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# SYNTHETIC STUDIES DIRECTED AT (±)-QUADRONE. A NEW END GAME.

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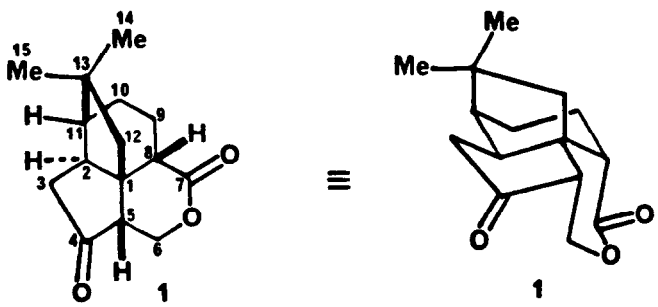
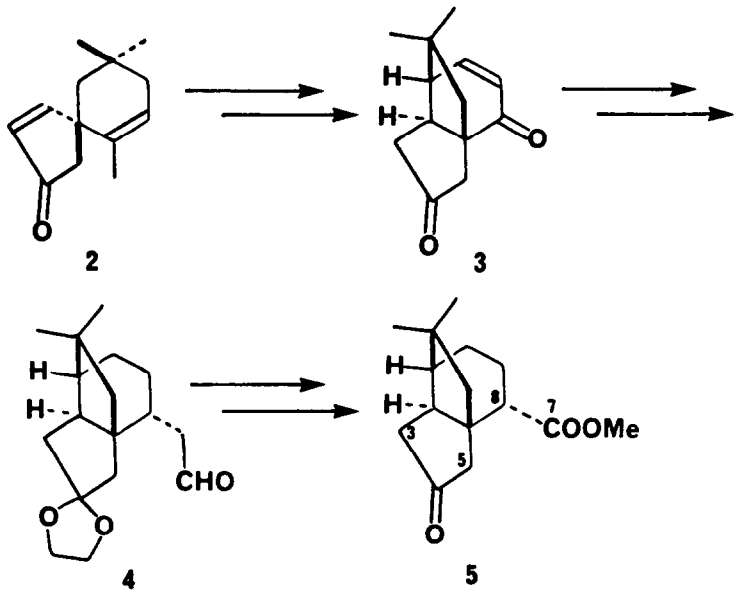
Summary: A synthesis of (±)-quadrone (1) is described, featuring an intramolecular delivery of the C(6)-carbon, thus avoiding possible regio- and stereochemical complications in the δ-lactone construction.

Sir: We recently reported[1] a formal total synthesis of (±)-quadrone (1), a fungal metabolite from Aspergillus terreus which exhibits in vitro and in vivo cytotoxicity.[2] This effort proceeded from the spiro[4.5]decadienone 2, via the tricyclic enedione 3, to the acetaldehyde derivative 4. Oxidative dehomologation followed by deketalization afforded the tricyclic keto




ester 5, a point of intersection with an earlier synthesis of (±)-quadrone by Danishefsky and co-workers.[3a] Although this one-carbon degradation was serviceable in securing a formal synthesis, we were dissatisfied with the excision of a carbon atom from 4, only to face the non-trivial introduction of the incipient C(6)-carbon at the C(5)-site.[4] We describe herein a sequence by which 4 is converted directly to (±)-quadrone (1), thus avoiding the wasteful dehomologation.

