An Asymmetric Synthesis of Optically Pure α,α-Disubstituted Amino Aldehydes, α,α-Disubstituted Amino Acids, and Sterically Demanding Dipeptides

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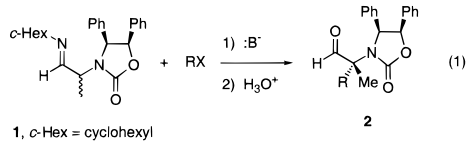
Abstract: Optically pure α-methyl-α-alkyl amino aldehydes were efficiently synthesized from the cyclohexylimine of propanal bearing an α-4(*R*),5(*S*)-diphenyl-2-oxazolidinone by asymmetric alkylation of the imine anion. α-Methylphenylalanine and α-methylleucine were synthesized in two steps from the corresponding amino aldehydes. Utilizing an oxaziridine rearrangement, amino aldehydes were converted to dipeptides in which both the amino and carboxy components were α,α-disubstituted.

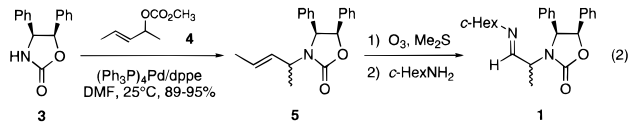
Introduction

Optically active α-amino aldehydes have been used in many synthetic applications.[1] Manipulation of the aldehyde functional group provides easy access to amino alcohols,[1a,b] unusual amino acids,[1a] amino sugars,[1a] natural products,[1b,c] heterocycles,[1c] dipeptide isosteres,[1a,2] and vicinal 1,2-diamines.[3] Optically active α-amino aldehydes were originally obtained from naturally occurring amino acids, which limited their availability.[1a,2a,4] Recently, the number of new chemical syntheses that have appeared are testimony to the growing interest in these compounds.[5] In most of these syntheses, the chiral center is generated by nucleophilic addition of an organometallic reagent to a protected glyoxaldehyde imine, and the process is therefore limited to the synthesis of monosubstituted α-amino aldehydes. One exception is a recent report of a synthesis of optically active α-methyl-α-amino aldehydes that requires 11 steps.[6] A shorter, more practical synthesis would expand the scope of amino aldehyde chemistry. Herein we report an efficient, five-step synthesis of optically pure α-methyl-α-alkyl amino aldehydes, featuring an asymmetric alkylation of α-amino imine **1** (eq 1). This methodology is applied to the synthesis of α-methyl-α-amino acids and, via an oxaziridine rearrangement, dipeptides consisting of two quaternary amino acids.



Results/Discussion

Preparation of α-Amino Imine 1. 2-Oxazolidinones have been widely used as chiral auxiliaries.[7] In particular, 4,5-diphenyl-2-oxazolidinone has been successfully applied in these laboratories as the chiral auxiliary in several diastereoselective processes, including photochemical [2 + 2] cycloadditions of *N*-vinyl oxazolidinones with chromium carbene complexes,[8] copper-catalyzed conjugate additions of Grignard reagents to acetamidoacrylates,[9] and alkylation of *β*-lactams that lead to α-methyl-α-amino acids.[10] Thus, the approach to **1** started with the nucleophilic addition of diphenyl oxazolidinone **3** to allylic carbamate **4** to provide allylic oxazolidinone **5**. Subsequent ozonolysis and imine formation would lead to **1** (eq 2).



Pd(0)-catalyzed allylic amination was utilized for the synthesis of **5** since direct nucleophilic displacement of substituted allylic bromides was unsuccessful. Interestingly, some consideration of the reaction conditions was necessary to successfully effect this transformation.[11] The standard catalyst, bis(dibenzylide-

(1) Reviews: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (c) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825.

(2) For examples, see the following. (a) Hydroxyethylamine isostere: Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635. (b) Double bond, epoxide, dimethylene, diol, hydroxy double bond, trihydroxy, hydroxyethylene, methyleneamino, and methylenehydroxyamino isosteres: Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838.

(3) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103.

(4) Fehrents, J. A.; Castro, B. *Synthesis* **1983**, 676.

(5) (a) Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 418. (b) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359. (c) Muralidharan, K. R.; Mokhallalati, M. K.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 7489. (d) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038.

(6) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379.

(7) (a) For a general review on chiral oxazolidinones in asymmetric synthesis, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta*, **1997**, *30*, 3. (b) Akiba, T.; Tanura, O.; Terashima, S. *Org. Synth.* **1997**, *75*, 45.

(8) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

(9) Lander, P. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 8126 and references therein.

(10) Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918.

(11) To the best of our knowledge, an intermolecular Pd-catalyzed allylic amination with a carbamate anion nucleophile has not been reported. For an intramolecular example, see: Tamaru, Y.; Bando, T.; Kawamura, Y.; Okamura, K.; Yoshida, Z.; Shiro, M.; *J. Chem. Soc., Chem. Commun.* **1992**, 1498.

