C1–C2–C3 plane, as summarized in the exaggerated depiction 6—have been confirmed through a complete neutron diffraction structure determination for this monosubstituted methylenecyclopropane.[14] Such corroborative evidence is especially important as verification of the second distortion, for neutron diffraction is a physical method much better suited to accurate location of hydrogen atoms in organic crystal structure determinations than X-ray crystallography.

These geometrical distortions, derived from "orbital distortions" associated with σ–π mixing,[15] reflect the sense of stereochemical bias shown consistently by methylenecyclopropane rearrangements, as in the example 3 ⇄ 4. That C2 is the favored pivot atom is mirrored in the displacement of C4 toward C2. Which diastereotopic face of the C4 methylene unit will preferentially bond with C2 as the methylenecyclopropane rearrangement occurs, and thus the favored transposition of the trans-C3 substituent to the anti-C4 location as the suprafacial [1,3] shift takes place, is apparent in the dihedral angles between C2–C1–C3 and HA–C4–HB in the ground state.

Recent experimental[16] and theoretical[17] efforts have made it abundantly clear that "orbital distortion" may influence the ground-state geometry of an addend in a manner indicative of stereoselectivity in cycloaddition reactions. The present finding suggests that similar correlations between ground-state geometry and reaction stereochemistry may be found in and may provide useful insights relevant to sigmatropic rearrangements and other unimolecular thermal reactions.

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Supplementary Material Available: Experimental and data deduction details, tables of coordinates, bond lengths, and bond angles, and an ORTEP drawing for the X-ray structure determination of **5** (5 pages). Ordering information is given on any current masthead page.

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(16) See, inter alia: Watson, W. H.; Galloy, J.; Bartlett, P. D.; Roof, A. A. M. *J. Am. Chem. Soc.* **1981**, *103*, 2022–2031. Pinkerton, A. A.; Schwarzenbach, D.; Birbaum, J. L.; Carrupt, P. A.; Schwager, L.; Vogel, P. *Helv. Chim. Acta* **1984**, *67*, 1136–1153. Paquette, L. A.; Green, K. E.; Gleiter, R.; Schafer, W.; Gallucci, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 8232–8240.
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A Brief, Convergent, Regioselective Synthesis of Naphthoquinones. A Formal Synthesis of Nanaomycin A and Deoxyfrenolicin

Summary: A new synthetic route to naphthoquinones, which involves the thermal rearrangement of alkynyl-substituted benzocyclobutenones, is reported.

Sir: Reported here are convergent, regioselective syntheses of the naphthoquinones **1a** and **1b**, compounds which have been employed as key synthetic precursors to the biologically important quinones nanaomycin A (**2a**) and deoxyfrenolicin (**2b**).[1-3] In this regard, new chemistry is also presented in the form of a potentially general naphthoquinone synthesis which was employed as the key step in the construction of **1a,b**.

Recent results reported from our laboratory concerning the thermal rearrangement of 4-alkynylcyclobutenones to quinones suggested the retrosynthetic approach to **1a**, as depicted in Scheme I.[4,5] Specifically, it was found that alkynylation of dione **4** with the lithium salt of benzylethyne gave a 9:1 mixture of the regioisomeric benzocyclobutanones. Significantly, the major product was observed to rearrange cleanly to 2-benzyl-8-methoxy-1,4-naphthoquinone upon thermolysis in refluxing *p*-xylene.[5] Thus, an entry to the naphthoquinone nucleus was established. Still another model study was accomplished which determined that allyl ethers of 4-alkynylcyclobutenols undergo ring expansion with allyl group migration upon thermolysis in refluxing *p*-xylene (138 °C).[5]

These studies encouraged investigations directed toward the preparation and thermolysis of methoxybenzocyclobutenones such as **3**. Results from Liebeskind's laboratory as well as our own experience suggested that monoalkynylation of **4** might result in a mixture of regioisomers due to incomplete selection for alkynylation at the more electron-deficient carbonyl.[6] This proved to be true as evidenced by the fact that alkynylation of dione **4** with the lithium salt of 3-(tetrahydropyranyloxy)propyne (2:1 mixture of diastereomers) at −78 °C in THF gave **5a** (yellow oil) and its regioisomer in 85% yield in a respective ratio of 3:1; furthermore each regioisomer was formed as a 2:1 mixture of diastereomers (Scheme II).[7] Upon further experiment with **4** and other lithium acetylides it was found that regioselectivities of >95:5 were obtained at −100 °C in a mixed solvent of THF/diethyl ether (1:1).[8]

