

Enantioselective Synthesis of 2,3-Disubstituted Piperidines

Michael Calosso, Mathieu Wagner, Thomas Gendrineau and Morgane Petit, Catherine Kadouri-Puchot* and Luc Dechoux*

Université Pierre et Marie Curie-Paris 6, Laboratoire de chimie organique (UMR CNRS 7611), Institut de chimie moléculaire (FR 2769), case 47, 4 Place Jussieu, F-75252 Paris Cedex 05, France

Received September 08, 2006; Revised January 22, 2007; Accepted January 23, 2007

Abstract: Chiral derivative **3** has been recognized as a precursor of enantiopure 2,3-disubstituted piperidines. A study concerning the chemoselective reduction, using $\text{BH}_3\cdot\text{Me}_2\text{S}$, of highly functionalised compounds **6** and *N*-BOC aminoacid **12** is reported.

Keywords: Asymmetric synthesis, piperidines, phenylglycinol, aza-annulation.

In previous communications, we reported the enantioselective synthesis of *cis*- and *trans*-2,3-piperidinedicarboxylic acids **1** and **2** (Fig. 1) by using a methodology which provides access to a variety of conformationally restricted analogs of NMDA [1] such as 5-methylated derivatives [2]. The 2,3-disubstituted piperidine structures possess the basic skeleton of many pharmacologically active compounds, as for examples non-peptidic tacykinin receptor antagonists [3], cardiovascular drugs, tumor necrosis factor- α (TNF- α) converting enzyme inhibitors [4] that play a role in numerous autoimmune diseases such as rheumatoid arthritis [5]. More specifically, piperidinedicarboxylic acid are structurally rigidified aspartic acid derivatives that

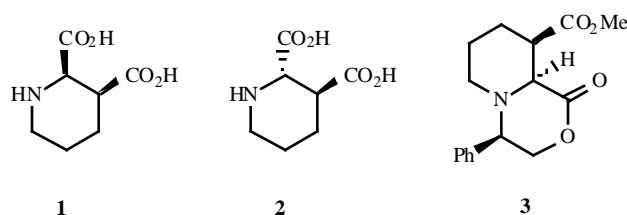
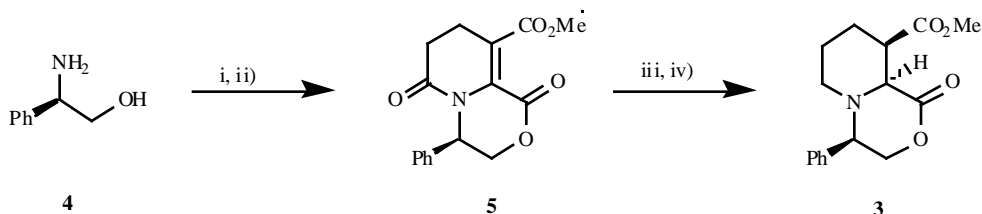


Fig. (1).

construction of biologically active peptidomimetics or non-peptide small molecule ligands. Potential application of 2,3-disubstituted piperidines to various lupine alkaloids are developed in our group, ranging from the simple lupinine to more elaborate, biologically active matrine and sophocarpine [7]. Herein, we reported the preliminary results of these studies based on the use of bicyclic heterocycle **3** (Fig. 1), which is a precursor of the α -amino acid **1**, in the enantioselective synthesis of diverse 2,3-difunctionalized piperidines.

Compound **3** was prepared as already described in 4 steps (Scheme 1) [2b]. The condensation of dimethyl acetylenedicarboxylate with (*R*)-phenylglycinol **4** and further aza-annulation with acryloyl chloride yielded the bicyclic enamido ester **5**. The ethylenic double bond of compound **5** was diastereoselectively hydrogenated to give the *cis*-adduct **6**. Then, the reduction of the amidic function with 2 equivalents of $\text{BH}_3\cdot\text{Me}_2\text{S}$ complex over two hours in THF afforded the bicyclic compound **3** after chromatography on silica gel. This new procedure, involving only one purification at the final step, furnished 20 grams of product **3** in 77% overall yield.

