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Optically Pure *N*-Hydroxy-*O*-triisopropylsilyl-α-L-amino Acid Methyl Esters from $AlCl_3$-Assisted Ring Opening of Chiral Oxaziridines by Nitrogen Containing Nucleophiles

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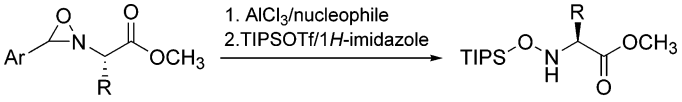

Ar = 4-methoxy-phenyl; R = H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, CH_2Ph

This article reports a straightforward and unprecedented process of $AlCl_3$-assisted oxaziridine ring opening by nitrogen containing nucleophiles, in a totally anhydrous milieu. Under these conditions, nucleophiles exclusively attack the carbon atom of the three-membered heterocycles, obtained from methyl esters of natural α-amino acids, generating *N*-hydroxy-α-L-amino acid methyl esters. No nitrones, amides, or other side products, either from unwanted rearrangements or due to the attack of the nucleophile on the *N* atom of the oxaziridine systems, are formed. The hydroxylamine compounds are recovered in excellent yields, after their site-specific conversion into the corresponding *O*-triisopropylsilyl derivatives, by exposure to triisopropylsilyl triflate in the presence of 1*H*-imidazole. Derivatization, performed immediately after the recovery of the *N*-hydroxylated precursors, allows the chiral integrity of the asymmetric α-carbon atoms in the amino acid methyl esters to be retained. It also protects the obtained compounds from frame degradation by disproportionation. *N*-Hydroxy-*O*-triisopropylsilyl-α-L-amino acid methyl esters are important intermediates in the study of natural α-L-amino acid metabolic pathways and are ideal candidates as starting materials in the synthesis of biologically, pharmacologically, and nutritionally important *N*-hydroxy peptides.

Introduction

Oxaziridines belong to one of the most appropriate families of molecules potentially offering easy synthetic routes to a broad range of chiral nitrogenated compounds.[1] Enantiomerically pure oxaziridines displaying natural α-L-amino acid frames can play a very central role as candidates in preparing *N*-hydroxy-α-L-amino acid derivatives: these compounds are relatively uncommon in nature, but possess attractive biological properties and occur as residues in several simple and more complex natural compounds.[2] They are often present as constituents in tri- and tetrapeptide segments which are useful scaffolds for making peptide sequences able to act as chiral ligands or chelators of iron(III). Peptide segments containing *N*-hydroxy-α-L-amino acids are also useful molecular devices, for example, in regulating the protein ubiquitin−proteasome pathway in Parkinson's desease.[3] In addition, peptides related to *N*-hydroxy-α-L-amino acid derivatives are of biological importance, because they show good activities as low molecular weight siderophores.[4] They can also mimic desferrioxamines,[5] acting as carrier systems which are vital to the microorganism's acquisition of iron from food and the environment. Finally, *N*-hydroxy-α-L-amino acid derivatives are important molecular signals that indicate pathologies related to some human and animal tumors.[6]

(1) (a) Schmitz, E. *Adv. Heterocycl. Chem.* **1963**, *2*, 83. (b) Dupin, J. F. *Bull. Soc. Chim. Fr.* **1967**, 3085. (c) Spence, G. G.; Taylor, E. C.; Buchardt, O. *Chem. Rev.* **1970**, *70*, 231. (d) Bellamy, F.; Streith, J. *Heterocycles* **1976**, *4*, 1391. (e) Schmitz, E. *Adv. Heterocycl. Chem.* **1979**, *24*, 63. (f) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

(2) Ottenheim, H. C. J.; Herscheid, J. D. M. *Chem. Rev.* **1986**, *86*, 697.

(3) Zhang, X.; Xie, W.; Qu, S.; Pan, T.; Wang, X.; Le, W. *Biochem. Biophys. Res. Commun.* **2005**, *333*, 544.

(4) Drechsel, H.; Jung, G. *J. Pept. Sci.* **1998**, *4*, 147.

(5) (a) Neilands, J. B. *Annu. Rev. Microbiol.* **1981**, *36*, 285. (b) Crosa, J. H. *Annu. Rev. Microbiol.* **1984**, *38*, 69. (c) Hara, Y.; Akiyama, M. *Inorg. Chem.* **1996**, *35*, 5173. (d) Roosenberg, J. M.; Lin, Y. M.; Lu, Y.; Miller, M. J. *Curr. Med. Chem.* **2000**, *7*, 159. (e) Surman, M. D.; Miller, M. J. *Org. Lett.* **2001**, *3*, 519.

(6) Neunhoeffer, O. *Z. Naturforsch., B: Chem. Sci.* **1970**, *25*, 299.

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A large number of syntheses of *N*-hydroxy-α-L-amino acid derivatives have been reported, but most have shown that the desired compounds can be realized only through nonstereoselective methods, and the final compounds are isolated in overall yields that are invariably low.[7] Disproportionation and the formation of nitrones and amides as side products are two crucial factors hampering the satisfactory synthesis of *N*-hydroxylated α-L-amino acid analogues.[8]

Ring opening of oxaziridines obtained from methyl esters of natural α-L-amino acids can offer a straightforward solution to the problems above. A series of biologically active *N*-hydroxy-α-L-amino acid derivatives has been prepared by transforming α-L-amino acids into oxaziridines and subsequent acid-catalyzed hydrolysis. In aqueous and anhydrous organic acids, oxaziridines were shown to undergo ring opening and cleavage to form carbonyl compounds and *N*-substituted hydroxylamines.[9] Hydrolitic methods previously employed to obtain pure *N*-hydroxy analogues of common α-L-amino acids, because of the presence of water, also produce nitrone side products accompanied by disproportionated products, thus seriously limiting overall yields.[10] Upon exposure to aqueous acidic media, oxaziridines displaying a natural α-L-amino acid methyl ester framework undergo structural rearrangement to the corresponding nitrones. Low temperatures reduce but do not eliminate this rearrangement.[11] Any increase in reaction temperature results in the formation of amides, and at higher *T* values and with prolonged reaction times, a notable lowering of the *N*-hydroxylated derivative yields has been observed, due to the activation of thermal rearrangement pathways. Formation of side products must be avoided if the aim of the oxaziridine ring opening is to obtain pure *N*-hydroxy-L-amino acid derivatives in high yields. Nonhydrolytic methods are also available in the literature[12] for the synthesis of *N*-hydroxy-α-L-amino acid derivatives, but all suffer from drawbacks. In many cases, in fact, the loss of the chiral integrity of the α-carbon atom in the *N*-hydroxy-α-L-amino acid derivatives cannot be controlled.

This work focuses on a novel, clean, and very efficient ring opening of chiral oxaziridines obtained from α-L-amino acid methyl esters. The method uses $AlCl_3$, in a totally anhydrous environment, to assist the ring opening of the heterocycle by nitrogen containing nucleophiles, provoking the desired C−O bond cleavage and directing the nucleophilic attack specifically to the carbon atom of the three-membered structure. The reaction proceeds with no production of unwanted nitrone, aldehyde, ketone, amide, or hydrazine side products. Site-specific derivatization, carried out after ring opening, is proposed to prepare the title compounds in excellent yields. This method opens a new pathway in the synthesis of optically pure *N*-hydroxy-α-L-amino acid derivatives, which are useful precursors in the preparation of *N*-hydroxy peptides of biological interest.

