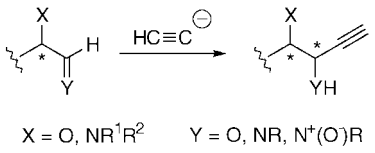
Asymmetric Addition Reactions of Lithium (Trimethylsilyl)acetylide with Chiral α-Amino Nitrones. Synthesis of Diastereomerically Pure *N*-Hydroxy-α-amino Acids†



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Received August 7, 1997

The nucleophilic addition of alkynyl organometallic reagents to unsaturated C=X systems (X = O, NR) is a very convenient and reliable strategy for carbon−carbon bond formation, but it has not been used as extensively as other organometallic nucleophilic additions to those systems.[1] Several reports on the addition of alkynyl organometallic reagents to carbonyl compounds can be found in the literature.[2] Also, successful examples of ethynylation of carbon−nitrogen double bonds have been reported.[3] In previous papers, we have described the stereoselective addition of (trimethylsilyl)acetylene to α-alkoxy nitrones;[4] in addition, we found that the stereochemical course of the reaction could be controlled by the appropriate use of Lewis acids. To expand our knowledge of nucleophilic additions to nitrones, we wish to extend this reaction toward the preparation of derivatives containing other functionalities such as an amino group at the α-position of the nitrone moiety.[5]

In this paper, the ethynylation of α-amino nitrones derived from L-serine is detailed. Of particular interest is the observation that the stereoselectivity of the reaction depends on the protecting groups in the starting material.[6] In addition, the obtained propargyl hydroxylamines can be further converted into the corresponding N-hydroxy-α-amino acids by the oxidation of the acetylene group.[2i] *N*-Hydroxy-α-amino acids are an important class of unnatural α-amino acids. These amino acid derivatives are both intermediates in metabolic pathways and components of naturally occurring metabolites such as mycelianamide.[7] Because of that interest, several methodologies for their synthesis[8] and those of some phosphonate derivatives[9] have recently been reported.

Nitrone **1** (Scheme 1), readily available from L-serine,[10] was treated with an excess amount (3.0 equiv) of lithium (trimethylsilyl)acetylide, at −80 °C, in THF as a solvent, to provide the propargyl hydroxylamine **2** in quantitative yield. The diastereoselectivity was sufficiently high so that the minor diastereomer was not observed by NMR spectroscopy. The 3*S*,4*R* configuration of **2** was confirmed by an independent synthesis (vide infra). Desilylation with tetrabutylammonium fluoride in anhydrous THF, followed by acetylation (Ac_2O, Py) of the *N*-hydroxy group, afforded compound **4** in 88% purified yield. The ethynyl group was oxidized according to the method of Czernecki.[2h,11] Unfortunately, the use of sodium bicarbonate in the reaction medium results in the loss of the acetyl group.[12] In addition, workup with sodium bisulfite gave a complex mixture from which we could not identify optimal conditions for purifying the desired carboxylic acid. As a remedy for this situation, a simple isolation procedure was developed, as follows. The oxidation was conducted in the usual way, with the exception that no sodium bicarbonate is added to the reaction mixture to prevent the hydrolysis of the acetyl group. At the completion of the reaction, water and ethyl acetate were added, and the organic layer was separated, filtered through a pad of Florisil, and eluted with ethyl acetate. The ruthenium is retained on the Florisil, while the filtrate contained only the desired carboxylic acid, which

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† Dedicated to the memory of Professor Stanislas Czernecki.

(1) For general treatises on nucleophilic additions to unsaturated systems see: (a) *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 1 (Schreiber, S. L., Ed.), Vol. 2 (Heathcock, C. H., Ed.). (b) *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Houben-Weyl, Thieme: Stuttgart, 1996; Vols. 2 and 3.

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(5) For other nucleophilic additions to α-amino nitrones see: (a) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2381−2401. (b) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1996**, *61*, 9028−9032. See also ref 6.

(6) Such a tunable stereoselectivity in the addition of organometallic reagents to α-amino nitrones has been well-demonstrated in our laboratory. See: Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett.* **1997**, *38*, 1813−1816.

