Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron

Tetrahedron 62 (2006) 4430–4434

Short and efficient preparations of isoxazole-3-carboxylic acid and imino-oxopentanoic acid potent precursors of 4-hydroxyisoleucine

Jean-Michel Becht, Sandra De Lamo Marin, Martine Maruani,
Alain Wagner* and Charles Mioskowski*

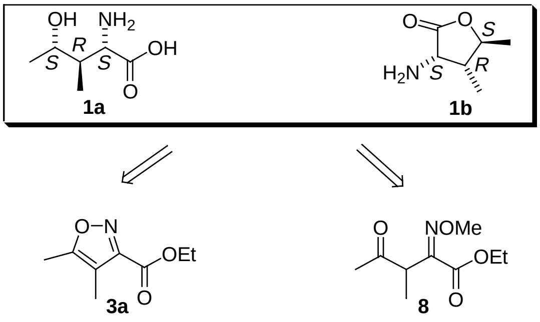
Laboratoire de Synthèse Bioorganique, UMR 7514 associée au CNRS, Faculté de Pharmacie,
Université Louis Pasteur de Strasbourg, 74 Route du Rhin, 67400 Illkirch, France

Received 18 January 2006; revised 14 February 2006; accepted 20 February 2006

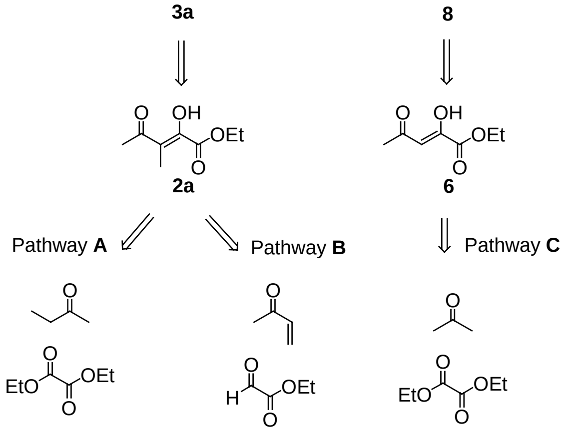
Abstract—Herein, we describe short and efficient syntheses of isoxazole-3-carboxylic acid **3a** and imino-oxopentanoic acid **8** achiral precursors of 4-hydroxyisoleucine. The developed procedures involve readily available and cheap starting materials and can easily be transposed to the large scale.

1. Introduction

It has been estimated that more than 200 million people in the world will have diabetes mellitus in the next decade. Therefore, the development of improved antidiabetic drugs has concentrated huge interest in medicinal chemistry.[1] (2*S*,3*R*,4*S*)-4-Hydroxyisoleucine **1a**, a natural product extracted from fenugreek seeds has emerged as a promising candidate.[2] However, production of this compound through an extraction process is not practicable for pharmaceutical supply. To date, only two stereoselective syntheses of (2*S*,3*R*,4*S*)-**1a** have been reported.[3,4] These syntheses suffer from many drawbacks that prohibit their use for the large scale production. For instance, they involve more than six steps and proceed with low overall yields. They also require the use of expensive starting materials, chiral auxiliaries as well as enzymatic resolutions. For these reasons, we have focused our attention to the development of a short and efficient synthesis of the natural occurring (2*S*,3*R*,4*S*)-**1a** and its corresponding lactone (3*S*,4*R*,5*S*)-3-amino-4,5-dimethyl-2-oxotetrahydrofuran **1b** from achiral 4,5-dimethyl-isoxazole-3-carboxylic acid ethyl ester **3a** and 2-methoxyimino-3-methyl-4-oxo-pentanoic acid ethyl ester **8** (Scheme 1). The compounds **1a** and **1b** can be obtained using as a key step stereoselective reductions and kinetic resolutions of **3a** and **8**.[5,6] Herein, we describe straightforward and inexpensive methodologies for large scale syntheses of substrates **3a** and **8** from readily available starting materials (Scheme 2).[7] The results concerning stereoselective reductions of **3a** and **8** will be reported in due course.



Scheme 1. Retrosynthetic analysis for the synthesis of **1a** and **1b**.



Scheme 2. Retrosynthetic analysis for the synthesis of **3a** and **8**.

