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A HIGH YIELD TOTAL SYNTHESIS OF *dl*-4-ISOAVENACIOLIDE

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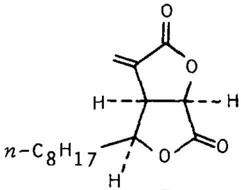
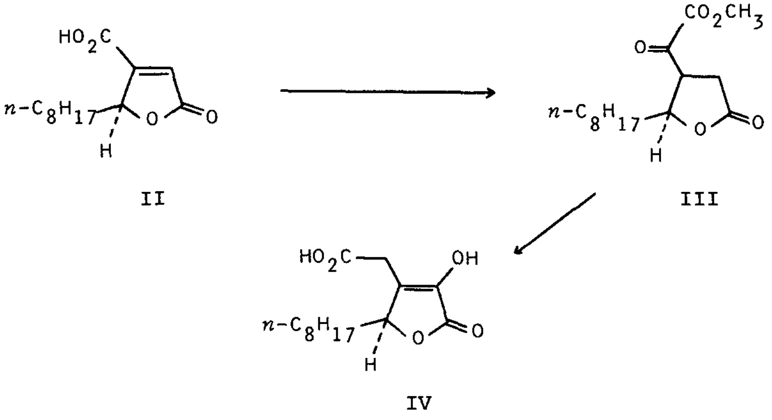
The application of latent functionality to the problem of organic synthesis is of considerable current interest.[1] In this regard, we report the use of latent carbonyl functionality applied to the stereospecific total synthesis of *dl*-4-isoavenaciolide (I), an antifungal minor metabolite of *Aspergillus avenaceus* [2]



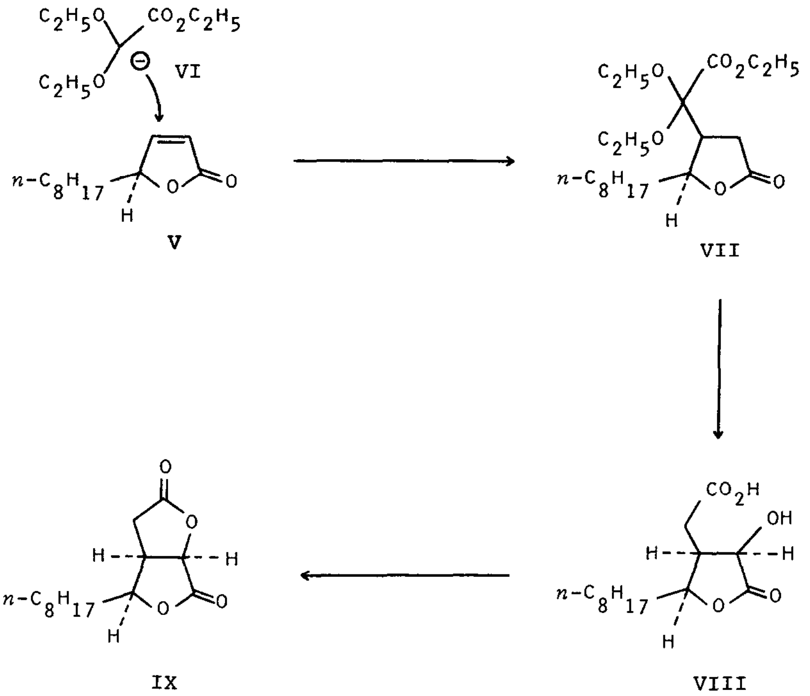
I

The bislactone I has recently been prepared in 3% overall yield by a twelve step route starting from the aconic acid II and proceeding through the α-keto ester III and the α-hydroxy butenolide IV.[3] Using a latent carbonyl anion, we have developed a five step construction of I in 51% overall yield starting from the butenolide V[4] proceeding through the intermediate IV. Thus, the key step in our synthesis is the conjugate addition of the latent carbonyl anion VI to the butenolide V.



Treatment of ethyl diethoxyacetate (1 equiv) with lithium diisopropyl amide (1 equiv, 1 M in THF) at -78° for 15 min affords the colorless carbonyl anion equivalent VI.[5] To this anion was slowly added a solution of the butenolide V (0.5 equiv, 1 M in THF) followed by immediate quenching at -78° with saturated ammonium chloride. Standard work-up afforded the adduct VII (oil) as the sole reaction product. Hydrolytic rearrangement of VII (1 equiv) was accomplished by heating at 100° for 48 hrs in 60% aqueous THF solution containing 10 equivalent of perchloric acid. Extraction of the acidic material from the resulting mixture gave pure α hydroxy butenolide IV (mp 69-71°, lit. 66-71°)[3] in 80% overall yield from V.[6]

Catalytic reduction of IV (100 atm, 0.5 M in acetic acid) with 5% rhodium on alumina gave the hydroxy lactone VIII which without purification was treated with boron trifluoride (gas) in methylene chloride solution (0.1 M) for 30 min at 0°. Crystallization of this reaction mixture from ether-hexane gave pure bislactone IX (mp 84°, lit. 81-82.5°)[3] in 80% overall yield from IV.



Elaboration of this bislactone IX into I was carried out using the procedure of F. Johnson.[7] Thus, reaction of IX with Stiles reagent at 150° for 2 hrs followed by treatment with aqueous formaldehyde and diethylamine in acetic acid buffered with sodium acetate afforded after standard work-up and crystallization from ether-hexane pure *dl*-4-isoavenaciolide (mp 99-99.5°, lit. 99-101°)[3] in 80% overall yield from IX.[8]

ACKNOWLEDGMENT We thank the National Institutes of Health, the Hoffmann LaRoche Corporation, and the Alfred P. Sloan Foundation for support of this work.

REFERENCES

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2. D. C. Aldridge and W. B. Turner, *J. Chem. Soc.*, (C), 2431 (1971).
3. K. Yamada, M. Kato, M. Iyoda, and Y. Hirata, *Chem. Comm.*, 499 (1973).
4. J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Amer. Chem. Soc.*, 95, 7923 (1973).
5. To our knowledge, the carbonyl anion equivalent VI represents the first dioxygenated system of this type to undergo the conjugate addition reaction. Anion VI is considerably less stable that its dithioethyl analogue, see *Tetrahedron Letts.*, 2595, 2599 (1973), but has the advantage of being much easier to hydrolyze into the corresponding carbonyl compound.
6. This hydrolytic rearrangement presumably involves the intermediacy of the α-keto ester III.
7. (a) W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, 91, 7208 (1969), (b) J. L. Finkbeiner and M. Stiles, *ibid.*, 85, 616 (1963).
8. All compounds exhibited satisfactory spectral and physical properties.