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Some Selective Reactions of Moenomycin A[†]

Stefan Vogel,[a] Andrij Buchynskyy,[a] Katka Stembera,[a] Karin Richter,[a] Lothar Hennig,[a]
Dietrich Müller,[b] Peter Welzel,[a,*] Françis Maquin,[c]
Christian Bonhomme[c] and Maxime Lampilas[c,*]

[a]*Universität Leipzig, Institut für Organische Chemie, Johannisallee 29, D-04103 Leipzig, Germany*
[b]*Fakultät für Chemie der Ruhr-Universität, D-44780 Bochum, Germany*
[c]*Aventis, F-93230 Romainville, France*

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Abstract—A number of new moenomycin A derivatives have been prepared. Their antibiotic properties highlight the very specific recognition of moenomycin A at the transglycosylase binding site which is the basis of the transglycosylase inhibiting property of moenomycin A (**4a**). © 2000 Elsevier Science Ltd. All rights reserved.

The transglycosylation reaction in peptidoglycan biosynthesis is a highly promising target for new antibiotics. Two classes of compounds, the moenomycins (see moenomycin A, **4a**) and (at least some of) the glycopeptides[1] have been shown to interfere with this biosynthetic step. Interestingly, their modes of action are completely different. Whereas glycopeptides have been shown to interfere with the substrates of the transglycosylation reaction,[2] the moenomycins interact with the enzyme(s).[3] Although the moenomycins are, thus, very interesting lead compounds for the development of new antibiotics, their complicated structures with many different functional groups has rendered it difficult to find reaction conditions allowing selective transformations.

- It has been demonstrated that the lipid part can be hydrogenated selectively. The decahydro derivative thus obtained has high antibiotic activity[4] but may suffer from poor pharmacokinetics.[5]
- $K_3[Fe(CN)_6]$ oxidation provides in high yield an antibiotically active compound lacking part A.[4] Starting from this derivative the lipid moiety has selectively been oxidized with singlet oxygen and with osmium tetroxide to provide antibiotically inactive analogues with hydroxylated side-chains.[6]
- The reaction of unit A of moenomycin A with an aromatic diazonium salt gave an azo compound which underwent a Japp–Klingemann cleavage of the five-membered ring to furnish an amidrazone which finally recyclized to provide a triazole. This reaction has been employed for attaching reporter groups to moenomycin. Since part A of moenomycin is not relevant for the antibiotic activity all reactions at this site of the molecule led to antibiotically active derivatives.[7]
- A number of periodate-based degradation reactions have been used to convert moenomycin A to tri- and disaccharide analogues.[8]
- An enzymatic cleavage of the phosphate bond at the anomeric carbon of unit F of moenomycin led to antibiotically inactive cleavage products.[9]
- A Pd(0)-mediated cleavage of the allyl ether bond has allowed to convert **4a** into compound **2**.[6]
- All other methods that have been employed to elucidate the structure of moenomycin A provided the degradation products only in moderate or low yields.[10]

In the present communication we wish to report a number of new reactions that permit to modify moenomycin A selectively. It should be noted that all reactions have to be performed in highly polar media.

Refluxing a moenomycin A solution in 2:8 butylamin:methanol for 48 h followed by silica gel flash chromatography (FC, ethyl acetate:1-propanol:water 4:5:3) furnished the decarbamoyl product **4b** in 35% yield.[11] The

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*Corresponding authors. P. Welzel, fax: +49-9736599; e-mail: welzel@organik.chemie.uni-leipzig.de; M. Lampilas, fax: +33-1-49915087; e-mail: maxime.lampilas@aventis.com

[†]Dedicated to Professor Günter Wulff on the occasion of his 65th birthday.