Results and Discussion

We initially prepared the optically pure chiral imines **1a** and **1b** (Scheme 1) in nearly quantitative yields from a $TiCl_4$-mediated condensation between 4-methoxybenzaldehyde and methyl esters of α-L-natural amino acids.[13] Imines were then subjected to treatment with anhydrous *m*-chloroperoxybenzoic acid (*m*-CPBA) in dry ethanol-free methylene chloride at −40 °C, −15 °C, and room temperature (rt). Conversion of the starting imines was monitored by GC−MS and TLC. Reactions were complete in 12−23 h, depending on the temperature chosen for the experiment. The oxidation was studied using imines **1a** and **1b** (Scheme 1) as models. The reaction showed good stereoselectivity: **1a** and **1b** were each converted into a mixture of four stable nonracemic oxaziridines, **2a**−**5a** and **2b**−**5b**, respectively.

The diastereomers were easily separated by flash column chromatography (FCC) techniques and fully characterized by ^{1}H NMR. Assignment was unequivocally confirmed by comparison with data already reported in the literature[14] for a series of diastereomeric oxaziridines bearing a chiral amine residue on the *N*-atom of the ring. Absolute configuration assignments were also supported by the already reported[14c,e,g] finding that the absolute configuration of the nitrogen atom in the three-membered heterocycle is the opposite of the absolute configuration

(7) (a) Snow, G. A. *J. Chem. Soc.* **1954**, 2588. (b) Emery, T. F. *Biochemistry* **1963**, *2*, 1041. (c) Zinner, G.; Moderhack, D.; Kliegel, W. *Chem. Ber.* **1969**, *101*, 2536. (d) Kneifel, H.; Bayer, E. *Angew. Chem.* **1973**, *85*, 542. (e) Buechi, G.; Luk, K. C.; Kobbe, B.; Townsend, J. M. *J. Org. Chem.* **1977**, *42*, 244. (f) Møller, B. L. *J. Labelled Compd. Radiopharm.* **1978**, *14*, 663. (g) Herscheid, J. D. M.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1978**, 5143. (h) Cooper, A. J. L.; Griffith, O. W. *J. Biol. Chem.* **1979**, *254*, 2748. (i) Lee, V. J.; Woodward, R. B. *J. Org. Chem.* **1979**, *44*, 2487. (j) Tijhuis, M. W.; Herscheid, J. D. M.; Ottenheijm, H. C. J. *Synthesis* **1980**, 890. (k) Herscheid, J. D. M.; Colstee, J. H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1981**, *46*, 3346. (l) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.

(8) (a) Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5739. (b) Horner, L.; Jürgens, E. *Chem. Ber.* **1957**, *90*, 2184.

(9) (a) Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 657. (b) Duhamel, P.; Bénard, D.; Plaquevent, J.-C. *Tetrahedron Lett.* **1985**, *26*, 6065. (c) Duhamel, P.; Goument, B.; Plaquevent, J.-C. *Tetrahedron Lett.* **1987**, *28*, 2595. (d) Grundke, G.; Keese, W.; Rimpler, M. *Synthesis* **1987**, 1115. (e) Plaquevent, J. C.; Bénard, D.; Goument, B. *New J. Chem.* **1991**, *15*, 579. (f) Giard, T.; Bénard, D.; Plaquevent, J.-C. *Synthesis* **1998**, 297.

(10) (a) O'Connor, C. J.; Fendler, E. J.; Fendler, J. H. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1744. (b) Połoński, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, *28*, 2453. (c) Połoński, T.; Chimiak, A. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1979**, *27*, 459. (d) Butler, A. R.; Challis, B. C.; Lobo, A. M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1035. (e) Butler, A. R.; White, J. G.; Challis, B. C.; Lobo, A. M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1039.

(11) (a) Sternbach, L. H.; Keechlin, B. A.; Reeder, E. *J. Org. Chem.* **1962**, *27*, 4671. (b) Bigot, B.; Roux, D.; Sevin, A.; Devaquet, A. *J. Am. Chem. Soc.* **1979**, *101*, 2560. (c) Sauer, J. *Tetrahedron* **1979**, *35*, 2109. (d) Boyd, D. R.; Coulter, P. B.; Hamilton, W. J.; Jennings, W. B.; Wilson, V. E. *Tetrahedron Lett.* **1981**, *22*, 2287. (e) Davis, F. A.; Jenkins, R. H., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 4.

(12) (a) Shin, C.; Masaki, M.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3219. (b) Novikov, V. T.; Avrutskaya, I. A.; Fioshin, M. Y.; Belikov, V. M.; Babievskii, K. K. *Elektrokhimiya* **1976**, *12*, 1061. (c) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1981. (d) Detomaso, A.; Curci, R. *Tetrahedron Lett.* **2001**, *42*, 755.

(13) Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Romeo, C.; Siciliano, C.; Sindona, G. *Synth. Commun.* **2003**, *33*, 4331.

(14) (a) Bełżecki, C.; Mostowicz, D. *J. Org. Chem.* **1975**, *40*, 3878. (b) Bogucka-Ledochowska, M.; Konitz, A.; Hempel, A.; Dauter, Z.; Bełżecki, C.; Mostowicz, D. *Tetrahedron Lett.* **1976**, 1025. (c) Bucciarelli, M.; Moretti, I.; Torre, G. *J. Chem. Soc., Chem. Commun.* **1976**, 60. (d) Mostowicz, D.; Bełżecki, C. *J. Org. Chem.* **1977**, *42*, 3917. (e) Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1339. (f) Bełżecki, C.; Mostowicz, D. *J. Chem. Soc., Chem. Commun.* **1977**, 51. (g) Forni, A.; Garati, G.; Moretti, I.; Torre, G.; Andreetti, G. D.; Bocelli, G.; Sgorabotto, P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 401. (h) Bogucka-Ledochowska, M.; Konetz, A.; Hempel, A.; Dantor, Z.; Borowski, E. *Z. Kristallogr.* **1979**, *149*, 49.

SCHEME 1. Diastereoselective Oxidation of Imines 1a,b: Preparation of Oxaziridines 2a−5a and 2b−5b

