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# An Efficient and Facile Synthesis of Racemic and Optically Active Fexofenadine

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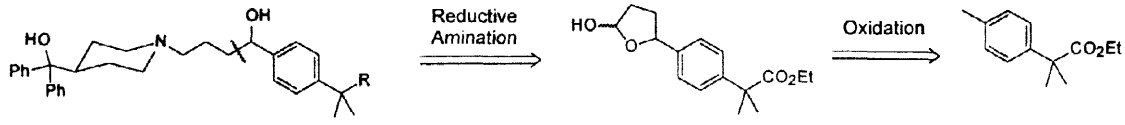
*Abstract: An efficient and practical method for the synthesis of racemic and optically active (96% ee) fexofenadine is described. The key racemic or optically active lactol intermediate 2 is prepared from readily available tolyl derivative 3.* 

Fexofenadine is the active acid metabolite of terfenadine (Seldane®). Both are selective $H_1$-histamine receptor antagonists that do not cause drowsiness. It has been documented that terfenadine can cause severe cardiovascular side effects when used in conjunction with certain antifungal (ketoconazole or itraconazole) or antibacterial (clarithromycin or erythromycin) agents.[1] Racemic fexofenadine reportedly does not cause ventricular arrhythmias and is an attractive alternative for the treatment of allergy symptoms, and currently it is marketed as Allegra®.

**Scheme 1**




**1a**: Terfenadine (R = Me)
**1b**: Fexofenadine (R = COOH)

**2**

**3**

In contrast to their structural similarities, the synthetic route for terfenadine, which employs the Friedel-Crafts reaction to introduce the *para* substitution of the phenyl ring, is not efficient or applicable for the synthesis of fexofenadine. It is reported that a statistical mixture of *meta* and *para* (2:1) products are obtained with the Lewis acid catalyzed acylation of ethyl α,α-1,1-dimethylphenylacetate with 4-chlorobutyryl acid chloride.[2] The lack of regioselectivity necessitated additional steps to obtain the pure *para*-isomer.[3] Recently, Just reported a regioselective synthesis of fexofenadine employing a Pd(0)-catalyzed coupling of a terminal alkyne and an aromatic bromide, followed by sequential regioselective hydration of the triple bond to give the ketone utilizing $HgO/H_2SO_4$ as the reagents.[4] This synthetic method established the *para*-substitution of the benzene ring regioselectively. However, it has limited applicability due to environmental hazards and a lack of impurity control. While an asymmetric synthesis of terfenadine has been reported,[5] there has been no publication related to the synthesis of fexofenadine enantiomers,[6] even though it has been reported that the enantiomers exhibit different pharmacokinetics.[7]

Several approaches can be devised for the synthesis of fexofenadine by analysis of the traditional bond disconnection strategy; however, for the development of a practical route, the following criteria had to be met: (a) availability of the starting materials; (b) the assembly of the target molecule should be simple; and (c) the approach needs to be general either for the synthesis of racemic or enantioselective variant. Herein, we disclose an unique and simple solution leading to an efficient and practical process for racemic and optically active fexofenadine by utilizing readily available tolyl derivative **3**, first elaborated into the strategic lactol **2**, which then rapidly transfers to fexofenadine derivatives via reductive amination-type protocol (Scheme 1).

The synthesis starts by the simple preparation of either the aldehyde **4a**[8a] or acid chloride **4b**[8b] from readily available tolyl derivative **3** by known oxidation processes. As illustrated in Scheme 2, chemoselective addition of the bromoethyl dioxolane Grignard **5**[9] (1.2 equiv.) to aldehyde **4a** at room temperature produces benzyl alcohol **6** in 92% yield.[10] After several experiments,[11] a mild hydrolysis method for dioxolane was developed. (Upon treatment of dioxolane **6** with Amberlyst-15 in a mixture of acetone /water (5:1) at 50 °C). Key aryl lactol **2** was produced in 85% yield as a mixture of 1:1 *cis/trans* isomers.[12] Reductive amination of

