Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 20, pp. 3489–3496, 1997

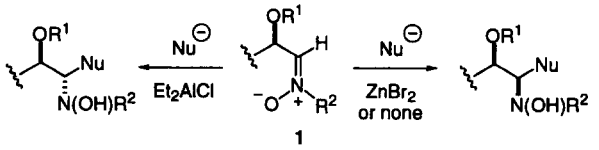
Printed in Great Britain
PII: S0957-4166(97)00438-2
0957-4166/97 $17.00 + 0.00

Diastereoselective nucleophilic addition of acetylide to *N*-benzyl-2, 3-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN). Stereodivergent synthesis of β-hydroxy-α-(hydroxyamino)- and β-hydroxy-α-amino acids

Pedro Merino,* Santiago Franco, Francisco L. Merchan and Tomas Tejero
Departamento de Química Orgánica, ICMA, Universidad de Zaragoza, E-50009 Aragon, Spain

Abstract: The stereocontrolled nucleophilic addition of lithium trimethylsilyl acetylide to the *N*-benzyl nitrone (BIGN) derived from 2,3-*O*-isopropylidene-D-glyceraldehyde, followed by oxidative cleavage of the ensuing propargyl hydroxylamines resulted in an efficient stereodivergent synthesis of fully protected epimeric *N*-hydroxy α-amino esters **8** and **13** as well as the corresponding α-amino esters **9** and **14**. © 1997 Published by Elsevier Science Ltd

Among the various strategies pursued for the synthesis of nitrogenated compounds bearing a hydroxyamino function, several procedures have in common the 1,3-addition of suitable nucleophiles to nitrones. Following this strategy, several syntheses of important natural products and related compounds have been reported.[1] In particular, chiral α-alkoxy nitrones **1** are useful building blocks for the asymmetric construction of several nitrogen-containing compounds of interest because they undergo stereocontrolled nucleophilic addition reactions depending on the nature of the Lewis acid used as a precomplexing agent of the nitrone[2] (Scheme 1).



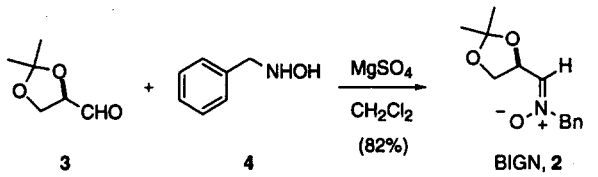
Scheme 1.

Indeed, recent studies in our laboratory have demonstrated the application of nitrones **1** in highly stereoselective asymmetric syntheses of amino nitriles, glycosyl amino acids, amino- and aza sugars and complex nucleosides.[3] In this context, we have recently described in a preliminary form, the asymmetric vinylation and ethynylation of the *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone **2**, namely BIGN, directed to the synthesis of allyl and propargyl amines, respectively.[4] Here, we describe further details of this work, including transformation of propargyl hydroxylamines into β-hydroxy-α-(hydroxyamino)- and β-hydroxy-α-amino esters, taking advantage of the ethynyl-carboxylic acid synthetic equivalence.[5]

The α-alkoxy nitrone **2** can be rapidly synthesized from D-glyceraldehyde[6] **3** and *N*-benzyl hydroxylamine[7] **4**, following our previously reported procedure[8] (Scheme 2). When that compound is prepared in modest scale (less than 2 g) the nitrone can be purified by column chromatography. However in larger runs (more than 5 g) the strong retention observed for **2** (even if neutral alumina is used instead of silica gel) makes the purification process a rather tedious step with considerable expenditure of solvents, otherwise appreciable loss of material is observed. In such a case a slight

* Corresponding author. Email: pmerino@posta.unizar.es

modification of the purification step (see experimental) allows isolation of **2** in pure form (as judged by elemental analysis and NMR spectroscopy) without using chromatography. Under that treatment no significant loss of chemical yield was observed.

