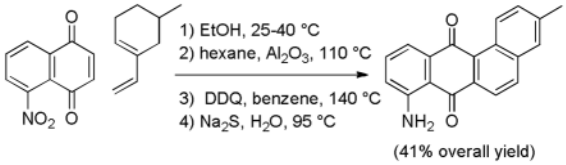
Published in final edited form as:
Org Lett. 2009 November 5; 11(21): 4926–4929. doi:10.1021/ol9020496.

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

Abstract



(41% overall yield)

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 coworkers 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 *Streptomycetes*.[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 is 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]

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 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-dimethoxyethylene preferentially (2.7:1) at

snider@brandei.edu.

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.

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**.

Addition of vinylmagnesium bromide to 3-methyl-cyclohexanone (**12**) followed by dehydration of the resulting tertiary allylic alcohol in 90:1 THF/H_2SO_4 for 72 hours 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 hours at 25 °C and 2 hours 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 hours in a tube sealed under air gave a 1:1 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 hours 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 hours, followed by replacing the oxygen and heating for an additional two hours. 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 equivalents of DDQ in benzene at 140 °C in a microwave oven for 20 minutes provided fully aromatic nitroquinone **19** in 71% yield (see Scheme 4).[12] Although only 2 equivalents of DDQ are required stoichiometrically, the reaction did not go to completion with 6 equivalents, 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 hours at 95 °C for 2 hours 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 12hours 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 hours 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 135–160 °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 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. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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.

References

1. Martin GDA, Tan LT, Jensen PR, Dimayuga RE, Fairchild CR, Raventos-Suarez C, Fenical W. J Nat Prod 2007;70:1406–1409. [PubMed: 17844998]

2. (a) Rohr J, Thierike R. Nat Prod Rep 1992:103–137. [PubMed: 1620493] (b) Krohn K, Rohr J. Topics in Current Chemistry 1997;188:127–195. (c) Carreño MC, Urbano A. Synlett 2005:1–25.

3. (a) Yadav JS, Reddy BVS, Rao KV, Raj KS, Prasad AR, Kumar SK, Kunwar AC, Jayaprakash P, Jagannath B. Angew Chem Int Ed 2003;42:5198–5201. (b) Yadav JS, Reddy BVS, Parimala G, Raju AK. Tetrahedron Lett 2004;45:1543–1546. (c) Yadav JS, Reddy BVS, Srinivas M, Padmavani B. Tetrahedron 2004;60:3261–3266. (d) Yadav JS, Reddy BVS, Padmavani B. Synthesis 2004:405–408. (e) Yadav JS, Reddy BVS, Meraj S, Vishnumurthy P, Narsimulu K, Kunwar AC. Synthesis 2006:2923–2926. (f) Rafiee E, Azad A. Bioorg Med Chem Lett 2007;17:2756–2759. [PubMed: 17400455] (g) Yadav JS, Subba Reddy BV, Srinivas M, Divyavani Ch, Kunwarb AC, Madavi Ch. Tetrahedron Lett 2007;48:8301–8305. (h) Narasimhulu M, Reddy SM, 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 NV, Romanov VS, Moroz AA, Shvartsberg MS. 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, Md Sohrab H, Flörke U. Tetrahedron: Asymmetry 2004;15:713–718.

7. (a) Rozeboom MD, Tegmo-Larsson IM, Houk KN. J Org Chem 1981;46:2338–2345. (b) Pyrek J, St Achmatowicz O Jr, Zamojski A. Tetrahedron 1977;33:673–680.

8. Cameron DW, Feutrill GI, Patti AF. 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%.

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 RJ, Zubkov OA. Org React 2003;62:569–736.

14. (a) Anderson LL, Arnold J, Bergman RG. J Am Chem Soc 2005;127:14542–14543. [PubMed: 16231885] (b) Marcseková K, Doye S. Synthesis 2007:145–154. (c) Yin P, Loh TP. Org Lett 2009;11:3791–3793. [PubMed: 19708694]

15. (a) Jaunzems J, Kashin D, Schonberger 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 PS, Mahesh R, Venkateswara Rao G, Kalyanam N. Synth Commun 1996;26:2161–2164.

