Tetrahedron Letters,Vol.30,No.9,pp 1143-1146,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A NEW SYNTHESIS OF (±)-SARKOMYCIN FROM A β-KETOPHOSPHONATE

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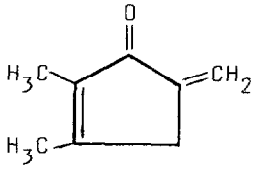
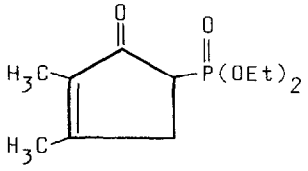
Summary: The total synthesis of (±)-sarkomycin starting from diethyl 2-oxopropanephosphonate is reported. The key step in this synthesis includes the Horner-Wittig reaction of 2-diethoxyphosphoryl-3-carboxy-cyclopentanone with formaldehyde

As a result of our study on the synthesis of cyclopentanoid antibiotics we have recently described several synthetic approaches to methylenomycin B (1) using organic phosphorus and sulphur reagents[1]. The general strategy employed was based on the synthesis and cyclization of the properly substituted 1,4-diketones followed by introduction of the exocyclic methylene moiety. Among the approaches devised to 1 that involving the synthesis of the cyclic β-oxo phosphonate 2 and its Horner-Wittig reaction with formaldehyde was found to be most efficient[2,3].



Methylenomycin B-1



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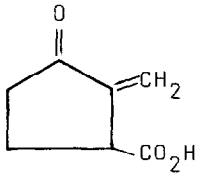
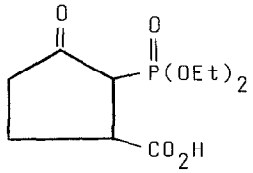


Sarkomycin - 3



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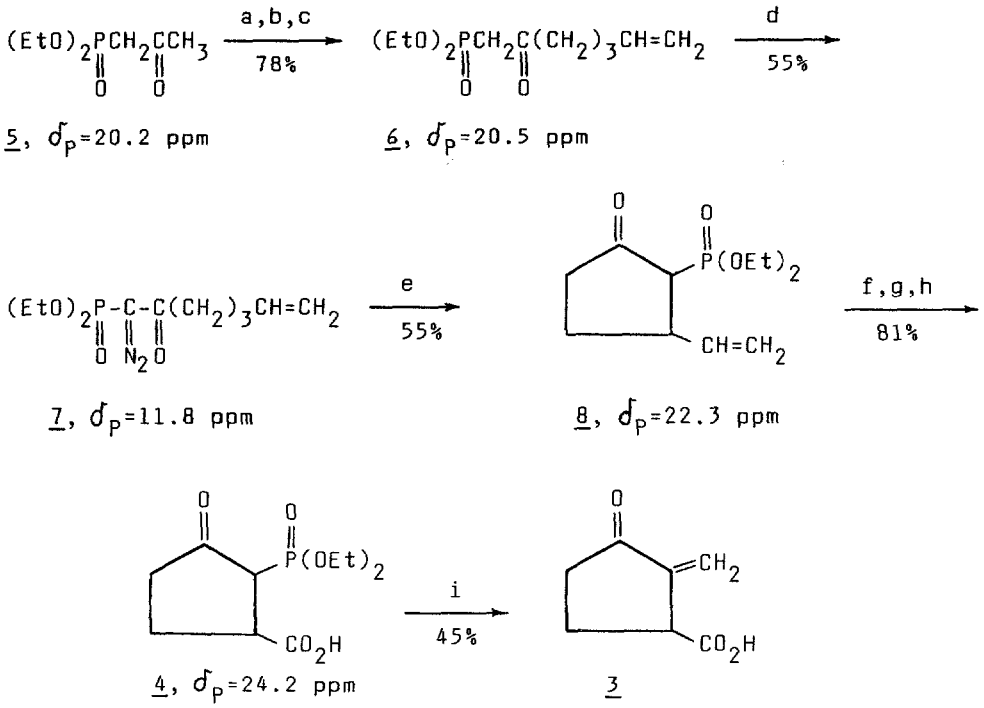
In continuing our interest in this area, we now wish to report the synthesis of the closely related antibiotic, (±)-sarkomycin (3)[4] - an antitumor agent clinically used is some countries. Since sarkomycin (3) like methylenomycin B (1) contains the reactive exocyclic methylene group and is a rather unstable compound, we decided to synthesize 2-diethoxyphosphoryl-3-carboxy--cyclopentanone (4) as a key intermediate which should be transformed into sarkomycin (3) via the Horner-Wittig reaction in the last step of the synthesis.

