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Application of Mn(III)-catalysed olefin hydration reaction to the selective functionalisation of avermectin B_1

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ABSTRACT

The $Mn(dpm)_3$-catalysed olefin hydration reaction of α,β-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_1. Different avermectin substrates such as 4″,7-OTMS-5-oxo-avermectin B_1 **3**, avermectin B_1 **1** and $\Delta^{2,3}$-avermectin B_1 **6** were thus treated with $Mn(dpm)_3$, $PhSiH_3$ in isopropanol under oxygen atmosphere to afford several novel analogues, including 3,4-dihydro-3-hydroxy-avermectin B_1 **8** with high level of regio- and stereoselectivity, 2-hydroxy-3,4-dihydro-avermectin B_1 **7**, the first example of a 2-substituted avermectin and the novel 22,23-dihydro-22-hydroxy-avermectin B_1 **9a** and **9b**, epimeric at C(22). Biological activity of these new avermectin derivatives is also reported.

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®, Agrimec®), a mixture of avermectin B_1a and avermectin B_1b, 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®, Affirm®), a semi-synthetic insecticide with a complementary spectrum, was introduced to the market by Novartis (now Syngenta Crop Protection AG) in 1997.[1,2]

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.[3]

In 1990, Mukaiyama reported a single-step procedure for the conversion of α,β-unsaturated esters into α-hydroxylated esters.[4] This interesting methodology, which results in the formal hydration of an olefin,[5] consists of the reaction with phenylsilane in isopropanol under dioxygen atmosphere in the presence of (dipivaloylmethanato)-manganese(III) ($Mn(dpm)_3$) as a catalyst. It was further investigated and extended to unsaturated ketones and nitriles by Magnus in 2000,[6b,c] and since then regularly applied in total synthesis[7] or natural product functionalisation.[6a,d] Other Mn(III)[8] or Co(III)[9] catalysts have also been successfully used, and a related method for the hydrohydrazination of olefins was also published.[10] 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_1 **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_2. 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.[11] Interestingly, the diastereoselectivity was reversed using the catalytic system $Mn(dpm)_3$/$PhSiH_3$/*i*PrOH/O_2 (conditions B), which afforded the α-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 $NaBH_4$ 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_1 **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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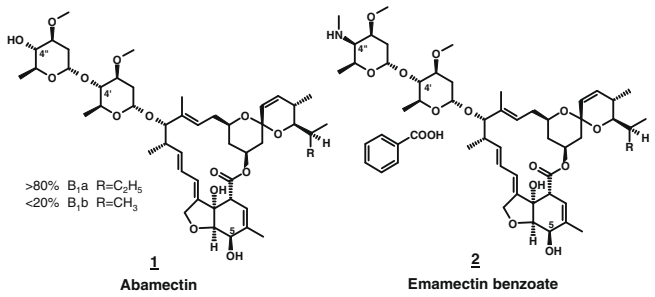


Scheme 1. Abamectin **1** and Emamectin benzoate **2**.

contrary to **5a**, **5b** displayed strong NOE effect between H-2 and CH_3-4a (both substituents axial).[12]

