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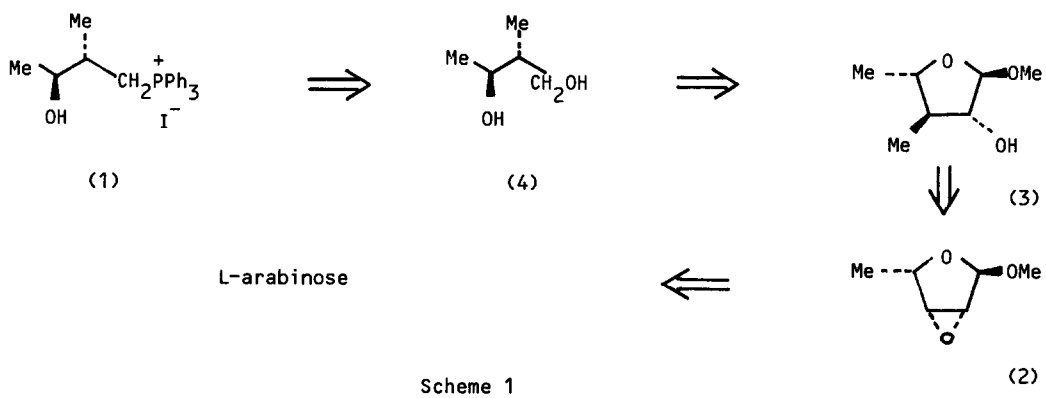
ENANTIOSPECIFIC SYNTHESIS OF (3S-HYDROXY-2S-METHYL) BUTYLTRIPHENYLPHOSPHONIUM IODIDE, A PRECURSOR FOR THE CHIRAL SIDE CHAIN OF PSEUDOMONIC ACID C

G.W.J. Fleet and T.K.M. Shing,

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford.

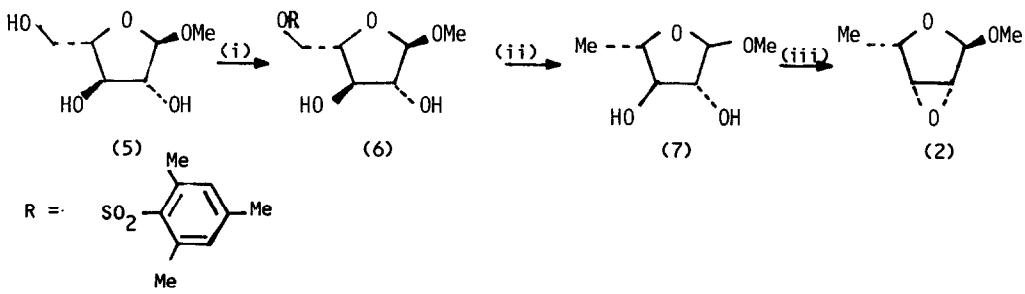
Abstract: The enantiospecific synthesis of (3S-hydroxy-2S-methyl)butyl triphenylphosphonium iodide from L-arabinose is described.

The accompanying paper[1] describes the total synthesis of pseudomonic acid C in which (3S-hydroxy-2S-methyl) butyltriphenylphosphonium iodide (1) is the intermediate used for the introduction of the chiral side chain; there are no previous reports of the synthesis of chiral phosphonium salt (1). The stereochemistry at the two chiral centres in (1) may be controlled by the regioselective ring opening of methyl 2,3-anhydro-5-deoxy--α-L-lyxofuranoside (2) by dimethylcopper lithium to yield the branched sugar (3) which may then be converted to 2R-methylbutan-1,3S-diol(4) and to the phosphonium salt (1). (Scheme 1).