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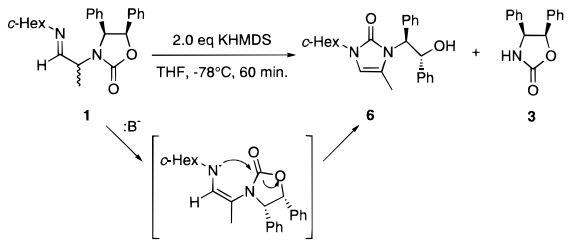
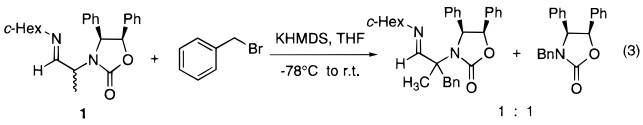
Scheme 1



neacetone)palladium ($Pd(dba)_2$), was unreactive with either triphenylphosphine or diphenylphosphinoethane (dppe) as the added ligand. Tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) was an active catalyst but was limited to conversions of 50%, even with loadings as high as 10 mol %. The stabilizing effect of an additional equivalent (to the catalyst) of triphenylphosphine (PPh_3) increased the conversion to 83%. The chelating ligand dppe was most effective in this regard; the catalyst system of 2.5 mol % $Pd(PPh_3)_4$/3.8 mol % dppe achieved conversions of ≥95% and provided **5** routinely in 89−95% yield as a 3:1 mixture of diastereomers on a 5 g (21 mmol) reaction scale. Purification was easily accomplished by oxidization of the phosphorus ligands with hydrogen peroxide and filtering the crude material through a plug of silical gel. Ozonolysis and condensation with cyclohexylamine proceeded uneventfully in quantitative yield to form α-amino imine **1** as a stable white solid which turned yellow upon standing. Imine **1** was used in the alkylation studies without further purification.

Alkylation of α-Amino Imine 1. Direct α-alkylation of aldehydes is problematic because of competing aldol reactions. Alkylation of their imine derivatives obviates this problem and has become a well-established prodecure in organic synthesis.[12] For the alkylation of imine **1**, however, this methodology was not straightforward. Ultimately, the oxazolidinone at the α-position became the source of a number of decomposition products unless the reaction conditions were carefully controlled.

Attempted α-alkylation by generation of the anion of imine **1** with base followed by addition of an electrophile was unsuccessful. In a control reaction, exposure to KHMDS[13] in the absence of an electrophile converted imine **1** to two products, urea **6** and oxazolidinone **3**,[14] in a ∼2:1 ratio (Scheme 1). The presence of urea **6** implied that the imine anion indeed formed, that the (*Z*)-configuration was predominant,[15] and that intramolecular attack of the imine anion nitrogen on the oxazolidinone carbonyl was rather facile. To inhibit formation of **6**, the imine anion needs to be trapped as formed, requiring the presence of an electrophile upon deprotonation. In the event, when an excess of KHMDS was added to a solution of **1** and benzyl bromide in THF at −78 °C, followed by warming to room temperature, alkylation occurred smoothly, accompanied by only a trace amount of urea **6**. However, decompostition of imine **1** to oxazolidinone **3** was still a competitive process. Under the reaction conditions, oxazolidinone **3** was benzylated, and this decomposition product was formed in a ∼1:1 ratio to the desired alkylation product (eq 3).



A method for inhibiting formation of byproduct **3** was discovered by running a series of low-temperature control alkylations. It was found that, at −45 °C, alkylation of imine **1** with benzyl bromide was complete within minutes, while the rate of decomposition to oxazolidinone **3** was very low. Decomposition to oxazolidinone **3** must be favorable over alkylation only at higher temperatures. The conditions for alkylation were thus established as follows: an excess (2.2 equiv) of KHMDS was added to a solution of imine **1** and BnBr at −78 °C in THF. The reaction was stirred for 15 min, warmed to −45 °C for 15 min, and quenched with MeOH. Under these conditions, imine **1** was alkylated with BnBr, accompanied by ≤5% of oxazolidinone **3**. Subsequent hydrolysis to the aldehyde was easily accomplished with 1 N $HCl_{(aq)}$/THF.

Additives had deleterious effects on the alkylation, so KHMDS generated from KH and HMDS in THF[16] was used as base. By using commercial KHMDS (1.0 M in toluene), the excess required for alkylation introduced a significant cosolvent in the reaction. The negative effect of this nonpolar additive was demonstrated in a control alkylation for which toluene alone was used as solvent. The major products in this reaction were urea **6** (∼50%) and oxazolidinone **3** (∼30%). Alkylation occurred in only minor amounts (∼20% total) and with little diastereoselectivity. When the polar additive HMPA was used as cosolvent with THF, a small increase in diastereoselectivity was observed. However, the alkylation was contaminated with >10% of oxazolidinone **3**.

Synthesis of α-Methyl-α-Amino Aldehydes. With a procedure for alkylating α-amino imine **1** established, a series of electrophiles was examined to determine the reaction scope (Table 1). In general, α-methyl-α-amino aldehydes were synthesized in the highest yields when ozonolysis, amine condensation, alkylation, and hydrolysis were performed as a four-step sequence without purification of intermediates. In each case, the major diastereomer could be isolated by column chromatography. The diastereoselectivity of alkylation was good (≥9:1), as were the overall yields over four steps (47−75%). Activated bromides were the most reactive electrophiles (entries 1−3); only 1 or 2 equiv was necessary for clean alkylation of **1**. Alkyl iodides were also satisfactory electrophiles (entries 4−6) but were required in an excess (10 equiv) to inhibit formation of urea **6**. Of note was alkylation with the secondary iodide, 2-iodopropane (entry 5). This bulky electrophile gave the respective amino aldehyde in good yield and in excellent diastereoselectivity. The main limitation of the methodology was the requirement that the electrophile be present upon imine anion formation. Electrophiles that are susceptible to nucleophilic attack or deprotonation by KHMDS (methoxymethyl chloride, iodomethylphthalimide, methyl bromoacetate, chloroformates) were incompatible with the reaction conditions.

Synthesis of α-Methyl-α-Amino Acids and Proof of the Stereochemical Course of Alkylation. An obvious application of α-methyl-α-amino aldehydes **2a**−**f** is the synthesis of α-methyl-α-amino acids, an important class of nonproteinogenic amino acids which has remained a synthetic challenge for years.[17] Two of these amino acids, α-methylphenylalanine **9**[6] and α-methylleucine **10**,[18] were synthesized as an application of the methodology, as a demonstration of optical purity, and,

(12) For a review, see: Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.