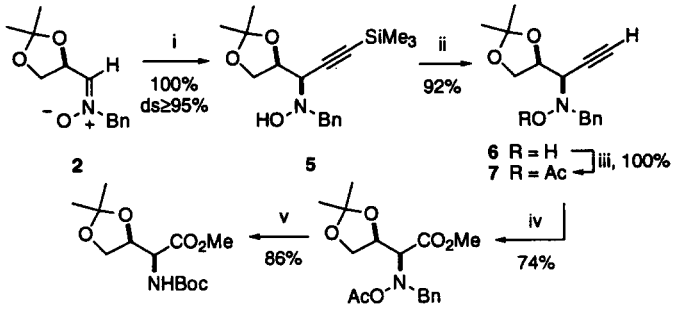


3 **4** BIGN, **2**

Scheme 2.

The nitrone **2** is a crystalline stable compound which can be stored under an inert atmosphere at 5°C for months. The Z configuration of **2** was assessed by n.O.e. experiments which established that the azomethine proton and the benzyl group were on the same side of the nitrone function.

Reaction of nitrone **2** with lithium trimethylsilyl acetylide (generated *in situ* from trimethylsilyl acetylene and butyllithium) gave hydroxylamine **5** in quantitative chemical yield as a sole diastereomer (Scheme 3). Models for explaining the high syn diastereoselectivity in nucleophilic additions to **2** have been proposed.[9]



2 **5** **9** **8**

Reagents and conditions: i) $LiC{\equiv}CSiMe_3$, THF, -80°C, 1 h. ii) Bu_4NF, THF, r.t., 2 min. iii) Ac_2O, Py, r.t., 4 h. iv) $RuCl_3$, $NaIO_4$, CH_3CN-CCl_4-H_2O, r.t., 2 min; then CH_2N_2, Et_2O, 0°C, 15 min. v) H_2, $Pd(OH)_2$-C, Boc_2O, r.t., 80psi, 6 days.

Scheme 3.

Desilylation of the propargyl hydroxylamine **5** with Bu_4NF (r.t., 2 min) demonstrated the remarkable lability of the trimethylsilyl group in these compounds. Subsequently, acetylation with acetic anhydride and pyridine quantitatively afforded compound **7** which was in turn oxidized under Sharpless conditions.[10] It has been reported that the optimum conditions for the oxidation of a triple bond are the use of ruthenium (III) chloride in a basic medium;[5,10] however, the use of such conditions led to intractable mixtures of products. This could be reasonable considering the lability of the acetoxyamino group in a basic medium. In order to circumvent that difficulty, a minor modification to the original oxidation procedure was introduced (see experimental).[11] The *N*-hydroxy-α-amino acid then obtained was isolated as the methyl ester **8** in 74% yield from **7**. (2*S*,3*S*)-3-(Hydroxymethyl)serine was obtained by hydrogenolysis over 20% palladium hydroxide on charcoal in the presence of an excess of ditert-butyldicarbonate. Also in this case, the acid was isolated as the corresponding methyl ester **9**.

In our previous communication[4] the absolute configuration of **5** had been demonstrated by chemical correlation. Fortunately, compound **6** was a crystallizable solid whose structure was unambiguously determined by X-ray crystallographic analysis (Figure 1). This product turned out to have a relative syn configuration between the two asymmetric centers, thus confirming our previous assignment.

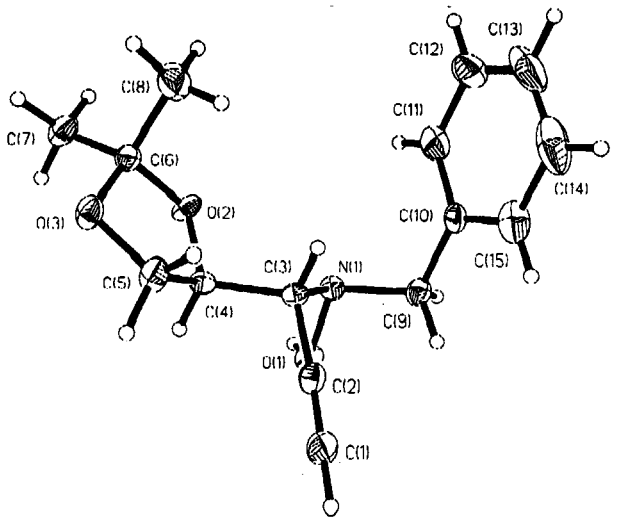
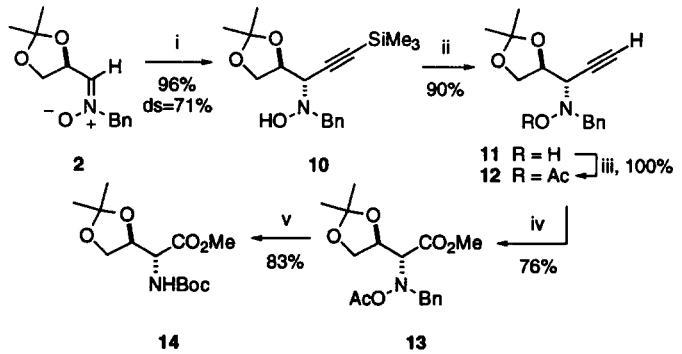


