Selective Nosylation of 1-Phenylpropane-1,3-diol and Perchloric Acid Mediated Friedel–Crafts Alkylation: Key Steps for the New and Straightforward Synthesis of Tolterodine

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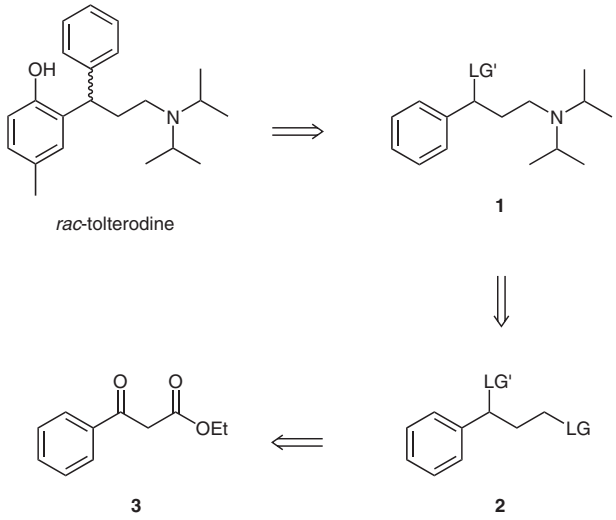
Abstract: We have developed a new and straightforward synthesis of racemic tolterodine [*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine]. The synthesis involves selective nosylation on the primary alcohol of 1-phenylpropane-1,3-diol using 4-nitrobenzenesulfonyl chloride, subsequent diisopropylamine substitution, and Friedel–Crafts alkylation using aqueous perchloric acid.

Key words: drugs, diol, selective sulfonation, nucleophilic substitution, Friedel–Crafts alkylation

Tolterodine is the drug of choice for most patients for the treatment of urinary urge incontinence resulting from an overactive bladder as it has fewer side effects.[1] Through the years there have been myriad ways published for its racemic[2] and asymmetric synthesis.[3] Mostly these methods made used of coumarin or hydrocoumarin derivatives as starting material or intermediates. Most of these methods employed protection and deprotection techniques. This makes the routes lengthy, hence requiring more reagents and solvents. In addition, some of these routes entail longer reaction times and an inert environment while others utilize harsh conditions and hazardous chemicals such as diisobutylaluminum hydride, lithium aluminum hydride, methyl iodide, among others. There are also shorter routes, however, they gave lower yields or enantioselectivities whereas others require tedious workup. For asymmetric synthesis, the use of chiral auxiliaries[3a,c] or expensive metal catalysts such as rhodium[2b,3b,d] is impractical due to the cost incurred. Recently, we published a new route for the synthesis of tolterodine that also employed a protection–deprotection technique via a two-phase reaction.[4] This route is simple and short, however, we have found a new route that is even simpler and eliminates the use of protecting groups. It is straightforward and has very short reaction times making it advantageous over other known procedures. We believed that this new method is economical and strategically feasible for industrial application. Thus, we wish to report here our new approach towards the synthesis of *rac*-tolterodine.

Our aim was to develop a method of synthesizing tolterodine without using the protection–deprotection strategy impelled us to study thoroughly the structure of tolterodine. We considered the retrosynthetic analysis shown in Scheme 1. We reported recently that 1-phenylpropane-1,3-diol could be produced easily from the reduction of ethyl benzoylacetate (**3**) in excellent yield.[4] Thus, we thought that converting the hydroxy functionality into a better leaving group would easily facilitate diisopropylamine substitution and subsequent Friedel–Crafts alkylation to form tolterodine in a straightforward manner.



