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Enantiospecific synthesis of 3,4-disubstituted glutamic acids via controlled stepwise ring-opening of 2,3-aziridino-γ-lactone

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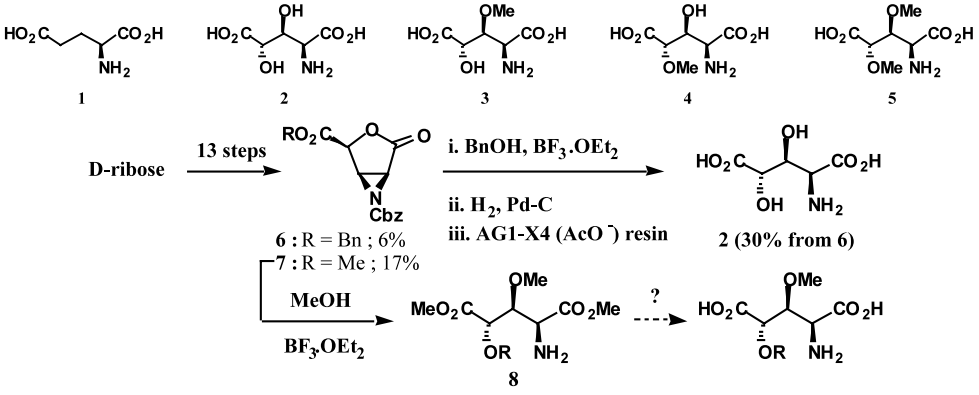
Abstract—The preparation of enantiomerically pure 3,4-disubstituted glutamic acids is described starting from D-ribose. This preparation involved the use of a 2,3-aziridino-γ-lactone whose reactivity towards nucleophiles could be efficiently controlled to allow selective functionalization at the β-position. A key step of the strategy was a titanate-mediated transesterification of a dimethyl ester into a dibenzyl analogue, allowing efficient deprotection to the free amino acid by hydrogenolysis.

The conformational flexibility of L-glutamic acid **1**, the major excitatory neurotransmitter of the central nervous system, confers the ability to bind to several types of glutamic acid receptors which are divided into two main classes: the ionotropic receptors (iGluRs) which are associated with cation-gated channels, and the metabotropic receptors (mGluRs) coupled to second messenger systems through GTP-binding proteins.[1] Each receptor class is divided into three subclasses which are in turn subdivided into several subtypes.

In order to gain insight into the physiological role of each of these receptor subtypes, the development of selective ligands is needed. To this end, several C-3 or C-4 substituted glutamic acids have been prepared[2] but few syntheses have been dedicated to the obtention of C-3 and C-4 substituted derivatives.[3] Recently, our interest in 2,3-aziridino-γ-lactone methodology[2l,4] culminated in the first stereoselective total synthesis of such a compound, namely (3*S*,4*S*)-3,4-dihydroxy-L-glutamic acid [(3*S*,4*S*)-DHGA] **2**[5] which was subsequently shown to be selective mGluR1 agonist.[6] For the purpose of structure–activity studies, we decided to prepare the methoxy and dimethoxy analogues of **2**, i.e. the amino acids **3**, **4** and **5**.

The synthesis of compound **2** involved the use of the bicyclic intermediate **6**. Simultaneous nucleophilic lactone and aziridine ring-opening by benzyl alcohol afforded, after removal of all the blocking groups by hydrogenolysis, (3*S*,4*S*)-DHGA **2** (Scheme 1).[5] However, although successful, the efficiency of this strategy



Scheme 1.

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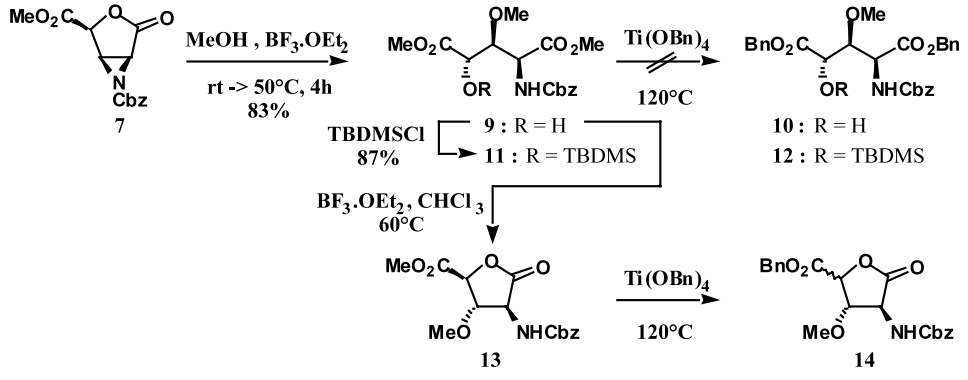
was hampered by the sensitivity of the benzyl ester which made the preparation of the aziridino-γ-lactone **6** tedious, the latter being synthesized in 13 steps from D-ribose in only 6% overall yield.

