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Stereoselective synthesis of conformationally constrained (2*S*,3*S*)-3-hydroxyornithine

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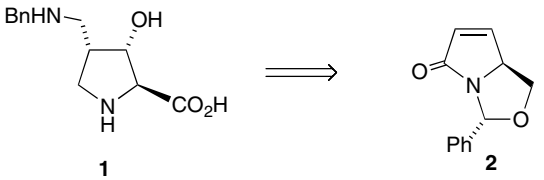
Abstract—A convenient and efficient route is described for the highly stereoselective synthesis of δ-amino protected and conformationally restricted (2*S*,3*S*)-3-hydroxyornithine through the *N*-benzylnitrone adduct to the α,β-unsaturated bicyclic lactam **2** derived from (*S*)-pyroglutaminol.

1. Introduction

Conformationally constrained amino acids have received much attention due to their ability to be incorporated into novel peptides and peptidomimetics.[1,2] They can also be used as tools to define the shape of subunits in bioactive peptides and to understand their activities better.[3,4] The restricted conformation is generally induced by the presence of rings and it is well known that cyclic amino acids, such as proline, exert a considerable influence on the conformation of peptides containing them.[5] In α,ω-diamino acids, five membered rings can also produce a restriction confined to the side chain.[6]

To the best of our knowledge, although several rigidified ornithine derivatives have already been reported,[6,7] no conformationally restricted 3-hydroxyornithine analogues have been described so far. We designed the (2*S*,3*S*)-δ-*N*-benzyl-3-hydroxyornithine chimera **1** as our target. Herein we report the practical and efficient synthesis of **1** as an extension of our methodology involving *N*-alkylnitrone cycloaddition to α,β-unsaturated bicyclic lactam **2** to introduce suitable functionalities at the C-3 and C-4 positions.[8–10]



1 **2**

2. Results and discussion

Bicyclic lactam **2** is a rigid and versatile substrate derived from (*S*)-pyroglutaminol, which gave highly regio- and stereoselective 1,3-dipolar cycloaddition with *N*-benzylnitrone, giving the adduct **3** in 90% yield.[8,10] The compound **3** was converted into **1** as shown in Scheme 1.

In this simple scheme, appropriate protection of the functional groups was not obvious but shown to be crucial. In the case of **3**, the best reagent to cleave the *N*–*O* bond of the isoxazolidine ring was $LiAlH_4$ in THF at reflux. Under these conditions the aminoacetal *C*–*O* bond was also cleaved with quantitative formation of (2*R*,3*S*,4*S*)-1-benzyl-4-benzylaminomethyl-3-hydroxy-2-hydroxymethylpyrrolidine **4**.[10] Several attempts to selectively protect the primary alcohol group of **4** as a *tert*-butyldimethylsilyl ether gave moderate results (48% as the highest yield). On the other hand, the protection of both the secondary alcohol and the δ-amino groups of **4** as oxazinone **5** with CDI in dichloromethane could only be performed in poor yield (30%). Thus, the protective oxazolidine ring of **3** was first hydrolyzed into **6** (100%) with trifluoroacetic acid in a mixture of THF–H_2O. Attempts to directly oxidize this primary alcohol into a carboxylic acid were unsuccessful but this route allowed the formation of amides or carbamates as intermediates before the oxidation step.

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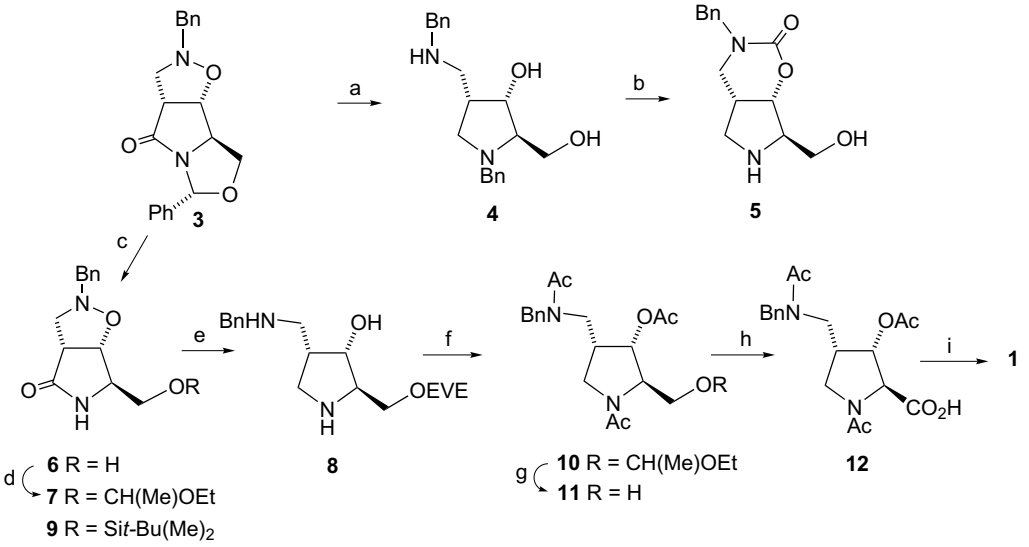

