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Use of the *Vicinal* Element Effect for Regiochemical Control of Quinone Substitutions and Its Implication for Convergent Mitomycin Construction

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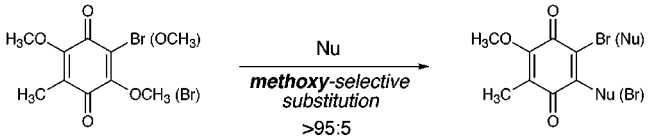
ABSTRACT



Nucleophilic substitution reactions of 2-methoxy-3-alkyl-*p*-benzoquinones are described as they relate to the construction of the mitomycin backbone. Normally controlled by activating groups attached to the olefin, the observed regioselection in these cases is determined by the deactivating substituent. Approximation of carbonyl activating ability would not have predicted the behavior of two systems investigated in which the poorer of two leaving groups is substituted in each case.

The chemistry of the quinone has been studied for over a century and continues to demand attention by virtue of its presence in antitumor quinone natural products such as (−)-saframycin A[1] and *nat*-mitomycin C[2,3] (Figure 1). Most quinone transformations fall within the classifications of redox, cycloaddition, and substitution reactions, and attendant reactivity is generally predictable by approximation of the electronics of each enone π-system.[4]

Our interest in the mitomcyins led us to reinvestigate the disconnections C9−C8a/N4−C4a studied extensively by Rapoport.[5] The straightforward nature of this strategy notwithstanding, attempts by Rapoport to effect direct C9−C8a coupling between dibromoquinone **1** and vinylogous amide **2** resulted only in the opposite (C9−C4a) regiochemical outcome (**3a**).[6] In this Letter, we describe the development of a straightforward solution to this problem that emphasizes the fact that the addition step of nucleophilic additions to activated olefins is rate-limiting.[7]

Our studies have focused on the behavior of pyrrolidinyl enamine **4**. Although substantially more reactive than **2**, enamine **4** behaved similarly by producing the undesired regioisomer **5** in the coupling process (Scheme 1). This behavior follows from examination of the intermediate

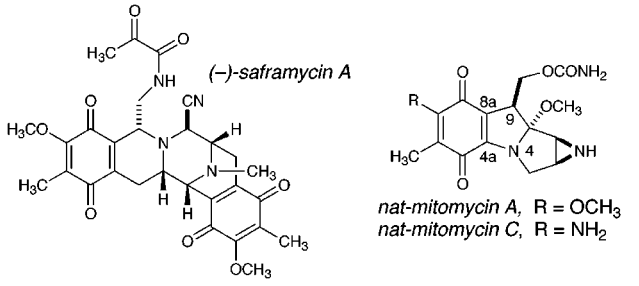


Figure 1. Representative quinone-derived alkaloids.

(1) Leading reference: Myers, A. G.; Plowright, A. T. *J. Am. Chem. Soc.* **2001**, *123*, 5114−5115, and ref 9 therein.

(2) Total synthesis of *rac*-mitomycin C: (a) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549−568. (b) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303−8304.

(3) Recent synthetic studies: (a) Coleman, R. S.; Chen, W. *Org. Lett.* **2001**, *2*, 1141−1144. (b) Papaionnou, N.; Evans, C. A.; Blank, J. T.; Miller, S. J. *Org. Lett.* **2001**, *3*, 2879−2882.

(4) Finley, K. T. In *Supplement E: The Chemistry of Hydroxyl, Ether, and Peroxide Groups*; Patai, S., Ed.; Wiley: New York, 1993; Vol. 2, Chapter 19.

(5) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515−4523.

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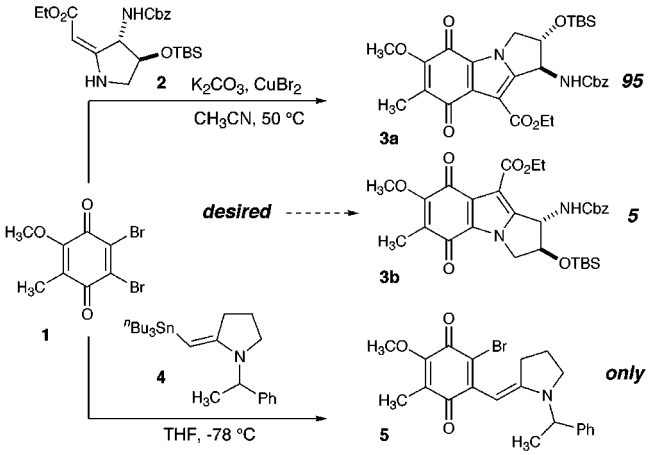
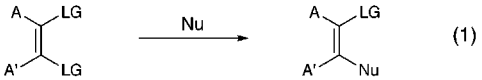
Scheme 1. Regioselective Quinone−Enamine Couplings



