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Ready access to enantiopure 5-substituted-3-pyrrolin-2-ones from *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN)

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Abstract

The reaction of the lithiated salt of methyl propiolate with *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN) afforded the corresponding propargyl hydroxylamines in a stereocontrolled way depending on the nature of the Lewis acid used as an additive. Subsequent reduction of the obtained hydroxylamines provided chiral 5-substituted-3-pyrrolin-2-ones, in high overall yields.

1. Introduction

Optically active 3-pyrrolin-2-ones are ubiquitous structural subunits found in a wide range of natural products including alkaloids, nucleosides, antineoplastic agents or immunosupresants.[1] The α,β-unsaturated-γ-butyrolactam moiety exists as a substructural unit in several biologically active natural products, e.g. biliverdin,[2] leuconolactam,[3] showdomycin,[4] dysidin,[5] pandamarine,[6] dolastatin 15,[7] or microcolins.[8]

Moreover, chiral 5-substituted-3-pyrrolin-2-ones are ideally suited as building blocks, as the combination of the chirality and inherent topology of a cyclic system provides a high degree of regio- and stereocontrol for the systematic functionalization of predetermined sites in the molecule. The α,β-unsaturated lactam moiety can be utilized as a Michael acceptor of a variety of nucleophiles including stabilized carbanions,[9] nitrogen nucleophiles[10–13] or several types of organocuprates.[14–17] Additionally, the double bond of the heterocycle is susceptible to both epoxidation[18,19] and hydroxylation[20–24] thus leading to polyhydroxylated compounds. More elaborated products are also accessible by using 3-pyrrolin-2-ones as substrates in cycloaddition reactions.[25–27]

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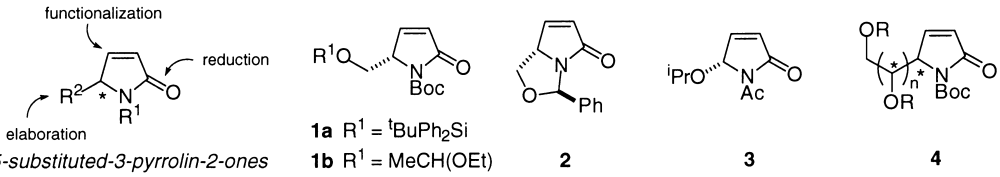


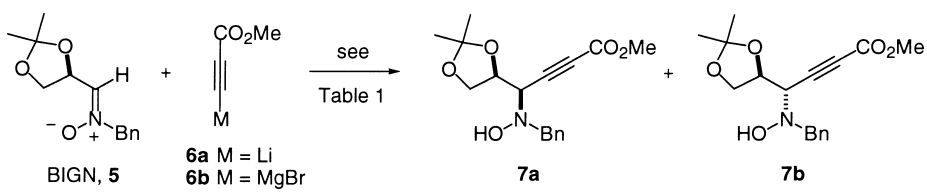
Therefore, the synthesis of such optically active building blocks are currently receiving considerable attention.[28–30] Thus, the preparation of several differentially protected 5-substituted-3-pyrrolin-2-ones **1** and **2** has been described using pyroglutamic acid as the starting material.[16,29,31,32] Derivative **3** has been prepared both starting from (*S*)-malic acid[27] and by enzymatic resolutions of racemic lactams.[30] Casiraghi and co-workers prepared compounds **4**, bearing a polyhydroxylated side chain at C-5, by condensing a pyrrole derivative, designed as a four-carbon synthon, with α-alkoxy aldehydes[33] and α-amino aldehydes.[34]

In connection with our efforts on the syntheses of biologically active nitrogenated compounds, starting from nitrones, we have developed new synthetic routes for diamines,[35] (hydroxyamino) nitriles,[36] complex nucleosides,[37] diamino acids,[38] and analogues of nucleosides.[39] All these strategies were based on nucleophilic addition reactions to chiral nitrones. In this context, we have recently reported, in a preliminary form, a new approach to 3-pyrrolin-2-ones.[40] Our strategy was based on the nucleophilic addition of a methyl propiolate acetylide to the *N*-benzyl nitrone derived from 2,3-*O*-isopropylidene-D-glyceraldehyde; during the course of our investigations quite similar chemistry was independently adopted by Vallee and co-workers in a study designed to provide a general means to prepare γ-amino-α,β-ethylenic acid derivatives.[41]

Herein we report in full the stereocontrolled addition of organometallic derivatives of methyl propiolate to *N*-benzyl 2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN) **5**, which makes it possible to furnish propargyl hydroxylamines in excellent diastereomeric excess. We also explored the transformations of the products obtained towards 3-pyrrolin-2-ones bearing a polyhydroxylated chain at C-5; the utility of such compounds has been well-demonstrated by Casiraghi and co-workers in recent years.[23,24,34,42]

2. Results and discussion

Lithiated methyl propiolate **6a** was generated by treatment of methyl propiolate with n-butyllithium in THF at −80°C. Nitrone **5** was added to the mixture at −80°C, and aqueous work-up after 15 min provided *syn*-hydroxylamine **7a** in quantitative yield (Scheme 1).