Scheme 1. Reagents and conditions: (a) $LiAlH_4$, THF, Δ, 100%; (b) CDI, CH_2Cl_2; (c) CF_3CO_2H, THF–H_2O, 100%; (d) ethylvinylether, CCl_3CO_2H, CH_2Cl_2, 93%; (e) $LiAlH_4$, THF, Δ, 100%; (f) Ac_2O, py, 98%; (g) CH_3CO_2H–H_2O, 96%; (h) Jones' reagent, acetone, 91%; (i) 3 M HCl (98%).

After efficient protection of the alcohol **6** as ethoxyethoxy derivative **7** with ethylvinylether and catalytic CCl_3CO_2H in CH_2Cl_2 (93%; OTHP gave a similar result in 72% yield), the reduction of the lactam carbonyl and the opening of the isoxazoline ring were accomplished in the same step by using an excess of $LiAlH_4$ in THF at reflux. The formation of 4-*N*-benzylaminomethyl-2-(1-ethoxyethoxymethyl)-3-hydroxypyrrolidine **8** was quantitative, whereas the *tert*-butyldimethylsilylether **9** was shown to be unstable under the same conditions. The loss of the silyl group during $LiAlH_4$ reduction has already been reported in similar cases and could be explained by intramolecular hydride transfer from the neighbouring NH group.[11] Peracetylation of **8** with acetic anhydride in pyridine furnished triacetate **10** (98%), which was selectively deprotected in a mixture of CH_3CO_2H–H_2O at 20 °C to afford the primary alcohol **11** in high yield (96%). Jones' oxidation of **11** gave rise to **12** (91%) and the target diamino acid **1** was obtained as a dihydrochloride by acid hydrolysis of **12** (3 M HCl, 70 °C, 98%).

3. Conclusion

In conclusion, we have developed a practical, highly stereoselective and efficient route to (2*S*,3*S*,4*S*)-4-(benzylaminomethyl)-3-hydroxyproline, a constrained 3-hydroxyornithine chimera, in 70% overall yield from **2**.

4. Experimental

4.1. General

Optical rotations were measured on a Jasco P-1010 polarimeter and the concentrations were given in g/100 mL. IR spectra (film, $CHCl_3$) were recorded on Perkin Elmer Spectrum BX (FT). ^1H NMR spectra were obtained ($CDCl_3$, $CHCl_3$ $\delta = 7.27$ ppm, unless otherwise indicated) from Bruker AM 300 or 500 (s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets and multiplet, respectively). ^{13}C NMR spectra were recorded on AM 300 or 500 (75 or 125 MHz, $CDCl_3$ centred at 77.14 ppm). Mass spectra and high-resolution mass spectra were measured on a Navigator (ESI), or a Micromass LC-TOF spectrometer. Chromatography was performed on silica gel (SDS 230–400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Usual workup means that the organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure.

4.2. (3a*R*,6*R*,6a*S*)-2-Benzyl-6-(1-ethoxyethoxymethyl)tetrahydro-2*H*-pyrrolo[3,4-*d*]isoxazol-4(5*H*)-one 7