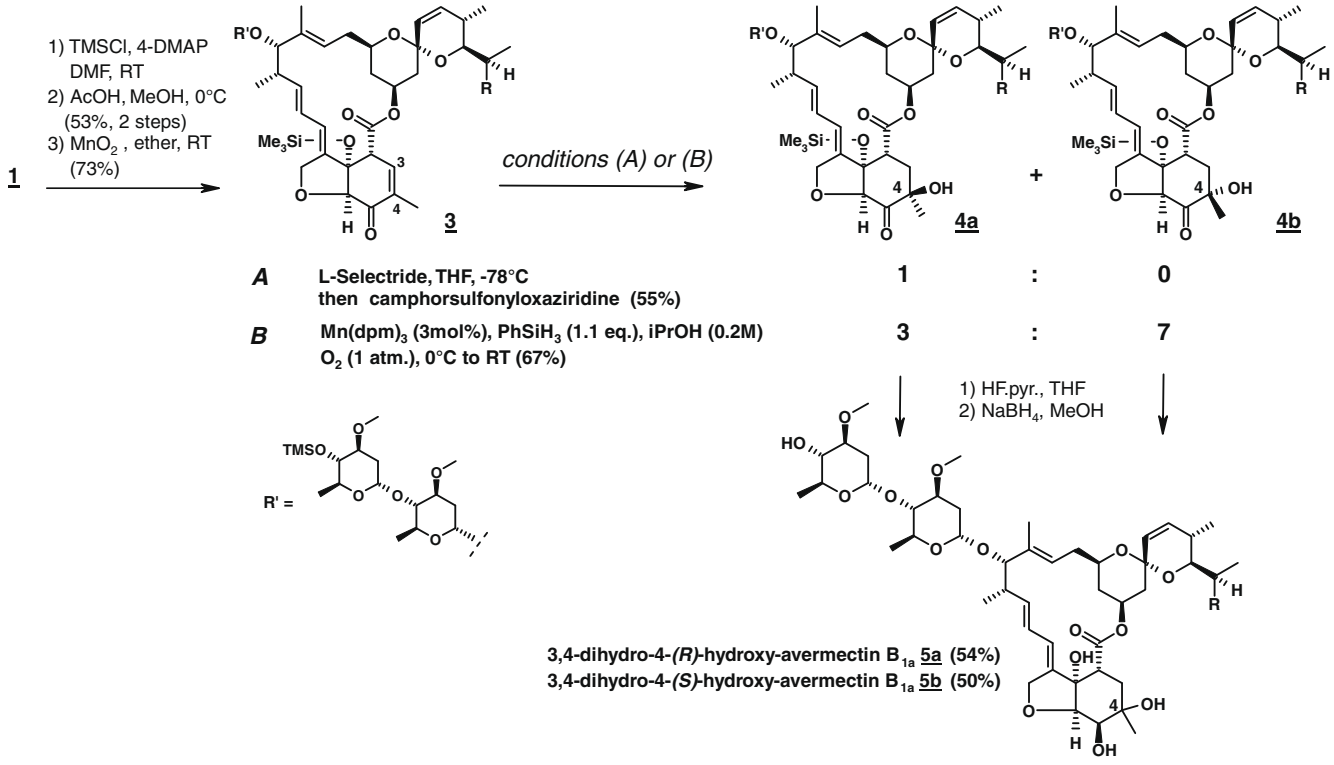
The first experiment demonstrated the tolerance of avermectin to these hydration reaction conditions, and encouraged us to further explore the potential application of this method with other avermectin substrates.[13]

Avermectin B_1 can be easily converted into its conjugated isomer $\Delta^{2,3}$-avermectin B_1 **6** upon treatment with DBU in dichloromethane (80% yield).[14] 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_1. To the best of our knowledge, this would represent the first example of an avermectin derivative substituted at the C(2)-position.

