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Synthesis of a building block for phosphonate analogues of moenomycin A_{12} from D-tartaric acid

Jalal Zahra,[a] Lothar Hennig,[a] Matthias Findeisen,[a] Peter Welzel,[a,*] Dietrich Müller[b] and William S. Sheldrick[b]

[a]*Universität Leipzig, Fakultät für Chemie und Mineralogie Johannisallee 29, D-04103 Leipzig, Germany*
[b]*Ruhr-Universität Bochum, Institut für Analytische Chemie, D-44780 Bochum, Germany*

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Abstract—An approach for the synthesis of moenomycin A_{12} *C*-glycoside partial structures is reported based on allyltin chemistry.
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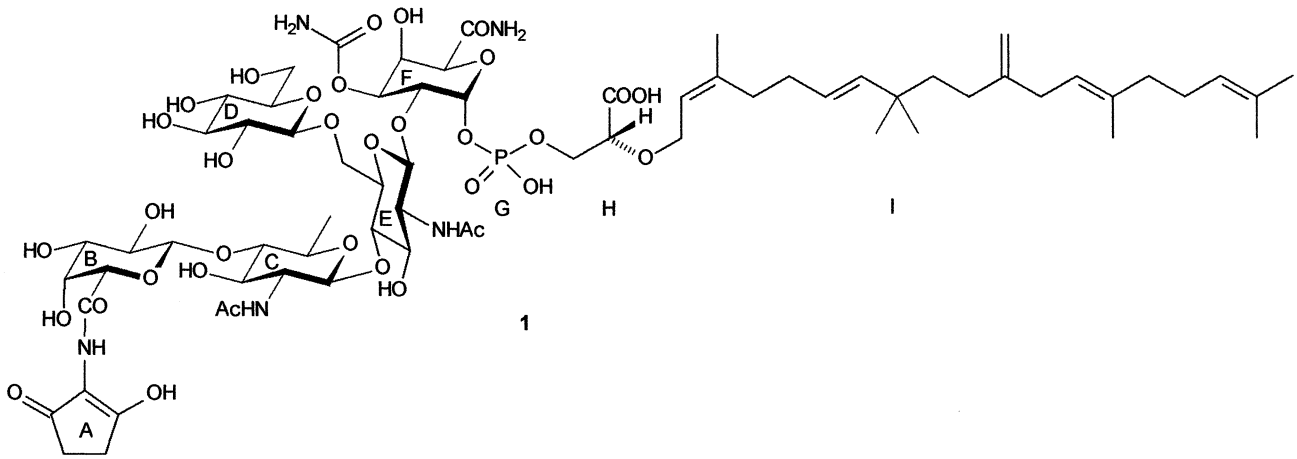
The transglycosylation reaction in peptidoglycan biosynthesis is a highly promising target for new antibiotics. The moenomycins (see moenomycin A_{12}, **1**[1]) have been shown to interfere with this biosynthetic step interacting with the enzyme(s).[2] A mechanism for their mode of action has been proposed.[3,4] It is assumed that they are anchored to the cytoplasmic membrane via the lipid part and bind highly selectively to the active site of the enzyme via the C–E–F trisaccharide. Units A, B, and D have been shown to be of minor importance for the antibiotic activity.[5] The moenomycins do not induce resistance readily. A weak point in this respect may be, however, the phosphate bond to unit F. Its cleavage by a yet poorly characterized enzyme is the only enzymatic degradation reaction of the moenomycins that is known to-date.[6] With this in mind we embarked on a programme aimed at synthesizing trisaccharide analogues of moenomycin A_{12} in which the phosphate oxygen at C-1 of unit F is replaced by a CH_2 group. It seemed important to retain all other functional groups in ring F as present in moenomycin since they are known to be of major importance as far as antibiotic activity is concerned.[5] Some mono- and disaccharide phosphonate models of moenomycin A have already been prepared but obviously their structures were too simple to elicit antibiotic activity.[7]

It appeared to us that D-tartaric acid would be an interesting starting material for such C_7 analogues of the uronamide part of moenomycins of the A_{12} type.



