Tetrahedron Letters,Vol.26,No.49,pp 6133-6136,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHETIC UTILITY OF OXYALLYLS: PREPARATION OF AN ANALOGUE OF HELMINTHOSPORIC ACID

John Mann* and Helen J. Overton

Department of Chemistry, University of Reading,

Whiteknights, P.O.Box 224, Reading, Berkshire, RG6 2AD, U.K.

Terence Lewis

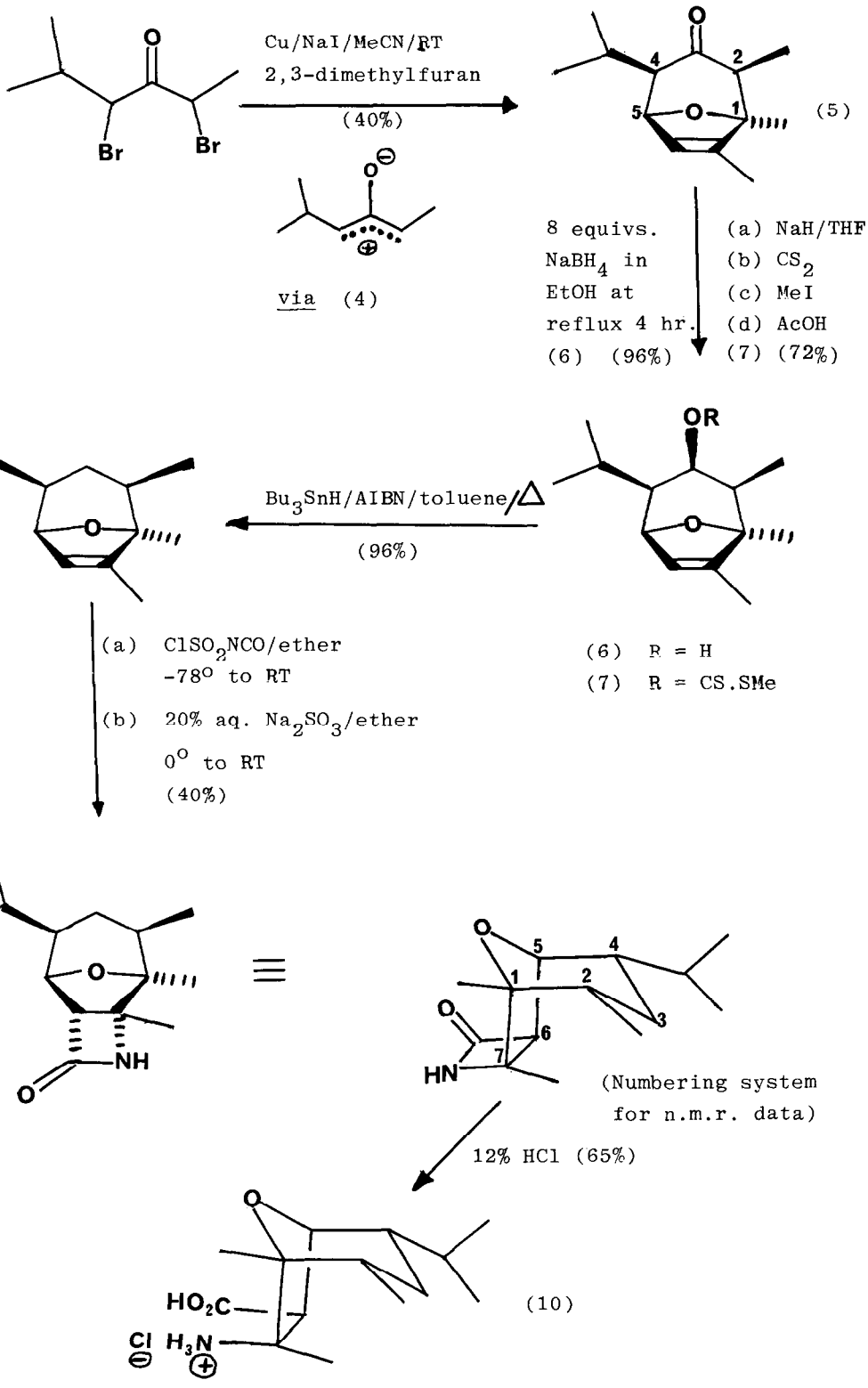
I.C.I.(Plant Protection Division) PLC, Jealott's Hill,
Bracknell, Berkshire, RG12 6EY, England.

