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TESOTf-Induced Rearrangement of Quinols. Efficient Construction of the Fully Functionalized Carbon Skeleton of the Griseusins by a Divergent–Reconvergent Approach

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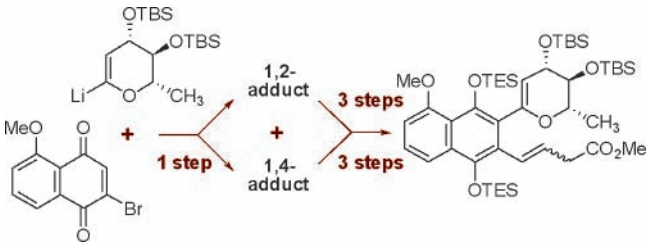
ABSTRACT



The "reverse polarity" or "umpolung" strategy for the total synthesis of aryl C-glycosides was developed in the context of the antibiotic (–)-griseusin B. Although a key reaction in a model sequence for the total synthesis produced two structurally divergent products, both were converted to the same advanced model intermediate that contains the complete carbon skeleton and (except for the extraneous oxygen substituent in the model series) the functional group pattern of the griseusins.

(−)-Griseusin A (**1a**) and B (**2a**),[1,2] their more recently isolated 4′-deacetyl derivatives **1b** and **2b**,[3] and the more complex 3′-*O*-α-D-forosaminyl-(+)-griseusin A (**3**)[4] are aromatic, polyketide-derived antibiotics produced by the actinomycete strain *Streptomyces griseus* (Figure 1).

The griseusins belong to the growing family of pyrano naphthoquinones that includes the well-known kalafungin, nanaomycins, medermycin, and granaticin.[5] Members of this class display a variety of interesting biological activities. Moore and Czerniak proposed that the pyrano naphthoquinones, including the griseusins, act as bioreductive alkylation agents via quinone methide intermediates in a manner similar to that of the anticancer agent mitomycin C.[6] The griseusins are active against gram-positive bacteria; the deacetyl griseusins **1b** and **2b** and the forosaminyl griseusin A **3** have demonstrated activity against methicillin-resistant *Staphylococcus aureus* (MRSA), a growing health problem.[7]

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(1) (a) Tsuji, N.; Kobayashi, M.; Wkisaka, Y.; Kawamura, Y.; Mayama, M.; Matsumoto, K. *J. Antibiot.* **1976**, *29*, 7. (b) Tsuji, N.; Kobayashi, M.; Terui, Y.; Tori, K. *Tetrahedron* **1976**, *32*, 2207.

(2) For the elucidation of the absolute stereochemistry of (−)-griseusin A (**1**) and B (**2**), see: (a) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 2311. (b) Tsuji, N.; Kamigauchi, T.; Nakai, H.; Shiro, M. *Tetrahedron Lett.* **1983**, *24*, 389. (c) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4725.

(3) Igarashi, M.; Chen, W.; Tsuchida, T.; Umekita, M.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1502.

(4) Maruyama, M.; Nishida, C.; Takhashi, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 952.

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(6) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

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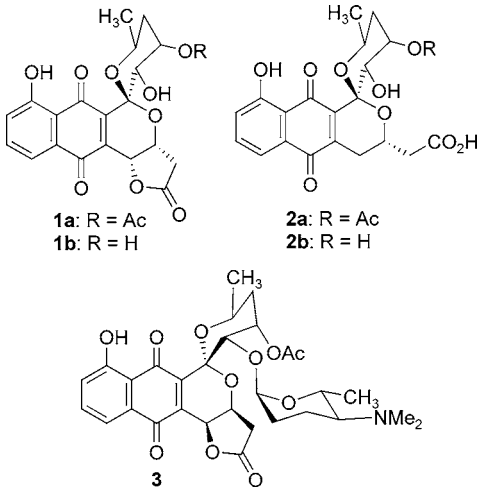


