

The Synthesis of 4-Hydroxypipelic Acids by Stereoselective Cycloaddition of Configurationally Stable Nitrones

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The diastereoselective synthesis of *trans*- and *cis*-4-hydroxypipelic acids has been achieved with geometry-controlled nitron cycloaddition chemistry. The cycloaddition of 3-butenol to enantiopure C-aminocarbonyl and C-alkoxycarbonyl nitrones having a definite (*Z*) and (*E*) configuration, respectively, occurs with complete regio- and *exo* selectivity. The acyclic (*Z*)-nitron **12** affords two cycloadducts in a 1:1 ratio, which can be separated and converted into (2*R*,4*R*)- and

(2*S*,4*S*)-4-hydroxypipelic acids, respectively, in four steps. The cyclic (*E*)-nitron **17** reacts with complete diastereofacial selectivity and the elaboration of its sole adduct gives the methyl ester of (2*R*,4*S*)-4-hydroxypipelic acid, albeit in low yield.

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Introduction

4-Hydroxypipelic acids **1** and **2** (Figure 1) are non-proteinogenic amino acids which have been isolated from several plants^[1] and, together with the 4-oxo derivatives, are present in many biologically active natural and synthetic products such as depsipeptide antibiotics,^[2] HIV protease inhibitors,^[3] and NMDA receptor antagonists.^[4] Recently, the 4-oxygenated pipelic acids have also been used as key intermediates in the syntheses of conformationally constrained amino acids and peptidomimetics.^[5]

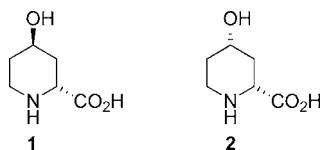
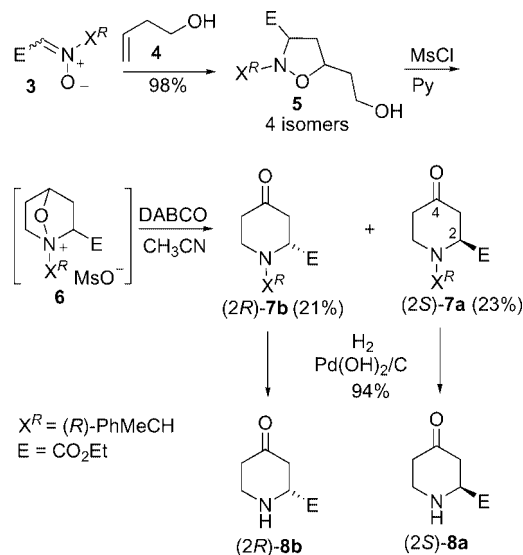


Figure 1. *trans*- and *cis*-hydroxypipelic acids.

Because of their biological importance and synthetic value, much effort has been devoted to their preparation, and several different synthetic approaches have been reported,^[6] including the nitron 1,3-dipolar cycloaddition (1,3-DC).^[7]

Nitron 1,3-DC followed by suitable elaboration of cycloadducts is a well-established and valuable tool for the synthesis of variously substituted nitrogen heterocycles.^[8] This approach has been applied to the multigram synthesis

of both enantiomers of 4-oxopipelic ester **8** using the chiral nitron **3** derived from *N*-(1*R*)-phenylethyl]hydroxylamine and ethyl glyoxylate (Scheme 1).^[7a]



Scheme 1.

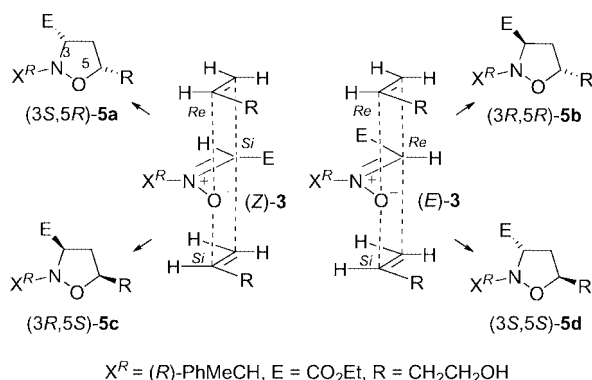
The cycloaddition of **3** to butenol **4** proceeded in high yield (98%) with complete regioselectivity but was totally stereo-random, affording all four possible isomers of **5** in an equimolar mixture. No attempt was made to separate this complex mixture, which was sequentially treated with MsCl/TEA and DABCO in acetonitrile to afford a two-component mixture of easily separable 4-oxopipelic acid derivatives **7**.

The poor stereoselectivity of the 1,3-DC can be ascribed to the nitron counterpart. C-Alkoxycarbonyl nitrones such as **3** exist as rapidly equilibrating mixtures of (*E*) and (*Z*)

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isomers in solution.^[9] Accordingly, diastereomers **5** arise from the reaction of both (*E*)-**3** and (*Z*)-**3** with butenol **4** with no π -facial discrimination (Scheme 2).



Scheme 2. The *exo* approach of **4** to both faces of (*Z*)-**3** and (*E*)-**3**.

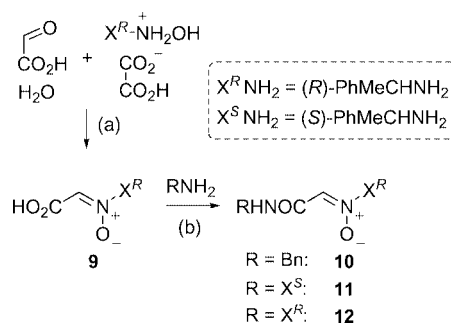
A high *exo* selectivity of the dipolarophile is expected in the cycloaddition,^[10] but it cannot be observed as the *exo* adducts of (*Z*)-**3** are identical to the *endo* adducts of (*E*)-**3**, and vice versa.

In a logical extension of the nitron approach to pipercolic acid derivatives, we studied the cycloaddition and subsequent adduct elaboration of nitrones closely related to **3** but having a definite configuration. Here, we report on the preparation of *trans*- and *cis*-4-hydroxypipercolic acids **1** and **2** in an enantiopure form by diastereoselective cycloaddition of butenol **4** to an acyclic (*Z*)-*C*-aminocarbonyl nitron and a cyclic (*E*)-*C*-alkoxycarbonyl nitron, respectively.

Results and Discussion

The simplest *C*-carboxy nitron **9**,^[11] which is readily prepared by condensation of glyoxylic acid with *N*-(1*R*)-1-phenylethyl]hydroxylamine ($X^R\text{NHOH}$)^[12] in the presence of molecular sieves (Scheme 3), exists exclusively in a (*Z*) configuration. Unfortunately, nitron **9** does not react appreciably with butenol **4** at temperatures up to 50–60 °C, even with extended reaction times, and decomposes at higher temperatures. In search for an alternative, **9** was converted into nitrones **10**, **11**, and **12** by coupling with benzylamine and (1*S*)- and (1*R*)-1-phenylethylamine, respectively. The *C*-aminocarbonyl nitrones **10–12** also exist entirely as (*Z*) isomers in solution^[11] (Scheme 3).

