

HETEROCYCLES, Vol. 77, No. 1, 2009, pp. 279 - 291. © The Japan Institute of Heterocyclic Chemistry  
 Received, 9th April, 2008, Accepted, 18th August, 2008, Published online, 21st August, 2008.  
 DOI: 10.3987/COM-08-S(F)9

## BENZOTHIAZINES IN ORGANIC SYNTHESIS. AN APPROACH TO THE SYNTHESIS OF *SECO*-PSEUDOPTEROXAZOLE

Michael Harmata\* and Pinguan Zheng

Department of Chemistry, University of Missouri-Columbia, Columbia, Missouri 65211, U. S. A.; E-mail: HarmataM@Missouri.edu

**Abstract** – As part of our approach to the synthesis of *seco*-pseudopteroxazole, we have succeeded in establishing the stereochemistry of the methyl-bearing stereocenter (C-11) with good diastereoselectivity. Though seemingly straightforward, the process was not simple and revealed some interesting aspects of benzothiazine chemistry.

### INTRODUCTION

We recently reported the synthesis of the antitubercular agent pseudopteroxazole (**1**)<sup>1</sup> using benzothiazine chemistry developed in our laboratories.<sup>2</sup> One difficulty in that process was establishing the configuration

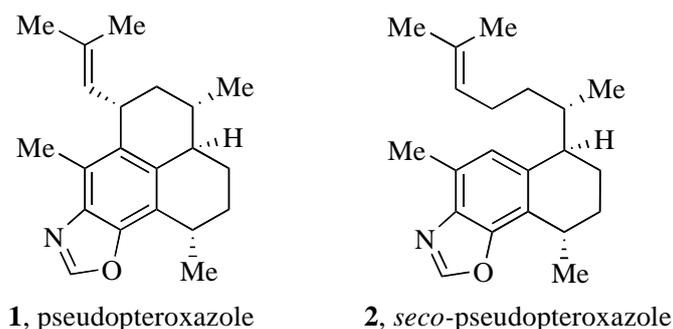
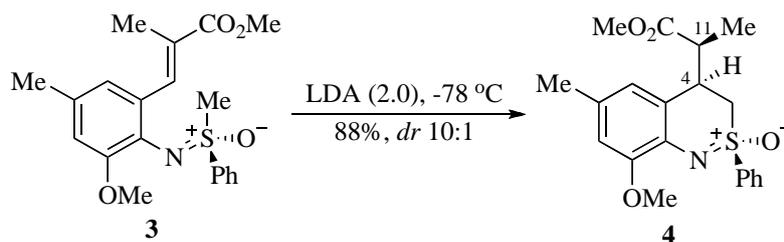


Figure 1

of the C-11 stereocenter in **1**. The reaction of enantiomerically pure **3** with LDA afforded **4** as a 10:1 mixture of diastereomers, unfortunately in the direction opposite to that desired (Scheme 1).

While steps could be taken to ameliorate this situation so that **1** could be synthesized, we wanted to develop one or more routes that would avoid this complication. We chose to do that in the context of the synthesis of the natural product *seco*-pseudopteroxazole (**2**).



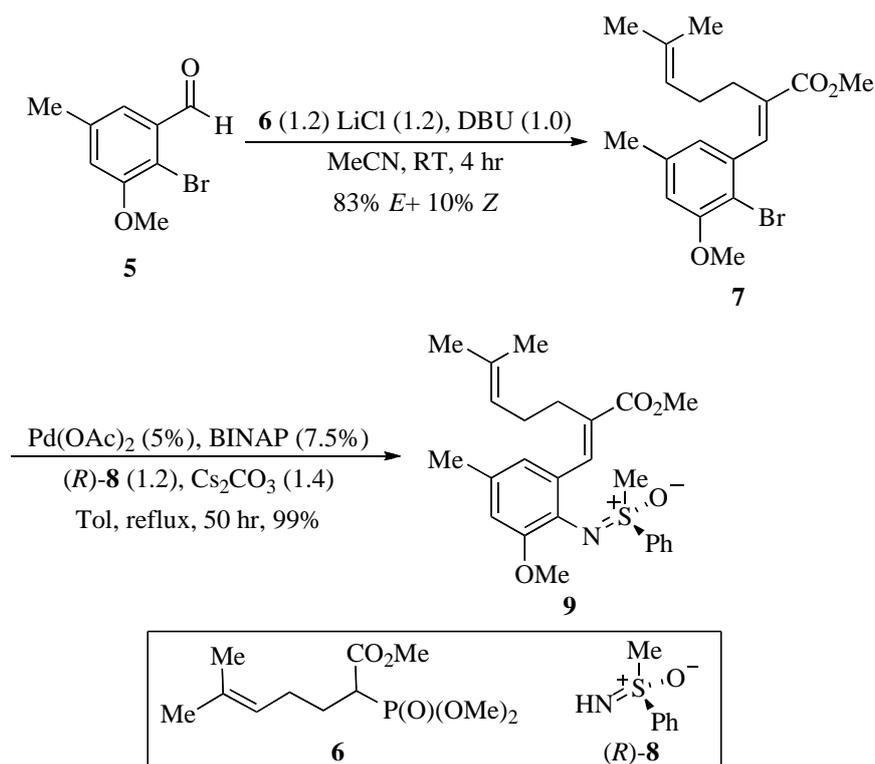
Scheme 1

*Seco*-pseudopteroxazole (**2**) was isolated by Rodriguez and coworkers from *Pseudopteroxorgia elisabethae*.<sup>3</sup> Like pseudopteroxazole, it showed antituberculosis activity, though its potency was less than that of pseudopteroxazole. No synthesis of *seco*-pseudopteroxazole has been reported, and this target appeared to be one through which we could demonstrate new strategies for establishing the common stereochemical centers at C-4 and C-11 of both pseudopteroxazole and *seco*-pseudopteroxazole.

While several approaches can be conceived for the establishment of the appropriate C-4/ C-11 relationship, we chose to simply reverse the roles of the substituents on the  $\alpha,\beta$ -unsaturated ester of the benzothiazine precursor, relative to how those were used in the synthesis of pseudopteroxazole.

