Total Synthesis of (±)-Quadrone

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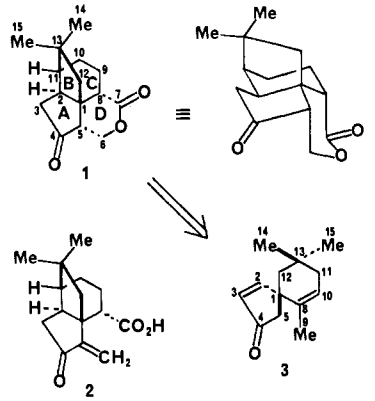
Abstract: Synthetic studies resulting in both formal and total syntheses of the cytotoxic fungal metabolite quadrone (**1**) in racemic form are described. The spiro[4.5]decadienone **3** is converted to the tricyclic carbon skeleton (**4**) of quadrone via an oxidative cleavage/Michael addition/aldol cyclization sequence. The formal synthesis, culminating with the tricyclic keto ester **14b**, proceeds from **3** in 14 steps. A partially coincident 19-step sequence provides (±)-quadrone (**1**) in 6.2% overall yield. A noteworthy aspect of this synthesis is that all carbon–carbon bond-forming reactions in the conversion **3** → **1** are intramolecular.

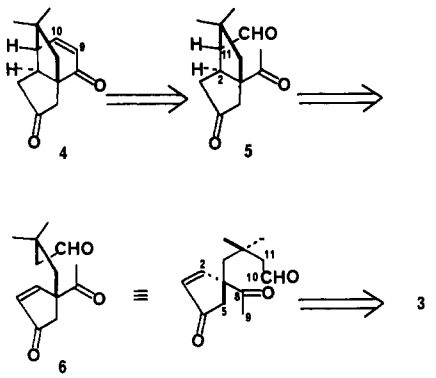
Quadrone (**1**) has provided a popular test of design and execution for synthetic organic chemists since 1978, when two reports emanated from the W. R. Grace Co. describing the isolation, structure, and biological properties of this fungal metabolite from *Aspergillus terreus*.[1] We,[2] among others,[3] yielded to the combined temptations offered by the structural challenge and the cytotoxic properties of this *quad*icyclic ket*one*, and began a program directed at the total synthesis of (±)-quadrone (**1**).



The biological incentive behind our involvement was the reported cell-growth inhibitory activity of quadrone.[1,4] At first inspection, these cytotoxic properties are somewhat surprising in that the quadrone molecule is devoid of the electrophilic functionality common in sesquiterpene antitumor agents.[5] There arose general speculation[3a,6] that quadrone may actually serve as a progenitor of the α-methylene ketone **2**, a more plausible cytotoxic agent. The prescience of both Danishefsky[3a] and Helquist[3b] in preparing the α-methylene ketone **2** in the penultimate stages of their syntheses was underscored by the recent isolation of **2**, christened terrecyclic acid A, from a different strain of *A. terreus* and the observation that **2** shows significantly greater acute toxicity than quadrone itself.[7]

The most striking structural features of the quadrone molecule are the unusual system of four rings and the five contiguous asymmetric centers. To date, quadrone (**1**) and terrecyclic acid A (**2**) are the only natural products known to possess this carbon skeleton. Two bicyclooctane structural subunits are in evidence; rings AB constitute a cis-fused bicyclo[3.3.0]octane system, while rings BC describe a bicyclo[3.2.1]octane system. Although each of these bicyclic subunits is widely represented among natural products (e.g., the cedrane, gymnomitrane, hirsutane, isocomane, kaurane, and gibberellane skeletons), the C(8)–C(10) propano bridge across the exo face of the former and the C(3)–C(5) fusion to the one-carbon bridge in the latter are distinctive. The five

Scheme I



centers of asymmetry are evenly distributed about the structure, such that the four rings contain four, three, three, and three stereocenters, respectively. Four of the asymmetric carbon atoms in **1** are neopentyl centers; the fifth is a quaternary carbon. Our attention was focused upon this quaternary center of asymmetry [C(1) in **1**] in that it is common to each of four rings.

Experimental reality compelled us to employ a route in which *all* new carbon–carbon bonds were formed by *intramolecular* delivery. Described herein with full details are the formal and total syntheses of (±)-quadrone (**1**) from the spiro[4.5]decadienone **3**, which was readily available in large quantities from a previous

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(1) (a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499. (b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38.

(2) (a) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *J. Am. Chem. Soc.* **1982**, *104*, 872. (b) Burke, S. D.; Murtiashaw, C. W.; Oplinger, J. A. *Tetrahedron Lett.* **1983**, *24*, 2949.

(3) (a) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136. (b) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *Ibid.* **1981**, *103*, 4647. (c) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *Ibid.* **1982**, *104*, 5808. (d) Takeda, K.; Shimono, Y.; Yoshii, E. *Ibid.* **1983**, *105*, 563. (e) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146. (f) Dewanckele, J. M.; Zutterman, F.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3235. For approaches to the synthesis of quadrone, see: (g) Smith, A. B., III; Wexler, B. A.; Slade, J. *Tetrahedron Lett.* **1982**, *23*, 1631. (h) Monti, S. A.; Dean, T. R. *J. Org. Chem.* **1982**, *47*, 2679. (i) Paquette, L. A.; Annis, G. D.; Schostarez, H. *J. Am. Chem. Soc.* **1982**, *104*, 6646.

(4) Quadrone showed activity in vitro against human epidermoid carcinoma of the nasopharynx (KB, ED_{50} 1.3 μg/mL) and in vivo against P388 lymphocytic leukemia in mice. The intraperitoneal LD_{50} value in mice was found to be >340 mg/kg.[1b]

(5) (a) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147. (b) Kupchan, S. M.; *Fed. Proc.* **1974**, *33*, 2288.

(6) See ref 16 in Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III *J. Am. Chem. Soc.* **1980**, *102*, 3904.

(7) (a) Nakagawa, M.; Hirota, A.; Sakai, H.; Isogai, A. *J. Antibiot.* **1982**, *35*, 778. (b) Hirota, A.; Nakagawa, M.; Sakai, H.; Sakai, H.; Isogai, A. *Ibid.* **1982**, *35*, 783. The intraperitoneal LD_{50} value in mice was found to be between 125 and 63 mg/kg.

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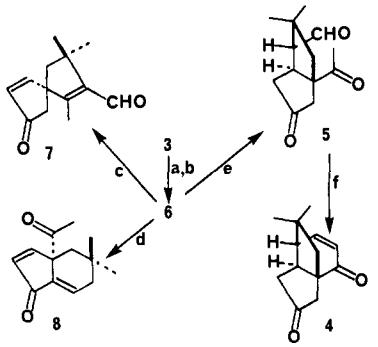
Scheme II



(a) OsO_4 (catalytic), *N*-methylmorpholine *N*-oxide, 1:1 acetone/H_2O. (b) $NaIO_4$ (8 equiv), 1:1 THF/H_2O. (c) $TiCl_4$, TAMA,[12] THF, $-35 \rightarrow 25$ °C. (d) *p*-TsOH (catalytic), PhH, reflux. (e) morpholine (2 equiv), *p*-TsOH, PhH, reflux. (f) KOH (powdered), dibenzo-18-crown-6, PhH, reflux.

study in our laboratories.[8] Note that in the spiro[4.5]decadienone **3** the numerical correlations with the carbon atoms in **1** are shown, with the center of spiro fusion corresponding to the central quaternary C(1) site in the target.

The antithetic strategy relating the carbon skeleton of quadrone to the starting material **3** is put forth in Scheme I. The divestment of the D-ring δ-lactone and an adjustment of oxidation level in the C-ring simplified **1** to the tricyclic enedione **4**, which represented the carbon skeleton subgoal. Scission of the C(9)–C(10) bond in **4** by application of a retro-aldol transform leads to the functionalized bicyclo[3.3.0]octane system **5**. This leads in turn to the γ,γ-disubstituted cyclopentenone **6** upon application of the indicated retro-Michael cleavage of the C(11)–C(2) bond.

In the synthetic sense (Scheme II), conversion of **3** to **6** was initially achieved by ozonolysis in the presence of pyridine,[9] while carefully monitoring the disappearance of the starting material by TLC. However, the product obtained was only ~95% pure by NMR analysis and suffered extensive degradation upon attempted silica gel chromatography. We turned to a two-stage process involving vicinal diol formation and oxidative cleavage as discrete steps. The first of these was accomplished with a catalytic amount of OsO_4, fueled by a variety of reoxidants such as $NaIO_4$, $NaClO_3$, and (most effectively) *N*-methylmorpholine *N*-oxide.[10] The crystalline mixture of diastereomeric diols was cleaved with $NaIO_4$ (8 equiv, 1:1 THF/H_2O). Rapid chromatography on silica gel provided a 97% overall yield of the cyclopentenone **6**.

The synthetic conversion of **3** → **6** → **5** → **4** required a sequence of oxidative cleavage, Michael addition, and aldol cyclization steps. Although it was obvious that the latent functional reactivity at C(2), C(5), C(8), C(9), C(10), and C(11) in **3** would be unleashed in **6**, it was not clear how these various electrophilic and nucleophilic sites would interact.

In practice, reactivity along three distinct pathways was observed (Scheme II), as detailed elsewhere.[11] We had envisioned a one-pot conversion of **6** (MW 222) to **4** (MW 204) via a tandem Michael addition/aldol cyclization, resulting in a net dehydration. When **6** was subjected to a mixture of $TiCl_4$ and *N*-methylanilinium trifluoroacetate (TAMA)[12] in THF (−35 → 25 °C, 8 h), the crystalline spiro[4.4]nonadiene **7** (mol wt 204, mp 108–111 °C) was formed in 50% yield. Under a second set of conditions (*p*-TsOH, PhH, reflux), **6** was converted to a mixture of the tetrahydrindenone **8** (45%, mol wt 204, mp 65–67 °C) and **7** (15%). In short, although products of net dehydration could be formed directly, the desired tricyclic enedione **4** was not among them. However, a third set of reaction conditions [morpholine (2 equiv), *p*-TsOH, PhH, reflux, 11 h] afforded the Michael addition product, formulated as **5**, in 92% yield.