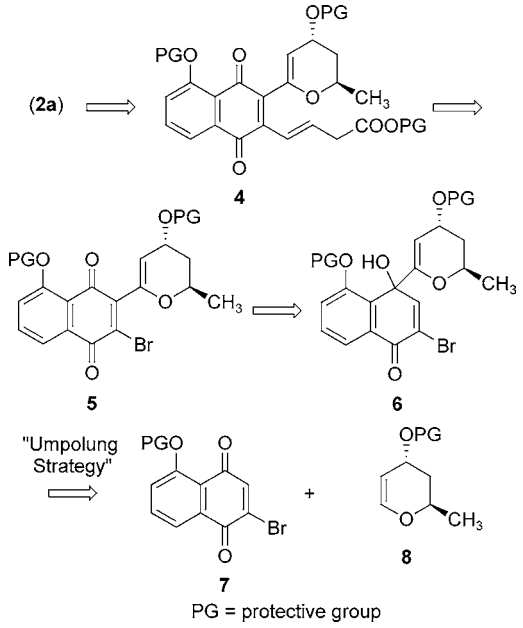
Figure 1. (−)-Griseusin A and B, the 4′-deacetyl griseusins, and 3′-*O*-α-D-forosaminyl-(+)-griseusin A.

The pyrano naphthoquinones have attracted interest in both the biosynthesis/bioengineering[8−10] and organic synthesis[11] communities. Total syntheses of (+)-griseusin A[2a] and (+)-9-deoxy griseusin B[2b] and a synthesis of a mixture of protected (−)-griseusin A isomers have been reported.[12]

Our own work on the synthesis of the griseusins is one component of a broad program focused on the synthesis of naturally occurring aryl C-glycosides with a variety of substitution patterns on the aromatic aglycone.[13] The oxidation pattern of the naphthyl C-glycoside moiety in the griseusins is the same as that in the mederrhodins,[8b] an arrangement that we have designated the group IV substitution pattern.[14] The synthesis of one of these compounds by the "reverse polarity" or "umpolung" strategy would provide a demonstration of its power for the preparation of members of the group IV aryl C-glycosides.

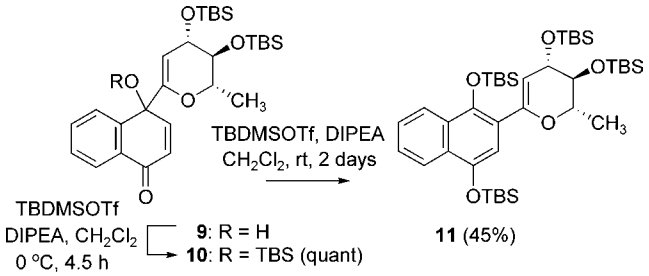
Our retrosynthetic analysis of (−)-griseusin B (**2a**) suggested the elaboration of quinone glycal **4**, envisioned as the Stille coupling product of bromoquinone glycal **5** with an appropriate stannane compound (Scheme 1). On the basis of our previous work, we anticipated that key intermediate **5** would be available from a dienone−phenol-type rearrangement[15] of quinol intermediate **6**. Quinol **6**, in turn, should be the product of regioselective addition[16] of the lithiated reagent from a 4-deoxy glycal **8**[17] to 2-bromojuglone derivative **7**.

Scheme 1. Retrosynthesis of (−)-Griseusin B (**2a**)



To test what appeared to be a reasonable but not directly precedented dienone−phenol rearrangement, we examined the behavior of the model quinol **9** (Scheme 2).[16] In experiments intended to effect the protection of the tertiary hydroxyl group of this compound (TBDMSOTf, DIPEA, 0 °C, 4.5 h),[18] we had noticed that extended reaction times or higher temperatures led to the appearance of aromatized product **11**. Indeed, when the intermediate silyl ether **10** was subjected to the silyl triflate reagent for 2 days at room

Scheme 2. Dienone−Phenol Rearrangement to the Group 4 Substitution Pattern of Aryl C-Glycosides