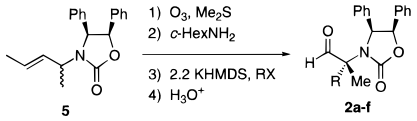
(13) A number of bases were screened, including LDA, LiHMDS, LiTMP, KH, and KOtBu. KHMDS was most effective in completely converting imine **1** without degradation.

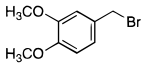
(14) It has not been determined exactly how imine **1** decomposes to oxazolidinone **3** in the presence of a strong base.

(15) Unbranched aldehyde and ketone imines are reported to favor (*E*)-isomer formation upon kinetic deprotonation: Knorr, R.; Low, P *J. Am. Chem. Soc*. **1980**, *102*, 3241. However, the α-branched heteroatom substituent of imine **1** will likely alter the (*E*)/(*Z*) selectivity.

(16) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

Table 1. Diastereoselective Synthesis of Aldehydes **2a**−**f** from Allylic Oxazolidinone **5**



entry	product	RX	d.s.[a]	%yield[b]
1)	**2a**		94:6	62
2)	**2b**		90:10[c]	47
3)	**2c**		92.5:7.5	62
4)	**2d**		93.5:6.5	62
5)	**2e**		97.5:2.5	48
6)	**2f**		92:8	75

[a] Diastereoselectivity measured by gas chromatography. [b] Isolated yield of major diastereomer in four steps from **3**. [c] Diastereoselectivity measured by ^{1}H NMR integration.

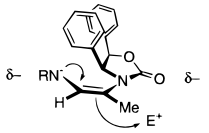
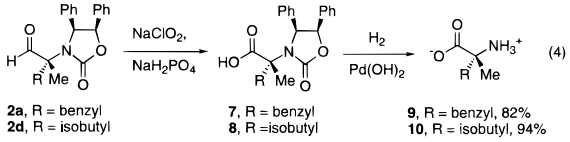


Figure 1. Proposed conformation.

by comparison of the sign of optical rotations to the literature values, as a proof of the stereochemical course of alkylation.

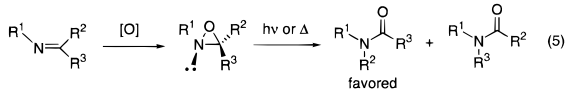
Oxidation of amino aldehydes **2a** and **2d** to amino acid derivatives **7** and **8** with buffered sodium chlorite and deprotection by catalytic hydrogenolysis with Pearlman's catalyst provided the amino acids α-methylphenylalanine **9** and α-methylleucine **10** in good overall yield (eq 4). A comparison of



the signs of rotation for amino acids **9** and **10** with those from the literature indicated that the new stereocenter generated by the alkylation was (*R*) when 4(*R*),5(*S*)-diphenyl-2-oxazolidinone was used as chiral auxiliary. From this fact, and the observation that the imine anion is in the (*Z*)-configuration (Scheme 1), a model can be proposed to explain the stereochemistry of alkylation. With no strong counterion to bind the imine nitrogen to the oxazolidinone carbonyl,[19] the oxazolidinone ring may adopt a conformation to minimize dipole interaction (Figure 1). In this conformation, the bulky phenyl substituents on the oxazolidinone ring will block the *si* face of the imine anion double bond, resulting in alkylation on the opposite, or *re*, face.

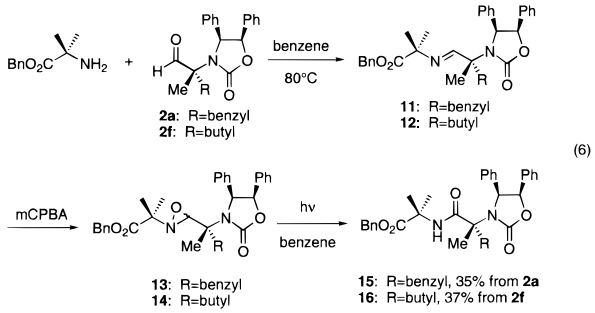
Gas chromatographic analysis of their Mosher amide derivatives indicated that amino acids **9** and **10** were optically pure within the limits of detection. The stereochemistry and optical purity of amino aldehydes **2a** and **2f** were thus established and inferred for the rest of amino aldehydes **2**.

Synthesis of Sterically Demanding Dipeptides via a Photolytic Oxaziridine Rearrangement. Imines can be converted to substituted amides by oxidation to an oxaziridine followed by thermal or photochemical rearrangement[20] (eq 5). This



methodology has been used to form the peptide bond of aspartame, for which the imine was synthesized from phenylalanine methyl ester and the α-amino aldehyde of aspartic acid protected as the β-lactam.[21] The availability of α,α-disubstituted amino aldehydes could extend this methodology to the synthesis of sterically demanding dipeptides. Of particular interest was the synthesis of dipeptides for which both the amino and carboxy coupling components were α,α-disubstituted, compounds difficult to synthesize by standard peptide coupling methods.[22]

Condensation of amino aldehydes **2a** and **2f** with benzyl 2-aminoisobutyrate in benzene at reflux cleanly formed imines **11** and **12** (eq 6). The crude imines were oxidized with mCPBA



to a ∼1:1 mixture of diastereomeric oxaziridines **13** and **14**, which were used directly in the photolytic rearrangement. As shown in eq 5, either substituent on the ring carbon may migrate to nitrogen. Both theoretical studies[23] and mechanistic evidence[24] indicate that the substituent anti to the nitrogen lone pair rearranges selectively.[25] As the oxidation products of trans imines **11** and **12**, substituted oxaziridines **13** and **14** are presumed to be trans substituted as well. Hydrogen should, therefore, be anti to the nitrogen lone pair and migrate selectively. Unfortunately, the photolytic oxaziridine rearrangement produced these protected dipeptides **15** and **16** in poor yields (35 and 37% overall). Numerous byproducts were detected that, upon preliminary examination, seemed to be formed by migration of the syn alkyl group followed by decomposition. Rearrangement under thermal conditions led to even greater decomposition. A detailed examination of the

(17) (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Organic Shemistry Series 7; Pergamon Press: Oxford, 1989. (b) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (d) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (e) Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225.