Keywords: Achiral precursors; Organic phase; Stereoselective.

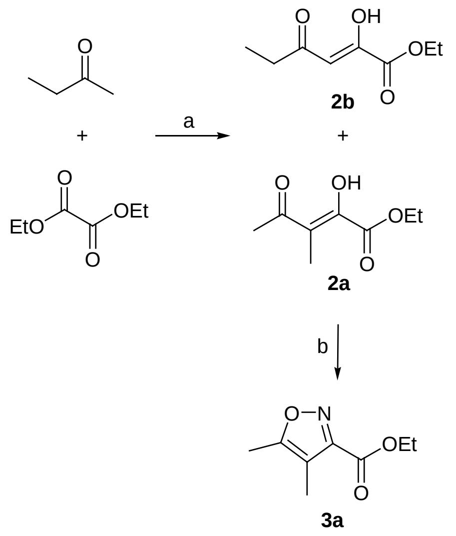
* Corresponding authors. Tel.: +33 (0)3 90 24 42 97; fax: +33 (0)3 90 24 43 06; e-mail: mioskowski@bioorga.u-strasbg.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.056

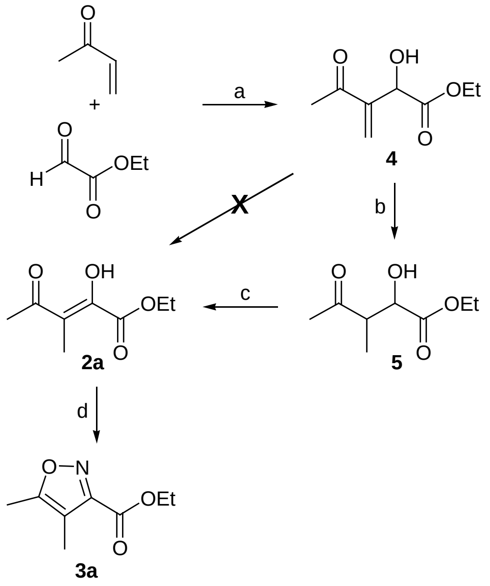
2. Results and discussion

The most common strategy for the synthesis of isoxazoles involves cycloaddition reactions of a nitrone or a nitrile oxide and an alkene or an alkyne.[8] The major drawbacks of these procedures are the low reactivity of the dipolarophiles and the dimerisation side reactions of the nitrile oxides to generate furoxanes.[8] Moreover, these reactions require expensive starting materials and are not easily amenable to the large scale. Therefore, we have turned our attention to the reaction of 2-hydroxy-3-methyl-4-oxo-pent-2-enoic acid ethyl ester **2a** with hydroxylamine to generate **3a** (Scheme 3). The first approach for the synthesis of **2a** involves the aldol condensation of the cheap and commercially available butanone and diethyloxalate in the presence of EtONa in EtOH at rt for 10 min (Scheme 2, pathway A).[9] As expected, a mixture of 2-hydroxy-3-methyl-4-oxo-pent-2-enoic acid ethyl ester **2a** and 2-hydroxy-4-oxo-hex-2-enoic acid ethyl ester **2b** were obtained in quantitative yield (Scheme 3). The separation of **2a** and **2b** by crystallization, distillation or flash-chromatography on silica-gel or alumina failed. Interestingly, we found a simple and efficient method to isolate the desired compound **2a**. EtOH was firstly distillated under reduced pressure and the crude reaction mixture dissolved in AcOEt. The organic phase was washed with a saturated solution of brine and the aqueous phase was extracted three times with AcOEt. ^{1}H NMR showed that compound **2b** was selectively extracted from the crude reaction mixture. The aqueous phase was then carefully acidified to pH 6 with HCl 10% and extracted three times with AcOEt. Noteworthy, by lowering the pH of the aqueous phase below 6, lactonisation of **2a** took place to afford 3-ethoxy-3-hydroxy-4,5-dimethyl-3*H*-furan-2-one.[10] We observed that washing the organic phase with water or by using diethylether for the extraction, the separation of **2a** and **2b** was much less efficient. After drying the combined organic phases with $MgSO_4$ and removal of the solvent under vacuum, **2a** was isolated in 35% yield (70% of the presence in the crude reaction mixture).[11a] We then turned our attention to the functionalization of **2a** with hydroxylamine. The reaction of the carbonyl group at the α position of an ester function with an amine is generally performed in the presence of an acid catalyst and an excess of amine.[12] By reacting non-symmetrical 1,3-diketones with amines, mixtures of regioisomers are generally obtained.[13] In some cases, the regioselectivity of this reaction can be controlled by adjusting the pH of the reaction medium.[13c,d] We have shown that a regioselective reaction occurs at the α position of the ester group by using hydroxylamine hydrochloride and at the γ position by using the free amine.[11b] Hydroxylamine hydrochloride was then added slowly at rt to a solution of **2a** in a 1:1 mixture of EtOH/THF, giving **3a** as the only product in 71% isolated yield.