Figure 1. ORTEP view of compound **5** showing ellipsoids at a 30% probability level.

We then focused our attention on the synthesis of epimeric (2*R*,3*S*) derivatives **13** and **14**, which requires essentially an inversion of the stereochemical outcome of the initial nucleophilic addition.

Therefore BIGN **2** was treated with 1.0 equivalent of diethylaluminum chloride and then with lithium trimethylsilyl acetylide (Scheme 4). This reaction yielded, preferentially, the anti isomer (ds=71%), the enantiomerically pure hydroxylamine **10** being obtained after purification by column chromatography. The inversion of the stereochemical course of the reaction when diethylaluminum chloride was used as a precomplexing agent is in good agreement with our previous reports and can be understood by considering a β-chelate model as proposed by us.[2] Next, the anti hydroxylamine **10** was converted into α-(hydroxyamino) ester **13** following a similar reaction pathway to that used for **5** (i.e. desilylation, acetylation and oxidation). The (2*R*,3*S*)-3-(hydroxymethyl)serine **14** was obtained after hydrogenolysis under the same conditions that those used for **8**. Thus, β-hydroxy-α-amino ester **14** was obtained in 83% yield.



Reagents and conditions: i) Et_2AlCl, r.t., 5 min; then $LiC{\equiv}CSiMe_3$, THF, -80°C, 1 h. ii) Bu_4NF, THF, r.t., 2 min. iii) Ac_2O, Py, r.t., 4 h. iv) $RuCl_3$, $NaIO_4$, CH_3CN-CCl_4-H_2O, r.t., 2 min; then CH_2N_2, Et_2O, 0°C, 15 min. v) H_2, $Pd(OH)_2$-C, Boc_2O, r.t., 80psi, 6 days.

Scheme 4.

In conclusion, we have developed an efficient and stereocontrolled route for homologating D-glyceraldehyde into fully protected α-(hydroxyamino) and α-amino esters. The salient features of this route are (i) the use of nitrone **2** (BIGN) as a key intermediate thus illustrating the synthetic utility of the nitrone functionality and (ii) the use of the ethynyl group as an efficient surrogate of the carboxyl group.

Experimental section

General methods

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried over standard drying agents[12] and freshly distilled prior to use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 300 Varian Unity spectrometer at room temperature, unless otherwise specified. Chemical shifts are given in parts per million downfield from tetramethylsilane. Optical rotations were measured using a Perkin Elmer 214 polarimeter with a thermally jacketed 10 cm cell at 25°C (concentration c given as g/100 mL). IR spectra were recorded in nujol or chloroform and measured in cm^{-1}, using a Perkin–Elmer 1600 FTIR infrared spectrophotometer; only representative bands are given. Elemental analyses were performed on a 1106 Microanalyzer Carlo Erba. All reactions were monitored by TLC on silica gel plates (Merck Kiesel gel 60 F254) and visualized by spraying with either 1 M aqueous $KMnO_4$ or a solution of 2,4-dinitrophenylhydrazine in methanolic sulfuric acid and heated. Flash column chromatography was performed on silica gel 60 F254.[13] D-Glyceraldehyde[6] and *N*-benzylhydroxylamine[7] were prepared as described.