This selectivity is almost certainly due to the strong hydrogen bond that stabilizes the (*Z*) configuration of the nitron (Figure 2). The existence of an intramolecular hydrogen bond was confirmed by the FT-IR spectra of **10–12** recorded under conditions at which aggregation is not significant (room temp., about 2 mM CDCl_3 solution). In particular, all the samples show a band at 3243–3254 cm^{-1} ascribed to the hydrogen-bonded N–H stretch. In addition, the high value of the amide hydrogen chemical shifts measured in 2 mM CDCl_3 solutions ($\delta_{\text{NH}} = 10.13\text{--}10.19$ ppm), and the low temperature coefficient recorded for a represen-



Scheme 3. (a) NEt_3 , molecular sieves (4 Å), CH_2Cl_2 , room temp., 65 h, 68% (crude). (b) DIC, HOBT, NEt_3/Pr_2 , CH_2Cl_2 , room temp., 24 h; **10**: 55%; **11**: 50%; **12**: 52%.

tative nitron (**11**: $\Delta\delta/\Delta T = -1.11$ ppb/K), are in agreement with the involvement of the amide proton in a strong intramolecular hydrogen bond in **10–12**.^[13]

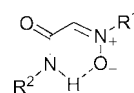
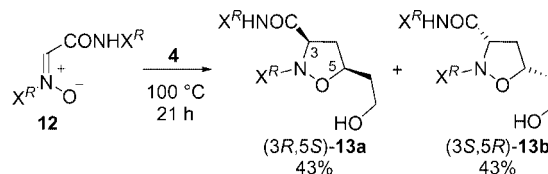


Figure 2. Hydrogen bonding in the (*Z*)-*C*-aminocarbonyl nitrones.

Nitrones **10–12** are thermally more stable than **9** and react with butenol **4** at 90–100 °C to give a roughly equimolar mixture of only two diastereomers. This result suggests that no (*E*)/(*Z*) isomerization of nitrones occurs upon heating. Accordingly, the relative configuration of the resulting isoxazolidines was assumed to be 3,5-*cis* as a result of the approach of reagents in an *exo* manner.

The lack of stereocontrol by the benzylic stereogenic center in **10** is consistent with the previous results obtained with nitron **3**, as the chiral auxiliary at the nitrogen atom of the acyclic nitrones experiences a considerable configurational freedom and is not able to discriminate the nitron faces. However, **11** and **12** also afforded a mixture of two cycloadducts in roughly equal proportions, thereby revealing that the introduction of a second stereogenic center does not affect the cycloaddition stereochemistry either.

The treatment of nitron **12** with butenol **4** at 100 °C for 22 h afforded the readily separable isoxazolidines **13a** and **13b** in good overall yield (86%) after chromatographic separation (Scheme 4). The pairs of diastereomeric cycloadducts derived from **10** and **11** could not be separated by chromatography on silica gel, therefore they were not studied further.

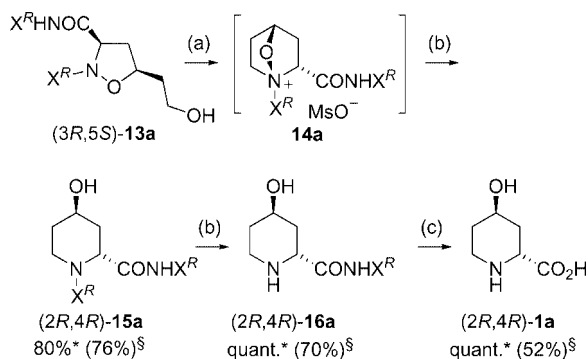


Scheme 4.

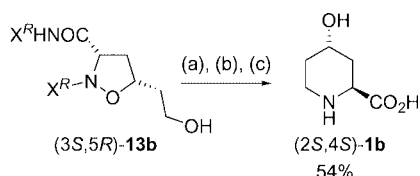
The relative and absolute configurations of **13a** and **13b**, as shown in Scheme 4, were determined by chemical correlation and comparison of their specific rotations with the known enantiopure *trans*-4-hydroxypipercolic acids (see be-

low). The 3,5-*cis* configuration of adducts **13** confirmed the assumed reaction pathway through the *exo* addition of the dipolarophile to both the diastereotopic faces of the (*Z*)-*C*-aminocarbonyl nitrene.

Isoxazolidines **13a** and **13b** were converted into (+)- and (–)-*trans*-4-hydroxypipelicolic acids (**1a** and **1b**), respectively, by mesylation followed by catalytic hydrogenation and hydrolysis of the [(1-phenylethyl)amino]carbonyl moiety under acidic conditions (Schemes 5 and 6). All the crude intermediates were used in the following step without purification, although samples of pure derivatives **15a** and **16a** could be easily obtained by chromatography on silica gel and fully characterized.



Scheme 5. (a) MsCl, NEt₃, CH₂Cl₂, 0 °C → room temp.; (b) (i) H₂, 10% Pd/C, MeOH, 1 atm, room temp., 19–22 h, (ii) Ambersep 900 OH, MeOH, room temp., 2 h; (c) 6 N HCl, reflux, 22 h. *: Yield of crude product; §: Yield of purified product from **13a**.



Scheme 6. (a) MsCl, NEt₃, CH₂Cl₂, 0 °C → room temp.; (b) (i) H₂, 10% Pd/C, MeOH, 1 atm, room temp., 19 h, (ii) Ambersep 900 OH, MeOH, room temp., 2 h; (c) 6 N HCl, reflux, 22 h.

Catalytic hydrogenation of salts **14** [catalyst: Pd/C or Pd(OH)₂/C, room temp., 1 atm, 15–96 h] induced the complete opening of the isoxazolidinium ring, whereas the debenzoylation of the endocyclic nitrogen atom was not reproducible, giving a mixture of **15** and **16** in most cases. Eventually, a second run of the hydrogenation step gave the complete conversion of **15**. Both catalysts Pd/C and Pd(OH)₂/C give similar results in the debenzoylation of **15**.

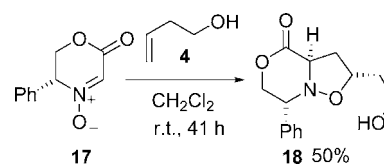
The synthesis of both enantiomers of **1** was completed by amide hydrolysis in refluxing 6 N aqueous HCl. After purification on a cation-exchange resin (Dowex 50W X8), the *trans*-4-hydroxypipelicolic acids **1a** and **1b** were recovered in 52–54% yield based on the corresponding isoxazolidines **13** (Schemes 5 and 6).

The relative and absolute configurations of **1a** and **1b** were unambiguously determined by comparison of the optical rotations and NMR spectra of the resulting amino acids with literature values.^[1f,14] Consequently, the stereo-

chemical assignment for the cycloaddition step and the configurations of all the intermediates were also established.

The present synthesis of enantiopure 4-hydroxypipelicolic acids by 1,3-DC of (*Z*)-*C*-aminocarbonyl nitrene **12** is far superior to that using the *C*-alkoxycarbonyl nitrene **3**.^[7a] The remarkable configurational stability of **12** allows the complete control of the relative configuration in the cycloaddition step, and this is maintained in the final products. The use of such a nitrene is suggested for other applications in 1,3-dipolar cycloaddition chemistry.

A similar reaction sequence was applied to the enantiopure (*E*)-*C*-carboxy nitrene **17**^[15] in search of the *cis*-4-hydroxypipelicolic acid. The cyclic nitrene **17** prepared from (*2R*)-2-amino-2-phenylethanol was more reactive and selective than the acyclic nitrene **12**, and afforded the sole cycloadduct **18** upon treatment with butenol **4** in CH₂Cl₂ at room temperature (Scheme 7). The structure and configuration of **18** were unambiguously established by X-ray analysis of a single crystal (Figure 3).^[16] As expected,^[15] isoxazolidine **18** forms by *exo* addition of **4** to the less-hindered side of the (*E*)-nitrene **17**, opposite the phenyl ring. In this case, the complete π -facial selectivity is ascribed to the more rigid structure of **17** with the chiral auxiliary embedded in the ring system.