Scheme 1 Retrosynthetic analysis of *rac*-tolterodine

We first considered chlorination of 1-phenylpropane-1,3-diol using 2,4,6-trichloro-1,3,5-triazine and *N*,*N*-dimethylformamide[5] followed by Friedel–Crafts alkylation using graphite[6] in chlorobenzene. The reactions proceeded quite well. Chloride is a better leaving group than the hydroxy group thus we expected diisopropylamine substitution to be smooth, however, we failed to obtain our desired product. This scenario prompted us to consider selective functionalization of the primary alcohol to make it a better leaving group (Scheme 2). Commonly, selective sulfonation of a diol is carried out using 4-toluenesulfonyl chloride with various catalysts.[7] Thus, we first tried the sulfonation of diol **4** with 4-toluenesulfonyl chloride. The yield with or without catalyst is relatively the same and both conditions require long reaction times so, we preferred doing it without the catalyst. The long reaction times prompted us to consider another reagent for

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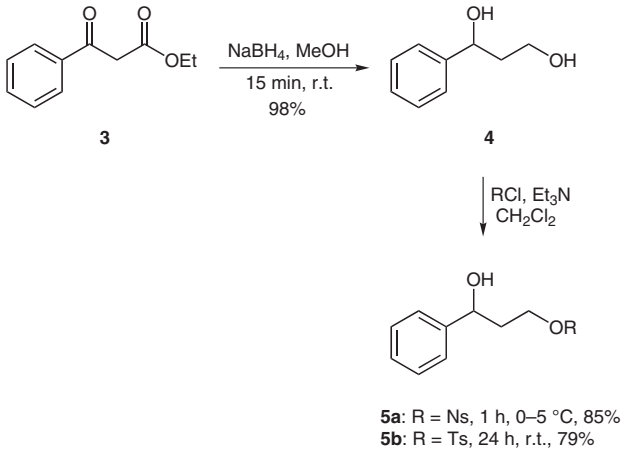
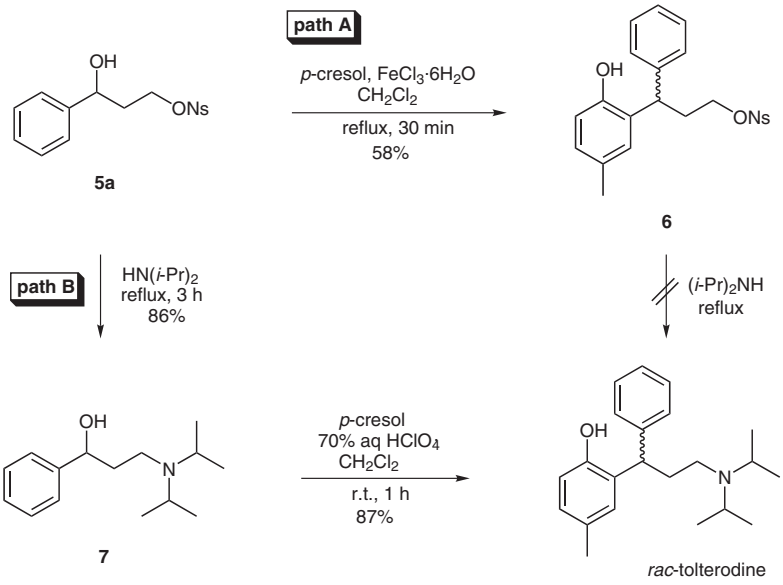
functionalization. There have been reports on the considerable higher reactivity of 4-nitrobenzenesulfonate (nosylate) as a leaving group, which results in improved subsequent nucleophilic displacement.[8] We have proven these ourselves in our previous study.[4] Thus we tried it for selective primary alcohol functionalization as well. As far as we know this is the first attempt at using 4-nitrobenzenesulfonyl chloride (NsCl) for the selective sulfonation of primary alcohols, such as diol **4**. The reaction proceeded smoothly in one hour giving **5a** in 85% yield.[9]



