mate is very rapid (complete within 20 min at room temperature) and that the free amine could be obtained in good yield after chromatography. Competing N-allylation[3] is apparently not a problem since the deprotected material exists in the reaction mixture as a silylated carbamate[11] rather than the free amine.

Conversion of the acetoacetate ester (entry 6) to a trimethylsilyl ester is interesting in light of results[12] obtained from the reaction of allyl acetoacetate with palladium catalysts in the absence of nucleophiles. It appears that in the present instance, desilylation of the π-allyl complex by the acetoacetate ion occurs more readily than decarboxylation and subsequent alkylation. This result encouraged an examination of the deprotection of the β-keto ester **3**, a key intermediate in the synthesis of thienamycin.[13] However under standard conditions it was predominantly converted to the novel ketone **5** (entry 7). Indications of the origin of this compound came from the following observations. If the reaction were stopped prior to reaching completion (after 40 min) an intermediate, the silyl ether of **3**, could be isolated (20% yield at 54% conversion). When the reaction was conducted in the presence of MeOH, the hydroxy ketone **4** was obtained as the major product. These results suggest that a trimethylsilyl ester is formed in the usual manner but that the silyl group is then transferred intermolecularly to any alcohol present. The β-keto acid then formed undergoes a facile decarboxylation to give the observed products.

Registry No. **1**, 90933-84-9; **2**, 92097-18-2; **3**, 92097-19-3; **3** (TMS ether), 92097-28-4; **4**, 92097-20-6; **5**, 92097-21-7; (*E*)-PhCH=CHCOCl, 17082-09-6; (*E*)-PhCH=CHCO$_2$H (1 ester), 92097-23-9; (*E*)-PhCH=CHCO$_2$H, 140-10-3; PhNCO, 103-71-9; PhNHCO$_2$H (1 ester), 92097-25-1; PhNH$_2$, 62-53-3; *p*-MeOC$_6$H$_4$NCO, 5416-93-3; *p*-MeOC$_6$H$_4$NHCO$_2$H (1 ester), 92097-26-2; *p*-MeOC$_6$H$_4$NH$_2$, 104-94-9; CH$_3$COCH$_2$CO$_2$H (1 ester), 92097-27-3; CH$_3$COCH$_2$CO$_2$TMS, 18457-02-8; CH$_3$COC(=N$_2$)CO$_2$H (1 ester), 92097-29-5; HC≡CCH$_2$TMS, 13361-64-3; CH$_2$O, 50-00-0; Pd(PPh$_3$)$_4$, 14221-01-3; cyclohexanecarbonyl chloride, 2719-27-9; cyclohexanecarboxylic acid (1 ester), 92097-22-8; cyclohexanecarboxylic acid, 98-89-5; Penicillin V (1 ester), 92097-24-0; Penicillin V (K salt), 132-98-9; diketene, 674-82-8; (3*S*,4*R*)-3-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-acetoxyazetidin-2-one, 76855-69-1.

(11) For practical reasons, these intermediates were not isolated but their existence was inferred from the gas evolution observed when the reaction mixture was poured onto a silica gel column.

(12) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199.

(13) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. C.; Bouffard, F. A.; *J. Am. Chem. Soc.* **1980**, *102*, 6161.

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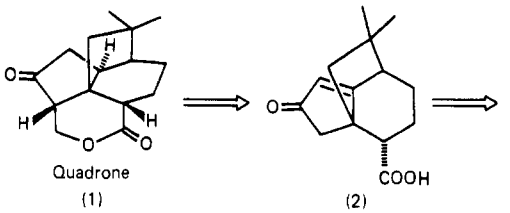
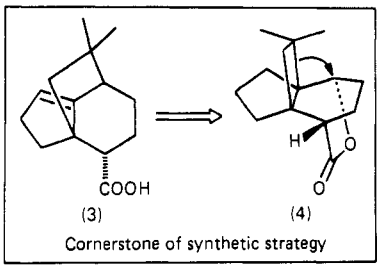
Total Synthesis of (+)-Quadrone: Assignment of Absolute Stereochemistry

Summary: The first total synthesis of quadrone in chiral nonracemic form is disclosed; assignment of the absolute stereochemistry is thereby secured.

Sir: Quadrone (**1**), a biologically active sesquiterpene, has been the focus of intense synthetic interest since its structure elucidation in 1978.[2] We also were enchanted with the quadrone architecture and report here the first total synthesis of quadrone in chiral nonracemic form. We note in advance that our approach is both short and highly efficient and permits for the first time assignment of the absolute stereochemistry.

