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REGIOCHEMICALLY CONTROLLED SYNTHESES OF 3-HYDROXYNAPHTHO [b] CYCLOBUTENE BY VICINAL DIESTER DIANION CONDENSATION.

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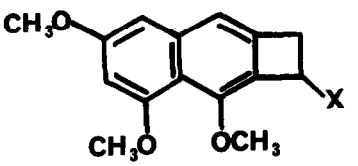
Summary: Utilization of the dianion derived from dimethyl trans-1,2-cyclobutane dicarboxylate allows for the rapid construction of an unsymmetric naphtho [b] cyclobutene by two different routes.

Our interest in the total synthesis of the aureolic acids requires the synthesis of the complex naphtho [b] cyclobutene 1 which will later serve as a diene in a Diels-Alder reaction.



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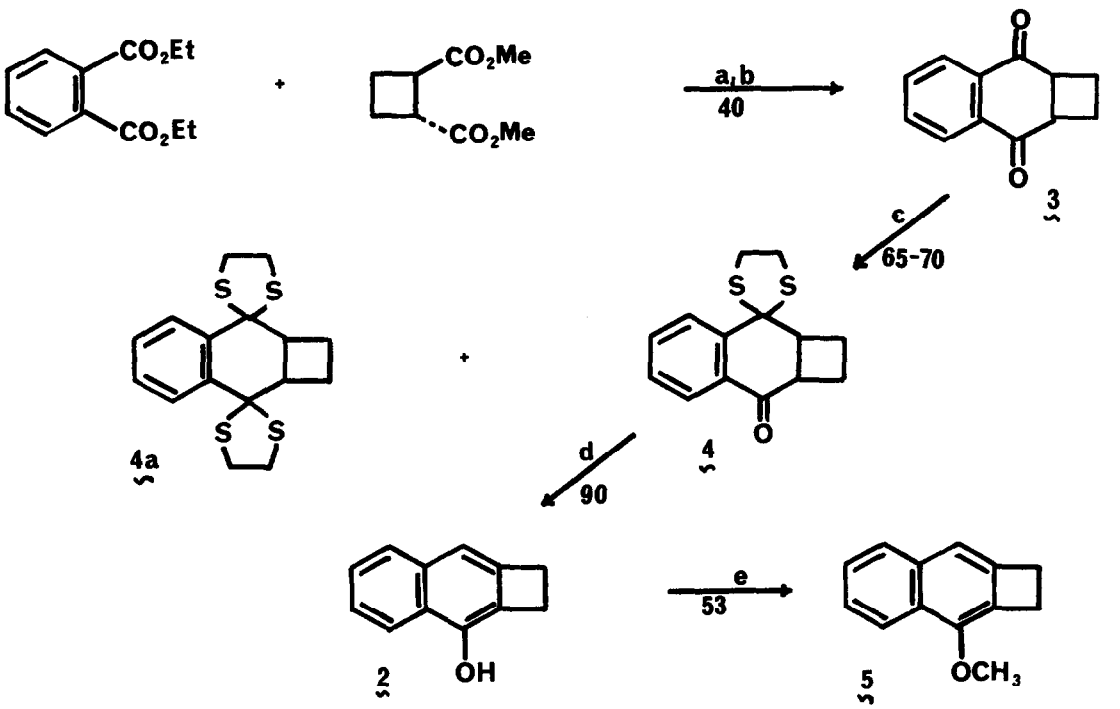
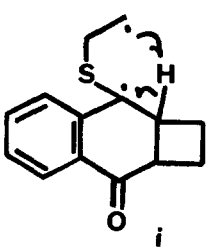
We wish to report in this letter our methodologies for the construction of the novel unsymmetric 3-hydroxynaphtho [b] cyclobutene, 2, in good overall yield from readily available starting materials.

The initial formation of known tricycle 3 was based on the diester dianion condensation of Garratt[2] utilizing dimethyl trans-1,2-cyclobutane dicarboxylate and diethyl phthalate (Scheme 1). Dione 3 was protected as the monothioketal[8,9] 4 in approximately 70% yield after careful silica gel chromatography to remove undesired diketal 4a and unchanged starting material. Thioketal 4 was then allowed to react with W-2 Raney nickel in refluxing acetone to afford naphthol 2 in 90% yield.[8,9] The Raney nickel had been previously deactivated by refluxing over acetone for 24 hours.[3] This type of deactivated Raney nickel reaction has been used for the introduction of an olefinic bond in the steroid field,[3] but to our knowledge, no report of this type of desulfurative aromatization is extant. This reaction may involve the intermediacy of diradical i which collap-

SCHEME 1



Reagents: a. 2.1 eq. LDA, THF, -78°c; b. CH_3COOH/H_2O/conc. H_2SO_4 (7:5:1). 100° C. N_2; c. 1 eq. $HSCH_2CH_2SH$, BF_3 -etherate, CH_2Cl_2, 24 h. reflux; d. W-2 Raney nickel, acetone, 24 h. reflux; e. FSO_3CH_3, KO-t-C_4H_9, DME, 45 min, r.t. ses to naphthol 2 as indicated. Air sensitive 2 exhibited H_1 NMR, and infrared spectra consistent with the assigned structure.[8,9]



