maniyan, P.; Balasubramaniyan, V. *J. Am. Chem. Soc.* **1969**, *90*, 5930–5931.
(16) Honig, B.; Hudson, B.; Sykes, B. D.; Karplus, M. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1289–1293.
(17) Ebrey, T.; Govindjee, R.; Honig, B.; Pollock, E.; Chan, W.; Crouch, R.; Yudd, A.; Nakanishi, K. *Biochemistry* **1975**, *15*, 3933–3941.

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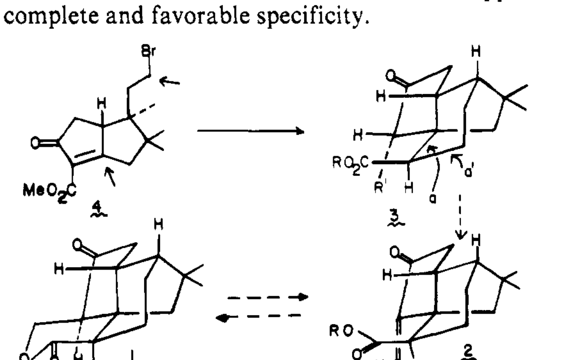
## Total Synthesis of *dl*-Quadrone

*Sir:*

Interest in the total synthesis of the *Aspergillus terreus* derived quadrone (**1**)[1,2] arises from its novel tetracyclic ring system and from its reported antitumor properties. Though the efficacy, not to speak of the mode of action, of quadrone remains to be clarified, it is recognized that **2**, formally derivable from **1** by $\beta$ elimination, is at least reminiscent, in its $\alpha$-methylenecarbonyl arrangement, of a large number of known antitumor agents.[3]

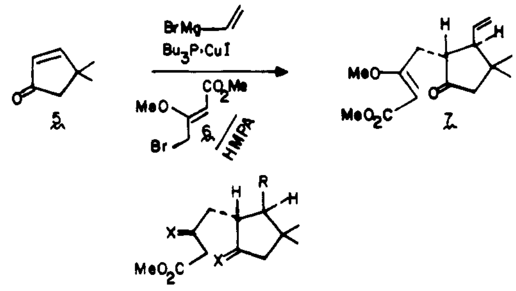
Our plan for synthesizing quadrone envisioned the reverse of the bioactivation process hypothesized above, i.e., the conversion of **2** (R = H) into **1**. Thus, systems such as **2** (R = H or alkyl) emerged, on chemical and biological considerations, as attractive subgoals. The scheme **4** → **3** → **2** → **1** (see dotted lines) presented itself as a plausible scenario. In our original formulation, we envisioned the possibility that the carbomethoxyl group in structure **4** would become a control element in structure **3** (see function R′). Regiochemical guidance for proper placement of the $\alpha$-methylene group in **2** thus would be provided.[4]

The conversion of **4** → **3** can be perceived to involve, overall, the attachment of the nucleophilic $CH_3$-$CO_2R$ through two of its CH bonds to two potentially electrophilic centers (see arrows in **4**), *with the added proviso that the $CO_2R$ function must emerge in an axial disposition.* Either mode of cyclization leading from structure **4** → structure **3** (see disconnection arrows a and a′) involves the closing of a propano bridge on the convex face of a bicyclo[3.3.0]octanone system—a risky and, therefore, interesting proposition for research. Below we report the first total synthesis of *dl*-quadrone wherein all regiochemical and stereochemical issues were resolved apparently with complete and favorable specificity.




A viable synthesis of compound **4** was our first concern. Conjugate addition of vinyl magnesium bromide to enone **5**,[5] followed by trapping of the resultant metalloenolate specie with **6**,[6] afforded **7**[7] (40–55% yield). While the $\beta,\alpha$-dialkylation of cycloalkenones, as a general concept, is well precedented,[8,9] the use of **6** as a $\gamma$-electrophilic equivalent of acetoacetate in a trapping context had not been demonstrated.[10]

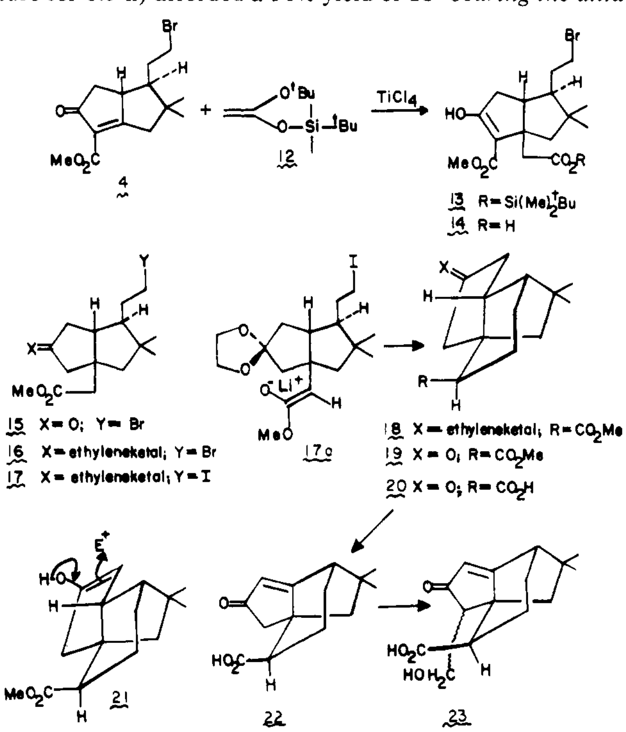
The diketal **8**, derived (ethylene glycol, $p$-TsOH, toluene, reflux) from **7**, was subjected to hydroboration ($BH_3$, THF, 0 °C → room temperature, 1.5 h) followed by oxidation with alkaline hydrogen peroxide to afford alcohol **9**. The latter was converted (mesyl chloride, triethylamine, ether, 0 °C → room temperature, 3 h) to **10** which, after treatment with lithium bromide in acetone (reflux, 6 h) and deketalization, gave **11**[11] in 55% overall yield from **7**. Exposure of **11** to 0.5 equiv of sodium methoxide in methanol at 0 °C provided the desired **4**,[7,11] mp 57–58 °C, in 76% yield.




