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Synthesis and reactivity of 4″-phenylsulfinimine-avermectin B_1 and 4′-phenylsulfinimine-avermectin B_1 monosaccharide derivative

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Abstract—A short, efficient synthesis of 4″-(*R* or *S*)-4″-deoxy-4″-amino-4″-C substituted avermectin B_1 and 4′-(*R* or *S*)-4′-deoxy-4′-amino-4′-C substituted avermectin B_1 monosaccharide **3** and **4** has been developed through the nucleophilic addition of an organometallic reagent to an intermediate phenylsulfinimide **7**. These new derivatives of avermectin B_1 exhibited potent, broad spectrum insecticidal activity.

Avermectin B_1 is a member of the naturally occurring macrocyclic lactones with high activity against mites, dipterous leafminers, thrips and lepidoptera.[1] The successful commercialization of the two members of the class of avermectins in crop protection (abamectin and emamectin) prompted us to investigate new interesting analogues of avermectins (Fig. 1).

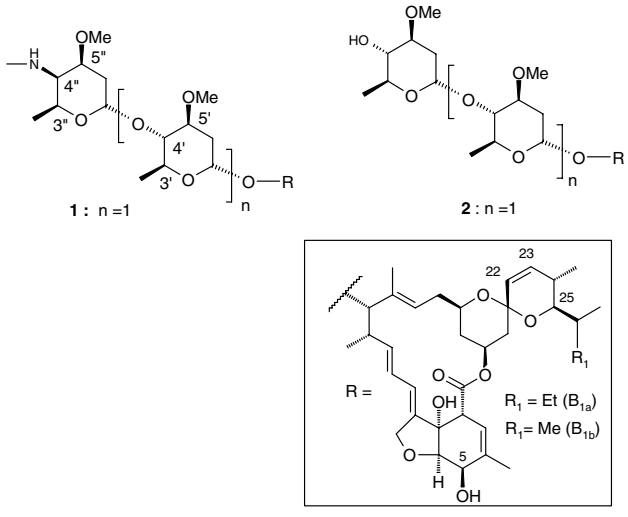

Figure 1. (1) Emamectin, (2) abamectin B_1.

One of the most promising classes of avermectins are the 4″-aminoavermectins. For example, the use of 4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 benzoate (emamectin's salt) as an agriculture insecticide has achieved commercial success. Our interest in these complex natural products has led to the preparation of a new class of analogues having an quaternary carbon in the 4″ position. Consequently, we became interested in developing a practical synthesis of **3** and **4** that could serve as a general route to 4″-(*S* or *R*)-4″-deoxy-4″-amino-4″-C substituted avermectin B_1 and 4′-(*S* or

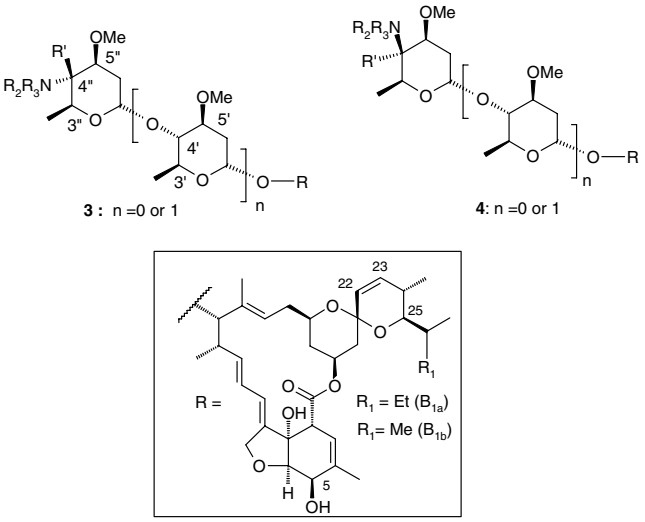

Figure 2. Targets.

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R)-4′-deoxy-4′-amino-4′-C substituted avermectin B_1 monosaccharide (Fig. 2).