(8) See, for example: (a) Taguchi, T.; Kunieda, K.; Takeda-Shitaka, M.; Takaya, D.; Kawano, N.i; Kimberley, M. R.; Booker-Milburn, K. I.; Stephenson, G. R.; Umeyama, H.; Ebizuka, Y.; Ichinose, K. *Bioorg. Med. Chem.* **2004**, *12*, 5917. (b) Ichinose, K.; Ozawa, M.; Itou, K.; Kunieda, K.; Ebizuka, Y. *Microbiol.* **2003**, *149*, 1633 and references therein. (c) Tang, Y.; Lee, T. S.; Kobayashi, S.; Khosla, C. *Biochemistry* **2003**, *42*, 6588.

(9) For an early example of bioengineering in this series, see: Ômura, S.; Ikeda, H.; Malpartida, F.; Kieser, H. M.; Hopwood, D. A. *Antimicrob. Agents Chemother.* **1986**, *29*, 13.

(10) Unlike the medermycin family and the granaticins, which are glycosylated octaketides, the griseusins are decaketides. See: Yu, T. W.; Bibb, M. J.; Revill, W. P.; Hopwood, S. A. *J. Bacteriol.* **1994**, *176*, 2627.

(11) Review: Brimble, M. A.; Nairn, M. R. *Tetrahedron* **2000**, *56*, 1937.

(12) Brimble, M. A.; Nairn, M. R.; Park, J. S. O. *Perkin Trans. 1* **2000**, 697.

(13) Parker, K. A.; Georges, A. T. *Org. Lett.* **2000**, *2*, 497 and references therein.

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(15) (a) Goodwin, S.; Witkop, B. *J. Am. Chem. Soc.* **1957**, *79*, 179. (b) Dodge, J. A.; Chamberlin, A. R. *Tetrahedron Lett.* **1988**, *29*, 4827.

(16) Parker, K. A.; Coburn, C. A.; Johnson, P. D.; Aristoff, P. *J. Org. Chem.* **1992**, *57*, 5547.

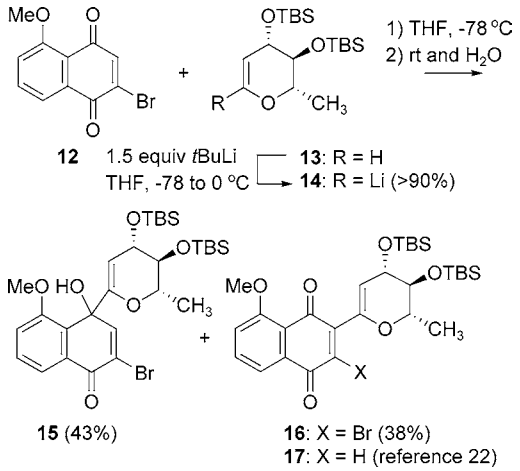
(17) (a) Moilanen, S. B.; Tan, D. S. *Org. Biomol. Chem.* **2005**, *3*, 798. (b) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2003**, *68*, 8798.

(18) Parker, K. A.; Koh, Y.-h. *J. Am. Chem. Soc.* **1994**, *116*, 11149.

temperature, the protected, rearranged naphthalenehydroquinone was isolated in 45% yield (not optimized).

Next, we investigated the 1,2-addition reaction that is the foundation of the umpolung strategy with 2-bromojuglone methyl ether (**12**).[19] For these feasibility studies (Scheme 3),

