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Enantioselective synthesis of protected forms of (3*R*,5*R*)-5-hydroxypiperazic acid useful for synthesis

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Abstract

Protected versions of (3*R*,5*R*)-5-hydroxypiperazic acid were synthesized enantioselectively in two novel ways. The first derives its chirality from *D*-glutamic acid while the second uses an Evans amination and a diastereoselective bromolactonization to establish the two chiral centers. Given that this amino acid is a component of several depsipeptides, these two routes enable the synthesis of multigram quantities of protected versions of **2**.

Keywords: amination; amino acid derivatives; annulation; lactonisation.

Hexahydro-3-pyridazinecarboxylic acid (piperazic acid, **1**) is a subunit often found in cyclic depsipeptides. These include the azinothricins[1] and luzopeptins,[2] and other natural products such as the matlystatins[3] and sanglifehrin A.[4] In itself, (3*S*)-**1**, is a GABA-uptake antagonist.[5] It is also a key element found in a class of angiotensin-converting enzyme inhibitors typified by Cilazapril™, a drug of considerable therapeutic importance for the treatment of hypertension and congestive heart failure.[6] A less common derivative of **1** is (3*R*,5*R*)-5-hydroxypiperazic acid (**2**), which is also found in cyclic depsipeptides such as polyoxypeptin[7] and the dumbbell-shaped dimer himastatin (**3**) (Fig. 1).[8] Our recent total synthesis of **3**[9] required **2** in protected form (**2p**) suitable for incorporation during the assemblage of the peptide backbone.

Early synthetic studies en route to **1** employed a hetero-Diels–Alder reaction of pentadienoic acid with *N*-phenyltriazolinedione[7b,10] and led to racemic product.[10b,11] A route to *ent*-**2** had been described.[12] While alternative strategies towards systems akin to **1** or **2** were devised, they were problematic[10,13] in terms of our goal. The only enantiospecific synthesis of **1** reported thus far was accomplished by Hale and co-workers[14] using electrophilic amination.[15]

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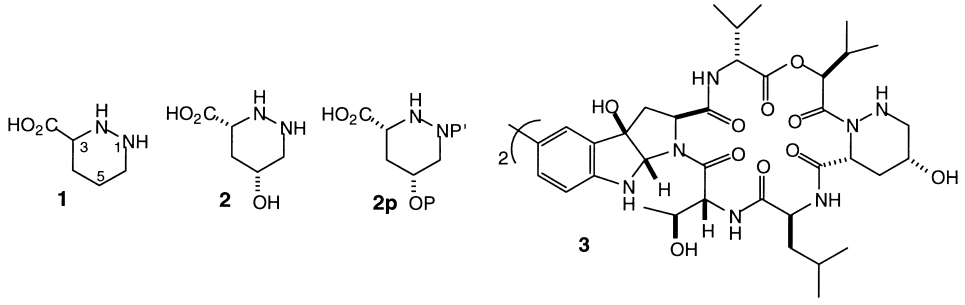
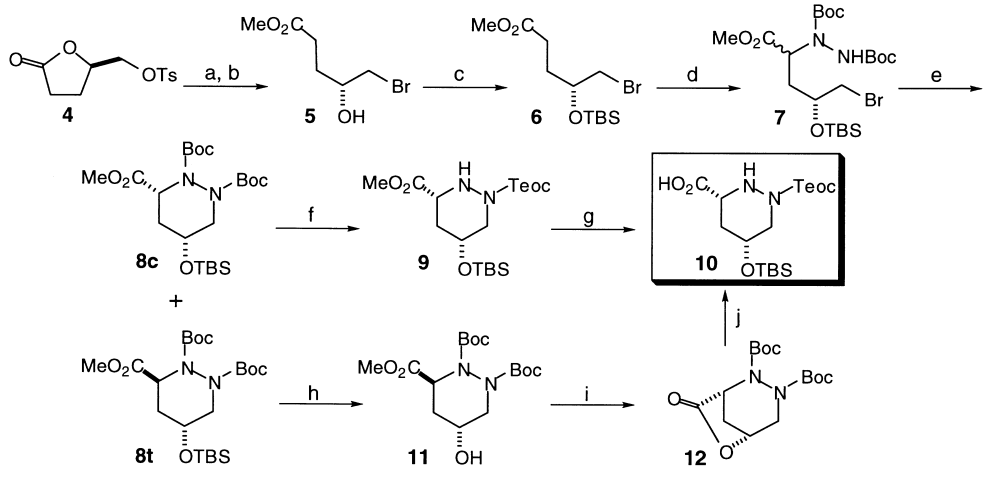


Figure 1.

For our purposes, a strategy had to be devised to enable selective deprotection of the four reactive groups of **2** while avoiding epimerization of the carboxyl function *cis*-related to the protected oxygen function. With these goals and challenges in mind, we devised two routes, which are described herein.