Ethylvinylether (0.30 mL, 3.13 mmol) and CCl_3CO_2H (15.6 mg, 0.095 mmol) were successively added at rt to a stirred solution of compound **6**[8] (435 mg, 1.75 mmol) in dry CH_2Cl_2 (2.8 mL). The mixture was stirred at rt for 4 h before a second addition of ethylvinylether (0.30 mL), and the stirring was maintained for an additional 19 h. An aqueous solution of Na_2CO_3 (10% w/v) was added after dilution with CH_2Cl_2 and the product was extracted four times with CH_2Cl_2. After the usual workup, the crude product was purified by chromatography (eluent CH_2Cl_2–MeOH 94:6) to afford compound **7** as a colourless oil (521 mg, 93%). IR: 3221, 2975, 2926, 1702, 1694, 1682, 1496, 1454, 1385 cm^{-1}. MS (ESI, MeOH) *m*/*z*: 343 (MNa^+, 100%). HRMS calcd for $C_{17}H_{24}N_2O_4Na$: 343.1634, found: 343.1609. ^1H NMR (300 MHz, $CDCl_3$): 7.32 (5H, H–Ar), 6.42 (broad s, 1H, NH), 4.69 (q, 1H, OCHO), 4.52 (m, 1H, H-6a), 3.97 (broad s, 2H, NCH_2Ph), 3.79 (m, 1H), 3.7–3.3 ($2OCH_2$, Ha-3), 3.37 (H-3a), 2.82 (m, 1H), 1.27 (d, 3H, $CHCH_3$), 1.18 (t, 3H, CH_2CH_3). ^{13}C NMR (75 MHz): 176.76 (CO), 136.80 (qC, Ar), 128.81, 128.51, 127.51 (CH, Ar), 99.85 (OCHO), 78.77 (C-6a), 66.14 (OCH_2), 61.68 (CH_2Ph), 61.30 (OCH_2), 61.23,

58.15 (C-3), 50.44–50.35 (C-3a), 19.68–19.49 ($CHCH_3$), 15.32 (CH_2CH_3).

4.3. (2*R*,3*S*,4*S*)-4-(Benzylaminomethyl)-2-(1-ethoxyethoxymethyl)pyrrolidin-3-ol 8

A solution of $LiAlH_4$ (658 mg, 17.3 mmol) in dry THF (28 mL) was added to a solution of **7** (696 mg, 2.17 mmol) in dry THF (7.1 mL), stirred at 0 °C under argon. The mixture was then heated at reflux for 15 h, cooled at 0 °C and the excess of reagent carefully destroyed by addition of some drops of a saturated aqueous solution of Na_2SO_4. The residue was obtained after usual workup (669 mg, 100%), as a colourless oil, and was used directly in the next step. IR: 3297, 2924, 1540, 1409 cm^{-1}. MS (ESI, MeOH) *m*/*z*: 331 (MNa^+). HRMS (MeOH): cald for $C_{17}H_{28}N_2O_3Na$: 331.1998, found 331.1985. ^1H NMR (300 MHz): 7.23 (m, 5H, H–Ar), 4.63 (q, 1H, OCHO), 4.01 (dd, 1H, H-3), 3.70 (centre of 2d, 2H, CH_2Ph), 3.57, 3.40 (2m, 4H, $2OCH_2$), 3.04 (2m, 2H, NCHa, H-2), 2.80 (m, 2H, NCH_2), 2.61 (m, 1H, NCHb), 2.18 (m, 1H, H-4). ^{13}C NMR (75 MHz, 2 diastereomers): 139.27 (qC, Ar), 128.62, 128.23, 127.39 (CH, Ar), 100.06, 99.90 (OCHO), 75.20 (C-3), 66.16, 65.89 (OCH_2), 65.89 (C-2), 61.31 (OCH_2), 54.04 (NCH_2Ph), 49.12 (NCH_2), 48.93 (NCH_2), 19.89 ($CHCH_3$), 15.37 (CH_2CH_3).

4.4. (2*R*,3*S*,4*S*)-3-Acetoxy-1-acetyl-4-(benzylacetamidomethyl)-2-(1-ethoxyethoxymethyl)pyrrolidine 10

Pyridine (15.0 mL) and Ac_2O (5.3 mL) were successively added under argon to this crude reduction product **8** (646 mg, 2.1 mmol) at 0 °C. The mixture was stirred at rt for 6 h, cooled again at 0 °C before the addition of MeOH (15 mL) and the mixture was stirred at rt for 0.5 h and then evaporated to dryness. A solution of the residue in CH_2Cl_2 was washed with an aqueous solution of Na_2CO_3 and the aqueous layer extracted three times with CH_2Cl_2. Usual workup gave the crude triacetate **10** as a colourless oil, pure enough to be used in the next step (891 mg, 98%). IR: 2976, 2931, 2881, 1737, 1640, 1416, 1376. MS (ESI, $CH_3CN + H_2O$) *m*/*z*: 457 (MNa^+, 100%). HRMS calcd for $C_{23}H_{34}N_2O_6Na$ (MNa^+): 457.2315, found: 457.2326. ^1H NMR (300 MHz): 7.34 and 7.12 (5H, H–Ar), 5.21 (d, 1H, H-3), 4.70–4.36 (OCHO, NCH_2Ph), 4.10 (m, H-2), 3.77–3.17 ($2OCH_2$, 2 NCH_2), 2.99 (m, 1H, H-4), 2.16–1.98 ($3COCH_3$), 1.30 ($CHCH_3$), 1.14 (CH_2CH_3). ^{13}C NMR (75 MHz): 171.47, 170.42, 170.09 (CO), 136.28 (qC, Ar), 129.22, 128.87, 128.02, 126.26, 126.15 (CH, Ar), 100.39, 100.15 (OCHO), 76.11, 75.84 (C-3), 64.48 (C-2), 64.18, 63.47 (OCH_2), 61.97, 61.86 (OCH_2), 52.44, 52.37 (NCH_2Ph), 50.62, 50.48 (NCH_2), 43.11 (NCH_2), 40.28, 40.19 (C-4), 22.77, 22.74 ($COCH_3$), 22.05, 21.91 ($COCH_3$), 21.17, ($COCH_3$), 20.14 ($CHCH_3$), 15.40 (CH_2CH_3).