Scheme 3. Lithiated Glycal Addition to 2-Bromojuglone Methyl Ether

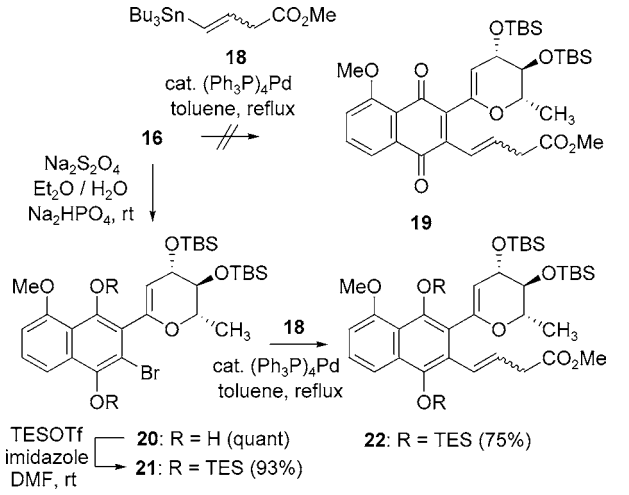


we used readily available rhamnal derivative **13**[20] as a model for the less accessible deoxy glycal **8**. Thus, lithiated rhamnal **14**[21] was added to quinone **12**. Quenching of the reaction with water *at room temperature*[22] led to the isolation of an approximately 1:1 mixture[23] of the expected diastereomeric mixture of quinol glycal **15** and the surprising but attractive quinone glycal **16**. In the context of a synthesis of griseusins, the appearance of this functionalized quinone was potentially advantageous.

The mechanism of formation of quinone **16** is not clear. It is presumably the result of air oxidation of the corresponding hydroquinone, formed by quenching the product of conjugate addition or of coupling of a radical anion/radical cation pair.[24] In any case, attempts to convert adduct **15** to the rearranged and oxidized **16** under the conditions of the addition reaction were unsuccessful.[23] Although we were unable to alter the ratio of these two adducts in the product mixture, we found that this 1:1 mixture was consistently produced in combined yields of >80%. Therefore, we set out to discover the chemistry that would convert each of the products to the same advanced (model) intermediate.

We first examined the elaboration of quinone glycal **16**. Stille coupling with vinyl stannane **18**[25] as proposed in our retrosynthetic analysis did not afford the desired compound **19** but, instead, a complex mixture of inseparable products (Scheme 4). This result is not surprising in light of the ease

Scheme 4. Transformation of Quinone Glycal **16** to Advanced Intermediate **22**



by which vinyl quinones undergo cyclization reactions under thermal and photochemical conditions and the inherent instability of the products of these conversions.[26,27]

Focusing again on progress toward the griseusins, we resorted to an indirect strategy that utilizes protected bromohydroquinone substrates for the Stille coupling with vinyl stannanes.[26] Thus, reduction of quinone glycal **16** yielded hydroquinone **20**, which was directly protected as hydroquinone **21**. Stille coupling of intermediate **21** with vinyl stannane **18** yielded protected vinyl hydroquinone glycal **22** in good yield. This readily available compound contains the complete carbon skeleton of the griseusins and, except for the extra hydroxyl equivalent on the dihydropyran ring, it is appropriately functionalized for completion of a total synthesis.

Next we turned our attention to the potential of quinol glycal **15** as a precursor for this same advanced model intermediate **22** (Scheme 5). In an attempt to effect the conversion of quinol **15** to intermediate **23**, we subjected it to the TESOTf rearrangement conditions (Hunig's base at room temperature, Scheme 2). However, this experiment yielded only the TES-protected quinol glycal **24**. Next, we

