Samarium diiodide-induced reductive coupling of chiral nitrones prepared from D-isoascorbic acid with methyl acrylate

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Dedicated to Professor Henk van der Plas on the occasion of his 80th birthday

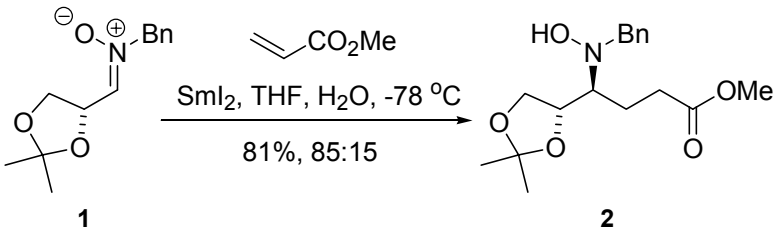
Abstract

Chiral nitrones **13-15** prepared from D-isoascorbic acid were found to effectively undergo an SmI_2-mediated radical addition to methyl acrylate affording γ-*N*-hydroxylamino esters **19-22** with high diastereomeric control. The unsubstituted nitrone **14** afforded in the SmI_2-induced coupling with methyl acrylate the γ-*N*-hydroxylamino ester **21** as minor product. The pyrrolidinones **23-25** were prepared in a single step from **19** and **22** involving N-O bond cleavage with Zn/AcOH or SmI_2 and subsequent spontaneous cyclization.

Keywords: Nitrones, samarium diiodide, chiral, hydroxylamino acids, pyrrolidinones

Introduction

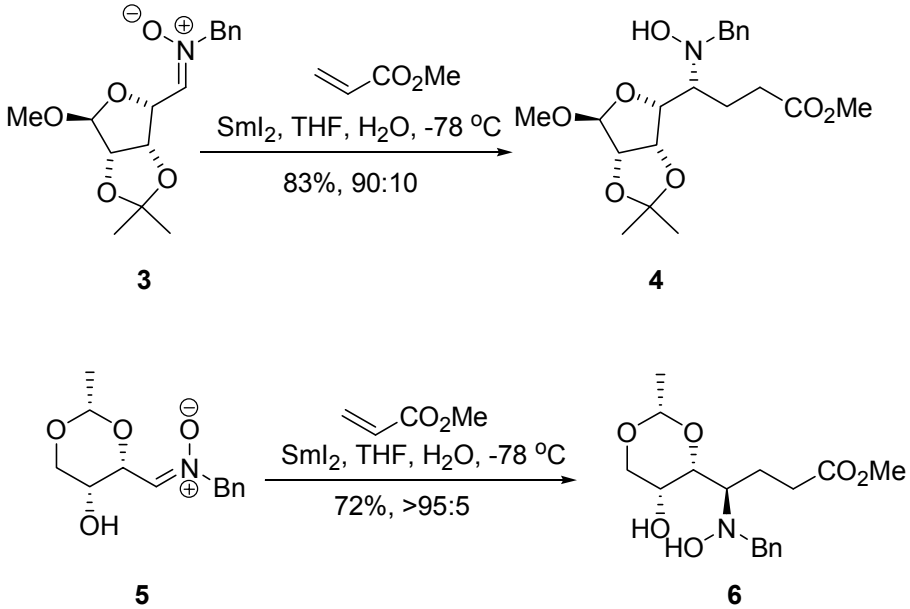
Nitrogen-containing heterocycles and their derivatives have broad application in synthetic materials, and biological chemistry, and as a result their synthesis and reactivity is subject of considerable interest. Over the years, nitrones have become important building blocks in organic synthesis.[1] During the last years we have learned know-how about the preparation of optically active nitrone templates for the asymmetric 1,3-dipolar cycloadditions.[2,3] Py, Vallée and coworkers[4a,b] have recently described the first samarium diiodide-induced umpolung of nitrones, which were able to undergo reductive coupling with α,β-unsaturated esters. D-Glyceraldehyde derived nitrone **1** reacted with methyl acrylate in presence of 3 equivalents SmI_2 in THF at –78 °C with the formation of γ-*N*-hydroxylamino esters **2** in fairly good yields, with a 85:15 diastereomeric ratio (Scheme 1). When chiral nitrones were used as substrates, significant diastereoselectivities were observed in this reactions.[4]



