Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1333–1336

TETRAHEDRON: *ASYMMETRY*

Synthesis of the nonproteinogenic amino acid (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline, a constituent of echinocandins

Nicole Langlois *

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cedex, France

Received 5 February 1998; accepted 13 March 1998

Abstract

An enantioselective synthesis of the unusual 3,4-disubstituted proline **2**, a constituent of antifungal echinocandins, has been achieved through 1,3-dipolar cycloaddition of *N*-methylnitrone to the α,β-unsaturated lactam **4** derived from (*S*)-pyroglutaminol.

(2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline **2** is a common component of antimicrobial echinocandins B, C and D, **1**,[1] and several related natural cyclopeptides such as pneumocandins A_0–A_4, sporiofungin A, mulundocandin and deoxymulundocandin.[2] An enantioselective synthesis of this unusual amino acid **2** could be useful for the preparation of structural analogs of these lipopeptides which are inhibitors of 1,3-β-D-glucan synthase and exhibit interesting specific fungicidal activities, specially against *Candida albicans* and *Pneumocystis carinii*.[3]

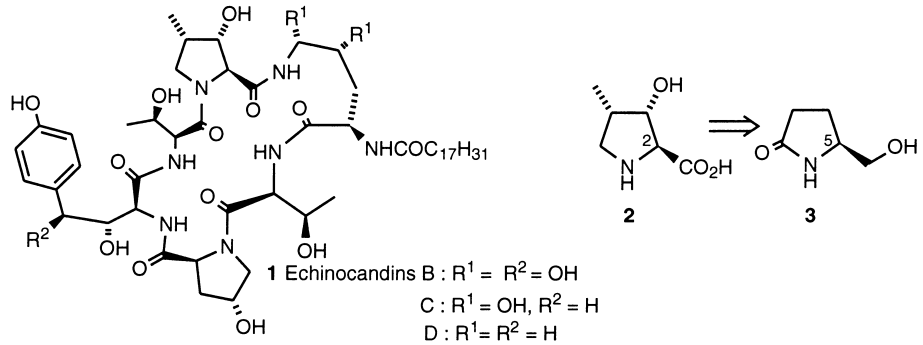
Two syntheses of **2**[4–6] and a synthesis of **2** methyl ester[7] have already been described, all of them involving aminocyclizations of suitably functionalized acyclic precursors. As part of a project towards the synthesis of several substituted proline derivatives,[8–11] it was planned to prepare **2** using inexpensive (*S*)-pyroglutaminol **3** as the starting material (Scheme 1).

In a simple and direct strategy, it was anticipated that both hydroxyl groups and the additional carbon of the methyl group in **2** could be introduced in the same step, through a 1,3-dipolar cycloaddition of a nitrone to α,β-unsaturated derivative **4**,[12] as shown in Scheme 2. In this way, an appropriate precursor of **2**, as the trisubstituted pyrrolidin-2-one **8**, could be accessible through hydrogenolysis of the cycloadduct **5** with cleavage of the isoxazolidine N–O bond, subsequent elimination of *N*-methylamine followed by hydrogenation of a 3-exomethylene intermediate.

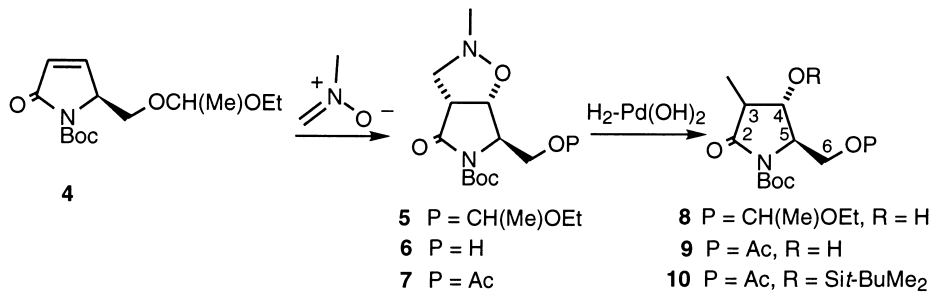
The cycloaddition of *N*-methylnitrone to the unsaturated pyrrolidinone **4** was achieved with 70% yield by heating in toluene. This improved yield (compared to our preliminary work[12]) was reached when the *N*-methylnitrone was prepared with a large excess of paraformaldehyde with regard to the *N*-methyl hydroxylamine and prolonged reaction time. The enantiopurity of the deprotected primary alcohol **6** was

