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Efficient Enantioselective Synthesis of Sertraline, a Potent Antidepressant, *via* a Novel Intramolecular Nucleophilic Addition to Imine

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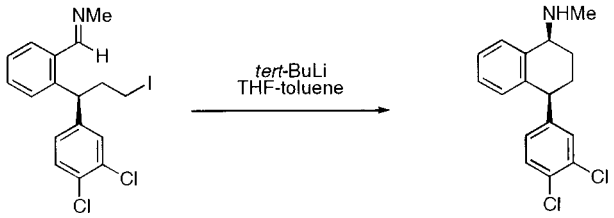
ABSTRACT



Sertraline

An efficient enantioselective synthesis of sertraline, an antidepressant, utilizing anionic imine ring closure is described.

Sertraline (**1**), a selective competitive inhibitor of synaptosomal serotonin uptake, is an important pharmaceutical agent for the treatment of depression.[1] The commercial production of sertraline relies on the resolution of the racemate with D-mandelic acid.[2] Two asymmetric syntheses for sertraline were reported: both focus on the efficient preparation of the sertraline penultimate, tetralone **2** (equation 1).[3] Obviously, reductive amination is expected to give the desired product as in the commercial production route. We herein wish to disclose a different approach to the synthesis of sertraline utilizing the metal−halide exchange of iodoimine **3** followed by an intramolecular, stereoselective anionic addition to the imine moiety (eq 1).[4]

As illustrated in Scheme 1, the stereo center at C4 bearing two aryl groups was established via a conjugated addition of arylmagnesium bromide to the imide conjugate derived from 3,4-dichlorocinnamic acid.[5] Incorporation of a chiral auxiliary such as phenyloxazolidinone allowed us to introduce the stereocenter in a reliable manner. Thus, 2-bromobenzaldehyde (**4**) was protected as its dimethyl acetal and subsequently converted to arylmagnesium bromide **5**. The cinnamic imide **7** was prepared in 94% yield from the corresponding acid **6** and (*S*)-2-phenyloxazolidine using Ho's procedure.[6] Addition of arylmagnesium bromide **5** (2 equiv) mediated by CuBr−SMe_2 (0.2 equiv) to the cinnamic imide **7** produced imide **8** in 90% yield with complete diastereoselectivity.[7] The imide was reduced to alcohol **9** (91% yield)

(1) Welch, W. M.; Kraska, A. R.; Sarges, R.; Coe, K. B. *J. Med. Chem.* **1984**, *27*, 1508. Coe, B. K.; Weissman, A.; Welch, W. M.; Broune, R. G. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686.

(2) Recemate route to sertraline has been reviewed, see: William, M.; Quallich, G. *Chem. Ind.* (*London*) **1990**, *10*, 315.

(3) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373. Quallich, G. J.; Woodall, T. M. *Tetrahedron* **1992**, *48*, 10239.

(4) The intramolecular addition of the imine is not precedented in the literature although the intermolecular version has been extensively studied. For recent reviews, see: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

(5) For an excellent review on asymmetric conjugate addition reaction, see: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

(6) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

(7) Nicolas, E.; Russell, K. C.; Hruby, V. J. Vane, J. *J. Org. Chem.* **1993**, *58*, 766. Hruby, V. J.; Han, Y. *Tetrahedron Lett.* **1997**, *38*, 7317. Lin, J.; Lian, S.; Hruby, V. J. *Tetrahedron Lett.* **1998**, *39*, 5373. Anderssen, P. G.; Schink, H. E.; Osterlund, K. *J. Org. Chem.* **1998**, *63*, 8067.

