

An Approach to Aminonaphthoquinone Ansamycins Using a Modified Danishefsky Diene

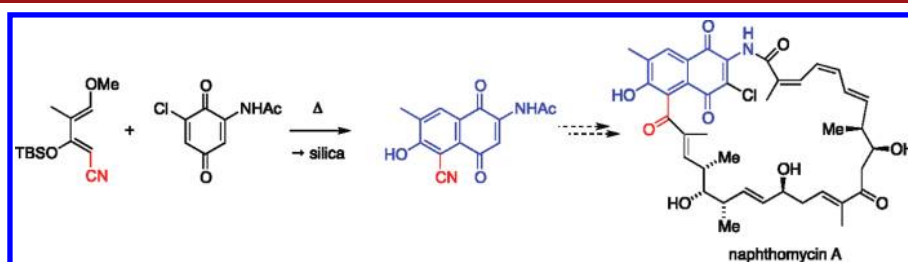
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ABSTRACT



A robust and scalable synthesis of a novel, cyano-substituted Danishefsky-type diene and its use in the Diels–Alder reaction with various dienophiles is reported. The diene allows for the rapid construction of highly substituted aminonaphthoquinones that occur in numerous ansamycin antibiotics.

Ansamycins are an important class of natural products that show potent antibacterial and antiviral activities. In addition to members of the family that have long been known, such as rifamycin or naphthomycin A (**1a**),¹ several new aminonaphthoquinone ansamycins with intriguing structures have recently been reported, including naphthomycin K (**1b**),² ansalactam (**2**),³ and divergolides C (**3a**) and D (**3b**).⁴ As depicted in Figure 1, these molecules possess structurally diverse *ansa* chains of varying lengths that are mounted to a shared naphthoquinone core (depicted in blue) through an acyl linkage in position 5 and an amide in position 2 (naphthoquinone nomenclature). Several members have additional C–C bonds between the aromatic core and the *ansa* chain, which is remarkable from both a synthetic and biosynthetic point of view.

Our interest in the total synthesis of these natural products prompted us to devise a unified approach to their

aminonaphthoquinone core (Scheme 1). We reasoned that due to steric compression, attachment of an *ansa* chain to the arene would be a challenge. This led us to consider cyano naphthalene **4** as a key intermediate, which in turn could be traced back to cyano-substituted Danishefsky diene **5** and substituted aminoquinone **6** via Diels–Alder reaction.

The original Danishefsky diene⁵ has been widely used in organic synthesis along with several variations, which have been developed to improve its reactivity and synthetic scope.⁶ These include alterations of the electron-donating substituents in positions 1 and 3, as well as the introduction of further substituents in positions 2 and 4 (diene nomenclature) that are not lost following cycloaddition.⁷ However, to the best of our knowledge, there is little, if any,

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precedence for Danishefsky-type dienes that bear electron-withdrawing groups. We now report the synthesis of such a diene, compound **5**, as well as studies on its reactivity and use toward the synthesis of ansamycin antibiotics.

