Pergamon

Tetrahedron Letters 42 (2001) 7805–7807

TETRAHEDRON LETTERS

A short formal synthesis of paroxetine. Diastereoselective cuprate addition to a chiral racemic olefinic amido ester

Janine Cossy,[a,*] Olivier Mirguet,[a] Domingo Gomez Pardo[a] and Jean-Roger Desmurs[b]

[a]*Laboratoire de Chimie Organique ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France*
[b]*Rhodia, 190 avenue Thiers, 69457 Lyon Cedex 06, France*

Received 26 June 2001; accepted 4 September 2001

Abstract—A diastereoselective conjugate addition of an organocopper reagent to a chiral racemic olefinic amido ester has been used as the key step in a formal total synthesis of paroxetine. © 2001 Published by Elsevier Science Ltd.

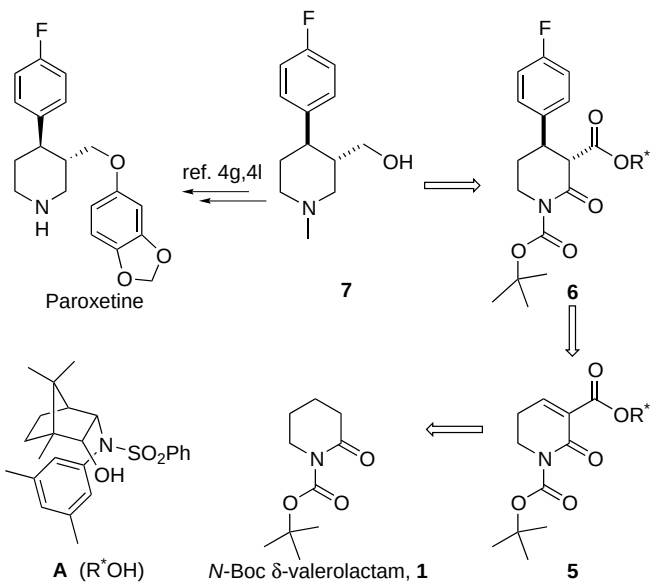
Drugs that modulate the physiological and pathophysiological actions of serotonin are useful or potentially useful in the treatment of a variety of human diseases, including depression, anxiety, alcoholism, chronic pain, emesis and eating disorders.[1]

For example, paroxetine which is an enantiomerically pure (−)-*trans*-3,4-disubstituted piperidine, is used in the treatment of depression, obsessive compulsive disorder and panic disorder.[2] Moreover, it has a reduced propensity to cause the side effects usually associated with tricyclic antidepressants.[3] Due to the importance of its biological properties, several syntheses of this compound have been achieved.[4]

Here we report the formal synthesis of paroxetine according to the following retrosynthetic scheme (Scheme 1). The key step for obtaining paroxetine was the conjugate addition of an organocopper compound to a chiral olefinic amido carboxylate of the concave chiral racemic alcohol **A**,[5] which can be easily prepared from *N*-Boc protected δ-valerolactam **1**.

The treatment of *N*-Boc δ-valerolactam **1** with Li-HMDS at −78°C (1.3 equiv., THF) followed by the addition of methyl chloroformate afforded the corresponding methyl amidocarboxylate **2**[6] in 93% yield. The asymmetric shielded amido ester **3** was readily available by a transesterification reaction of **2** with the chiral racemic auxiliary **A** (1 equiv.) mediated by DMAP (2 equiv., toluene, reflux).[7] A 65/35 mixture of two diastereomers **3a** and **3b** was obtained in 50% yield. Phenylselenation of the mixture of **3a**/**3b** gave a mixture of diastereomeric selenides **4a** and **4b** (75/25) which were not separated but oxidized with H_2O_2 (CH_2Cl_2, 0°C) to furnish the oxidative deselenation product **5** in quantitative yield. The addition of lithium di(4-fluorophenyl)cuprate (4 equiv., THF, −78°C) to the asymmetric olefinic amido ester **5** led to the conjugate addition product **6** in 80% yield (Scheme 2).

