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Reduction of Ethyl Benzoylacetate and Selective Protection of 2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol: A New and Facile Synthesis of Tolterodine

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Abstract:

A new and facile synthesis of tolterodine using ethyl benzoylacetate as the starting material was developed. Reduction using sodium borohydride in methanol followed by Friedel–Crafts alkylation utilizing $FeCl_3 \cdot 6H_2O$ as catalyst lead to the known 2-(3-hydroxy-1-phenylpropyl)-4-methylphenol intermediate. Consecutive protection of phenolic OH with *p*-toluenesulfonyl chloride via two-phase reaction and conversion of aliphatic OH using *p*-nitrobenzenesulfonyl chloride facilitates direct substitution of diisopropylamine. After simultaneous deprotection of the tosyl group, optically pure (*R*)-tolterodine·L-tartrate was obtained by resolution using L-tartaric acid with 99.99% purity.

Introduction

Tolterodine is the first muscarinic receptor antagonist specifically developed to treat overactive bladder. Overactive bladder results from the uncontrolled spontaneous activity of the bladder muscle (detrusor) during the filling phase, leading to the symptoms of urinary urgency and increased frequency of micturition with or without incontinence.[1] Clinical studies showed that it is equipotent with oxybutynin but possesses fewer side effects, especially on salivary glands.[2,3] This makes tolterodine the drug of choice by most patients for treatment of overactive bladder. In view of this, research to improve the known synthetic routes or to develop new routes has never stopped. There are various approaches published and patented, and most of them involved formation of hydrocoumarin[4–7] as intermediate, which was mostly synthesized from the coupling of *p*-cresol and *trans*-cinnamic acid. Others used hydrocoumarin also to produce intermediate 2-(3-hydroxy-1-phenylpropyl)-4-methylphenol (**3**).[8,9] Some of these routes are long and employ longer reaction times and inert conditions. Others utilize harsh conditions and hazardous chemicals. Some make use of shorter routes but have lower yield or enantioselectivity, whereas other routes require tedious workup. A number of published procedures utilized asymmetric reactions and employed chiral auxiliaries[10,11] or expensive metal catalyst such as rhodium.[12,13] However, the use of transition metal catalyst or other chiral auxiliaries make the process unsuitable for industrial scale as a result of the cost incurred. Thus, looking for a cheaper and economical process well suited for industrial production is still necessary.

We report herein a new and facile synthesis of tolterodine utilizing ethyl benzoylacetate, a relatively cheap starting material.

Results and Discussion

Our strategy (Scheme 1) took advantage of known chemistry such as reduction and Friedel–Crafts alkylation. Ethyl benzoylacetate (**1**), a relatively cheap reagent, was used as the starting material. Reduction of **1** to the corresponding 1-phenylpropane-1,3-diol (**2**) was carried out at various conditions (Table 1). At first, we attempted to use calcium borohydride for the reduction; however, such condition required a longer time for in situ preparation of calcium borohydride and reflux condition for the reduction per se. In our quest to find a milder condition, we considered using $NaBH_4$ in THF or MeOH as solvent instead of just additive,[14] as some literature reported, under reflux condition. Surprisingly the reaction proceeds excellently using $NaBH_4$ in MeOH at room temperature with 98% yield in a shorter time (Table 1, entry 10). The mechanism behind such observation is still under study. As shown in Table 1, the use of 3 or 4 molar equiv of $NaBH_4$ shows no significant difference in terms of yield. Thus, we recommend using 3 molar equiv. We believe that this finding is a new and better condition especially for industrial scale.

