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The Role of *N*-Substitution in Regio- and Stereoselective Vinylogous Imidonaphthoquinone (VINAquinone) [2 + 2] Photocycloadditions

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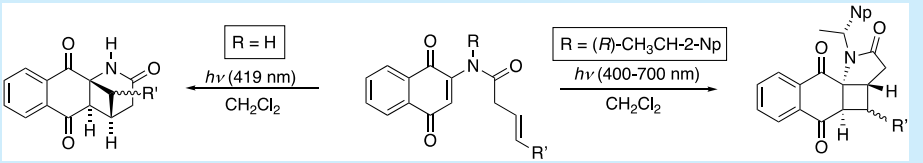

ABSTRACT: Described in this manuscript are intramolecular [2 + 2] photocycloadditions of readily available vinylogous imidonaphthoquinones whose regio- and diastereoselectivity is dependent on the substitution on the vinylogous imide. When exposed to 419 nm light, 2° vinylogous imidonaphthoquinones give novel bridged tetracyclic aza-anthraquinones from a rare crossed [2 + 2] cycloaddition reaction. In contrast, exposure of the corresponding 3° substrates to white light leads to linear adducts. Also outlined here are auxiliary controlled diastereoselective reactions and cyclobutane fragmentations as a means of generating the spirofused γ-lactam moiety present in the ansalactam family of natural product.

INTRODUCTION

The ansalactam natural products were first isolated by Fenical, Moore, Nam, and co-workers from the fermentation broth of a *Streptomyces sp.* (strain CNH-189) that was found off the coast of Southern California (Figure 1).[1,2] Following isolation, single-crystal X-ray analysis was used to determine whether the isolates were members of the ansamycin family but with a distinct twist. In addition to the "normal" ansa-ring that was linked through the naphthoquinone, the new compounds contained a unique and intriguing spiro-fused γ-lactam. We considered the ansalactams to be important and worthy of study both because of their interesting architectures and because the ansamycin family has repeatedly demonstrated biological activity.[3,4]

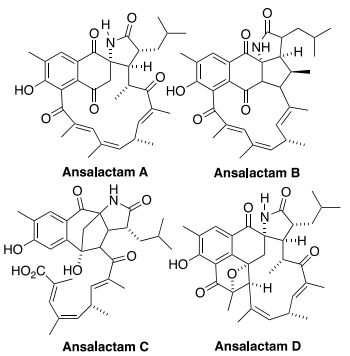

Figure 1. Ansamycin and ansalactam natural products.

While the total syntheses of members of the ansalactam family have not been reported to date, they have received attention from the synthetic community. In 2014 Trauner and co-workers reported that the γ-lactam could not be synthesized using an intramolecular radical cyclization.[5] In contrast to this, Pierce and co-workers described a successful [3 + 2] cycloaddition approach to a spiro-fused γ-lactam analog in 2021.[6]

Our fascination with the ansalactams came both from a general interest in aza-anthraquinones and our eagerness to build the spiro-fused γ-lactam moiety using a sequence that would begin with an intramolecular [2 + 2] cycloaddition.[7,8] As highlighted in Scheme 1, we proposed that ansalactam precursor **3** would result from a chemoselective fragmentation reaction of a cyclobutane such as **2**. In turn, **2** would be synthesized using an intramolecular [2 + 2] cycloaddition of an appropriately substituted Vinylogous ImidoNAphthoquinone (VINAquinone) **1**.

Although cyclobutane formation and fragmentation sequences have been employed previously,[9] we were unaware of their use to generate spiro-fused quinones or naphthoquinones.[10,11] In addition to this, only a few examples of intramolecular [2 + 2] photocycloadditions of naphthoquinones have been reported.[12,13] The most relevant of these to our proposed sequence was communicated by Mori, Bach, and co-workers in 2022.[14,15] They described the intramolecular photocycloaddi-