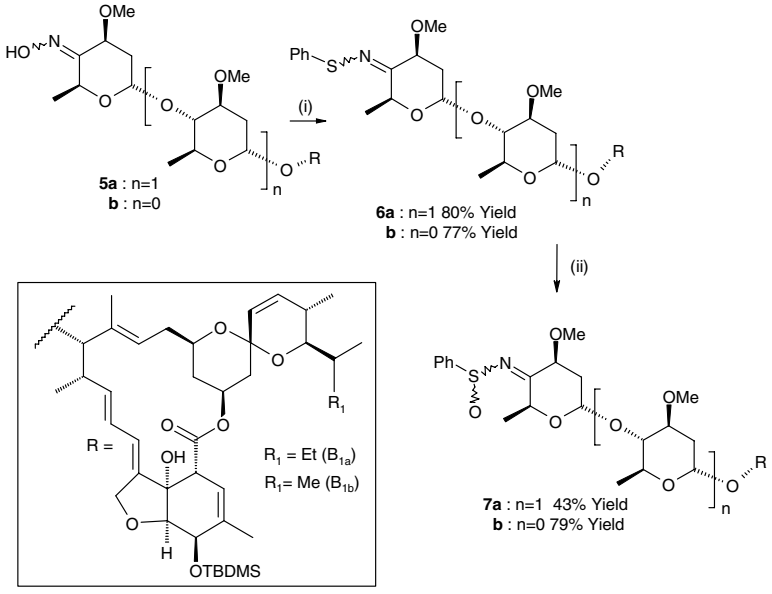
We have recently described the use of an intermediate *tert*-butylsulfinimide in the synthesis of modified nucleoside building blocks.[2] We applied this concept to the synthesis of 4″-*R* and *S*-amino-4″-C-avermectin B_1 derivatives and want to disclose our preliminary results. Our initial approach towards the synthesis of sulfinimine was to use the commercial (*S*)-*tert*-butylsufinamide.[3] The classical method to synthesize sulfinimine involves the reaction of a carbonyl compound with the (*S*)-*tert*-butylsufinamide in the presence of tetraethyl orthotitanate in THF at 60 °C. This experiment failed to provide any of the desired compound with the 5-OTBDMS-4″-deoxy-4″-oxo-avermectin B_1, even after extended reaction times and elevated temperature. In addition we tried, without success, other conditions such as azeotropic distillation of water with benzene, with or without copper sulfate. In every case, we obtained only the starting material or decomposition products.

In order to solve this problem, we turned our attention to the synthesis of *S*-phenylsulfinimines as an alternative approach. It is known from the literature[4] that an oxime derivative can react with the diphenyl disulfide and tributylphosphine to give the corresponding *S*-phenylsulfinimine. The oxidation of this *S*-phenylsulfinimine could give the desired sulfinimide.

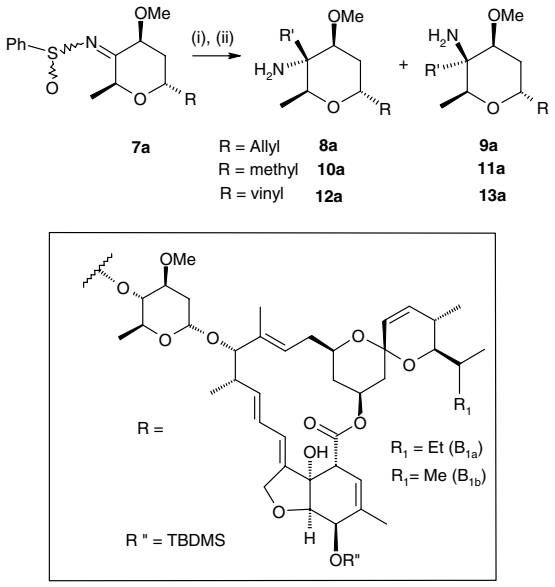
All avermectin B_1 derivatives synthesized are a mixture of B_{1a} and B_{1b} components,[5] present already in the commercially available starting material. The required oxime **5** was synthesized in one step from the corresponding ketone in 90–94% yield.[6] The reaction of oxime **5** with the diphenyl disulfide and tributylphosphine in tetrahydrofuran at 0 °C gave the *S*-phenylsulfinimine **6** in 77–80% yield. The oxidation of **6** with *m*-CPBA in a biphasic system gave a mixture of two diastereoisomers of the *S*-phenylsulfinimine **7**.[7] The same reaction in single-phase (CH_2Cl_2) oxidation gave a low yield and a complex mixture. The acid sensibility of the S–N bond in *S*-phenylsulfinimine **6**[7] could explain this result. It should be noted that for the oxime **5**, the *S*-phenylsulfinimine **6** and the *S*-phenylsulfinimine **7** the geometry of the double bond is unknown. The two mixtures of diastereoisomers *S*-phenylsulfinimine **7a** and **7b** are unstable on silica gel as well as in basic or acidic solvents. Consequently, it is highly challenging to separate them through purification techniques and so in general we worked with the mixture, after a fast purification by chromatography. The *S*-phenylsulfinimine **6a** and **6b** is also unstable, but less so than **7a** and **7b** (Scheme 1).

