Progress Towards the Total Synthesis of Nogalamycin using a Benzyne Cycloaddition Strategy.

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Supporting Information Placeholder

ABSTRACT: Nogalamycin (NOG) is a member of the anthracycline glycoside natural products; no total syntheses have yet been reported and there is minimal understanding of how the aglycone substitution pattern and the identities of the A- and D-ring sugar impact anticancer activity and toxicity. This paper reports progress towards a modular approach to NOG that could enable systematic structure-activity relationship studies. Key steps include a regioselective benzyne cycloaddition and a reductive ring-opening to assemble a versatile AB core for analogue synthesis.

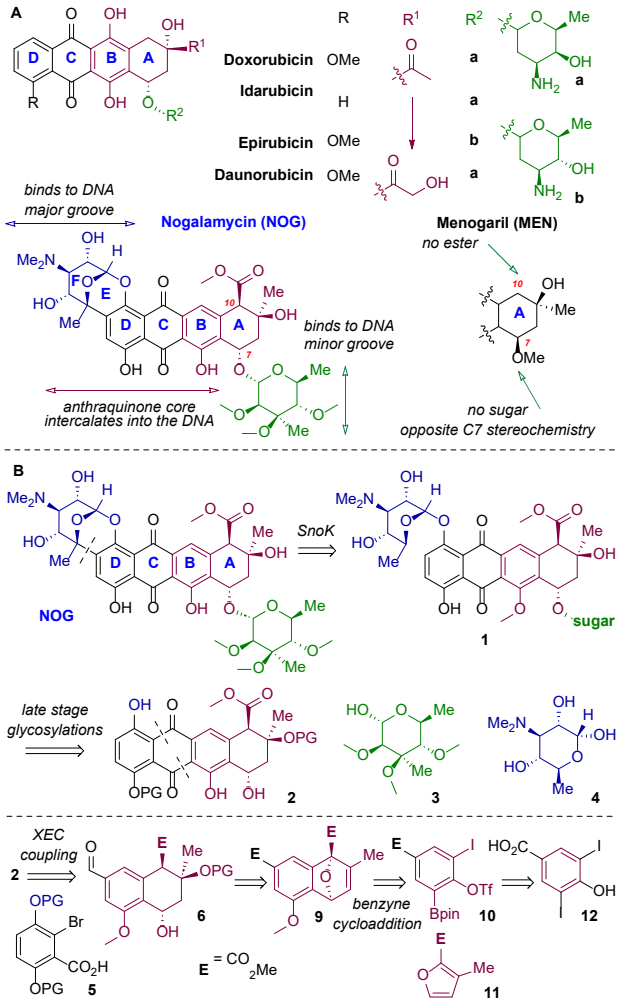
The anthracycline glycoside natural products are a class of molecules with potent antineoplastic activities that have attracted attention over the years for treatment of cancer. FDA-approved drugs in this class include doxorubicin (DOX), daunorubicin, epirubicin, and idarubicin (Scheme 1A), but cardiotoxicity and multidrug resistance limit their use as chemotherapeutics.[1-4] While DOX[5] surpassed a market value of $1.08 billion in 2020,[6] its toxicity and unclear mechanism of action[7,8] make the search for less toxic compounds with comparable activity attractive.

Nogalamycin (NOG), isolated from *Streptomyces nogalator*, contains a unique D-ring bicyclic amino sugar and an A-ring nogalose sugar, with the overall structure resembling a dumbbell. The tetracyclic core is proposed to intercalate DNA, with the D-ring sugar binding in the major groove and the A-ring sugar in the minor groove.[9] A cocrystal structure of NOG and a DNA hexamer suggest unfolding of the hexamer to bind to NOG, followed by adoption of a distorted helix post-binding. While the exact details of the mechanism-of-action are unclear, it is known that binding of NOG to an up-stream site can induce highly specific topoisomerase I-mediated DNA cleavage. NOG also inhibits Gram-positive bacteria and shows promising cytotoxicity against L1210 and KB cell lines in vitro; however, it shows only weak activity against solid tumors in vivo and high toxicity in mammalian subjects. Menogaril (MEN, Scheme 1A) is a semisynthetic derivative of NOG[10] that lacks the A-ring ester and sugar; the weaker binding of MEN to DNA may be due to the latter circumstance. While NOG and other anthracyclines are type II topoisomerase inhibitors, MEN selectively inhibits type I topoisomerase. MEN successfully entered Phase II clinical trials against non-Hodgkin lymphomas,[11] but no other NOG analogs have been reported in the clinic. We were interested in developing a modular approach to NOG that would enable systematic study of the impact of the identity of A- and D-ring sugars on the anti-cancer activity and toxicity of new analogues.

