A Modular, Stereoselective Approach to Spiroketal Synthesis

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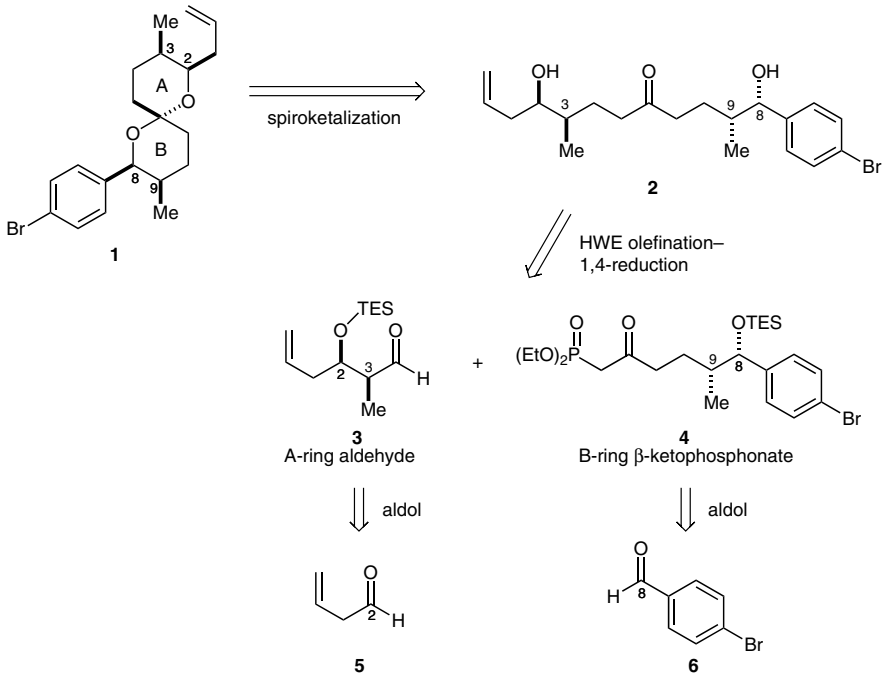
Abstract: A highly convergent and flexible synthetic approach to stereochemically defined spiroketals is reported. Substituents can be incorporated at various positions around the spiroketal framework without significant disruption to the synthetic scheme. The approach has been exploited to prepare the spiroketal fragment of milbemycin β_{14}.

Key words: spiroketals, asymmetric aldol addition, milbemycin

The spiroketal is a substructure that is commonly found in natural products.[2] Spiroketal-containing natural products range from elegantly simplistic pheromones[3] to complex polyketides[4] and marine toxins.[5] The spiroketal framework is a rigid structure owing to stabilization by the unique stereoelectronic phenomenon known as the anomeric effect.[6]

Due to the frequent occurance of spiroketals in biologically active natural products, and the potential of spiroketals as privileged structures in medicinal chemistry, a general strategy for the construction of spiroketals with substituents strategically and interchangeably positioned in various locations around the structural framework would hold considerable value to synthetic and medicinal chemists. A modular approach to the synthesis of spiroketals with significant versatility and minimal operational complexity for substituent interchange is reported here.

The general retrosynthetic approach is illustrated in Scheme 1. Spiroketal **1** would arise from pseudo-C_2-symmetrical dihydroxyketone **2**. Hydroxyketone **2** would be bisected to give A-ring chiral aldehyde **3** and B-ring β-ketophosphonate **4**. The relative and absolute stereochemistry of each fragment would be readily accessible from diastereoslective *N*-acylthiazolidinethione aldol addition methodology.[7,8] The bisection of the dihydroxyketone to the chiral aldehyde and chiral β-ketophosphonate is noteworthy, since the convergent, modular nature of the synthesis was an essential component of this approach. By disconnecting as shown, the functionality of the A- and B-rings can be independently changed obviating the need to repeat the entire synthesis. Only the shorter synthesis of one chiral fragment is required. In this manner, 'aldehyde' and 'phosphonate' fragments can be mixed and matched with ease to create a variety of novel spiroketals.



