Pergamon

Tetrahedron Letters 41 (2000) 2991–2994

TETRAHEDRON LETTERS

Synthesis of a *C*-glycosylpyranonaphthoquinone related to medermycin

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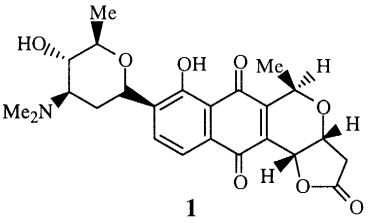
Received 14 January 2000; accepted 14 February 2000

Abstract

The synthesis of a 2-deoxyglucosyl analogue **2** of the pyranonaphthoquinone antibiotic medermycin **1** is reported. The critical β *C*-glycoside linkage was introduced at an early stage in the synthesis by direct *C*-glycosylation of naphthol **7** with benzyl protected glycosyl donor **4**. Conversion of *C*-glycoside **8** to 2-acetyl-1,4-naphthoquinone **3** then allowed assembly of the pyranonaphthoquinone skeleton via a furofuran annulation–oxidative rearrangement strategy.

Keywords: *C*-glycosides; naphthols; 2-trimethylsilyloxyfuran; pyranonaphthoquinones.



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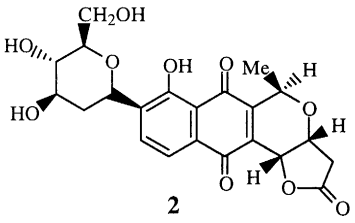

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The pyranonaphthoquinone antibiotic medermycin **1** was isolated[1] from *Streptomyces tanashiensis* and was shown to contain a *C*-glycoside linkage to the aminosugar, D-angolosamine. Medermycin **1** exhibits significant activity against Gram-positive bacteria,[2] including *staphylococci* which are resistant to several antibiotics. It showed cytotoxity for cell lines of K-562 human myeloid leukemia, P-388 murine leukemia and antibiotic-resistant cell lines of L5178Y lymphoblastoma in culture.[3] Platelet aggregation[4] and biomolecule synthesis are also inhibited by medermycin **1**.[5]

The only synthesis of medermycin **1** to date has been reported by Tatsuka et al.[6] and requires over 30 steps with the key step involving assembly of a pyranonaphthalene via addition of a sulfonyl-phthalide to an enone. The key sulfonyl-phthalide itself required 17 steps for its preparation. Our approach to the synthesis of analogues of medermycin **1** has focused on construction of the *C*-glycoside linkage in a flexible manner such that various *C*-glycosides can be attached to the pyranonaphthoquinone skeleton. We herein report an efficient synthesis of the 2-deoxyglucosyl analogue of medermycin

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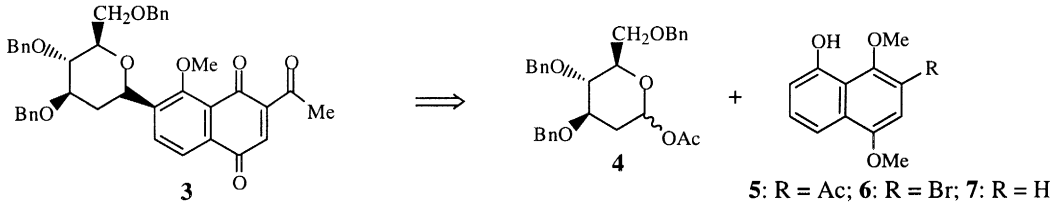
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00289-6

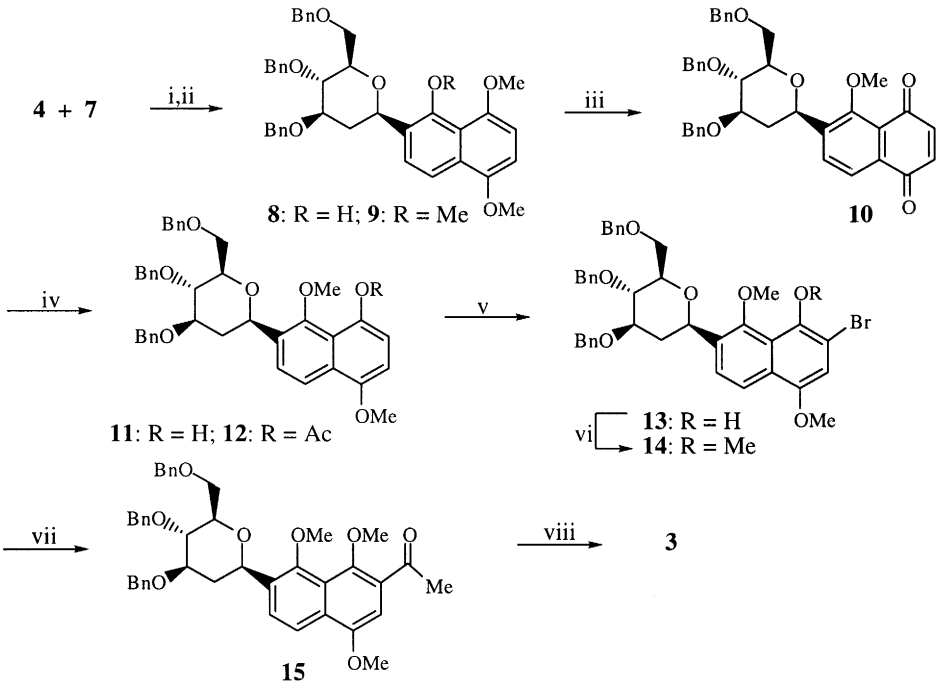
2, from 2-deoxyglucosylnaphthoquinone **3**, making use of our furonaphthofuran annulation–oxidative rearrangement strategy, as previously applied to the synthesis of the aglycone, kalafungin.[7]