Scheme 2

Next, we tried Friedel–Crafts alkylation using iron(III) chloride hexahydrate[10] to facilitate C–C bond formation giving compound **6** in a short period (Scheme 3, path A). Unfortunately, we were unsuccessful in obtaining *rac*-tolterodine from diisopropylamine substitution even for a prolonged period. Based on our ^{1}H NMR analysis, it gave a cyclic product instead. We presumed that under basic conditions the phenolic hydroxy group was readily deprotonated and acted as nucleophile to the carbon to which the nosylate group was attached, undergoing cyclic etherification. Nucleophilic reaction occurs rapidly due to the higher reactivity of nosylate as leaving group as aforementioned. This scenario prompted us to modify our strategy. Since we identified that the problem was the nucleophilicity of the phenolic hydroxy group under basic conditions and the greater ability of nosylate to leave, we decided to perform the diisopropylamine substitution prior to the Friedel–Crafts alkylation (Scheme 3, path B). Substitution proceeded efficiently in three hours giving compound **7** in 86% yield. This substitution reaction is very quick compare to the known procedures.[2,3] This is attributed to the leaving group ability of the nosylate moiety. The use of 4-nitrobenzenesulfonyl chloride is better than 4-toluenesulfonyl chloride because the former requires much shorter reaction times (3 h) than the latter (52 h). Furthermore, the used of tosylated alcohol **5b** gave only the diisopropylamine substitution product **7** in only 65% yield. This further supports the reactivity of nosylate.

The last step was the Friedel–Crafts alkylation. Initially we tried our procedure using iron(III) chloride hexahydrate, but unfortunately the reaction was unsuccessful and simply gave the starting material, compound **7**. The presence of two electron-donating groups, both capable of coordinating with the metal, suppressed the reaction. We thought that increasing the amount of iron(III) chloride hexahydrate to more than one equivalent would work, but it did not. We tried another stronger acid catalyst, 12-tungstophosphoric acid[11] ($H_3PW_{12}O_{40}$); however, it also gave the starting material, compound **7**. This strengthens our speculation that a metal catalyst will not work in a compound having two electron-donating groups. There has been a study using the superacid trifluoromethanesulfonic acid to ionize initially the alcohol in amino alcohols to generate dicationic intermediates.[12] However, this acid is very expensive. Thus, we considered using a strong inorganic acid, like aqueous perchloric acid, which is relatively stronger than sulfuric acid. In addition, there has been reports in the literature on the effectivity of perchlo-



Scheme 3

ric acid in dichloromethane at room temperature for organocatalytic Friedel–Crafts alkylations.[13] Using this acid in excess protonates the amine moiety, which removes its nucleophilicity while the benzylic alcohol group readily reacts with *p*-cresol to give the coupling product, *rac*-tolterodine. This reaction proceeded cleanly and quickly at room temperature. All reactions described used simple aqueous workup and purification methods to give the desired products.

In conclusion, we have developed a new route for tolterodine without using the common protection–deprotection strategy. The used of 4-nitrobenzenesulfonyl chloride for selective functionalization of the primary alcohol and aqueous perchloric acid for Friedel–Crafts alkylation are new ideas. These enable us to obtain *rac*-tolterodine in a straightforward manner. The chiral resolution of *rac*-tolterodine to (*R*)-tolterodine using L-tartaric acid has been achieved using our previous reported method.[4] In addition, all our steps require simple, inexpensive, and readily available reagents as well as simple purification methods giving an overall yield of *rac*-tolterodine of 62%. We believed that this route is a better alternative for tolterodine synthesis especially from an economic standpoint. The reduction of a β-keto ester with sodium borohydride in methanol solvent and the general application of Friedel–Crafts alkylation using perchloric acid are under investigation.

^{1}H and ^{13}C NMR spectra were obtained using a Varian 300 spectrometer (300 and 75 MHz respectively) with TMS as internal standard. IR spectra were recorded on a Bio-Rad FTS 6000 FT-IR spectrophotometer as KBr pellets. Uncorrected melting points were determined with a Gallenkamp melting point apparatus. HRMS were obtained on a JMS 700 spectrometer. Analytical TLC was conducted on E. Merck 60 F254 aluminum-backed silica gel plates (0.2 mm). Developed plates were visualized using UV light or 2.0% phosphomolybdic acid stain. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh).

