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TETRAHEDRON: *ASYMMETRY*

Rapid access to enantiopure bupropion and its major metabolite by stereospecific nucleophilic substitution on an α-ketotriflate

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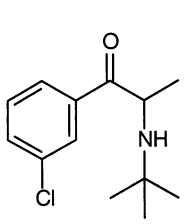
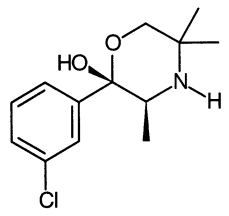
Abstract

A stereospecific method for the synthesis of enantiopure α-aminoketone from its corresponding α-hydroxy-ketone via the triflate intermediate is discussed. This strategy provides a rapid and efficient route for the preparation of either enantiomer of bupropion and its biologically active hydroxylated metabolite.

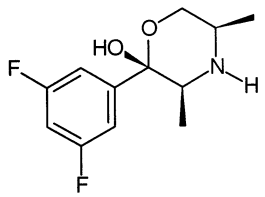
Racemic bupropion **1** is the active ingredient of Wellbutrin® (Glaxo Wellcome) marketed for the treatment of depression. Recently, it has also been approved as an aid to smoking cessation under the brand name of Zyban® (Glaxo Wellcome). Bupropion is extensively metabolized in the body and the major active metabolite is hydroxybupropion **2**.[1] Enantiopure bupropion has been prepared by chemical synthesis and hydroxybupropion has been separated by chiral columns.[2] Studies have shown that α-aminoketones readily racemize in neutral and basic media.[3] It has been reported that bupropion's therapeutic activity may result from the active hydroxylated metabolite (hydroxybupropion)[4] and structure–activity relationship studies of 2-phenylmorpholinols led to the discovery of 155U888 **3**.[5] In order to explore further the biological activities of single enantiomers of these compounds, and to develop analogs with novel biological activities, a general and rapid synthetic method for the synthesis of this class of compounds was required.[6]



1, Bupropion



2, Hydroxybupropion



3, 1555U88

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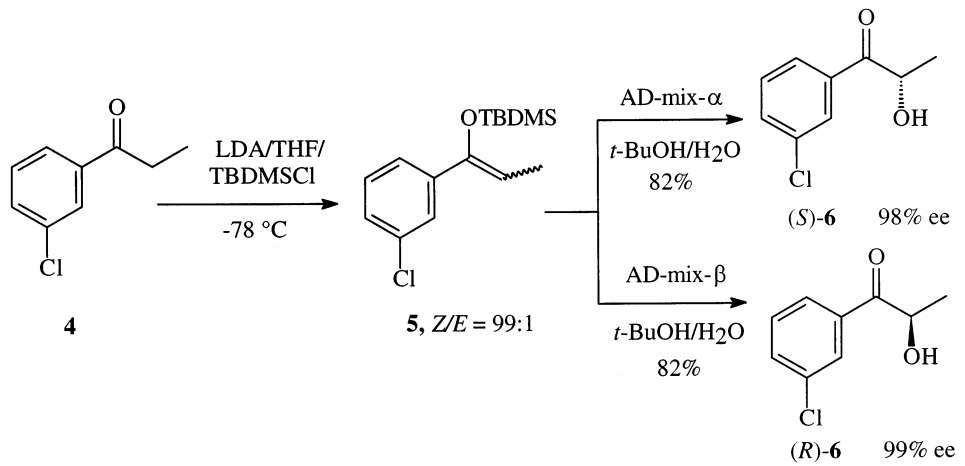
During the last two decades, numerous methods for the synthesis of enantiopure α-hydroxy ketones have been developed.[7] With the advancement of these technologies, α-hydroxy ketones with high enantiopurity are readily available. At the onset of our studies, the stereoselective replacement of the hydroxyl group in α-hydroxy ketones with an alkylamine appeared to be the most efficient approach to generate enantiomers of α-amino-ketones, such as bupropion and hydroxybupropion. Interestingly, conversion of chiral α-hydroxy esters to chiral α-amino esters (or acid) with complete inversion of stereochemistry is well established and practiced extensively,[8] however, to the best of our knowledge, no work has been published on the stereospecific conversion of α-hydroxy ketones to α-amino ketones, even though this transformation has been applied to racemic substrates.[9] In addition, Creary reported that α-keto mesylates, triflates, and trifluoroacetates can undergo solvolysis in polar solvents through a cationic transition state,[10] which indicates the possibility of racemization during the substitution reaction. Herein, we wish to report the stereospecific nucleophilic substitution of α-hydroxy ketones with alkylamines utilizing α-ketotriflate intermediates to prepare enantiomers of bupropion and hydroxybupropion.

