Tetrahedron Letters,Vol.27,No.22,pp 2443-2446,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF OUDEMANSINS A AND B

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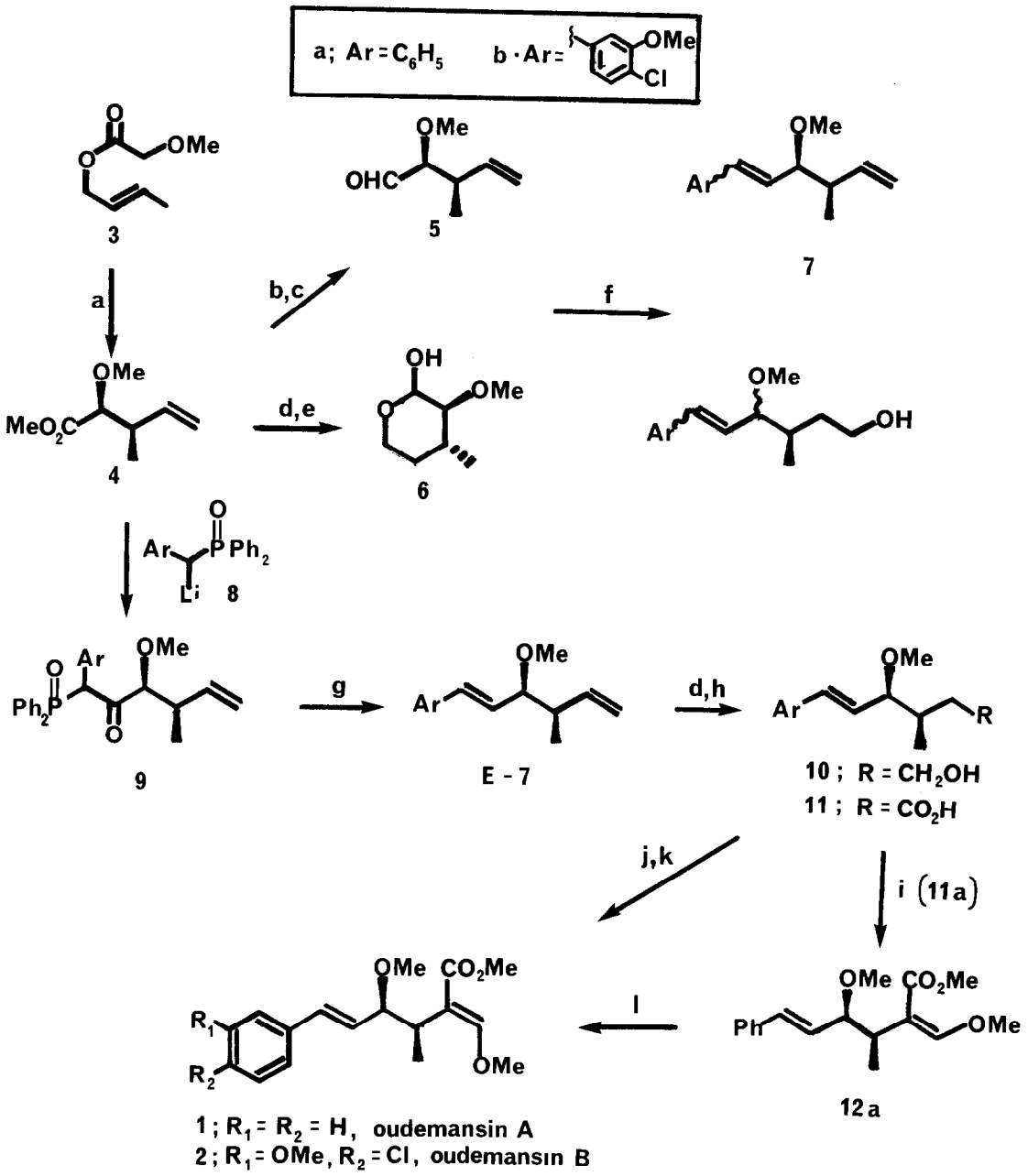
Summary: Efficient, stereocontrolled syntheses of the antifungal metabolites oudemansin A and B are described.

The oudemansins A (1) and B (2) are members of a class of naturally-occurring β-methoxy acrylates isolated from mycelial cultures of Basidiomycetes.[1,2] Recent interest in the oudemansins and related compounds stems from their broad spectrum antibiotic and antifungal activity and their ability to inhibit eukaryotic respiration. As part of an ongoing program to evaluate the antifungal activity of the oudemansins and their analogs, we required an efficient synthetic route to these compounds in which the vicinal acyclic stereochemistry and olefin geometries are rigorously defined.[2] Herein we report a short, highly-stereocontrolled route to oudemansin A and the previously unprepared oudemansin B.

