Tetrahedron Letters,Vol.26,No.48,pp 5907-5910,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

STIPITATIC ACID: SYNTHESIS *VIA* CYCLOPROPANATED QUINONES*

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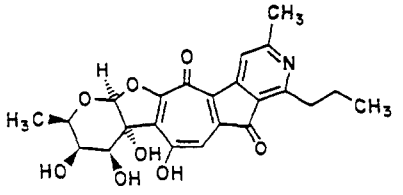
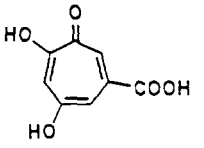
Abstract: A new synthesis of stipitatic acid incorporating a cyclopropanated quinone intermediate is reported.

The red, water soluble, microbial pigment rubrolone was shown by x-ray analysis of a heavy atom derivative to have structure 1.[1] The aromatic portion of rubrolone consists of a fused pyridine, cyclopentadienone and tropolone, thus forming a new and unique chromophore. As part of an interest in the synthesis of 1, we required a new method for the preparation of tropolones. Our work towards this goal is illustrated herein with a new synthesis of the mold metabolite, stipitatic acid (2)[2,3] which has a substitution pattern similar to the tropolone in rubrolone.



1

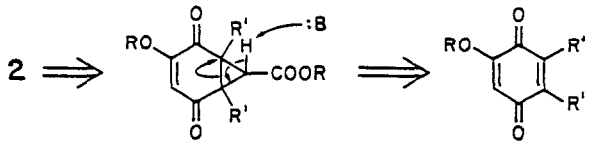


2

The concept behind this synthesis is shown in Scheme 1. It was felt that upon treatment with base, the bicyclic enedione 3, where the R' moieties are easily removable anion stabilizing groups, would form a seven-membered ring by cleavage of the internal carbon-carbon bond common to the three-membered and six-membered rings. Formation of either "stabilized" ketone enolate (one mode of fragmentation is illustrated in Scheme 1) would direct the course of reaction to this end. The bicyclic enedione 3 would be obtained by regiospecific cyclopropanation of quinone 4.

* Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

Scheme 1



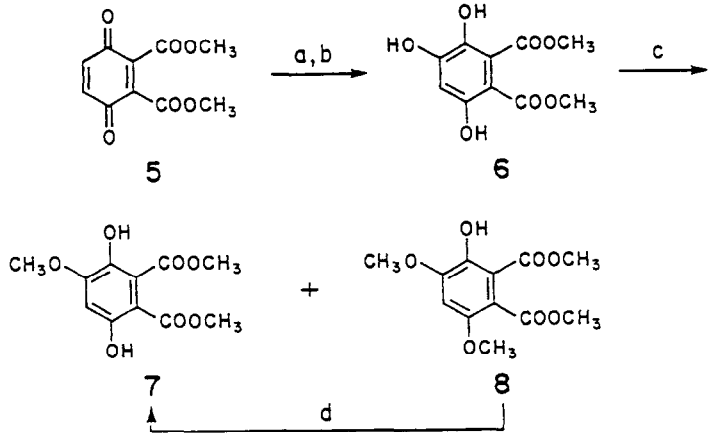
For the electron withdrawing groups R', methoxycarbonyl residues were chosen with the intent that they would eventually be removed by decarboxylation. Methyl groups were selected to serve as R, thus making 2,3-dimethoxycarbonyl-5-methoxy-p-benzoquinone (**4**, R = CH_3-, R' = CH_3O_2C-) the required starting material. A description of the synthesis of **4** follows:

Exposure of 2,3-dimethoxycarbonyl-p-benzoquinone (**5**)[4] to Thiele-Winter conditions (H_2SO_4, Ac_2O)[5] followed by acetate hydrolysis in methanolic sulfuric acid gave in 92% yield hydroxyhydroquinone **6**[6] (Scheme 2). Etherification of **6** with diazomethane at 0° in ether resulted in a mixture from which methoxyhydroquinone **7**[6] and the dimethyl ether **8**[6] were isolated in a 1.4:1 ratio (combined yield, 92%). The yield of **7**, however, was maximized (91%, overall) by treatment of **8** with boron trichloride in CH_2Cl_2 at -78° which effected selective cleavage of the methyl ether adjacent to the ester residue.[7] Oxidation of hydroquinone **7** with silver oxide at 50° in benzene gave in 95% yield the material required for cyclopropanation studies, methoxy-p-benzoquinone **9**[6] (**4**, R = CH_3-, R' = CH_3O_2C-).