Scheme 1 Retrosynthesis of spiroketal **1**

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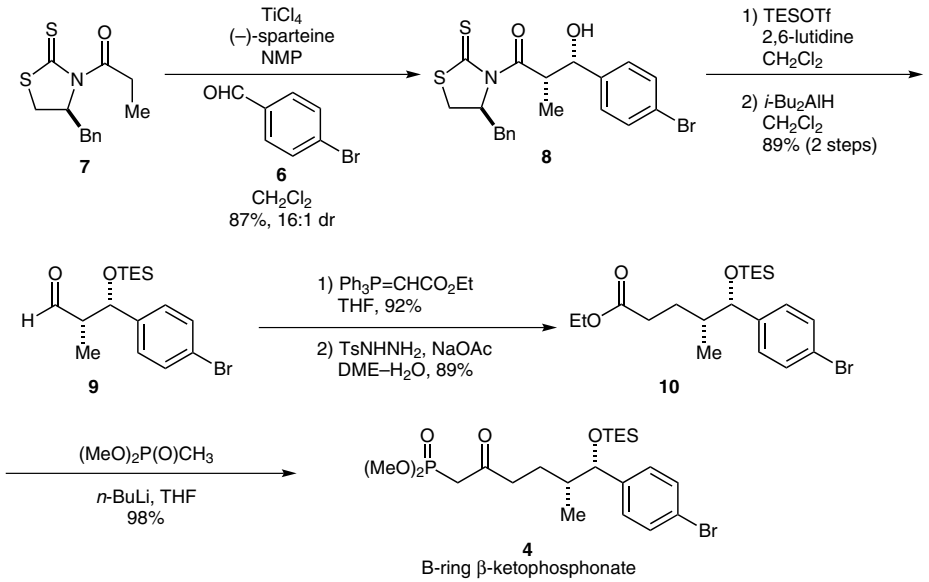
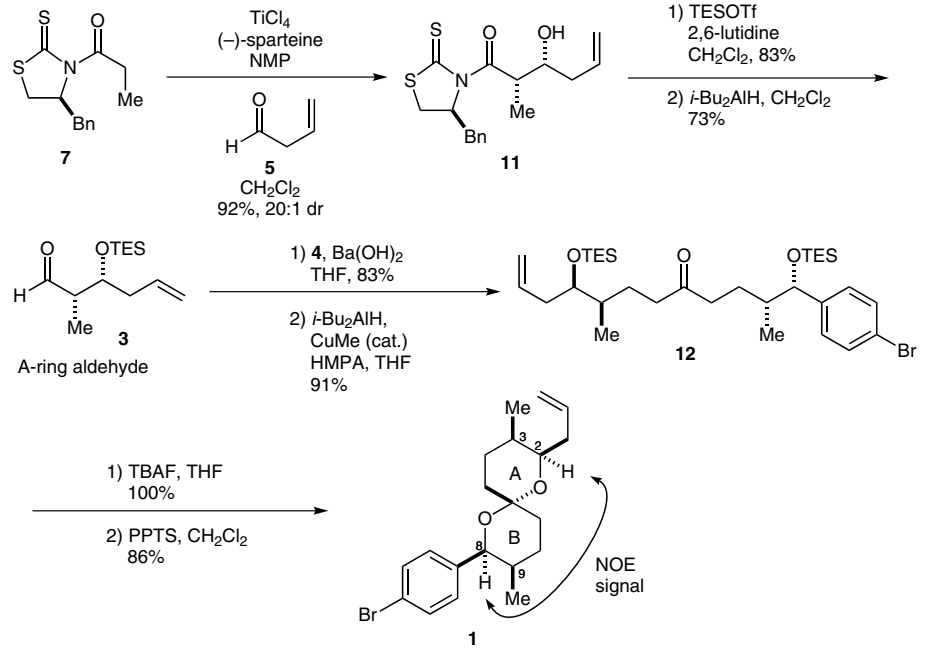