N-*Benzyl-2,3*-O-*isopropylidene*-D-*glyceraldehyde nitrone (BIGN) 2*

To a well-stirred solution of freshly distilled D-glyceraldehyde (10 g, 76.84 mmol) in dichloromethane (750 ml), anhydrous magnesium sulfate (10.23 g, 85 mmol) and *N*-benzylhydroxylamine (9.46 g, 76.84 mmol) were added sequentially and the resulting mixture was stirred at 20°C for 4 h. The reaction mixture was filtered and the filtrate rotatory evaporated to yield a residue which was triturated with cold diethyl ether, the product (14.82 g, 82%) being isolated by filtration as a white solid; mp 90°C; $[\alpha]_D$ +96.8 (c 0.50, $CHCl_3$); IR ν 1599; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.37 (s, 3H), 3.82 (dd, 1H, J=8.7, 5.9 Hz), 4.35 (dd, 1H, J=7.1, 8.7 Hz), 4.80 (bs, 2H), 5.08 (ddd, 1H, J=7.1, 5.9, 4.6 Hz), 6.78 (d, 1H, J=4.6 Hz), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.9, 26.2, 67.8, 67.0, 72.0, 109.8, 129.1, 129.2, 129.4, 132.1, 139.1. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.04; N, 6.11.

(*3*R,*4*S)-N-*Benzyl-4,5-dihydroxy-3-(hydroxyamino)-4,5*-O-*isopropylidene-1-(trimethylsilyl)-1-pentyne 5*

To a solution of trimethylsilyl acetylene (0.69 g, 7.0 mmol) in THF (25 mL) at −20°C was added n-butyllithium (4.45 mL, 1.6 M in hexanes, 7.12 mmol). This solution was stirred for 15 min and then cooled to −80°C. A cold (−80°C) solution of nitrone **2** (1.41 g, 6.0 mmol) in THF (50 mL) was then quickly added with a cannula over a period of 45 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 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 (3×30 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 (10:90 EtOAc:hexane) to give the hydroxylamine **5** as a clear oil (2.0 g, 100%); $[\alpha]_D$ −28.2 (c 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.21 (s, 9H), 1.31 (s, 3H), 1.33 (s, 3H), 3.68 (d, 1H, J=6.9 Hz), 3.87 (d, 1H, J=12.5 Hz), 3.92 (dd, 1H, J=8.8, 6.3 Hz), 4.08 (dd, 1H, J=8.8, 6.2 Hz), 4.16 (d, 1H,

J=12.5 Hz), 4.34 (ddd, 1H, J=6.9, 6.3, 6.2 Hz), 5.01 (bs, 1H, ex. D_2O), 7.28–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 0.0, 25.7, 26.6, 61.5, 62.5, 67.3, 75.75, 94.1, 98.3, 109.5, 127.7, 128.4, 129.6, 136.1. Anal. Calcd for $C_{18}H_{27}NO_3Si$: C, 64.83; H, 8.16; N, 4.20. Found: C, 64.66; H, 8.33; N, 4.06.

(3R,4S)-N-Benzyl-4,5-dihydroxy-3-(hydroxyamino)-4,5-O-isopropylidene-1-pentyne **6**

A solution of hydroxylamine **5** (1.33 g, 4.0 mmol) in THF (30 mL) at ambient temperature was treated with 4.5 mL (4.5 mmol) of a 1.0 M solution of Bu_4NF in anhydrous THF. After 2 min 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 ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The resulting oil was chromatographed on silica gel (40:60 Et_2O:hexane) to give propargyl hydroxylamine **6** (0.96 g, 92%) as a white solid; mp 113–115°C; $[\alpha]_D$ −24.4 (c 0.72, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.33 (s, 3H), 2.45 (d, 1H, J=2.2 Hz), 3.56 (dd, 1H, J=7.5, 2.2 Hz), 3.94 (d, 1H, J=12.4 Hz), 3.98 (dd, 1H, J=8.8, 5.6 Hz), 4.08 (dd, 1H, J=8.8, 6.3 Hz), 4.16 (d, 1H, J=12.4 Hz), 4.41 (ddd, 1H, J=7.5, 6.3, 5.6 Hz), 6.25 (bs, 1H, ex. D_2O), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.5, 26.6, 60.4, 62.4, 67.2, 75.5, 76.6, 77.1, 109.7, 127.7, 128.5, 129.7, 135.9. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.02; H, 7.51; N, 5.49.