Scheme 7.

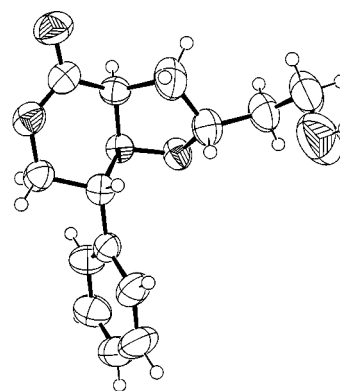
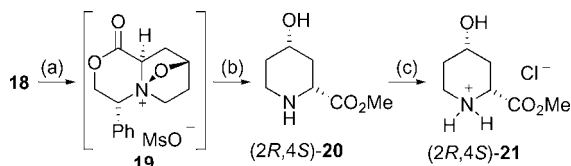


Figure 3. ORTEP drawing of the X-ray crystal structure of cycloadduct **18**.^[16]

Mesylation of **18** followed by spontaneous cyclization by nucleophilic substitution afforded the tricyclic intermediate **19**, which was directly hydrogenated in the presence of Pd/C in methanol to cleave the isoxazolidine N–O bond and the *N*-benzyl moiety. The reduction mixture was then treated with a basic ion-exchange resin (Ambersep 900 OH) to remove the mesylate anion and induce methanolysis of the lactone. The pipelicolic ester **21** was finally recovered in 8% yield, based on **18**, after silica gel chromatography of

the multistep reaction mixture. The rather low yield of **21** is probably caused by difficulty in forming the strained tricyclic isoxazolidinium salt **19** (Scheme 8).



Scheme 8. (a) MsCl, NEt₃, CH₂Cl₂, 0 °C → room temp.; (b) (i) H₂, 10% Pd/C, MeOH, 1 atm, room temp., 4 d, (ii) Ambersep 900 OH, MeOH, room temp., 2 h; (d) TMS-Cl, MeOH, 0 °C.

The structure and configuration of **20** were verified by comparison of the optical rotation and NMR spectra of the corresponding piperidinium chloride salt **21** with literature values.^[17]

Conclusions

The synthesis of both enantiomers of *trans*-4-hydroxypipicolinic acid has been accomplished in five steps in a combined overall yield of 45.6% starting from nitrone **12**. The relative configuration of the two stereocenters of **1** was set up through the 1,3-DC of butenol **4** to the (*Z*)-nitrone **12**, which occurs exclusively in an *exo* manner. Similarly, the (*E*)-nitrone **17** affords a derivative of the (2*R*,4*S*) enantiomer of the *cis*-4-hydroxypipicolinic acid. In this case, the cycloaddition is completely diastereoselective, although subsequent elaboration of the adduct afforded the methyl ester of **2** in a lower yield (4% over five steps starting from **17**).

Experimental Section

General: All reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were dried appropriately before use. NMR spectra were recorded in CDCl₃ (unless otherwise stated) and the data are reported in δ (ppm) from TMS. The multiplicities of the ¹³C NMR signals were determined by means of APT and HSQC experiments. Relative percentages in the mass spectra are given in parentheses. *R_f* values refer to TLC on 0.25-mm silica gel plates (Merck F₂₅₄).

(2*Z*)-{Oxido[(1*R*)-1-phenylethyl]imino}ethanoic Acid (9**):** [(1*R*)-1-(hydroxyammonio)ethyl]benzene oxalate (9.08 g, 0.04 mol) and TEA (5.53 mL, 0.04 mol) were added to a suspension of glyoxylic acid monohydrate (3.68 g, 0.04 mol) and activated powdered molecular sieves in CH₂Cl₂ (50 mL). The reaction mixture was stirred at room temperature for 65 h and then washed with water. The organic phase was dried with Na₂SO₄, filtered, and the solvent was removed under reduced pressure to give crude **9** as an orange oil (5.28 g, 68%), which was used in the next step without further purification. ¹H NMR (200 MHz): δ = 1.90 (d, *J* = 6.9 Hz, 1 H, CH₃), 5.16 (q, *J* = 6.9 Hz, 1 H, CHCH₃), 7.32 (s, 1 H, HC=N), 7.44 (br. s, 5 H, Ph) ppm.

(2*Z*)-*N*-Benzyl-2-{oxido[(1*R*)-1-phenylethyl]imino}ethanamide (10**):** Diisopropylcarbodiimide (DIC; 121 μ L, 0.78 mmol) was added dropwise to a solution of crude nitrone **9** (150 mg, 0.78 mmol) and hydroxybenzotriazole hydrate (HOBt; 12 wt.-% H₂O; 117 mg,

0.77 mmol) in CH₂Cl₂ (0.8 mL). Benzylamine (102 μ L, 0.93 mmol) and diisopropyl(ethyl)amine (DIPEA; 135 μ L, 0.78 mmol) were then added sequentially. The reaction mixture was stirred at room temperature for 24 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with 5% KHSO₄ aqueous solution (3 $\times$ 3 mL) and H₂O (3 $\times$ 3 mL). The organic phase was dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/petroleum ether = 1:3 then 1:2) to give **10** (120 mg, 55%) as a colorless oil. *R_f* = 0.1 (EtOAc/petroleum ether = 1:3). $[\alpha]_D^{20}$ = −14.4 (*c* = 0.88, CHCl₃). ¹H NMR (400 MHz): δ = 1.83 (d, *J* = 6.9 Hz, 3 H, CH₃), 4.47 (A part of an ABX system, *J* = 15.0, 5.7 Hz, 1 H, NCHH), 4.55 (B part of an ABX system, *J* = 15.0, 6.0 Hz, 1 H, NCHH), 5.08 (q, *J* = 6.9 Hz, 1 H, CHCH₃), 7.21 (s, 1 H, HC=N), 7.34–7.23 (m, 5 H, Ph), 7.38–7.45 (m, 5 H, Ph), 10.13 (br. s, 1 H, NH) ppm. ¹³C NMR (100 MHz): δ = 18.7 (q, CH₃), 43.1 (t, NCH₂), 76.4 (d, CH₃CHNO), 127.4 (d, C=N), 127.5 (d, 2 C, Ph), 127.9 (d, 2 C, Ph), 128.6 (d, 2 C, Ph), 129.0 (d, 2 C, Ph), 129.5 (d, 2 C, Ph), 136.6 (s, Ph), 137.5 (s, Ph), 160.7 (s, CO) ppm. IR (CDCl₃): $\tilde{\nu}$ = 3254, 3033, 2930, 1651, 1529, 1455 cm^{−1}. MS (70 eV, EI): *m/z* (%) = 282 (7) [M⁺], 177 (17), 161 (13), 104 (100), 76 (62). C₁₇H₁₈N₂O₂ (282.34): calcd. C 72.32, H 6.43, N 9.92; found C 72.21, H 6.30, N 10.09.