ABSTRACT: We describe a synthesis of a novel amino acid resembling helminthosporic acid. The route is short (six steps) and uses oxyallyl methodology to establish the correct regio- and stereochemistry in the required bicyclic system.

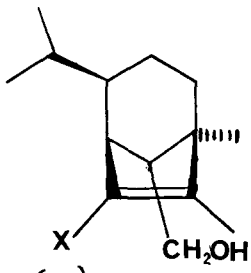
The sesquiterpenes helminthosporol (1a), and sativene diol (2) are produced by the cereal pathogens Helminthosporium sativum[1] and Cochliobolus setariae[2] respectively. They cause plant growth effects similar to those produced by the gibberellins[3], and a number of structural analogues of (1a) have been produced[4] in order to probe structure-activity relationships. In particular, this work established that the hydroxymethyl group in (1a) was not essential for activity, and we thus chose to design a route to analogues of helminthosporic acid (1b), which lacked this group and which would also have good water solubility. We give details here of our synthetic approach to compounds of general form (3).

The chemistry of oxyallyl carbocations (e.g. (4)) has been reviewed recently[5], and we have also made a number of contributions in this area[6]. By careful choice of reaction conditions and oxyallyl precursors the cycloaddition reactions with furans proceed with a high degree of regio- and stereoselectivity. For our purposes we chose the cycloaddition between oxyallyl (4) (formed from 2-methyl-3,5-dibromohexan-4-one) and 2,3-dimethylfuran (see Scheme for yields and conditions). [It would have been better to employ 2,3-dimethyl-4-furoic acid, but cycloadditions with this diene were impractical due to inaccessibility and the low yields obtained in cycloaddition reactions.] The cycloaddition proceeded (on a 50 mM scale) in good yield (73% of total cycloadducts; and 40% of the desired regio- and stereoisomer) to produce (5).[7]

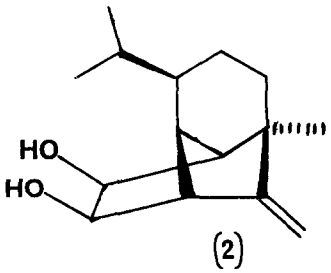
Reduction with excess sodium borohydride produced primarily the axial alcohol (6)[8] (ratio of axial:equatorial alcohols of 8:1 as judged by n.m.r.); and this was converted into the xanthate (7). Deoxygenation was then accomplished according to the method of Barton et al.[9] to yield


Cu/NaI/MeCN/RT
2,3-dimethylfuran
(40%)
via (4)
(5)
8 equivs. NaBH4 in EtOH at reflux 4 hr.
(6) (96%)
(a) NaH/THF
(b) CS2
(c) MeI
(d) AcOH
(7) (72%)
Bu3SnH/AIBN/toluene/Δ
(96%)
(8)
(6) R = H
(7) R = CS.SMe
(a) ClSO2NCO/ether -78° to RT
(b) 20% aq. Na2SO3/ether 0° to RT
(40%)
(9)
(Numbering system for n.m.r. data)
12% HCl (65%)
(10)

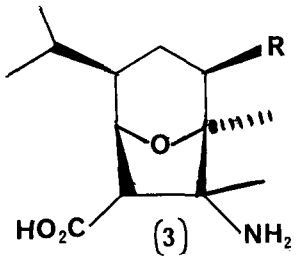
the oxabicyclo[3.2.1]octene (8) ; and this provided the tricyclic β-lactam (9)[10] upon reaction with chlorosulphonylisocyanate (and subsequent reduction). Finally, cleavage of the lactam was accomplished using 12% aq. HCl to produce the novel amino acid (10) (as its HCl salt, m.p. 224-5°), and this compound and lactam (9) were evaluated as plant growth regulators. Both compounds showed modest phytotoxic activity against a variety of weeds, but although this was a significant effect it was too small to warrant further evaluation.



