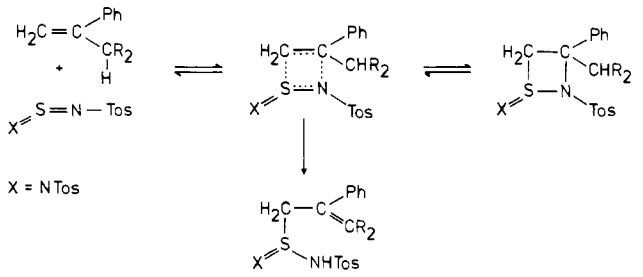
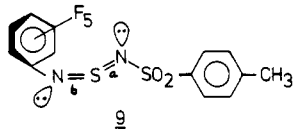
Scheme II



certain others the [2 + 2] cycloaddition is noted to be the only reaction occurring. Two categories of results, each implicating the intervention of a four-membered cyclic complex in its reaction pathway, have thus far been identified. For example, in a series of propenylbenzenes (illustrated in Scheme I) competition exists for the formation of two different orientations of the reactant planes, only one of which can achieve the ene-reaction product while the other results in the [2 + 2] cycloaddition. The most electron-releasing substituents on the aromatic (Ar) group tend to foster the complex which precedes (only) the cyclic product, since an allylic H in this complex is not available for abstraction by the nonbonding pair of the nitrogen. Even where the phenyl ring is unbiased by substitution, the ease of formation of the pre-ene-reaction complex is greatly diminished compared to 1-alkyl-substituted propenes; thus, the ene product from propenyl benzene is found to form at rates which are orders of magnitude lower.[2b,c]

Circumstances have also been encountered where difficulties of steric, conformational and/or bond-strength origin can arise in the rate-controlling H-abstraction step, while formation of the preliminary complex is uninhibited by substitution. Here, it is often detected that the kinetic product is the [2 + 2] cycloadduct which is rapidly and reversibly formed; in fact, this side product can frequently be isolated. A class of examples where the development of the equilibrium ene-reaction product takes place at the expense of the more rapidly formed [2 + 2] cycloadduct is depicted in Scheme II. Analogous observations of steric and conformational substituent effects have been made in the hydroperoxidation of allylic olefins with singlet oxygen[9a], an ene-like reaction for which an actual intermediate or a complex between the reactants prior to the rate-determining allylic-H-abstraction step has been deduced[9b] through KIE studies.

Further evidence supporting this proposal is to be found in the reactions of unsymmetrical (potentially) bifunctional superenophiles. For example, the reagent **9**, *N*-(pentafluorophenyl)-*N'*-tosylsulfur diimide, compared with ditosylsulfur diimide, exhibits very greatly diminished reactivity (ca. factor of >1000 in rate reduction) in the ene reaction at bond b. The X-ray-determined structure of **9** shows[6] that the fluorinated benzene ring is *not* coplanar with the bond b orbitals and tends to sterically mask the *n* orbitals of the nitrogen at bond a from participating in any such "pseudopericyclic" process depicted in Figure 1.



9

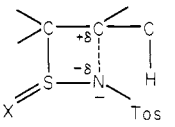
The full details of these and other arguments supporting a mechanism of the superene reaction requiring four-center preliminary complex formation,[10] from which a "pseudopericyclic" TS of nonlinear H transfer emerges, will be discussed in future publications. But this reaction scheme is not unprecedented. Thus, even homolytic processes of allylic H abstraction have been most recently shown[11] to involve the formation of an orienting complex between an abstracting *tert*-butoxy radical and the double bond, preliminary to a nonlinear H transfer occurring in a "pseudopericyclic" TS‡.

Acknowledgment. The collaboration between our laboratories in carrying out this study was made possible by a U.S. Senior Scientist award (to H.K.) of the Alexander von Humboldt Stiftung and the support of the National Science Foundation under Grant CHE-7911110. The work at Munich was supported by the Deutsche Forschungsgemeinschaft and the Fond der Chemischen Industrie; this support is gratefully acknowledged.

