The Reaction of β-Amino Alcohols with 1,1′-Carbonyldiimidazole − Influence of the Nitrogen Substituent on the Reaction Course

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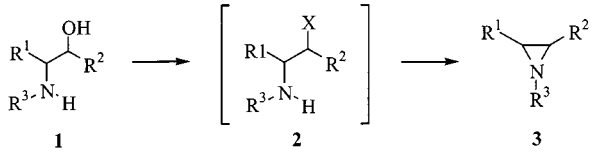
The reaction of β-amino alcohols with 1,1′-carbonyldiimidazole in dichloromethane is affected by the size of the nitrogen substituent. 1,3-Oxazolidin-2-ones are exclusively obtained from *N*-H, *N*-methyl and *N*-arylmethyl derivatives. *O*-(1-Imidazolyl)carbonyl derivatives are formed as intermediates from *N*-[1-(2-pyridyl)alkyl]-(*S*)-valinol and are mainly or exclusively converted into aziridines in the presence of water, although the cyclization is impeded by large *N*-substituents such as triphenylmethyl.

Introduction

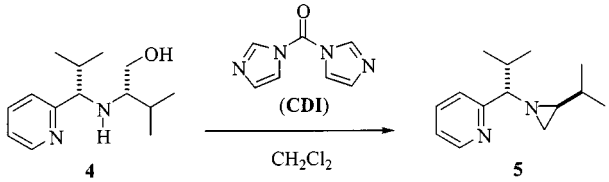
β-Amino alcohols **1** can be converted into aziridines **3** by a cyclodehydration reaction which usually takes place by the two step mechanism described in Scheme 1, where the intermediate **2** is either isolated or converted in situ into the target **3**. Enantiomerically pure, ring substituted aziridines can be prepared from β-amino alcohols available from the "chiral pool" or by asymmetric methodologies.[1] Several methods and reagents have been described for this purpose. For example, the reaction of β-amino alcohols with sulfuric acid afforded the β-aminoalkyl sulfates **2** (X = OSO_3H), from which aziridines were obtained by alkali treatment at high temperature.[2] On the other hand, the one-pot formation of the aziridines **3**, avoiding the isolation of intermediate **2**, was accomplished by the treatment of **1** with triphenylphosphane/carbon tetrachloride/triethylamine,[3] diethyl azodicarboxylate (Mitsunobu reaction),[3c,4] or dihalo-[5] or dialkoxytriphenylphosphoranes.[6] Moreover, starting from β-amino alcohols carrying bulky *N*-substituents, the corresponding *O*-tosyl and *O*-mesyl derivatives were prepared and then cyclized to aziridines by means of triethylamine in refluxing solvents,[4g,7] although the one-pot formation of aziridines at low temperature was sometimes observed.[4g,7d,7e] The reaction of β-amino alcohols with sulfuryl chloride generally afforded 2,2-dioxo-1,2,3-oxathiazolidines, but *N*-trityl-L-serine and -threonine benzyl esters were converted into the corresponding aziridines.[8] The treatment of chiral β-amino alcohols with thionyl chloride gave 2-oxo-1,2,3-oxathiazolidines or β-chloro amines, which were then converted into aziridines.[8,9] Finally, triflic anhydride has been used to convert valinol to 1-trifluoromethanesulfonyl-2-isopropylaziridine with excellent yield, although further examples were not provided.[7e] These methods often give aziridines with high yields, but suffer from certain disadvantages, since they require acidic or hard conditions, hazardous or poisonous reagents, tedious separation of by-products, or lack generality.



Scheme 1

In the course of our studies directed towards the synthesis of enantiopure 1-(2-pyridyl)alkylamines,[10] we discovered that the reaction of the β-amino alcohol **4** with 1,1′-carbonyldiimidazole (CDI) in dichloromethane unexpectedly yielded the aziridine **5** (Scheme 2).[10e] This result has no precedent in the previously reported reactions of β-amino alcohols with CDI, as the 1,3-oxazolidin-2-ones **7**, **9**, **11** and **13** were obtained from the β-amino alcohols **6**, **8**, **10** and **12**, respectively (Scheme 3).[11] Cyclic carbamates were recently prepared from 1,3-amino alcohols by reaction with CDI in the presence of triethylamine or imidazole.[12] Moreover, the reaction of 1,2-diols[13] and *N*-mono-substituted 1,2- and 1,4-diamines[14a,14b] with CDI follows analogous pathways affording 1,3-oxazolidin-2-ones and cyclic ureas, respectively. On the other hand, primary 1,2- and 1,4-diamines did not afford the cyclic ureas by treatment with CDI, phosgene and other phosgene equivalents; this goal was achieved by the use of gaseous carbonyl sulfide.[14c,14d]

We envisioned that the nitrogen substituent must have a remarkable effect on the reaction course and decided to investigate in depth the reaction of β-amino alcohols with CDI. Especially, we aimed to verify the scope of this new method for the construction of the aziridine ring and to



Scheme 2

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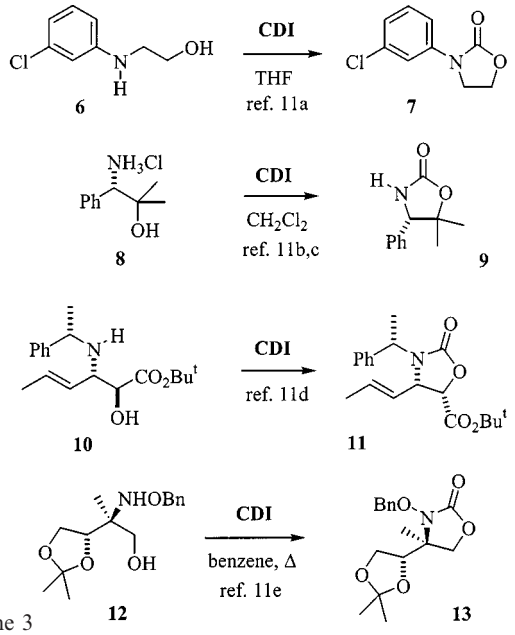
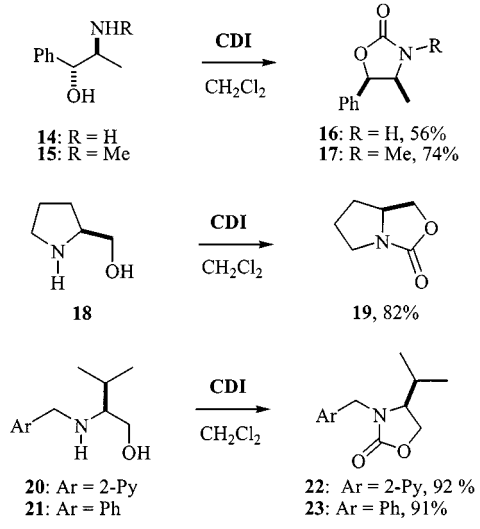


