

Efficient Synthesis of the Tetracyclic
Aminoquinone Moiety of Marmycin A

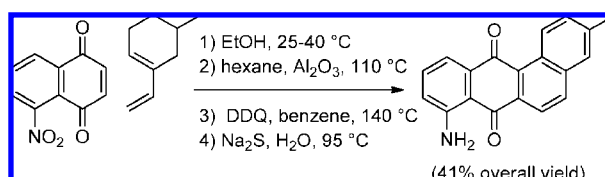
Nathan Maugel and Barry B. Snider*

Department of Chemistry MS 015, Brandeis University,
Waltham, Massachusetts 02454-9110

snider@brandeis.edu

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ABSTRACT



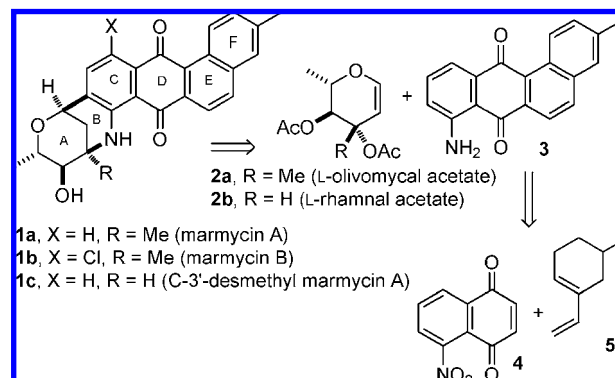
An efficient four-step route to the tetracyclic aminoquinone moiety of marmycin A that proceeds in 41% overall yield from 5-nitronaphthoquinone and 5-methyl-1-vinylcyclohexene will facilitate preparation of marmycin A analogues for biological evaluation. The Diels–Alder reaction gave exclusively the desired adduct that is favored by steric considerations rather than the regioisomeric adduct that is favored by electronic considerations.

Fenical and co-workers recently isolated two cytotoxic quinones of the angucycline family, marmycins A (**1a**) and B (**2**), from a marine sediment-derived actinomycete related to the genus *Streptomyces* (Scheme 1).¹ The structures were determined by spectroscopic analysis and X-ray crystallography. C-Glycosidic linkages are quite common in angucyclines,² but the C- and N-glycosidic linkages resulting in a hexacyclic skeleton are unique to the marmycins. Marmycin A (**1a**) showed potent activity against 12 human tumor cell lines with a mean IC₅₀ value of 22 nM. The combination of the novel skeleton and potent biological activity of **1a** prompted us to undertake its synthesis.

We envisioned that condensation of glycol **2a** with tetracyclic aminoquinone **3** would provide the acetate of **1a**. Yadav has extensively studied related condensations of simple anilines with glycols such as **2b** that contain hydrogen on C-3 to form the tricyclic ABC ring system of the marmycins with a hydrogen rather than a methyl group at C-3'.³ While our work was in progress, Yao and Zhang

reported a ten-step synthesis of tetracyclic aminoquinone **3** and the InBr₃-catalyzed condensation of **3** and **2b** to afford C-3'-desmethyl marmycin A (**1c**).⁴