(2*Z*)-2-{Oxido[(1*R*)-1-phenylethyl]imino}-*N*-[(1*S*)-1-phenylethyl]ethanamide (11**):** The crude nitrone **9** (502 mg, 2.60 mmol) was coupled with (1*S*)-1-phenylethylamine (402 μ L, 3.12 mmol) under the same conditions as described for the synthesis of **10**. The purification of the crude product by chromatography on silica gel (EtOAc/petroleum ether = 1:3 then 1:2) afforded nitrone **11** (390 mg, 50%) as a pale-yellow oil. *R_f* = 0.3 (EtOAc/petroleum ether = 1:2). $[\alpha]_D^{20}$ = +30.0 (*c* = 0.27, CHCl₃). ¹H NMR (400 MHz): δ = 1.52 (d, *J* = 6.9 Hz, 3 H, CH₃CHNH), 1.84 (d, *J* = 6.9 Hz, 3 H, CH₃CHNO), 5.07 (q, *J* = 6.9 Hz, 1 H, CH₃CHNO), 5.15 (pseudo-quint, *J* = 7.2 Hz, 1 H, CHNH), 7.16 (s, 1 H, HC=N), 7.20–7.33 (m, 5 H, Ph), 7.37–7.43 (m, 5 H, Ph), 10.17 (br. d, *J* = 7.1 Hz, 1 H, NH) ppm. ¹³C NMR (50 MHz): δ = 18.7 (q, CH₃CHNO), 22.4 (q, CH₃CHNH), 48.8 (d, CHNH), 76.3 (d, CH₃CHNO), 126.2 (d, 2 C, Ph), 127.2 (d, C=N), 127.4 (d, 2 C, Ph), 128.6 (d, 2 C, Ph), 129.0 (d, 2 C, Ph), 129.4 (d, Ph), 129.7 (d, Ph), 136.5 (s, Ph), 142.8 (s, Ph), 159.8 (s, CO) ppm. IR (CDCl₃): $\tilde{\nu}$ = 3243, 3032, 2929, 1649, 1554, 1526, 1455 cm^{−1}. MS (70 eV, EI): *m/z* (%) = 296 (1) [M⁺], 192 (13), 175 (11), 145 (7), 130 (14), 104 (100), 76 (86). C₁₈H₂₀N₂O₂ (296.36): calcd. C 72.95, H 6.80, N 9.45; found C 72.90, H 6.94, N 9.36.

(2*Z*)-2-{Oxido[(1*R*)-1-phenylethyl]imino}-*N*-[(1*R*)-1-phenylethyl]ethanamide (12**):** The crude nitrone **9** (1.71 g, 8.86 mmol) was coupled with [(1*R*)-1-phenylethyl]amine (400 μ L, 1.29 g, 10.64 mmol) under the same conditions as described for the synthesis of **10**. The purification of the crude product by chromatography on silica gel (EtOAc/petroleum ether = 1:3 then 1:2) afforded nitrone **12** (1.35 g, 52%) as a white solid. *R_f* = 0.40 (EtOAc/petroleum ether = 1:2); m.p. 120–122 °C. $[\alpha]_D^{23}$ = −88.8 (*c* = 1.09, CHCl₃). ¹H NMR (400 MHz): δ = 1.50 (d, *J* = 6.9 Hz, 3 H, CH₃CHNH), 1.83 (d, *J* = 6.9 Hz, 3 H, CH₃CHNO), 5.08 (q, *J* = 6.9 Hz, 1 H, MeCHNO), 5.15 (pseudo-quint, *J* = 7.2 Hz, 1 H, CHNH), 7.18 (s, 1 H, HC=N), 7.21–7.36 (m, 5 H, Ph), 7.37–7.47 (m, 5 H, Ph), 10.19 (br. d, *J* = 7.0 Hz, 1 H, NH) ppm. ¹³C NMR (50 MHz): δ = 18.6 (q, CH₃CHNO), 22.4 (q, CH₃CHNH), 48.7 (d, CHNH), 76.3 (d, MeCHNO), 126.2 (d, 2 C, Ph), 127.3 (d, C=N), 127.5 (d, 2 C, Ph), 128.6 (d, 2 C, Ph), 129.0 (d, 2 C, Ph), 129.5 (d, Ph), 129.7 (d, Ph), 136.5 (s, Ph), 142.9 (s, Ph), 159.8 (s, CO) ppm. IR (CDCl₃): $\tilde{\nu}$ = 3243, 2983, 1649, 1526, 1454 cm^{−1}. MS (70 eV, EI): *m/z* (%) = 192

(4) [$M^+ - 104$], 175 (4), 147 (5), 131 (6), 119 (5), 104 (100), 77 (20). $C_{18}H_{20}N_2O_2$ (296.36): calcd. C 72.95, H 6.80, N 9.45; found C 73.09, H 7.01, N 9.77.

Cycloadducts of Nitrone 12 with 3-Buten-1-ol (Representative Cycloaddition)

(3*R*,5*S*)- and (3*S*,5*R*)-5-(2-Hydroxyethyl)-*N*,2-bis[(1*R*)-1-(phenylethyl)]-3-isoxazolidinecarboxamide (13a and 13b): A solution of nitrone 12 (1.35 g, 4.56 mol) in butenol 4 (96% purity, 2 mL) was heated at 100 °C for 21 h. The solution was then cooled and the excess of butenol was removed under reduced pressure. The crude mixture of the two diastereomers 13a and 13b was separated by chromatography on silica gel (EtOAc/petroleum ether, 2:1) to give 13a (715 mg, 43%) and 13b (729 mg, 43%) as colorless oils.

13a: R_f = 0.1 (EtOAc/petroleum ether = 2:1). $[a]_D^{20}$ = -13.9 (c = 0.28, $CHCl_3$). 1H NMR (400 MHz): δ = 1.33 (d, J = 6.6 Hz, 3 H, CH_3CHNO), 1.51 (d, J = 7.0 Hz, 3 H, CH_3CHNH), 1.69–1.76 (m, 2 H, CH_2CH_2OH), 2.23 (ddd, J = 12.6, 7.7, 5.7 Hz, 1 H, 4-H), 2.72 (ddd, J = 12.6, 8.9, 6.9 Hz, 1 H, 4-H), 3.58 (t, J = 5.8 Hz, 2 H, CH_2OH), 3.87 (dd, J = 8.9, 5.7 Hz, 1 H, 3-H), 3.94 (q, J = 6.6 Hz, 1 H, CH_3CHNO), 4.19 (br. quint, J = 6.8 Hz, 1 H, 5-H), 5.12 (dq, J = 8.0, 7.0 Hz, 1 H, CH_3CHNH), 7.27–7.29 (m, 10 H, Ph), 7.77 (br. d, J = 8.0 Hz, 1 H, NH) ppm. ^{13}C NMR (50 MHz): δ = 20.2 (q, CH_3), 21.5 (q, CH_3), 35.8 (t, CH_2CH_2OH), 38.7 (t, C-4), 48.0 (d, CH_3CHNH), 59.3 (t, CH_2OH), 63.7 (d, CH_3CHNO), 65.2 (d, C-3), 75.5 (d, C-5), 125.5 (d, 2 C, Ph), 126.9 (d, 3 C, Ph), 127.1 (d, Ph), 128.0 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 141.6 (s, Ph), 142.6 (s, Ph), 170.8 (s, CO) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3367, 3031, 2978, 2932, 1664, 1515, 1454 cm^{-1} . MS (70 eV, EI): m/z (%) = 368 (1) [M^+], 220 (41), 116 (46), 105 (100), 77 (33). $C_{22}H_{28}N_2O_3$ (368.47): calcd. C 71.71, H 7.66, N 7.60; found C 71.25, H 7.99, N 7.64.