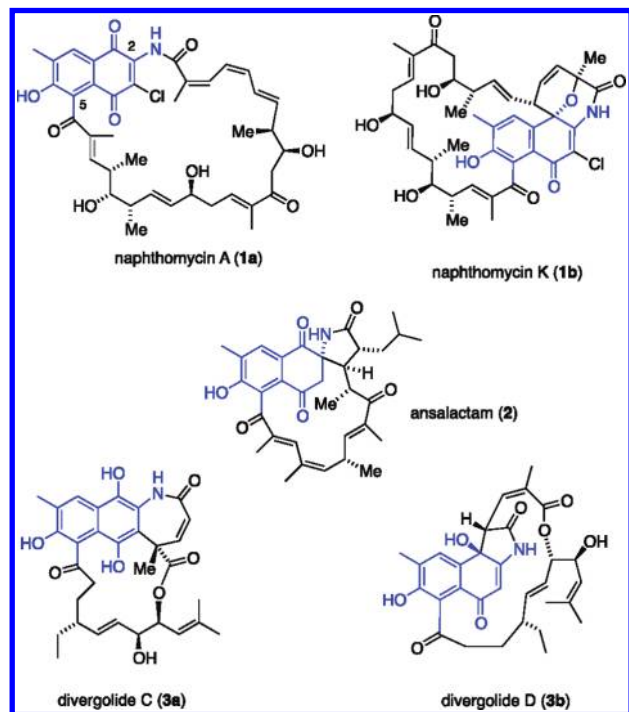
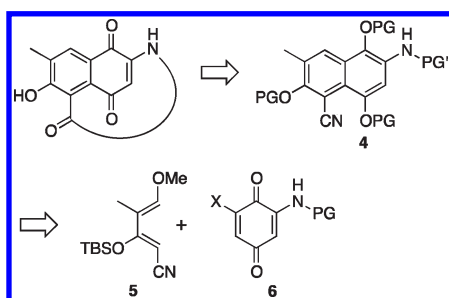


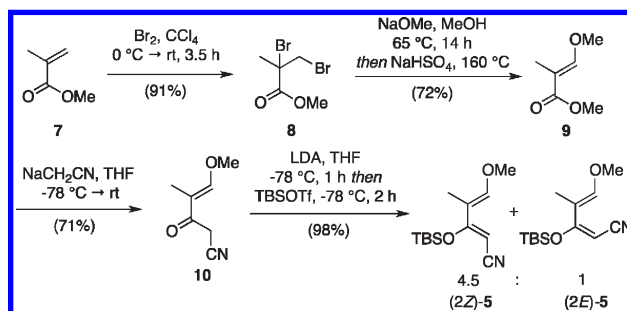
Figure 1. Structurally intriguing ansamycin antibiotics containing an aminonaphthoquinone core.

Scheme 1. Retrosynthetic Analysis of the Aminonaphthoquinone Core of Ansamycins with Suitable Functionalization



Our synthesis of **5** commenced with the bromination of commercially available methyl methacrylate⁸ (**7**), followed by nucleophilic substitution and elimination to introduce a β -methoxy substituent (Scheme 2). Subsequent Claisen-type condensation with deprotonated acetonitrile gave ketonitrile **10**, which proved to be surprisingly stable. Next, conditions for its enolization and subsequent silylation were screened. Attempts to synthesize the TMS enol ether