Scheme 1.

The absolute configuration of **7a** was established by comparison of the physical and spectroscopic properties of a further derivative with a known compound (*vide infra*). The diastereoselectivity was

Table 1
Stereoselective addition of metallated methyl propiolates to BIGN **5**

entry	M[a]	solvent	T[a](°C)	Lewis acid[c]	time (min)	*syn:anti*[d]	yield (%)[e]
1	Li	THF	-80	none	15	>20:1	100
2	Li	THF	-80	$ZnBr_2$	60	>20:1	98
3	Li	THF	-80	Et_2AlCl	60	43:57	90
4	Li	Et_2O	-80	Et_2AlCl	60	30:70	92
5	MgBr[b]	THF	-60	none	60	85:15	86
6	MgBr[b]	Et_2O	-60	Et_2AlCl	120	34:66	88

[a] 2.0 equiv. were added. [b] prepared by metal-exchange with $MgBr_2$. [c] 1.0 equiv. were added. [d] measured from the intensities of NMR signals. [e] determined on isolated mixture.

sufficiently high so that the minor diastereomer was not observed. In such instances the minimal diastereomeric ratio is given as >20:1, the limit of detectability by ^{13}C NMR spectroscopy.†

Lithiated derivative **6a** also added smoothly to BIGN **5** when the latter was precomplexed with Lewis acids (Table 1). According to our previous results[43] on the addition of organometallic compounds to **5**, prior treatment of the nitrone with $ZnBr_2$ also led to the *syn*-adduct (Table 1, entry 2). Guided by our previous experiments[44] and in order to reverse the diastereoselectivity of the addition, we used Et_2AlCl as a precomplexing agent of the nitrone (Table 1, entries 3 and 4). The *syn*:*anti* ratio of 30:70, when diethyl ether was used as a solvent, demonstrates that Et_2AlCl displays reasonable diastereofacial selectivity, comparable to that of other addition reactions to **5** in the presence of such an additive.[43,44] The Grignard derivative **6b** was also examined both in the presence and in the absence of Et_2AlCl (Table 1, entries 5 and 6). Slight reductions in both the diastereoselectivities and chemical yields were observed. All these behaviours are fully consistent with those of the previously reported nucleophilic additions to BIGN **5**.[38,43–45] In consequence, the results can be rationalized by applying models previously proposed by us.[43]

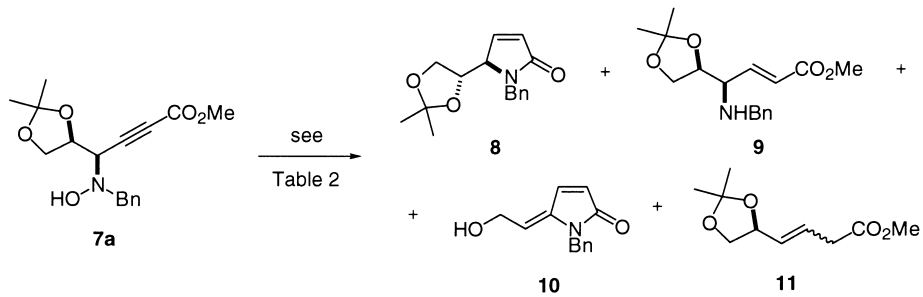
One possible method to convert propargyl hydroxylamines **7** into preparatively useful 3-pyrrolin-2-ones is the reduction with a considerable excess (20 equiv.) of Zn in the presence of a protic and acidic solvent system (e.g. AcOH–MeOH, AcOH–H_2O or HCO_2H–H_2O). This strategy has been successfully applied to propargyl hydroxylamines derived from α-amino nitrones.[41]

However, when we evaluated this procedure for concomitant reduction and cyclization of **7a**, moderately useful results were obtained by using a 1:9 AcOH–MeOH mixture as a solvent, compound **8** being isolated in only 40% chemical yield (Scheme 2). Moreover, the three by-products **9**–**11** could be identified from the reaction mixture. Compound **9** was obtained as a consequence of the partial *E*/*Z* selectivity of the reaction. A deacetonization with elimination to the allyl alcohol derivative **10** was also observed.‡ Likewise, the considerable excess of reducing agent presumably induces partial elimination of the hydroxyamino moiety, thus leading to **11** which was identified as an *E*–*Z* mixture of compounds. Subjection of hydroxylamine **7b** to a range of similar conditions (Table 2), including those using the Zn–Cu(II) couple (Table 2, entry 4),[46] led only to increasing amounts of undesired side products.