Registry No. 1 (R = D), 63523-01-3; (*S*)-1 (R = Me), 58717-85-4; *2* (R' = Tos), 4104-47-6; *3* (R = Me; R' = Tos), 81654-84-4.

(9) (a) Foote, C. S. *Acc. Chem. Res.* **1968**, *1*, 104. (b) Frimer, A. A.; Bartlett, P. D.; Boshung, A. F.; Jewett, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 7977. (c) See also for full discussions: Frimer, A. A. *Chem. Rev.* **1979**, *79*, 359. Gorman, A. A. *Chem. Soc. Rev.* **1981**, 205.

(10) The possibility that this complex may be better represented by a dipolar structure such as **10** or the corresponding diradical structure



10

has not as yet been resolved. Whatever the outcome, however, the evidence indicating the involvement of the lone pair on nitrogen in a "pseudopericyclic" TS of this superene reaction is unaffected by the nature of the carbon–nitrogen bonding in this complex.

(11) Kwart, H.; Brechbiel, M.; Miles, W.; Kwart, L. D., submitted for publication in *J. Org. Chem.*

(12) Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1956.

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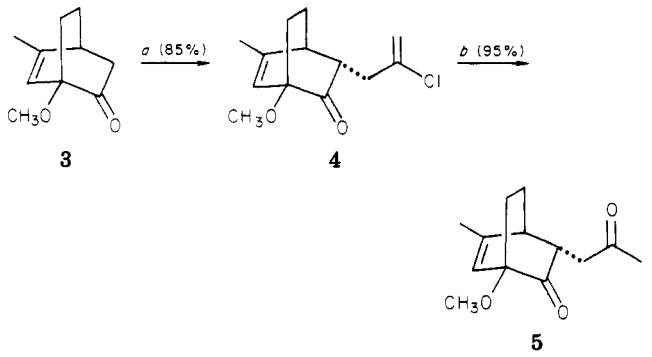
An Approach to the Quadrone Skeleton via a Tandem Aldol–Pinacol[1]

Summary: The preparation of a key tricyclic intermediate for the synthesis of quadrone has been accomplished efficiently from a bicyclo[2.2.2]octenone precursor by a regioselective rearrangement to a substituted bicyclo[3.2.1]octenedione and then generation of the tricyclic nucleus by a novel intramolecular aldol–pinacol rearrangement.

Sir: The tetracyclic lactone quadrone (1) represents a novel class of sesquiterpenes which possess significant

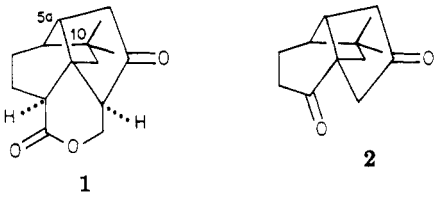
(1) This investigation was supported by Grant No. CA 26985, awarded by the National Cancer Institute, DHHS.

Scheme I



[a] (i) $(Me_3Si)_2NLi$, THF/HMPA, −78 °C; (ii) ICH_2CClCH_2, −78 °C. [b] (i) $Hg(OAc)_2$, HCOOH; (ii) 10% aqueous HCl.

antitumor properties.[2] The presence of a substituted bicyclo[3.2.1]octane moiety within the core of the quadrone skeleton suggests that a rearrangement methodology[3] for preparing these derivatives from synthetically accessible bicyclo[2.2.2]octenones might provide a facile route to the quadrone nucleus.[4] Herein we report the efficient synthesis of dione **2**, a key intermediate which incorporates the basic quadrone structural features and which contains functionality appropriate for introduction of the required δ-lactone unit.