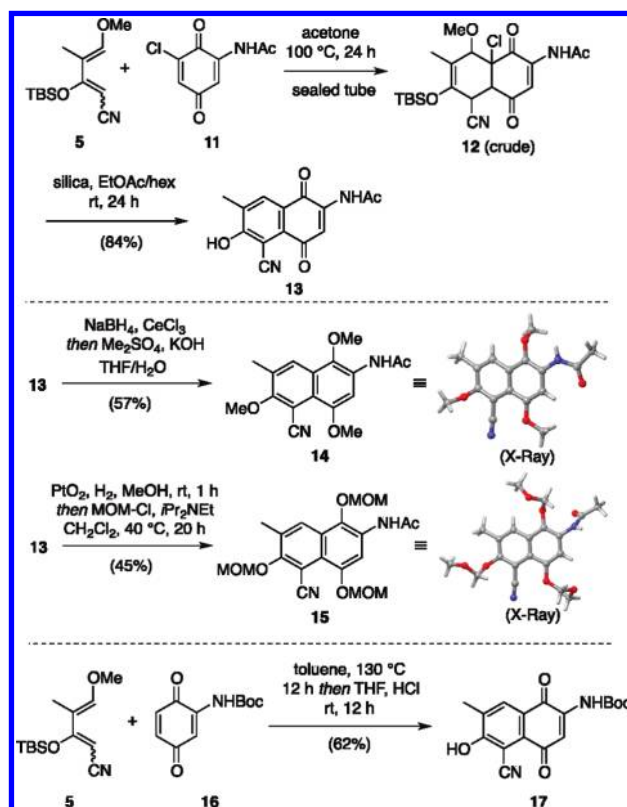
Scheme 2. Synthesis of Diene **5**



of **10** failed due to its high lability toward various workup conditions. However, we found that deprotonation with LDA and subsequent silylation with TBSOTf delivered silyloxy diene **5** as a 4.5:1 mixture of (2Z)- and (2E)-isomers in excellent overall yield. These isomers could be separated (see Supporting Information) but were usually employed as a mixture in subsequent reactions.

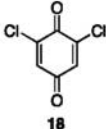
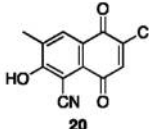
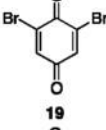
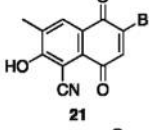


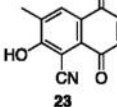
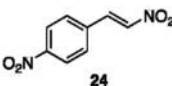
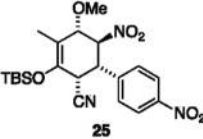
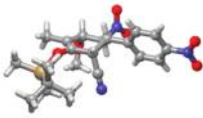
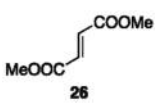
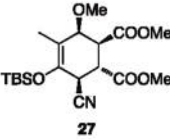
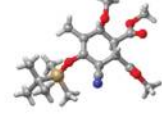
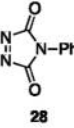
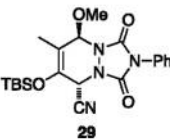
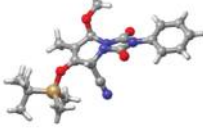
With multigram quantities of diene **5** in hand, we investigated its utility in the synthesis of naphthoquinones. Diels–Alder reaction of **5** with the known benzoquinone derivative **11**⁹ gave intermediary product **12** as a mixture of stereoisomers, which was not further characterized. Treatment of this crude material with oven-dried silica gel in

Scheme 3. Synthesis of the Aminonaphthoquinone Core and Subsequent Reduction and Protection



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Table 1. Results of Diels–Alder Reactions of Diene **5** (4.5:1 Mixture of Stereoisomers) with Different Dienophiles

entry	dienophile	conditions	isolated product	crystal structure	yield [%]
1	 18	toluene, 120 °C, 29 h then silica, acetone, rt, 12 h	 20	—	79
2	 19	toluene, 150 °C, 3 h then THF, HCl, silica, rt, 12 h	 21		43
3	 22	AlCl ₃ , CH ₂ Cl ₂ , 0 °C, 3 h then silica	 23	—	79
4	 24	toluene, 120 °C, 2 h	 25		75
5	 26	toluene, 140 °C, 14 d	 27		23
6	 28	benzene, 80 °C, 12 h	 29		63

ethyl acetate/hexanes resulted in desilylation and aromatization to afford our key naphthoquinone **13** in 84% overall yield. Notably, only a single regioisomer was isolated.

To elaborate **13** into a more useful building block and confirm its structure, the naphthoquinone was reduced to the corresponding naphthohydroquinone using sodium borohydride. *In situ* protection of the phenolic hydroxy groups as methyl ethers then afforded hexasubstituted naphthalene **14**, the crystal structure of which is depicted in Scheme 3. Analogous protection of the three hydroxy groups as MOM ethers required reduction with hydrogen in the presence of Adam's catalyst, followed by treatment with MOM chloride and Hünig's base. This gave naphthalene derivative **15**, which was also characterized by X-ray crystallography. It should be noted that the alkylations required careful optimization to avoid *N*-methylation while ensuring that all three hydroxy groups were affected. Interestingly, the aromatization following the cycloaddition did not require an "inbuilt oxidant" in the form of a halogen substituent on the benzoquinone. Reaction of diene **5** with Moody's Boc-protected

aminobenzoquinone **16**¹⁰ gave naphthoquinone **17**, presumably through air oxidation of the intermediary cycloadduct.

