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Stereo- and substituent-enabled divergent synthesis of 5,6-spiroketal analogs of avermectin containing a triazole function

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ABSTRACT

Stereo-divergent construction of a 5,6-spiroketal moiety, together with an efficient strategy to access various avermectin analogs containing a triazole group, has been accomplished. In the spirocyclization event, a C21*R* spiroketal product was selectively obtained using $Zn(OTf)_2$ as a Lewis acid. Conversely, use of $Sc(OTf)_3$ afforded a C21S spiroketal compound as the major product. One pot triazole formation between three TMS-alkyne substrates and organic azides effectively provided the corresponding anti-triazole products. This strategy generates stereochemical and substituent diversity among avermectin analogs. Some of the 5,6-spiroketal analogs showed anti-nematodal activity comparable to ivermectin.

Introduction

The avermectins were isolated from a culture broth of *Streptomyces avermitilis* (renamed *avermectinius*), discovered in the Kitasato Institute, as a mixture of eight chemical components.[1] The avermectins demonstrated potent anthelmintic and insecticidal activity with a novel mode of action.[2] The commercialized product arising from this research and development, ivermectin, is an approximate 4:1 mixture of ivermectin B_{1a} (**1**) and B_{1b} (**2**), two hydrogenated derivatives of avermectin B_{1a} (**3**) and B_{1b} (**4**) (Fig. 1). Ivermectin has been used to an extraordinary extent in veterinary medicine against a broad range of parasites in a variety of livestock and pets. Since 1987, it has also been used for treatment of parasitic infections in humans, such as onchocerciasis, lymphatic filariasis, strongyloidiasis, gnathostomiasis, ascariasis, trichuriasis and some parasitic skin diseases, including scabies and head lice infestation.[3–7] Over 300 million people take ivermectin annually, the drug being the primary tool in global programs to eliminate onchocerciasis and lymphatic filariasis. Ivermectin has proved to be extremely safe for human use and appears to have a wide range of efficacy. Therefore, ivermectin or its derivatives are considered to have great potential against a range of infectious agents and diseases, such as streptocerciasis, trichinosis and myiasis, as an antiviral (against HIV, dengue), as an antibacterial (for *Chlamydia trachomatis*, *Mycobacterium tuberculosis* and *M. ulcerans*), as an anti-cancer agent, as well as to control insect vectors of parasites that cause malaria, leishmaniasis, trypanosomiasis, and schistosomiasis.[3,8] However, ivermectin resistance has become a serious problem for parasite control in livestock and there is a concern about resistance development and spread in nematode parasites occurring in humans.[9] Consequently, there is significant stimulus to produce a broad range of avermectin analogs and create a library of compounds for use in developing new drugs and treatments to combat a variety of diseases, parasite vectors or which will help overcome the problem of parasite resistance.

Since discovery of the avermectins, many structure activity relationship (SAR) studies have been undertaken.[10] Most research has focused on a modification of the disaccharide part of the avermectins.[11–13] Therefore, we opted for a different approach, namely modification of the spiroketal moiety, with only a few such studies being reported in the past by the Merck group.[14–18]

Ivermectin is an allosteric agonist of glutamate-gated chloride ion channels (α (GluCl)). The X-ray structure of the GluCl-Fab complex, with respect to ivermectin, was determined by Hibbs and Gouaux.[19] According to their X-ray analysis, a tetrahydrobenzofuran moiety is bound to a GluCl on the inside of the pocket. Conversely, the disaccharide and spiroketal moiety are located

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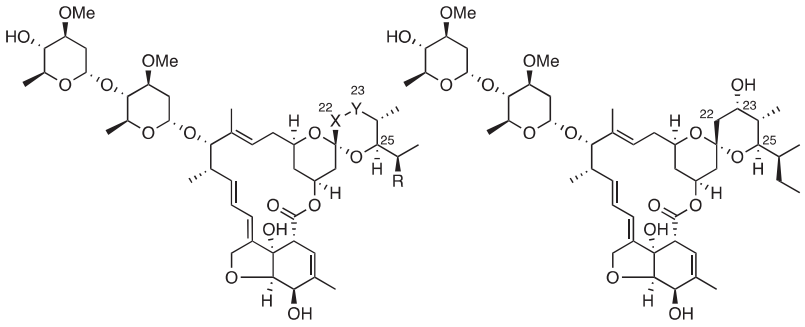