C-Glycosylnaphthoquinone **3**, which contains an acetyl group at C-3 (required in order to control the regiochemistry of the ensuing furofuran annulation), was the focus of our initial attention (Scheme 1). Whilst direct *C*-glycosylation[8] of 3-acetylnaphthol **5** or 3-bromonaphthol **6** with 2-deoxyglucosyl donor **4** appeared an obvious route to the required *C*-glycosylnaphthoquinone **3**, this approach was hampered by the formation of rearranged bicyclic acetals in which the glycosyl donor **4** had undergone an unusual 1,6-hydride shift.[9] Our successful synthesis of *C*-glycosylnaphthoquinone **3**, therefore, focused on the *C*-glycosylation of naphthol **7** followed by regioselective introduction of the required 3-acetyl group.



Scheme 1.

Addition of boron trifluoride diethyletherate to naphthol **7**[10] and glycosyl acetate **4**[11] in dry acetonitrile at 0°C afforded the desired β *C*-glycoside **8**[12,13] in 73% yield after flash chromatography (Scheme 2). After protection of naphthol **8** as a methyl ether **9**,[14] conversion to naphthoquinone **10**, followed by reductive monomethylation, afforded naphthol **11** which allows regioselective introduction of an acetyl substituent at C-3.

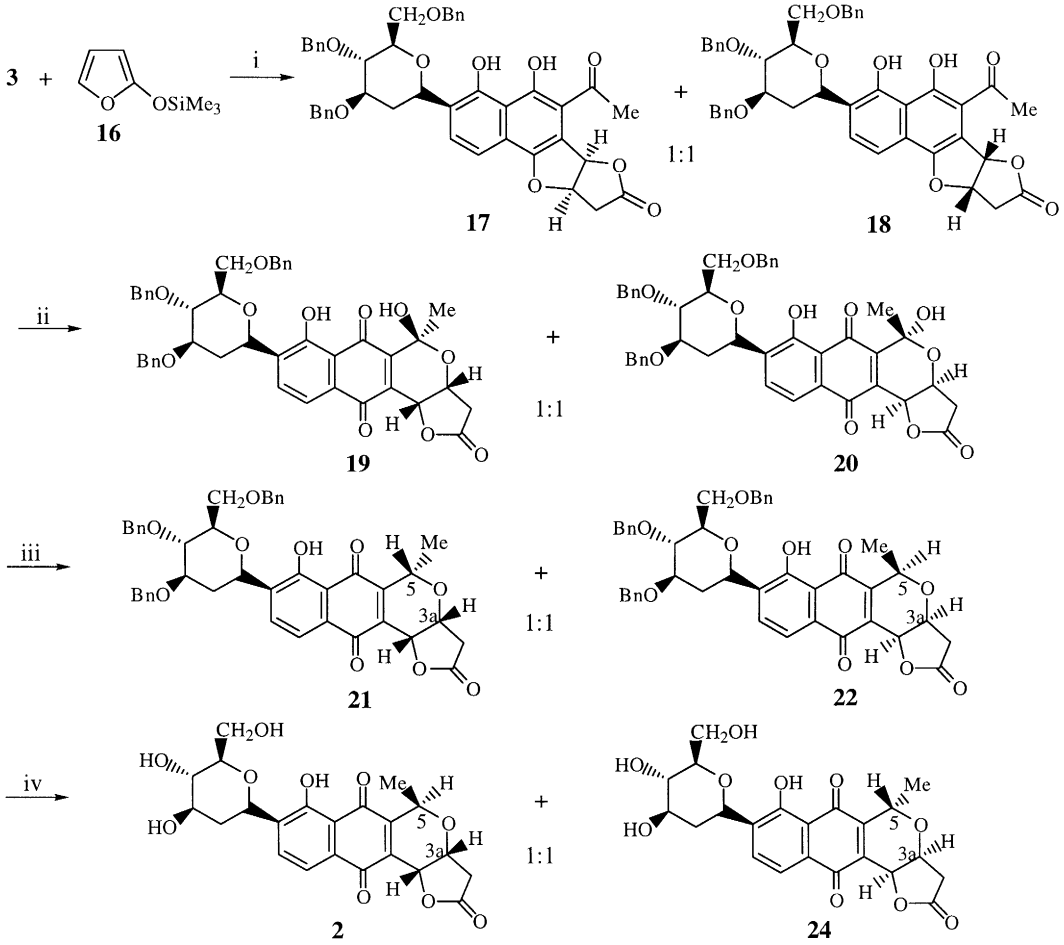


Scheme 2. *Reagents and conditions*: (i) $BF_3 \cdot Et_2O$, CH_3CN, 0°C, 20 min, 73%; (ii) MeI, NaH, DMF, 0°C, 12 h, 85%; (iii) CAN, CH_3CN, 0.5 h, 93%; (iv) $Na_2S_2O_4$ then Me_2SO_4, K_2CO_3, acetone, reflux, 2–4 h, 82%; (v) Br_2, CCl_4, 0°C, 2 min, 77%; (vi) NaOH, Me_2SO_4, DMF/H_2O, 15 min, 0°C, 84%; (vii) $Pd(PPh_3)_2Cl_2$, $Bu_3SnC(OEt)=CH_2$, toluene, 100°C, N_2, 16 h then H_3O^+, 97%; (viii) AgO, HNO_3, dioxane, 20 min, 93%

Attempted Fries' rearrangement of acetate **12** derived from naphthol **11** was ineffective and, therefore, the acetyl group was introduced indirectly from bromide **13**. After conversion of bromonaphthol **13**

to bromomethoxynaphthalene **14**, introduction of the acetyl group via lithiation of the bromide was unsuccessful due to the highly basic nature of the naphthyl anion. An alternative approach employing α-ethoxyvinyltributyl tin as a masked acetylating agent afforded 3-acetylnaphthalene **15** which was smoothly oxidised to naphthoquinone **3**.

