



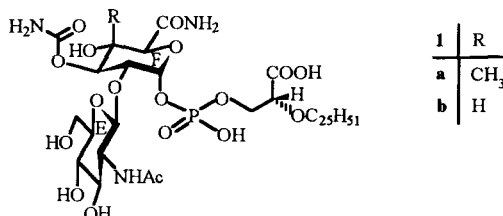
New Protecting Group Chemistry in the Synthesis of Moenomycin Analogues

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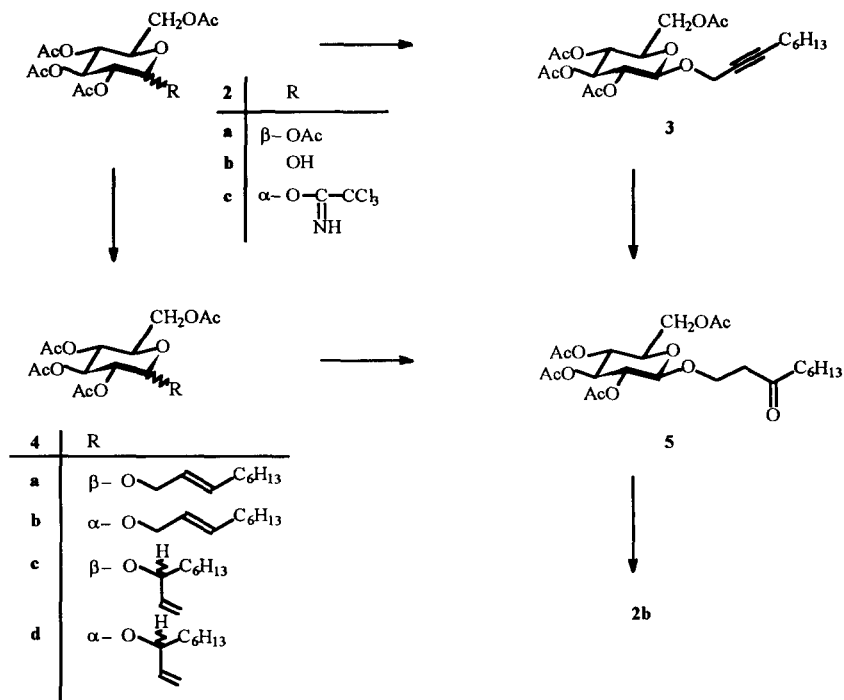
Abstract - Two new C₉ protecting groups for the anomeric position of carbohydrates are reported. Methods both for their introduction and removal are described. The C₉-protected compounds are much less polar than the corresponding allyl protected analogues.

The moenomycins are antibiotics that inhibit the transglycosylation step of peptidoglycan biosynthesis. Extensive degradation and synthetic studies have shown that compound **1a** is the smallest moenomycin A analogue with full transglycosylase-inhibiting and antibiotic activities.¹ A severe problem frequently encountered in the synthesis of compounds related to **1a** is the very low solubility of synthetic intermediates. Thus, for the introduction of the carbamoyl group special conditions had to be found in certain cases.² Similarly, removal of the allyl protecting group from the anomeric position of oligosaccharide intermediates using the standard procedures turned out to be impossible in several instances, and a new method for the cleavage of allyl glycosides was developed based on Wacker oxidation of the allyl part.^{3,4} In an especially annoying case, we were unable to perform disaccharide formation,⁴ and as a result of this, until now the synthesis of the highly interesting moenomycin A analogue **1b** has not yet been achieved. **1b** would allow to probe the role of the unit F C-methyl group in the structure-activity relationships of the moenomycin A series.⁵