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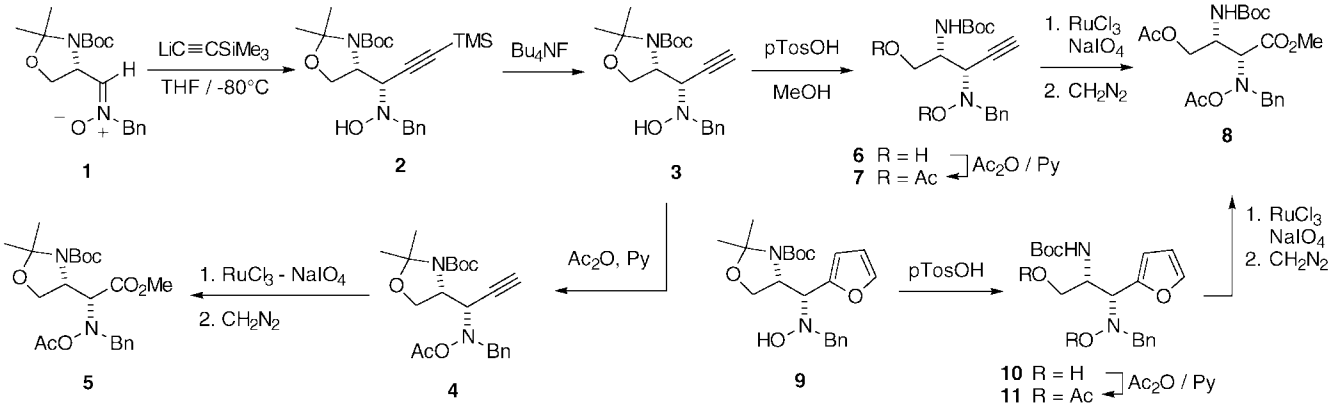
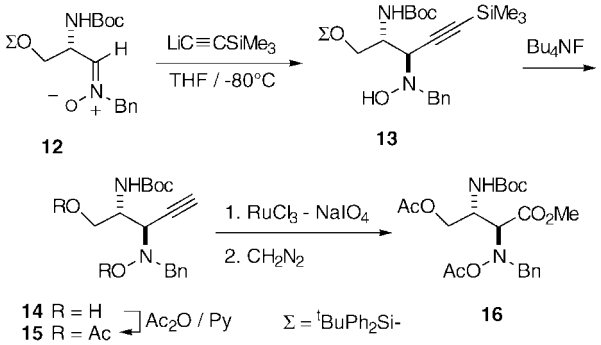
(12) The lability of the acetoxyamino group under both basic and acidic conditions has been registered in several instances in our laboratory.

S0022-3263(97)01477-1 CCC: $15.00
Published on Web 07/17/1998

Scheme 1



Scheme 2



can be purified as the corresponding methyl ester **5**. With this procedure, which is more similar to that originally reported by Sharpless,[13] the *N*-hydroxy-α-amino ester **5** was isolated in 72% yield.

Markedly, the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ at room temperature showed compounds **4** and **5** to be rather complex mixtures of rotamers, due to the amide conformational isomers. First-order spectra could be obtained in most cases by registering them in DMSO-d_6 at high temperatures (80−120 °C). The existence of a high-energy dynamic equilibrium for 4-substituted 3-(*tert*-butoxycarbonyl)oxazolidines had been reported by Garner and Park.[14]

For comparison purposes (vide infra), hydroxylamine **3** was deprotected to afford amino alcohol **6** (94%), which was diacetylated to give **7** in 97% yield. Ruthenium-mediated oxidation of compound **7** as described above followed by esterification with diazomethane provided the corresponding methyl ester **8** in 80% overall yield.

The assigned 3*S*,4*R* stereochemistry of **2** was confirmed by an independent synthesis of the *N*-hydroxy-α-amino ester **8** starting from the furan derivative[15] **9**, whose absolute configuration had been unambiguously confirmed by us.[16] The strategy for that synthesis is illustrated in Scheme 1.

It is worth mentioning that oxidation of the furan ring according to our previous report[17] needed more reaction time than the ethynyl group. As a consequence, some byproducts coming from the oxidation of the benzyl groups were observed.[17] In such cases, the acetylene route becomes a more advisable option. Unfortunately, oxidation of **9** after acetylation of the hydroxylamino group following our own procedure failed. All efforts to find conditions that would promote furan oxidation over side reactions were unsuccessful. We thus turned to change the protecting group arrangement of the furfurylhydroxylamine **9**, and compound **11** was synthesized. The oxidation of compound **11** followed by esterification (CH_2N_2, Et_2O) afforded the expected hydroxyamino ester **8** in an acceptable yield (45%). Their physical and spectroscopic (^{1}H and ^{13}C NMR) properties were identical to those of the compound obtained from **3**.