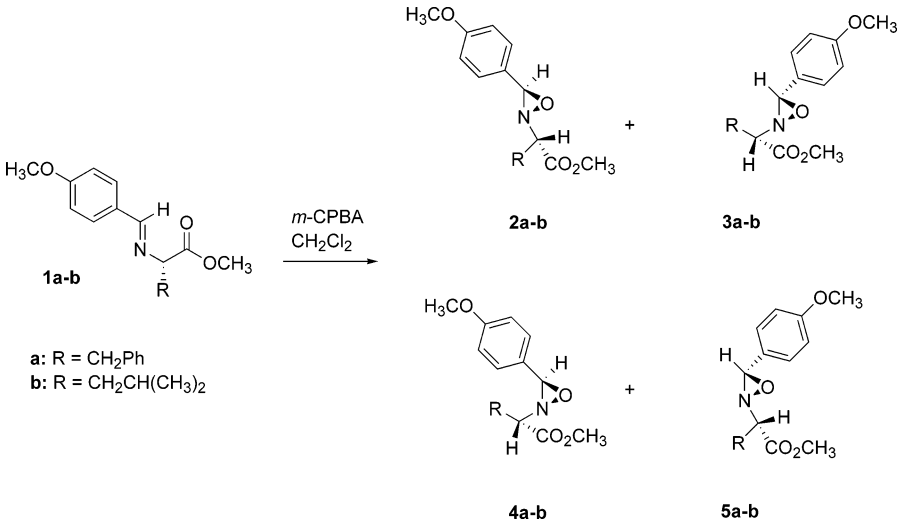


TABLE 1. Yields of the Oxaziridines 2a−5a and 2b−5b

	T (°C)	t (h)	total yield[a] (%) (**2**+**3**+**4**+**5**)	product distribution[b] (**2**:**3**:**4**:**5**)	trans:cis ratio[b] (**2**+**3**):(**4**+**5**)	recovered product ratio[c] (2:3:4:5)
a: R = CH_2Ph	−40	23	78	69:19:7:5	88:12	68:18:7:3
	−15	19	75	67:19:8:6	86:14	68:18:6:4
	rt	12	71	68:17:9:6	85:15	67:14:8:5
b: R = $CH_2CH(CH_3)_2$	−40	23	70	71:19:7:3	90:10	70:18:6:3
	−15	19	68	61:22:10:7	83:17	59:22:10:5
	rt	12	63	60:20:12:8	80:20	58:19:12:7

[a] Expressed as oxaziridine products recovered by FCC. [b] Determined by ^1H NMR. [c] Obtained for each diastereomer after recovery by FCC.

of the chiral substituent connected to the nitrogen atom of the C=N bond in the parent imines. ^1H NMR analysis of the respective crude materials also proved useful in determining the effective yields of each stereomeric oxaziridine formed by oxidation of **1a** and **1b**. The calculation was made on the basis of the intensities of the well distinguished resonances related to the methyl group of the amino acid ester moiety and agreed closely to the results obtained via FCC (Table 1).

The presence of a second chiral atom, the *C*3 term of the heterocyclic ring, proved to be a valuable feature that facilitated the separation and quantification of all diastereomers from their respective mixture. The *trans*-oxaziridines were always the predominant oxidation products. Treatment of imines **1a** and **1b** with *m*-CPBA at −15 °C proceeded diastereoselectively, giving *trans*/*cis* ratios of 86:14 and 83:17 for oxaziridines **2a**−**5a** and **2b**−**5b**, respectively. At temperatures from −40 °C to rt, the diastereomeric distributions were quite constant for oxaziridines containing the L-phenylalanine residue, while a slight change was observed for oxaxiridines derived from L-leucine when the process was carried out at very low temperature. Values, summarized in Table 1, are between 88:12 and 85:15 for oxaziridines **2a**−**5a** at all temperatures employed. For oxaziridines **2b**−**5b**, values between 80:20 and 90:10 were found, the higher ratio being observed when oxidation takes place at −40 °C. The stereoselectivity was in accordance with the data reported in the literature for other hindered chiral systems.[15]

The instrumental analysis of the unseparated product mixtures recovered showed that no nitrones or amides were formed at any of the reaction temperatures employed, unlike previously reported methods.[16] Selection of the appropriate thermal conditions can improve the total yields of oxaziridine products. Yields were lower at room temperature than at −40 °C, varying from 71 to 78%, for oxidation of imine **1a**, and from 63 to 70% in the case of imine **1b**. Similar results were obtained for the oxidation of the imine containing the leucine motif in its structural framework. In addition, by using anhydrous *m*-CPBA, reactions are clean and there is no formation of other undesired species such as acids or bisperoxides.

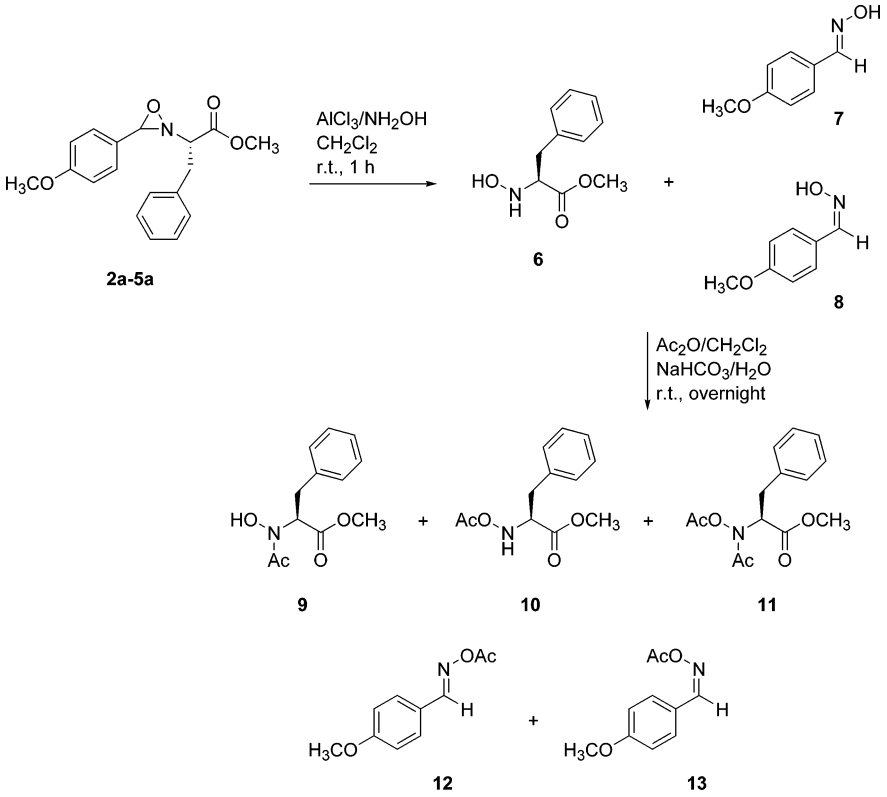
When oxaziridines are obtained from natural α-L-amino acids, of particular interest is the possibility to conduct the hydrolytic ring opening cleanly to produce the corresponding *N*-hydroxylated derivatives. The previously reported hydrolytic methods exploit the oxaziridine ring opening by using concentrated acidic media in an aqueous environment.[9,10] We found these systems to be impractical due to the large amount of nitrone and amide derivatives produced. Moreover, these procedures did not facilitate the recovery of the final compounds, whose total yields were generally low and limited by disproportionation of the *N*-hydroxylated α-L-amino acid derivatives.

To define a straightforward and efficient synthesis of the desired *N*-hydroxy-α-L-amino acid derivatives, we

(15) Boyd, D. R.; Neill, D. C.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1813.

(16) (a) Krimm, H. *Chem. Ber.* **1958**, *91*, 1057. (b) Splitter, J. S.; Calvin, M. *J. Org. Chem.* **1965**, *30*, 3427. (c) Splitter, J. S.; Su, T. M.; Ono, H.; Calvin, M. *J. Am. Chem. Soc.* **1971**, *93*, 4075. (d) Toda, F.; Tanaka, K. *Chem. Lett.* **1987**, 2283. (e) Aubé, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, 2283.

