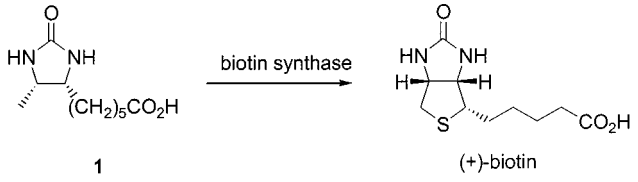
Synthesis of the Diastereomers of Dethiobiotin Using the Conjugate Addition of 4-Phenyloxazolidin-2-one to a Nitroalkene

Denis Lucet,[a] Philippe Heyse,[a] Arnaud Gissot,[a] Thierry Le Gall,*[a] and Charles Mioskowski*[a,b]

Keywords: Asymmetric synthesis / Conjugate addition / Dethiobiotin / Imidazolidin-2-one / Nitroalkene

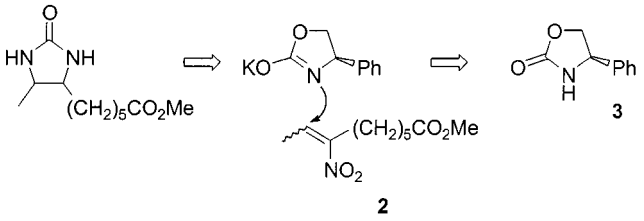
Natural D-dethiobiotin and its three stereoisomers were prepared from a single nitroalkene **2**. Conjugate addition of the potassium salt of (*R*)-4-phenyloxazolidin-2-one **3** to **2** led to two diastereomeric nitro compounds **6** and **7**. Their enantiomers were prepared from (*S*)-**3**. These compounds were converted in three analogous steps into the dethiobiotin isomers as their methyl esters.

In the course of a study into the biosynthesis of biotin, a vitamin which acts as a cofactor for carboxylase reactions, we were interested in the synthesis of the various diastereomers of the biotin precursor dethiobiotin **1**. This *cis*-substituted imidazolidin-2-one, derived from the corresponding diamine, is converted into biotin under the action of the enzyme biotin synthase (Scheme 1).[1–3] In this article, we describe the synthesis of all four diastereomers of dethiobiotin.



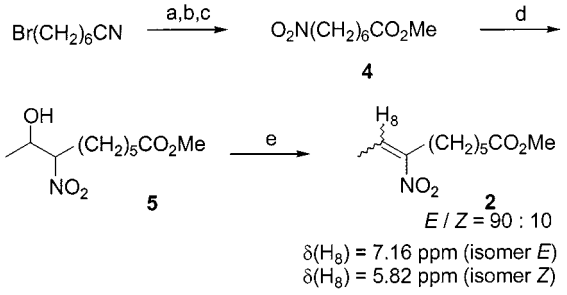
Scheme 1. Biosynthesis of biotin

The retrosynthetic analysis for the dethiobiotin isomers is presented in Scheme 2. The two nitrogen-containing functional groups could be introduced using the conjugate addition of a nitrogen nucleophile to nitroalkene **2** of the appropriate chain length and the carboxylic function. We have previously reported the highly stereoselective conjugate addition of the potassium salt of 4-phenyloxazolidin-2-one **3** to monosubstituted nitroalkenes and the conversion of a corresponding adduct into an enantiomerically pure monosubstituted imidazolidin-2-one.[4,5] When applied to disubstituted nitroalkenes, pairs of diastereomers should be obtained. Furthermore, since both enantiomers of **3** are commercially available, the method would allow for the synthesis of the four isomers of dethiobiotin.



Scheme 2. Retrosynthetic analysis of dethiobiotin diastereomers

Nitroalkene **2** was prepared according to the sequence described in Scheme 3. Commercially available 7-bromoheptanenitrile was converted in three efficient steps into the known methyl 7-nitroheptanoate **4**.[6] Nitroaldolisation of **4** with acetaldehyde afforded nitro alcohol **5**. Acetylation of **5** followed by treatment with basic alumina yielded nitroalkene **2** as a 90:10 mixture of (*E*)- and (*Z*)-isomers.



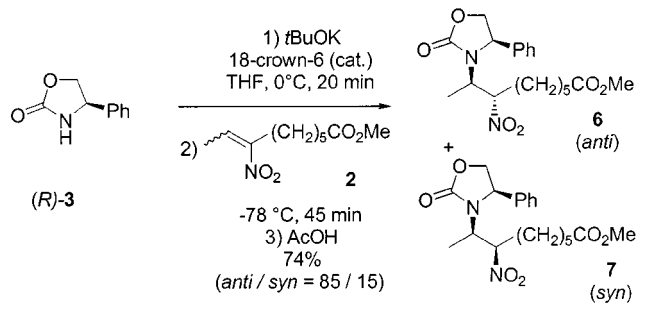
Scheme 3. Preparation of nitroalkene **2**; reagents and conditions: (a) H_2SO_4, MeOH, 40 h, reflux, 66%; (b) NaI, acetone, 30 h, reflux, 94%; (c) $AgNO_2$, ether, 3 days, room temp., 80%; (d) CH_3CHO, KOH, MeOH, 19 h, 0 °C, 84%; (e) i) DMAP, Ac_2O, ether, 16 h, room temp., ii) DMAP, basic alumina, 4 h, reflux, 63% (two steps)