In order to circumvent these troubles we turned our attention to the two-step procedure previously devised in our laboratory.[40] The strategy that exclusively provides the cyclized product **8**, is outlined in Scheme 3. Optimum conditions for the reduction of the triple bond involved catalytic hydrogenation at

† This is the signal-to-noise limit of detection. For previous use of ^{13}C NMR in the determination of diastereomeric ratios see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett*. **1977**, *18*, 2183–2186.

‡ The *E*-stereochemistry of the exocyclic double bond in **10** was confirmed by NOE experiments.



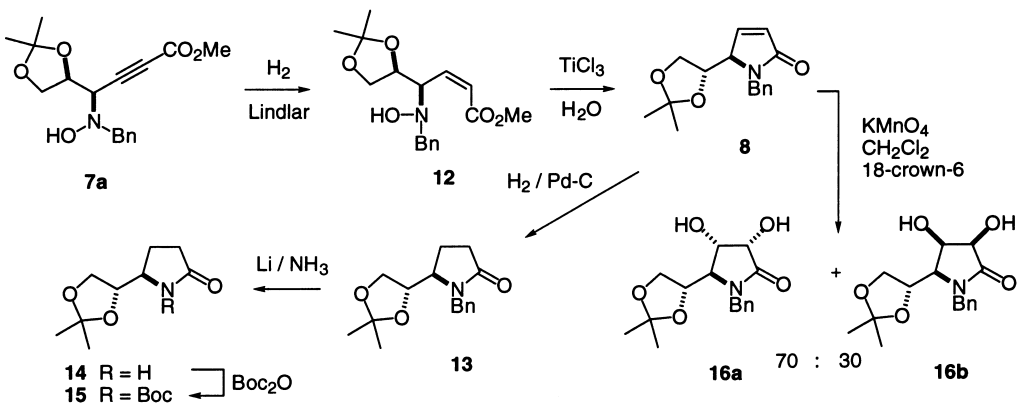
Scheme 2.

Table 2
Reduction of hydroxylamine **7a**[a]

entry	solvent	time (min)	**8**	**9**	**10**	**11**	yield (%)[c]
1	1:9 AcOH / MeOH	60	8	2	1	1	60
2	1:9 AcOH / H_2O	60	5	1	10	traces	72
3	1:15 AcOH / MeOH	90	1	1	10	1	66
4	5:1 AcOH / H_2O[b]	60	2	1	3	0	60

[a] All reactions were carried out with 20 equiv. of Zn. [b] 5 equiv. of Zn were used and 1.0 equiv of $Cu(AcO)_2$ was added. [c] determined on isolated mixture.

atmospheric pressure using Lindlar's catalyst for 45 min.¶ This led to intermediate **12** in quantitative yield, no purification being needed for its further use. Finally, reduction of the hydroxyamino moiety in **12** by using a 20% aqueous solution of $TiCl_3$, as described,[47] provided the targeted 3-pyrrolin-2-one **8** in 91% isolated yield after column chromatography. Thus compound **8** has been synthesized in three steps from BIGN **5** in an overall yield of 91% and with total diastereoselectivity.



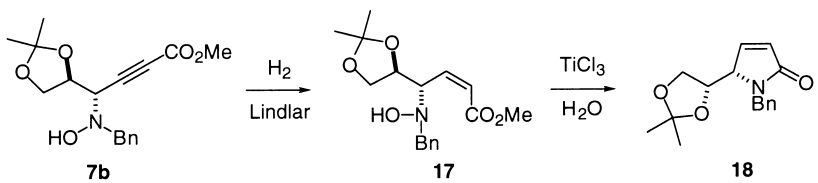
Scheme 3.

