Synthesis of Functionalized Nitrogen Heterocycles by Radical Decarboxylation of β- and γ-Amino Acids

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Iodinated or oxygenated nitrogen heterocycles are obtained by radical decarboxylation of β- and γ-amino acids. This mild, versatile reaction is applied to the synthesis of bioactive products, such as 4-arylpiperidines, hydroxylated piperidines, and new antifungal agents.

Introduction

Intense research has been devoted to the synthesis of functionalized piperidine and pyrrolidine rings, since these nitrogen heterocycles can be found in the structure of many natural products,[1] synthetic drugs[2] and chiral ligands or catalysts.[3] For example, the ant defensive alkaloids (2*R*)- and (2*S*)-solenopsin-A (**1**; Figure 1),[1a] and the potent antipsychotic (±)-haloperidol (**2**)[2a] contain functionalized piperidine rings, while Corey's catalyst **3**[3a] possesses a 2-substituted pyrrolidine ring.

Among the synthetic methodologies used to obtain nitrogen heterocycles,[4] we have reported a tandem radical decarboxylation of α-amino acids/oxidation, and addition of nucleophiles.[5] When α-amino acids **4** (Scheme 1) were treated with (diacetoxyiodo)benzene (DIB) and iodine, a radical decarboxylation process took place that generated a *C*-radical **5** stabilized by the nitrogen atom. This radical was then oxidized by excess reagent to the acyliminium ion

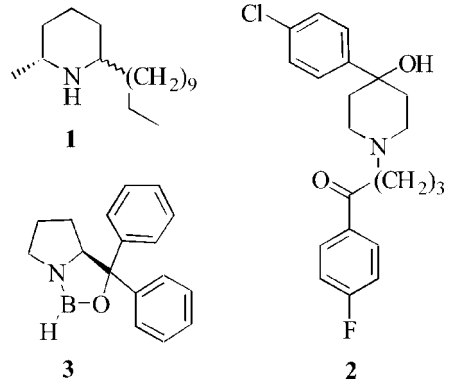
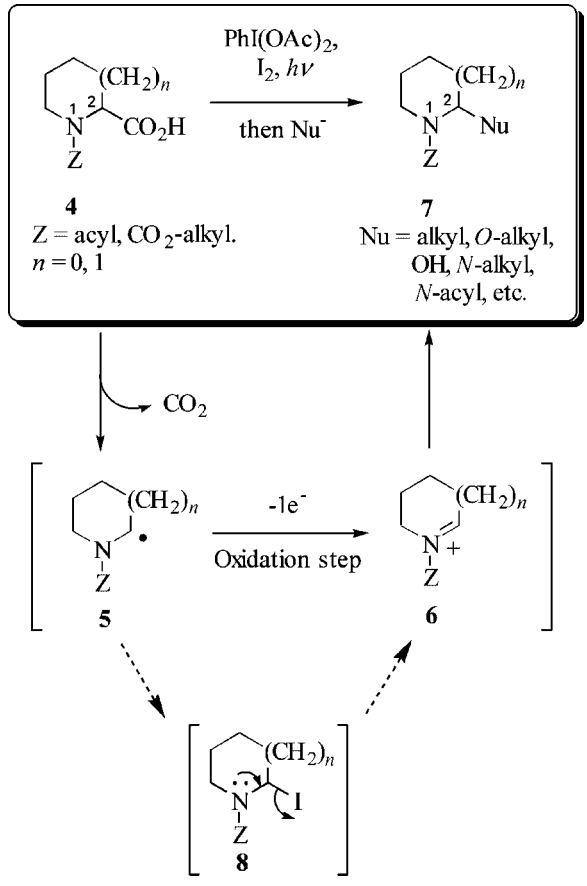


Figure 1. Piperidine and pyrrolidine rings in natural products, synthetic drugs and chiral catalysts



Scheme 1. Synthesis of substituted nitrogen heterocycles from α-amino acids

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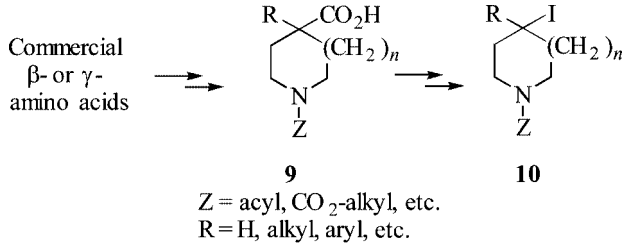
6, which was trapped with oxygen, nitrogen or carbon nucleophiles. The resultant 2-functionalized piperidines (n = 1) or pyrrolidines (n = 0) **7** were obtained in good to excellent yields.

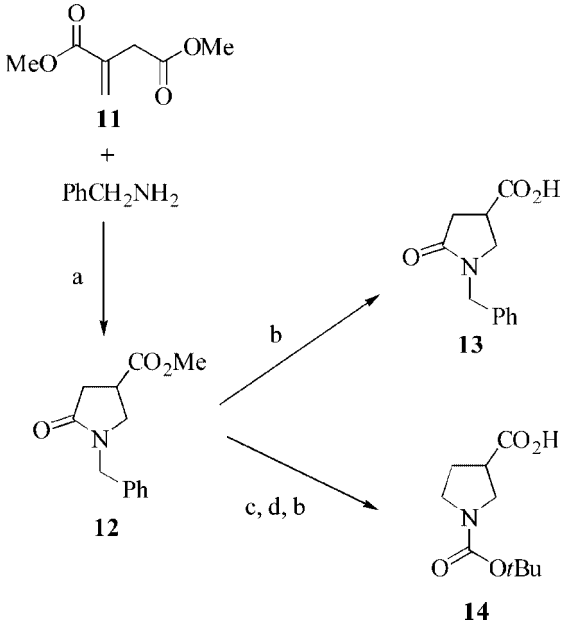
The mechanism of the oxidation step is unclear. However, we reasoned that a plausible pathway would involve the trapping of the *C*-radical by iodine. The resulting α-iodo piperidines or pyrrolidines **8** are unstable compounds,[6] and extrusion of the iodo group with concomitant formation of the acyliminium ion would then take place.

According to this proposal, the decarboxylation of the related β- and γ-amino acids **9** (Scheme 2) should generate β- or γ-iodo derivatives **10**, which, unlike the α-iodo derivatives, are generally isolable and stable compounds.[7] Since the iodo group can be easily replaced by other functionalities,[8] the heterocycles **10** would be useful synthetic building blocks.

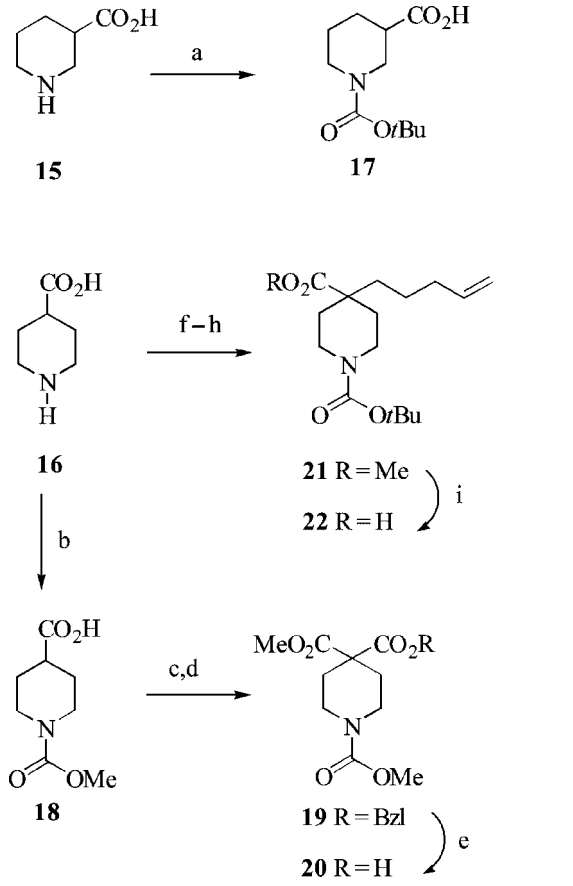


Scheme 2. Synthesis of substituted nitrogen heterocycles from β- and γ-amino acids