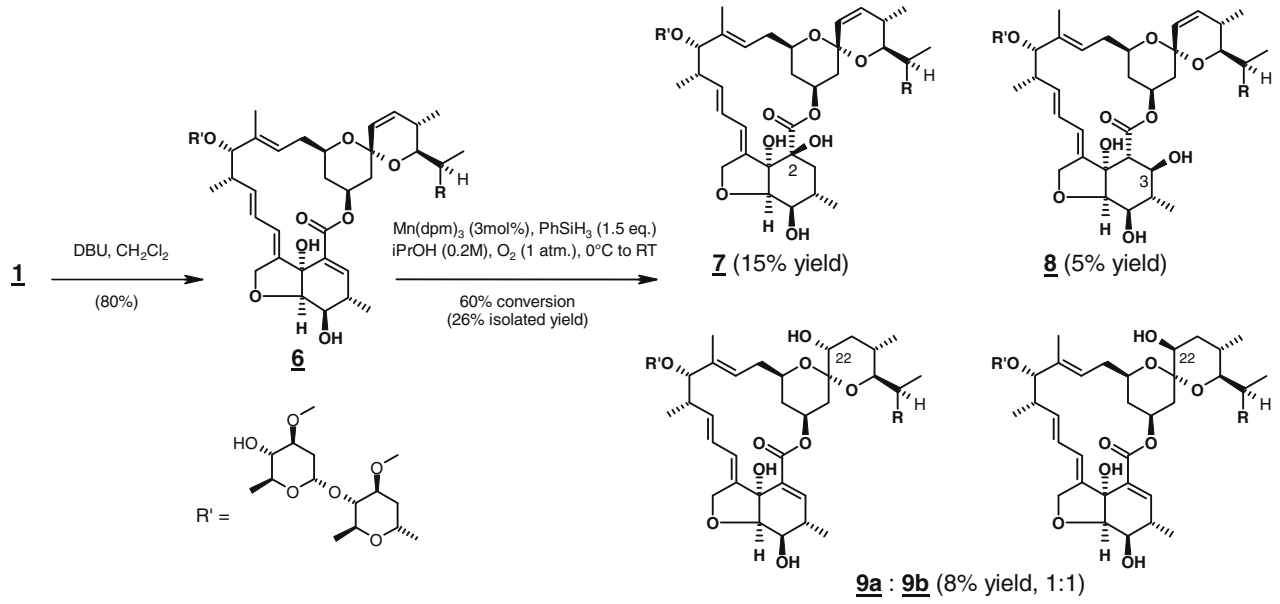
The standard procedure (method B in Scheme 1) was thus applied to the conjugated ester **6** (Scheme 2) and afforded after reductive work-up a mixture of four different monohydrated products, which were carefully separated by reverse phase preparative HPLC. 2-Hydroxy-3,4-dihydro-avermectin B_1 **7** 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_1 **8** in 5% yield.[15] 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**).[16] It is noteworthy that the transformation does not involve any protecting group, and although the reaction of **6** did not proceed regiospecifically, 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[17] led us next to consider avermectin B_1 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_1 **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.[18]

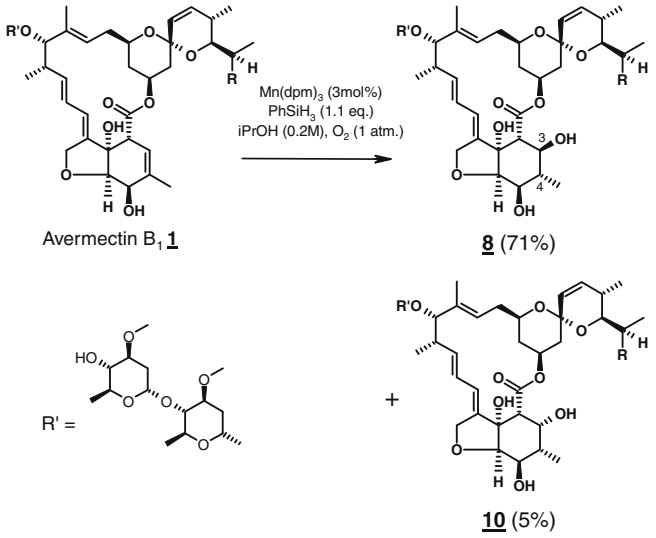
Although this Mn(III)-catalysed hydration reaction has already been applied to other substrates than unsaturated ketones, esters or nitriles,[5,9] the reaction with allylic alcohols is unprecedented and might represent a new application of this methodology as well as an attractive synthetic transformation for avermectin functionalisation. Thus, 4″,7-OTMS-avermectin B_1 **11** was converted into 4″,7-OTMS-3,4-dihydro-3-hydroxy-avermectin B_1 **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–