Scheme 3

prepare new optically pure aziridines useful in the field of asymmetric catalysis.[10e]

Results

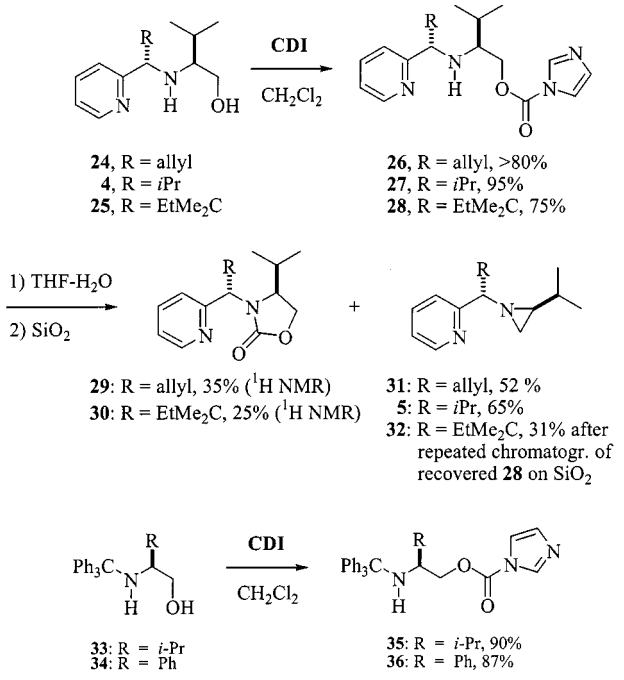
Despite the previously reported reactions of β-amino alcohols with CDI described in Scheme 3, we performed analogous reactions with the commercially available and optically pure β-amino alcohols (−)-norephedrine **(14)**, (−)-ephedrine **(15)** and (*S*)-prolinol **(18)**, and obtained the corresponding known oxazolidinones **16**,[15] **17**[15] and **19**,[16] respectively, in good yields (Scheme 4).



Scheme 4

Then we examined the reaction of (*S*)-valinol and (*S*)-phenylglycinol derivatives carrying different *N*-substituents; some of them were known compounds, others were prepared by routine methods, as described in the Experimental Section. In particular, the size of the *N*-substituent in the (*S*)-valinol derivatives was finely tuned by the addition of different organometallic reagents to the imine derived from 2-pyridinaldehyde, according to the protocols described previously by us.[10] The compounds **20** and **21**, carrying the 2-pyridylmethyl and benzyl groups as the *N*-substituent, were converted with high yields to the 1,3-oxazolidin-2-ones **22** and **23**, respectively (Scheme 4).

Different outcomes were obtained from the reaction of (*S*)-valinol derivatives having more bulky substituents, i.e. compounds **24** and **25** (Scheme 5). This lead us to repeat the reaction of **4**, but, to our great disappointment, we did not succeed in preparing the aziridine **5** in quantitative yield, as previously described:[10e] instead, in different experiments apparently carried out by following the same experimental procedure, the yields were low to good. As a matter of fact, all the reaction mixtures derived from the β-amino alcohols **24**, **4** and **25** contained the *O*-(1-imidazolyl)-carbonyl derivatives **26**−**28** (Scheme 5). These compounds were identified only by ^{1}H NMR spectroscopy, since only low molecular weight products were revealed by GC-MS analyses.



Scheme 5

It should be underlined that the products were isolated after stirring or washing the reaction mixtures (CH_2Cl_2) with H_2O to remove the imidazole formed as a by-product. After considerable experimentation, we finally discovered that the aziridine **5** was formed during the aqueous treatment. In fact, when the aqueous workup was avoided and the solvent evaporated, ^{1}H NMR analyses of the crude mixtures coming from the substrates **24**, **4** and **25** indicated that the *O*-(1-imidazolyl)carbonyl derivatives were mainly or almost exclusively formed, being accompanied in all cases by imidazole. The mixture coming from **24** also contained traces amounts of the oxazolidinone **29** and about 15% of the aziridine **31**; the intermediate **28** was accompanied by

the oxazolidinone **30** (25%). On the other hand, only traces of the aziridine **5** were formed from **4**. The yield of the aziridine **5** was seemingly affected by the relative amounts of water in the workup and by the duration of stirring the heterogeneous mixture CH_2Cl_2/H_2O. In order to obtain reproducible results, it was preferable to evaporate the CH_2Cl_2 solvent and then stir the reaction residues in a diluted homogeneous medium THF/H_2O (1:3). In this way, after 2 h, the complete cyclization of the intermediates **26**−**28** to 1,3-oxazolidin-2-ones and/or aziridines was observed. Starting from the compound **26** carrying the less bulky *N*-substituent, a mixture of oxazolidinone **29** and aziridine **31** was obtained, but only the aziridine **31** was isolated pure in 52% yield after column chromatography (SiO_2). On the other hand, the aziridine **5** was exclusively formed from **27**. It is noteworthy that from the compound **28**, with the most bulky *N*-substituent, the aziridine **32** was not formed in the aqueous medium, but during the attempted purification of **28** by chromatography on an SiO_2 column: an overall 31% yield of aziridine **32** was obtained by repeating the chromatography of recovered **28**.