Conjugate additions of the potassium salt generated from either (*R*)- or (*S*)-**3**, by treatment with potassium *tert*-butoxide in THF in the presence of 0.1 equivalent of 18-crown-6, with nitroalkene **2** were then performed. The results obtained from (*R*)-**3** are summarized in Scheme 4. After 45 minutes at −78 °C, the reaction mixture was quenched with acetic acid. Only two diastereomeric adducts were formed

[a] CEA-Saclay, Service des Molécules Marquées
Bât. 547, 91191 Gif-sur-Yvette cedex, France
Fax: (internat.) +33 (0)1 69 08 79 91
E-mail: legall@dsvidf.cea.fr
[b] Université Louis Pasteur, Laboratoire de Synthèse Bio-Organique associé au CNRS, Faculté de Pharmacie
74 route du Rhin, B. P. 24, 67401 Illkirch, France
E-mail: mioskowski@dsvidf.cea.fr

  1434–193X/00/1121–3575 $ 17.50+.50/0

according to ^1H and ^{13}C NMR spectra of the crude product. Chromatography allowed for the separation of compounds **6** (*anti*-adduct) and **7** (*syn*-adduct). The indicated relative and absolute configurations were not known at this time, but derived by comparison of the final products with an authentic sample.



Scheme 4. Conjugate addition of the potassium salt of (*R*)-**3** on nitroalkene **2**

The *anti*/*syn* ratio (85:15) was sufficient to carry out the following steps from the major adduct **6**. However, larger quantities of *syn*-adduct **7** were needed. For this purpose, the isomerization of compound **6** to its epimer **7** was briefly studied under various basic conditions, as described in Table 1. By stirring a solution of compound **6** in dichloromethane in the presence of triethylamine at room temperature, it was possible to obtain after 2.5 days a *anti*/*syn* ratio of 60:40, with no noticeable degradation. When this isomerization was applied to the crude product of the conjugate addition, a 46:54 *anti*/*syn* ratio was obtained, with an 83% combined yield of adducts.

Table 1. Study of the isomerization of *anti*-nitro compound **6**

(*anti*)-**6** ⟶ (*anti*)-**6** + (*syn*)-**7**

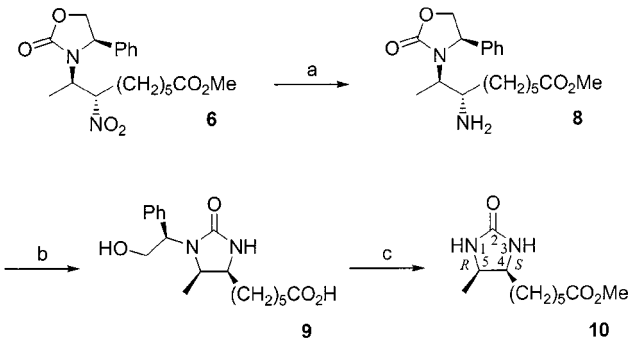
Reagent	Conditions	**6**/**7** Ratio[a]
MeONa, MeOH	3 h at reflux	[b]
K_2CO_3, THF	24 h, room temp.	> 99:1
K_2CO_3, MeOH	24 h, room temp.	86:14
Et_3N, CH_2Cl_2	60 h, room temp.	60:40

[a] Determined by ^1H NMR spectroscopy. – [b] Degradation had occurred, probably because of a retroaddition process.

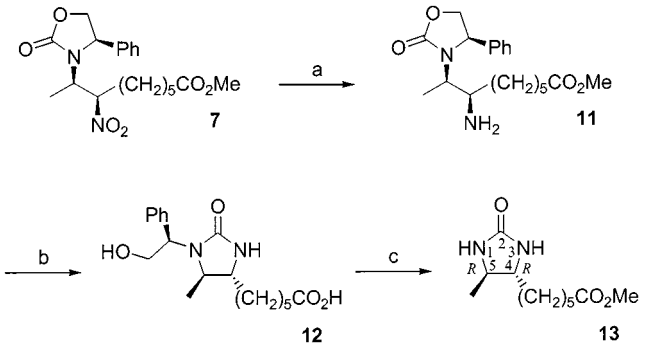
The adducts **6** and **7**, and their enantiomers *ent*-**6** and *ent*-**7** obtained from (*S*)-4-phenyloxazolidin-2-one were then all converted into the dethiobiotin methyl ester or into its stereoisomers in a similar manner as described in Scheme 5, starting from **6**.

Treatment of **6** with ammonium formate in the presence of palladium on carbon in methanol afforded the corresponding amine **8**. Heating this compound at reflux with potassium hydroxide in methanol led to the more stable imidazolidinone **9**. The methyl ester was hydrolyzed to a carboxylic acid under these conditions. The last step consisted of the hydrogenolysis of the remains of the original source of chirality, and the concomitant formation of the methyl ester, leading to imidazolidinone **10**.

The same sequence was carried out from nitro compound **7**, as summarized in Scheme 6.



