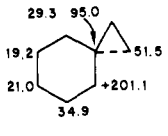

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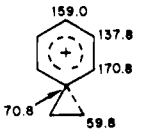

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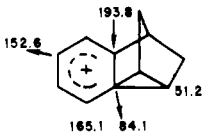

7

The secondary spiro cation **1** upon warming to −10 °C irreversibly rearranges to the thermodynamically more stable, well characterized,[15] rapidly equilibrating bicyclo[3.3.0] oct-1-yl cation (**5**). We are continuing our studies on the effect of a spiro cyclopropane ring adjacent to a carbocationic center in various medium and small sized rings.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

(15) G. A. Olah, G. Liang, and P. W. Westerman, *J. Org. Chem.*, **39**, 367–369 (1974).

Preparation of Lactone Systems. Total Synthesis of (±)-Quadrone

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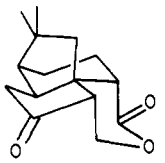
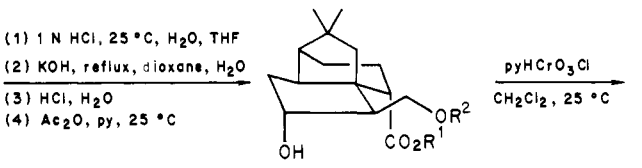
A few years ago, quadrone (**1**) was obtained as a metabolite of the fungus *Aspergillus terreus* and was found to display significant in vitro activity against KB human epidermoid carcinoma of the nasopharynx (ED_{50} 1.3 μg) and in vivo activity against P388 lymphocytic leukemia in mice. The structure of **1** was determined definitively by single-crystal X-ray diffraction, although the absolute configuration of the compound was not demonstrated.[1]



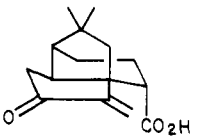
1

Because of its biological activity and the intriguing nature of its tetracyclic ring system, which includes a δ-valerolactone moiety, quadrone appeared to be an attractive synthetic target for the application of our recently developed methodology for the construction of various types of six-membered lactone ring systems.[2] However, while we were nearing the completion of our work, a synthesis was reported by Professor Danishefsky.[3] Although the basic strategy of our approach to quadrone overlaps considerably with that of the earlier synthesis, key elements of the methodology employed in the two routes are quite different. Most importantly, the use of our lactone annulation procedure[2] permits us to avoid the serious regiochemical difficulties encountered by Danishefsky in the introduction of the lactone ring of the natural product.

The starting material, 5,5-dimethylcyclopenten-3-one (**2**),[4] is subjected to copper-catalyzed 1,4-addition of vinylmagnesium bromide,[5] and the resulting enolate is trapped[6] as the trimethylsilyl enol ether **3** (Scheme I). Subsequent application of the cyclopentenone annulation procedure recently developed by Piers[7] affords the bicyclic enone **4**[8,9] in 37% overall yield for the four-step transformation (enolate regeneration, alkylation, enol ether hydrolysis, and intramolecular Horner–Emmons reaction). Through use of our approach to δ-valerolactone systems,[2] we planned next to fuse the lactone ring of quadrone onto **4**. Because of the highly folded nature of bicyclo[3.3.0]octane systems, we assumed that the overall process of 1,4-addition of the lithium enolate of methyl phenylmercaptoacetate and formaldehyde condensation would occur in a syn fashion on the convex face of the ring system. When this sequence is employed, a β-hydroxy ketone is indeed obtained in 68% yield, but lactonization with the acetate group fails to occur under the usual conditions. Instead the hydroxy ketone undergoes facile dehydration to an unstable α-methylene ketone. These findings led us to hypothesize that the 1,4-addition/condensation sequence occurs with anti stereochemistry, as confirmed by X-ray analysis of a later intermediate (vide infra). To offset these difficulties, the initially obtained hydroxy ketone, without purification, is reduced with sodium borohydride to a diol which is then protected as the acetonide to give **5**[9,10] in an overall yield of 47% from **4**. Desulfurization with lithium in liquid ammonia yields the olefinic ester **6**[9] which is modified for intramolecular alkylation by hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN),[11] tosylation of the resulting alcohol **7**,[9] and conversion of the crude tosylate into the iodo ester **8**.[9] Alkylative cyclization of the lithium enolate of **8** efficiently produces **9**,[9] having the desired α orientation of the carbomethoxy group[12] as indicated most clearly by the later X-ray analysis. Acid-catalyzed hydrolysis of the acetonide gives the dihydroxy ester **10** which may then be



10, $R^1 = CH_3$; R^2 = H (70%)
11, $R^1 = R^2$ = H (100%)
12, R^1 = H; R^2 = Ac (95%)



