Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 707–709

First example of an Ugi type reaction on phenylsulfinimine-avermectin B_1 derivatives

Emmanuel Callens, Ottmar Hüter, Emmanuel Lamy, Patrick Lüthi, Tammo Winkler and Pierre M. J. Jung*

Syngenta Crop Protection AG, CH-4002 Basel, Switzerland

Received 25 October 2006; revised 13 November 2006; accepted 14 November 2006
Available online 8 December 2006

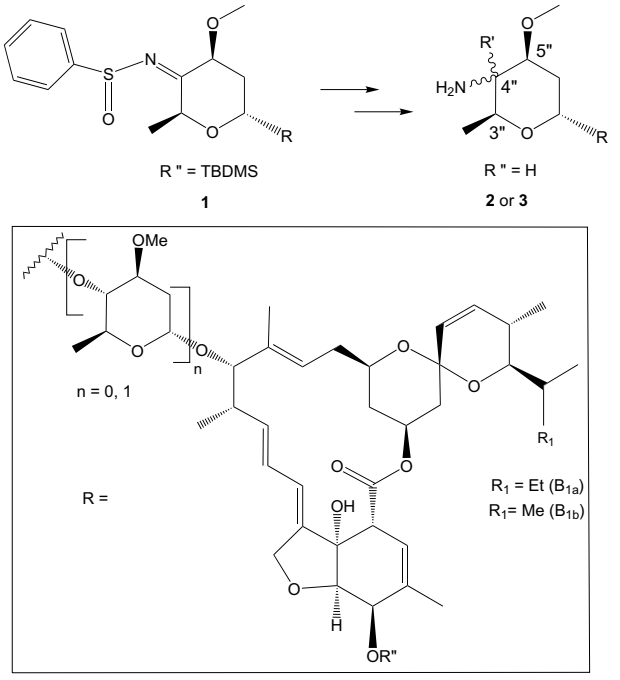
Abstract—A short synthesis of 4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-alkylcarbamoyl-avermectin B_1 **4** has been developed through the diastereoselective Ugi reaction to an phenylsulfinimide intermediate.

Avermectin B_1 is a member of a group of naturally occurring macrocyclic lactones having high levels of activity against mites, dipterous leafminers, thrips and lepidoptera.[1]

In our effort to identify new interesting analogues of avermectin, we have shown that an *S*-phenyl sulfinimine group in position 4″ of avermectin derivatives (Scheme 1, compound **1**) could be used as an activating group for the preparation of 4″-(*S* or *R*)-4″-deoxy-4″-amino-4″-alkyl-avermectin B_{1a} derivatives and 4′-(*S* or *R*)-4′-deoxy-4′-amino-4′-alkyl-avermectin B_{1a} monosaccharide derivatives (Scheme 1, compounds **2** and **3**).[2] In addition, these new types of avermectin derivatives have shown an improved biological profile (highly active against mites, dipterous leaf miners, thrips and lepidoptera) compared with the standard avermectin derivatives.[3]

In the context of this program directed towards the synthesis of modified avermectin B_{1a} with improved biological properties, we became interested in developing a synthesis of **4** (Fig. 1).

Multiple component reactions are of great value for the contemporary synthesis, because large arrays of compounds with diverse substitution patterns can be prepared in one step under mild reaction conditions.



Scheme 1. $n = 1$. Compound **1**: 5-OTBDMS-4″-deoxy-4″-phenylsulfinimine-avermectin B_1 derivatives, **2**: 4″-(*S*)-4″-deoxy-4″-amino-4″-R′-avermectin B_{1a} derivatives and **3**: 4″-(*R*)-4″-deoxy-4″-amino-4″-R′-avermectin B_{1a} derivatives.

A classical example of a multiple component reaction is the four-component Ugi reaction, which has emerged as a powerful tool for rapid identification of lead

Keywords: Avermectin; Ugi reaction.
* Corresponding author. Tel.: +41 613236904; fax: +41 613238529; e-mail: pierre.jung@syngenta.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.089

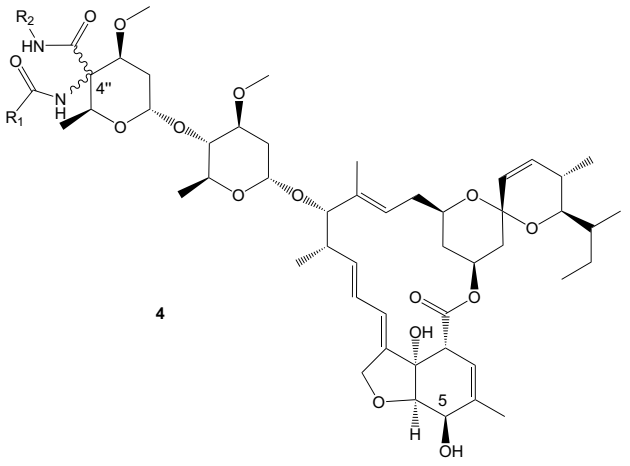
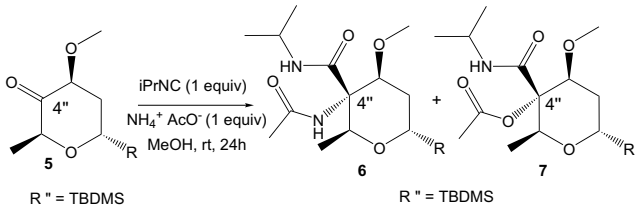