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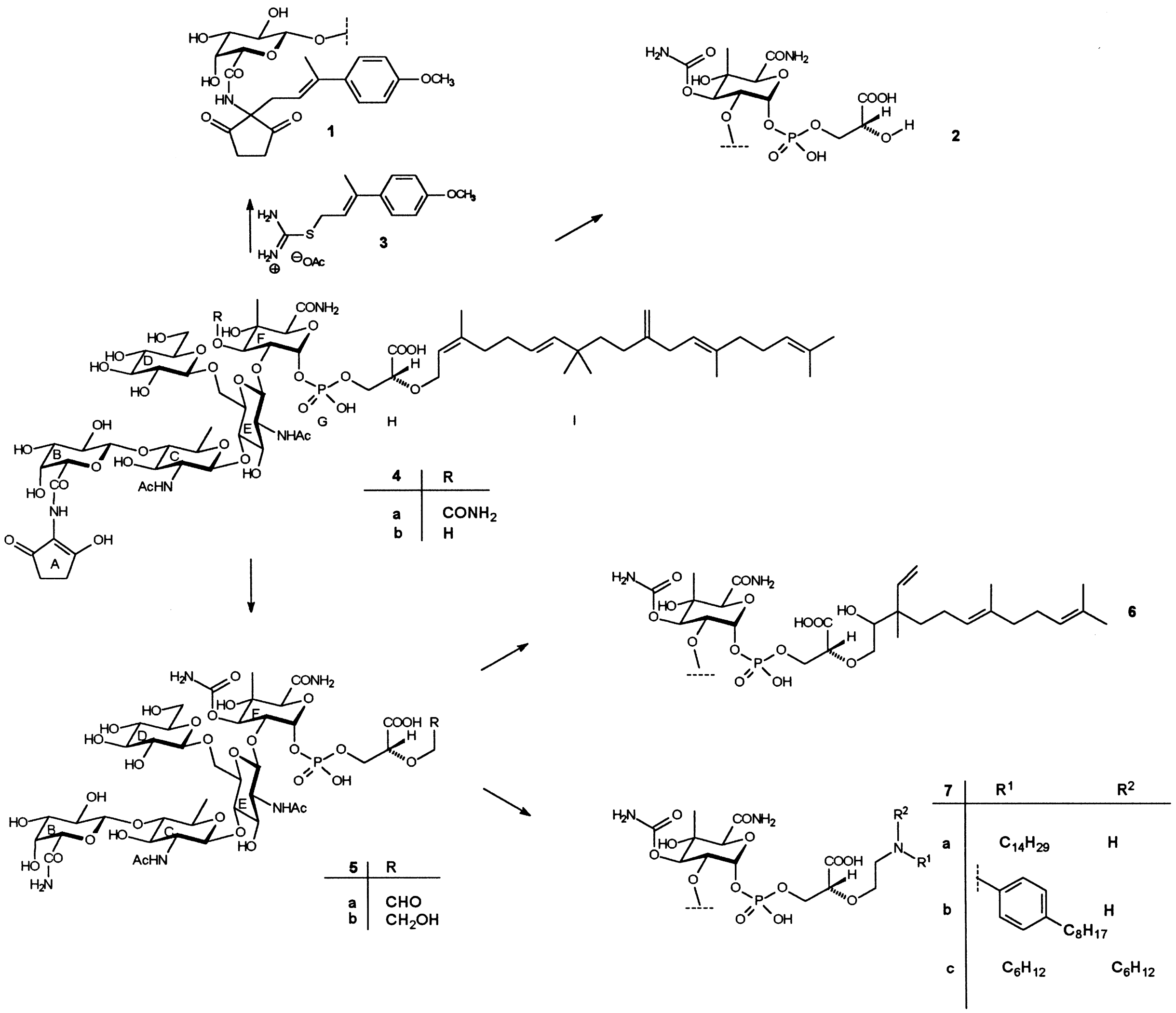

Formulae 1–7.

minimal inhibitory concentration (MIC) against several *Staphylococcus aureus* strains[12] was in the range of 2.7×10^{-6} mol/L, whereas under identical conditions moenomycin A had a MIC of 6.9×10^{-9} mol/L. This very remarkable result is a compelling evidence for the great importance of the moenomycin unit F and the carbamoyl group in particular as regards the transglycosylase-inhibiting properties of **4a**.

