

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

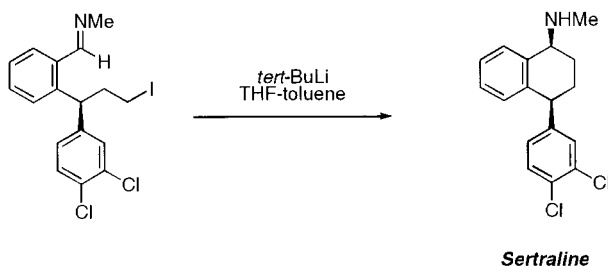
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ABSTRACT



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–SMe₂ (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)

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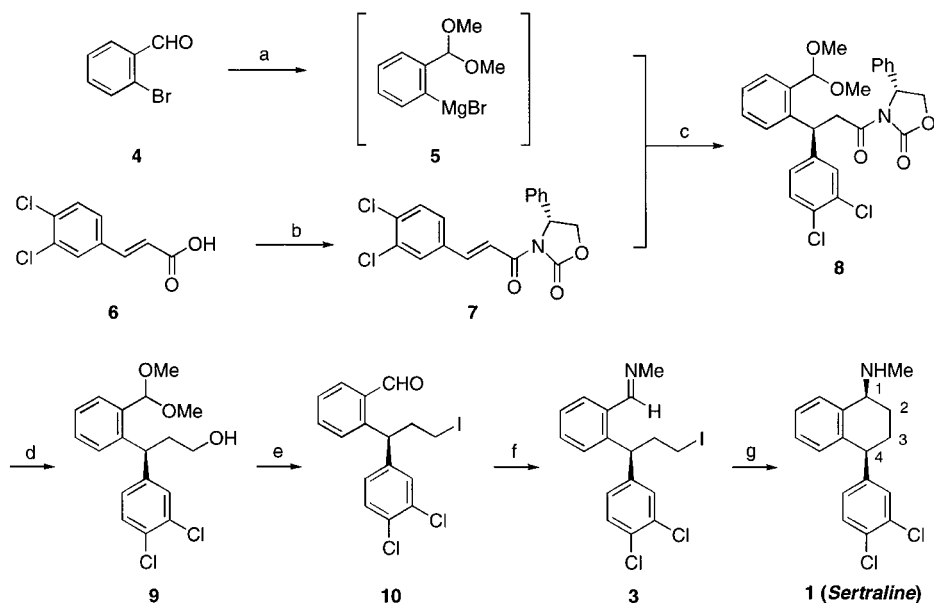
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Scheme 1



Conditions: a) 1. (MeO)₃CH, MeOH, cat. *p*-TsOH, 2. Mg, THF; b) Me₃CCOCl, Et₃N, LiCl, (*S*)-2-phenyl oxazolidine; c) 0.2 eq CuBrSMe₂, THF, -30 °C to 0 °C; d) NaBH₄ (3 eq), THF-H₂O; e) 1. PPh₃-I₂-imidazole, 2. N HCl; or 1. MsCl, Et₃N, 2. excess NaI, acetone, Δ; f) 2.0 M MeNH₂ in THF; g) *t*-BuLi (2.0 eq) in THF-toluene, -78 °C.

smoothly using NaBH₄/THF-H₂O.⁸ Treatment of alcohol **9** with I₂-PPh₃-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 precursor, iodoimine **3**, was formed quantitatively from the aldehyde and methylamine (2.0 M in THF). Ring closure was facilitated 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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(10) The sertraline free base was fully characterized: ¹H NMR (500.1 MHz, C₆D₆) 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); ¹³C NMR (125.8 MHz, C₆D₆) 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).