We therefore decided to reconsider use of the methyl ester analogue of **6**, i.e. compound **7**, that we previously prepared for the same purpose.[2l] Due to the increased stability of the methyl ester, its synthesis from D-ribose was performed in a more acceptable 17% overall yield (Scheme 1). But we failed to complete the total synthesis of substituted glutamic acids from **7** since acidic hydrolysis or saponification of the methyl esters were not compatible with the high functionality of these molecules. In order to fully explore the synthetic opportunities provided by the 2,3-aziridino-γ-lactone **7**, we turned our attention to a possible transesterification of the methyl esters into benzyl esters based on the pioneering work of Seebach[7] recently revisited by Shapiro[8] related to the titanate-mediated transesterification of functionalized substrates.

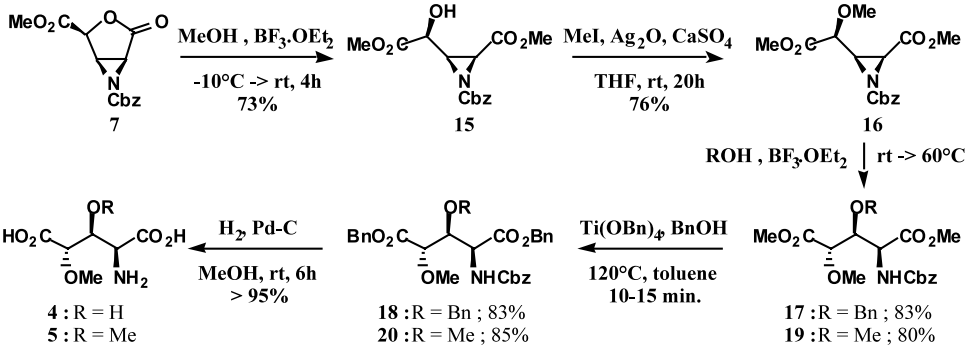
Initial efforts were devoted to the preparation of amino acid **3**. Reaction of compound **7** in methanol in the presence of boron trifluoride etherate led to the formation of the glutamate analogue **9** in 83% yield (Scheme 2). However, application of the titanate-mediated transesterification did not afford the expected dibenzyl ester **10**. Reaction of the silylated derivated **11** with $Ti(OBn)_4$ also failed while the lactone **13**, obtained after acidic cyclization of compound **9**, afforded the desired benzyl ester **14** but as an inseparable 1:1 mixture of diastereoisomers.[9] These results prompted us to turn our attention to the aziridine 2-carboxylate **15** for the preparation of amino acids **4** and **5**.

Thus, by working at a lower temperature, reaction of compound **7** in methanol in the presence of boron trifluoride etherate could efficiently be controlled to give only the lactone ring-opened product **15** in 73% yield (Scheme 3).[10] Transesterification at this stage of the synthesis was envisaged but it appeared to us that the Lewis acidity of the titanium complex could activate the aziridine ring towards ring opening by the free hydroxyl group. The latter was thus methylated to give the protected derivative **16** in 76% yield. The reaction of **16** with benzyl alcohol then occurred at the C-3 position as expected affording compound **17** in 83% yield while aziridine ring-opening with methanol led to the dimethoxy derivative **19** in 80% yield. Finally, the key step, i.e. the titanate-mediated transesterification, was investigated. After several experiments, it was found that the reaction was best run with freshly prepared $Ti(OBn)_4$[11] in toluene at reflux and was complete within 10–15 minutes. The resulting dibenzyl esters **18** and **20** were isolated, in 83 and 85% yield, respectively, after careful purification by flash chromatography. No traces of monobenzyl esters could be detected under these conditions. Hydrogenolysis of all the protecting groups then afforded the desired amino acids **4** and **5** in quantitative yield.[12]

In conclusion, use of the 2,3-aziridino-γ-lactone methyl ester **7** allowed preparation of (2*S*,3*S*,4*S*)-3-hydroxy-4-



Scheme 2.



Scheme 3.

methoxy- and (2*S*,3*S*,4*S*)-3,4-dimethoxyglutamic acids in 18 steps starting from D-ribose with an overall yield of 6%. Key steps are, on one hand, the selective lactone ring-opening of compound **7** to afford the useful aziridine 2-carboxylate **15** and, on the other hand, the titanate-mediated transesterification of the dimethyl ester into the more easily deprotected dibenzyl analogue. The pharmacological activity of these substituted glutamic acids with respect to GluRs will be reported elsewhere.

