ORGANIC LETTERS

2009
Vol. 11, No. 21
4926−4929

Efficient Synthesis of the Tetracyclic Aminoquinone Moiety of Marmycin A

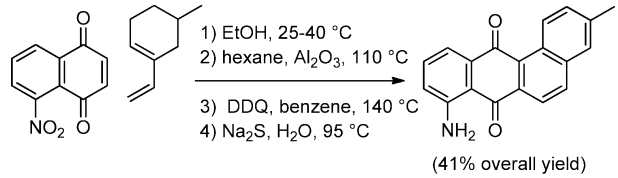
Nathan Maugel and Barry B. Snider*

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

snider@brandei.edu

Received September 3, 2009

ABSTRACT

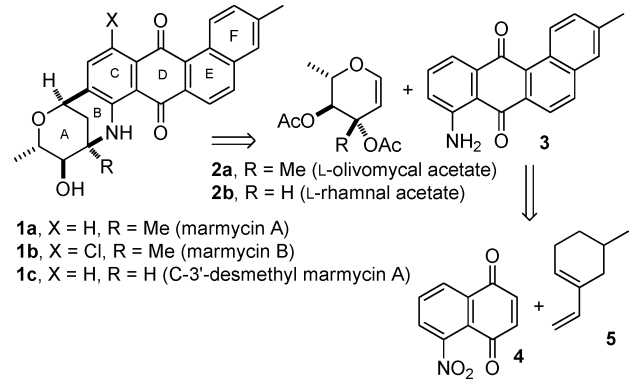


An efficient four-step route to the tetracyclic aminoquinone moiety of marmycin A that proceeds in 41% overall yield from 5-nitronaphthoquinone and 5-methyl-1-vinylcyclohexene will facilitate preparation of marmycin A analogues for biological evaluation. The Diels−Alder reaction gave exclusively the 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 IC_{50} 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 glycal **2a** with tetracyclic aminoquinone **3** would provide the acetate of **1a**. Yadav has extensively studied related condensations of simple anilines with glycals 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 $InBr_3$-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

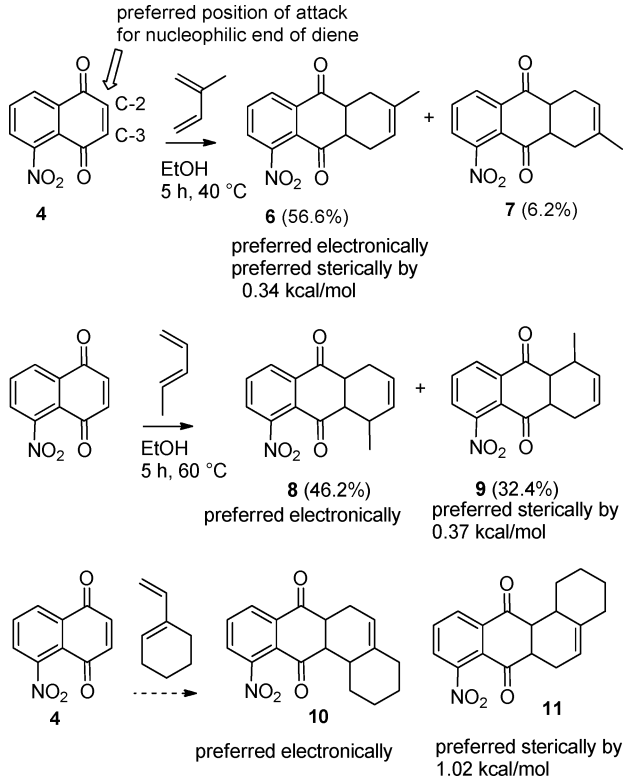
(1) Martin, G. D. A.; Tan, L. T.; Jensen, P. R.; Dimayuga, R. E.; Fairchild, C. R.; Raventos-Suarez, C.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 1406–1409.

(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.

10.1021/ol9020496 CCC: $40.75 © 2009 American Chemical Society
Published on Web 10/05/2009

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**.

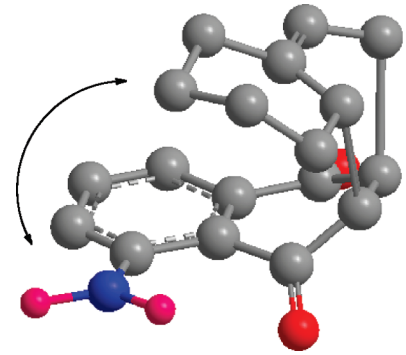


Figure 1. MMX calculated structure for the Diels−Alder reaction leading to **11** with the arrow showing steric repulsion between the nitro group and cyclohexene ring.

Addition of vinylmagnesium bromide to 3-methylcyclohexanone (**12**) followed by dehydration of the resulting tertiary allylic alcohol in 90:1 THF/H_2SO_4 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.; Kunwarb, A. C.; Madavi, Ch. *Tetrahedron Lett.* **2007**, *48*, 8301–8305. (h) Narasimhulu, 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.