The unsaturated lactam **8** has proven to be a useful intermediate in organic synthesis (Scheme 3). Saturated pyrrolidin-2-one **13** was obtained from **8** after catalytic hydrogenation (H_2, Pd–C) of the double bond; subsequent debenzylation by using Li in liquid ammonia furnished deprotected lactam **14**. The physical and spectroscopic properties of **14** were identical to those reported in the literature[48]

¶ It should be noted that this reaction was quite sensitive to reaction time. Hydrogenation for less than 45 min resulted in recovery of starting material. Above the indicated time an over-reduced product appeared: the longer the reaction time, the higher the amount of saturated derivative.

for the same compound (see Experimental), thus confirming the *syn* arrangement of the heteroatoms at the stereogenic centres. This result also establishes that the previously assigned stereochemistry for hydroxylamines **7** was correct. Compound **14** was also characterized as the corresponding *N*-(tert-butoxycarbonyl) derivative **15**. Hydroxylation of **8** was carried out with $KMnO_4$ following Casiraghi's conditions.[34] A 70:30 mixture of diastereomeric diols **16** was obtained, the stereochemistry of the adducts being assumed on the basis of the absolute configuration of the side chain at C-5 and conformational analysis of **8** using Chem3D®.[§]

In order to illustrate the convenience of the two-step reduction sequence of propargyl hydroxylamines we also prepared the *anti*-diastereomer **18** from **7b** as indicated in Scheme 4. Hydrogenation of **7b** in the presence of Lindlar's catalyst was accomplished in 40 min and compound **17** was obtained in quantitative yield. Treatment of **17** with aqueous $TiCl_3$ afforded *anti*-**18** in 91% isolated yield. The overall yield for the synthesis of **18** from BIGN **5** was 58.6% (three steps).



Scheme 4.

3. Conclusions

In conclusion, we have developed a short and efficient synthesis (three steps) of epimeric 5-substituted-3-pyrrolin-2-ones **8** (91% overall yield) and **18** (58.6% overall yield) from the *N*-benzyl nitrone derived from 2,3-*O*-isopropylidene-D-glyceraldehyde. We expect 3-pyrroline-2-ones **8** and **18** to find utility for the synthesis of highly functionalized pyrrolidines. The efficiency and convenience of this chemistry recommends this approach for the synthesis of these and related systems.

4. Experimental

4.1. General methods

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried over standard drying agents[49] and freshly distilled prior to use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 300 Varian Unity spectrometer in $CDCl_3$, 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). 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 with iodine or by spraying with 1 M aqueous $KMnO_4$ and heating. Flash column chromatography was performed on silica gel 60 F254.[50] *N*-Benzyl 2,3-*O*-isopropylidene-D-glyceraldehyde nitrone **5** was prepared as described.[44]

[§] We use semiempirical methods (MOPAC 97®, PM3 and AM1) in Chem3D Pro® v. 4.0.

4.2. Methyl (4R,5S)-N-benzyl-5,6-dihydroxy-4-(hydroxyamino)-5,6-O-isopropylidene-2-hexynoate **7a**

To a solution of methyl propiolate (0.716 g, 8.52 mmol) in THF (25 mL) at −80°C was added n-butyllithium (5.4 mL, 1.6 M in hexanes, 8.64 mmol), the resulting solution being stirred for 15 min. A cold (−80°C) solution of nitrone **5** (1.0 g, 4.26 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 mixture was quenched with saturated NH_4Cl (5 mL) and 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 ≥20:1 by NMR). The crude product was chromatographed on silica gel (hexane:ethyl acetate=85:15) to give the hydroxylamine **7a** as a clear oil (1.36 g, 100%): $[\alpha]_D$ −49.1 (c 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.31 (s, 3H), 3.69 (d, 1H, J=7.4 Hz), 3.79 (s, 3H), 3.91 (d, 1H, J=12.4 Hz), 3.96 (dd, 1H, J=5.3, 9.0 Hz), 4.08 (dd, 1H, J=6.2, 9.0 Hz), 4.15 (d, 1H, J=12.4 Hz), 4.40 (ddd, 1H, J=5.3, 6.4, 7.4 Hz), 6.20 (bs, 1H, ex. D_2O), 7.28–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.5, 26.6, 52.8, 60.5, 62.5, 67.1, 75.1, 79.4, 81.6, 109.9, 127.9, 128.5, 129.6, 135.6, 153.4. Anal. calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.10; H, 6.55; N, 4.61.