The starting material for our synthesis of the naturally occurring oudemansins is ester 4, available as an 10:1 mixture of syn:anti diastereomers[3] from the enolate Claisen rearrangement[4] of glycolate 3. Our synthetic plan called for introduction of the requisite styryl subunit followed by development of the sensitive β-methoxy acrylate moiety in the final stages of our scheme. Initial attempts to introduce the aromatic group were complicated by our inability to control olefin geometry. Thus Wittig olefinations of aldehyde 5 afforded intractable mixtures of E and Z dienes 7. Similar results were obtained for the lactol 6. Wittig reactions of 6 were further complicated by epimerization of the C_2-methoxy substituent, presumably due to intramolecular proton abstraction by the transient δ-alkoxy aldehyde resulting from deprotonation of the lactol. An examination of alternative olefination procedures ultimately led to a protocol which was completely selective for the desired E isomer of 7.[5] Treatment of ester 4 with the lithium anion of phosphine oxide 8a[6] afforded the β-ketophosphine oxide 9a. Reduction to the corresponding alcohol and elimination gave diene E-7a (32% from 4) as the only detectable olefin isomer.[7]



REAGENTS: a) LDA, Me_3SiCl, THF, -78-0°, then aq. NH_4Cl; CH_2N_2, Et_2O; b) $LiAlH_4$, Et_2O, 0°; c) $(COCl)_2$, DMSO, NEt_3; d) 9-BBN, THF, 0°, then H_2O_2; e) DIBAL, PhH, 0°; f) Ph_3PCHAr or $(EtO)_2OPCHArLi$; g) $LiBH_4$, THF, 0°; h) Jones; i) t-BuLi (2 eq.), HCO_2CH_3, then $(MeO)_2SO_2$; j) CH_2N_2, Et_2O; k) LDA, N-formylimidazole, then K_2CO_3, $(MeO)_2SO_2$; l) MeOH, TsOH.

Regioselective hydroboration of E-7a afforded alcohol 10a[8], from which the minor anti diastereomer (a residual product from the original Claisen rearrangement) could be conveniently removed by flash chromatography. Alcohol 10a was smoothly oxidized to the corresponding acid 11a[2] with Jones reagent (98%). Initially, we attempted to introduce the β-methoxymethylene group by acylation of the dianion[9] of 11a (2 eq. t-BuLi, methyl formate) and alkylation with dimethyl sulfate. Obtained from this procedure was the E-isomer 12a (52%) accompanied by traces (<3%) of the desired 1. Treatment of this mixture with acidic methanol resulted in isomerization[10] of the undesired isomer to give as the only product, *oudemansin A*, 1[11] (37% *from* 11a). *Alternatively, 1 could be obtained directly from ester* 11a by acylation of the enolate with N-formylimidazole[12] and O-alkylation of the resulting β-formyl ester with dimethyl sulfate/K_2CO_3[2c] to give oudemansin A, 1 (57% from 11a).

A similar sequence was used to prepare oudemansin B. Addition of phosphine oxide 8b[6] to 4 and reduction with $LiBH_4$ gave diene E-7b (30%) which was transformed to acid 11b as described above (82% from E-7b). Esterification, acylation with N-formylimidazole and methylation afforded the previously unprepared oudemansin B, 2 (44% from 11b), which exhibited physical and spectral properties in close agreement with literature data.[11]

In summary, we have developed a short synthetic route to the oudemansins which effectively controls both the stereochemistry and olefin geometries of these compounds. Our synthetic scheme is well-suited to the preparation of multigram quantities of derivatives of 1 and 2; the synthesis and biological activity of oudemansin analogs will be the subject of a future report.

Acknowledgement: We are pleased to acknowledge the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work. High-field NMR spectra were obtained from the N.I.H. Research Resource facility (RR-01317) at Syracuse University.

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2. *For previously reported syntheses of oudemansin A see:* a) T. Nakata, T. Kuwabara, Y. Tani and T. Oishi, Tetrahedron Letts. 1015 (1982); b) H. Akita, H. Koshiji, A. Furuichi, K. Horikoshi and T. Oishi, ibid. 2009 (1983); c) H.H. Meyer, Leibigs Ann. Chem. 791 (1984); d) C.J. Kowalski, M.S. Haque and K.W. Fields, J. Amer. Chem. Soc. 107, 1429 (1985).

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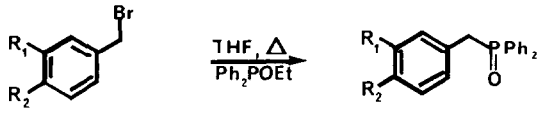
6. Phosphine oxides 8a and 8b were prepared by reaction of the corresponding benzyl halides with diphenylethoxyphosphine:



8a ; $R_1 = R_2 = H$
8b ; $R_1 = OMe$ $R_2 = Cl$

7. The olefin ratio is extremely sensitive to reaction conditions and reducing agent. For example, reduction of 9a with $LiAlH_4$ gave a 3:1 ratio of E:Z olefins. Olefin mixtures were analyzed by 250 MHz ^1H NMR and GC; limit of detection for E:Z mixtures is >50:1.