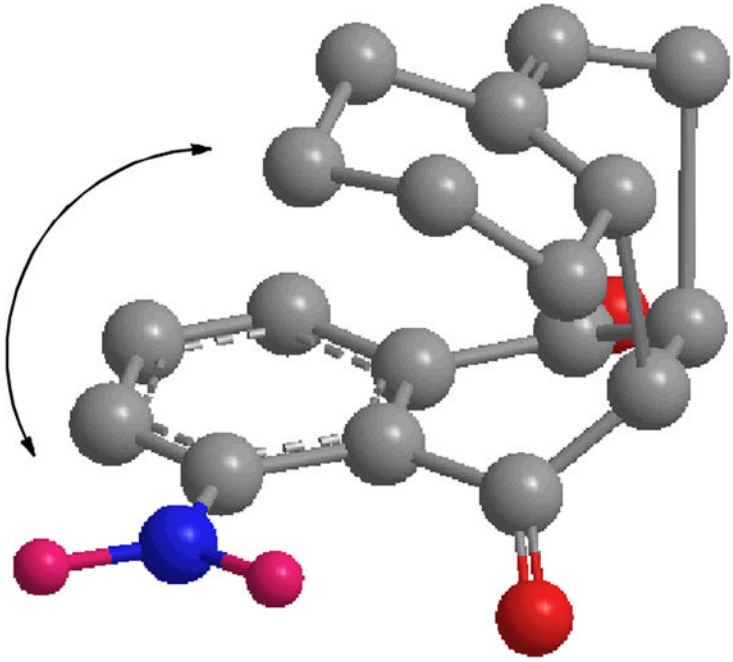
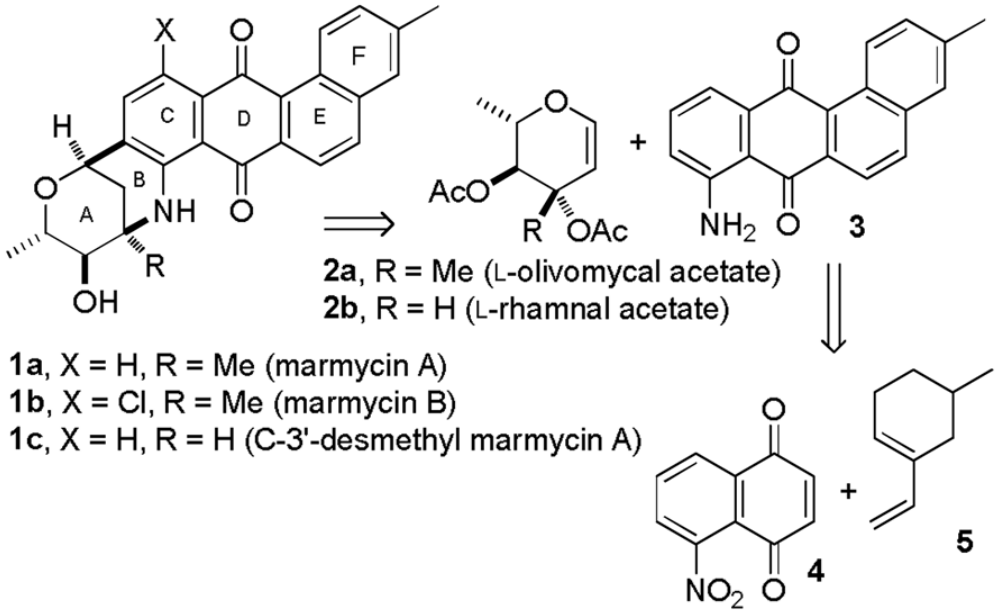
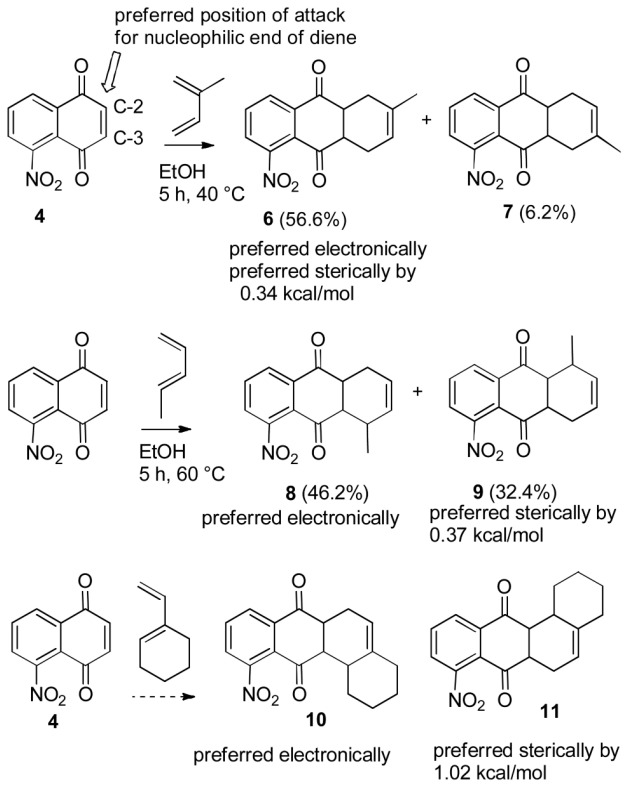


