



Pergamon

Tetrahedron Letters 41 (2000) 2991–2994

TETRAHEDRON
LETTERS

Synthesis of a C-glycosylpyranonaphthoquinone related to medermycin

Margaret A. Brimble* and Timothy J. Brenstrum

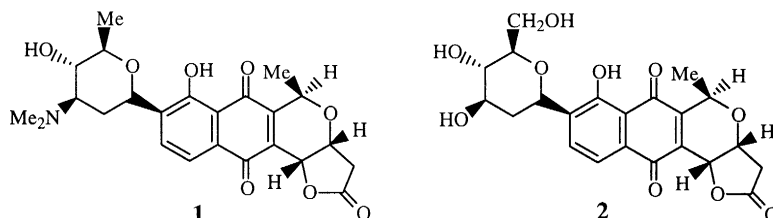
School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia

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. © 2000 Elsevier Science Ltd. All rights reserved.

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



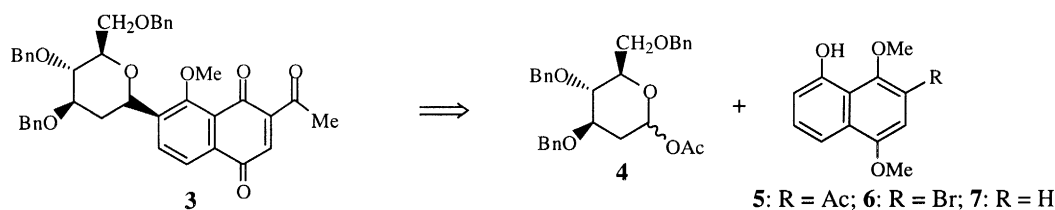
The pyranonaphthoquinone antibiotic medermycin **1** was isolated¹ from *Streptomyces tanashiensis* and was shown to contain a C-glycoside linkage to the aminosugar, D-angolosamine. Medermycin **1** exhibits significant activity against Gram-positive bacteria,² including *staphylococci* which are resistant to several antibiotics. It showed cytotoxicity 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 aggregation⁴ 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

* Corresponding author. Department of Chemistry, 23 Symonds St., Auckland, New Zealand. Tel: +64 9 3737599, ext. 8259; fax: +64 9 3737422; e-mail: m.brimble@auckland.ac.nz (M. A. Brimble)

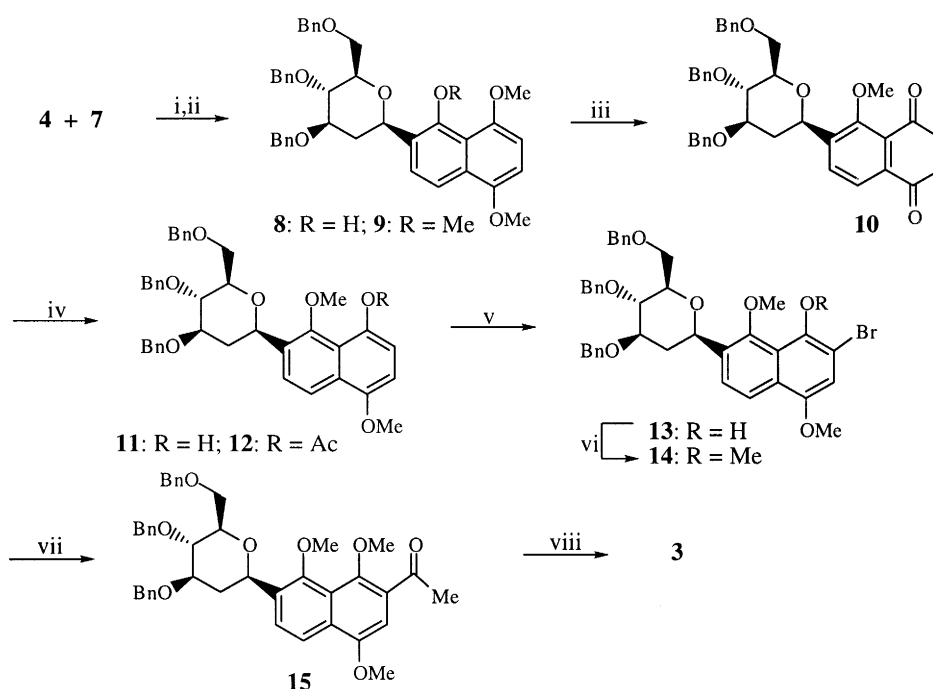
2, from 2-deoxyglucosyl naphthoquinone **3**, making use of our furonaphthofuran annulation–oxidative rearrangement strategy, as previously applied to the synthesis of the aglycone, kalafungin.⁷

C-Glycosyl naphthoquinone **3**, which contains an acetyl group at C-3 (required in order to control the regiochemistry of the ensuing furfuran annulation), was the focus of our initial attention (Scheme 1). Whilst direct C-glycosylation⁸ of 3-acetylnaphthol **5** or 3-bromonaphthol **6** with 2-deoxyglucosyl donor **4** appeared an obvious route to the required C-glycosyl naphthoquinone **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-glycosyl naphthoquinone **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.