A number of synthetic approaches towards NOG and MEN have been reported,[12-26] culminating in an enantioselective synthesis of MEN by Terashima in 1988[19,20] and a racemic synthesis by Hauser in 1991.[26] However, while there is no reported total synthesis of NOG, there are approaches to the simpler analogue MEN.[19-20,25] Terashima used a Diels-Alder cycloaddition between a CDEF-ring quinone fragment and an AB-ring diene to furnish MEN with 28 steps in the longest linear sequence. Hauser[26] employed a key Hauser annulation to give racemic MEN with a longest linear sequence of 30 steps and published an enantioselective synthesis of the DEF-ring system in 2000.[27] Related model studies towards the preparation of the CDEF fragment include work by the groups of Krohn[12-14] and Franck,[15] while strategies to forge the anthracycline core were reported by Wulff.[28,29] The VanNieuwenhze group achieved the most advanced partial synthesis of NOG[30] using a late-stage convergent synthesis involving a key Hauser annulation. Despite this success, approaches to the shared CDEF ring of MEN and NOG are lengthy and scaffold diversification must be done early in the synthesis. From a practical standpoint, late-stage installation of the A and D-ring sugars would allow easier access to diverse analogs. Similarly, common approaches to the aglycone core lack versatility, as Hauser annulation is limited to chemistries tolerant of the pre-installed phthalide and Michael acceptor, while Diels-Alder approaches require electronic matching for high selectivity. A more efficient route to install as much functionality as possible in a few steps would be enabling.

Our goal is to develop a modular, convergent approach to NOG to provide opportunities to probe structure-activity

Scheme 1. A) Representative anthracycline glycosides. B) Retrosynthetic analysis of nogalamycin.

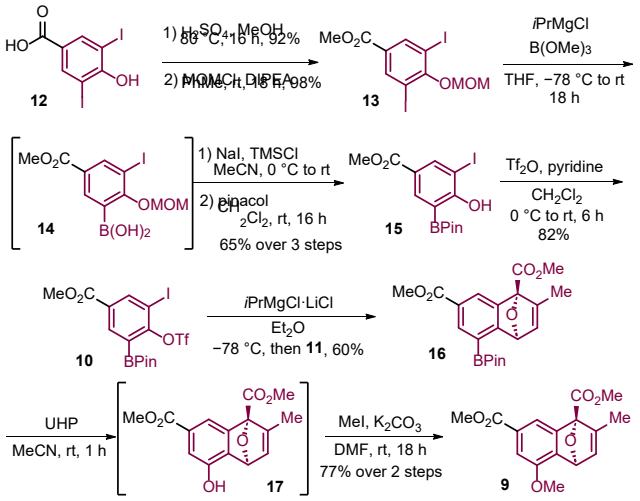


relationships in a straight-forward manner. This would enable systematic study of how the A- and D-ring sugars, as well as substitution on the aglycone core,[17-21] impacts both the desirable and off-target activities. Our proposed retrosynthesis of NOG (Scheme 1) involves a three-fragment convergent approach that couples the anthracycline core **2**, the A-ring sugar (nogalose **3** in NOG) and a nogalamine aminosugar **4**. The final step is inspired by the biosynthetic pathway, where native SnoK or an enzyme modified by directed evolution forges the challenging C_{aryl}–$C_{glycoside}$ bond in **1**.[32] While a bold strategy, postponing glycosylation until the penultimate steps allows greater flexibility for efficient analog preparation, where appending any accessible sugar or aminosugar to the aglycone can be explored.