Scheme 1

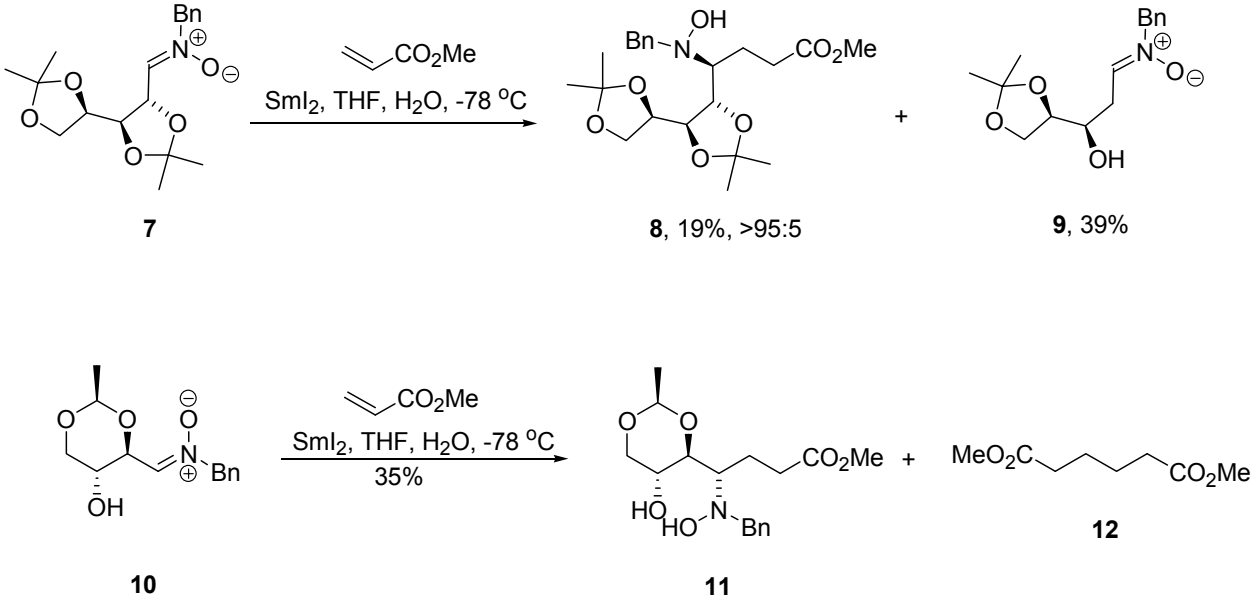
Moreover, Skrydstrup et al. have found that alkyl nitrones possessing *N*-substituted sugars as chiral auxiliaries effectively undergo an SmI_2-mediated radical addition to *n*-butyl acrylate affording γ-amino acid derivatives with high diastereomeric control.[5] This methodology opens a direct route to γ-*N*-hydroxylamino esters.[4,5] The derivatives of γ-amino buryric acid (GABA) could be potential, selective and irreversible inhibitors of GABA amino transferase, the enzyme involved in the catabolism of GABA.[6,7] As in principle γ-lactams should be easily obtained from the corresponding γ-*N*-hydroxylamino esters we have paid our attention to the synthesis of biologically important γ-amino acids from the sugar-derived nitrones previously used by us in the chiral cycloadditions.[2,3]

In our first two papers we have found that the reaction course of samarium diiodide-induced reductive coupling of chiral sugar derived nitrones with methyl acrylate is dependant on the structure of the starting chiral nitrone.[8] The nitrones **3** and **5** possessing C–2/C–3 *threo* configuration were found to effectively undergo an SmI_2 induced reductive coupling to methyl acrylate affording γ-*N*-hydroxylamino esters **4** and **6** with high diastereomeric control (Scheme 2).[8]



Scheme 2

On the other hand, the coupling of the nitrones **7** and **10** possessing C–2/C–3 *erythro* configuration with methyl acrylate proceeded slower, the expected γ-*N*-hydroxylamino esters **8** and **11** were obtained as minor products along with products resulting from unusual reductive deoxygenation **9** and dimethyl adipate (**12**), the product of the radical dimerisation/addition step involving the acrylate (Scheme 3).[8]



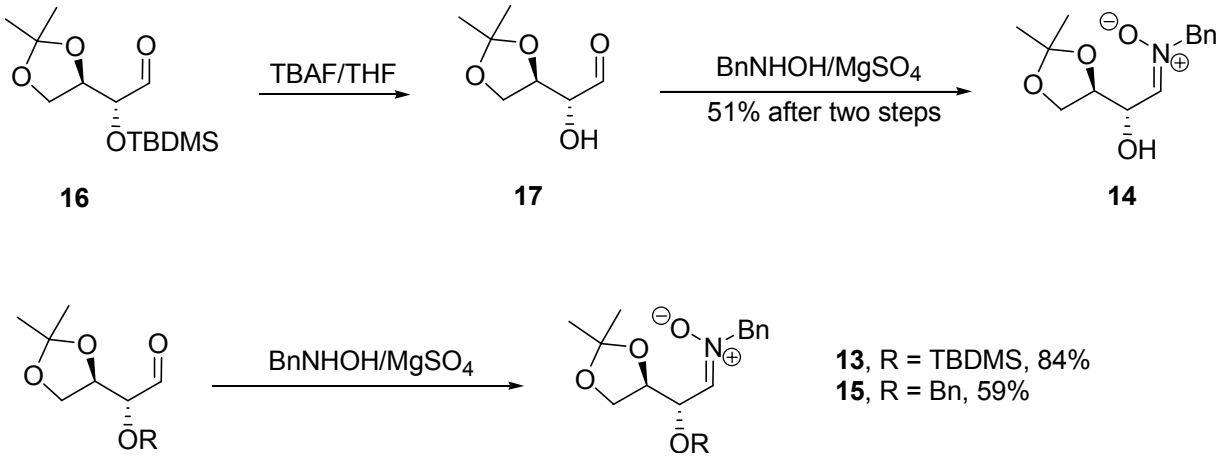
Scheme 3

In this communication we wish to describe the SmI_2-induced coupling of *N*-benzylsubstituted D-*erythro* nitrones **13-15** prepared from D-isoascorbic acid with methyl acrylate with the subsequent conversion of the formed γ-*N*-hydroxylamino esters into γ-lactams. The TBDMS substituted nitrone **13** has been employed in [3+3] cyclizations with lithiated alkoxyallenes and a subsequent rearrangement of the resulting 1,2-oxazine derivatives to novel carbohydrates mimetics.[9]