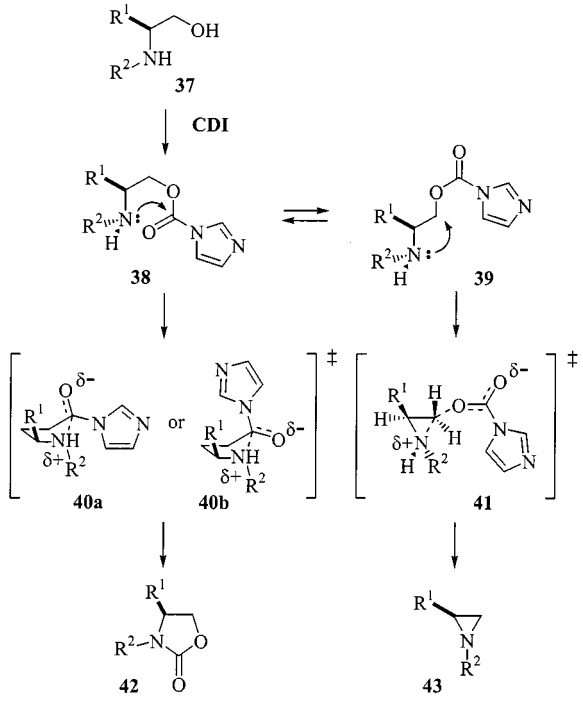
Finally, we carried out the reaction of *N*-triphenylmethyl-(*S*)-valinol **(33)** and *N*-triphenylmethyl-(*S*)-phenylglycinol **(34)**, and observed the formation of the *O*-(1-imidazolyl)-carbonyl derivatives **35** and **36**, respectively, in high yields (Scheme 5). No cyclic product was obtained either by stirring **35**,**36** for several hours in the homogeneous system THF/H_2O or by heating them in refluxing THF or toluene, even in the presence of triethylamine;[12a] instead, unidentified by-products were sometimes formed.

Reaction Pathways

The construction of 1,3-oxazolidin-2-ones and aziridines by the reaction of chiral *N*-substituted β-amino alcohols **37** with CDI can be explained by the reaction course described in Scheme 6. The *O*-imidazolecarbonyl derivatives **40**[17] can be envisaged as the preliminarily formed intermediates in the pathways leading to both the 1,3-oxazolidin-2-ones **42** and aziridines **43**. In fact, it is known that 3-methylamino-1,2-propandiol gives the cyclic carbonate instead of the cyclic carbamate, demonstrating that the primary hydroxyl function reacts preferentially to the secondary amine.[13d]

The 1,3-Oxazolidin-2-ones **42** are then formed from **38** by the intramolecular attack of the secondary amine function at the carbonyl group of the carbamate moiety, through the diastereomeric transition states **40a,b**. On the other hand, aziridines **43** are formed from the conformers **39** of the same intermediates by an intramolecular S_N2 reaction in which nitrogen attacks the carbon atom bearing the *O*-imidazolecarbonyl leaving group, through the transition state **41**. This view is in agreement with the known reactivity of amines, since the presence of substituents at nitrogen favours the S_N2 displacement rather than attack at the carbonyl group.[18,19]

Our results demonstrate that the rate of cyclization to 1,3-oxazolidin-2-ones is affected by the size of the *N*-substituent R^2. This can be explained by considering the nonbonding interactions in the transition states, i.e. R^2-imidazole in **40a** and R^1-imidazole in **40b**. However, the aziridines **43** were formed even with bulky R^2 substituents, although the cyclization required the presence of water, and did not occur at all when the size of R^2 was excessive, e.g. in **25**.



Scheme 6

It is noteworthy that both the rate and the regioselectivity of the ring closure to aziridines **43** is enhanced by an aqueous medium. This outstanding solvent effect can be understood, in our opinion, by considering that the transition state **41** is more dipolar than the transition states **40a,b**, because the opposite charges are more separated; hence, it is better solvated and more stabilized by water, which has higher dipole moment and dielectric constant than aprotic organic solvents.

Conclusions

The nature of the *N*-substituent is the determining factor deciding the outcome of the reaction of β-amino alcohols with 1,1′carbonyldiimidazole (CDI). 1,3-Oxazolidin-2-ones are exclusively produced from substrates having a small *N*-substituent, whereas the cyclization to aziridines is favoured by a larger *N*-alkyl substituent, e.g. 1-(2-pyridyl)alkyl, and requires the presence of H_2O. The *O*-imidazolecarbonyl derivatives of the β-amino alcohols (imidazole carboxylic esters) are the intermediates in these cyclizations. Only the latter compounds are isolated from β-amino alcohols carrying very bulky *N*-substituents, e.g. trityl, and do not undergo cyclization even at high temperature.

In our continuing efforts to synthesize other optically pure 1-[(2-pyridyl)alkyl]aziridines, we intend to verify if this procedure can be applied to other β-amino alcohols, especially (*S*)-phenylglycinol derivatives.

We wish to underline that the use CDI for the construction of aziridines and 1,3-oxazolidin-2-ones from β-amino alcohols, and similarly of cyclic ureas and carbonates from ω-amino alcohols and 1,n-diols, respectively, is convenient for the simplicity of the procedure and the mildness of the experimental conditions. Moreover, CDI is a stable (although hygroscopic), crystalline and safe reagent. These uses of CDI, despite a few reports,[11−14] have been heretofore neglected with respect to other methods, which generally require phosgene or phosgene substitutes,[20] which can result in better conversion and selectivity but are more hazardous. Recently developed procedures making use of CO/O_2/Pd-Cu,[16c] CO/PdI_2/KI[16e] or electrogenerated tetraethylammonium carbonate or peroxydicarbonate with a large excess of tosyl chloride[20f] have drawbacks, too.

Experimental Section

General Conditions: Melting points are uncorrected. − Solvents were distilled under N_2 prior to use: THF over sodium benzophenone ketyl and then over $LiAlH_4$, and CH_2Cl_2 over P_2O_5. − Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$ values are given in 10^{-1} deg cm^3 g^{-1}. − ^{1}H NMR spectra were recorded on a Varian Gemini instrument at 300 or 200 MHz for samples in $CDCl_3$ which had been stored over Mg. ^{1}H Chemical shifts are reported in ppm relative to $CHCl_3$ (δ_H = 7.27) and *J* values are given in Hz. − MS spectra were taken at an ionizing voltage of 70 eV on a Hewlett-Packard 5970 or 5890 spectrometer with GLC injection. − Chromatographic purifications were carried out on columns of silica gel (Merck, 230−400 mesh) at medium pressure. − 2-Pyridinealdehyde and benzaldehyde (Aldrich) were distilled before use. − Chlorotriphenylmethane was purchased from Aldrich and used as received. − All organometallic reactions were performed in flame-dried apparatus under a static atmosphere of dry N_2. − (*S*)-*N*-Benzyl valinol **(21)** was prepared according to a reported procedure;[21] the β-hydroxy amines **4**,[10d,10e] **24**,[10d,10e] and **25**[10e] and aziridines **5**[10e] and **32**[10e] were prepared as previously described.