A Ni-catalyzed cross-electrophile coupling (XEC) between **5** and **6**[33] followed by cyclization via EAS forms **2**. The aryl aldehyde AB-ring fragment **6** is traced back to the oxa-benzonorbornadiene (OBD) **9**, obtained from a regioselective boron-directed benzyne cycloaddition between benzyne precursor **10** and furan **11**.[34] The iodotriflate **10** is accessed from commercially available diiodobenzoic acid **12**.

The benzyne cycloaddition strategy to construct the AB ring (Scheme 2) commenced with esterification of **12** and MOM protection of the phenol to afford **13** in 90% yield over the 2 steps. Magnesium-halogen exchange and trapping with trimethyl borate gave boronic acid **14**, which was carried forward without purification due to its insolubility. MOM deprotection and formation of the boronic ester delivered **15**, which was characterized and isolated in a 65% yield over the three-step sequence. Formation of the benzyne triflate precursor **10** proceeded smoothly in 82% yield. In situ formation of the benzyne utilized the Turbo Grignard *i*PrMgCl•LiCl; trapping with furan **11** gave **16** as the major regioisomer in 60% yield (10.1:1 *rr*), plus a small amount of a minor regioisomer **16a** (not shown). The inseparable OBD regioisomers were carried forward into the next step.

Scheme 2. Synthesis of OBD intermediate **9**.

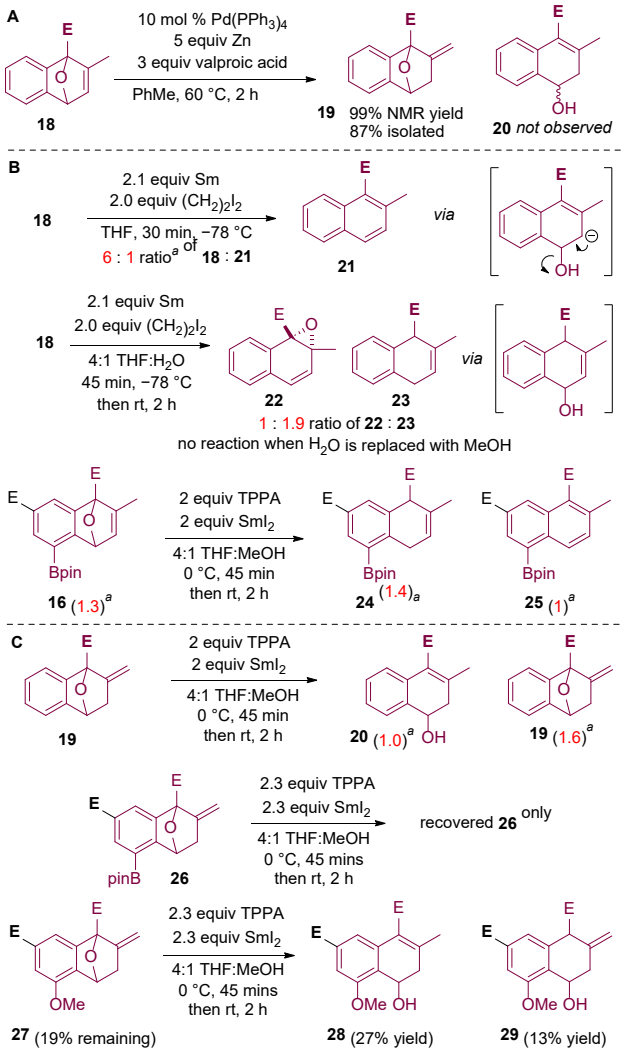


Oxidation of the boronic ester of **16** with urea hydrogen peroxide (UHP) and separation of the desired OBD regioisomer **17** was followed by methylation of the phenol to furnish **9** in 77% yield over the two steps. This oxidation-methylation strategy proved advantageous, as removal of the boronic ester rendered purification of the later intermediates much easier and a free phenol could later be easily accessed for the B ring.