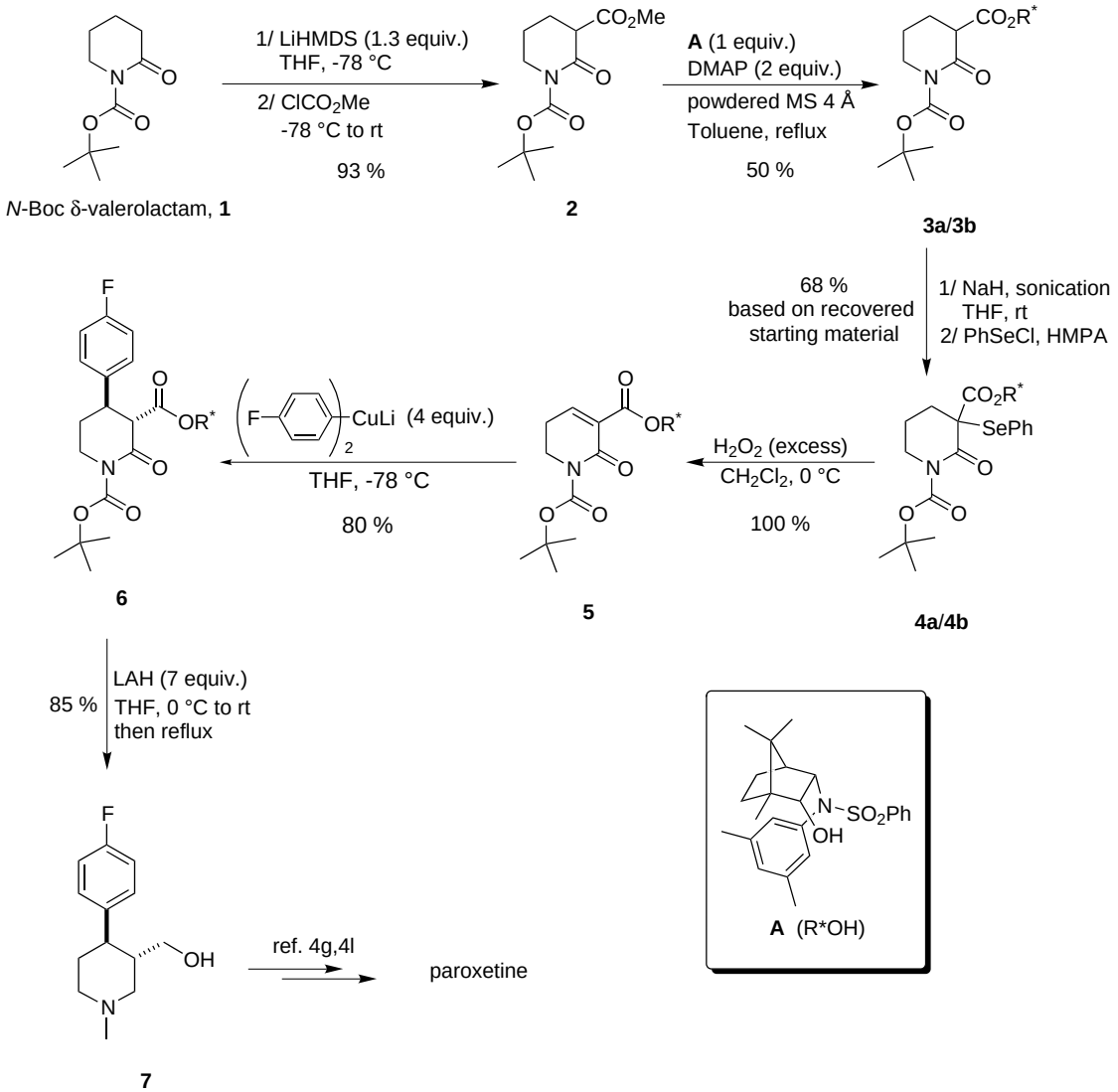
It is worth noting that the NMR spectrum of the unpurified conjugate addition product indicated excel-



Scheme 1. Retrosynthetic analysis.