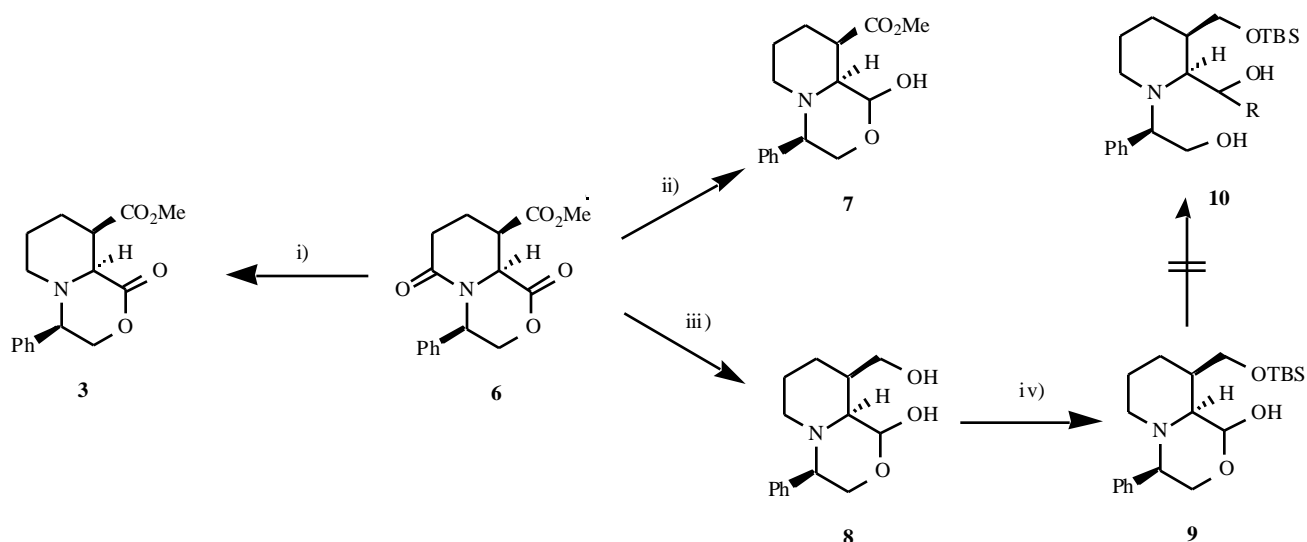


Scheme 1. i) Dimethyl acetylenedicarboxylate, MeOH, reflux 12h ii) Acryloyl chloride 1.1 equiv. THF, reflux, 2h; iii) H_2 / Pd/C, MeOH, 12h; iv) $\text{BH}_3\cdot\text{Me}_2\text{S}$ (2 equiv), THF, RT, 2h, 77% (four steps).

appeared to be ligands of the NMDA receptor [6]. These heterocycles possess functional groups for structural diversification and could be useful as chiral scaffolds for

It appeared that the reduction of the amide function of **6** was chemoselective using 2 equivalents of $\text{BH}_3\cdot\text{Me}_2\text{S}$ leading to derivative **3** when the reaction was quenched with water after 2 hours [8]. If the reaction was stopped after 18 hours, hemiacetal **7** was recovered as a single stereoisomer [9] after chromatography on silica gel in 45% yield. Moreover, when the reaction was conducted with 6 equivalents of $\text{BH}_3\cdot\text{Me}_2\text{S}$ in refluxing THF for 2.5 hours,

*Address correspondence to these authors at the Université Pierre et Marie Curie-Paris 6, Laboratoire de chimie organique (UMR CNRS 7611), Institut de chimie moléculaire (FR 2769), case 47, 4 Place Jussieu, F-75252 Paris Cedex 05, France; Fax: (33) 01 44 27 26 20; E-mail: dechoux@ccr.jussieu.fr; kadouri@ccr.jussieu.fr



Scheme 2. i) $\text{BH}_3\text{-Me}_2\text{S}$ (2 equiv), THF, RT, 2h 80%; ii) $\text{BH}_3\text{-Me}_2\text{S}$ (2 equiv), THF, RT, 18h 45%; iii) $\text{BH}_3\text{-Me}_2\text{S}$ (6 equiv), THF, reflux, 2.5 h 56%; iv) Imidazole (2.4 equiv.), TBDMSCl (1.3 equiv.), CH_2Cl_2 , RT, 24 h, 90%.

