



## Application of Mn(III)-catalysed olefin hydration reaction to the selective functionalisation of avermectin B<sub>1</sub>

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### ABSTRACT

The Mn(dpm)<sub>3</sub>-catalysed olefin hydration reaction of  $\alpha,\beta$ -unsaturated esters and ketones discovered by Mukaiyama in 1990 and further developed by Magnus in 2000 was applied to the challenging environment of avermectin B<sub>1</sub>. Different avermectin substrates such as 4'',7-OTMS-5-oxo-avermectin B<sub>1</sub> **3**, avermectin B<sub>1</sub> **1** and  $\Delta^{2,3}$ -avermectin B<sub>1</sub> **6** were thus treated with Mn(dpm)<sub>3</sub>, PhSiH<sub>3</sub> in isopropanol under oxygen atmosphere to afford several novel analogues, including 3,4-dihydro-3-hydroxy-avermectin B<sub>1</sub> **8** with high level of regio- and stereoselectivity, 2-hydroxy-3,4-dihydro-avermectin B<sub>1</sub> **7**, the first example of a 2-substituted avermectin and the novel 22,23-dihydro-22-hydroxy-avermectin B<sub>1</sub> **9a** and **9b**, epimeric at C(22). Biological activity of these new avermectin derivatives is also reported.

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Naturally occurring avermectins and their semi-synthetic analogues have been the subject of intensive research for more than 20 years. In crop protection, two compounds have been successfully introduced to the market: Abamectin **1** (Vertimec<sup>®</sup>, Agrimec<sup>®</sup>), a mixture of avermectin B<sub>1a</sub> and avermectin B<sub>1b</sub>, is an acaricide and insecticide launched in 1985 by Merck Sharp and Dohme Agvet (now marketed by Syngenta Crop Protection AG) and Emamectin benzoate **2** (Proclaim<sup>®</sup>, Affirm<sup>®</sup>), a semi-synthetic insecticide with a complementary spectrum, was introduced to the market by Novartis (now Syngenta Crop Protection AG) in 1997.<sup>1,2</sup>

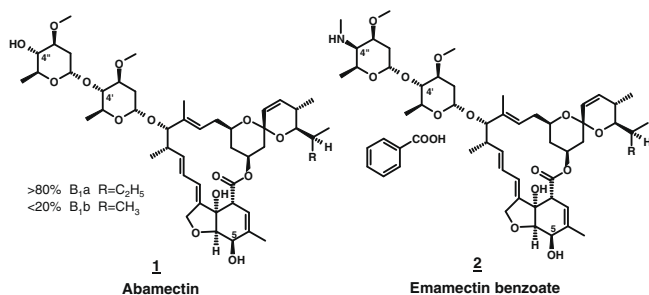
Following the successful development and commercialisation of these two products, considerable effort has been dedicated towards the identification of novel derivatives with improved biological activity or spectrum at Syngenta Crop Protection Research. This has stimulated in our group an intensive chemical research for selective, site-specific functionalisation of the macrolide.<sup>3</sup>

In 1990, Mukaiyama reported a single-step procedure for the conversion of  $\alpha,\beta$ -unsaturated esters into  $\alpha$ -hydroxylated esters.<sup>4</sup> This interesting methodology, which results in the formal hydration of an olefin,<sup>5</sup> consists of the reaction with phenylsilane in isopropanol under dioxygen atmosphere in the presence of (dipivaloylmethanato)-manganese(III) (Mn(dpm)<sub>3</sub>) as a catalyst.

It was further investigated and extended to unsaturated ketones and nitriles by Magnus in 2000,<sup>6b,c</sup> and since then regularly applied in total synthesis<sup>7</sup> or natural product functionalisation.<sup>6a,d</sup> Other Mn(III)<sup>8</sup> or Co(III)<sup>9</sup> catalysts have also been successfully used, and a related method for the hydrohydrazination of olefins was also published.<sup>10</sup> The several reported applications of this methodology prompted us to share our own results of the application of this Mn(III)-catalysed hydration reaction to the challenging environment of avermectins.