Scheme 1

The epoxide (2) is synthesised from L-arabinose by the route outlined in Scheme 2. Methyl α-L-arabinofuranoside (5), available as the kinetic glycoside from L-arabinose in 57% yield,[2] reacted with trimsyl chloride in pyridine to give a crystalline trimsylate (6),[3] m.p. 70°, $[\alpha]_D^{20}$-73.3 (c, 1.35 in $CHCl_3$) (77%) which was quantitatively converted to the corresponding iodide (2 equiv. of NaI in butanone) and subsequently hydrogenolysed (palladium on charcoal, methanol in the presence of triethylamine) to give crystalline methyl 5-deoxy-α-L-arabinofuranoside (7)[4] (96% yield). Reaction of the trans-diol (7) with triphenylphosphine - diethyl azodicarboxylate[5] gave stereospecifically[6] methyl

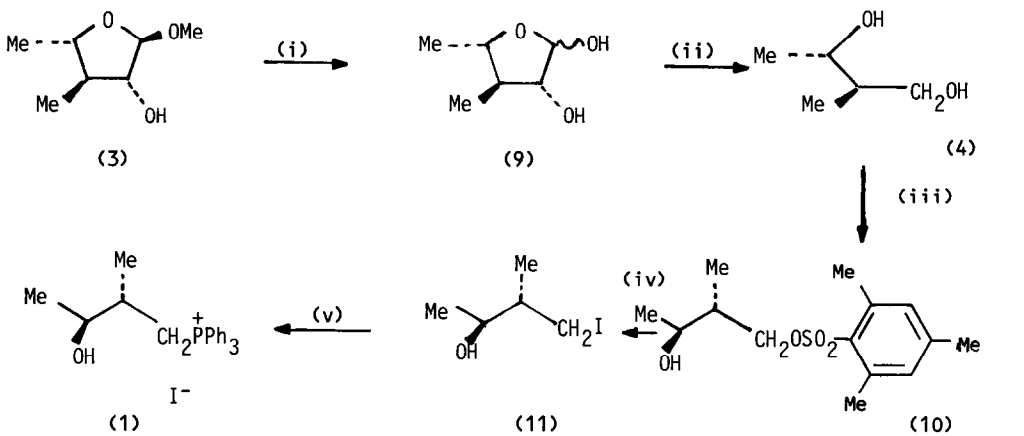


(i) Trimsyl chloride, pyridine, 0° (ii) NaI in refluxing butanone (8 hr) followed by Pd/C, methanol, triethylamine (iii) Ph_3P, $EtO_2CN{=}NCO_2Et$, tetrahydrofuran, 0°

Scheme 2

2,3-anhydro-5-deoxy-α-L-lyxofuranoside (2), m.p. 58°, $[\alpha]_D^{20}$-87.7, (c, 0.4 in $CHCl_3$) (87% yield). The overall yield of epoxide (2) from furanoside (5) is 65%.

The epoxide (2), on treatment with 3 equivalents of $Me_2Cu(CN)Li_2$[7] at room temperature

