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Approach Toward the Total Synthesis of 5-Hydroxyaloin A

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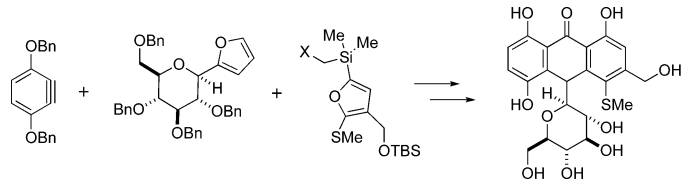
ABSTRACT



The synthesis of a thiomethyl analogue of 5-hydroxyaloin A has been achieved using benzyne and naphthyne [4 + 2] cycloadditions with substituted furans. A regiocontrolled cycloaddition was achieved using a silicon tether, and a regioselective ring opening was accomplished using a sulfide as a directing group.

Over the past three decades, there have been numerous synthetic approaches to the *C*-aryl glycoside class of natural products, owing to both their significant anticancer properties and the challenges associated with forming the *C*-glycosidic linkage.[1] Toward addressing this problem, we have developed a unified strategy for preparing the four major classes of *C*-aryl glycosides.[2] The approach features benzyne-furan [4 + 2] cycloadditions and has been applied to a formal synthesis of galtamycinone[3] and total syntheses of vineomycinone B_2 methyl ester[4] and isokidamycin.[5] We also envisioned that this methodology might be extended to enable facile access to the novel class of anthrone *C*-glycosides as represented by 5-hydroxyaloin A (**1**),[6] aloin (**2**),[7] and cassialoin (**3**) (Figure 1).[8,9] These *C*-glycosides, which are not technically categorized as *C*-aryl glycosides, contain a sugar moiety bonded to C(10) of an anthrone ring via a C−C bond. We thus became interested in the *aloe*-derived glycoside 5-hydroxyaloin A (**1**), which has not yet been prepared by total synthesis.

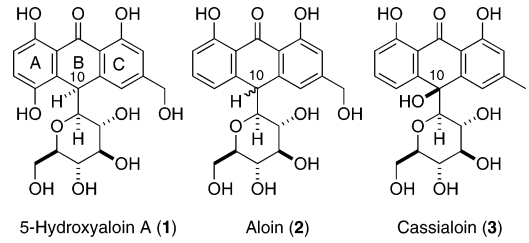


Figure 1. Anthrone *C*-glycosides.

(1) For reviews on the synthesis of *C*-aryl glycosides, see: (a) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1–20. (b) Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 2175–2178. (c) Levy, D. E.; Tang, C. In *The Chemistry of C-Glycosides*; Elsevier Science: Tarrytown, NY, 1995. (d) Du, Y. G.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959. (e) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133–1167.

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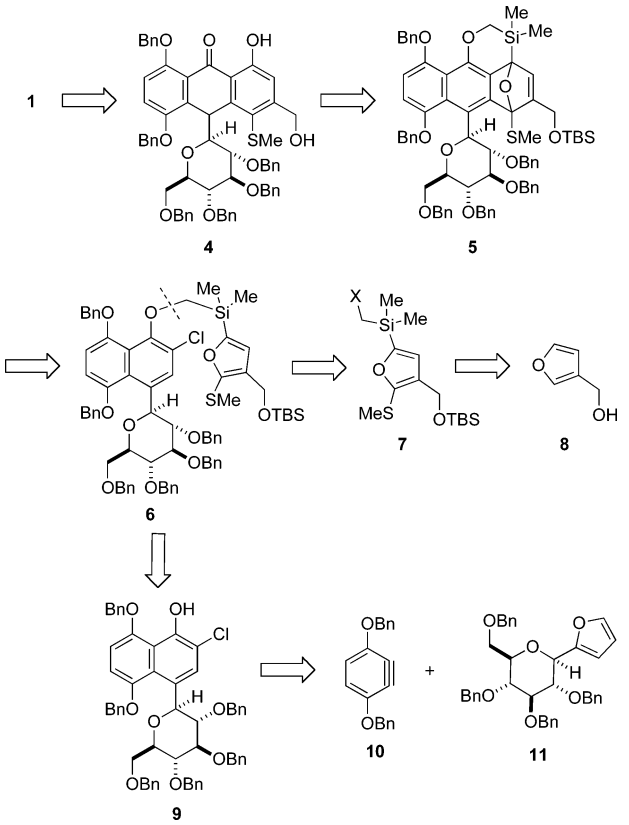
In our retrosynthetic analysis, we envisioned that 5-hydroxyaloin A (**1**) would be formed by desulfurization of **4**, which would arise from desilylation and acid-catalyzed ring opening of **5** (Scheme 1). The intermediate **5** would be

