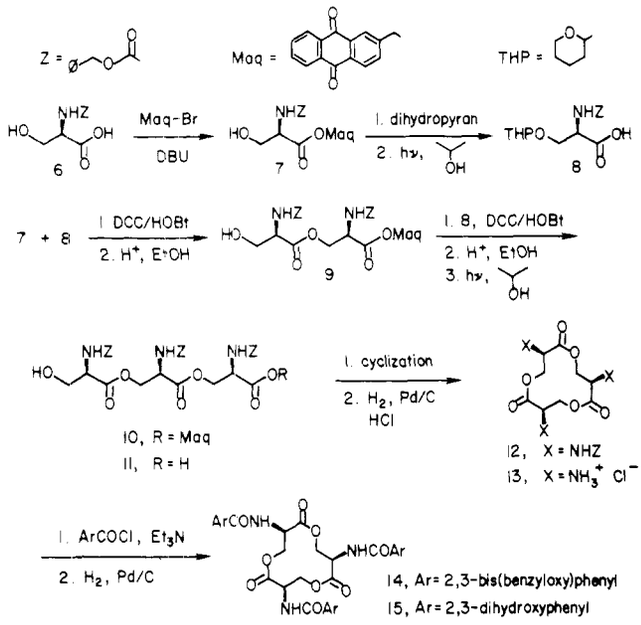
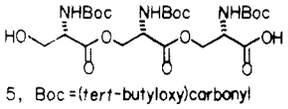
Scheme I



and 4. Nonetheless, the DCC/HOBt-mediated coupling yields an approximately 1:1 mixture of diastereomeric dimers (66%).[11] Despite the success achieved with DCC/HOBt for the coupling of *N*-benzoyl amino acids,[10e] no satisfactory solution could be found to limit racemization of protected *N*-(2,3-dihydroxybenzoyl)serine monomers.

The Corey synthesis of enterobactin[12] via the enantiomer of D-serine cyclic trimer **13** (Scheme I) showed the viability of the urethane approach. Our application of the DCC/HOBt coupling method to urethane-protected monomers revealed the lack of racemization during coupling. However, (*tert*-butyloxy)carbonyl-protected trimer hydroxy acid **5**[8,13] produced by sequential DCC/HOBt couplings failed to cleanly cyclize under a variety of conditions, including those used by Corey et al.[12] for cyclization of the corresponding *N*-[(benzyloxy)carbonyl]-protected trimer hydroxy acid (see enantiomer **11**, Scheme I). Crude cyclization mixtures derived from **5** could not be purified nor deprotected to give a cyclic triammonium salt (see enantiomer **13**, Scheme I).



5, Boc = (*tert*-butyloxy)carbonyl

Our successful approach to enantioenterobactin (and enterobactin) is outlined in Scheme I. *N*-[(Benzyloxy)carbonyl]-D-serine[14] (**6**) was alkylated with 2-(bromomethyl)anthraquinone[15] (MaqBr), giving acid-protected monomer **7**[8,13] (92%). Hydroxyl-protected monomer **8**[8,12] was derived from **7** by reaction with dihydropyran followed by photoreductive deprotection[15] of the Maq ester (82% overall). Coupling of **7** and **8** and removal of the THP protecting group yielded crystalline dimer alcohol **9**[8,13] (88% overall). Further coupling of **9** with **8** and THP removal yielded crystalline trimer alcohol **10**[8,13] (95% overall). Removal of the Maq ester generated the enantiomer (**11**[8]) of Corey's linear trimer enterobactin precursor[12] (67–82%).

Trimer **11** could be cyclized in low yield by DCC/HOBt coupling by Masamune's *tert*-butyl thioester/cuprous triflate method[16] or, preferably, by Corey's imidazolyl disulfide procedure.[12] Hydrogenolysis of crystalline **12**[8,13] in the presence of HCl proceeded smoothly to trihydrochloride salt **13** which was acylated without isolation to give hexabenzylenantioenterobactin (**14**,[8,13] 61–69% overall). Further hydrogenolysis yielded enantioenterobactin (**15**,[13] 56–89%) which was indistinguishable from natural enterobactin by ^{1}H NMR, IR, TLC, UV, field-desorption mass spectrometry (M^+, m/e 669), and melting point. Ferric enantioenterobactin (**2**) displays a CD spectrum which in intensity and sign of rotation is exactly the mirror image of that measured[17] for the natural ferric complex (**1**).