Scheme 2 Synthesis of phosphonate **4**

The first spiroketal **1** targeted incorporated an A-ring terminal alkene and a B-ring aryl bromide in the 2- and 8-positions of the spiroketal, respectively. The synthesis of the B-ring β-ketophosphonate fragment commenced with a thiazolidinethione-mediated 'Evans *syn*'-aldol addition[7a] with *p*-bromobenzaldehyde (**6**) to yield aldol adduct **8** in 87% isolated yield of the major diastereomer and a 16:1 diastereomeric ratio overall (Scheme 2). Protection of the secondary alcohol followed by reductive removal of the chiral auxiliary yielded aldehyde **9** in 89% yield over two steps. Wittig olefination followed by diimide reduction[9] provided ethyl ester **10**. Completion of the B-ring β-ketophosphonate was achieved through a Claisen condensation in 98% yield to give B-ring β-ketophosphonate **4** in six steps and 62% overall yield.

The A-ring aldehyde fragment was also prepared through thiazolidinethione-mediated 'Evans *syn*'-aldol addition[7a] with 3-butenal[10] (**5**) to give aldol adduct **11** in 92% yield and 20:1 diastereomeric ratio (Scheme 3). Alcohol protection directly followed by chiral auxiliary reduction provided A-ring aldehyde fragment **3** in three steps and 56% overall yield.

The two fragments were coupled in a Horner–Wadsworth–Emmons olefination utilizing barium hydroxide[11] as mild base to provide the α,β-unsaturated ketone in 83% yield. Selective reduction of the α,β-unsat-



Scheme 3 Synthesis of spiroketal **1**

urated ketone in the presence of the terminal olefin was accomplished using diisobutylaluminum hydride with HMPA and catalytic methyl copper as an additive, forming saturated ketone **12** in 91% yield without over reduction.[12]

To access the desired spiroketal, the triethylsilyl ether protective groups were removed with TBAF in quantitative yield, providing the open-chain dihydroxyketone. Immediate treatment with a catalytic amount of PPTS converted the dihydroxyketone into desired spiroketal **1** in 86% yield as a single diastereomer. The spiroketal was prepared in ten longest linear steps and provided gram quantities of the desired spiroketal in 40% overall yield. Relative stereochemistry was ultimately determined through 2-D NOESY analysis (see Supporting Information).

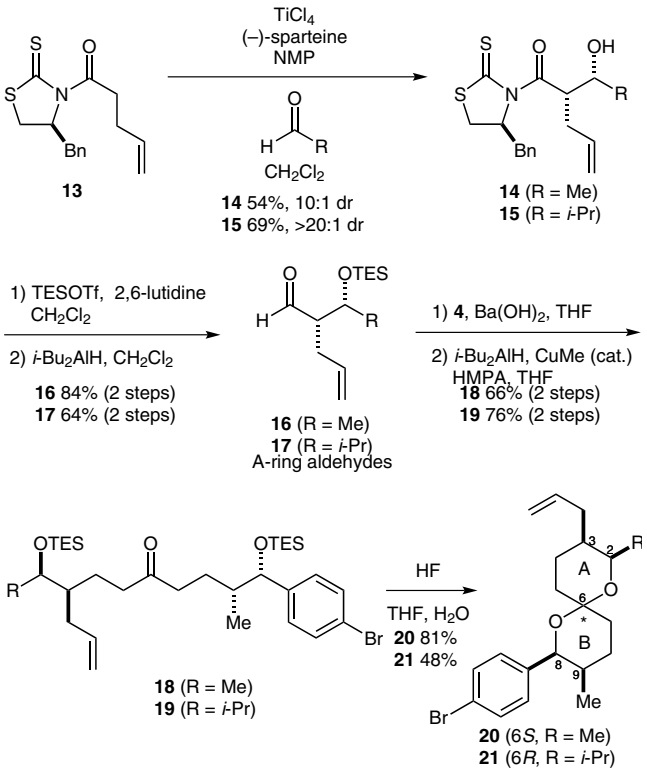
Two further spiroketals were targeted (**20** and **21**) with a B-ring aryl bromide identical to **1**, and a modified A-ring architecture. The terminal alkene was shifted to the 3-position and either a methyl group (**20**) or isopropyl group (**21**) was located in the 2-position. Demonstrating the modular approach to spiroketal synthesis, only the A-ring aldehyde fragment needed to be prepared in each case, as the B-ring β-ketophosphonate needed (**4**) is the same as previously prepared.