When a solution of moenomycin A and isothiuronium salt **3** (2.5 equiv) was stirred in water at 60 °C for 49 h compound **1** was obtained in 52% yield after lyophilization, FC (silica gel, 1-propanol:water 5:1) and medium pressure chromatography (RP_{18}, acetonitrile:water 1:1, FAB MS, $m/z = 1764.7$, $[M+Na]^+$). This is another reaction of the chromophore unit A with a soft electrophile[7] which may be useful for the attachment of reporter groups to moenomycin.

Stirring of moenomycin A under argon in a 0.01 M acetate buffer (pH 5.5) at 80 °C for 94 h caused cleavage of the allyl ether bond to provide **2** in 45% yield after FC (1-propanol:water 7:2) and Sephadex G-10® gel filtration. The same compound has previously been obtained by Pd(0)-mediated allyl ether cleavage and was found to be devoid of antibiotic activity.[6] It is conceivable that loss of the lipid part under the solvolytic conditions is of relevance in the context of the moenomycin stability problem. Previously it was assumed that oxidation of the side chain causes loss of antibiotic activity.[6,7]

On ozonolytic degradation of moemoycin A (in methanolic solution at −78 °C) a precipitate was formed in 98% yield which according to all spectroscopic data is aldehyde **5a** (soluble in water). The structure **5a** is well in agreement with the ESI MS spectrum (negative mode, $m/z = 1186.7$, $[M-H]^-$). According to the NMR spectra the aldehyde is mainly hydrated (chemical shift of the hydrated aldehyde carbon: $\delta = 88.0$). On reduction with sodium borohydride in aqueous solution, primary alcohol **5b** was formed in 91% yield (purification by Sephadex LH20® gel filtration (GF), elution with water:methanol 1:4, $m/z = 1189.1$, $[M-H]^-$). Aldehyde **5a** offers the opportunity for preparing large libraries of moenomycin derivatives.[13] In fact, numerous analogues have been synthesized starting from **5a**. We shall describe here only a few. Indium-mediated reaction[14] of

5a with farnesyl bromide in 1:4 methanol-water solution (100 mesh In, sonication for 10 min, stirring at 20 °C for 24 h, purification by Sephadex LH20® GF, 1:4 water: methanol, followed by LC, silica gel, ethyl acetate: isopropanol:water 6:4:3 and another LH-20 GF) provided **6** as a mixture of stereoisomers in 25% yield. **6** Displayed the expected spectroscopic properties ($m/z=1393.6$, $[M-H]^-$). Another class of compounds was prepared from **5a** by reductive amination. Thus, **5a** on reaction with the appropriate amine (5 equiv) and sodium cyanoborohydride (2 equiv) in 3:1:8 water, 0.2 mol/L phosphate buffer (pH 7), methanol, adjusted with 1 mol/L acetic acid to pH 6.5 provided **7a** (69% yield), **7b** (42% yield), and **7c** (34% yield). The purification was performed as above for the In-mediated reaction. The compounds **6** and **7a–c** were tested in an *Escherichia coli* in-vitro assay[15] and showed appreciable transglycosylase-inhibiting properties. The IC_{50} values (in 10^{-9} mol/L) were as follows: 106 for **6**, 247 for **7a**, 31 for **7b**, compared to 1.5 for **4a**. Tertiary amine **7c** was inactive in this test. As far as the antibiotic properties of the compounds against *S. aureus* are concerned, all of them proved inactive. Again, this result nicely matches with earlier observations. It has been shown that the free glyceric acid carboxyl group is an absolute prerequisite of the antiobiotic activity[4] and that introduction of polar groups at the end of the lipid side-chain also destroys the antibiotic activity.[6,7] These results have been taken as evidence that interactions of the glycerophospholipid part of moenomycin with the membrane serves to facilitate the highly selective interaction of the binding site at the enzyme and the first three sugars of moenomycin.[16] In compounds **6** and **7a–c** a polar group at C-2 of the lipid chain is obviously sufficient to disturb this well-adjusted recognition phenomenon.

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