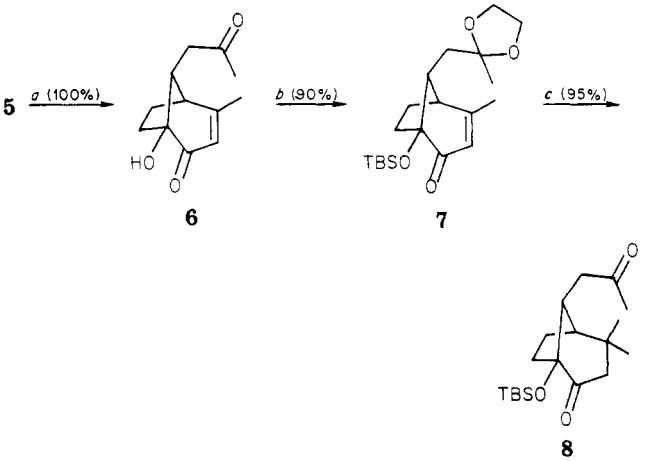


1 2

The synthesis of dione **2** can be divided into three distinct stages involving establishing the correct stereochemistry at C-5a (quadrone numbering), rearrangement to a bicyclo[3.2.1]octane nucleus and introduction of the C-10 *gem*-dimethyl group, and finally a tandem intramolecular aldol–pinacol rearrangement to give dione **2**.

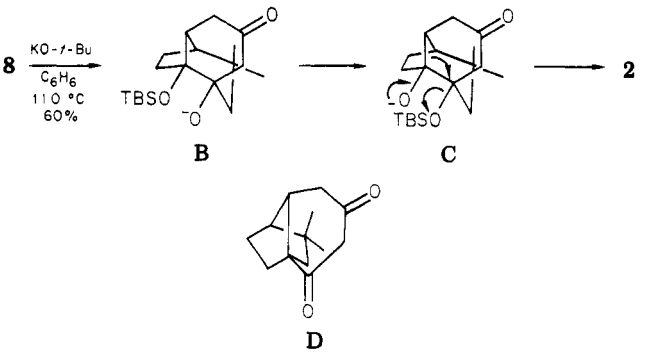
Introduction of the C-5a stereochemistry was accomplished by the low-temperature alkylation of the lithium enolate of the readily available[3a] bicyclo[2.2.2]octenone **3** with 3-iodo-2-chloropropene to give a single[5] vinyl chloride[6] **4**, which was hydrolyzed to dione[6] **5** (Scheme I). This kinetic preference for alkylation from the presumed less hindered face of **3** (i.e., syn to the double bond) may be contrasted to earlier observations[3b] that nucleophilic addition to the ketone moiety of **3** furnishes mixtures (syn/anti = ca. 2/1).

Scheme II



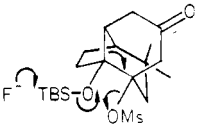
[a] HCOOH. [b] (i) $HOCH_2CH_2OH$, MsOH (cat.), Ph-H, heat: (ii) NaH, THF; (iii) *t*-$BuMe_2SiCl$ (TBSCl), THF; (iv) 10% aqueous HCl. [c] (i) Me_2CuLi, Et_2O; (ii) $(CH_3)_2CO$, MsOH (cat.).

Scheme III



Acid-catalyzed rearrangement of dione **5** afforded the more stable[7] conjugated bicyclo[3.2.1]octenedione[6] **6** in which the key syn stereochemical relationship between the methyl ketone group and the enone is maintained. After functional group protection, the *gem*-dimethyl group was introduced by conjugate addition of dimethylcopper lithium to enone[6] **7**, which upon hydrolysis furnished bicyclic dione[6] **8** in good yield (Scheme II).

The final, critical conversion of dione **8** to the target molecule **2** was envisioned via a sequence in which the key step would involve the rearrangement of an isolable intermediate such as A (see arrows). In practice, treatment



A

of dione **8** under normal aldol conditions (KO-*t*-Bu) yielded the desired tricyclic dione[6] **2** as the *single* isolable product in 60% yield[8] (Scheme III). This unique tandem aldol–

(2) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499–502.

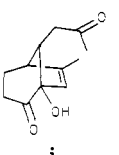
(3) Cf. (a) Monti, S. A.; Chen, S-C.; Yang, Y-L.; Yuan, S-S.; Bourgeois, O. P. *J. Org. Chem.* **1978**, *43*, 4062–4069. (b) Monti, S. A.; Chen, S-C. *Ibid.* **1979**, *44*, 1170–1172. (c) Monti, S. A.; Yang, Y-L. *Ibid.* **1979**, *44*, 897–898.