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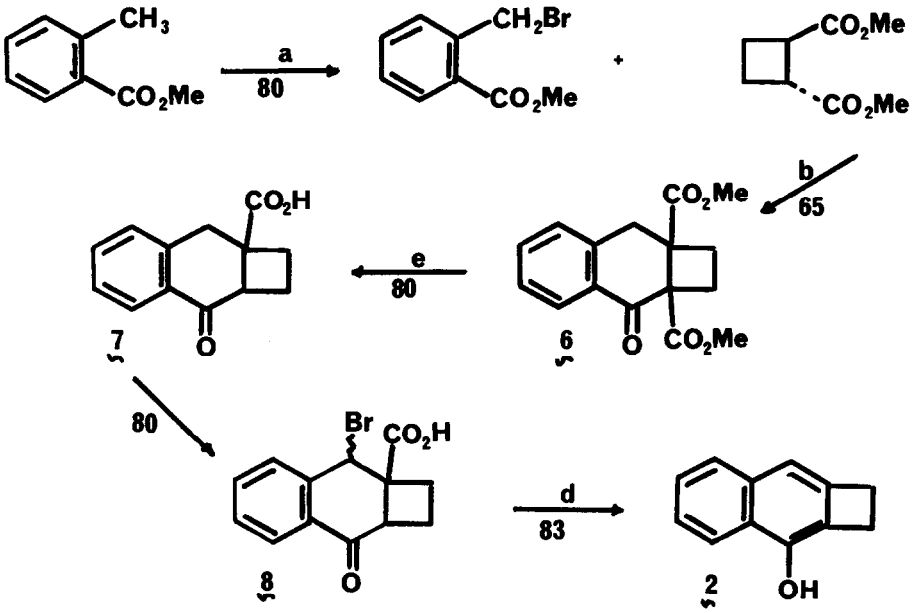
Naphthol 2 was further characterized as its methyl ether 5, mp 59-60°C,[8,9] which was prepared with methyl fluorosulfonate and potassium t-butoxide in DME.[4]

Scheme 1 illustrates a bis-acylative annulation for the formation of dihydroquinone 3. Recently Garratt et al. reported an acylative-alkylative annulation in a synthesis of a terpene precursor.[5] We also have exploited an acylative-

SCHEME 2



Reagents: a. NBS, CCl_4, h, reflux; b. 2.1 eqv. LDA, THF, -78° C, 6h; c. CH_3COOH/H_2O/conc. H_2SO_4 (5:5:1), 100°C, N_2, 16 h; d. $(C_2H_5)_3N$, silica gel, trace H_2O, CH_3CN, reflux, 3 h.

alkylative annulation to produce keto diester 6 which with straightforward manipulation of the peripheral functionality can afford naphthol 2. This approach is shown in Scheme 2.

Bromination of methyl o-toluate gives methyl o-bromomethyl toluate[6] in high yield. Submission of this substrate to acylative-alkylative annulation with the cyclobutane diester dianion affords internally differentiated tricyclic diester 6, mp 83-5°C, in 65% yield.[8,9] Hydrolysis of 6 then produces keto-acid 7 in good yield.[8,9] Crude 7 could be purified by reversed phase silica gel

chromatography, however, the crude material was of sufficient purity for the subsequent reactions. Benzylic bromination of 7 with NBS affords bromo acid 8 as a mixture of stereoisomers in 80% yield. Submission of 8 to a Grob fragmentation cleanly produces naphthol 2 in 83% yield. The use of the above described methodologies for the construction of more highly functionalized naphtho(b) cyclobutenes will be described in due course.

Acknowledgement We are grateful for the support of NIH grant CA 27116 and for the communication of some experimental detail from Dr. Garratt.

References and Notes

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8. Infrared spectra were consistent with the assigned structures.
9. H-NMR (CDCl) 100 Mhz, 4, 1.7-2.6 (4H,m), 3.2-3.7 (6H,m), 7.2-7.6 (2H, m), 7.95 (2H, m); 2 3.24 (4H, s), 5.26 (1H, br s, exchanges with D O), 7.08 (H8, s), 7.36 (H5, H6, m), 7.74 (H7, m), 8.10 (H4, m); 5 3.28 (2H, m). 3.50 (2H, m), 4.02 (3H, s), 7.05 (H8, s). 7.34 (H5, H6, m), 7.68 (H8, m). 8.10 (H4, m); 6 2.16 (3H, m), 3.00 (1H, half of AB Quartet, J=16 hz). 3.22 (1H, m), 3.46 (1H, half of AB quartet, J= 16 hz), 3.70 (3H, s), 3.76 (3H, s), 7.40 (3H, m), 7.98 (1H, d, J=7 hz); 7 2.10 (2H,m), 2.54 (2H, m). 2.98 (1H, half of AB quartet, J=16 hz), 3.28 (1H, half of AB quartet, J=16 hz), 3.60 (1H, m), 7.40 (3H, m), 7.86 (1H, d, J=8 hz), 11.50 (1H, br s); 8 2.3 (2H, m), 2.7 (2H, m), 4.64 (1H, m), 5.58 (0.83H, s), 5.94 (0.17H, s), 7.45 (3H, m), 7.96 (1H, m), 9.0 (1H, br s).
MS (70 ev) m/e 5 M+ 184, 170; 6 M+ 288, 229, 170; 7 M+ 216, 188.
(CI) m/e 4 M^++ 1 263, 201, 175.

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