Totally Stereocontrolled Nitrone−Ketene Acetal Based Synthesis of (2*S*,3*S*)-*N*-Benzoyl- and *N*-Boc-phenylisoserine†

Sylvie Jost, Yves Gimbert, and Andrew E. Greene*

Université Joseph Fourier de Grenoble, Chimie Recherche (LEDSS), 38041 Grenoble Cedex, France

Frédéric Fotiadu

Université d'Aix-Marseille, ENSSPICAM, 13397 Marseille Cedex 20, France

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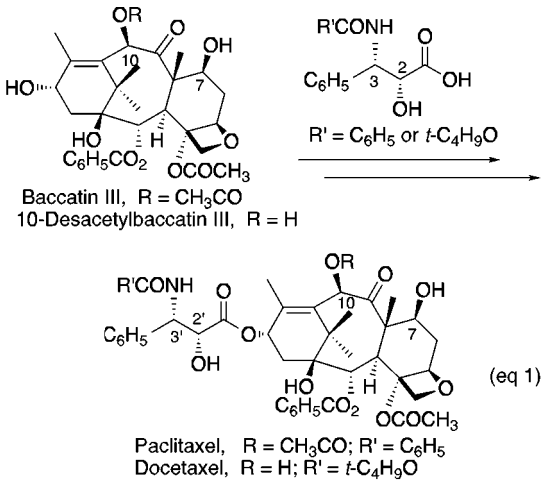
A novel, nitrone−ketene acetal based approach to enantiopure (2*S*,3*S*)-*N*-benzoyl- and *N*-boc-phenylisoserine has been realized. The convergent approach, which involves the intermediacy of isoxazolidinones, proceeds in up to 59% overall yield and requires only three operations from the starting nitrones.

The important cancer chemotherapeutic agents paclitaxel (Taxol®) and docetaxel (Taxotere®) are currently best secured by a partial synthesis approach that, formally, joins baccatin III with (2*R*,3*S*)-*N*-benzoylphenylisoserine and 10-desacetylbaccatin III with (2*R*,3*S*)-*N*-boc-phenylisoserine, respectively (eq 1).[1] This conceptually simple approach, which was first demonstrated to be viable in 1988,[2] has to date fostered an impressive number of often highly imaginative routes to the (2*R*,3*S*)-phenylisoserine side chains for use in the esterification reactions.[1]

In 1994 we disclosed the surprising result that cyclically protected (2*S*,3*S*)-phenylisoserine derivatives could also be employed in these esterifications for they too yielded paclitaxel and docetaxel on deprotection.[3] Interest today in this anti stereoisomer also stems from the disclosure by Kingston and co-workers[4] that (4*S*,5*R*)-2,4-diphenyloxazoline-5-carboxylic acid, which is prepared conveniently from (2*S*,3*S*)-phenylisoserine derivatives,[5] is an effective esterification partner for protected baccatin III. While syntheses of the 2*R*,3*S* (syn) side chains are



far more numerous than those of the 2*S*,3*S* (anti), there are several different routes to the latter. These include enzymatic resolution,[5a,6] enzymatic reduction,[7] enantio- and diastereoselective condensation and Michael addition,[5b,c,8] and chiral pool[9] based approaches. In most of the approaches, however, high enantiomeric and diastereomeric excesses are largely offset by mediocre yields and/or the number of steps required.

Tomoda, Takeuchi, and Nomura first demonstrated the feasiblity of the addition of *O*-silylated ketene acetals to nitrones to afford racemic β-amino ester derivatives, although with modest (2−3:1) diastereoselectivity at the alkyl(or aryl)-substituted α and β centers.[10] It was felt

‡ This paper is dedicated to Prof. Maitland Jones, Jr., on the occasion of his 60th birthday.

* Tel: (33) 4-76-51-46-86. FAX: (33) 4-76-51-43-82; E-mail: Andrew.Greene@ujf.grenoble-fr. Correspondence concerning the theoretical calculations should be directed to Dr. F. Fotiadu.

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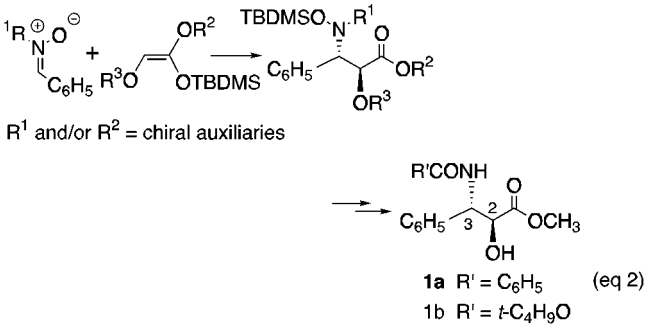
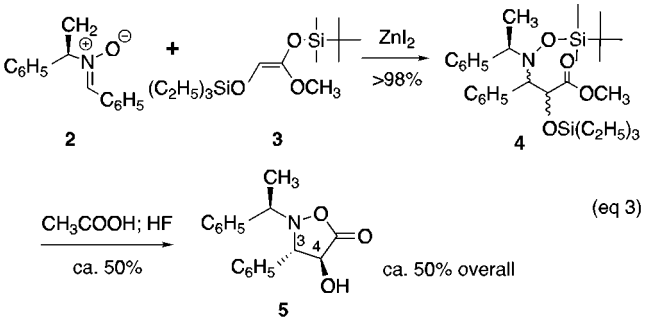
a chiral nitrone or a chiral *O*-silylated ketene acetal, or both in combination, if well chosen, might through this reaction provide stereoselective access to the *N*-benzoyl- and *N*-boc-phenylisoserine side chains (eq 2).[11] In this paper we detail an effective, alternative approach to the 2*S*,3*S* side chains based on such nitrone−*O*-silylated ketene acetal couplings. To the best of our knowledge, these are the first examples of chirality control in this reaction through the use of removable auxiliary groups.