Friedel–Crafts alkylation of alcohols using $FeCl_3 \cdot 6H_2O$ was recently reported,[15] and this technique with little modification was used to facilitate the carbon–carbon bond formation to get 2-(3-hydroxy-1-phenylpropyl)-4-methylphenol (**3**). An excess

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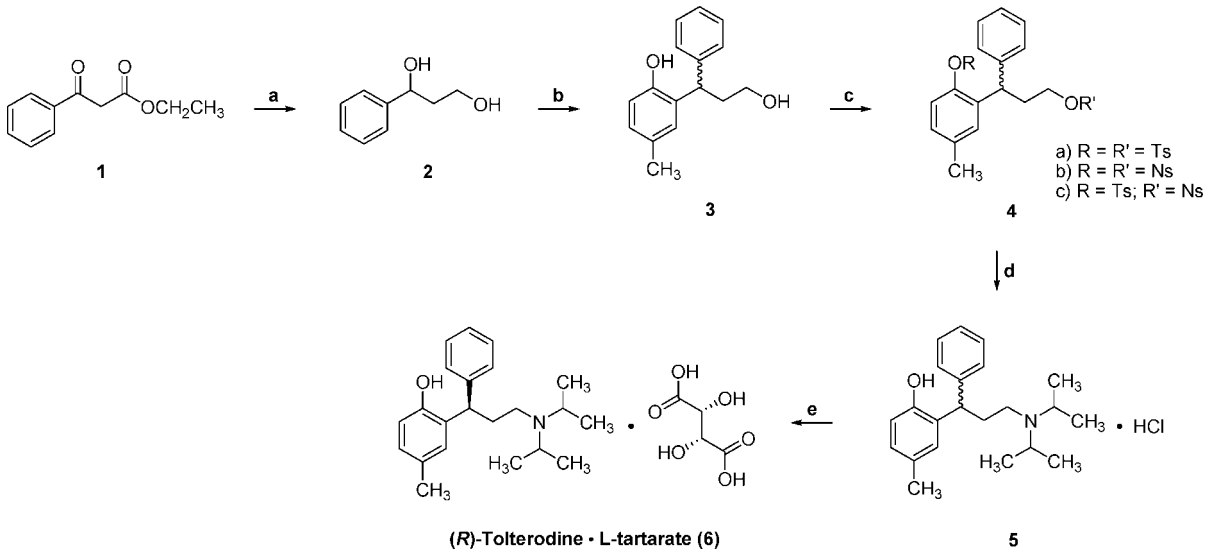
Scheme 1[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 30 min (98%); (b) *p*-cresol, $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, reflux, 1 d (70%); (c) (1) TsCl, NaOH, H_2O, CH_2Cl_2, 40 °C, 1 h, (2) NsCl, NEt_3, 0 °C, 2 h (88%); (d) (1) $NHPr^i_2$, CH_3CN, reflux, 12 h, (2) NaOH, MeOH, reflux, 4 h, (3) HCl, CH_2Cl_2, rt, 1 h (77%); (e) (1) NaOH, Na_2CO_3, CH_2Cl_2, rt, 1 h. (2) L-tartaric acid, MeOH, acetone, reflux, 1 h (88%).

Table 1. **Reduction of ethyl benzoylacetate (1)**

	reaction condition					
entry	reducing agent	molar equiv	solvent	time (h)	temp	yield (%)
1	$Ca(BH_4)_2$[a]	2.0	dry THF	72	reflux	71
2	$Ca(BH_4)_2$[a]	2.0	THF	24	reflux	32
3	$Ca(BH_4)_2$[b]	2.0	dry THF	30	reflux (inert)	66
4	$Ca(BH_4)_2$[c]	2.0	dry THF	91	reflux	69
5	$NaBH_4$	3.0	dry THF	52	reflux	78
6	$NaBH_4$	3.0	MeOH	2	reflux	91
7	$NaBH_4$	3.0	MeOH	3	reflux	92
8	$NaBH_4$	3.0	MeOH	4	reflux	93
9	$NaBH_4$	4.0	MeOH	1	rt	99
10	$NaBH_4$	3.0	MeOH	0.50	rt	98

[a] Prepared in situ, stirred for 24 h at rt. [b] Prepared in situ, stirred for 1 h at reflux condition. [c] Prepared in situ, stirred for 48 h at rt.

amount of *p*-cresol (4.0 equiv) and only 0.05 equiv of $FeCl_3 \cdot 6H_2O$ catalyst in dichloromethane solvent were necessary to effect the reaction.

