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SYNTHESIS OF (±)-DESCARBOXYLQUADRONE

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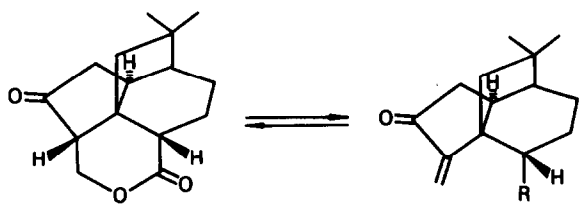
Summary: The synthesis of a biologically active analogue of the antitumor agent quadrone, termed descarboxylquadrone (3), is described.

In 1978 the structure including stereochemistry of the fungal metabolite quadrone (1) was shown by a group at W. R. Grace Co., through aegis of a single crystal X-ray analysis, to be a novel polycyclic sesquiterpene.[2] Although lacking the functionality commonly associated with many antitumor agents (i.e. electrophilic centers such as an α-methylene lactone or ketone),[3] quadrone did display significant inhibitory activity *in vitro* against the cell line developed from human epidermoid carcinoma of the nasopharynx (KB) and presumptive activity *in vivo* against P-388 lymphocytic leukemia in mice (PS).[2] No explanation for the reported antineoplastic activity however was put forth at the time the structure was announced. Towards this end two groups (Smith at Penn[4] and Danishefsky at Yale[5]) suggested that quadrone is an ideal latent α-methylene cyclopentanone (1→ 2) and that it is the α-methylene ketone functionality that is responsible for the observed cytotoxic activity. Interestingly, the ability to control the equilibrium between quadrone and the presumed biologically active, open form (2) served as the ultimate transformation in each of the successful total synthesis of this most challenging synthetic target.[5-7]

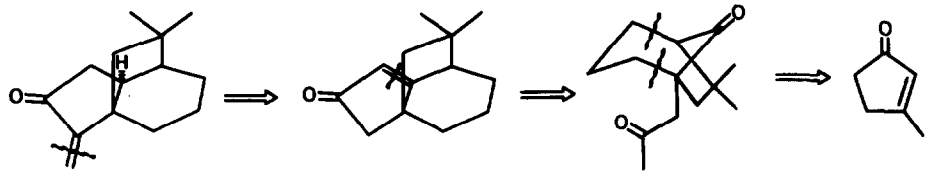


(1)
Quadrone

(2) R = COOH
(3) R = H

In connection with our ongoing program in this area, we wish to record here the synthesis of the *first biologically active analogue* of the quadrone skeleton; we term this analogue descarboxylquadrone (3).

As way of background, we note that by and large most active (and some passive) approaches to quadrone have been built on the premise of constructing initially a bicyclic [3.3.0]octane skeleton, with the subsequent goal of closing the required six membered carbocyclic ring and then in the final stages of the synthesis, elaboration of the δ-lactone system.[5-7] After careful consideration of this and several other strategies, we undertook construction of the model system, descarboxylquadrone (3), via the strategy illustrated below.



(3) (4) (5) (6)