Two disturbing uncertainties regarding the *cis*-fused bicyclo[3.3.0]octane product **5** and its conversion to the tricyclic enedione **4** remained. Clearly, the conversion **5** → **4** required that the formyl residue at C(11) have an exo orientation, on the same (convex) side of the bicyclic framework as the angular acetyl group. Although the ^1H (400 MHz) and ^{13}C NMR data clearly indicated that **5** was a single isomer, homonuclear ($^3J_{H2-H11}$)[13] and heteronuclear ($^3J_{H11-C10}$)[14] coupling constants of 11.20 and 5.40 Hz, respectively, were inconclusive with respect to this exo/endo ambiguity at C(11). In addition, examination of molecular models of **5** in the desired C(11) configuration revealed an exceptionally long internuclear distance between the C(9) and C(10) reactive centers. This, in concert with the high rigidity of the cis-fused bicyclo[3.3.0]octane framework, cast some doubt on the aldol closure to give **4**. Single-crystal X-ray diffraction analysis of the bicyclic substance **5** showed that the requisite C(11) configuration was present.[15] However, the internuclear distance between C(8) and C(10) was 4.75 Å in the crystal. Little reassurance regarding the critical C(9)–C(10) closure could be gleaned from these data.

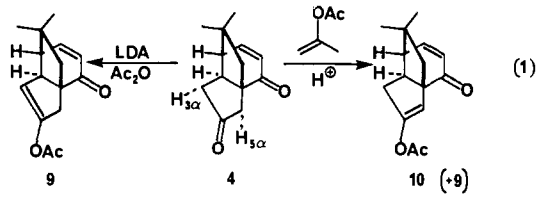
Attempted intramolecular aldolization of **5** under a variety of standard conditions was uniformly unsuccessful. Neither secondary amine/acetic acid combinations nor hydroxide or alkoxide bases in hydroxylic solvents and mixtures thereof ever gave evidence of the production of the tricyclic enedione **4**. However, upon treatment of **5** with lithium hydroxide solubilized in refluxing benzene with a phase-transfer catalyst (Adogen 464),[16] a new UV-active substance was formed in modest yield. Carbonyl stretching frequencies at 1740 and 1680 cm^{-1}, a prominent parent ion at *m/e* 204 in the mass spectrum, and olefinic resonances in the ^1H NMR spectrum at δ 7.29 (1 H, dd, J = 9.6, 9.3 Hz) and at δ 5.90 (1 H, d, J = 9.6 Hz) all suggested that this crystalline product (mp 59–61 °C) was the elusive tricyclic enedione **4**. Optimization of the reaction parameters (finely ground KOH, dibenzo-18-crown-6, refluxing benzene, high dilution) allowed the ready conversion of **5** → **4** in yields as high as 96%.[17]

It was felt that the tricyclic substance **4** was especially attractive for further elaboration in that the two carbonyls would be chemically differentiable by enolization or enolate formation. Enolization of the cyclohexenone unit would be precluded by the bridgehead nature of the derived intermediate.[18] Selective involvement of the cyclohexenone carbonyl would be possible by "protecting" the cyclopentanone as its enolate.[19]

The hydrogens flanking the C(4) carbonyl on the less hindered face of the enedione **4** are shown in eq 1. We had felt that $H_{5\alpha}$ could be selectively removed over $H_{3\alpha}$ based on a stereoelectronic argument similar to that recently demonstrated by Stork.[20] This would have allowed a selective functionalization at C(5) via the enolate. Inspection of molecular models revealed that in the highly

(8) Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Strickland, S. M. S.; Saunders, J. O. *J. Org. Chem.* **1981**, *46*, 2400.
(9) Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.
(10) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(11) Burke, S. D.; Murtiashaw, C. W.; Dike, M. S. *J. Org. Chem.* **1982**, *47*, 1349.
(12) Gras, J.-L. *Tetrahedron Lett.* **1978**, 2111.
(13) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.
(14) (a) Aydin, R.; Loux, J.-P.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 449. (b) Hansen, P. E. *Prog. Nucl. Magn. Reson. Spectrosc.* **1981**, *14*, 175.
(15) We are indebted to Dr. Lukasz Lebioda of this department for this structure determination.
(16) Kieczykowski, G. R.; Pogonowski, C. S.; Richman, J. E.; Schlessinger, R. H. *J. Org. Chem.* **1977**, *42*, 175.
(17) For pertinent reviews of phase-transfer chemistry, see: (a) Dehmlow, E. V. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 170. (b) Gokel, G. W.; Durst, H. D. *Aldrichimica Acta* **1976**, *9*, 3. Although yields exceeded 90% in several runs, a more representative yield of 84% is reflected in the Experimental Section.
(18) (a) Buchanan, G.-L. *Chem. Soc. Rev.* **1974**, *3*, 41. (b) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 464.
(19) For examples of this form of carbonyl protection, see: (a) Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 4262. (b) Kieczykowski, G. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 1938. (c) Barton, D. H. R.; Hesse, R. H.; Wilshire, C.; Pechet, M. M. *J. Chem. Soc., Perkin Trans.* **1977**, 1075. (d) Goldsmith, D. J.; Lewis, A. J.; Still, W. C. *Tetrahedron Lett.* **1973**, 4807.
(20) (a) Stork, G.; Still, W. C.; Singh, J. *Tetrahedron Lett.* **1979**, *5077*. For a similar example, see: (b) ref 7 in Quallich, G. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 7627.

rigid framework of **4**, the C(5)–$H_{5\alpha}$ bond has a much higher degree of overlap with the flanking carbonyl π system than does the C(3)–$H_{3\alpha}$ bond. On the basis of a stereoelectronic argument, one would therefore predict a greater kinetic acidity for $H_{5\alpha}$. In fact, kinetic deprotonation of **4** with lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C followed by an acetic anhydride quench gave a single product. Extensive homonuclear decoupling in the ^{1}H NMR spectrum at 400 MHz revealed that this product was the undesired $\Delta^{3,4}$-enol acetate **9**. Evidently steric factors invalidate the stereoelectronic argument in this case. Although enol acetylation under thermodynamic conditions with isopropenyl acetate/H_2SO_4 in refluxing benzene gave a 1:1 mixture of **9** and the desired $\Delta^{4,5}$-enol acetate **10** (eq 1), this was not considered useful and was not pursued.

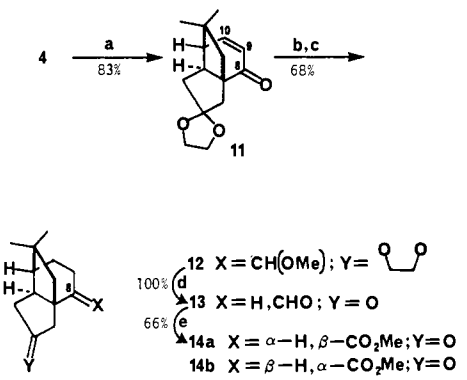


9 4 10 (•9) (1)

With the failure of this initial strategem for selective functionalization at C(5), we sought to complete a formal total synthesis of (±)-quadrone before mounting a second attempt at the regioselective construction of the δ-lactone unit bridging C(5) and C(8). Since Danishefsky[3a] had by this time completed a total synthesis via the tricyclic keto ester **14b** (Scheme III), our interim goal appeared to be close at hand. The conversion of **4** to the gross structure **14** would require only the removal of the C(9)–C(10) unsaturation and a reductive homologation at C(8). However, it quickly became clear that the latter requirement would not be so easily met.

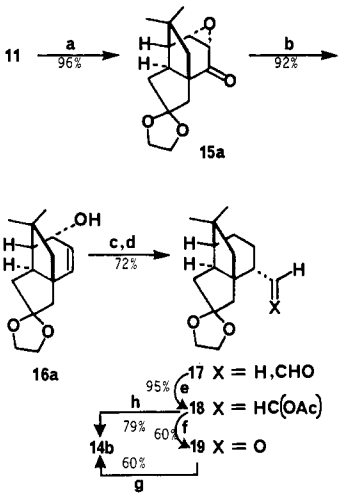
Selective ketalization (Scheme III) of **4** under standard conditions gave **11** (mp 81–83 °C) in 83% yield, together with a 13% recovery of starting material. Catalytic hydrogenation of the C(9)–C(10) olefin in **11** gave the corresponding saturated ketone (mp 58–60 °C) in 99% yield. The neopentyl C(8) carbonyl in **11** and in the derived saturated ketone proved to be resistant to attack by a number of nucleophiles, including 2-lithio-2-trimethylsilyl-1,3-dithiane,[21] methoxymethylenetriphenylphosphorane,[22] dimethylsulfonium methylide,[23] and the organolithium reagent derived from chloromethyltrimethylsilane.[24] In contrast, 1-(diphenylphosphonio)-1-methoxymethyllithium[25] proved to be a capable nucleophile in these systems. Reaction of the latter with the saturated derivative of **11**, followed by alkoxide quenching with MeOH and quaternization with iodomethane, gave an oily mixture of enol ethers **12** in 68% yield. There was also recovered a 32% yield of starting ketone, presumably reflecting competing enolate formation. Hydrolysis of the enol ether and ketal functions in **12** was accomplished in near-quantitative yield with aqueous HCl. Although analysis of the aldehyde **13** by ^{13}C NMR indicated that a single diastereomer was present, the C(8) stereochemistry was not discernible at this stage. Oxidation of **13** with Jones reagent gave the corresponding carboxylic acid (mp 155–157 °C) in high yield. Esterification with ethereal diazomethane gave a keto ester of gross structure **14** as an oil. Although this too was clearly a single diastereomer, we were concerned about the stereochemistry at C(8). In the ^{1}H NMR spectrum of **14** at 400 MHz there was observed a doublet of doublets (J = 11.77, 6.25 Hz) at δ 2.63. This pattern for the C(8) methine hydrogen was clearly consistent with the unwanted C(8) configuration exemplified by structure **14a**. In addition, Danishefsky had reported **14b** as a crystalline solid, and had

Scheme III



(a) ethylene glycol (1.2 equiv), p-TsOH (catalytic), PhH, reflux. (b) H_2 (1 atm), 5% Pd/C, EtOH, 25 °C. (c) $PH_2PCHOCH_3$, THF, −95 → 25 °C. (d) 3:1 THF/5% aqueous HCl, acetone, 25 °C. (e) Jones reagent, 0 → 25 °C; CH_2N_2, Et_2O, 0 → 25 °C.

Scheme IV



(a) t-BuOOH, NaOH, MeOH, H_2O, 25 °C. (b) $H_2NNH_2 \cdot xH_2O$, MeOH, HOAc. (c) Ethyl vinyl ether, $Hg(OAc)_2$; 240 °C, 4 h, o-xylene, diisopropylethylamine, sealed tube. (d) H_2 (1 atm), 5% Pd/C, abs EtOH, 25 °C. (e) Ac_2O, KOAc, reflux, 1.5 h. (f) OsO_4 (catalytic), $NaIO_4$ (8 equiv), 1:1 THF/H_2O, 25 °C. (g) Jones reagent, 0 → 25 °C; CH_2N_2, Et_2O, 0 → 25 °C. (h) $RuCl_3 \cdot 3H_2O$, (catalytic), $NaIO_4$ (8 equiv), $CCl_4/CH_3CN/H_2O$, 25 °C, 2 h; CH_2N_2, Et_2O, 0 → 25 °C.

generated **14a** as a minor product.[3a] Direct comparison by high-field ^{1}H NMR of our sample and authentic **14b** confirmed that the wrong C(8) epimer, **14a**, had been generated. A variety of attempts to epimerize **14a** to **14b** were uniformly unsuccessful, thus forcing us to discontinue this route.