13b: R_f = 0.2 (EtOAc/petroleum ether = 2:1). $[a]_D^{20}$ = -17.1 (c = 0.34 in $CHCl_3$). 1H NMR (400 MHz): δ = 1.43 (d, J = 7.0 Hz, 3 H, CH_3CHNH), 1.50 (d, J = 6.4 Hz, 3 H, CH_3CHNO), 1.67–1.76 (m, 2 H, CH_2CH_2OH), 2.24 (ddd, J = 12.8, 7.0, 3.5 Hz, 1 H, 4-H), 2.68 (ddd, J = 12.8, 8.8, 8.5 Hz, 1 H, 4-H), 3.63–3.69 (m, 3 H, 3-H and CH_2OH), 3.90 (q, J = 6.4 Hz, 1 H, CH_3CHNO), 4.42 (dq, J = 5.3, 7.3 Hz, 1 H, 5-H), 4.96 (dq, J = 8.3, 7.0 Hz, 1 H, CH_3CHNH), 7.26–7.36 (m, 10 H, Ph), 7.72 (br. d, J = 8.3 Hz, 1 H, NH) ppm. ^{13}C NMR (50 MHz): δ = 21.4 (q, CH_3CHNO), 22.2 (q, CH_3CHNH), 36.6 (t, CH_2CH_2OH), 36.8 (t, C-4), 48.3 (d, CH_3CHNH), 60.4 (t, CH_2OH), 63.8 (d, CH_3CHNO), 65.8 (d, C-3), 76.0 (d, C-5), 125.9 (d, 2 C, Ph), 127.0 (d, Ph), 127.4 (d, 2 C, Ph), 128.1 (d, Ph), 128.5 (d, 2 C, Ph), 128.9 (d, 2 C, Ph), 141.8 (s, Ph), 143.4 (s, Ph), 170.9 (s, CO) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3372, 3032, 2931, 1664, 1518, 1454 cm^{-1} . MS (70 eV, EI): m/z (%) = 368 (2) [M^+], 220 (43), 116 (46), 105 (100), 77 (32). $C_{22}H_{28}N_2O_3$ (368.47): calcd. C 71.71, H 7.66, N 7.60; found C 71.60, H 7.98, N 7.44.

Cycloadducts of Nitrone 10 with 3-Buten-1-ol

(3*R*,5*S*)- and (3*S*,5*R*)-*N*-Benzyl-5-(2-hydroxyethyl)-2-[(1*R*)-1-phenylethyl]-3-isoxazolidinecarboxamide (mixture of two inseparable diastereomers): R_f = 0.27 (EtOAc). 1H NMR (400 MHz): *one isomer*: δ = 1.47 (d, J = 6.4 Hz, 3 H, CH_3CHNO), 1.80–1.88 (m, 2 H, CH_2CH_2OH), 2.35 (ddd, J = 12.9, 7.2, 3.5 Hz, 1 H, 4-H), 2.74 (ddd, J = 12.9, 9.3, 7.9 Hz, 1 H, 4-H), 3.69 (dd, J = 9.5, 3.4 Hz, 1 H, 3-H), 3.74 (pseudo-t, J = 5.9 Hz, 2 H, CH_2OH), 3.90 (q, J = 6.4 Hz, 1 H, CH_3CHNO), 4.31 (A part of an ABX system, J = 15.0, 5.4 Hz, 1 H, CH_3CHNH), 4.49 (B part of an ABX system, J = 15.0, 7.0 Hz, 1 H, CH_3CHNH), 4.42–4.49 (m, 1 H, 5-H), 7.16–7.37 (m, 10 H, Ph), 7.75 (m, 1 H, NH) ppm; *other isomer*: δ = 1.38 (d, J = 6.6 Hz, 3 H, CH_3CHNO), 1.64–1.72 (m, 2 H, CH_2CH_2OH), 2.25 (ddd, J = 12.9, 7.7, 5.3 Hz, 1 H, 4-H), 2.74

(ddd, J = 12.9, 9.3, 7.9 Hz, 1 H, 4-H), 3.53 (pseudo-t, J = 5.8 Hz, 2 H, CH_2OH), 3.96 (dd, J = 8.2, 5.1 Hz, 1 H, 3-H), 3.97 (q, J = 6.6 Hz, 1 H, CH_3CHNO), 4.19 (dq, J = 4.9, 7.5 Hz, 1 H, 5-H), 4.44 (A part of an ABX system, J = 15.0, 5.7 Hz, 1 H, CH_3CHNH), 4.53 (B part of an ABX system, J = 15.0, 6.4 Hz, 1 H, CH_3CHNH), 7.16–7.37 (m, 10 H, Ph), 7.84 (m, 1 H, NH) ppm. ^{13}C NMR (100 MHz) selected data: *one isomer*: δ = 21.3 (q, CH_3), 36.6 (t, CH_2CH_2OH), 36.7 (t, C-4), 43.0 (t, CH_2Ph), 60.4 (t, CH_2OH), 63.6 (d, CH_3CHNO), 65.8 (d, C-3), 76.1 (d, C-5), 138.2 (s, Ph), 141.7 (s, Ph), 171.8 (s, CO) ppm; *other isomer*: δ = 20.8 (q, CH_3), 36.0 (t, CH_2CH_2OH), 39.0 (t, C-4), 43.1 (t, CH_2Ph), 60.5 (t, CH_2OH), 64.3 (d, CH_3CHNO), 65.6 (d, C-3), 76.4 (d, C-5) ppm.

Cycloadducts of Nitrone 11 with 3-Buten-1-ol

(3*R*,5*S*)- and (3*S*,5*R*)-5-(2-Hydroxyethyl)-2-[(1*R*)-1-phenylethyl]-*N*-[(1*S*)-1-phenylethyl]-3-isoxazolidinecarboxamide (mixture of two inseparable diastereomers): R_f = 0.12 (EtOAc/petroleum ether = 1.5:1). 1H NMR (400 MHz): *one isomer*: δ = 1.48 (d, J = 6.4 Hz, 3 H, CH_3CHNO), 1.50 (d, J = 6.8 Hz, 3 H, CH_3CHNH), 1.83–1.90 (m, 2 H, CH_2CH_2OH), 2.33 (ddd, J = 12.8, 7.3, 3.6 Hz, 1 H, 4-H), 2.72 (ddd, J = 12.8, 9.4, 7.8 Hz, 1 H, 4-H), 3.63 (dd, J = 9.4, 3.6 Hz, 1 H, 3-H), 3.77 (tm, J = 5.8 Hz, 2 H, CH_2OH), 3.89 (q, J = 6.4 Hz, 1 H, CH_3CHNO), 4.47 (dq, J = 5.3, 7.3 Hz, 1 H, 5-H), 5.00 (dq, J = 8.1, 7.0 Hz, 1 H, CH_3CHNH), 7.16–7.37 (m, 10 H, Ph), 7.68 (br. d, J = 8.6 Hz, 1 H, NH) ppm; *other isomer*: δ = 1.42 (d, J = 6.6 Hz, 3 H, CH_3CHNO), 1.52 (d, J = 6.8 Hz, 3 H, CH_3CHNH), 1.58 (q, J = 5.7 Hz, 2 H, CH_2CH_2OH), 2.13 (ddd, J = 12.7, 7.3, 5.6 Hz, 1 H, 4-H), 2.66 (ddd, J = 12.7, 8.9, 6.6 Hz, 1 H, 4-H), 3.49 (pseudo-t, J = 5.8 Hz, 2 H, CH_2OH), 3.91 (dd, J = 8.9, 5.6 Hz, 1 H, 3-H), 3.99 (q, J = 6.6 Hz, 1 H, CH_3CHNO), 4.16 (br. quint, J = 6.9 Hz, 1 H, 5-H), 5.09 (dq, J = 8.3, 7.0 Hz, 1 H, CH_3CHNH), 7.16–7.37 (m, 10 H, Ph), 7.78 (br. d, J = 7.5 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz): *one isomer*: δ = 21.2 (q, CH_3), 21.7 (q, CH_3), 36.4, 36.6 (t, CH_2CH_2OH , C-4), 48.2 (d, CH_3CHNH), 60.3 (t, CH_2OH), 63.8 (d, CH_3CHNO), 65.8 (d, C-3), 76.3 (d, C-5), 126.0 (d, 2 C, Ph), 127.1 (d, Ph), 127.5 (d, 2 C, Ph), 128.1 (d, Ph), 128.5 (d, 2 C, Ph), 128.9 (d, 2 C, Ph), 141.7 (s, Ph), 143.0 (s, Ph), 170.8 (s, CO) ppm; *other isomer*: δ = 20.6 (q, CH_3), 22.2 (q, CH_3), 36.0 (t, CH_2CH_2OH), 39.1 (t, C-4), 48.4 (d, CH_3CHNH), 60.4 (t, CH_2OH), 64.4 (d, CH_3CHNO), 65.7 (d, C-3), 76.4 (d, C-5), 125.9 (d, 2 C, Ph), 127.2 (d, Ph), 127.4 (d, 2 C, Ph), 127.7 (d, Ph), 128.5 (d, 2 C, Ph), 128.6 (d, 2 C, Ph), 141.7 (s, Ph), 143.2 (s, Ph), 170.8 (s, CO) ppm.