(4) For other synthesis, see (a) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262–4263; **1981**, *103*, 4136–4141. (b) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *Ibid.* **1981**, *103*, 4647–4648. (c) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *Ibid.* **1982**, *104*, 872–874.

(5) Alkylation at higher temperature furnished variable amounts of the epimeric alkylation product.

(6) This compound was fully characterized by ^1H and ^{13}C NMR, IR, high-resolution mass spectroscopy, and/or combustion analysis. Data for **2**: mp 99–100 °C; IR (CCl_4) 3000–2810, 1745, 1712 cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 1.24 (s, 3), 1.31 (s, 3), 1.70 (d, 1, J = 14.7 Hz), 1.75 (m, 1), 1.96 (d, 1, J = 14.7 Hz), 2.11 (m, 1), 2.16 (s, 1), 2.23 (d, 1, J = 18.9 Hz), 2.4–2.7 (m, 5), 2.78 (d, 1, J = 18.9 Hz).

(7) Under controlled conditions, the nonconjugated isomer i could be



i

isolated.

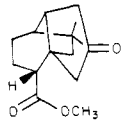
pinacol transformation appears to involve formation of the aldol product B, intramolecular silyl migration[9] to give C, and finally rearrangement[10] of the antiperiplanar carbon–carbon bond to give dione 2. The alternative pinacol-like rearrangement of intermediate B to give the bicyclo[2.2.1]heptane derivative D is apparently precluded due to steric/strain considerations.

The conversion of tricyclic dione 2, prepared from bicyclic[2.2.2]octenone 3 in 40% overall yield, into quadrone 1 and examination of the scope of this tandem aldol–pinacol transformation are in progress.

Acknowledgment. We thank Professor Steven D. Burke for generously providing a sample of tricyclic dione.

Registry No. 2, 81740-63-8; 3, 67316-12-5; 4, 81740-64-9; 5, 81740-65-0; 6, 81740-66-1; 7, 81740-67-2; 8, 81740-68-3; 3-iodo-2-chloropropene, 39557-31-8.

(8) Subsequent confirmation of this structural assignment was made by comparison (IR, ^{1}H NMR, ^{13}C NMR) of dione 2 with a sample prepared independently and generously provided by Professor S. Burke and by conversion of 2 into the epi ester ii prepared previously.[4a]



ii

(9) Jones, S. S.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2762–2764.

(10) For a silyl oxide leaving group analogy, see Monti, S. A.; Larsen, S. D. *J. Am. Chem. Soc.* **1977**, *99*, 8015–8020.

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Directed Ortho Lithiation of Isophthalonitrile. New Methodology for the Synthesis of 1,2,3-Trisubstituted Benzenes

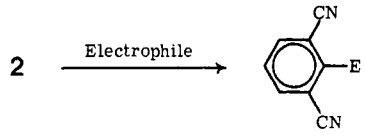
Summary: The lithiation of 1,3-dicyanobenzene with lithium diisopropylamide occurs in high yield, regiospecifically at the 2-position, to give aryllithium species stable at temperatures below −90 °C.

Sir: Directed ortho lithiations of benzenes with heteroatom-containing substituents have been extensively studied.[1,2] Cyano groups have been employed as activating groups to effect direct lithiation of thiophene,[3] selenophene,[3b] and dihydropyridines,[4] using a nonnucleophilic lithium dialkylamide as lithiating agent. Parham and Jones generated quenching products from 2-lithiobenzonitrile prepared from the halogen–metal exchange of 2-bromobenzonitrile and *n*-butyllithium at −78 °C.[5] The only reported benzonitrile to undergo directed ortho lithiation is 3-chlorobenzonitrile[2] in which a chelating effect of the chlorine can be invoked to explain the regiospecificity. The 2-lithio derivative was trapped in 30% yield with dimethyl disulfide. We report conditions for the efficient ortho lithiation of 1,3-dicyanobenzene (1), an example of ortho lithiation of a substituted benzene directed by a functional group lacking lone pairs of electrons which can plausibly be invoked in a stabilizing chelation of the lithium ion.