Scheme 1. Retrosynthesis of Marmycin A



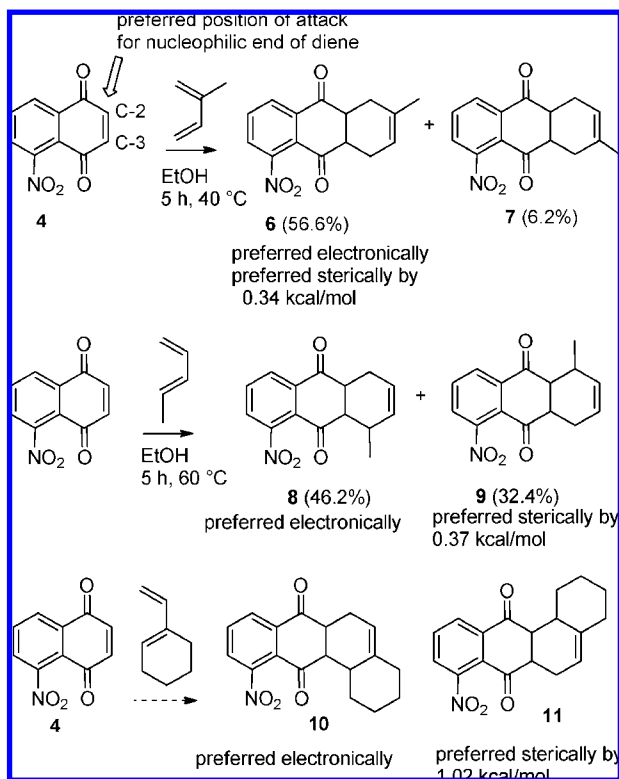
Our approach to tetracyclic aminoquinone **3** by the Diels–Alder reaction of 5-nitronaphthoquinone (**4**)⁵ with 5-methyl-1-vinylcyclohexene (**5**)⁶ will form the complete carbon skeleton in a single step. However, the regiochemistry

(1) Martin, G. D. A.; Tan, L. T.; Jensen, P. R.; Dimayuga, R. E.; Fairchild, C. R.; Raventos-Suarez, C.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 1406–1409.

(2) (a) Rohr, J.; Thierike, R. *Nat. Prod. Rep.* **1992**, 103–137. (b) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127–195. (c) Carreño, M. C.; Urbano, A. *Synlett* **2005**, 1–25.

of the proposed Diels–Alder reaction was of some concern. Naphthoquinones with electron-withdrawing substituents on C-5 react preferentially with nucleophiles, including the nucleophilic end of a diene, at C-2, not C-3, which should lead to the undesired regioisomer in the Diels–Alder reaction (see Scheme 2).⁷ Nitroquinone **4** reacts with 1,1-dimethoxy-

Scheme 2. Diels–Alder Reactions of **4** with Unsymmetrical Dienes



ethylene preferentially (2.7:1) at C-2.⁸ Oda studied the Diels–Alder reactions of **4** with isoprene, which gave a 9.2:1 mixture favoring the expected major isomer **6**.⁹ However, with piperylene, the expected major isomer **8** was favored by only 1.4:1. Molecular mechanics calculations of the

Diels–Alder transition states provide a possible explanation for this loss of selectivity.¹⁰ The formation of **6** is preferred sterically by 0.34 kcal/mol in addition to the electronic preference. However, the formation of **9** is preferred sterically by 0.37 kcal/mol due to repulsion between the nitro and methyl groups in the transition state that leads to the electronically preferred adduct **8**. Competing electronic and steric preferences should result in reduced selectivity. Calculations for the Diels–Alder reaction of **4** with 1-vinylcyclohexene suggest that the transition state for the desired adduct **11** is favored over that for the electronically preferred adduct **10** by 1.02 kcal/mol due to steric repulsion between the nitro group and cyclohexene ring (see Figure 1). We therefore decided to investigate this route to aminoquinone **3**.

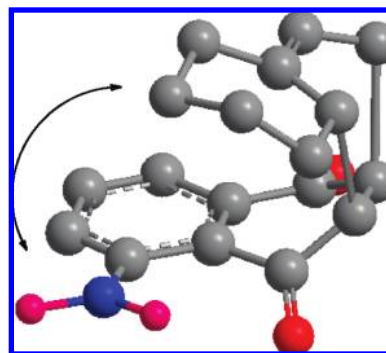


Figure 1. MMX calculated structure for the Diels–Alder reaction leading to **11** with the arrow showing steric repulsion between the nitro group and cyclohexene ring.