## RESULTS AND DISCUSSION

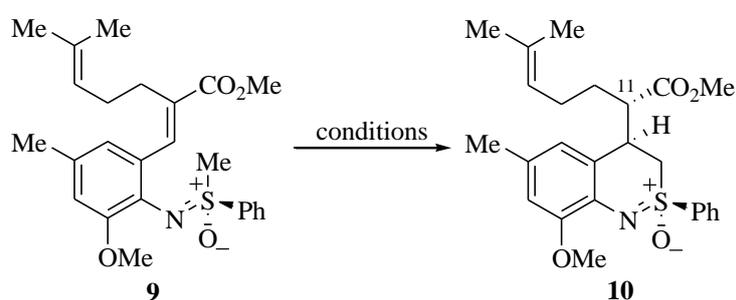
We began with aldehyde **5**, which is readily prepared from 3,5-dimethylanisole in a 4-step sequence.<sup>4</sup> A Horner-Emmons reaction with known phosphonate **6**<sup>5</sup> using the modification introduced by Roush and

Scheme 2. Synthesis of sulfoximine **9**

Masamune<sup>6</sup> afforded the ester **7** in 83% yield along with a 10% yield of the corresponding *Z* isomer. Coupling of this compound with enantiomerically pure sulfoximine **8** under standard conditions led to sulfoximine **9** in 99% yield (Scheme 2).<sup>7</sup> We were thus prepared to develop an intramolecular conjugate addition/protonation sequence that would be highly diastereoselective.

Based on earlier results,<sup>1</sup> we knew that the key to selectivity would be the protic quench itself. A selection of quenching procedures attempted are illustrated in Table 1.

**Table 1.** Optimization of intramolecular Michael reaction



entry	base (2.0)	electrophile <sup>a</sup>	<i>d.r.</i> <sup>b</sup>	Yield (%)
1	LDA	MeOH	3.8: 1.0	85
2	LiHMDS	MeOH	4.6: 1.0	95
3	LDA	1N HCl in MeOH	5.8: 1.0	NA <sup>c</sup>
4	LiHMDS	1N HCl in MeOH	9.2: 1.0	99
5	LDA	DIPA·HCl in MeOH	4.4: 1.0	98
6	LiHMDS	DIPA·HCl in MeOH	5.6: 1.0	80

<sup>a</sup>Pre-cooled to  $-78$  °C. <sup>b</sup>Determined by <sup>1</sup>H NMR of the crude reaction mixture  
<sup>c</sup>AN = Not Available

Initial attempts utilizing cold methanol as quenching reagent afforded the desired product in good yield, but with only fair diastereoselectivity. This might result from the rapid epimerization at C-11 position during the protonation of enolate, due to the formation of methoxide. A stronger proton donor was necessary to achieve better stereoselectivity. When the reaction was quenched by rapid addition of cold 1N HCl in methanol solution at  $-78$  °C, the product was obtained in quantitative yield with a diastereomeric ratio of up to 9.2:1.0 (entry 4). Interestingly, a sterically-hindered proton donor (diisopropylamine-HCl) afforded product with only moderate diastereoselectivity (entry 6). Further, the reaction utilizing LDA as a base generally gave lower diastereoselectivity than LiHMDS, which might suggest that the role of free amines (HMDS and DIPA) in the reaction mixture should not be overlooked (entries 3 and 5). The stereochemical outcome of the reaction could be rationalized by a model analogous to one developed by Kocienski (**11**, Figure 2).<sup>8</sup> Protonation on the *Re* face of **11** avoids an untoward interaction with the hydrogen on the aryl ring (Figure 2) and is thus favored.

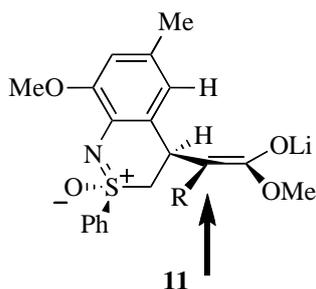
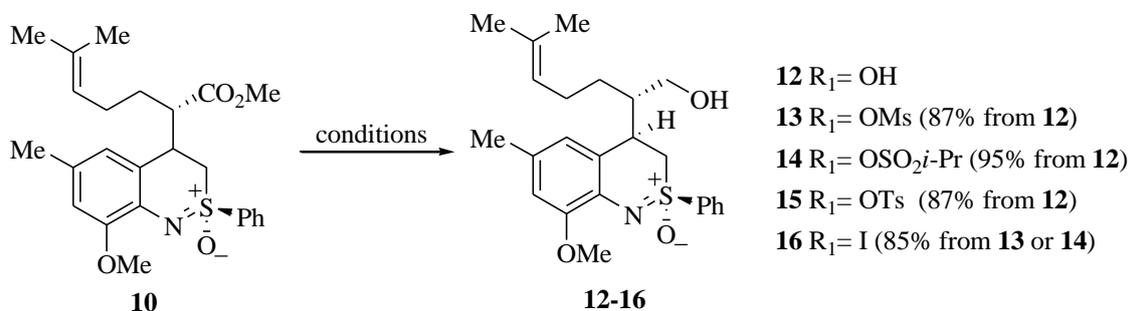


Figure 2. Model for diastereoselective enolate quench

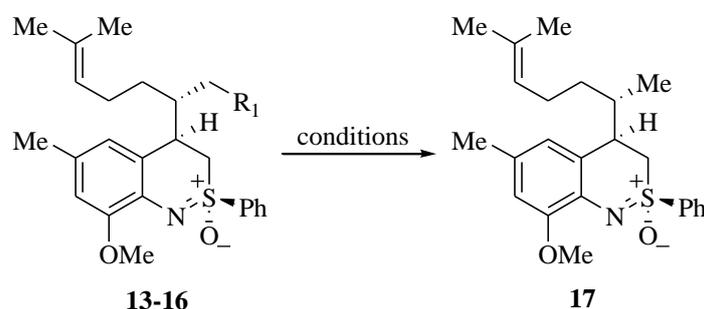
After successfully establishing the stereocenters at carbons 4 and 11 (**2** numbering), we set out to convert the methyl ester in **10** to a methyl group. One step procedures were not successful.<sup>9</sup> LAH reduction gave only moderate yields (43-57%) of the corresponding alcohol after silica gel column chromatography, despite the fact that relatively clean conversion was achieved on a 200 mg scale (entry 1, Table 2). The low yield of this reaction might be attributed to the lability of alcohol **12**, which was prone to undergo decomposition under the reaction conditions and during silica gel chromatography.