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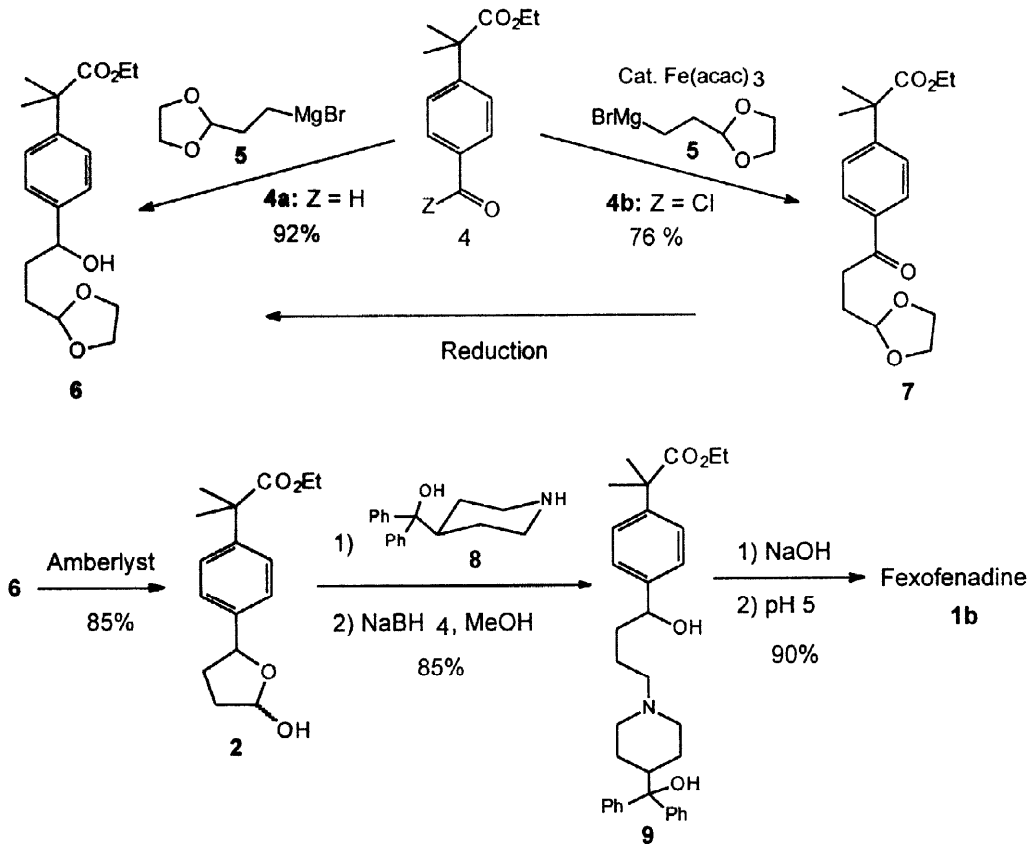
lactol **2** with azacyclonol **8** (1 equiv.) in MeOH at 50 °C in the presence of sodium borohydride (0.4 equiv.) at room temperature cleanly yields fexofenadine ethyl ester **9** in 85% yield.[13] Ester **9** is conveniently converted to fexofenadine in 90% yield by simple saponification with sodium hydroxide in methanol.[4] This highly effective synthesis has been consistantly repeated to provide a non-chromatographic, multigram process to racemic fexofenadine (> 99 A% pure) with an overall yield of 60% from aldehyde **4a**.

**Scheme 2**




Viability of this new strategy was extended to the synthesis of (*S*)- or (*R*)-fexofenadine (1b), by utilizing the enantiomerically enriched (95% ee) benzyl alcohol **6**. Optically active **6** is prepared by the asymmetric reduction of the phenyl ketone **7** using oxazaborolidine based catalysts **10**,[14a] **11**, **12**,[14c] or **13**[15] as outlined in Scheme 3. The prochiral ketone **7** is readily prepared by the Fe(acac)3 catalyzed Grignard **5** addition to aromatic acid chloride **4b** in 76% yield[16] (Scheme 2).