(2*R*,4*R*)-4-Hydroxy-*N*,1-bis[(1*R*)-1-phenylethyl]-2-piperidinecarboxamide (15a): Freshly distilled $MsCl$ (166 μL , 2.13 mmol) was cooled in an ice/water bath and then added dropwise to a solution of isoxazolidine 13a (715.3 mg, 1.94 mmol) and anhydrous NEt_3 (403 μL , 2.91 mmol) in anhydrous CH_2Cl_2 (6.5 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 2 h, diluted with THF (18 mL), and concentrated under reduced pressure. The residue was dissolved in MeOH (28 mL) and hydrogenated in the presence of 10% Pd/C (310 mg) at room temperature and atmospheric pressure for 19 h. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH, treated with Ambersep 900 OH at room temperature for 2 h, filtered, and concentrated under reduced pressure to give crude 15a, containing traces of 16a, as a yellow oil (546 mg, 80% based on 13a), which was used in the next step without further purification. A sample purified by chromatography on silica gel ($CH_2Cl_2/MeOH/NH_3$ = 50:1:0.01) afforded analytically pure 15a as a colorless oil (76% yield based on 13a). R_f = 0.21

(CH₂Cl₂/MeOH/NH₃ = 50:1:0.01). [α]_D²⁰ = +24.7 (*c* = 0.45 in CHCl₃). ¹H NMR (400 MHz): δ = 1.32 (d, *J* = 6.7 Hz, 3 H, CH₃CHNCH₂), 1.50 (d, *J* = 7.0 Hz, 3 H, CH₃CHNH), 1.52–1.64 (m, 4 H, 3-H, 2 $\times$ 5-H, OH), 2.33 (br. dt, *J* = 12.9, 4.4 Hz, 1 H, 3-H), 2.54–2.70 (m, 2 H, 2 $\times$ 6-H), 3.65 (br. t, *J* = 4.7 Hz, 1 H, 2-H), 3.78–3.87 (m, 1 H, 4-H), 3.93 (q, *J* = 6.7 Hz, 1 H, CHNCH₂), 5.12 (dq, *J* = 7.9, 7.0 Hz, 1 H, CHNH), 7.21–7.38 (m, 10 H, Ph), 7.45 (br. d, *J* = 7.9 Hz, 1 H, NH) ppm. ¹³C NMR (100 MHz): δ = 21.1 (q, CH₃CHNCH₂), 22.1 (q, CH₃CHNH), 29.9 (t, C-5), 32.2 (t, C-3), 42.5 (t, C-6), 48.4 (d, CHNH), 58.2 (d, C-2), 59.0 (d, CHNCH₂), 65.5 (d, C-4), 126.0 (d, 2 C, Ph), 127.3 (d, Ph), 127.4 (d, Ph), 127.6 (d, 2 C, Ph), 128.5 (d, 2 C, Ph), 128.7 (d, 2 C, Ph), 142.9 (s, Ph), 143.4 (s, Ph), 172.2 (s, CO) ppm. IR (CDCl₃): $\tilde{\nu}$ = 3609, 3358, 3031, 2932, 1664, 1505, 1453 cm⁻¹. MS (70 eV, EI): *m/z* (%) = 352 (0.1) [M⁺], 204 (97), 105 (100), 100 (90), 77 (53). C₂₂H₂₈N₂O₂ (352.47): calcd. C 74.97, H 8.01, N 7.95; found C 74.48, H 8.45, N 8.04.

(2*R*,4*R*)-4-Hydroxy-*N*-[(1*R*)-1-phenylethyl]-2-piperidinecarboxamide (16a): Crude **15a** (546 mg, 1.55 mmol) was dissolved in MeOH (22 mL) and hydrogenated in the presence of 10% Pd/C (247 mg) at room temperature and atmospheric pressure for 22 h. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH, treated with Ambersep 900 OH at room temperature for 2 h, filtered, and concentrated under reduced pressure to give crude **16a** as a yellow oil (quantitative yield), which was used in the next step without further purification. A sample purified by chromatography on silica gel (EtOAc followed by EtOAc/MeOH/NH₃ = 10:1:0.01, then MeOH/NH₃ = 1:0.01) afforded analytically pure **16a** as a colorless oil (87% yield based on **15a**; 70% yield based on **13a**). *R*_f = 0.28 (MeOH/NH₃ = 1:0.01). [α]_D²⁰ = +40.6 (*c* = 0.18 in CHCl₃). ¹H NMR (400 MHz): δ = 1.48 (d, *J* = 6.9 Hz, 3 H, CH₃), 1.50–1.60 (m, 1 H, 5-H), 1.70–1.88 (m, 4 H, 3-H, 5-H, NHCH₂, OH), 1.94–2.02 (m, 1 H, 3-H), 2.80 (ddd, *J* = 12.9, 5.6, 4.4 Hz, 1 H, 6-H), 3.11 (ddd, *J* = 12.9, 9.4, 3.5 Hz, 1 H, 6-H), 3.73 (dd, *J* = 8.5, 4.0 Hz, 1 H, 2-H), 4.04 (m, 1 H, 4-H), 5.08 (pseudo-quint, *J* = 7.2 Hz, 1 H, MeCH), 7.22–7.36 (m, 5 H, Ph), 7.41 (br. d, *J* = 7.6 Hz, 1 H, NHCO) ppm. ¹³C NMR (100 MHz): δ = 21.9 (q, CH₃), 33.3 (t, C-5), 36.7 (t, C-3), 40.3 (t, C-6), 48.2 (d, CHCH₃), 55.0 (d, C-2), 64.4 (d, C-4), 126.1 (d, 2 C, Ph), 127.2 (d, Ph), 128.6 (d, 2 C, Ph), 143.2 (s, Ph), 172.7 (s, CO) ppm. IR (CDCl₃): $\tilde{\nu}$ = 3609, 3367, 3032, 2929, 1661, 1512, 1451 cm⁻¹. MS (70 eV, EI): *m/z* (%) = 248 (0.4) [M⁺], 104 (29), 100 (100), 82 (54). C₁₄H₂₀N₂O₂ (248.32): calcd. C 67.71, H 8.12, N 11.28. found C 67.22, H 7.78, N 11.41.