Table 2. Reduction and subsequent functionalization of **10**

entry	condition	yield (%) <b>12</b> or <b>16</b>
1	LAH (1.5), THF, 0 °C, 0.5 h	43-57
2	Red-Al (3.0), 0 °C, 2 h, rt, 5 h	a
3	DIBAL (3.0), 0 °C, 1.5 h, rt	46 <sup>b</sup>
4	LiEt <sub>3</sub> BH (3.0), THF, 0 °C, 0.5 h	Quant.
5	1. LiEt <sub>3</sub> BH, THF; 2. I <sub>2</sub> , PPh <sub>3</sub> , imid.	80-89 <sup>c</sup>

<sup>a</sup>Decomposition of **10** was observed. <sup>b</sup>8% recovery of starting material. <sup>c</sup>Iodide **16** was obtained in 80-89% yield.

Compound **10** afforded a complex mixture of products upon with the treatment of Red-Al (Table 2, entry 2). Attempted reduction with DIBAL afforded product in 46% yield along with a small amount of starting material (Table 2, entry 3). LiEt<sub>3</sub>BH<sup>10</sup> was found to work perfectly to give a quantitative yield of alcohol, which was directly converted to iodide **16** in 80-89% yield (Table 2, entries 4 and 5).<sup>11</sup> Other substrates (**13-15**), bearing different sulfonate functionalities, were also prepared from **12** in good yields.

**Table 3.** Reductions of sulfonate esters and iodides

entry	educt	conditions	Yield (%) <b>17</b>	Yield (%) <b>18</b> or <b>19</b>
1	<b>13</b>	LAH (3.0), Et <sub>2</sub> O -25 °C, 12 h	45 (60 <sup>a</sup> )	15 ( <b>18</b> )
2	<b>13</b>	LiEt <sub>3</sub> BH (3.0), THF 0 °C, 12 h	b	NA
3	<b>13</b>	LiAlH(OMe) <sub>3</sub> , CuI THF, 0 °C, 12 h	b	NA
4	<b>13</b>	LiH <sub>3</sub> BNMe <sub>2</sub> , Et <sub>3</sub> B THF, 65 °C, 12 h	c	NA
5	<b>13</b>	NaBH <sub>4</sub> , DMSO 50 °C, 24 h	71, <40 <sup>d</sup>	NA
6	<b>14</b>	LAH (3.0), Et <sub>2</sub> O 0 °C, 1 h; rt, 1 h	e	NA
7	<b>14</b>	LiEt <sub>3</sub> BH (3.0), THF rt, 12 h	e	NA
8	<b>15</b>	LAH (3.0), Et <sub>2</sub> O 0 °C, 3 h	50	24 ( <b>18</b> ) 4 ( <b>19</b> )
9	<b>15</b>	LAH (3.0), Et <sub>2</sub> O -25 °C, 12 h	53	NA
10	<b>15</b>	LAH (1.2), Et <sub>2</sub> O 0 °C, 12 h	35 (62 <sup>a</sup> )	5 ( <b>18</b> ) 2 ( <b>19</b> )
11	<b>15</b>	LiEt <sub>3</sub> BH (3.0), THF rt, 24 h	23 <sup>e</sup>	NA
12	<b>16</b>	5% Pd/C (20%) EtOAc, 12 h	38 <sup>f</sup>	NA
13	<b>16</b>	NaBH <sub>4</sub> , DMSO, 50 °C 24 h	e	NA
14	<b>16</b>	LiEt <sub>3</sub> BH (3.0), THF 0 °C, 2 h	80-91	5-12 ( <b>20</b> )

<sup>a</sup>Yield was calculated based on recovered starting material. <sup>b</sup>Only starting material was recovered. <sup>c</sup>Complex mixture. <sup>d</sup>900 mg scale. <sup>e</sup>Decomposition observed. <sup>f</sup>The yield was calculated based on <sup>1</sup>H NMR analysis of the crude reaction mixture; see text.

Substrates **13-16** were subjected to different conditions of reductive cleavage of the C-X bond (Table 3). When **13** was first exposed to 3.0 equivalents of LAH at -25 °C, compound **17** was obtained in 45% yield (60% based on recovered starting material). A 15% yield of overreduction product **18** was isolated (entry 1). Compound **13** reacted very slowly upon treatment of LiEt<sub>3</sub>BH or LiAlH(OMe)<sub>3</sub> combined with CuI<sup>12</sup> (entries 2 and 3). An unidentified complex mixture was obtained when **13** was treated with lithium dimethylaminoborohydride and 20% Et<sub>3</sub>B<sup>13</sup> (entry 4). NaBH<sub>4</sub> dissolved in DMSO<sup>14</sup> was also applied to the deoxygenation of **13**. A 71% yield of **17** was obtained in a small-scale reaction, but the yield dropped precipitously on a larger scale. When sulfonate **14**<sup>15</sup> was treated with either LAH or LiBHEt<sub>3</sub>, only decomposition of starting material was observed (entries 6 and 7). When tosylate **15** was subjected to

reaction with LAH at 0 °C, significant amounts of over-reduction products **18** and **19** were isolated (entry 8).<sup>16</sup> A lower temperature (-25 °C) and lower loading of LAH suppressed the side reactions leading to these compounds (entries 9 and 10), but the yield of **17** was still not satisfactory. Decomposition of **15** was observed when it was reacted with LiEt<sub>3</sub>BH (entry 11).