With the completion of an efficient synthesis of the (3*S*,4*R*)-3-amino-4-hydroxy-2-(hydroxyamino)butanoic acid derivatives with two different protecting groups[18] (**5** and **8**), we focused our attention on the preparation of the 3*R*,4*R* isomer. The precursor nitrone **12** (Scheme 2) was prepared following our previously published procedure.[10] The choice of protecting groups was described by our previous results.[6] Addition of lithium (trimethylsilyl)-acetylide to **12** under the conditions described above gave an 85:15 mixture of diastereomers. The desired 3*R*,4*R* diastereomer **13** was isolated in 68% yield by chromatography. To improve the obtained results from the nitrone **12**, we set out to examine other conditions for the nucleophilic addition of the acetylide moiety. These included (i) addition at lower temperatures, (ii) change of solvent, and (iii) addition in the presence of HMPT.[19] Unfortunately, none of these attempts afforded better results than that obtained in THF at −80 °C (80% yield, ds = 85%). Addition at lower temperatures (−100 °C)

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(15) Compound **9** was prepared by us from nitrone **1** and 2-lithiofuran. See: Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Electronic Conference on Trends in Organometallic Chemistry*; Rzepa, H. S., Leach, C., Eds.; Royal Society of Chemistry: London, 1997; Article 003, CD-ROM, ISBN 0-85404-889-8. Internet: http://www.ch.ic.ac.uk/ectoc/ectoc-3/.

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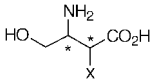
(18) Homologated serines having different functionalities at the α-position are versatile building blocks for asymmetric synthesis. X = N_3: Nitta, H.; Ueda, I.; Hatanaka, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1793−1798. X = OH: Wagner, R.; Tilley, J. W. *J. Org. Chem.* **1990**, *55*, 6289−6291. X = N(OR)R: This work.



(19) The addition in the presence of Lewis acids (in a way similar to that described by us for α-alkoxy nitrones) were not considered due to the lower chemical yield observed under these conditions with other nucleophiles (Merino, P.; Franco, S.; Lanaspa, A.; Merchan, F. L.; Tejero, T. Unpublished results).

gave a poor conversion (20% after 24 h) without substantial increasing of the diastereoselectivity. The use of diethyl ether as a solvent or HMPT as an additive afforded lower selectivities (55% and 65%, respectively) without increasing the chemical yield.

Desilylation of **13** (Bu_4NF, THF) provided **14** (70%), whose physical and spectroscopic (^1H and ^{13}C NMR) properties were rather different than those of its diastereomer **6**, whose relative stereochemistry had been proven by an independent synthesis as described above. Hence, the 3*R*,4*R* stereochemistry of compound **13** had been established.

Protection of **14** as the di-*O*-acetyl derivative **15** and subsequent cleavage of the ethynyl group by the ruthenium protocol afforded the anti *N*-hydroxy-α-amino ester **16** in 76% isolated yield. Also, the physical and spectroscopic properties of this compound were quite different from those of **8**. This further confirmed the stereodivergency of the described process.

In summary, we have demonstrated that secondary *N*-hydroxy-α-amino esters derived from L-serine can be prepared in a highly stereocontrolled manner by changing the protecting groups in the starting α-amino nitrones **1** and **12**. Thus, quite conveniently, both **8** (ds ≥ 95%) and **16** (ds = 85%) are available from L-serine via three- and five-step routes that diverge following the initial acetylide nucleophilic addition to the corresponding nitrones. The use of the ethynyl group as a surrogate of the carboxylic acid, instead of the furan ring, allows releasing of the carboxyl moiety under milder conditions.

Experimental Section

General Methods. For general experimental information see ref 5a. Nitrones **1** and **12** were prepared as described.[10] Compound **9** was prepared as described.[15] Commercial-grade (trimethylsilyl)acetylene was used without further purification.