1-Phenylpropane-1,3-diol (4)[4]

Ethyl benzoylacetate (**3**, 25.80 mL, 149.9 mmol) was dissolved in MeOH (300 mL) and $NaBH_4$ (17.02 g, 449.8 mmol) was added slowly to the mixture at r.t.; the mixture was stirred for 15 min. All of the MeOH was evaporated and EtOAc was added (50 mL). The mixture was shaken with supersaturated brine soln (30 mL) and the mixture was filtered to remove the solid. The layers were separated and the aqueous layer was extracted using EtOAc (50 mL as many times necessary). The organic phases were combined, dried (anhyd $MgSO_4$), filtered, and concentrated using rotary evaporator. The mixture was further purified using short column chromatography (silica gel, hexane–EtOAc, 2:1) to give **4** (22.36 g, 98%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (m, 2 H), 2.79 (s, 1 H), 3.23 (s, 1 H), 3.84 (m, 2 H), 4.94 (dd, *J* = 8.3, 6.0 Hz, 1 H), 7.30 (m, 5 H).

^{1}H NMR (300 MHz, $CDCl_3$): δ (upon D_2O exchange) = 1.96 (m, 2 H), 3.83 (t, *J* = 5.5 Hz, 1 H), 4.79 (s, 2 H), 4.94 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.31 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.7, 61.6, 74.5, 125.9, 127.8, 128.8, 144.6.

3-Hydroxy-3-phenylpropyl 4-Nitrobenzenesulfonate (5a)

1-Phenylpropane-1,3-diol (**4**, 0.6215 g, 4.084 mmol) was dissolved in CH_2Cl_2 (8.2 mL). NsCl (0.9503 g, 4.288 mmol) was slowly added using a solid dropping funnel while the mixture was stirred in an ice bath (0–5 °C). Et_3N (0.85 mL, 6.126 mmol) was finally added and the mixture was continuously stirred at 0–5 °C for 1 h. The mixture was immediately filtered through a thin pad of silica gel (EtOAc). The mixture was concentrated using a rotary evaporator. It was further purified using column chromatography (silica gel, hexane–EtOAc, 2:1) to give **5a** (1.172 g, 85%) as a white solid; mp 83–85 °C.

IR (KBr): 3559, 1534, 1357, 1323, 1179, 1107, 1073 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (m, 2 H), 2.48 (s, 1 H), 4.14 (m, 1 H), 4.35 (m, 1 H), 4.76 (t, *J* = 6.2 Hz, 1 H), 7.28 (m, 5 H), 8.06 (d, *J* = 8.7 Hz, 2 H), 8.36 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.0, 69.2, 70.3, 124.8, 125.9, 128.3, 128.9, 129.5, 141.7, 143.5, 151.0.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{15}NO_6S$: 337.0620; found: 337.0620.

3-Hydroxy-3-phenylpropyl 4-Toluenesulfonate (5b)[7c]

1-Phenylpropane-1,3-diol (**4**, 1.439 g, 9.458 mmol) was dissolved in CH_2Cl_2 (18.9 mL). TsCl (1.803 g, 9.458 mmol) was slowly added while the mixture was stirred at r.t. Et_3N (0.85 mL, 6.126 mmol) was finally added and the mixture was continuously stirred for 24 h. The mixture was washed with H_2O (3 × 30 mL). The combined organic phase was dried (anhyd $MgSO_4$), filtered, and concentrated using a rotary evaporator. The mixture was further purified using column chromatography (silica gel, hexane–EtOAc, 3:1) to give **5b** (2.280 g, 79%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (s, 1 H), 2.03 (m, 2 H), 2.46 (s, 3 H), 4.06 (m, 1 H), 4.29 (m, 1 H), 4.81 (t, *J* = 6.7 Hz, 1 H), 7.31 (m, 7 H), 7.80 (d, *J* = 8.5 Hz, 2 H).