Literature reports describe the nucleophilic attack of allylmagnesium chloride[8] or benzyl magnesium chloride[9] on *S*-phenylsulfinimine derivatives. In the case of other Grignard reagents, the possible outcome of the reaction appears to be the deprotonation at the alpha imino carbon[7] or the nucleophilic addition on the sulfur atom.[8,9] Reaction of allylmagnesium bromide with **7a** in diethyl ether at 0 °C, followed by the cleavage of the S–N bond with a mixture of isopropanol, trifluoroacetic acid in dichloromethane[10] gave compounds (**8a**/**9a**) resulting from the desired nucleophilic attack to the imine bond. The addition of other Grignard reagents to *S*-phenylsulfinimine **7a** leads, after the cleavage of the S–N bond, to 4″-(*S* or *R*)-4″-deoxy-4″-amino-4″-C-avermectin B_{1a} derivatives (see Scheme 2, Table 1).

As a 5-O protected form it was possible to separate stereoisomers **8a**, **9a** and **10a**, **11a**. For compounds **12a** and **13a**, resulting from the nucleophilic attack of vinyl magnesium bromide, separation was possible only after deprotection of the 5-hydroxyl group with a complex of 70% HF–pyridine in tetrahydrofuran.



Scheme 1. Preparation of *S*-phenylsulfinimines derivatives **7**. Reagents and conditions: (i) tributylphosphine, diphenyl disulfide, THF, 0 °C; (ii) chloroform, saturated solution of sodium hydrogencarbonate, *m*-chloroperbenzoic acid, 0 °C.



Scheme 2. Addition of Grignard reagents to *S*-phenylsulfinimines derivatives **7a**. Reagents and conditions: (i) Grignard reagent, diethyl ether, 0 °C; (ii) dichloromethane, isopropanol, trifluoroacetic acid, 0 °C.

Table 1. Reaction of Grignard reagents with **7a**

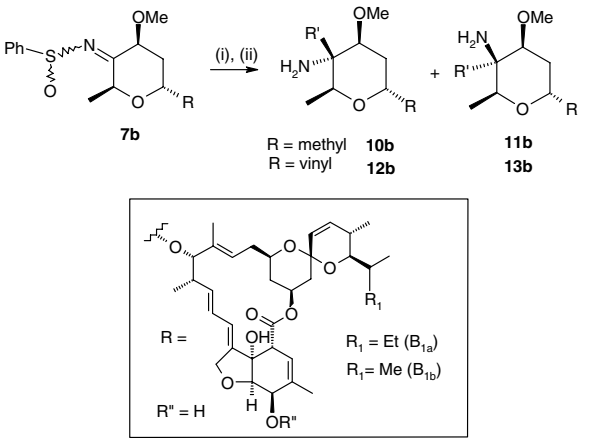
Entry	R′MgX	Yield for two steps[a] (%)	Ratio
1	AllylMgBr	31	**8a/9a**: 3/7[b]
2	MeMgCl	19	**10a/11a**: 1/1[b]
3	VinylMgBr	43	**12a/13a**: 4/7[c]

[a] Not optimized.
[b] Ratio determined after isolation.
[c] Ratio determined by NMR.