The formation of halogenated heterocycles following this strategy, and their application to the synthesis of bioactive aza compounds, are discussed herein.[9]



Scheme 3. Synthesis of substrates **13** and **14**; reagents and conditions: (a) MeOH, reflux, 99%; (b) 2 N NaOH, MeOH, room temp., 85% for **13**, 85% for **14**; (c) BBN, THF, reflux, 70%; (d) H_2, Pd (10 wt.% on C), [*t*BuO(O)C]$_2$O, EtOAc, 92%



Scheme 4. Synthesis of substrates **17**, **18**, **20** and **22**; reagents and conditions: (a) [*t*BuO(O)C]$_2$O, 1 N aq. NaOH, THF, 91%; (b) ClCOOMe, THF/sat. aq $NaHCO_3$, 75%; (c) NaI, K_2CO_3, BzlBr, MeCN, 0 °C to room temp., 79%; (d) LDA, THF, –78 °C; then $ClCO_2Me$ in THF, –78 °C to room temp., 94%; (e) H_2, $Pd(OH)_2$ (20 wt.% on C), EtOAc, room temp., 99%; (f) $SOCl_2$, MeOH, –12 °C to room temp.; (g) CH_2Cl_2, Et_3N, $(BOC)_2O$, DMAP (cat.), 79% for the two steps; (h) LDA, THF, –78 °C; then 5-bromo-1-pentene, –78 °C to room temp., 78%; (i) 2 N NaOH, MeOH, reflux, 87%

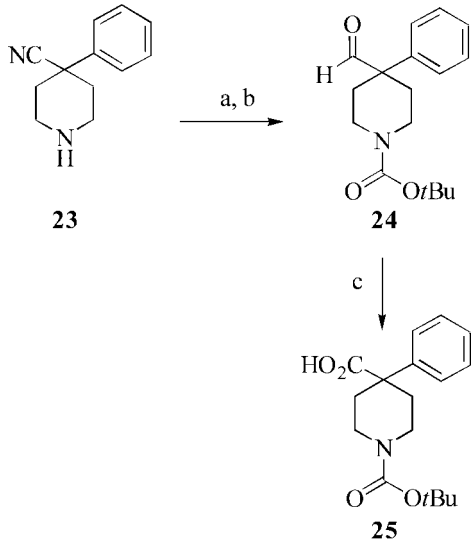
Results and Discussion

To study the radical decarboxylation, differently substituted β- or γ-amino acid derivatives (Scheme 3) were prepared from commercial products. For instance, condensation of dimethyl itaconate (**11**) with benzylamine gave the 3-carboxypyrrolidine ester **12**,[10] from which the acid **13**[10,11] was obtained. Reduction of the lactam **12**,[10,12] followed by hydrogenolysis,[10,12b] *N*-carbamoylation[13] and ester hydrolysis gave the β-amino acid **14**.[13,14]

The carbamoylation of commercial nipecotic acid (**15**) (Scheme 4) and isonipecotic acid (**16**) gave the amino acids **17**[15] and **18**, respectively.[16] The malonate derivative **19** was obtained from compound **18** in two steps, and hydrogenolysis of the benzyl ester afforded the acid **20** in good yield.

The 4-pentenyl derivative **21** was also efficiently synthesized in three steps starting from isonipecotic acid **16**. Saponification of the methyl ester gave the 4-substituted acid **22**.

Finally, commercial 4-cyano-4-phenylpiperidine hydrochloride (**23**) afforded, after formation of its methyl carbamate and reduction of the cyano group, the aldehyde **24** in good yield.[17] This compound was easily oxidized to the aryl acid **25** (Scheme 5).[18] It must be noted that many other α-aryl acids can be synthesized by palladium-catalysed arylation of ester enolates, followed by saponification.[19] Alternatively, they can be obtained in a two-step sequence from commercial aryl acetic esters and nitrogen mustards.[20]



Scheme 5. Synthesis of substrate **25**; reagents and conditions: (a) [*t*BuO(O)C]$_2$O, CH_2Cl_2, Et_3N, room temp., 94%; (b) DIBAL-H, toluene, –78 °C, 4 h; then NH_4Cl (aq), –78 °C to room temp., 53%; (c) aq. NaH_2PO_4, H_2O_2, aq. $NaClO_2$, MeCN, 95%

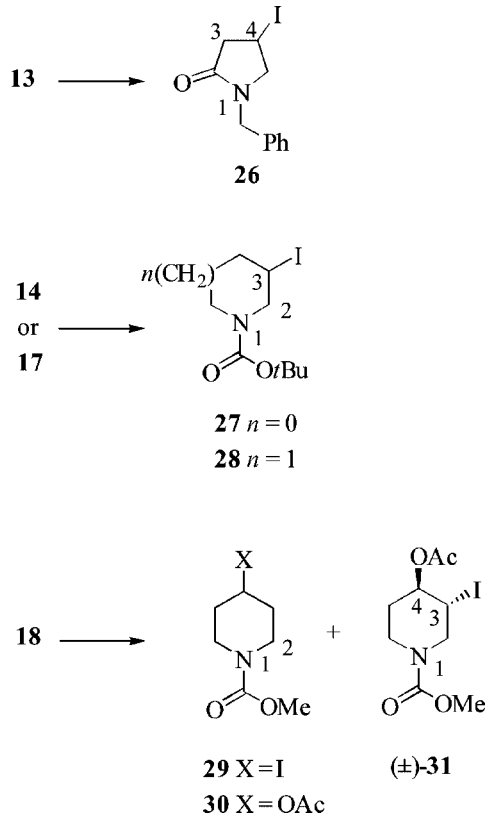
The decarboxylation of the β- or γ-amino acids **13**, **14**, **17**, **18**, **20**, **22** and **25** was studied under different conditions, as shown in Table 1.

Table 1. Synthesis of nitrogen heterocycles by radical decarboxylation of β- and γ-amino acids

Entry	Substrate	Reaction condition,[a] *t*1 [h], *t*2 [h]	Products (yield, %)[b]
1	**13**	A, 4 h	**26** (81)
2	**14**	B, 4 h, 4 h	**27** (66)
3	**17**	A, 6 h	**28** (81)
4	**18**	A, 5 h	**29** (72)
5	**18**	C, 5 h, 5 h	**30** (34), **31** (39)
6	**18**	D, 5 h, 5 h	**30** (17), **31** (24)

[a] Conditions: Method A: DIB (2 equiv.), I_2 (1 equiv.), *hv* with two 80-W tungsten-filament lamps, CCl_4, 80 °C, for the time *t*1; then work-up with saturated aq. $Na_2S_2O_3/CH_2Cl_2$; Method B: Similar to Method A, but after *t*1 the same amounts of DIB and iodine were added, and then the reaction mixture was irradiated for the time *t*2; Method C: Similar to Method B, but using sunlight; Method D: Similar to Method B, but in the dark. [b] Yields are given for products purified by chromatography on silica gel.

The pyrrolidinone derivative **13**, on treatment with (diacetoxyiodo)benzene (DIB) and iodine, afforded the iodo derivative **26** (Scheme 6) in good yield (Table 1, entry 1). Remarkably, due to the mild reaction conditions, no elimination was observed. The 3-carboxypyrrolidine **14** and its 3-carboxypiperidine analogue **17** were treated under similar conditions, and yielded the desired iodo derivatives **27** and **28**, respectively (entries 2 and 3).