3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl 4-Nitrobenzenesulfonate (6)

3-Hydroxy-3-phenylpropyl 4-nitrobenzenesulfonate (**5a**, 1.199 g, 3.555 mmol) and $FeCl_3$ 6 H_2O (0.0961 g, 0.3555 mmol) were dissolved in CH_2Cl_2 (14.6 mL). *p*-Cresol (1.538 g, 14.22 mmol) was then added and the mixture was refluxed vigorously for 30 min. The mixture was allowed to cool to r.t. and was quenched with H_2O (15 mL) for 25 min. The layers were separated. The organic phase was washed with H_2O (2 × 15 mL). It was dried (anhyd $MgSO_4$), filtered, and concentrated using a rotary evaporator. The mixture was further purified using column chromatography twice (silica gel, hexane–EtOAc, 5:1 and hexane–EtOAc, 8:1) to give **6** (0.8896 g, 59%) as a gummy yellow solid.

IR (KBr): 3487, 1534, 1349, 1311, 1183, 1092 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 2.41 (m, 2 H), 4.11 (t, *J* = 6.3 Hz, 2 H), 4.32 (t, *J* = 7.8 Hz, 1 H), 6.56 (d, *J* = 7.2 Hz, 1 H), 6.85 (d, *J* = 7.2 Hz, 1 H), 6.86 (s, 1 H), 7.20 (m, 5 H), 8.00 (d, *J* = 8.7 Hz, 2 H), 8.30 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 33.6, 40.0, 70.5, 116.1, 124.6, 126.9, 128.1, 128.4, 128.6, 128.9, 129.0, 129.4, 130.4, 141.7, 142.7, 150.8, 151.1.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{22}H_{21}NO_6S$: 427.1090; found: 427.1085.

3-(Diisopropylamino)-1-phenylpropan-1-ol (7)[14]

3-Hydroxy-3-phenylpropyl 4-nitrobenzenesulfonate (**5a**, 3.501 g, 10.38 mmol) was refluxed with *i*-Pr_2NH (29.30 mL) for 3 h. The mixture was allowed to cool to r.t. and was filtered using CH_2Cl_2 for washing. The filtrate was washed with H_2O and brine alternately several times until the salt was completely removed. All the organic

phase was combined, dried (anhyd $MgSO_4$), filtered, and concentrated using a rotary evaporator. The product was further dried under vacuum to give **7** (2.102 g, 86%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.6 Hz, 6 H), 1.16 (d, *J* = 6.9 Hz, 6 H), 1.66 (m, 1 H), 1.84 (m, 1 H), 2.79 (m, 2 H), 3.20 (m, 2 H), 4.90 (dd, *J* = 9.9, 2.5 Hz, 1 H), 7.32 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 21.9, 35.3, 44.2, 47.5, 76.3, 125.8, 127.0, 128.4, 145.5.

***rac*-Tolterodine**

3-(Diisopropylamino)-1-phenylpropan-1-ol (**7**, 2.084 g, 8.855 mmol) was dissolved in CH_2Cl_2 (4.00 mL) and *p*-cresol (0.9576 g, 8.855 mmol) was added to the soln followed by 70% aq $HClO_4$ (5.35 mL). The mixture was stirred at r.t. for 3 h. Ice was added to the mixture and it was neutralized with aq NaOH; the mixture was quenched for 30 min. The layers were separated and the organic layer was washed with brine and distilled H_2O. The organic phases were combined, dried (anhyd $MgSO_4$), filtered, and concentrated using a rotary evaporator. The product was further dried under vacuum to give the product (2.507 g, 87%) as a gummy yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.3 Hz, 6 H), 1.13 (d, *J* = 6.9 Hz, 6 H), 2.11 (s, 3 H), 2.36 (m, 2 H), 2.72 (m, 2 H), 3.23 (m, 2 H), 4.49 (dd, *J* = 11.1, 3.9 Hz, 1 H), 6.53 (br s, 1 H), 6.83 (m, 2 H), 7.23 (m, 1 H), 7.32 (d, *J* = 4.5 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 20.2, 21.0, 33.3, 39.5, 42.2, 48.2, 118.4, 126.4, 128.0, 128.5, 128.8, 128.9, 129.6, 132.7, 144.9, 153.5.