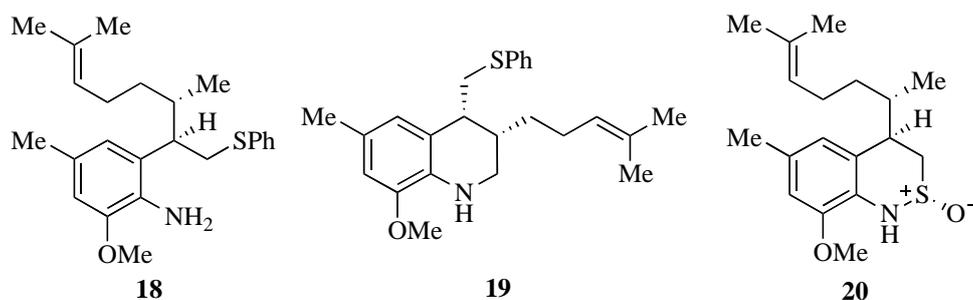
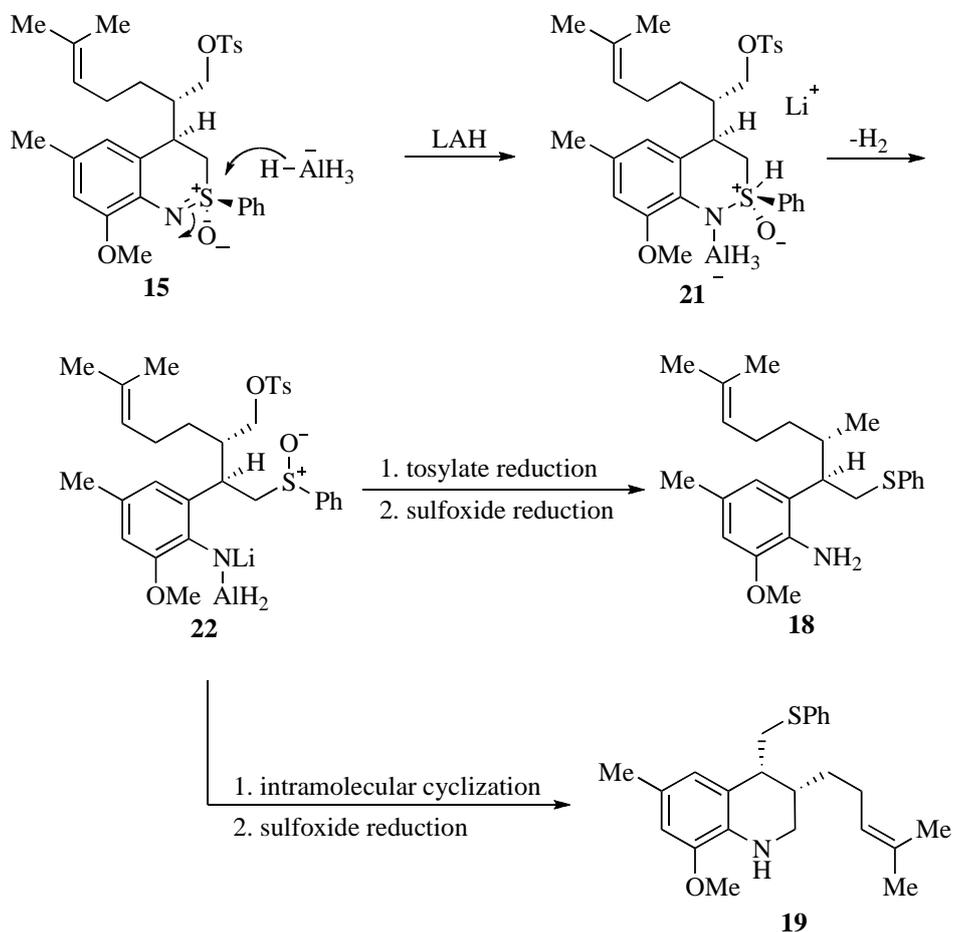


Figure 3

Alkyl iodide **16** was first subjected to catalytic hydrogenolysis.<sup>17</sup> Only a 38% conversion to product was observed through <sup>1</sup>H NMR analysis of crude reaction mixtures (entry 12). Heating **16** in the presence of

Scheme 3. Formation of **18** and **19**

NaBH<sub>4</sub> in DMSO resulted in the decomposition of starting material (entry 13). However, treatment with 3.0 equivalents of LiEt<sub>3</sub>BH at 0 °C for 2 h afforded **17** in up to 91% yield, together with 5-12% of sulfonamide **20**.<sup>18</sup> This reaction was generally very clean and was easily scaled up to gram-scale.

A possible mechanism for the formation of byproducts **18** and **19** is shown in Scheme 3. Based on proposed mechanisms for the LAH reduction of sulfones and sulfoxides,<sup>19</sup> we suggest that reduction might occur through initial S-N bond cleavage to afford **22**. Tosylate reduction followed by sulfoxide reduction would afford **18**. If displacement of the leaving group at the nascent C-11 methyl group has not yet occurred, cyclization is possible and subsequent sulfoxide reduction would give **19**. The exact timing of tosylate reduction is open to question, but formation of an anilide must presumably precede reduction during the formation of **19**.

If reagents and reaction conditions could be manipulated to selectively produce **18** or **19**, a powerful methodology for the synthesis of such compounds would be available.

## CONCLUSION

We have developed a reliable 6-step sequence to benzothiazine **17**, a key intermediate in our projected total synthesis of *seco*-pseudopteroxazole (**2**), featuring our completely stereoselective benzothiazine chemistry. Enolate protonation provided high levels of diastereoselectivity in setting the C-11 stereochemistry of **2**. The total synthesis of *seco*-pseudopteroxazole is still in progress and the results will be reported in due course.

## EXPERIMENTAL

**General.** All reactions were carried out under an atmosphere of nitrogen or argon in flamed-dried glassware. All commercial grade reagents and solvents were used as supplied with the following exceptions. Ethyl ether (Et<sub>2</sub>O), tetrahydrofuran (THF) and toluene were freshly distilled from sodium-benzophenone before use. Triethylamine, dichloromethane and acetonitrile were distilled from calcium hydride. Chromatographic separations were carried out using Silicycle ultra pure silica gel (230-400 mesh). Analytical thin layer chromatography was performed on EM reagent 0.25 mm silica gel 60-F plates with F-254 indicator. Melting points were measured with a Fisher-Johns melting point apparatus. Infrared spectra were recorded on a Thermo Nicolet NEXUS 670 FT-IR spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter with a sodium lamp and are reported as follows:  $[\alpha]_D^{25}$  (*c* g/100 mL, solvent). High-resolution mass was measured on a Bruker 12 Tesla FRICR-MS with an Apollo II ion source in Old Dominion University. Elemental analysis was performed by the MHW laboratories, Phoenix, AZ. <sup>1</sup>H and <sup>13</sup>C-NMR spectra were recorded on a Bruker ARX-250 (250 MHz), DRX-300 (300 MHz), DRX-500 (500 MHz) spectrometer. Chemical shifts were reported in ppm using tetramethylsilane (TMS; δ 0.0 ppm) as an internal standard. Data are reported as follows:

chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration.