4.3. Methyl (4S,5S)-N-benzyl-5,6-dihydroxy-4-(hydroxyamino)-5,6-O-isopropylidene-2-hexynoate **7b**

To a well-stirred solution of nitrone **5** (1.0 g, 4.26 mmol) in diethyl ether (80 mL), Et_2AlCl (4.3 mmol, 4.3 mL of a 1.0 M solution in hexanes) was added in one portion at room temperature and the resulting mixture was stirred for 5 min. The mixture was cooled to −80°C and a solution of lithiated methyl propiolate [prepared as described above from methyl propiolate (0.716 g, 8.52 mmol) and n-butyllithium (5.4 mL, 1.6 M in hexanes, 8.64 mmol)], was then quickly added with a cannula over a period of 15 min. The mixture was stirred for 1 h at −80°C and then treated with 1 N aqueous NaOH (25 mL). After additional stirring for 15 min at ambient temperature the mixture was extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to give the crude product. The diastereoselectivity (ds=70%) was established by NMR analysis. Purification by column chromatography on silica gel (hexane:diethyl ether=70:30) gave pure **7b** (0.88 g, 65%) as a white solid: mp 116–118°C; $[\alpha]_D$ +6.9 (c 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.45 (s, 3H), 3.64 (dd, 1H, J=7.2 Hz), 3.81 (s, 3H), 3.87 (d, 1H, J=12.9 Hz), 4.01 (dd, 1H, J=4.9, 8.9 Hz), 4.07 (dd, 1H, J=6.1, 8.9 Hz), 4.15 (d, 1H, J=12.9 Hz), 4.41 (ddd, 1H, J=4.9, 6.1, 7.2 Hz), 4.85 (bs, 1H, ex. D_2O), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3, 26.7, 52.8, 61.4, 62.5, 67.2, 75.9, 78.9, 82.3, 110.4, 127.9, 128.6, 129.4, 136.2, 153.6. Anal. calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.79; H, 6.59; N, 4.54.

4.4. Methyl (4R,5S)-(Z)-N-benzyl-5,6-dihydroxy-4-(hydroxyamino)-5,6-O-isopropylidene-2-hexenoate **12**

A mixture of the hydroxylamine **7a** (0.80 g, 2.50 mmol) and 5% palladium on calcium carbonate, poisoned with lead (Lindlar's catalyst) (80 mg) in ethyl acetate (50 mL) was degassed under vacuum and saturated with hydrogen three times. The resulting suspension was stirred in a Parr hydrogenation apparatus at ambient temperature for 45 min at atmospheric pressure, then filtered through a plug of

Celite, and concentrated to give the crude product, which was purified by column chromatography on silica gel (hexane:diethyl ether=70:30) to afford 0.804 g (100%) of pure **12** as a colourless oil: $[\alpha]_D$ +69.3 (c 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 11.34 (s, 3H), 1.38 (s, 3H), 3.63 (s, 3H), 3.76 (d, 1H, J=12.2 Hz), 3.82 (dd, 1H, J=6.8, 8.6 Hz), 3.86 (d, 1H, J=12.2 Hz), 3.87 (dd, 1H, J=6.6, 8.6 Hz), 4.37 (ddd, 1H, J=6.6, 6.8, 7.1 Hz), 4.63 (dd, 1H, J=7.1, 10.1 Hz), 6.11 (d, 1H, J=11.9 Hz), 6.21 (bs, 1H, ex. D_2O), 6.53 (dd, 1H, J=10.1, 11.9 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.7, 26.5, 51.2, 62.2, 64.1, 66.4, 76.4, 109.4, 124.2, 127.2, 128.2, 129.4, 137.6, 142.1, 166.2. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.48; H, 7.00; N, 4.29.

*4.5. (5R)-1-Benzyl-5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-pyrrolin-2-one **8***

*Method A (from **7a**).* To a solution of the hydroxylamine **7a** (1.0 g, 3.14 mmol) in an AcOH:MeOH (1:9) mixture (10 mL), Zn dust (4.1 g, 62.8 mmol) was added and the mixture was stirred for 60 min at 60°C. After cooling to 0°C the solution was made alkaline (pH=9) by the addition of 1 M NaOH. The resulting solution was extracted with ethyl acetate (3×20 mL); the combined extracts were washed with saturated aqueous EDTA (3×25 mL) and with brine (25 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which was purified by column chromatography on silica gel (hexane:ethyl acetate=50:50).

Eluted first (R_f=0.75, hexane:ethyl acetate=50:50) was **11** (60:40 mixture of *E*:*Z* isomers): 32 mg (5%). *E*-Isomer: ^1H NMR ($CDCl_3$), selected signals δ 1.37 (s, 3H), 1.41 (s, 3H), 3.10 (m, 2H), 3.61 (m, 1H), 3.67 (s, 3H), 4.04 (m, 1H), 4.50 (m, 1H), 5.60 (m, 1H), 5.90 (dt, 1H, J=7.1, 15.4 Hz). *Z*-Isomer: ^1H NMR ($CDCl_3$), selected signals δ 1.38 (s, 3H), 1.41 (s, 3H), 3.20 (m, 2H), 3.63 (m, 1H), 3.68 (s, 3H), 4.02 (m, 1H), 4.53 (m, 1H), 5.53 (ddd, 1H, J=7.3, 9.6, 11.0 Hz), 5.80 (dt, 1H, J=7.6, 11.0 Hz).