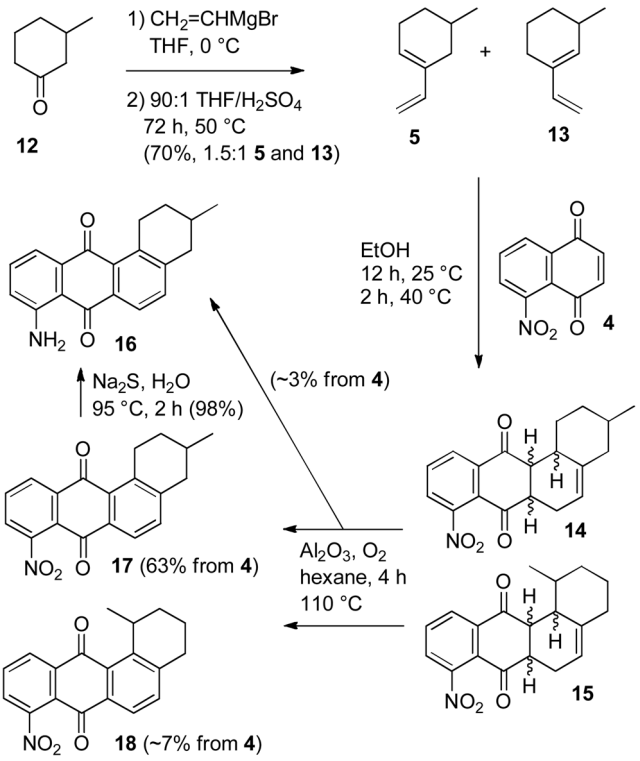
Figure 1.
MMX calculated structure for the Diels-Alder reaction leading to **11** with arrow showing steric repulsion between the nitro group and cyclohexene ring.