### Preparation of (*E*)-methyl 2-(2-bromo-3-methoxy-5-methylbenzylidene)-6-methylhept-5-enoate **7**

To a stirred suspension of LiCl (2.21 g, 52.3 mmol) in dry MeCN (170 mL) under N<sub>2</sub> atmosphere at rt, were sequentially added phosphonate **6** (13.8 g, 52.3 mmol), DBU (6.5 mL, 43.6 mmol) and aldehyde **5** (10 g, 43.6 mmol). The resulting mixture was stirred for overnight (12 h) before it was diluted with EtO<sub>2</sub>C. The organic solution was washed with water and brine, then dried over MgSO<sub>4</sub>. Concentration of the solvent *in vacuo* afforded the crude product. NMR analysis of crude reaction mixture showed the ratio of *E*: *Z* isomer is 10: 1.0. Flash column chromatography (5% EtOAc/hexanes) gave 13.3 g (83%) of *E*-**7** and 1.6 g (10%) of an *E/Z* mixture. *E*-**7**: Yellow liquid; IR:  $\nu$  2945, 2851, 1715, 1572, 1425, 1323, 1258, 1090, 1029, 833 cm<sup>-1</sup>; <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  7.60 (s, 1H), 6.68 (s, 1H), 6.64 (s, 1H), 5.03 (t, *J* = 7.5 Hz, 1H), 3.84 (d, *J* = 1.9 Hz, 3H), 3.79 (d, *J* = 1.6 Hz, 3H), 2.32-2.39 (m, 2H), 2.29 (s, 3H), 2.10-2.16 (m, 2H), 1.61 (s, 3H), 1.51 (s, 3H); <sup>13</sup>C-NMR (62.5 MHz, CDCl<sub>3</sub>):  $\delta$  168.1, 155.7, 139.0, 137.7, 137.5, 134.0, 132.1, 123.4, 122.4, 112.0, 109.6, 56.1, 51.8, 27.7, 27.4, 25.5, 21.3, 17.4; HRMS calcd for C<sub>18</sub>H<sub>23</sub>BrO<sub>3</sub>Na<sup>+</sup> [M+ Na]<sup>+</sup> 389.0722, found 389.0716.

### Procedure for Buchwald-Hartwig coupling reaction

To a 500 mL round bottomed flask equipped with a reflux condenser under N<sub>2</sub> atmosphere were sequentially added bromoester **7** (10 g, 27.2 mmol), *R*-sulfoximine **8** (5.0 g, 32.6 mmol), Pd(OAc)<sub>2</sub> (312 mg, 1.36 mmol), *rac*-BINAP (1.31 g, 2.04 mmol), Cs<sub>2</sub>CO<sub>3</sub> (12.4 g, 38.0 mmol) and then toluene (270 mL). The reaction mixture was heated in an oil bath at 110-115 °C for 50 hr. The solution was cooled to rt and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic solution was filtered through a pad of Celite. Concentration of solvent *in vacuo* afforded the crude product as brown oil. Purification of the product was carried out by flash chromatography (30% EtOAc/hexane) afforded **9** as a pale yellow semi-solid 12.0 g (99%). IR:  $\nu$  2929, 1703, 1462, 1335, 1258, 1204, 1160, 1090, 739 cm<sup>-1</sup>; <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  8.06 (s, 1H), 8.00-8.04 (m, 2H), 7.47-7.57 (m, 3H), 6.77 (s, 1H), 6.60 (d, *J* = 1.3 Hz, 1H), 5.17 (tt, *J* = 7.3, 1.3 Hz, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 3.12 (s, 3H), 2.46-2.52 (m, 2H), 2.28 (s, 3H), 2.22-2.25 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H); <sup>13</sup>C-NMR (62.5 MHz, CDCl<sub>3</sub>):  $\delta$  169.0, 151.9, 142.6, 139.1, 132.3, 131.9, 131.8, 131.5, 130.0, 128.8, 127.4, 123.8, 122.0, 112.9, 55.4, 51.6, 46.0, 28.0, 27.8, 25.6, 21.2, 17.6; HRMS calcd for C<sub>25</sub>H<sub>31</sub>NO<sub>4</sub>SNa<sup>+</sup> [M+ Na]<sup>+</sup> 464.1849, found 464.1849; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +15.66 (c 1.66, acetone).

### Procedure for the intramolecular Michael reaction

To a 1 L round bottom flask under N<sub>2</sub> atmosphere were added **9** (9.6 g, 21.7 mmol) and THF (430 mL).

The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  before it was added dropwise LiHMDS (1.0 M in THF, 43 mL, 43.4 mmol). The stirring was continued for 1 h. The mixture was vigorously stirring with the rapid addition of a cold 1N HCl in MeOH solution, which was precooled to  $-78\text{ }^{\circ}\text{C}$ . The resulting mixture was warmed to rt and diluted with EtOAc and  $\text{H}_2\text{O}$ . The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over  $\text{MgSO}_4$ . Concentration of solvent *in vacuo* afforded crude product (*d.r.* 9.2: 1.0). Purification was carried out using column chromatography (30% EtOAc/hexane) to afford 9.5 g of **10** (> 99%). **10**: Yellow foam; IR:  $\nu$  2929, 1732, 1458, 1254, 1159, 1012, 747  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.11 (d,  $J = 7.8$  Hz, 2H), 7.50-7.65 (m, 3H), 6.68 (s, 1H), 6.60 (s, 1H), 4.96 (t,  $J = 7.0$  Hz, 1H), 3.86 (s, 3H), 3.52-3.58 (m, 2H), 3.37 (s, 3H), 3.29-3.37 (m, 1H), 3.11-3.20 (m, 1H), 2.30 (s, 3H), 1.85-1.91 (m, 2H), 1.65 (s, 3H), 1.56-1.62 (m, 1H), 1.52 (s, 3H), 1.45-1.52 (m, 1H);  $^{13}\text{C-NMR}$  (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  174.9, 152.7, 139.5, 133.3, 132.6, 131.4, 130.2, 129.1, 129.0, 125.3, 122.7, 120.1, 111.9, 55.9, 52.4, 51.2, 44.3, 38.5, 31.4, 25.6, 21.3, 17.5; HRMS caclcd for  $\text{C}_{25}\text{H}_{31}\text{NO}_4\text{SNa}^+ [\text{M} + \text{Na}]^+$  464.1866, found 464.1853.