Thiazolidinethione-mediated 'Evans *syn*'-aldol addition[7a] with known thiazolidinethione **13**[7] and either acetaldehyde or isobutyraldehyde gave aldol adducts **14** and **15** in 54% yield (10:1 dr) and 69% yield (>20:1 dr), respectively (Scheme 4). Alcohol protection followed by reduction of the auxiliary completed the new A-ring aldehyde fragments **16** and **17** in a three-step overall yield of 45% and 47%, respectively.

Horner–Wadsworth–Emmons coupling[11] of previously prepared B-ring β-ketophosphonate **4** and A-ring aldehydes **16** or **17**, followed by selective 1,4-reduction,[12] resulted in 66% and 76% yields of ketones **18** and **19**, respectively. One-pot HF-promoted deprotection–cyclization of ketone **18** proceeded in 81% yield to give spiroketal **20**. Based on extensive 1D and 2D NMR analysis, spiroketal **20** was formed in a 13:1 dr favoring the singly anomeric 6*S* diastereomer at the C6 spiroketal carbon atom. The analogous deprotection of ketone **19** yielded spiroketal **21** in 48% yield. A single diastereomer favoring the doubly anomeric 6*R* diastereomer at the C6 spiroketal carbon atom was formed, as determined by extensive 1D and 2D NMR analysis. Both spiroketal **20** and **21** were prepared in nine longest linear steps and overall yields of 34% and 23%, respectively.

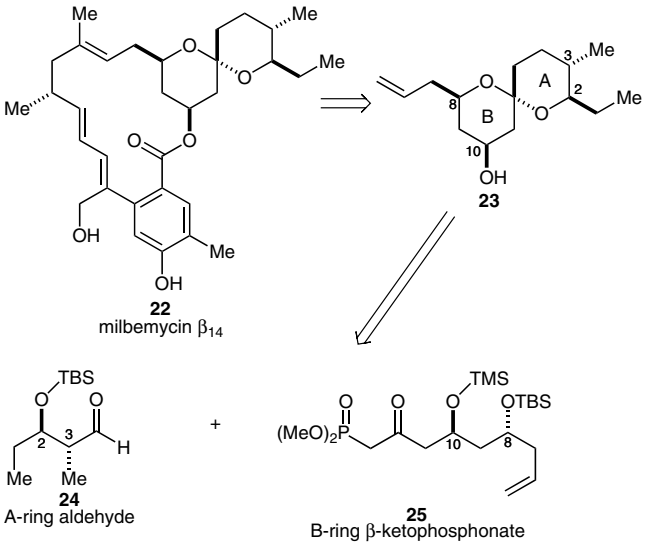
This modular approach to spiroketal synthesis has also been incorporated into natural product synthesis. We have previously reported the total synthesis of spirofungins A and B[13] incorporating this versatile spiroketal synthesis.

Our recent attention was turned to milbemycin β_{14} (**22**) as a possible target. Milbemycin β_{14} is an acaricidal and nematocidal macrolactone isolated from the fermentation broth of a strain of *Streptomyces bingchenggensis*.[14] Ret-