SCHEME 2. $AlCl_3$-Assisted Ring Opening of Oxaziridines 2a−5a with Hydroxylamine



subjected all the obtained oxaziridines to a ring opening performed by nitrogenated nucleophiles, in the presence of $AlCl_3$ and under totally anhydrous conditions. To our knowledge, only a few applications of Lewis acids in oxaziridine reactivity studies have been reported.[17] Examples include the use of BF_3 to produce the only known stable boronate derivatives of nitrones in very high yields, but no formation of *N*-hydroxylamine compounds by BF_3-assisted C−O bond activation in oxaziridines has been reported.[17a,b] Moreover, no data are available in the literature concerning the role played by $AlCl_3$ in assisting oxaziridine ring opening in reactions conducted by nitrogenated nucleophiles.

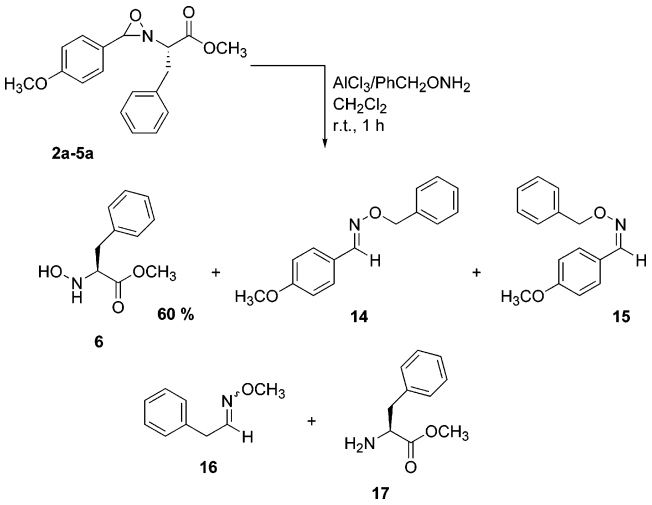
The ring opening was initially attempted by exposing a mixture of **2a**−**5a** to 2 equiv of $AlCl_3$ and 1 equiv of hydroxylamine (Scheme 2). The 2 equiv of $AlCl_3$ are required because of the two potential O atom coordination sites present in the oxaziridine molecule, namely the one in the carbonyl moiety and of course the target O atom in the three-membered ring. The nucleophile was prepared by treating the commercially available hydrochloride with a stoichiometric amount of sodium methoxide in dry methanol at 0 °C for 10 min and then evaporating the solvent. Reaction was performed in dry ethanol-free methylene chloride for 1 h at room temperature. After this time, reaction was complete and gave a surprisingly complex mixture of products. To characterize the desired *N*-hydroxylated compound **6**, formed together with an equivalent amount of oximes **7** and **8**, the crude mixture recovered from the reaction was treated overnight with an excess of acetic anhydride at room temperature (Scheme 2). GC−MS analysis of samples taken from the reaction mixture revealed acetylation to be unsatisfactory, because it led to the formation of complex mixtures of the *N*- and *O*-monoacetylated derivatives **9** and **10**. The *N*,*O*-bisacetyl-α-L-amino acid methyl ester **11** and the *O*-acetylated oximes **12** and **13** were also produced during the derivatization process. This made separation of the mixture difficult. Despite these partially negative results, GC−MS and ^{1}H NMR controls of the crude material recovered from the acetylation demonstrated that the aromatic moiety on the L-phenylalanine side chain remained totally unaffected by the reaction with $AlCl_3$. This fact illustrates the total compatibility between aromatic substrates and the experimental conditions selected for the Lewis acid-assisted oxaziridine ring opening. The results also prompted the changing of the nucleophile used in the process, specifically those not containing free hydroxyl functions.

We thus selected *O*-benzylhydroxylamine as the nucleophile. The free base was obtained by reaction of the commercial hydrochloride salt with 1 equiv of sodium methoxide dissolved in dry methanol, exactly as previously discussed for hydroxylamine. One equivalent of the freshly prepared nucleophile, a sticky white solid, was added to the dry ethanol-free methylene chloride solution containing 1 equiv of the substrate and 2 equiv of $AlCl_3$ (Scheme 3).

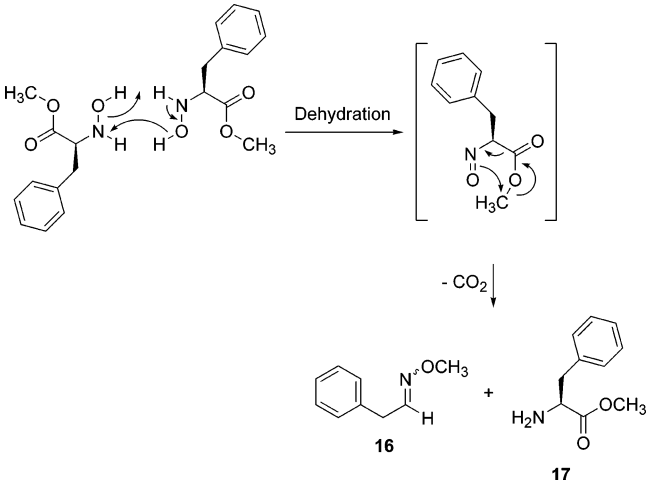
After 1 h at room temperature, the crude reaction mixture was chromatographed to isolate the *N*-hydroxy-α-L-amino acid methyl ester **6** in a 60% yield, calculated on the basis of the amount of oxaziridine precursor, and of the two *anti*- and *syn*-*O*-benzylaldoximates **14** and **15**, obtained in a 95% yield with respect to the starting

(17) (a) Emmons, W. D. *Chem. Heterocycl. Compd.* **1964**, *19*, 624. (b) Milliet, P.; Lusinchi, X. *Tetrahedron Lett.* **1971**, 3763. (c) Schoumacker, S.; Hamelin, O.; Téti, S.; Pécaut, J.; Fontecave, M. *J. Org. Chem.* **2005**, *70*, 301.

SCHEME 3. $AlCl_3$-Assisted Ring Opening of Oxaziridines 2a−5a with *O*-Benzylhydroxylamine



SCHEME 4. Mechanism of Disproportionation of *N*-Hydroxy-α-L-amino Acid Methyl Ester 6



material, and as an equimolar mixture of both the geometric isomers. Chromatography also furnished the *O*-methyl aldoximate **16** and L-phenylalanine methyl ester **17** in 18 and 15% yields, respectively, estimated in this case also on the basis of the starting substrate amount. Recovery of both the *O*-benzylaldoximates **14** and **15** allowed us to calculate the conversion of the initial substrate. From the chromatography data it was seen that oxaziridines subjected to the ring opening, under these conditions, were totally consumed. Nevertheless, in all the tests performed, yield of the recovered product **6** was rather modest and never exceeded 60%. Comparison of GC−MS and TLC analyses performed on the crude reaction mixture during the treatment and after the reaction workup step did not show the presence of **16** and **17** as side products. Their formation may be supposed to happen, probably via the initial dehydration of **6**, on the chromatography column during product purification. Compounds **16** and **17** could form from **6** via a nitroso intermediate (Scheme 4), similarly to the mechanism already reported[18] for the disproportionation of *N*-hydroxy-α-L-amino acids.

The disproportionation occurs even using neutral Al_2O_3. The amounts of **16** and **17** recovered are practically the same as those obtained when using a SiO_2 stationary phase.

It is worth noting that the *N*-hydroxy-α-L-amino acid methyl ester **6** showed identical optical activity to the same product obtained by hydrolytic methods.[9,10] Since the stereochemistry of the α-L-amino acid residue is maintained during the oxidation of the imine starting materials, we suppose, on the basis of the results mentioned above for compound **6**, that the $AlCl_3$-assisted ring opening of oxaziridines does not alter the chirality of the α-carbon atom.