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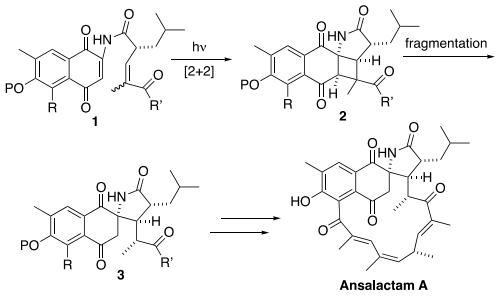
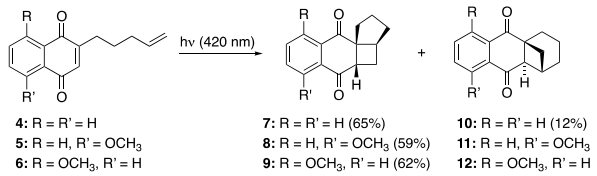
Scheme 1. Proposed Use of Cyclobutanes to Synthesize Spiro-Fused γ-Lactams and Ansalactam A



tions of naphthoquinones **4**–**6** having a three-carbon tether between a terminal alkene and the naphthoquinone (Scheme 2). Interestingly, while the reaction of **4** gave **7** as the major

Scheme 2. Mori, Bach, and Co-workers Intramolecular [2 + 2] Photocycloadditions of Naphthoquinones[14]

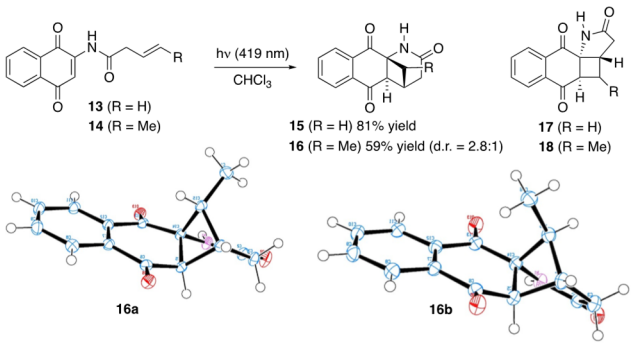


product, it also gave a small amount of crossed-cycloadduct **10**. In contrast, the closely related substrates **5** and **6** only provided linear adducts **8** and **9**, respectively. In related work, Nielsen and Wege and later Mori, Bach, and co-workers examined the corresponding intramolecular naphthoquinone enol ether [2 + 2] photocycloadditions as a means of generating the natural product elecanacin; both groups reported the exclusive formation of linear products from these studies.[16]

RESULTS AND DISCUSSION

With the above precedent as the background, we were reasonably confident about our plan for the ansamycin skeleton. As models to develop the ideas expressed in Scheme 1, we synthesized VINAquinone cyclization precursors **13** and **14** (see the Supporting Information) and were pleased to find that they underwent the expected intramolecular cycloaddition reaction when exposed to 419 nm light (Scheme 3). After extensive spectroscopic analysis that initially had us convinced that the reaction had resulted in the desired linear adducts **17** and **18**, single crystal X-ray analysis showed that our assignments had been incorrect. As depicted for **16a** and

Scheme 3. Photocycloaddition of VINAquinones 13 and 14



16b, the reactions resulted in the corresponding crossed adducts **15** and **16**.

These results were surprising to us. As mentioned above, dienyl substrates having three-atom tethers between the alkenes generally give linear products.[17,18] In contrast, substrates having a two-atom tether between the reactive π-systems generally give crossed [2 + 2] photocycloaddition products.[19−21]

We found that the cycloadditions of **13** and **14** were slow and required about 13 h for the starting material to be consumed. In an effort to increase the rate of the reaction, we explored the effect of substitution on the vinylogous imide *N*-atom on the photocycloaddition reaction. To this end, we synthesized 3° vinylogous imide **20** from the corresponding vinylogous amide **19** by slightly modifying our previously reported one-pot acylation strategy. (see Scheme 4 and Table

Scheme 4. Photocycloaddition Reactions of 3° VINAquinone 20

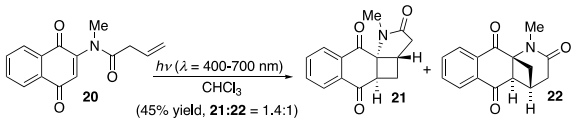
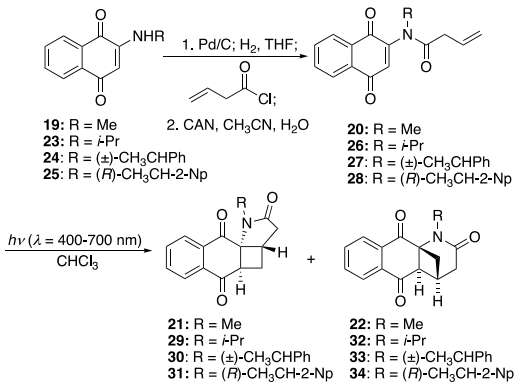