The ultimately successful method for the introduction of the contrathermodynamic (axial) carbon substituent at C(8) for the completion of both the formal and total syntheses of (±)-quadrone is outlined in Scheme IV. It was reasoned that the enone moiety in **11** could serve as the locus for successive allylic rearrangements, the first of which would establish an axial C(10) α-oxygen substituent. This C(10)–O linkage could then serve to deliver, in an intramolecular sense, the C(8) α-oriented carbon substituent via a second allylic transposition. Critical to the success of this strategy was the steric shielding of the β-face of the enone unit in **11** by the C(1) to C(11) ethano bridge bearing the occlusive geminal methyl groups. Thus, conjugate epoxidation of **11** with basic t-BuOOH in aqueous methanol[26] gave a single product (mp 91–92 °C), formulated as the epoxy ketone **15a**, in 96% yield.

The first allylic transposition was efficiently accomplished (92%) *on a small scale* with hydrazine hydrate in MeOH/HOAc[27] to

(21) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.
(22) (a) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150. (b) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373.
(23) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(24) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536.
(25) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.
(26) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.

give the allylic alcohol **16a** (mp 69–71 °C). However, all attempts to scale this procedure up resulted in drastically reduced yields of **16a**; the reaction was repeated on small scale to accumulate sufficient material to proceed. The resulting α-oriented hydroxyl group at the C(10) position was properly situated for the delivery of a C(8) α-oriented carbon substitutent by a second allylic transposition.

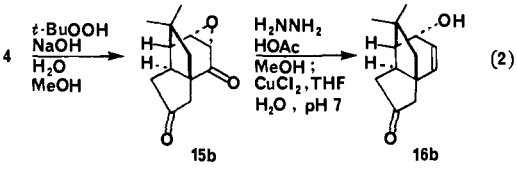
Several methods existed which seemed appropriate for the delivery of a single carbon to C(8) via a [2,3] sigmatropic rearrangement. Attempted application of Still's method[28] for the conversion of allylic alcohols to transposed homoallylic alcohols failed in this case, as did Büchi's method[29] for the transpositive conversion of allylic alcohols to β,γ-unsaturated amides. A final attempt at effecting a [2,3] sigmatropic delivery of the C(8) carbon substituent employed the sequence developed by Nakai,[30] involving the dianion of an α-allyloxyacetic acid. This also failed to provide detectable amounts of the desired rearrangement product. We believe that the failure of these [2,3] sigmatropic rearrangements is related to the lack of conformational mobility in the bridged cyclohexene unit common to the rearrangement substrates derived from **16a**.

Attempts to utilize [3,3] sigmatropic rearrangement methods to deliver two carbons to the C(8) site in **16a** also met with initial failure. Whitesell's method[31] for the synthesis of β-γ-unsaturated esters involves the enolate Claisen rearrangement of esters derived from allylic alcohols and methoxyacetyl chloride. In our case, attempted rearrangement via such an ester enolate derived from **16a** was thwarted by an elimination process which resulted in the regeneration of the **16a**. Similarly, the variants of the Claisen rearrangement developed by Eschenmoser and Meerwein (amide acetal)[32] and by Johnson (orthoester)[33] were not successful in this case.

Success was achieved with the most classical form of the Claisen rearrangement.[34] Conversion of the allylic alcohol **16a** to the corresponding allyl vinyl ether and thermolysis in a sealed tube in *o*-xylene in the presence of Hünig's base proceeded at 240 °C to give the γ,δ-unsaturated aldehyde. Hydrogenation over 5% Pd/C afforded the acetaldehyde derivative **17** in 78% overall yield from **16a** (Scheme IV). Thus the reluctant C(8)–C(7) α-oriented bond had been introduced by the sequential allylic transposition strategy as originally formulated.

In order to complete the formal synthesis of (±)-quadrone it was necessary to effect a net oxidative decarbonylation of the acetaldehyde unit in **17** to lead, after deketalization, to the keto ester **14b**. This conversion was accomplished in two ways (Scheme IV). Upon treatment with $Ac_2O/KOAc$,[35] **17** afforded an oily mixture of enol acetates **18** in 95% yield. In one pathway, the enol acetate unit was oxidatively cleaved with $OsO_4/NaIO_4$ to provide the homogeneous aldehyde **19** as an oil in 60% yield.[36] Jones oxidation gave the corresponding carboxylic acid, with concomitant deketalization. Esterification with ethereal diazomethane gave **14b** (mp 47–49 °C; lit.[3a] 49–51 °C) in 60% overall yield. This material proved to be identical by IR spectroscopy, MS, TLC, and 400-MHz ^1H NMR spectroscopy with an authentic sample. A more streamlined **18** → **14b** transformation utilizing $RuCl_3 \cdot H_2O/NaIO_4$ in $CCl_4/CH_3CN/H_2O$[37] resulted in the cleavage of the enol acetate double bond, upward adjustment to the carboxylic acid oxidation state, *and* deketalization. The crude carboxylic acid thus obtained was esterified as before to give **14b** in 79% yield from **18**.

In addition, direct epoxidation of the tricyclic enedione **4**, again with basic *t*-BuOOH,[26] gave the epoxy diketone **15b** (mp 119–120 °C) in 95% yield (eq 2). Subjection of **15b** to the conditions of the Wharton reaction[27] as before gave intractable, highly polar material which was not characterized. However, a workup procedure in which this crude product was stirred in aqueous THF in the presence of pH 7 phosphate buffer and $CuCl_2$[38] afforded the desired product **16b** (69%). Presumably, the cyclopentanone carbonyl suffers hydrazone formation and is liberated by the hydrolytic workup.



(2)

With the formal synthesis thus completed, we turned to the problem of how to convert the functionalized tricyclic substance **17** into quadrone itself. It should be noted that in **17** (Scheme IV), we had available the correct number of carbon atoms necessary for the production of the target (disregarding the ketal carbons). Although the oxidative dehomologation sequence described above was successful for the formal total synthesis, we were dissatisfied with the excision of a carbon atom from **17**, only to face the nontrivial introduction of the incipient C(6) carbon at the C(5) site. It seemed possible that the aldehyde residue in **17** could be delivered intramolecularly to C(5), thus offering a potential solution to the regio- and stereochemical problems associated with the α-functionalization of the C(4) carbonyl (vide supra).[39]

The requirements for the conversion of **17** to (±)-quadrone (**1**) were as follows: (a) the formation of the C(5)–C(6) bond, with the aldehyde carbon serving as C(6); (b) the upward and downward adjustments of oxidation state, respectively, at the incipient C(7) and C(6) sites; (c) the disconnection of these two carbons in **17** and their reattachment through oxygen to give the requisite δ-lactone D-ring.

Deketalization of **17** with aqueous acid gave the keto aldehyde **20** (mp 77–79 °C) in 86% yield (Scheme V). Intramolecular aldol cyclization of **20** proceeded at ambient temperature in glacial acetic acid containing a small amount of H_2SO_4. The resulting mixture of diastereomeric β-acetoxy ketones **21a,b**, obtained in 79% yield, was judged by ^1H NMR analysis to favor **21a** by a 4:1 ratio.[40] This mixture was subjected to pyrolysis in a sealed tube at 400 °C for 4 min, yielding a mixture of the desired β,γ-unsaturated ketone **22a** (61%) and the conjugated enone **22b** (33%).[41] The major isomer was reduced by ethereal lithium aluminum hydride to give the C(4) alcohol, which was directly protected as the *tert*-butyldimethylsilyl (TBS) ether **23**.[42] It should be noted that, although a single diastereomer resulted from the reduction step, the relative configuration at C(4) in **23** was

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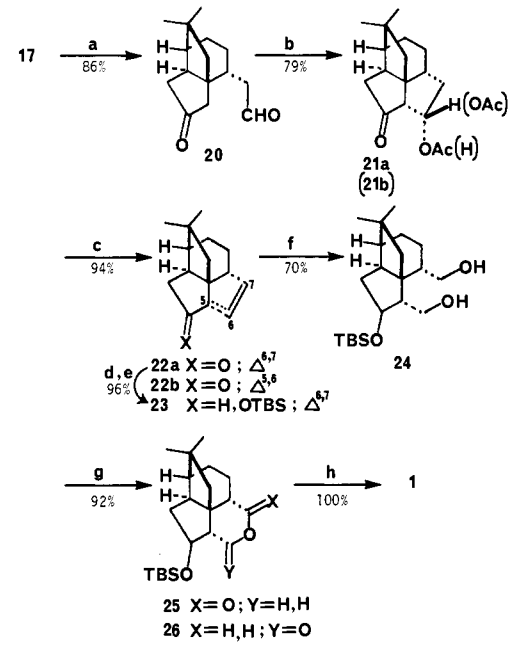
(37) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(38) (a) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 3667. (b) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054.
(39) Danishefsky[3a] and Helquist[3b] had already observed intermolecular α-functionalization of the cyclopentanone in similar systems to occur either with the wrong regiochemistry [at C(3), not C(5)] or with the wrong stereochemistry [β at C(5)].
(40) When the aldolization was effected under basic conditions (K_2CO_3, MeOH, 25 °C), the ratio of **21a**:**21b**, obtained after acetylation, was reversed to 1:2.
(41) When the acetate mixture described above[40] was subjected to pyrolysis under these conditions, the α,β-unsaturated ketone **22b** was formed in preponderance.
(42) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Scheme V



(a) 2 M aqueous HCl, acetone, 25 °C, 3 h. (b) HOAc, H_2SO_4, 25 °C, 27 h. (c) neat, sealed tube, 400 °C, 4 min. (d) $LiAlH_4$, Et_2O, −25 → 25 °C, 1 h. (e) *t*-$BuMe_2SiCl$ (2 equiv), imidazole (4 equiv), DMF, 25 °C, 2.5 h. (f) O_3, 1:1 CH_2Cl_2/MeOH, −78 °C; Me_2S, −78 → 25 °C; $NaBH_4$, EtOH, 0 → 25 °C. (g) Ag_2CO_3-Celite (5 equiv), PhH, reflux, 40 min. (h) Jones reagent, acetone, 0 → 25 °C, 1 h.

not determined. Since this center was subsequently reoxidized, this was of little practical importance.