Scheme 1. Retrosynthetic Analysis of 5-Hydroxyaloin A (**1**)



formed from an intramolecular [4 + 2] cycloaddition of a furanyl naphthyne that would be generated from **6**, which in turn would be assembled by etherification of **9** with **7**. The bromosilane **7** would then be accessed in three steps from commercially available 3-furanmethanol (**8**). The [4 + 2] cycloaddition of benzyne **10** and glycosyl furan **11** would lead to the substituted *C*-aryl glycoside **9**.

There are several issues associated with the regiochemical outcomes of reactions in our retrosynthetic analysis that merit additional comment. The first of these involves the regiochemistry of the ring opening of **5** to give **4**. Given the known propensity of related compounds *lacking an electron-donating group* at the bridgehead to undergo acid-catalyzed ring opening in the opposite regiochemical sense,[2a,10c] the placement of an electron-donating group at the bridgehead to direct the ring opening was deemed essential. Indeed, the importance of using such a directing group for the ring opening of compounds related to **5** was validated in preliminary model studies. Either an alkoxy or a thioalkyl substituent could serve this purpose, but a thioalkyl, in particular, a thiomethyl, group was viewed as being easier to remove at a late stage in the synthesis. A second feature of the approach is the use of an intramolecular [4 + 2] cycloaddition of a furan and a naphthyne as a regiocontrol element. Although [4 + 2] cycloadditions involving benzynes and furans can proceed with good regioselectivity,[10] examination of the literature suggests that the polarization of a naphthyne generated from a derivative of **9** and a 2-thiomethylfuran would likely proceed preferentially in the undesired regiochemical sense (Figure 2). In an exploratory experiment, we found that this

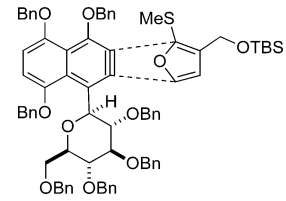
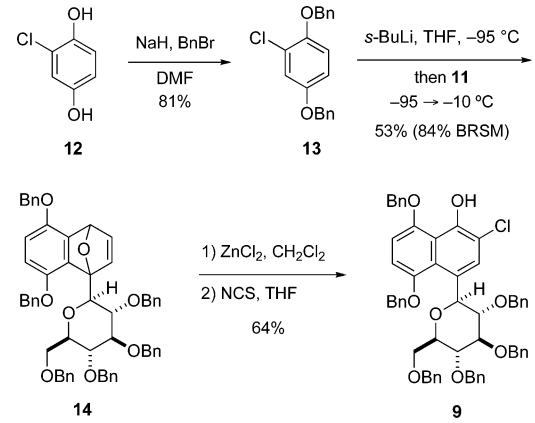


Figure 2. Predicted preferential regioselectivity of bimolecular [4 + 2] naphthyne-furan cycloaddition.

intermolecular cycloaddition did in fact deliver a mixture of cycloadducts. To address such problems of low regioselectivity in intermolecular benzyne cycloadditions, we had previously shown that silicon tethers can be nicely exploited as disposable linkers to circumvent this problem by rendering the reaction intramolecular.[2c]

We initiated our efforts with the preparation of the naphthol derivative **9**. In the event, the benzyne precursor **13** was formed in 81% yield upon treatment of chlorohydroquinone (**12**) with BnBr and NaH (Scheme 2). Deproto-

Scheme 2. Synthesis of Naphthol **9**



nation of **13** with *s*-BuLi at −95 °C and addition of the known glycosyl furan **7**,[11] followed by warming to −10 °C, provided cycloadduct **14** in 53% yield (84% BRSM). Ring