Scheme 6. Synthesis of functionalized pyrrolidines and piperidines by radical decarboxylation of β- and γ-amino acids; see Table 1 for conditions and yields

The influence of the reaction conditions was studied with the piperidine-4-carboxylic acid **18**, which, on treatment with DIB/iodine (entry 4), afforded the 4-iodopiperidine **29**. To determine whether the decarboxylation reaction needed irradiation or it was mainly thermal, two reactions were conducted (entries 5 and 6) using solar light and without irradiation, respectively. In the first case, the iodo compound **29** was not isolated, and two new compounds were formed instead: the acetate **30** and the iodoacetate **31**. The acetate **30** was formed from **29** by nucleophilic substitution of the iodo group by acetate ions from the reagent. The iodoacetate **31** could be generated from product **29** by elimination of the iodo group followed by an iodoesterification reaction.[21] To check this hypothesis, a solution of **29** in CCl_4 was treated with DIB (1.5 equiv.) and iodine (1.3 equiv.) and refluxed for 5 h in sunlight to give the acetate **30** (37%) and the iodoacetate **31** (44%).

Interestingly, when the reaction was conducted in the dark, compounds **30** and **31** were still formed, but the reaction times were longer and the yields decreased. These results show that both irradiation and heating play a significant role in the reaction outcome.

The decarboxylation of the 4-substituted acids **20**, **22** and **25** was studied next. When the malonate derivative **20** was

treated under the usual conditions (Table 2, entry 1), the 4-iodo ester **32** was obtained in moderate yield. The preparation of quaternary α-iodo esters is difficult by other methodologies since an elimination reaction usually takes place to give the α,β-unsaturated ester.[22] In fact, an elimination reaction did take place in the decarboxylation of substrate **22** (entry 2). The reaction generated a complex mixture of products of similar polarity. The NMR spectrum of the crude reaction mixture contains olefinic signals, and when this mixture was treated with DBU and refluxed for 6 h, two olefinic products **33** and **34** were obtained (44% global yield, **33**:**34** = 1:3).

Table 2. Synthesis of nitrogen heterocycles by radical decarboxylation of 4-substituted β- and γ-amino acids

Entry	Substrate	Reaction conditions,[a] *t*1 [h], *t*2 [h]	Products (%)[b]
1	**20**	A, 5 h	**32** (41)
2	**22**	E, 2 h	**33** (12), **34** (32)
3	**25**	B, 5 h, 5 h	**35** (48)
4	**25**	F,[c] 5 h, 6 h	**36** (81)

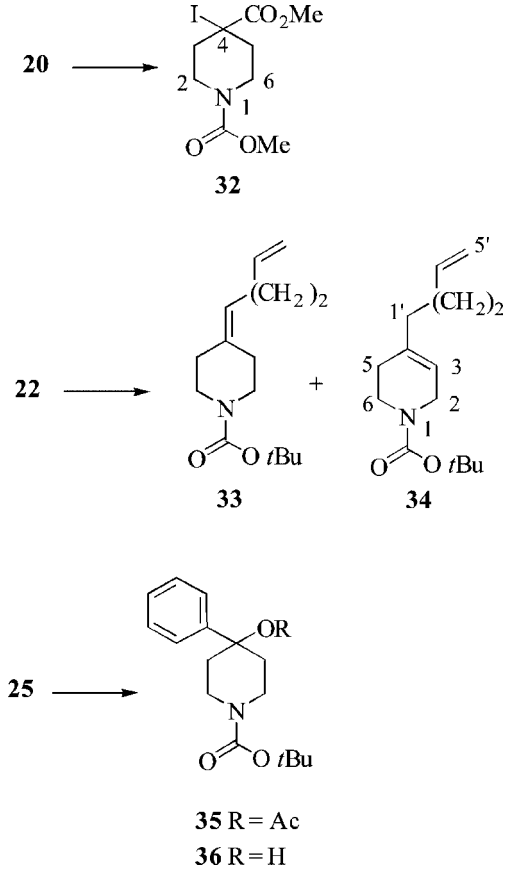
[a] Conditions: Method A: See footnote to Table 1; Method B: See footnote to Table 1; Method E: Initially as in Method A, and after the work-up, the residue was dissolved in CH_2Cl_2 and treated with DBU for 6 h; Method F: PhIO (2 equiv.), I_2 (2 equiv.), *hv* with two 80-W tungsten-filament lamps, MeCN, reflux, 5 h, then the same amounts of PhIO and iodine were added. Stirring proceeded for another 6 h, followed by work-up as in Method A. [b] Yields are given for products purified by chromatography on silica gel. [c] Since the solubility of PhIO in CCl_4 is low, the solvent was changed to MeCN.

To our surprise, in the decarboxylation of the 4-phenyl substrate **25** (entry 3), no iodo or elimination derivatives were isolated, the main product being the acetate **35**.[23] This result can be explained by initial formation of a tertiary benzylic iodide followed by nucleophilic substitution by acetate ions from the reagent. When the reaction was carried out with PhIO instead of DIB (entry 4), the hydroxy derivative **36**[24] was isolated in 81% yield. Compound **36** is probably formed by replacement of the iodo group by water during the work-up.

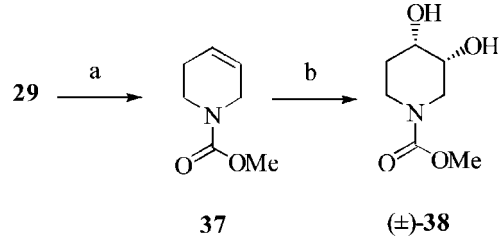
The formation of the oxygenated derivative **36** is interesting, since several drugs with a potent action on the nervous system have similar structures,[25] such as the widely used antipsychotic **2** and several new opiate analogues. These oxygenated derivatives are usually obtained by addition of Grignard reagents to ketones,[25,26c,26f,26g] conditions that are not compatible with aryl substituents such as Br, I, OAc, etc. Our methodology could offer an alternative route towards new members of this class of compounds.

Following our current interest in biologically active products, we decided to apply the decarboxylation reaction to the synthesis of imino sugars. Many of these compounds are potent glycosidase inhibitors, and possess antiviral, antitumour and hypoglucemic activities.[26] In order to improve their bioavailability or modulate their activity, new derivatives are continually being sought.

The decarboxylation product **29** can be transformed into different imino sugars in a few steps.[27] For example, treatment of **29** with DBU gives the alkene **37**[28] (Scheme 8) in good yields. This product reacts with OsO_4 to afford the dihydroxylated piperidine (±)-**38**[28c] in satisfactory yields.



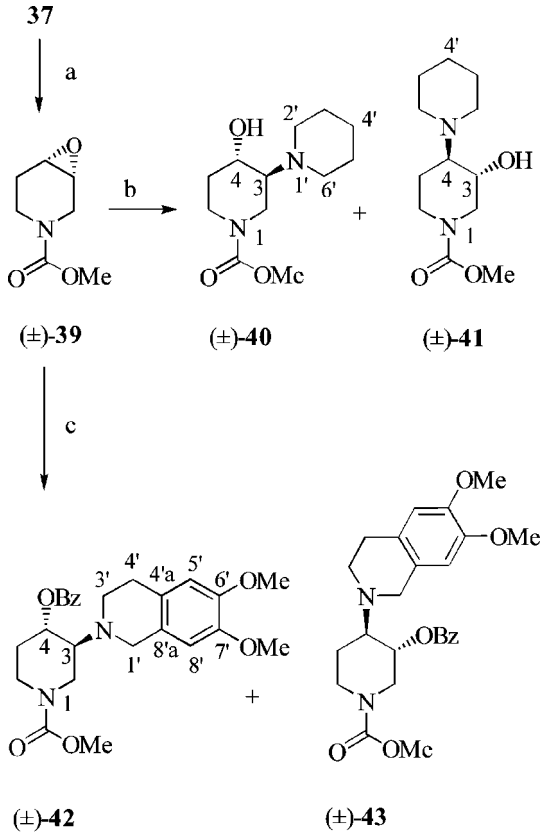
Scheme 7. Synthesis of functionalized nitrogen heterocycles by radical decarboxylation of 4-substituted β- and γ-amino acids; see Table 2 for conditions and yields



Scheme 8. Synthesis of imino sugar (±)-**38**; reagents and conditions: (a) DBU, CH_2Cl_2, room temp., 84%; (b) acetone/H_2O (2:1), 0 °C, then OsO_4 in *t*BuOH, NMO, 57%

Finally, the decarboxylation of γ-amino acids was applied to the development of new antifungal agents. Thus, epoxidation of the alkene **37** (Scheme 9), followed by opening of the epoxide **39** with piperidine, yielded the alcohols (±)-**40** and (±)-**41**.[29a] These alcohols show promising activity against opportunistic fungi of the genus Saccharomyces (IC_{50} = (108 ± 9) × 10^{-3} μmol mL^{-1} for (±)-**40**; IC_{50} = (105 ± 9) × 10^{-3} μmol mL^{-1} for (±)-**41**], so other derivatives were synthesized in order to increase this effect. For

instance, treatment of the epoxide **39** with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, followed by benzoylation, afforded the benzoate esters (±)-**42** and (±)-**43**.[21b] To our satisfaction, both compounds showed a potent antifungal effect (IC_{50} = (10 ± 4) × 10^{-3} μmol mL^{-1} for (±)-**42**; IC_{50} = (14 ± 7) × 10^{-3} μmol mL^{-1} for (±)-**43**] (Scheme 9). We are currently testing their activities against different strains of pathogenic fungi, and synthesizing other derivatives to study the structure-activity relationship. The complete biological results will be published elsewhere.