Figure 1. Targets.

compounds in drug discovery.[4] We designed a synthetic approach using a modification of the Ugi reaction with avermectin B_1 derivatives.

Initial studies demonstrated that the nucleophilic addition of an isocyanide to a 4″-imine gave only trace amounts of the desired product along with a side product derived from the Passerini reaction.[5]

For example, the reaction of 5-TBDMS-4″-oxo-avermectin B_{1a} **5**[6] in the presence of ammonium acetate and isopropyl isocyanide in methanol at room temperature[7] gave a mixture of **6** and **7**. The desired compound **6** was obtained in low yield (<10%, Scheme 2).

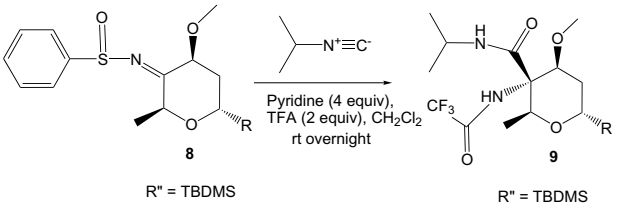


Scheme 2. Initial studies for the synthesis of 4″-(*S*) or (*R*)-4″-deoxy-4″-acetylamino-4″-isopropylcarbamoyl-avermectin B_{1a}.

In order to improve the yields, we turned our attention to the more reactive and stable imine derived from *S*-phenylsulfinimine. The reaction of a sulfinimine under Ugi conditions is, to the best of our knowledge, not described in the literature. Only the use of *S*-phenylsulfonylimine derivatives with isocyanide for the synthesis of heterocycles mediated by 1,3 dipoles and zwitterionic intermediates was found in the literature.[8] The direct addition of an isocyanide to *S*-phenylsulfonylimines was described using a metal catalyst[9] for the synthesis of heterocycles. More interestingly, the reaction of isocyanoacetamides with *S*-phenylsulfonylimine derivatives gives 2,4-disubstituted-5-amino-1,3-oxazoles via the addition of isocyanide to *N*-sulfonylimines.[10]

The required phenylsulfinimine **8** was synthesized from the corresponding oxime derivatives in two steps via the sequence already described in previous studies.[2,3]

The reaction of 5-OTBDMS-4″-deoxy-4″-phenylsulfinimine-avermectin B_1 **8** with a mixture of pyridine (4 equiv), trifluoroacetic acid (2 equiv) and isopropylisocyanide (1 equiv) in dichloromethane gave, after purification, a mixture of 5-OTBDMS-4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-isopropylcarbamoyl-avermectin B_{1a} **9** and 5-OTBDMS-4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-isopropylcarbamoyl-avermectin B_{1b} **9** in 23% yield (Scheme 3).[11]



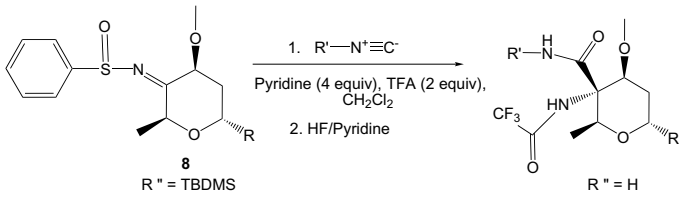
Scheme 3. Synthesis of 5-OTBDMS-4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-isopropylcarbamoyl-avermectin B_{1a} **9**.

We isolated compound **9** only with the *S* configuration in 4″ position. One of the side products identified was the compound resulting from the Passerini reaction. The crude mixture was complex and we were not able to identify the other by-products. It should be made clear that the instability of **8** to acidic and basic conditions lowers the yield of the reaction and gives a complex mixture of by-products. Consequently, we cannot affirm that this diastereomer with the *R* configuration in 4″ position is not formed during this reaction. However, we never isolated or observed this diastereoisomer.