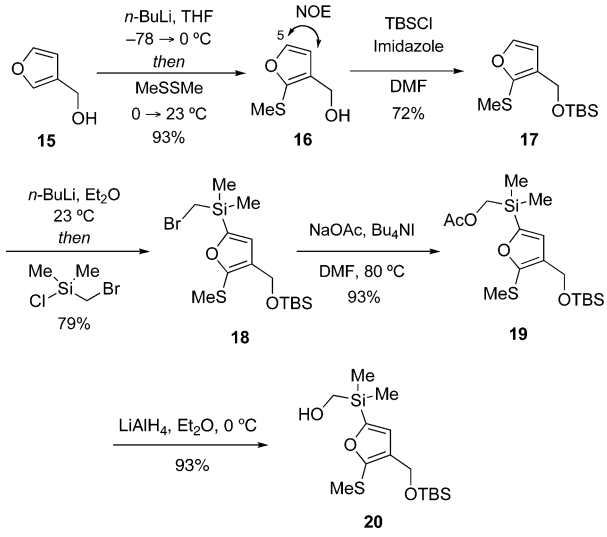
(10) For example: (a) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736. (b) Giles, R. G. F.; Hughes, A. B.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1581–1587. (c) Baker, R. W.; Baker, T. M.; Birkbeck, A. A.; Giles, R. G. F.; Sargent, M. V.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1589–1600.

(11) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610–612.

opening of the oxabicycloheptadiene ring was achieved upon treating **14** with $ZnCl_2$ to give an intermediate phenol that was regioselectively chlorinated by the action of *N*-chlorosuccinimide to give **9** in 64% overall yield.

The next stage of the synthesis required the preparation of a suitably substituted furan that would eventually give rise to the unsymmetrically substituted C ring of **1**. Regioselective lithiation of 3-furanmethanol (**15**) at C(2), followed by reaction with dimethyl disulfide, gave **16** (Scheme 3).[12]

Scheme 3. Synthesis of the Furan Precursor of the C Ring

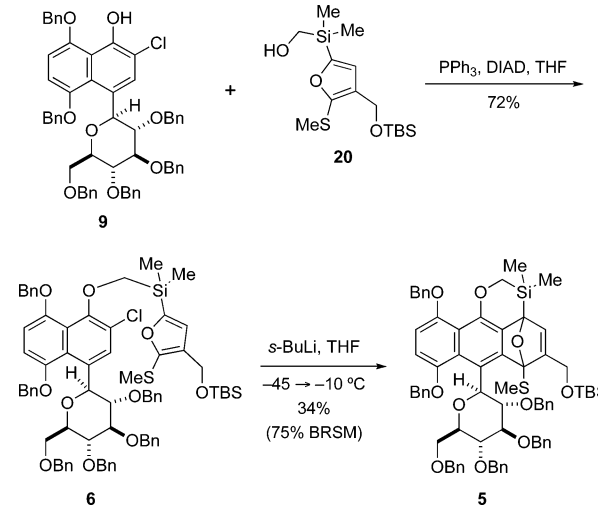


Treatment of sulfide **16** with TBSCl and imidazole furnished silyl ether **17** in about 60% overall yield from **15**. The conversion of **17** into **18** was achieved by sequential lithiation of **17** at C(5) and treatment with bromomethyl chlorodimethylsilane. Unfortunately, we discovered that the etherification of the naphthol **9** with **18** under a variety of conditions was problematic, giving complex mixtures of compounds. This difficulty was not completely unexpected as we had previously encountered problems with similar alkylations.[2c] Indeed, during the course of those investigations, we had also developed a solution to this problem wherein a Mitsunobu reaction was employed to prepare phenolic ethers. Accordingly, bromide **18** was converted to the acetate **19** by treatment with NaOAc and TBAI; subsequent reduction of **19** with $LiAlH_4$ then provided the requisite alcohol **20**.