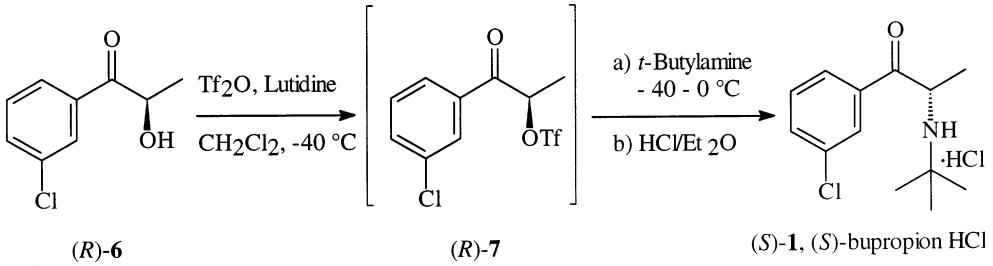
The synthesis of either enantiomer of compound **6** was accomplished by Sharpless's asymmetric dihydroxylation of silyl enol ether **5**[11] in multi-gram quantities, as outlined in Scheme 1.



Scheme 1.

3′-Chlorophenyl propanone was treated with LDA at −78°C, followed by addition of TBDMS-Cl to give the silyl enol ether. The Z/E ratio of the vinyl ethers was estimated to be 99:1 by ^{1}H NMR analysis. Asymmetric dihydroxylation of the silyl ether with AD-mix-α and AD-mix-β as catalysts in t-BuOH/H_2O yielded the corresponding hydroxyketones. (*R*)-**6** and (*S*)-**6** were isolated from the reaction mixture and purified by flash chromatography in 82% yield with 98 and 99% ee, respectively. These α-hydroxyphenylketones can be stored at −10°C under nitrogen atmosphere for one month without any racemization.

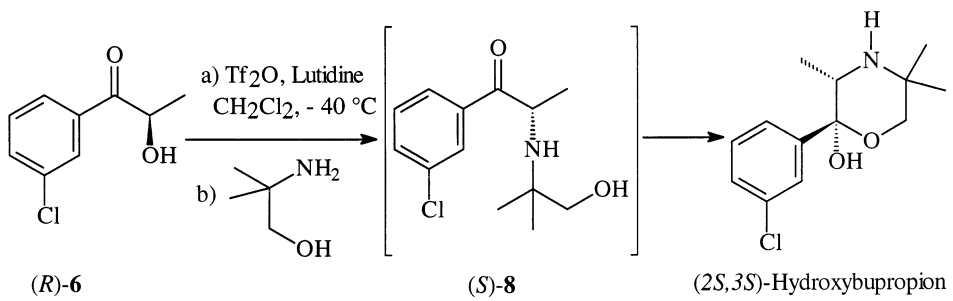
Stereospecific nucleophilic substitution on α-ketotriflate **7** readily available from α-hydroxyketone **6** with t-butylamine for the synthesis of (*S*)-bupropion is outlined in Scheme 2.



Scheme 2.