The configuration of C(4″) in the isomeric pairs was established by measuring the ^{13}C chemical shift of the allyl CH_2 or the CH_3 groups, since it is well documented that an axial CH_2 or CH_3 absorbs at 5–7 ppm higher field than the equatorial equivalent.[11] The deprotected isomers of **12a** and **13a** were distinguished by the NOEs observed between the vinyl group in equatorial position and the two axial protons H-3″ and H-5″ in **13a**. In the case of the two deprotected isomers of **11a** and **10a**, the observation of an analogous NOE effect between the equatorial CH_3 group and the two axial protons H-3″ and H-5″ corroborates the results based upon the ^{13}C chemical shifts.

We then turned our attention to the 5-OTBDMS-4′-deoxy-4′-phenylsulfinimine-avermectin B_1 monosaccharide **7b**. Reaction of Grignard reagents with **7b** in diethyl ether at 0 °C, followed by the cleavage of the S–N bond and deprotection of the hydroxyl group in position 5 with a mixture of methanol and methanesulfonic acid gave the desired compounds (Scheme 3, Table 2).

As before, the vinyl derivatives **12b** and **13b** were distinguished by the NOEs observed between the vinyl group in equatorial position and the two axial protons H-3′ and H-5′ in **13b**. In the case of the methyl derivatives



Scheme 3. Addition of Grignard reagents to *S*-phenylsulfinimines derivatives **7b**. Reagents and conditions: (i) Grignard reagent, diethyl ether, 0 °C; (ii) methanol, methanesulfonic acid, 0 °C.

Table 2. Reaction of Grignard with **7b**

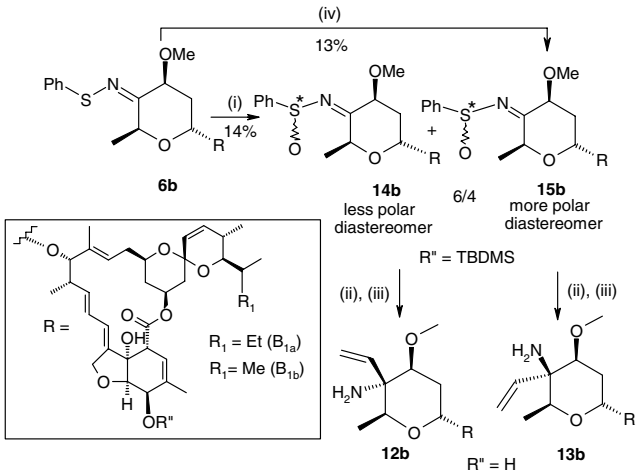
Entry	R′MgX	Yield for two steps (%)	Ratio
1	MeMgCl	31	**10b/11b**: 10/1[a]
2	VinylMgBr	59	**12b/13b**: 4/3.2[a]

[a] Ratio determined after isolation.

10b and **11b**, we based our analysis again on the ^{13}C chemical shifts: the methyl of **10b** is axial (14.5 ppm) and the methyl of **11b** is equatorial (22.1 ppm).

In this case, the mixture of the diastereoisomers of *S*-phenylsulfinimine **7b** was separated on silica gel to give **14b** and **15b** in total of 14% yield. This low yield is explained by the instability of **7b**. Reaction of vinylmagnesium bromide with **14b** in diethyl ether at 0 °C, followed by the cleavage of the S–N bond and deprotection of the hydroxyl in the 5 position with a mixture of methanesulfonic acid in methanol gave **12b** in 65% yield. The same reaction with **15b** gave **13b** in 59% yield. Consequently, we propose that the sulfoxide could direct the addition of the organometallic on the imine bond via either Ellman model[12a] or Davis model.[12b] Unfortunately, we were not able to determine the configuration of the *S*-phenylsulfinimine **14b** or **15b** (Scheme 4) and consequently understand clearly the factors governing the addition of the organometallic. In addition, it should be made clear that the instability of **6**, **7** and avermectin B_1 to acidic and basic conditions lowers the yield of the reactions.