(*S*)-*N*-[(2-Pyridyl)methyl]valinol (20): To a solution of (*S*)-valinol (0.824 g, 8 mmol) in CH_2Cl_2 (10 mL) cooled at 0 °C was added anhydrous $MgSO_4$ (4 g) and freshly distilled 2-pyridinealdehyde (0.856 g, 8 mmol). The mixture was stirred for 2 h, then the solution was filtered and concentrated to leave an oily residue of the imine.[10d] This was dissolved in MeOH (10 mL) and $NaBH_4$ (0.300 g, 8 mmol) was added. The mixture was stirred at room temp. for 4 h, then the solvent was evaporated at reduced pressure, H_2O (5 mL) was added, and the organic phase was extracted with Et_2O (3 × 10 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to leave an oily residue. Chromatography on a short column of SiO_2 eluting with cyclohexane/ethyl acetate (60:40) gave compound **20** as an oil: 1.101 g (65%); $[\alpha]_D^{25}$ = +30.7 (*c* = 0.96, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 5.7 Hz, 1 H, Py), 7.65 (m, 1 H, Py), 7.30 (d, *J* = 7.6 Hz, Py), 7,18 (m, 1 H, Py), 4.01 (q, 2 H, PyCH_2), 3.70 (dd, *J* = 3.9 and 11.4 Hz, 1 H, CHCH_2), 3.47 (dd, *J* = 7.2 and 11.4 Hz, 1 H, CHCH_2), 3.1 (br, 2 H, NH and OH), 2.50 (m, 1 H, C*H*CH_2), 1.85 (m, 1 H C*H*Me_2), 1.0 and 0.95 (2 d, *J* = 6.7 Hz, 6 H, CH*Me*$_2$). − MS: *m*/*z* (%) = 163 (100) [M^+ − CH_2OH], 93 (92), 92 (46), 151 (38) [M^+ − *i*Pr], 94 (24), 65 (20).

Preparation of *N*-Triphenylmethyl β-Amino Alcohols: To a solution of (*S*)-valinol or (*S*)-phenylglycinol (10 mmol) in dry CH_2Cl_2 (25 mL) cooled at 0 °C was added Et_3N (1.4 mL, 10 mmol), then diphenylmethyl bromide (2.480 g, 10 mmol) or triphenylmethyl chloride (2.800 g, 10 mmol). The mixture was stirred for 7−8 h, then filtered, washed with brine, dried over Na_2SO_4, and concentrated and the residue was chromatographed on an SiO_2 column (cyclohexane/ethyl acetate 90:10).

***N*-Triphenylmethyl-(*S*)-valinol (33):** Yellowish oil; the compound was >95% pure by ^{1}H NMR analyses: 3.044 g, 90%; $[\alpha]_D^{20}$ = −20 (*c* = 1.16, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.6−7.05 (m, 15 H, Ph), 3.33 (dd, *J* = 3.7 and 11.0 Hz, 1 H, CHCH_2), 3.10 (dd, *J* = 5.4 and 11.0 Hz, 2 H, CHCH_2), 2.42 (m, 1 H, C*H*CH_2), 2.05 (broad, 2 H, NH and OH), 1.26 (m, 1 H, C*H*Me_2), 0.80 and 0.66 (2 d, *J* = 6.9 Hz, CH*Me*$_2$). − $C_{24}H_{27}NO$ (345.48): calcd. C 83.44, H 7.88, N 4.05; found C 83.54, H 8.03, N 3.99.

***(S)*-*N*-Triphenylmethyl-phenylglycinol (34):** White solid; 3.41 g (90%); m.p. 55−56 °C; $[\alpha]_D^{20}$ = −96 (*c* = 1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.7−7.1 (m, 20 H, Ph), 3.81 (t, 1 H, CHN), 3.24 (dd, *J* = 4.1 and 10.5 Hz, 1 H, CHCH_2), 2.83 (dd, *J* = 5.4 and 10.5 Hz, 1 H, CHCH_2), 1.50 (broad, 2 H, NH and OH). − $C_{27}H_{25}NO$ (379.49): calcd. C 85.45, H 6.64, N 3.69; found C 85.50, H 6.69, N 3.60.

Reactions of β-Amino Alcohols with 1,1′-Carbonyldiimidazole

A) Preparation of 1,3-Oxazolidin-2-ones: To a solution of the β-amino alcohol (5 mmol) in dry CH_2Cl_2 (20 mL) was added 1.1′-carbonyldiimidazole (0.810 g, 5 mmol) and the solution was stirred with a magnetic bar for 1−2 h, after which time the reaction was apparently complete, as judged by TLC analysis (sometimes the products and starting material were not well separated). The reaction mixture was washed with H_2O (2 × 10 mL), then dried (Na_2SO_4) and concentrated, and the residue was chromatographed on a column of SiO_2 eluting with cyclohexane/ethyl acetate mixtures.

(4*S*,5*R*)-4-Methyl-5-phenyl-1,3-oxazolidin-2-one (16): White solid; 0.523 g (56%); $[\alpha]_D^{20}$ = −170 (*c* = 1.2, $CHCl_3$), m.p. 116−117 °C {ref.[15b] $[\alpha]_D^{20}$ = −158.4 (*c* = 0.44, $CHCl_3$), m.p. 116−117 °C; ref.[15c] $[\alpha]_D^{20}$ = −149.6 (*c* = 0.51, $CHCl_3$), m.p. 102−105 °C}. − The ^{1}H NMR spectrum was identical to that reported in the literature. − MS: *m*/*z* (%) = 107 (100), 79 (55), 77 (23), 105 (20), 51 (18), 177 (17) [M^+].

(4*S*,5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolidin-2-one (17): White solid; 0.707 g (74%); $[\alpha]_D^{20}$ = −122 (*c* = 1.2, $CHCl_3$), m.p. 91−92 °C {ref.[15b] $[\alpha]_D^{20}$ = −118.3 (*c* = 0.23, $CHCl_3$), m.p. 91−92 °C; ref.[15a] $[\alpha]_D$ = −110.6 ($CHCl_3$), m.p. 91−92 °C; ref.[15d] $[\alpha]_D$ = −125 (*c* = 1.0, $CHCl_3$), m.p. 91−92 °C; ref.[15f] $[\alpha]_D$ = −120 (*c* = 1.18, $CHCl_3$), m.p. 90−92 °C}. − The ^{1}H NMR spectrum was identical to that reported in the literature. − MS: *m*/*z* (%) = 57 (100) [MeCHNMe], 191 (30) [M^+], 117 (28), 105 (25), 77 (24), 132 (20), 91 (14), 147 (10) [M^+ − CO_2], 176 (9) [M^+ − Me].