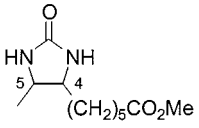
Scheme 5. Preparation of imidazolidinone **10** from nitro compound **6**; reagents and conditions: (a) HCO_2NH_4, Pd/C, MeOH, 3 days, 64%; (b) KOH, MeOH, 16 h, reflux, 89%; (c) H_2, $Pd(OH)_2/C$, MeOH, H_2SO_4 (cat.), 2 days, 64%



Scheme 6. Preparation of imidazolidinone **13** from nitro compound **7**; reagents and conditions: (a) HCO_2NH_4, Pd/C, MeOH, 3 days, 72%; (b) KOH, MeOH, 16 h, reflux, 89%; (c) H_2, $Pd(OH)_2/C$, MeOH, H_2SO_4 (cat.), 2 days, 63%

The structures of the four imidazolidinones prepared were determined (a) by comparison of their spectroscopical properties (Table 2) with those of a sample prepared by esterification of authentic D-dethiobiotin (MeOH, H_2SO_4, 12 h, room temp., 91%) and (b) by comparison of their optical rotation values (Table 3) with those reported in the literature.[7]

Table 2. Spectroscopic characteristics of imidazolidinones **10** and **13**



	H_4 δ (ppm)	H_5 δ (ppm)	$J(H_4-H_5)$ (Hz)	C_4 δ (ppm)	C_5 δ (ppm)	CH_3CH δ (ppm)
10 (*cis*)	3.70–3.60	3.83	7.7	55.8	51.3	15.5
13 (*trans*)	3.13	3.33	5.5	60.2	54.0	21.0

Table 3. Optical rotations of imidazolidinones **10**, *ent*-**10**, **13**, *ent*-**13**

	10	*ent*-**10**	**13**	*ent*-**13**	D-dethiobiotin methyl ester[7]
$[\alpha]_D$	−2.3	+2.1	+42.5	−39.7	+2.6
c ($CHCl_3$)	0.865	0.74	1.15	1.28	2.00

The product *ent*-**10** was found to be identical to D-dethiobiotin methyl ester and thus its absolute configuration is (4*R*,5*S*). Hence, the absolute configurations of the three other diastereomers **10**, **13**, and *ent*-**13** are (4*S*,5*R*), (4*R*,5*R*), and (4*S*,5*S*), respectively.

The (*R*) absolute configuration observed for carbon 5 in compounds **10** and **13**, which are both derived from 4-phenyloxazolidin-2-one (*R*)-**3**, was expected on the basis of our previous study of the conjugate addition to nitroalkenes.[4,5]

In conclusion, the highly stereoselective conjugate addition of 4-phenyloxazolidin-2-one to nitroalkene **2** served as the key step in the synthesis of the methyl esters of natural D-dethiobiotin and its diastereomers. The action of the unnatural isomers on biotin biosynthesis will be evaluated.

Experimental Section

General: THF was freshly distilled from sodium benzophenone ketyl. − TLC: Silica Gel 60F_{254} plates (Merck), with detection by UV light or with an acidic solution of ninhydrin in *t*BuOH or with a solution of phosphomolybdic acid in EtOH. − Column chromatography: 40−63 μm Merck Silica Gel. − IR: Perkin−Elmer 2000. − Optical rotations: Perkin−Elmer 341 micropolarimeter. Melting points (uncorrected): Büchi 535. − NMR: Bruker AM 300 (300.13 and 75.47 MHz for ^{1}H and ^{13}C, respectively). − MS: Finnegan-Mat 4600 (70 eV).

Methyl 7-Bromoheptanoate: Concentrated sulfuric acid (20 g) was slowly added to methanol (25 mL) cooled at 0 °C. 7-Bromoheptanenitrile (8.45 g, 44.5 mmol) was then added and the mixture was heated at reflux for 40 h. After cooling to room temp., cold water (50 mL) was added, the organic phase was separated and the aqueous phase was extracted with ether (4 × 50 mL). The combined organic phases were then dried with magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (95:5 pentane/AcOEt) afforded methyl 7-bromoheptanoate (6.49 g, 66%) as a colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.40 (m, 4 H, CH_2CH_2CH_2CH_2Br), 1.61 (m, 2 H, CH_2CH_2CO), 1.83 (m, 2 H, CH_2CH_2Br), 2.29 (t, *J* = 7.5 Hz, 2 H, CH_2CO), 3.37 (t, *J* = 6.8 Hz, 2 H, CH_2Br), 3.63 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 24.5, 27.5, 28.0, 32.3, 33.4, 33.6 (C2-C7), 51.2 (CH_3O), 173.8 (C1).

Methyl 7-Iodoheptanoate: Sodium iodide (3.36 g, 22.4 mmol) was added to a solution of methyl 7-bromoheptanoate (1.00 g, 4.50 mmol) in acetone (15 mL). The suspension was heated at reflux for 30 h under argon, in the dark. After cooling to room temp., aqueous sodium thiosulfate (0.1 N, 20 mL) was added, the organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water (2 × 10 mL), then dried with magnesium sulfate. After filtration and concentration in vacuo, methyl 7-iodoheptanoate (1.14 g, 94%) was obtained as a colorless oil, which was used in the next step without further purification. − ^{1}H NMR ($CDCl_3$): δ = 1.37 (m, 4 H, CH_2CH_2CH_2CH_2I), 1.62 (m, 2 H, CH_2CH_2CO), 1.80 (m, 2 H, CH_2CH_2I), 2.29 (t, *J* = 7.5 Hz, 2 H, CH_2CO), 3.16 (t, *J* = 7.0 Hz, 2 H, CH_2I), 3.65 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 6.6 (CH_2I), 24.4, 27.8, 29.9, 33.0, 33.7 (C2-C6), 51.2 (CH_3O), 173.8 (C1).