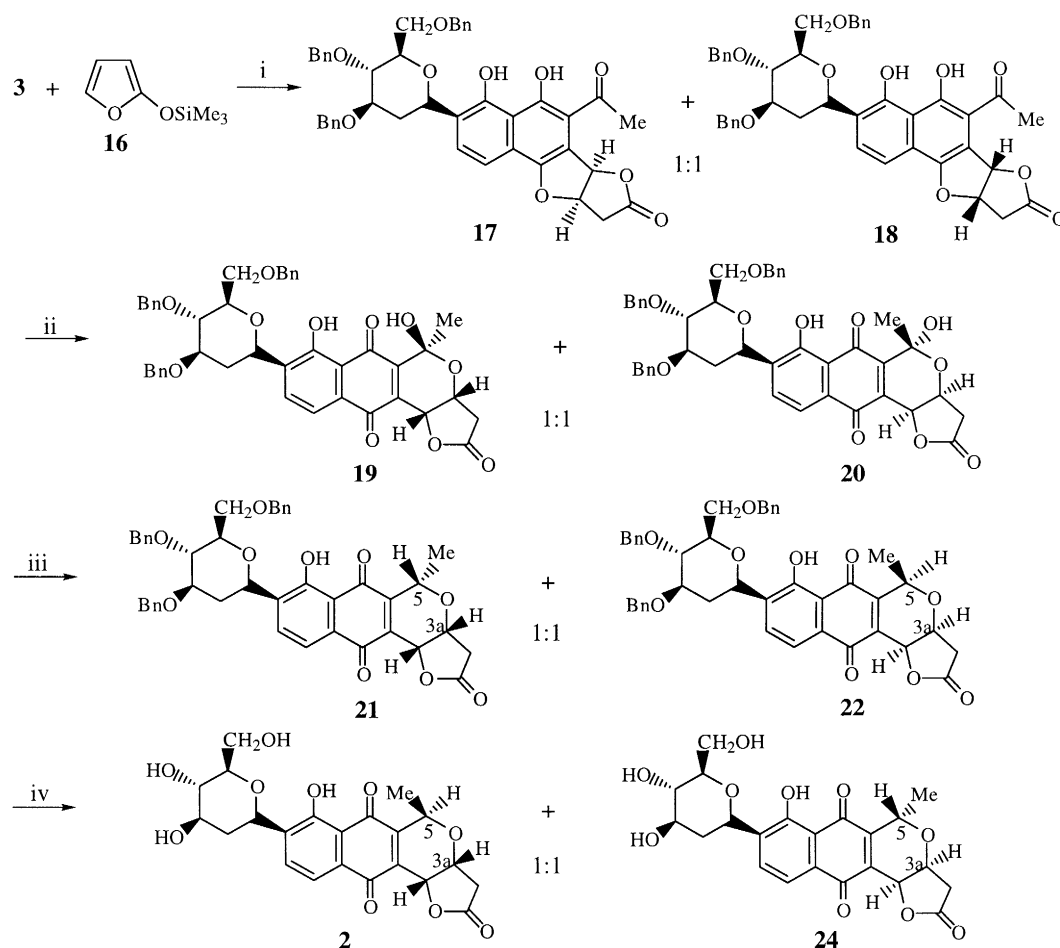


Scheme 2. *Reagents and conditions*: (i) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_3CN , 0°C, 20 min, 73%; (ii) MeI, NaH, DMF, 0°C, 12 h, 85%; (iii) CAN, CH_3CN , 0.5 h, 93%; (iv) $\text{Na}_2\text{S}_2\text{O}_4$ then Me_2SO_4 , K_2CO_3 , acetone, reflux, 2–4 h, 82%; (v) Br_2 , CCl_4 , 0°C, 2 min, 77%; (vi) NaOH, Me_2SO_4 , DMF/ H_2O , 15 min, 0°C, 84%; (vii) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, $\text{Bu}_3\text{SnC}(\text{OEt})=\text{CH}_2$, 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) $\text{CF}_3\text{CO}_2\text{H}$, 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.

References

1. Takano, S.; Hasuda, K.; Ito, A.; Koide, Y.; Ishii, F.; Haneda, I.; Chihara, S.; Koyami, T. *J. Antibiot.* **1976**, *29*, 765.
2. Tanaka, N.; Okabe, T.; Isono, F.; Kashiwagi, M.; Namoto, K.; Takahashi, M.; Shimazu, A.; Nishimura, T. *J. Antibiot.* **1985**, *38*, 1327.
3. Japanese Patent 62 10086, 1987; *Chemical Abstracts* 106: 212564u.
4. Nakagawa, A.; Fukamachi, N.; Yamaki, K.; Hayashi, M.; Ohishi, S.; Kobayashi, B.; Omura, S. *J. Antibiot.* **1987**, *40*, 1075.
5. Nomoto, K.; Okabe, T.; Suzuki, H.; Tanaka, N. *J. Antibiot. (Tokyo)*. **1988**, *41*, 1124.
6. Tatsuka, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.* **1990**, *31*, 5495.
7. Brimble, M. A.; Stuart, S. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 881.
8. For recent reviews on C-glycosidation, see: (a) Du, Y.; Lindhart, R. J. *Tetrahedron* **1998**, *54*, 9913; (b) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700; (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995. (d) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Oxford, 1995.
9. Brimble, M. A.; Brenstrum, T. J. *Tetrahedron Lett.* **2000**, *41*, 1107.
10. Wurm, G.; Goessler, B. *Arch. Pharm.* **1989**, *322*, 569.
11. Miokowski, C.; Bolitt, V.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.
12. Andrews, F. L.; Larsen, D. S. *Tetrahedron Lett.* **1994**, *35*, 8693.
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.
17. Brimble, M. A.; Phythian, S. J.; Prabakaran, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2855.