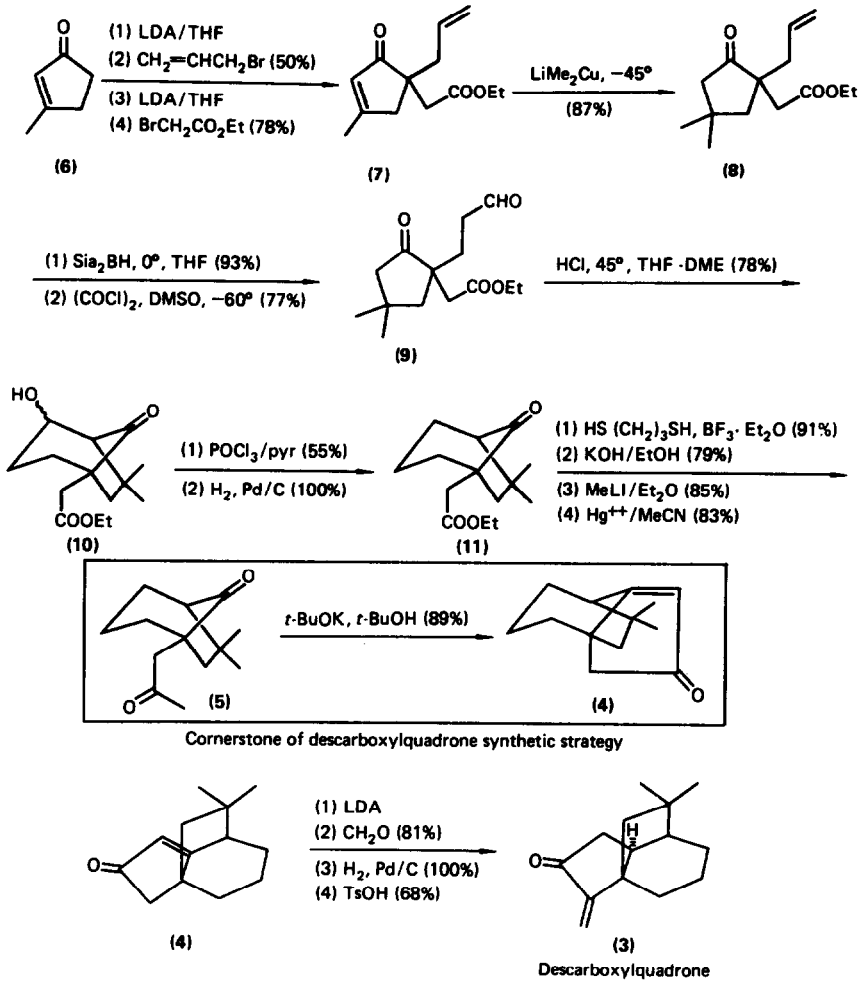
Central to this approach is the elaboration of a bicyclo[3.2.1]octane skeleton (i.e. 5). Subsequent closure of the five membered ring via aldol condensation and then introduction of the α-methylene ketone group taking advantage of the regioselectivity provided by the cyclopentenone functionality would then lead to descarboxylquadrone (3).

With the above goal in mind, we initiated this venture via alkylation of the kinetically derived enolate of 3-methyl-2-cyclopentenone [1.1 eq LDA/THF, -78°],[8] first with allyl bromide and then again with ethyl bromoacetate. Conjugate addition[9] of lithium dimethyl copper [Et_2O, -45°] to the resultant enone (7)[10] then afforded saturated ketone 8[10] in 89% yield.[10c] Completion of the three carbon unit requisite for construction of the bicyclo[3.2.1]octane system was accomplished by hydroboration[11] of the terminal olefinic linkage with disiamylborane [2 eq/THF, 0°] followed by Swern oxidation[12] to give the desired aldehyde-ester 9[10] in 72% overall yield. Then, employing the procedure Corey utilized to great advantage in his picrotoxin synthesis,[13] 9 was treated with 2.0 eq of 3.5 N HCl in THF-DME [5:1 v/v] at 45° for 16 h to afford bicyclic alcohol 10[10] as a mixture of isomers.

With a viable approach to bicyclo[3.2.1]octanone 10 assured, we turned next to preparing the way for the aldol condensation proposed to complete the carbon skeleton of descarboxylquadrone. Towards this end it was necessary first to remove the hydroxyl group as well as homologate the side chain to an acetonyl unit. Without separation of the epimers of 10, the former was accomplished via dehydration with $POCl_3$ in pyridine at reflux [2.5 h, 55%] followed by hydrogenation [Pd/C, MeOH, 100%]. Chain homologation in turn entailed: (a) protection of the ketone carbonyl group as the thioketal [$HSCH_2CH_2CH_2SH/BF_3 \cdot Et_2O/CH_2Cl_2$, rt, 16 h],[14] (b) saponification of the ester functionality [10% KOH/EtOH], (c) reaction with 2.2 eq methyllithium [Et_2O/rt, 2 h][15] and (d) deprotection [$HgCl_2$-HgO/CH_3CN/H_2O(4:1 v/v), at reflux, 2 h][16] to afford 5.[10] The overall yield for this series of transformations was 51%, or an average yield of 85%/step.