(*R*)-3′-Chloro-2-hydroxypropiophenone **6** (98% ee) was treated with trifluoromethyl sulfonic anhydride at −40°C in the presence of lutidine to form the ketotriflate intermediate **7**. Without isolation, the triflate intermediate was treated with *t*-butylamine at −40°C to give (*S*)-bupropion in 60% yield after chromatographic purification (lower yield of the product was obtained when Et_3N or pyridine was used as base). Based on chiral HPLC analysis, enantiomeric excess of the product was 98% with complete inversion of the stereogenic center.[12] (*R*)-Bupropion was obtained similarly starting from (*S*)-**6**. Bupropion free base is prone to racemization and was converted to its hydrochloride salt in ethyl ether (>95% yield). Racemization studies of the HCl salt of the bupropion isomer in phosphate buffer (pH 7.4) at 25°C indicated that racemization readily takes place (42% in 2 h, 62% in 4 h, and >94% in 24 h, based on chiral HPLC analysis).

Due to the rapid racemization of bupropion enantiomers, our attention was focused on the synthesis of configurationally more stable active metabolites. Since the biologically active hydroxylated metabolite of bupropion is a hemiketal (2-phenylmorpholinol), it would be less subject to racemization, and the biological testing results of the enantiomers would be more reliable and desirable.[2b] This newly developed mild synthetic entry for the α-aminoketone was extended to the preparation of the hydroxybupropion isomer, as outlined in Scheme 3.



Scheme 3.

When inexpensive and readily available 2-amino-2-methyl-1-propanol is reacted with (*R*)-triflate **7**, conformationally locked (2*S*,3*S*)-hydroxybupropion is isolated in 65% yield without any racemization (98% ee) as the only product, and (2*R*,3*S*)-isomer was not observed.[13] The absolute configuration of the product was determined unambiguously by single-crystal X-ray analysis of its di-toluoyl-L-tartrate salt (Fig. 1).[14] Racemization studies of the hydroxy metabolite at 25°C and pH 7.4 phosphate buffer were conducted, and as expected, racemization takes place slowly (0.1% in 2 h, and ca. 2% in 24 h), which makes it much more desirable as an enantiomerically pure drug candidate. (2*R*,3*R*)-Hydroxybupropion was obtained similarly from (*S*)-**6**.