(18) Kruizinga, W. H.; Bolster, J.; Kellogg, R. M. *J. Org. Chem.* **1988**, *53*, 1826.

(19) This chelation model was invoked to explain the selectivity of Grignard addition in ref 9.

(20) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269.

(21) Duhamel, P.; Goument, B.; Plaquevent, J.-C. *Tetrahedron. Lett.* **1987**, *28*, 2595.

(22) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.

(23) Oliveros, E.; Rivière, M.; Malrieu, J. P.; Teichteil, C. *J. Am. Chem. Soc.* **1979**, *101*, 318.

(24) Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929.

(25) The barrier to inversion of an oxazirine is ≥30 kcal/mol. See ref 23.

oxaziridine rearrangement on this type of system is in progress and will be reported in due course.

Conclusion

An efficient five-step synthesis of optically pure, α-methyl-α-alkyl amino aldehydes was achieved featuring a diastereoselective alkylation of an α-amino imine. The amino aldehydes served as common precursors in the synthesis of α-methyl-α-amino acids and dipeptides consisting of two quaternary amino acids, compounds difficult to synthesize by other methods. Further studies of α-methyl-α-alkyl amino aldehydes as chiral synthetic intermediates are underway.

Experimental Section

General Methods. THF was distilled from sodium−benzophenone ketyl, and CH_2Cl_2, DMF, *t*-BuOH, and benzene were distilled from CaH_2. 300-MHz ^{1}H NMR and 75-MHz ^{13}C NMR were recorded in $CDCl_3$, D_2O, or D_2O/CD_3OD, and chemical shifts are given in ppm relative to Me_4Si (0 ppm, ^{1}H), $CDCl_3$ (77.0 ppm, ^{13}C), and CD_3OD (49.0 ppm, ^{13}C). Photolyses were performed in a Rayonet photochemical reactor, which was equipped with eight RPR 2537-Å lamps. Column chromatography was performed with ICN 32−63 nm, 60 Å silica gel using flash column techniques. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All reactions were performed under an atmosphere of Ar unless otherwise noted.

Preparation of Allylic Oxazolidinone 5. In a 250-mL Airless flask, 402 mg (10.0 mmol) of NaH (60% dispersion in mineral oil) was washed 2× with hexanes. A 250-mL addition funnel was attached, and a solution of 4(*R*),5(*S*)-2-oxazolidinone **4** (2.00 g, 8.37 mmol) in 60.0 mL of dry DMF was added. The flask was cooled to 0 °C, and the solution of **4** in DMF was added dropwise to the NaH with stirring. The apparatus was rinsed with an additional 20.0 mL of DMF, and the solution was allowed to warm to room temperature and stir for 45 min. To this mixture were added 150 mg of dppe (0.38 mmol), 290 mg of $Pd(PPh_3)_4$ (0.25 mmol), and 1.50 mL of carbonate **3** (10.0 mmol). After the mixture was stirred for 12 h, 0.94 mL of 30% H_2O_2 was added and stirred for 10 min, and then 30.0 mL of $Na_2S_2O_3$ was added and stirred for 10 min. The solution was partitioned between EtOAc and H_2O. The aqueous layer was extracted 1× with EtOAc, and the combined organics were washed with H_2O (3×) and brine (1×) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the resulting oil was filtered through a plug of SiO_2 with the aid of 4:1 hexanes/EtOAc. The solvent was removed by rotary evaporation, giving 2.43 g of **5** (95%) as a white solid. Analysis by gas chromatography revealed a 3:1 mixture of diastereomers, 99% pure: IR (film, cm^{-1}) 1747 (s); ^{1}H NMR (major diastereomer) δ 7.05−7.07 (m, 6H), 6.97−7.00, (m, 2H), 6.80−6.93 (m, 2H), 5.80 (d, J = 8.3 Hz, 1H), 5.51−5.67 (m, 2H), 4.98 (d, J = 8.3 Hz, 1H), 4.40−4.49 (m, 1H), 1.73 (d, J = 5.1 Hz, 1H), 0.99 (d, J = 6.9 Hz, 1H) [peaks for minor diastereomer, 6.80−7.07 (m), 5.13−5.77 (m), 5.02 (d J = 8.2 Hz), 4.67−4.77 (m), 3.99−4.08 (m), 1.61 (dd, J = 1.5, 6.8 Hz), 1.43−1.49 (m), 1.03 (d J = 7.0 Hz)]; ^{13}C NMR (asterisk denotes minor diastereomer) δ 157.5, 157.4*, 136.3, 135.5*, 134.8*, 134.6, 130.1*, 129.9, 128.0, 127.9, 127.8, 127.7, 127.6, 125.9, 79.9, 79.4*, 64.1*, 63.1, 52.5*, 51.8, 18.6, 18.4*, 17.6, 17.3*. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.26; H, 7.00; N, 4.53.