Eluted second (R_f=0.40, hexane:ethyl acetate=50:50) was **9**: 96 mg (10%); oil; $[\alpha]_D$ −49.0 (c 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.33 (s, 3H), 2.16 (bs, 1H, ex. D_2O), 3.22 (ddd, 1H, J=0.8, 7.0, 8.3 Hz), 3.57 (d, 1H, J=13.4 Hz), 3.74 (s, 3H), 3.75 (dd, 1H, J=5.6, 8.3 Hz), 3.84 (d, 1H, J=13.4 Hz), 3.92 (dd, 1H, J=6.4, 8.3 Hz), 4.04 (ddd, 1H, J=5.6, 6.4, 7.0 Hz), 6.02 (dd, 1H, J=0.8, 15.8 Hz), 6.72 (dd, 1H, J=8.3, 15.8 Hz), 7.22–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3, 26.7, 51.1, 51.7, 61.6, 66.4, 76.8, 109.7, 124.2, 127.1, 128.1, 128.4, 139.7, 146.5, 166.3. Anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.75; H, 7.42; N, 4.71.

Eluted third (R_f=0.25, hexane:ethyl acetate=50:50) was **8**: 342 mg (40%); oil; $[\alpha]_D$ +32.1 (c 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.40 (s, 3H), 3.48 (dd, 1H, J=5.1, 8.5 Hz), 3.76 (dd, 1H, J=6.1, 8.5 Hz), 4.06–4.20 (m, 2H), 4.44 (d, 1H, J=15.0 Hz), 4.97 (d, 1H, J=15.0 Hz), 6.30 (dd, 1H, J=1.5, 6.1 Hz), 6.90 (dd, 1H, J=1.5, 6.1), 7.19–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.7, 26.2, 44.9, 64.3, 64.9, 75.5, 110.2, 127.6, 128.0, 128.7, 129.5, 137.6, 143.7, 171.6. Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.46; H, 6.88; N, 5.27.

Eluted fourth (R_f=0.12, hexane:ethyl acetate=50:50) was **10**: 34 mg (5%); oil; ^1H NMR ($CDCl_3$) δ 2.58 (bs, 1H, ex. D_2O), 4.36 (d, 2H, J=7.5 Hz), 4.83 (s, 2H), 5.49 (dt, 1H, J=1.5, 7.5 Hz), 6.31 (dd, 1H, J=1.5, 5.9 Hz), 7.11–7.29 (m, 5H), 7.32 (d, 1H, J=5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 42.7, 58.1, 113.1, 124.5, 126.8, 127.4, 128.7, 133.1, 136.9, 140.8, 170.3. Anal. calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.65; H, 5.89; N, 6.63.

*Method B (from **12**).* To a solution of **12** (0.8 g, 2.48 mmol) in methanol (10 mL), water (9 mL) and sodium acetate (2.48 g, 30 mmol) were added and the resulting mixture was vigorously stirred at ambient temperature while 3.8 mL of a 20% $TiCl_3$ solution in water was added dropwise. After 1 h, the suspension was poured into 35 mL of water and then extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (25 mL) and brine

(25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the crude material by column chromatography (hexane:ethyl acetate=50:50) afforded pure **8** (0.612 g, 91%) as an oil. The physical and spectroscopic properties of the obtained compound were identical to those of the same compound obtained from **12** as described above.

*4.6. (5R)-1-Benzyl-5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-pyrrolidinone **13***

