*-spiro[cyclohexane-1,6′-imidazo[1,5-*b*]isoxazol]-4′(5′*H*)-one 9

A solution of nitrone (−)-**1** (1.55 mmol, 370 mg) and *Z*-but-2-en-1,4-diol (4.65 mmol, 411 mg) was stirred in toluene (10 mL) for 48 h at 110 °C. TLC showed the complete conversion of nitrone. The solution was evaporated and the residue purified by flash chromatography ($CHCl_3$-isopropanol 98:2) to afford **8** (247 mg) contaminated with a small amount of unreacted *Z*-but-2-en-1,4-diol. This residue was dissolved in acetone (10 mL). Then KOH (pellets, in excess) and $Bu_4N^+Br^-$(27 mg, 0.08 mmol) were added. To the mixture, cooled to 0 °C, CH_3I (0.024 mol, 1.5 mL) was added dropwise. The reaction was allowed to proceed at room temperature for 18 h. After acetone was evaporated under reduced pressure, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with NH_4Cl solution and water, then dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc–petroleum ether 3:7) to afford compound **9** (424 mg, 77% yield from nitrone) as a colorless syrup. R_f 0.21 (EtOAc–petroleum ether 7:3); $[\alpha]_D^{22} = +26$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83 (d, 3H, $J = 6.6$ Hz, $CH(CH_3)_2$), 0.84 (d, 3H, $J = 6.6$ Hz, $CH(CH_3)_2$), 0.92 (d, 3H, $J = 6.6$ Hz, CH_3), 0.93 (m, 1H), 1.33 (m, 3H), 1.61 (m, 2H, CH_2), 1.81 (m, 1H), 2.03 (dt, 1H, $J = 12.6$ Hz, $J = 2.4$ Hz), 2.09 (m, 1H), 2.74 (s, 3H, NCH_3), 3.10 (m, 1H), 3.34, 3.36 (2s, 6H, 2 OCH_3), 3.40 (dd, 1H, $J = 6.9$ Hz, $J =$ 12.3 Hz, $HCHOCH_3$), 3.42 (dd, 1H, $J = 7.8$ Hz, $J =$ 11.4 Hz, $HCHOCH_3$), 3.54 (dd, 1H, $J = 8.1$ Hz, $J =$ 12.3 Hz, $HCHOCH_3$), 3.70 (dd, 1H, $J = 3.0$ Hz, $J = 11.4$ Hz, $HCHOCH_3$), 3.81 (br s, 1H), 4.01 (ddd, 1H, $J = 3.3$ Hz, $J = 4.5$ Hz, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.1 ($CH(CH_3)_2$), 22.0 (CH_2), 22.2 (CH_3), 23.9 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$), 25.9 (NCH_3), 29.4 (CH), 34.3 (CH_2), 40.2 (CH_2), 47.7 (CH), 48.0 (CH), 58.5, 59.0 ($2OCH_3$), 68.1 (CH), 69.7 (CH_2OCH_3), 70.2 (CH_2OCH_3), 78.8 (CH), 89.7 (C^{IV}), 172.1 (C=O). HRMS, (ESI) calcd for $C_{19}H_{35}N_2O_4$ $(MH)^+$ 355.2597, found: 355.2595.

4.13. (1*R*,2*R*,2′*R*,3′*R*,3′a*R*,5*S*)-2′,3′-Bis(methoxymethyl)-2-isopropyl-5,5′-dimethyl-3′,3′a-dihydro-2′*H*-spiro[cyclohexane-1,6′-imidazo[1,5-*b*]isoxazol]-4′(5′*H*)-one 9a

The previous procedure applied to (+)-**1** (1.13 mmol, 270 mg) and *Z*-but-2-en-1,4-diol (6.07 mmol, 500 μL) afforded compound **9a** (305 mg, 76% yield from nitrone) as a colorless syrup. R_f 0.55 (EtOAc–petroleum ether 1:1); $[\alpha]_D^{22} = -26$ (*c* 1.0, CH_2Cl_2). HRMS, (ESI) calcd for $C_{19}H_{35}N_2O_4$ $(MH)^+$ 355.2597, found: 355.2593.

4.14. (3*S*,5*R*,6*S*,9*R*)-3-[(1*S*,2*S*)-2-Hydroxy-3-methoxy-1-(methoxymethyl)propyl]-6-isopropyl-1,9-dimethyl-1,4-diaza-spiro[4.5]decan-2-one 10