In order to improve the yield obtained for the synthesis of **2a** (Scheme 3), we have investigated another pathway based on a Baylis–Hillmann condensation of methylvinylketone (MVK) and ethylglyoxalate (Scheme 2, pathway B).[14] In the presence of catalytic amounts of DABCO in dioxane, the Baylis–Hillmann adduct **4** was isolated in 77% yield after rapid filtration on silica-gel (Scheme 4). Noteworthy, another Baylis–Hillmann strategy for the synthesis of **2a** implies as a key-step the condensation of 2-oxo-but-3-enoic acid ethyl ester and acetaldehyde. Several reaction conditions were tested for this purpose but we observed only dimerisation of 2-oxo-but-3-enoic acid ethyl ester. Interestingly, the C–C double bond isomerisation of **4** into **2a** failed under acidic (i.e., formic acid, HCl, TFA) or basic (i.e., K_2CO_3, *t*-BuOK, DBU) conditions. Similar results were obtained in the presence of transition metal catalysts (i.e., Ir, Ni, Pd, Ru, Rh). In each case, **4** was quantitatively recovered. Compound **4** was then reduced with H_2/Pd/$CaCO_3$ in EtOH at rt for 3 h to give **5** in 85% yield, followed by Swern oxidation to afford **2a** in 81% isolated yield.[15] The extraction of **2a** was firstly performed with a phosphate buffer (pH 6.8) or a borax buffer (pH 9.6). The desired compound was, respectively, isolated in 42 and 75% yield. Improved yield was obtained by performing the extraction



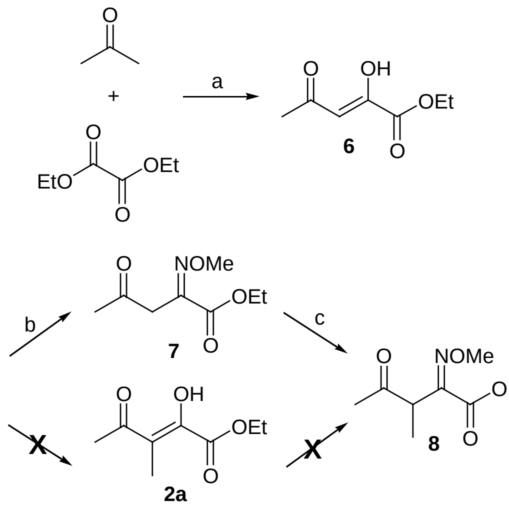
Scheme 3. Reagent and conditions: (a) Na, EtOH, rt, 10 min, 35%. (b) $HONH_2$.HCl, EtOH/THF 1:1, rt, 24 h, 71%.



Scheme 4. Reagent and conditions: (a) DABCO, dioxane, rt, 30 h, 77%. (b) Pd/$CaCo_3$, H_2, EtOH, rt, 3 h, 85%. (c) TFAA, DMSO, DCM, −78 °C, 2 h then TEA, −78 °C to rt, 2 h, 81% (d) $HONH_2$.HCl, EtOH/THF 1:1, rt, 24 h, 71%.

at pH 6 by using a KCl/NaOH buffer (pH 12). Under these work-up conditions, pure **2a** was obtained in 81% yield and did not require further purification. Finally, by reacting **2a** with hydroxylamine hydrochloride in a 1:1 mixture of EtOH/THF, **3a** was isolated in 71% yield.