* Fax: (0)1 69077247; e-mail: nicole.langlois@icsn.cnrs-gif.fr

0957-4166/98/$19.00
PII: S0957-4166(98)00112-8



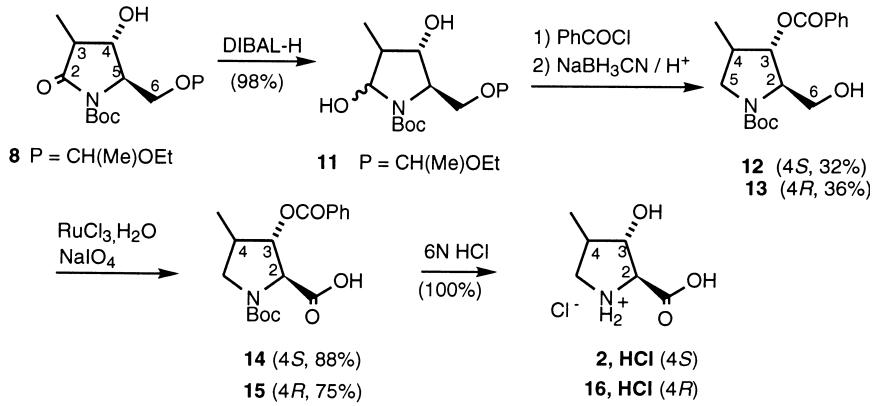
Scheme 1.



Scheme 2.

deteremined through its Mosher's ester obtained with (−)-MTPA-Cl, and compared to the diastereomeric esters prepared from racemic (±)-**6** and the same acid chloride. Thus, the stereogenic C-5 center of (*S*)-pyroglutaminol **3** was preserved under the cycloaddition conditions, unlike the partial racemization of **4**, recently observed during aminonucleophilic conjugate addition.[13] The cycloadduct **5** was hydrolyzed over Pearlman's catalyst (H_2, 1 atm, r.t.) with concomitant elimination of methylamine to directly afford the compound **8** in 72% yield, as a mixture of two inseparable diastereomers A and B. The ratio A:B was evaluated as 2:3 by ^{1}H NMR. The relative configurations were tentatively assigned in the acetates **9** prepared under the same conditions (73%, **9A**:**9B**=2:3) from the acetoxy derivative **7**, since it does not possess the additional stereogenic center. A *cis* relationship between the substituents at C-3 and C-4 in **9A** was supported by the strong NOE between H-3 and H-4, while in **9B** an NOE was observed between CH_3-3 and H-4, and between H-4 and H-6. The ^{1}H and ^{13}C chemical shifts of the methyl groups and adjacent H-C-3 are rather different in **8A** and **8B** [$CDCl_3$, ^{13}C δ ppm: **8A**: 8.19 (CH_3), 42.90 (C-3); **8B**: 15.29 (CH_3), 46.76 (C-3)]. They are respectively very close to those of **9A** and **9B**, and therefore informative [**9A**: 8.19 (CH_3), 42.73 (C-3); **9B**: 13.85 (CH_3), 46.80 (C-3)]. The diastereomer **9A** could be obtained as a major compound (A:B=2:1) by a deprotonation–protonation sequence of the initial mixture **9**. The formation of another diastereomer through a retro-aldol reaction with cleavage of the C-3–C-4 bond was not observed.