Methyl 7-Nitroheptanoate (4): Silver nitrite (6.68 g, 43.4 mmol) was added to a solution of methyl 7-iodoheptanoate (5.86 g, 21.7 mmol) in diethyl ether (75 mL). The suspension was stirred for 3 d under argon, in the dark. The solid phase was removed by filtration and washed with methanol (2 × 20 mL). The combined organic phases were filtered to remove residual solids. After filtration and concentration in vacuo, chromatography on silica gel (90:10 pentane/AcOEt) afforded methyl 7-nitroheptanoate (3.28 g, 80%) as a colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.35−1.44 (m, 4 H, CH_2CH_2CH_2C$H_2$$NO_2$), 1.57−1.65 (m, 2 H, C$H_2CH_2$CO), 2.01 (m, 2 H, C$H_2CH_2$$NO_2$), 2.30 (t, *J* = 7.3 Hz, 2 H, CH_2CO), 3.65 (s, 3 H, OCH_3), 4.36 (t, *J* = 7.1 Hz, 2 H, CH_2NO_2). − ^{13}C NMR ($CDCl_3$): δ = 24.0, 25.4, 26.7, 27.8 (C3−C6), 33.4 (C2), 50.8 (CH_3O), 75.0 (CH_2NO_2), 173.2 (C1).

Methyl 8-Hydroxy-7-nitrononanoate (5): To a solution of nitroester **4** (5.2 g, 27.5 mmol) in methanol (50 mL) cooled at 0 °C were added successively a solution of potassium hydroxide (1.54 g, 27.5 mmol) in methanol (25 mL) and acetaldehyde (1.55 mL, 27.5 mmol). Additional acetaldehyde was added after 4 h (1.55 mL), and after 11 h (1.55 mL). After 19 h, acetic acid was added. After concentration in vacuo, water (2 mL) was added and the aqueous phase was extracted with diethyl ether (4 × 10 mL). The combined organic phases were then dried with magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (70:30 pentane/AcOEt) afforded nitroalcohol **5** (5.37 g, 84%, mixture of two diastereomers) as a colorless oil. − IR (film): $\tilde{\nu}$ = 3469 cm^{-1} (broad, OH), 2938, 2864, 1737 (C=O), 1550, 1371. − ^{1}H NMR ($CDCl_3$): δ = 1.28 (d, *J* = 6.7 Hz, 3 H, CHCH_3, diastereomer 1), 1.28 (d, *J* = 6.6 Hz, 3 H, CHCH_3, diastereomer 2), 1.30−1.40 (m, 4 H, CH_2CH_2CH_2CH_2CO), 1.57−1.63 (m, 2 H, CH_2CH_2CO), 1.77−1.82 (m, 1 H, C*H*HCHNO_2), 1.97−2.07 (m, 1 H, CH*H*CHNO_2), 2.21 (d, *J* = 7.0 Hz, 1 H, OH, diastereomer 1), 2.28 (broad s, 1 H, OH, diastereomer 2), 2.30 (t, *J* = 7.3 Hz, 2 H, CH_2CO), 3.66 (s, 3 H, OCH_3), 4.10 (m, 1 H, C*H*OH, diastereomer 1), 4.18 (m, 1 H, C*H*OH, diastereomer 2), 4.36−4.41 (m, 1 H, C*H*NO_2). − ^{13}C NMR ($CDCl_3$): δ = 18.8 (C9, diastereomer 1), 19.4 (C9, diastereomer 2), 24.1, 25.0 (diastereomer 1), 25.3 (diastereomer 2), 28.0 (diastereomer 1), 28.1 (diastereomer 2), 29.6 (C3−C6), 33.4 (C2), 51.3 (CH_3O), 68.2 (C8), 92.9 (C7, diastereomer 1), 94.0 (C7, diastereomer 2), 173.0 (C1). − $C_{10}H_{19}NO_5$ (233.3): calcd. C 51.49, H 8.21, N 6.01; found C 51.63, H 8.11, N 5.91.

Methyl 8-Acetoxy-7-nitrononanoate: To a solution of nitroalcohol **5** (5.2 g, 22.3 mmol) in anhydrous diethyl ether (150 mL) was added a solution of DMAP (4-dimethylaminopyridine, 1.36 g, 11.2 mmol) in acetic anhydride (21.1 mL). After stirring for 16 h at room temp., saturated aqueous sodium hydrogen carbonate (30 mL) was added. Solid sodium hydrogen carbonate was then added until gas evolution ceased. The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic phases were then dried with magnesium sulfate. Filtration and concentration in vacuo afforded an oil (4.5 g) containing mostly the expected nitro acetate and a little nitroalkene **2**. The crude product was used as such in the next step. Characteristics of the major diastereomer: − ^{1}H NMR ($CDCl_3$): δ = 1.29 (d, *J* = 6.5 Hz, 3 H, CHCH_3), 1.24−1.38 (m, 4 H, CH_2CH_2CH_2CH_2CO), 1.59−1.66 (m, 2 H, CH_2CH_2CO), 1.66−1.68 (m, 1 H, C*H*HCHNO_2), 1.98−2.02 (m, 1 H, CH*H*CHNO_2), 2.01 (s, 3 H, CH_3CO), 2.29 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.66 (s, 3 H, OCH_3), 4.52 (ddd, *J* = 11.3, 8.2, 3.2 Hz, 1 H, C*H*NO_2), 5.25 (qd, *J* = 8.2, 6.5 Hz, 1 H, C*H*CH_3). − ^{13}C NMR ($CDCl_3$): δ = 16.3 (C9), 20.5 (*C*H_3CO), 24.1, 24.9, 28.0, 29.2 (C3−C6), 33.4 (C2), 51.1 (CH_3O), 69.8 (C8), 90.7 (C7), 169.3 (CH_3*C*O), 173.4 (C1).