(*S*)-Tetrahydro-1*H*,3*H*-pyrrolo[1,2-c]oxazol-3-one 19: Yellowish oil; 0.521 g (82%); $[\alpha]_D^{20}$ = −33 (*c* = 1, $CHCl_3$) {ref.[16a] $[\alpha]_D^{20}$ = −35.1 (*c* = 0.72, $CHCl_3$); ref.[16b] $[\alpha]_D^{20}$ = +37.1 (*c* = 1.61, $CHCl_3$) for the (*R*)-enantiomer}. − The ^{1}H NMR spectrum was identical to that reported for the authentic compound.[16c]

(4*S*)-Isopropyl-3-[(2-pyridyl)methyl]-1,3-oxazolidin-2-one (22): Yellowish oil; 1.011 g (92%). − $[\alpha]_D^{20}$ = −6.0 (*c* = 1.2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.56 (d, *J* = 4.8 Hz, 1 H, Py), 7.75 (m, 1 H, Py), 7.44 (d, *J* = 8.1 Hz, 1 H, Py), 7.27 (m, 1 H, Py), 4.86 (d, *J* = 15.5 Hz, 1 H, PyCH_2), 4.32 (d, *J* = 15.5 Hz, 1 H, PyCH_2), 4.25 (dd, *J* = 9.0 and 12.0 Hz, 1 H, CHCH_2), 4.11 (dd, *J* = 14.7

and 9.0 Hz, 1 H, CHCH_2), 3.78 (m, 1 H, CHCH$_2$), 2.19 (m, 1 H, CHMe$_2$), 0.86 and 0.84 (2 d, J = 7.0 Hz, CHMe_2). − MS: m/z (%) = 93 (100), 92 (44), 177 (26) [M$^+$ − iPr], 65 (15), 133 (11). − $C_{12}H_{16}N_2O_2$ (220.27): calcd. C 65.43, H 7.32, N 12.72; found C 65.72, H 7.43, N 12.70.

3-Benzyl-(4*S*)-isopropyl-1,3-oxazolidin-2-one (23): Colourless oil; 0.996 g (91%); $[\alpha]_D^{20}$ = −25.5 (c = 1.1, CHCl$_3$). − IR: $\tilde{\nu}$ = 1747 (C=O). − ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.27 (m, 5 H, Ph), 4.89 (d, J = 15 Hz, 1 H, PhCH_2), 4.19 (dd, J = 9.0 and 17.7 Hz, CHCH_2), 4.09 (dd, J = 5.7 and 9.0 Hz, CHCH_2), 3.98 (d, J = 15 Hz, 1 H, PhCH_2), 3.56 (m, 1 H, CHCH$_2$), 2.08 (m, 1 H, CHMe$_2$), 0.88 and 0.84 (2 d, J = 6.9 Hz, 6 H, CHMe_2). − MS: m/z (%) = 91 (100), 176 (18) [M$^+$ − iPr], 65 (10), 92 (8), 219 (4) [M$^+$]. − $C_{13}H_{17}NO_2$ (219.28): calcd. C 71.21, H 7.81, N 6.39; found C 71.29, H 7.85, N 6.35.

B) Preparation of *O*-[(1-imidazole)carbonyl] Derivatives: The same procedure previously described for the synthesis of 1,3-oxazolidin-2-ones was followed for the preparation of the compounds **26**−**28**, **35** and **36**. The reactions could not be monitored by GC-MS analyses because these high molecular weight compounds were not eluted. In order to detect the compounds **26** and **27**, which were more labile due to aqueous treatment, the reaction mixtures were analysed by ^{1}H NMR spectroscopy after evaporating the solvent and dissolving the residue in CDCl$_3$; in these cases, imidazole was present in the reaction mixtures.

(*S*)-*O*-[(1-Imidazolyl)carbonyl]-*N*-[(1*S*)-1-(2-pyridyl)but-3-en-1-yl)]valinol (26): The crude oily product contained also the aziridine **31** (ca. 15%) and trace amounts of the starting material **24**.
26: ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 8.56 (m, 1 H, Py), 8.16 (s, 1 H, Im), 7.64 (m, 1 H, Py), 7.44 (s, 1 H, Im), 7.36 (d, J = 4.3 Hz, 1 H, Py), 7.20−7.05 (m, 2 H, Py and Im), 5.70 (m, 1 H, CH=CH$_2$), 5.12−4.86 (m, 2 H, CH=CH_2), 4.53 and 4.36 (2 m, 2 H, CH$_2$O), 3.91 (t, 1 H, PyCHN), 2.56−2.28 (m, 4 H, CH$_2$=CHCH_2, NCHCH$_2$O and NH), 1.74 (m, 1 H, CHMe$_2$), 0.93 and 0.86 (2 d, J = 6.6 Hz, 6 H, CHMe_2).

(*S*)-*O*-[(1-Imidazolyl)carbonyl]-*N*-[(1*S*)-1-(2-pyridyl)-2-methylpropyl]valinol (27): The crude oily product contained imidazole and trace amounts of the starting material **4** and aziridine **5**.
27: ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 8.58 (d, J = 4.3 Hz, 1 H, Py), 8.17 (s, 1 H, Im), 7.64 (m, 1 H, Py), 7.46 (s, 1 H, Im), 7.30−7.10 (m, 3 H, Py and Im), 4.45 (m, 2 H, CH$_2$O), 3.48 (d, J = 6.8 Hz, 1 H, PyCHN), 2.39 (q, 1 H, NCHCH$_2$O), 1.93 and 1.75 (2 m, 2 H, CHMe$_2$), 1.27 (broad, 1 H, NH), 1.0, 0.91, 0.84 and 0.75 (4 d, J = 6.6 Hz, 12 H, CHMe_2).

(*S*)-*O*-[(1-Imidazolyl)carbonyl]-*N*-[(1*S*)-1-(2-pyridyl)-2,2-dimethylbutyl]valinol (28): The crude oily product contained about 25% of the oxazolidinone **30**.
28: ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 8.56 (m, 1 H, Py), 8.15 (s, 1 H, Im), 7.6 (m, 1 H, Py), 7.44 (s, 1 H, Im), 7.25−7.10 (m, 2 H, Py), 7.08 (s, 1 H, Im), 4.42 (d, J = 4.9 Hz, CH$_2$O), 3.58 (s, 1 H, PyCHN), 2.16 (m, 1 H, NCHCH$_2$), 1.72 (m, 1 H, CHMe$_2$), 1.35 (m, 2 H, CH_2Me), 0.85−1.0 (m, 15 H, CHMe_2, MeCH$_2$CMe_2).