Addition of vinylmagnesium bromide to 3-methylcyclohexanone (**12**) followed by dehydration of the resulting tertiary allylic alcohol in 90:1 THF/H₂SO₄ for 72 h at 50 °C afforded a 1.5:1 mixture of the desired diene **5** and **13** in 70% yield, which was used directly because previous studies of Diels–Alder reactions with other naphthoquinones indicated that the more hindered minor isomer **13** was much less reactive than **5** (see Scheme 3).⁶ Nitration of naphthoquinone with sodium nitrate in sulfuric acid afforded **4** in 75% yield.⁵ Treating **4** with 2 equiv of the 1.5:1 mixture of **5** and **13** in EtOH for 12 h at 25 °C and 2 h at 40 °C afforded a complex mixture of stereo- and regioisomeric Diels–Alder adducts **14** and **15** that was oxidized to the quinone and aromatic E ring prior to purification.

Oda oxidized **6–9** to anthraquinones by aeration in ethanolic potassium hydroxide or by heating in hexane containing alumina.⁹ Stirring the mixture of **14** and **15** in 0.1 M KOH in EtOH at 25 °C for 24 h in a tube sealed under air gave a 1:1

(3) (a) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V.; Raj, K. S.; Prasad, A. R.; Kumar, S. K.; Kunwar, A. C.; Jayaprakash, P.; Jagannath, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5198–5201. (b) Yadav, J. S.; Reddy, B. V. S.; Parimala, G.; Raju, A. K. *Tetrahedron Lett.* **2004**, *45*, 1543–1546. (c) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Padmavani, B. *Tetrahedron* **2004**, *60*, 3261–3266. (d) Yadav, J. S.; Reddy, B. V. S.; Padmavani, B. *Synthesis* **2004**, 405–408. (e) Yadav, J. S.; Reddy, B. V. S.; Meraj, S.; Vishnumurthy, P.; Narsimulu, K.; Kunwar, A. C. *Synthesis* **2006**, 2923–2926. (f) Rafiee, E.; Azad, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2756–2759. (g) Yadav, J. S.; Subba Reddy, B. V.; Srinivas, M.; Divyavani, Ch.; Kunwar, A. C.; Madavi, Ch. *Tetrahedron Lett.* **2007**, *48*, 8301–8305. (h) Narasimulu, M.; Reddy, S. M.; Rajesh, K.; Suryakiran, N.; Ramesh, D.; Venkateswarlu, Y. *Heteroatom Chem.* **2008**, *19*, 429–433.

(4) Ding, C.; Tu, S.; Li, F.; Wang, Y.; Yao, Q.; Hu, W.; Xie, H.; Meng, L.; Zhang, A. *J. Org. Chem.* **2009**, *74*, 6111–6119.

(5) Ivashikina, N. V.; Romanov, V. S.; Moroz, A. A.; Shvartsberg, M. S. *Bull. Acad. Sci. USSR, Ser. Chem.* **1984**, *33*, 2345–2348; *Izv. Akad. SSSR, Ser. Khim.* **1984**, *33*, 2261–2265.