Methyl 7-Nitronon-7-enoate (2): To a solution of the crude product obtained above (4.5 g) in dichloromethane (20 mL) were added DMAP (6.8 g, 55.6 mmol) and basic alumina (7.5 g, activity I). The reaction mixture was heated at reflux for 4 h, cooled to room temp., and then filtered over a short pad of celite. After concentration in vacuo, chromatography on silica gel (85:15 pentane/AcOEt) afforded nitroalkene **2** (3.00 g, 63% from nitro alcohol **5**) as a 90:10 mixture of (*E*)- and (*Z*)-isomers. Characteristics of the major isomer: ^{1}H NMR ($CDCl_3$): δ = 1.31−1.39 (m, 2 H, C*H*$_2$CH$_2$CH$_2$CO), 1.45−1.52 (m, 2 H, CH$_2$*H*$_2$C=), 1.58−1.67 (m, 2 H, C*H*$_2$CH$_2$CO), 1.87 (d, *J* = 7.4 Hz, 3 H, C*H*$_3$CH=), 2.30 (t, *J* = 7.4 Hz, 2 H, CH$_2$CO), 2.58 (t, *J* = 7.5 Hz, 2 H, CH$_2$C=), 3.66 (s, 3 H, OCH$_3$), 7.16 (q, *J* = 7.4 Hz, 1 H, CH$_3$C*H*=). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (C9), 24.3, 25.6, 27.0, 28.3 (C3−C6), 33.6 (C2), 51.1 (CH$_3$O), 130.9 (C8), 152.4 (C7), 173.6 (C1).

Nitrooxazolidinones 6 and 7: A mixture of (*R*)-4-phenyloxazolidin-2-one (989 mg, 6.06 mmol), potassium *tert*-butoxide (680 mg, 6.06 mmol) and 18-crown-6 (123 mg, 0.47 mmol) in THF (35 mL) was stirred under argon at 0 °C for 20 min, and then cooled to −78 °C. A solution of nitroalkene **2** (1.00 g, 4.66 mmol) in THF (5 mL) cooled at −78 °C was added dropwise. After 45 min at −78 °C, no more nitroalkene remained in the reaction mixture. Acetic acid (0.67 mL, 11.65 mmol) was added and the flask was allowed to warm to room temp. Water (20 mL) and dichloromethane (100 mL) were added, the phases were separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were then dried with magnesium sulfate. After filtration and concentration in vacuo, the yellow oil obtained was dissolved in dichloromethane (100 mL) and triethylamine (4 mL) was added. After 5 d at room temp., the solution was concentrated in vacuo. Chromatography on silica gel (75:25 pentane/AcOEt) afforded the two nitro compounds **6** (0.6775 g, 38%, less polar) as a slightly yellow oil and **7** (0.7824 g, 45%, more polar) as a slightly yellow solid.

6: $[\alpha]_D^{28}$ = −33.3 (*c* = 0.650, CH$_3$OH). − IR (film): $\tilde{\nu}$ = 2948 cm^{-1}, 2864, 1748, 1552, 1417, 1215, 1039. − ^{1}H NMR ($CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CH), 1.18−1.33 (m, 4 H, C*H*$_2$C*H*$_2$CH$_2$CH$_2$CO), 1.53−1.64 (m, 3 H, C*H*$_2$CH$_2$CO, C*H*HCHNO$_2$), 1.67−1.80 (m, 1 H, CH*H*CHNO$_2$), 2.26 (t, *J* = 7.4 Hz, 2 H, CH$_2$CO), 3.62 (m, 1 H, C*H*CH$_3$), 3.65 (s, 3 H, OCH$_3$), 4.21 (dd, *J* = 8.5, 6.9 Hz, 1 H, OC*H*HCHN), 4.62 (t, *J* = 8.5 Hz, 1 H, OCH*H*CHN), 4.71 (dd, *J* = 8.5, 6.9 Hz, 1 H, CHPh), 5.15 (ddd, *J* = 10.7, 8.5, 3.3 Hz, 1 H, CHNO$_2$), 7.30−7.43 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$) δ = 12.9 (C9), 24.1, 24.9, 27.9, 30.4 (C3−C6), 33.5 (C2), 51.2 (CH$_3$O), 51.8 (C8), 59.8 (*C*HPh), 70.2 (O*C*H$_2$CHN), 89.8 (C7), 127.2, 129.2, 129.4 (Ar-C), 137.4 (*ipso*-Ar-C), 157.2 (NCOO), 173.6 (C1). − $C_{19}H_{26}N_2O_6$ (378.4): calcd. C 60.30, H 6.93, N 7.40; found C 60.35, H 6.83, N 7.52.

ent-**6**: Same characteristics as **6** except for the optical rotation. $[\alpha]_D^{28}$ = +37.0 (*c* = 0.732, CH$_3$OH).