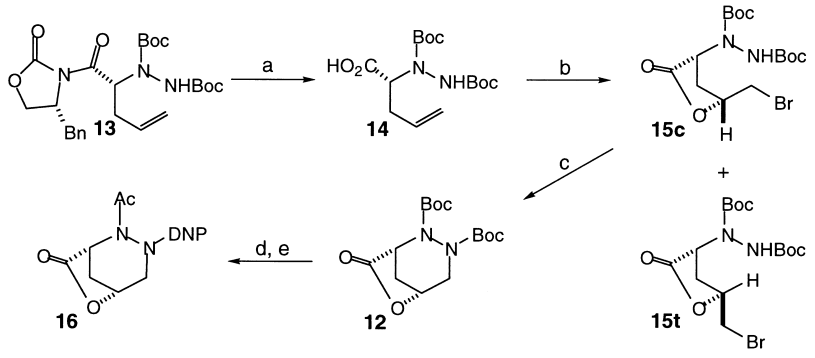
Starting from *D*-glutamic acid, the conversion to *R*-dihydro-5-(*p*-tolylsulfonyloxymethyl)-2(3*H*)-furanone (**4**) required three steps, which can be conducted on a large scale (Scheme 1).[16] Advancement of **4** to the known epoxy ester[17] was followed by opening with LiBr and HOAc to provide hydroxy ester **5**. Protection of the secondary alcohol as its *t*-butyldimethylsilyl ether afforded **6** in good overall yield for the three steps. Following amination of **6** with di-*tert*-butyl azodicarboxylate (DBAD), diastereomers **7** (ca. 1:1), and thence piperazic esters **8c** and **8t** were obtained. Removal of the Boc groups from **8c** and selective protection of the more reactive nitrogen (N1) with a TEOC group gave amino ester **9**. Conversion to amino acid **10**, suitable for interpolation into peptides (e.g. **3**), occurred in quantitative yield through facile hydrolysis with LiOH. The *trans* ester **8t** could also be converted to **10** via alcohol **11** and the *cis* piperazic lactone **12**. An important advantage of this approach is its ease of scale-up and minimal number of purifications.



Scheme 1. (a) NaOMe, MeOH; (b) LiBr, HOAc/THF (93%, two steps); (c) TBSOTf, 2,6-lutidene, CH_2Cl_2, −78°C, 65%; (d) NaHMDS, THF, −78°C; DBAD, CH_2Cl_2, 79%; (e) NaH, DMF, 0°C, 37% **8c**, 44% **8t**; (f) (i) TFA, CH_2Cl_2, 0°C; (ii) TEOC-Cl, *i*-Pr_2NEt, CH_2Cl_2 (92% overall); (g) LiOH, THF, 100%; (h) TBAF, THF, 80%; (i) DBU, toluene, 69%; (j) (i) TFA, MeOH, 0°C; (ii) TEOC-Cl, *i*-Pr_2NEt, CH_2Cl_2; (iii) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2; (iv) LiOH, THF (82% from **12**)

Concurrently, a second stereoselective route to the 5-hydroxypiperazic acid system from **13** was developed[14,15] (Scheme 2). Thus, cleavage of the auxiliary acyloxazolidinone bond followed by bromolactonization of the resultant acid gave a ca. 4.5:1 ratio[18] of **15c**:**15t**.[19] The bromine function was

displaced upon deprotonation of N1 to provide lactone **12**, which could be converted to **10** as described above.



Scheme 2. (a) LiOH, THF/H_2O, 0°C, 80%; (b) NBS, toluene, 0°C, 70% (4:5:1 **15c**:**15t**); (c) NaHMDS, DMF, 0°C, 64%; (d) (i) TFA, CH_2Cl_2, 0°C; (ii) 2,4-dinitrofluorobenzene, pyridine, THF, 50%; (e) acetyl chloride, 5 h, 100%

To vouchsafe the absolute stereochemistry of **12**, it was converted in three steps to the known (3*R*,5*R*)-N1-(2,4-dinitrophenyl)-N2-(acetyl) piperazic acid lactone (**16**).[8c,20] Thus, the two Boc groups of **15c** were removed, a DNP group was appended to the more reactive N1 nitrogen, and the N2 nitrogen was acetylated to give **16** $[\alpha]_D^{27}$ −482° (*c*=0.065, dioxane).

In conclusion, both independent routes to **2** allow for control in the management of each of the four reactive functionalities through the progression. Furthermore, because **8c** can be epimerized to **8t**, this chemistry can also be used to synthesize the 3*S*,5*R* isomer. In principle, the capability of starting with either *L*-glutamic acid or with the 4*S*-oxazolidinone should provide access to the 3*S*,5*S* and 3*R*,5*S* isomers.