(eq 2)

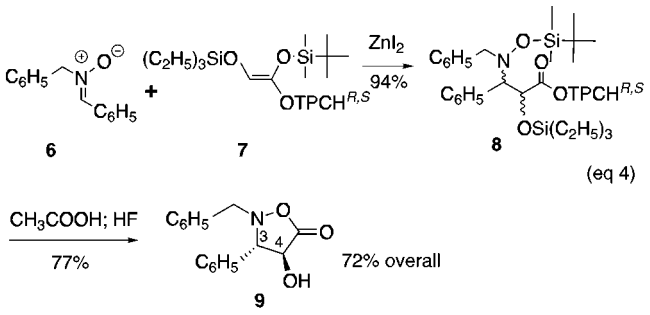
The chiral nitrone (*R*)-*N*-(α-methylbenzyl)-*C*-phenylnitrone (**2**) was readily prepared by condensation of (*R*)-*N*-(α-methylbenzyl)hydroxylamine[12] with benzaldehyde. In combination with the achiral *E* ketene acetal **3**, derived from methyl (triethylsilyloxy)glycolate,[13] in acetonitrile−dichloromethane under zinc iodide catalysis[10b] thio nitrone provided a 93:7 mixture of anti and syn diastereomers **4** in better than 98% yield (eq 3). The two



(eq 3)

anti diastereomers, the major products, were present in an 80:20 ratio and the two syn in a 65:35 ratio.[14−16] Conveniently, the mixture of diastereomers on treatment with acid smoothly underwent deprotection with concomitant cyclization to afford an easily separated mixture of the corresponding isoxazolidinones. The 3*S*,4*S* diastereomer **5** was isolated pure in ca. 50% overall yield. This transformation was of considerable importance for it not only facilated the purification and identification of the diastereomers but also served, as will be seen, to labilize the N−O bond and to simplify the removal and recovery of the chiral auxiliaries of starting chiral *O*-silylated ketene acetals.

A second approach to a diastereo- and enantiomerically pure isoxazolidinone intermediate involved the use of a chiral ketene acetal with *N*-benzyl-*C*-phenylnitrone. The initial, and ultimately the best, chiral ketene acetal examined was that derived from readily available (1*R*,2*S*)-2-phenylcyclohexanol (TPCH^{R,S}):[17] the known[18] glycolate was converted into its triethylsilyl derivative, which was then transformed to the *Z* ketene acetal (**7**, *Z*:*E* = 95:5) in 73% overall yield. In the presence of *N*-benzyl-*C*-phenyl nitrone (**6**)[19] and zinc iodide in acetonitrile−dichloromethane, this ketene acetal reacted smoothly to give the expected adduct **8** as a 90:10 mixture of anti and syn diastereomers in 94% yield (eq 4). The two anti diastereomers were present in a 97:3 ratio and the two syn in a 80:20 ratio.[14] After removal of the two minor diastereomers by silica gel chromatography, the mixture was subjected to acidic conditions to effect deprotection and cyclization, which afforded the enantiopure isoxazolidinone **9** in 77% yield (72% overall) and intact (1*R*,2*S*)-2-phenylcyclohexanol in 82% yield.



(eq 4)

Double induction, however, proved the most remarkable: while (*S*)-*N*-(α-methylbenzyl)-*C*-phenylnitrone in combination with the above ketene acetal **7** provided a mixture of diastereomers (anti:syn, 85:15; 87% yield), *the matched*[20] *antipodal nitrone* ***2*** *delivered only the desired 2S,3S diastereomer* ***10*** *in essentially quantitative yield*. Exposure of this derivative to acid afforded the expected isoxazolidinone **5** in pure form in 74% yield (73% overall) together with the chiral auxiliary in 79% yield (eq 5).

Tomada[10a] and Kita[10b] have both proposed a stepwise mechanism for the nitrone−*O*-silylated ketene acetal

(11) For examples of the application of chiral nitrones and chiral dipolarophiles in asymmetric synthesis, see: Murahashi, S.-I.; Imada, Y.; Kohno, M; Kawakami, T. *Synlett* **1993**, 395. For an alternative approach, see: Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett*. **1994**, *35*, 4419. Seerden, J.-P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron: Asymmetry* **1995**, *6*, 1441.

(12) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455.

(13) Ketene acetal **3** was prepared by a modification of the procedure described by Hattori and Yamamoto: Hattori, K.; Yamamoto, H. *J. Org. Chem*. **1993**, *58*, 5301. The *E*:*Z* ratio was 74:26. The *tert*-butyldimethylsilyl and benzyl protecting groups were found to be less effective in this work.

(14) These ratios were determined by proton NMR analysis. The anti−syn stereochemical assignments were established by NMR after cyclization of the purified or partially purified components to the corresponding isoxazolidinones; the absolute stereochemistry was assigned after conversion of the isoxazolidinones to the known isoserine derivatives.

(15) The corresponding *Z* ketene acetal produced a 63:37 anti to syn ratio in 63% yield.

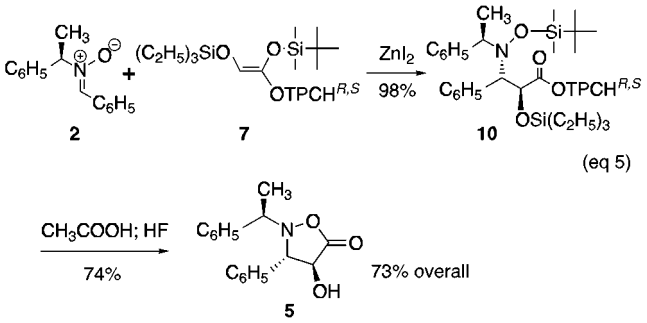
(16) One other chiral nitrone, the α,α′-dichlorophenyl analogue of **2**, was also tested with the above ketene acetal **3**. (*R*)-1-(2,6-Dichlorophenyl)ethylamine, which in several instances has been shown to be a more effective inductor than α-methylbenzylamine (Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859. Polniaszek, R. P.; Dillard, L. W. *Tetrahedron Lett.* **1990**, *31*, 797. Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. J. *J. Org. Chem*. **1990**, *55*, 215), was prepared as previously described (Polniaszek, R. P.; Lichti, C. F. *Synth. Commun*. **1992**, *22*, 171) and then transformed[12] to the corresponding hydroxylamine, which was condensed with benzaldehyde to give the nitrone. Disappointingly, although the ratio of the anti diastereomers improved (89:11) while the combined yield remained high (92%), the anti and syn products were now formed in similar amounts (56:44).