(3*S*,4*R*)-3-(*N*-Benzyl-*N*-hydroxyamino)-5-hydroxy-4,5-*N*,*O*-isopropylidene-4-[(*tert*-butoxycarbonyl)amino]-1-(trimethylsilyl)-1-pentyne (2). To a solution of (trimethylsilyl)-acetylene (0.89 g, 9.0 mmol) in THF (25 mL) at −20 °C was added *n*-butyllithium (5.7 mL, 1.6 M in hexanes, 9.12 mmol). This solution was stirred for 15 min and then cooled to −80 °C. A cold (−80 °C) solution of nitrone **1** (1.0 g, 3.0 mmol) in THF (40 mL) was then quickly added with a cannula over a period of 15 min. The solution turned yellow and orange as the addition progressed. Stirring at −80 °C was continued for an additional 15 min until all the nitrone was consumed (TLC). The reaction was quenched with saturated NH_4Cl (5 mL), and the result mixture was allowed to warm to room temperature. The reaction mixture was partitioned between Et_2O (25 mL) and saturated aqueous NH_4Cl (50 mL) and then shaken vigorously. The layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure to give a slightly yellow oil (ds ≥ 95% by ^1H NMR). The crude product was chromatographed on silica gel (15:85 EtOAc/hexane) to give the hydroxylamine **2** as a clear oil (1.26 g, 97%): R_f 0.28; $[\alpha]_D$ +37.9 (*c* 1.70, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.22 (s, 9H), 1.31 (s, 3H), 1.47 (s, 3H), 1.54 (s, 9H), 3.43 (d, 1H, J = 10.0 Hz), 3.88 (d, 1H, J = 12.9 Hz), 3.95 (dd, 1H, J = 5.0, 9.2 Hz), 4.07 (d, 1H, J = 9.2 Hz), 4.18 (d, 1H, J = 12.9 Hz), 4.22 (dd, 1H, J = 5.0, 10.0 Hz), 7.18−7.28 (m, 5H), 7.43 (bs, 1H, ex. D_2O); ^{13}C NMR ($CDCl_3$) δ 0.1, 24.6, 27.3, 28.4, 58.5, 60.8, 61.1, 65.9, 81.0, 92.6, 94.0, 100.9, 127.1, 128.1, 128.9, 137.8, 154.2. Anal. Calcd for $C_{23}H_{36}N_2O_4Si$: C, 63.85; H, 8.39; N, 6.48. Found: C, 63.80; H, 8.09; N, 6.40.

(3*S*,4*R*)-3-(*N*-Benzyl-*N*-hydroxyamino)-5-hydroxy-4,5-*N*,*O*-isopropylidene-4-[(*tert*-butoxycarbonyl)amino]-1-pentyne (3). A solution of hydroxylamine **2** (1.0 g, 2.3 mmol) in THF (30 mL) at ambient temperature was treated with 2.5 mL (2.5 mmol) of a 1.0 M solution of Bu_4NF in anhydrous THF. After 1 h, the reaction was quenched by the addition of saturated $NaHCO_3$ and the resulting mixture partitioned between Et_2O (30 mL) and H_2O (50 mL). The layers were separated, and the aqueous solution was extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and filtered under reduced pressure. The resulting oil was chromatographed on silica gel (20:80 EtOAc/hexane) to give propargyl hydroxylamine **3** (0.73 g, 88%) as a white solid: mp 73−75 °C; R_f 0.33; $[\alpha]_D$ +37.1 (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.46 (s, 3H), 1.52 (s, 9H), 2.43 (d, 1H, J = 2.2 Hz), 3.39 (dd, 1H, J = 2.2, 10.1 Hz), 3.87 (d, 1H, J = 13.0 Hz), 3.94 (dd, 1H, J = 5.0, 9.3 Hz), 4.03 (d, 1H, J = 9.3 Hz), 4.18 (d, 1H, J = 13.0 Hz), 4.23 (dd, 1H, J = 5.0, 10.1 Hz), 7.14−7.31 (m, 5H), 7.52 bs, 1H, ex. D_2O); ^{13}C NMR ($CDCl_3$) δ 24.6, 27.3, 28.4, 58.6, 60.2, 60.8, 65.7, 75.4, 79.0, 81.2, 94.1, 127.2, 128.1, 128.9, 137.6, 154.3. Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.57; H, 7.99; N, 7.53.