X-Ray crystallographic data of compound **6**: $C_{15}H_{19}NO_3$, trigonal, space group $P3_2$, a=13.240(5), c=7.157(5) Å (from 39 orientation reflections, 9.192°<θ<24.916°), V=1086.5(10) $Å^3$, Z=3, D_{calcd}=1.198 g/cm^3, F(000)=420, μ=0.083 (MoKα radiation, λ=0.71069 A). Intensity data were recorded on a Siemens P4 diffractometer (θ–2θ scans, θ_{max}=25.49°). The intensities of the three standard reflections remeasured every 97 reflections during data collection to monitor crystal stability, indicated a decay of 6.64%. From a total of 1604 measurements those 14,028 reflections with I>2σ(I) were retained for the analysis. The crystal structure was solved by direct methods (SIR-92, Giacovazzo). All non-hydrogen atoms were refined anisotropically and the hydrogen atoms at calculated positions. The final cycle of full-matrix least-squares refinement was based on 1553 observed reflections and 178 variable parameters with one restraint, and converged with agreement factors of: R=0.0409, wR_2=0.1018, S=1.062. Crystallographic calculations were performed on a Micro–Vax Alpha (SHELXL-93, Sheldrick 1993). In the least-square iterations $w=1/[\sigma^2(Fo^2)+(0.0643P)^2+0.0988P]$, $P=(Fo^2-2Fc^2)/3$ was minimized.

(3R,4S)-3-(Acetoxyamino)-N-benzyl-4,5-dihydroxy-4,5-O-isopropylidene-1-pentyne **7**

A solution of hydroxylamine **6** (0.78 g, 3.0 mmol) in CH_2Cl_2 (5 mL) at room temperature was treated sequentially with pyridine (6 mL) and acetic anhydride (6 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 stirring 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 which was subjected to purification by column chromatography on silica gel (30:70 EtOAc:hexane) to give the acetylated product **7** as a colorless oil (0.91 g, 100%); $[\alpha]_D$ −1.8 (c 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.35 (s, 3H), 1.94 (s, 3H), 2.49 (d, 1H, J=2.4 Hz), 3.91 (dd, 1H, J=7.5, 2.4 Hz), 3.98 (dd, 1H, J=8.1, 6.6 Hz), 4.03 (dd, 1H, J=8.1, 5.7 Hz), 4.08 (d, 1H, J=12.9 Hz), 4.25 (ddd, 1H, J=7.5, 6.6, 5.7 Hz), 4.30 (d, 1H, J=12.9 Hz), 7.24–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 19.4, 25.4, 26.5, 59.8, 60.7, 66.7, 75.9, 76.8, 76.6, 109.5, 128.0, 128.4, 129.7, 135.0, 169.4. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.48; H, 7.12; N, 4.44.

Methyl (2S,3S)-2-(acetoxyamino)-N-benzyl-3,4-dihydroxy-3,4-O-isopropylidenebutanoate **8**

To a well-stirred mixture of CH_3CN (2.6 mL), CCl_4 (2.6 mL) and H_2O (4 mL) were added $NaIO_4$ (0.530 g, 2.48 mmol) and $RuCl_3$ H_2O (19.4 mg, 0.086 mmol) sequentially. The resulting yellowish mixture was allowed to stir for 30 min, at which time it was poured into a flask containing pure

7 (0.455 g, 1.50 mmol). The resulting mixture turned black and additional $NaIO_4$ (0.266 mg, 1.24 mmol) was added. After 5 min the reaction mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL), the layers were separated, and the aqueous layer was extracted with additional portions of EtOAc (5×20 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 **8** (0.374 mg, 74%) as a colorless oil; $[\alpha]_D$ −21.7 (c 2.90, $CHCl_3$); IR ν 1730; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.35 (s, 3H), 1.89 (s, 3H), 3.77 (s, 3H), 3.80 (d, 1H, J=7.2 Hz), 3.89 (dd, 1H, J=8.7, 6.5 Hz), 4.05 (dd, 1H, J=8.7, 6.5 Hz), 4.27 (d, 1H, J=13.2 Hz), 4.34 (d, 1H, J=13.2 Hz), 4.55 (dt, 1H, J=7.2, 6.5 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.2, 25.1, 26.3, 52.0, 60.9, 66.5, 69.2, 73.6, 109.7, 127.8, 128.3, 129.6, 135.4, 168.7, 169.5. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.81; H, 6.72; N, 3.88.