At this stage, certain of the stated requirements for the conversion **17** → **1** had been satisfied in full or in part. The C(5)–C(6) connection had been made and the readjustment of the C(6) and C(7) oxidation states had been partially accomplished. The remaining requirements followed directly.

Cleavage of the C(6)–C(7) olefinic linkage in **23** with ozone followed by a reductive workup with sodium borohydride gave the crystalline diol **24** (mp 139–140 °C) in 70% yield. In the penultimate step of the total synthesis, oxidation of the diol **24** with Fetizon's reagent (Ag_2CO_3 on Celite)[43] in refluxing benzene gave in 92% yield a 1:1 mixture of the regioisomeric lactones **25** (mp 139–140 °C) and **26** (mp 76–78 °C). A variety of attempts, including oxidation with pyridinium chlorochromate,[44] pyridinium dichromate,[45] nickel(II) benzoate/Br_2,[46] and PtO_2/O_2,[47] all failed to enhance the ratio of **25**/**26**. The mixture of lactone regioisomers was easily separated by chromatography on silica gel, and **25** was exposed to Jones reagent. This resulted in the hydrolysis of the TBS ether and oxidation of the resultant alcohol to give (±)-quadrone (**1**), (mp 139–140 °C; lit.[3a] 140–142 °C) in quantitative yield. The racemic quadrone so produced was identical by IR spectroscopy, MS, TLC, and 400-MHz ^1H NMR spectroscopy with a sample provided by Professor Danishefsky.

In summary, the spiro[4.5]decadienone **3** was converted in 14 steps to the tricyclic keto ester **14b**,[3a] thus completing a formal total synthesis of (±)-quadrone. A partially coincident 19-step sequence was employed to transform **3** into (±)-quadrone (**1**) in 6.2% overall yield. A noteworthy aspect of this **3** → **1** conversion is that *all* carbon–carbon bond-forming reactions were *intramolecular* in nature. Finally, it must be conceded that, although a method was developed by which the δ-lactone moiety was appended to the C(5) position without interference from the C(3) site,[39] our inability to produce the desired δ-lactone in preponderance from the pseudosymmetrical diol **24** serves to vilify this approach.

Experimental Section

General Procedures. Melting points were recorded on a Büchi capillary melting point apparatus. Melting and boiling points are uncorrected. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 90 or 400 MHz as indicated. Chemical shifts for proton and carbon resonances are reported in parts per million (δ) relative to Me_4Si (δ 0.0).

Analytical thin-layer chromatography (TLC) was done on Analtech TLC plates precoated with silica gel GHLF (250-μm layer thickness). Column chromatography was done on E. Merck silica gel 60 (70–230 mesh ASTM).

Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl immediately before use. Benzene and toluene were dried over sodium ribbon. Methylene chloride (CH_2Cl_2) was passed through a column of alumina. Ethyl vinyl ether and xylenes were distilled from sodium just prior to use.

Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ.

4-(2,2-Dimethyl-4-oxo-*n*-butyl)-4-(1-oxoethyl)cyclopent-2-en-1-one (6). A solution of 1.70 g (8.94 mmol) of the spirodienone **3**[8] in 115 mL of acetone and 115 mL of distilled H_2O at room temperature was treated first with 5 mg of OsO_4 and then with 1.45 g (14.0 mmol) of *N*-methylmorpholine *N*-oxide (NMO).[10] The resulting solution was allowed to stir at room temperature for 13 days, during which time three extra portions of OsO_4 (2 mg) and NMO (0.5 g) were added at 4-day intervals. On the 14th day a slurry of 5.5 g of sodium dithionite and 5.5 g of Florisil in 25 mL of distilled H_2O was added, and the solution was stirred vigorously for 1 h and filtered. The filtrate was saturated with NaCl and extracted seven times with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to furnish 2.0 g of a mixture of diol diastereomers which solidified slowly on standing. Further purification was unnecessary.

To a solution of 2.0 g (8.9 mmol) of the diol mixture in 130 mL of THF and 130 mL of distilled H_2O at room temperature was added 15.3 g (8 equiv) of $NaIO_4$. The initially clear solution was stirred at room temperature for 11 h, eventually producing a voluminous white precipitate. This suspension was saturated with NaCl and extracted six times with ether. The combined ether extracts were dried with $MgSO_4$, filtered, and concentrated to give 1.93 g (97%) of the cyclopentenone **6** as a light yellow unstable oil: R_f 0.4 (ether); IR (film) 3020, 2005, 2961, 2935, 2875, 2839, 2740, 1722, 1710, 1588, 1467, 1408, 1390, 1370, 1357, 1295, 1225, 1180, 1150, 1060, 840, 800 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.81 (t, 1 H, J = 2.7 Hz), 7.77 (d, 1 H, J = 5.7 Hz), 6.17 (d, 1 H, J = 5.7 Hz), 2.62 (AB q, 2 H, J_{AB} = 18.3 Hz, $\Delta\nu_{AB}$ = 47.0 Hz), 2.36 (d, 2 H, J = 2.1 Hz), 2.22 (s, 3 H), 2.10 (s, 2 H), 1.11 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 206.48, 206.25, 201.66, 165.22, 133.14, 61.41, 55.71, 48.22, 44.19, 34.24, 28.20, 27.83, 26.35; MS (70 eV) parent 222, base peak 95.

3,3a,4,5,6,6aα-Hexahydro-3aα-acetyl-5,5-dimethyl-6α-formyl-2-(1*H*)-pentalenone (5). To a solution of 174 mg (0.78 mmol) of **6** in 20 mL of dry benzene at room temperature was added 137 mg (2 equiv) of morpholine. The resulting solution was stirred at room temperature for 11 h, treated with 1 mg of *p*-TsOH, and then heated at reflux under a Dean–Stark trap for 3 h. The reaction was cooled to room temperature and stirred with 3 mL of distilled H_2O for 3 h, followed by extraction (five times) with ether. After the combined organic phases were dried ($MgSO_4$), filtered, and concentrated, column chromatography on silica gel (elution with 3:1 ether–hexanes) afforded 164 mg (92%) of the crystalline diketo aldehyde **5**, melting at 68–70 °C: R_f 0.47 (ether); IR ($CHCl_3$) 3022, 2958, 2930, 2870, 2822, 2729, 2380, 1742, 1713, 1460, 1402, 1390, 1372, 1356, 1304, 1228, 1162, 1140, 1088, 1036, 1017, 975, 941, 908, 882, 857, 838, 805, 682, 645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, 1 H, J = 2.2 Hz), 3.64 (ddd, 1 H, J = 11.20, 10.17, 1.65 Hz), 2.72 (d, 1 H, J_{gem} = 18.67 Hz), 2.60 (ddd, 1 H, J = 19.25, 9.35, 1.10 Hz), 2.40 (d, 1 H, J_{gem} 13.75 Hz), 2.33 (dd, 1 H, J = 11.20, 2.20 Hz), 2.26 (dd, 1 H, J = 18.67, 1.65 Hz), 2.25 (s, 3 H), 2.14 (d, 1 H, J_{gem} = 19.25 Hz), 1.78 (d, 1 H, J_{gem} = 13.75 Hz), 1.31 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.07 (C), 208.45 (C), 201.98 (CH), 67.77 (CH), 60.10 (C), 53.02 (CH_2), 48.93 (CH_2), 43.31 (C), 42.43 (CH_2), 40.64 (CH), 29.02 (CH_3), 25.53 (CH_3), 23.70 (CH_3); MS (70 eV) parent 222, base peak 43. An analytical sample was obtained by recrystallization from hexanes.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.32; H, 8.08.

(1*R,5*S**,6*S**)-11,11-Dimethyltricyclo[4.3.2.0^{1,5}]undec-7-ene-3,9-dione (4).**[48] To a rapidly stirring solution of 1.045 g (4.70 mmol) of the

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(44) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(45) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(46) Doyle, M. P.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 4806.
(47) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899.

diketo aldehyde **5** in 1800 mL of dry benzene was added a finely ground suspension of KOH (three pellets) in 5 mL of benzene. Dibenzo-18-crown-6 (30 mg) was added and the mixture was heated at reflux for 3.25 h, then cooled to room temperature. To this golden yellow solution was then added 30 mL of saturated aqueous NH_4Cl and the resulting mixture was allowed to stir at room temperature for 3 h. After decanting the benzene, the remaining aqueous portion was extracted five times with ether, combining the ether extracts with the benzene for drying ($MgSO_4$) and filtration. Upon concentration, the resulting oily solid was dissolved in a small amount of $CHCl_3$ and chromatographed on silica gel (8:5 ether–hexanes) to provide 0.806 g (84%) of the white crystalline enedione **4**, melting at 59–61 °C: R_f 0.67 (ether); IR ($CHCl_3$) 3010, 2961, 2939, 2879, 2860, 1742, 1682, 1597, 1467, 1454, 1409, 1380, 1290, 1240, 1192, 1151, 1115, 887, 857, 823, 800, 690, 660, 622 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 7.29 (dd, 1 H, J = 9.6, 9.3 Hz), 5.90 (d, 1 H, J = 9.6 Hz), 2.81–2.26 (m, 6 H), 1.73 (s, 2 H), 1.4 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.58 (C), 202.44 (C), 158.70 (CH), 127.78 (CH), 55.00 (C), 52.69 (CH), 46.74 (CH), 45.07 (CH_2), 43.43 (C), 42.67 (CH_2), 31.90 (CH_2), 30.87 (CH_3), 29.62 (CH_3); MS (70 eV) parent 204, base peak 149. Recrystallization from hexanes provided an analytical sample.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.52; H, 7.97.

(1*R,5*S**,6*S**)-3,3-Ethylenedioxytricyclo[4.3.2.0^{1,5}]undec-7-en-9-one (11).** A mixture of 1.163 g (5.70 mmol) of the enedione **4**, 40 mg of *p*-TsOH, 0.381 mL (1.2 equiv) of ethylene glycol, and 530 mL of benzene was heated at reflux under a Dean–Stark trap for 5.5 h. At this point the solution was cooled and a second addition of ethylene glycol (95 μL, 0.3 equiv) and *p*-TsOH (5 mg) was made; heating at reflux was continued for 11 h. The solution was cooled to room temperature and then poured into a 1:1 mixture of saturated aqueous $NaHCO_3$/saturated aqueous Na_2CO_3, and ice. After extraction with ether (six times), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel, eluting with 1:3 ether–hexanes, to yield 220 mg (13%) of starting material and 1.170 g (83%) of the colorless crystalline ketal **11**, melting at 81–83 °C: R_f 0.62 (4:1 ether–hexanes); IR ($CHCl_3$) 3024, 3003, 2982, 2955, 2928, 2890, 2880, 2855, 1678, 1598, 1459, 1436, 1380, 1370, 1349, 1328, 1296, 1289, 1270, 1232, 1178, 1144, 1112, 1086, 1050, 1027, 1001, 948, 890, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, 1 H, J = 9.7, 9.6 Hz), 5.90 (d, 1 H, J = 9.6 Hz), 3.88 (m, 4 H), 2.63–1.50 (m, 8 H), 1.40 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.25 (C), 158.48 (CH), 127.62 (CH), 117.57 (C), 64.08 (CH_2, CH_2), 63.42 (CH_2), 56.69 (CH), 52.51 (CH), 46.79 (CH_2), 44.24 (C), 40.78 (CH_2), 40.76 (C), 31.57 (CH_3), 30.59 (CH_3); MS (20 eV) parent 248, base peak 193. An analytical sample was prepared by recrystallization from ether–hexanes.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.33; H, 8.30.