Despite the wealth of literature on the ring-opening of OBDs, there are few reported methods capable of accessing the substitution required for NOG. Most reported OBD ring-openings introduce substitution on the cyclohexane ring located β to the newly generated alcohol;[35-37] anthracyclines typically do not have substitution at this position. Thus, we opted to first synthesize a model OBD **18** (Scheme 3) to evaluate the likelihood of success in the application of known literature conditions to the advanced OBD scaffold that is needed for NOG.

Initial attempts to open the OBD **18** using Lauten's Ni-catalyzed conditions[35] gave a variety of undesired products, while Pd-catalyzed conditions reported by Cheng gave a 99% yield of the *exo*-alkene **19** (Scheme 3A).[36] Variations on the Cheng conditions (see the Supporting Information for details) still favored isomerization. Thus, we shifted our

Scheme 3. A) Pd-catalyzed OBD ring-opening using a model compound. B) Efforts using Sm-mediated OBD ring-opening. C) Successful OBD ring-opening with advanced NOG AB ring scaffolds.



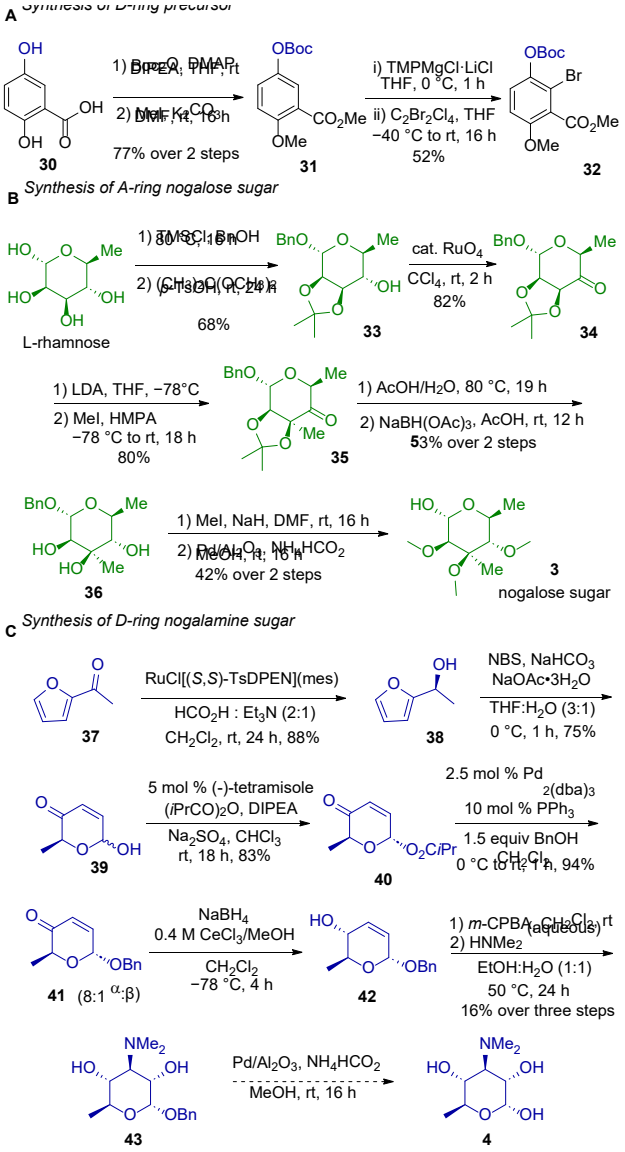
[a]NMR ratios of all products observed.

approach and took inspiration from Molander's reductions of vinyloxiranes to allylic alcohols.[38] We hypothesized that an anionic ring-opening to eliminate the C–O bond of the OBD would circumvent formation of the undesired regioisomer. Applying a modified version of Molander's conditions (Scheme 3B) to **18** gave recovered **18** and the naphthalene **21** in a 6:1 ratio. While the production of **21** was mitigated using H_2O as a cosolvent, ligation of H_2O to SmI_2 generated a mixture of reducing SmI_2 species, which gave epoxide **22** and overreduction to **23**. Use of unligated SmI_2 in THF/MeOH gave no reaction. The Baran group used tris(pyrrolidino)phosphoramide (TPPA) as an alternative to HMPA as a ligand in a SmI_2 electroreduction of arenes.[39] Treatment of the actual substrate **16** with TPPA/SmI_2 in THF/MeOH still gave competing overreduction and recovered starting material.