(2*R*,4*R*)-4-Hydroxy-2-piperidinecarboxylic Acid (1a): Crude **16a** from the previous step was dissolved in 6 N aqueous HCl (19 mL) and the resulting solution was refluxed for 22 h. After concentration under vacuum, the product was treated with saturated aqueous Na₂CO₃ and washed with EtOAc to remove the (*R*)-(phenylethyl)-amine. The aqueous solution was acidified to pH = 1 with 6 N HCl and then the solvent was completely removed under reduced pressure. The residue was redissolved in a minimum amount of H₂O and adsorbed on a column of cation-exchange resin (Dowex 50W X-8, 100–200 mesh). The resin was washed with distilled water until neutral and then the amino acid was eluted with 6% aqueous ammonia. The collected solution was concentrated under reduced pressure to give a yellow solid, which was washed with EtOH and lyophilized to give **1a** (147 mg, 65% yield based on **15a**; 52% yield based on **13a**) as a white solid. [α]_D²⁰ = +12.6 (*c* = 0.3, H₂O) {ref.^{[14]}} [α]_D²⁰ = +12.6 (*c* = 0.8, H₂O)}. ¹H NMR (400 MHz, D₂O): δ = 1.81–1.97 (m, 3 H, 3-H + 5-H₂), 2.16–2.23 (m, 1 H, 3-H), 3.26–3.29 (m, 2 H, 6-H₂), 3.89 (dd, *J* = 11.9, 3.7 Hz, 1 H, 2-H), 4.21 (m, 1 H, 4-H) ppm.

(2*S*,4*S*)-4-Hydroxy-2-piperidinecarboxylic Acid (1b): Freshly distilled MsCl (169 μ L, 2.18 mmol) was cooled in an ice/water bath and then added dropwise to a solution of isoxazolidine **13b** (728.8 mg, 1.98 mmol) and anhydrous NEt₃ (411 μ L, 2.97 mmol) in anhydrous CH₂Cl₂ (6.6 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 2 h, diluted with THF (18 mL), and concentrated under reduced pressure. The residue was dissolved in MeOH (28 mL) and hydrogenated in the presence of 10% Pd/C (316 mg) at room temperature and atmospheric pressure for 19 h. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH, treated with Ambersep 900 OH at room temperature for 2 h, filtered, and concentrated under reduced pressure. The residue was dissolved in 6 N aqueous HCl (19 mL) and the resulting solution was treated under the same conditions as described for the hydrolysis of **16a**. The purification of the crude product by ion-exchange chromatography afforded the amino acid **1b** (156 mg, 54% yield based on **13b**) as a white solid. [α]_D²⁰ = –11.7 (*c* = 0.5, H₂O) {ref.^{[14]}} [α]_D²⁰ = –12.6 (*c* = 0.8, H₂O); ref.^{[14]}} [α]_D²⁰ = –13 $\pm$ 0.4 (1% in H₂O)}. ¹H NMR spectrum identical with that of the enantiomer **1a**.

(2*R*,3*aR*,7*R*)-2-(2-Hydroxyethyl)-7-phenyltetrahydroisoxazolo-[3,2-*c*][1,4]oxazin-4(2*H*)-one (18): A solution of nitron **17**^[15] (1.44 g, 7.55 mmol) and butenol **4** (1.3 mL, 15 mmol) in CH₂Cl₂ (3.7 mL) was stirred at room temperature for 41 h. The mixture was concentrated under reduced pressure and the pale-yellow solid obtained was recrystallized (*i*Pr₂O/EtOAc = 1:1) to give the product **18** (989 mg, 50%) as white crystals. *R*_f = 0.48 (EtOAc/petroleum ether = 1:2); m.p. 126–128 °C (*i*Pr₂O/EtOAc = 1:1). [α]_D²³ = –123.4 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz): δ = 1.75–1.92 (m, 2 H, CH₂CH₂OH), 2.18 (br. s, 1 H, OH), 2.52 (ddd, *J* = 12.8, 9.3, 6.3 Hz, 1 H, 3-H), 2.88 (dt, *J* = 12.8, 7.5 Hz, 1 H, 3-H), 3.66 (br. t, *J* = 5.9 Hz, 2 H, CH₂OH), 4.11 (A part of an ABC system, *J* = 10.0, 3.6 Hz, 1 H, 7-H), 4.22 (B part of an ABC system, *J* = 11.6, 10.0 Hz, 1 H, 6-H), 4.28 (C part of an ABC system, *J* = 11.6, 3.6 Hz, 1 H, 6-H), 4.32–4.41 (m, 2 H, 3a-H, 2-H), 7.30–7.44 (m, 5 H, Ph) ppm. ¹³C NMR (100 MHz): δ = 36.2 (t, CH₂CH₂OH), 38.8 (t, C-3), 59.6 (t, CH₂OH), 61.9 (d, C-7), 62.1 (d, C-3a), 69.6 (t, C-6), 74.0 (d, C-2), 127.4 (d, 2 C, Ph), 128.6 (d, Ph), 128.8 (d, 2 C, Ph), 135.4 (s, Ph), 169.7 (s, C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3557, 3035, 2926, 1724, 1247, 1063 cm⁻¹. MS (70 eV, EI): *m/z* (%) = 263 (2) [M⁺], 160 (3), 130 (12), 105 (100), 90 (12). C₁₄H₁₇NO₄ (263.29): calcd. C 63.87, H 6.51, N 5.32; found C 63.65, H 6.36, N 5.45.

Methyl (2*R*,4*S*)-4-Hydroxy-2-piperidinecarboxylate (20): Freshly distilled MsCl (136 μ L, 1.75 mmol) was cooled in an ice/water bath and then added dropwise to a solution of **18** (419 mg, 1.59 mmol) and anhydrous NEt₃ (330 μ L, 2.39 mmol) in anhydrous CH₂Cl₂ (5.3 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 4 h and then at room temperature for 30 min, diluted with THF (2.5 mL), and concentrated under reduced pressure. The residue was dissolved in MeOH (26.6 mL) and hydrogenated in the presence of 10% Pd/C (34 mg) at room temperature and atmospheric pressure for 4 d. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH, treated with Ambersep 900 OH at room temperature under magnetic stirring for 2 h, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH/NH₃ = 15:1:0.01), to give the oxazinone **20** (20 mg, 8% yield) as a yellow oil. ¹H NMR (200 MHz): δ = 1.24–1.56 (m, 2 H, 3-H, 5-H), 1.86–2.00 (m, 1 H, 5-H), 2.23–2.36 (m, 1 H, 3-H), 2.63 (br. s, 2 H, NH, OH), 2.64 (dt, *J* = 2.6, 12.1 Hz, 1

H, 6-H), 3.22 (dt, $J = 12.7, 3.9$ Hz, 1 H, 6-H), 3.40 (dd, $J = 10.7, 3.1$ Hz, 1 H, 2-H), 3.64–3.81 (m, 1 H, 4-H), 3.74 (s, 3 H, CH₃) ppm. ¹³C NMR (50 MHz): $\delta = 34.7$ (t, C-5), 37.8 (t, C-3), 42.7 (t, C-6), 52.0 (q, OCH₃), 56.7 (d, C-2), 67.8 (d, C-4), 172.9 (s, CO) ppm.