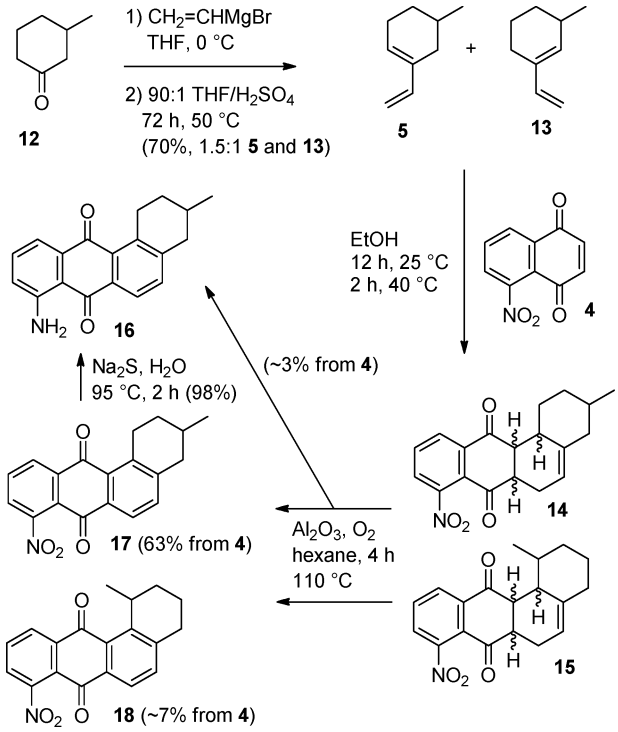
(7) (a) Rozeboom, M. D.; Tegmo-Larsson, I. M.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338–2345. (b) Pyrek, J. St; Achmatowicz, O., Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673–680.

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

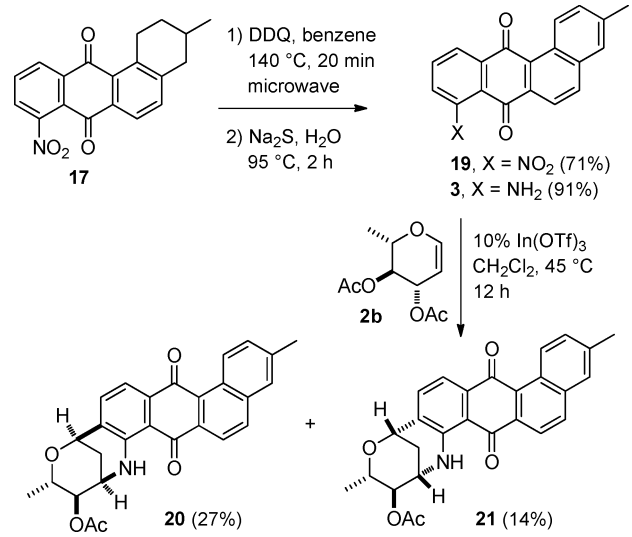
(9) Oda, N.; Kobayashi, K.; Ueda, T.; Ito, I. *Chem. Pharm. Bull.* **1978**, *26*, 2578–2581.

(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**



Scheme 4. Synthesis of Aminoquinone **3**



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.

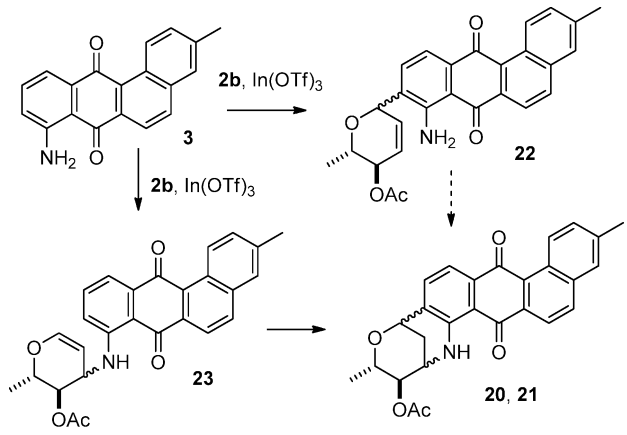
Oxidation of **17** with 10 equiv of DDQ in benzene at 140 °C in a microwave oven for 20 min provided fully aromatic nitroquinone **19** in 71% yield (see Scheme 4).[12] Although only 2 equiv of DDQ are required stoichiometrically, the reaction did not go to completion with 6 equiv, even after heating 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 $In(OTf)_3$ was less moisture sensitive; use of 10% $In(OTf)_3$ 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) Ghaieni, H.; Sharifi, M.; Fattollahy, M. *Dyes Pigm.* **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.

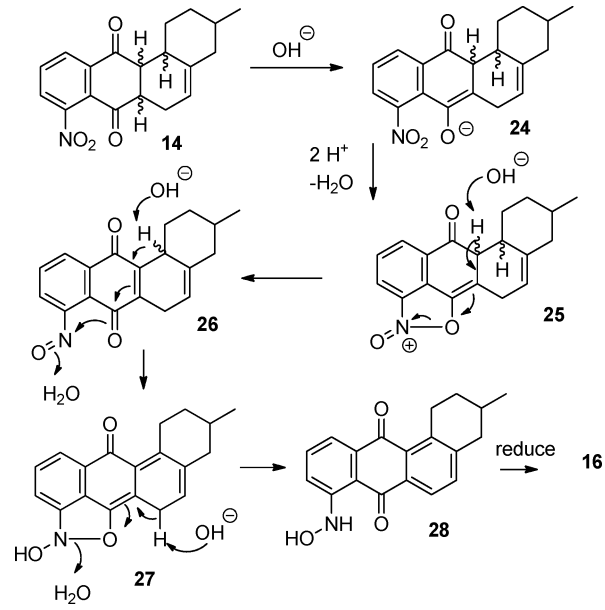
Scheme 5. Mechanistic Considerations



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 BF_3•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.

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.

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for support of this work. We thank the National Science Foundation for partial support of this work through grant CHE-0521047 for the purchase of a new X-ray diffractometer.

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.

OL9020496

(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.