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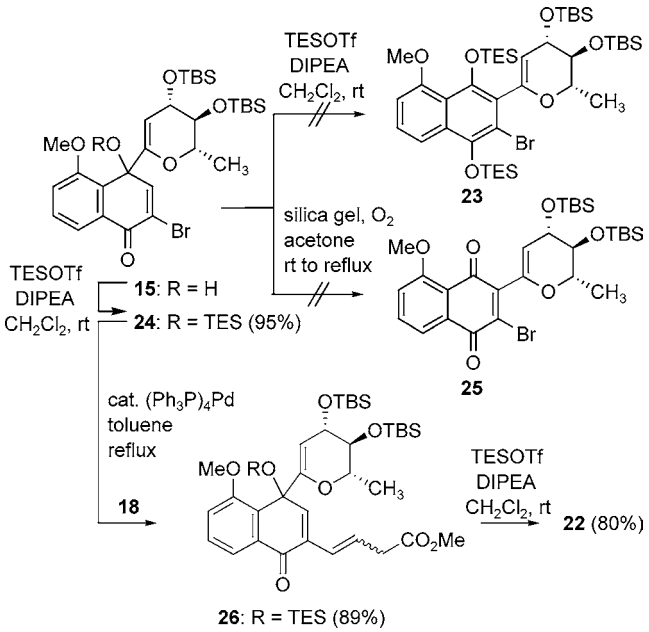
(20) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107.
(21) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, *48*, 4187. The success of the lithiation of glycal **13** was verified by quenching samples of the reaction mixture with D_2O and NMR analysis of the product. Integration of the diminished signal of the vinyl proton indicated >90% lithiation of substrate **13**.
(22) Addition of water at low temperature (−78 °C) resulted in the formation of a mixture of quinol **15** and quinone **17** in which the bromo substituent had been lost. In this experiment, the isolated yields of **15** and **17** were 35 and 37%, respectively.
(23) The ratio of the two products **15** and **16** could not be influenced by altering the reaction conditions. The same 1:1 mixture of adducts in varying yields was isolated from experiments at different temperatures (−100 to 0 °C) and after extended reaction time (warming to room temperature over 8 h), in different solvents (THF, Et_2O, *t*-BuOMe) and at different concentrations of quinone **12** (0.1 M or 20 mM).
(24) Wigal, C. T.; Grunwell, J. R.; Hershberger, J. *J. Org. Chem.* **1991**, *56*, 3759.
(25) Presumably a *cis*/*trans* mixture; the NMR spectra of this compound are complex because of coupling with the tin nucleus. For the preparation of vinyl stannane **18**, see: Collins, P. W.; Kramer, S. W.; Gasiecki, A. F.; Weier, R. M.; Jones, P. H.; Gullikson, G. W.; Bianchi, R. G. *J. Med. Chem.* **1987**, *30*, 193.
(26) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2001**, *3*, 3875.
(27) Iwamoto, H.; Takuwa, A.; Hamada, K.; Fujiwara, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 575.

Scheme 5. Elaboration of Advanced Intermediate **22** from Quinol Glycal **15** by a Dienone−Phenol-type Rearrangement



attempted the silica gel-promoted rearrangement of quinols as reported by Wigal.[28] However, substrate **15** proved to be stable under the applied conditions, and no rearranged product **25** was observed. These results are consistent with related observations that suggest that a bromo substituent retards a dienol−phenol rearrangement.[29]

To access a suitable and useful substrate for the dienone−phenol-type rearrangement, we converted TES-protected quinol **24** to protected quinol **26** by Stille coupling with vinyl stannane **18** (Scheme 5). When protected quinol **26** was treated with excess TESOTf and Hunig's base at room temperature, it was cleanly converted to quinone **22**, identical in all respects to the product derived from bromoquinone **16**.

With this achievement, both quinol glycal **15** and quinone glycal **16** have been converted to advanced model intermediate **22**, each in only three steps and each in good overall yield (approximately 70%). This result provides an unusual example of the utility of two regioisomeric products, obtained from a single reaction mixture, for the preparation of the same, desired compound.

Despite the additional manipulations associated with processing two intermediates, only seven steps total are required to prepare a complex structure that contains the complete carbon skeleton and (except for the extraneous C-oxygen substituent in the model **22**) the functional group pattern of the griseusins from a bromoquinone and a protected glycal.

Application of the divergent−reconvergent approach to the total synthesis of (−)-griseusin B (**2a**) is currently being investigated. The modular assembly nature of the synthetic scheme suggests that it might be efficiently applied to the preparation of griseusin analogues for structure−activity relationship (SAR) studies.

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Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1964**, *29*, 509.