(1*R,5*S**,6*S**)-3,3-Ethylenedioxy-11,11-dimethyl-9-methoxymethylenetricyclo[4.3.2.0^{1,5}]undecane (12).** A mixture of 276 mg (1.11 mmol) of the enone ketal **11**, 20 mg of 5% Pd/C, and 15 mL of absolute EtOH was stirred vigorously under 1 atm of H_2 for 40 min at room temperature. Filtration through a Celite pad followed by evaporation of the solvent provided 277 mg (99%) of the corresponding saturated ketone as a white crystalline solid melting at 58–60 °C: R_f 0.62 (4:1 ether–hexanes); IR ($CHCl_3$) 2975, 2942, 2875, 1710, 1454, 1434, 1417, 1390, 1368, 1345, 1332, 1311, 1294, 1219, 1166, 1123, 1089, 1074, 1042, 1020, 997, 947, 920, 890, 847, 811, 792, 752, 718 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.87 (s, 4 H), 2.58–1.60 (m, 12 H), 1.32 (s, 3 H), 1.19 (s, 3 H).

To a solution of 2.67 mL of 1.33 M *sec*-butyllithium (4.5 equiv) in 10 mL of dry THF at −95 °C (toluene–liquid N_2) was added 9.06 mL (5.0 equiv) of a methoxymethyldiphenylphosphine/THF solution (100 mg/mL) dropwise over a period of 25 min. The resulting orange solution was stirred −95 °C for an additional 15 min; then a solution of 197 mg (0.788 mmol) of the ketal ketone from above in 3 mL of dry THF was added in a dropwise fashion. After the addition was complete, the mixture was stirred at −95 °C for 45 min and was then allowed to warm to room temperature. The solution was treated first with 143 μL of MeOH, then 3.5 mL of MeI, and was allowed to continue stirring at room temperature for 1 h, whereupon it was poured into H_2O and extracted four times with ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated to provide a crude oil which was chromatographed on silica gel. Elution with 1:8 ether–hexanes afforded 149 mg (68%) of the enol ether **12** as an oily mixture of olefinic isomers: R_f 0.63 (2:1 ether/hexanes); ^1H NMR (90 MHz, $CDCl_3$) δ 5.52 (t, 1 H, J = 1.5 Hz), 3.88 (m, 4 H), 3.45 (s, 3 H), 2.45–1.27 (m, 12 H), 1.17 (s, 3 H), 1.02 (s, 3 H). In addition, 63 mg (32%) of starting material was recovered.

(1*R,5*S**,6*S**,9*R**)-11,11-Dimethyltricyclo[4.3.2.0^{1,5}]undecan-3-one-9-carboxaldehyde (13).** A mixture of 44 mg of the enol ether **12**, 3 mL of THF, and 1 mL of aqueous 5% HCl was stirred at room temperature for 8 h. The solution was then treated with 2 mL of acetone and stirred for an additional 13 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted five times with ether. After the combined ether layers were dried ($MgSO_4$) and concentrated, chromatography of the residue on silica gel (3:4 ether–hexanes) yielded 35 mg (100%) of the slightly impure keto aldehyde **13** as an oil: R_f 0.46 (3:1 ether–hexanes); IR ($CHCl_3$) 3010, 2985, 2920, 2868, 2720, 1734, 1718, 1448, 1404, 1364, 1348, 1316, 1280, 1252, 1229, 1190, 1162, 1147 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.60 (d, 1 H, J = 0.71 Hz), 2.72–1.26 (m, 13 H), 1.22 (s, 3 H), 1.11 (s, 3 H).

Methyl (1*R,5*S**,6*S**,9*R**)-11,11-Dimethyltricyclo[4.3.2.0^{1,5}]undecan-3-one-9-carboxylate (14a).** To a cooled (0 °C) solution of 35 mg (0.16 mmol) of ketoaldehyde **13** in 3.5 mL of acetone was added 0.5 mL (2 equiv) of 0.66 M Jones reagent. After the reaction mixture was allowed to come slowly to room temperature and had stirred for 5 h, it was poured into saturated aqueous Na_2CO_3; the basic solution was extracted three times with ether. The aqueous layer was adjusted to pH 2 with 5% HCl, and then extracted five times with ether. The combined extracts of the acidified aqueous layer were dried ($MgSO_4$) and concentrated to yield 37 mg (100%) of slightly impure carboxylic acid. Recrystallization from ether afforded a white solid melting at 155–157 °C.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.14; H, 8.54. Found: C, 70.91; H, 8.87.

An ethereal solution of 30 mg (0.13 mmol) of the carboxylic acid was treated with an excess of diazomethane (in ether) at 0 °C. The mixture was stirred for 5 min and then allowed to warm to room temperature. Concentration and chromatography on silica gel (5:2 hexanes–ether) provided 21 mg (66%) of the pure ester **14a** as a colorless oil: R_f 0.56 (2:1 ether–hexanes); IR ($CHCl_3$) 3021, 2995, 2950, 2925, 2868, 1725, 1450, 1434, 1405, 1360, 1330, 1311, 1291, 1230, 1191, 1162, 1198, 1019, 976, 946, 890, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3 H), 2.63 (dd, 1 H, J = 11.77, 6.25 Hz), 2.51 (m, 2 H), 2.33 (AB q, 2 H, J_{AB} = 18.02 Hz, $\Delta\nu_{AB}$ = 38.54 Hz), 2.15–1.81 (m, 4 H), 1.6–1.5 (m, 1 H), 1.29 (d, 1 H, J = 15.07 Hz), 1.19 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 218.46, 174.27, 55.48, 52.66, 51.81, 51.23, 50.35, 48.38, 46.43, 42.16, 41.16, 34.57, 29.90, 26.71, 22.95. Microdistillation provided an analytical sample.

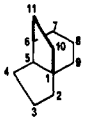
Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.24; H, 8.49. Found: C, 72.30; H, 8.73.

(1*R,5*S**,6*S**,7*S**,8*S**)-7,8-Epoxy-3,3-ethylenedioxy-11,11-dimethyltricyclo[4.3.2.0^{1,5}]undecan-9-one (15a).** To a methanolic solution (55 mL) of 821 mg (3.31 mmol) of the ketal **11** and 6.6 mL of aqueous 0.05 M NaOH at room temperature was gradually added 7.4 mL of 70% aqueous *tert*-butyl hydroperoxide. After the solution had stirred at room temperature for 8 h, it was cooled to 0 °C and subjected to the dropwise addition of 7.3 g of sodium sulfite in 37 mL of distilled H_2O. The resulting white suspension was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was then saturated with NaCl and extracted five times with ether. The combined ether layers were dried ($MgSO_4$), filtered, and concentrated to give a white solid that was recrystallized from ether/hexanes to provide 840 mg (96%) of the epoxide **15a**, mp 91–92 °C: R_f 0.60 (2:1 ether–hexanes); IR ($CHCl_3$) 3670, 3470, 3400, 3003, 2956, 2873, 2440, 2388, 1740, 1715, 1602, 1458, 1436, 1392, 1369, 1332, 1312, 1302, 1281, 1227, 1126, 1101, 1056, 1027, 1018, 1000, 968, 946, 897, 881, 861, 843, 815, 803, 715, 657, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90–3.82 (m, 4 H), 3.52 (t, 1 H, J = 3.87 Hz), 3.20 (d, 1 H, J = 3.87 Hz), 2.85 (dd, 1 H, J = 12.46, 8.17 Hz), 2.49 (d, 1 H, J = 4.30 Hz), 2.25 (d, 1 H, J = 12.89 Hz), 2.18 (d, 1 H, J = 14.61 Hz), 2.01 (m, 3 H), 1.64 (d, 1 H, J = 14.61 Hz), 1.37 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.29 (C), 117.81 (C), 64.16 (CH_2), 63.51 (CH_2), 61.52 (C), 54.45 (CH), 53.02 (CH), 49.21 (CH_2), 46.34 (CH), 41.29 (C), 40.80 (CH), 40.61 (CH_2), 38.55 (CH_2), 32.25 (CH_3), 27.04 (CH_3); MS (17 eV) parent 264, base peak 264. An analytical sample was prepared by recrystallization from hexanes.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.49; H, 7.77.

(1*S,5*S**,6*S**,7*R**)-3,3-Ethylenedioxy-7-hydroxy-11,11-dimethyltricyclo[4.3.2.0^{1,5}]undec-8-ene (16a).** This procedure was carried out on 150 mg (0.57 mmol) of the ketal epoxide **15a** which was evenly distributed among 11 small vials (~13 mg each). Each vial was treated as

(48) All tricyclic compounds were named according to the von Baeyer system. The numbering scheme is shown below:



follows: after the addition of 160 μL of MeOH (reagent grade) and 0.5 mL of glacial acetic acid, the solution was cooled in a −78 °C bath until frozen. The vial was then removed from the bath and the mixture was allowed to thaw. Just as the solid began to melt, 32 μL of 64% aqueous hydrazine hydrate was added and the yellowing solution was allowed warm to room temperature and stirred for 1 h. The contents of all the vials were combined and poured into saturated aqueous Na_2CO_3. Ether extraction (five times), followed by drying ($MgSO_4$) and concentration of the organic layers, provided a yellow residue which was chromatographed on silica gel. Elution with 1:1 ether–hexanes and evaporation of the solvent furnished 130 mg (92%) of the allylic alcohol **16a** as a white solid melting at 69–71 °C: R_f 0.54 (ether); IR ($CHCl_3$) 3660, 3598, 3460, 3025, 2998, 2970, 2955, 2927, 2872, 2675, 2460, 2380, 1723, 1670, 1628, 1460, 1432, 1395, 1388, 1363, 1330, 1303, 1285, 1231, 1180, 1155, 1122, 1097, 1057, 1030, 1012, 994, 952, 947, 909, 871, 839, 821, 798, 685, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, 1 H, J = 9.23 Hz), 5.56 (ddd, 1 H, J = 9.23, 4.10, 1.54 Hz), 4.21 (m, 1 H), 3.88 (m, 4 H), 2.29 (dd, 1 H, J = 12.31, 8.72 Hz), 2.06 (m, 4 H), 1.86 (d, 1 H, J = 13.84 Hz), 1.76 (d, 1 H, J = 12.82 Hz), 1.52 (m, 2 H), 1.23 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.05 (CH), 125.93 (CH), 118.84 (C), 69.47 (CH), 64.20 (CH_2), 63.53 (CH_2), 54.47 (CH), 51.60 (C), 49.10 (CH), 48.94 (CH_2), 44.93 (CH_2), 40.38 (CH_2), 39.11 (C), 34.12 (CH_3), 28.94 (CH_3); MS (15 eV) parent 250, base peak 153. Recrystallization from hexanes provided an analytical sample.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.66; H, 8.69.