Naphthol **9** and alcohol **20** were then coupled by a Mitsunobu etherification to give **6** in 72% yield (Scheme 4). Deprotonation of **6** with *s*-BuLi led to naphthyne generation and intramolecular cycloaddition to furnish **5** in 34% yield (75% BRSM). Unfortunately, it was not possible to optimize this reaction by using excess *s*-BuLi because Si−C bond cleavage intervened as a major side reaction. Fortunately, however, it was possible to recover and recycle **6**.

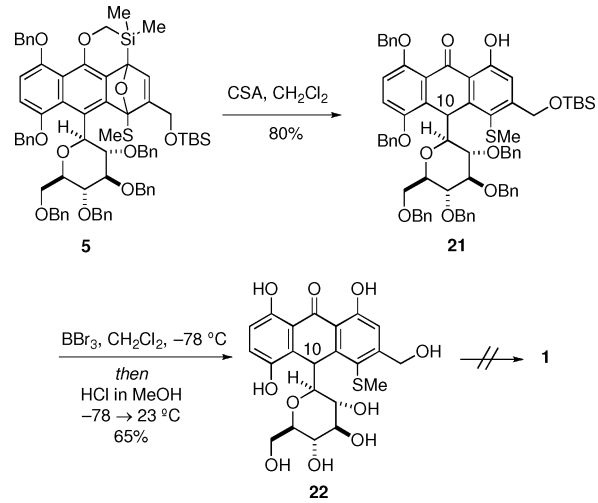
(12) For a similar reaction, see: Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835–5838.

Scheme 4. Etherification and Naphthyne Cycloaddition



With the cycloadduct **5** in hand, it remained to cleave the silicon tether, open the oxabicycloheptadiene, and remove the benzyl protecting groups and the thiomethyl moiety. In prior work, we had developed an effective two-step procedure for removing the silicon tether with TBAF in DMF, followed by opening the oxabicyclo ring with a Brønsted or Lewis acid to give a naphthol.[2c] In the present instance, however, we found that when **5** was simply treated with camphorsulfonic acid (CSA) the anthrone **21** was obtained as a single diastereomer in 80% yield (Scheme 5).

Scheme 5. Synthesis of the Thiomethyl Analogue of 5-Hydroxyaloin A



Attempts to desulfurize **21** using a variety of reagents, including deactivated Raney-Ni,[13] nickel boride,[14] and NiCRAs,[15] were uniformly unsuccessful, giving either no reaction or intractable mixtures. We thus postponed the desulfurization step and effected global deprotection of the

benzyl and silyl ethers on **21** using BBr_3 to furnish **22** as a single diastereomer in 65% yield. Once again, however, all efforts to effect desulfurization of **22** to give 5-hydroxyaloin A (**1**) using Raney nickel, nickel boride, and NiCRAs were unsuccessful. We also explored the possibility of desulfurizing the sulfoxide and the sulfone derived from **22** using Raney nickel, Na/Hg amalgam in the presence of dibasic sodium phosphate,[16] and SmI_2,[17] but these attempts were also fruitless. We were therefore reluctantly compelled to accept the synthesis of the thiomethyl 5-hydroxyaloin A derivative **22** as the terminal goal for these efforts. Although both **21** and **22** were isolated as single diastereomers, we were unable to determine the relative stereochemistry at C(10) in either. Efforts to obtain crystals suitable for X-ray analysis were unsuccessful, and NOE experiments were ambiguous.

In summary, we have applied a variant of our benzyne-furan [4 + 2] cycloaddition strategy for the synthesis of a thiomethyl analogue of 5-hydroxyaloin A. Although the thiomethyl group served admirably in its appointed task of directing the regiochemistry of the ring opening of the cycloadduct **5**, difficulties encountered in its removal precluded us from completing the synthesis of 5-hydroxyaloin A. An alternate plan must now be developed. Nevertheless, we did discover a useful one-step procedure for converting cycloadducts such as **5** into naphthol derivatives, thus improving upon our prior art. Further applications of our general strategy for the synthesis of *C*-aryl glycosides are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures, chromatographic data, and characterization and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) SmI_2 generation: Concello, J. M.; Rodrýguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, *2003*, 1775–1778. For an example of desulfurization using SmI_2, see: Adrio, J.; Carretero, J. C.; García, J. L.; Ruano, L. M.; Cabrejas, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1623–1631.