Scheme 9. Synthesis of new antifungal compounds; reagents and conditions: (a) MCPBA, CH_2Cl_2, room temp., 98%; (b) piperidine, EtOH, Et_3N, 29% for (±)-**40**, 19% for (±)-**41**; (c) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, EtOH, Et_3N; then BzCl, CH_2Cl_2, Et_3N, 35% for (±)-**42**, 16% for (±)-**43**

Conclusions

The decarboxylation of β- and γ-amino acids is a direct way to obtain iodinated or oxygenated piperidines and pyrrolidines. The formation of the halogenated products supports the hypothesis that a 2-iodo derivative, which serves as precursor of the acyliminium intermediate, is formed in the decarboxylation of related α-amino acids.

The present methodology is a mild and efficient way to obtain different functionalized nitrogen heterocycles, which are useful intermediates in the synthesis of a variety of compounds, such as 4-arylpiperidines and imino sugars. The discovery of potent antifungal agents, which were synthesized from a halogenated piperidine, has also been reported.

Experimental Section

General Remarks: Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under nitrogen. The spray reagents for TLC analysis were 0.5% vanillin in H_2SO_4/EtOH (4:1) or 0.25% ninhydrin in ethanol. Merck silica gel 60 PF (0.063–0.2 mm) was used for chromatography.

Acronyms: BBN = 9-borabicyclo[3.3.1]nonane, MCPBA = 3-chloroperbenzoic acid, DBU = 1,8-diazabicyclo[5.4.0]undecene, DIB = (diacetoxyiodo)benzene, DIBAL-H = diisobutylaluminium hydride, DMAP = 4-(dimethylamino)pyridine, NMO = 4-methylmorpholine *N*-oxide.

The melting points were determined with a hot-stage apparatus. IR spectra were recorded in $CHCl_3$ solution. NMR spectra were recorded from $CDCl_3$ solutions using TMS as an internal standard, unless otherwise stated.

For some compounds, a mixture of two rotamers was observed at room temperature, which caused broadening or splitting of the NMR signals. The rate of rotamer interconversion usually increased on heating, and in many cases only one rotamer could be detected at 70 °C. When the NMR resolution improved significantly on heating, the spectra at 70 °C are described.

General Procedure for Radical Decarboxylation. Method A: (Diacetoxyiodo)benzene (DIB) (0.6 mmol) and iodine (0.3 mmol) were addedto a solution of the starting acid (0.3 mmol) in CCl_4 (15 mL) under nitrogen. The reaction mixture was refluxed for the time stated in Table 1 and Table 2, under irradiation with two 80-W tungsten-filament lamps. Afterwards, it was poured into 10% aqueous sodium thiosulfate ($Na_2S_2O_3$) and extracted with dichloromethane. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvents evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc) to give the purified reaction product(s).

Method B: (Diacetoxyiodo)benzene (DIB) (0.4 mmol) and iodine (0.3 mmol) were addedto a solution of the starting acid (0.3 mmol) in CCl_4 (15 mL) under nitrogen. The reaction mixture was stirred for 4 h, under irradiation with two 80 W tungsten-filament lamps. Since the TLC analysis showed that some starting material remained unchanged, more DIB (0.4 mmol) and iodine (0.3 mmol) were added, and the mixture was refluxed for the stated time. Work-up and chromatography as in Method A gave the purified reaction product(s).

Method C: As in Method B, but the reaction was conducted in ambient light.

Method D: As in Method B, but the reaction was conducted in the dark.

Method E: As in Method A, but after the work-up, the residue was dissolved in CH_2Cl_2 (2 mL) and treated with DBU (0.2 mL, 1.34 mmol) for 6 h at room temperature; the reaction mixture was then poured into 10% aq. HCl and extracted with CH_2Cl_2. The organic layer was dried and evaporated as usual, and the residue was purified by chromatography on silica gel (hexanes/EtOAc).

Method F: PhIO (44 mg, 0.2 mmol) and iodine (51 mg, 0.2 mmol) were added to a solution of the acid (0.1 mmol) in dry CH_3CN (5 mL) under nitrogen. The reaction mixture was refluxed for 5 h, and was irradiated with two 80 W tungsten-filament lamps. Since it was observed by TLC that starting material still remained, more PhIO (44 mg, 0.2 mmol) and iodine (51 mg, 0.2 mmol) were added. After refluxing for another 6 h, usual work-up and chromatography afforded the oxygenated product.

1-Benzyl-4-iodo-2-pyrrolidinone (26): Method A, (81%), crystalline solid, m.p. 72.1–74.2 °C (from ethyl acetate/*n*-hexane). IR ($CHCl_3$): $\tilde{\nu}$ = 1689 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.88 (dd, J = 5.1, 17.7 Hz, 1 H, 3-H_a), 3.07 (dd, J = 7.6, 17.7 Hz, 1 H, 3-H_b), 3.56 (dd, J = 4.4, 11.5 Hz, 1 H, 5-H_a), 3.74 (dd, J = 6.5, 11.4 Hz, 1 H, 5-H_b) 4.39 (m, 1 H, 4-H), 4.45 (d, J = 14.8 Hz, 1 H, C$H_a$$H_b$Ph), 4.52 (d, J = 14.8 Hz, 1 H, C$H_a$$H_b$Ph), 7.26 (d, J = 7.2 Hz, 2 H, arom.), 7.29 (dd, J = 7.1, 7.3 Hz, 1 H, arom.), 7.34 (dd, J = 7.0, 7.5 Hz, 2 H, arom.) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 9.7 (CH, 4-C), 44.7 (CH_2, 3-C), 46.4 (CH_2, *C*H_2Ph), 58.0 (CH_2, 5-C), 127.8 (CH, arom.), 128.2 (2 × CH, arom.), 128.8 (2 × CH, arom.), 135.6 (C, arom.), 171.8 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 301 (61) [M^+], 174 (10) [M^+ – I], 91 (100) [Bzl]. HRMS (EI, 70 eV): calcd. for $C_{11}H_{12}INO$ 300.9964; found 300.9937. $C_{11}H_{12}INO$ (301.13): calcd. C 43.88, H 4.02, N 4.65; found C 44.16, H 4.19, N 4.89.

***tert*-Butyl 3-Iodo-1-pyrrolidinecarboxylate (27):** Method B, (66%), yellowish oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) some signals were broadened due to equilibrium between rotamers: δ = 1.46 (s, 9 H, *t*Bu), 2.21 (br. m, 1 H, 4-H_a), 2.25 (br. m, 1 H, 4-H_b), 3.42 (br. m, 1 H, 5-H_a), 3.57 (br. m, 1 H, 5-H_b), 3.74 (br. m, 1 H, 2-H_a), 3.81 (br. m, 1 H, 2-H_b), 4.35 (m, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$) two rotamers A/B were observed: δ = 19.8 (CH, 3-C), 28.4 (3 × CH_3, *t*Bu), 37.5/38.3 (CH_2, 4-C), 44.7/44.9 (CH_2, 5-C), 57.0/57.3 (CH_2, 2-C), 79.7 (C, O*C*Me_3), 154.1 (C, N-CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 297 (3) [M^+], 57 (100) [*t*Bu]. HRMS (EI, 70 eV): calcd. for $C_9H_{16}INO_2$ 297.0226; found 297.0194. $C_9H_{16}INO_2$ (297.14): calcd. C 36.38, H 5.43, N 4.71; found C 36.56, H 5.23, N 4.60.