The cornerstone of our strategy was envisioned to be the acid-catalyzed rearrangement of propellane **4** to olefin **3** (or a closely related derivative).[3] Allylic oxidation would then afford **2**, an advanced intermediate in the Danishefsky synthesis.[2c]





Our synthesis begins with the [2 + 2]-photochemical cycloaddition of isobutylene to bicyclic enone **5**[4] to afford a mixture of isomeric propellanes **6**[5] and **7**[5] (2:1, 74%). Treatment of this mixture with sodium methoxide in methanol leads via epimerization at C(5) to a new mixture enriched in the desired *anti*-propellanone **7** (1:5 of **6** to **7**, 84%), from which pure **7** could be obtained by crystallization (mp 48–50 °C). Reduction of **7** with NaBH$_4$, followed by reaction of the resulting alcohol with methanesulfonyl chloride and pyridine, afforded trans-substituted **8**[5,6] in quantitative yield from **7**.

Treatment of **8** with lithium methanethiolate in HMPA[7] afforded lactone **4**,[5] substrate for the key acid-catalyzed rearrangement; the yield was 65%.[8] To our delight,

(1) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; National Institute of Health (National Cancer Institute) Career Development Award, 1980–1985.

(2) For the isolation of quadrone, see: (a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499–502. (b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38–42. For total synthesis of *racemic* quadrone, see: (c) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. J. *J. Am. Chem. Soc.* **1981**, *103*, 4136–4141; **1980**, *102*, 4262–4263. (d) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *Ibid.* **1981**, *103*, 4647–4648. (e) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *Ibid.* **1982**, *104*, 872–874. (f) Takeda, K.; Shimono, Y.; Yoshii, E. *Ibid.* **1983**, *105*, 563–568. (g) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *Ibid.* **1982**, *104*, 5808–5810. (h) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146–1147. (i) Dewanckele, J. M.; Zutterman, F.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3235–3244.

(3) For a discussion of the stereoelectronic requirements for this rearrangement, see: Smith, A. B., III; Wexler, B. A. *Tetrahedron Lett.* **1984**, *25*, 2317–2320.

(4) Smith, A. B.; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845–1855.

(5) All new compounds gave 250-MHz ^{1}H NMR, IR, high-resolution mass spectra and/or satisfactory C, H combustion analysis in accord with the structure given. All yields recorded here are based upon isolated material which was 97% pure.

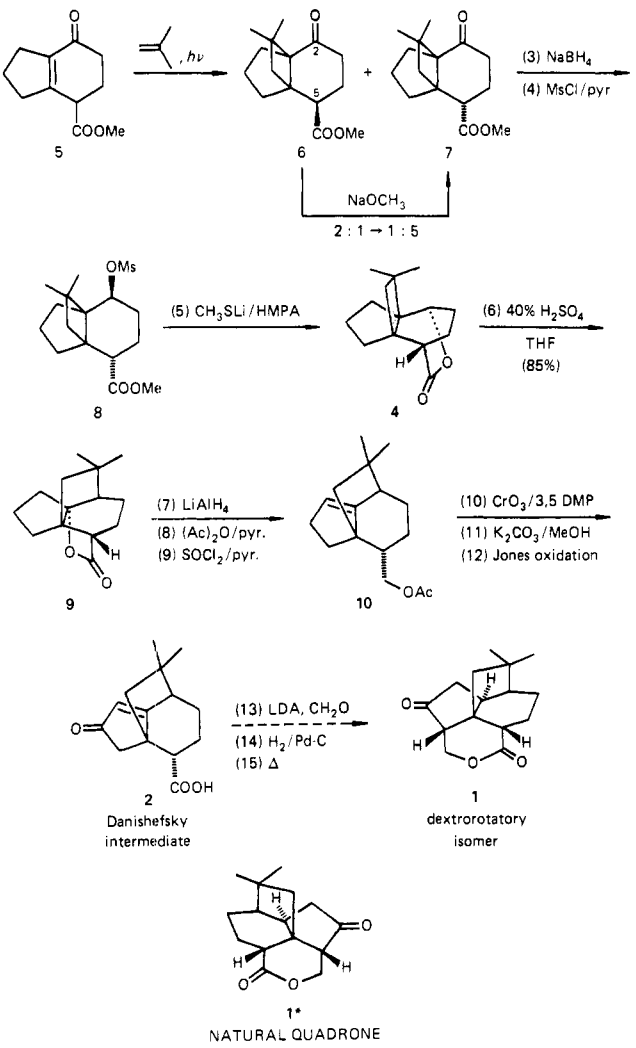
(6) Reduction occurs stereoselectivity from the anti face of the molecule.

(7) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859–3860.

(8) We have also explored the reaction of **8** with KO$_2$/18-crown-6. While we obtained yields of **4** as high as 70%, the reaction proved capricious and was abandoned for the methanethiolate procedure. For the use of KO$_2$/18-crown-6, see: Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183–3186.