8 R = vinyl, X = ethyleneketal
9 R = $CH_2CH_2OH$, X = ethyleneketal
10 R = $CH_2CH_2OMs$, X = ethyleneketal
11 R = $CH_2CH_2Br$, X = O ⟶ 4

The tricyclic acid **20** was reached as follows. A Mukaiyama[12] reaction of **4** with 1-*tert*-butoxy-1-*tert*-butyldimethylsilyloxyethylene[13] (**12**) (1 equiv of **4**, 1.1 equiv of $TiCl_4$, 5 equiv of **12**, $CH_2Cl_2$, −78 °C, 10 min) afforded a high yield of crude **13** *in which the tert-butyl group had been cleaved.* Desilylation with $Bu_4N^+F^-$ afforded the acid, **14**[7], mp 159–161 °C, in 70% overall yield. However, for our purpose, crude diester **13** was subjected to the action of 1 M HCl in dioxane under reflux for 1 h. After esterification of the crude *monoacid*[14] with diazomethane, the keto ester **15**[7] was in hand in 63% overall yield from **4**. Ketalization (ethylene glycol, $p$-TsOH, toluene, reflux, 6 h) afforded **16**[7] which, after Finkelstein reaction (sodium iodide–acetone containing a trace of pyridine, reflux, 12 h), gave rise to **17** (87% from **15**).

Reaction of **17** with lithium hexamethyl disilazide in THF (−78° → −23 °C, ~40 min, followed by addition of 20% HMPA, followed by stirring from −23 °C → room temperature for 6.5 h) afforded a 56% yield of **18**[7] *bearing the axial*

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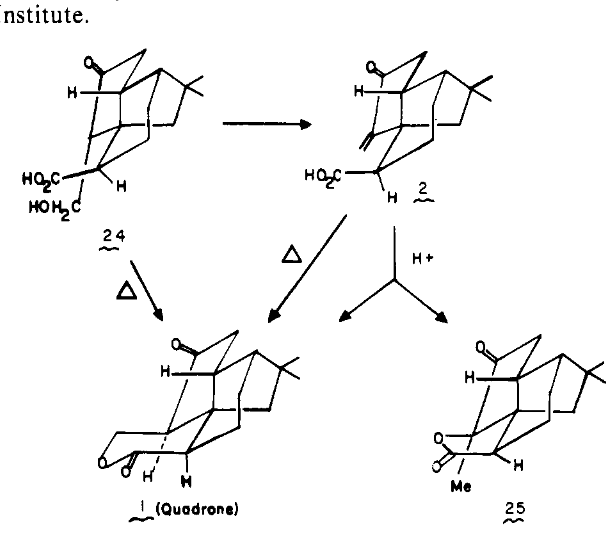
*carbomethoxy group.* NMR examination of the crude reaction mixture did not reveal the presence of epimeric tricyclic ketal ester.[15] The formation of **18** implies that the reacting enolate derived from **17** is in the rotameric state shown in **17a.** The reasons for this conformational specificity remain to be understood.

Deprotection ($p$-TsOH, acetone) of **18** afforded the keto ester **19**,[7] mp 49-51 °C, which upon alkaline hydrolysis (aqueous KOH, dioxane, reflux 1 h) gave acid **20**,[7] mp 132-135 °C, in 90% yield from **18.** A variety of experiments probing the regiochemistry of $\alpha$-substitution reactions about the ketone in compounds **19** and **20** indicated the exclusive formation of products derived from enol **21.**[16-18] Accordingly, keto acid **20** was subjected to selenenylation[18] (PhSeCl, ethyl acetate, room temperature 2.5 h). Oxidative treatment ($CH_2Cl_2$, $H_2O_2$, pyridine, room temperature) of the resultant $\alpha$-phenylseleno ketone afforded the enone acid, **22**,[7] mp 142-146 °C, in 87% yield from **20.** *It was our intention to use the $\alpha,\beta$ unsaturation in* **22** *to force enolization in the required $\alpha'$ sense. Thus, enolization in the extended mode is prohibited by the bridgehead nature of the $\gamma$ carbon.*

Treatment of **22** with 3 equiv of lithium diisopropylamide (THF, −23 °C, 1 h), followed by quenching of the resultant dianion with gaseous formaldehyde, afforded a 62% yield of crystalline hydroxymethyl keto acid **23**,[7] mp 156-158 °C, which, upon catalytic reduction ($H_2$, Pd/C, EtOAc-MeOH, room temperature, ~1 atm), gave a nearly quantitative yield of **24**,[7,19] mp 153-155 °C.