Results and Discussion

Initial experiments were performed with the TBDMS-substituted D-*erythro*-nitrone **13**. Whereas the synthesis of D-erythrose derived nitrone **13** starting from D-isoascorbic acid has been reported in the literature,[10] the preparation of the new nitrones **14** and **15** is described here. The D-erythrose derived nitrone **14** possessing a free hydroxy group was synthesized by condensation of *O*-isopropenylidene-D-erythrose **17** with *N*-benzylhydroxylamine according to the method of Dondoni and Merino.[10] The required aldehyde *O*-isopropenylidene-D-erythrose **17** was prepared from known[11] aldehyde **16** by desilylation with TBAF in THF and was used directly without any

isolation in the condensation with *N*-benzylhydroxylamine (Scheme 4). The synthesis of *O*-benzylated *O*-isopropenylidene-D-erythrose **18** starting from D-isoascorbic acid has been reported in the literature.[12]

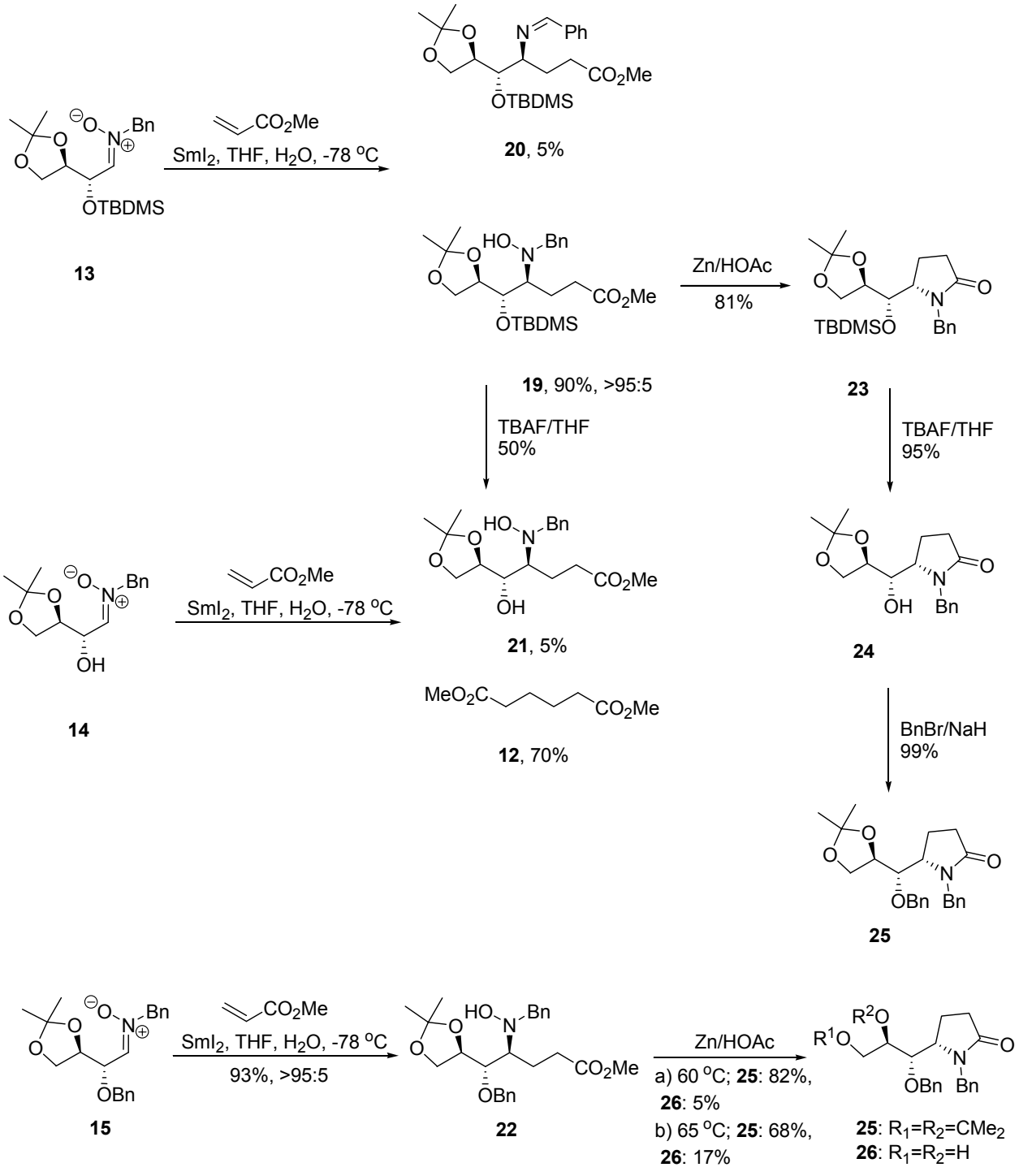


Scheme 4

The TBDMS-substituted D-*erythro*-nitrone **13** reacted smoothly with methyl acrylate in THF in the presence of three equivalents of samarium diiodide[13,14] and eight equivalents of H_2O at –78° C over two hours to give γ-*N*-hydroxylamino ester **19** in 90% yield along with ester **20** (5%) (Scheme 5). The formation of conjugated imine **20** can be rationalized by dehydratation of the primary formed ester **19**. The analogous formation of the imine derivative by SmI_2-mediated radical addition of nitrones to methyl acrylate was also observed by Py and Greene.[4h] The addition proceeded with excellent (>95:5) diastereoselectivity, with only the *anti*-diastereomer **19** being detected. The *O*-benzylsubstituted D-*erythro*-nitrone **15** reacted with methyl acrylate in THF in the presence of three equivalents of samarium diiodide and eight equivalents of H_2O at –78° C over two hours fully analogously to afford exclusively (>95:5) *anti*-γ-*N*-hydroxylamino ester **22** in 93% yield (Scheme 5).

In contrast, when D-erythrose derived nitrone **14** possessing a free hydroxyl group was treated with three equivalents of SmI_2 and eight equivalents of H_2O in THF at –78° C over two hours with methyl acrylate, the expected γ-*N*-hydroxylamino ester **21** was obtained in low 5% yield along with dimethyl adipate (70%) and substantial amounts of unreacted nitrone **14** (44%, Scheme 6). On the other hand the reaction is completely diastereoselective (>95:5) within the limits of NMR analysis of the crude product. The TBDMS substituted γ-*N*-hydroxylamino ester **19** was deprotected with TBAF in THF to afford after separation the γ-*N*-hydroxylamino ester **21** in 50% yield. All structures described were determined by ^1H and ^{13}C MNR measurements. The relative stereochemistry, previously determined through single-crystal X-ray structure analysis,[8] has been assigned in the other adducts by analogy. The formation of *anti* isomers **19-22** is