Ivermectin : mixture of dihydro derivatives of
B_{1a} (**1**) [R = Et; X–Y = H_2C–CH_2]
B_{1b} (**2**) [R = Me; X–Y = H_2C–CH_2]
Avermectin B_{1a} (**3**) [R = Et; X–Y = ⌇═⌇]
Avermectin B_{1b} (**4**) [R = Me; X–Y = ⌇═⌇]

Avermectin B_{2a} (**5**)

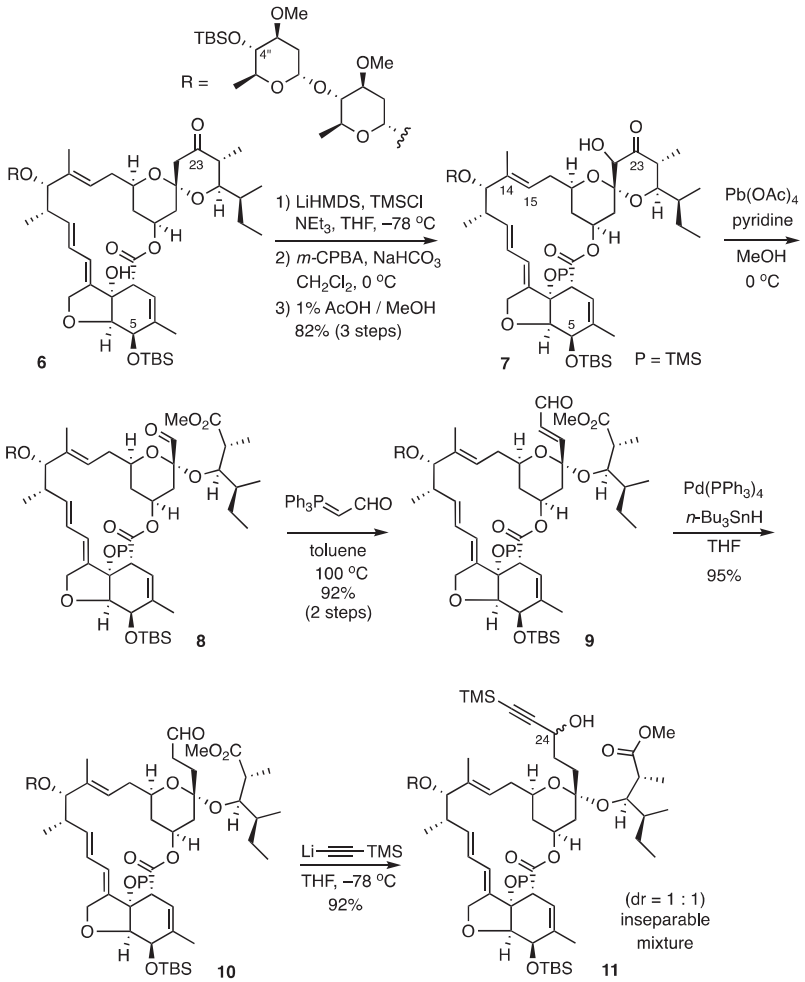
Fig. 1. Ivermectin, Avermectin B_{1a} (**3**) B_{1b} (**4**), B_{2a} (**5**).

outside the pocket. Taking into consideration this binding difference, elongation of the C25 substituent may help increase affinity to GluCl.

In this manuscript, we report the stereo-divergent construction of the 5,6-spiroketal moiety from an appropriate acyclic hemiacetal, derived from avermectin B_{2a}. Subsequently, utilizing click chemistry,[20] triazole formation between the organic azide and alkyne[21] effectively provided various triazole analogs.

Results and discussion

Meinke and co-workers reported the synthesis of an avermectin derivative containing a 5,6-spiroketal ring using avermectin B_{2a} (**5**) as the starting point.[16] Following their methodology, we prepared aldehyde **10** from **5** obtained from a culture broth of *S. avermectinius* (Scheme 1).[22] According to Shih and colleagues, ketone **6**, prepared from **5** in 2 steps,[14] can be converted to the silyl enol



Scheme 1. Synthesis of propargyl alcohol **11**.