Total Synthesis of Olivanic Acids and Related Compounds: Preparation of (±)-MM 22383 and (±)-*N*-Acetyldehydrothienamycin

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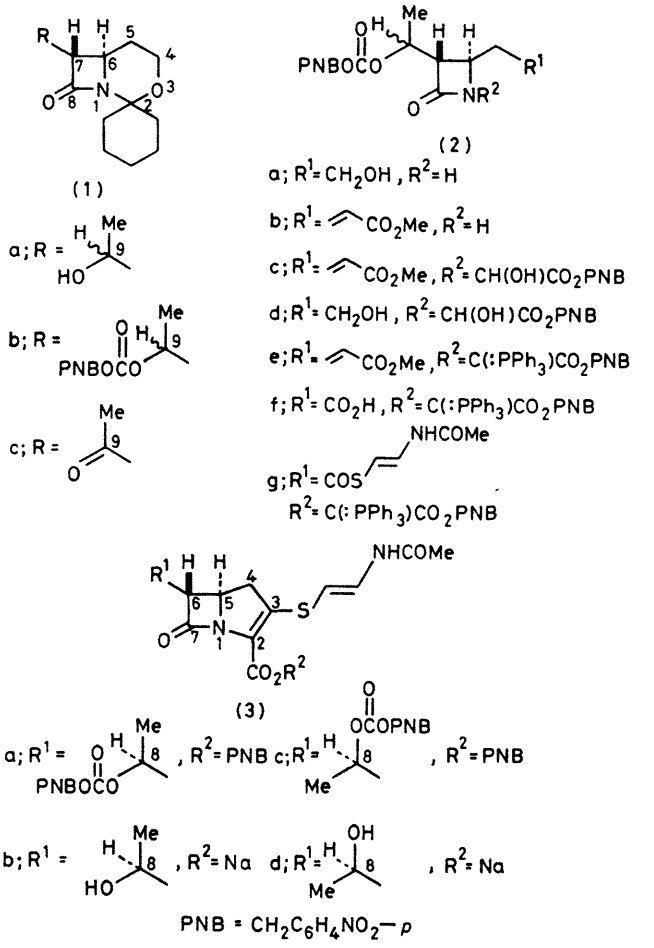
Summary 7-(1-Hydroxyethyl)-8-oxo-3-oxa-1-azabicyclo-[4.2.0]octanespiro-2-cyclohexane has been elaborated to provide appropriately substituted thioester-phosphoranes; these have been cyclised *via* an intramolecular Wittig reaction and the products deprotected to furnish (±)-MM-22383 and (±)-*N*-acetyldehydrothienamycin.

WE have previously described[1] the methodology for preparing β-lactam intermediates having the 1-hydroxyethyl substituent α- to the carbonyl group of the β-lactam ring. In addition 3-(2-acetamidoethenylthio)-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylates have been prepared[2] by us using an intramolecular Wittig reaction with thioesters. We now report the application of these methods to provide

a total synthesis of the racemic forms of the olivanic acid MM 22383 (**3b**)[3] and its C-8 epimer (**3d**) *i.e.* *N*-acetyl-dehydrothienamycin.[4]

7-(1-Hydroxyethyl)-8-oxo-3-oxa-1-azabicyclo[4.2.0]octanespiro-2-cyclohexane (**1a**),† obtained[1] as a 1:1 mixture of diastereoisomers, was initially protected by treatment with n-butyl-lithium and *p*-nitrobenzyl chloroformate (tetrahydrofuran; −78 °C) to provide (**1b**)‡ in 90% yield. Removal of the nitrogen–oxygen blocking group using 0·25 M concentrated sulphuric acid in 10% aqueous acetone (50 °C; 3 h) gave (**2a**)‡ (70%). Oxidation (pyridinium chlorochromate, methylene chloride, 3 h) of the alcohol (**2a**) and trapping of the intermediate aldehyde using a stabilised Wittig reagent ($Ph_3P{=}CHCO_2Me$) afforded the β-lactam (**2b**)‡ (45%). Condensation of (**2b**) with *p*-nitrobenzyl glyoxylate and elaboration of the alcohol (**2c**)‡ to the phosphorane (**2e**)‡ (thionyl chloride, 2,6-lutidine, triphenylphosphine) followed by ozonolysis (methylene chloride, trifluoroacetic acid; −70 °C) and oxidation with *m*-chloroperbenzoic acid gave the acid (**2f**)‡ in 52% overall yield as a crisp foam. Alternatively, improved yields of (**2c**) could be obtained by prior condensation of (**2a**) with *p*-nitrobenzyl glyoxylate leading to (**2d**)‡ (75%) followed by oxidation of the diol (**2d**) with pyridinium chlorochromate. Selective oxidation at the primary alcohol occurred providing, after trapping with the stabilised phosphorane, a 65% yield of (**2c**). Treatment of (**2f**) as the acid chloride ($SOCl_2$, C_5H_5N, MeCN) followed by reaction with silver (*E*)-2-acetamidoethenethiolate[2] afforded the thioester-phosphorane (**2g**)‡ (55%), m.p. 110—112 °C.

Cyclisation of the thioester-phosphorane (**2g**) (1:1 mixture of diastereoisomers) in dry toluene under argon over 48 h gave, after chromatography on silica gel, two products of greater polarity than the starting thioester-phosphorane. The more polar product (**3a**)‡ (15%) was found to be identical spectroscopically with an authentic sample of protected MM 22383§ (8*S*-stereochemistry¶). The second diastereoisomer (**3c**) (8%) (8*R*-stereochemistry¶) was isolated after careful rechromatography of the recovered thioester-phosphorane. Alternatively, separation of the isomers could be achieved at an early stage in the synthesis. Chromatography of (**1b**) gave the diastereoisomer with the (9*S*)-side chain stereochemistry but the second diastereoisomer could not be completely purified. However, reduction of the ketone[1] (**1c**) using potassium Selectride (tetrahydrofuran; 5 °C) gave excellent stereocontrol and almost exclusive formation of the (9*R*)-side chain diastereoisomer which could be processed as previously described.



Hydrogenolysis of the diastereoisomers (**3a**) and (**3c**) (H_2–Pd/C; aqueous dioxan) followed by addition of 1 equiv. of sodium hydrogen carbonate gave the sodium salts (**3b**) and (**3d**). The salt (**3b**) was found to be identical with an authentic sample of MM 22383 (spectroscopically and by h.p.l.c.) and as expected showed approximately half the biological activity of the natural product in *in vitro* antibacterial tests. The C-8 epimer (**3d**) corresponding to *N*-acetyldehydrothienamycin, λ_{max} (H_2O) 308 and 228 nm, ν_{max} (KBr) 1755 cm^{-1}, also showed broad spectrum antibacterial activity, details of which will be reported later.

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† All compounds are racemic mixtures, but only one enantiomer is depicted for convenience.

‡ All new compounds were satisfactorily characterised.

§ Prepared by acylation of MM 22383 *p*-nitrobenzyl ester using n-butyl-lithium and *p*-nitrobenzyl chloroformate in dry tetrahydrofuran.

¶ The (8*S*)-diastereoisomer is distinguishable from the (8*R*)-diastereoisomer in the position and coupling constants of the C-6 proton; for the (8*S*)-diastereoisomer the C-6 H appears at δ 3·47 (dd, *J* 3·0, 4·5 Hz) and for the (8*R*)-diastereoisomer it appears at δ 3·32 (dd, *J* 2·5, 8·0 Hz).

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