consistent with a β-chelated transition state suggested by Py and Skrydstrup[4,5] as well as with our previous results.[8]



Scheme 5

Considering the well-known propensity of *N*-hydroxylamines to be reduced to amines, we have prepared chiral pyrrolidinones **23** (81%) and **25** (82%) in a single step from aforementioned obtained γ-*N*-hydroxylamino esters **19** and **22** involving N-O bond cleavage with Zn/AcOH at 60 °C and subsequent spontaneous cyclization (Scheme 5). The reduction of ester **22** at higher temperature (65 °C) afforded additionaly to pyrrolidinone **25** (68%) also the pyrrolidinone **26** (17%). The reduction γ-*N*-hydroxylamino ester **19** with SmI_2 in THF proceeded in lower yield and gave pyrrolidinone **23** in 68% yield. The TBDMS substituted pyrrolidinone **23** was deprotected with TBAF in THF to afford after separation the pyrrolidinone **24** in 95% yield. The subsequent benzylation using BnBr/NaH in THF yielded pyrrolidinone **25** in 99% yield.

In conclusion, the reductive cross-coupling of chiral sugar derived D-*erythro*-nitrones **13-15** prepared from D-isoascorbic acid with alkyl acrylates allows the stereoselective synthesis of 4-substituted γ-*N*-hydroxylamino esters and their reduction provides entry to the optically active pyrrolidinones possessing structural similarities to the glycosidase inhibitors.[15] This method opens a novel, short, and general route for the synthesis of biologically important trihydroxysubstituted γ-amino acids and pyrrolidinones. We are currently extending the scope of this synthetically useful reaction to various chiral sugar derived nitrones.

Experimental Section

General Procedures. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VRX-300 and Varian INOVA-600 in $CDCl_3$ solution using TMS as internal standard. Chemical shifts are reported in ppm. IR spectra were recorded on FTIR NICOLET MAGNA 750 instrument. Specific rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell. Elemental analyses were conducted using the Fisons EA 1108 Analysator. TLC analysis was carried out using Merck TLC silica gel 60 F254 aluminium sheets and visualized by UV light or oxidize in $KMnO_4$ solution ($NaOH/KMnO_4/K_2CO_3/H_2O$ 1:8:80:1200). The *O*-isopropenylidene-D-erythrose derived nitrone **13**,[10] *O*-isopropenylidene-D-erythrose **16**[11] and *O*-benzylated *O*-isopropenylidene-D-erythrose **18**[12] were prepared by literature procedure.