***tert*-Butyl 3-Iodo-1-piperidinecarboxylate (28):** Method A, (81%), yellowish solid, m.p. 63.9–66.7 °C (EtOAc/*n*-pentane). IR ($CHCl_3$): $\tilde{\nu}$ = 1685 cm^{-1}. ^1H NMR (60 °C, 500 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, *t*Bu), 1.57 (m, 1 H, 5-H_a), 1.71 (m, 1 H, 5-H_b), 2.00 (m, 1 H, 4-H_a), 2.26 (m, 1 H, 4-H_b), 3.08 (ddd, J = 3.1, 10.1, 13.2 Hz, 1 H, 6-H_a), 3.34 (dd, J = 10.8, 11.4 Hz, 1 H, 2-H_b), 3.77 (ddd, J = 4.5, 4.5, 13.4 Hz, 1 H, 6-H_b), 4.08 (m, 1 H, 2-H_a), 4.14 (m, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 25.4 (CH, 3-C), 27.1 (CH_2, 4-C or 5-C), 28.4 (3 × CH_3, *t*Bu), 37.6 (CH_2, 4-C or 5-C), 43.8 (CH_2, 6-C), 53.7 (CH_2, 2-C), 80.0 (C, O*C*Me_3), 154.2 (C, N-CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 237 (11) [M^+ – O*t*Bu], 184 (24) [M^+ – I], 128 (69) [M^+ + H – I – *t*Bu], 57 (100) [*t*Bu]. HRMS (EI, 70 eV): calcd. for C_6H_9INO 237.9729; found 237.9699. $C_{10}H_{18}INO_2$ (311.16): calcd. C 38.60, H 5.83, N 4.50; found C 38.71, H 5.80, N 4.67.

Methyl 4-Iodo-1-piperidinecarboxylate (29): Method A, (72%), a yellowish oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.98 (m, 4 H, 3-H_2 + 5-H_2), 3.31 (ddd, J = 5.5, 5.5, 11.6 Hz, 2 H, 2-H_a + 6-H_a), 3.57 (m, 2 H, 2-H_b + 6-H_b), 3.64 (s, 3 H, OMe), 4.41 (dddd, J = 5.8, 5.9, 5.9, 5.9 Hz, 1 H, 4-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.1 (CH, 4-C), 37.0 (2 × CH_2, 3-C + 5-C), 43.7 (2 × CH_2, 2-C + 6-C), 52.6 (CH_3, OMe), 155.7 (C, N-*C*O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 269 (2) [M^+], 238 (3) [M^+ – OMe], 142 (100) [M^+ – I]. HRMS (EI, 70 eV): calcd. for $C_7H_{12}INO_2$ 268.9913; found 268.9939. $C_7H_{12}INO_2$ (269.08): calcd. C 31.25, H 4.50, N 5.21; found C 31.41, H 4.38, N, 5.25.

Methyl 4-Acetyloxy-1-piperidinecarboxylate (30) and Methyl (3*R,4*R**)-4-Acetyloxy-3-iodo-1-piperidinecarboxylate (31):** Method C: Compounds **30** (34%) and **31** (39%); Method D: Compounds **30** (17%) and **31** (24%).

Methyl 4-Acetyloxy-1-piperidinecarboxylate (30): Oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1728, 1690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.60 (dddd, J = 4.0, 8.4, 8.5, 12.9 Hz, 2 H, 3-H_a + 5-H_a), 1.84 (m, 2 H, 3-H_b + 5-H_b), 2.04 (s, 3 H, CH_3CO), 3.26 (ddd, J = 3.6, 8.7, 13.6 Hz, 2 H, 2-H_a + 6-H_a), 3.68 (s, 3 H, OMe), 3.73 (m, 2 H, 2-H_b + 6-H_b), 4.90 (m, 1 H, 4-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.2 (CH_3, MeCO), 30.4 (2 × CH_2, 3-C + 5-C), 41.1 (2 × CH_2, 2-C + 6-C), 52.6 (CH_3, OMe), 69.5 (CH, 4-C), 155.8 (C, N-CO), 170.3 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 201 (9) [M^+], 158 (11) [M^+ – COMe], 141 (100) [M^+ – HOAc]. HRMS (EI, 70 eV): calcd. for $C_9H_{15}NO_4$ 201.1001; found 201.0987. $C_9H_{15}NO_4$ (201.22): calcd. C 53.72, H 7.51, N 6.96; found C 53.94, H 7.27; N 6.77.

Methyl (3*R,4*R**)-4-Acetyloxy-3-iodo-1-piperidinecarboxylate (31):**[30] Oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1738, 1701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.60 (m, 1 H, 5-H_a), 2.00 (s, 3 H, MeCO), 2.10 (m, 1 H, 5-H_b), 3.17 (ddd, J = 3.2, 10.7, 13.9 Hz, 1 H, 6-H_a), 3.31 (m, 1 H, 2-H_a), 3.62 (s, 3 H, OMe), 3.85 (ddd, J = 4.4, 9.5, 9.7 Hz, 1 H, 3-H), 4.00 (m, 1 H, 6-H_b), 4.35 (m, 1 H, 2-H_b), 4.88 (ddd, J = 4.4, 9.2, 9.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.0 (CH_3, MeCO), 25.9 (CH, 3-C), 30.9 (CH_2, 5-C), 41.6 (CH_2, 6-C), 50.8 (CH_2, 2-C), 52.9 (CH_3, OMe), 74.7 (CH, 4-C), 155.2 (C, N*C*O), 169.8 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 296 (<1) [M^+ – OMe], 268 (1) [M^+ – OAc], 158 (24) [M^+ – I – CH_2=CO], 140 (100) [M^+ – HOAc – I]. HRMS (EI, 70 eV): calcd. for $C_8H_{11}INO_3$ 295.9784; found 295.9792. $C_9H_{14}INO_4$ (327.12): calcd. C 33.05, H 4.31, N 4.28; found C 33.35, H 3.95; N 4.28.

Transformation of Methyl 4-Iodo-1-piperidinecarboxylate (29) into Products 30 and 31: A solution of the 4-iodo compound **29** (69 mg, 0.26 mmol) in dry CCl_4 (5 mL) was treated with (diacetoxyiodo) benzene (133 mg, 0.41 mmol) and iodine (83 mg, 0.33 mmol) and refluxed under nitrogen for 5 h. Work-up and purification as in Method A afforded the acetate **30** (19 mg, 37%) and the 3-iodo-4-acetate derivative **31** (37 mg, 44%).

Dimethyl 4-Iodo-1,4-piperidinedicarboxylate (32): Method A, (41%), white crystals, m.p. 91.7–93.5 °C (EtOAc/*n*-pentane). IR ($CHCl_3$): $\tilde{\nu}$ = 1728, 1697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.84 (ddd, J = 3.9, 8.8, 13.4 Hz, 2 H, 3-H_a + 5-H_a), 2.27 (m, 2 H, 3-H_b + 5-H_b), 3.32 (ddd, J = 3.1, 8.8, 13.4 Hz, 2 H, 2-H_a + 6-H_a), 3.68 (s, 3 H, OMe), 3.70 (m, 2 H, 2-H_b + 6-H_b), 3.80 (s, 3 H, OMe) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 38.2 (2 × CH_2, 3-C + 5-C), 42.0 (C, 4-C), 42.5 (2 × CH_2, 2-C + 6-C), 52.8 (CH_3, OMe), 53.2 (CH_3, OMe), 155.7 (C, N-CO), 172.2 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 327 (1) [M^+], 296 (<1) [M^+ – OMe], 200 (100) [M^+ – I]. HRMS (EI, 70 eV): calcd. for $C_9H_{14}INO_4$ 326.9968; found 327.0007. $C_9H_{14}INO_4$ (327.12): calcd. C 33.05, H 4.31, N 4.28; found C 33.39, H 4.44, N 3.92.