Table 1. 3° VINAquinone [2 + 2] Cycloaddition Reaction



Entry	Precursor	Products	Yield (3 steps) (%)	L:C	d.r.
1	**20**	**21**/**22**	45	1.4:1	-----
2	**26**	**29**/**32**	76	5.9:1	-----
3	**27**	**30**/**33**	62	22:1	4.5:1
4	**28**	**31**/3431/34	78	>22:1[a]	>22:1[a]

[a]**31** was only observed in the crude ^{1}H NMR as a single diastereomer.

1).[22] When **20** was exposed to light several interesting features of these reactions were uncovered: (1) As anticipated the cycloaddition proceeded more rapidly than the corresponding 2° VINAquinone derivatives (starting material was completely consumed after 4 h instead of the 13 h required for **13** and **14**). (2) Not anticipated was that the reaction could be carried out using longer wavelength light (white light (λ = 400−700 nm)). While advantageous, this discovery presented several challenges. 3° Vinyloguous naphthoquinones had to be protected from ambient light to avoid spontaneous [2 + 2] cycloaddition reactions. (3) We found it intriguing that the reaction could also occur in the absence of solvent. (4) Finally, and arguably most importantly for our ansalactam strategy, the reaction gave

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a 1.4:1 mixture of linear and crossed products favoring the linear cycloadduct **21** in an overall yield of 45%.

With the surprising result from **20** in hand, we decided to further examine the effect of substitution on nitrogen on the ratio of crossed to linear products and synthesized *N*-isopropyl VINAquinone **26** from vinylogous amide **23** (Table 1, entry 2).[23,24] We were pleased to find that **26** underwent the desired cycloaddition reaction when it was exposed to white light providing **29** and **32** in a 5.9:1 ratio favoring linear adduct **29**. We next turned to phenethyl- and naphthethyl-substituted VINA quinones **27** and **28**, respectively. In addition to examining the effect of sterics on the reaction, these substrates contain a chiral center and therefore offered opportunities for controlling the facial selectivity of the cycloaddition reaction. As precedent for their use, we had previously demonstrated that phenethyl and naphthethyl bis-aryl pyridones underwent diastereoselective photoelectrocyclization reactions.[25] The VINAquinone cycloaddition precursors were generated by combining Poulson's Michael addition technology to give **24** and **25** from naphthoquinone (see Supporting Information) with the same two-step reductive acylation chemistry that was used for the synthesis of **20** and **26**.[26] We initially examined the [2 + 2] cycloaddition of **27** and were pleased to find that it underwent a spontaneous cycloaddition reaction when exposed to ambient light giving cyclobutanes **30** and **33** in a 22:1 ratio and a 62% yield from **24** (entry 3). Equally satisfying was that **30** existed as a 5:1 mixture of diastereomers, demonstrating that the phenethyl amine moiety was not only controlling the regioselectivity but also helping to control the facial selectivity of the cycloaddition reaction. Interestingly, when the cycloaddition of **27** was carried out in the absence of solvent, the diastereomeric ratio was 2.2:1. Even more significant improvements were observed with naphthethyl derivative **28**. When **28** was subjected to ambient light we isolated linear adduct **31** as a single regio- and stereoisomer (entry 4). These results clearly demonstrate that it is possible to flip the inherent tendency for crossed products in 2° VINAquinone cycloadditions with relatively simple modifications on the *N*-atom and that the absolute stereochemistry of the products can also be controlled. That the enantioselective [2 + 2] cycloaddition of **4** using chiral Lewis acids is complicated by the propensity of the Lewis acids to coordinate to both naphthoquinone carbonyl groups makes the results with **28** all the more impactful.[14]