For the next steps, a suitable protection of the hydroxyl group at C-4 was required to allow a further selective deprotection of the primary alcohol before oxidation to the carboxylic acid. Attempts to silylate **9** under the usual conditions (*t*-$BuMe_2SiCl$, Im, DMF)[14] gave rise to only a moderate yield (47%) of the silylated derivative **10**. As the sensitivity towards elimination reactions of β-carbonylated hydroxy derivatives has also to be taken into account, the lactams **8** were reduced before protection of the secondary hydroxyl group. The straightforward sequence depicted in Scheme 3 was applied to the mixture **8** without separation of the intermediates leading to **12** and **13**.



Scheme 3.

Accordingly, the α-hydroxycarbamates **11** obtained in 98% yield by DIBAL-H reduction of **8** (in hexane, 3 equiv., −78°C) was directly benzoylated (PhCOCl, Et_3N–CH_2Cl_2). Subsequent reduction with $NaBH_3CN$ in acetic acid[15] and removal of EVE protection were achieved in one pot, giving rise to **12** and **13**. The diastereomeric alcohols **12** and **13** were separated by chromatography on silica gel, with 32% and 36% yield respectively for the two steps. They were oxidized under Sharpless conditions ($NaIO_4$–$RuCl_3$, H_2O, CCl_4–CH_3CN–H_2O)[16] into the carboxylic acids **14** (88%) and **15** (75%) which were quantitatively deprotected to **2** and **16** as hydrochloride salts, by heating in 6 N HCl. The amino acid **2** showed identical spectroscopic data to those reported.[1]

This synthesis demonstrated that the unsaturated pyrrolidin-2-one **4** is a good precursor of (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **2**, which was synthesized in seven steps and 14% yield, despite the lack of selectivity in the C-3 stereocenter formation. The improvement of this diastereoselectivity is currently under investigation.

Acknowledgements

We thank M.-T. Martin and J.-F. Gallard (ICSN, Gif-sur-Yvette) for NMR spectra.

References

1. Benz, F.; Knüsel, F.; Nüesch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlin, W. *Helv. Chim. Acta* **1974**, *57*, 2459–2477.
2. Hammond, M. L. Chemical and structure–activity studies of the echinocandin lipopeptides, in *Cutaneous Antifungal Agents*, 1993, Chapter 28, pp. 395–420; Rippon, J. W.; Fromtling, R. A., Ed., Marcel Dekker Inc.
3. Bouffard, F. A.; Zambias, R. A.; Dropinski, J. F.; Balkovec, J. M.; Hammond, M. L.; Abruzzo, G. K.; Bartizal, K. F.; Marrinan, J. A.; Kuntz, M. B.; McFadden, D. C.; Nollstadt, K. H.; Powles, M. A.; Schmatz, D. M. *J. Med. Chem.* **1994**, *37*, 222–225 and references therein.
4. Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc*. **1986**, *108*, 6041–6043.
5. Kurokawa, N.; Ohfune, Y. *Tetrahedron* **1993**, *49*, 6195–6222.
6. Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, *111*, 7500–7504.
7. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc*. **1987**, *109*, 7151–7151.
8. Langlois, N.; Andriamialisoa, R. Z. *Tetrahedron Lett.* **1991**, *32*, 3057–3058.
9. Panday, S. K.; Griffart-Brunet, D.; Langlois N. *Tetrahedron Lett*. **1994**, *35*, 6673–6676.
10. Panday, S. K.; Langlois, N. *Synth. Commun*. **1997**, 1373–1384.
11. Langlois, N.; Radom, M.-O. *Tetrahedron Lett*. **1998**, *39*, 857–860.

12. Langlois, N.; van Bac, N.; Dahuron, N.; Delcroix, J.-M.; Deyine, A.; Griffart-Brunet, D.; Chiaroni, A.; Riche, C. *Tetrahedron* **1995**, *51*, 3571–3586.
13. Langlois, N.; Calvez, O.; Radom, M.-O. *Tetrahedron Lett*. **1997**, *38*, 8037–8040.
14. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
15. Rojas, A. PhD thesis, Paris XI, Orsay, 1994, order number 3264.
16. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem*. **1981**, *46*, 3936–3938.