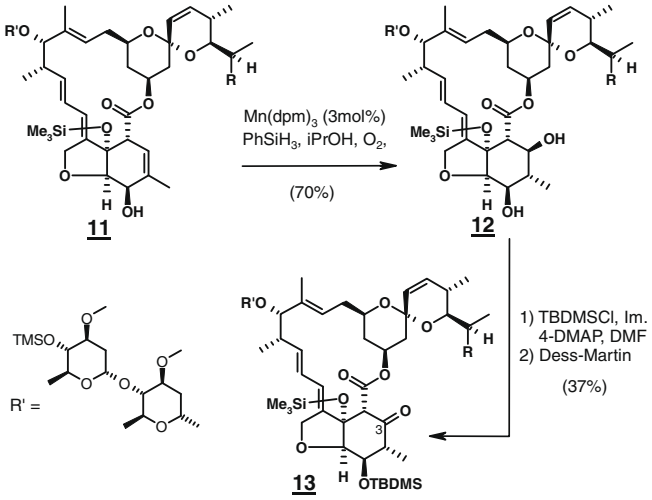
Scheme 2. Synthesis of 3,4-dihydro-4-hydroxy-avermectin B_1.



Scheme 3. Mn(III)-catalysed hydration reaction on $\Delta^{2,3}$-avermectin B_1.



Scheme 4. Mn(III)-catalysed hydration reaction on avermectin B_1.



Scheme 5. synthesis of 3,4-dihydro-3-keto-avermectin B_1.

Martin periodinane afforded ketone **13**, an attractive keto-lactone intermediate for further functionalisation at C(2).

Finally, the biological activity of some of these new hydrated avermectin derivatives was evaluated (Table 1). Although most of the new analogues displayed reduced activity compared to Abamectin **1**, (*S*)-3,4-dihydro-4-hydroxy avermectin B_1 **5b**, which could only be obtained via the Mn(III)-catalysed reaction (see Scheme 1), showed good level of activity against *Tetranychus urticae* (two-spotted spider mite) and similar level of activity than Abamectin against *Frankliniella occidentalis* (western flower thrips). Noteworthy is the difference of activity with its 4-epimer **5a**.

In summary, different avermectin substrates were subjected to the Mn(III)-catalysed hydration reaction discovered by Mukaiyama in 1990. This resulted in a straightforward access to several novel semi-synthetic avermectin derivatives: (1) 2-hydroxy-3,4-dihydro-avermectin B_1 **7**, the first example of a 2-substituted avermectin; (2) four regio- and diastereoisomers of the hydrated product of the 3,4-double bond **5a**, **5b**, **8** and **10** and (3) the novel 22,23-dihydro-22-hydroxy-avermectin B_1 **9a** and **9b**, epimeric at C(22).[19] The precise mechanism of this catalytic transformation has not yet been fully established although several hypothesis have been proposed,[5,6a,10] but there is no doubt that it has high potential for the selective transformation of complex natural products such as avermectins and the semi-synthesis of novel derivatives of biological interest, competing in that respect with biocatalytic transformations.[20]

Table 1
insecticidal and acaricidal activity of new avermectins

Compound	Fo[a]	Tu[b]
Abamectin **1**	3	0.01
5a	>3	0.8
5b	3	0.2
7	>3	3
8	>3	0.8
10	>3	0.8

Biological activities in the table are given as EC_{80} in ppm.
[a] *Frankliniella occidentalis* mixed population activity.
[b] *Tetranychus urticae* contact activity against adults.

Acknowledgements

Armando Cicchetti is thanked for the HPLC separation of the products of the reaction on Scheme 3. Marion Petrzika-Kitzka is thanked for LC–MS measurements. Dr. Jean Wenger and Dr. Alain De Mesmaeker are thanked for their support and availability for scientific discussion.

Supplementary data

Supplementary data (copies of ^{1}H NMR spectra for compounds **5a**, **5b**, **7**, **8**, **9a**, **9b** and **10**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.080.