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* Corresponding author. Fax: (49) 341 9736599; e-mail: welzel@organik.chemie.uni-leipzig.de

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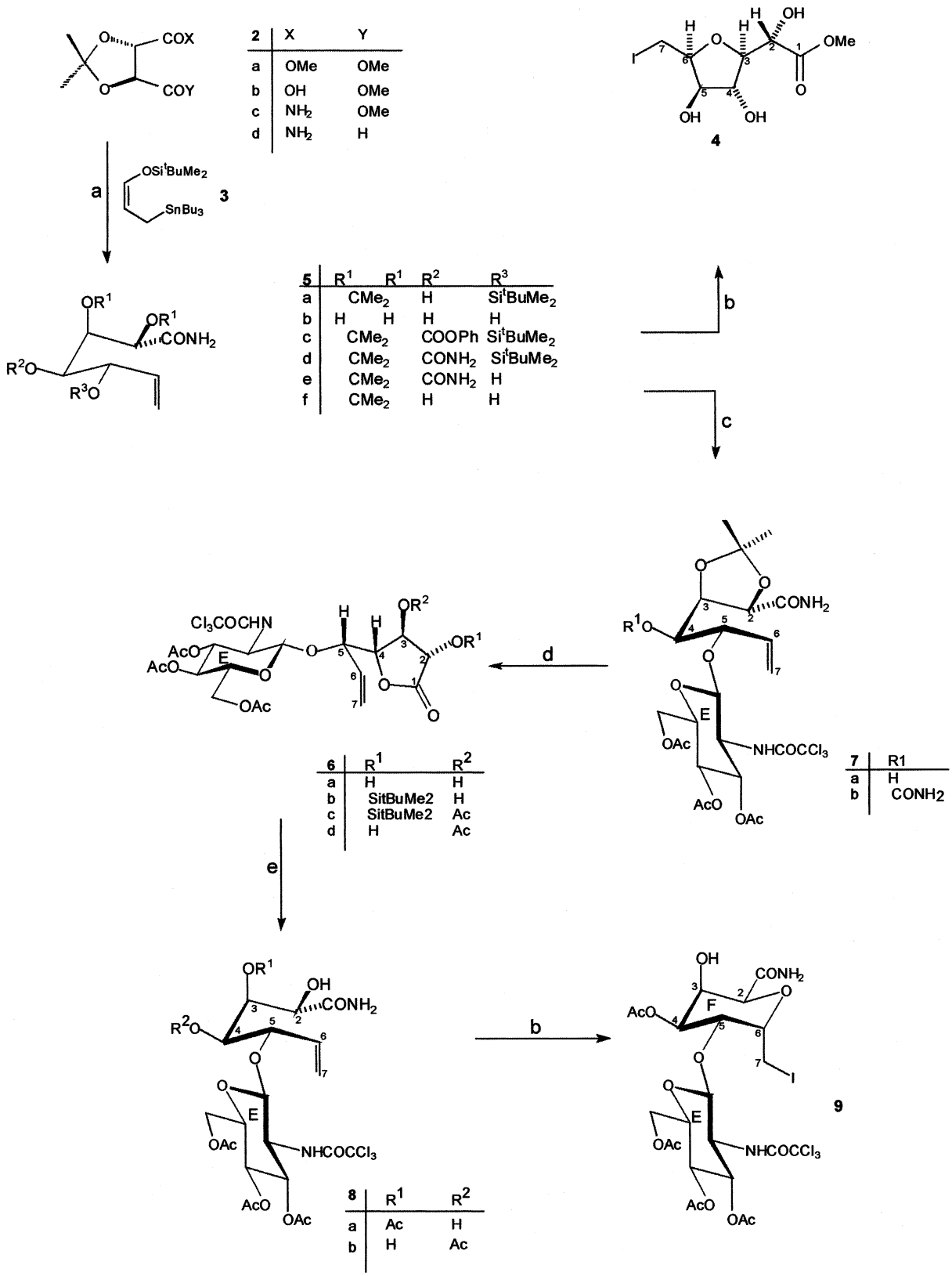
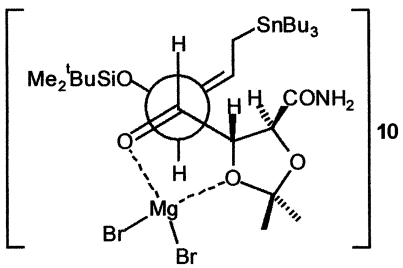
Thus, the known derivative **2a** of D-(−) tartaric acid was hydrolyzed with KOH (1 equiv.) in methanol to give monoester **2b** in 73% yield.[8] The free carboxylic acid group was converted into the amide making use of Staab's procedure (**2b**→**2c**, 91%).[9] Reduction of **2c** with DIBAL-H in dichloromethane furnished aldehyde **2d** in



Scheme 1. (a) (i) **2d**, $MgBr_2OEt_2$, CH_2Cl_2, (ii) **3**, 48 h, 20°C, 50%; (b) (i) **5b**, $Hg(OCOCF_3)_2$, THF, 20°C, 60 h, (ii) aqueous KCl, (iii) FC ethyl acetate–methanol 9:1, (iv) I_2, THF, (v) $FCCHCl_3$–methanol 95:5, (vi) cryst. from methanol; (c) Ref. 5, 32%; (d) **7a**, $CuCl_2{\cdot}2H_2O$, acetonitrile, reflux, 5 h, 94%; (e) **6d**, THF, gaseous ammonia, 0°C, 8 h.