**Scheme 3**

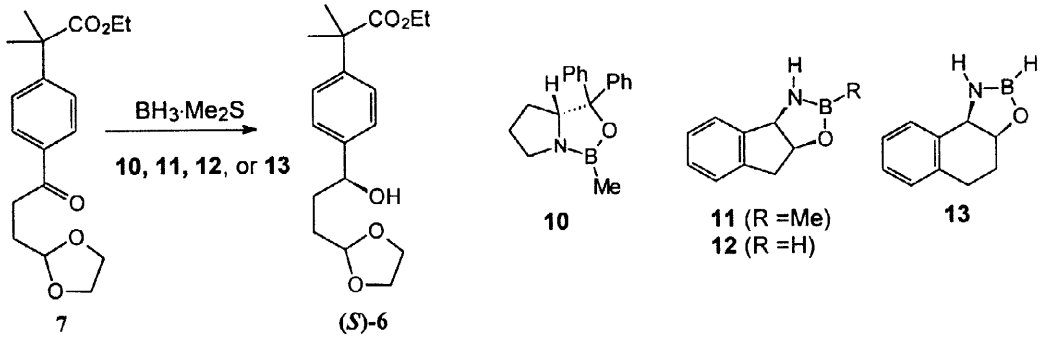


**Table 1:** Asymmetric reduction of ketone **7** catalyzed by oxazaborolidines.

| Entry | Reagent (equiv.) | Cat. (mol%) | Temp. °C | Yield (crude) | ee | Config. |
|---|---|---|---|---|---|---|
| 1 | $BH_3$•THF (1.0) | **10** (10) | -10 | 85 | 95.0 | *S* |
| 2 | $BH_3$•THF (1.8) | **10** (100) | 0 | 84 | 92.0 | *S* |
| 3 | $BH_3$•$Me_2S$ (0.7) | **11** (100) | -10 | (99) | 89.0 | *S* |
| 4 | $BH_3$•THF (1.2) | **12** (20) | 20 | 82 | 84.0 | *S* |
| 5 | $BH_3$•THF (1.8) | **13** (100) | 0 | 79 | 89.0 | *S* |
| 6 | $BH_3$•THF (1.2) | **13** (20) | 0 | (99) | 85.5 | *S* |

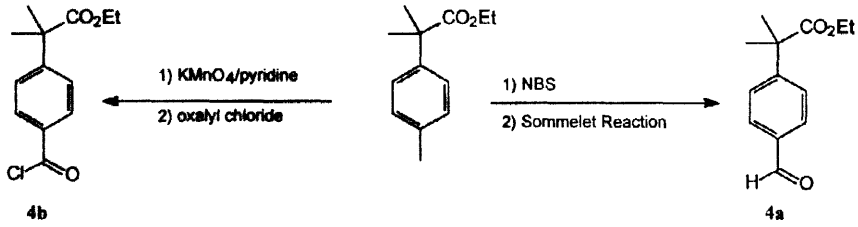
The results of the asymmetric reduction of ketone **7** with catalysts **10-13** are summarized in Table 1. Catalysts **12** and **13** are prepared *in situ* by allowing (*1R, 2S*)-aminoindanol or (*1R, 2S*)-aminotetrahydronaphathalenol to react with one equivalent of borane at 0 °C. A THF solution of ketone **7** is added to a THF solution of borane in the presence of a oxazaborolidine catalyst (0.1 to 1 eq) at a specified temperature (Table 1). The reaction mixture is stirred for 15 min at 0 °C followed by quenching with methanol.[17] CBS catalyst **10** (10 mol%) provided alcohol **6** in the highest enantiomeric purity (95% ee), while catalysts **12** and **13** (20 mol%) gave lower ee's (84.0 and 85.5% respectively).[18] The absolute configuration of alcohol **6** is based on the optical rotation of **9** which is prepared from **6** (from entry 1) according to Scheme 2.[6] The absolute stereochemistry of (*S*)-**6** is also in agreement with the prediction based on the configuration of catalyst **10**.[14a]

The optically active alcohol (*S*)-**6** (95% ee from entry 1) is then subjected to the reaction sequence, as depicted in Scheme 2, to yield (*S*)- fexofenadine ((*S*)-**1b**) *with no detectable epimerization*[19a] throughout the process with a 96% ee, which is determined by chiral HPLC assay.[19b]

In conclusion, we have developed a practical and efficient process for the preparation of both racemic and optically active (96% ee) fexofenadine from readily available tolyl derivative **3**. Novel lactol **2** is anticipated to be an extremely versatile intermediate for the synthesis of other biologically important analogues.