(17) Whitesell, J. K.; Lawrence, R. M. *Chim*. **1986**, *40*, 318. The other chiral auxiliaries examined were 8-phenylmenthol, phenylethanol, and 3,3-dimethyl-2-butanol.

(18) Georg. G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R.; Burke, C. T. *J. Med. Chem*. **1992**, *35*, 4230.

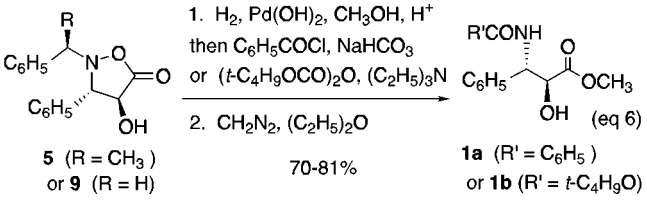
(19) Murahasi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem*. **1990**, *55*, 1736. Murahashi, S.-I.; Shiota, T.; Imada, Y. *Org. Synth*. **1991**, *70*, 265.

(20) See: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.



reaction involving an initial transfer of the silyl group to the nitrone followed by combination of the resultant *N*-(silyloxy)imminium ion and ester enolate through an open transition state. While such a mechanism cannot be completely ruled out, a well-organized, closed transition state would seem more likely, particularly in the presence of zinc iodide. The zinc should facilitate adjacency of the reactants, which would be expected to lead to the formation of a pentacoordinated silicon. Theoretical calculations support the involvement of a pentacoordinated silicon and indicate that the carbon−carbon bond formation will occur through a pseudochair or a pseudotwist transition state.[21] Adduct **4** would then arise through reaction of the *E* ketene acetal **3** with the nitrone primarily through the former, whereas adducts **8** and **10** would be formed from the *Z* ketene acetal **7** and the nitrones through the latter, in which unfavorable nonbonded steric interactions between the triethylsilyloxy group and the nitrone phenyl are avoided (Figure 1).

Both isoxazolidinones **5** and **9** efficiently provided the desired phenylisoserine derivatives on one-pot double hydrogenolysis−benzoylation/*tert*-butoxycarbonylation (eq 6). The isoxazolidinones in methanol containing acetic acid or a catalytic amount of perchloric acid in the presence of Pearlman's catalyst were smoothly converted at room temperature under hydrogen at 1 atm to (2*S*,3*S*)-phenylisoserine, which was treated in situ with benzoyl chloride and sodium bicarbonate or boc anhydride and triethylamine to yield the anti side chains **1a** and **1b**. The corresponding methyl esters, obtained in 70−81% overall yield, were identical in all respects with independently prepared samples.



5 (R = CH_3) or **9** (R = H)

1a (R' = C_6H_5) or **1b** (R' = *t*-C_4H_9O)

(21) In this preliminary study the AM1 semiempirical molecular orbital method was employed (Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902). All calculations were performed with the AMPAC 4.5 code (Semichem, Shawnes, KS 66216). The RHF, closed-shell, ground state was used in all cases. Force calculations were performed on the local minima and the transition states to verify that they had no and one and only one negative force constant, respectively. In addition, some *ab initio* calculations have been carried out with the 3-21G* basis set using the Gaussian 92 program on stationary points found at the semiemprical level (Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, W. P. M.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Reploge, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92*; Gausssian Inc.: Pittsburgh, PA, 1992). Details can be found in the Supporting Information.

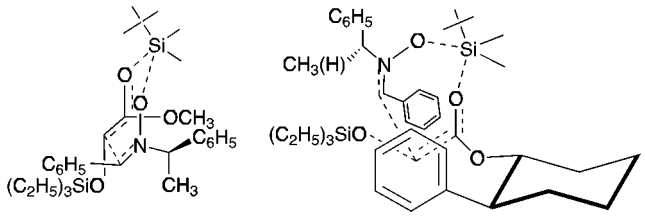


Figure 1. Proposed transition states for the formation of (2*S*,3*S*)-phenylisoserines **4** (left) and **8** and **10** (right).

In summary, a novel, nitrone−ketene acetal based approach to enantiopure (2*S*,3*S*)-*N*-benzoyl- and *N*-boc-phenylisoserine has been realized. The convergent approach, which proceeds in up to 59% overall yield and requires only three operations from the starting nitrones, may also prove useful for the enantioselective synthesis of other β-amino acid derivatives.

Experimental Section

Isolation of the crude product was generally accomplished by pouring the reaction mixture into water and then thoroughly extracting the separated aqueous phase with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhydrous Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium−benzophenone, and methanol was distilled from magnesium. Pentane, dichloromethane, acetonitrile, *N*,*N*-dimethylformamide, HMPA, and triethylamine were distilled from calcium hydride.[22]

(*R*)-(−)-*N*-(α-Methylbenzyl)-*C*-phenylnitrone (2). To a solution of 11.36 g (50.0 mmol) of (*R*)-(+)-*N*-(α-methylbenzyl)-hydroxylammonium oxalate[12] in 250 mL of dry THF under argon was added 16.8 g (200 mmol) of sodium bicarbonate, 5.08 mL (5.30 g, 50.0 mmol) of benzaldehyde, and an excess of anhydrous magnesium sulfate. The reaction mixture was stirred at 20 °C overnight and then filtered through a pad of anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure to leave an oil, which was purified by silica gel chromatography with 20% ethyl acetate in hexane to give 11.04 g (98%) of nitrone **2**: $[\alpha]^{20}_D$ −48.2 (*c* 1.0, $CHCl_3$); mp 52 °C; ^{1}H NMR (200 MHz) δ 1.87 (d, J = 6.9 Hz, 3 H), 5.16 (q, J = 6.9 Hz, 1 H), 7.20−7.40 (m, 3 H), 7.40−7.60 (m, 6 H), 8.15−8.30 (m, 2 H); ^{13}C NMR (50.3 MHz) δ 18.8 (CH_3), 74.6 (CH), 126.9 (2 CH), 128.1 (2 CH), 128.3 (3 CH), 128.4 (2 CH), 129.9 (CH), 130.4 (C), 132.6 (CH), 138.3 (C); mass spectrum (CI) m/z 226 (MH^+, 100%), 210, 122, 105.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.76; H, 6.73; N, 5.93.