94% yield. The missing three carbons were introduced by coupling **2d** with the (*Z*)-substituted γ-silyloxyallyl stannane **3**.[10] The yield and the stereoselectivity of this addition was strongly dependent on the activating Lewis acid. The best results were obtained using magnesium dibromide etherate.[11] Under these conditions heptonic acid amide **5a** was obtained as the major stereoisomer in 50% yield. All the protecting groups were removed on refluxing an ethanol–water solution of **5a** in the presence of Dowex 50-H^+ to afford **5b** (quant.). Electrophilic cyclization[12] (for conditions, see Scheme 1) produced a compound that according to the NMR spectra was a methyl ester. After crystallization from methanol an X-ray analysis[13] yielded structure **4**, confirming the presence of a methyl ester and demonstrating the lability of the amide group in this system. Not unexpectedly, a furanoid cyclization product had been formed. But most importantly, the X-ray structure proved that the addition of allyl stannane **3** to aldehyde **2d** had given a D-*galacto* product (L-*galacto* according to the nomenclature rules) exactly as desired and as present in unit F of moenomycin A_{12}.



The outcome of the addition of the allylstannane to **2d** can be explained on the basis of a transition state geometry, as indicated in formula **10**, in which it is assumed that the $MgBr_2$-promoted addition involves chelation control and that the C=O and C=C bonds are in an antiperiplanar relationship as suggested previously.[11]

In order to achieve the desired cyclization to a pyranoid ring, functional group manipulations blocking the 3-OH group became necessary. The 4-OH group of **5a** was converted into an urethane via the phenyl carbonate (**5a**→**5c**→**5d**). The silyl protecting group was removed and disaccharide **7b** was formed making use of the Beau–Jacquinet procedure.[14] From this compound we were unable to remove the acetonide group. Many of the known methods failed. Thus, we cleaved the silyl protecting group from **5a** with TBAF in THF. The resulting **5f** was glycosylated using again the Beau–Jacquinet procedure. Disaccharide **7a** was obtained in 32% yield. In addition, the 1→4 disaccharide (4%) and the trisaccharide (10%) were isolated. Then an attempt was made to remove the acetonide protecting group from **7a** using cupric chloride dihydrate in acetonitrile.[15] Under these conditions lactone **6a** was obtained (94%) demonstrating again the lability of the amide group. In principle the lactone is a very nice compound since it contains the 4-OH group in a protected form. Thus, protecting the 3-OH group and opening the lactone ring with ammonia would set the stage for the 6-*exo*-trig cyclization. Unfortunately, all attempts to selectively protect the 3-OH group failed. In all cases the 2-OH group was more reactive. Consequently, a two-step protocol had to be used. The 2-OH group of **6a** was converted into a *t*butyldimethylsilyl ether (**6b**, 89%) and the 3-OH group was acetylated (**6c**, 94%). Silyl group removal with TBAF then gave **6d** (98%).[16] Opening of the lactone ring with NH_3 in THF furnished two products, 3-acetate **8a** (46%) and the 4-isomer **8b** (38%). Cyclization of **8a** under the conditions described for the formation of **3** (see Scheme 1) gave the desired cyclization product **9** with migration of the acetyl group from the 3- to the 4-position (28%).[16]

In conclusion, D-tartaric acid can nicely be converted into L-galactoheptonamides (D-galactohepturonamides).