(1*S,5*S**,6*S**,9*R**)-3,3-Ethylenedioxy-11,11-dimethyltricyclo-[4.3.2.0^{1,5}]undecane-9-acetaldehyde (17).** A solution of 1.00 g (4.00 mmol) of allylic alcohol **16a** in 85 mL of ethyl vinyl ether was heated at reflux and treated with a series of five additions of $Hg(OAc)_2$ (1.7 g each) at 2 h intervals. The resulting clear solution was maintained at reflux for a total of 18 h, at which time 0.43 mL of glacial acetic acid was added, followed by continued refluxing for 50 min. The solution was cooled, diluted with 80 mL of ether, poured into cold 5% aqueous KOH, and extracted three times with ether. The combined extracts were dried over K_2CO_3, filtered, concentrated, and redissolved in 35 mL of hexanes. This solution was swirled with 1.0 g of alumina (activity grade 3) for 1 min and then filtered immediately through a pad of alumina (activity grade 3). Evaporation of the solvent gave 961 mg (87%) of the derived allyl vinyl ether in the form of a light yellow oil: R_f 0.61 (1:1 ether–hexanes); IR (CCl_4) 3112, 3068, 3013, 2991, 2949, 2925, 2868, 2760, 2673, 1735, 1629, 1603, 1472, 1460, 1448, 1433, 1403, 1387, 1364, 1344, 1329, 1318, 1303, 1295, 1286, 1255, 1240, 1189, 1179, 1158, 1124, 1098, 1056, 1039, 1008, 995, 980, 964, 945, 915, 896, 878, 830, 810, 730, 715, 691, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (dd, 1 H, J = 13.85, 6.67 Hz), 6.23 (d, 1 H, J = 9.23 Hz), 5.56 (ddd, 1 H, J = 9.23, 4.10, 1.54 Hz), 4.29 (m, 2 H), 4.00 (dd, 1 H, J = 6.67, 1.54 Hz), 3.87 (m, 4 H), 2.46 (t, 1 H, J = 10.26 Hz), 2.11 (m, 4 H), 1.87 (d, 1 H, J = 13.85 Hz), 1.80 (d, 1 H, J = 12.82 Hz), 1.53 (d, 1 H, J = 12.82 Hz), 1.24 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.56 (CH), 143.16 (CH), 122.41 (CH), 118.54 (C), 87.70 (CH_2), 76.49 (CH), 64.10 (CH_2), 63.51 (CH_2), 51.43 (C), 51.26 (CH), 49.15 (CH_2), 49.05 (CH), 44.82 (CH_2), 40.28 (CH_2), 39.05 (C), 34.03 (CH_3), 29.05 (CH_3); MS (15 eV) parent 276, base peak 133.

A solution of 741 mg (2.68 mmol) of the allyl vinyl ether in 72.5 mL of *o*-xylene was evenly distributed among five sealable glass tubes. Each tube was charged with 75 μL of diisopropylethylamine and then degassed (accomplished by three freeze–thaw cycles) and sealed under vacuum. The resulting sealed tubes were totally immersed in a salt bath at 240 °C for 4 h and then cooled to room temperature.[49] The tubes were opened and the combined colorless solutions were placed directly on a column of silica gel. After flushing first with hexanes, elution was performed with (1) 2:9 ether–hexanes and (2) 2:5 ether–hexanes. Evaporation of the solvent yielded 667 mg (90%) of the rearranged aldehyde as a colorless oil: R_f 0.58 (2:1 ether–hexanes); IR (CCl_4) 3105, 2990, 2960, 2939, 2880, 2822, 2702, 1732, 1550, 1459, 1410, 1390, 1370, 1350, 1339, 1306, 1290, 1252, 1230, 1123, 1053, 1022, 1005, 951 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, 1 H, J = 1.72 Hz), 5.98 (t, 1 H, J = 8.21 Hz), 5.33 (dd, 1 H, J = 9.23, 3.08), 3.89 (m, 4 H), 2.72 (m, 2 H), 2.49–1.58 (m, 9 H), 1.25 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.04, 137.15, 127.67, 119.04, 64.35, 63.52, 55.55, 53.02, 50.15, 48.59, 47.11, 46.81, 45.15, 44.35, 39.66, 32.20, 30.96; MS (19 eV) parent 276, base peak 248.

A mixture of 104 mg (0.38 mmol) of the unsaturated aldehyde, 11 mg of 5% Pd/C, and 10 mL of absolute ethanol was stirred under 1 atm of H_2 gas for 10 h at room temperature. Filtration through a Celite pad followed by removal of the solvent provided 106 mg (100%) of the saturated aldehyde **17** as a white solid, mp 45–47 °C: R_f 0.53 (2:1 ether–hexanes); IR (film) 2906, 2706, 2242, 1718, 1470, 1447, 1432, 1406, 1385, 1360, 1345, 1337, 1315, 1300, 1285, 1258, 1226, 1207, 1191, 1169, 1147, 1112, 1092, 1070, 1043, 1020, 1002, 991, 943, 910, 893, 843, 827, 787, 729, 673, 640 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 9.68 (s, 1 H), 3.76 (s, 4 H), 2.70–1.41 (m, 15 H), 1.23 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.46 (CH), 118.3 (C), 64.21 (CH_2), 63.33 (CH_2), 54.74 (CH_2), 53.14 (C), 50.26 (CH), 48.84 (CH), 46.10 (CH_2), 45.53 (CH_2), 40.37 (CH_2), 39.47 (C), 36.79 (CH), 34.51 (CH_3), 27.47 (CH_2), 26.71 (CH_3), 24.86 (CH_2); MS (17 eV) parent 278, base peak 250.

(1*R,5*S**,6*S**,9*R**)-3,3-Ethylenedioxy-11,11-dimethyltricyclo-[4.3.2.0^{1,5}]undecan-9-(2-acetoxy)ethene (18).** A solution of 108 mg (0.39 mmol) of the aldehyde **17** and 5 mg of anhydrous KOAc in 4.0 mL of distilled acetic anhydride was heated at reflux for 1.5 h.[35] The cooled solution was then poured into a 1:1 mixture of brine and saturated aqueous Na_2CO_3 and extracted five times with ether. The combined ether extracts were then dried, filtered, and concentrated to yield a residue which was chromatographed on silica gel. Elution with 1:5 ether–hexanes provided 118 mg (95%) of the enol acetate **18** as an oily mixture of olefin isomers: R_f 0.48 (1:1 ether–hexanes); IR (CCl_4) 2980, 2942, 2890, 2865, 1755, 1663, 1470, 1450, 1430, 1386, 1367, 1332, 1309, 1286, 1220, 1118, 1099, 1040, 1022, 991, 929, 805, 721 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 6.95 (m, 1 H), 5.31 (m, 1 H), 3.78 (s, 4 H), 2.03 (s, 3 H), 2.35–1.42 (m, 13 H), 1.25 (s, 3 H), 1.15 (s, 3 H).

(1*R,5*S**,6*S**,9*S**)-3,3-Ethylenedioxy-11,11-dimethyltricyclo-[4.3.2.0^{1,5}]undecane-9-carboxaldehyde (19).** A mixture of 31 mg (0.096 mmol) of the enol acetate **18**, 1.5 mL of THF, 1.5 mL of distilled H_2O, and 1 mg of OsO_4 was stirred at room temperature for 10 min. The darkened solution was treated with 166 mg (8 equiv) of $NaIO_4$ and allowed to stir at room temperature for 8.5 h. The reaction mixture was extracted three times with ether, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (1:4 ether–hexanes) to give 15.3 mg (60%) of the oily aldehyde **19** with the ketal still intact: R_f 0.56 (1:1 ether–hexanes; ^1H NMR (90 MHz, CCl_4) δ 9.82 (d, 1 H, J = 1.8 Hz), 3.78 (s, 4 H), 2.34–1.34 (m, 13 H), 1.22 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR δ 202.46, 118.41, 64.21, 63.33, 54.75, 53.14, 50.26, 48.84, 46.11, 45.54, 40.38, 39.47, 36.80, 34.52, 27.47, 26.72, 24.86.

Methyl (1*R,5*S**,6*S**,9*S**)-11,11-Dimethyltricyclo[4.3.2.0^{1,5}]undecan-3-one-9-carboxylate (14b). A. From Aldehyde 19.** To a solution of 15 mg (0.057 mmol) of the aldehyde **19** in 1.0 mL of acetone at 0 °C was added 75 μL of 2.67 M Jones reagent. The solution was allowed to warm to room temperature and stirred for 2 h during which time another 12 equiv of Jones reagent was added. The resulting solution was poured into a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2CO_3 and extracted four times with ether. The remaining aqueous layer was adjusted to pH 2 with 5% aqueous HCl and extracted six times with ether. The extracts of the acidic aqueous phase were combined, dried ($MgSO_4$), filtered, and concentrated to afford 10 mg (80%) of the crude carboxylic acid.

An ethereal solution of the crude acid was exposed to excess diazomethane in ether at 0 °C. After the reaction had stirred at room temperature for 30 min, the solvent was evaporated and the residue chromatographed on silica gel (1:2 ether–hexanes) to yield 8.5 mg (75%) of the keto ester **14b**, which crystallized slowly (mp 47–49 °C): R_f 0.56 (2:1 ether–hexanes); IR (CCl_4) 3000, 2960, 2931, 2872, 1748, 1453, 1439, 1412, 1393, 1368, 1339, 1304, 1264, 1240, 1196, 1162, 1096, 1044, 1013, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3 H), 2.87 (t, 1 H, J = 10.25 Hz), 2.75 (d, 1 H, J = 7.32 Hz), 2.48 (d, 2 H, J = 10.25 Hz), 2.36 (AB q, 2 H, J_{AB} = 17.58 Hz, $\Delta\nu_{AB}$ = 38.40 Hz), 2.0–1.72 (m, 6 H), 1.56 (d, 1 H, J = 14.65 Hz), 1.18 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 218.52, 175.77, 53.26, 51.42, 51.27, 49.77, 49.08, 48.66, 47.41, 42.30, 40.18, 34.45, 28.76, 27.18, 22.52; MS (15 eV) parent 250, base peak 235. An analytical sample was prepared by sublimation (80 °C bath temperature, 0.100 mmHg).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.67; H, 8.65.