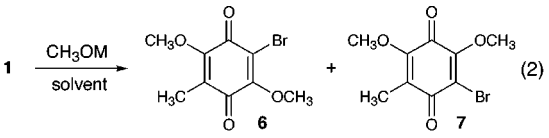
adducts whose relative energies might be reflected by the difference in pK_a between *tert*-butyl acetate (30.3) and acetone (26.5) in DMSO.[8] The possibility that Lewis acid might reverse the sense of regioselection according to the Engler protocol[9] was investigated but found to be uniformly unsuccessful. This was not entirely unexpected since coupling of **1** with **4** at −78 °C is instantaneous and indicated by an immediate color change from orange (**1**) to deep blue (**5**). Hence, the substitutionally labile olefin of dibromoquinone **1** conforms to the *vicinal* element effect (eq 1). [10]



It was therefore reasonable to assume that substitution first with methoxy might be both (1) highly regioselective in direction and magnitude by analogy to substitutions with **2** and **4** and (2) a means to electronically differentiate the two olefinic sites of substitution such that C9−C8a coupling can be effected. This was not the case.

Treatment of **1** with buffered methanol was significantly less regioselective than enamine addition, providing a 1.5:1 ratio of bromoquinones **6** and **7** (Table 1, entry 3).[11,12] Selectivity could be increased only marginally by addition of preformed sodium methoxide (Table 1, entry 2). Although the same level of regioselection was observed using sodium

Table 1. Regioselective Substitutions of **1** with Methoxide (eq 2)[a]



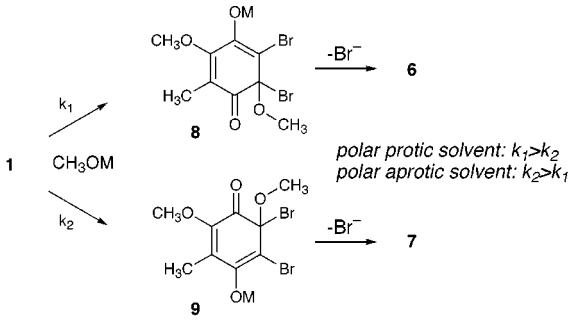
entry	Nu	solvent	**6**:**7**[b]	yield (%)[c]
1	$Mg(OCH_3)_2$	CH_3OH	2:1	55/30
2	$NaOAc/NaOCH_3$	CH_3OH	2.2:1	–
3	NaOAc	CH_3OH	1.5:1	–
4	$NaOCH_3$	CH_3CN	1:1.4	–
5	$KOCH_3$	CH_3CN	1:2	24/54

[a] See Supporting Information for full experimental details. [b] Measured using ^{1}H NMR (400 MHz). [c] Isolated yield.

and magnesium counterions, the latter provided significantly shorter reaction times (2 h vs 3 d). During an optimization process that included both acidic (Lewis and protic acids) and basic conditions (including the use of counterion-sequestering reagents), it was found that additions using polar aprotic solvents reversed the regioselection in favor of **7**. Again, a maximum of 2:1 selectivity could be achieved by use of potassium methoxide (Table 1, entry 5).

A possible explanation for the divergent behavior of these substitutions follows from rate-limiting methoxide addition. Product ratios might simply reflect a solvent-induced reversal of the addition rates to form **8** and **9** (Scheme 2). A 1,2-

Scheme 2. Solvent-Induced Reversal of Regioselection



carbonyl addition/1,2-migration to the enone cannot be discounted, but we observe no product formation using protic acid conditions that might favor this process.[4,13]

To model couplings relevant to mitomycin construction, quinones **6** and **7** were independently exposed to enamine **4** (Scheme 3). The blue quinones formed rapidly at 0 °C, and inspection of the ^{1}H NMR of the crude reaction mixture suggested the presence of only one coupling product of **4** in each case. The thermally labile adducts could be retrieved in pure form after chromatography over neutral alumina (jacketed column, ice−water cooling), and structural assignments were possible by HMBC. Additionally, the same product was formed upon coupling of **4** with either **1** or **6**. The isolated yields reflect the sensitivity of these adducts to

(6) Recourse was eventually made to N4−C4a bond formation prior to C9−C8a, but this sequence has not yet enabled the total synthesis. (a) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1671−1672. (b) Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.* **1983**, *105*, 2859−2866. (c) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745−2752.

(7) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73.

(8) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463. (b) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327−4331.

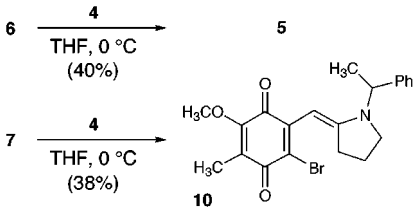
(9) (a) Engler, T. A.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444−2457. (b) Engler, T. A.; Iyengar, R. *J. Org. Chem.* **1998**, *63*, 1929−1934.

(10) (a) Bunnett, J. F.; Garbisch, E. W. Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**,*79*, 385. (b) Bunnett, J. F. *Q. Rev. (London)* **1958**, *12*, 1.