Methyl 4-(4-Pentenylidene)-1-piperidinecarboxylate (33) and Methyl 4-(4-Pentenyl)-1,2,5,6-tetrahydro-1-pyridinecarboxylate (34): Method A, (44%), **33**:**34** (*exo*:*endo*) = 1:3.

Dienes 33 and 34: Oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1688, 1603 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$). Mixture of the two stereoisomers. Compound **33**: δ = 1.45 (s, 9 H, *t*Bu), 1.95–2.1 (m, 4 H, 2′-H_2 + 3′-H_2), 2.10 (m, 2 H, 3-H_a + 5-H_a), 2.20 (dd, J = 5.6, 5.6 Hz, 2 H, 3-H_b + 5-H_b), 3.37 (ddd, J = 5.5, 5.6, 5.8 Hz, 4 H, 2-H_2 + 6-H_2), 4.94 (d, J = 11 Hz, 1 H, 5′-H_a), 4.97 (d, J = 16 Hz, 1 H, 5′-H_b), 5.20 (m, 1 H, 1′-H), 5.79 (m, 1 H, 4′-H) ppm; compound **34**: δ = 1.46 (s, 9 H, *t*Bu), 1.48 (m, 2 H, 2′-H_2), 1.96–2.15 (m, 6 H, 5-H_2 + 1′-H_2 + 3′-H_2), 3.47 (dd, J = 5.5, 5.6 Hz, 2 H, 6-H_2), 3.83 (m, 2 H, 2-H_2), 4.94 (d, J = 11 Hz, 1 H, 5′-H_a), 4.98 (d, J = 15 Hz, 1 H, 5′-H_b), 5.33 (m, 1 H, 3-H), 5.79 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): Compound **33**: δ = 28.3 (2 × CH_2, 3-C + 5-C), 28.5 (3 × CH_3, *t*Bu), 34.0 (CH_2, 3′-C), 35.8 (CH_2, 2′-C), 46.0 (2 × CH_2, 2-C + 6-C), 79.4 (C, *t*Bu), 114.5 (CH_2, 5′-C), 123.1 (CH, 1′-C), 135.4 (C, 4-C), 138.3 (CH, 4′-C), 154.8 (C, N-CO) ppm; compound **34**: δ = 26.6 (CH_2, 2′-C), 28.5 (CH_2, 5-C), 28.6 (3 ×

CH_3, *t*Bu), 33.2 (CH_2, 3′-C or 1′-C), 36.6 (CH_2, 1′-C or 3′-C), 40.3 (CH_2, 6-C), 43.1 (CH_2, 2-C), 79.3 (C, *t*Bu), 114.6 (CH_2, 5′-C), 117.9 (CH, 3-C), 136.5 (C, 4-C), 138.6 (CH, 4′-C), 154.9 (C, N-CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 252 (<1) [M^+ + H], 194 (20) [M^+ – *t*Bu], 57 (100) [*t*Bu]. HRMS (EI, 70 eV): calcd. for $C_{15}H_{26}NO_2$ 252.1964; found 252.2006. $C_{15}H_{25}NO_2$ (251.37): calcd. C 71.67, H 10.02, N 5.57; found C 71.52, H 10.02, N 5.86.

***tert*-Butyl 4-Acetyloxy-4-phenyl-1-piperidinecarboxylate (35):** Method B, (48%), crystals, m.p. 62.8–65.9 °C (EtOAc/*n*-pentane). IR ($CHCl_3$): $\tilde{\nu}$ = 3028, 1698, 1684 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 1.93 (ddd, *J* = 4.8, 13.3, 13.6 Hz, 2 H, 3-H_a + 5-H_a), 2.06 (s, 3 H, OMe), 2.48 (d, *J* = 12.3 Hz, 2 H, 3-H_b + 5-H_b), 3.11 (m, 2 H, 2-H_a + 6-H_a), 4.12 (m, 2 H, 2-H_b + 6-H_b), 7.27 (m, 1 H, arom.), 7.34 (m, 4 H, arom.) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.9 (CH_3, CH_3CO_2), 28.4 (3 × CH_3, $OC(CH_3)_3$], 35.3 (2 × CH_2, 3-C + 5-C), 40.1 (2 × CH_2, 2-C + 6-C), 79.6 (C, O*C*Me$_3$ or 4-C), 80.3 (C, O*C*Me$_3$ or 4-C), 124.4 (2 × CH, arom.), 127.4 (CH, arom.), 128.4 (2 × CH, arom.), 143.8 (C, arom.), 154.7 (C, NCO), 169.3 (C, CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 260 (<1) [M^+ – OAc], 259 (4) [M^+ – HOAc], 203 (65) [M^+ – OAc – *t*Bu], 57 (100) [*t*Bu]. HRMS (EI, 70 eV): calcd. for $C_{16}H_{22}NO_2$ 260.1651; found 260.1575. $C_{18}H_{25}NO_4$ (319.40): calcd. C 67.69, H 7.89, N 4.39; found C 67.58, H 7.96, N 4.53.

tert*-Butyl 4-Hydroxy-4-phenyl-1-piperidinecarboxylate (36):** Method E, (81%), oil. IR ($CHCl_3$): $\tilde{\nu}$ = 3597, 3450, 1682 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 1.73 (d, *J* = 13 Hz, 2 H, 3-H_a + 5-H_a), 2.00 (m, 2 H, 3-H_b + 5-H_b), 3.25 (m, 2 H, 2-H_a + 6-H_a), 4.00 (m, 2 H, 2-H_b + 6-H_b), 7.27 (dd, *J* = 7.1, 7.4 Hz, 2 H, arom.), 7.36 (dd, *J* = 7.5, 8.0 Hz, 1 H, arom.), 7.47 (d, *J* = 7.8 Hz, 2 H, arom.) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.5 (3 × CH_3, *t*Bu), 38.1 (2 × CH_2, 3-C + 5-C), 39.9 (2 × CH_2, 2-C + 6-C), 71.5 (C, 4-C), 79.5 (C, O*C*Me$_3$), 124.4 (2 × CH, arom.), 127.3 (CH, arom.), 128.5 (2 × CH, arom.), 147.9 (C, arom.), 154.9 (C, N-CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 277 (2) [M^+], 259 (<1) [M^+ – H_2O], 220 (4) [M^+ – ***tBu], 203 (23) [M^+ – OH – *t*Bu], 57 (100) [*t*Bu]. HRMS (EI, 70 eV): calcd. for $C_{16}H_{23}NO_3$ 277.1678; found 277.1648. $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.34, H 8.72, N 4.75.