We first considered 4'',7-OTMS-5-oxo-avermectin B<sub>1</sub> **3** as an initial substrate, expecting high chemoselectivity for the 3,4-conjugated double bond of the macrolide (Scheme 1). Compound **3** was prepared by tris-silylation of **1** followed by mild deprotection of the 5-OTMS group and oxidation with MnO<sub>2</sub>. Previously, we could achieve the conjugated reduction of **3** with L-Selectride followed by trapping of the enolate with (*R*)- or (*S*)-camphorsulfonyloxaziridine (conditions A) to afford the hydroxy-ketone **4a** in 55% yield as a single diastereoisomer.<sup>11</sup> Interestingly, the diastereoselectivity was reversed using the catalytic system Mn(dpm)<sub>3</sub>/PhSiH<sub>3</sub>/iPrOH/O<sub>2</sub> (conditions B), which afforded the  $\alpha$ -hydroxy-ketones **4a** and **4b** in 67% yield as a 3:7 separable mixture of diastereoisomers. After removal of the trimethylsilyl-protecting groups with HF/pyridine and NaBH<sub>4</sub> reduction of the 5-ketone, both the isomers could be converted to the epimeric 4-(*R*)- and 4-(*S*)-3,4-dihydro-4-hydroxy-avermectin B<sub>1</sub> **5a** and **5b** in 55% and 50% yield, respectively (9% and 18% of the 5-epimeric alcohols were also obtained in both the cases, not displayed on the scheme). In

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Scheme 1. Abamectin **1** and Emamectin benzoate **2**.

contrary to **5a**, **5b** displayed strong NOE effect between H-2 and CH<sub>3</sub>-4a (both substituents axial).<sup>12</sup>

The first experiment demonstrated the tolerance of avermectin to these hydration reaction conditions, and encouraged us to further explore the potential application of this method with other avermectin substrates.<sup>13</sup>

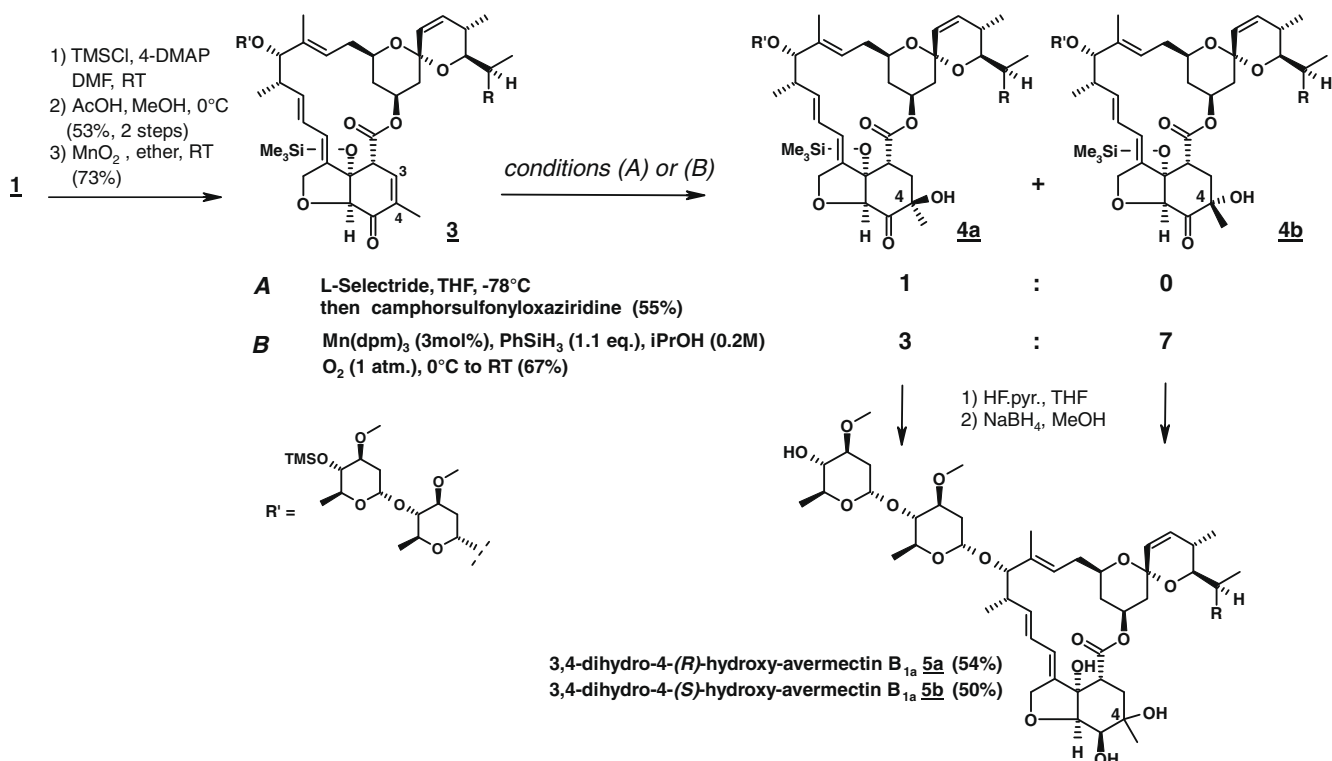
Avermectin B<sub>1</sub> can be easily converted into its conjugated isomer Δ<sup>2,3</sup>-avermectin B<sub>1</sub> **6** upon treatment with DBU in dichloromethane (80% yield).<sup>14</sup> We wondered if the conjugated ester **6** would react under the Mn(III)-catalysed hydration conditions to afford 2-hydroxy-3,4-dihydro-avermectin B<sub>1</sub>. To the best of our knowledge, this would represent the first example of an avermectin derivative substituted at the C(2)-position.