We were able to obtain a single-crystal X-ray structure of **31** (see Figure 2). The X-ray structure not only confirmed our structural assignment, but it also hinted at a reason for the reaction's diastereoselectivity. In the crystal, the naphthyl group is stacked underneath the quinone with the methyl group oriented into a less congested region. Assuming that similar phenomena are operative during the reaction of **28**, we propose that conformer **B** having the naphthyl group stacked under the naphthoquinone directs the alkene to attack the quinone from the top face while conformer **A** having the naphthyl group stacked on top of the quinone positions the alkene on the bottom face. The difference between conformers **B** and **A** lies in the orientation of the methyl group relative to that of the alkene. As the alkene approaches the naphthoquinone, the methyl group in **B** is *anti* to the alkene and less sterically congested while the methyl group in **A** is *syn* to the alkene and presumably suffers from nonbonded interactions with the alkene and the naphthoquinone. While we propose that both the phenethyl and naphthethyl auxiliaries behave

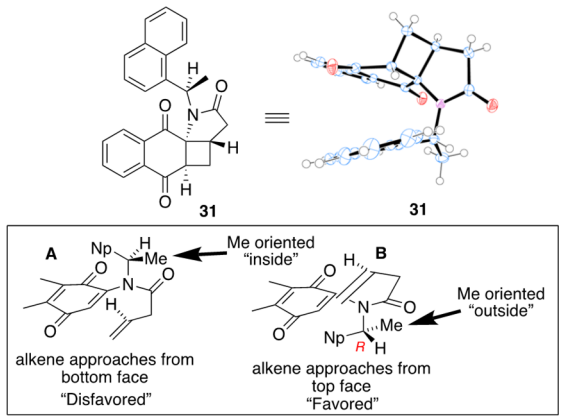
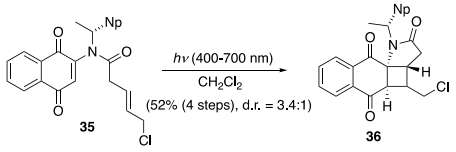


Figure 2. X-ray crystal structure of linear adduct **31** and the proposed conformation for the cycloaddition.

similarly, the naphthethyl auxiliary's larger π-surface area makes it more selective.

Having had success with the cycloaddition of terminal alkenes, we next examined the effect of the 3° naphthethylimide on the cycloaddition reaction of internal alkenes beginning with chloro derivative **35** (Scheme 5). We utilized

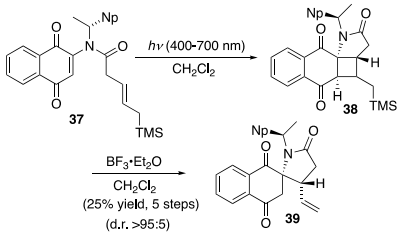
Scheme 5. Photocycloaddition of Allyl Chloride 35



cross-metathesis to construct **35** from **28** (see the Supporting Information). In the event, by exposing **35** to ambient light we were able to affect the cycloaddition isolating **36** as a 3.4:1 mixture of diastereomers at the chloromethyl bearing stereocenter in 52% yield from vinylogous amide **25** (4 steps).

To determine whether the linear cyclobutanes would be susceptible to fragmentation and thus serve as an entry into spiro-fused γ-lactams,[27] we next examined the [2 + 2] photocycloaddition reaction of allyl silane **37** (Scheme 6). As

Scheme 6. Cyclobutane Formation and Fragmentation to the Spiro-Fused γ-Lactam 39



with **35**, **37** was synthesized from **28** using cross metathesis (see Supporting Information). When exposed to white light, **37** underwent a [2 + 2] photocycloaddition to give linear adduct **38**. Although our attempts to purify **38** were largely unsuccessful, by subjecting **38** to $BF_3 \bullet Et_2O$ directly after its formation we were able to isolate spiro-fused γ-lactam **39** in 25% yield from **25** (5 steps). Although there remains a significant amount of work to be accomplished to synthesize the ansalactams, the generation of **39** bodes favorably for the

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use of a cyclobutane degradation strategy to accomplish this goal.

CONCLUSIONS

To summarize our findings, while the [2 + 2] cycloaddition reactions of 2° VINAquinones provide bridged tetracyclic azaanthraquinone products, the use of the analogous 3° VINAquinones provides the corresponding linear adducts. Gaining a better understanding of this unique reactivity and the application of this chemistry to ansalactams and other interesting problems in organic chemistry will be the focus of future studies.

ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c01418.

Experimental protocols for the preparation and purification of **13**−**16**, **20**, **21**, **25**, **20**−**26**, and **29**−**31** (PDF)

NMR data (PDF)

Accession Codes

CCDC 2257558−2257559 and 2305544 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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