Acknowledgements

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13. Crystal data for $C_8H_{13}IO_6$: Siemens P4 diffractometer, Mo-Kα radiation, orthorhombic, space group $P2_12_12_1$, $a=6.283(2)$, $b=8.481(3)$, $c=20.440(8)$ Å, $U=1089.2(6)$ Å^3, $F(000)=648$, $Z=4$, $D_c=2.025$ g cm^{-3}, $R=0.029$ [$I>2\sigma(I)$], $wR_2=0.072$ for 1831 unique reflections ($2\theta\max=60°$), Flack absolute structure parameter 0.01(3). Full crystallographic details been deposited with the Cambridge Crystallographic Data Center (CCDC 150778). Copies may be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@chemcrys.cam.ac.uk).
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16. **6d**: ^{1}H NMR (400 MHz, $CDCl_3$, HH COSY): $\delta=1.95$, 1.96, 2.03, 2.06 (4s, 12H, $COCH_3$), 3.66 (ddd, 1H, 5^E-H), 3.97–4.12 (m, 3H, 2^E-H, CH_2-6^E), 4.18–4.26 (m, 2H, 4-H, 5-H), 4.47 (d, 1H, 2-H), 4.82 (d, 1H, 1^E-H), 5.02 (dd, 1H, 4^E-H), 5.22–5.36 (m, 4H, 7-H$_a$, 7-H$_b$, 3^E-H, 3-H), 5.85 (ddd, 1H, 6-H), 7.26 (d, 1H, NH). $J_{5,6}=7.4$, $J_{6,7a}=10.6$, $J_{6,7b}=17.7$, $J_{1E,2E}=8.1$, $J_{2E,NH}=9.2$, $J_{4E,5E}=9.9$, $J_{5E,6E}=2.5$, 4.6 Hz.—^{13}C NMR (50.3 MHz, $CDCl_3$, HMQC, HMBC): $\delta=20.74$, 20.89, 21.10, 21.19 ($CO\underline{C}H_3$), 56.13 (C-2^E), 62.15 (C-6^E), 68.59 (C-4^E), 72.06, 72.17 (C-3^E, C-5^E), 72.80 (C-2), 75.73 (C-3), 81.42, 81.55 (C-4, C-5), 92.45 (CCl_3), 100.57 (C-1^E), 120.49 (C-7), 132.93 (C-6), 162.47 ($\underline{C}OCCl_3$), 169.53, 170.87, 170.91, 171.21, 172.50 (C-1).—$C_{23}H_{28}Cl_3NO_{14}$ (648.83, 647.06), FAB MS: m/z 648.1 [M+H]$^+$, 670.1 [M+Na]$^+$.
9: ^{1}H NMR (300 MHz, $CDCl_3$, HH COSY): $\delta=2.01$, 2.05, 2.12, 2.16 (4s, 12H, $COCH_3$), 3.92 (dd, 1H, 7^F-H), 4.00 (ddd, 1H, 5^E-H), 4.14 (dd, 1H, 7^F-H′), 4.29 (m, 1H, 2^E-H), 4.36 (dd, 1H, 6^E-H), 4.50 (dd, 1H, 6^E-H′), 4.78 (d, 1H, 2^F-H), 4.91 (m, 1H, 6^F-H), 5.06 (dd, 1H, 5^F-H), 5.37 (m, 1H, 3^F-H), 5.53 (dd, 1H, 4^E-H), 5.68–5.72 (m, 2H, 4^F-H, 1^E-H), 6.18 (dd, 1H, 3^E-H), 7.79, 8.60 (2s, 2H, $CONH_2$), 10.66 (d, 1H, NH). $J_{2F,3F}=1.7$, $J_{4F,5F}=9.8$, $J_{5F,6F}=5.9$, $J_{6F,7F}=3.3$, $J_{6F,7'F}<1$, $J_{7F,7F'}=11.3$, $J_{NHF,NHF}=2.2$, $J_{1E,2E}=10.2$, $J_{2E,NH}=8.0$, $J_{2E,3E}=10.6$, $J_{3E,4E}=9.2$, $J_{4E,5E}=9.9$, $J_{5E,6E}=2.5$, $J_{5E,6'E}=4.7$, $J_{6E,6'E}=12.1$ Hz.—^{13}C NMR: (75.5 MHz, $CDCl_3$, HMQC, HMBC): $\delta=3.60$ (C-7^F), 20.10, 20.19, 20.42, 21.07 ($CO\underline{C}H_3$), 56.98 (C-2^E), 61.92 (C-6^E), 67.47 (C-3^F), 69.24 (C-4^E), 71.22 (C-3^E), 71.84 (C-5^E), 72.66, 72.71 (C-2^F, C-4^F), 74.68 (C-5^F), 76.43 (C-6^F), 93.33 (CCl_3), 100.40 (C-1^E), 162.70 ($\underline{C}OCCl_3$), 169.48, 170.01, 170.10, 170.13 ($\underline{C}OCH_3$), 171.45 ($CONH_2$).—$C_{23}H_{30}Cl_3IN_2O_{14}$ (791.76, 789.98), FAB MS: m/z 789.9 [M+H]$^+$, 812.9 [M+Na]$^+$.