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References

(1) (a) Nilvebrant, L. *Life Sci.* **2001**, *68*, 2549. (b) Chancellor, M. B.; Appell, R. A.; Sathyan, G.; Gupta, S. K. *Clin. Therapeut.* **2001**, *23*, 753. (c) Kaur, K.; Aeron, S.; Bruhaspathy, M.; Shetty, S. J.; Gupta, S.; Hegde, L. H.; Silamkoti, A. D. V.; Mehta, A.; Chugh, A.; Gupta, J. B.; Sarma, P. K. S.; Kumar, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2093.

(2) (a) Gage, J. R.; Cabaj, J. E. WO 199829402, **1998**. (b) Botteghi, C.; Corrias, T.; Marchetti, M.; Paganelli, S.; Piccolo, O. *Org. Process Res. Dev.* **2002**, *6*, 379. (c) Kumar, Y.; Prasad, M.; Misra, S. WO 2003014060, **2003**. (d) Kankan, R. N.; Rao, D. R. WO 2005061432, **2005**. (e) Srinivas, K.; Srinivasan, N.; Reddy, K. S.; Ramakrishna, M.; Reddy, C. R.; Arunagiri, M.; Kumari, R. L.; Venkatarman, S.; Mathad, V. T. *Org. Process Res. Dev.* **2005**, *9*, 314. (f) Venkataraman, S.; Mathad, V. T.; Reddy, K. S.; Srinivasan, N.; Reddy, C. R.; Arunagiri, M.; Kumari, R. L. US 20060094904, **2006**. (g) Toplak, R. WO 2006066931, **2006**. (h) Turchetta, S.; Ciambecchini, U.; Massardo, P. US 20060079716, **2006**.

(3) (a) Anderson, P. G.; Schink, H. E.; Osterlund, K. *J. Org. Chem.* **1998**, *63*, 8067. (b) Colombo, L.; Rossi, R.; Castaldi, G.; Allegrini, P. CA 2502640, **2005**. (c) Hedberg, C.; Anderson, P. G. *Adv. Synth. Catal.* **2005**, *347*, 662. (d) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285. (e) Ulgheri, F.; Marchetti, M.; Piccolo, O. *J. Org. Chem.* **2007**, *72*, 6056.

(4) De Castro, K. A.; Ko, J.; Park, D.; Park, S.; Rhee, H. *Org. Process Res. Dev.* **2007**, *5*, 918.

(5) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553.

(6) Sereda, G. A. *Tetrahedron Lett.* **2004**, *45*, 7265.

(7) (a) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447. (b) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L. *Tetrahedron* **2000**, *56*, 7291. (c) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578. (d) Das, B.; Reddy, V. S.; Reddy, M. R. *Tetrahedron Lett.* **2004**, *45*, 6717. (e) Fazaeli, R.; Tangestaninejad, S.; Aliyan, H. *Can. J. Chem.* **2006**, *84*, 812.

(8) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(9) The flash column chromatography may be avoided by using crystallization. This is for industrial consideration.

(10) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913.

(11) Heydari, A.; Khaksar, S.; Akbari, J.; Esfandyari, M.; Pourayoubi, M.; Tajbakhsh, M. *Tetrahedron Lett.* **2007**, *48*, 1135.

(12) Li, A.; Kindelin, P. J.; Klump, D. A. *Org. Lett.* **2006**, *8*, 1233.

(13) Li, D.; Guo, Y.; Ding, Y.; Xiao, W. *Chem. Commun.* **2006**, 799.

(14) Razzetti, G.; Mantegazza, S.; Rossi, R.; Allegrini, P. EP 20060823, **2006**.