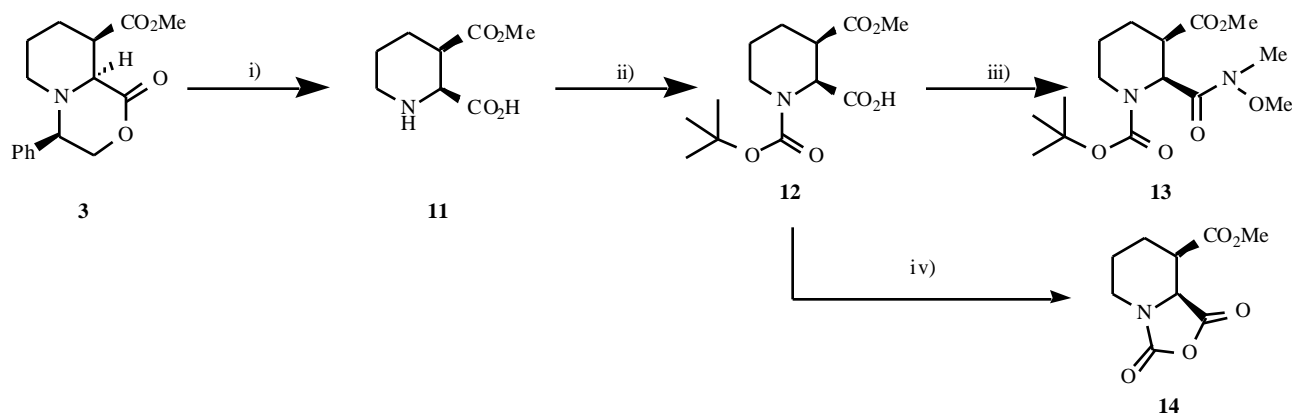
the over-reduced compound **8** was isolated in 56% yield (Scheme 2).

Next, in order to introduce a functionalized substituent (*R*) such as in **10**, derivative which would be an advanced intermediate in the synthesis of optically active indolizidines or quinolizidines, we examined the possibility to alkylate the hemiacetalic function (Scheme 2). Therefore, in a series of experiment, we studied the reactivity of hemiacetal **9** toward allyl- and vinyl-magnesium bromide and allyltrimethylsilane in the presence of TiCl_4 [10]. Unfortunately it has not been possible to obtain traces of the desired product **10**, large amount of starting material being recovered from the reaction mixture. These results show the extreme stability of such hemiacetal.

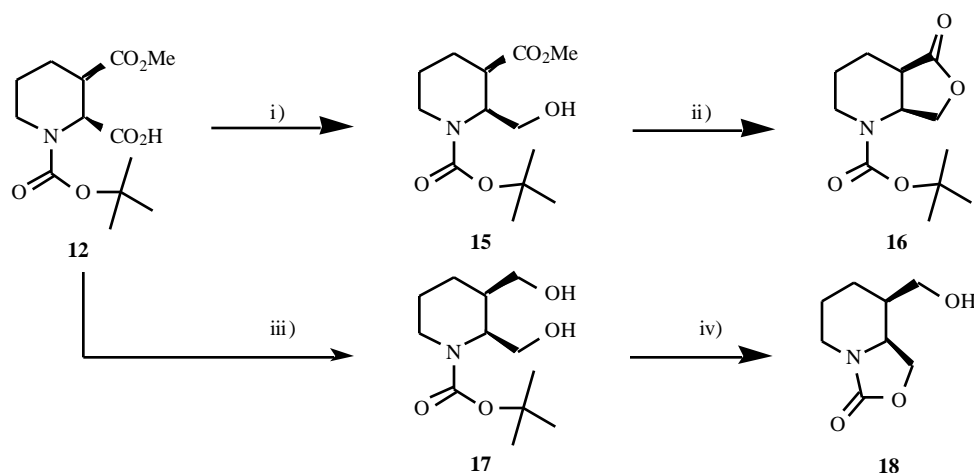
Next we envisaged that *N*-protected aminoacid **12** should be a good candidate for the chemoselective introduction of various substituents on the α position relative to nitrogen. The hydrogenolysis of aminolactone **3** led directly to α -aminoacid **11** and the protection of the amino function with $(\text{BOC})_2\text{O}$ gave product **12** in good yield (Scheme 3). The carboxylic acid was then transformed into Weinreb amide **13** derivative using EDCI as coupling reagent [11].

