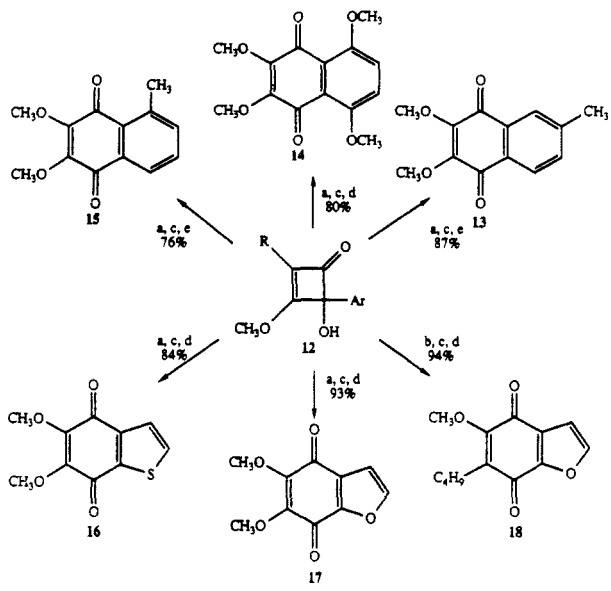
Scheme IV[a]



[a] (a) R = CH_3O; (b) R = n-C_4H_9; (c) 138 °C, p-xylene; (d) Ag_2O, K_2CO_3, C_6H_6, 1 h; (e) Ce(IV)/SiO_2, CH_2Cl_2, 10 min.

rangement is envisaged to involve the (2-alkynylethenyl)ketene **7** which cyclizes to the zwitterionic species **8**. Subsequent intramolecular electrophilic attack on the allyl double bond and C–O bond cleavage leads to **9**.

The cyclobutenol precursor to **6** was also subjected to thermolysis at 138 °C for 1 h. This gave a 71% isolated yield of 2-benzyl-5,6-dimethoxy-1,4-benzoquinone.[6] Still another example of this reaction mode is given in Scheme III. This case not only illustrates the unusual hydrogen migration but also presents a potentially general regiospecific route to naphthoquinones. Here, the benzocyclobutenone **10**, obtained in 75% yield upon alkynylation of the corresponding methoxybenzocyclobutenedione, gave **11** in 84% yield when subjected to thermolysis.[7]

Finally, we report that 4-aryl-4-hydroxycyclobutenones **12** undergo facile rearrangement to the corresponding hydroquinones in refluxing p-xylene after 2 h.[8,9] These were oxidized (Ag_2O or Ce(IV)/SiO_2)[10] to the respective quinones **13**–**18** which were isolated in 76–93% overall yields (Scheme IV). Particular note is made of the **12** to **18** transformation since this was accomplished with complete regiocontrol starting from 3-butyl-4-methoxycyclobutenedione and 3-lithiofuran.[11,12] The starting cyclobutenones were prepared in 59–73% isolated yields by treating the cyclobutenediones (THF, −78 °C) with the appropriate aryllithium reagent and quenching the reaction with 5% NH_4Cl at −78 °C.

The results presented here represent very general and efficient synthetic routes to highly functionalized quinones and hydroquinones. Further details will be reported subsequently.

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Registry No. **6**, 102683-41-0; **9**, 102683-43-2; **10** (isomer 1), 102683-45-4; **10** (isomer 2), 102696-56-0; **10** (dione), 62416-22-2; **11**, 102683-46-5; **12** (R = OCH_3, Ar = H), 102683-47-6; **12** (R = C_4H_9, Ar = H), 102683-48-7; **13**, 102632-08-6; **14**, 51783-58-5; **15**, 102632-07-5; **16**, 102683-49-8; **17**, 102683-50-1; **18** (isomer 1), 102683-51-2; **18** (isomer 2), 102683-53-4; $C_6H_5CH_2C{\equiv}CLi$, 102683-42-1; $ICH_2CH{=}CH_2$, 556-56-9; 2,3-dimethoxycyclobutenedione, 5222-73-1; 2-benzyl-5,6-dimethoxy-1,4-benzoquinone, 102683-44-3; 3-butyl-4-methoxycyclobutenedione, 102683-52-3; 3-lithiofuran, 53101-93-2; 2-lithiofuran, 2786-02-9.