B. From Enol Acetate 18. To a solution of 50 mg (0.156 mmol) of the enol acetate mixture **18** in 0.35 mL of carbon tetrachloride, 0.35 mL of acetonitrile, and 0.5 mL of water were added 267 mg (8 equiv) of $NaIO_4$ and approximately 1 mg of $RuCl_3 \cdot 3H_2O$.[37] The reaction mixture was stirred at room temperature for 2 h, at which time TLC analysis indicated complete consumption of the starting material **18**. The reaction mixture was extracted three times with methylene chloride and the combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in ether and this solution was filtered through Celite. The filtrate was concentrated and the crude carboxylic acid was esterified with an ethereal solution of diazomethane (0 → 25 °C). After evaporation of the ether solvent, the residue was purified by chroma-

(49) As a nonflammable, stable, high-temperature bath, we utilized a molten salt mixture comprising 40% $NaNO_2$, 7% $NaNO_3$, and 53% KNO_3 by weight. See: Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972; p 450.

tography on 15 g of silica gel (elution with hexanes followed by 1:3 ether/hexanes) to give 30 mg (79% from **18**) of the keto ester **14b**, identical in all respects with that described above and elsewhere.[3a]

(1R*,5S*,6S*,7S*,8S*)-7,8-Epoxy-11,11-dimethyltricyclo-[4.3.2.0^{1,5}]undecane-3,9-dione (15b). To a solution of 0.5 g (2.45 mmol) of the tricyclic enedione **4** in 40 mL of MeOH at 25 °C were added 4.8 mL of 0.05 N NaOH and 5.2 mL of 70% aqueous *tert*-butyl hydroperoxide. The reaction mixture was stirred at room temperature for 3 h, at which time TLC analysis indicated that all of the starting enone had been consumed. The reaction mixture was cooled to 0 °C and a solution of 6.0 g of Na_2SO_3 in 26 mL of H_2O was added. After the resulting mixture had warmed to room temperature, 25 mL of H_2O was added and the solution was extracted six times with ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated to yield 514 mg (95%) of the crystalline epoxide **15b** (mp 119–120 °C): R_f 0.42 (2:1 ether–hexanes); IR ($CHCl_3$) 3027, 3008, 2973, 2937, 2878, 1730, 1712, 1447, 1401, 1364, 1333, 1309, 1271, 1218, 1151, 1100, 1055, 1010, 959, 884, 859, 839 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.59 (t, 1 H, J = 3.8 Hz), 3.28 (d, 1 H, J = 3.8 Hz), 2.98 (m, 1 H), 2.60 (d, 1 H, J = 4.0 Hz), 2.55 (s, 1 H), 2.42 (m, 3 H), 1.76 (AB q, 2 H, J_{AB} = 15 Hz, $\Delta\nu_{AB}$ = 10 Hz), 1.36 (s, 3 H), 1.25 (s, 3 H).

(1S*,5S*,6S*,7R*)-7-Hydroxy-11,11-dimethyltricyclo[4.3.2.0^{1,5}]undec-8-en-3-one (16b). A solution of the epoxy diketone **15b** (50 mg, 0.227 mmol) in 1.25 mL of MeOH and 3.0 mL of glacial acetic acid was degassed with a stream of nitrogen for 30 min. The solution was cooled to −78 °C until it solidified, at which point it was removed from the cooling bath. Just as the mixture began to melt, 55 μL of 64% aqueous hydrazine hydrate was added and the yellowing solution was allowed to warm to room temperature and stirred for 1.25 h. The reaction mixture was poured into saturated brine and the aqueous layer was extracted five times with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was dissolved in 3.3 mL of THF, 0.75 mL of a pH 7 phosphate buffer, and 2 mL of aqueous $CuCl_2$ (3 equiv). The reaction mixture was stirred at room temperature for 22 h, at which time the THF was removed under reduced pressure and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexanes followed by 1.5:1 ether–hexanes gave 32.1 mg (69%) of the allylic alcohol **16b**: R_f 0.51 (ether); IR ($CHCl_3$) 3600, 3448, 3302, 3001, 2958, 2928, 2867, 1734, 1627, 1454, 1406, 1389, 1363, 1311, 1296, 1268, 1226, 1170, 1140, 1102, 1070, 1011, 996, 968, 941, 899, 867, 833, 812, cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 6.18 (d, 1 H, J = 9.0 Hz), 5.60 (dd, J = 9.0, 4.6 Hz), 4.28 (t, 1 H, J = 4.6 Hz), 2.78–1.29 (m, 9 H), 1.20 (s, 3 H), 1.06 (s, 3 H).

(1S*,5S*,6S*,9R*)-11,11-Dimethyltricyclo[4.3.2.0^{1,5}]undecan-3-one-9-acetaldehyde (20). To a solution of 198 mg (0.71 mmol) of ketal aldehyde **17** in 15 mL of acetone at room temperature was added 5 drops of 2 M aqueous HCl. The mixture was stirred at room temperature for 3 h, during which time an additional 4 mL of 2 M HCl was added. The mixture was then extracted three times with ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was chromatographed on silica gel, eluting with 3:4 ether–hexanes, to yield 143 mg (86%) of the crystalline keto aldehyde **20** melting at 77–79 °C: R_f 0.42 (3:1 ether–hexanes); IR ($CHCl_3$) 3000, 2928, 2881, 2822, 2722, 1738, 1725, 1452, 1410, 1390, 1230, 1205, 1179, 1150, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1 H), 2.54–1.12 (m, 15 H), 1.16 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 218.22 (C), 201.61 (CH), 52.90 (CH_2), 52.78 (C), 49.52 (CH), 47.40 (CH_2), 47.32 (CH), 45.74 (CH_2), 42.20 (CH_2), 39.69 (C), 36.14 (CH), 34.28 (CH_3), 27.65 (CH_2), 26.62 (CH_3), 24.63 (CH_2); MS (15 eV) parent 234, base peak 177. Recrystallization from hot hexanes provided an analytical sample.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.74; H, 9.62.

(1S*,2S*,5R*,8R*,11S*)-6-Acetoxy-12,12-dimethyltetracyclo-[6.5.0.0^{1,5}.0^{2,11}]tridecan-4-one (21a,b).[50] To a solution of 347 mg (1.48 mmol) of keto aldehyde **20** in 48 mL of glacial acetic acid was added 0.8 mL of concentrated H_2SO_4 at room temperature. After stirring for 27 h at room temperature, the light brown solution was poured into saturated aqueous Na_2CO_3 and neutralized with additional solid Na_2CO_3. The resulting solution was extracted four times with ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated to provide a residue which was chromatographed on silica gel. Elution with 2:5 ether–hexanes and removal of the solvent furnished 323 mg (79%) of the keto acetates **21a,b** as a crystalline 4:1 mixture of diastereomers: R_f 0.43 (1:1 ether–hexanes); IR ($CHCl_3$) 3001, 2955, 2932, 2873, 1742, 1740, 1457, 1415, 1392, 1380, 1249, 1192, 1152, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (m, 1 H), 2.69–1.47 (m , 17 H), 1.18 (s, 6 H); MS (15 eV) parent 276, base peak 216.

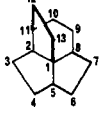
(1S*,2S*,5S*,8R*,11S*)-12,12-Dimethyltetracyclo[6.5.0.0^{1,5}.0^{2,11}]-tridec-6-en-4-one (22a). A solution of 23 mg (0.083 mmol) of the keto acetates **21a,b** in ether was transferred into two sealable tubes. Using a stream of N_2, the ether was carefully evaporated so that the sides of the tubes were evenly coated with the compound. The tubes were then evacuated, sealed, and totally submerged in a salt eutectic bath at 400 °C for 4 min.[49] The contents of the tubes were then combined and chromatographed on silica gel, eluting with 1:22 ether–hexanes. Evaporation of the solvent provided 6 mg (33%) of the conjugated isomer **22b** and 11 mg (61%) of the deconjugated keto olefin **22a**. Data for **22a**: R_f 0.73 (1:1 ether–hexanes); IR ($CHCl_3$) 3053, 3028, 3008, 2958, 2930, 2870, 2378, 1730, 1590, 1476, 1453, 1411, 1388, 1365, 1331, 1260, 1231, 1189, 1157, 1133, 1090, 1077, 1054, 1038, 1025, 992, 977, 953, 915, 892, 862, 840, 826, 815, 625, 610 cm^{-1}; ^{1} H NMR (400 MHz, $CDCl_3$) δ 5.68 (br s, 1 H), 5.51 (br s, 1 H), 3.16 (br s, 1 H), 2.92 (br s, 1 H), 2.40 (m, 2 H), 2.21 (dd, 1 H, J = 13.83, 7.42 Hz), 1.95 (m, 2 H), 1.85 (d, 1 H, J = 5.15 Hz), 1.71 (m, 2 H), 1.60 (m, 2 H), 1.18 (s, 3 h), 1.17 (s, 3 H). Data for **22b**: R_f 0.64 (1:1 ether–hexanes); IR ($CHCl_3$) 3005, 2959, 2930, 2870, 1710, 1614, 1457, 1428, 1407, 1385, 1362, 1268, 1230, 1189, 1175, 1143, 1125, 1096, 1080, 950, 915, 856, 843 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.89 (s, 1 H), 2.92 (dd, 1 H, J = 20.8, 10.4 Hz), 2.38 (dd, 1 H, J = 18.5, 12.1 Hz), 2.21–1.16 (m, 11 H), 0.95 (s, 3 H), 0.88 (s, 3 H).

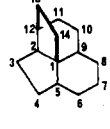
(1S*,2S*,5S*,8R*,11S*)-4-(*tert*-Butyldimethylsiloxy)-12,12-dimethyltetracyclo[6.5.0.0^{1,5}.0^{2,11}]tridec-6-ene (23). To a solution of 18 mg (0.083 mmol) of the unconjugated enone **22a** in 3.0 mL of dry ether at −25 °C was added 0.5 mL of a 1M ethereal $LiAlH_4$ solution. The resulting mixture was allowed to stir at −25 °C for 1 h and then warmed to room temperature over a period of 30 min. The excess $LiAlH_4$ was quenched by the sequential addition of 0.5 mL of distilled H_2O, 0.5 mL of 15% aqueous NaOH, and 1.5 mL of distilled H_2O, all at 0 °C.[51] After warming to room temperature, the white suspension was first treated with $MgSO_4$, then filtered, and concentrated to provide 18 mg (100%) of the corresponding alcohol as an oil, homogeneous by TLC and NMR analysis: R_f 0.46 (2:1 ether–hexanes); IR ($CHCl_3$) 3600, 3420, 3018, 2925, 2865, 1600, 1460, 1385, 1364, 1326, 1260, 1240, 1162, 1145, 1094, 1055, 1012, 999, 966, 903, 884, 856 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.43 (AB q, 2 H, J_{AB} = 5.7 Hz, $\Delta\nu_{AB}$ = 19.2 Hz), 3.95 (m 1 H) 2.60 (m, 2 H), 2.17–1.42 (m, 11 H), 1.18 (s, 3 H), 1.05 (s, 3 H).