(*Z*)-*N*-((*S*)-2-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethylidene)-1-phenylmethanamine oxide (14). To stirred solution of crude aldehyde **16** (1.17 g, 4.26 mmol) in THF (50 mL) $TBAF.3H_2O$ (1.34 g, 4.26 mmol) and water (1 mL) were added. The reaction mixtures was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. Reaction mixtures was filtrated through pad of silica gel and washed with EtOAc at the end. Filtrate was concentrated under reduced pressure. A crude aldehyde **17** was dissolved in dichloromethane (30 mL) and anhydrous of magnesium sulfate (1.53 g, 14.04 mmol) and *N*-benzylhydroxylamine (0.576 g, 4.68 mmol) were added. The reaction mixtures was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC. After end of the

reaction magnesium sulfate was removed and the solvent was removed under reduced pressure. The residue was isolated with column chromatography (silica gel, EtOAc). The nitrone **14** was obtained as a yellow crystals (0.576 g, 51%), mp: 77-80 °C; Rf: 0.18 (hexanes/EtOAc, 20:80, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: -103.3 (c = 0.21; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 1.31, 1.33 (2s, 6H), 3.98 (dd, 1H, *J* = 4.3, 9.1 Hz), 4.12 (dd, 1H, *J* = 6.2, 9.1 Hz), 4.23-4.30 (m, 1H), 4.39-4.43 (m, 1H), 4.91 (s, 2H), 5.95-6.08 (bs, 1H), 7.07 (d, 1H, *J* = 4.0 Hz), 7.41 (s, 5H); ^{13}C NMR (75 MHz) δ: 24.9, 26.7, 66.9, 69.4, 69.3, 75.2, 109.7, 129.0, 129.1, 129.2, 131.9, 138.6; IR (KBr, cm^{-1}) ν: 3156, 3066, 3031, 2986, 2939, 2887, 1603, 1587, 1497, 1459; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.21; H, 7.25; N, 5.26.

(*Z*)-*N*-((*S*)-2-(Benzyloxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethylidene)-1-phenyl-methanamine oxide (15). To stirred solution of crude aldehyde **18** (1.78 g, 7.18 mmol) in dichloromethane (35 mL) anhydrous of magnesium sulfate (8.61 g, 71.8 mmol) and *N*-benzylhydroxylamine (0.88 g, 7.18 mmol) were added. The reaction mixtures was stirred at room temperature for 18 h. The progress of the reaction was monitored by TLC. After end of the reaction magnesium sulfate was removed and the solvent was removed under reduced pressure. The residue was isolated with column chromatography (silica gel, hexanes/EtOAc, 12:88). The nitrone **15** was obtained as a colorless crystals (1.52 g, 59%), mp: 79-82 °C; R_f: 0.3 (hexanes/EtOAc, 12:88, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: -9 (c = 0.2; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 1.30, 1.31 (2s, 6H), 3.75 (dd, 1H, *J* = 5.8, 8.7 Hz), 3.97 (dd, 1H, *J* = 6.7, 8.7 Hz), 4.33 (dt, 1H, *J* = 4.8, 6.0 Hz), 4.51-4.61 (2d, 2H, *J* = 11.9 Hz), 4.86 (s, 2H), 4.90 (dd, 1H, *J* = 4.8, 7.4 Hz), 6.72 (d, 1H, *J* = 7.4 Hz), 7.28-7.38 (m, 10H); ^{13}C NMR (75 MHz) δ: 24.9, 26.2, 65.7, 70.1, 72.7, 72.8, 76.4, 109.5, 127.8, 128.0, 128.3, 128.9, 129.0, 129.2, 132.4, 137.6, 136.4; IR (KBr, cm^{-1}) ν: 3064, 2978, 2879, 1586, 1496, 1455; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.17; H, 7.26; N, 3.89.

General procedure for preparation of 19-22

A stirred and carefully deoxygented solution on corresponding nitrone (1 mmol) in dry THF (10 mL) was cooled to –78 °C under nitrogen. Methyl acrylic ester and water were degassed by boiling under a stream of nitrogen for 20 min. Methyl acrylic ester (1.4 mmol), water (8 mmol) and solution of SmI_2 (30 mL of 0.1 M in THF, 3 mmol) were then added. The temperature was kept at –78 °C until the reaction was judged to be complete by TLC, whereupon a solution of $Na_2S_2O_3$ (50 mL, 1 M in water) was added. The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtred, and concentrated in rotatory evaporator. The residue was purified by silica gel column chromatography.

(4*S*,5*S*)-Methyl 4-(benzyl(hydroxy)amino)-5-(*tert*-butyldimethylsilyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (19) prepared from nitrone **13**. The adduct **19** was isolated by column chromatography (silica gel, hexanes/EtOAc, 88:12) as colorless oil (0.421g, 90%), R_f: 0.65 (hexanes/EtOAc, 50:50, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: +40 (c = 0.203; $CHCl_3$);

^{1}H NMR (300 MHz) δ: 0.15 (s, 6H), 0.90 (s, 9H), 1.34, 1.43 (2s, 6H), 1.68-1.82 (m, 1H), 2.13-2.26 (m, 1H), 2.41-2.55 (m, 2H), 2.85-2.92 (m, 1H), 3.59 (s, 3H), 3.78 (d, 1H, *J* = 13.6 Hz), 3.91 (t, 1H, *J* = 6.5 Hz), 3.99-4.19 (m, 4H), 4.85-4.95 (bs, 1H), 7.29-7.32 (m, 5H); ^{13}C NMR (75 MHz) δ: -4.5, -3.9, 18.3, 22.1, 25.1, 26.0, 26.5, 32.4, 51.6, 61.5, 66.9, 68.3, 71.8, 77.4, 108.7, 127.0, 128.1, 128.9, 138.7, 175.4; IR (KBr, cm^{-1}) ν: 3446, 2985, 2953, 2932, 2894, 2857, 1739, 1472; Anal. Calcd for $C_{24}H_{41}NO_6Si$: C, 61.64; H, 8.84; N, 2.99. Found: C, 61.71; H, 8.46; N, 2.79.

