Tetrahedron Letters,Vol.24,No.25,pp2531-2532,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

THE SYNTHESIS OF ASPERSITIN

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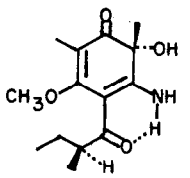
Summary: Aspersitin, a new metabolite produced by Aspergillus parasiticus, was synthesized in racemic form by a six step sequence starting with dimethylphloroglucinol.

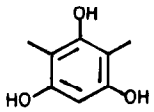
Recent work[2] on a strain of Aspergillus parasiticus brought to light a new metabolite which was named aspersitin. An X-ray analysis performed by Dr. J. F. Blount at Hoffmann-La Roche, Nutley, N.J. revealed structure 1 and other physical properties measured in this laboratory were in accord with his findings. Aspersitin (1) belongs to a new class of nitrogen containing fungal metabolites, and to explore its chemical properties attention was focused on synthesis.

Dimethylyphloroglucinol (2)[3] was condensed with excess racemic 2-methylbutanoic acid in the presence of gaseous boron trifluoride (85°, 4h). The resulting acyl phloroglucinol 3, obtained in 74% yield, was selectively protected at the non-hydrogen bonded p-hydroxy group by treatment with t-butyldimethylsilyl chloride and imidazole[4] (DMF, 20°, 3h, 73% yield) giving intermediate 4.[5] Dimethyl ether 5,[6] was formed in 92% yield when 4 was methylated with dimethyl sulfate (acetone, potassium carbonate, 20°, 15h). Deprotection with tetra-n-butylammonium fluoride[7] (THF, 1h, 82% yield) produced phenol 6, mp 58.5-59°,[8] which was oxidized to 7[9] with lead tetraacetate (acetic acid, 10 min, 93% yield). ^{1}H NMR spectroscopy revealed the product to be a mixture of the two diastereomeric 2-acetoxycyclohexadienones 7.

To complete the synthesis of aspersitin (1), the acetate had to be hydrolyzed, and, more critically, one of the methoxy groups in the dimethyl ether 7 had to be replaced by an amino group. It was reasoned that 1,6-addition of ammonia to the dienone 7 should occur more readily than 1,4-addition because of more extensive charge delocalization in the former mode of addition. Indeed, treatment of 7 with methanolic ammonium hydroxide (20°, 12-15h) afforded a mixture of diastereomeric aspersitins, in 20-30% yield, after thin layer chromatographic purification on silica gel (cyclohexane-acetone 70:30). Separation of the two diastereomers formed in approximately equal yield was accomplished by HPLC (column: Whatman 9M 10/50 ODS-3, reverse phase C_{18}; solvent:methanol-water 50:50; flow rate: 4 ml/min at 1800 psi; detection at 260nm). A ^{1}H NMR spectrum[10] of the more readily eluting isomer was different from that of aspertin (1).[2] The spectrum of the latter[2], however, was superimposable on that of the more slowly eluted diastereomer. Identity of synthetic and natural metabolites were confirmed by chromatographic behavior using HPLC and by ultraviolet spectroscopy.



1



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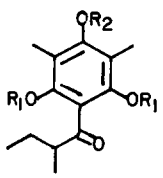

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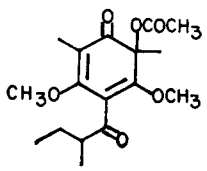
3 $R_1 = R_2 = H$.
4 $R_1 = H$; R_2 = TBDMS.
5 $R_1 = CH_3$; R_2 = TBDMS.
6 $R_1 = CH_3$; $R_2 = H$.



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Acknowledgments. This work was supported by a National Research Service Award (No. 2T32CA09112) from the National Cancer Institute, DHEW, the National Institutes of Health (Grant GM 09868), and the Hoffmann-La Roche Foundation. High-resolution mass spectra were provided by the facility, supported by the National Institutes of Health (Grant RR 00317) (Principal Investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources.

References and Notes

1. NIH Predoctoral Trainee, 1979-1981.
2. Büchi, G.; Francisco, M. A.; Murray, W. V.; Kachholz, T.; Demain, A. L.; Blount, J. F., accompanying letter.
3. Robertson A.; Whalley, W. B. J. Chem. Soc. 1951, 3355.
4. Corey, E. J.; Venkateswarlu, H., J. Amer. Chem. Soc. 1972, 94, 6190.
5. UV max (EtOH) (ε) 346 (2900), 288 (15,300), 222 (sh) (13,500) nm; UV max (EtOH, NaOH) (ε) 400 (3700) nm.
6. UV max (EtOH) 253 (4300), 218 (sh) (16,100) nm.
7. Fowler, D. L.; Loebenstein, W. V.; Pall, D. B.; Kraus, D. A., J. Am. Chem. Soc. 1940, 62, 1140.
8. UV max (EtOH) (ε) 262 (4000), 217 (sh) (13,300); UV max (EtOH, NaOH) 331 (8800) nm.
9. UV max (EtOH) (ε) 348 (sh) (4000), 334 (4100), 324 (4100), 327 (sh) (6100) nm.
10. Measured in $CDCl_3$ at 250 MHz: 10.10 (br, 1); 6.55 (br, 1); 4.11 (br, s, 1), 3.78 (s, 3); 3.21 (sext, 1, J = 6.7 Hz); 1.91 (s, 3); 1.62 (m, 1), 1.57 (s, 3); 1.30 (m, 1); 1.12 (d, 3, J = 6.7 Hz); 0.81 (t, 3, J = 7.4 Hz).

(Received in USA 28 February 1983)