A mixture of 21 mg (0.96 mmol) of the homoallylic alcohol, 1.5 mL of dimethylformamide (DMF), 26 mg (4 equiv) of recrystallized imidazole, and 29 mg (2 equiv) of *tert*-butyldimethylsilyl chloride was stirred at room temperature for 2.5 h. The resulting clear solution was poured into saturated aqueous $CuSO_4$ and extracted two times with pentane. The combined organic layers were washed, first with H_2O, then brine, and then dried over $MgSO_4$. Evaporation of the solvent and chromatography on silica gel (hexanes) provided 31 mg (96%) of the silyl ether **23** as a colorless oil: R_f 0.37 (hexanes); IR ($CHCl_3$) 3050, 2987, 2940, 2870, 1466, 1410, 1393, 1370, 1262, 1114, 1087, 1078, 1043, 1013, 944, 901, 867, 842 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.51 (AB q, 2 H, J_{AB} = 5.9 Hz, $\Delta\nu_{AB}$ = 16.8 Hz), 4.01 (m, 1 H), 2.63 (m, 2 H), 2.22–1.29 (m, 10 H), 1.23 (s, 3 H), 1.09 (s, 3 H), 0.94 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 136.47 (CH), 132.08 (CH), 81.58 (CH), 63.05 (CH), 60.94 (C), 52.14 (CH), 50.93 (CH_2), 49.59 (CH), 46.23 (CH), 41.30 (CH_2), 39.38 (C), 35.09 (CH_3), 29.29 (CH_3), 28.06 (CH_2), 25.99 (CH_3), 20.78 (CH_2), 18.16 (C), −4.58 (CH_3); MS (15 eV) base peak 275.

(1R*,2S*,5S*,6S*,9S*)-3-(*tert*-Butyldimethylsiloxy)-2,9-bis(hydroxymethyl)-11,11-dimethyltricyclo[4.3.2.0^{1,5}]undecane (24). A solution of 58 mg (0.16 mmol) of homoallylic silyl ether **23** in 2.5 mL of CH_2Cl_2 and 2.5 mL of MeOH was placed in a flask equipped with a drying tube and oil bubbler. Ozone was then bubbled through the solution at −78 °C until a distinct blue color persisted. After the solution had stirred an additional 15 min at −78 °C, 140 μL of Me_2S was added and the mixture was allowed to warm to room temperature. Evaporation of the solvent provided a colorless oil which was redissolved in 8.3 mL of EtOH. To this ethanolic solution at 0 °C were then added 2 drops of H_2O and 42 mg of $NaBH_4$ at 0 °C. The resulting mixture was stirred at 0 °C for 45 min, warmed to room temperature for 5 h, and then treated once again

(50) All tetracyclic compounds were named according to the von Baeyer system. The numbering schemes are shown below:





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with 1 drop of H_2O and 25 mg of $NaBH_4$. Stirring was continued for a total of 18 h, at which time the reaction mixture was poured into H_2O and extracted three times with ether. The combined ether extracts were dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica gel. Elution with 1:2 ether-hexanes yielded 41 mg (70%) of the diol **24** as a solid melting at 139-140 °C: R_f 0.41 (1:1 ether-hexanes); IR ($CHCl_3$) 3590, 3360, 2950, 2928, 2860, 1720, 1460, 1400, 1380, 1360, 1250, 1134, 1104, 1089, 1057, 1004, 881, 860, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.86 (dd, 1 H, J = 10.27, 4.74 Hz), 4.07 (m, 1 H), 3.90 (dd, 1 H, J = 11.73, 3.99 Hz), 3.38 (dd, 1 H, J = 11.76, 3.85 Hz), 2.40 (d, 1 H, J = 4.66), 2.07-1.50 (m, 14 H), 1.26 (s, 3 H), 1.11 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); MS (5 eV) base peak 189.

(1S*,2S*,5R*,9S*,12S*)-4-(*tert*-Butyldimethylsiloxy)-13,13-dimethyl-7-oxatetracyclo[7.5.0.0.^{1,5}.$0^{2,12}$]tetradecan-8-one (25). A suspension of 35 mg (0.097 mmol) of diol **24** and 540 mg (5 equiv) of Fetizon's reagent (Ag_2CO_3 on Celite) in 10.6 mL of benzene was heated at reflux for 40 min. The suspension, initially a light green color, rapidly turned black. After filtration through a pad of Celite, the clear liquid was concentrated and chromatographed (silica gel, 1:5 ether-hexanes) to give 16 mg each of the two regioisomeric lactones **25** and **26** with a total yield of 92%. Both compounds were solids with **25** melting at 139-140 °C and **26** melting at 76-78 °C. Data for **25**: R_f 0.55 (1:1 ether-hexanes); IR ($CHCl_3$) 3030, 2960, 2933, 2900, 2861, 1740, 1470, 1460, 1383, 1359, 1345, 1335, 1320, 1302, 1292, 1275, 1255, 1188, 1157, 1133, 1113, 1081, 1070, 1058, 1042, 1005, 968, 957, 939, 908, 879, 869, 850, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (br s, 2 H), 4.04 (m, 1 H), 2.54 (d, 1 H, J = 6.94 Hz), 2.22 (dd, 1 H, J = 13.48, 6.13 Hz), 2.06-1.50 (m, 10 H), 1.25 (s, 3 H), 1.12 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.08, 77.85, 67.18, 54.21, 53,31, 52.89, 51.20, 48.69, 46.39, 39.42, 38.92, 35.06, 28.02, 26.83, 25.86, 18.71, 18.00, -4.38, -4.68; MS (18 eV) parent 364, base peak 307. Data for **26**: R_f 0.44 (1:1 ether-hexanes); IR ($CHCl_3$) 2980, 2959, 2931, 2910, 2860, 1730, 1471, 1461, 1390, 1371, 1361, 1330, 1308, 1295, 1264, 1228, 1181, 1170, 1136, 1103, 1077, 1063, 1055 1045 1030, 1005, 980, 962, 938, 920, 895, 861, 838, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (t, 1 H, J = 11.99 Hz), 4.21 (m, 1 H), 4.09 (dd, 1 H, J = 11.21, 4.69 Hz), 2.71 (d, 1 H, J = 6.09 Hz), 2.11-1.69 (m, 11 H), 1.26 (s, 3 H), 1.12 (s, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H).

(1S*,2S*,5R*,9S*,12S*)-13,13-Dimethyl-7-oxatetracyclo[7.5.0.0.^{1,5}.$0^{2,12}$]tetradecane-4,8-dione. (±)-Quadrone (1). To a solution of 16 mg (0.044 mmol) of the lactone **25** in 1.5 mL of acetone at 0 °C was added 50 μL of 2.67 M Jones reagent. The stirred mixture was allowed to warm to room temperature over a period of 1 h and was then treated with 3 drops of isopropyl alcohol. The green suspension was poured into saturated $NaHCO_3$ and extracted three times with ether. The combined ether extracts were dried over $MgSO_4$, filtered, concetrated, and chromatographed on silica gel. Elution with 1:1 ether-hexanes yielded 10.8 mg (100%) of (±)-quadrone (**1**) as a white solid, mp 139-141 °C (lit.[3a] 140-142 °C): R_f 0.62 (ether); IR ($CHCl_3$) 3014, 2997, 2980, 2958, 2930, 2902, 2895, 2873, 1742, 1700, 1495, 1488, 1469, 1450, 1438, 1411, 1385, 1371, 1353, 1346, 1320, 1298, 1285, 1270, 1252, 1208, 1190, 1178, 1166, 1141, 1129, 1113, 1091, 1074, 1062, 1044, 1021, 1002, 958, 910, 897, 870, 857, 845, 831, 718, 660, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (d, 1 H, J = 11.75 Hz), 4.20 (dd, 1 H, J = 11.75, 5.52 Hz), 2.73 (d, 1 H, J = 6.84 Hz), 2.66 (dd, 1 H, J = 17.28, 14.26), 2.39 (, 3 H), 2.09-1.61 (m, 7 H), 1.27 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 216.57, 173.98, 65.26, 52.47, 52.18, (2C), 49.83, 48.66, 45.92, 43.17, 40.42, 34.79, 28.04, 26.87, 19.28; MS (15 eV) parent 248, base peak 248. An analytical sample was prepared by recrystallization from hexanes.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.29; H, 8.11.

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Ketenes. 18.[1] Evidence for an Intermediate in the Reaction of Ketenes with Silyl Enol Ethers

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Abstract: The reactions of diethylketene and diphenylketene with various silyl enol ethers and the chemistry of some of the reaction products have been investigated. The formation of a rearranged adduct, in addition to the normally expected cyclobutanone, was taken as an indication that the reaction proceeds by an ionic mechanism. The same rearranged product arose from the thermolysis of a 3-silyloxycyclobutanone and a 2-silyloxyoxetane, which suggests that a zwitterionic intermediate occurs in all three reactions.

One tool with which to distinguish between concerted and stepwise [2 + 2] cycloadditions is the use of reactants that should give "abnormal" products if a zwitterionic or diradical intermediate is formed. Nishida has used the propensity of cyclopropylcarbinyl carbonium ions and radicals to rearrange to differentiate concerted, diradical, and zwitterionic mechanisms in [2 + 2] cycloadditions to olefins.[2] For instance, extensive rearrangement occurred and none of the normal [2 + 2] cycloadduct was formed when 1,1-diphenyl-2-vinylcyclopropane was reacted with tetracyanoethylene (TCNE). Since 1,1-diphenyl-2-vinylcyclopropane gave a normal Diels-Alder adduct, its rearrangement with TCNE was taken as an indication that the reaction was not concerted and that it proceeded via an intermediate.[2b] The same concept can be applied to the addition of ketenes to enol ethers, a reaction generally thought to be concerted.[3]

Many useful synthetic methods rely on the rearrangement of α-silyloxy carbonium ions to carbonyl compounds. Catalyzed aldol-type condensations of silyl enol ethers and acetals are known,[4]

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