The next step is believed to be a major breakthrough in the protection and deprotection technique, as well as in the direct substitution of diisopropylamine employed in the synthesis of tolterodine. In most cases, a methyl, benzyl, or *p*-toluenesulfonyl (tosyl) unit is usually used to protect the phenolic OH, while a tosyl unit is used to convert the alcoholic OH into a better leaving group using an organic base simultaneously.[5–8] However, such technique necessitates a longer reaction time (hours or even days) under pressurized and high temperature conditions to facilitate substitution of diisopropylamine. In some cases, an additional step is required to convert the tosyl moiety into a much better leaving group such as iodide,[8] but still, doing so requires the same drastic conditions mentioned above. With these scenarios at hand, a more appropriate condition fitted for industrial scale is essential. At first, we tried to use tosyl chloride for protection and conversion of phenolic and aliphatic OH, respectively, followed by direct substitution of diisopropylamine, as done in the literature. However, contrary to the published results, we obtained a very poor yield of substitution product (20–30%) and mostly starting material. Diisopropylamine substitution did not proceed well, presumably because the tosyl unit is not good enough as a leaving group. A new protecting group and at the same time a better leaving group is needed; hence we considered *p*-nitrobenzenesulfonyl chloride (nosyl chloride, NsCl). As far as we know, nobody has tried to use this moiety before. Initially, we did simultaneous protection and substitution of the two OH groups using triethylamine in dichloromethane. We failed to achieve complete conversion because the aliphatic OH is more nucleophilic than the phenolic OH. It is therefore necessary to change the phenolic OH into phenoxide ion. To facilitate such transformation, we did nosylation in a stepwise manner. First, one nosyl unit was added using 1 M NaOH as base in dichloromethane via a two-phase reaction. This makes nosylation at the phenolic OH. Then, another nosyl unit was added to convert finally the aliphatic OH. This stepwise procedure leads to an 87% yield of 2-(3-(4-nitrobenzenesulfonyloxy)-1-phenylpropyl)-4-methylphenyl *p*-nitrobenzenesulfonate (**4b**). The protection and conversion of the two OH groups proceeded easily, and diisopropylamine undergoes substitution smoothly. This shows that the nosyl unit is really a better leaving group. However, nosyl chloride is

somewhat more expensive than tosyl chloride. Therefore, we considered protecting the phenolic OH with tosyl chloride instead of nosyl chloride for economic consideration and converting the aliphatic OH using nosyl chloride consecutively in the same manner aforementioned. The idea materialized easily to give 2-(3-(4-nitrobenzenesulfonyloxy)-1-phenylpropyl)-4-methylphenyl *p*-toluenesulfonate (**4c**). It gave the same yield as that when using nosyl chloride for both OH groups. Simultaneous diisopropylamine substitution and deprotection of the phenolic OH were carried out without difficulty, and the following treatment with hydrochloric acid produced tolterodine·
HCl salt (**5**) in 77% isolated yield. Finally, the racemic salt formed was resolved using L-tartaric acid in hot methanol to produce optically pure (*R*)-tolterodine·L-tartarate (**6**) in 88% yield with 99.99% chemical purity based on the established and validated HPLC method.[16]

Conclusion

In conclusion, we have developed a new route for tolterodine utilizing available chemistry. The reduction of ethyl benzoylacetate using $NaBH_4$ in MeOH at room temperature is very practical. The successive selective protection and conversion of the two OH groups using tosyl and nosyl chloride, respectively, via a two-phase reaction is a new idea. It is believed that this route is practical for industrial purposes because ethyl benzoylacetate is a relatively cheap starting material and each step employs mild reaction conditions coupled with cheap reagents and easy handling.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were obtained using a Varian 300-MR spectrometer (300 or 500 MHz) in $CDCl_3$ or DMSO solvents. The chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr pellets on a Varian FTS 1000 FT-IR spectrometer. HRMS were obtained on a JMS 700 spectrometer. The purity of the final product was checked using chiral AGP column (100 mm × 2.0 mm, 5 μm, Chromtech Co.). Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was conducted on E. Merck 60 F_{254} aluminum-backed silica gel plates. Developed plates were visualized with UV light or with a 2.0% phosphomolybdic acid staining solution. Uncorrected melting points were determined with a Gallenkamp melting point apparatus.