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(6) We have documented 10 examples of this rearrangement.
(7) Alkynylation of the methoxybenzocyclobutenedione gave a 9:1 mixture of regioisomers. From electronic considerations, **10** is assumed to be the major regioisomer.
(8) In principle this is analogous to the metal-mediated synthesis of naphthols from alkynes and chromium carbene complexes. See, for example: Dotz, K-H.; Pruskil, I.; Muhlemeir, V. *Chem. Ber.* **1982**, *115*, 1278. Semmelhack, M. F. "Regioselectivity in Metal Promoted Carbon–Carbon Coupling Reactions" in *Selectivity–A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M. Eds., Verlag Chemie: Weinheim, 1984.
(9) It is necessary to protonate the initially formed alkoxide at −78 °C. If not, other chemistry dominates. For analogies see: Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6182. Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1801.
(10) Fisher, A.; Henderson, J. *Synthesis* **1985**, 641.
(11) 3-Butyl-4-methoxycyclobutenedione was prepared in 47% yield by treating 2,3-dimethoxycyclobutenedione with butyllithium followed by mild acid hydrolysis. On the basis of previous analogy (ref 9, for example) as well as upon NMR arguements, the regiochemistry of the cyclobutenol obtained upon arylation of the above dione is assigned as shown.
(12) The regioisomer of **18** was obtained in 91% when 2-lithiofuran was employed.

The Structure and Kinetic Reactivity of a Pyrrolidine-Derived Vinylogous Urethane Lithium Enolate

Summary: NMR data show the enolate **1** possesses a highly twisted diene skeleton. This enolate undergoes kinetic and anti selective aldol reactions at its distal C-4 position.

Sir: We have described some novel anti selective aldol reactions of the lithium enolate **1**.[1] To more thoroughly control this enolate, an examination of both its structure and its mode of reaction with aldehydes was undertaken. Data which delineate both an unusual structure for **1** and establish the kinetic nature of its aldol reactivity are detailed below.

The E configuration of substituents [$(CH_2)_4N$ and CO_2CH_3] for substances like **2** is known to be thermodynamically favored.[2] An s-cis orientation of olefin and carbonyl residues predominated in **2** as evidenced by a 20% NOE found between the methoxy group of the ester and the C-2 vinyl proton.[3] ^1H NMR studies of **2** indicate a C-1–C-2 bond rotation of 7.4 kcal/mol (T_c = 154 K, THF-d_8) and 13.4 kcal/mol (T_c = 286 K, THF-d_8) for the degenerate rotation of the pyrrolidine ring.[4]

Deprotonation of **2** with LDA (THF/−78 °C) followed by reaction with Me_3SiCl gave a single distillable (0 °C, 10^{-6} torr) ketene acetal enamine, **3** (Scheme I). Desilylation of **3** with CH_3Li (THF/−78 °C) gave enolate **1**.[5] Z

(1) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777–1778 and references cited therein.
(2) Smith, D. *Spectrochim. Acta Part A* **1976**, *32A*, 1477–1488, 1489–1502.
(3) Infrared studies verify this conclusion, see ref 2.
(4) Dabrowski, J.; Kozerski, L. *Org. Magn. Reson.* **1973**, *5*, 469–470.

