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A New Synthetic Route to Methylenomycin B Via Rhodium(II)-Mediated Decomposition of α,β-Unsaturated α'-Diazoketones

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A NEW SYNTHETIC ROUTE TO METHYLENOMYCIN B VIA RHODIUM(II)-MEDIATED DECOMPOSITION OF α,β-UNSATURATED α'-DIAZOKETONES

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A new synthesis of methylenomycin B, involving Rh(II)-catalyzed, intramolecular carbon-hydrogen insertion of diazoketone **2c**, derived from 2,3-dimethyl-2-butenoic acid **2b**, is reported.

Many biologically active natural compounds are characterized by a cyclopentanone moiety as a main structural feature, hence improved syntheses are being continually developed to provide substituted cyclopentanones.[1] We have recently reported,[2] a new general cyclopentanone synthesis based on the carbon-carbon bond formation through dirhodium tetraacetate

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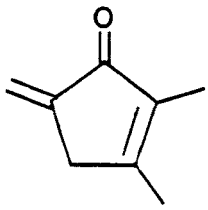
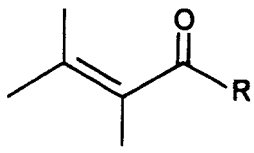
catalysed decomposition of α,β -unsaturated α'-diazoketones. To further demonstrate the synthetic utility of this methodology, a short, expeditious synthesis of the cyclopentenoid antibiotic methylenomycin B 1[3,4] was carried out.

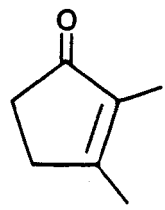
The trimethyl acrylic acid (2b) was selected as the crucial cyclization substrate for the proposed formal synthesis of 1. This compound, obtained in relatively modest overall yield[5], was now prepared following a new procedure. Thus Wittig-Horner reaction of acetone and triethyl-2-phosphono-propionate, and subsequent hydrolysis with iodotrimethylsylane,[6] yielded 2b in 71% yield.



1



2a R = OEt
b R = OH
c R = CHN_2



3

Treatment of the acid 2b with oxalyl chloride produced the corresponding acid chloride, whose exposure to

diazomethane and triethylamine afforded diazoketone 2c in 51% yield. Reaction of 2c with dirhodium tetraacetate[7] in methylene chloride gave 2,3-dimethyl-2-cyclopenten-1-one 3 in 75% yield. The IR, ^{1}H NMR and ^{13}C NMR spectra were in good accordance with those reported.[4a] Compound 3 has been converted in to methylenomycin B[3b,4i] and therefore this study constitutes a formal total synthesis of this antibiotic.

Experimental Section

Melting points were obtained on a Reichert micro hotstage and are uncorrected. Infrared spectra of chloroform solutions were observed on a Perkin-Elmer 1320 spectrophotometer. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded on a Bruker AC 200 spectrometer operating at 200.1 and 50.3 MHz, respectively, in the Fourier transform mode. The carbon shifts are in parts per million downfield from Me_4Si; $(Me_4Si) = (CDCl_3) + 76.9$ ppm. Column chromatography was executed on 0.0063-0.200 mesh Merck silica gel. All reactions were carried out under nitrogen, and all extracts were dried over Na_2SO_4.

2,3-Dimethyl-2-butenoic acid ethyl ester (2a). Triethyl-phosphonopropionate[8] (4.1 g, 17 mmol) was added to a

solution of sodium ethoxide (1.2 g, 17 mmol) in 20 ml of ethanol. After stirring for 10 min a solution of acetone (1.3 ml, 17 mmol) in 5 ml of ethanol was added dropwise. The mixture was poured into water and extracted with ether. The extract was washed with water, dried, and evaporated. Chromatography of the residue and elution with 49:1 hexane-ethyl acetate gave 2.3 g (87%) of liquid ester **2a**. [I.R. : C=O 1720 (s) cm^{-1}]. ^{1}H NMR 1.16 (t, 3, OCH_2-$\underline{C}H_3$), 1.68, 1.72, 1.88 (each s, 9, methyls), 4.05 (q, 2, $O\underline{C}H_2$-CH_3); ^{13}C NMR 13.96 (OCH_2-$\underline{C}H_3$), 15.2, 22.0, 22.4 (methyls), 59.5 ($O\underline{C}H_2$-CH_3), 122.3 (C = $\underline{C}$-CO), 142.3 ($\underline{C}$=C-CO), 169.1 (C=O).

2,3-Dimethyl-2-butenoic acid (2b). A solution of ester **2a** (1.8 g, 13 mmol) in 75 ml of carbon tetrachloride was treated with iodotrimethylsilane[6] (6g, 30 mmol) at reflux for 24 h. The reaction mixture was taken up in 100 ml of ether, washed with water, 10% aqueous sodium thiosulfate solution, 15% aqueous bicarbonate solution, and brine. The organic layers were, then, dried, and evaporated. Chromatography of the residue and elution with 25:1 chloroform-ethyl acetate afforded 1.2 g (81%) of colourless, crystalline acid **2b**, m.p. 72-73 °C [lit.[5] 70-71 °C]. ^{1}H NMR 1.91 (s, 6, methyls), 2.16

(s, 3, methyl); ^{13}C NMR 15.4, 23.2, 23.3 (methyls), 121.6 (C=C-CO), 147.9 (C=C-CO), 174.8 (C=O).