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References

1. Maehr, H.; Liu, C.-M.; Palleroni, N. J.; Smallheer, J.; Todaro, L.; Williams, T. H.; Blount, J. F. *J. Antibiot.* **1986**, *39*, 17.
2. (a) Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Am. Chem. Soc*. **1981**, *103*, 1241; (b) Arnold, E.; Clardy, J. *J. Am. Chem. Soc*. **1981**, *103*, 1243.
3. Tamaki, K.; Tanzawa, K.; Kurihara, S.; Oikawa, T.; Monma, S.; Shimada, K.; Sugimura, Y. *Chem. Pharm. Bull*. **1995**, *43*, 1883.
4. Int. Pat. Appl. WO 97/22085 A1 970123, 1997, Sandoz Ltd., Switzerland.
5. Johnston, G. A. R.; Stephanson, A. L.; Twitchin, B. *J. Pharm. Pharmacol*. **1977**, *29*, 240.
6. For a lead reference, see: Attwood, M. R.; Hassall, C. H.; Krohn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1011.

7. (a) Umezawa, K.; Nakazawa, K.; Uemura, T.; Ikeda, Y.; Kondo, S.; Naganawa, H.; Kinoshita, N.; Hashizume, H.; Hamada, M.; Takeuchi, T.; Ohba, S. *Tetrahedron Lett*. **1998**, *39*, 1389; (b) For the enantiomer, (3*S*,5*S*)-5-hydroxypiperazic acid, found in the monamycins, see: Hassall, C. H.; Ogihara, Y.; Thomas, W. A. *J. Chem. Soc. (C)* **1971**, 514.
8. (a) Lam, K. S.; Hesler, G. A.; Mattei, J. M.; Mamber, S. W.; Forenza, S.; Tomita, K. *J. Antibiot.* **1990**, *43*, 956; (b) Leet, J. E.; Schroeder, D. R.; Krishnan, B. S.; Matson, J. A. *J. Antibiot.* **1990**, *43*, 961; (c) Leet, J. E.; Schroeder, D. R.; Golik, J.; Matson, J. A.; Doyle, T. W.; Lam, K. S.; Hill, S. E.; Lee, M. S.; Whitney, J. L.; Krishnan, B. S. *J. Antibiot*. **1996**, *49*, 299.
9. (a) Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2993; (b) Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2995.
10. (a) Davies, C. R.; Davies, J. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2390; (b) Adams, C. E.; Aguilar, D.; Hertel, S.; Knight, W. H.; Paterson, J. *Synth. Commun*. **1988**, *18*, 2225.
11. Hassall, C. H.; Johnson, W. H.; Theobald, C. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1451.
12. Hassall, C. H.; Ramachandran, K. L. *Heterocycles* **1977**, *7*, 119.
13. (a) Hughes, P.; Clardy, J. *J. Org. Chem*. **1989**, *54*, 3260; (b) Aspinall, I. H.; Cowley, P. M.; Mitchell, G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun*. **1993**, 1179; (c) Schmidt, U.; Riedl, B. *Synthesis* **1993**, 809; (d) Rutjes, F. P. J. T.; Teerhuis, N. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1993**, *49*, 8605; (e) Ciufolini, M. A.; Xi, N. *J. Chem. Soc., Chem. Commun*. **1994**, 1867.
14. Hale, K. J.; Cai, J.; Delisser, V.; Manaviazar, S.; Peak, S. A.; Bhatia, G. S.; Collins, T. C.; Jogiya, N. *Tetrahedron* **1996**, *52*, 1047.
15. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria Jr., J. F. *Tetrahedron* **1988**, *44*, 5525 and references cited therein.
16. (a) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449; (b) Gringore, O. H.; Rouessac, F. P. *Org. Synth. Coll. Vol. VII* **1990**, 99.
17. (a) Ho, P.-T.; Davies, N. *Synthesis* **1983**, 462; (b) Le Corre, M.; Hercouet, A.; Bessieres, B. *Tetrahedron: Asymmetry* **1995**, *6*, 683.
18. Rainin Microsorb-MV (86-100-C8) Si 8 μm (100 Å), 50% ethyl acetate in hexanes, 2.0 mL/min, refractive index detection; **15t**, 1.78 min; **15c**, 1.98 min.
19. (a) Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett*. **1986**, *50*, 6079; (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Walchli, M. *J. Am. Chem. Soc*. **1989**, *111*, 2582; (c) Hutton, C.; White, J. M. *Tetrahedron Lett*. **1997**, *38*, 1643.
20. Hassall, C. H.; Ogihara, Y.; Thomas, W. A. *J. Chem. Soc. (C)* **1971**, 522.