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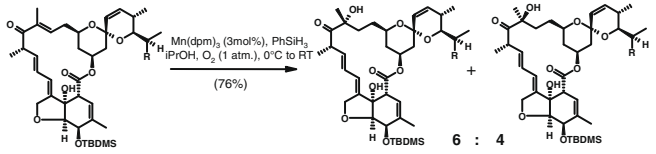
11. A full account on 1,4-hydride addition on 5-keto-avermectin B_1 and subsequent functionalisation at C(4) will be published separately.
12. See Ref. 18 for general procedure: Analytical data for **5a**: $C_{48}H_{74}O_{15}$, MW: 890.5. LC–MS: t_{RT}, B_{1a}: 7.85 min, 913.5 (M+Na), 891.5 (M+H), B_{1b}: 7.11 min. ^{1}H NMR (500 MHz, $CDCl_3$) selected data: 1.31 (s, 3H), 1.85 (dd, 1H, $J_{3eq,2}$ 3.5 Hz, H-3eq), 2.00 (t, 1H, $J_{3ax,2}$ and $J_{3ax,2}$ 12.5 Hz, H-3ax), 2.40 (d, 1H, J 10 Hz, 5-OH), 2.85 (dd, $J_{2,3}$ 3.5, 12.5 Hz, H-2), 3.66 (m, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) selected data: 25.7 (C-4a), 36.1 (C-3), 41.7 (C-2), 71.1 (C-5). Analytical data for **5b**: $C_{48}H_{74}O_{15}$, MW: 890.5. LC–MS: t_{RT}, B_{1a}: 7.36 min, 913.5 (M+Na), 891.5 (M+H). ^{1}H NMR (500 MHz, $CDCl_3$) selected data: 1.39 (s, 3H), 1.84 (dd, 1H, $J_{3eq,2}$ 3.5 Hz, H-3eq), 2.08 (t, 1H, $J_{3ax,2}$ and $J_{3ax,2}$ 12.5 Hz, H-3ax), 2.71 (dd, $J_{2,3}$ 3.5, 12.5 Hz, H-2), 3.63 (m, 1H, H-5); strong NOE effect (4.8%) observed between H-2 and CH_3-4a ^{13}C NMR (125 MHz, $CDCl_3$) selected data: 23.5 (C-4a), 36.1 (C-3), 44.5 (C-2), 79.5 (C-5).
13. C13–C14 position was also hydrated under those conditions from 4″,5-TBDMS-12-oxo-avermectin B_{1a} aglycon.