Scheme I applied to *N*-[(benzyloxy)carbonyl]-L-serine[14] yielded enterobactin indistinguishable in all respects (vide supra) from natural material.

Synthetic L-serylenterobactin is fully active in iron transport in *E. coli*, whereas D-serylenterobactin (enantioenterobactin, **15**) is completely inactive.[7]

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Registry No. **1**, 61481-53-6; **2**, 75363-12-1; **6**, 6081-61-4; **7**, 75299-15-9; **8**, 75299-16-0; **9**, 75299-17-1; **10**, 75299-18-2; **11**, 75299-19-3; **12**, 75363-09-6; **13**, 75363-10-9; **14**, 75299-20-6; **15**, 75363-11-0; 2-(bromoethyl)anthraquinone, 7598-10-9.

(11) Separated by LC.
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(18) Firmenich Assistant Professor of Natural Products Chemistry, Alfred P. Sloan Fellow, 1980–1982.

William H. Rastetter,*[18] Thomas J. Erickson
Michael C. Venuti
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received September 23, 1980

Selective Catalysis of Diels–Alder Reactions of 2-Methoxy-5-methyl-1,4-benzoquinone

Summary: The poor regioselectivity of Diels–Alder reactions of 2-methoxy-5-methylbenzoquinone with alkyl-substituted dienes can be directed to favor either isomeric adduct by using stannic chloride or boron trifluoride catalysts.

Sir: Diels–Alder reactions of *p*-benzoquinones have been used to advantage in many well-known syntheses (e.g., steroids,[1] reserpine,[2] and gibberellic acid[3]). Indeed,

(1) (a) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. *J. Am. Chem. Soc.* **1952**, *74*, 4223. (b) Cohen, N.; Banner, B.; Eichel, W.; Valenta, Z.; Dickenson, R. *Synth. Commun.* **1978**, *8*, 427. (c) Das, J.; Kubela, R.; MacAlpine, G.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308.

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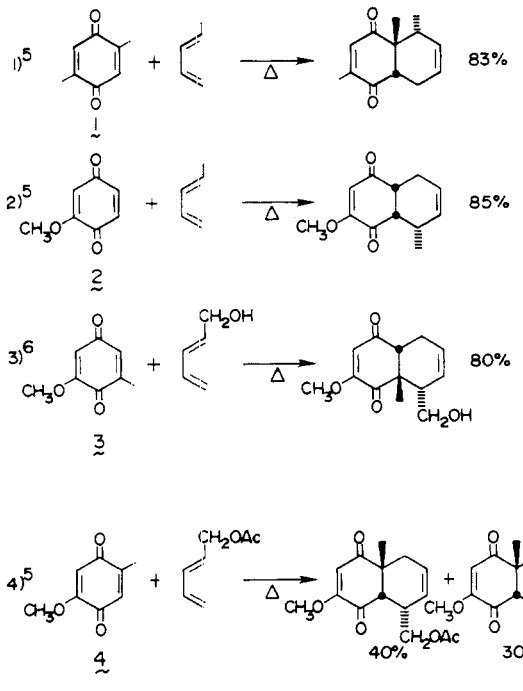
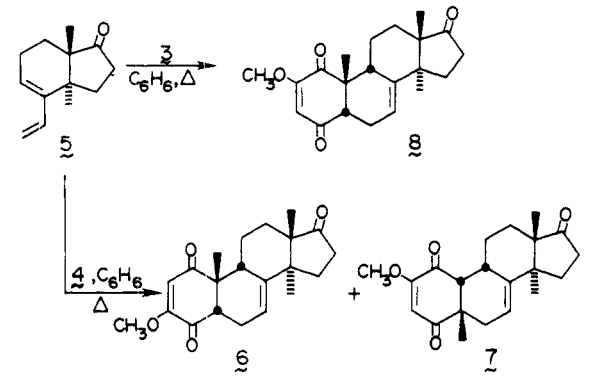
Scheme I