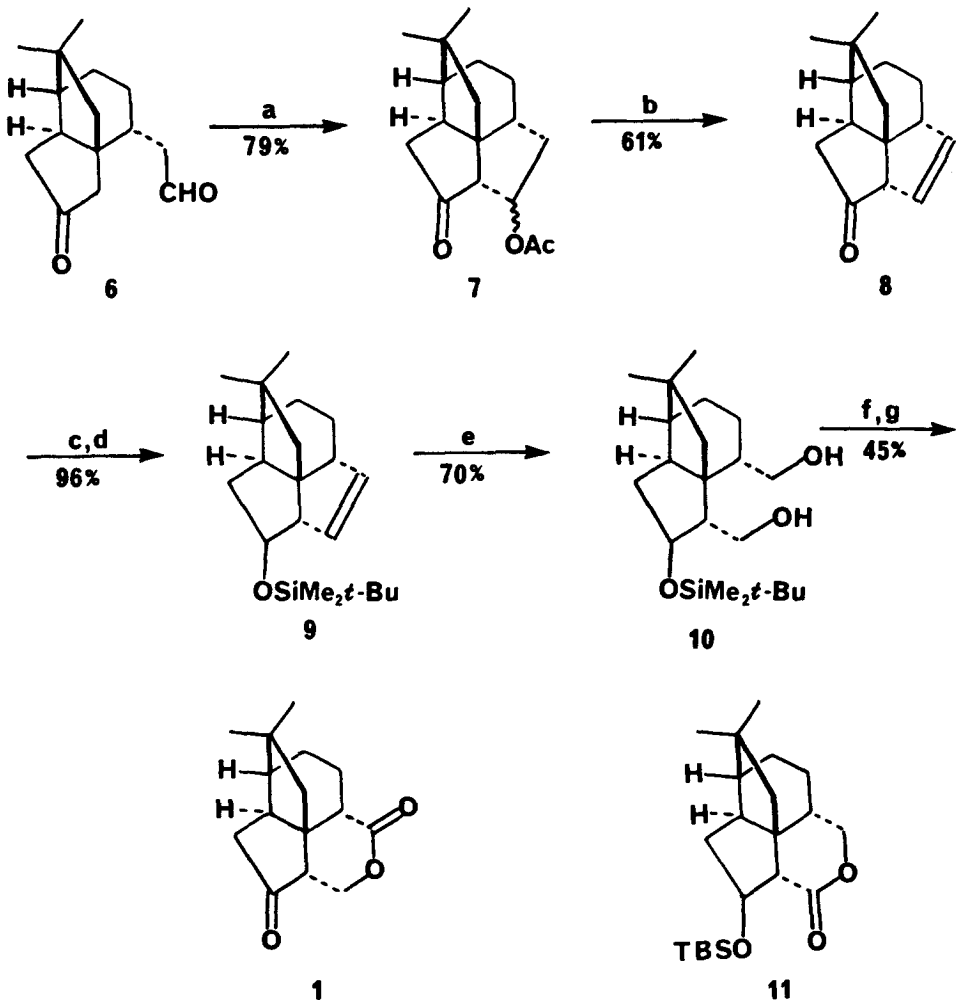



The requirements for the conversion of 4 to 1 were as follows: (1) the formation of the C(5)-C(6) bond, with the aldehyde carbon serving as C(6); (2) the upward and downward adjustments of oxidation state, respectively, at the incipient C(7) and C(6) sites; (3) the disconnection of these two carbons in 4 and their reattachment through oxygen to give the δ-lactone unit in 1. These requirements were met as outlined in the Scheme.

Deketalization of 4 (2N HCl, acetone, 25°C, 3 h) gave the aldehyde 6 (mp 77-79°C) in 86% yield. Acid-catalyzed aldol cyclization (HOAc, $H_2SO_4$, 25°C, 27 h) provided a mixture (4:1 by $^1H$ NMR) of the β-acetoxyketones 7 (79%) which, upon thermolysis (neat, sealed tube, 400°C, 4 min), afforded a 61% yield of tetracyclic, β,γ-unsaturated ketone 8, along with a 33% yield of the corresponding α,β-unsaturated isomer. Reduction of the ketone carbonyl ($LiAlH_4$, $Et_2O$, -30°C, 1 h), followed by hydroxyl protection [t-$BuMe_2SiCl$ (2 equiv), imidazole (4 equiv), DMF, 25°C, 2 h][5] gave a single t-butyldimethylsilyl ether 9 in 96% yield.[6] Ozonolysis of 9 followed by reductive work-up of the crude product ($NaBH_4$, EtOH, 0→25°C) provided a 70% yield of the crystalline diol 10 (mp 139-140°C).

A two-stage oxidation of 10 to give (±)-quadrone (1) was accomplished by two methods, with comparable efficiency. Treatment of 10 with pyridinium chlorochromate[7] (3 equiv, NaOAc, $CH_2Cl_2$, 0→25°C) followed by Jones oxidation[8] (0→25°C, 25 min) gave (±)-quadrone (1) (mp 139-141°C; lit.[3a] 140-142°C) in 45% yield. Alternatively, treatment of 10 with Fetizon's reagent[9] ($Ag_2CO_3$-Celite, PhH, reflux, 40 min) followed by Jones oxidation[9] also afforded a 45% yield of crystalline (±)-quadrone (1). In each case, the racemic quadrone so produced was identical by IR, MS, TLC, and 400 MHz $^1H$ NMR data to a sample generously supplied by Professor Danishefsky. The modest overall yields of quadrone from these two-stage oxidations reflect a lack of regioselectivity in the diol-to-δ-lactone conversion. The regioisomeric lactone 11 was isolated in 43% and 47% yields, respectively, after the initial oxidation steps by PCC or Fetizon's reagent.[10]

Scheme[a]




[a](a) HOAc, $H_2SO_4$, 25°C, 27 h. (b) neat, sealed tube, 400°C, 4 min. (c) $LiAlH_4$, $Et_2O$, -30°C, 1 h. (d) t-$BuMe_2SiCl$ (2 equiv), imidazole (4 equiv), DMF, 25°C, 2.5 h. (e) $O_3$, $CH_2Cl_2$/MeOH, -78°C; $Me_2S$, -78°C; $NaBH_4$, EtOH, 0 → 25°C. (f) PCC (3 equiv), $CH_2Cl_2$, NaOAc, 0 → 25°C or $Ag_2CO_3$-Celite, PhH, reflux, 40 min. (g) Jones reagent, 0 → 25°C, 25 min.

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(2) (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.

(3) (a) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. J. Am. Chem. Soc. 1981, 103, 4136. For other syntheses of (±)-quadrone, see:
(b) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. Ibid. 1981, 103, 4647. (c) Kende, A. S.; Roth, B.; Sanfilippo, J.; Blacklock, T. J. Ibid. 1982, 104, 5808. (d) Takeda, K.; Shimono, Y.; Yoshii, E. Ibid. 1983, 105, 563. The Kende and Yoshii syntheses are formally based upon the Danishefsky total synthesis.

(4) The observations by Danishefsky (ref. 3a) and Helquist (ref. 3b) indicate that the α-functionalization of the cyclopentanone in 5 and similar systems proceeds selectively, but with the wrong regiochemistry [at C(3), not C(5)] or with the undesired stereochemistry [β at C(5)]. Both authors were able to skirt these unfortunate tendencies.

(5) Corey, E. J.; Venkateswarlu, A. J. Am. Chem. Soc. 1972, 94, 6190.

(6) Note that although the reduction is completely stereoselective, the orientation of the siloxy-substituent is unassigned. This is of little consequence in that the stereocenter is subsequently obliterated.

(7) Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 2647.

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(9) Fetizon, M.; Golfier, M.; Louis, J.-M. Tetrahedron 1975, 31, 171.

(10) All yields reported herein refer to chromatographically homogeneous, isolated material. All structural assignments are fully supported by IR, MS, $^{13}C$ NMR, 400 MHz $^{1}H$ NMR, and combustion analysis data.

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