Scheme 4 Synthesis of spiroketals **20** and **21**

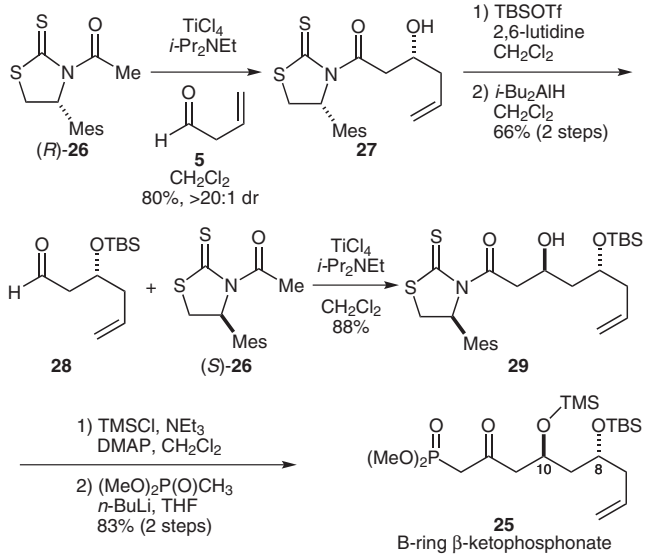
rosynthetically, milbemycin β_{14} could be derived from key spiroketal **23** (Scheme 5). Spiroketal **23** can readily be constructed utilizing this modular approach through preparation of B-ring β-ketophosphonate **25** and A-ring aldehyde **24**.



Scheme 5 Milbemycin β_{14} partial retrosynthesis

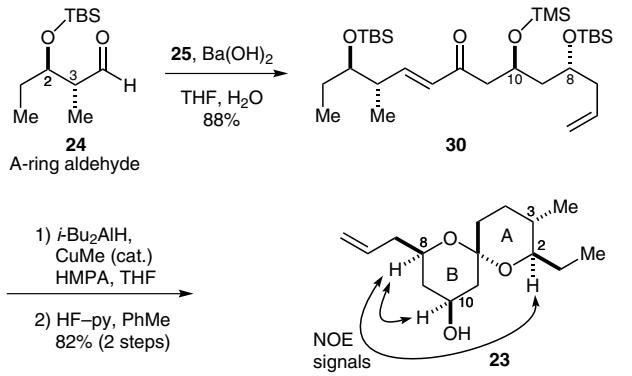
The B-ring β-ketophosphonate fragment was prepared through an iterative thiazolidinethione-mediated acetate aldol addition[7b] developed in our laboratory. Addition of 3-butenal (**5**)[10] to a solution of the chlorotitanium enolate of *N*-acetylthiazolidinethione (*R*)-**26** produced the aldol

adduct **27** in 80% yield and greater than 20:1 diastereomeric ratio (Scheme 6). Protection of the secondary alcohol followed by reductive cleavage of the chiral auxiliary provided aldehyde **28** in 66% yield over two steps. The second acetate aldol addition[7b] with thiazolidinethione (*S*)-**26** provided iterative aldol adduct **29** in 88% yield as a single stereoisomer. Protection of the C10 secondary alcohol as its TMS ether and direct displacement of the auxiliary with lithiated dimethyl methyl phosphonate provided B-ring β-ketophosphonate **25** in 83% yield over two steps. The B-ring phosphonate fragment was synthesized in six steps and 39% overall yield.



Scheme 6 Synthesis of β-ketophosphonate **25**

Horner–Wadsworth–Emmons coupling[11] of B-ring β-ketophosphonate **25** with known protected A-ring aldehyde **24**[15] provided unsaturated ketone **30** in 88% yield. Selective 1,4-reduction[12] of the enone followed by one-pot tris-silyl ether deprotection–cyclization yielded spiroketal **23** as a single isomer in 84% yield over two steps. Spiroketal **23** was completed in nine overall steps (longest linear sequence) and 29% overall yield (Scheme 7). The relative configuration of the spiroketal was confirmed through 2D NOESY analysis.



Scheme 7 Synthesis of spiroketal **23**

In conclusion, we have demonstrated a versatile, modular synthesis of stereochemically defined spiroketals where individual rings can be mixed and matched. Spiroketal substituents can be easily translated to various positions without disrupting the overall synthetic approach. The modular approach to spiroketals can be applied toward the total synthesis of spiroketal-containing natural products.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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