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15. Analytical data for **7**: $C_{48}H_{74}O_{15}$, MW: 890.5. LC–MS: t_{RT}, B_{1a}: 8.43 min, 913.4 (M+Na), 891.5 (M+H). ^{1}H NMR (500 MHz, $CDCl_3$) selected data: 1.19 (d, 3H, $J_{4a,4}$ 5.5 Hz, H-4a), 1.57 (dd, 1H, $J_{3,3}$ 15.0 Hz, $J_{3,4}$ 2.5 Hz, H-3eq), 1.97 (m, 1H), 2.20 (dd, 1H, $J_{3,3}$ 15.0 Hz, $J_{3,4}$ 10 Hz, H-3ax), 3.89 (dd, 1H, $J_{5,4}$ 9.0 Hz, $J_{5,6}$ 2.5 Hz, H-5), 3.92 (d, 1H, $J_{6,5}$ 2.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) selected data: 20.9 (C-4a), 31.3 (C-4), 34.3 (C-3), 73.3 (C-5), 87.6 (C-6).
16. Analytical data for **9a**: $C_{48}H_{74}O_{15}$, MW: 890.5. LC–MS: t_{RT}, B_{1a}: 7.10 min, 913.5 (M+Na), 323.3 (spiroketal fragment + 18); ^{1}H NMR (500 MHz, $CDCl_3$) selected data: 0.80 (d, 2H, $J_{24a,24}$ 5.5 Hz, H-24a), 1.40 (m, 1H, $J_{23ax,23eq}$ 25 Hz, $J_{23ax,22}$ 14.5 Hz, H-23ax), 1.69 (m, 1H, H-24),1.83 (m, 1H, H-23eq), 3.16 (m, 1H, H-25), 3.31 (dd, $J_{22,23ax}$ 14.5 Hz, $J_{22,23eq}$ 5.5 Hz, H-22); ^{13}C NMR (125 MHz, $CDCl_3$) selected data: 17.1 (C-24a), 31.7 (C-24), 37.2 (C-23), 71.6 (C-22), 76.1 (C-25). Analytical data for **9b**: $C_{48}H_{74}O_{15}$, MW: 890.5. LC–MS: t_{RT}, B_{1a}: 7.17 min, 913.5 (M+Na), 323.3 (spiroketal fragment + 18); B_{1b}: 6.52 min; ^{1}H NMR (500 MHz, $CDCl_3$) selected data: 0.80 (d, 2H, $J_{24a,24}$ 5.5 Hz, H-24a), 1.68 (m, 1H, H-23), 1.80 (m, 1H, H-23), 1.81 (m, 1H, H-24), 3.25 (m, $J_{24,25}$ 10 Hz, H-25), 3.44 (m, 1H, H-22); ^{13}C NMR (125 MHz, $CDCl_3$) selected data: 17.2 (C-24a), 25.5 (C-24), 35.5 (C-23), 70.2 (C-22), 76.8 (C-25).
17. The unsaturated spiroketal can be seen as a masked unsaturated ketone, which can explain the reactivity and the regiochemistry observed.
18. *Typical experiment*: Avermectin B_1 (1.75 g, 2 mmol) was dissolved in isopropanol (10 ml) and the resulting solution was cooled to 0 °C. The catalyst $Mn(dpm)_3$ (60 mg, 0.1 mmol, prepared as described by Magnus Ref. 6a, was added and the reaction mixture was placed under dioxygen (balloon). Phenylsilane (0.6 ml, 5 mmol) was added and the solution was stirred at 0 °C for 30 min then at room temperature for 2 h. Triethylphosphite (0.38 ml, 2.2 mmol) was added and the resulting mixture was stirred for 30 min, poured into water, extracted with ethyl acetate, washed with 1 N sodium hydroxide, water and then brine. The organic layer was dried over sodium sulfate then concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/ethyl acetate 65:35) to afford 4-(*S*)-3,4-dihydro-3-(*S*)-hydroxy-avermectin B_1 **8** (1.2 g, 71%) and 4-(*S*)-3,4-dihydro-3-(*R*)-hydroxy-avermectin B_1 **10** (0.1 g, 5%). Analytical data for **8**: $C_{48}H_{74}O_{15}$, MW: 890.5. LC–MS: t_{RT}, B_{1a}: 6.60 min, 913.5 (M+Na), 891.5 (M+H), B_{1b}: 6.00 min ^{1}H NMR (500 MHz, $CDCl_3$) selected data: 1.75 (m, 1H, H-4), 2.62 (d, 1H, $J_{2,3}$ 11.5 Hz, H-2), 3.60 (dd, 1H, $J_{5,4}$ 11.0 Hz, $J_{5,6}$ 4.0 Hz, H-5), 3.70 (d, 1H, $J_{2,3}$ 11.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) selected data: 42.5 (C-4), 55.1 (C-2), 71.8 (C-3), 72.3 (C-5). Analytical data for **10**: $C_{48}H_{74}O_{15}$, MW: 890.5. LCMS: t_{RT}, B_{1a}: 8.07 min, 913.5 (M+Na). ^{1}H NMR (500 MHz, $CDCl_3$) selected data: 1.76 (m, 1H, H-4), 2.54 (d, 1H, $J_{2,3}$ <2 Hz, H-2), 3.87 (m, 1H, H-5), 4.11 (br s, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) selected data: 36.2 (C-4), 48.4 (C-2), 68.7 (C-3), 73.6 (C-5).
19. Compounds **9a** and **9b** are the C(22) regioisomeric analogues of avermectin B_2, another natural product of this family. They did not show any activity at the highest tested concentration.
20. For a recent review, see: Holland, H. L. *Curr. Opin. Chem. Biol.* **1999**, *3*, 22–27.