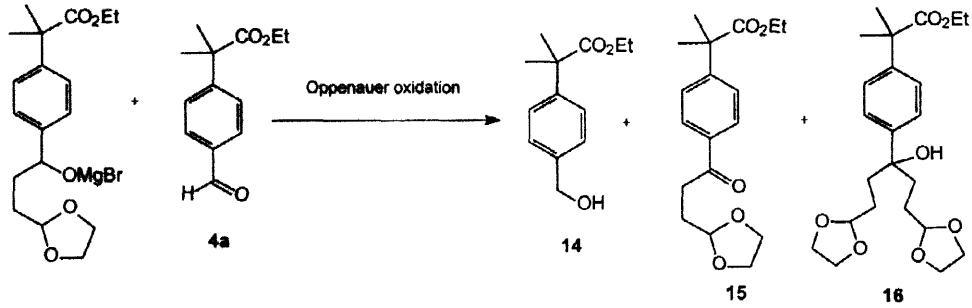
**References and Notes:**


1. (a) Honig, P. K.; Woosley, R. L.; Zamani, K.; Conner, D. P.; Cantilena, L. R., Jr. *Clin. Pharmacol. Ther.* **1992**, *52*, 231. (b) Honig, P. K. *JAMA*, **1993**, *269*, 1513. (c) Woosley, L.; Young, J. W.; Chen, Y. US Patent 5375693.
2. Carr, A. A.; Dolfini, J. E.; Wright, G. J. US patent 4254130 and Carr, A. A.; Dolfini, J. E.; Wright, G. J. US Patent 4285958.
3. D'Ambra, T. E. US Patent 5581011 and US Patent 5578610.
4. Kawai, S. H.; Hambalek, R. J.; Just, G. *J. Org. Chem.* **1994**, *59*, 2620
5. Zhang, M. Q.; Ter Laak, A. M.; Timmerman, H. *Bioorg. Med. Chem. Lett.* **1991**, 387.
6. (a) Nakamura, M.; Shiga, M. PCT., Int. Appl. WO9531436 describes the resolution of fexofenadine and its ethyl ester with (+)-di-*para*-toluoyltartaric acid to give the (*R*)-(+)- (96%) and (*S*)-(-)- isomers 99% (ee) respectively. Optical rotation for the (*R*)-(+)-ester: [α] = +49 (c=1, $CHCl_3$). (b) Chan, K. Y.; George, R. C.; Chen, T.; Okerhoan, R. A. *J. Chromatogr.* **1991**, *571*, 291 described the separation of the enantiomer by chiral column chromatography.
7. Surapaneni, S.; Khalil, S. K. W. *Chirality* **1994**, *6*, 479.
8. (a) Aldehyde **4a** was prepared in large scale by bromination of ethyl α,α-dimethyl(4-methylphenyl)acetate (**3**) with NBS (75%), followed by Sommelet reaction (74%). **4a** could also be prepared from ethyl α,α-dimethylphenyl acetate according to the procedure of Maillard, J.; Langlois, M.; Delaunay, P.; Tri, V. *Chim. Ther.* **1973** *4*, 487. (b) Compound **4b** is prepared by oxidation of ethyl α,α–dimethyl(4-methylphenyl)acetate (**3**) to the corresponding acid with $KMnO_4$, followed by acid chloride formation (43%, not optimized). See, Larner, P. *J. Chem. Soc.* **1952**, 680, 683.




