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## A formal total synthesis of *anti-Helicobacter pylori* agent (+)-spiroloxine methyl ether

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### ABSTRACT

A convergent, formal enantioselective synthesis of *anti-Helicobacter pylori* agent, (+)-spiroloxine methyl ether **2** has been achieved in high enantiomeric purity starting from commercially available 1,5-pentane-diol. The strategy mainly comprises of the Noyori's asymmetric reduction and Brown allylation/Cu-catalyzed lactonization as the key step for the construction of key chiral intermediates, spiroketal **3** and phthalide fragment **4**.

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### Introduction

*Helicobacter pylori* is a Gram-negative microaerophilic bacterium that has infected a significant proportion of the human population.<sup>1,2</sup> Its helical shape is believed to have evolved to penetrate the mucoid lining of the stomach.<sup>3</sup> It is also the primary agent responsible for gastric and duodenal ulcers and has been further linked with distal gastric cancer and mucose-associated lymphoid tissue (MALT) lymphoma.<sup>4,5</sup> The current treatments for *H. pylori* infections are not able to completely remove the bacteria, providing opportunity to investigate new structural units that are potent helicobacterial compounds (see Fig. 1).<sup>6</sup>

Spiroloxine (**1**) and its methyl ether (**2**) were isolated from various strains of white rot fungi belonging to the genera *Sporotrichum* and *Phanerochaete*.<sup>7</sup> Structurally, they contain a 7-methoxy-5-hydroxyphthalide nucleus linked through a polymethylene chain to a [6,5]-spiroacetal group. Biologically, spiroloxine and its derivative possess helicobactericidal properties and could become potential lead compounds in the development of drugs that treat gastroduodenal disorder and for the prevention of gastric cancer.<sup>8</sup> Also, spiroloxines have been reported to exhibit cholesterol-lowering activity, and cytotoxic activity toward endothelial cells as well as a variety of tumor cell lines.

Due to its unique structural features and potent biological activity, many reports on the total synthesis of spiroloxine have appeared.<sup>9</sup> Brimble's convergent approach utilizes a Julia–Kocienski

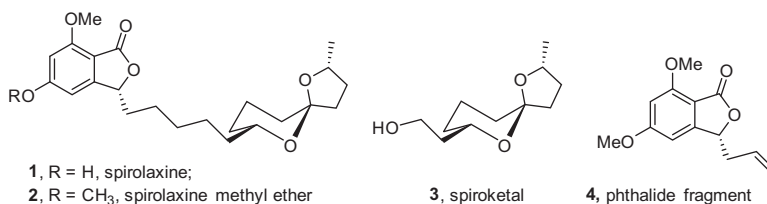
olefination to afford spiroloxine methyl ether in 16 steps from (S)-aspartic acid.<sup>9c</sup> Dallavalle et al.<sup>9a</sup> have reported a concise, 12-step total synthesis utilizing Prins cyclization to form the spiroketal unit and Horner–Wadsworth–Emmons condensation to couple the main subunits. Trost et al. synthesis introduces the stereochemistry in both the phthalide portion and the spiroketal portion via ProPhenol catalyst-controlled asymmetric alkylation chemistry in 14 steps with an overall yield of 3.4%.<sup>9d</sup> Yadav et al.<sup>9f</sup> have employed Sharpless asymmetric epoxidation as the key reaction whereas Argade et al. approach utilized chiral building blocks to achieve the formal synthesis of **2** in 11 steps.<sup>9g</sup>

However, the reported methods for the synthesis of spiroloxine methyl ether **2** suffer from certain limitations such as the use of chiral building blocks, introduction of chirality in the early stages, long reaction sequences, and low enantiomeric excess and are often not amenable for scale-up studies.<sup>9</sup> In this context, a more practical and convergent method for the synthesis of (+)-spiroloxine methyl ether **2** is highly desirable. In this Letter, we describe a practical, and high yielding synthesis of crucial spiroketal part **3** and phthalide fragment **4** with an improved enantiomeric excess (96% ee) thereby constituting a formal synthesis of **2**. The synthesis entails Noyori's asymmetric reduction and Brown allylation as the key chirality inducing steps that establishes complete stereochemistry of spiroloxine methyl ether **2** (Schemes 2–5).

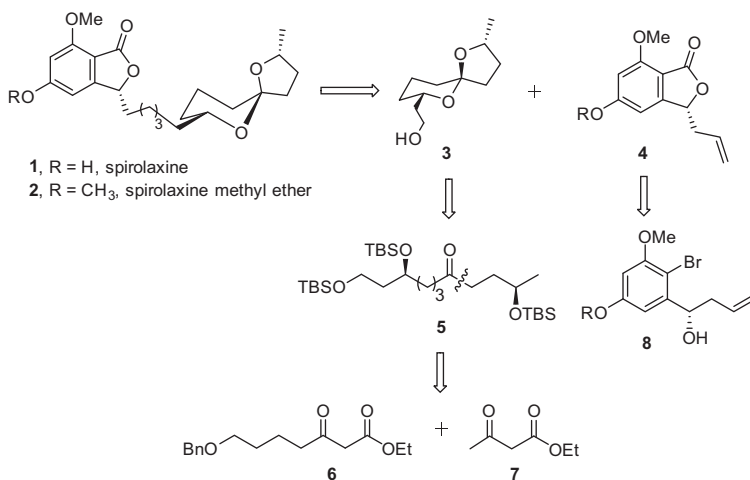
The retrosynthesis of spiroloxine methyl ether **2** is shown in Scheme 1. We envisioned that the synthesis of **2** could be achieved from the key chiral intermediates spiroketal **3** and phthalide segment **4**. Spiroketal moiety **3** could be prepared by acid catalyzed cyclization of ketone **5** which in turn can be obtained from  $\beta$ -keto

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**Figure 1.** Structure of spirolaxine (1), its methyl ether (2), spiroketal (3) and phthalide unit (4).