General Procedure for the Preparation of 1. In a round-bottom flask, a 0.04 M solution of **5** in CH_2Cl_2 was cooled to −78 °C. Ozone was bubbled through until a faint blue color persisted. Oxygen was bubbled through until the blue color disappeared, and Me_2S (1.0 mL/mmol) was added by syringe. The reaction was allowed to warm to room temperature and was stirred for 4 h. The solution was washed with H_2O (3×) and brine (1×) and dried over Na_2SO_4. The solvent was removed by rotary evaporation to yield the aldehyde as a clear oil. This oil was dissolved in CH_2Cl_2 (0.16 M solution), and $MgSO_4$ was added followed by cyclohexylamine (1.1 equiv). The solvent was removed by rotary evaporation to yield a white solid which was filtered through Celite with the aid of CH_2Cl_2. The solvent was removed by rotary evaporation to yield a diastereomeric mixture of imines as a white solid which was used immediately for alkylation.

General Procedure for the Preparation of α-Amino Aldehydes. To a solution of amino imine **1** and 1.1−10.0 equiv of alkyl halide in THF at −78 °C was added 2.8 equiv of 1.10 M KHMDS/THF dropwise over 1 min. The reaction was stirred for 15 min, warmed to −45 °C (Dry Ice/CH_3CN), and stirred for another 15 min, quenched with 5 equiv of MeOH, and warmed to room temperature. EtOAc was added, and the solution was washed with H_2O (3×) and brine (1×) and dried over Na_2SO_4. Removal of the solvent by rotary evaporation gave the crude amino imine as a yellow oil. The amino imine was dissolved in 2:1 THF/1 N HCl, and the solution was stirred for 1 h. EtOAc was added, and the solution was washed with H_2O (3×) and brine (1×) and dried over Na_2SO_4. Removal of the solvent by rotary evaporation gave the diastereomeric mixture of amino aldehydes as a yellow oil or yellow solid. Column or radial chromatography provided the indicated products as white solids.

2a. According to the general procedure, α-amino imine **1** was prepared from 500 mg (1.63 mmol) of allylic oxazolidinone **5**, 1.63 mL of Me_2S (1 mL/mmol **5**), and 0.21 mL (1.79 mmol) of cyclohexylamine. Imine **1** was alkylated with 0.21 mL (1.79 mmol) of benzyl bromide in 10.0 mL of THF and 3.60 mL (3.96 mmol) of 1.10 M KHMDS. The imine was hydrolyzed with 60.0 mL of 2:1 THF/1 N HCl, and the diastereomeric amino aldehydes were isolated by column chromatography (SiO_2/4:2:1 hexanes/CH_2Cl_2/Et_2O), giving 390 mg (62%) of the major diastereomeric amino aldehyde **2a** and 48.0 mg (8%) of the minor.

2a: mp 157−159 °C (EtOAc/hexanes); $[\alpha]^{20}_D$ +34.3 (*c* 1, CH_2Cl_2); IR (film, cm^{-1}) 1750 (s); ^{1}H NMR δ 9.65 (s, 1H), 7.24−7.26 (m, 3H), 6.92−7.12 (m, 10H), 6.74 (d, J = 9.0 Hz, 1H), 5.83 (d, J = 8.4 Hz, 1H), 5.09 (d, J = 8.4 Hz, 1H), 3.32 (d, J = 6.0 Hz, 1H), 3.28 (d, J = 6.0 Hz, 1H), 1.30 (s, 3H); ^{13}C NMR δ 198.7, 158.1, 136.3, 134.8, 134.1, 130.9, 128.3, 128.2, 128.1, 127.9, 127.7, 127.4, 127.1, 126.0, 80.6, 66.8, 64.5, 39.9, 19.3. Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.83; H, 6.13; N, 3.53. Minor diastereomer: IR (CH_2Cl_2, cm^{-1}) 1744 (s); ^{1}H NMR δ 9.84 (s, 1H), 7.42−7.45 (m, 3H), 7.30−7.32 (m, 3H), 7.01−7.04 (m, 7H), 6.85−6.87 (m, 2H), 5.61 (d, J = 8.0 Hz, 1H), 4.08 (d, J = 8.0 Hz, 1H), 3.60 (d, J = 13.8 Hz, 1H), 3.00 (d, J = 13.8 Hz, 1H), 0.97 (s, 3H); ^{13}C NMR δ 199.5, 157.9, 136.8, 135.8, 133.5, 130.5, 128.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.4, 127.0, 126.9, 125.9, 81.0, 65.9, 63.6, 38.5, 19.3.

2b. According to the general procedure, α-amino imine **1** was prepared from 250 mg (0.81 mmol) of allylic oxazolidinone **5**, 0.81 mL of Me_2S (1 mL/5 mmol), and 0.10 mL (0.89 mmol) of cyclohexylamine. Imine **1** was alkylated with 206 mg (0.89 mmol) of 3,4-dimethoxybenzyl bromide in 5.00 mL of THF and 1.80 mL (1.98 mmol) of 1.10 M KHMDS. The imine was hydrolyzed with 30.0 mL of 2:1 THF/1 N HCl, and the diastereomeric amino aldehydes were isolated by radial chromatography (SiO_2, 2 mm plate/2:1:1 hexanes/CH_2Cl_2/Et_2O), giving 16 mg (5%) of the minor diastereomeric amino aldehyde. The fractions containing the major amino aldehyde were recrystallized from toluene to give 170 mg (47%) of **2b**: mp 126−128 °C (toluene); $[\alpha]^{20}_D$ +40.7 (*c* 1, CH_2Cl_2); IR (film, cm^{-1}) 1745 (s); ^{1}H NMR δ 9.64 (s, 1H), 6.92−7.07 (m, 8H), 6.74−6.78 (m, 3H), 6.61−6.64 (m, 2H), 5.85 (d, J = 8.1 Hz, 1H), 5.08 (d, J = 8.1 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.30 (d, J = 13.1 Hz, 1H), 3.20 (d, J = 13.1 Hz, 1H), 1.32 (s, 3H); ^{13}C NMR δ 198.8, 158.0, 148.6, 148.1, 136.2, 134.0, 128.1, 127.8, 127.5, 127.3, 125.9, 123.1, 114.0, 110.9, 80.6, 66.8, 64.4, 55.8, 39.5, 19.4. Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.63; H, 6.05; N, 3.12. Minor diastereomer: IR (film, cm^{-1}) 1745 (s); ^{1}H NMR δ 9.86 (s, 1H), 6.81−7.05 (m, 13H), 5.62 (d, J = 8.0 Hz, 1H), 4.21 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.58 (d, J = 14.0 Hz, 1H), 2.94 (d, J = 14.0 Hz, 1H), 0.99 (s, 3H); ^{13}C NMR δ 199.8, 158.0, 148.9, 148.4, 136.9, 133.6, 128.4, 128.3, 128.1, 128.0, 127.8, 125.9, 122.6, 113.7, 111.2, 81.0, 66.0, 63.7, 56.0, 38.1, 19.4.