4.5. (2*R*,3*S*,4*S*)-3-Acetoxy-1-acetyl-4-(benzylacetamidomethyl)-2-hydroxymethylpyrrolidine 11

To compound **10** (888 mg, 2.05 mmol) were successively added H_2O (20.7 mL) and AcOH (19.5 mL). The mixture was stirred at rt for 6.5 h, cooled at 0 °C diluted with CH_2Cl_2 and carefully neutralized by the slow addition of Na_2CO_3. After removing the salts by filtration, the solution was washed with aqueous Na_2CO_3 (10%) and the small aqueous layer extracted three times with CH_2Cl_2. The solution was dried over $MgSO_4$ and gave, after usual workup, the primary alcohol **11** as a colourless foam (710 mg, 96%). $[\alpha]_D^{24} = -60.2$ (*c* 1.34, $CHCl_3$). IR: 3391, 2935, 2879, 1738, 1630, 1423, 1375. MS (ESI, MeOH) *m*/*z*: 385 (100%, MNa^+). HRMS: calcd for $C_{19}H_{26}N_2O_5Na$ (MNa^+): 385.1739, found: 385.1734. ^1H NMR (300 MHz): 7.37 (m, 3H, H–Ar), 7.15 (m, 2H, H–Ar), 5.03 (d, 1H, H-3), 4.62 and 4.42 (2d, 2H, CH_2Ph), 4.13 (m, 1H, H-2), 3.77 and 3.62 (2m, 2H, OCH_2), 3.70 (m, 1H) and 3.26 (dd, 1H): NCH_2, 3.60 (masked m) and 3.42 (dd, 1H): NCH_2, 2.77 (m, 1H, H-4), 2.17 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz): 172.05 (CO), 171.69 (CO), 170.34 (CO), 136.22 (qC, Ar), 129.27, 128.15, 126.39, 126.19 (CH, Ar), 75.32 (C-3), 66.86 (C-2), 63.72 (OCH_2), 52.86 (NCH_2Ph), 50.70 (NCH_2), 43.29 (NCH_2), 40.55 (C-4), 22.58 ($COCH_3$), 21.87 ($COCH_3$), 21.07 ($COCH_3$).

4.6. (2*S*,3*S*,4*S*)-3-Acetoxy-1-acetyl-4-(benzylacetamidomethyl)pyrrolidine-2-carboxylic acid 12

Jones' reagent (690 μL) in acetone (8.7 mL) was added to a stirred solution of primary alcohol **11** (241 mg, 0.67 mmol) in acetone (9.4 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. After the addition of a few drops of 2-propanol at 0 °C and H_2O, the acid was extracted four times with EtOAc. The organic layers were dried over $MgSO_4$. Usual workup and washing with pentane afforded **12** (229 mg, 91%), as a colourless solid. $[\alpha]_D^{24} = -56.3$ (*c* 1.37, $CHCl_3$). IR: 3393, 1732, 1603, 1422, 1376. MS (ESI, MeOH) *m*/*z*: 399 (MNa^+, 100%). HRMS calcd for $C_{19}H_{24}N_2O_6Na$: 399.1532, found 399.1545. ^1H NMR (500 MHz): 7.38, 7.32, 7.15 (H–Ar), 5.54 (m, 1H, H-3), 4.62 and 4.47 (2d, 2H, $J = 16$, N–CH_2Ph), 4.57 (masked m, 1H, H-2), 3.77 and 3.27 (2m, 2H, N–CH_2), 3.68 and 3.57 (2m, 2H, NCH_2), 2.77 (m, 1H, H-4), 2.16, 2.07 (3s, $3COCH_3$). ^{13}C NMR (75 MHz): 172.23, 170.00 (CO), 135.85 (qC, Ar), 129.29, 128.13, 126.33 (CH, Ar), 74.26 (C-3), 65.97 (C-2), 52.39 (NCH_2Ph), 50.42 (NCH_2), 42.79 (NCH_2), 40.98 (C-4), 22.08, 21.77, 21.01 ($COCH_3$).