1-Phenylpropane-1,3-diol (2). Ethyl benzoylacetate (**1**) (3.44 mL, 19.99 mmol) was dissolved in MeOH (40 mL), and sodium borohydride (2.27 g, 59.97 mmol) was added slowly to the mixture at room temperature. The mixture was stirred until the reaction was complete based on TLC monitoring (hexane/ethyl acetate = 2:1, v/v). After completion (30 min), all of the MeOH was evaporated, and ethyl acetate was added (20 mL). The mixture was shaken with brine solution (20 mL), and the organic layer was extracted using ethyl acetate (20 mL as many times as necessary). The mixture was further purified using silica gel column chromatography with hexane/ethyl acetate (2:1, v/v) eluent system to give compound **2**[17] in 98% yield (2.98 g) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.94 (dd, J = 8.3, 6.0 Hz, 1H), 3.84 (m, 2H), 3.23 (s, 1H), 2.79 (s, 1H), 1.95 (m, 2H). ^{1}H NMR (300 MHz, $CDCl_3$) upon D_2O exchange: 7.31 (m, 5H), 4.94 (dd, J = 8.5, 4.1 Hz, 1H), 4.79 (br s, 2H), 3.83 (t, J = 5.5 Hz, 1H), 1.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 128.7, 127.8, 125.9, 74.2, 61.4, 40.6.

2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol (3). 1-Phenylpropane-1,3-diol (**2**) (1.48 g, 9.72 mmol) was dissolved in CH_2Cl_2 (10 mL). *p*-Cresol (4.07 mL, 38.88 mmol) and $FeCl_3 \cdot 6H_2O$ (0.13 g, 0.48 mmol) were added to the solution. The resulting mixture was stirred and heated at reflux for 1 day. The reaction progress was monitored via TLC (hexane/ethyl acetate = 2:1, v/v). Upon completion, the mixture was cooled down to room temperature and quenched with water (10 mL). The product was extracted using CH_2Cl_2 (20 mL) as many times as necessary. The organic layer was dried using anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure and further dried using vacuum. The crude product was purified using silica gel column chromatography with hexane/ethyl acetate (2:1, v/v) eluent system to give compound **3**[8] in 70% yield (1.64 g) as a white crystalline powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J = 4.0 Hz, 4H), 7.23 (m, 1H), 6.88 (dd, J = 8.3, 1.8 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 4.58 (dd, J = 10.3, 5.8 Hz, 1H), 3.77 (m, 1H), 3.55 (m, 1H), 2.39 (m, 1H), 2.17 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.7, 144.3, 130.6, 130.5, 129.4, 128.7, 128.5, 128.2, 126.5, 116.2, 60.9, 38.6, 37.1, 21.0.