Treatment of **24** with $p$-TsOH in benzene at 40-50 °C smoothly afforded the presumed biologically active intermediate **2**,[7] as a nicely crystalline solid, mp 177-179 °C. The stage was now set to conclude the total synthesis of quadrone. Treatment of **2,** so generated, with $p$-TsOH in benzene under reflux afforded the long sought *dl*-quadrone **1** (vide infra), but only as the minor product. Surprisingly, the major product of this reaction was its isomer **25**[7,20] (**25:1** $\simeq$ 7:3).

Fortunately for our purposes, when **2** was heated in the absence of solvent from 190 to 195 °C for 5 min, there was produced *dl*-quadrone, mp 140-142 °C, free of its isomer **25.** Adding still further to the simplicity of the synthesis was the finding that pyrolysis of **24**[21] under the same conditions also afforded only *dl*-quadrone. The solution ($CHCl_3$) IR, NMR ($CDCl_3$, 270 MHz), and mass spectra of the *dl*-quadrone, as well as its chromatographic mobility, were indistinguishable from those obtained from a sample of the natural product furnished by Dr. Matthew Suffness of the National Cancer Institute.




The total synthesis of quadrone was thus achieved in 19 steps in 1.4% yield from cyclopentenone **5.** Efforts to improve the overall yield are in progress. The results of those investigations as well as a full description of the studies described herein will be provided in due course.

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## References and Notes

(1) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978,** 499.
(2) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978,** *31,* 38.
(3) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971,** *14,* 1147.
(4) While considerable progress in the direction of this esthetically commendable goal has been achieved (R. C. Gadwood, unpublished results), this objective has not been fully met. On the other hand, the method described here (**20** → **22** → **23** → **24** → **2**), while somewhat lengthy, is in fact easily carried out in high yield).
(5) Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *J. Am. Chem. Soc.* **1976,** *98,* 6317.
(6) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975,** *97,* 2503.
(7) The structure assigned to this compound is consistent with its IR, NMR, and mass spectra.
(8) Boeckman, R. K., Jr. *J. Org. Chem.* **1973,** *38,* 4450.
(9) Welch, S. C.; Chayabunjonglerd, S. *J. Am. Chem. Soc.* **1979,** *101,* 6768.
(10) For a recent use of compound **6** as an alkylating agent see Stork, G.; Taber, D. F.; Marx, M. *Tetrahedron Lett.* **1978,** 2445.
(11) Typically the sequence **7** → **11** was carried out without purification of the intermediates; **11** was purified in only a preliminary fashion (silica gel flash chromatography) prior to cyclization. The overall yield from **7** → homogeneous **4** in this way was 40-42%.
(12) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976,** 163.
(13) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973,** *3,* 67.
(14) With this decarboxylation, the potential for regiochemical control implicit in the $\beta$-dicarbonyl system was forfeited. The solution described here circumvents the need for this control. In ongoing investigations, we are still attempting to exploit more fully the functionality in **13.**[4]
(15) In addition to **18** there could be found smaller amounts of bromide **16** (due to incomplete Finkelstein reaction) and more complex material possibly arising from intermolecular alkylation.
(16) These included (i) reaction of either **19** or **20** with formaldehyde under various acidic conditions, (ii) reaction of **19** with Bredereck's[17] reagent, and (iii) selenenylation **19** (as well as **20**) under standard conditions.[18] It should also be noted that enol silylation of **19** using lithium diisopropylamide afforded the silyl enol ether corresponding to **21.**
(17) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, R. *Chem. Ber.* **1968,** *107,* 41.
(18) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973,** *95,* 6137.
(19) The stereochemistry of the hydroxymethyl group in compounds **23** and **24** is not known. The nonspontaneity of lactonization may be taken to suggest an $\alpha$ configuration of this group, though this is not clear.
(20) The formation of **25** under acidic conditions may involve prior enolization of the ketone. Lactonization to **25** would occur via the allylic carbonium ion derived from protonation of this enol at the methylene carbon. The equilibria between **2**, **25**, and **1** are currently being studied.
(21) Careful TLC monitoring of this transformation demonstrated that it proceeds through intermediate **2**, rahter than by direct lactonization to **1**.[19]

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## Asymmetric Induction in the Reaction of Osmium Tetroxide with Olefins

*Sir:*

Of the existing methods[1,2] for direct conversion of olefins into cis-vicinal diols, the most reliable method continues to be the reaction of an olefin with a stoichiometric amount of os-

 