2c. According to the general procedure, α-amino imine **1** was prepared from 250 mg (0.81 mmol) of allylic oxazolidinone **5**, 0.81 mL of Me_2S (1 mL/5 mmol), and 0.10 mL (0.89 mmol) of cyclohexylamine. Imine **1** was alkylated with 0.14 mL (0.89 mmol) of allyl bromide in 5 mL of THF and 1.80 mL (1.98 mmol) of 1.10 M KHMDS.

The imine was hydrolyzed with 30.0 mL of 2:1 THF/1 N HCl, and the diastereomeric amino aldehydes were isolated by radial chromatography (SiO_2, 2 mm plate/4:1:1 hexanes/CH_2Cl_2/Et_2O), giving 168 mg (62%) of the major diastereomeric amino aldehyde **2c** and 19 mg (7%) of the minor.

2c: mp 127−129 °C (EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 1749 (s); ^1H NMR δ 9.66 (s, 1H), 7.04−7.10 (m, 10H), 6.01 (d, J = 8.1 Hz, 1H), 5.63 (dddd, J = 7.2, 7.2, 9.9, 17.1 Hz, 1H), 5.20 (d, J = 7.8 Hz, 1H), 5.04 (d, J = 9.9 Hz, 1H), 4.95 (d, J = 17.1 Hz, 1H), 2.44 (d, J = 7.2 Hz, 2H), 1.40 (s, 3H); ^{13}C NMR δ 198.3, 157.7, 136.1, 133.8, 131.3, 128.3, 128.2, 127.7, 127.6, 125.8, 119.5, 80.9, 65.5, 63.3, 38.4, 18.8. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.38; H, 6.47; N, 4.07. Minor diastereomer: IR (CH_2Cl_2, cm^{-1}) 1748 (s); ^1H NMR δ 9.75 (s, 1H), 7.00−7.11 (m, 10H), 5.84−6.01 (m, 1H), 5.93 (d, J = 7.8 Hz, 1H), 5.31 (d, J = 9.3 Hz, 1H), 5.30 (d, J = 18.3 Hz, 1H), 5.03 (d, J = 7.8 Hz, 1H), 2.86 (dd, J = 7.8, 14.1 Hz, 1H), 2.55 (dd, J = 7.2, 14.1 Hz, 1H), 1.05 (s, 3H); ^{13}C NMR δ 199.1, 157.8, 136.5, 133.6, 131.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.3, 125.9, 120.5, 81.1, 65.4, 63.9, 38.3, 19.0.

2d. According to the general procedure, α-amino imine **1** was prepared from 1.00 g (3.25 mmol) of allylic oxazolidinone **5**, 3.25 mL of Me_2S (1 mL/5 mmol), and 0.41 mL (0.89 mmol) of cyclohexylamine. Imine **1** was alkylated with 3.74 mL (0.89 mmol) of 1-iodo-2-methylpropane in 20.0 mL of THF and 1.80 mL (1.98 mmol) of 1.10 M KHMDS. The imine was hydrolyzed with 120 mL of 2:1 THF/1 N HCl, and the diastereomeric amino aldehydes were isolated by column chromatography (SiO_2/4:1:1 hexanes/CH_2Cl_2/Et_2O), giving 709 mg (62%) of the major diastereomeric amino aldehyde **2d** and 68 mg (6%) of the minor.

2d: mp 127−129 °C (Et_2O/hexanes); $[\alpha]^{20}_D$ −73.6 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2, cm^{-1}) 1747 (s); ^1H NMR δ 9.64 (s, 1H), 7.08−7.11 (m, 7H), 7.01−7.03 (m, 3H), 5.94 (d, J = 7.8 Hz, 1H), 5.14 (d, J = 7.8 Hz, 1H), 1.53−1.68 (m 3H), 1.44 (s, 3H), 0.86 (d, J = 6.0 Hz, 3H), 0.70 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ 198.8, 157.8, 136.5, 133.9, 128.4, 128.3, 127.8, 127.6, 125.9, 81.1, 66.5, 63.5, 43.0, 24.4, 24.2, 23.6, 19.4. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.92; H, 7.20; N, 4.01. Minor diastereomer: IR (CH_2Cl_2, cm^{-1}) 1746 (s); ^1H NMR δ 9.72 (s, 1H), 7.03−7.12 (m, 10H), 5.98 (d, J = 7.4 Hz, 1H), 5.07 (d, J = 7.4 Hz, 1H), 1.74−1.91 (m, 3H), 1.11 (s, 3H), 1.02 (d, J = 6.0 Hz, 1H), 0.98 (d, J = 6.0 Hz, 1H); ^{13}C NMR δ 199.7, 157.6, 136.1, 133.6, 128.6, 128.4, 128.0, 127.9, 127.8, 125.9, 81.0, 66.0, 64.4, 43.0, 24.8, 24.4, 23.5, 19.3.