2-(3-(4-Nitrobenzenesulfonyloxy)-1-phenylpropyl)-4-methylphenyl *p*-Nitrobenzenesulfonate (4b). 2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol (**3**) (10.0 g, 41.27 mmol) and *p*-nitobenzenesulfonyl chloride (9.60 g, 43.33 mmol) were dissolved in CH_2Cl_2 (100 mL) at room temperature. Aqueous NaOH (1.0 M, 83 mL) was added to the mixture, which was stirred at 0–5 °C. The reaction was monitored by TLC. Upon completion, the organic layer was separated and washed with water (50 mL each time) until the pH of the aqueous layer was approximately 6–7. The organic layer was collected and dried with anhydrous $MgSO_4$. *p*-Nitrobenzenesulfonyl chloride (10.06 g, 45.40 mmol) was then added to the dried organic layer, and the mixture was stirred at 0–5 °C. Then triethylamine (8.35 g, 82.54 mmol) was added slowly using a dropping funnel. The resulting mixture was stirred for 2 h at room temperature. Afterwards, the mixture was washed with water (50 mL) twice. The organic layer was collected and dried with anhydrous $MgSO_4$. The filtrate was concentrated to half its original volume under reduced pressure, and the product was recrystallized using acetone (75 mL). The resulting solid was filtered and vacuum dried at 60 °C to give compound **4b** in 87% yield (21.99 g) as a white powder. Mp: 115–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (m, 3H), 8.05 (m, 3H), 7.18 (m, 2H), 6.95 (m, 4H), 4.31 (t, J = 7.5 Hz, 1H), 4.03 (m, 2H), 2.37 (m, 1H), 2.27 (s,

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3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.2, 150.9, 145.2, 141.4, 141.3, 140.9, 138.1, 135.6, 130.0, 129.5, 129.5, 129.0, 128.0, 127.2, 124.8, 124.7, 121.7, 69.6, 40.7, 39.4, 34.3, 21.4. IR (KBr, cm^{-1}): 1536, 1492 (NO_2), 1371, 1313 (NO_2, S═O), 1182 (S═O), 1095 (S–O); HRMS *m/z* calcd for $C_{28}H_{24}N_2O_{10}S_2$ + H 613.0951, found 613.0955.

2-(3-(4-Nitrobenzenesulfonyloxy)-1-phenylpropyl)-4-methylphenyl *p*-Toluenesulfonate (4c). 2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol (**3**) (100.0 g, 412.69 mmol) and *p*-toluenesulfonyl chloride (78.68 g, 412.69 mmol) were dissolved in CH_2Cl_2 (500 mL) at room temperature. Next, 50% aqueous NaOH (40 mL) was added, and the mixture was heated for 1 h at 40 °C. The reaction mixture was cooled down to room temperature, and the organic layer was separated. The organic layer was washed with 1.0 M HCl (250 mL) and with water (250 mL) twice. The organic layer was collected, dried with anhydrous $MgSO_4$ and filtered. *p*-Nitrobenzenesulfonyl chloride (96.03 g, 433.31 mmol) was then added to the dried organic layer at room temperature. The mixture was cooled down to 0 °C, and triethylamine was added dropwise. The resulting mixture was stirred for 2 h at 0 °C. The mixture was washed with 1.0 M HCl (250 mL) and with water (250 mL) twice. The organic layer was collected and dried with anhydrous $MgSO_4$. The filtrate was concentrated to half its original volume under reduced pressure, and the product was recrystallized using *n*-hexane (750 mL). The resulting solid was filtered and vacuum dried at 60 °C to give compound **4c** in 88% yield (211.24 g) as a dirty white powder. Mp: 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (m, 2H), 8.05 (m, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.16 (m, 3H), 6.99 (dd, J = 8.0, 2.2 Hz, 2H), 6.88 (m, 2H), 6.81 (d, J = 8.3 Hz, 1H), 4.31 (dd, J = 8.8, 6.9 Hz, 1H), 4.04 (m, 2H), 2.48 (s, 3H), 2.34 (m, 2H), 2.23(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.8, 145.9, 145.4, 141.5, 141.2, 137.5, 136.4, 133.0, 130.3, 129.6, 129.0, 128.9, 128.7, 128.6, 128.1, 127.1, 124.7, 122.1, 69.9, 39.5, 33.9, 22.1, 21.4. IR (KBr, cm^{-1}): 1534, 1491 (NO_2), 1350, 1311 (NO_2, S═O), 1184 (S═O), 1091 (S–O). HRMS *m/z* calcd for $C_{29}H_{27}NO_8S_2$ + H 582.1256, found 582.1251.