* Corresponding author. Tel.: 00.33.1.40.79.46.63; fax: 00.33.1.40.79.46.60; e-mail: janine.cossy@espci.fr

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)01666-5



Scheme 2. Formal total synthesis of paroxetine.

lent diastereoselectivity (>98:2). However, the ^{1}H and ^{13}C NMR spectroscopic data of **6**[8] did not reveal the relative stereochemistry between the newly introduced groups and the chiral auxiliary. Fortunately **6** was crystalline (mp = 215–217°C) and its structure could be determined by X-ray diffraction spectroscopy (Fig. 1).[9]

Attack of the organocopper reagent to the asymmetric olefinic amido ester **5** occured from the less hindered face of the s-*trans* enoate double bond leading to the formation of **6** with a very high level of diastereoselectivity (Fig. 2).[5]

Cleavage of the chiral auxiliary from the sterically crowded olefinic amido ester **6** was accomplished by reduction with LAH in THF (7 equiv., 0°C to rt, then reflux), which gave the known amino alcohol **7** in 85% yield.

Since piperidine **7** has been converted into paroxetine,[4g,4l] the present transformation of the *N*-Boc protected δ-valerolactam (six steps, 21% overall yield) constitutes a formal synthesis of paroxetine. As the auxiliary **A** can be prepared enantiomerically pure, (−)-paroxetine can be obtained by using this synthetic route. Furthermore, our work demonstrates for the first time that highly diastereoselective addition of cuprates can be performed on chiral facially shielded cyclic olefinic amido ester.

Acknowledgements

The authors would like to thank Rhône-Poulenc-Rhodia for financial support and Dr. Lee Tai LIU for sending us the ^{1}H NMR spectrum of compound **7**.[4f] One of us, O.M. thanks the MRET for a grant.

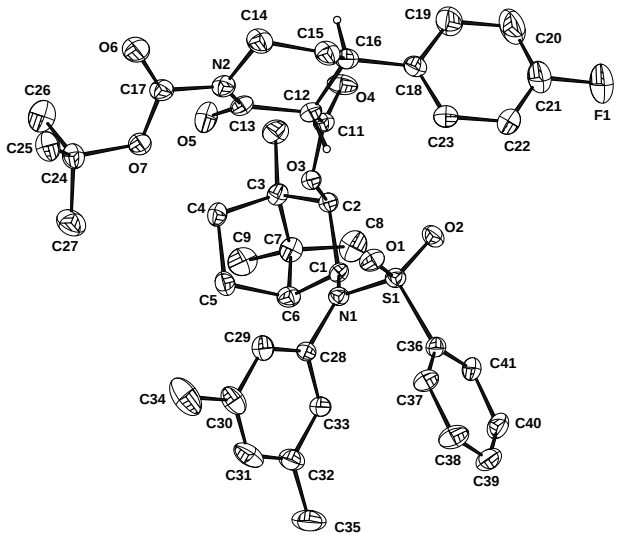


Figure 1. ORTEP plot for compound **6**.

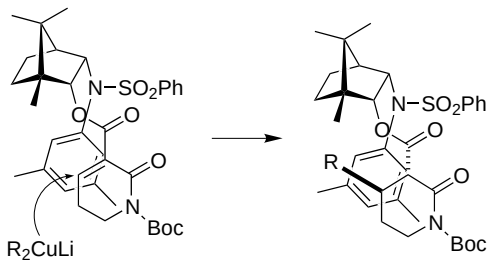


Figure 2.