The reactions of Weinreb amide **13** with various Grignard reagents did not lead to the expected ketone. Polyalkylated products could be identified in the crude mixture of the reaction. At our knowledge, no study concerning the chemoselective alkylation of Weinreb amides in the presence of an ester function has been published [12]. The transformation of the acidic function into aldehyde failed also [13]. At least the treatment of aminoacid **12** with oxalylchloride in presence of a catalytic amount of DMF in THF, led quantitatively to bicyclic compound **14** by intramolecular addition of the *N*-BOC group [14] onto the acyl chloride intermediate (Scheme 3).

Owing to the difficulties to introduce a substituent (*R* such as in target **10**), it was envisaged the selective reduction of the carboxylic function in compound **12** by using $\text{BH}_3\text{-Me}_2\text{S}$ (2.3 equiv.) in THF. In these conditions and by quenching the reaction after one night with H_2O , the crude product was chromatographed on silica gel. The NMR analyses are consistent with compound **15** and diol **17** and a small amount of lactone **16** which was formed on silica gel from compound **15**. Moreover, the hydroxyester **15** could be quantitatively transformed into lactone **16** by treatment with



Scheme 3. i) $\text{Pd}(\text{OH})_2$, H_2 , MeOH, 12 h 78% ; ii) $(\text{BOC})_2\text{O}$, $\text{H}_2\text{O}/\text{THF}$, NaOH, 12 h 84%, iii) EDCI (1.1 equiv.), $\text{NH}(\text{OMe})\text{Me}$ (3 equiv.), NEt_3 (5 equiv.), DMAP (1equiv.), CH_2Cl_2 , 8 h 70%, iv) oxalyl chloride (1.2 equiv.), DMF, toluene, 99%.



Scheme 4. i) $\text{BH}_3\text{-Me}_2\text{S}$ (2.3 equiv.), THF, 12 h ii) SiO_2 , CH_2Cl_2 , 48 h 70% (2 steps); iii) $\text{BH}_3\text{-Me}_2\text{S}$ (5 equiv.), THF, 12 h 89%; iv), NaH (1.5 equiv.), THF, 8 h 72%.

SiO_2 in dichloromethane over 48 hours. Thus, lactone **16** was prepared efficiently in two steps in 70% yield. Diol **17** was also efficiently prepared by using 5 equivalents of the reducing agent. Our objective was again to distinguish between the two functionalities for further application in synthesis. Basic treatment of compound **17** in THF furnished oxazolidinone **18** selectively in 72% yield (Scheme 4).

In summary, compounds **14**, **16** and **18** were synthesized efficiently in enantiopure form, and we can envision their use in the access to other 2,3-disubstituted piperidine derivatives. Furthermore, the aliphatic substitution and the creation of a stereogenic center on the 2'-position relative to the nitrogen would allow the construction of more elaborate bicyclic skeletons.