We then focused our attention to the synthesis of **8**. Compound **2a**, synthesized as described above, was firstly reacted with methoxylamine hydrochloride or with free methoxylamine and catalytic amounts of acids in various solvents (i.e., EtOH, EtOH/H_2O, THF, THF/H_2O). Unfortunately, **8** was never obtained in reasonable yield (Scheme 5). Complex reaction mixtures were generally observed. We tried a completely different pathway based on the reaction of 2-hydroxy-4-oxo-pent-2-enoic acid ethyl ester **6** with methoxylamine hydrochloride, followed by methylation reaction to generate **8** (Scheme 2, pathway C). The aldol condensation of acetone and diethyloxalate in the presence of EtONa in EtOH at rt for 2 h gave pure **6** in 89% yield (Scheme 5).[9] This reaction has been transposed efficiently on a 100 g scale without any noticeable loss in efficacy. Several attempts to perform the methylation of **6** before the amination reaction failed by using various bases (i.e., EtONa, *t*-BuOK, K_2CO_3), solvents (i.e., EtOH, DMF, THF, acetone) or methylating reagents (i.e., MeI or dimethylsulfate). Complex reaction mixtures or dimethylated product were generally obtained. Compound **6** was then firstly reacted with benzyloxyamine, benzylamine and methoxylamine hydrochlorides at rt for 12 h in a 1:1 mixture EtOH/H_2O to afford the expected products in 43, 74 and 88% yields, respectively.[16] The methylation reaction conditions were then optimized with **7** as model substrate. The use of MeI, various bases (i.e., K_2CO_3, NaH, $NaNH_2$) and solvents (i.e., EtOH, DMF, acetone) did not afford the expected product. Similar results were obtained with dimethylsulfate as a methylating reagent. Degradation by-products were also observed in this case. Better results were obtained by reacting **7** in the presence of *t*-BuOK and MeI in THF. Under these reaction conditions, we isolated **8** in 90% yield after rapid filtration on silica-gel.



Scheme 5. Reagent and conditions: (a) Na, EtOH, rt, 2 h, 89%. (b) $MeONH_2$.HCl, EtOH/H_2O 1:1, rt, 12 h, 88%. (c) *t*-BuOK, THF, 0 °C, 30 min then MeI, 0 °C to rt, 12 h, 90%

3. Conclusions

We have described short and efficient syntheses of achiral 4-hydroxyisoleucine precursors **3a** and **8**. The described procedures require only cheap and readily available substrates and can efficiently be transposed on the large scale. The results concerning stereoselective reductions of **3a** and **8** to generate optically pure 4-hydroxyisoleucine will be reported in due course.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded using whether a 200 or 300 MHz instrument in $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield from TMS. Spin multiplicities are indicated by the following symbol: s (singlet), d (doublet), t (triplet) and m (multiplet). IR absorbances are reported in reciprocal centimeters (cm^{-1}). The mass spectra were recorded by the ionization technique using ammonia gas. THF was distilled from sodium/benzophenone. Acetone, EtOH and DMSO were dried on molecular sieves 4 Å.

4.1.1. Preparations of 2-hydroxy-3-methyl-4-oxo-pent-2-enoic acid ethyl ester (2a). *Procedure 1.* A solution of EtONa is generated by reacting sodium (528 mmol, 12.1 g, 1.2 equiv) in anhydrous EtOH (800 mL) at rt for 2 h. Butanone (440 mmol, 39.4 mL, 1.0 equiv) is then added dropwise at rt and the reaction mixture is stirred at rt for 1 h. Diethyloxalate (880 mmol, 119.5 mL, 2.0 equiv) is quickly added at rt. After 10 min vigorous stirring, the solvent is removed under reduced pressure and the crude reaction mixture is dissolved in AcOEt (900 mL). The organic phase is washed with a saturated solution of brine (900 mL). The aqueous phase is again extracted with AcOEt (3×900 mL). The aqueous phase is carefully acidified to pH 6 by adding dropwise a solution of HCl 10% under vigorous stirring. The aqueous phase is then extracted with AcOEt (3×900 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure to give **2a** and a dimeric structure in 35% yield (26.6 g).