A mixture of compound **8** (0.60 g, 2.20 mmol) and 20% palladium on charcoal (50 mg) in methanol (30 mL) was degassed under vacuum and saturated with hydrogen three times. The resulting suspension was stirred in a Parr hydrogenation apparatus at ambient temperature for 24 h at atmospheric pressure, then filtered through a plug of Celite, and concentrated to give the crude product, which was purified by column chromatography on silica gel (hexane:ethyl acetate=60:40) to afford compound **13** (0.606 g, 100%) as an oil: $[\alpha]_D$ −134.9 (c 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.35 (s, 3H), 1.55 (dddd, 1H, J=4.9, 6.0, 9.8, 13.3 Hz), 2.00 (dddd, 1H, J=7.3, 8.4, 9.9, 13.3 Hz), 2.36 (ddd, 1H, J=6.0, 9.9, 17.1 Hz), 2.50 (ddd, 1H, J=7.3, 9.8, 17.1 Hz), 3.45 (ddd, 1H, J=4.9, 8.4, 7.5 Hz), 3.53 (dd, 1H, J=6.9, 8.4 Hz), 3.93 (dd, 1H, J=6.6, 8.4 Hz), 4.11 (ddd, 1H, J=6.6, 6.9, 7.5 Hz), 4.34 (d, 1H, J=14.7 Hz), 4.98 (d, 1H, J=14.7 Hz), 7.20–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.6, 25.2, 26.4, 29.9, 45.4, 59.5, 66.3, 79.0, 110.2, 127.3, 128.4, 128.5, 137.3, 175.1. Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.57; H, 7.52; N, 5.19.

*4.7. (5R)-5-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-pyrrolidinone **14***

A solution of pyrrolidinone **13** (0.606 g, 2.20 mmol) in THF (15 mL) was added dropwise to liquid ammonia (75 mL), cooled to −35°C. Then lithium in small portions was added slowly until a blue colour persisted for 15 min. At this time absolute ethanol (5 mL) was added and the solution became colourless. The solvent was evaporated and the residue partitioned between brine (25 mL) and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2×25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (hexane:ethyl acetate=20:80) afforded the saturated lactam **14** (0.354 g, 87%) as an oil which solidified upon standing: mp 103–105°C; $[\alpha]_D$ −52.1 (c 0.67, $CHCl_3$) [lit.[48] mp 102–104°C; $[\alpha]_D$ −54 (c 0.10, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.42 (s, 3H), 1.65–1.74 (m, 1H), 2.05–2.15 (m, 1H), 2.20–2.34 (m, 2H), 3.59 (dd, 1H, J=6.2, 8.1 Hz), 3.63 (dd, 1H, J=5.1, 8.1 Hz), 3.92 (pseudo q, 1H, J=6.5 Hz), 4.11 (pseudo q, 1H, J=6.6 Hz), 6.44 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 24.8, 26.6, 28.7, 47.1, 59.4, 79.4, 110.2, 174.8. Anal. calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.19; H, 7.83; N, 7.74.

*4.8. (5R)-1-(tert-Butoxycarbonyl)-5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-pyrrolidinone **15***

To a solution of **14** (0.354 g, 1.91 mmol) in dichloromethane (30 mL) were added triethylamine (0.27 mL, 1.91 mmol), di-tert-butyldicarbonate (0.83 g, 15.8 mmol), and 4-(dimethylamino)pyridine (0.23 g, 1.91 mmol). The solution was stirred for 7 h at 25°C under an argon atmosphere at which time the reaction mixture was treated with 1 M aqueous solution of $KHSO_4$ (25 mL). The organic layer was separated and washed with brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate=60:40) to give **15** (0.512 g, 94%) as an oil: $[\alpha]_D$ +47.9 (c 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 55°C) δ 1.26 (s, 3H), 1.31 (s, 3H), 1.47 (s, 9H), 1.90–2.14 (m, 3H), 2.64 (ddd, 1H, J=9.6, 10.6, 17.6 Hz), 3.75 (dd, 1H, J=6.6, 8.8 Hz), 3.90 (dd,

1H, J=6.4, 8.8 Hz), 4.23 (pseudo dt, 1H, J=3.3, 6.5 Hz), 4.31 (ddd, 1H, J=1.7, 3.4, 8.9 Hz); ^{13}C NMR ($CDCl_3$, 55°C) δ 21.7, 25.3, 25.9, 28.0, 32.2, 57.5, 65.9, 78.4, 82.9, 109.4, 150.6, 174.2. Anal. calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.05; H, 8.26; N, 4.76.

*4.9. (3*R*,4*R*,5*S*)-1-Benzyl-3,4-dihydroxy-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-pyrrolidinone* ***16a*** *and (3*S*,4*S*,5*S*)-1-benzyl-3,4-dihydroxy-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-pyrrolidinone* ***16b***

To a solution of **8** (0.60 g, 2.20 mmol) in anhydrous dichloromethane (20 mL) were added *cis*-dicyclohexano-18-crown-6 ether (0.16 g, 0.44 mmol) and powdered potassium permanganate (0.21 g, 1.31 mmol) under an argon atmosphere at −12°C. After stirring at this temperature for 12 h, a saturated aqueous Na_2SO_3 solution and a 5% citric acid solution were added to the reaction mixture. The resulting mixture was extracted with dichloromethane (3×30 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated in vacuo. The diastereoselectivity (ds=70%) was established by NMR analysis. The crude product was chromatographed on silica gel (hexane:ethyl acetate=40:60) to afford pure diols **16**.