7: $[\alpha]_D^{29}$ = −78.9 (*c* = 1.041, CH$_3$OH). − IR (film): $\tilde{\nu}$ = 2945 cm^{-1}, 1756, 1548, 1242, 1032. − ^{1}H NMR ($CDCl_3$): δ = 1.07 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH), 1.19−1.37 (m, 4 H, C*H*$_2$C*H*$_2$CH$_2$CH$_2$CO), 1.51−1.76 (m, 4 H, C*H*$_2$CH$_2$CO, C*H*$_2$CHNO$_2$), 2.22 (t, *J* = 7.4 Hz, 2 H, CH$_2$CO), 3.65 (s, 3 H, OCH$_3$), 3.72 (m, 1 H, C*H*CH$_3$), 4.08 (m, 1 H, OC*H*HCHN), 4.50 (t, *J* = 8.5 Hz, 1 H, OCH*H*CHN), 4.75 (t, *J* = 7.8 Hz, 1 H, CHPh), 5.16 (td, *J* = 10.8, 3.5 Hz, 1 H, CHNO$_2$), 7.22−7.37 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$) δ = 13.6 (C9), 24.1, 25.0, 28.0, 30.3 (C3−C6), 33.4 (C2), 51.2 (CH$_3$O), 52.6 (C8), 59.6 (*C*HPh), 70.0 (O*C*H$_2$CHN), 89.1 (C7), 127.3, 129.0, 129.3 (Ar-C), 137.0 (*ipso*-Ar-C), 157.3 (NCOO), 173.5 (C1). − $C_{19}H_{26}N_2O_6$ (378.4): calcd. C 60.30, H 6.93, N 7.40; found C 60.53, H 6.92, N 7.24.

ent-**7**: Same characteristics as **7** except for the optical rotation. $[\alpha]_D^{21}$ = +75.2 (*c* = 0.938, CH$_3$OH).

Aminooxazolidinone 8: To a solution of nitro compound **6** (0.676 g, 1.79 mmol) in methanol (60 mL) were added palladium on carbon (10% , 0.300 g) and anhydrous ammonium formate (0.563 g, 8.93 mmol). After stirring for 3 d at room temp., the suspension was filtered through a short pad of celite which was then washed with methanol. After concentration in vacuo, chromatography on silica gel (95:3:0.5 MeOH/CH_2Cl_2/Et_3N) afforded amine **8** (0.399 g, 64%) as a viscous, colorless oil. **8**: $[\alpha]_D^{26}$ = −28.5 (*c* = 0.68, CH$_3$OH). − IR (film): $\tilde{\nu}$ = 3379 cm^{-1}, 2937, 2860, 1736 (C=O), 1591, 1222, 705. − ^{1}H NMR ($CDCl_3$): δ = 1.10 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH), 1.13−1.44 (m, 6 H, C*H*$_2$C*H*$_2$C*H*$_2$CHNH$_2$), 1.48 (m, 2 H, C*H*$_2$CH$_2$CO), 2.20 (t, *J* = 7.3 Hz, 2 H, CH$_2$CO), 3.18 (m, 1 H, C*H*NH$_2$), 3.31 (m, 1 H, C*H*CH$_3$), 3.61 (s, 3 H, OCH$_3$), 4.13 (dd, *J* = 8.5, 6.6 Hz, 1 H, OC*H*HCHN), 4.32 (broad s, 2 H, NH$_2$), 4.62 (t, *J* = 8.5 Hz, 1 H, OCH*H*CHN), 4.88 (dd, *J* = 8.5, 6.6 Hz, 1 H, CHPh), 7.30−7.38 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$) δ = 11.6 (C9), 24.4, 25.2, 28.4, 32.9 (C3−C6), 33.6 (C2), 51.1 (CH$_3$O), 53.0 (C7), 54.8 (C8), 60.6 (*C*HPh), 70.4 (O*C*H$_2$CHN), 127.0, 128.9, 129.0 (Ar-C), 138.8 (*ipso*-Ar-C), 158.5 (NCOO), 173.7 (C1). − $C_{19}H_{30}N_2O_5$ (**8** + H_2O, 366.2): calcd. C 62.27, H 8.25, N 7.64; found C 62.42, H 7.75, N 7.26.

ent-**8**: Same characteristics as **8** except for the optical rotation. $[\alpha]_D^{27}$ = +27.9 (*c* = 0.84, CH$_3$OH).