Tolterodine·HCl Salt (5). Diisopropylamine (34.79 g, 343.84 mmol) was added to 2-(3-(4-nitrobenzenesulfonyloxy)-1-phenylpropyl)-4-methylphenyl *p*-toluenesulfonate (**4c**) (40.00 g, 34.38 mmol) in acetonitrile (50 mL). The reaction mixture was heated at reflux for 12 h and dried under reduced pressure. The residue was dissolved in MeOH (80 mL), and then aqueous NaOH (6.88 g in 35 mL of H_2O) was added to the mixture. The reaction mixture was heated at reflux for 4 h and then concentrated under reduced pressure. Water (250 mL) was added, and the reaction was extracted with CH_2Cl_2 (75 mL). The extract was washed with brine solution, and aqueous HCl solution (1.88 mL of concentrated HCl in 5.64 mL of H_2O) was added to the organic layer. The mixture was stirred for 1 h, and the resulting solid was filtered and washed with CH_2Cl_2 (20 mL). The solid was dried under vacuum at 60 °C to give tolterodine·HCl salt (**5**)[18] in 77% yield (9.59 g) as a white powder. ^{1}H NMR (300 MHz, CD_3OD): δ 7.25 (m, 5H); 6.94 (br s, 1H), 6.85 (dd, J = 8.3, 1.9 Hz, 1H), 6.70 (dd, J = 8.3, 1.4 Hz, 1H), 4.38 (t, J = 7.7 Hz, 1H), 3.64 (m, 2H), 3.01 (t, J = 8.7 Hz, 2H), 2.50 (m, 2H), 2.18 (s, 3H), 1.27 (m, 12H). ^{13}C NMR (75 MHz, CD_3OD): δ 152.5, 143.4, 129.2, 128.7, 128.5, 128.4, 128.0, 126.4, 115.0, 55.2, 41.9, 32.7, 19.6, 17.7, 15.9.

(*R*)-Tolterodine-L-tartarate (6). Tolterodine·HCl salt (**5**) (14.56 g, 40.23 mmol), CH_2Cl_2 (73 mL), and H_2O (73 mL) were mixed. Aqueous NaOH solution (50%, 1.09 g, 27.31 mmol) and Na_2CO_3 (1.46 g, 13.74 mmol) were added to the mixture, which was stirred for 1 h. The organic layer was extracted and washed with H_2O (73 mL). The solution was dried under reduced pressure, and the residue was dissolved in acetone (80 mL) and warmed to 60–70 °C. The dissolved L-tartaric acid (6.64 g, 44.26 mmol) in hot MeOH (41 mL) was added at 60–70 °C, and the resulting mixture was heated at reflux for 1 h. The reaction mixture was cooled down to 0 °C and was held at that temperature for 1 h. The resulting solid was filtered and dried under vacuum at 60 °C to give optically pure (*R*)-tolterodine·L-tartarate in 88% yield with 99.99% chemical purity (8.42 g) as a white crystalline powder. The purity of the product was checked using a chiral AGP column (100 mm × 2.0 mm, 5 μm, Chromtech Co.) based on the known validated procedure.[16] ^{1}H NMR (300 MHz, DMSO): δ 7.29 (m, 5H), 7.16 (m, 1H), 7.03 (d, J = 1.7 Hz, 1H), 6.80 (dd, J = 8.0, 1.4 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.29 (t, J = 7.6 Hz, 1H), 4.03 (s, 2H), 3.46 (m, 2H), 2.75 (m, 3H), 2.37 (m, 2H), 2.16 (s, 3H), 1.12 (d, J = 6.3 Hz, 12H). ^{13}C NMR (75 MHz, DMSO): δ 175.0, 153.1, 144.7, 130.2, 128.9, 128.5, 128.2, 128.0, 126.7, 115.8, 72.6, 53.4, 45.9, 41.5, 33.0, 21.0, 18.5.

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Supporting Information Available

^{1}H and ^{13}C spectra for compounds **2**–**6** and HRMS and IR spectra for compounds **4b** and **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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