Eluted first (R_f=0.32, hexane:ethyl acetate=50:50) was **16a** (0.332 g, 49%) as a sticky foam; $[\alpha]_D$ −62.5 (c 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.36 (s, 3H), 3.20 (bs, 2H, ex. D_2O), 3.40 (d, 1H, J=6.1 Hz), 3.76 (dd, 1H, J=5.0, 8.1 Hz), 4.01–4.10 (m, 3H), 4.21 (d, 1H, J=15.4 Hz), 4.51–4.55 (m, 1H), 5.19 (d, 1H, J=15.4 Hz), 7.20–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.0, 26.3, 45.9, 64.8, 66.8, 69.8, 70.2, 75.0, 110.5, 127.6, 128.1, 128.7, 135.1, 174.3. Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.47; H, 7.09; N, 4.61.

Eluted second (R_f=0.26, hexane:ethyl acetate=50:50) was **16b** (0.142 g, 21%) as a sticky oil; $[\alpha]_D$ −31.5 (c 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.34 (s, 3H), 2.80 (bs, 2H, ex. D_2O), 3.49 (dd, 1H, J=3.8, 8.1 Hz), 3.71 (d, 1H, J=3.8 Hz), 4.03–4.12 (m, 2H), 4.24 (d, 1H, J=14.7 Hz), 4.24–4.31 (m, 2H), 4.90 (d, 1H, J=14.7 Hz), 7.20–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3, 26.5, 45.2, 62.7, 66.6, 67.3, 70.6, 75.9, 109.7, 127.4, 128.3, 128.4, 136.9, 174.0. Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.67; H, 7.14; N, 4.39.

*4.10. Methyl (4*S*,5*S*)-(*Z*)-*N*-benzyl-5,6-dihydroxy-4-(hydroxyamino)-5,6-*O*-isopropylidene-2-hexenoate* ***17***

The hydroxylamine **7b** (0.8 g, 2.50 mmol) was treated as described above for the preparation of **12**. Column chromatography on silica gel (hexane:diethyl ether=70:30) of the crude product gave 0.803 g (100%) of **16** as a white solid: mp 83°C; $[\alpha]_D$ −80.5 (c 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.34 (s, 3H), 3.66 (s, 3H), 3.82 (s, 2H), 3.95 (dd, 1H, J=5.8, 8.6 Hz), 4.07 (dd, 1H, J=6.2, 8.6 Hz), 4.41 (ddd, 1H, J=5.8, 6.2, 6.6 Hz), 4.69 (ddd, 1H, J=0.8, 6.6, 10.0 Hz), 4.98 (bs, 1H, ex. D_2O), 6.10 (dd, 1H, J=0.8, 11.8 Hz), 6.59 (dd, 1H, J=10.0, 11.8 Hz), 7.22–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.4, 26.3, 51.3, 62.0, 65.6, 67.6, 76.6, 109.5, 124.4, 127.3, 128.3, 129.4, 137.7, 143.1, 166.4. Anal. calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.62; H, 7.43; N, 4.49.

*4.11. (5*S*)-1-Benzyl-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-pyrrolin-2-one* ***18***

The hydroxylamine **17** (0.8 g, 2.48 mmol) was treated as described above for the preparation of **8**. Column chromatography on silica gel (hexane:ethyl acetate=50:50) of the crude product gave 0.62 g (91%) of **18** as an oil; $[\alpha]_D$ −20.3 (c 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.41 (s, 3H), 3.64 (dd, 1H, J=6.0, 8.5 Hz), 3.92 (dd, 1H, J=6.6, 8.5 Hz), 4.12 (dd, 1H, J=1.8, 6.0 Hz), 4.25 (d, 1H, J=15.1

Hz), 4.26 (ddd, 1H, J=1.8, 6.0, 6.6 Hz), 5.20 (d, 1H, J=15.1 Hz), 6.26 (dd, 1H, J=1.7, 6.0 Hz), 6.99 (dd, 1H, J=1.7, 6.0 Hz), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.6, 26.0, 44.7, 63.1, 65.3, 74.8, 109.7, 127.5, 128.0, 128.5, 128.7, 137.3, 144.7, 172.1. Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.57; H, 7.21; N, 4.98.

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