**Scheme 1.** Retrosynthetic analysis of spirolaxine methyl ether (2).

esters **6** and **7** by Noyori's chiral reduction strategy and Grignard reaction. Phthalide fragment **4** could be obtained by Cu-catalyzed CN-assisted lactonization of chiral alcohol **8** which can be obtained by Brown allylation of the corresponding 3,5-dimethoxybenzaldehyde **21**.

## Results and discussion

The formal synthesis of spirolaxine methyl ether **2** was commenced with the construction of the key chiral intermediate spiroketal **3**, which was synthesized from commercially available 1,5-pentanediol (**9**). Selective benzylation of **9** resulted in monobenzyl ether **10** in 89% yield followed by its oxidation using TEMPO and di(acetoxyiodo)benzene conditions furnished aldehyde **11** in 95% yield. Noyori's asymmetric reduction is a very useful tool for the chiral reduction of  $\beta$ -keto esters giving  $\beta$ -hydroxy esters in high enantioselectivity.<sup>10</sup>

In view of this, we have planned our synthesis to achieve the chiral  $\beta$ -hydroxy ester **13**. Thus, we have treated benzyl protected aldehyde **11** with ethyl bromoacetate under Reformatsky reaction conditions (Zn, NH<sub>4</sub>Cl, THF, 0 °C) that furnished racemic  $\beta$ -hydroxy ester **12** in 90% yield followed by its oxidation using IBX provided precursor  $\beta$ -keto ester **6** in excellent yield (87%).

Now, racemic  $\beta$ -keto-ester **6** was subjected to asymmetric reduction using Noyori's catalytic conditions: {[(*R*)-Ru(BINAP)Cl<sub>2</sub>]<sub>2</sub>·NEt<sub>3</sub>, 2 M HCl (0.1 mol %), MeOH, H<sub>2</sub> (100 psi), 50 °C} to afford the corresponding chiral  $\beta$ -hydroxyester **13** with excellent yield (95%) and enantiopurity (96% ee by chiral HPLC analysis). The reduction of ester **13** with LiAlH<sub>4</sub> resulted in the formation of chiral 1,3-diol **14** in 90% yield. Further, protection of diol **14** as silyl ether followed by deprotection of benzyl ether to the corresponding alcohol and its oxidation to aldehyde **16** has been achieved following the literature procedure<sup>9f</sup> (Scheme 2).

With aldehyde fragment **16** in hand, we have turned our attention toward the synthesis of alkyl fragment **20**, which was

synthesized by the asymmetric reduction of commercially available ethyl acetoacetate **7** using Noyori's condition {[(*R*)-Ru(BINAP)Cl<sub>2</sub>]<sub>2</sub>·NEt<sub>3</sub>, 2 M HCl (0.1 mol %), MeOH, H<sub>2</sub> (100 psi), 50 °C} to produce chiral (*R*)-ethyl 3-hydroxybutyrate **17** in 94% yield and 98% enantiomeric excess. Its specific rotation was in close agreement with the reported value [ $\alpha$ ]<sub>D</sub><sup>20</sup> –45.0 (c 1.0, CHCl<sub>3</sub>); lit.<sup>12</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> –46.0 (c 1.0, CHCl<sub>3</sub>)]. Secondary hydroxyl functionality in **17** was protected as its silyl ether **18** in 90% yield. The resulting ester **18** was subjected to complete reduction with DIBAL-H at 0 °C to provide the corresponding alcohol **19** in 85% yield. Now, free primary hydroxyl group was converted into the corresponding bromide under Appel reaction protocol (CBr<sub>4</sub>, Ph<sub>3</sub>P, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C) that provided alkyl bromide derivative **20** in 89% yield<sup>11</sup> (Scheme 3).

Both the fragments **16** and **20** were treated under Grignard conditions that resulted in the formation of alcohol *in situ*, which was subsequently oxidized using IBX to furnish keto derivative **5** in 75% yield for two steps, without affecting the silyl ether functionality. Finally, acid catalyzed cyclization of keto derivative **5** to spiroketal moiety **3** was achieved in 76% yield following the literature protocol.<sup>9f</sup> Its specific rotation value was in complete agreement with the literature value {[ $\alpha$ ]<sub>D</sub><sup>20</sup> +65.2 (c 1.0, CHCl<sub>3</sub>); lit.<sup>9f</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> +65.4 (c 1.0, CHCl<sub>3</sub>)} (Scheme 4).

Having synthesized spiroketal **3**, our next task was to undertake the preparation of the phthalide precursor **4**, which was crucial for the total synthesis of spirolaxine methyl ether **2**. Recently, we have developed a general single step protocol for the synthesis of phthalide unit by a simple annulation using CuBr as catalyst and NaCN as C1 source in stoichiometric amounts.<sup>13</sup> This simple synthetic methodology has been utilized in the synthesis of phthalide precursor **4**. Thus, regioselective *ortho* bromination of 3,5-dimethoxybenzaldehyde **21** with NBS gave 2-bromo-3,5-dimethoxybenzaldehyde followed by its Brown allylation using (–)-Ipc<sub>2</sub>B(allyl)borane at –78 °C afforded bromo allylic alcohol **8** in excellent yield and good enantiomeric excess (89% yield; 87% ee). The Cu(I)-mediated displacement of bromide with cyanide was achieved using NaCN

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