(*S*)-*O*-[1-(Imidazolyl)carbonyl]-*N*-triphenylmethylvalinol (35): White solid, 1.980 g (90%); m.p. 106−107 °C (cyclohexane). − $[\alpha]_D^{20}$ = −50.4 (c = 0.96, CHCl$_3$). − IR (nujol): $\tilde{\nu}$ = 3252 (N−H), 1769 (C=O) cm^{-1}. − ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 8.04 (s, 1 H, Im), 7.57 (m, 5 H, Ph), 7.35 (m, 1 H, Im), 7.31−7.16 (m, 10 H, Ph), 7.08 (m, 1 H, Im), 4.10 (dd, J = 4.2 and 10.8 Hz, 1 H, CHCH_2), 3.94 (dd, J = 5.4 and 11.1 Hz, 1 H, CHCH_2), 2.66 (m, 1 H, CHCH$_2$), 2.03 (m, 1 H, NH), 1.60 (m, 1 H, CHMe$_2$), 0.90 and 0.86 (2 d, J = 6.9 Hz, CHMe_2). − $C_{28}H_{29}N_3O_2$ (439.55): calcd. C 76.51, H 6.65, N 9.56; found C 76.55, H 6.70, N 9.51.

(*S*)-*O*-[(1-Imidazolyl)carbonyl]-*N*-triphenylmethylphenylglycinol (36): White solid; 2.065 g (87%); m.p. 132 °C. − $[\alpha]_D^{20}$ = −46 (c = 1, CHCl$_3$). − IR: $\tilde{\nu}$ = 3298, 3156, 1760 cm^{-1}. − ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.89 (m, 1 H, Im), 7.48 (m, 5 H, Ph), 7.27 (s, 1 H, Im), 7.25−7.06 (m, 15 H, Ph), 7.0 (m, 1 H, Im), 4.05 (m, 2 H, CHCH_2), 3.88 (dd, J = 6.0 and 9.6 Hz, 1 H, CHCH_2), 2.60 (d, J = 7.2 Hz, 1 H, NH). − MS: m/z (%) = 243 (100) [CPh$_3$], 165 (23), 244 (20), 348 (9) [M$^+$ − CH$_2$OCOIm], 91 (5), 360 (4). − $C_{31}H_{27}N_3O_2$ (473.57): calcd. C 78.62, H 5.75, N 8.87; found C 78.71, H 5.85, N 8.80.

C) Preparation of the Aziridines 5, 31 and 32: The procedure previously described for the preparation of oxazolidinones was followed. After the reaction was complete, as indicated by disappearance of the starting β-amino alcohol (TLC analysis), the solvent was evaporated and the residue was taken up with 120 mL of a THF/H$_2$O mixture (1:3). After stirring for 2 h, most of the THF was evaporated at reduced pressure and the aqueous phase extracted with Et$_2$O (3 × 50 mL), the collected ethereal layers were dried (Na$_2$SO$_4$) and concentrated.

(2*R*)-Isopropyl-1-[(*S*)-1-(2-pyridyl)but-3-en-1-yl]aziridine (31): yellowish oil; 0.571 g (52%) was obtained after column chromatography (SiO$_2$) eluting with cyclohexane/ethyl acetate (80:20); $[\alpha]_D^{20}$ = −45.1 (c = 0.96, CHCl$_3$). − ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 8.57 (d, J = 4.2 Hz, 1 H, Py), 7.70 (m, 1 H, Py), 7.46 (d, J = 8.2 Hz, 1 H, Py), 7.08 (m, 1 H, Py), 5.70 (m, 1 H, CH=CH$_2$), 5.06−4.84 (m, 2 H, CH=CH_2), 2.68 (m, 2 H, PyCHCH_2), 2.57 (m, 1 H, PyCH), 1.72 (d, J_{cis} = 3.4 Hz, 1 H, NCH$_2$), 1.50 (d, J_{trans} = 6.6 Hz, 1 H, NCH$_2$), 1.36−1.22 (m, 2 H, NCH-iPr and CHMe$_2$), 0.79 and 0.49 (2 d, J = 6.6 and 6.2 Hz, 6 H, CHMe_2). − $C_{14}H_{20}N_2$ (216.32): calcd. C 77.73, H 9.32, N 12.95; found C 77.77, H 9.36, N 12.90.
0.450 g of a 2:1 mixture of 1,3-oxazolidin-2-one **(29)** and aziridine **31** was also obtained by column chromatography; from the ^{1}H NMR spectrum (CDCl$_3$, 200 MHz), the signals due to the oxazolidinone **29** could be discerned: δ = 8.57 (d, J = 4.3 Hz, 1 H, Py), 7.65 (m, 2 H, Py), 7.10 (m, 1 H, Py), 5.82 (m, CH=CH$_2$), 5.31−4.95 (m, 3 H, CH=CH_2 and PyCH), 4.11 (dd, J = 8.8 and 12.4 Hz, 1 H, CH$_2$O), 4.07 (dd, J = 8.8 and 4.8 Hz, 1 H, CH$_2$O), 3.82 (m, 1 H, NCHCH$_2$O), 3.04 (m, 2 H, CH$_2$=CHCH_2), 1.74 (m, 1 H, CHMe$_2$), 0.75 and 0.47 (2 d, J = 7.4 and 6.6 Hz, 6 H, CHMe_2).

(2*R*)-Isopropyl-1-[(*S*)-1-(2-pyridyl)-2-methylpropyl]aziridine (5): Yellowish oil; 1.029 g (95%, >95% pure by GC-MS and ^{1}H NMR analyses); chromatography on a SiO$_2$ column eluting with cyclohexane/ethyl acetate (85:15) gave pure **5** as a colourless oil: 0.708 g (65%); $[\alpha]_D^{20}$ = −19.1 (c = 0.96, CHCl$_3$). − The ^{1}H NMR spectrum was identical to that previously described.[10e]

(2*R*)-Isopropyl-1-[(*S*)-1-(2-pyridyl)-2,2-dimethylbutyl]aziridine (32): Chromatography of the crude reaction product on an SiO$_2$ column eluting with cyclohexane/ethyl acetate (80:20) gave a small amount of the aziridine **32**; the fractions mainly containing recovered compound **28** were concentrated and the residue was again chromatographed to obtain further aziridine; the collected aziridine **32**, obtained as a yellowish oil, weighed 0.382 g (31%) and was identical to that previously described.[10e]

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[1] The synthesis of chiral aziridines has recently been reviewed: [1a] D. Tanner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599−639. − [1b] H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715.