(*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-methoxy-2-(triethylsilyloxy)ethylene (3). A mixture of 7.7 mL (9.0 g, 100 mmol) of methyl glycolate, 17.0 g (250 mmol) of imidazole, and 20.3 mL (18.2 g, 120 mmol) of triethylsilyl chloride in 100 mL of dry DMF was stirred at 20 °C overnight. Pentane and saturated aqueous sodium bicarbonate were added to the mixture, and the product was then isolated in the usual manner to give 21.0 g of methyl (triethylsilyloxy)acetate: ^{1}H NMR (200 MHz) δ 0.65 (qd, J = 8.0, 1.5 Hz, 6 H), 0.98 (t, J = 8.0 Hz, 9 H), 3.75 (s, 3 H), 4.25 (s, 2 H); ^{13}C NMR (75.5 MHz) δ 4.1 (3 CH_2), 6.2 (3 CH_3), 51.3 (CH_3), 61.1 (CH_2), 171.8 (C); IR 1766, 1149, cm^{-1}; mass spectrum (CI) m/z 222 (69%), 205 (MH^+, 62%), 175 (100%), 132, 117.

Anal. Calcd for $C_9H_{20}O_3Si$: C, 52.90; H, 9.86. Found: C, 52.78; H, 9.84.

To a stirred solution of 1.98 mL (1.66 g, 11.7 mmol) of tetramethylpiperidine in 48 mL of THF at 0 °C under argon

(22) For the analytical instruments used in this work, see: B. M. de Azevedo, M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940.

was added dropwise 4.30 mL (10.8 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes. The resulting solution was stirred for 15 min at 0 °C and then cooled to −100 °C and treated dropwise first with a solution of 1.93 g (12.8 mmol) of *tert*-butyldimethylsilyl chloride in 4.0 mL of THF and then with a solution of 2.04 g (10.0 mmol) of the above ester in 8.0 mL of THF. The reaction mixture was stirred at −100 °C for an additional 10 min, whereupon it was allowed to warm slowly to 20 °C. After being stirred for 1 h at this temperature, the reaction mixture was diluted with 400 mL of hexane and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in hexane, which was washed with saturated aqueous sodium bicarbonate and water and dried over anhyd magnesium sulfate. The crude product was then isolated in the normal manner and purified by evaporative distillation (40 °C/0.005 mbar) to give 1.83 g (58%) of ketene acetal **3** (*E*:*Z*, 74:26) as a colorless oil: ^{1}H NMR (200 MHz, *E*-isomer) δ 0.13 (s, 6 H), 0.63 (q, J = 7.8 Hz, 6 H), 0.91 (s, 9 H), 0.96 (t, I = 7.8 Hz, 9 H), 3.61 (s, 3 H), 5.41 (s, 1 H); ^{13}C NMR (50.3 MHz, *E*-isomer) δ −5.0 (2 CH_3), 4.3 (3 CH_2), 6.5 (3 CH_3), 18.0 (C), 25.6 (3 CH_3), 56.0 (CH_3), 108.7 (CH), 148.9 (C); IR 3061,1701, 1229, 1178 cm^{-1}; mass spectrum (CI) *m*/*z* 394, 319 (MH^+, 100%), 305, 275, 132.

Anal. Calcd for $C_{15}H_{34}O_3Si_2$: C, 56.55; H, 10.76. Found: C, 56.53; H, 10.89.

(*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-(((1*R*,2*S*)-2-phenylcyclohexyl)oxy)-2-(triethylsilyloxy)ethylene (7). A mixture of 3.89 g (16.6 mmol) of (1*R*,2*S*)-2-phenylcyclohexyl glycolate,[18] 2.80 g (41.1 mmol) of imidazole, and 3.35 mL (3.01 g, 20.0 mmol) of triethylsilyl chloride in 41 mL of dry DMF was stirred at 20 °C overnight. Pentane and saturated aqueous sodium bicarbonate were added to the mixture, and the product was then isolated in the usual manner to give 5.80 g (100%) of (1*R*,2*S*)-2-phenylcyclohexyl (triethylsilyloxy)-acetate: $[\alpha]^{23}_D$ −16.7 (*c* 2.2, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.47 (qd, J = 8.0, 1.0 Hz, 6 H), 0.86 (t, J = 8.0 Hz, 9 H), 1.20−1.75 (m, 4 H), 1.75−2.00 (m, 3 H), 2.05−2.30 (m, 1 H) ; 2.64 (td, J = 11.0, 3.7 Hz, 1 H), 3.89 (ABq, J_{AB} = 16.7 Hz, δA-δB = 36.1 Hz, 2 H), 5.06 (deformed td, J = 10.5, 4.5 Hz, 1 H), 7.10−7.30 (m, 5 H); ^{13}C NMR (75.5 MHz) δ 4.1 (3 CH_2), 6.4 (3 CH_3), 24.7 (CH_2), 25.7 (CH_2), 32.2 (CH_2), 33.9 (CH_2), 49.7 (CH), 61.0 (CH_2), 76.0 (CH), 126.3 (CH), 127.3 (2 CH), 128.2 (2 CH), 142.8 (C), 170.8 (C); IR 3085, 3063, 3030, 1755, 1603, 1149 cm^{-1}; mass spectrum (CI) *m*/*z* 366, 349 (MH^+, 100%), 319, 208, 191, 178, 159, 132, 117, 108.

Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.33; H, 9.23.

To a stirred solution of 2.20 mL (1.68 g, 10.4 mmol) of hexamethyldisilazane in 34 mL of THF at 0 °C under argon was added dropwise 4.50 mL (9.45 mmol) of a 2.1 M solution of *n*-butyllithium in hexanes. The resulting solution was stirred for 15 min at 0 °C and then cooled to −78 °C, and 8.60 mL of HMPA was slowly added. After 5 min, the solution was cooled to −100 °C and treated first with a solution of 3.00 g (8.62 mmol) of the above ester in 3.4 mL of THF over 5 min and then with a solution of 1.69 g (11.2 mmol) of *tert*-butyldimethylsilyl chloride in 1.7 mL of THF. The reaction mixture was stirred at −100 °C for an additional 10 min, whereupon it was allowed to warm slowly to 20 °C. After being stirred for 1 h at this temperature, the reaction mixture was diluted with 260 mL of cold hexane and 86 mL of saturated aqueous sodium bicarbonate was added. The crude product was isolated in the usual way and purified by evaporative distillation (150−160 °C/0.03 mbar) to give 2.92 g (73%) of ketene acetal **7** (*E*:*Z*, 5:95) as a colorless oil: ^{1}H NMR (300 MHz) δ −0.06 (s, 3 H), 0.01 (s, 3 H), 0.55 (q, J = 7.9 Hz, 6 H), 0.86 (s, 9 H), 0.91 (t, J = 7.9 Hz, 9 H), 1.20−1.95 (m, 7 H), 2.25−2.35 (m, 1 H), 2.55 (td, J = 11.2, 3.8 Hz, 1 H), 3.83 (deformed td, J = 10.0, 4.2 Hz, 1 H), 5.11 (s, 1 H), 7.10−7.35 (m, 5 H); ^{13}C NMR (75.5 MHz) δ −4.4 (2 CH_3), 4.7 (3 CH_2), 6.6 (3 CH_3), 18.2 (C), 24.8 (CH_2), 25.7 (3 CH_3) ; 25.9 (CH_2), 32.4 (CH_2), 34.0 (CH_2), 50.5 (CH), 81.1 (CH), 109.9 (CH), 126,1 (CH), 128.0 (2 CH), 128.1 (2 CH), 144.2 (C), 145.9 (C); IR 3083, 3063, 3030, 1704, 1604, 1202, 1159 cm^{-1}.

Anal. Calcd for $C_{26}H_{46}O_3Si_2$: M_r, 462.2985. Found: M_r (mass spectrum), 462.2965.

Nitrone−Ketene Acetal Condensations. General Procedure. The pure ketene acetal was added over 1 h to a stirred solution at 20 °C under argon of the nitrone in 1:1 acetonitrile−dichloromethane containing zinc iodide (0.5−1 equiv, dried under vacuum for 10 min at 300 °C). After being stirred for an additional 1 h at 20 °C, the reaction mixture was processed with ether in the normal manner and the crude product was purified by silica gel chromatography with ether in hexane to give the adduct.

(A) (*R*)-(−)-*N*-(α-Methylbenzyl)-*C*-phenylnitrone (2) with (*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-methoxy-2-(triethylsilyloxy)ethylene (3) To Give 4. From 293 mg (1.30 mmol) of nitrone **2** and 831 mg (2.61 mmol) of ketene acetal **3** in 2.6 mL of solvent was obtained 696 mg (98%) of a mixture (**4**) of the four diastereomers (93% anti (80:20), 7% syn (65:35)),[14] which could be partially separated by repeated chromatography: ^{1}H NMR (300 MHz) major anti (2*S*,3*S*) δ 0.20−0.40 (m, 6 H), 0.26 (s, 3 H), 0.51 (s, 3 H), 0.62 (t, J = 7.9 Hz, 9 H), 0.96 (s, 9 H), 1.26 (d, J = 6.6 Hz, 3 H), 3.71 (s, 3 H), 3.80 (q, J = 6.6 Hz, 1 H), 4.14 (d, J = 10.4 Hz, 1 H), 4.68 (d, J = 10.4 Hz, 1 H), 7.10−7.50 (m, 10 H); minor anti (2*R*,3*R*, selected resonances) δ 1.02 (d, J = 6.9 Hz, 3 H), 3.57 (s, 3 H), 4.23 (q, J = 6.9 Hz, 1 H), 4.55 (d, J = 9.7 Hz, 1 H); major syn δ 0.18 (s, 3 H), 0.26 (s, 3 H), 0.59 (q, J = 7.6 Hz, 6 H), 0.90−1.00 (m, 18 H), 1.35 (d, J = 6.6 Hz, 3 H), 3.23 (s, 3 H), 3.94 (q, J = 6.6 Hz, 1 H), 4.00 (d, J = 7.8 Hz, 1 H), 4.72 (d, J = 7.8 Hz, 1 H), 7.10−7.50 (m, 10 H); minor syn δ −0.07 (m, 3 H), 0.13 (s, 3 H), 0.59 (q, J = 7.6 Hz, 6 H), 0.90−0.95 (m, 18 H), 1.01 (d, J = 6.9 Hz, 3 H), 3.38 (s, 3 H), 4.2 (deformed d, 1 H), 4.44 (q, J = 6.9 Hz, 1 H), 4.58 (d, J = 6.1 Hz, 1 H), 7.10−7.50 (m, 10 H); IR 3088, 3063, 3029, 1743, 1605, 1118 cm^{-1}; mass spectrum (CI) *m*/*z* 544 (MH^+), 340 (100%), 236, 105.

Anal. Calcd for $C_{30}H_{49}O_4NSi_2$: C, 66.25; H, 9.08; N, 2.58. Found: C, 66.54; H, 9.24; N, 2.54.