#### Procedure for $\text{LiEt}_3\text{BH}$ reduction of ester **10**

In a 300 mL flask were placed **10** (3.6 g, 8.15 mmol) and THF (160 mL). The flask was cooled to  $0\text{ }^{\circ}\text{C}$  with ice cooling.  $\text{LiEt}_3\text{BH}$  (1.0 M in THF, 24.4 mL, 24.4 mmol) was added dropwise in 30 min with vigorous stirring. The stirring was continued for an additional 30 min. The reaction was quenched by sequential addition of MeOH, 1 N NaOH and 30%  $\text{H}_2\text{O}_2$ . The resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic extract was washed with  $\text{H}_2\text{O}$  and brine. The organic extract was dried over  $\text{MgSO}_4$ . Concentration of solvent *in vacuo* afforded **12** (3.4 g, >99% yield), which was pure enough to carry out next step without further purification. **12**: Yellow semi-solid; IR:  $\nu$  3440, 2925, 1470, 1249  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.01 (d,  $J = 7.2$  Hz, 2H), 7.43-7.59 (m, 3H), 6.64 (s, 1H), 6.59 (s, 1H), 5.03 (t,  $J = 7.1$  Hz, 1H), 3.82 (s, 3H), 3.48-3.54 (m, 1H), 3.30-3.43 (m, 3H), 3.15-3.21 (m, 1H), 2.28 (s, 3H), 2.24-2.33 (m, 2H), 1.94-2.03 (m, 2H), 1.66 (s, 3H), 1.54 (s, 3H), 1.24-1.36 (m, 2H);  $^{13}\text{C-NMR}$  (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.3, 139.1, 133.4, 132.1, 131.9, 129.6, 129.0, 129.0, 126.1, 123.8, 118.9, 111.1, 61.4, 55.8, 49.9, 38.4, 29.3, 25.6, 21.4, 17.6; HRMS caclcd for  $\text{C}_{24}\text{H}_{32}\text{NO}_3\text{S}^+ \text{M}^+$  414.2097, found 414.2097.

#### Procedure for the preparation of sulfonate ester **13**, **14** and **15**

To the dichloromethane solution (17 mL) of alcohol **12** (360 mg, 0.87 mmol) were successively added sulfonyl chloride (1.30 mmol), DMAP (10.6 mg, 0.09 mmol) and TEA (365  $\mu\text{L}$ , 2.60 mmol). The resulting mixture was stirred at rt for a few hours before it was diluted with water. The organic layer was washed with brine and dried over  $\text{MgSO}_4$ . Flash chromatography (50% EtOAc/hexane) provided the

desired sulfonate ester.

**13:** Yellow oil, 87% yield; IR:  $\nu$  2929, 1462, 1254, 1168  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.11 (d,  $J = 8.0$  Hz, 2H), 7.53-7.69 (m, 3H), 6.70 (s, 1H), 6.59 (s, 1H), 5.04 (t,  $J = 6.5$  Hz, 1H), 4.17-4.21 (m, 1H), 3.85-3.93 (m, 1H), 3.88 (s, 3H), 3.42-3.46 (m, 2H), 3.14 (dd,  $J = 13.7, 9.5$  Hz, 1H), 2.87 (s, 3H), 2.65-2.67 (m, 1H), 2.33 (s, 3H), 2.03-2.10 (2H), 1.70 (s, 3H), 1.44-1.70 (m, 2H), 1.59 (s, 3H);  $^{13}\text{C-NMR}$  (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.7, 138.8, 133.8, 132.8, 132.0, 130.1, 129.3, 129.1, 124.7, 122.8, 118.7, 111.5, 68.7, 55.9, 49.4, 37.0, 36.4, 36.1, 29.1, 25.6, 25.2, 21.4, 17.7; HRMS calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_5\text{S}_2\text{Na}^+ [\text{M}+\text{Na}]^+$  514.1692, found 514.1695.

**14:** Yellow solid, 95% yield, mp 103-4  $^\circ\text{C}$ ; IR:  $\nu$  2929, 1462, 1331, 1254, 1151  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.08-8.11 (m, 2H), 7.54-7.66 (m, 3H), 6.70 (d,  $J = 1.2$  Hz, 1H), 6.59 (s, 1H), 5.04 (td,  $J = 7.0, 1.5$  Hz, 1H), 4.14-4.19 (m, 1H), 3.89-3.92 (m, 1H), 3.89 (s, 3H), 3.41-3.47 (m, 2H), 3.12-3.21 (m, 2H), 2.60-2.70 (m, 1H), 2.33 (s, 3H), 2.02-2.15 (m, 2H),  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.7, 138.9, 133.8, 132.8, 132.0, 130.1, 129.3, 129.0, 124.9, 122.9, 118.8, 111.5, 67.7, 56.0, 52.0, 49.5, 36.4, 36.2, 29.3, 25.7, 25.3, 21.4, 17.7, 16.5, 16.4; HRMS calcd for  $\text{C}_{27}\text{H}_{37}\text{NO}_5\text{S}_2\text{Na}^+ [\text{M}+\text{Na}]^+$  542.2005, found 524.2004.

**15:** Yellow foam, 87% yield. IR:  $\nu$  2913, 1450, 1168, 1086  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02 (d,  $J = 7.4$  Hz, 2H), 7.48-7.65 (m, 5H), 7.24 (d,  $J = 8.1$  Hz, 2H), 6.65 (s, 1H), 6.46 (s, 1H), 4.91 (t,  $J = 6.7$  Hz, 1H), 3.90 (dd,  $J = 10.3, 3.0$  Hz, 1H), 3.85 (s, 3H), 3.63 (dd,  $J = 10.0, 4.3$  Hz, 1H), 3.28-3.38 (m, 2H), 2.99-3.09 (m, 1H), 2.42-2.50 (m, 1H), 2.39 (s, 3H), 2.26 (s, 3H), 1.83-1.89 (m, 2H), 1.64 (s, 3H), 1.47 (s, 3H), 1.22-1.55 (m, 2H);  $^{13}\text{C-NMR}$  (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.6, 144.9, 138.9, 133.7, 132.5, 132.2, 131.8, 130.1, 129.8, 129.2, 129.0, 127.6, 124.9, 122.9, 119.0, 111.5, 69.0, 55.9, 49.8, 36.5, 36.0, 28.9, 25.6, 25.1, 21.5, 21.3, 17.6.