(4*S*,5*S*)-Methyl 4-(benzylideneamino)-5-(*tert*-butyldimethylsilyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (20) prepared from nitrone **13**. The product **20** was isolated by column chromatography (silica gel, hexanes/EtOAc, 88:12) as colorless oil (0.023g, 5%), R_f: 0.51 (hexanes/EtOAc, 50:50, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: +43 (c = 0.22; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 0.14, 0.18 (2s, 6H), 0.91 (s, 9H), 1.31, 1.39 (2s, 6H), 2.01-2.11 (m, 1H), 2.26-2.37 (m, 1H), 2.44-2.57 (m, 2H), 3.66 (s, 3H), 3.80 (t, 1H, *J* = 6.9 Hz), 4.01 (t, 1H, *J* = 6.9 Hz), 4.06-4.15 (m, 2H), 4.38 (dt, 1H, *J* = 3.7, 6.6 Hz), 7.34 (s, 1H), 7.41-7.43 (m, 3H), 8.19-8.23 (m, 2H); ^{13}C NMR (75 MHz) δ: -4.48, -4.26, 18.1, 23.6, 24.6, 25.8, 26.3, 30.0, 51.6, 64.8, 73.2, 76.1, 78.2, 108.3, 128.5, 128.6, 130.2, 130.4, 135.8, 173.2; IR (KBr, cm^{-1}) ν: 2985, 2953, 2931, 2895, 2857, 1738, 1577, 1562, 1472; Anal. Calcd for $C_{24}H_{39}NO_5Si$: C, 64.11; H, 8.74; N, 3.11. Found: C, 64.27; H, 8.52; N, 3.03.

(4*S*,5*S*)-Methyl 4-(benzyl(hydroxy)amino)-5-(benzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (22) prepared from nitrone **15**. The adduct **22** was isolated by column chromatography (silica gel, hexanes/EtOAc, 50:50) as colorless oil (0.412g, 93%), R_f: 0.43 (hexanes/EtOAc, 50:50, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: +33 (c = 0.229; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 1.34, 1.42 (2s, 6H), 1.75-1.85 (m, 1H), 2.19-2.32 (m, 1H), 2.41-2.55 (m, 2H), 2.93-2.98 (m, 1H), 3.58 (s, 3H), 3.79 (d, 1H, *J* = 13.5 Hz), 3.89 (dd, 1H, *J* = 5.9, 8.1 Hz), 3.94 (dd, 1H, *J* = 2.6, 6.7 Hz), 3.99 (d, 1H, *J* = 13.5 Hz), 4.08 (dd, 1H, *J* = 6.4, 8.1 Hz), 4.17 (t, 1H, *J* = 6.7 Hz), 4.62-4.90 (2d, 1H, *J* = 11.2 Hz), 5.25-5.35 (bs, 1H), 7.24-7.36 (m, 10H); ^{13}C NMR (75 MHz) δ: 21.7, 25.2, 26.6, 32.3, 51.6, 60.9, 66.8, 67.3, 73.5, 76.8, 77.7, 109.1, 127.1, 127.5, 127.9, 128.1, 128.3, 128.9, 138.4, 138.5, 175.5; IR (KBr, cm^{-1}) ν: 3400, 3030, 2984, 2947, 2932, 2881, 1732, 1575, 1494; Anal. Calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16. Found: C, 67.63; H, 7.58; N, 3.12.

(4*S*,5*S*)-Methyl 4-(benzyl(hydroxy)amino)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-hydroxypentanoate (21) prepared from nitrone **14**. The adduct **21** was isolated by column chromatography (silica gel, hexanes/EtOAc, 50:50) as colorless crystals (0.018 g, 5%), mp: 112-114 °C; R_f: 0.54 (hexanes/EtOAc 20:80, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: +66 (c = 0.207; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 1.32 1.40 (2s, 6H), 1.72-1.81 (m, 1H), 2.33-2.54 (m, 3H), 2.81-2.88 (m, 1H), 3.58 (s, 3H), 3.65-3.75 (bs, 1H), 3.77 (d, 1H, *J* = 13.3 Hz), 3.94 (ddd, 1H, *J* = 4.5, 6.1, 9.2 Hz), 4.07 (dd, 1H, *J* = 4.4, 8.6 Hz), 4.14 (dd, 1H, *J* = 6.1, 8.6 Hz,), 4.20 (d, 1H, *J* = 13.3 Hz), 4.28 (dd, 1H, *J* = 0.9, 9.1 Hz), 5.60-5.80 (bs, 1H), 7.24-7.31 (m, 5H); ^{13}C NMR (75 MHz) δ: 19.5, 25.1, 26.9, 31.9, 51.8, 60.5, 64.6, 67.8, 70.9, 75.1, 109.2, 127.3, 128.2, 128.9, 137.8, 176.5;

IR (KBr, cm^{-1}) ν: 3516, 3407, 2989, 2925, 1705, 1455, 1444; Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.08; H, 7.81; N, 3.91.