The stage was now set for closure of the five membered ring, cornerstone of our synthetic strategy to descarboxylquadrone. After several unsuccessful attempts we were delighted to learn that treatment of 5 with 10 equivalents of potassium tert-butoxide in anhydrous tert-butanol at the reflux point afforded the desired tricyclic system (4)[10] in 89% yield.

Final conversion of enone 4 to descarboxylquadrone was then accomplished via the protocol employed by Danishefsky et al.[5] in their successful quadrone synthesis. More specifically, generation of the kinetic enolate of 4 [1.1 eq LDA/THF, -78°] and condensation with carefully distilled gaseous formaldehyde followed by hydrogenation [Pd/C, EtOAc, 92%] and acid catalyzed dehydration [TsOH/benzene] afforded descarboxylquadrone (3),[10] the overall yield from enone 4 being 68%. Confirmation that descarboxylquadrone (3) was indeed in hand derived from careful comparison of the 250 MHz ^1H NMR spectra of 3 with that of the open form of quadrone (2), the latter provided by Professor Danishefsky through the good auspices of Professor Schlessinger.[18]



Cornerstone of descarboxylquadrone synthetic strategy

In summation, the synthesis of the first biologically active[17] analogue of quadrone has been achieved in 16 steps and 3.2% overall yield based on 3-methyl-2-cyclopentenone (6). To demonstrate the efficacy of this approach several hundred milligrams of descarboxylquadrone were prepared for biological screening. Finally, to the best of our knowledge the key aldol closure (5 → 4) is unprecedented. Indeed, a central reason for initiating this model study was to demonstrate the feasibility of this transformation.

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References and Notes

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10. a) The structure assigned to each new compound was in accord with its infrared and 60 and/or 250 MHz NMR spectra as well as appropriate parent ion identification by high resolution mass spectrometry. b) In addition, analytical samples of new compounds, obtained by recrystallization or chromatography (LC or TLC) gave satisfactory C and H combustion analyses within 0.4% c) All yields recorded here are based upon isolated material which was > 97% pure. IR and 250 MHz NMR spectra data of representative intermediates are recorded below. 4: IR (CCl_4) 1705(s), 1640(m) cm^{-1}; NMR ($CDCl_3$) δ 0.94 (s, 3H), 1.26(s, 3H), 1.34 (d, J = 13 Hz, 1H), 1.44-2.0 (m, 5H), 2.0-2.18 (m, 2H), 2.29 (bs, 1H), 2.49 (bs, 1H), 2.49 (brs, 1H) 5.80 (s, 1H); 3: IR (CCl_4) 1720(s), 1625(w) cm^{-1}; NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.17 (s, 3H), 1.40-1.98 (m, 10H), 2.40 (d,d, J = 7.6 and 16.8 Hz, 1H), 2.62 (d,d, J = 10.6 and 16.8 Hz, 1H) 5.0 (d, J = 1.2 Hz, 1H), 5.80 (d, J = 1.2 Hz, 1H).
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17. As illustrated below, descarboxylquadrone displayed significant activity in the anti-HeLa test. We thank Dr. Tomohisa Takita [Director, Department of Chemistry, Microbial Chemistry Research Foundation, Institute of Microbial Chemistry, Tokyo, Japan] for screening descarboxylquadrone.

ANTI HeLa ACTIVITY OF QUADRONE AND DESCARBOXYLQUADRONE

Sample	*Dose (mcg/ml)*	*Cell number (× 10^5 cells/plate)*	*Inhibition (percent)*	*IC_{50} (mcg/ml)*
Quadrone	10	toxic	—	2.3
(1)	5	0.21	110.89	
	2.5	2.21	60.62	
	1.25	3.90	13.37	
Descarboxylquadrone	10	0.39	106.03	4.0
(3)	5	0.97	90.84	
	2.5	4.39	0.78	
	1.25	5.09	−17.66	
Control		4.42		

Cell number at drug addition: 0.62 × 10^5 cells/plate.

18. We wish to thank Professor Danishefsky and Schlessinger for valuable discussions and for making available a sample of the open form of quadrone (2).

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