2e. According to the general procedure, α-amino imine **1** was prepared from 250 mg (0.81 mmol) of allylic oxazolidinone **5**, 0.81 mL of Me_2S (1 mL/5 mmol), and 0.10 mL (0.89 mmol) of cyclohexylamine. Imine **1** was alkylated with 0.81 mL (8.13 mmol) of 2-iodopropane in 5.00 mL of THF and 1.80 mL (1.98 mmol) of 1.10 M KHMDS. The imine was hydrolyzed with 30.0 mL of 2:1 THF/1 N HCl, and the diastereomeric amino aldehydes were isolated by radial chromatography (SiO_2, 2 mm plate/4:1:1 hexanes/CH_2Cl_2/Et_2O), giving 132 mg (48%) of the major diastereomeric amino aldehyde **2e:** mp 133−140 °C (EtOAc/hexanes); $[\alpha]^{20}_D$ −48.8 (*c* 1, CH_2Cl_2); IR (film, cm^{-1}) 1743 (s); ^1H NMR δ 9.63 (s, 1H), 7.01−7.09 (m, 10H), 5.94 (d, J = 8.1 Hz, 1H), 5.10 (d, J = 8.1 Hz, 1H), 2.68 (m, 1H), 1.34 (s, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 199.0, 158.0, 136.3, 134.0, 128.3, 128.1, 127.9, 127.8, 127.7, 125.8, 80.6, 69.5, 64.0, 31.1, 17.6, 17.5, 15.6. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.61; H, 6.92; N, 4.15.

2f. According to the general procedure, α-amino imine **1** was prepared from 500 mg (1.63 mmol) allylic oxazolidinone **5**, 1.63 mL Me_2S (1 mL/5 mmol), and 0.21 mL (1.79 mmol) cyclohexylamine. Imine **1** was alkylated with 1.85 mL (1.79 mmol) 1-iodobutane in 10.0 mL THF and 3.60 mL (3.96 mmol) 1.10 M KHMDS. The imine was hydrolyzed with 60.0 mL of 2:1 THF:1 N HCl and the diastereomeric amino aldehydes were isolated by column chromatography (SiO_2/4:2:1 hexanes:CH_2Cl_2:Et_2O) giving 369 mg (73%) of the major diastereomeric amino aldehyde **2f** and 38 mg (9%) of the minor.

2f: mp 116.5−118.5 °C; $[\alpha]^{20}_D$ −62.7 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2-CH_2Cl_2, cm^{-1}) 1749 (s); ^1H NMR δ 9.61 (s, 1H), 7.02−7.10 (m, 10H), 5.98 (d, J = 8.1 Hz, 1H), 5.14 (d, J = 8.1 Hz, 1H), 1.57−1.72 (m, 1H), 1.40−1.49 (m, 1H), 1.49 (s, 3H), 0.99−1.25 (m, 4H), 0.71−0.76 (m, 3H); ^{13}C NMR δ 198.3, 157.8, 136.5, 133.8, 128.2, 128.1, 127.7, 127.6, 125.7, 80.9, 66.1, 63.0, 33.8, 25.3, 22.6, 18.6, 13.4. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.96; H, 7.03; N, 4.10. Minor diastereomer: IR (CH_2Cl_2, cm^{-1}) 1747 (s); ^1H NMR δ 9.67 (s, 1H), 7.06−7.11 (m, 10H), 6.00 (d, J = 7.6 Hz, 1H), 5.07 (d, J = 7.6 Hz, 1H), 1.87−1.97 (m, 1H), 1.71−1.81 (m, 1H), 1.34−1.36 (m, 4H), 1.09 (s, 3H), 0.91−0.95 (m, 3H); ^{13}C NMR δ 199.5, 157.6, 136.1, 133.6, 128.5, 128.3, 127.9, 127.5, 125.8, 81.1, 65.6, 64.0, 34.0, 25.3, 22.9, 18.7, 13.8.

6: IR (CH_2Cl_2, cm^{-1}) 3323 (m), 1660 (s), 1633 (s); ^1H NMR δ 7.12−7.26 (m, 7H), 6.98−7.01 (m, 2H), 6.91−6.92 (m, 1H), 5.96 (s, 1H), 5.68 (s, 1H), 4.86 (d, J = 2.4 Hz, 1H), 4.00−4.07 (m, 1H), 1.66−1.97 (m, 8H), 1.81 (s, 3H) 1.48−1.66 (m, 4H), 1.11−1.20 (m, 1H); ^{13}C NMR δ 152.9, 141.3, 135.8, 128.5, 127.5, 127.3, 127.2, 127.0, 126.3, 118.9, 104.1, 73.9, 66.8, 51.6, 32.4, 32.3, 25.3, 25.1, 10.6; HRMS *m*/*z* 377.2221 (M^+ + 1) (calcd for $C_{24}H_{28}N_2O_2$ 377.2229).

11. Benzyl 2-aminoisobutyrate·HCl (92 mg, 0.4 mmol) was dissolved in 10% $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The solvent was removed by rotary evaporation. The resulting oil and **2a** (96 mg, 0.25 mmol) were dissolved in 6 mL of benzene, 4-Å molecular seives were added, and the mixture was heated to reflux for 26 h. The solution was filtered through Celite, and the solvent was removed by rotary evaporation to give **11** as a clear oil which was used in the next step without further purification: IR (film, cm^{-1}) 1745 (s), 1729 (s), 1668 (m); ^1H NMR δ 7.61 (s, 1H), 7.24−7.35 (m, 11H), 6.80−7.00 (m, 7H), 6.60 (bs, 2H), 5.49 (d, J = 8.2 Hz, 1H), 5.13 (s, 1H), 4.70 (d, J = 8.2 Hz, 1H), 3.63 (d, J = 13.4 Hz, 1H), 3.36 (d, J = 13.4 Hz, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR δ 173.9, 162.1, 158.1, 137.0, 136.6, 135.9, 134.5, 131.1, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.3, 126.7, 126.1, 79.8, 66.6, 65.1, 65.0, 63.5, 41.5, 25.9, 24.9, 23.1.