Procedure 2. Trifluoroacetic anhydride (82.5 mmol, 11.5 mL, 2.9 equiv) is added at −78 °C to a solution of DMSO (6.5 mL) in DCM (100 mL). After 10 min stirring, a solution of **5** (28.4 mmol, 5.0 g, 1.0 equiv) in DCM (30 mL) is added dropwise at −78 °C. The resulting solution is stirred at −78 °C for 2 h. Triethylamine (187 mmol, 26.1 mL, 6.6 equiv) is then added dropwise. The reaction mixture is stirred for another 2 h at −78 °C, warmed to rt and poured into a pH 12 buffer (12 mL) obtained from KCl 0.2 M (25 mL) and NaOH 0.2 M (6 mL). The aqueous phase is extracted with DCM (2×50 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is purified by flash-chromatography on silica-gel (eluant: hexane/AcOEt 7:3) to give **2a** and a dimeric structure as an orange oil in 81% yield (3.98 g). Orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (m, 6H), 1.97 (s, 3H), 2.24 (s, 3H), 2.30 (s, 2H), 4.32 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.2, 13.6, 28.8, 62.5, 101.1, 160.2, 190.5, 205.0. IR ($CHCl_3$): 3452, 3054, 2987, 1731, 1264, 742, 703. M.S: $[M+H]^+=173$.

4.1.2. Preparation of 4,5-dimethyl-isoxazole-3-carboxylic acid ethyl ester (3a). Hydroxylamine hydrochloride (13.2 mmol, 917 mg, 1.2 equiv) is slowly added in 12 portions over 3 h to a solution of **2a** (11.0 mmol, 1.90 g, 1.0 equiv) in a 1:1 mixture of EtOH/THF (30 mL). The reaction mixture is stirred at rt for 24 h. The solvent is removed under reduced pressure. The crude reaction mixture is poured into a saturated solution of NaCl (40 mL). The aqueous phase is extracted with AcOEt (3× 50 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude product is purified by flash-chromatography on silica-gel (eluant: hexane/AcOEt 95:5) to give **3a** in 71% yield (1.32 g). Colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ 1.39 (t, 3H, $J=7.2$ Hz), 2.10 (s, 3H), 2.36 (s, 3H), 4.40 (q, 2H, $J=7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.5, 10.9, 14.2, 61.8, 111.4, 154.9, 161.0, 167.6. IR (CH_2Cl_2): 2985, 2943, 1783, 1631, 1389, 1295, 1083, 934, 787, 650. M.S: $[M+H]^+=170$.

4.1.3. Preparation of 5-hydroxy-3,4-dimethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (3b). Hydroxylamine hydrochloride (13.2 mmol, 917 mg, 1.2 equiv) and sodium acetate (13.2 mmol, 1.08 g, 1.2 equiv) are added in one portion to a solution of **2a** (11.0 mmol, 1.90 g, 1.0 equiv) in EtOH (60 mL). The reaction mixture is stirred at rt for 4 h. The solvent is removed under reduced pressure. The crude reaction mixture is poured into a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase is extracted with dichloromethane (3×40 mL). The combined organic phases are washed with distilled water (2×20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is purified by crystallization in diethyl ether to give **3b** in 92% yield (1.81 g). White solid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, 3H, $J=7.5$ Hz), 1.35 (t, 3H, $J=7.2$ Hz), 1.99 (s, 3H), 3.70 (q, 1H, $J=7.5$ Hz), 4.32 (q, 2H, $J=7.2$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.3, 10.9, 13.6, 49.7, 62.8, 102.5, 159.3, 168.6. M.S: $[M+H]^+=188$.

4.1.4. Preparation of 3-acetyl-2-hydroxy-but-3-enoic acid ethyl ester (4). DABCO (5.3 mmol, 594 mg, 0.09 equiv) is added in one portion at 0 °C to a solution of methylvinylketone (60 mmol, 4.9 mL, 1.0 equiv) and ethylglyoxalate 50% w in toluene (72.0 mmol, 14.2 mL, 1.2 equiv) in dioxane (30 mL). The reaction mixture is warmed to rt for 30 h. The crude reaction mixture is then poured in HCl 10% (10 mL) and the aqueous phase is extracted with AcOEt (2×50 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is rapidly filtered on silica-gel (eluant: hexane/AcOEt 1:2) to give **4** in 77% yield (7.98 g). Orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, $J=7.2$ Hz), 2.37 (s, 3H), 3.44 (d, 1H, $J=6.1$ Hz), 4.23 (q, 2H, $J=7.2$ Hz), 4.82 (d, 1H, $J=6.1$ Hz), 6.14 (s, 1H), 6.22 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 26.0, 62.1, 70.9, 128.7, 146.1, 172.6, 198.5. IR (CH_2Cl_2): 3481, 2985, 2938, 1741, 1681, 1636, 1371, 1216, 1027, 912, 741, 585. M.S: $[M+H]^+=173$.