[2] [2a] H. Wenker, *J. Am. Chem. Soc.* **1935**, 57, 2328. − [2b] E. D. Bergmann, A. Kaluszyner, *Recl. Trav. Chim. Pay-Bas* **1959**, *78*, 289−314. − [2c] Y. Minoura, M. Takebayashi, C. C. Price, *J. Am. Chem. Soc.* **1959**, *81*, 4689−4692. − [2d] D. V. Kashelikar, P. E. Fanta, *J. Am. Chem. Soc.* **1960**, *82*, 4930−4931. − [2e] S. J. Brois, G. P. Beardsley, *Tetrahedron Lett.* **1966**, 5113−5119. − [2f] P. G. Gassman, A. Fentman, *J. Org. Chem.* **1967**, *32*, 2388−2391. − [2g] C. S. Dewey, R. A. Bafford, *J. Org. Chem.* **1967**, *32*, 3108−3110. − [2h] H. Rubinstein, B. Feibush, E. Gil-Av, *J. Chem. Soc., Perkin Trans. 2* **1973**, 2094−2097. − [2i] A. Nabeya, T. Shigemoto, Y. Iwakura, *J. Org. Chem.* **1975**, *40*, 3536−3539. − [2j] G. S. Bates, M. A. Varelas, *Can. J. Chem.* **1980**, *58*, 2562−2565. − [2k] M. E. Perlman, T. J. Bardos, *J. Org. Chem.* **1988**, *53*, 1761−1767.

[3] [3a] R. Appel, R. Kleinstuck, *Chem. Ber.* **1974**, *107*, 5−12. − [3b] K. J. Shaw, J. R. Luly, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 4515−4523. − [3c] P. G. Andersson, D. Guijarro, D. Tanner, *Synlett.* **1996**, 727−728.

[4] [4a] J. R. Pfister, *Synthesis* **1984**, 969−970. − [4b] M. A. Poelert, R. P. Hof, C. M. W. Peper, R. M. Kellog, *Heterocycles* **1994**, *37*, 461−475. − [4c] N. Fujii, K. Nakai, H. Habashita, Y. Hotta, H. Tamamura, A. Otaka, T. Ibuka, *Chem. Pharm. Bull.* **1994**, *42*, 2241−2246. − [4d] P. G. Andersson, A. Harden, D. Tanner, P.-O. Norrby, *Chem. Eur. J.* **1995**, *1*, 12−16. − [4e] T. Ibuka, N. Mimura, H. Aoyama, M. Akaji, H. Ohno, Y. Miwa, T. Taga, K. Nakai, H. Tamamura, N. Fujii, Y. Yamamoto, *J. Org. Chem.* **1997**, *62*, 999−1015. − [4f] T. Ibuka, N. Mimura, H. Ohno, K. Nakai, M. Akaji, H. Habashita, H. Tamamura, Y. Miwa, T. Taga, N. Fujii, Y. Yamamoto, *J. Org. Chem.* **1997**, *62*, 2982−2991. − [4g] D. A. Alonso, P. G. Andersson, *J. Org. Chem.* **1998**, *63*, 9455−9461.

[5] [5a] I. Okada, K. Ichimura, R. Sudo, *Bull. Chem. Soc. Jpn* **1970**, *43*, 1185−1189. − [5b] J. C. Pommelet, J. Cluche, *Can. J. Chem.* **1976**, *54*, 1571−1581. − [5c] N. Manisse, J. Cluche, *J. Am. Chem. Soc.* **1977**, *99*, 1271−1272.

[6] [6a] J. W. Kelly, N. L. Eskew, S. A. Evans, Jr., *J. Org. Chem.* **1986**, *51*, 95−97. − [6b] J. W. Kelly, P. L. Robinson, S. A. Evans, Jr., *J. Org. Chem.* **1986**, *51*, 4473−4475. − [6c] J. W. Kelly, S. A. Evans, Jr., *J. Org. Chem.* **1986**, *51*, 5492−5494. − [6d] E. Kuyl-Yeheskiely, C. M. Dreef-Tromp, G. A. van der Marel, J. H. van Boom, *Recl. Trav. Chim. Pay-Bas* **1989**, *108*, 314−316. − [6e] J. E. Baldwin, C. N. Farthing, A. T. Russell, C. J. Schofield, A. C. Spivey, *Tetrahedron Lett.* **1996**, *37*, 3761−3764.

[7] [7a] K. Nakajima, F. Takai, T. Tanaka, K. Okawa, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1577−1578. − [7b] T. Tanaka, K. Nakajima, K. Okawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1352−1355. − [7c] T. Wakamiya, K. Shimbo, T. Shiba, K. Nakajima, M. Neya, K. Okawa, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3878−3881. − [7d] M. Poch, X. Verdaguer, A. Moyano, M. A. Pericas, A. Riera, *Tetrahedron Lett.* **1991**, *32*, 6935−6938. − [7e] M. Cernerud, H. Adolfsson, C. Moberg, *Tetrahedron: Asymmetry* **1997**, *8*, 2655−2662. − [7f] C. Anaya de Parrodi, G. E. Moreno, L. Quintero, E. Juaristi, *Tetrahedron: Asymmetry* **1998**, *9*, 2093−2099. − [7g] J.-W. Chang, J. H. Bae, S.-H. Shin, C. S. Park, D. Choi, W. K. Lee., *Tetrahedron Lett.* **1998**, *39*, 9193−9196.

[8] E. Kuyl-Yeheskiely, M. Lodder, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **1982**, *30*, 3013−3016.

[9] [9a] J. A. Deyrup, C. L. Moyer, *J. Am. Chem. Soc.* **1969**, *34*, 175−179. − [9b] L. Kniezo, P. Kristian, M. Budesinsky, K. Havrilova, *Coll. Czech. Chem. Commun.* **1981**, *46*, 717−728. − [9c] J. E. Baldwin, A. C. Spivey, C. J. Schofield, *Tetrahedron: Asymmetry* **1990**, *1*, 881−884. − [9d] B. K. Cuthbert, G. Lowe, *J. Chem. Soc., Chem. Commun.* **1989**, 1702−1703. − [9e] A. Flores-Parra, P. Suarez-Moreno, S. A. Sanchez-Ruiz, M. Tlahuextl, J. Iaen-Gaspar, H. Tlahuextl, R. Salas-Coronado, A. Cruz, H. Noth, R. Contreras, *Tetrahedron: Asymmetry* **1998**, *9*, 1661−1671.