The results obtained from the treatment of oxaziridines bearing the L-phenylalanine methyl ester frame surprisingly showed that the attack of the nitrogen nucleophile takes place exclusively at the carbon atom of the heterocyclic ring. No hydrazine-like compounds from possible interaction between the nitrogen of the nucleophile and the *N* term of the three-membered ring are generated during the process. This evidence is a novel acquisition in the field of oxaziridine chemistry, since the literature[19] reports that nitrogenated nucleophiles preferentially attack the N atom rather than the *C*3 term of the heterocycle, even in the cases of substrates containing at least one aromatic substituent on the same carbon atom. Moreover, *N*-hydroxy-α-L-amino acid methyl esters can be synthesized without altering the chirality of the parent α-L-amino acid methyl esters employed in the preparation of the starting oxaziridines.

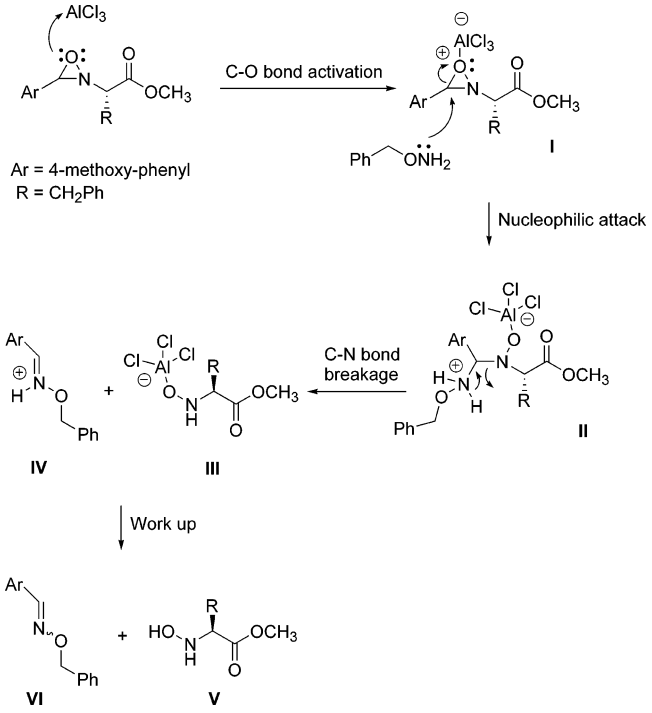
To study the temperature dependence of the ring-opening process, a mixture of the model oxaziridines **2a**−**5a** was refluxed with 2 equiv of $AlCl_3$ and 1 equiv of *O*-benzylhydroxylamine in dry ethanol-free methylene chloride. The reaction rate increased and the substrate was totally converted in 25 min, but no traces of products coming from thermal transposition or decomposition of the starting material and/or the formed products were detected, as demonstrated by GC−MS analysis. The yields of the final products were not affected by raising the reaction temperature from the rt value to that of the refluxing solvent.

The study of the process was concluded by demonstrating that the nucleophile plays a fundamental role in the ring opening of oxaziridines to produce *N*-hydroxy derivatives of natural α-L-amino acids. This was shown by refluxing **2a**−**5a** dissolved in dry ethanol-free methylene chloride with $AlCl_3$. After 12 h, the mixture of oxaziridines subjected to conversion was recovered totally unmodified as confirmed by GC−MS runs and ^{1}H NMR analysis. On the other hand, the necessity for the Lewis acid with regard to the ring-opening development was definitively illustrated by carrying out an experiment in which a mixture of **2a**−**5a** was treated with *O*-benzylhydroxylamine in the required molar ratio, in refluxing dry ethanol-free methylene chloride for 12 h. GC−MS and ^{1}H NMR analysis of samples taken during the reaction, as well as at the end, showed no change in the substrate

(18) (a) Ahmad, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2583. (b) Møller, B. L.; McFarlane, I. J.; Conn, E. E. *Acta Chem. Scand. B* **1977**, *31*, 343.

(19) (a) Schirmann, J.-P.; Weiss, F. *Tetrahedron Lett.* **1972**, 635. (b) Schmitz, E.; Ohme, R.; Schramm, S.; Striegler, H.; Heyne, H. U.; Rusche, J. *J. Prakt. Chem.* **1977**, *319*, 195. (c) Hata, Y.; Watanabe, M. *J. Am. Chem. Soc.* **1979**, *101*, 6671. (d) Hata, Y.; Watanabe, M. *J. Org. Chem.* **1981**, *46*, 610. (e) Rastetter, W. H.; Wagner, W. R.; Findeis, M. A. *J. Org. Chem.* **1982**, *47*, 419.

SCHEME 5. Mechanism of the $AlCl_3$-Assisted Oxaziridine Ring Opening with *O*-Benzylhydroxylamine



and no formation of either the desired compound or other side products. These data confirm the role that the nucleophile plays in the process and also provide evidence for the assistance of the Lewis acid to the reaction. The use of completely anhydrous conditions is strategic in this ring-opening step, since formation of unwanted side products arising from the action of water as a nucleophile can easily be avoided.

The kinetics of the ring opening is noticeably quickened by the intervention of the Lewis acid, which coordinates the apical O atom of the three-membered heterocycle activating the C−O linkage and regiospecifically addressing the nucleophilic attack onto the *C*3 atom, the most electrophilic term of structure **I** (Scheme 5). The attack of *O*-benzylhydroxylamine produces the tetrahedral zwitterionic intermediate **II**, which, in turn, can evolve to compounds **III** and **IV** through C−N bond breakage. The final compounds **V** and **VI** are then generated after the reaction workup. Our hypothesis of the mechanism is supported by the evidence that oxaziridines do not isomerize when they are treated under the conditions adopted for the experiment, but solely when $AlCl_3$ is used.

Because of the drawbacks discussed above, we coupled the $AlCl_3$-assisted ring opening to a derivatization of the *N*-hydroxylated α-L-amino acid analogues. This last step must be performed immediately after the total consumption of the starting substrates and a minimal workup to remove the residual Lewis acid, without purification of the crude reaction mixture. Triisopropylsilyl triflate (TIPSOTf) was chosen as the derivatizing reagent.