(B) *N*-Benzyl-*C*-phenylnitrone (6) with (*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-(((1*R*,2*S*)-2-phenylcyclohexyl)oxy)-2-(triethylsilyloxy)ethylene (7) To Give 8. From 662 mg (3.14 mmol) of nitrone **6** and 2.90 g (6.27 mmol) of ketene acetal **7** in 6.3 mL of solvent was obtained 1.99 g (94%) of a mixture (**8**) of the four diastereomers (90% anti (97:3), 10% syn (80:20)),[14] which could be partially separated by repeated chromatography: ^{1}H NMR (200 MHz) major anti (2*S*,3*S*) δ 0.55 to −0.25 (m, 3 H), −0.15 to 0.10 (m, 3 H), 0.46 (qd, J = 7.9, 2.7 Hz, 6 H), 0.80−0.96 (m, 18 H), 1.10−2.05 (m, 8 H), 2.66 (deformed td, J = 11.2, 3.4 Hz, 1 H), 3.50−3.80 (m, A of an AB, 1 H), 3.93 (d, B of an AB, J = 13.3 Hz, 1 H), 4.46 (d, J = 4.1 Hz, 1 H), 4.90−5.10 (m, 1 H), 4.99 (deformed td, J = 10.5, 3.7 Hz, 1 H), 7.05−7.40 (m, 13 H), 7.55−7.75 (m, 2 H); major syn (selected resonance) δ 4.37 (d, J = 6.2 Hz, 1 H); ^{13}C NMR (75.5 MHz) major anti (2*S*,3*S*) δ −5.5 (CH_3), −4.9 (CH_3), 4.7 (3 CH_2), 6.8 (3 CH_3), 18.3 (C), 24.6 (CH_2), 25.8 (CH_2), 26.2 (3 CH_3), 32.1 (CH_2), 34.0 (CH_2), 49.9 (CH), 59.3 (CH_2), 71.7 (CH), 71.9 (CH), 76.5 (CH), 126.4 (CH), 126.9 (CH), 127.3 (CH), 127.5 (2 CH), 127.6 (2 CH), 127.7 (2 CH), 128.3 (2 CH), 130.4 (2 CH), 130.6 (2 CH), 135.7 (C), 139.2 (C), 143.0 (C), 172.5 (C); major syn (selected resonances) δ −4.3 (CH_3), 26.9 (CH_2), 30.9 (CH_2), 49.4 (CH), 61.0 (CH_2), 73.6 (CH), 78.0 (CH), 127.1 (CH), 131.6 (CH), 135.1 (C), 138.3 (C), 143.3 (C), 171.4 (C); IR 3087, 3063, 3030, 1748, 1604, 1140 cm^{-1}; mass spectrum (EI) *m*/*z* 674 (M^+), 658, 644, 616, 588, 326, 159, 91 (100%).

Anal. Calcd for $C_{40}H_{59}O_4NSi_2$: C, 71.27; H, 8.82; N, 2.08. Found: C, 71.33; H, 9.07; N, 2.01.

(C) (*R*)-(−)-*N*-(α-Methylbenzyl)-*C*-phenylnitrone (2) with (*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-(((1*R*,2*S*)-2-phenylcyclohexyl)oxy)-2-(triethylsilyloxy)ethylene (7) To Give 10. From 110 mg (0.49 mmol) of nitrone **2** and 450 mg (0.97 mmol) of ketene acetal **7** in 1.0 mL of solvent was obtained 329 mg (98%) of the 2*S*,3*S* anti diastereomer **10** as a viscous oil: $[\alpha]^{20}_D$ 2.0 (*c* 1.6, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.04 (q, J = 7.9 Hz, 6 H), 0.25 (s, 3 H), 0.38 (s, 3 H), 0.55 (t, J = 7.9 Hz, 9 H), 0.96 (s, 9 H), 1.29 (d, J = 6.7 Hz, 3 H), 1.40−1.70 (m, 4 H), 1.75−2.05 (m, 3 H), 2.35−2.50 (m, 1 H), 2.77 (deformed td, J = 11.0, 3.4 Hz, 1 H), 3.97 (q, J = 6.7 Hz, 1 H), 4.18 (d, J = 7.9 Hz, 1 H), 4.51 (d, J = 7.9 Hz, 1 H), 4.96 (deformed td, J

= 10.2, 4.5 Hz, 1H), 7.05−7.45 (m, 15 H); ^{13}C NMR (75.5 MHz) δ −3.8 (CH_3), −2.6 (CH_3), 4.4 (3 CH_2), 6.5 (3 CH_3), 18.8 (C), 21.0 (CH_3), 24.8 (CH_2), 25.9 (CH_2), 26.6 (3 CH_3), 32.3 (CH_2), 34.6 (CH_2), 49.7 (CH), 64.9 (CH), 71.5 (CH), 71.9 (CH), 77.4 (CH), 126.5 (CH), 126.7 (2 CH), 126.9 (CH), 127.6 (2 CH), 127.8 (2 CH), 128.2 (2 CH), 128.4 (2 CH), 128.7 (CH), 131.8 (2 CH), 135.3 (C), 143.3 (C), 143.7 (C), 172.5 (C); IR 3087, 3062, 3030, 1744, 1605, 1246, 1123 cm^{-1}; mass spectrum (EI) m/z 688 (M^+), 672, 658, 630, 602, 340, 236, 159, 105 (100%), 91, 75, 41.

Anal. Calcd for $C_{41}H_{61}O_4NSi_2$: C, 71.57; H, 8.94 ; N, 2.04. Found: C, 71.90; H, 8.96; N, 2.15.

Deprotection−Cyclization of Condensation Products to Isoxazolidinones. General Procedure. A stirred solution of the condensation product in acetic acid under argon was heated at 50 °C until no starting material remained (TLC). After being allowed to cool to 20 °C, the reaction mixture was treated with a solution of HF in water and then stirred until no further evolution was observed (TLC), whereupon it was partially concentrated under reduced pressure. The crude product was isolated with ether in the usual manner and purified by silica gel chromatography with ethyl acetate in hexane to give the isoxazolidinone as a white solid.