8. New compounds were characterized by IR, HPLC or GC, 500 MHz PMR, 126 MHz CMR and elemental analysis. Analytical data for key intermediates:
E-7a- IR (neat oil) 1090 cm^{-1}; PMR ($CDCl_3$) δ 7.39 (d, J=7.4 Hz, 2H), 7.31 (t, J=7.4 Hz, 2H), 7.24 (t, J=7.4 Hz, 1H), 6.51 (d, J=15.9 Hz, 1H), 6.05 (dd, J=8.1, 15.9 Hz, 1H), 5.86 (m, 1H), 5.07 (m, 2H), 3.56 (dd, J=8.1, 5.8 Hz, 1H), 3.32 (s, 3H), 2.49 (m, 1H), 1.07 (d, J=6.8 Hz, 3H); CMR ($CDCl_3$) ppm 140.2, 136.6, 133.2, 128.5, 128.3, 127.6, 126.4, 114.6, 86.3, 56.6, 42.5, 15.6.
E-7b - IR (neat oil) 1490, 1410, 1060 cm^{-1}; PMR ($CDCl_3$) δ 7.23 (d, J=8.6 Hz, 1H), 6.88 (m, 2H), 6.43 (d, J=16.1 Hz, 1H), 5.99 (dd, J=7.8, 16.1 Hz, 1H), 5.81 (m, 1H), 5.02 (m, 2H), 3.85 (s, 3H), 3.50 (dd, J=7.8, 6.2 Hz, 1H), 3.28 (s, 3H), 2.44 (m, 1H), 1.02 (d, J=7.0 Hz, 3H); CMR ($CDCl_3$) ppm 154.7, 139.9, 136.4, 132.0, 129.9, 128.8, 121.4, 119.3, 114.6, 109.6, 85.9, 56.6, 55.8, 42.3, 15.4.
10a - IR (neat oil) 3400 br, 1450 cm^{-1}; PMR ($CDCl_3$) δ 7.40 (d, J= 7.3 Hz, 2H), 7.33 (t, J=7.3, 2H), 7.25 (m, 1H), 6.53 (d, J= 16.0 Hz, 1H), 6.12 (dd, J= 8.2, 16.0 Hz, 1H), 3.75 (m, 1H), 3.64 (m, 2H), 3.33 (s, 3H), 2.56 (br s, 1H), 1.98 (m, 1H), 1.76 (m, 1H), 1.45 (m, 1H), 0.96 (d, J=6.9 Hz, 3H); CNMR ($CDCl_3$) ppm 136.5, 133.8, 128.6, 127.7, 127.2, 126.5, 86.8, 61.4, 56.5, 35.9, 35.7, 16.6.
10b - IR (neat oil) 3400 br cm^{-1}; PMR ($CDCl_3$) δ 7.30 (d, J=8.6 Hz, 1H), 6.93 (m, 2H), 6.49 (d, J= 16.0 Hz, 1H), 6.10 (dd, J=8.1, 16.0 Hz, 1H), 3.93 (s, 3H), 3.59 - 3.79 (m, 3H), 3.34 (s, 3H), 2.56 (br s, 1H), 1.98 (m, 1H), 1.77 (m, 1H), 1.45 (m, 1H), 0.97 (d, J=6.8 Hz, 3H); CMR ($CDCl_3$) ppm 154.8, 136.2, 132.6, 129.9, 127.9, 121.6, 119.3, 109.6, 86.4, 61.1, 56.5, 55.9, 35.6, 35.4, 16.3,
11b (methyl ester) - IR (neat oil) 1730, 1460, 1290, 1060 cm^{-1}; PMR ($CDCl_3$) δ 7.30 (d, J=8.3 Hz, 1H), 6.93 (m, 2H), 6.50 (d, J=16.2 Hz, 1H), 6.04 (dd, J=16.2, 7.6 Hz, 1H), 3.93 (s, 3H), 3.64 (s, 3H), 3.59 (dd, J=7.6, 5.1 Hz, 1H), 3.31 (s, 3H), 2.53 (dd, J=15.3, 5.7 Hz, 1H), 2.30 (m, 1H), 2.16 (dd, J=15.3, 8.3 Hz, 1H), 1.01 (d, J=7.0 Hz, 3H); CNMR ($CDCl_3$) ppm 173.3, 154.8, 136.3, 132.2, 130.0, 128.5, 121.6, 119.4, 109.6, 85.3, 56.7, 55.9, 51.4, 37.3, 35.0, 15.5.

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11. Synthetic oudemansins A and B exhibit physical and spectral properties in close agreement with those reported for natural[1] and synthetic[2] material. The 250 MHz ^1H spectrum of isomer 12a was consistent with literature data.[2a]

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(Received in USA 14 February 1986)