13 (67%)

saponified to the acid **11**. In order to confirm the stereochemical assignments made on the basis of spectroscopic data and chemical

(1) (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.
(2) Bornack, W. K.; Bhagwat, S. S.; Helquist, P., submitted for publication.
(3) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262–4263.
(4) Ryono, D. E.: Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 1889–1899.
(5) House, H. O.; Chu, C.-Y.; Phillips, W. V.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1977**, *42*, 1709–1717.
(6) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396–1403.
(7) Piers, E.; Abeysekera, B.; Scheffer, J. R. *Tetrahedron Lett.* **1979**, 3279–3282. See also: Begley, M. J.; Cooper, K.; Pattenden, G. *Ibid.* **1981**, *22*, 257–260. Klipa, D. K.; Hart, H. *J. Org. Chem.* **1981**, *46*, 2815–2816.
(8) The stereochemistry of this compound was ultimately assigned on the basis of the X-ray analysis of the later intermediate **11** but was initially inferred from the stereochemical outcome of 1,4-addition/alkylation sequences of related systems. See: Mitra, A. "The Synthesis of Prostaglandins"; Wiley: New York, 1977; pp 247–266.
(9) This compound was fully characterized spectroscopically, and the molecular composition was confirmed by elemental analysis and/or high-resolution mass spectrometry.
(10) This compound was obtained as a 1.5:1 mixture (^1H NMR) of diastereomers with respect to the relative configuration of the carbon atoms bearing the phenylthio substituent.
(11) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765–7770.
(12) Although the reasons for this stereochemical result are obscure, an analogous observation was made by Professor Danishefsky.[3] If the carbomethoxy group had been introduced in the equatorial β position, we had planned to epimerize this center at a later stage in which the lactone ring had been constructed and for which the desired configuration would clearly be the more stable orientation.

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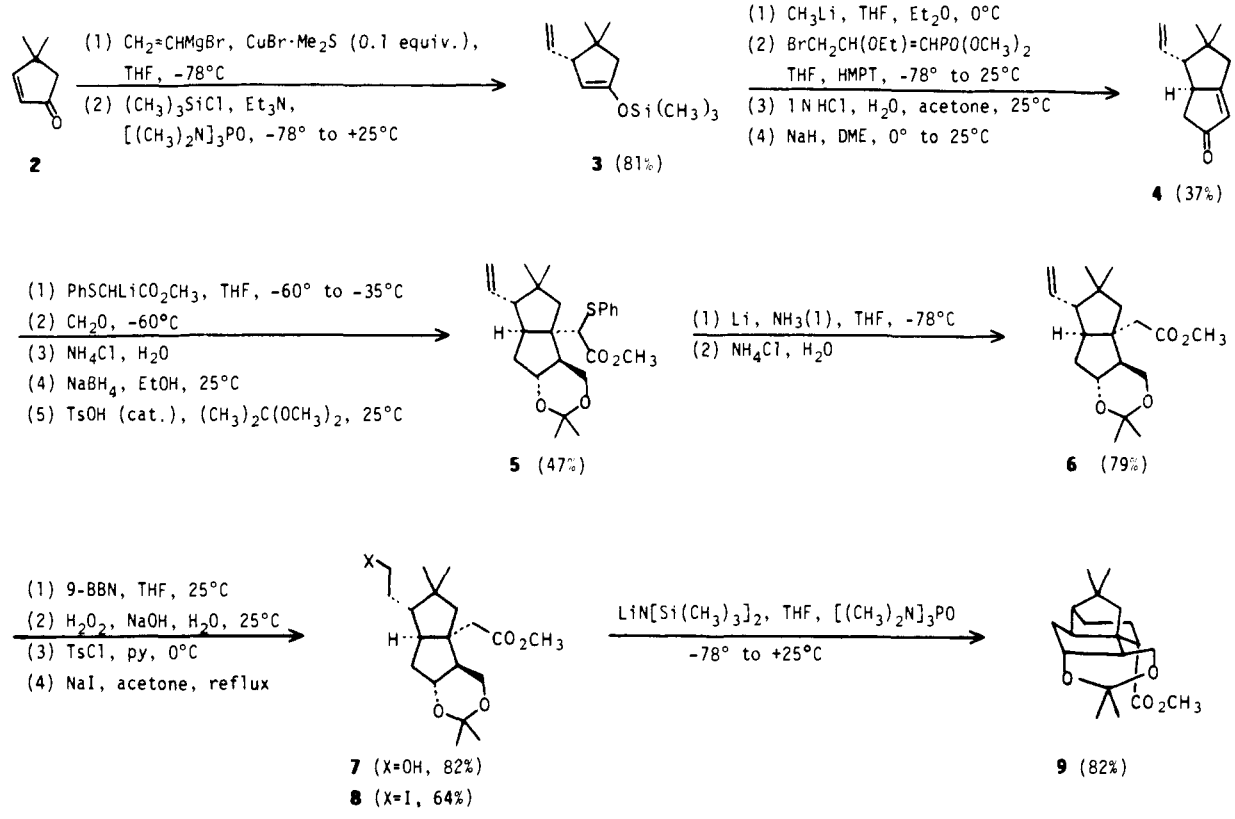
Scheme I