(A) (3*S*,4*S*)-4-Hydroxy-3-phenyl-*N*-(1-phenylethyl)isoxazolidinone (5) from 4. From 800 mg (1.47 mmol) of the mixture (**4**) of the four diastereomers, 30 mL of acetic acid, and 15 mL of 0.1 M HF, 188 mg (45%) of isoxazolidinone **5** and 37.4 mg (6%) of the corresponding *O*-*tert*-butyldimethylsilyl derivative were obtained, together with small amounts of the diastereomeric products. Minor trans diastereomer: ^{1}H NMR (200 MHz) δ 1.51 (d, J = 7.8 Hz, 3 H), 2.95 (br s, 1 H), 4.13 (q, J = 6.8 Hz, 1 H), 4.23 (d, J = 10.3 Hz, 1H), 4.60 (d, J = 10.3 Hz, 1 H), 7.10−7.20 (m, 4 H), 7.20−7.35 (m, 6 H); ^{13}C NMR (50.3 MHz) δ 15.8 (CH_3), 65.0 (CH), 74.1 (CH), 76.2 (CH), 127.6 (2 CH), 127.9 (CH), 128.1 (2 CH), 128.2 (2 CH), 128.6 (CH), 128.8 (2 CH), 135.8 (C), 139.5 (C), 173.3 (C); IR 3425, 3088, 3064, 3034, 1782, 1135 cm^{-1}; mass spectrum (CI) *m*/*z* 284 (MH^+,100%), 210 , 120, 105. Major cis diastereomer: ^{1}H NMR (200 MHz) δ 1.59 (d, J = 6.9 Hz, 3 H), 2.10−2.55 (br s, 1H), 3.99 (q, J = 6.9 Hz, 1 H), 4.20−4.50 (m, 2 H), 7.05−7.40 (m, 10 H). Minor cis diastereomer: ^{1}H NMR (200 MHz) δ 1.47 (d, J = 6.5 Hz, 3 H), 2.00 (br s, 1 H), 4.26 (q, J = 6,5 Hz, 1 H), 4.71 (deformed ABq, J_{AB} = 7.7 Hz, $\delta_A-\delta_B$ = 23.8 Hz, 2 H), 7.10−7.60 (m, 10 H). Isoxazolidinone **5**: mp 37−40 °C; $[\alpha]^{20}_D$ 148 (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz) δ 1.56 (d, J = 7.1 Hz, 3 H), 2.64 (deformed d, J = 3.2 Hz, 1 H), 3.86 (d, J = 10.9 Hz, 1 H), 3.95 (q, J = 7,1 Hz, 1 H), 4.56 (deformed dd, J = 10.9, 3.2 Hz, 1 H), 7.15−7.27 (m, 2 H), 7.28−7.36 (m, 3 H), 7.38−7.45 (m, 5 H); ^{13}C NMR (50.3 MHz) δ 20.0 (CH_3), 63.4 (CH), 73.1 (CH), 75.8 (CH), 127.7 (2 CH), 128.3 (4 CH), 129.1 (4 CH), 172.8 (C); IR 3342, 3089, 3064, 3032, 1782, 1131 cm^{-1}; mass spectrum (EI) *m*/*z* 283 (M^+), 226, 120, 105 (100%), 91, 77, 65, 51, 39.

Anal. Calcd for $C_{17}H_{17}O_3N$: M_r, 283.1208. Found: M_r (mass spectrum), 283.1216.

(B) (3*S*,4*S*)-4-Hydroxy-3-phenyl-*N*-(1-phenylethyl)isoxazolidinone (5) from 10. From 168 mg (0.24 mmol) of adduct **10**, 4.8 mL of acetic acid, and 2.44 mL of 0.1 M HF, 51.2 mg (74%) of isoxazolidinone **5**, identical with that above, was produced.

(C) (3*S*,4*S*)-*N*-Benzyl-4-hydroxy-3-phenylisoxazolidinone (9) from 8. From 400 mg (0.59 mmol) of adduct **8** (92% 2*S*,3*S*), 12 mL of acetic acid, and 0.100 mL of 48% HF was obtained 130 mg (72% overall) of isoxazolidinone **9**: mp 96−97 °C; $[\alpha]^{20}_D$ 166 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.84 (d, J = 3.9 Hz, 1 H), 3.92 (d, J = 14.8 Hz, 1 H), 4.15 (d, J = 10.8 Hz, 1 H), 4.24 (d, J = 14.8 Hz, 1 H), 4.65 (dd, J = 10.8, 3.9 Hz, 1 H), 7.28−7.38 (m, 5 H), 7.40−7.48 (m, 3 H), 7.50−7.55 (m, 2 H); ^{13}C NMR (75.5 MHz) δ 60.9 (CH_2), 75.6 (CH), 76.3 (CH), 127.7 (2 CH), 128.0 (CH), 128.5 (2 CH), 129.3 (4 CH), 129.4 (CH), 134.5 (C), 134.7 (C), 172.8 (C); IR 3418, 3107, 3088, 3063, 3032, 1779, 1603, 1136 cm^{-1}; mass spectrum (CI) m/z 287, 270 (MH^+, 100%), 226, 196, 124, 106, 76.

Anal. Calcd for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61 ; N, 5.20. Found: C, 71.38; H, 5.71; N, 5.00.

(−)-Methyl (2*S*,3*S*)-3-Benzamido-2-hydroxy-3-phenylpropanoate (1a). (A) From Isoxazolidinone 5. A mixture of 55.5 mg (0.20 mmol) of isoxazolidinone **5** and 19.4 mg of $Pd(OH)_2$ on carbon (Pearlman's catalyst) in 3.2 mL of methanol containing a few drops of perchloric acid was vigorously stirred under hydrogen until no starting material remained (TLC) and then placed under an argon atmosphere and neutralized with 10% aqueous sodium bicarbonate. The resulting mixture was cooled to 0 °C and treated with an additional 4.7 mL of 10% aqueous sodium bicarbonate followed by 68 μL (82 mg, 0.59 mmol) of benzoyl chloride. After completion of the reaction (TLC), the mixture was acidified to pH 1 with 6 N HCl and thoroughly extracted with dichloromethane, which was then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue, dissolved in a minimum amount of acetone, yielded 57 mg of acid on addition of hexane. Treatment of the acid with CH_2N_2 in ether at 0 °C provided the corresponding methyl ester, which was purified by silica gel chromatography with ethyl acetate in hexane to give 42.6 mg (73%) of **1a** as a white solid.