(3*S*,4*R*)-3-(*N*-acetoxy-*N*-benzylamino)-5-hydroxy-4,5-*N*,*O*-isopropylidene-4-[(*tert*-butoxycarbonyl)amino]-1-pentyne (4). A solution of hydroxylamine **3** (0.70 g, 1.94 mmol) in CH_2Cl_2 (5 mL) at room temperature was treated sequentially with pyridine (5 mL) and acetic anhydride (5 mL). The resulting mixture was allowed to stir for 1 h, at which time it was diluted with CH_2Cl_2 (15 mL) and then poured into saturated aqueous $CuSO_4$ (25 mL). After the mixture was stirred vigorously for 5 min, the layers were separated, and the organic layer was sequentially washed with saturated aqueous $CuSO_4$, water, and brine. The solution was dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil that was subjected to purification by column chromatography on silica gel (20:80 EtOAc/hexane) to give the acetylated product **4** as a colorless oil (0.78 g, 100%): R_f 0.19; $[\alpha]_D$ −29.8 (*c* 0.50, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 1.35 (s, 9H), 1.41 (s, 3H), 1.49 (s, 3H), 1.85 (s, 3H), 3.31 (bs, 1H), 3.95 (dd, 1H, J = 6.2, 8.9 Hz), 4.07 (d, 1H, J = 13.0 Hz), 4.09 (m, 1H), 4.14 (m, 1H), 4.21 (m, 1H), 4.26 (d, 1H, J = 13.0 Hz), 7.30−7.47 (m, 5H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 18.5, 25.9, 26.8, 27.5, 58.0, 58.6, 59.6, 64.2, 77.8, 78.6, 80.9, 93.1, 127.1, 127.6, 129.0, 135.1, 151.1, 168.3. Anal. Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.73; H, 7.79; N, 7.11.

1,1-Dimethylethyl [*R*-(*R*)]-4-[[(*N*-Acetoxy-*N*-benzylamino)-methoxycarbonyl]methyl]-2,2-dimethyl-3-oxazolidinecarboxylate (5). To a well-stirred mixture of CH_3CN (1.3 mL), CCl_4 (1.3 mL), and H_2O (2 mL) were added $NaIO_4$ (0.265 g, 1.24 mmol) and $RuCl_3 \cdot H_2O$ (9.7 mg, 0.043 mmol) sequentially. The resulting yellowish mixture was allowed to stir for 30 min, at which time it was poured into a flask containing pure **4** (0.3 g, 0.75 mmol). The resulting mixture turned black, and additional $NaIO_4$ (0.133 mg, 0.62 mmol) was added. After 5 min, the reaction mixture was partitioned between EtOAc (25 mL) and H_2O (25 mL), the layers were separated, and the aqueous layer was extracted with additional portions of EtOAc (5 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and filtered through a short plug of Florisil, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid. This crude material was dissolved in Et_2O and treated with an ethereal solution of diazomethane to give, after purification by column chromatography on silica gel (15:85 EtOAc/hexane), the ester **5** (0.236 mg, 72%) as a colorless oil: R_f 0.24; $[\alpha]_D$ −30.7 (*c* 0.66, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 1.41 (bs, 6H), 1.43 (s, 9H), 1.82 (s, 3H), 3.96 (s, 3H), 3.93 (m, 1H), 4.10 (d, 1H, J = 13.7 Hz), 4.13 (d, 1H, J = 4.2 Hz), 4.18 (d, 1H, J = 13.7 Hz), 4.26−4.31 (m, 2H), 7.19−7.43 (m, 5H); ^{13}C NMR (DMSO-d_6, 100 °C) δ 18.8, 25.2, 27.2, 28.3, 60.6, 63.1, 64.6, 71.9, 82.9, 83.3, 109.4, 126.1, 126.9, 128.4, 135.3, 150.2, 168.8, 173.5. Anal. Calcd for $C_{22}H_{32}N_2O_7$: C, 60.54; H, 7.39; N, 6.42. Found: C, 60.79; H, 7.13; N, 6.69.

(3*S*,4*R*)-3-(*N*-Benzyl-*N*-hydroxyamino)-4-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-1-pentyne (6). A solution of hydroxylamine **3** (0.5 g, 1.39 mmol) in MeOH (35 mL) at room temperature was treated with catalytic *p*-TosOH (10 mg, 2% w/w). The resulting solution was warmed to reflux, where it was maintained until all starting material disappeared (TLC, 3 h). The mixture was allowed to cool to room temperature, at which time the solvent was removed under reduced pressure. The crude product was then partitioned between CH_2Cl_2 (30 mL)

