

# A Cyclopropanol-Based Strategy for Subunit Coupling: Total Synthesis of (+)-Spirolaxine Methyl Ether

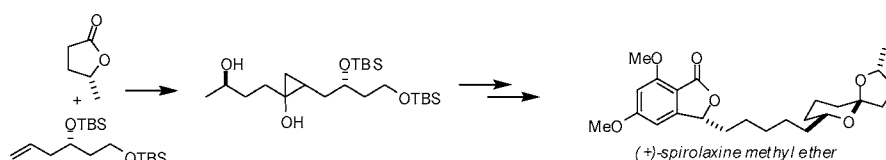
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## ABSTRACT



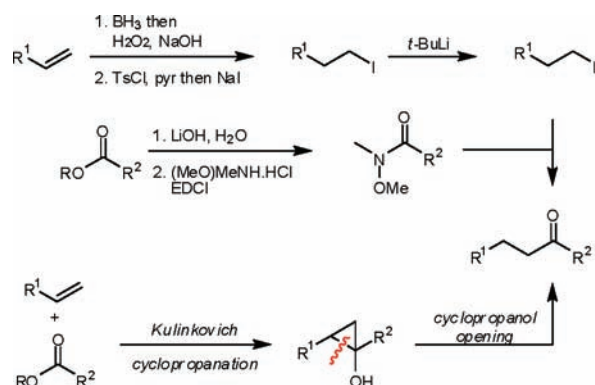
A strategy for ketone synthesis with cyclopropanols as intermediates and its application to (+)-spirolaxine methyl ether is described. The synthesis also features an application of Fu's alkyl–alkyl Suzuki coupling.

In the course of studies directed toward the synthesis of polyketide natural products, we sought a convenient method for the reductive coupling of an olefin with an ester. Although current dogma dictates that this process is best achieved by a multistep sequence involving conversion of the olefin to a main group organometallic and reaction with a Weinreb amide, we were attracted to a straightforward alternative that consists of sequencing a Kulinkovich cyclopropanation<sup>1,2</sup> and subsequent cyclopropanol opening (Scheme 1).<sup>3–5</sup>

Our initial studies focused on the combination of olefin **1** with ethyl acetate (Scheme 2). Although a variety of conditions for the Kulinkovich reaction are known, the straightforward application of cyclohexylmagnesium bromide<sup>6</sup> as reductant in the presence of  $\text{Ti}(i\text{-PrO})_4$  was effective

in producing **2**.<sup>7</sup> After exploring acidic and basic conditions for the opening of cyclopropanol **2**, we settled on the  $\text{Fe}(\text{III})$ -based conditions first promulgated by DePuy<sup>8</sup> and Saegusa.<sup>9,10</sup> In the presence of  $\text{Bu}_3\text{SnH}$ ,  $\text{Fe}(\text{NO}_3)_3$  provided **3** in 86% yield. Other hydrogen atom or hydride donors<sup>11</sup> such as 1,3-cyclohexadiene or  $\text{Et}_3\text{SiH}$  were also suitable, although with lower yield in this example (50 and 37%, respectively).

Scheme 1



(1) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Priytskaya, T. S. *Zh. Org. Chim.* **1989**, 25, 2244. (b) Cha, J. K.; Kim, H.; Lee, J. *J. Am. Chem. Soc.* **1996**, 118, 4198.

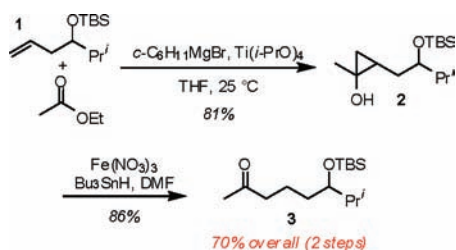
(2) For review of the Kulinkovich cyclopropanation, see: de Meijere, A.; Kulinkovich, O. G. *Chem. Rev.* **2000**, 100, 2789.

(3) A substantial portion of the early work on cyclopropanols was carried out by DePuy and co-workers. For a review, see: Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, 74, 605.

(4) For a recent review of the chemistry of cyclopropanols, see: Kulinkovich, O. G. *Chem. Rev.* **2003**, 103, 2597.

(5) For other examples of  $\text{Ti}$ -based subunit couplings, see: (a) Keaton, K. A.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, 128, 408. (b) Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, 46, 1440.

Scheme 2

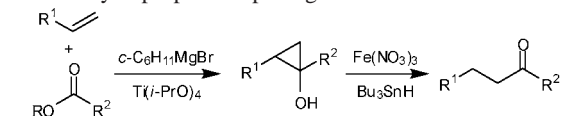


Some measure of the utility of this reaction for the acylation of other homoallylic alcohols is provided in Table 1. As can be seen from this survey presented, there is tolerance of simple functionality, and the yields for the two-step process range from ~50 to 80% (an average of 75–90% each step).