(1a) X = CHO
(1b) X = CO_2H



(2)



(3)

R = alkyl or aryl

In conclusion, we have demonstrated the viability of this approach to oxabicycles resembling helminthosporic acid, and other analogues including elimination products of (3) should now be accessible.

References and Notes

1. A.Sakurai and S.Tamura, Agric.Biol.Chem., 1964, 28, 337.
2. H.Hattori, S.Marumo and M.Nukina, J.Amer.Chem.Soc., 1975, 97, 2542.
3. L.N.Mander, Synthesis, 1983, 48;
   J.R.Hanson, Biochem.Soc.Trans., 1983, 11, 522; and refs. therein.
4. L.N.Mander, J.V.Turner, and B.G.Coombe, Austral.J.Chem., 1974, 27, 1985.
5. H.M.R.Hoffmann, Angewandte Chemie, 1984, 1.
   R.Noyori and Y.Hayakawa, Organic Reactions, 1983, 29, 163.
6. A.P.Cowling and J.Mann, J.C.S.Perkin Trans.I, 1978, 1564.
   A.P.Cowling, J.Mann and A.A.Usmani, J.C.S.Perkin Trans.I, 1981, 2116.
   W.J.Cummins, M.G.B.Drew, J.Mann and E.B.Walsh, J.C.S.Perkin Trans.I, 1983, 167.
   K.G.Bowers and J.Mann, Tetrahedron Letters, 1985, 4411.
7. Satisfactory high resolution mass spectral data or microanalytical data were obtained for all new compounds. In addition n.m.r. data for (5) is given: δ($CDCl_3$, 100 MHz), 0.85-1.13 (m, 9H, 2-Me and isopropyl methyls), 1.45 (s, 3H, 1-Me), 1.8 (d, J2Hz, 3H, 7-Me), 2.54 (dd, J5 and 7Hz, 1H, 4-H), 2.55 (q, J 7.5Hz, 1H, 2-H), 4.85 (m, J3 and 5Hz, 1H, 5-H), and 5.75 (m, J2 and 3Hz, 1H, 6-H).
8. N.m.r. data for (6): δ($CDCl_3$, 100 MHz), 0.9-1.1 (m, 9H, 2-Me and

isopropyl methyl), 1.26 (s, 3H, 1-Me), 1.5-2.1 (complex m, 4H, isopropyl H, 2-H, 4-H, OH), 1.86 (dd, 3H, J1 and 1.5 Hz, 7-Me), 3.7-3.95 (broad m, 1H, 3-H, 4.66 (broad m, 1H, 5-H), 5.92 (dd, 1H, J1.5 and 2Hz, 6-H). (The equatorial alcohol had an olefinic proton resonance at δ 5.7).

9. For an excellent review of this methodology see: W.Hartwig, Tetrahedron, 1983, 39, 2609.

10. M.pt. 151-161°; n.m.r. data for (9) δ C_6D_6, 220 MHz) (the numbering system used for the preceding compounds has been retained), 0.52 (ddd, 1H, J 11,11 and 12.5 Hz, 3_{ax}-H), 0.65-0.75 (m, 9H, 2-Me and isopropyl methyls), 0.75-0.95 (complex m, 1H, isopropyl H), 1.07 and 1.08 (2s, 6H, 1-Me and 7-Me), 1.36 (m, 1H, J3, 5, 9 and 11 Hz, 4-H), 1.47 (m, 1H, J 1.5, 5, 5 and 12.5 Hz, $3_{eq.}$-H), 1.74 (m, 1H, J5, 7 and 11Hz, 2-H), 2.84 (d, 1H, J 2Hz, 6-H), 4.56 (dd, 1H, J1.5 and 3Hz, 5-H), and 6.69 (broad s, 1H, NH).

A full X-ray structural analysis has also been carried out on this compound, and this will be described elsewhere.

Acknowledgements

H.J.O. thanks the S.E.R.C. and I.C.I. Plant Protection for a CASE Award.

(Received in UK 1 October 1985)