and saturated aqueous $NaHCO_3$ (30 mL), the layers were separated, and the aqueous layer was extracted with additional portions of CH_2Cl_2 (3 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the crude product on silica gel (40:60 EtOAc/hexane) gave 0.42 g (94%) of amino alcohol **6** as a sticky foam: R_f 0.38; $[\alpha]_D$ +13.8 (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.85 (bs, 1H, ex. D_2O), 2.50 (d, 1H, J = 2.3 Hz), 3.50 (dd, 1H, J = 2.3, 9.9 Hz), 3.83 (m, 2H), 3.86 (dt, 1H, J = 2.5, 9.9 Hz), 4.12 (bd, 1H, J = 9.1 Hz), 4.19 (d, 1H, J = 13.3 Hz), 5.13 (d, 1H, J = 9.5 Hz), 6.71 (bs, 1H, ex. D_2O), 7.17−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3, 53.1, 59.7, 61.0, 62.1, 76.2, 78.4, 80.2, 127.1, 128.1, 128.7, 137.6, 157.7. Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.52; H, 7.40; N, 8.88.

(3*S*,4*R*)-5-Acetoxy-3-(*N*-Acetoxy-*N*-benzylamino)-4-[(*tert*-butoxycarbonyl)amino]-1-pentyne (7). Applying the procedure described above for the preparation of **4**, 0.50 g (1.56 mmol) of compound **6** was converted to **7**. Chromatography of the crude product on silica gel (25:75 EtOAc/hexane) gave 0.61 g (97%) of **7** as a colorless oil: R_f 0.24; $[\alpha]_D$ +15.6 (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 55 °C) δ 1.42 (s, 9H), 1.90 (s, 3H), 1.96 (s, 3H), 2.51 (d, 1H, J = 2.3 Hz), 3.87 (dd, 1H, J = 2.3, 8.7 Hz), 4.00 (ddd, 1H, J = 3.7, 5.0, 8.7 Hz), 4.08 (d, 1H, J = 12.9 Hz), 4.28 (d, 1H, J = 12.9 Hz), 4.30 (dd, 1H, J = 5.0, 11.4 Hz), 4.41 (dd, 1H, J = 3.7, 11.4 Hz), 5.02 (d, 1H, J = 6.8 Hz), 7.21−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 19.1, 20.5, 28.4, 51.7, 57.6, 59.6, 63.8, 76.7, 77.1, 79.7, 127.9, 128.4, 129.6, 135.3, 155.5, 168.9, 170.4. Anal. Calcd for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.60; H, 7.29; N, 6.73.

Methyl (2*R*,3*R*)-4-Acetoxy-2-(*N*-acetoxy-*N*-benzylamino)-3-[(*tert*-butoxycarbonyl)amino]butanoate (8). **From 7.** Applying the procedure described above for the preparation of **5**, 0.30 g (0.74 mmol) of compound **7** was converted to **8**. Chromatography of the crude product on silica gel (30:70 EtOAc/hexane) gave 0.26 g (80%) of **8** as a colorless oil: R_f 0.33; $[\alpha]_D$ +13.4 (*c* 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.88 (s, 3H), 1.94 (s, 3H), 3.80 (s, 3H), 3.82 (d, 1H, J = 8.3 Hz), 4.09 (dd, 1H, J = 4.9, 11.5 Hz), 4.10 (d, 1H, J = 12.9 Hz), 4.16 (dd, 1H, J = 4.6, 11.5 Hz), 4.25 (ddd, 1H, J = 4.6, 4.9, 8.3 Hz), 4.27 (d, 1H, J = 12.9 Hz), 5.21 (bd, 1H, J = 6.6 Hz), 7.21−7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.1, 20.6, 28.3, 49.2, 52.1, 59.2, 63.7, 65.6, 79.8, 127.9, 128.4, 129.4, 135.4, 155.4, 168.5, 169.1, 170.4. Anal. Calcd for $C_{21}H_{30}N_2O_8$: C, 57.52; H, 6.90; N, 6.39. Found: C, 57.76; H, 6.68; N, 6.54.

From 10. A solution of furfurylhydroxylamine **10** (0.15 g, 0.41 mmol) in CH_2Cl_2 (2 mL) was treated as described above for the preparation of **4** to afford crude **11** (0.183 g, 100%; 95% pure by ^{1}H NMR), which was used for the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.88 (s, 3H), 1.92 (s, 3H), 3.65 (d, 1H, J = 12.9 Hz), 3.82 (dd, 1H, J = 4.2, 11.1 Hz), 4.51 (d, 1H, J = 12.9 Hz), 4.18−4.28 (m, 3H), 5.30 (bs, 1H), 6.37 (bd, 1H, J = 3.8 Hz), 6.41 (dd, 1H, J = 3.8, 1.9 Hz), 7.25−7.36 (m, 5H), 7.43 (bd, 1H, J = 1.9 Hz).