*Methyl (2S,3S)-2-(tert-butoxycarbonylamino)-3,4-dihydroxy-3,4-*O*-isopropylidenebutanoate* ***9***

To a solution of **8** (0.30 g, 0.9 mmol) in methanol (20 mL), Boc_2O (0.46 g, 2.1 mmol) and 20% palladium hydroxyde on activated charcoal (Pearlman's catalyst) (20 mg) were added. The resulting mixture was hydrogenated at 80 psi for 6 days (Parr hydrogenation apparatus). Filtration of the catalyst and evaporation of the solvent afforded a colourless oil which was purified by column chromatography on silica gel (10:90, Et_2O:hexane) to give 0.224 g (86%) of pure **9** as a colourless oil; $[\alpha]_D$ −66.5 (c 0.50, $CHCl_3$); IR ν 1725; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.31 (s, 3H), 1.43 (s, 9H), 3.76 (s, 3H), 3.78 (dd, 1H, J=8.5, 6.7 Hz), 4.06 (dd, 1H, J=8.5, 6.7 Hz), 4.37 (dd, 1H, J=9.4, 2.3 Hz), 4.56 (td, 1H, J=6.7, 2.3 Hz), 5.18 (bd, 1H, J=9.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.8, 26.1, 28.3, 52.7, 54.3, 66.0, 75.3, 80.3, 109.8, 156.0, 170.8. Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 54.13; H, 8.23; N, 4.78.

*(3S,4S)-*N*-Benzyl-4,5-dihydroxy-3-(hydroxyamino)-4,5-*O*-isopropylidene-1-(trimethylsilyl)-1-pentyne* ***10***

To a solution of nitrone **2** (1.41 g, 6.0 mmol) in Et_2O (80 mL) was added Et_2AlCl (6.0 ml of a 1.0 M solution in hexanes, 6.0 mmol) and the resulting mixture was stirred at ambient temperature for 5 min. The reaction mixture was cooled to −80°C and quickly added with a cannula to a solution of lithium trimethylsilyl acetylide (7.0 mmol), prepared as described above. Stirring at −80°C was continued for an additional 60 min until all the nitrone was consumed (TLC). The reaction was quenched with saturated NH_4Cl (5 mL) and the result 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 (3×30 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=71% by ^1H NMR). The crude product was chromatographed on silica gel (10:90 EtOAc:hexane) to give the hydroxylamine **10** (1.334 g, 68%) as a white solid; mp 132°C; $[\alpha]_D$ +43.5 (c 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.23 (s, 9H), 1.34 (s, 3H), 1.40 (s, 3H), 3.53 (d, 1H, J=6.5 Hz), 3.82 (d, 1H, J=12.9 Hz), 3.95 (dd, 1H, J=8.9, 5.1 Hz), 4.05 (dd, 1H, J=8.9, 6.2 Hz), 4.12 (d, 1H, J=12.9 Hz), 4.36 (ddd, 1H, J=6.5, 6.2, 5.1 Hz), 4.84 (bs, 1H, ex. D_2O), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 0.1, 25.6, 26.5, 61.9, 62.4, 67.3, 76.4, 93.6, 98.7, 110.0, 127.6, 128.4, 129.4, 136.5. Anal. Calcd for $C_{18}H_{27}NO_3Si$: C, 64.83; H, 8.16; N, 4.20. Found: C, 64.77; H, 8.39; N, 4.31.

*(3S,4S)-*N*-Benzyl-4,5-dihydroxy-3-(hydroxyamino)-4,5-*O*-isopropylidene-1-pentyne* ***11***

Compound **11** was prepared following the procedure used for the preparation of compound **6**. Purification of the crude product by column chromatography on silica gel (40:60 Et_2O:hexane) gave 0.941 g (90%) of **11** as an oil; $[\alpha]_D$ +1.8 (c 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.42 (s, 3H), 2.52 (d, 1H, J=2.2 Hz), 3.50 (dd, 1H, J=7.7, 2.2 Hz), 3.84 (d, 1H, J=12.8 Hz), 3.95 (dd, 1H,

J=8.9, 5.1 Hz), 4.05 (dd, 1H, J=8.9, 6.2 Hz), 4.12 (d, 1H, J=12.8 Hz), 4.36 (ddd, 1H, J=7.7, 6.2, 5.1 Hz), 5.12 (bs, 1H, ex. D_2O), 7.23–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3, 26.7, 61.4, 62.4, 67.4, 75.8, 76.3, 77.6, 110.0, 127.7, 128.5, 129.4, 136.5. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.03; H, 7.27; N, 5.29.