Given the challenges with opening **18** or **16** in the desired manner, attention was turned to employing the *exo*-alkene **19** obtained in Scheme 3A as the starting OBD. Gratifyingly, treatment of **19** with TPPA/SmI_2 in THF/MeOH (Scheme 3C) gave remaining **19** and the desired **20** in a 1.6:1.0 ratio with no observed overreduction or aromatization. The more functionalized **26** gave no product, likely due to the empty *p* orbital on B. However, anisole **27** gave a 27% yield of the desired **28**, along with 13% of the isomer **29** and 19% remaining **27**. Further optimization was not carried out at this point, but will be pursued in the application of this strategy to the synthesis of other anthracycline glycosides and their analogues.

With a viable approach in hand to access intermediates that could be used to elaborate the AB-ring in a flexible manner, we next prepared the D-ring fragment and the A-

Scheme 4. A) Synthesis of the D ring aryl bromide fragment. B) Synthesis of nogalose **3**. C) Synthesis of nogalamine **4**.



and D-ring sugars of NOG (Scheme 4). The D-ring fragment involved Boc protection and methylation of gentisic acid **30** to afford **31**. Directed *ortho*-lithiation[40] was unsuccessful

for arene bromination, perhaps due to tight chelation of the aryllithium to the -OBoc and ester groups. While arylmagnesium bases are not as well-studied for *ortho*- lithiation, directed magnesiation of **31** with a TMPMgCl·LiCl complex successfully delivered **32** in 52% yield (Scheme 4A).[41]

Finally, the nogalose **3** and nogalamine **4** sugars were prepared from modifications to commercially available L-rhamnose and precedented sugar chemistry, respectively (Scheme 4B-C). L-Rhamnose[42] was first converted to the *O*-benzyl glycoside and protected as the acetonide **33**. Oxidation at the C4 position gave ketone **34**, enabling the introduction of the C3-methyl substituent by kinetic deprotonation and trapping with MeI to give **35**. Acetonide removal and hydride reduction directed by the C3-OH furnished triol **36**. Global methylation and benzyl deprotection by catalytic transfer hydrogenation gave **3**.

Synthesis of the nogalamine fragment **4** began with Noyori asymmetric reduction of achiral **37** to give **38**, followed by oxidative ring expansion via an Achmatowicz reaction to yield dihydropyranone **39** (Scheme 4C).[43] Tang's chiral catalyst-directed acylation and Pd-catalyzed glycosidation strategies afforded intermediate **41** as an 8:1 mixture of α:β anomers.[44] Luche reduction, epoxidation and ring-opening with $HNMe_2$ afforded **43** in 16% yield over the three-step sequence. A final debenzylation is all that is required for the nogalamine sugar **4**, but at this stage, the alcohol was left protected as the benzyl ether.

In conclusion, we have successfully accessed a functionalized OBD as an AB-ring precursor for NOG and analogues through a highly regioselective benzyne cycloaddition strategy to give an oxa-benzonorbornadiene (OBD) A-ring fused to a functionalized aromatic B-ring. A new variation on a SmI_2-mediated ring-opening gave regioselective ring-opening of the OBD to furnish a precursor for the A ring of NOG. More importantly, our studies on reductive ring-opening of the OBD led to several other platforms that could be readily elaborated to novel NOG analogues for SAR studies. Ongoing studies are implementing our proposed convergent three-fragment strategy to couple the AB-ring to the D-ring via XEC and a carbonylative intramolecular Friedel-Crafts reaction. Late-stage glycosylations of both the A- and D-ring sugars will be followed by biocatalysis with SnoK to close the E-ring and afford NOG. More excitingly, demonstration of this modular synthetic strategy will afford a great degree of flexibility to probe the interplay of the appended sugars or aminosugars on analog activity.

ASSOCIATED CONTENT

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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The supporting information contains NMR characterization data for all new and old compounds, reaction optimization conditions, unsuccessful substrates, and relevant references.

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Author Contributions

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