(2R,4S)-4-Hydroxy-2-(methoxycarbonyl)piperidinium Chloride (21): Chlorotrimethylsilane (0.2 mL, 1.58 mmol) was added to a solution of **20** (4.3 mg, 0.027 mmol) in MeOH (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h, then the solvent was evaporated under reduced pressure to give **21** (5.3 mg, quantitative yield). $[\alpha]_D^{25} = -9.6$ ($c = 0.45$, MeOH) {ref.^[17] $[\alpha]_D^{25} = +9.9$ ($c = 1.01$, MeOH) for the (2S,4R) enantiomer}.

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- [1] a) G. C. Kite, J. J. Wieringa, *Biochem. Syst. Ecol.* **2003**, *31*, 279–292; b) G. C. Kite, H. Ireland, *Phytochemistry* **2002**, *59*, 163–168; c) J. T. Romeo, L. A. Swain, A. B. Bleeker, *Phytochemistry* **1983**, *22*, 1615–1618; d) V. U. Ahmad, M. A. Khan, *Phytochemistry* **1971**, *10*, 3339–3340; e) V. W. Schenk, H. R. Schutte, *Flora* **1963**, *153*, 426–443; f) J. W. Clark-Lewis, P. I. Mortimer, *J. Chem. Soc.* **1961**, 189–201.
- [2] a) T. A. Mukhtar, G. D. Wright, *Chem. Rev.* **2005**, *105*, 529–542; b) M. Di Giambattista, E. Nyssen, A. Percher, C. Cocito, *Biochemistry* **1990**, *29*, 9203–9211; c) J. W. Reed, M. B. Purvis, D. G. I. Kingston, A. Blot, F. Gossele, *J. Org. Chem.* **1989**, *54*, 1161–1165; d) H. Kessler, M. Kühn, T. Löschner, *Liebigs Ann. Chem.* **1986**, 1–20; e) U. Hollstein, *Chem. Rev.* **1974**, *74*, 625–652; f) H. Vanderhaeghe, G. Parmentier, *J. Am. Chem. Soc.* **1960**, *82*, 4414–4422.
- [3] a) P. L. Beaulieu, P. C. Anderson, D. R. Cameron, G. Croteau, V. Gorys, C. Grand-Maitre, D. Lamarre, F. Liard, W. Paris, L. Plamondon, F. Soucy, D. Thibeault, D. Wernic, C. Yoakim, *J. Med. Chem.* **2000**, *43*, 1094–1108; b) D. Lamarre, G. Croteau, L. Bourgon, D. Thibeault, E. Wardrop, C. Clouette, M. Vailancourt, E. Cohen, C. Pargellis, C. Yoakim, P. C. Anderson, *Antimicrob. Agents Chemother.* **1997**, *41*, 965–971.
- [4] a) R. Sakai, H. Matsubara, K. Shimamoto, M. Jimbo, H. Kamiya, M. Namikoshi, *J. Nat. Prod.* **2003**, *66*, 784–787; b) P. L. Ornstein, M. B. Arnold, W. H. W. Lunn, L. J. Heinz, J. D. Leander, D. Lodge, D. D. Schoepp, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 389–394; c) J. W. Skiles, P. P. Giannousis, K. R. Fales, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 963–966; d) G. Mannaioni, M. Alesiani, V. Carlà, B. Natalini, M. Marinozzi, R. Pellicciari, F. Moroni, *Eur. J. Pharmacol.* **1994**, *251*, 201–207; e) R. Pellicciari, B. Natalini, G. Constantino, A. Garzon, R. Luneia, M. R. Mahmoud, M. Marinozzi, M. Roberti, G. C. Rosato, S. A. Shiba, *Farmaco* **1993**, *48*, 151–157.
- [5] a) F. Machetti, F. M. Cordero, F. De Sarlo, A. M. Papini, M. C. Alcaro, A. Brandi, *Eur. J. Org. Chem.* **2004**, 2928–2935; b) A. S. Golubev, H. Schedel, G. Radics, J. Sieler, K. Burger, *Tetrahedron Lett.* **2001**, *42*, 7941–7944; c) B. Bellier, S. Da Nascimento, H. Meudal, E. Gincel, B. P. Roques, C. Garbay, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1419–1424.
- [6] For a recent review on the synthesis of enantiopure pipecolic acid derivatives, including 4-hydroxy- and 4-oxopipecolic acids, see: C. Kadouri-Puchot, S. Comesse, *Amino Acids* **2005**, *29*, 101–130.
- [7] a) F. Machetti, F. M. Cordero, F. De Sarlo, A. Brandi, *Tetrahedron* **2001**, *57*, 4995–4998; b) F. Machetti, F. M. Cordero, F. De Sarlo, A. Guarna, A. Brandi, *Tetrahedron Lett.* **1996**, *37*, 4205–4208.
- [8] a) E. Breuer, H. G. Aurich, A. Nielsen, *Nitrones, Nitronates and Nitroxides*, John Wiley & Sons, Chichester, **1989**; b) K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, New York, **1988**; c) J. J. Tufariello, in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa); John Wiley & Sons, New York, **1984**, vol. 5, p. 83; d) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863–909; e) M. Frederickson, *Tetrahedron* **1997**, *53*, 403–425.
- [9] a) Y. Inouye, K. Takaya, H. Kakisawa, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3541–3542; b) Y. Inouye, J. Hara, H. Kakisawa, *Chem. Lett.* **1980**, 1407–1410; c) C. Belzecki, I. Panfil, *J. Org. Chem.* **1979**, *44*, 1212–1218.
- [10] J. Hara, Y. Inouye, H. Kakisawa, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3871–3872.
- [11] D. Keirs, K. Overton, *Heterocycles* **1989**, *28*, 841–848.
- [12] P. M. Wovkulich, M. R. Uskoković, *Tetrahedron* **1985**, *41*, 3455–3462.
- [13] L. Belvisi, C. Gennari, A. Mielgo, D. Potenza, C. Scolastico, *Eur. J. Org. Chem.* **1999**, 389–400.
- [14] F. A. Davis, T. Fang, B. Chao, D. M. Burns, *Synthesis* **2000**, 2106–2112.
- [15] a) O. Tamura, K. Gotanda, J. Yoshino, Y. Morita, R. Terashima, M. Kikuchi, T. Miyawaki, N. Mita, M. Yamashita, H. Ishibashi, M. Sakamoto, *J. Org. Chem.* **2000**, *65*, 8544–8551; b) S. W. Baldwin, B. G. Young, A. T. McPhail, *Tetrahedron Lett.* **1998**, *39*, 6819–6822; c) A. Long, S. W. Baldwin, *Tetrahedron Lett.* **2001**, *42*, 5343–5346.
- [16] CCDC-274773 contains the supplementary data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
- [17] J. Gillard, A. Abraham, P. C. Anderson, P. L. Beaulieu, T. Bogri, Y. Bousquet, L. Grenier, I. Guse, P. Lavallée, *J. Org. Chem.* **1996**, *61*, 2226–2231.

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