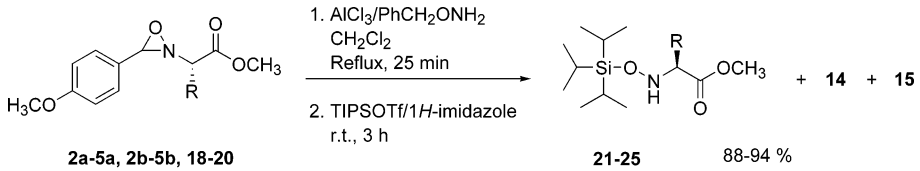
The capabilities of this methodology, in which the $AlCl_3$-assisted oxaziridine ring opening is the key step, were exploited by treating a mixture of **2a**−**5a** with 2 equiv of the Lewis acid and 1 equiv of *O*-benzylhydroxylamine, in refluxing dry ethanol-free methylene chloride. After 25 min, the reaction mixture was cooled to room temperature, workup was carried out, and the crude material recovered was immediately subjected to derivatization with a stoichiometric amount of the reagent system TIPSOTf/1*H*-imidazole in dry ethanol-free methylene chloride at room temperature (Scheme 6). Treatment was complete in 3 h, as demonstrated by GC−MS and TLC analysis of the crude reaction mixture. Chromatography on silica gel of the crude product recovered from the final workup allowed the separation of the *anti*- and *syn*-*O*-benzylaldoximates **14** and **15**, in an amount equivalent to that obtained for the desired *N*-hydroxy-*O*-triisopropylsilyl-α-L-amino acid methyl ester **21**, which was isolated in a 94% overall yield, calculated on the basis of the oxaziridine substrate. Compounds **14**, **15**, and **21** were the only products. The use of TIPSOTf resulted in the site-specific derivatization at the O atom of the *N*-hydroxylated compound. The silylated product **21** obtained was optically pure and isolated with ease. Since the process of O-masking is performed immediately after workup of the reaction mixture obtained from the Lewis acid-assisted oxaziridine ring opening, the overall yield registered for the silyl derivative at the end of the treatment is directly related to that actually obtainable for the nonsilylated product, as could be determined by ^{1}H NMR analysis of the respective crude material observed before functionalization. Furthermore, *O*-triisopropylsilylation suppresses the tendency toward spontaneous disproportionation of the *N*-hydroxy-α-L-amino acid methyl ester, since the OH group of the hydroxylamine moiety is not available to begin dehydration, the process responsible for the unwanted structural transformation of the α-L-amino acid derivative (Scheme 4).

The stability of the *O*-triisopropylsilylated derivative **21** was checked by repeating the TLC, GC−MS, and ^{1}H NMR analyses on the same sample, both as a solid and in deuteriochloroform solution, stored at room temperature and in the light. Even after long periods, up to three weeks, the sample remained pristine. To test its thermal stability, one analytical sample of **21** was refluxed in dry toluene for up to 12 h. In this case also, neither molecular degradation nor rearrangement into amide products was observed. The optical purity of the chiral *N*-hydroxy-*O*-triisopropylsilyl-α-L-amino acid methyl ester obtained was established by ^{1}H NMR in titration experiments performed with the shift reagent Eu(hfc)$_3$: no residual resonances attributable to the D optical antipode of **21** were individuated, and only the spin system signals of the desired molecule were visible in the 1D spectrum.

To fully exploit the capabilities of the studied methodology, the application of the same synthetic approach was extended to the preparation of a series of *N*-hydroxy-*O*-triisopropylsilyl-α-L-amino acid methyl esters (Scheme 6). Attention was devoted to the preparation of lipophilic *N*-hydroxy-α-L-amino acid methyl esters, as these are known to occur as constituents of the iron(III)-chelating crowns in *N*-hydroxy peptides of biological importance.[20]

Oxidation with anhydrous *m*-CPBA of the respective imine precursors[13] gave mixtures of the corresponding oxaziridines **2b**−**5b** and **18**−**20** in 70−77% yields. The heterocycles were refluxed in dry ethanol-free methylene chloride in the presence of 2 equiv of $AlCl_3$ and 1 equiv of *O*-benzylhydroxylamine.

SCHEME 6. Synthesis of *N*-Hydroxy-*O*-triisopropylsilyl-α-L-amino Acid Methyl Esters



2a-5a, 2b-5b, 18-20 **21-25** 88-94 %

2a-5a: R = CH_2Ph
2b-5b: R = $CH_2CH(CH_3)_2$
18: R = $CH(CH_3)_2$
19: R = CH_3
20: R = H

21: R = CH_2Ph
22: R = $CH_2CH(CH_3)_2$
23: R = $CH(CH_3)_2$
24: R = CH_3
25: R = H

TABLE 2. Yields of the *N*-Hydroxy-*O*-triisopropylsilyl-α-L-amino Acid Methyl Esters

compound	R	overall yields (%)[a]
21	CH_2Ph	94
22	$CH_2CH(CH_3)_2$	94
23	$CH(CH_3)_2$	92
24	CH_3	90
25	H	88

[a] Obtained after FCC and calculated on the basis of the parent oxaziridine amounts.

All reactions were complete in 25 min, as checked by TLC and GC−MS analysis of the reaction mixtures. After treatment with TIPSOTf and 1*H*-imidazole in dry ethanol-free methylene chloride at room temperature for 3 h, the crude products were chromatographed to separate the *O*-benzylaldoximates **14** and **15** from the *O*-triisopropylsilyl derivatives **22**−**25**, which were then isolated in excellent overall yields (88−94%), calculated with respect to the amount of oxaziridine precursors (Table 2). ^1H NMR analysis of the pure compounds, accomplished using the shift reagent Eu(hfc)$_3$, showed the obtained chiral α-L-amino acid derivatives **22**−**25** to be enantiomerically pure.

Conclusions

Methyl esters of natural α-L-amino acids can be *N*-hydroxylated using a strategy in which the respective imine derivatives are oxidized stereoselectively to the corresponding oxaziridines. Ring opening of these heterocycles, assisted by the Lewis acid $AlCl_3$ and carried out by free *O*-benzylhydroxylamine, is the key step of the procedure. In the absence of water, and different from all previously reported methods, reactions are rapid and clean, giving rise only to *N*-hydroxy-α-L-amino acid methyl esters which are generated through the regiospecific attack of the nitrogenated nucleophile at the *C*3 atom of the parent oxaziridines. The site-specific *O*-triisopropylsilylation of the *N*-hydroxy α-L-amino acid analogues obtained is the conclusive step of the proposed synthetic route. After derivatization, the desired optically pure compounds are isolated in excellent overall yields. No side products arising from disproportionation of the *N*-hydroxylated α-L-amino acid derivatives or molecular rearrangement of the oxaziridine precursor are generated, and no loss of the chiral integrity of the parent amino acid frames is observed.

Experimental Section

Optical rotations of all new chiral compounds (oxaziridines and *N*-hydroxy-*O*-triisopropylsilyl-α-L-amino acid methyl esters) were measured in a 1-dm (2-mL volume) tube. All measurements were carried out on chloroform solutions of each compound (*c* 2), and $[\alpha]_D$ values were determined at 20 °C by using a digital polarimeter.

Synthesis of Oxaziridines 2a−5a and 2b−5b. General Procedure. The appropriate imine (5.75 mmol) was dissolved in dry ethanol-free methylene chloride (15 mL) and maintained at 0 °C under magnetic stirring. A solution of anhydrous *m*-chloroperoxybenzoic acid (1.1 g, 6.33 mmol) in dry ethanol-free methylene chloride (15 mL) was added dropwise in 20 min. After being stirred for 23 h at −40 °C, TLC showed the reaction to be complete (Et_2O/*n*-hexane 60:40, v/v), and the *m*-chlorobenzoic acid precipitated was rapidly removed by filtration under vacuum. The mother liquor was treated with a 1 N NaOH aqueous solution (20 mL) and brine (10 mL) and then extracted with ethanol-free chloroform (5 × 10 mL). Organic layers were separated, washed once with brine (10 mL), and dried on $MgSO_4$. Solvent was then removed under reduced pressure conditions, and the mixture of diastereomeric oxaziridines recovered was subjected to flash column chromatography.