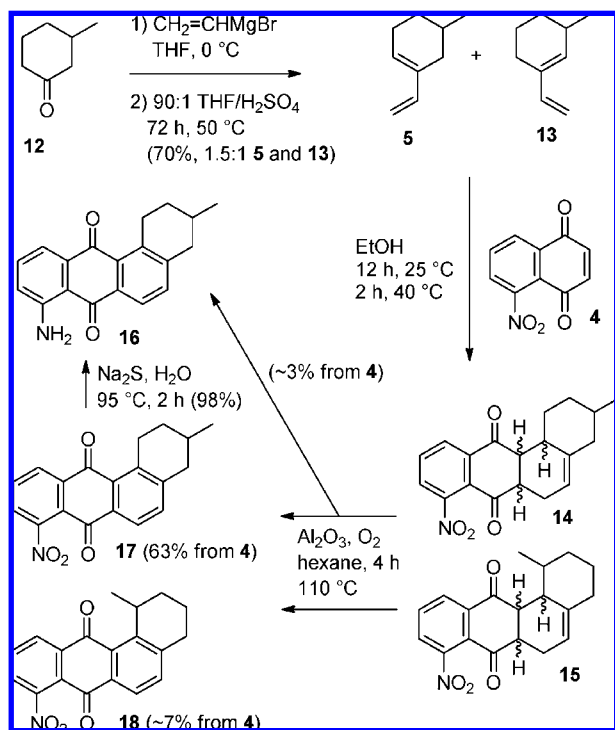
(6) (a) Motoyoshiya, J.; Masue, Y.; Iwayama, G.; Yoshioka, S.; Nishii, Y.; Aoyama, H. *Synthesis* **2004**, 2099–2102. (b) Krohn, K.; Sohrab, Md. H.; Flörke, U. *Tetrahedron: Asymmetry* **2004**, *15*, 713–718.

(7) (a) Rozeboom, M. D.; Tegmo-Larsson, I. M.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338–2345. (b) Pyrek, J. St.; Achmatowicz, O., Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673–680.

(8) Cameron, D. W.; Feutrill, G. I.; Patti, A. F. *Aust. J. Chem.* **1980**, *33*, 1805–1816.

(9) Oda, N.; Kobayashi, K.; Ueda, T.; Ito, I. *Chem. Pharm. Bull.* **1978**, *26*, 2578–2581.

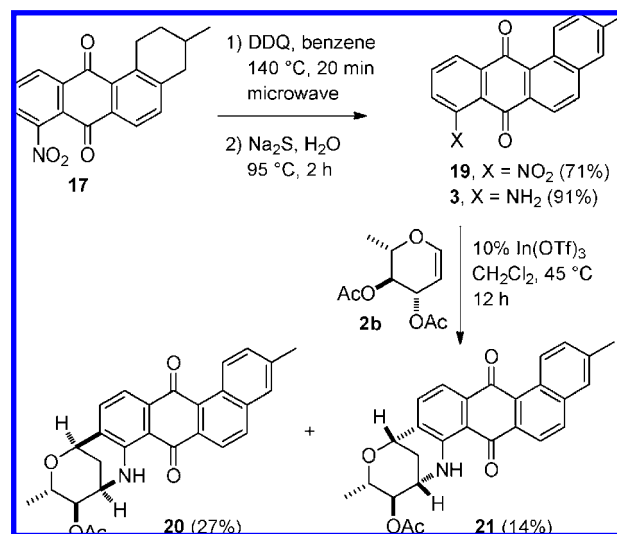
(10) PCMODEL version 8.0 from Serena Software was used. MMX calculations were performed with transition state bond formation of 30%.

Scheme 3. Diels–Alder Reaction to Form **17**

mixture of the desired nitroquinone **17** and the unexpected aminoquinone **16** in low yield. The structure of amine **16** was confirmed by reduction of **17** with aqueous Na_2S at 95 °C for 3 h to give **16** in 98% yield.¹¹ This suggested that both oxygen and the nitro group could function as oxidants for the aromatization of the E ring. Bubbling air into the reaction through a dispersion tube decreased the formation of **16**, giving a 10:1 mixture of **17** and amine **16**, but in only 24% yield from naphthoquinone **4**. A possible mechanism for the formation of **16** is presented below in Scheme 6.

Much better results were obtained by heating the mixture of **14** and **15** in 90:10 hexane/benzene containing alumina in a sealed tube under oxygen (~0.7 equiv) for 2 h, followed by replacing the oxygen and heating for an additional 2 h. This gave a 9:1 mixture of the desired adduct **17** and adduct **18** (formed from the undesired diene **13**) that contained only 2–4% of amine **16**. Recrystallization from CHCl_3 afforded pure nitroquinone **17** in 63% overall yield from naphthoquinone **4**. The oxidation was not complete and more amine was formed if the reaction was heated for 4 h without replacement of the oxygen after 2 h. The structure of **17** was established by X-ray crystal structure determination of **3** as described below. We were delighted to find that the Diels–Alder reaction was very selective for the desired product **17** that was expected on steric grounds rather than the undesired regioisomer corresponding to **10** that was expected on the basis of electronic considerations.