### Procedure for the preparation of iodide 16

To a stirred, cooled (0  $^\circ\text{C}$ ) MeCN (30 mL) and Et<sub>2</sub>O (30 mL) mixture were successively added **12** (3.30 g, 8.15 mmol), triphenylphosphine (4.27 g, 16.3 mmol) and imidazole (1.11 g, 16.3 mmol). Iodine (4.10 g, 16.3 mmol) was slowly added. After the resulting pale yellow suspension was stirred for 5 hr (monitored by TLC), the reaction mixture was diluted with ether and sequentially washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, saturated aqueous CuSO<sub>4</sub> and water. The organic layer was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford crude iodide. Flash chromatography (30% EtOAc/hexanes) gave 3.79 g of desired iodide **16** (89% over the two steps). Yellow seimi-solid; IR:  $\nu$  2921, 1462, 1254, 1151, 1017, 747  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.12 (d,  $J = 7.9$  Hz, 2H), 7.51-7.67 (m, 3H), 6.70 (s, 1H), 6.55 (s, 1H), 4.97 (t,  $J = 7.0$  Hz, 1H), 3.88 (s, 3H), 3.42 (d,  $J = 5.3$  Hz, 2H), 3.09-3.14 (m, 2H), 2.51 (dd,  $J = 10.4, 5.7$  Hz, 1H), 2.33 (s, 3H), 1.80-1.96 (m, 3H), 1.68 (s, 3H), 1.55 (s, 3H), 1.23-1.52 (m, 2H);

$^{13}\text{C}$ -NMR (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.9, 139.4, 133.7, 132.4, 131.6, 130.5, 129.3, 129.0, 125.7, 123.0, 120.3, 111.7, 56.0, 50.7, 40.6, 36.5, 31.8, 25.7, 25.1, 21.3, 17.7, 11.1; HRMS caclcd for  $\text{C}_{24}\text{H}_{31}\text{INO}_2\text{S}^+ \text{M}^+$  524.1114, found 524.1109.

### Procedure for the preparation of **17**

In a 300 mL flask were placed iodide **16** (4.62 g, 8.82 mmol) and THF (175 mL). The flask was immersed into an ice bath (0 °C).  $\text{LiEt}_3\text{BH}$  (1.0 M in THF, 26.3 mL, 26.3 mmol) was added dropwise in 50 mins using syringe pump (0.49 mL/min) with vigorous stirring. After addition was complete, stirring was continued for an additional 1 hr. The reaction was quenched by sequential addition of MeOH, 1 N NaOH and 30%  $\text{H}_2\text{O}_2$ . The reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with  $\text{H}_2\text{O}$  and brine. The combined organic layer was dried over  $\text{MgSO}_4$ . Concentration of solvent *in vacuo* afforded crude **17**. Flash chromatography (30% EtOAc/Hexane) afforded 3.19 g of **17** (91% yield) and 260 mg of **20** (*ca.* 10% yield). **17**: Yellow semi-solid; IR:  $\nu$  2913, 1458, 1241, 1012  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H}$ -NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.08-8.12 (m, 2H), 7.52-7.67 (m, 3H), 6.68 (s, 2H), 5.12 (tt,  $J = 7.1, 1.3$  Hz, 1H), 3.89 (s, 3H), 3.30-3.44 (m, 2H), 2.85 (t,  $J = 12.0$  Hz, 1H), 2.49-2.56 (m, 1H), 2.34 (s, 3H), 2.03-2.09 (m, 2H), 1.71 (s, 3H), 1.62 (s, 3H), 1.27-1.51 (m, 2H), 0.80 (d,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$ -NMR (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.2, 139.2, 133.5, 132.3, 131.9, 129.4, 129.1, 125.7, 123.8, 118.3, 110.9, 55.9, 47.9, 40.2, 38.0, 35.2, 31.4, 25.8, 25.6, 21.4, 17.6, 14.7; HRMS caclcd for  $\text{C}_{24}\text{H}_{31}\text{NO}_2\text{SNa}^+ [\text{M}+\text{Na}]^+$  420.1967, found 420.1958.

**Byproduct 18**: Red oil; *d.r.*: 3.3: 1.0; IR:  $\nu$  3444, 3366, 2913, 1585, 1486, 1290, 1160, 735  $\text{cm}^{-1}$ ; major isomer:  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.25-7.32 (m, 4H), 7.16 (t,  $J = 7.0$  Hz, 1H), 6.53 (s, 2H), 5.02 (t,  $J = 6.8$  Hz, 1H), 3.86 (s, 3H), 3.64 (s, 2H,  $\text{NH}_2$ ), 3.43 (dd,  $J = 12.2, 4.2$  Hz, 1H), 3.20 (dd,  $J = 12.5, 10.5$  Hz, 1H), 2.89 (ddd,  $J = 10.6, 6.8, 3.8$  Hz, 1H), 2.29 (s, 3H), 1.85-2.0 (m, 5H), 1.68 (s, 3H), 1.56 (s, 3H), 1.38-1.40 (m, 1H), 1.13-1.17 (m, 1H), 1.03 (d,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  147.4, 137.4, 132.0, 131.4, 128.8, 128.7, 127.9, 127.0, 125.5, 124.5, 119.6, 109.0, 55.3, 43.5, 36.5, 36.4, 34.3, 25.6, 25.4, 21.3, 17.5, 16.8; HRMS caclcd for  $\text{C}_{24}\text{H}_{33}\text{NOSNa}^+ [\text{M}+\text{Na}]^+$  406.2175, found 406.2165.

The presence of  $\text{NH}_2$  group was clearly shown in IR spectrum (doublet: 3444, 3366  $\text{cm}^{-1}$ ). A peak of doublet at 1.03 ppm with coupling constant of 6.5 Hz indicated that the tosylate group was cleaved. Furthermore, a careful comparison of proton NMR of desired product **17**, a lower chemical shift of *S*-phenyl group (7.15-7.32 ppm in **18**, as compared 7.52-8.12 ppm in **17**) suggested the more shielding from sulfur atom, and thus low valence of sulfur in the molecule, which was later confirmed to be thiophenyl ether by the high resolution mass spectrum. Thus, the structure of **18** was assigned.