4.1.5. Preparation of 2-hydroxy-3-methyl-4-oxo-pentanoic acid ethyl ester (5). $Pd/CaCO_3$ (26.1 mmol, 1.8 g, 0.5 equiv) is added to a solution of **4** (52.2 mmol, 9.03 g, 1.0 equiv) in EtOH (200 mL). The mixture is purged several times with H_2. After 3 h vigorous stirring at rt, the crude mixture is filtered with Celite®, washed with EtOH (2× 50 mL) and concentrated under reduce pressure. The crude product is purified by flash-chromatography on silica-gel (eluant: hexane/AcOEt 7:3) to give a 62:38 mixture of diastereoisomers **5** in 85% yield (7.76 g). Orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, 1.8H, $J=7.2$ Hz), 1.17 (d, 1.2H, $J=7.2$ Hz), 1.18 (t, 1.2H, $J=7.2$ Hz), 1.22 (t, 1.8H, $J=7.2$ Hz), 2.11 (s, 1.2H), 2.16 (s, 1.8H), 2.89 (m, 1H), 3.24 (d, 0.6H, $J=3.7$ Hz), 3.37 (d, 0.4H, $J=6.9$ Hz), 4.19 (m, 2.4H), 4.51 (m, 0.6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4, 12.8, 14.2, 28.4, 28.9, 50.0, 50.1, 61.8, 62.1, 71.0, 72.5, 173.3, 173.4, 209.2, 210.2. IR (CH_2Cl_2): 3429, 2984, 1714, 1739, 1615, 1365, 1218, 1027, 973, 741, 585. M.S: $[M+H]^+=175$.

4.1.6. Preparation of 2-hydroxy-4-oxo-pent-2-enoic acid ethyl ester (6). A solution of EtONa is generated by reacting sodium (336 mmol, 7.72 g, 1.2 equiv) in anhydrous EtOH (800 mL) at rt for 2 h. A solution of diethyloxalate (280 mmol, 38.0 mL, 1.0 equiv) in acetone (280 mmol, 20.6 mL, 1.0 equiv) is then added dropwise at rt. The reaction mixture is vigorously stirred at rt for 2 h. The solvent is then removed under reduced pressure and water (400 mL) is poured to the crude reaction mixture. Ice (100 g) is added, followed by concentrated sulfuric acid (30 mL). The aqueous phase is extracted with AcOEt (3× 500 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure to give **6** in 89% yield (39.4 g). Orange oil. ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, 3H, $J=7.1$ Hz), 2.24 (s, 3H), 4.32 (q, 2H, $J=7.1$ Hz), 6.36 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 27.7, 62.6, 102.2, 162.1, 167.0, 200.1. IR ($CHCl_3$): 3561, 2987, 1739, 1643, 1602, 1465, 1419, 1370, 1269, 1212, 1119, 1018, 910, 776, 732. M.S: $[M+NH_4]^+=176$.

4.1.7. Preparation of 2-methoxyimino-4-oxo-pentanoic acid ethyl ester (7). A solution of *N*-methoxylamine hydrochloride (190 mmol, 15.9 g, 1.0 equiv) in water (150 mL) is added dropwise at rt to a solution of **6** (190 mmol, 33.4 g, 1.0 equiv) in a mixture of EtOH (300 mL) and water (150 mL). The reaction mixture is stirred at rt for 12 h. The solvent is then removed under vacuum and water (200 mL) is poured to the crude reaction mixture. The aqueous phase is extracted with AcOEt (3× 400 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is rapidly filtered on silica-gel to give **7** in 88% yield (34.4 g). Orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, 3H, $J=7.2$ Hz), 2.21 (s, 3H), 3.72 (s, 2H), 4.07 (s, 3H), 4.34 (q, 2H, $J=7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 29.5, 40.0, 61.9, 63.3, 146.3, 162.8, 203.8. IR ($CHCl_3$): 2982, 2941, 1716, 1375, 1308, 1215, 1230, 1049, 1026, 732. M.S: $[M+NH_4]^+=205$.