Acknowledgements

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References

1. For recent and relevant reviews on excitatory amino acids pharmacology, see: (a) Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645; (b) Moloney, M. G. *Nat. Prod. Rep.* **1999**, *16*, 485–498; (c) Doble, A. *Pharmacol. Ther.* **1999**, *81*, 163–221.
2. For recent examples, see: (a) Bunch, L.; Johansen, T. H.; Bräuner-Osborne, H.; Stensbøl, T. B.; Johansen, T. N.; Krogsgaard-Larsen, P.; Madsen, U. *Bioorg. Med. Chem.* **2001**, *9*, 875–879; (b) Pedregal, C.; Collado, I.; Escribano, A.; Ezquerra, J.; Dominguez, C.; Mateo, A. I.; Rubio, A.; Baker, S. R.; Goldsworthy, J.; Kamboj, R. K.; Ballyk, B. A.; Hoo, K.; Bleakman, D. *J. Med. Chem.* **2000**, *43*, 1958–1968; (c) Baker, S. R.; Bleakman, D.; Ezquerra, J.; Ballyk, B. A.; Deverill, M.; Ho, K.; Kamboj, R. K.; Collado, I.; Dominguez, C.; Escribano, A.; Mateo, A. I.; Pedregal, C.; Rubio, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1807–1810; (d) Ma, D.; Tang, G.; Tian, H.; Zou, G. *Tetrahedron Lett.* **1999**, *40*, 5753–5756; (e) Guillena, G.; Mancheño, B.; Nájera, C.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1998**, *54*, 9447–9456; (f) Escribano, A.; Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Baker, S. R.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 765–770; (g) Receveur, J.-M.; Guiramand, J.; Récasens, M.; Roumestant, M.-L.; Viallefont, P.; Martinez, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 127–132; (h) Helaine, V.; Bolte, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3855–3861; (i) Dominguez, E.; O'Donnell, M. J.; Scott, W. L. *Tetrahedron Lett.* **1998**, *39*, 2167–2170; (j) Wermuth, C. G.; Mann, A.; Schoenfelder, A.; Wright, R. A.; Johnson, B. G.; Burnett, J. P.; Mayne, N. G.; Schoepp, D. D. *J. Med. Chem.* **1996**, *39*, 814–816; (k) Gu, Z. Q.; Hesson, D. P.; Pelletier, J. C.; Maccechini, M. L.; Zhou, L. M.; Skolnick, P. *J. Med. Chem.* **1995**, *38*, 2518–2520; (l) For a review of previous syntheses of substituted glutamic acids, see: Dauban, P.; Chiaroni, A.; Riche, C.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2488–2496.
3. (a) Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron Lett.* **2001**, *42*, 5901–5902; (b) Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 8801–8803.
4. (a) Dubois, L.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 901–910; (b) Dubois, L.; Mehta, A.; Tourette, E.; Dodd, R. H. *J. Org. Chem.* **1994**, *59*, 434–441; (c) Dauban, P.; Dubois, L.; Tran Huu Dau, E.; Dodd, R. H. *J. Org. Chem.* **1995**, *60*, 2035–2043; (d) Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1997**, *62*, 4277–4284; (e) Dauban, P.; Hofmann, B.; Dodd, R. H. *Tetrahedron* **1997**, *53*, 10743–10752; (f) De Saint-Fuscien, C.; Tarrade, A.; Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2000**, *41*, 6393–6397.
5. Dauban, P.; De Saint-Fuscien, C.; Dodd, R. H. *Tetrahedron* **1999**, *55*, 7589–7600.
6. Dauban, P.; De Saint-Fuscien, C.; Acher, F.; Prézeau, L.; Brabet, I.; Pin, J.-P.; Dodd, R. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 129–133.
7. Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138–141.
8. Shapiro, G.; Marzi, M. *J. Org. Chem.* **1997**, *62*, 7096–7097.
9. The epimerization at the C-4 position could be related to the Lewis acidity of the titanium complexes.
10. It should be mentioned that such a controlled lactone ring-opening reaction was also performed with 2,3-aziridino-γ-lactone **6** in the presence of benzyl alcohol, but in rather poor yield (<35%).
11. $Ti(OBn)_4$ was prepared by refluxing a solution of $Ti(O\textit{i}\text{-}Pr)_4$ in toluene in the presence of 5 equiv. of benzyl alcohol.
12. Selected data: compound **4**: mp 192–193°C; $[\alpha]_D^{21}$ −19.1 (*c* 0.115, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 3.42 (s, 3H), 3.91 (m, 1H), 4.04 (m, 1H), 4.48 (m, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 53.0, 59.2, 70.0, 84.9, 163.8, 169.2. Compound **5**: mp 191–193°C; $[\alpha]_D^{21}$ −35.2 (*c* 0.125, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 3.42 (s, 3H), 3.46 (s, 3H), 3.85 (m, 1H), 4.16 (m, 1H), 4.20 (m, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 53.4, 58.0, 79.2, 82.9, 173.0, 178.2.