Scheme II



quinone dienophiles not only incorporate an extraordinary confluence of functional groups but generally display a high selectivity in reactions with various dienes. Several important directing effects have been observed for these Diels–Alder reactions. (a) Electron-donating substituents on the quinone deactivate the double bond to which they are attached (CH_3O > CH_3). (b) Substituents on the dienophilic double bond usually direct addition reactions with 1-substituted dienes to give ortho adducts (eq 1, Scheme I) and addition with 2-substituted dienes to give the para adduct.[4] (c) A remote methoxy substituent exerts a strong influence on the orientation of addition reactions at the unsubstituted double bond (eq 2, Scheme I).

In Diels–Alder reactions of 2-methoxy-6-methylbenzoquinone (**3**) we note that directing effects b and c act in concert (eq 3), but in the 2-methoxy-5-methyl isomer **4** they are opposed (eq 4). The nonspecificity of the latter reaction can be tipped in favor of the ortho adduct by replacing the 1-alkyl substituent on the diene with an electron-withdrawing group[5] or in favor of the meta adduct

Table I. Diels–Alder Reactions of 4 with Piperylene

	thermal (100 °C)	$SnCl_4$ (−16 °C)	BF_3 (−16 °C)
ratio of **9**/**10**	1:1	<1:20	4:1
yield, %	80	>85	>85

Table II. Diels–Alder Reactions of 4 with Isoprene

	thermal (100 °C)	$SnCl_4$ (−16 °C)	BF_3 (0 °C)
ratio of **11**/**12**	1:1	<1:20	2.4:1
yield (%)	70	>80	>70

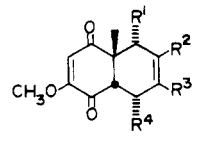
by replacement with an electron-donating group.[7]

We find that the lack of regioselectivity in Diels–Alder reactions of **4** with alkyl-substituted dienes can be directed to favor either isomeric adduct by using appropriate Lewis acid catalysts.[8] The most dramatic results were obtained with bicyclic diene **5**, which reacted with **4** in refluxing benzene to give a 3:2 mixture of adducts **6** and **7**[9] in approximately a 40% isolated yield. In contrast, **5** reacted with quinone **3** to give adduct **8** in over 55% yield (Scheme II).

Stannic chloride catalysis (1:1 catalyst–quinone) of the reaction of **4** and **5** in methylene chloride solution at 0 °C resulted in a 75% yield of adduct **7**. No isomeric adduct **6** was detected by ^1H NMR analysis of the crude product. The corresponding boron trifluoride catalyzed reaction at −16 °C gave a 50–55% yield of **6**, contaminated by no more than 10% of **7**. This minor product was easily removed by crystallization.

Similar reactions of **4** with piperylene and isoprene gave the results shown in Tables I and II.

The assignment of structure **9** has been made with the help of an unexpected tautomerism. On being allowed to stand, the 4:1 mixture of **9** and **10**, prepared by boron



9, $R^1 = CH_3$; $R^{2,3,4} = H$
10, $R^4 = CH_3$; $R^{1,2,3} = H$
11, $R^3 = CH_3$; $R^{1,2,4} = H$
12, $R^2 = CH_3$; $R^{1,3,4} = H$

trifluoride catalyzed cycloaddition, slowly deposited a crystalline isomer (mp 120–123 °C) which we have identified as the enol tautomer **13** of adduct **9**. This assignment is based on the ^1H NMR spectrum (see below), homonuclear decoupling experiments, infrared absorption (KBr) at 3300, 1675, and 1601 cm^{-1}, a UV λ_{max} (ethanol) at 340