References

1. Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412–1417.
2. Mathis, C. A.; Gerdes, J. M.; Enas, J. D.; Whitney, J. M.; Taylor, S. E.; Zhang, Y.; McKenna, D. J.; Havlik, S.; Peroutka, S. J. *J. Pharm. Pharmacol.* **1992**, *44*, 801–805.
3. Gunasekara, N. S.; Noble, S.; Benfield, P. *Drugs* **1998**, *55*, 85–120.
4. For other asymmetric synthesis of paroxetine, see: (a) Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *Tetrahedron Lett.* **2001**, *42*, 5705–5707; (b) Liu, L. T.; Hong, P.-C.; Huang, H.-L.; Chen, S.-F.; Wang, C.-L. J.; Wen, Y.-S. *Tetrahedron: Asymmetry* **2001**, *12*, 419–426; (c) Johnson, A. J.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004–1005; (d) Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647–5651; (e) Amat, M.; Bosch, J.; Hidalgo, J.; Canto, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084; (f) Shih, K.-S.; Liu, C.-W.; Hsieh, Y.-J.; Chen, S.-F.; Ku, H.; Liu, L.-T.; Lin, Y.-C.; Huang, H.-L.; Wang, C.-L. J. *Heterocycles* **1999**, *51*, 2439–2444; (g) Murthy, K. S. K.; Rey, A. W. WO Patent 9907680, 1999; *Chem. Abstr.* **1999**, *130*, 182361; (h) Patil, V. D.; Viswanathan, C. L. *Indian Drugs* **1998**, *35*, 686–692; (i) Kreidl, J.; Czibula, L.; Deutschné, J.; Werkné Papp, E.; Nagyné Bagdy, J.; Dobay, L.; Hegedus, I.; Harsanyi, K.; Borza, I. WO Patent 9801424, 1998; *Chem. Abstr.* **1998**, *128*, 127941; (j) Sugi, K.; Itaya, N.; Katsura, T.; Igi, M.; Yamazaki, S.; Ishibashi, T.; Yamaoka, T.; Kawada, Y.; Tagami, Y. Eur. Patent 0812827 A1, 1997; *Chem. Abstr.* **1998**, *128*, 75308; (k) Adger, B. M.; Potter, G. A.; Fox, M. E. WO Patent 9724323, 1997; *Chem. Abstr.* **1997**, *127*, 149075; (l) Engelstoft, M.; Hansen, J. B. *Acta Chem. Scand.* **1996**, *50*, 164–169; (m) Zepp, C. M.; Gas, Y.; Heefner, D. L. US Patent 5,258,517, 1993; *Chem. Abstr.* **1994**, *120*, 217289; (n) Willcocks, K.; Barnes, R. D.; Rustidge, D. C.; Tidy, D. J. D. *J. Label. Cmpds. Radiopharm.* **1993**, *33*, 783–794; (o) Christensen, J. A.; Squires, R. F. US Patent 4,007,196, 1977; *Chem. Abstr.* **1974**, *81*, 152011; (p) Stemp, J. A.; Miller, D.; Martin, R. T. Eur. Patent 0190496, 1985.
5. (a) Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051–6054; (b) Urban, E.; Riehs, G.; Knühl, G. T. *Tetrahedron* **1995**, *41*, 11149–11164.
6. Imbroisi, D. O.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1815–1823.
7. Taber, D. F.; Amedio, Jr., J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618–3619.
8. Compound **6**: mp 215–217°C; IR (KBr): 1742, 1730, 1708, 1332, 1297, 1185, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (m, 1H), 7.48–7.27 (5H), 7.06 (br s, 1H), 7.03 (m, 2H), 6.81 (br s, 1H), 5.86 (br s, 1H), 5.43 (d, 1H, $J=8.5$ Hz), 4.23 (dd, 1H, $J=8.5$ and 3.3 Hz), 4.08 (m, 1H), 3.93 (d, 1H, $J=5.1$ Hz), 3.83 (ddd, 1H, $J=13.2$, 6.6 and 4.8 Hz), 3.66 (ddd, 1H, $J=13.2$, 9.2 and 4.0 Hz), 2.44 (m, 1H), 2.27 (s, 3H), 2.00 (s, 3H), 1.99–1.82 (2H), 1.67 (m, 1H), 1.54 (s, 9H), 1.34–0.99 (3H), 1.03 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8 (s), 167.3 (s), 161.7 (d, $J=244.8$ Hz), 152.1 (s), 138.8 (s), 138.7 (d, $J=3.7$ Hz), 138.3 (s), 137.1 (s), 136.9 (s), 132.5 (d), 130.1 (d), 129.4 (d), 128.8 (dd, $J=7.9$ Hz), 128.2 (d), 127.5 (d), 115.6 (dd, $J=21.4$ Hz), 83.1 (d), 78.0 (s), 59.0 (d), 57.4 (d), 51.2 (s), 49.2 (d), 45.8 (s), 43.5 (t), 39.7 (d), 30.5 (t), 28.0 (q), 26.7 (t), 21.1 (q), 20.9 (q), 19.5 (q), 19.4 (t), 19.3 (q), 14.4 (q); MS CI^+ (NH_3) (relative intensity): 750 ($M+NH_4^+$, 11), 634 (37), 633 (92), 593 (20), 493 (40), 415 (29), 414 (100), 274 (23), 174 (20); HRMS (CI^+, NH_3): calcd for $C_{41}H_{50}FN_2O_7S$ ($M+H^+$): 733.3323. Found: 733.3317.
9. Crystallographic data (excluding structural factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 162939. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].