4b 4a


9. Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122.
10. Compound **6**: $^1$H NMR ($CDCl_3$). δ 1.15-1.19 (t, *J* = 7.1 Hz, 3H), 1.55 (s, 6H), 1.65-1.90 (m, 4H), 2.92 (broad s, 1H), 3.75-3.88 (m, 2H), 3.90-3.97 (m, 2H), 4.06-4.13 (q, *J* = 7.0 Hz, 2H), 4.65-4.69 (m, 1H), 4.86-4.89 (m, 1H). 7.29 (s, 4H). Reaction by-products are identified as **14**, **15**, and **16**. They are possibly formed by magnesium alkoxide-catalyzed Oppenauer oxidation. Their formation can be minimized to < 5% by adding **4a** to Grignard **5** in THF at room temperature.


4a 14 15 16


11. Under standard acidic cleavage conditions (e.g. 5% HCl, THF/$H_2O$), a complex mixture of products are formed (**2** in 60%). See Greene, T. W.; Wuts, P. M in "Protective Groups in Organic Synthesis". John Wiley & Sons, Inc. New York, Sec. Ed. **1991**, 190-192.
12. $^1$H NMR of one isomer of **2**, δ: 1.18 (t, J =7.2 Hz, 3H), 1.56 (s, 6H), 1.65-2.44 (m, 4H) 2.88 (s, 1H), 3.65-3.85 (m, 4H), 4.12-4.16 (q, J =7.3 Hz, 2H), 5.10 (m, 1H), 5.35 (m, 1H), 7.27 (m, 4H). $^1$H NMR of the other isomer. δ: 1.18 (t, J -7.2 Hz, 3H), 1.56 (s, 6H), 1.65-2.44 (m, 4H) 2.58 (s, 1H), 3.65-3.85 (m, 4H), 4.12-4.16 (q, J = 7.3 Hz, 2H), 5.0 (m, 1H), 5.22 (m, 1H), 7.32 (s, 4H).
13. Compound **9**: $^1$H NMR ($CDCl_3$) δ 1.12-1.17 (t, *J* = 7.1 Hz), 1.53 (s, 6H), 1.40-1.80 (m, 6H), 1.88-2.10 (m, 4H), 2.3-2.50 (m, 4H), 2.93-2.96 (d, *J* =10 Hz, 1H), 3.11-3.15 (d, *J* =11 Hz), 4.04-4.11 (q, *J* = 7.3 Hz, 2H), 4.56-4.59 (dd, *J1* = 2.7 Hz, *J2* = 8.4 Hz, 1H), 7.15-7.18 (m, 2H), 7.25-7.30 (m, 8H), 7.45-7.50 (m, 4H).
14. (a) Corey, E. J.; Bakshi, R. K.; Shibita, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Carrol, J. D.; Corley, E. G.; Grabowski, E. J. *J. Org. Chem.* 1993, 58, 2880. (c). Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 6631, and 5551.
15. Asymmetric reductions utilizing (*1R, 2S*)-1-amino-2-tetrahydronaphathelenol see: Hett, R.; Senanayake, H. C.; Wald, A. S.; *Tetrahedron Lett.* **1998**, 0000.
16. For Fe(acac)$_3$ catalyzed Grignard addition reaction see: Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, 4805.
17. With prolonged stirring of the reaction mixture (for example, reaction time is > 3h, ~ 30% of alcohol was observed) an over-reduced by-product (ethyl ester of **6** to the corresponding alcohol) was detected.
18. The ee of **6** was determined by HPLC analysis: Chiracel OD, 10 mm, 25 cm x 4.6 mm; UV 220 nm, mobile phase hexane/i-propanol (9:1), ambient temperature, flow rate 1.0 mL/min, retention times R (13.4 min), S (15.9 min).
19. (b) Surprisingly, no epimerization is observed for the conversion of (S)-**6** to lactol **7** with Amberlyst. (b) Ultron-ES-OVM (Shinwa Chemical Industries), 5 mm, UV 210, mobile phase: sodium phosphate buffer (0.05M, pH 4.5):MeCN = 6:94. R (8.7 min), S (6.8 min). See ref. 6. [α] = -32 (c = 0.4, $CHCl_3$), (lit. [α] = -33, c = 0.41, $CHCl_3$ for *S*-**1b**).