[10] [10a] G. Alvaro, D. Savoia, *Tetrahedron: Asymmetry* **1996**, *7*, 2083−2092. − [10b] G. Alvaro, D. Savoia, M. R. Valentinetti, *Tetrahedron* **1996**, *52*, 12571−12586. − [10c] G. Alvaro, P. Pacioni, D. Savoia, *Chem. Eur. J.* **1997**, *3*, 726−731. − [10d] G. Alvaro, G. Martelli, D. Savoia, *J. Chem. Soc., Perkin Trans. 1* **1998**, 775−783. − [10e] K. Fiore, G. Martelli, M. Monari, D. Savoia, *Tetrahedron: Asymmetry* **1999**, *10*, 4803−4810.

[11] [11a] W. B. Wright, Jr., *J. Heterocyclic Chem.* **1965**, *2*, 41−43. − [11b] S. G. Davies, H. J. Sanganee, *Tetrahedron: Asymmetry* **1995**, *6*, 671−674. − [11c] S. G. Davies, H. J. Sanganee, P. Szolcsanyi, *Tetrahedron* **1999**, *55*, 3337−3354. − [11d] S. G. Davies, D. R. Fenwick, O. Ichihara, *Tetrahedron: Asymmetry* **1997**, *8*, 3387−3391. − [11e] M. Carda, J. Murga, S. Rodriguez, F. Gonzalez, E. Castillo, J. A. Marco, *Tetrahedron: Asymmetry* **1998**, *9*, 1703−1712.

[12] [12a] D. L. Comins, J. T. Kuethe, H. Hong, F. J. Lakner, *J. Am. Chem. Soc.* **1999**, *121*, 2651−2652. − [12b] M. Demarcus, S. N. Figheddu, A. Mann, M. Taddei, *Tetrahedron Lett.* **1999**, *40*, 4417−4420.

[13] [13a] J. P. Kutney, A. H. Ratcliffe, *Synth. Commun.* **1975**, *5*, 47−52. − [13b] J. Adams, B. J. Fitzsimmons, Y. Girard, Y. Leblanc, J. F. Evans, J. Rokach, *J. Am. Chem. Soc.* **1985**, *107*, 464−469. − [13c] S.-K. Kang, D.-C. Park, H.-S. Rho, S.-M. Han, *Synth. Commun.* **1993**, *23*, 2219−2224. − [13d] S. P. Rannard, N. J. Davis, *Org. Lett.* **1999**, *1*, 933−936.

[14] [14a] J. Armbruster, S. Grabowski, T. Ruch, H. Prinzbach, *Angew. Chem. Int. Ed.* **1998**, *37*, 2242−2245. − [14b] J. P. Freeman, L. Laurian, J. Szmuszkovicz, *Tetrahedron Lett.* **1999**, *40*, 4493−4496. − [14c] S. G. Davies, A. A. Morlock, *Tetrahedron Lett.* **1991**, *32*, 4791−4794. − [14d] H. Ulrich, B. Tucker, R. Richter, *J. Org. Chem.* **1978**, *43*, 1544−1547. In our hands no reaction occurred between *N,N′*-bis(1-phenylethyl)-1,2-diamines and CDI in CH_2Cl_2 at 25 °C.

[15] [15a] J. B. Hyne, *J. Am. Chem. Soc.* **1959**, *81*, 6058−6061. − [15b] G. Fodor, J. Stefanovsky, B. Kurtev, *Monatsh. Chem.* **1967**, *98*, 1026−1042. − [15c] S. L. Spassov, J. N. Stefanovsky, B. J. Kurtev, G. Fodor, *Chem. Ber.* **1972**, *105*, 2462−2466. − [15d] G. Caccia, S. Gladiali, R. Vitali, R. Gardi, *J. Org. Chem.* **1973**, *38*, 2264−2265. − [15e] S. Kano, T. Yokomatsu, H. Iwasawa, S. Shibuya, *Tetrahedron Lett.* **1987**, *28*, 6331−6334. − [15f] M. Moreno-Manas, I. Pedros, *J. Heterocyclic Chem.* **1993**, *30*, 1235−1239. − [15g] C. Agami, F. Couty, L. Hamon, O. Venier, *Tetrahedron Lett.* **1993**, *34*, 4509−4512.

[16] [16a] W. Wiegrebe, E.-G. Herrmann, U. P. Schlunegger, H. Budzikiewicz, *Helv. Chim. Acta* **1974**, *57*, 301−314. − [16b] Y. Aoyagi, T. Manabe, A. Ohta, T. Kurihara, G.-L. Pang, T. Yuhara, *Tetrahedron* **1996**, *52*, 869−876. − [16c] Y. Imada, Y. Mitsue, K. Ike, K.-I. Washizuka, S.-I. Murahashi, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2079−2090. − [16d] B. A. Aitken, K. Ali, S. T. E. Mosher, *Tetrahedron Lett.* **1997**, *38*, 4179−4182. − [16e] B. Gabriele, G. Salerno, D. Brindisi, M. Costa, G. P. Chiusoli, *Org. Lett.* **2000**, *5*, 625−627.

[17] Analogous derivatives of alcohols (imidazole carboxylic esters) have seldom been prepared (see ref.[13d]); moreover, 1-imidazolecarbonyl glycosides were obtained as intermediates in the preparation of glycosides by reaction of anomeric hydroxyl groups with CDI: M. J. Ford, S. V. Ley, *Synlett* **1990**, 255−256.

[18] [18a] M. J. Cravey, H. Kohn, *J. Am. Chem. Soc.* **1980**, *102*, 3928−3939.

[19] S. K. Sharma, M. J. Miller, S. M. Payne, *J. Med. Chem.* **1989**, *32*, 357−367.

[20] See, for example: [20a] M. E. Dien, D. Swern, *Chem. Rev.* **1967**, *67*, 197−246. − [20b] J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 77−82. − [20c] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835−875. − [20d] A.-A. G. Shaikh, S. Sivaram, *Chem. Rev.* **1996**, *96*, 951−976. − [20e] T. Hintermann, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 2093−2126. − [20f] M. Feroci, A. Inesi, V. Mucciante, L. Rossi, *Tetrahedron Lett.* **1999**, *40*, 6059−6060.

[21] S. K. Davidsen, M. Y. Chu-Moyer, *J. Org. Chem.* **1989**, *54*, 5558−5567.

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