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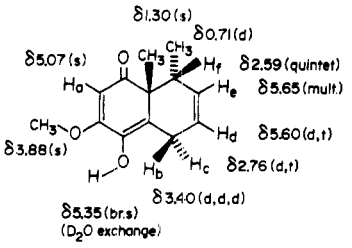
(9) The structures of the new compounds are based on microanalysis,[15] mass spectrometry, 250-MHz ^1H NMR, 20-MHz ^{13}C NMR, and infrared spectroscopy. X-ray diffraction analysis[16] of adducts **6** (mp 260–261 °C), **7** (mp 239–241 °C), and **8** (mp 228–230 °C) confirms their structures. Adducts of **10** (mp 70–73 °C) and **12** (mp 116–118 °C) have been reported in the literature,[5,10] and our samples correspond in all respects with the recorded properties. Compound **11** (mp 86–88 °C) was previously described in an unpublished report[11] from R. B. Woodward's laboratory. Its ^1H NMR spectrum ($CDCl_3$) [δ 1.31 (s, 3 H), 200 (s, 3 H), 2.10–2.80 (m, 4 H), 2.93 (t, J = 6.5 Hz, 1 H), 3.79 (s, 3 H), 5.31 (m, 1 H), 5.83 (s, 1 H)] is different from that of **12** and agrees well with the cis-fused structure drawn. A pure sample of **9** was never obtained; however, in a 4:1 mixture with **10**, compound **9** exhibited ^1H NMR signals at δ 0.81 (d, J = 7.4 Hz, 3 H), 1.40 (s, 3 H), 2.05–2.20 (m, 2 H), 2.90–3.00 (m, 2 H), 3.80 (s, 3 H), 5.60 (br s, 2 H), 6.00 (s, 1 H).



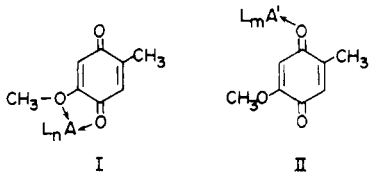
13

nm (ε 3300), and other data.[9] Both **10** and its trans-fused epimer were characterized by Bohlmann et al.[5] and are stable, crystalline compounds. The spontaneous tautomerization of **9** is unique among all the Diels–Alder adducts of **4** that we have studied. Nonbonded interactions of the vicinal methyl groups may provide some driving force for this transformation.

A report by Ayer et al.[10] that the thermal cycloaddition of isoprene with **4** gave pure **12** conflicts with our findings, as well as an unpublished study by Knowles.[11] The product obtained by the Canadian group was well characterized and corresponds in melting point to our own **12**. In fact, our assignment of this structure rests heavily upon their degradative work. A possible explanation for these contradictory results is that a metal ion catalyst may inadvertently have been incorporated in the Canadian experiments. For example, **4** prepared by the method of Ashley[12] often contains zinc salts that are difficult to remove.[1a]

The profound influence that Lewis acid catalysts have on the rate and selectivity of Diels–Alder reactions of quinones was first noted by Valenta and co-workers.[13] Their landmark study demonstrated a clean reversal of regioselectivity in reactions of 2,6-dimethylquinone with various dienes in the presence of Lewis acid catalysts, as compared with the corresponding thermal reactions. A regioselective complexation of the catalyst with one of the carbonyl groups is believed to be responsible for this effect.

Our work extends the findings of the Valenta group to the useful methoxy quinone **4**. The remarkable catalyst



I II

selectivity we have observed with **4** apparently depends on whether the catalyst–quinone complex is stabilized by chelation, as in I, or is fixed at an unhindered site on the more basic ester-like carbonyl group, as in II. Since boron can accept only four ligands, it will tend to form a type II complex, and this should activate the less substituted carbon atom of the dienophilic double bond. Complexes of type I appear to be favored by $SnCl_4$ and $TiCl_4$[14] and activate the more substituted carbon atom of the dienophile.

Finally, it is instructive to compare catalyst effects (BF_3 vs. $AlCl_3$) in Diels–Alder reactions of juglone derivatives[17] with the results reported here. Boeckman et al. note that the regioselectivity of many such reactions is dominated by diene polarity and suggest that this polarity can be significantly altered by complexation. Simple alkyl-substituted dienes are unlikely to exhibit such complexation in competition with the more basic quinone dienophiles. In fact, isoprene did not show the same reversal of adduct orientation in catalyzed reactions with juglone as did 1,4-dimethoxyisoprene.[17a] Thus the relative importance of competitive complexation, steric hindrance, and charge-transfer effects in these different systems is difficult to assess at this time.

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Jacob S. Tou, William Reusch*
Department of Chemistry
Michigan State University
East Lansing, Michigan 48824
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