Oxidation of **17** with 10 equiv of DDQ in benzene at 140 °C in a microwave oven for 20 min provided fully aromatic

Scheme 4. Synthesis of Aminoquinone **3**

nitroquinone **19** in 71% yield (see Scheme 4).¹² Although only 2 equiv of DDQ are required stoichiometrically, the reaction did not go to completion with 6 equiv, even after heating for 30 min at 140 °C, suggesting that DDQ decomposes at a rate competitive with the oxidation of **17**. Oxidation with DDQ at lower temperatures was less effective. The DDQ byproducts are very polar and easily removed by flash chromatography. Reduction of the nitro group of **19** with aqueous sodium sulfide for 2 h at 95 °C provided the desired fully aromatic tetracyclic aminoquinone **3** in 91% yield.¹¹ The structure of **3** was established by X-ray crystallography. The spectral data are identical to those reported by Yao and Zhang.⁴ This sequence provides tetracyclic aminoquinone **3** in only 4 steps from naphthoquinone **4** in 41% overall yield.

Yao and Zhang reported that the reaction of **3** with **2b** was very sluggish with many catalysts but gave a 2:1 mixture of **20** (56%) and **21** (28%) by reaction for 12 h at 25 °C with 10% InBr_3 in CH_2Cl_2 . In our hands, this reaction with InBr_3 appeared to be exceedingly moisture sensitive. Reaction with $\text{In}(\text{OTf})_3$ was less moisture sensitive; use of 10% $\text{In}(\text{OTf})_3$ in CH_2Cl_2 for 12 h at 45 °C provided **20** (27%) and **21** (14%).

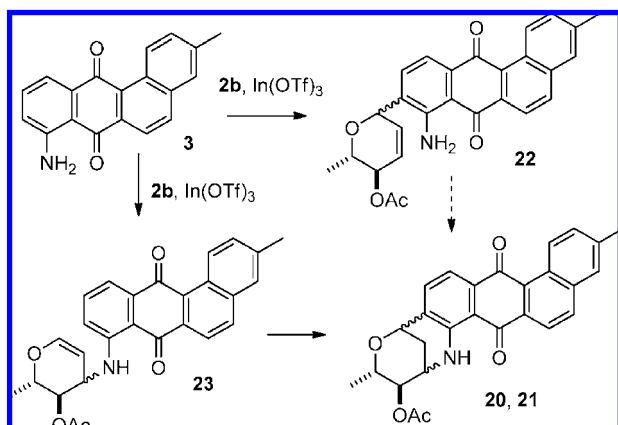
Yadav proposed that these reactions proceed by a Friedel–Crafts reaction (C-glycosylation) to give **22** followed by an intramolecular hydroamination to form **20** and **21** (see Scheme 5).^{3a,4} The formation of C-glycoside **22** is well precedented.¹³ Although hydroaminations of unactivated alkenes catalyzed by acid or lanthanum triflates have recently been reported, they require temperatures between 135 and 160 °C.¹⁴ Therefore, the intramolecular hydroamination of **22** to give **20** and **21** is unlikely to take place at 25 °C. It seems more likely that the first step involves loss of acetate

(11) Ghaeni, H.; Sharifi, M.; Fattollahy, M. *Dyes Pigment.* **2007**, *72*, 97–100.

(12) Mal, D.; Dey, S. *Tetrahedron* **2006**, *62*, 9589–9602.

(13) Ferrier, R. J.; Zubkov, O. A. *Org. React.* **2003**, *62*, 569–736.