Dimethylsulfonium carbomethoxymethylide **10** has been used to cyclopropanate electron deficient double bonds,[8] and seemed an ideal initial choice for the present study. The treatment of quinone **9** with ylid **10**[9] (Scheme 3) led smoothly to the bicyclic enedione **11**[6] (~100%). Although it is not rigorously shown, the available evidence (eg. a single singlet in the vinyl region of the NMR at δ 5.97) suggests that only one of the two possible cyclopropane isomers was formed. The critical conversion of the bicyclic enedione to a cycloheptatrienone, was accomplished by exposure of **11** to potassium hydride in dry glyme. Evolution of hydrogen gas ensued, and after routine workup, the 1,4-tropolone **12** was isolated in 59% yield as a crystalline solid.[6,10] To complete the synthesis, **12** was heated at 110° in 48% HBr for 6 hrs. Under these conditions the three methyl esters and the methyl ether were cleaved, and the resultant β-ketoacids underwent decarboxylation to give directly stipitatic acid, which was identical to an authentic sample of the natural product.[11] Progress has been made towards applying this methodology to a synthesis of rubrolone which will be published at a later date.

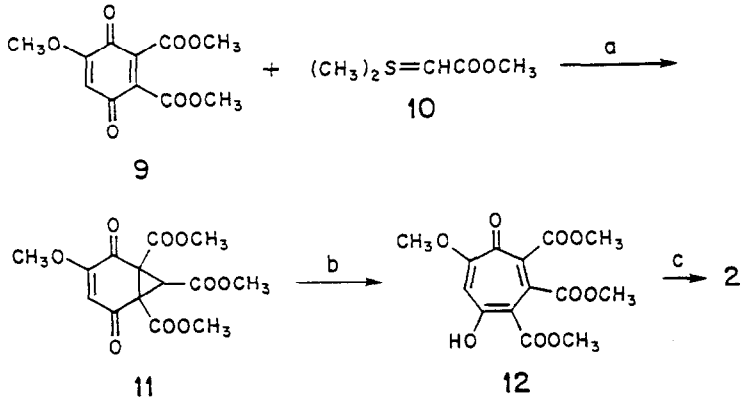
Acknowledgement: The able technical assistance of R. Yang and J. Tortora is gratefully acknowledged. Spectral and microanalytical analyses were carried out by the Physical Chemistry Department at Hoffmann-La Roche Inc.

Scheme 2



(a) H_2SO_4, Ac_2O, 25 °C, 6 days, 97%; (b) H_2SO_4, CH_3OH, reflux, 45 min, 95%; (c) CH_2N_2, Et_2O/CH_3OH, 0 °C, 53% (7); (d) BCl_3, CH_2Cl_2, −78 °C → 25 °C, 2 hr, 98%.

Scheme 3



(a) THF/DMSO, 0 °C, 1 hr, ~100%; (b) KH, Glyme, 25 °C, 2 hr, 59%; (c) 48% HBr, 110 °C, 6 hr, 50%.

References and Footnotes

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2. For isolation and structure determination of stipitatic acid, see: a) Birkinshaw, J. H.; Chambers, A. R.; Raistrick, H. *Biochem. J.* **1942**, *36*, 242. b) Dewar, M. *Nature* **1945**, *155*, 50-51. c) Corbett, R. E.; Johnson, A. W.; Todd, A. R. *J. Chem. Soc.* **1950**, 147-149.

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4. Ansell, M. E.; Nash, B. W.; Wilson, D. A. *J. Chem. Soc.* **1963**, 3028-3036.

5. Thiele, J; Winter, E. *Ann.* **1900**, *311*, 341.

6. Structure assignments for new compounds are supported by spectral data (including IR, NMR, UV and MS) and microanalysis.

7. Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, 4153-4159.

8. Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351-3355.

9. The ylid **10** was prepared by stirring a suspension of dimethyl methoxycarbonylmethyl sulfonium bromide and sodium hydride in dry THF/DMSO under an inert atmosphere at ambient temperature. After 4 hrs, a voluminous white precipitate (NaBr) was removed by filtration, and the filtrate placed in an addition funnel in preparation for addition to a solution of quinone **9**.

10. By showing the product of this reaction as 12, it is not intended to rule out the other possible tautomer. It may well be that the cyclopropane opening proceeds as shown in 3, which would give rise to the other tautomer. Opening the cyclopropane as shown in 3 gives rise to the enolate of a ketone, whereas the other mode of opening leads to the presumably less stable enolate of a vinylogous ester. In any event, the subsequent conversion of the product, whether it be 12, its tautomer, or a mixture of the two, to stipitatic acid makes the question of exact structure moot at least as far as the synthesis is concerned.

11. We gratefully acknowledge a gift of crude stipitatic acid from Professor Ian Scott. Recrystallization from water gave an analytically pure sample.

(Received in USA 18 June 1985)