General procedure for preparation of 23, 25 and 26

Method A. The γ-hydroxylamino ester was dissolved in mixture (AcOH/THF/H_2O, 2:1:1, 10 mL). Zinc dust was added and reaction mixture was stirred at 60 °C for 1h. Reaction was controlled with TLC. Water (100 mL) was added after reaction and obtained mixture was treated with Na_2CO_3 to basic reaction (pH > 10). The solution was extracted with EtOAc (4 x 50 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtred, and concentrated in rotatory evaporator. The residue was purified by silica gel column chromatography using AcOEt:hexanes (1:1).

Method B. The γ-hydroxylamino ester was dissolved in dry THF and this mixture was treated with solution of SmI_2 (0.1 M in THF) and stirred at room temperature under nitrogen atmosphere. The reaction was confirmed to be complete by TLC, whereupon a solution of $Na_2S_2O_3$ (50 mL, 1 M in water) was added. The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtred, and concentrated in rotatory evaporator. The crude product was dissolved in mixture (MeOH/H_2O/ethyl ether, 1:1:1, 60 mL) and K_2CO_3 (0.3 g) was added. The obtained mixture was stirred at room temperature for 20 min. After this period reaction mixture was extracted with EtOAc (4 x 40 mL) and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtred, and concentrated in rotatory evaporator. The residue was purified by silica gel column chromatography using AcOEt:hexanes (1:1).

1-Benzyl-5-((*S*)-(*tert*-butyldimethylsilyloxy)((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)pyrrolidin-2-one (23)

Method A. Prepared from **19** (0.1 g, 0.214 mmol), zinc dust (0.28 g, 4.28 mmol), reaction time 4 h, yield of product **23** (0.072g, 81%). Colorless oil, R_f: 0.58 (hexanes/EtOAc, 20:80, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: +71 (c = 0.216; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 0.04, 0.13 (2s, 6H), 0.88 (s, 9H), 1.26 (s, 6H), 1.87-2.17 (m, 2H), 2.35 (ddd, 1H, *J* = 4.3, 10.5, 15.0 Hz), 2.51 (ddd, 1H, *J* = 4.3, 9.1, 17.7 Hz), 3.67-3.91 (m, 5H), 3.98-4.06 (m, 1H), 5.23 (d, 1H, *J* = 14.8 Hz), 7.22-7.35 (m, 5H); ^{13}C NMR (75 MHz) δ: -4.6, -3.8, 17.1, 18.1, 25.1, 26.6, 25.7, 25.8, 30.6, 44.2, 58.2, 67.2, 71.5, 76.1, 109.3, 127.6, 128.2, 128.7, 136.1, 175.9; IR (KBr, cm^{-1}) ν: 2953, 2929, 2885, 2857, 2683, 1683, 1472, 1435, 1419; HRMS: [M+H^+] Calcd: 420.2570, Found: 420.2569; [M+Na^+] Calcd: 442.2390, Found: 442.2388; [M+K^+] Calcd: 458.2129, Found: 458.2125.

Method B. Prepared from **19** (0.29 g, 0.62 mmol) in THF (5 mL), SmI_2 solution in THF (19 mL, 3 eq.), reaction time 1 h, yield of product **23** (0.176g, 68%).

(*S*)-1-Benzyl-5-((*S*)-benzyloxy-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)pyrrolidin-2-one (25)

Method A. Prepared from **22** (0.1 g, 0.225 mmol), zinc dust (0.294 g, 4.5mmol), reaction time 1 h, yield of product **25** (0.072g, 82%). Colorless oil, R_f: 0.6 (hexanes/EtOAc, 20:80, $KMnO_4$,

yellow spot); $[\alpha]_D^{25}$: +39 (c = 0.209; $CHCl_3$); ^{1}H NMR (600 MHz) δ: 1.28, 1.33 (2s, 6H), 1.91-1.98 (m, 1H), 2.10 (dddd, 1H, *J* = 2.8, 2.9, 10.0, 12.9 Hz), 2.35 (ddd, 1H, *J* = 3.3, 10.4, 16.8 Hz), 2.61 (ddd, 1H, *J* = 8.4, 9.4, 17.9 Hz), 3.67 (d, 1H, *J* = 8.3 Hz), 3.77 (bd, 1H, *J* = 7.6 Hz), 3.83 (dd, 1H, *J* = 5.5, 8.3 Hz), 3.85 (d, 1H, *J* = 16.0 Hz), 3.99 (ddd, 1H, *J* = 6.0, 7.1, 13.1 Hz), 4.05 (dd, 1H, *J* = 6.2, 8.2 Hz), 4.45-4.49 (2d, 2H, *J* = 11.1 Hz), 5.03 (d, 1H, *J* = 14.9 Hz), 7.21-7.37 (m, 10H); ^{13}C NMR (150 MHz) δ: 18.6, 25.1, 26.7, 30.6, 44.5, 57.9, 67.1, 74.3, 75.2, 78.3, 109.3, 127.6, 128.0, 128.1, 128.2, 128.5, 128.7, 136.5, 137.4, 175.8; IR (KBr, cm^{-1}) ν: 3030, 2984, 2932, 2882, 1682, 1495, 1453; Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.68; H, 7.27; N, 3.41.