Methyl 1,2,5,6-Tetrahydro-1-pyridinecarboxylate (37): DBU (1 mL, 6.7 mmol) was added dropwise to a solution of compound **29** (311 mg, 1.16 mmol) in dichloromethane (18 mL). The reaction mixture was stirred at room temperature for 7 h and was then poured into 10% aqueous HCl and extracted with dichloromethane. The organic layers were washed with brine, dried with Na_2SO_4, filtered and the solvents evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 95:5) to yield the alkene **37** (137 mg, 84%) as a colourless, volatile oil. An alternative synthesis of alkene **37** has been reported previously.[28a,28b]

Methyl (3*S,4*R**)-3,4-Dihydroxy-1-piperidinecarboxylate (38):** A solution of OsO_4 (20 mg, 0.08 mmol) in *t*BuOH (2 mL) was added to a solution of compound **37** (40 mg, 0.26 mmol) in acetone/water (2:1, 3 mL) at 0 °C. After 5 min, NMO was added (34 mg, 0.29 mmol). The reaction mixture was stirred for 12 h and was then poured into brine and extracted with EtOAc. The organic layers were dried with Na_2SO_4, filtered and the solvents evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 50:50) to yield the diol **38** (28 mg, 57%) as a colourless oil. An alternative synthesis of diol **38** has been reported previously.[28c]

Methyl (3*S,4*R**)-1,2,5,6-Tetrahydro-1-pyridinecarboxylate 3,4-Oxide (39):** *meta*-Chloroperbenzoic acid (MCPBA; 240 mg, 1.4 mmol) was added to a solution of compound **37** (100 mg, 0.70 mmol) in dichloromethane (10 mL) and the mixture was stirred at room temperature for 4 h. Afterwards, it was poured into a saturated aqueous $NaHCO_3$ solution and was extracted with CH_2Cl_2. The organic layers were dried with Na_2SO_4, filtered and the solvents evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 90:10) to yield the epoxide **39** (109 mg, 98%) as a colourless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1694 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$). Mixture of two rotamers: δ = 1.90 (m, 1 H, 5-H_a), 2.02 (br. m, 1 H, 5-H_b), 3.16 (m, 1 H, 6-H_a), 3.18 (m, 1 H, 3-H or 4-H), 3.26 (m, 1 H, 3-H or 4-H), 3.43 (br. m, 1 H, 6-H_b), 3.65 (s, 3 H, OMe), 3.74 (m, 1 H, 2-H_a), 3.82/3.82 (m/m, 1 H, 2-H_b) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.1/24.5 (CH_2, 5-C), 37.3 (CH_2, 6-C), 42.3 (CH_2, 2-C), 49.9/50.2 (CH, 3-C or 4-C), 50.5 (CH, 4-C or 3-C), 52.6 (CH_3, OMe), 156.0 (C, N-CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 158 (7) [M^+ + H], 157 (54) [M^+], 140 (50) [M^+ – OH], 126 (18) [M^+ – OMe], 114 (100) [CH_2=N(CO_2Me)CH=CH_2]. HRMS (EI, 70 eV): calcd. for $C_7H_{12}NO_3$ 158.0817; found 158.0799; calcd. for $C_7H_{11}NO_3$ 157.0739; found 157.0730. $C_7H_{11}NO_3$ (157.17): calcd. C 53.49, H 7.05, N 8.91, found C 53.45, H 6.96, N 8.60.

Compounds (±)-40 and -41: Triethylamine (0.7 mL, 5 mmol) and piperidine (0.15 mL, 1.5 mmol) were added to a solution of the epoxide **39** (79 mg, 0.5 mmol) in dry ethanol (10 mL). The reaction mixture was refluxed under nitrogen for 24 h, and then most of the solvent was removed under vacuum. The concentrated mixture was poured into brine and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvents evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 70:30) to yield **40** (39 mg, 32%) and **41** (24 mg, 20%) as oils. Two rotamers at room temperature, one rotamer at 70 °C for both compounds.

Methyl (3*S,4*S**)-4-Hydroxy-3-(1-piperidinyl)-1-piperidinecarboxylate (40):** IR ($CHCl_3$): $\tilde{\nu}$ = 3447, 1686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 70 °C): δ = 1.47 (m, 3 H, 4′-H_2 + 5-H_a), 1.65 (m, 4 H, 3′-H_2 + 5′-H_2), 2.05 (dddd, *J* = 2.6, 2.6, 4.9, 12.8 Hz, 1 H, 5-H_b), 2.28 (ddd, *J* = 4.1, 10.7, 10.8 Hz, 1 H, 3-H), 2.47 (ddd, *J* = 3.4, 6.9, 10.7 Hz, 2 H, 2′-H_b + 6′-H_b), 2.65 (dd, *J* = 11.7, 12.5 Hz, 1 H, 2-H_a), 2.71 (ddd, *J* = 2.8, 13.3, 13.3 Hz, 1 H, 6-H_a), 2.82 (ddd, *J* = 3.5, 7.2, 11.1 Hz, 2 H, 2′-H_b + 6′-H_b), 3.57 (ddd, *J* = 4.6, 10.3, 10.3 Hz, 1 H, 4-H), 3.69 (s, 3 H, OMe), 4.13 (d, *J* = 13.7 Hz, 1 H, 6-H_b), 4.25 (d, *J* = 11.8 Hz, 1 H, 2-H_b) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, 70 °C): δ = 24.2 (CH_2, 4′-C), 26.0 (2 × CH_2, 3′-C + 5′-C), 32.6 (CH_2, 5-C), 41.1 (CH_2, 2-C), 42.4 (CH_2, 6-C), 50.4 (2 × CH_2, 2′-C + 6′-C), 52.8 (CH_3, OMe), 67.4 (CH, 4-C), 68.0 (CH, 3-C), 155.9 (C, N-CO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 243 (17) [M^+ + H], 242 (100) [M^+], 140 (27) [M^+ – H_2O – $C_5H_{10}N$]. HRMS (EI, 70 eV): calcd. for $C_{12}H_{23}N_2O_3$ 243.1709; found 243.1681; calcd. for $C_{12}H_{22}N_2O_3$ 242.1630; found 242.1655; calcd. for $C_7H_{10}NO_2$ 140.0712; found 140.0712.

Methyl (3*R,4*R**)-3-Hydroxy-4-(1-piperidinyl)-1-piperidinecarboxylate (41):** IR ($CHCl_3$): $\tilde{\nu}$ = 3428, 1688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 70 °C): δ = 1.44 (m, 1 H, 5-H_a), 1.46 (m, 2 H, 4′-H_2), 1.66 (m, 4 H, 3′-H_2 + 5′-H_2), 1.77 (m, 1 H, 5-H_b), 2.40 (m, 1 H, 4-H), 2.47 (m, 2 H, 2′-H_a + 6′-H_a), 2.58 (dd, *J* = 10.5, 12.4 Hz, 1 H, 2-H_a), 2.69 (ddd, *J* = 2.5, 12.8, 13.2 Hz, 1 H, 6-H_a), 2.74 (m, 2 H, 2′-H_b + 6′-H_b), 3.45 (ddd, *J* = 5.1, 10.0, 10.1 Hz, 1 H, 3-H), 3.69 (s, 3 H, OMe), 4.25 (d, *J* = 12.6 Hz, 1 H, 6-H_b), 4.43 (d, *J* = 9.7 Hz, 1 H, 2-H_b) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, 70 °C): δ = 22.0 (CH_2, 4′-C), 24.4 (CH_2, 5-C), 26.1 (2 × CH_2, 3′-C + 5′-C), 43.6 (CH_2, 6-C), 49.2 (CH_2, 2-C), 49.9 (2 × CH_2, 2′-C + 6′-C), 52.7 (CH_3, OMe), 65.4 (CH, 3-C), 69.8 (CH, 4-C), 155.8 (C, NCO) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 243 (5) [M^+ + H], 242 (32) [M^+], 111 (100) [(M^+ + H) – OMe – OH – piperidine]. HRMS (EI, 70 eV): calcd. for $C_{12}H_{23}N_2O_3$ 243.1709; found 243.1706; calcd. for $C_{12}H_{22}N_2O_3$ 242.1630; found 242.1607.

Compounds (±)-42 and (±)-43: Triethylamine (0.35 mL, 2.5 mmol) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[31] (118 mg, 0.62 mmol) were added to a solution of the epoxide **39** (39 mg, 0.25 mmol) in dry ethanol (5 mL). The reaction mixture was refluxed under nitrogen for 24 h, and then most of the solvent was removed under vacuum. The concentrated mixture was poured into brine and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvents evaporated under vacuum. The residue was dissolved in dry CH_2Cl_2 (5 mL), and then dry triethylamine (1.8 mL, 13 mmol) and a catalytic amount of DMAP (5 mg, 0.05 mmol) were added. The solution was cooled to 0 °C and benzoyl chloride (0.09 mL, 109 mg, 0.75 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 24 h. Afterwards, it was poured into saturated $NaHCO_3$ and extracted with EtOAc. The organic layers were dried with sodium sulfate, filtered and the solvents evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 90:10) to yield the benzoates (±)-**42** (48 mg, 42%) and (±)-**43** (22 mg, 19%). Two rotamers at room temperature, one rotamer at 70 °C for both compounds.