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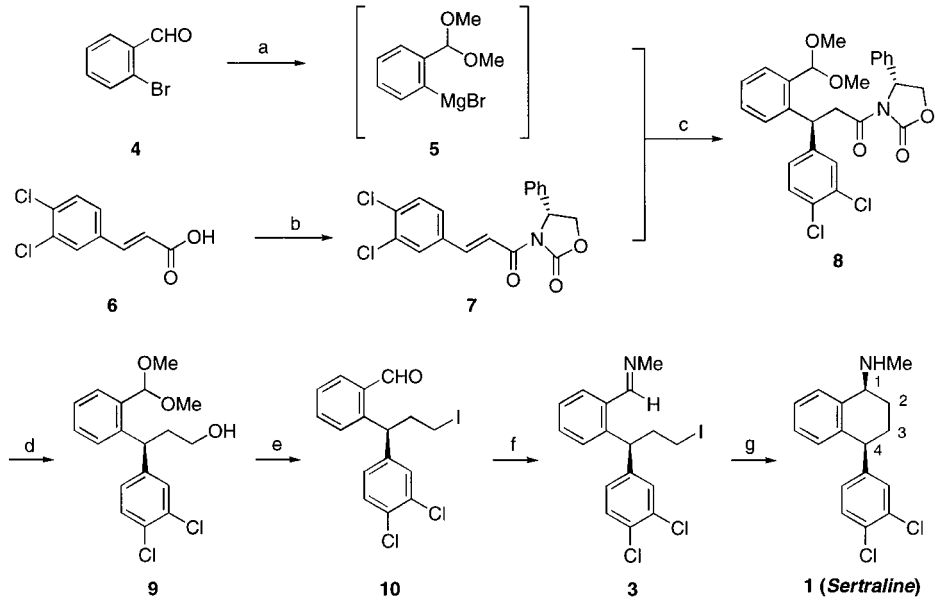
Scheme 1



Conditions: a) 1. $(MeO)_3CH$, MeOH, cat. *p*-TsOH, 2. Mg, THF; b) Me_3CCOCl, Et_3N, LiCl, (*S*)-2-phenyl oxazolidine; c) 0.2 eq $CuBrSMe_2$, THF, -30 °C to 0 °C; d) $NaBH_4$(3 eq), THF-H_2O; e)1. PPh_3-I_2-imidazole, 2. 2 N HCl; or 1. MsCl, Et_3N, 2. excess NaI, acetone, Δ; f) 2.0 M $MeNH_2$ in THF; g) *t*-BuLi (2.0 eq) in THF-toluene, -78 °C.

smoothly using $NaBH_4$/THF−H_2O.[8] Treatment of alcohol **9** with I_2−PPh_3−imidazole followed by in situ hydrolysis of the acetal moiety using 2 N HCl led to the formation of iodoaldehyde **10** (83%). Alternatively, the alcohol was converted to its mesylate which was displaced by iodide using Finkelstein's conditions.[9] Interestingly, deprotection of the acetal moiety was also effected in the reaction to give the iodoaldehyde **10** directly in 85% overall yield. The ring-closure precusor, iodoimine **3**, was formed quantitatively from the aldehyde and methylamine (2.0 M in THF). Ring closure was faciliated with *t*-BuLi (2.0 equiv) in THF−toluene (1:1) to give sertraline in 69% yield as a single diastereoisomer.[10]

In summary, the asymmetric synthesis of sertraline was accomplished in 45% overall yield in six steps from 3,4-dichlorocinnamic acid. To the best of our knowledge, the intramolecular anionic ring closure on imine is literature unprecedented.[4] The high efficiency of the stereoselective ring closure is remarkable and could potentially be extended to the synthesis of other chiral amines.

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(8) Prashd, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067.

(9) Finkelstein H. *Ber.* **1910**, *43*, 1528.

(10) The sertraline free base was fully characterized: ^{1}H NMR (500.1 MHz, C_6D_6) δ 7.18 (br d, J = 7.6, 1 H), 7.15 (obscured d, 1 H), 7.04 (m, 1 H), 6.99 (d, J = 8.3, 1 H), 6.96 (m, 1 H), 6.67 (d, J = 7.6, 1 H), 6.59 (dd, J = 8.3, 2.4, 1 H), 3.56 (dd, J = 9.5, 6.0, 1 H), 3.43 (t, J = 4.4 1 H), 2.26 (s, 3 H), 1.99 (m 1 H), 1.70 (m, 1 H), 1.61 (m, 1 H), 1.45 (m, 1 H); ^{13}C NMR (125.8 MHz, C_6D_6) δ 148.2, 140.1, 139.0, 132.6, 131.1, 130.6, 130.4, 130.0, 129.5, 128.5, 127.4, 126.7, 57.7, 45.5, 34.3, 28.4, 26.0. The free base was converted to its hydrochloride salt: mp 241−244 °C (lit.[1] mp 243−245 °C).