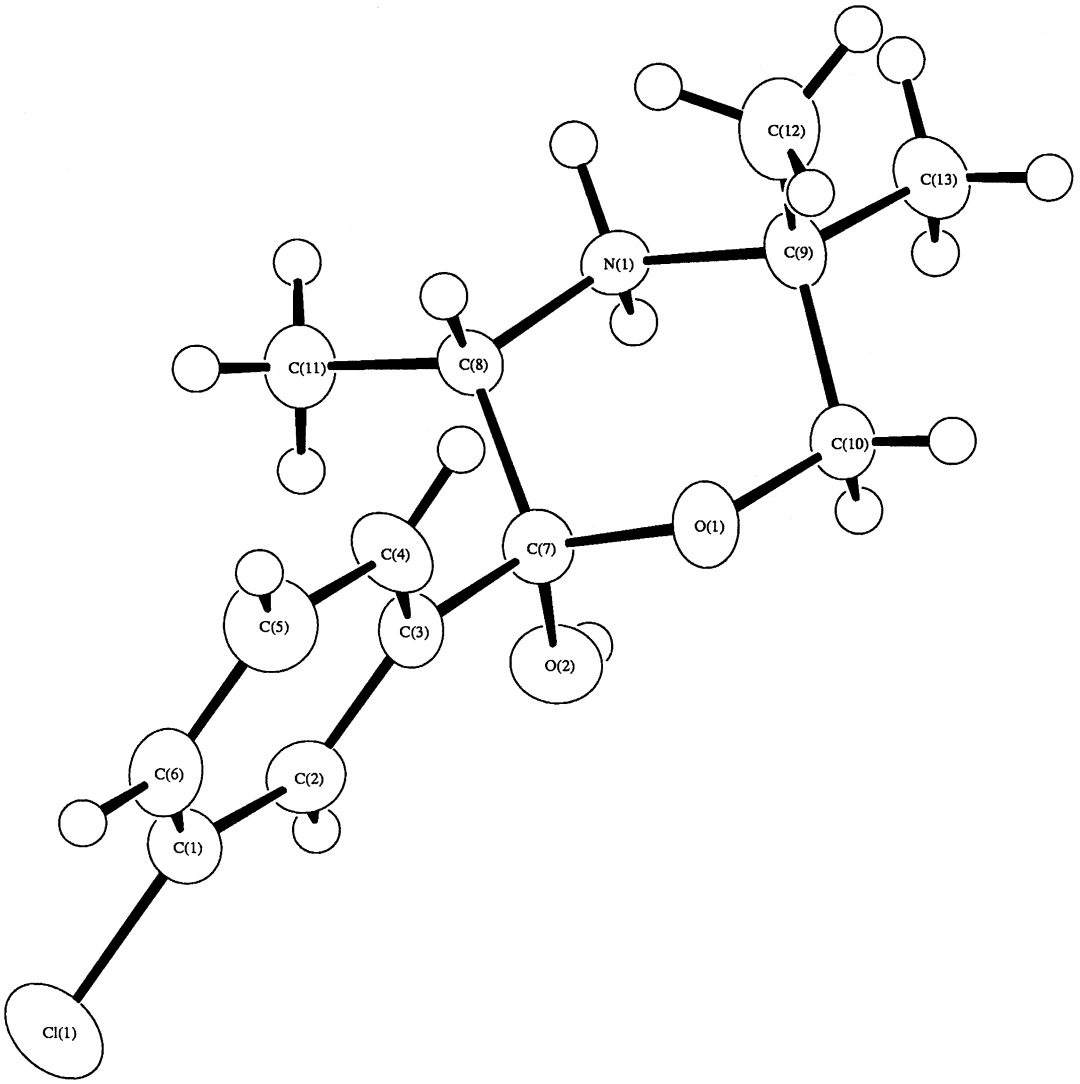


Figure 1. Perspective view (ORTEP) showing the crystallography labels for (2*S*,3*S*)-hydroxybupropion

In summary, we have developed a mild stereospecific displacement reaction for the transformation of readily available enantiopure α-hydroxy ketone to enantiopure α-aminoketone, which allows the production of either enantiomer of bupropion and hydroxybupropion from readily available ethyl 3′-chlorophenyl ketone. This is the first asymmetric synthesis of bupropion and its biologically active metabolite. The scope of this reaction utilizing other ketones to prepare biologically active targets is under investigation.