Although it is possible that chelation involving the π electrons of the cyano triple bond plays a role in this reaction, the π-electron density of the cyano function (in the Hückel approximation) is approximately 4 times greater at the more remote nitrogen than at the proximal carbon.[6]

The preparation of 2 by lithium–hydrogen exchange using lithium diisopropylamide (LDA) is complete within 3 min at −96 °C. The 220-MHz ^{1}H NMR spectrum of the crude product obtained by quenching the lithiation reaction mixture with CH_3OD reveals that 100% of 2 is formed.[8] When benzonitrile was subjected to the same reaction conditions, no 2-deuteriobenzonitrile was detected by ^{1}H NMR.[9]

Table I. Reaction of 2 and 4 with Electrophiles



3 - 8

electrophile	product[a]	mp, °C	% yield[b]
I_2	3, E = I	208–209	79
$(CBrCl_2)_2$	4, E = Br	189–190 (lit. 190–190.5)[c]	81
C_2Cl_6	5, E = Cl[d]	154–156	77
PhSSPh	6, E = SPh	109–110	68
$(CH_3)_3SiCl$	7, E = $(CH_3)_3Si$	86–88	83
CH_3I	8, E = CH_3	132–134 (lit. 135–136)[e]	83[f]
PhCHO	9,[g]	162–163	71

[a] Satisfactory analytical data (±0.4% for C, H, N and, when appropriate, halogen or S) were reported for all new compounds listed in the table. Compounds 3, 5, 6, and 7 gave AB_2 patterns and compound 9 gave an ABC pattern in the aromatic region of the ^{1}H NMR spectrum ($CDCl_3$, 220 MHz). [b] Isolated material, after purification. [c] Fendler, E. J.; Fendler, J. H.; Griffin, C. E.; Larsen, J. W. *J. Org. Chem.* **1970**, *35*, 287. [d] Turner, N. J.; Battershell, R. D. *Contrib. Boyce Thompson Inst.* **1970**, *24*, 203. No physical data were reported. [e] Lindsay, W. S.; Stokes, P.; Humber, L. G.; Boekelheide, V. *J. Am. Chem. Soc.* **1961**, *83*, 943. [f] This yield was obtained when a 10-fold excess of methyl iodide was added to 2. [g] Isolated after the crude reaction mixture was warmed with dilute hydrochloric acid.

(1) See, for example: (a) Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 521. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463. (c) Meyers, A. I.; Lutomski, K. *Ibid.* **1979**, *44*, 4465. (d) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457. (e) Figuly, G. D.; Martin, J. C. *J. Org. Chem.* **1980**, *45*, 3728.

(2) For a recent comprehensive review, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(3) (a) Gronowitz, S.; Eriksson, B. *Arkiv. Kemi* **1963**, *21*, 335 [*Chem. Abstr.* **1963**, *59*, 13918f]. (b) Dubus, P.; Decroix, B.; Morel, J.; Pastour, P. *Bull. Soc. Chim. Fr.* **1976**, 628.

(4) Schmidt, R. R.; Berger, G. *Chem. Ber.* **1976**, *109*, 2936.

(5) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187.

(6) Such π-electron-based chelation could more plausibly be invoked for the recently reported reaction of phenylacetylene with *n*-butyllithium and potassium *tert*-butoxide, which was postulated to give ring potassiation (Hommes, H.; Verkruijsse, H. D.; Brandsma, L. *Tetrahedron Lett.* **1981**, 2495), or the reaction of diphenylacetylene with 2 mol of *n*-butyllithium, which gives addition to the triple bond followed by ortho lithiation of the phenyl ring adjacent to the added butyl group.[7] In both cases the π-electron density in the intermediate monolithio derivative, which is subject to ring metalation, is expected to be greater at the carbon nearer the ring which is lithiated.

(7) Mulvaney, J. E.; Gardlund, Z. G.; Gardlund, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 3897.

(8) ^{1}H NMR for 1 ($CDCl_3$, 220 MHz): δ 7.96 (s, 1), 7.90 (d, 2), 7.65 (t, 1).

0022-3263/82/1947-2681$01.25/0