Aminooxazolidinone 11: The same procedure described for the preparation of amine **8** was applied to nitro compound **7** (0.75 g, 1.98 mmol), and afforded amine **11** (0.496 g, 72%) as a viscous, slightly yellow oil. **11**: $[\alpha]_D^{27}$ = −27.5 (*c* = 0.86, CH$_3$OH). − IR (film): $\tilde{\nu}$ = 3382 (broad) cm^{-1}, 2939, 2860, 1733 (C=O), 1603, 1223, 704. − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CH), 1.11−1.48 (m, 8 H, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CHNH$_2$), 2.22 (t, *J* = 7.3 Hz, 2 H, CH$_2$CO), 3.09 (m, 1 H, C*H*NH$_2$), 3.41 (m, 1 H, C*H*CH$_3$), 3.58 (s, 3 H, OCH$_3$), 4.06 (dd, *J* = 8.2, 6.9 Hz, 1 H, OC*H*HCHN), 4.33 (broad s, 2 H, NH$_2$), 4.55 (t, *J* = 8.2 Hz, 1 H, OCH*H*CHN), 4.90 (dd, *J* = 8.2, 6.9 Hz, 1 H, CHPh), 7.30 (m, 5 H, Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 15.9 (C9), 24.4, 24.9, 28.9, 33.0 (C3−C6), 33.7 (C2), 51.2 (CH$_3$O), 53.3 (C7), 54.2 (C8), 58.9 (*C*HPh), 70.4 (O*C*H$_2$CHN), 127.3, 128.8, 128.9 (Ar-C), 139.3 (*ipso*-Ar-C), 158.9 (NCOO), 173.9 (C1).

ent-**11**: Same characteristics as **11** except for the optical rotation. $[\alpha]_D^{27}$ = +28.1 (*c* = 1.63, CH$_3$OH).

Imidazolidinone 9: A solution of amine **8** (0.430 g, 1.23 mmol) and potassium hydroxide (0.300 g) in methanol (60 mL) was heated at reflux for 16 h. The reaction mixture was cooled to room temp. and concentrated in vacuo. Water (50 mL) and dichloromethane (50 mL) were then added, and an aqueous solution of HCl (0.1 N) was added until pH = 3 was achieved. The organic phase was then washed with water and dried with magnesium sulfate. After filtration and concentration in vacuo, imidazolidinone **9** (0.368 g, 89%) was obtained as a thick white gum, which was used in the next step without further purification. − **9**: IR (film): $\tilde{\nu}$ = 3383 cm^{-1}, 3300, 2949, 1705, 1634, 1490, 1452, 1213. − ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, *J* = 6.0 Hz, 3 H, C*H*$_3$CH), 1.10−1.50 (m, 6 H, C*H*$_2$C*H*$_2$C*H*$_2$CHNH), 1.60 (m, 2 H, C*H*$_2$CH$_2$CO), 2.29 (t, *J* = 7.0 Hz, 2 H, CH$_2$CO), 3.52 (qd, *J* = 7.9, 6.0 Hz, 1 H, C*H*CH$_3$), 3.60 [m, 1 H, C*H*(NH)CH$_2$], 3.90 (m, 1 H), 4.20 (dd, *J* = 11.9, 8.3 Hz, 1 H), 4.39 (m, 1 H), 6.53 (broad s, 1 H, *H*OCH$_2$), 7.26−7.31

(m, 5 H, CHPh), 8.20 (broad s, 1 H, HOCO). − ^{13}C NMR ($CDCl_3$): δ = 11.9 (CH_3CH), 24.4, 25.7, 28.7, 29.2 ($CH_2CH_2CH_2CH_2CH_2CO$), 33.8 (CH_2CO), 54.5, 54.9 (CHNH, CH_3CH), 60.8 (*C*HPh), 64.2 (CH_2OH), 127.0, 127.6, 128.5 (Ar-C), 137.8 (*ipso*-Ar-C), 163.3 (NCON), 177.6 (COOH).

Imidazolidinone 12: The same procedure described for the preparation of imidazolidinone **9** was applied to amine **11** (0.43 g, 1.23 mmol), and afforded imidazolidinone **12** (0.368 g, 89%) as a white gum, which was used in the next step without further purification. − IR (film): $\tilde{\nu}$ = 3316 cm^{-1}, 2930, 1705, 1450, 1250, 1074. − ^{1}H NMR ($CDCl_3$): δ = 1.14 (d, *J* = 5.6 Hz, 3 H, CH_3CH), 0.84−1.39 (m, 6 H, $CH_2CH_2CH_2CHNH$), 1.60 (m, 2 H, CH_2CH_2CO), 2.29 (t, *J* = 6.6 Hz, 2 H, CH_2CO), 3.11 (qd, *J* = 5.9, 5.6 Hz, 1 H, $CHCH_3$), 3.21 [m, 1 H, C*H*(NH)CH_2], 3.95 (m, 1 H), 4.24 (dd, *J* = 11.8, 8.0 Hz, 1 H), 4.39 (m, 1 H), 6.51 (broad s, 1 H, $HOCH_2$), 7.22−7.34 (m, 5 H, CHPh). − ^{13}C NMR ($CDCl_3$): δ = 18.1 (CH_3CH), 24.4, 25.0, 28.5, 33.7, 34.7 ($CH_2CH_2CH_2CH_2CH_2CO$), 57.5, 58.2 (CHNH, CH_3CH), 60.6 (*C*HPh), 64.2 (CH_2OH), 127.1, 127.6, 128.5 (Ar-C), 137.4 (*ipso*-Ar-C), 162.7 (NCON), 177.5 (COOH).