REFERENCES AND NOTES

- [1] *The NMDA Receptor*: Collingridge, G.L.; Watkins, J.C., Eds.; Oxford University Press: Oxford, 1994.
- [2] (a) Agami, C.; Kadouri-Puchot, C.; Le Guen, V.; Vaissermann, J. *Tetrahedron Lett.*, **1995**, *36*, 1657; (b) Agami, C.; Hamon L.; Kadouri-Puchot, C.; Le Guen, V. *J. Org. Chem.*, **1996**, *61*, 5736.
- [3] Harrison, T.; Williams, B.J.; Swain, C.J.; Ball, R.G. *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 2545.
- [4] (a) Aggarwal, B.B.; Kohr, W.J.; Hass, P.E.; Moffat, B.; Spencer, S.A.; Henzel, W.J.; Bringman, T.S.; Nedwin, G.E.; Goeddel, D.V.; Harkins, R.N. *J. Biol. Chem.*, **1985**, *260*, 2345; (b) Xue, C.B.; Chen, X.T.; He, X.; Roderick, J.; Corbett, R.L.; Ghavimi, B.; Liu, R.Q.; Covington, M.B.; Qian M.; Ribadeneira, M.D.; Vaddi, K.; Trzaskos, J.M.; Newton, R.C.; Duan, J.J.W.; Decicco, C.P. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 4453.
- [5] (a) Aggarwal, B.B.; Natarajan, K. *Eur. Cytokine Network*, **1996**, *7*, 93; (b) Eigler, A.; Sinha, B.; Hartmann, G.; Endres, S. *Immunol. Today*, **1997**, *18*, 487; (c) Newton, R.; Decicco, C.P. *J. Med. Chem.*, **1999**, *42*, 2295.
- [6] (a) Davies, J.; Evans, R.H.; Francis, A.A.; Jones, A.W.; Smith, D.A.S.; Watkins, J.C. *Neurochem. Res.*, **1982**, *7*, 119; (b) Olverman, H.J.; Jones, A.W.; Mewett, K.N.; Watkins, J.C. *Neuroscience*, **1988**, *26*, 17; (c) Madsen, U.; Brehm, L.; Schaumburg, K.; Joergensen, F.S.; Krosggaard-Larsen, P. *J. Med. Chem.*, **1990**, *33*, 374.
- [7] Aslanov, K.A.; Kushmuradov, Y.K.; Sadykov, S. *Alkaloids*, **1987**, *31*, 117.
- [8] Russ, P.A.; Heim, P.; Caress, E.A. *J. Org. Chem.*, **1976**, *41*, 149.
- [9] The absolute configuration of the newly formed stereocenter has not been determined.
- [10] Tomooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.*, **1987**, *28*, 6339.
- [11] Cupps, T.L.; Boutin, R.H.; Rapoport, H. *J. Org. Chem.*, **1985**, *50*, 3972.
- [12] Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.*, **1981**, *22*, 3815.
- [13] Rosenmund, K.W. *Berichte*, **1918**, *51*, 585.
- [14] Agami, C.; Couty, F. *Tetrahedron*, **2002**, *58*, 2701.
- [15] NMR analysis of compounds **16**: ^1H NMR: 1.47 (s, 9H); 1.51-1.60 (m, 1H); 1.67-1.79 (m, 2H); 1.93-1.97 (m, 1H); 2.63-2.72 (m, 1H); 3.06 (td, $J = 3.8$ and 9.5 Hz, 1H); 3.68-3.73 (m, 1H); 4.20 (dd, $J = 7.0$ and 9.5 Hz, 1H); 4.41 (dd, $J = 7.0$ and 9.5 Hz, 1H); 4.72 (q, $J = 7.0$ Hz, 1H). ^{13}C NMR: 22.0; 22.1; 28.7; 37.6; 41.2; 50.6; 69.3; 81.2; 166.0; 177.6. Compound **17**: ^1H NMR: 1.38 (s, 9H); 1.42-1.47 (m, 2H); 1.59-1.64 (m, 2H); 1.85-1.92 (m, 1H); 2.60 (s, 2H, OH); 2.62-2.71 (m, 1H); 3.46-3.61 (m, 3H); 3.76-3.91 (m, 2H); 4.34 (m, 1H). ^{13}C NMR: 22.9; 25.6; 28.8; 40.9; 53.8; 59.6; 64.6; 68.3; 80.3; 156.0. Compound **18**: ^1H NMR: 1.40-1.50 (m, 2H); 1.80-2.05 (m, 3H); 2.75-2.85 (m, 1H); 3.64 (dd, $J = 5.0$ and 11.2 Hz, 1H); 3.80-3.90 (m, 2H); 3.99 (dd, $J = 7.5$ and 10.5 Hz, 1H); 4.31 (t, $J = 8.5$ Hz, 1H); 4.52 (dd, $J = 6.75$ and 9 Hz, 1H). ^{13}C NMR: 19.7; 26.6; 37.4; 41.9; 57.2; 60.7; 65.4; 168.0.