Oxaziridine 2a: Pale yellow oil (1.224 g. 3.91 mmol; 68%). $[\alpha]^{20}_D$ −48.9 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.68. FT-IR (neat) 3031, 2953, 2862, 1745, 1613, 1517, 1252, 1170, 1032 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.67 (d, 2 H, J = 8.0 Hz), 6.70−7.39 (m, 7 H), 4.65 (s, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.05−3.42 (m, 3 H). ^{13}C NMR ($CDCl_3$) δ 172.6, 158.7, 140.2, 129.3, 128.8, 128.0, 127.4, 126.2, 114.2, 80.1, 68.5, 56.1, 52.0, 32.0. MS (EI) *m/z* (relative intensity %) 313 ($M^{+\bullet}$, 2.1), 298 (1.1), 282 (2.1), 254 (1.0), 163 (4.5), 151 (71.2), 135 (100), 120 (12.3), 107 (10.9), 92 (9.8), 77 (12.8), 64 (7.9), 51 (4.2). HRMALDI: calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$, 314.13923; found 314.13919.

Oxaziridine 3a: Pale yellow oil (0.33 g, 1.04 mmol; 18%). $[\alpha]^{20}_D$ −49.2 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.67. FT-IR (neat) 3031, 2865, 1748, 1612, 1517, 1252, 1168, 1033 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.67 (d, 2 H, J = 8.0 Hz), 6.69−7.39 (m, 7 H), 4.64 (s, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.04−3.43 (m, 3 H). ^{13}C NMR ($CDCl_3$) δ 171.9, 158.2, 141.0, 129.1, 128.8, 128.0, 127.1, 126.0, 114.1, 79.2, 68.1, 57.2, 51.8, 31.8. MS (EI) *m/z* (relative intensity %) 313 ($M^{+\bullet}$, 1.0), 298 (1.0), 282 (1.9), 254 (1.0), 163 (4.7), 151 (68.5), 135 (100), 120 (13.3), 107 (11.9), 92 (9.8), 77 (10.8), 64 (7.7), 51 (4.0). HRMALDI: calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$, 314.13923; found 314.13921.

Oxaziridine 4a: Pale yellow oil (0.13 g, 0.40 mmol; 7%). $[\alpha]^{20}_D$ −22.4 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.65. FT-IR (neat) 3030, 2954, 2838, 1754, 1613, 1516, 1251, 1170 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.68 (d, 2 H, J = 8.1 Hz), 6.71−

(20) (a) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816. (b) Shimizu, K.; Nakayama, K.; Akiyama, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2456. (c) Akiyama, M.; Katoh, A.; Iijima, M.; Takagi, T.; Natori, K.; Kojima, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1356. (d) Yakirevitch, P.; Rochel, N.; Albrecht-Gary, A. M.; Libman, J.; Shanzer, A. *Inorg. Chem.* **1993**, *32*, 1779. (e) Bianco, A.; Zabel, C.; Walden, P.; Jung, G. *J. Pept. Sci.* **1998**, *4*, 471. (f) Braslau, R.; Axon, J. R.; Lee, B. *Org. Lett.* **2000**, *2*, 1399. (g) Ye, Y.; Liu, M.; Kao, J. L.-K.; Marshall, G. R. *Biopolymers* **2003**, *71*, 489.

7.38 (m, 7 H), 4.74 (s, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.18−3.47 (m, 3 H). ^{13}C NMR ($CDCl_3$) δ 172.3, 158.2, 142.0, 129.0, 128.7, 128.0, 127.1, 126.0, 114.4, 78.5, 68.3, 57.8, 52.3, 33.0. MS (EI) *m/z* (relative intensity %) 313 ($M^{+\bullet}$, 0.9), 298 (1.2), 282 (2.2), 254 (1.4), 163 (3.9), 151 (70.1), 135 (100), 120 (13.1), 107 (14.9), 92 (9.3), 77 (11.8), 64 (7.9), 51 (4.2). HRMALDI: calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$, 314.13923; found 314.13926.

Oxaziridine 5a: Pale yellow oil (53.2 mg, 0.17 mmol; 3%). $[\alpha]^{20}_D$ −23.5 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.63. FT-IR (neat) 3029, 2957, 2833, 1751, 1618, 1517, 1250, 1168 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.68 (d, 2 H, J = 8.1 Hz), 6.70−7.39 (m, 7 H), 4.72 (s, 1 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 3.19−3.47 (m, 3 H). ^{13}C NMR ($CDCl_3$) δ 172.3, 159.0, 142.0, 128.8, 128.5, 128.0, 127.3, 126.3, 114.8, 80.1, 69.0, 57.9, 52.7, 32.1. MS (EI) *m/z* (relative intensity %) 313 ($M^{+\bullet}$, 1.2), 298 (1.2), 282 (1.9), 254 (1.1), 163 (4.9), 151 (72.0), 135 (100), 120 (11.3), 107 (10.7), 92 (10.1), 77 (12.2), 64 (7.2), 51 (3.9). HRMALDI: calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$, 314.13923; found 314.13920.

Oxaziridine 2b: Pale yellow oil (1.124 g; 4.03 mmol; 70%). $[\alpha]^{20}_D$ −49.2 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.79. FT-IR (neat) 3170, 2958, 2770, 1752, 1621, 1512, 1235, 1170 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2 H, J = 8.1 Hz), 7.04 (d, 2 H, J = 8.1 Hz), 4.51 (s, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.23 (dd, 1 H, J = 9.2 Hz, J = 6.3 Hz), 1.61−1.82 (m, 3 H), 0.87 (d, 6 H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 172.6, 159.3, 130.1, 127.6, 115.0, 79.3, 63.5, 56.0, 51.8, 35.0, 23.1, 22.0. MS (EI) *m/z* (relative intensity %) 279 ($M^{+\bullet}$, 0.1), 223 (14.4), 191 (9.3), 151 (4.5), 135 (100), 107 (8.7), 92 (5.4), 76 (7.2), 64 (13.1), 59 (34.0), 43 (72.3). HRMALDI: calcd for $C_{15}H_{22}NO_4$ $(M + H)^+$, 280.15488; found 280.15484.

Oxaziridine 3b: Pale yellow oil (0.29 g, 1.04 mmol; 18%). $[\alpha]^{20}_D$ −45.3 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.77. FT-IR (neat) 3168, 2949, 2771, 1750, 1622, 1518, 1235, 1171 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2 H, J = 8.0), 7.05 (d, 2 H, J = 8.0), 4.54 (s, 1 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.23 (dd, 1 H, J = 9.2 Hz, J = 6.2 Hz), 1.61−1.83 (m, 3 H), 0.88 (d, 6 H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 171.9, 159.1, 130.0, 127.5, 114.8, 78.1, 64.3, 57.1, 52.8, 34.8, 23.0, 21.8. MS (EI) *m/z* (relative intensity %) 279 ($M^{+\bullet}$, 0.1), 223 (14.4), 191 (9.8), 151 (7.8), 135 (100), 107 (10.7), 92 (7.4), 76 (7.1), 64 (12.8), 59 (34.3), 43 (70.0). HRMALDI: calcd for $C_{15}H_{22}NO_4$ $(M + H)^+$, 280.15488; found 280.1548.

