

SYNTHESIS OF THOMASIDIOIC ACID

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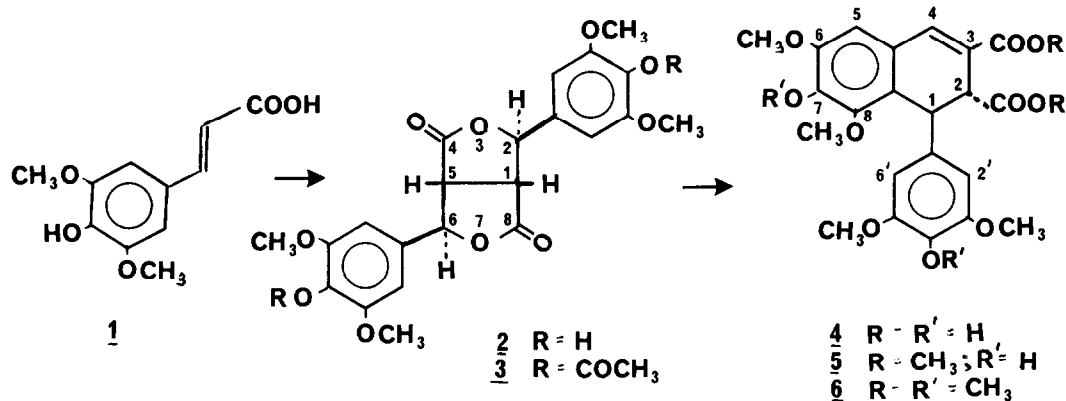
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Thomasidioic acid is a phenolic lignan isolated^{1,2} from aqueous extracts of the heartwood of Ulmus thomasii Sarg., one of several elms growing in the United States and known generally as "rock elm". Scrutiny of the proposed structure (4) for this product^{2,3} reveals features significantly unusual within the lignan class of natural products. Particularly noteworthy are the facts that thomasidioic acid and the congener thomasic acid (a) are the only known naturally-occurring members of the 1-aryl-1,2-dihydronaphthalene lignan structure group, (b) that they occur in racemic form despite the presence of two asymmetric centres (c) that they possess a free carboxyl group (only one other known lignan has this feature and (4) is the only known dicarboxylic acid) and (d) that they provide examples of an interesting steric environment in which vicinal trans substituents (at C-1 and 2) adopt diaxial conformations.³⁻⁵ The further noteworthy observation has been made in chemotaxonomic studies of Ulmus species⁶ that the same phenolic heartwood extractives, although absent in the sapwood, are found in the outer "brown ring" area, characteristically symptomatic of Dutch elm disease.

We report here a convenient biogenetic-type two-step synthesis of the novel lignan, thomasidioic acid (4) starting from the readily available⁷ sinapic

acid (1). Oxidative coupling of (1) in aqueous methanol by ferric chloride and oxygen (method first used by Erdtman⁸ and Haworth⁹ with ferulic acid) gives "dehydrodisinapic acid dilactone" (2) [m.p. 227-235° (softens ca. 200°)¹⁰; λ 5.63 μ (lactone); δ 3.85 (OCH₃), 3.94 d. (J=1.5Hz, H-1 and 5), 5.77 br.s. (H-2 and 6) and 6.75 (Ar-H)]. The derived diacetate (3) had m.p. 232-234° [δ 2.23 (acetate), 3.85 (OCH₃), 4.20 d. (J=1.5Hz, H-1,5), 5.88 br.s. (H-2 and 6) and 6.83 (Ar-H)]. The configuration assignments implied in formula (2) are in accord with these p.m.r. data.

Mechanism considerations suggested that acid-catalyzed hydrolytic cleavage of the dilactone (2) under appropriate conditions might lead to the aryl 1,2-dihydronaphthalene system with the substituents in the required trans configuration.



This we have substantiated by heating (2) with a mixture of concentrated hydrochloric acid (1 part)-water (9 parts)-dioxan (12.5 parts) for 45 minutes at steam bath temperature to give in 80 - 90% yield thomasidic acid (4) as a solid¹¹ [λ 5.88 and 5.92 μ ; δ 3.65 (C-8 OMe), 3.70 (C-3' and 5' OMe), 3.90 (C-6 OMe), 4.02 d. (J=1.5Hz, H-2), 5.08 br.s. (H-1), 6.42 (H-2' and 6'), 6.97 (H-5) and 7.70 (H-4)].

Alternatively, by heating a solution of the dilactone (2) in methanol saturated with hydrogen chloride, there was obtained in quantitative yield

thomasidiolic acid dimethyl ester (5) as plates from aqueous methanol [m.p. 201-203°; λ 5.78 and 5.88 μ ; δ 3.65 (C-8 OMe and C-2 CO₂Me), 3.75 (C-3' and 5' OMe, and C-3 CO₂Me), 3.92 (C-6 OMe), 4.03 d. (J=1.5Hz, H-2), 5.02 br.s. (H-1), 6.30 (H-2' and 6'), 6.72 (H-5) and 7.65 (H-4)] which could be converted to (4) by base hydrolysis. Both (4) and (5) were characterized by treatment with diazomethane to give the previously reported¹² dimethyl ether dimethyl ester (6) [m.p. 121-122° or 143-143.5°; λ 5.76 and 5.86 μ ; δ 3.67 (C-8 OMe and C-2 CO₂Me), 3.73 (C-3' and 5' OMe), 3.78 (C-4' OMe and C-3 CO₂Me), 3.89 (C-6 and C-7 OMe), 4.07 d. (J=1.5Hz, H-2), 5.00 br.s. (H-1), 6.28 (H-2' and 6'), 6.73 (H-5) and 7.65 (H-4)].

Comparison of the infrared and n.m.r. spectra of synthetic and natural (4) and (6) established their identity.^{13,14}

We consider that appropriate modification of this procedure to yield aryl-dihydronaphthalene analogues of (4) should facilitate synthesis of the numerous aryl-naphthalene and aryl-tetralin lignan systems.

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FOOTNOTES AND REFERENCES

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 10. K. Freudenberg and H. Schraube, Chem. Ber., 88, 16 (1955) report m.p. 208° and m.p. 228-230° for (2) and (3) respectively.
 11. Thomasidic acid was described as amorphous and no m.p. was reported. We obtained (4) as a white solid from acetone-chloroform with indefinite m.p., typically turning brown and decomposing ca. 210° and fully liquified ca. 250°.
 12. The reported² m.p. for (6) was 142.5-143° (from aqueous methanol). From this solvent, we obtained (6) as rosettes of needles, m.p. 121-122°; seeding of a solution of this form with the higher melting form gave prismatic needles, m.p. 143-143.5°. The higher melting form was also obtained by crystallization from aqueous acetone.
 13. We are grateful to Dr. J. W. Rowe (Forest Products Laboratory, U.S. Department of Agriculture) for making these comparisons and providing an authentic specimen of compound 5.
 14. The p.m.r. spectra of compounds (2), (3) and (4) were determined in hexadeuterioacetone, and (5) and (6) in deuteriochloroform solution. Infrared spectra were determined for KBr discs.
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