0022-3263/84/1949-4094$01.50/0

Scheme I

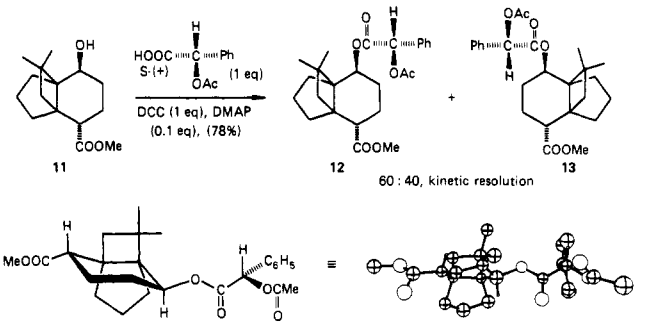


acid-catalyzed rearrangement of **4** (40% H_2SO_4, THF, 50 °C, 1 h, 85%) yielded a new lactone assigned structure **9**[5] by virtue of a strong IR band at 1760 cm^{-1}, by the absence of a resonance in the ^1H NMR spectrum for the functionality $R_2C(H)O$, and by the subsequent transformation of **9** to quadrone (vide infra).

With the carbocyclic skeleton of quadrone intact, reduction of **9** with $LiAlH_4$ to the corresponding diol (95%), followed by protection of the primary hydroxyl group [$(Ac)_2O$, pyridine], and elimination of the tertiary hydroxyl group [$SOCl_2$, pyridine, 85% for the two steps], afforded olefin **10**.[5] Transformation of **10** to **2** involved allylic oxidation (CrO_3, 3,5-dimethylpyrazole),[9] hydrolysis of the acetate functionality (K_2CO_3, methanol, 72% for the two steps), and Jones oxidation (90%). The resulting crystalline material was identical (250-MHz NMR, IR, and TLC) with an authentic sample kindly provided by Professor Kende.[10] Since compound **2** has been converted into (±)-quadrone in three steps (36%),[2c] the synthesis presented in Scheme I would afford racemic quadrone in 15 steps and 6.3% overall yield from **5**.[11]

For the synthesis of quadrone in nonracemic form, trans hydroxy ketone **11**[5] was reacted with (*S*)-(+)-*O*-acetylmandelic acid[12] (DCC, DMAP, CH_2Cl_2, 78%) to yield a

Scheme II



diastereomeric mixture of adducts separable by HPLC (see Scheme II). The major isomer[13] was subjected to single-crystal X-ray analysis. The derived ORTEP diagram indicates that, given the *S* configuration of the mandelate residue, the crystalline diastereomer has structure **12**.[5]

Removal of the chiral auxiliary[14] was then effected with $NaOCH_3$ (96%) to afford the dextrorotatory enantiomer of **11** (absolute configuration as shown in Scheme II). Submission of (+)-**11** to the synthetic sequence,[15] including the three steps needed for the transformation of **2** to quadrone, afforded **1** [mp 177–178 °C; $[\alpha]_D$ +49.8° (*c* 0.62, EtOH)], the enantiomer of the natural product [mp 181–182 °C; $[\alpha]_D$ −51.8° (*c* 0.59, EtOH)]. It follows therefore, that the naturally occuring levorotatory enantiomer of quadrone has the opposite absolute configuration to **1** and should be depicted by **1***.

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Registry No. **1**, 87480-01-1; **1***, 66550-08-1; (±)-**2**, 78739-64-7; (±)-**4**, 92096-28-1; (±)-**5**, 80953-80-6; (±)-**6**, 92096-22-5; (±)-**7**, 92216-07-4; (±)-**8**, 92096-23-6; (±)-**9**, 92096-24-7; (±)-**10**, 92096-25-8; (+)-**11**, 92216-09-6; (±)-**11**, 92096-26-9; **12**, 92096-27-0; **13**, 92216-08-5; (*S*)-(+)-*O*-acetylmandelic acid, 7322-88-5; isobutylene, 115-11-7.

(9) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **19788**, *43*, 2057–2059.

(10) We thank Professor Kende (Rochester) for kindly providing an authentic sample of racemic **2**.

(11) Confirmation of the 6.3% overall yield derives from completion of the chiral nonracemic synthesis (vide infra).

(12) Breitholle, E. G.; Stammer, C. H. *J. Org. Chem.* **1974**, *39*, 1311–1312.

(13) An approximately 3:2 mixture of **12** to **13** was obtained even in the presence of excess reagents.

(14) For preparative purposes, (*S*)-(+)-*O*-methylmandelic acid was employed as the resolving agent. The same 3:2 ratio of diastereomers was obtained, with the major diastereomer again producing the dextrorotatory enantiomer of **11**. For the synthesis of (*S*)-(+)-*O*-methylmandelic acid from (*S*)-(+)-mandelic acid, see: Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126–3132.

(15) Circular dichroism analysis suggested that the absolute configuration of natural quadrone was **1** (Scheme I), indicating that (+)-**11** should be employed in the synthesis. The error of this analysis is unknown at the present time; however, it should be noted that the CD analysis of cyclopentanones has proven to be problematic; see: Tichy, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2673–2684. Snatzke, G. *Tetrahedron Lett.* **1972**, 4275–4278.

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