Method B. Prepared from **22** (0.355 g, 0.80 mmol) in THF (10 mL), SmI_2 solution in THF (23 mL, 3 eq.), reaction time 3 h, yield of product **25** (0.033g, 10%).

(*S*)-1-Benzyl-5-((1*S*,2*R*)-1-(benzyloxy)-2,3-dihydroxypropyl)pyrrolidin-2-one (26). Colorless oil, (0.04 g, 5%); R_f: 0.16 (hexanes/EtOAc, 20:80, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: +37 (c = 0.285; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 1.85-1.95 (m, 1H), 2.09-2.18 (m, 1H), 2.30 (ddd, 1H, *J* = 2.6, 10.3, 19.6 Hz), 2.54-2.65 (m, 1H), 2.60-2.80 (bs, 1H), 2.90-3.10 (bs, 1H), 3.64-3.75 (m, 4H), 3.79 (d, 1H, *J* = 14.7 Hz), 3.86 (d, 1H, *J* = 7.7 Hz), 4.38-4.50 (2d, 2H, *J* = 11.1 Hz), 4.91 (d, 1H, *J* = 14.9 Hz), 7.20-7.38 (m, 10H); ^{13}C NMR (75 MHz) δ: 18.8, 30.8, 44.2, 58.2, 63.5, 71.2, 74.1, 76.7, 127.6, 128.1, 128.2, 128.3, 128.5, 128.6, 136.4, 137.4, 176.2; IR (KBr, cm^{-1}) ν: 3368, 2929, 2873, 1651, 1495, 1452, 1418; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.78; H, 7.37; N, 4.02.

(*S*)-1-Benzyl-5-((*S*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)pyrrolidin-2-one (24). The TBAF (0.127 g, 0.403) and water (0.2 mL) were put to solution of pyrrolidinone **23** (0.169 g, 0.403 mmol) in THF (10 mL) and mixture was stirred at room temperature for 2.5 h. The reaction was controlled by TLC. At the end of the reaction THF was removed on rotatory evaporator. The pyrrolidinone **24** was obtained after purification by column chromatography (silica gel, EtOAc) as a colorless crystals (0.117 g, 95%), mp: 159-162°C; R_f: 0.14 (hexanes/EtOAc, 20:80, $KMnO_4$, yellow spot); $[\alpha]_D^{25}$: +58 (c = 0.209; $CHCl_3$); ^{1}H NMR (300 MHz) δ: 1.23, 1.26 (2s, 6H), 1.85-1.98 (m, 1H), 2,14 (ddd, 1H, *J* = 3.9, 9.9, 17.0 Hz), 2.36 (ddd, 1H, *J* = 4.3, 10.4, 17.0 Hz), 2.46-2.58 (m, 1H), 3.78 (dd, 1H, *J* = 3.1, 8.7 Hz), 3.67-3.96 (m, 2H), 4.01-4.14 (m, 3H), 4.75-4.85 (bs, 1H), 5.10 (d, 1H, *J* = 15.1 Hz,), 7.22-7.35 (m, 5H); ^{13}C NMR (75 MHz) δ: 17.2, 25.1, 26.7, 30.9, 44.2, 58.7, 67.7, 69.7, 74.9, 109.4, 127.7, 128.1, 128.7, 136.0, 176.5; IR (KBr, cm^{-1}) ν: 3298, 3066, 2982, 2954, 2887, 1651, 1464, 1455, 1444; Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.98; H, 7.73; N, 4.67.

(*S*)-1-Benzyl-5-((*S*)-benzyloxy-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)pyrrolidin-2-one (25). The hydroxypyrrolidinone **24** (0.046 g, 0.15 mmol) was dissolved in THF (5 mL) and NaH (0.040 g, 1.66 mmol) was added. The mixture was stirred at room temperature for 1 h. After then benzylbromide (0.035, 0.30 mmol) was added and reaction mixture was stirred at room temperature for 3 h. The reaction mixture was controlled by TLC. The water and toluene were added at the end of the reaction and solvents were removed by reduced pressure. The

pyrrolidinone **25** was obtained after purification by column chromatography (silica gel, hexanes/EtOAc, 40:60) as a colorless oil (0.058 g, 98%).

Acknowledgements

The authors are grateful to the Slovak Grant Agency (No. 1/3549/06) and APVV (No. 20/000305). NMR experimental part was facilitated by the support of Slovak National Research (No 2003SP200280203).

References and Notes

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