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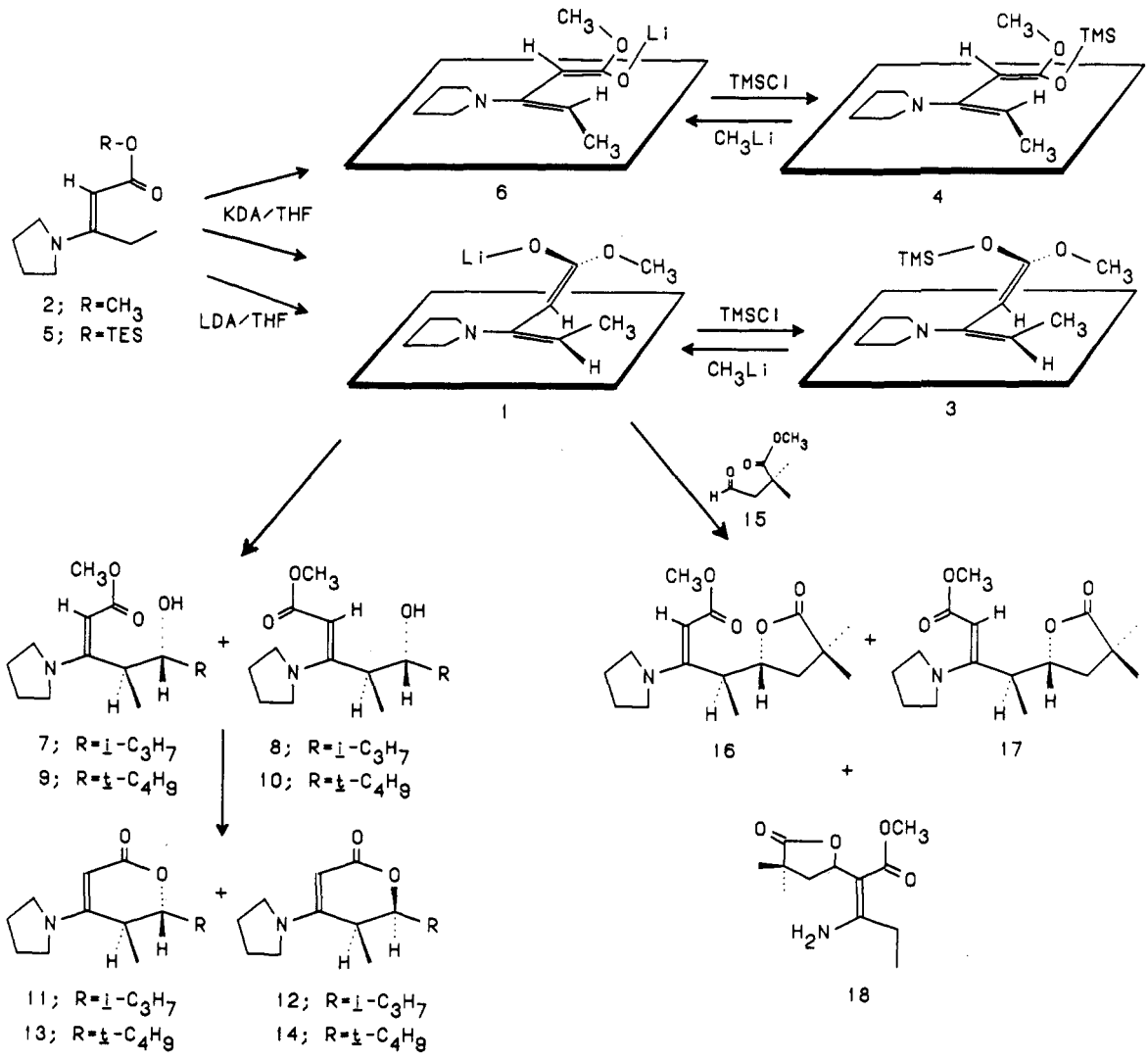
Scheme I



geometry for the ketene acetal portion of **3** follows both from a 20% NOE between the vinyl proton at C-2 and the *O*-methyl group and from the observation that the *O*-silyl residue of **3** undergoes a first-order migration (22 °C) to the C-4 atom.[6]

(*E*)-Enamine geometry for **3** was demonstrated by a C-4 signal at 92.40 ppm (typical ^{13}C-β value for (*E*)-enamines).[7] Further, a 1:1 mixture of **3** [(*E*)-enamine] and **4** [(*Z*)-enamine] was obtained by deprotonating **2** with KDA (THF/−78 °C) and reaction with Me_3SiCl.[8] A C-4 resonance at 106.40 ppm (^{13}C-β value for (*Z*)-enamines) was observed for **4**.[7] The (*E*)- and (*Z*)-enamine geometry of **3** and **4** was confirmed by generating a symmetrically substituted ketene acetal residue from the Et_3Si ester derivative **5** (done by deprotonation of **5** with KDA/THF followed by trapping with Et_3SiCl to generate a 1:1 mixture of (*E*)- and (*Z*)-enamine species).

A twisted diene structure should be present in both **3** and its enolate analogue **1**, due to the substitution pattern of their olefinic residues.[9] On the other hand, a relatively more planar diene structure ought to be present in both **4** and its enolate analogue **6**. We wished to investigate this supposition, since a twisted diene structure for **1** could profoundly influence the pathway by which it undergoes reaction. ^{13}C NMR proved useful in this regard, because it can be used to determine the relative degree of increased electron density experienced at C-2 and C-4 on conversion of **3** and **4** into their respective enolates **1** and **6**.