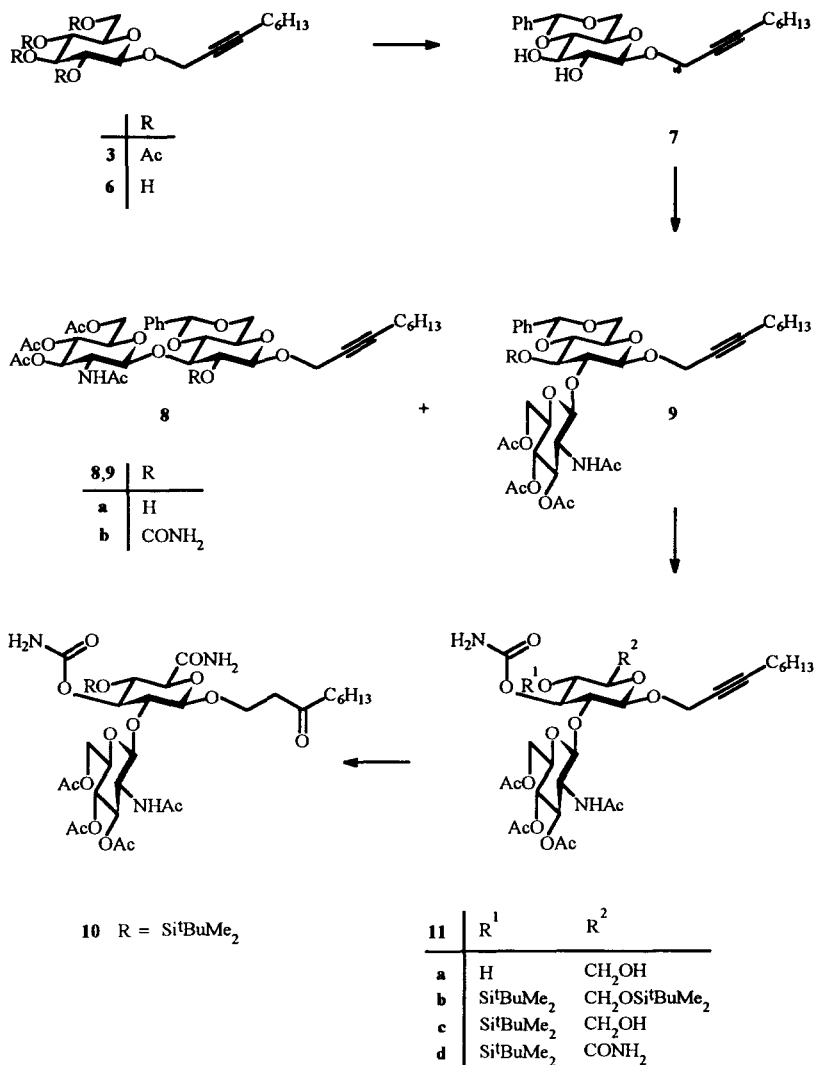
We reasoned that most of the problems discussed above would become less severe if for the anomeric position of unit F instead of the allyl protecting group⁶ a more lipophilic one was used. This structural change was hoped to render the synthetic intermediates less polar and, furthermore, would allow to purify them by reversed-phase chromatography. Thus, we decided to replace the allyl protecting group by an appropriate C₉ chain.

Treatment of **2a** with (E)-2-nonen-1-ol⁷ (2 equiv) in the presence of boron trifluoride etherate⁸ (4 equiv, CH₂Cl₂, -10°C, 48 h) gave a complex mixture from which compounds **4a-4d** have been isolated in a total yield of 39%. The desired β-glycoside **4a** was obtained in disappointingly low yields (26%). Recourse was then made to Schmidt's procedure. The sequence **2a** → **2b** (hydrazinium acetate,⁹ 1.4 equiv, DMF, 0°C, 6.5 h), **2b** → **2c**¹⁰ (trichloroacetonitrile, 2 equiv, DBU,¹¹ 0.33 equiv, 0°C, 7.5 h), **2c** → **4a** ((E)-2-nonen-1-ol, 1 equiv, CH₂Cl₂, BF₃•OEt₂, 0.1 equiv, -78°C,¹² 3 h, then → -10°C, 20 h) provided **4a** in an overall yield of 75%. In the course of these studies it was found, that BF₃•OEt₂-mediated reaction⁸ (2 equiv) of **2a** with 2-nonyl-1-ol (1 equiv, 20°C, 4.5 h) was quite efficient and provided β-glycoside **3** in 69% (isolated) yield.



Removal of the C₉-protective groups was achieved via β-alkoxy ketone **5**. Treatment of **4a** with PdCl₂ (3 equiv) in 6:1 DMF-water (45°C, 24 h) furnished **5** in 97% yield.¹³ Water addition to **3** was accomplished by treatment with 5 mol% Hg²⁺ (from HgSO₄)¹⁴ in 5:1 methanol-water (20°C, 22 h) and gave **5** in 69 % yield along with 15 % of the target compound **2b**.¹³ Finally, eliminative deprotection of **5** occurred on reaction with DBU (5 equiv, CH₂Cl₂, 20°C, 30 min)¹⁵ and gave **2b** in 82% yield. In conclusion, both the introduction of two new C₉ protecting groups and their removal have been achieved in reasonable yields.