12. As described above for **11**, 88 mg of **2f** (0.25 mmol) gave imine **12** as a clear oil: IR (film, cm^{-1}) 1747 (s), 1732 (s), 1668 (m); ^1H NMR δ 7.61 (s, 1H), 7.33 (s, 5H), 6.94−7.01 (m, 10H). 5.82 (d, J = 7.8 Hz, 1H), 5.14 (s, 2H), 4.97 (d, J = 7.8 Hz, 1H), 2.05−2.12 (m, 1H), 1.78−1.85 (m, 1H), 1.14 (s, 3H), 1.23−1.41 (m, 4H), 1.36 (s, 3H), 1.20 (s, 3H), 0.82−0.86 (m, 3H); ^{13}C NMR δ 174.0, 162.8, 157.5, 137.1, 135.8, 134.4, 128.4, 128.1, 128.0, 127.8, 127.7, 127.5, 127.4, 125.9, 79.9, 66.4, 64.7, 64.3, 62.7, 35.9, 25.8, 25.6, 24.9, 22.7, 21.8, 13.8.

15. A slurry of *m*-CPBA (94 mg, ∼0.38 mmol) in 10% $NaHCO_3$ was extracted with CH_2Cl_2 (3×), and the solvent was removed by rotary evaporation. The resulting white solid was dissolved in 2.00 mL of toluene and cooled to −78 °C. To this solution was added a solution of imine **11** in 2.00 mL of toluene under air. The reaction was stirred at −78 °C for 30 min and warmed to room temperature for 15 min. The reaction was washed with 10% $Na_2S_2O_3$ (1×), $NaHCO_3$ (1×), and brine (1×) and dried over Na_2SO_4. The solvent was removed by rotary evaporation, giving a 1:1 mixture of diastereomeric oxazolidinones **13** as a clear oil. In a quartz tube, this oil was dissolved in 4.00 mL of benzene and degassed for 45 min by bubbling argon through the solution. The quartz tube containing the oxaziridine was photolyzed at 254 nm for 2.5 h. The solvent was removed by rotary evaporation, and purification by radial chromatography (10:1:1 hexanes/CH_2Cl_2/Et_2O) gave 50 mg (35%) of **15** as a white solid: mp 157−158 °C; $[\alpha]^{20}_D$ +35.0 (*c* 1, CH_2Cl_2); IR (film, cm^{-1}) 3383 (w), 1737 (s), 1667 (m); ^1H NMR δ 7.33−7.38 (m, 5H), 7.21−7.26 (m, 5H), 7.06 (bs, 1H), 7.00−7.04 (m, 3H), 6.78−6.94 (m, 4H), 6.43 (d, J = 6.0 Hz, 2H), 5.72 (d, J = 8.3 Hz, 1H), 5.23 (d, J = 6.6 Hz, 1H), 5.21 (d, J = 8.3 Hz, 1H), 5.19 (d, J = 6.6 Hz, 1H), 3.90 (d, J = 13.2 Hz, 1H), 3.20 (d, J = 13.2 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.20 (s, 3H); ^{13}C NMR δ 174.3, 172.2, 159.2, 136.8, 135.7, 134.5, 131.1, 128.5, 128.3, 128.1, 127.8, 127.6, 127.5, 127.4, 127.2, 126.9, 126.1, 80.1, 67.2, 65.1, 64.8, 57.0, 41.6, 24.6, 24.4, 22.6. Anal. Calcd for $C_{36}H_{36}N_2O_5$: C, 74.98; H, 6.29; N, 4.86. Found: C, 74.87; H, 6.33; N, 4.98.

16. As described above for **15**, imine **12** was oxidized with 94 mg (∼0.38 mmol) of *m*-CPBA to give **14** as a clear oil. Photolysis at 254 nm for 6 h and purification by radial chromatography (SiO_2, 2 mm plate/6:1:1 hexanes/CH_2Cl_2/Et_2O) gave 50 mg (37%) of **16** as a clear oil: $[\alpha]^{20}_D$ −39.2 (*c* 2.2, CH_2Cl_2); IR (film, cm^{-1}) 3350 (w), 1739 (s), 1673 (m); ^1H NMR δ 7.35−7.37 (m, 5H), 7.23 (bs, 1H), 7.04−7.08

(m, 6H), 6.93−6.96 (m, 4H), 5.76 (d, J = 7.9 Hz, 1H), 5.24 (d, J = 12.3 Hz, 1H), 5.14 (d, J = 12.3 Hz, 1H), 5.05 (d, J = 7.9 Hz, 1H), 1.93−2.09 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.34 (s, 3H), 1.08−1.38 (m, 4H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 174.1, 171.7, 158.1, 136.9, 135.7, 134.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.4, 125.9, 80.4, 67.0, 64.6, 64.3, 56.6, 36.4, 26.3, 25.0, 24.3, 22.9, 21.5, 13.9. Anal. Calcd for $C_{33}H_{38}N_2O_5$: C, 73.04; H, 7.06; N, 5.16. Found: C, 73.10; H, 7.16; N, 4.98.

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Supporting Information Available: Experimental procedures and compound characterization for compounds **7**−**10** (3 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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