Since this type of experiment had heretofore not been carried out on unsaturated esters, we first examined the behavior of the Me_3Si ketene acetal and lithium enolate derived from methyl-3,3-dimethylacrylate.[10] As expected, conversion of the ketene acetal into the enolate resulted in ^{13}C upfield shifts at both C-2 and at C-4; specifically, a 9.97 ppm (81.95 to 71.98) upfield shift for C-2 and a 7.34 ppm (107.96 to 100.62) upfield shift for C-4. We then prepared a mixture of **3** and **4** by deprotonation of **2** with KDA followed by trapping with Me_3SiCl. After evaporation of the volatiles at 0 °C (10^{-6} torr), the residue was diluted with THF-d_8, and the ^{13}C chemical shift values at

(5) House, H. O.; Prabhu, A. V.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209–1214. 1 generated in this fashion undergoes reactions with the same stereoselectivity and in the same yields as 1 formed by deprotonation of **2** with LDA.

(6) For similar 1,5-silicon migrations, see: Bell, S. H.; Cameron, D. W.; Feutrill, G. I.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **1985**, *26*, 6519–6522.

(7) Stradi, R.; Trimarco, P.; Vigevani, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1–4.

(8) The origin of this interesting result is unknown at this time.

(9) Dreiding and CPK molecular models of **1** and **3** suggest a twist around the C-2–C-3 bond of at least 50°, due to nonbonded interactions experienced by the *E* enamine residue.

(10) (a) Vogt, H. H.; Gompper, R. *Chem. Ber.* **1981**, *114*, 2884–2897. (b) For leading references on the lithium enolate of methyl 3,3-dimethylacrylate, see: Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1333–1336; **1985**, *26*, 1939–1942.

C-2 and C-4 of both **3** and **4** were recorded at −40 °C. Next, the mixture of **3** and **4** was desilylated with methyllithium (−40 °C, 4 h), the solvent removed (0 °C, 10^{-6} torr), and the enolate mixture redissolved in THF-d_8, and the ^{13}C chemical shift values at C-2 and C-4 of the lithium enolates **1** and **6** were recorded at −40 °C. In the case of the ketene acetal (*Z*)-enamine **4** and its enolate analogue **6**, upfield shifts at C-2 of 13.2 ppm (75.7 to 62.6) and at C-4 of 4.9 ppm (106.4 to 101.5) were observed on conversion of **4** into **6**. In marked contrast, conversion of the ketene acetal (*E*)-enamine **3** into its lithium enolate **1** resulted in an upfield shift at C-2 of 11.3 ppm (74.5 to 63.2) while at C-4 only 0.9 ppm (92.4 to 91.5) of upfield shift was observed.[11] These data, with respect to the NMR time scale, support the notion that the (*E*)-enamine containing systems **3** and **1** are considerably twisted around the C-2–C-3 bond compared to the (*Z*)-enamine containing systems **4** and **6**.[12]

Interestingly, the aldol reactions of **1** occurred exclusively at C-4 and not at C-2 even though the electron density at C-2 was observed to be greater than at C-4 in the ^{13}C NMR. This called into question the pathway by which these aldol products were formed. Specifically, was the reaction at C-4 kinetic or thermodynamic, and was this condensation subsequent to a reversible aldol process at C-2?[13] We began to study this point by reacting **1** with an equivalent of isobutyraldehyde at −78 °C for periods varying from 15 s to 30 min. These reactions gave, in excellent yield, compounds **7** and **8**, which are C-4 aldol adducts that hold only anti geometry at C-4–C-5, differing as *E*/*Z* isomers about the C-2–C-3 olefinic moiety.[14] The condensation of **1** with pivalaldehyde also was examined. In this instance, the adducts **9** and **10**, as *E*/*Z* isomers possessing only anti geometry at C-4–C-5, were formed.

We were curious to see if the anti geometry at C-4–C-5 was maintained on cyclization of these adducts. This was examined in two ways; either by generating the adducts at −78 °C and allowing them to slowly cyclize at −78 °C or by raising the temperature, after 5 min, to 0 °C to allow rapid cyclization. The adducts **7** and **8** (*E*/*Z* isomers) cyclized under either protocol (90% yield) to give a 20:1 mixture of anti lactone **11** and syn lactone **12**, respectively. This is a detectable (^1H NMR) corruption of C-4–C-5 anti geometry during cyclization. More spectacularly, the adducts **9** and **10** cyclized at −78 °C to give an 18:1 ratio of anti lactone **13** and syn lactone **14**, while at 0 °C the ratio was 7.8:1.[15] These data indicate that the aldol reactions of **1** occur at C-4 to afford anti geometry via a kinetic process. However, lactonization of these adducts leads to some compromise of stereochemistry, presumably by a retro aldol process.[16]