Oxaziridine 4b: Pale yellow oil (97.7 mg, 0.35 mmol; 6%). $[\alpha]^{20}_D$ −23.0 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.76. FT-IR (neat) 3170, 2959, 2770, 1749, 1620, 1510, 1238, 1171 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 2 H, J = 8.1 Hz), 6.98 (d, 2 H, J = 8.1 Hz), 4.62 (s, 1 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.19 (dd, 1 H, J = 9.1 Hz, J = 6.4 Hz), 1.62−1.81 (m, 3 H), 0.87 (d, 6 H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 172.3, 159.6, 129.8, 127.6, 115.1, 80.1, 65.5, 56.7, 52.3, 35.3, 23.2, 22.1. MS (EI) *m/z* (relative intensity %) 279 ($M^{+\bullet}$, 0.4), 223 (13.4), 191 (10.1), 151 (3.5), 135 (100), 107 (8.9), 92 (8.4), 76 (7.2), 64 (10.1), 59 (34.0), 43 (72.3). HRMALDI: calcd for $C_{15}H_{22}NO_4$ $(M + H)^+$, 280.15488; found 280.15490.

Oxaziridine 5b: Pale yellow oil (47.4 mg, 0.17 mmol; 3%). $[\alpha]^{20}_D$ −24.4 (*c* 1.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.75. FT-IR (neat) 3167, 2954, 2772, 1751, 1620, 1518, 1234, 1165 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 2 H, J = 8.0 Hz), 6.97 (d, 2 H, J = 8.0 Hz), 4.60 (s, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.16 (dd, 1 H, J = 9.2 Hz, J = 6.1 Hz), 1.60−1.83 (m, 3 H), 0.88 (d, 6 H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 171.8, 159.0, 129.5, 127.3, 114.6, 80.4, 64.4, 57.0, 51.9, 34.6, 23.6, 21.7. MS (EI) *m/z* (relative intensity %) 279 ($M^{+\bullet}$, 0.4), 223 (15.9), 191 (11.2), 151 (5.5), 135 (100), 107 (8.9), 92 (10.4), 76 (8.2), 64 (11.8), 59 (32.4), 43 (71.3). HRMALDI: calcd for $C_{15}H_{22}NO_4$ $(M + H)^+$, 280.15488; found 280.15485.

Synthesis of *N*-Hydroxy-*O*-triisopropylsilyl-α-L-amino Acid Methyl Esters 21 and 22. General Procedure. To a solution of the appropriate oxaziridine (used as mixture of diastereomers; 2.2 mmol) dissolved in dry ethanol-free methylene chloride (10 mL), $AlCl_3$ (0.59 g, 4.4 mmol) was added. After 5 min at rt, a solution of the free *O*-benzylhydroxylamine (0.6 g; 2.2 mmol) in dry ethanol-free methylene chloride (10 mL) was added, and the resulting mixture was refluxed under magnetic stirring for 25 min. After this time, TLC (Et_2O/*n*-hexane 60:40, v/v) showed the reaction to be complete. The solution was cooled at rt, then treated with a 1 N HCl aqueous solution (pH = 3). The aqueous phase was separated, and the organic layer, after drying on $MgSO_4$, was filtered and evaporated to dryness. The residue was treated with a dry ethanol-free methylene chloride (10 mL) solution containing 1*H*-imidazole (0.15 g, 2.2 mmol) and triisopropylsilyl triflate (TIPSOTf; 0.52 mL, 2.2 mmol) under magnetic stirring at rt. Reaction was complete in 3 h, as checked by TLC (Et_2O/*n*-hexane 60:40, v/v). The organic solvent was removed under reduced pressure conditions, and the solid residue was dissolved in a 5% $NaHCO_3$ aqueous solution (5 mL). The aqueous phase was extracted with AcOEt (3 × 5 mL), and the collected organic layers were washed once with a 5% $KHSO_4$ aqueous solution (5 mL) and once with brine (5 mL). After drying on $MgSO_4$, the solvent was removed under reduced pressure conditions to give a pale yellow crude material, which was chromatographed to afford the title compounds in 92−94% overall yields.

***N*-Hydroxy-*O*-triisopropylsilyl-α-L-amino Acid Methyl Ester 21:** White powder (0.73 g, 2.07 mmol; 94%), mp 122−124 °C. $[\alpha]^{20}_D$ +22.1 (*c* 2.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.72. FT-IR (KBr) 3350, 3310, 3065, 2870, 2810, 1752, 1554, 1352, 1102 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.31−7.36 (m, 5 H), 6.11 (d, 1 H, J = 10.1 Hz), 3.87 (ddd, 1 H, J = 10.1 Hz, J = 9.1 Hz, J = 6.3 Hz), 3.71 (s, 3 H), 3.02 (dd, 1 H, J = 13.5 Hz, J = 6.3 Hz), 2.89 (dd, 1 H, J = 13.5 Hz, J = 9.1 Hz), 1.81 (septet, 3 H, J = 7.1 Hz), 0.93 (d, 18 H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 171.9, 140.1, 128.7, 127.1, 125.9, 67.7, 52.3, 33.4, 17.8, 10.2. MS (EI) *m/z* (relative intensity %) 351 ($M^{+\cdot}$, 21.9), 336 (21.6), 320 (3.4), 308 (9.8), 292 (10.8), 274 (24.3), 260 (9.7), 194 (8.8), 188 (21.7), 178 (11.2), 173 (7.8), 163 (9.9), 157 (15.7), 91 (100), 77 (87.5), 65 (56.9), 59 (34.9), 51 (45.3), 43 (87.9), 31 (34.0). HRMALDI: calcd for $C_{19}H_{34}NO_3Si$ $(M + H)^+$, 352.23080; found 352.23075.

***N*-Hydroxy-*O*-triisopropylsilyl-α-L-amino Acid Methyl Ester 22:** White powder (0.64 g, 2.024 mmol; 92%), mp 90−92 °C. $[\alpha]^{20}_D$ +18.5 (*c* 2.0, $CHCl_3$). TLC (Et_2O/*n*-hexane 60:40, v/v) R_f 0.74. FT-IR (KBr) 3348, 3299, 2875, 2820, 1751, 1550, 1349, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.10 (d, 1 H, J = 10.4 Hz), 3.68 (s, 3 H), 3.40−3.52 (m, 1 H), 1.79 (septet, 3 H, J = 7.2 Hz), 1.53−1.71 (m, 1 H), 1.27−1.36 (m, 2 H), 0.85−0.92 (m, 24 H). ^{13}C NMR ($CDCl_3$) δ 172.2, 65.7, 52.2, 37.8, 23.1, 22.8, 17.8, 10.1. MS (EI) *m/z* (relative intensity %) 317 ($M^{+\bullet}$, 12.2), 302 (10.2), 286 (8.9), 274 (34.2), 260 (12.6), 258 (44.1), 188 (24.0), 173 (28.7), 160 (22.3), 157 (15.8), 144 (11.0), 129 (12.4), 59 (22.1), 57 (100), 43 (87.0), 31 (23.1). HRMALDI: calcd for $C_{16}H_{36}NO_3Si$ $(M + H)^+$, 318.24645; found 318.24640.

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Supporting Information Available: General experimental methods and detailed descriptions of procedures used for the synthesis of oxaziridines **18**−**20** and *N*-hydroxy-*O*-triisopropylsilyl-α-L-amino acid methyl esters **23**−**25**, spectral characterization of *O*-benzylaldoximates **14** and **15**, and elemental analysis of compounds **2a**−**5a**, **2b**−**5b**, **14**, **15**, and **21**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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