4.7. (2*S*,3*S*,4*S*)-4-(Benzylaminomethyl)-3-hydroxypyrrolidine-2-carboxylic acid 1

Acid **12** (125.2 mg, 0.33 mmol) in 3 M HCl (6.9 mL) was heated at 70 °C for 48 h. After evaporation to dryness, the residue was washed with Et_2O and dissolved in H_2O. The solution was then filtered and evaporated to give **1**, as dihydrochloride crystallized in a mixture of MeOH–Et_2O (105.4 mg, 98%). Mp with decomposition: 226 °C. $[\alpha]_D^{24} = +2.2$ (*c* 1.22, MeOH). IR: 3350, 3205, 2959, 1737, 1632, 1454, 1422, 1230. MS (ESI, MeOH) *m*/*z*: 251 $(MH)^+$. HRMS calcd for $C_{13}H_{19}N_2O_3$ $(MH)^+$: 251.1396, found: 251.1379. ^1H (300 MHz, D_2O $\delta = 4.8$ ppm): 7.50 (5H, H–Ar), 4.69 (broad d, 1H, $J = 4.5$, H-3), 4.29 (m, 3H, NCH_2Ph, H-2), 3.77 (dd, 1H, $J = 11.6$, $J' = 8.6$) and 3.27 (dd, 1H, $J \sim J' \sim 11.6$): NCH_2, 3.39 (dd, 1H, $J = 13.0$, $J' = 7.6$) and 3.23 (dd, $J = 13.0$, $J' = 6.2$): NCH_2, 2.61 (m, 1H, H-4). ^{13}C (125 MHz, D_2O): 170.10

(CO), 129.85, 129.82, 129.39 (CH, Ar), 72.94 (C-3), 69.10 (C-2), 51.74 (NCH_2Ph), 46.28 (NCH_2), 43.48 (NCH_2), 38.75 (C-4).

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References

1. (a) Hanessian, S.; Mc Naughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854; (b) Fletcher, M. D.; Campbell, M. M. *Chem. Rev.* **1998**, *98*, 763–795.
2. (a) Gante, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1699–1720; (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180.
3. Gutiérrez-Rodríguez, M.; Martín-Martínez, M.; García-López, M. T.; Herranz, R.; Cuevas, F.; Polanco, C.; Rodríguez-Campos, I.; Manzanares, I.; Cárdenas, F.; Feliz, M.; Lloyd-Williams, P.; Giralt, E. *J. Med. Chem.* **2004**, *47*, 5700–5712.
4. Gibson (née Thomas), S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585–615.
5. As examples: (a) Webb, T. R.; Eigenbrot, C. *J. Org. Chem.* **1991**, *56*, 3009–3016; (b) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202–209, and references cited therein.
6. (a) Murray, P. J.; Starkey, I. D.; Davies, J. E. *Tetrahedron Lett.* **1998**, *39*, 6721–6724; (b) Eustache, J.; Grob, A.; Lam, C.; Sellier, O.; Schulz, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2961–2966; (c) Surman, M. D.; Miller, M. J. *Org. Lett.* **2001**, *3*, 519–521.
7. (a) Goswami, R.; Moloney, M. G. *J. Chem. Soc.* **1999**, 2333–2334; (b) Mamai, A.; Hughes, N. E.; Wurthmann, A.; Madalengoitia, J. S. *J. Org. Chem.* **2001**, *66*, 6483–6486; (c) Mamai, A.; Madalengoitia, J. S. *Org. Lett.* **2001**, *3*, 561–564.
8. Langlois, N.; Van Bac, N.; Dahuron, N.; Delcroix, J.-M.; Deyine, A.; Griffart-Brunet, D.; Chiaroni, A.; Riche, C. *Tetrahedron* **1995**, *51*, 3571–3586.
9. Langlois, N.; Rakotondradany, F. *Tetrahedron* **2000**, *56*, 2437–2448.
10. Deyine, A.; Delcroix, J.-M.; Langlois, N. *Heterocycles* **2004**, *64*, 207–214.
11. De Vries, E. F. J.; Brussee, J.; Van der Gen, A. *J. Org. Chem.* **1994**, *59*, 7133–7137.