**Byproduct 19:** Red liquid; single diastereomer; IR: 3423, 2908, 1585, 1507, 1262, 1102, 833, 735, 690  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.13-7.37 (m, 5H), 6.55 (s, 1H), 6.49 (d,  $J = 1.4$  Hz, 1H), 5.10 (td,  $J = 7.0, 1.3$  Hz, 1H), 4.17 (s, 1H), 3.81 (s, 3H), 3.36 (ddd,  $J = 11.5, 4.2, 1.2$  Hz, 1H), 3.22 (dd,  $J = 11.8, 10.3$  Hz, 1H), 3.21 (dd,  $J = 12.0, 4.7$  Hz, 1H), 3.05-3.09 (m, 1H), 3.02-3.05 (m, 1H), 2.25 (s, 3H), 2.02-2.10 (m, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.25-1.55 (m, 2H);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  145.9, 137.3, 131.8, 130.6, 129.0, 128.7, 125.6, 124.2, 124.0, 123.2, 121.6, 109.1, 55.3, 42.9, 39.4, 35.3, 34.9, 29.5, 25.7, 25.6, 20.9, 17.6; HRMS calcd for  $\text{C}_{24}\text{H}_{31}\text{NOSNa}^+ [\text{M}+\text{Na}]^+$  404.2018, found 404.2014.

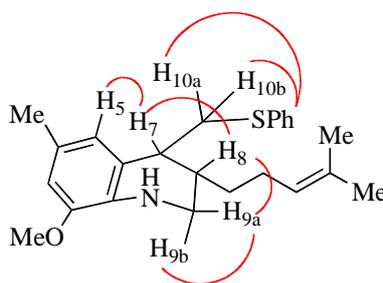


Figure 4. Key NOE Correlations of **19**

The structure of minor byproduct **19** was assigned based on the extensive NMR studies. Coupling constants of  $\text{H}_9$  and  $\text{H}_{10}$  were calculated based on 2D J-resolved NMR spectrum. As shown in  $^1\text{H-NMR}$ , the sulfoximine moiety was reduced as clearly indicated by the lower chemical shift of *S*-phenyl group. The absence of tosylate group and no distinct doublet around 1.00 ppm (methyl group), together with the evidence of free NH group, suggested the presence of tetrahydroquinoline moiety in the molecule. The attempts to calculate the coupling constants of  $\text{H}_7$  based on the  $^1\text{H-NMR}$  turned out to be fruitless, because  $\text{H}_7$  overlapped with  $\text{H}_{10a}$  and the spectrum turned into second-order spectrum ( $\Delta\delta/J$ : 1.87). Thus, the stereochemistry of  $\text{H}_7$  and  $\text{H}_8$  were assigned based on the stereochemistry of the starting material. The structural assignment was also supported by NOESY experiment (Figure 4).

## ACKNOWLEDGEMENTS

We are grateful to the National Institutes of Health (1R01-AI59000-01A1).

## REFERENCES

1. (a) M. Harmata, X. Hong, and C. L. Barnes, *Org. Lett.*, 2004, **6**, 2201. (b) M. Harmata and X. Hong, *Org. Lett.*, 2005, **7**, 3581.
2. M. Harmata and X. Hong, *J. Am. Chem. Soc.*, 2003, **125**, 5754.
3. A. D. Rodriguez, C. Ramirez, I. I. Rodriguez, and E. Gonzalez, *Org. Lett.*, 1999, **1**, 527.
4. G. Qabaja and G. B. Jones, *J. Org. Chem.*, 2000, **65**, 7187.

5. (a) W. Biernacki and A. Gdula, [Synthesis, 1979, 37](#). (b) Z. Liu, W. Z. Li, L. Peng, Y. Li, and Y. Li, [J. Chem. Soc., Perkin Trans. 1, 2000, 4250](#).
6. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essinfeld, S. Masamune, W. R. Roush, and T. Sakai, [Tetrahedron Lett., 1984, 25, 2183](#).
7. (a) C. Bolm and J. P. Hildebrand, [Tetrahedron Lett., 1998, 39, 5731](#). (b) C. Bolm and J. P. Hildebrand, [J. Org. Chem., 2000, 65, 169](#). (c) M. Harmata and N. Pavri, [Angew. Chem. Int. Ed., 1999, 38, 2419](#).
8. R. Chow, P. J. Kocienski, A. Kuhl, J.-Y. LeBrazidec, K. Muir, and P. Fish, [J. Chem. Soc., Perkin Trans. 1, 2001, 2344](#).
9. V. Gevorgyan, M. Rubin, J. X. Liu, and Y. Yamamoto, [J. Org. Chem., 2001, 66, 1672](#).
10. S. Krishnamurthy and H. C. Brown, [J. Org. Chem., 1976, 41, 3064](#).
11. J. A. Marshall and D. G. Cleary, [J. Org. Chem., 1986, 51, 858](#).
12. S. Masamune, P. A. Rossy, and G. S. Bates, [J. Am. Chem. Soc., 1973, 95, 6452](#).
13. S. Thomas, T. Huynh, V. Enriquez-Rios, and B. Singaram, [Org. Lett., 2001, 3, 3915](#).
14. H. M. Bell, C. W. Vanderslice, and A. Spehar, [J. Org. Chem., 1969, 34, 3923](#).
15. D. H. Hua, G. Sinai-Zingde, and S. Venkataraman, [J. Am. Chem. Soc., 1985, 107, 4088](#).
16. The structures of these side products were assigned on the basis of one and two-dimensional NMR data. See experimental section.
17. A. H. G. Siebum, W. S. Woo, and J. Lugtenburg, [Eur. J. Org. Chem., 2003, 4664](#).
18. M. Harmata and P. Zheng, [Org. Lett., 2007, 9, 5251](#).
19. (a) T. A. Whitney and D. J. Cram, [J. Org. Chem., 1970, 35, 3964](#). (b) F. G. Bordwell and W. H. McKellin, [J. Am. Chem. Soc., 1951, 73, 2251](#).