1-Diazo-3,4-dimethyl-3-penten-2-one (2c). A solution of acid **2b** (1.2 g, 10 mmol) in 25 ml of methylene chloride was treated with 18 mmol of freshly distiled oxalyl chloride at 35 °C for 2 h. It was thene vaporated under vacuum. A solution of the residue in 30 ml of ether was added dropwise over a 0.5 h period to a stirring solution of 13 mmol of diazomethane and 10 mmol of distilled triethylamine in 50 ml of ether at 0 °C, and stirring was continued for 1 h. The mixture was filtered, and the filtrate was evaporated. Chromatography of the residue through a short column of neutral alumina (activity III) and elution with 25 : 1 hexane: ethyl acetate produced 0.7 g (51%) of yellow amorphous solid diazoketone **2c**. [IR: $C=N_2$ 2100 (s), C=O 1628 (s) cm^{-1}]. ^1H NMR 1.70, 1.80, 1.88 (each s, 9, methyls), 5.20 (s, 1, $\underline{CH}N_2$).

2,3-Dimethyl-2-cyclopenten-1-one (3). A solution of diazoketone **2c** (0.5 g, 4 mmol) 100 ml of methylene chloride was added dropwise over a 6 h period to a suspension of 0.08 mmol of dirhodium tetraacetate in 50 ml of methylene chloride. The mixture was evaporated

under vacuum. Chromatography of the residue and elution with 30 : 1 hexane: ethyl acetate yielded 0.30 g (75%) of cyclopentenone 3 as colourless oil. I.R., ^{1}H NMR, and ^{13}C NMR spectrally identical with those reported in literature.[4a]

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REFERENCES

1) Rizzo, L.J.; Dunlop, N.K.; Smith III, A. J. Org. Chem., **1987**, 52, 5280.
2) Ceccherelli, P.; Curini, M.; Marcotullio, M.C.; Rosati, O.; Wenkert, E. J. Org. Chem., **1990** , 55, 311.
3) For the isolation and structure reassignment see: (a) Haneishi, T.; Kitohara, N.; Takiguchi, Y.; Arai, M. J. Antibiotic, **1974**, 27, 386. (b) Jernow, J.; Fautz, W.; Rosen, P.; Williams, T.H. J. Org. Chem., **1979**, 44, 4212.
4) For other synthetic approaches see: (a) Tonari, K.; Machiya, K.; Ueda, H. Agric. Biol. Chem., **1981**, 45, 295. (b) Newton, R.F.; Reynolds, D.P.; Eyre, T.Synth. Commun., **1981**, 11 527. (c) Siwapinyoyos, T.; Thebtaranonth, Y.J. J. Org. Chem., **1982**, 47, 598. (d) Mikolajczyk, M.; Grzejszczak, S.; Lyzwa, P. Tetrahedron Lett., **1982**, 23, 2237. (e) Takahashi, Y.; Kosugi, H.; Uda, H. J. Chem. Soc., Chem. Commun., **1982**, 496. (f) Billington, D.C.; Pauson, P.L. Organometallics, **1982**, 1, 1560. (g) Strunz, G.M.; Lal, G.L.S. Can. J. Chem., **1982**, 60, 2528. (h) Doutheau, A.; Sartoretti, J.; Gore, J. Tetrahedron, **1983**, 39, 3059. (i) Negishi, E.I.; Miller, J.A. J.Am. Chem. Soc., **1983**, 105, 6761. (j) Ho, T.L. Synth. Commun., **1983**, 13, 435. (k) Cameron, A.G.; Hewson, A.T.; Osammor, M.I. Tetrahedron Lett., **1984**, 25, 2267. (l) Mikolajczyck, M.; Midura, W.; Grzejszczak, S.

Tetrahedron Lett., **1984**, 25, 2489. (m) Mikolajczyk, M.; Balczewski, P. Synthesis, **1984**, 691. (n) Pohmakotr, M.; Chancharuee, S. Tetrahedron Lett., **1984**, 25, 4141. (o) Stetter, H.; Haese, W. Chem. Ber., **1984**, 117, 682. (p) Patterson, G.M.L.; Astrab, D.P. J. Antibiot., **1985**, 38, 1061. (q) Camps, F.; Coll, J.; Moreto, J.M.; Torras, J. Tetrahedron Lett., **1985**, 26, 6397. (r) Tins, M.A.; Astrab, D.P.; Fauq, A.H.; Ousset, J.B.; Trehan, S. J. Am. Chem. Soc., **1986**, 108, 3438. (s) Mathew, J.; Alink, B. J. Org. Chem., **1990**, 55, 3880. Also see ref. 1. (t) Welch, S.C.; Assercq, J.M.; Loh, J.P.; Glase, S.A. J. Org. Chem., **1987**, 52, 1440. (u) Mikolajczy, K.M.; Balczewski, P. Synthesis, **1987**, 659. See also ref. 1.

5) Brande, E.A.; Evans, E.A. J. Chem. Soc., **1955**, 3331 and references cited therein.
6) Ho, T.L.; Olah, G.A. Synthesis, **1977**, 417 and references cited therein.
7) Hubert, A.; Noels, A.F.; Anciaux, A.J.; Teyssie', P. Synthesis, **1976**, 600.
8) Gallagher jr., G.; Webb, R.L. Synthesis, **1974**, 122.

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