With the key *C*-glycosylnaphthoquinone **3** in hand, attention then focused on conversion to *C*-glycosylpyranonaphthoquinone **2** (Scheme 3). Addition of 2-trimethylsilyloxyfuran **16** to naphthoquinone **3** afforded a 1:1 mixture of the furonaphthofuran adducts **17** and **18** in moderate yield. Treatment of furo[3,2-*b*]naphthofurans **17** and **18** with aqueous ceric ammonium nitrate (CAN) effected smooth conversion to furonaphthopyrans **19** and **20** which were separable upon purification by low temperature (−20°C)[15] flash chromatography. Subsequent reduction of the lactols **19** and **20**, using triethylsilane and trifluoroacetic acid, afforded cyclic ethers **21** and **22** which were also separable by low temperature flash chromatography.[15] Finally, use of boron tribromide to effect deprotection of the benzyl ethers on pyranonaphthoquinones **21** and **22**, in which the bridgehead proton at C3a is *cis* to the methine proton at C5, afforded the more stable epimeric pyranonaphthoquinones **2** and **24**, in which these two protons were *trans* to each other.[16] This epimerisation has been reported on simpler pyranonaphthoquinones.[17]



Scheme 3. *Reagents and conditions*: (i) CH_3CN, 0°C, 1 h, then MeOH, silica gel, 18 h, 60%; (ii) CAN, CH_3CN, 20 min, 85%; (iii) CF_3CO_2H, Et_3SiH, −10°C, 72 h, 86%; (iv) BBr_3, CH_2Cl_2, −48°C to room temperature, 30 min, 67%

In summary, the successful synthesis of the 2-deoxyglucosyl analogue **2** of the pyranonaphthoquinone antibiotic medermycin **1** has been achieved. Moreover, the synthesis can be easily modified for the

preparation of medermycin **1** itself, and other analogues, by simply varying the nature of the glycosyl donor used in the initial *C*-glycosylation step.

Acknowledgements

The authors thank the Australian Research Council and the University of Sydney for financial support and Dr. David Larsen (University of Otago) for helpful advice.

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13. The β stereochemistry was confirmed by vicinal coupling constants for the anomeric proton, $J_{1',2'ax}$=11.0 and $J_{1',2'eq}$=1.8 Hz.
14. All new compounds gave satisfactory elemental and spectroscopic analysis.
15. Performing flash chromatography at room temperature resulted in substantial decomposition of the product.
16. Lactols **19** and **20**, cyclic ethers **21** and **22**, and pyranonaphthoquinones **2** and **24**, were able to be separated by low temperature flash chromatography; however, assignment of exact stereochemistry to an individual compound in a given pair was not possible using NMR spectroscopy.
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