(B) From Isoxazolidinone 9. A mixture of 30.0 mg (0.11 mmol) of isoxazolidinone **9** and 11.0 mg of $Pd(OH)_2$ on carbon (Pearlman's catalyst) in 1.8 mL of methanol containing a few drops of perchloric acid was vigorously stirred under hydrogen until no starting material remained (TLC) and then placed under an argon atmosphere and neutralized with 10% aqueous sodium bicarbonate. The resulting mixture was cooled to 0 °C and treated with an additional 2.7 mL of 10% aqueous sodium bicarbonate followed by 39 μL (47 mg, 0.34 mmol) of benzoyl chloride. After completion of the reaction (TLC), the mixture was processed as above to give 27.4 mg of acid, which provided 23.3 mg (70%) of methyl ester **1a**, identical to that obtained in A: mp 158−159 °C (lit.[23] mp 158−159 °C); $[\alpha]^{21}_D$ −23.7 (*c* 1.1, $CHCl_3$) [lit.[5a] $[\alpha]^{20}_D$ −23 (*c* 1, $CHCl_3$)]; ^{1}H NMR (200 MHz) δ 3.05 (d, J = 6.5 Hz, 1 H); 3,71 (s, 3 H), 4.70 (dd, J = 6.5, 3.8 Hz, 1 H), 5.61 (dd, J = 8.6, 3.8 Hz, 1 H), 7.14 (deformed d, J = 8.6 Hz, 1 H), 7.25−7.36 (m, 5 H), 7.37−7.56 (m, 3 H), 7.76−7.84 (m, 2 H); ^{13}C NMR (75.5 MHz) δ 52.5 (CH_3), 55.6 (CH), 73.0 (CH), 127.0 (2 CH), 127.4 (2 CH), 128.2 (CH), 128.5 (4 CH), 131.6 (CH), 134.1 (C), 136.6 (C), 166.7 (C), 172.1 (C); IR (KBr) 3446, 3323, 3089, 3064, 3032, 3004, 1745, 1643, 1604, 1257 cm^{-1}; mass spectrum (CI) *m*/*z* 300 (MH^+, 100%).

Anal. Calcd for $C_{17}H_{17}O_4N$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.30; H, 5.60; N, 4.64.

(+)-Methyl (2*S*,3*S*)-3-(*N*-(*tert*-Butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoate (1b). (A) From Isoxazolidinone 5. A mixture of 58 mg (0.20 mmol) of isoxazolidinone **5** and 17.6 mg of $Pd(OH)_2$ on carbon (Pearlman's catalyst) in 3 mL of methanol−acetic acid (98:2) was vigorously stirred under hydrogen until no starting material remained (TLC) and then placed under an argon atmosphere and neutralized with triethylamine. The resulting mixture was treated with an additional 171 μL (124 mg, 1.23 mmol) of triethylamine followed by 223 mg (1.02 mmol) of di-*tert*-butyl dicarbonate. After being stirred overnight, the mixture was diluted with methanol and filtered to remove the catalyst, and the filtrate was partitioned between ether and water. The aqueous phase was separated, acidified at 0 °C to pH 2−4 with 2 N HCl, and thoroughly extracted with dichloromethane, which was then dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the acid as a white solid. Treatment of the acid with CH_2N_2 in ether at 0 °C provided the corresponding methyl ester, which was purified by silica gel chromatography with ethyl acetate in hexane to afford 49.0 mg (81%) of methyl ester **1b** as a white solid.

(B) From Isoxazolidinone 9. A mixture of 55.1 mg (0.20 mmol) of isoxazolidinone **9** and 20.5 mg of $Pd(OH)_2$ on carbon (Pearlman's catalyst) in 3.2 mL of methanol containing a few drops of perchloric acid was vigorously stirred under hydrogen until no starting material remained (TLC) and then placed under an argon atmosphere and neutralized with triethylamine. The resulting mixture was treated with an additional 171 μL (124 mg, 1.23 mmol) of triethylamine followed by 223 mg (1.02 mmol) of di-*tert*-butyl dicarbonate. After completion

(23) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.

of the reaction (TLC), the mixture was processed as above to give the acid, which provided 42.1 mg (70%) of methyl ester **1b**, identical to that obtained in A: mp 136−137 °C; $[\alpha]^{21}_D$ 30.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 Hz) δ 1.41 (br s, 9 H), 2.85 (deformed d, J = 6.9 Hz, 1 H), 3.68 (s, 3 H), 4.58 (deformed dd, J = 6.2, 3.4 Hz, 1 H), 5.08 (deformed dd, J = 8.7, 2.6 Hz, 1 H), 5.57 (deformed d, J = 7.9 Hz, 1 H), 7.15−7.40 (m, 5 H); ^{13}C NMR (100.6 MHz) δ 28.3 (3 CH_3), 52.6 (CH_3), 56.7 (CH), 73.3 (CH), 79.9 (C), 127.2 (2 CH), 128.1 (CH), 128.5 (2 CH), 136.7 (C), 155.0 (C), 172.3 (C); IR (KBr) 3387, 3362, 3038, 3024, 3008, 1722, 1693, 1234, 1172 cm^{-1}; mass spectrum (CI) m/z 313, 296 (MH^+, 100%), 257, 240.

Anal. Calcd for $C_{15}H_{21}O_5N$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.86; H, 7.10; N, 4.64.

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Supporting Information Available: Details on the theoretical calcuations (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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