Scheme I



(a) NaH,THF,rt; (b) n-BuLi,THF,0°C; (c) CH_2=CH(CH_2)$_2$Br,rt,1hr; (d) NaH, TsN_3,THF-Benzene 0-rt,6hr; (e) $Rh_2(OAc)_4$(1% mol),CH_2Cl_2, reflux; (f) O_3, MeOH,-78°C;(g) Me_2S,-30°-rt; (h) CrO_3,H_2SO_4, Acetone,0°; (i) NaH (two moles), CH_2O-gas, THF, rt-reflux

In our total synthesis of (±)-sarkomycin (3), which is depicted in Scheme I, diethyl 2-oxopropanephosphonate (5) was used as a starting material. The dianion generated from 5[5] upon subsequent treatment with sodium hydride and n-butyllithium was reacted with homoallyl bromide to give diethyl 2-oxo--hept-6-enephosphonate (6) in 78% yield [^{1}H-NMR($CDCl_3$) δ=1.30(t,J=7.1 Hz,6H), 1.65(quintet,J=7.3 Hz,2H),1.90-2.10(m,2H), 2.60(t,J=7.3 Hz,2H), 3.03 (d,J= =22.8 Hz), 4.0-4.30(m,4H), 4.90-5.05(m,2H), 5.73(ddt,J=6.7 Hz,J=10.2,10.7 Hz,

1H)][6]. Treatment of 6 with tosyl azide under the standard diazo-transfer reaction conditions[7] afforded the α-diazophosphonate 7 in 55% yield [^{1}H-NMR($CDCl_3$) δ=1.35(dt,J=7.1 Hz, J=0.8 Hz,6H), 1.72(quintet, J=7.3 Hz,2H), 2.00-2.10 (m, 2H), 2.54(t,J=7.4 Hz,2H),4.0-4.30(m,4H), 4.90-5.05(m,2H),5.75(ddt,J=6.7 Hz, J=10.2 Hz,J=17.0 Hz,1H); ^{13}C-NMR ($CDCl_3$) δ=16.2(d,6.4), 23.43,33.06,38.74, 63.46(d,J=5.3 Hz), 115.35, 137.80, 192.7 (d,J=13.4 Hz)]. The next, important step in the synthesis of (±)-3 was the intramolecular cyclization of 7[8] catalyzed by rhodium (II) acetate leading to 2-diethoxyphosphoryl-3-vinyl-cyclopentanone (8) in 55% yield [^{1}H-NMR($CDCl_3$) δ=1.35(dt,J=7.0 Hz,J=0.5 Hz,3H), 1.36(dt,J=7.0 Hz,J=0.4 Hz,3H), 1.65-1.90(m,1H), 2.20-2.50(m,3H), 2.59(dd, J=8.1 Hz,J=25.8 Hz,1H),3.15-3.45(m,1H), 4.00-4.30(m,4H), 5.12 (dt,J=1.2 Hz, J=10.3 Hz,1H), 5.18(dt,J=1.2 Hz,J=17.2 Hz,1H), 5.91(ddd,J=6.9 Hz,J=10.3 Hz, J=17.2 Hz,1H);^{13}C-NMR ($CDCl_3$) δ=16.97(d,J=5.4 Hz), 17.04(d,J=5.4 Hz),28.75 (d,J=11.0 Hz, 39.27,42.82,53,16 (d,J=137.2 Hz), 62.98(d,J=6.8 Hz), 63.57 (d,J=6.5 Hz), 115.82, 140.10(d,J=5.7 Hz), 211.65; M.S.:m/e=246(M^+,51),218(15), 191(100),163(46),139(27),135(70),109(68),75(43),53(31),29(34)]. Conversion of 8 into cyclopentanone 4, a precursor of sarkomycin (3), was effected in 81% yield by ozonolysis followed by reduction of the ozonide with dimethyl sulphide and subsequent oxidation of the corresponding aldehyde formed (δ_{31P}= 23.0), with the Jones reagent [4:^{1}H-NMR ($CDCl_3$) δ=1.30(t,J=7.1 Hz,3H),1.37 (t,J=7.0 Hz,3H), 1.85-2.10(m,1H), 2.10-2.45(m,3H),3.10-3.40(m,2H), 3.95-4.30 (m,4H); ^{13}C-NMR ($CDCl_3$) δ=16.98(d,J=6 Hz), 26.95(d,J=11.0 Hz),40.12, 46.84, 50.8(d,J=137.9 Hz),63.68(d,J=6.0),63.16(d,J=7.0), 180.49,211.80; M.S.: m/e= =264(M^+,<1),219(4),149(43),137(13),97(11),75(100),69(19),57(40),41(35),45(31), 28(55)]. To complete the preparation of (±)-3, cyclopentanone 4 was treated with two equivalents of sodium hydride and then with gaseous formaldehyde at room temperature and the reaction mixture was refluxed for 2 hr in tetrahydrofurane to give after usual work-up (±)-3 and diethyl phosphoric acid. Column chromatography using $CHCl_3$:MeOH (100:2) as an eluent gave pure (±)-sarkomycin (3) in 45% yield. The spectral data of the product obtained are fully consistent with the literature data[9].[^{1}H-NMR ($CDCl_3$) δ=2.0-2.8 (,4H),3.6-3.9(m,1H), 5.71(d,1H), 6.23 (d,1H), J=2.5 Hz, 9.8 (br.s.,1H)].