The value of the new method was tested in the synthesis of disaccharide **10**. **3** was converted to **7** via **6** by (i) base hydrolysis (Zemplén method,¹⁶ methanol, NaOCH₃, 5 mol%) and (ii) acetal formation¹⁷ (DMF, PhCH(OCH₃)₂, 2.7 equiv, *p*TsOH, 0.15 equiv) (89% overall). For the introduction of unit E¹⁸ the oxazoline method was used^{2,19} (oxazoline,²⁰ 1.15 equiv, camphorsulfonic acid, 0.1 equiv, CH₂Cl₂, 60°C, 6.5 h). The two isomers **8a** and **9a**²¹ could not be separated and were directly converted to urethanes **8b** and **9b** ((i) trichloroacetylisocyanate, 1.1 equiv, CH₂Cl₂, -7°C, 2.5 h, (ii) zinc, 11 equiv, methanol, 20°C, 19 h)²² and then, by acid hydrolysis, (2:1 ethanol-water, cation exchange resin, 100°C, 1 h)²³ to **11a** (31% overall yield) and the corresponding 1→3-isomer (48% overall yield). Chromatographic separation (silica gel, 20:1 CHCl₃-methanol) could easily be performed at this stage. The two free OH groups in **11a** were silylated (tBuMe₂SiCl, 4.9 equiv, imidazole, 6.6 equiv, DMF, 40°C, 4 d, quantitative),²⁴ and the silyl ether in the 6-position was selectively cleaved by acid hydrolysis (1:1:3 THF-water-acetic acid, 20°C, 20 h, 86%).²⁵ Two-stage oxidation ((i) *o*-iodoxybenzoic acid,²⁶ 3 equiv, DMSO, 20°C, 24 h, (ii) NaClO₂,²⁷ 5 equiv, 10:50:7.5 methyl-2-butene - *tert*-butanol - water, NaH₂PO₄, 3.3 equiv, 20°C, 3 h) and subsequent amide formation (N,N'-carbonyldiimidazole, 2.3 equiv, CH₂Cl₂, 20°C, 4 h, then NH₃, 0°C, 15 min)²⁸ provided **11d** in 62% overall yield. Finally, water addition to **11d** as described above²⁹ furnished **10** (58%).³⁰



In summary: The new protecting group chemistry has shown its merits. All compounds were nicely soluble in CH_2Cl_2 .³¹ **10** is the most advanced intermediate on the way to **1b** until now.⁴ Conversion of **10** into **1b** will be reported in due course.

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References and Notes

Dedicated to Professor Hans-Dieter Scharf on the occasion of his 65th birthday.

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- 29 1 equiv of HgSO_4 , 3 h.
- 30 The spectroscopic data of all new compounds (^1H NMR, ^{13}C NMR, FAB MS) are fully in accord with the structures assigned. Some characteristic ^1H NMR signals (δ values, 400 MHz spectra): **3** (CDCl_3): glucose part: 1-H 4.77 (d, $J = 8.0$ Hz), nonynyl part: CH_2 -1 4.33 (t, $^4J = 2.1$ Hz); **4a** (CDCl_3): glucose part: 1-H 4.54 (d, $J = 8.0$ Hz), nonenyl part: CH_2 -1 4.04 (ddd, $^2J = 12.5$ Hz, $^3J = 7.0$ Hz, $^4J = 1.0$ Hz) and 4.26 (ddd, $^3J = 5.5$ Hz, $^4J = 1.0$ Hz); **5** (CDCl_3): glucose part: 1-H 4.59 (d, $J = 8.1$ Hz), 3-oxo-nonan-1-yl part: CH_2 -1 3.83 (ddd, $^2J = 9.8$ Hz, $^3J = 5.4$ and 8.2 Hz) and 4.01 (ddd, $^3J = 5.4$ and 5.7 Hz); CH_2 -2 2.55 (ddd, $^2J = 17.1$ Hz) and 2.73 (ddd); **10** (pyridine- d_5): F part: 1-H 4.96 (d, $J = 6.3$ Hz), E part: 1-H 5.59 (d, $J = 8.4$ Hz), 3-oxo-nonan-1-yl part: CH_2 -1 3.97-4.03 (m) and 4.27-4.35 (m), CH_2 -2 2.80-2.85 (m), CH_2 -4 2.43-2.47 (m); **11d** (pyridine- d_5): F part: 1-H 5.30 (d, $J = 5.6$ Hz), E part: 1-H 5.73 (d, $J = 8.4$ Hz), nonynyl part: CH_2 -1 4.68-4.72 (m).
- 31 In the case of diol **11a** some methanol had to be added.

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