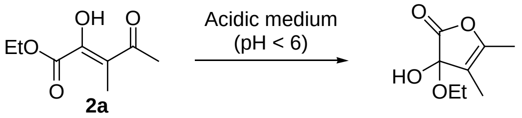
4.1.8. Preparation of 2-methoxyimino-3-methyl-4-oxo-pentanoic acid ethyl ester (8). A 1 M solution of *t*-BuOK in THF (174 mmol, 174.0 mL, 1.5 equiv) is added dropwise at 0 °C to a solution of **7** (116 mmol, 23.9 g, 1.0 equiv) in anhydrous THF (1200 mL). The reaction mixture is stirred at 0 °C for 30 min. Methyl iodide (174 mmol, 10.8 mL, 1.5 equiv) is then added at 0 °C. The reaction mixture is warmed to rt for 12 h. The solvent is removed under vacuum and HCl 10% (300 mL) is poured to the crude reaction mixture. The aqueous phase is extracted with AcOEt (3× 500 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is rapidly filtered on silica-gel to give **8** in 90% yield (21.4 g). White solid. ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (d, 3H, $J=7.1$ Hz), 1.37 (t, 3H, $J=7.1$ Hz), 2.10 (s, 3H), 3.92 (q, 1H, $J=7.1$ Hz), 4.07 (s, 3H), 4.35 (q, 2H, $J=7.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 13.7, 27.2, 45.0, 61.8, 63.1, 151.1, 162.4, 203.5. IR ($CHCl_3$): 2987, 2941, 1721, 1375, 1254, 1176, 1044, 913, 734, 652. M.S: $[M+NH_4]^+=219$.

Acknowledgements

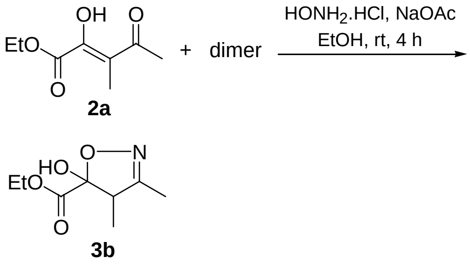
We thank the Ministère de la Recherche et de l'Enseignement Supérieur for financial support of this work through a MENRT grant to J.-M. Becht and Innodia through grants to S. De Lamo Marin and M. Maruani.