(1) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J. *J. Org. Chem.* **1985**, *50*, 5566.
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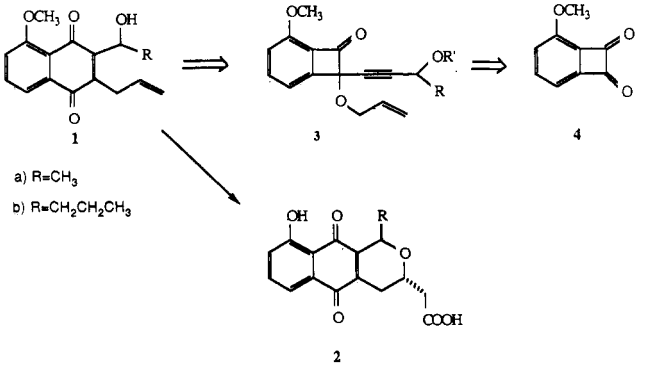
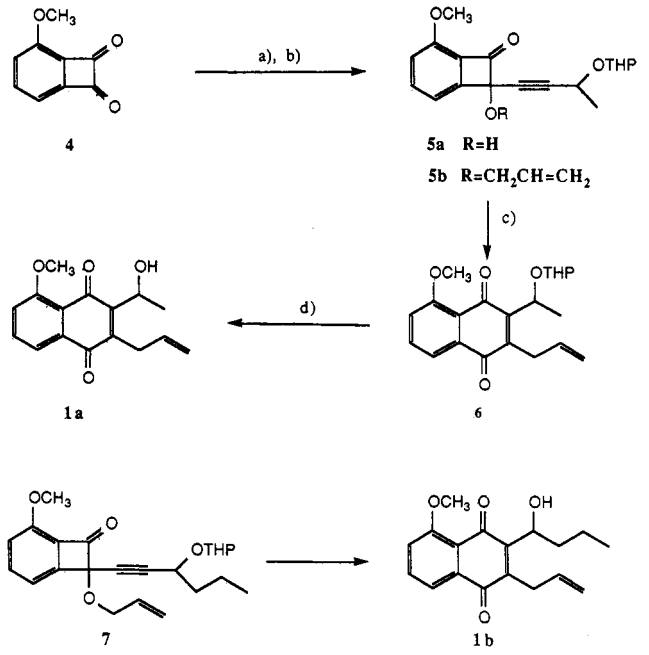
(3) Deoxyfrenolicin (**2b**) is a degradation product of the natural epoxy naphthoquinone, frenolicin: Ellestad, G. Z.; Kuntsmann, M. P.; Whaley, H. A.; Patterson, E. L. *J. Am. Chem. Soc.* **1968**, *90*, 1325.
(4) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.
(5) Perri, S. T.; Foland, L. D.; Decker, O. H.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.
(6) Liebeskind, L. S.; Jewell, C. F.; Iyer, S. *J. Org. Chem.* **1986**, *51*, 3066.
(7) Spectral and analytical properties for all new compounds are in strict agreement with their assigned structures.
(8) Related changes in the regioselectivity were noted by Liebeskind and his co-workers, who found that replacement of the methoxy group in **4** with a *tert*-butyldimethylsiloxy group improved regioselectivity in condensations with phenyllithium from 6.6:1 to >20:1. See ref 6.

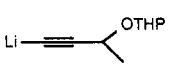
0022-3263/87/1952-1174$01.50/0

Scheme I



Scheme II[a]

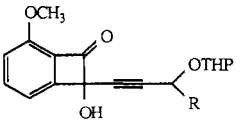


[a] (a)  , THF, −78 °C, 54% (2:1), (b)  , Ag_2CO_3, 99%; (c) *p*-xylene, 138 °C, 71%; (d) $CH_3COOH/H_2O/THF$ (4:2:1), 72%.

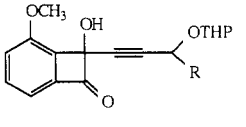
However, these conditions also resulted in a sacrifice in yields (Table I).

The fact that **5a** and its regioisomer were formed as 2:1 mixtures of diastereomers suggests that they differ stereochemically only at the chiral center in the tetrahydropyranyl group. This was confirmed by hydrolytic removal of the THP group of **5a** upon treatment with 4:2:1 $CH_3COOH/THF/H_2O$ at 50 °C, which yielded only one diol. Thus, the alkynylation of **4** is not only regioselective for reaction at the more electron-deficient and sterically less congested carbonyl but also stereoselective in its approach to that group.

Table I. Alkynylation of Benzocyclobutenedione 4



MAJOR ISOMER



MINOR ISOMER

R	conditions	yield, %	ratio
H	THF, −78 °C	83	2:1
CH_3	THF, −78 °C	85	3:1
$CH_2CH_2CH_3$	THF, −78 °C	85	4:1
H	1:1 THF/Et_2O, −100 °C	52	97:3
CH_3	1:1 THF/Et_2O, −100 °C	54	98:2
$CH_2CH_2CH_3$	1:1 THF/Et_2O, −100 °C	58	95:5

The allyl ether **5b** was formed in >95% yield as a yellow oil by treating **5a** with an excess of allyl iodide and Ag_2CO_3 in dioxane.[9] Thermolysis of this ether in refluxing *p*-xylene (138 °C) gave the naphthoquinone **6** as a yellow oil (71%). Removal of the THP protecting group with 4:2:1 $CH_3COOH/THF/H_2O$ gave **1a** (yellow crystals, mp, 76–78 °C, 72%) whose spectral data correlated with those reported in the literature.[1a,b]

Synthesis of **1b**, the precursor of deoxyfrenolicin, was accomplished by a procedure analogous to that described above. That is, alkynylation of **4** with the lithium salt of 3-(tetrahydropyranyloxy)hexyne gave a mixture of two diastereomeric tertiary alcohols contaminated with only 2% of a regioisomeric alcohol (Table I). The major regioisomer was conveniently purified by flash chromatography (ethyl acetate/hexane, silica gel), but the diastereomers were not easily separated. Allylation of the major product gave **7**, which was converted to **1b** by the method reported above.

The overall syntheses of **1a,b** are reasonably efficient. Quinone **1a** was obtained in 28% yield from **4** and **1b** in 22% yield. The dione **4** was obtained in 31% from 2-bromoanisole.[10] The brevity and simplicity of these syntheses recommend the overall approach as a viable method for the preparation of naphthoquinones of specific substitution patterns.

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