(11) Huisman, H. O. *Recueil* **1950**, *69*, 1133−1156.

(12) Structural assignments were made by HMBC and NOE measurements in both cases. See Supporting Information for details.

Scheme 3. Enamine−Methoxybromoquinone Couplings



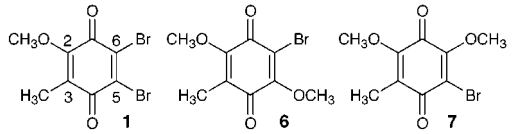
chromatography since 400 MHz ^{1}H NMR analysis of the unpurified reaction mixtures revealed clean conversion. A competition experiment involving equimolar amounts of **4**, **6**, and **7** confirmed the expectation that substitution of the vinylogous ester is more rapid (>95:5 **5**:**10**) than substitution of the vinylogous carbonate.

The results of the competition experiment are not consistent with a 1,2-addition/1,2-migration pathway, so only conjugate addition/β-elimination pathways are considered.[14] The observation that the poorer leaving group is preferentially substituted is consistent with a mechanism in which enamine addition to the enone π-bond is rate-determining.[15] That the methoxy would be substituted preferentially in the case of **7**, however, is nonobvious since *vicinal element effects predict control by the stronger activating group*, which in this case is the carbonyl at C1 (Table 2 numbering).[16]

We turned to semiempirical calculations (Table 2) to determine whether this behavior might be predictable, using the assumption that ground-state polarization of the accepting olefin might be extrapolated to the relative energies of the nucleophile−quinone Michael adducts.[17] The nearly identical charges at carbonyl C1 (vinylogous enone) and carbonyl C4 (enone) indicate that oxygen *n*-donation to the carbonyl π-bond is not detected in these calculations. However, oxygen *n*-donation to the C2−C3 π-bond is revealed by significant negative charge at C3. Hence, the calculations appear to identify only local electronic perturbations.

For enamine additions to **1**, the high degree of regioselectivity derives from, and is consistent with, the electronic nature of enones C5/C1 and C6/C4 as determined by a deactivating resonance contribution by the C2-methoxy into C4. The unique characteristic of enamine additions to **6** and **7** is that an overriding *vicinal* element effect by the bromine substituent is expressed. The methoxy carbon is more positive and carries a larger LUMO coefficient relative to the bromine-substituted carbon in both quinones. An alternative

Table 2. LUMO Coefficients and Charge for Each Carbon of Quinones **1**, **6**, and **7** Determined by Semiempirical (PM3) Calculations[a]



carbon	LUMO[b] (*charge*)		
1	-0.3216 (*0.3351*)	0.3095 (*0.3564*)	0.3528 (*0.3384*)
2	-0.3198 (*0.0011*)	0.3595 (*0.0255*)	0.3341 (*-0.0215*)
3	0.3184 (*-0.1299*)	-0.3166 (*-0.1722*)	-0.3711 (*-0.1193*)
4	0.3227 (*0.3425*)	-0.3624 (*0.3495*)	-0.2921 (*0.3680*)
5	**0.3862** (***-0.1770***)	**-0.3505** (***0.0645***)	-0.2913 (*-0.2996*)
6	**-0.3848** (***-0.1800***)	0.2956 (*-0.3074*)	**0.3309** (***0.0566***)

[a] Using PCModel (Serena Software) and the MOPAC suite. AM1 calculations revealed identical trends. Numbers in bold correspond to experimentally observed sites of nucleophilic substitution. [b] Raw coefficients must be squared for comparison.

view is that addition to the bromine-substituted carbon is strongly disfavored by a donating resonance effect by the methoxy group. That the methoxy substituent exerts a deactivating effect is supported by slower reaction of enamine **4** with **6** and **7** relative to **1**.

In closing, several unsymmetrical benzoquinone systems have been described that undergo substitution with moderate (2:1) to high (>95:5) regioselectivity. The present level offers an improvement in coupling selectivity toward construction of the mitomycin backbone but also identifies a new target (**7**) for coupling that might be prepared via a more direct route.

Additionally, interest in the development of nonlinear optics (NLO) based on quinonic systems[18] might now consider β-halo vinyl ether systems as alternatives to traditional 1,2-dihaloethylenic acceptors, since the former are more regioselective and utilize less halogenated substrates.

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Supporting Information Available: General experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Experiments suggest that these product ratios are kinetic distributions.

(15) Rappoport, Z. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic: London, 1969; Vol. 7, Chapter 1.

(16) For examples of the vicinal element effect (methoxy-substitution) in quinones where enone electronics are not overridden, see: (a) Tatsuta, K.; Mukai, H.; Mitsumoto, K. *J. Antibiot.* **2001**, *54*, 105−108. (b) Reference 11.

(17) Rozeboom, M. D.; Tegmo-Larsson, I.-M.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338−2345

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