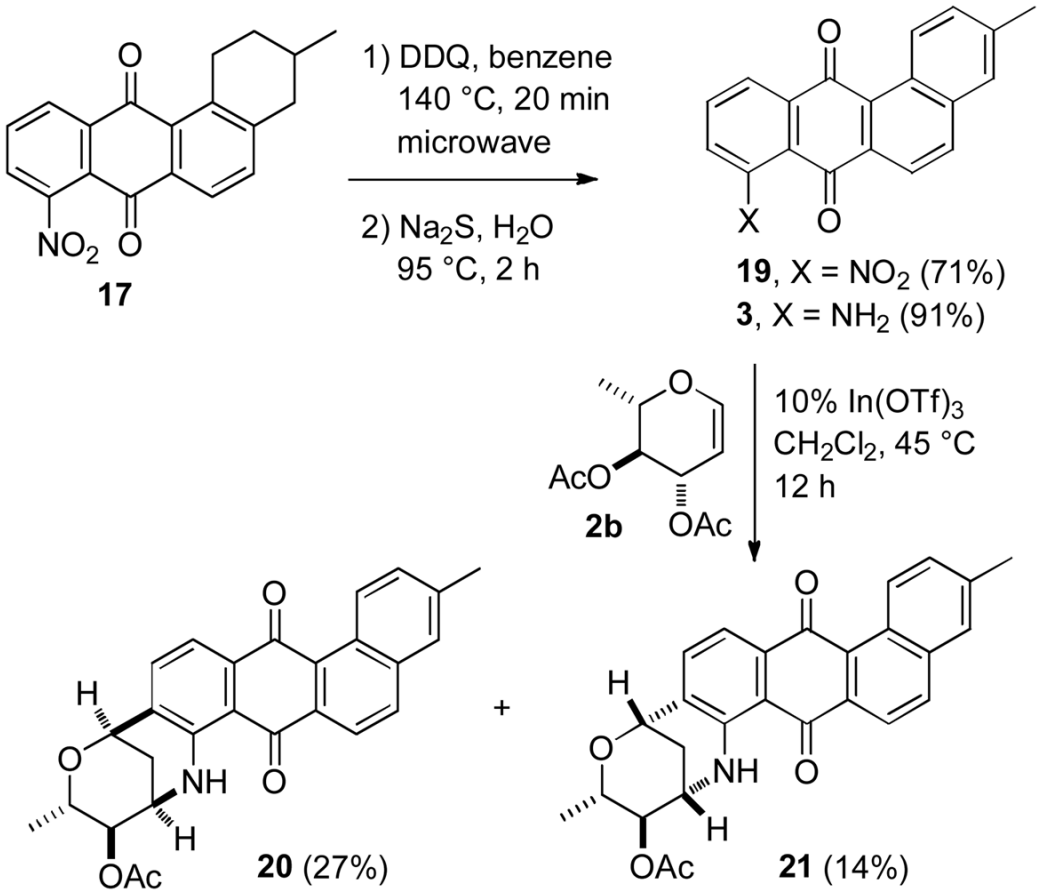
Scheme 1.
Retrosynthesis of Marmycin A



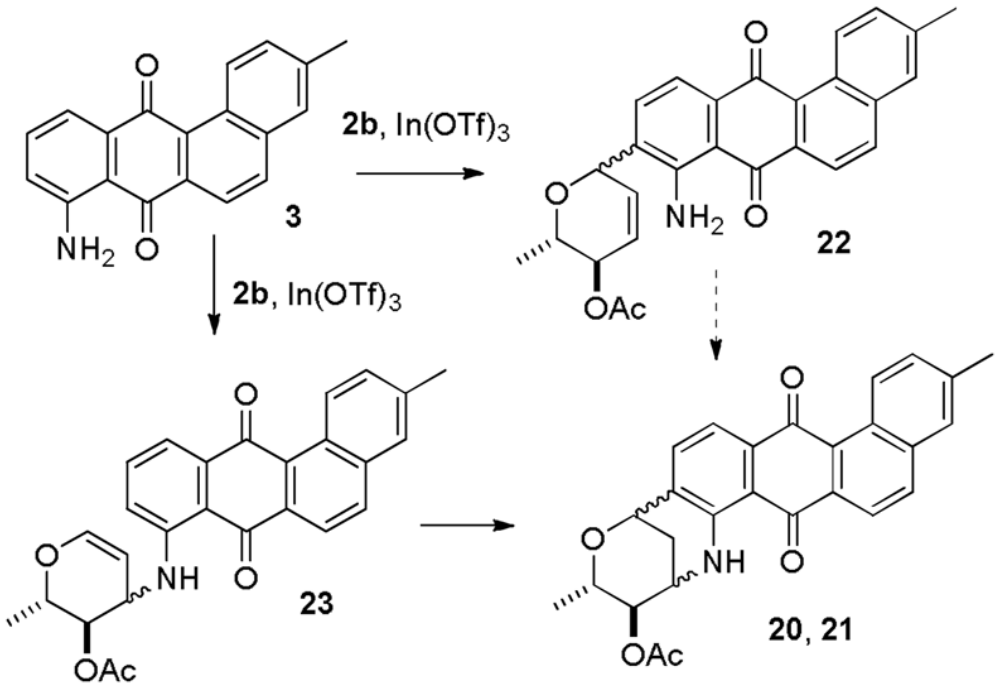
Scheme 2.
Diels-Alder Reactions of **4** with Unsymmetrical Dienes



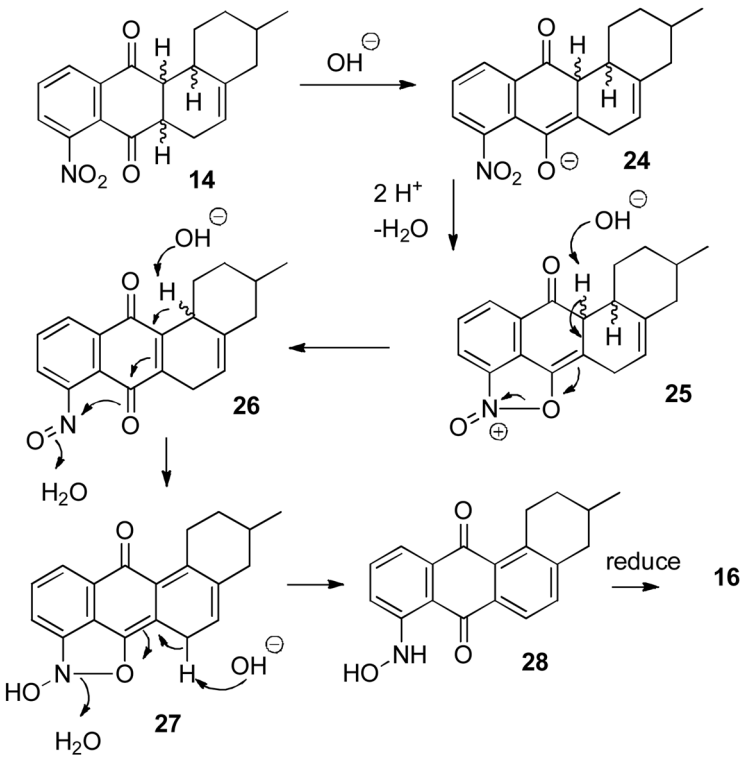
Scheme 3.
Diels-Alder Reaction to Form 17



Scheme 4.
Synthesis of Aminoquinone 3



Scheme 5.
Mechanistic Considerations



Scheme 6.
Oxidation to the Anthraquinone by the Nitro Group