References and notes

1. Amos, A. F.; McCarthy, D. J.; Zimmet, P. *Diabet. Med.* **1997**, *14*, 1.
2. (a) Ribes, G.; Sauvaire, Y.; Baccou, J. C.; Valette, G.; Chenon, D.; Trimble, E. R. *Ann. Nutr. Metab.* **1984**, *28*, 37. (b) Ribes, G.; Sauvaire, Y.; Costa, C. D.; Baccou, J. C.; Loubatieres-Mariani, M. M. *Proc. Soc. Exp. Biol. Med.* **1986**, *182*, 159. (c) Fowden, L.; Pratt, H. M.; Smith, A. *Phytochemistry* **1973**, *12*, 1707. (d) Sauvaire, Y.; Petit, P.; Broca, C.; Manteghetti, M.; Baissac, Y.; Fernandez-Alvarez, J.; Gross, R.; Roye, M.; Leconte, A.; Gomis, R.; Ribes, G. *Diabetes* **1998**, *47*, 206. (e) Broca, C.; Gross, R.; Petit, P.; Sauvaire, Y.; Manteghetti, M.; Tournier, M.; Masiello, P.; Gomis, R.; Ribes, G. *American Journal of Physiology* **1999**, *277*, E617.
3. (a) Wang, Q.; Ouazzani, J.; Sasaki, N. A.; Potier, P. *Eur. J. Org. Chem.* **2002**, 834. (b) Rolland-Fulcrand, V.; Rolland, M.; Roumestant, M.-L.; Martinez, J. *Eur. J. Org. Chem.* **2004**, *4*, 873.
4. Other isomers of 4-hydroxyisoleucine are known as part of natural products. Syntheses of the corresponding molecules have been reported: (a) Jamieson, A. G.; Sutherland, A.; Willis, C. L. *Org. Biomol. Chem.* **2004**, *2*, 808. (b) Kassem, T.; Wehbe, J.; Rolland-Fulcrand, V.; Roumestant, M.-L.; Martinez, J. *Tetrahedron: Asymmetry* **2001**, *12*, 2657. (c) Gull, R.; Schöllkopf, U. *Synthesis* **1985**, 1052. (d) Inghardt, T.; Fredj, T.; Svensson, G. *Tetrahedron* **1991**, *47*, 6469. (e) Englisch-Peters, S. *Tetrahedron* **1989**, *45*, 6127.
5. (a) Lee, S. Y.; Lee, B. S.; Lee, C.-W.; Oh, D. Y. *J. Org. Chem.* **2000**, *65*, 256. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (c) Baraldi, G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857. (d) Veronese, A. C.; Callegari, R.; Morelli, C. F.; Vincentini, C. B. *Tetrahedron Lett.* **1997**, *53*, 14497. (e) Zhou, P.; Natale, N. R. *Tetrahedron Lett.* **1998**, *39*, 8249. (f) Burkhart, D. J.; Twamley, D.; Natale, N. R. *Tetrahedron Lett.* **2001**, *42*, 8415. (g) Burkhart, D. J.; Zhou, P.; Blumenfeld, A.; Twamley, B.; Natale, N. R. *Tetrahedron* **2001**, *57*, 8039. (h) Chuang, C.-P.; Wu, Y.-L.; Jiang, M.-C. *Tetrahedron* **1999**, *55*, 11229. (i) Piaz, V. D.; Giovannoni, M. P.; Castellana, C. *J. Med. Chem.* **1997**, *40*, 1417.
6. (a) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A. *Tetrahedron Lett.* **2002**, *43*, 7441. (b) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123.
7. Becht, J.-M.; Catala, C.; De Lamo Marin, S.; Wagner, A.; Mioskowski, C., patent PCT/FR03/03542, 2002.
8. (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon: New York, 1992; pp 1069–1109. (b) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon: New York, 1992; pp 1111–1168. (c) Torsell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988. (d) Adams, J. P.; Patterson, J. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3695. (e) Ghorai, S.; Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron* **2005**, *61*, 2999. (f) Lautens, M.; Roy, A. *Org. Lett.* **2000**, *2*, 555.
9. Manfredini, S.; Simoni, D.; Zanirato, V.; Casolari, A. *Tetrahedron Lett.* **1988**, *29*, 3997.
10. Reaction of **2a** in acidic medium (pH < 6) leads to 3-ethoxy-3-hydroxy-4,5-dimethyl-3*H*-furan-2-one:



11. (a) Compound **2a** was isolated in the presence of a by-product, which is, as shown by mass spectrometry, a dimeric structure of **2a**. (b) The addition of hydroxylamine hydrochloride and sodium acetate to a mixture of **2a** and its dimer afforded compound **3b** with a 92% isolated yield. This result confirms that **2a** and its dimer exhibit the same reactivity.



12. (a) Boeykens, M.; Kimpe, N. D.; Tehrani, K. A. *J. Org. Chem.* **1994**, *59*, 6973. (b) Feistauer, H.; Neidlein, R. *Helv. Chim. Acta* **1995**, *78*, 1806.
13. (a) Brunnelle, H.; Singam, P. R.; Narayanan, B. A.; Bradshaw, C. W.; Liou, J. S. *Synthesis* **1997**, 439. (b) Seki, K.; Isegawa, J.; Fukuda, M.; Ohki, M. *Chem. Pharm. Bull.* **1984**, *32*, 1568. (c) Yokoyama, M.; Tsuji, K.; Kushida, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 67. (d) Baraldi, P. G.; Moroder, F.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, *12*, 2983.
14. (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1988**, *44*, 4653. (b) Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793.
15. Amon, C. M.; Banwell, M. G.; Lance Gravatt, G. *J. Org. Chem.* **1987**, *52*, 4851.
16. (a) Smith, L. I. *Chem. Rev.* **1938**, *23*, 193. (b) Beak, P.; Selling, G. W. *J. Org. Chem.* **1989**, *54*, 5574.