Prepared, as described for **4**, from **9** (0.15 mmol, 53 mg) to afford **10** (45 mg, 85%) as a colorless syrup. R_f 0.25 (EtOAc–petroleum ether 1:1); $[\alpha]_D^{22} = +4$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86 (d, 6H, $J = 6.9$ Hz, $CH(CH_3)_2$), 0.90 (m, 1H), 0.91 (d, 3H, $J = 6.6$ Hz, CH_3), 1.37 (m, 2H), 1.48 (m, 2H), 1.55 (m, 1H), 1.64 (m, 2H), 1.77 (m, 1H), 2.29 (m, 1H), 2.64 (br s, 1H, OH), 2.77 (s, 3H, NCH_3), 3.31, 3.38 (2s, 6H, 2 OCH_3), 3.39 (m, 1H), 3.53 (m, 2H), 3.69 (dd, 1H, $J = 4.5$ Hz, $J = 9.9$ Hz), 3.80 (d, 1H, $J = 2.7$ Hz), 4.05 (m, 1H), 5.25 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.1 (CH_3), 22.0 (CH_2), 22.1 (CH_3), 23.9 (CH_3), 24.4 (CH), 25.2 (NCH_3), 28.6 (CH), 34.3 (CH_2), 41.2 (CH), 46.6 (CH), 47.3 (CH_2), 58.6, 58.9 (2 OCH_3), 62.7 (CH), 69.9 (CH_2OCH_3), 70.7 (CHOH), 74.7 (CH_2OCH_3), 81.1 (C^{IV}), 173.5 (C=O). HRMS, (ESI) calcd for $C_{19}H_{37}N_2O_4$ $(MH)^+$ 357.2753, found: 357.2745.

4.15. (3*R*,5*S*,6*R*,9*S*)-3-[(1*R*,2*R*)-2-Hydroxy-3-methoxy-1-(methoxymethyl)propyl]-6-isopropyl-1,9-dimethyl-1,4-diaza-spiro[4.5]decan-2-one 10a

The previous procedure applied to **9a** (0.28 mmol, 100 mg) afforded compound **10a** (90 mg, 90%) as a colorless syrup. R_f 0.25 (EtOAc–petroleum ether 1:1); $[\alpha]_D^{22} = -4$ (*c* 1.0, CH_2Cl_2). HRMS, (ESI) calcd for $C_{19}H_{37}N_2O_4$ $(MH)^+$ 357.2753, found: 357.2742.

4.16. (2*S*,3*S*,4*S*)-2-Amino-4-hydroxy-5-methoxy-3-(methoxymethyl)-pentanoic acid 11

Prepared, as described for **6**, from **10** (0.12 mmol, 45 mg) to afford **11** (18 mg, 72%) as a colorless oil. R_f 0.65 (MeOH–

H_2O 9:1); $[\alpha]_D^{22} = +5$ (*c* 1.0, H_2O); ^1H NMR (D_2O, 300 MHz): δ 2.15 (m, 1H, H-3), 3.27, 3.31 (2s, 6H, 2 OCH_3), 3.48 (m, 3H), 3.62 (m, 2H), 4.01 (m, 1H, H-4); ^{13}C NMR (D_2O, 75 MHz): δ 42.5 (C-3), 57.2 (C-2), 58.5 (2 OCH_3), 69.8 (CH_2), 69.9 (C-4), 75.1 (CH_2), 178.5 (C=O). HRMS, (CI, isobutane) calcd for $C_8H_{18}NO_5$ $(MH)^+$ 208.1185, found: 208.1185.

4.17. (2*R*,3*R*,4*R*)-2-Amino-4-hydroxy-5-methoxy-3-(methoxymethyl)-pentanoic acid 11a

The previous procedure applied to **10a** (0.14 mmol, 50 mg) afforded compound **11a** (21.3 mg, 73%) as a colorless oil. R_f 0.65 (MeOH–H_2O 9:1); $[\alpha]_D^{22} = -5$ (*c* 1.0, H_2O). HRMS, (CI, isobutane) calcd for $C_8H_{18}NO_5$ $(MH)^+$ 208.1185, found: 208.1185.

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27. Crystal data of compound **2**: $C_{18}H_{32}N_2O_3$, $M = 324.24$, monoclinic, $P2_1$, $a = 8.352(5)$ Å, $b = 17.802(5)$ Å, $c = 12.568(5)$ Å, $V = 1856.6(14)$ Å^3, $Z = 2$, $D_x = 1.161$ Mg m^{-3},

μ (Mo-K$_\alpha$) = 0.08 mm^{-1}, colorless needle, 4201 reflections measured ($R_{int} = 0.140$), 4513 unique, $wR_2 = 0.052$, conventional $R = 0.050$ on F values of 3107 reflections with $I > 2.0\sigma(I)$, $(\Delta/\sigma)_{max} < 0.0001$, $S = 1.09$. Unit cell determination and intensity data collection ($\theta_{max} = 27.9°$) were performed on a Nonius KappaCCD at 150(2) K. Structure solutions were found by direct methods and refinements were achieved by full-matrix least-squares methods on F. Data collection: COLLECT (Nonius, 1997–2001). Cell refinement: DENZO/SCALEPACK (Otwinowski & Minor, 1997). Data reduction: DENZO/SCALEPACK (Otwinowski & Minor, 1997). Program(s) used to solve structure: SIR97 (Altomare et al., 1999). Program(s) used to refine structure: CRYSTALS (Betteridge et al., 2003). Molecular graphics: DIAMOND (Brandenburg et al., 1996). Software used to prepare material for publication: CRYSTALS (Betteridge et al., 2003). Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC Deposition No. 652568).

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