In parallel studies, we have applied this strategy to a remarkably direct synthesis of the spiroketal domain of (+)-spiroloxine methyl ether (Scheme 3) en route to a total synthesis.<sup>12</sup> The spiroloxines were isolated from various strains of white rot fungi (genera *Sporotrichum* and *Phanerochaete*) and have potent activity against *Helicobacter pylori*.<sup>13</sup> Spiroloxine **1** has also been reported to lower cholesterol and to inhibit the growth a variety of cell lines.<sup>14</sup> Some recent attention from the synthesis community has resulted in total syntheses of (+)-spiroloxine methyl ether by Brimble and co-workers<sup>15</sup> and Dallavalle and co-workers.<sup>16</sup>

The synthesis commences with the coupling of readily available olefin **4**<sup>17</sup> with commercially available (*R*)- $\gamma$ -

Table 1. Ketone Synthesis by Kulinkovich Reaction—Cyclopropanol Opening



entry	starting material	product	yield
1			62
2			76
3			52
4			60
5 <sup>a</sup>			66
6			61
7			77
8 <sup>a,b</sup>			62

<sup>a</sup> *c*-C<sub>6</sub>H<sub>11</sub>MgBr (6 equiv), Ti(*i*-PrO)<sub>4</sub> (3 equiv), PhMe, 25 °C. <sup>b</sup> The acylating agent was methyl isobutyrate.

- (6) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.  
 (7) The Kulinkovich cyclopropanation generally provides *cis*-cyclopropanols, although more highly substituted substrates can give mixtures of *cis*- and *trans*-cyclopropanols. For mechanistic studies, see: (a) Casey, C. P.; Strotman, N. A. *J. Am. Chem. Soc.* **2004**, *126*, 1699. (b) Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem. Soc.* **2001**, *123*, 5777.  
 (8) DePuy, C. H.; Van Lanen, R. J. *J. Org. Chem.* **1974**, *39*, 3360.  
 (9) It is known that FeCl<sub>3</sub> and Fe(NO<sub>3</sub>)<sub>3</sub> cleave (trimethylsilyl) cyclopropanols to give the enone or the  $\beta$ -chloroketone: (a) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073. (b) Blanco, L.; Mansour, A. *Tetrahedron Lett.* **1988**, *29*, 3239. (c) For the opening and subsequent 5-*exo* cyclization of trimethylsilylcyclopropanol-derived radicals, see: Booker-Milburn, K. I.; Jones, L. J.; Sibley, G. E. M.; Cox, R.; Meadows, J. *Org. Lett.* **2003**, *5*, 1107 and references cited therein.  
 (10) (a) For the photosensitized oxidation and opening of aminocyclopropanes, see: Lee, H. B.; Sung, M. J.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 11322. (b) For the opening of cyclopropanols to enones, see: Lysenko, I. L.; Lee, H. G.; Cha, J. K. *Org. Lett.* **2006**, *8*, 2671.  
 (11) Two possible limiting scenarios can be envisaged: radical opening of the cyclopropanol to give the  $\beta$ -keto radical and subsequent reaction with Bu<sub>3</sub>SnH or oxidation of the  $\beta$ -keto radical to the cation and then reaction with Bu<sub>3</sub>SnH in a polar manifold. Mechanistic studies will be reported in due course.

- (12) (a) Arnone, A.; Assante, G.; Nasini, G.; Vajna de Pava, O. *Phytochemistry* **1990**, *29*, 613. (b) Gaudiana, M. A.; Huang, L. H.; Kaneko, T.; Watts, P. C. PCT Int. Appl. W0 9605204, 1996. (c) Adachi, T.; Takagi, I.; Kondo, K.; Kawashima, A.; Kobayashi, A.; Taneoka, I.; Morimoto, S.; Hi, B. M.; Chen, Z. PCT Int. Appl. W0 9610020, 1996.  
 (13) (a) Blaser, M. J. *Clin. Infect. Dis.* **1992**, *15*, 386. (b) Walsh, J. H.; Peterson, W. L. *New Engl. J. Med.* **1995**, *333*, 984. (c) Rathbone, B. *Scrip Magazine* **1993**, 25.  
 (14) Bava, A.; Clericuzio, M.; Giannini, G.; Malpezzi, L.; Valdo Meille, S.; Nasini, G. *Eur. J. Org. Chem.* **2005**, 2292.  
 (15) Robinson, J. E.; Brimble, M. A. *Chem. Commun.* **2005**, 1560.

valerolactone in the presence of cyclohexylmagnesium bromide and Ti(*i*-PrO)<sub>4</sub> in toluene at room temperature to afford cyclopropanol **5** in 92% yield (Scheme 3). Immediate exposure of this material to Fe(NO<sub>3</sub>)<sub>3</sub> and Bu<sub>3</sub>SnH provided ketone **6** in 75% yield. Removal of the TBS ethers and concomitant cyclic ketal formation proceeded smoothly upon exposure of **6** to HF to yield **7** (89%). Subsequent Appel reaction with NBS and PPh<sub>3</sub> proceeded in quantitative yield to give primary bromide **8**.

At this juncture, we were presented with an opportunity to evaluate the alkyl–alkyl Suzuki coupling recently reported by Fu for the union of the two halves of the target.<sup>18</sup> To this end, a solution of olefin **11** in THF (prepared from **9** by

- (16) Nannei, R.; Dallavalle, S.; Merlini, L.; Bava, A.; Nasini, G. *J. Org. Chem.* **2006**, *71*, 6277.  
 (17) Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J.; White, J. D. *J. Org. Chem.* **2005**, *70*, 5449.  
 (18) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.  
 (19) This material was identical to the reported data for (+)-spiroloxine methyl ether (see refs 12 and 15).

In conclusion, we have described a new strategy for the synthesis of ketones and its application to a very concise synthesis of spiroloxine methyl ether. As well as highlighting the utility of this approach for subunit couplings, the synthesis also features a complex example of Fu's alkyl-alkyl Suzuki coupling.

**Supporting Information Available:** Experimental procedures, characterization data, and copies of spectra for compounds **3** and **5–12**, spirolaxine and the final compounds in Table 1. This material is available free of charge via the Internet at <http://pubs.acs.org>.