References

1. Welch, R. F.; Lai, A. A.; Schroeder, D. H. *Xenobiotica* **1987**, *17*, 287 and references cited therein.

2. (a) Kelley, J. L.; Musso, D. L.; Boswell, G. E.; Soroko, F. E.; Cooper, B. R. *J. Med. Chem.* **1996**, *39*, 347–349. (b) Musso, D. L.; Mehth, N. B.; Soroko, F. E.; Ferris, R. M.; Hollingsworth, E. B.; Kenney, B. T. *Chirality* **1993**, *5*, 495. (c) Musso, D. L.; Mehth, N. B.; Soroko, F. E. *Bioorg. Med. Chem. Lett.* **1997**, 1.
3. Mey, B.; Paulus, H.; Lamparter, E.; Blaschke, G. *Chirality* **1998**, 307.
4. Suckow, R. F.; Zhang, M. F.; Cooper, T. B. *Biomed. Chromatogr.* **1997**, *11*, 174 and references cited therein.
5. Boswell, G. E.; Musso, A. O.; Davis, D. L.; Kelley, J. L.; Soroko, F. E.; Cooper, B. R. *J. Heterocycl. Chem.* **1997**, *34*, 1813.
6. Due to the presence of chlorine substitution (*meta*) on the phenyl ring and the *t*-butylamine substitution on the side chain, common methods for the synthesis of arylketone (e.g. Friedel–Crafts reaction with enantiomerically enriched acid chloride) are not applicable to bupropion synthesis.
7. (a) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067–8; (b) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 708; (c) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919. (d) Davis, F. A.; Sheppard, A. C.; Chen, B. C. *J. Am. Chem. Soc.* **1990**, 6679. (e) Duh, T. H.; Wang, Y. F.; Wu, M. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1793. (f) Bradshaw, C. W.; Fu, H.; Shen, G. J.; Wong, C. H. *J. Org. Chem.* 1**992**, *57*, 1526. (g) Zhu, Y.; Manske, K. J.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4080. (h) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819.
8. (a) Coppola, G. M.; Schuster, H. F. α-*Hydroxy Acids in Enantioselective Synthesis*; Wiley–VCH: Weinheim, 1997. (b) Effenberger, F.; Burkard, U. *Liebigs Ann. Chem.* **1986**, 334. (c) Kunz, H.; Lerchen, H. G. *Angew. Chem.* **1984**, *84*, 798.
9. Giordani, A.; Carera, A.; Pinciroli, V.; Cozzi, P. *Tetrahedron: Asymmetry*, **1997**, *8*, 253. Synthesis of chiral ketone traflate has been reported and has been used for the preparation of chiral α-fluoroketone. See Liu, A.; Carlson, K. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **1992**, *35*, 2113.
10. Creary, X. *J. Am. Chem. Soc.* **1984**, *106*, 5568 and references cited therein.
11. In order to obtain high ee's of hydroxyketone TBS ether is crucial; when TMS was used 93% ee was obtained in the ADH reaction. When the TBS enol ether is replaced with vinyl chloride, the ee of the hydroxy ketone was 90% (also see Ref. 7a).
12. ^{1}H NMR data was identical to the racemate sample. Ee's were analyzed with ChiralPAK® AD column eluted with hexane/IPA/DEA (99/1/0.1). (*R*)-(−)-Isomer, 4.51 min; (*S*)-(+)-isomer, 5.66 min. (Absolute configuration of (*S*)-bupropion is established on AD chemistry.) Also see Ref. 14, which is further confirmed by X-ray analysis.
13. Typical experimental procedure: To a solution of (*R*)-3′-chloro-2-hydroxylpropiophenone (0.30 g) in CH_2Cl_2 (6 mL) at −78°C was added triflurometh ane sulfonic anhydride (0.50 g), followed by the addition of 2,6-lutidine (0.26 g). The reaction mixture was allowed to warm to −40°C and was stirred at this temperature for 40 min. Then 2-amino-2-methyl-1-propanol (0.40 g, 2.5 equiv.) was added and the mixture was stirred for 2 h at −40°C, warmed to 0°C and stirred overnight. CH_2Cl_2 (10 mL) was added and the organic phase was washed with aqueous sodium bicarbonate, water and brine. The organic phase was concentrated to give a residue, which was passed through a short column of silica gel eluted with CH_3CN to give the product (260 mg, free base), ee 98%. The ee was analyzed with ChiralCel® OD column eluted with hexane/IPA/DEA (98/2/0.1). (1*R*,2*R*)-Isomer, 7.45 min; (1*S*,2*S*)-isomer, 8.70 min. ^{1}H NMR ($CDCl_3$): δ 0.78 (d, 3H), 1.1 (s, 3H), 1.4 (s, 3H), 3.2 (q, 1H), 3.4 (d, 1H), 3.8 (d, 2H), 7.2–7.65 (m, 4H). $[\alpha]=+66$ ($c=1$, EtOH). (1*R*,2*R*)-Hydroxybupropion was prepared from (*S*)-**1** with 97% ee $[\alpha]=-56$ ($c=1$, EtOH).
14. Single crystals of (1*S*,2*S*)-hydroxybupropion ditoluoyl L-tartrate suitable for X-ray analysis were obtained first by salt formation and subsequent crystallization from ethanol. As shown in the crystal structure, the methyl group (C11) is clearly *cis* to the hydroxy group (O2) in the morpholine ring.