Methyl (3*S,4*S**)-4-(Benzoyloxy)-3-[6,7-dimethoxy-3,4-dihydro-2(1*H*)-isoquinolinyl]-1-piperidinecarboxylate (42):** IR ($CHCl_3$): $\tilde{\nu}$ = 3039, 3020, 1698, 1603 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 70 °C): δ = 1.73 (m, 1 H, 5-H_a), 2.23 (m, 1 H, 5-H_b), 2.67 (ddd, *J* = 5.2, 5.3, 15.8 Hz, 1 H, 4′-H_a), 2.74 (ddd, *J* = 5.6, 5.7, 16.7 Hz, 1 H, 4′-H_b), 2.88 (m, 2 H, 3′-H_a + 3-H), 3.06 (ddd, *J* = 5.4, 5.7, 11.4 Hz, 1 H, 3′-H_b), 3.18 (ddd, *J* = 3.3, 10.2, 13.5 Hz, 1 H, 6-H_a), 3.27 (dd, *J* = 9.1, 13.7 Hz, 1 H, 2-H_a), 3.73 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.83 (d, *J* = 14 Hz, 1 H, 1′-H_a), 3.90 (d, *J* = 14 Hz, 1 H, 1′-H_b), 3.93 (m, 1 H, 6-H_b), 4.11 (ddd, *J* = 1.3, 4.2, 13.7 Hz, 1 H, 2-H_b), 5.44 (ddd, *J* = 4.3, 8.7, 8.8 Hz, 4-H), 6.50 (s, 1 H, arom.), 6.53 (s, 1 H, arom.), 7.40 (dd, *J* = 7.7, 7.8 Hz, 2 H, arom.), 7.52 (dd, *J* = 7.4, 7.5 Hz, 1 H, arom.), 8.00 (d, *J* = 7.1 Hz, 2 H, arom.) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, 70 °C): δ = 29.5 (CH_2, 4′-C), 29.7 (CH_2, 5-C), 41.5 (CH_2, 6-C), 43.5 (CH_2, 2-C), 47.6 (CH_2, 3′-C), 51.9 (CH_2, 1′-C), 52.7 (CH_3, OMe), 55.9 (2 × CH_3, OMe), 62.8 (CH, 3-C), 70.5 (CH, 4-C), 109.3 (CH, arom., 5′-C or 8′-C), 111.4 (CH, arom., 5′-C or 8′-C), 126.5 (C, arom., 4′a-C or 8′a-C), 126.7 (C, arom., 4′a-C or 8′a-C), 128.3 (2 × CH, arom.), 129.6 (2 × CH, arom.), 130.1 (C, arom.), 133.0 (CH, arom.), 147.1 (C, arom., 6′-C or 7′-C), 147.3 (C, arom., 6′-C or 7′-C), 155.9 (C, N-*C*O), 165.6 (C, Ph*C*O_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 454 (5) [M^+], 453 (4) [M^+ – H], 349 (3) [M^+ – COPh], 332 (5) [M^+ – PhCOOH], 192 (100) [dimethoxytetrahydroisoquinoline]. HRMS (EI, 70 eV): calcd. for $C_{25}H_{30}N_2O_6$ 454.2104; found 454.2090; calcd. for $C_{25}H_{29}N_2O_6$ 453.2026; found 453.1976; calcd. for $C_{18}H_{25}N_2O_5$ 349.1763; found 349.1727; calcd. for $C_{18}H_{24}N_2O_4$ 332.1736; found 332.1756; calcd. for $C_{11}H_{14}NO_2$ 192.1024; found 192.1044.

Methyl (3*R,4*R**)-3-(Benzoyloxy)-4-[6,7-dimethoxy-3,4-dihydro-2(1*H*)-isoquinolinyl]-1-piperidinecarboxylate (43):** IR ($CHCl_3$): $\tilde{\nu}$ = 3030, 1701, 1604 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 70 °C): δ = 1.83 (m, 1 H, 5-H_a), 2.08 (m, 1 H, 5-H_b), 2.71 (m, 1 H, 4′-H_a), 2.81 (m, 1 H, 4′-H_b), 2.90 (m, 1 H, 3′-H_a), 3.00 (m, 1 H, 4-H), 3.05 (m, 1 H, 3′-H_b), 3.16 (ddd, *J* = 3.3, 10.2, 13.4 Hz, 1 H, 6-H_a), 3.22 (dd, *J* = 8.1, 13.2 Hz, 1 H, 2-H_a), 3.70 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × OMe), 3.7–3.9 (m, 2 H, 1′-H_2), 3.90 (m, 1 H, 6-H_b), 4.24 (m, 1 H, 2-H_b), 5.32 (m, 1 H, 3-H), 6.50 (s, 1 H, arom.), 6.53 (s, 1 H, arom.), 7.41 (dd, *J* = 7.6, 7.7 Hz, 2 H, arom.), 7.53 (dd, *J* = 7.4, 7.5 Hz, 1 H, arom.), 7.98 (d, *J* = 7.3 Hz, 2 H, arom.) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.9 (CH_2, 5-C), 29.3 (CH_2, 4′-C), 42.3 (CH_2, 6-C), 46.0 (CH_2, 2-C), 47.6 (CH_2, 3′-C), 52.8 (CH_3, OMe), 55.8 (2 × CH_3, OMe), 63.1 (CH, 4-C), 68.3 (CH, 3-C), 109.4 (CH, arom., 5′-C or 8′-C), 111.4 (CH, arom., 5′-C or 8′-C), 128.4 (2 × CH, arom.), 129.7 (2 × CH, arom.), 130.1 (C, arom.), 133.2 (CH, arom.) ppm; due to signal broadening, the signals for C-6′, C-7′, C-4′a, C-4′b and the CO groups were not clearly observed. MS (EI, 70 eV): *m*/*z* (%) = 454 (3) [M^+], 349 (2) [M^+ – COPh], 332 (4) [M^+ – PhCOOH], 192 (100) [dimethoxytetrahydroisoquinoline]. HRMS (EI, 70 eV): calcd. for $C_{25}H_{30}N_2O_6$ 454.2104; found 454.2103; calcd. for $C_{18}H_{25}N_2O_5$ 349.1763; found 349.1786; calcd. for $C_{18}H_{24}N_2O_4$ 332.1736; found 332.1765; calcd. for $C_{11}H_{14}NO_2$ 192.1025; found 192.1044.

Supporting Information: Synthesis and spectroscopic data of compounds **18**–**22** and **25** and the synthetic intermediates **44** and **45**. See also the footnote on the first page of this article.

Acknowledgments

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[30] The structure of methyl (3*R**,4*R**)-4-acetyloxy-3-iodo-1-piperidinecarboxylate (**31**) was supported by HSQC and COSY experiments. Thus, 3-H (CHI, δ_H = 3.85 and δ_C = 25.9 ppm) is coupled with 2-H_a (δ_H = 3.31 and δ_C = 50.8 ppm) and with 4-H (CHOAc, δ_H = 4.88 and δ_C = 74.7 ppm), and 4-H (CHOAc, δ_H = 4.88 ppm) is correlated with 5-H_a (δ_H = 1.60 and δ_C = 30.9 ppm) and 5-H_b (δ_H = 2.10 and δ_C = 30.9 ppm). Furthermore, 5-H_a (δ_H = 1.60 ppm) is coupled with 5-H_b (δ_H = 2.10 ppm) and with 6-H_a (δ_H = 3.17 and δ_C = 41.6 ppm). Finally, 6-H_a (δ_H = 3.17 and δ_C = 41.6 ppm) is correlated with 6-H_b (δ_H = 4.00 and δ_C = 41.6 ppm).

[31] 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline was prepared by adding its commercial chlorohydrate salt to a saturated aqueous $NaHCO_3$ solution, which was then extracted with EtOAc. The organic layer was dried, filtered and the solvents evaporated under vacuum to afford the free tetrahydroisoquinoline.

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