Scheme 5. Mechanistic Considerations



from C-3 of **2b** to give an allylic cation that reacts with the amine to give **23**. There is ample precedent for the formation of compounds analogous to **23** from glycals and other nucleophiles. The $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction of **2b** with NaN_3 occurs initially at C-1, but the major product formed after equilibration is the C-3 azide corresponding to **23**.^{15a} Similarly, the SnCl_4 -catalyzed reaction of glycals with aliphatic thiols occurs initially at C-1 but gives mainly 3-alkylthio glycals corresponding to **23** under equilibrium conditions.^{15b} Protonation of glycal **23** and an intramolecular Friedel–Crafts reaction will then form **20** and **21**. The intramolecular Friedel–Crafts reaction of **23** appears to be more likely for the cyclization step than the intramolecular hydroamination of unactivated alkene **22**.

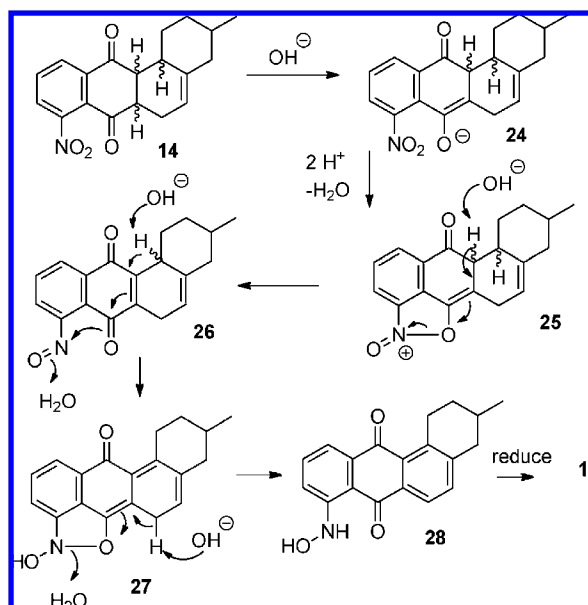
There is limited precedent for a nitro group functioning as an oxidant in the conversion of **14** to **16**.¹⁶ A possible mechanism involves enolization of **14** to give **24** followed by addition of the enolate to the nitro group, which will give **25** after protonation and loss of water (see Scheme 6). Deprotonation and elimination will convert **25** to nitrosoquinone **26**. Enolization of **26** followed by attack of the enolate on the nitroso group will give **27** after protonation.

(14) (a) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542–14543. (b) Marcseková, K.; Doye, S. *Synthesis* **2007**, 145–154. (c) Yin, P.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 3791–3793.

(15) (a) Jaunzems, J.; Kashin, D.; Schönberger, A.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3435–3446. (b) Priebe, W.; Zamojski, A. *Tetrahedron* **1980**, *36*, 287–297.

(16) (a) Rosenblum, M. *J. Am. Chem. Soc.* **1960**, *82*, 3796–3798. (b) Srinivasan, P. S.; Mahesh, R.; Venkateswara Rao, G.; Kalyanam, N. *Synth. Commun.* **1996**, *26*, 2161–2164.

Scheme 6. Oxidation to the Anthraquinone by the Nitro Group



Deprotonation and elimination will give anthraquinone **28** at the hydroxylamine oxidation state which must then be reduced to give **16**.

In conclusion, we have developed an efficient four-step route to aminoquinone **3** from naphthoquinone **4** that proceeds in 41% overall yield. This will facilitate the preparation of marmycin analogues for biological evaluation. The Diels–Alder reaction of **4** and **5** gave exclusively the desired Diels–Alder adduct **14** that is favored by steric considerations rather than the adduct corresponding to **10** that is favored by electronic considerations.

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Supporting Information Available: Complete experimental procedures, copies of ^1H and ^{13}C NMR spectral data, details of the structure determination of **3**, and CIF file of **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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