*(3S,4S)-3-(Acetoxyamino)-*N*-benzyl-4,5-dihydroxy-4,5-*O*-isopropylidene-1-pentyne* ***12***

Compound **12** was prepared following the procedure used for the preparation of compound **7**. Purification of the crude product by column chromatography on silica gel (30:70 EtOAc:hexane) gave 0.910 g (100%) of **12** as an oil; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.40 (s, 3H), 1.92 (s, 3H), 2.50 (d, 1H, J=2.3 Hz), 3.70 (dd, 1H, J=6.9, 2.3 Hz), 4.06 (m, 2H), 4.10 (d, 1H, J=12.9 Hz), 4.16 (m, 1H), 4.25 (d, 1H, J=12.9 Hz), 7.22–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.1, 25.1, 26.7, 60.3, 60.7, 67.6, 75.3, 75.9, 77.5, 109.9, 127.8, 128.4, 129.2, 135.2, 169.0. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.20; H, 6.82; N, 4.73.

*Methyl (2R,3S)-2-(acetoxyamino)-*N*-benzyl-3,4-dihydroxy-3,4-*O*-isopropylidenebutanoate* ***13***

Compound **13** was prepared following the procedure used for the preparation of compound **8**. Purification of the crude product by column chromatography on silica gel (15:85 EtOAc:hexane) gave 0.385 g (76%) of **13** as an oil; $[\alpha]_D$ +3.9 (c 0.30, $CHCl_3$); IR ν 1722; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.32 (s, 3H), 1.84 (s, 3H), 3.55 (d, 1H, J=9.2 Hz), 3.86 (s, 3H), 4.12 (dd, 1H, J=9.0, 6.2 Hz), 4.14 (d, 1H, J=13.2 Hz), 4.18 (d, 1H, J=13.2 Hz), 4.19 (dd, 1H, J=9.0, 4.5 Hz), 4.37 (ddd, 1H, J=9.2, 6.2, 4.5 Hz), 7.21–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.0, 25.1, 26.8, 51.9, 60.8, 67.3, 69.5, 73.8, 109.7, 127.9, 128.4, 129.2, 135.4, 168.5, 168.9. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.76; H, 6.94; N, 4.33.

*Methyl (2R,3S)-2-(tert-butoxycarbonylamino)-3,4-dihydroxy-3,4-*O*-isopropylidenebutanoate* ***14***

Compound **14** was prepared following the procedure used for the preparation of compound **9**. Purification of the crude product by column chromatography on silica gel (10:90 hexane:diethyl ether) gave 0.216 g (83%) of **14** as an oil; $[\alpha]_D$ −33.5 (c 1.60, $CHCl_3$); IR ν 1731; ^1H NMR ($CDCl_3$, 55°C) δ 1.24 (s, 3H), 1.28 (s, 3H), 1.40 (s, 9H), 3.73 (s, 3H), 3.76 (m, 1H), 4.20 (dd, 1H, J=5.1, 2.0 Hz), 4.28 (pseudo q, 1H, J=5.1 Hz), 4.36 (dd, 1H, J=7.2, 3.7 Hz), 5.15 (bs, 1H); ^{13}C NMR ($CDCl_3$, 55°C) δ 24.8, 26.3, 28.2, 52.4, 55.7, 65.7, 76.4, 80.2, 110.1, 155.1, 170.5. Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 54.05; H, 7.86; N, 4.92.

Acknowledgements

Financial support by DGICYT (Project PB94-0598, Madrid, Spain) is gratefully acknowledged. One of us (S.F.) thanks the Ministerio de Educacion y Cultura (Madrid, Spain) for a grant.

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(Received in UK 4 September 1997)