Various isocyanides were readily converted to the corresponding Ugi product in low to moderate yields. In general, the Ugi reaction was followed by the deprotection of the 5-hydroxyl group with a complex of 70% HF–pyridine in tetrahydrofuran (Scheme 4, Table 1).[2,3]

The configuration of C(4″) was determined on deprotected derivatives by NMR through the measurement of the coupling constant between H-5″ and the amide carbonyl carbon attached to C(4″). This three bond coupling constant shows the usual Karplus type dependence on the dihedral angle and has been measured, for example, in the two anomers of neuraminic acid.[12] Since the amide carbon couples also with the two NH protons and H-3″, the coupling to H-5″ cannot easily be extracted from the fully proton coupled carbon spectrum. It was therefore measured for two examples (entries 2 and 5) in the reverse configuration using a selective carbon pulse following the procedure of R. Freeman et al.[13] The coupling constant was determined to be 8.3 Hz, proving a trans diaxial arrangement.[12] Subsequently, an HMBC optimized for 8 Hz was measured for all compounds. All spectra show an intense cross peak between H-5″ and the amide carbonyl carbon attached to C(4″), which proves the trans arrangement as drawn for **9**.

In conclusion, we have shown that the *S*-phenyl sulfinimine group could be used as activating group for the



Scheme 4. General scheme for the synthesis of 4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-alkylcarbamoyl-avermectin B_{1a}.

Table 1. Reaction of isocyanides with sulfinimine **8**

Entry	R′	Yield (%) for two steps[a]
1	$CH_3CH_2OC(O)CH_2$	27
2	*t*-Bu	14
3	*cyclo*-Hexyl	19
4	Me_3SiCH_2	19
5	Bu	16
6	$CH_3OCH_2CH_2$	25
7	*N*-BocNHCH_2CH_2	10
8	Me	6
9	*cyclo*-Propyl	9
10	*cyclo*-Pentyl	10
11	Et	8

[a] Not optimized.

preparation of 4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-alkylcarbamoyl-avermectin B_1 derivatives. The method described here should be valuable in the synthesis of other sugar-containing macrolide antibiotics.

Acknowledgement

We would like to thank Johan Drapel for mass spectrometry analysis.

Supplementary data

Full ^{1}H NMR spectra and HPLC–MS data for compounds **9** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.089.

References and notes

1. For example: Rugg, D.; Buckingham, S. D.; Sattelle, D. B.; Jansson, R. K. *Comprehensive Molecular Insect Science* **2005**, *5*, 25; *Ivermectin and Abamectin*; Campbell, W. C., Ed.; Springer-Verlag: New York, 1989; Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.
2. Lamy, E.; Lüthi, P.; Paturel, C.; Winkler, T.; Jung, P. M. J. *Tetrahedron Lett.* **2006**, *47*, 5657.
3. Jung, P. M. J.; Pitterna, T.; Quaranta, L.; Hueter, O. F.; Murphy-Kessabi, F. M. WO 2005097816 A1.
4. For example: (a) Ugi, I.; Lohberger, S.; Karl, R. The Passerini and Ugi Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 1083; (b) Domling, A.; Ugi, I. *Angew. Chem.* **2000**, *39*, 3168.
5. Hüter, O. F.; Syngenta Crop Protection AG, unpublished results.
6. 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 and an isopropyl group. 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.
7. Bossio, R.; Marcaccini, S.; Paoli, P.; Papaleo, S.; Pepino, R.; Polo, C. *Liebigs Ann. Chem.* **1991**, 843.
8. For example: Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427; Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659.
9. For example: Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331.
10. For example: Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J. *Tetrahedron* **1998**, *54*, 12445.
11. Typical experiment: To a solution of 7.39 g of 5-OTBDMS-4″-deoxy-4″-phenylsulfinimine-avermectin B_1 **8** in 150 ml of dichloromethane at −78 °C was added successively 1970 μl of pyridine, 840 μl of isopropylisocyanide and 940 μl of trifluoroacetic acid. The mixture was stirred overnight at room temperature. The mixture was poured onto a mixture of a saturated solution of sodium hydrogenocarbonate and ethyl acetate. the aqeuous phase was extracted twice with ethyl acetate; the combined organic phases were dried over sodium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel with cyclohexane/ethyl acetate, yielding 5-OTBDMS-4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-isopropylcarbamoyl-avermectin B_{1a} **9** and 5-OTBDMS-4″-(*S*)-4″-deoxy-4″-trifluoroacetylamino-4″-isopropylcarbamoyl-avermectin B_{1b} **9** (1.63 g, 23% yield).
12. For example: Haverkamp, J.; Spoormaker, T.; Dorland, L.; Vliegenthart, J. F. G.; Schauer, R. *J. Am. Chem. Soc.* **1979**, *101*, 4851; Hori, H.; Nakajima, T.; Nishida, Y.; Ohrui, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317; Prytulla, S.; Lauterwein, J.; Klessinger, M.; Thiem, J. *Carbohydr. Res.* **1991**, *215*, 345.
13. Blechta, V.; del Rio-Portilla, F.; Freeman, R. *Magn. Reson. Chem.* **1994**, *32*, 134.