Methyl 6-[(4*S*,5*R*)-5-Methyl-2-oxoimidazolidin-4-yl]hexanoate (10): To a solution of imidazolidinone **9** (0.316 g, 0.946 mmol) in methanol (20 mL) were added palladium(II) hydroxide on carbon (20%, 0.500 g) and two drops of concentrated hydrochloric acid. The suspension was stirred for 48 h at room temp. under hydrogen (1 atm). The suspension was filtered through a short pad of celite which was washed with methanol. The solution obtained was concentrated in vacuo. Chromatography on silica gel (95:5 MeOH/CH_2Cl_2) afforded imidazolidinone **10** (0.137 g, 64%) as a white solid.

10: $[\alpha]_D^{26}$ = −2.3 (*c* = 0.865, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3222 cm^{-1}, 2932, 2861, 1742, 1699, 1461, 1171. − ^{1}H NMR ($CDCl_3$): δ = 1.12 (d, *J* = 6.2 Hz, 3 H, CH_3CH), 1.24−1.37 (m, 6 H, $CH_2CH_2CH_2CHNH$), 1.63 (m, 2 H, CH_2CH_2CO), 2.30 (t, *J* = 7.2 Hz, 2 H, CH_2CO), 3.66 (s, 3 H, CH_3O), 3.60−3.70 [m, 1 H, C*H*(NH)CH_2], 3.83 (qd, *J* = 7.7, 6.2 Hz, 1 H, $CHCH_3$), 4.69 (broad s, 1 H, NH), 4.95 (broad s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 15.5 (CH_3CH), 24.5, 25.9, 28.8, 29.3 ($CH_2CH_2CH_2CH_2CH_2CO$), 33.7 (CH_2CO), 51.2, 51.3 (CH_3O, CH_3CH), 55.8 (CHNH), 163.1 (NCON), 173.8 (CO_2CH_3). − $C_{11}H_{20}N_2O_3$ (228.3): calcd. C 57.87, H 8.83, N 12.27; found C 58.02, H 8.59, N 11.95.

Methyl 6-[(4*R*,5*S*)-5-Methyl-2-oxo-imidazolidin-4-yl]hexanoate (*ent*-10): Same characteristics as **10** except for the optical rotation. $[\alpha]_D^{22}$ = +2.1 (*c* = 0.74, $CHCl_3$).

Methyl 6-[(4*R*,5*R*)-5-Methyl-2-oxo-imidazolidin-4-yl]hexanoate (13): The same procedure described for the preparation of compound **10** was employed. Starting from compound **12** (0.316 g, 0.94 mmol), imidazolidinone **13** (0.137 g, 63%) was obtained.

13: $[\alpha]_D^{29}$ = +42.5 (*c* = 1.15, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3239 cm^{-1}, 2942, 2866, 1741, 1703, 1440, 1203. − ^{1}H NMR ($CDCl_3$): δ = 1.10−1.70 (m, 11 H, CH_3CH, $CH_2CH_2CH_2CH_2CHNH$), 2.30 (t, *J* = 7.2 Hz, 2 H, CH_2CO), 3.13 [m, 1 H, C*H*(NH)CH_2], 3.33 (m, 1 H, $CHCH_3$), 3.57 (s, 3 H, CH_3O), 5.85 (broad s, 1 H, NH), 6.00 (broad s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_3CH), 24.5, 25.1, 28.5, 33.6, 34.7 ($CH_2CH_2CH_2CH_2CH_2CO$), 51.2 (CH_3O), 54.0 (CH_3CH), 60.2 (CHNH), 163.3 (NCON), 173.8 (CO_2CH_3). − $C_{11}H_{20}N_2O_3$ (228.3): calcd. C 57.87, H 8.83, N 12.27; found C 57.89, H 8.65, N 12.05.

Methyl 6-[(4*S*,5*S*)-5-Methyl-2-oxo-imidazolidin-4-yl]hexanoate (*ent*-13): Same characteristics as **13** except for the optical rotation. $[\alpha]_D^{30}$ = −39.7 (*c* = 1.28, $CHCl_3$).

Acknowledgments

This study was partially supported by the Bioavenir program financed by Rhône-Poulenc with the contribution of the Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche. We thank Dr. Philippe Desbordes (Rhône-Poulenc Agro France) for helpful discussions.

[1] F. Escalettes, D. Florentin, B. Tse Sum Bui, D. Lesage, A. Marquet, *J. Am. Chem. Soc.* **1999**, *121*, 3571−3578, and references therein.
[2] F. Moreau, D. Florentin, A. Marquet, *Tetrahedron* **2000**, *56*, 285−293.
[3] A. Nudelman, A. Nudelman, D. Marcovici-Mizrahi, D. Flint, *Bioorg. Chem.* **1998**, *26*, 157−168.
[4] D. Lucet, L. Toupet, T. Le Gall, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 2682−2683.
[5] D. Lucet, S. Sabelle, O. Kostelitz, T. Le Gall, C. Mioskowski, *Eur. J. Org. Chem.* **1999**, 2583−2591.
[6] E. Bosone, P. Farina, G. Guazzi, S. Innocenti, V. Marotta, U. Valcavi, *Synthesis* **1983**, 942−944.
[7] V. du Vigneaud, D. B. Melville, K. Folkers, D. E. Wolf, R. Mozingo, J. C. Keresztesy, S. A. Harris, *J. Biol. Chem.* **1942**, *146*, 475.

Received April 17, 2000
[O00197]