behavior of the earlier intermediates, the structure of this nicely crystalline dihydroxy acid was determined by single-crystal X-ray diffraction[13] which firmly established the structure as depicted by **11**. Treatment of the diol with acetic anhydride in pyridine produces selectively the primary acetate **12** which upon reaction with pyridinium chlorochromate[14] undergoes both oxidation of the remaining alcohol function and elimination of acetic acid to provide the α-methylene ketone **13** which was the final precursor of quadrone in the Danishefsky synthesis.[3] Comparison of ^{1}H NMR spectra of our sample and the earlier workers' material indicated their identity. Indeed, when **13** is placed in a flask at ca. 200 °C under nitrogen for 5–10 min, quadrone (**1**) is obtained directly. The synthetic material is identical with an authentic sample according to ^{1}H NMR, TLC, and GLC data.

In summary, we have completed a rather direct, regioselective synthesis of quadrone which is accomplished with excellent stereochemical control over four of the five chiral centers of the natural product and which serves as an important application of our approach to the construction of lactone ring systems. Further work is under way to introduce the fifth chiral center with the correct configuration and determine the absolute configuration[15] of quadrone by circular dichroism and X-ray studies of optically active derivatives of **11**. The details of this work will be published subsequently in a full paper.

(13) Compound **11** crystallizes from a mixture of acetone and pentane as triclinic prisms belonging to the space group $P\bar{1}$ with a = 6.102 (2), b = 7.439 (3), c = 15.63 (1) Å; α = 88.21 (6), β = 84.76 (6), γ = 76.67 (3)°; Z = 2. The data set was collected on an Enraf–Nonius CAD4A diffractometer by using Mo Kα X radiation in the range $0 < 2\theta \leq 40°$. The structure was solved by using the Multan direct method programs and refined to unweighted and weighted R values of 0.088 and 0.100, respectively, for the 172 variables and 493 observations with $F_o \geq 3\sigma(F_o)$. The computations were performed on a PDP 1145 computer by using the Enraf–Nonius Structure Determination Package developed by Okaya and Frenz. See: Okaya, Y. In "Computing in Crystallography"; Schenk, H., Olthof-Hazekamp, R., van Koningsveld, H., Bassi, G. C., Eds.; Delft University Press: The Netherlands, 1978; pp 153–165. Frenz, B. A. *Ibid.*, pp 64–71.

(14) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.

(15) The absolute configuration of quadrone was not determined in the original structural studies of the natural material, although X-ray diffraction was used to assign the structure.[1]

Acknowledgment. We express our appreciation to Dr. R. L. Ranieri (W. R. Grace & Co.) for providing an authentic sample of quadrone, Professor S. Danishefsky and K. Vaughan (Yale University) for supplying NMR spectra of compound **13**, Professor E. Piers (University of British Columbia) for informing us of the experimental details of his annulation procedure,[7] and Professor J. W. Lauher (SUNY) for his assistance with the X-ray diffraction study. We also acknowledge financial support received from the National Institutes of Health, DHEW (Grant CA20701 and CA22741).

Evidence for Migratory Insertion of a Methylidene Ligand into a Transition Metal–Methyl Bond

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Recent evidence suggests that insertion of surface-bound methylidene groups into transition metal–alkyl linkages may be the key chain growth step in Fischer–Tropsch reactions,[1] and it has been believed for some time that similar insertions are involved in the formation of polymethylene from diazomethane in the presence of some organometallic complexes.[2] However, only one example has been reported of a stoichiometric reaction of a complex containing an alkylidene ligand, lacking stabilizing heteroatomic substituents, which appears to involve insertion of the alkylidene ligand into an adjacent transition metal–alkyl bond.[3]

†Undergraduate research participant.

(1) (a) Brady, R. C.; Pettit, R. *J. Am. Chem. Soc.* **1980**, *102*, 6181. (b) Ibid. **1981**, *103*, 1287.

(2) Mango, F. D.; Dvoretzky, I. *J. Am. Chem. Soc.* **1966**, *88*, 1654.

(3) Sharp, P. R.; Schrock, R. R. *J. Organomet. Chem.* **1979**, *171*, 43.

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