To a well-stirred solution of $NaIO_4$ (0.351 g, 1.65 mmol) in H_2O−CCl_4−CH_3CN 3:2:2 (7.4 mL) was added $RuCl_3$ (2.8 mg, 0.013 mmol). After 15 min of stirring, the 2-furyl derivative **11** (0.121 g, 0.27 mmol) in CH_3CN (0.5 mL) was added. The solution turned instantaneously from yellowish to black. Then enough $NaIO_4$ was added to restore the yellowish color. After 5 min, the mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL). The organic combined extracts were washed successively with 20% aqueous $NaHSO_3$ and brine until colorless and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O and treated with an ethereal solution of diazomethane to give, after purification by column chromatography on silica gel (30:70 EtOAc/hexane), the ester **8** (81 mg, 45%) as an oil. The characteristics of this material were identical to those of the product obtained from **7** as described above.

(1*R*,2*R*)-3-Acetoxy)1-(*N*-benzyl-*N*-hydroxyamino)-1-(2-furyl)-2-[(*tert*-butoxycarbonyl)amino]propane (10). By applying the procedure described above for the preparation of **6**, 0.20 g (0.50 mmol) of compound **9** was converted to **10**. Chromatography of the crude product on silica gel (40:60 EtOAc/hexane) gave 0.174 g (96%) of **10** as a sticky oil: R_f 0.34; $[\alpha]_D$ +6.6 (c 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H), 2.0 (bs, 1H, ex. D_2O), 3.39 (dd, 1H, J = 2.9, 11.2 Hz), 3.66 (dd, 1H, J = 2.9, 11.2 Hz), 3.70 (d, 1H, J = 13.9 Hz), 3.75 (d, 1H, J = 13.9 Hz), 3.87 (d, 1H, J = 10.3 Hz), 4.11 (tdd, 1H, J = 2.9, 9.3, 10.3 Hz), 5.30 (d, 1H, J = 9.3 Hz), 6.43 (dd, 1H, J = 1.7, 3.2 Hz), 6.46 (bd, 1H, J = 3.2 Hz), 6.68 (bs, 1H, ex. D_2O), 7.22−7.32 (m, 5H), 7.45 (bd, 1H, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 28.2, 53.3, 50.6, 62.5, 64.1, 80.1, 110.0, 110.6, 127.0, 128.1, 128.6, 138.9, 142.1, 150.5, 157.9. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.78; H, 7.59; N, 7.46.

(3*R*,4*R*)-3-(*N*-Benzyl-*N*-hydroxyamino)-4-[(*tert*-butoxycarbonyl)amino]-5-(*tert*-butyldiphenylsiloxy)-1-(trimethylsilyl)-1-pentyne (13). By applying the procedure described above for the preparation of **2**, 1.60 g (3.0 mmol) of nitrone **12** was converted to **13**. Chromatography of the crude mixture of diastereomers (ds = 85% by ^{1}H NMR) on silica gel (15:85 EtOAc/hexane) afforded 1.29 g (68%) of **13** as a colorless oil: R_f 0.29; $[\alpha]_D$ −37.4 (*c* 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 55 °C) δ 0.17 (s, 9H), 1.04 (s, 9H), 1.44 (s, 9H), 3.72 (dd, 1H, J = 6.6, 10.2 Hz), 3.76−3.87 (m, 3H), 4.19−4.35 (m, 1H), 4.32 (d, 1H, J = 13.6 Hz), 4.72 (d, 1H, J = 9.9 Hz), 5.94 (bs, 1H), 7.03−7.43 (m, 11H), 7.46−7.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 55 °C) δ −0.2, 19.1, 26.7, 28.2, 52.8, 61.3, 61.4, 63.6, 65.5, 79.5, 83.2, 126.9, 127.5, 127.6, 127.9, 129.0, 129.4, 129.6, 133.2, 134.7, 135.5 (2C), 137.7, 156.5. Anal. Calcd for $C_{36}H_{50}N_2O_4Si_2$: C, 68.53; H, 7.99; N, 4.44. Found: C, 68.39; H, 8.14; N, 4.09.