The standard procedure (method B in Scheme 1) was thus applied to the conjugated ester **6** (Scheme 2) and afforded after reductive work-up a mixture of four different monohydrated products, which were carefully separated by reverse phase preparative HPLC. 2-Hydroxy-3,4-dihydro-avermectin B<sub>1</sub> **7** was indeed isolated as a single diastereoisomer in 15% isolated yield (retaining the natural configuration of the lactone at C(2); the assigned configuration was supported by NMR experiments, in particular by the absence

of any cross peak in HMBC between H-3ax and C(2)) along with its regioisomer 3-hydroxy-3,4-dihydro-avermectin B<sub>1</sub> **8** in 5% yield.<sup>15</sup> Interestingly, two other minor products (8% yield) resulted from competitive hydration of the C(22)–C(23) double bond to afford the novel 22-hydroxy-avermectins **9a** and **9b** as a separable mixture of isomers (characterised by mass spectrometry and NMR; TOCSY experiment revealed in particular the *trans*-diaxial coupling between H-22 and H-23ax in **9a**).<sup>16</sup> It is noteworthy that the transformation does not involve any protecting group, and although the reaction of **6** did not proceed regioselectively, with only incomplete conversion and low isolated yield (28% overall), we were pleased with the high stereoselectivity observed at C(2) and C(3) and rewarded with the isolation of four novel semi-synthetic isomeric avermectin derivatives.

The observed reactivity of the unsaturated spiroketal<sup>17</sup> led us next to consider avermectin B<sub>1</sub> itself as a possible substrate for the reaction, in order to favour reactivity at the C(22)–C(23) double bond (Scheme 4). However, to our surprise, upon treatment under the standard conditions, no reaction was observed at the spiroketal double bond but instead a clean, fast and stereoselective reaction occurred at the C(3)–C(4) olefin, which afforded 4-(*S*)-3,4-dihydro-3-(*S*)-hydroxy-avermectin B<sub>1</sub> **8** in 70% yield (identical with the second compound obtained in the previous experiment, see Scheme 3) along with its 3-epimer **10** in 5% yield. The relative configuration at C(3) and C(4) in **8** was confirmed by NMR with *trans*-diaxial couplings observed between H-2, H-3, H-4 and H-5.<sup>18</sup>

Although this Mn(III)-catalysed hydration reaction has already been applied to other substrates than unsaturated ketones, esters or nitriles,<sup>5,9</sup> the reaction with allylic alcohols is unprecedented and might represent a new application of this methodology as well as an attractive synthetic transformation for avermectin functionalisation. Thus, 4',7-OTMS-avermectin B<sub>1</sub> **11** was converted into 4',7-OTMS-3,4-dihydro-3-hydroxy-avermectin B<sub>1</sub> **12** in 70% yield, which was selectively protected at the 5-position with a TBDMS group (Scheme 5). Oxidation of the 3-hydroxy group with Dess-

Scheme 2. Synthesis of 3,4-dihydro-4-hydroxy-avermectin B<sub>1</sub>.

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