To establish the synthetic scope of diene **5** in Diels–Alder reactions, we investigated its reactivity with other dienophiles (Table 1). Encouraged by our initial results, we first examined various quinones as dienophiles. Reaction of **5** with commercially available dichlorobenzoquinone (**18**) and the known dibromobenzoquinone (**19**)¹¹ provided naphthoquinones **20** and **21**, respectively, in satisfactory yields following aromatization (entries 1 and 2). When benzoquinone itself (**22**) was used as the dienophile, simple heating in toluene proved to be less effective than catalysis using AlCl₃ as a Lewis acid. Following aromatization, these catalytic conditions gave naphthoquinone **23** in good overall yield (entry 3). Reaction of **5** with nitrostyrene **24** afforded the desired cycloaddition product **25** as a single diastereomer (entry 4). Heating of diene **5** with dimethyl fumarate (**26**) over 14 days afforded cycloadduct **27** as a single diastereomer, but in only 23% yield. Reaction of **5** with phenyl triazoline dione (**28**) gave cycloadduct **29**,

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which has the opposite relative stereochemistry with respect to the OMe and CN substituents compared to **25** and **27**. This stereochemical outcome presumably reflects isomerization of the initial cycloadduct to the thermodynamically more stable product *via* reversible cleavage of the *N,O*-acetal. The structures of **21**, **25**, **27**, and **29** were confirmed by X-ray crystallography (Table 1 and Supporting Information). Attempted reactions of diene **5** with tetracyanoethylene or maleic anhydride failed to give the desired products despite extensive screening of conditions.

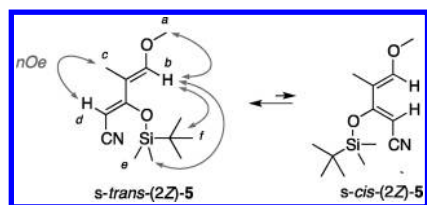


Figure 2. Conformational analysis of diene **5**.

From these data, it is apparent that diene **5** exhibits markedly reduced reactivity when compared to the parent Danishefsky diene. This can be partially attributed to the electronic effect of the cyano substituent but is probably also due to the influence of the methyl substituent on the preferred conformation of the diene. To undergo a [4 + 2] cycloaddition, **5** must adopt an *s-cis* conformation (Figure 2). NMR spectroscopy of pure (2*Z*)-**5** demonstrated a strong

NOE correlation between olefinic proton *d* and the protons of the methyl group along with weak interactions between olefinic proton *b* and protons *e* and *f* of the TBS group. By contrast, no NOE could be observed between protons *b* and *d* or between proton *c* and the protecting group substituents. This strongly suggests that (2*Z*)-**5** mostly adopts an *s-trans* conformation and that the requisite *s-cis* conformation is sparsely populated. We assume that this effect is even more pronounced in the (2*E*)-isomer of **5** and that this isomer is essentially unreactive in Diels–Alder cycloadditions, or it may isomerize to its (2*Z*)-diastereomer under the reaction conditions.

In summary, we have reported the synthesis of a novel Danishefsky-type diene, which allows for the rapid assembly of substituted aminonaphthoquinones or other highly functionalized small molecules. Related studies on Diels–Alder dienes that bear substituents with opposing electronic effects will be further pursued. Our ongoing attempts to implement our synthetic strategy in the total synthesis of ansamycin antibiotics will also be reported in due course.

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Supporting Information Available. Experimental procedures, spectroscopic and analytical data for compounds **5**–**29**, and X-ray data for compounds **14**, **15**, **21**, **25**, **27**, and **29**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.