The above data do not address the possibility that the C-4 reactivity observed for **1** could be preceeded by reversible aldol process at C-2 of the enolate. Hence, we condensed **1** with the aldehyde ester **15** feeling that the ester residue carried by **15** stood an excellent chance of intercepting the aldol generated alkoxide anion faster than the retro aldol process. The reaction of **1** with **15** (−78 °C) for periods ranging from 15 s to 1 h gave only the C-4 aldol adducts **16** and **17** (85% yield). **16** and **17** are *E*/*Z* isomers around the C-2–C-3 olefin, and in this instance it proved possible by ^1H NMR to demonstrate that the barrier for this isomerization was 15.0 kcal/mol (T_c = 331 K, THF-d_8).[17] We repeated the above experiment by adding [2.1.1]kryptand (1.0 equiv) to the enolate **1** followed by addition of **15**. A mixture of the C-4 aldol adducts **16** and **17** was isolated (35% yield) in this instance. Along with these C-4 adducts, a product, **18**, reflecting condensation at C-2, was isolated (35% yield), indicating that under certain conditions, reaction at this position of **1** can be realized.[18]

We are attempting to determine the role that the lithium counterion plays in the reactions of **1** in order to comprehend the mechanism by which this enolate undergoes the aldol process.

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Registry No. **1**, 102779-94-2; **2**, 102779-95-3; **3**, 102779-96-4; **4**, 102779-97-5; **5**, 102779-98-6; **6**, 102779-99-7; **7**, 102780-00-7; **8**, 102780-01-8; **9**, 102780-02-9; **10**, 102780-03-0; **11**, 102780-04-1; **12**, 102780-05-2; **13**, 102780-06-3; **14**, 102780-07-4; **15**, 51445-11-5; **16**, 102780-08-5; **17**, 102807-65-8; **18**, 102780-09-6; isobutyraldehyde, 78-84-2; pivaldehyde, 630-19-3.

(11) Methyl 3-pyrrolidino-2-butenoate could not be examined since it does not form a ketene acetal enamine, see: Chan, T. H.; Kang, G. J. *Tetrahedron Lett.* **1982**, *23*, 3011–3014.

(12) The species **4** and **6**, based on nonbonded interactions, are also twisted; however, the extent of twist in **4** and **6** must be less extreme than that observed for **3** and **1**.

(13) Reversible reactions at either C-2 or C-4 could result in *E*/*Z* isomerization of the enolate at the C-1–C-2 or C-3–C-4 bonds, rendering an accounting of the anti selective behavior of **1** futile. For appropriate examples, see: (a) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. (b) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162. See also ref 16.

(14) The degradation sequence used to confirm anti geometry at the C-4–C-5 bond was similar to that described by: Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357.

(15) Benzaldehyde was also examined and found to behave like pivaldehyde.

(16) To further demonstrate a retro aldol process, crossover experiments between pivalaldehyde and isobutyraldehyde were carried out. It was possible to exchange pivalaldehyde with isobutyraldehyde but not to exchange isobutyraldehyde with pivalaldehyde. Since this retro aldol process could have isomerized the (*E*)-enamine geometry of **1**, we conducted the following experiment to probe this possibility. **1** (1 equiv) in THF at −78 °C was treated with 0.5 equiv of pivalaldehyde. The reaction was brought to 0 °C, then cooled to −78 °C, and quenched with Et_3SiCl. After removal of the volatiles, the ^1H NMR of the residue was examined. Aside from **13** and **14** (7.8:1) and **2**, a Et_3Si-derived ketene acetal enamine was present. This substance possessed only (*E*)-enamine geometry and was identical with the ketene acetal enamine obtained by reacting **1** with Et_3SiCl.

(17) **16** and **17** exist as a 15:1 anti/syn mixture, respectively, of isomers at the C-4–C-5 bond. The anti/syn ratio obtained on reaction of **1** with butyraldehyde was 11:1.

(18) **18** arises on workup with aqueous NH_4Cl. The anti/syn ratio of **16** and **17** in this reaction changes from 15:1 to 2:1.

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An Enantio- and Erythro-Selective Lithium Enolate Derived from a Vinylogous Urethane: Its Application as a C_4 Synthon to the Virginiamycin M_2 Problem

Summary: A brief and efficient construction of the virginiamycin M_2 fragment **2** using an enantio- and erythro-selective lithium enolate derived from the vinylogous urethane **3** is described.

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