Another interesting result was obtained when we used *trans*-3-phenyl-2-(phenylsulfonyl)-oxaziridine (Davis reagent) in tetrachloromethane as oxidant. In this case, the reaction of **6b** with this reagent gave compound **15b** as the major product in 13% yield after purification. Use of *m*-CPBA gave **14b** and **15b** and to explain this, we suggest that the oxygen lone pair of an oxygen of the carbohydrate part of avermectin B_1 could have a moderate directing effect via hydrogen bonding with *m*-chloroperbenzoic acid during the formation of **6b**.[13] However, we propose that when Davis reagent is used as oxidant, hydrogen bonding is not possible with the



Scheme 4. Addition of Grignard reagents to pure *S*-phenylsulfinimines derivatives **14b** and **15b**. Reagents and conditions: (i) chloroform, saturated solution of sodium hydrogencarbonate *m*-chloroperbenzoic acid, 0 °C; (ii) Grignard reagent, diethyl ether, 0 °C; (iii) methanol, methanesulfonic acid, 0 °C; (iv) Davis reagent, CCl_4.

carbohydrate and consequently the reaction is controlled by steric hindrance. The reaction of **15b** (obtained with Davis reagent) with vinylmagnesium bromide gave **13b** in 38% yield after deprotection with a mixture of methane sulfonic acid in methanol.

In conclusion, we have shown that the *S*-phenylsulfinimine group could be used as activating group for the preparation of 4″-(*S* or *R*)-4″-deoxy-4″-amino-4″-C substituted avermectin B_{1a} derivatives and 4′-(*S* or *R*)-4′-deoxy-4′-amino-4′-C substituted avermectin B_{1a} monosaccharide derivatives. Complementary work on these types of avermectins is in progress and will be reported in future publications. These new types of avermectin derivatives have shown an improved biological profile (highly active against mites, dipteran leaf miners, thrips, and lepidoptera) by comparison with the known avermectin derivatives.[14] The method described here should be valuable in the synthesis of other sugar-containing macrolide antibiotics.

Acknowledgements

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Supplementary data

General experimental procedures, full ^1H NMR spectra and HPLC–MS procedures and data for compounds **6a**–**15b** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.019.

References and notes

1. For example: Rugg, D.; Buckingham, S. D.; Sattelle, D. B.; Jansson, R. K. *Comprehensive Molecular Insect Science* **2005**, Vol. 5, 25; *Ivermectin and Abamectin*; Campbell, W. C., Ed.; Springer: New York, 1989; Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.
2. Jung, P. M. J.; Beaudegnies, R.; De Mesmaeker, A.; Wendeborn, S. *Tetrahedron Lett.* **2003**, *44*, 293.
3. For example: Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913; Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.
4. For example: (a) Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1986**, *12*, 2243; (b) Esteban, J.; Costa, A. M.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **2004**, *45*, 5563.
5. The B series have an OH group in the 5-position. The 'a' series and the 'b' series are compounds in which the substituent in position 25 is, respectively, a *sec*-butyl radical and an isopropyl group, respectively. The number 1 in the name of the compounds means that carbon atoms 22 and 23 are linked by a double bond. The ratio of B_{1a}/B_{1b} is about 9/1.
6. For example: (a) Linn, B. O.; Mrozik, H. Merck and Co., Inc., USA. US 4873224 A, 1989; Application: US 88-197731 19880523; (b) Nagai, K.; Sunazuka, T.; Shiomi, K.; Harder, A.; Turberg, A.; Omura, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3943; (c) Meinke, P. T.; Sinclair, P.; Mrozik, H.; O'Connor, S.; Ostlind, D. A.; Shoop, W. L.; Arison, B. H.; Fisher, M. H. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 537.
7. Davis, F. A.; Friedman, A. J.; Nadir, U. K. *J. Am. Chem. Soc.* **1978**, *100*, 2844.
8. Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4; Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.
9. Moreau, P.; Essiz, M.; Mérour, J.-Y.; Bouzard, D. *Tetrahedron: Asymmetry* **1997**, *8*, 591.
10. For example: Asensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; Soler, J. G.; Meille, S. V.; Panzeri, W.; Viani, F.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, *8*, 1449.
11. Schneider, H. J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.
12. (a) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883; (b) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396.
13. De Sousa, S. E.; Kee, A.; O'Brien, P.; Watson, S. T. *Tetrahedron Lett.* **1999**, *40*, 387; Erzen, E.; Koller, J.; Plesnicar, B. *J. Org. Chem.* **2001**, *66*, 5155; Adam, W.; Mitchell, C. M.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **1999**, *64*, 785.
14. Jung, P. J. M.; Pitterna, T.; Quaranta, L.; Hueter, O. F.; Murphy-Kessabi, F. M. WO 2005097816 A1.