(3*R*,4*R*)-3-(*N*-Benzyl-*N*-hydroxyamino)-4-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-1-pentyne (14). By applying the procedure described above for the preparation of **3**, 1.50 g (2.38 mmol) of compound **13** was converted to **14**. Chromatography of the crude product on silica gel (40:60 EtOAc/hexane) gave 0.53 g (70%) of **14** as a white solid: mp 164−166 °C; R_f 0.32; $[\alpha]_D$ −65.7 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 55 °C) δ 1.42 (s, 9H), 1.60 (bs, 1H, ex. D_2O), 2.50 (d, 1H, J = 2.2 Hz), 3.71 (dd, 1H, J = 5.4, 11.4 Hz), 3.72 (dd, 1H, J = 2.2, 4.9 Hz), 3.81 (d, 1H, J = 13.1 Hz), 3.86 (dd, 1H, J = 4.9, 11.4 Hz), 4.10 (dt, 1H, J = 4.9, 5.4 Hz), 4.29 (d, 1H, J = 13.1 Hz), 5.04 (bd, 1H, J = 8.7 Hz), 6.05 (bs, 1H, ex. D_2O), 7.23−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 28.3, 53.4, 60.7, 61.8, 62.7, 76.6, 78.0, 80.0, 127.3, 128.2, 129.1, 137.1, 156.6. Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.66; H, 7.61; N, 8.68.

(3*R*,4*R*)-5-Acetoxy-3-(*N*-acetoxy-*N*-benzylamino)-4-[(*tert*-butoxycarbonyl)amino]-1-pentyne (15). By applying the procedure described above for the preparation of **4**, 0.25 g (0.78 mmol) of compound **14** was converted to **15**. Chromatography of the crude product on silica gel (25:75 EtOAc/hexane) gave 0.315 g (100%) of **15** as a colorless oil: R_f 0.19; $[\alpha]_D$ −31.8 (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 55 °C) δ 1.42 (s, 9H), 1.89 (s, 3H), 1.94 (s, 3H), 2.45 (d, 1H, J = 2.3 Hz), 3.79 (dd, 1H, J = 2.3, 6.9 Hz), 4.10 (d, 1H, J = 12.5 Hz), 4.10−4.21 (m, 2H), 4.22 (d, 1H, J = 12.5 Hz), 4.29 (dd, 1H, J = 5.3, 10.7 Hz), 4.85 (bs, 1H), 7.20−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 19.1, 20.4, 28.2, 51.1, 57.4, 60.5, 63.8, 76.2, 76.7, 79.7, 127.9, 128.4, 129.5, 135.0, 155.0, 168.8, 170.1. Anal. Calcd for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93. Found: C, 62.21; H, 6.85; N, 6.78.

Methyl (2*S*,3*R*)-4-Acetoxy-2-(*N*-acetoxy-*N*-benzylamino)-3-[(*tert*-butoxycarbonyl)amino]butanoate (16). By applying the procedure described above for the preparation of **5**, 0.20 g (0.49 mmol) of compound **15** was converted to **16**. Chromatography of the crude product on silica gel (30:70 EtOAc/hexane) gave 0.163 g (76%) of **16** as an oil: R_f 0.26; $[\alpha]_D$ −3.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 55 °C) δ 1.41 (s, 9H), 1.91 (s, 3H), 1.94 (s, 3H), 3.72 (d, 1H, J = 7.6 Hz), 3.81 (s, 3H), 4.13 (dd, 1H, J = 4.5, 11.2 Hz), 4.17 (d, 1H, J = 12.6 Hz), 4.22 (d, 1H, J = 12.6 Hz), 4.30−4.39 (m, 2H), 5.01 (bd, 1H, J = 11.2 Hz), 7.26−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 19.0, 20.4, 28.2, 49.2, 51.7, 60.4, 63.9, 66.1, 80.4, 127.9, 128.4, 129.6, 135.1, 154.9, 168.4, 168.8, 170.2. Anal. Calcd for $C_{21}H_{30}N_2O_8$: C, 57.52; H, 6.90; N, 6.39. Found: C, 57.71; H, 7.01; N, 6.60.

Acknowledgment. Financial support was provided by the Ministerio de Educación y Cultura (Madrid, Spain). We are also grateful to the MEC for a contract to S.F.

JO9714775