The overall yield of (±)-3 from 5 was 9%. Further experiments to optimize the yield of (±)-3 as well as to synthesise optically active sarkomycin are now in progress in our Laboratory.

Acknowlegement: This work was financially supported by the Polish Academy of Sciences within the program CPBP 01.13.

References and Notes

1. M.Mikołajczyk and P.Bałczewski, **Synthesis**, 659 (1986) and references cited therein.
2. M.Mikołajczyk, S.Grzejszczak, W,Midura and A.Zatorski, **Phosphorus and Sulfur**, 18, 175 (1983).
3. M.Mikołajczyk and A.Zatorski, Polish Patent 141948, 15 Jan.1988, Appl. 247247, 13 Apr.1984.
4. For other syntheses of sarkomycin see e.g.: B.Wexler, B.H.Toder, G.Minaskanian and A.B.Smith III, **J.Org.Chem.**, 47, 3333 (1982); J.N.Marx and G.Minaskanian, **J.Org.Chem.**, 47, 3306 (1982); R.K.Boeckman, Jr., P.C. Naegely and S.D.Arthur, **J.Org.Chem.**, 45, 752 (1980); Y.Kobayashi and J.Tsuji, **Tetrahedron Lett.**, 22, 4295 (1981); E.J.Barreiro,**Tetrahedron Lett.**,23, 3605 (1982); G.Helmchen, K.Ihring and H.Schindler, **Tetrahedron Lett.**, 28, 183 (1987) and references therein.
5. P.A.Grieco and C.S.Pogonowski, **J.Am.Chem.Soc.**, 95, 3071 (1973).
6. All new compounds (4,6,7 and 8) gave satisfatory combustion analyses for C,H and P.
7. P.Callant, L.D'Haenens, E.Van der Eycken and M.Vandewalle, **Synth.Commun.**, 14, 155 (1984).
8. When our work was in progress a publication of Sturtz et al appeared in which similar results were described: B.Corbel, D.Hernot, J.-P.Haelters and G.Sturtz, **Tetrahedron Lett.**, 28, 6605 (1987).
9. M.Kodpinid, T.Siwapinyoyos and Y.Thebtaranonth, **J.Am.Chem.Soc.**, 106, 4862 (1984).

(Received in UK 4 January 1989)