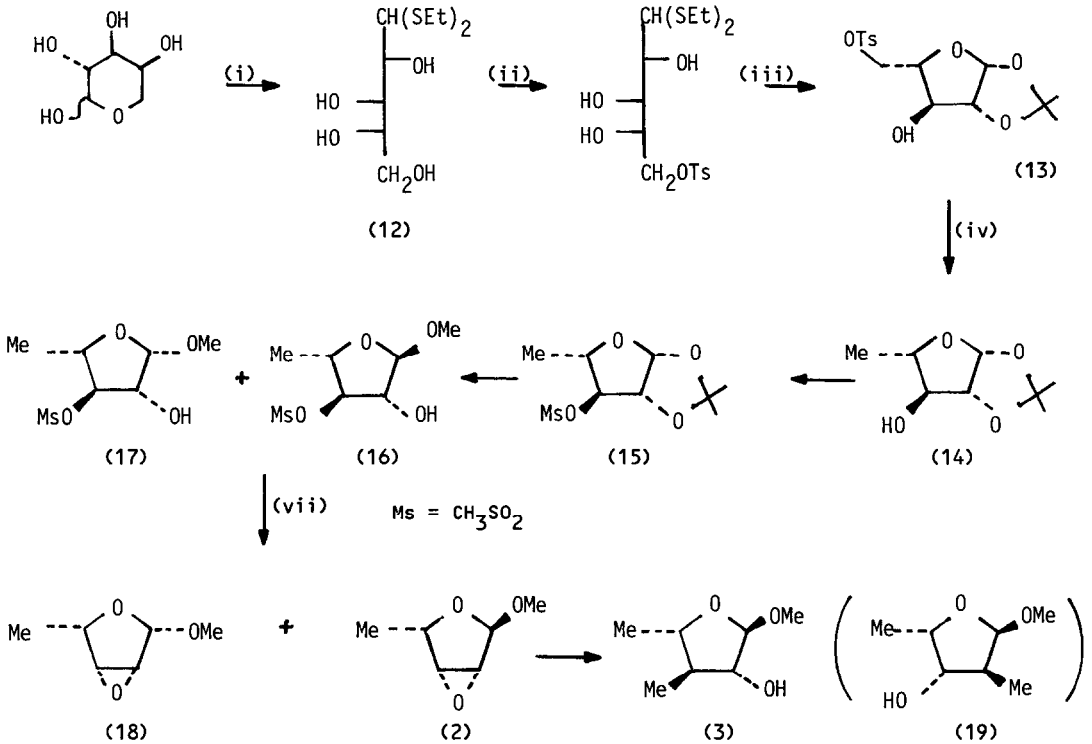


(i) Dowex 50W-8x resin (H^+), 60° (ii) $NaIO_4$, followed by $NaBH_4$ (iii) Trimsyl chloride, pyridine, 0° (iv) NaI in butanone, reflux, 2 hr (v) Ph_3P in refluxing toluene, 2 days

Scheme 3

for 36 h, gave the anticipated[8] regiospecific ring opening to the C-3-methyl alcohol (3) in 71% yield; the ^1H n.m.r. of (3) displayed a diagnostic upfield triplet of quartets at δ1.59 attributable to H-3 ($J_{3,2}$ 6.1, $J_{3,4}$ 6.1, $J_{3,Me}$ 6.8 Hz), an assignment confirmed by double resonance experiments.

Further elaboration of (3) now required carbon degradation of the carbon chain (Scheme 3). Hydrolysis of the methyl furanoside (3) gave lactol (9) which, without isolation, was subjected to glycol-cleavage oxidation with sodium periodate, followed by sodium borohydride reduction of the liberated aldehyde; the resulting diol (4) was then isolated in 60% yield from (3). Selective esterification of the primary hydroxyl group[9] in (4) by trimsyl chloride produced trimsylate (10), $[\alpha]_D^{20}$+5.0 (c, 1.36 in $CHCl_3$), which on treatment with sodium iodide formed the volatile iodide (11) (90% yield). Reaction of iodide (11)

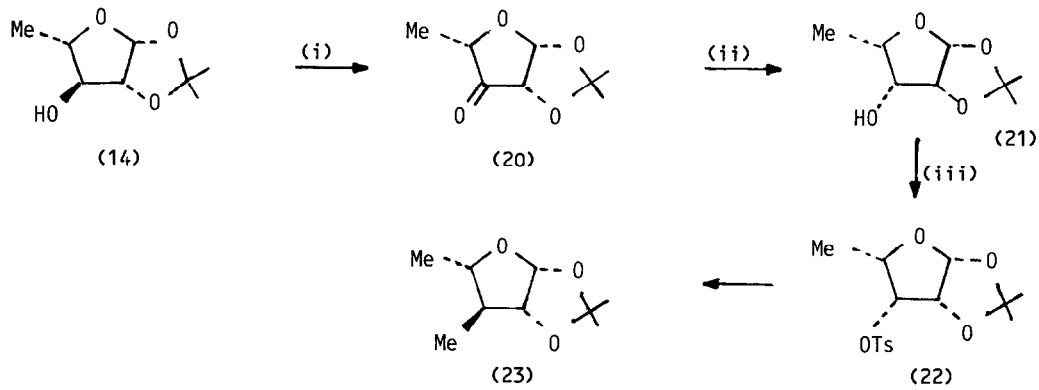


(i) EtSH, HCl (ii) 1.1 equiv. TsCl, pyridine, 0° (iii) Hg^{++}, acetone (iv) excess $LiAlH_4$ in tetrahydrofuran (v) MsCl, pyridine (vi) MeOH, Dowex 50W-8(H^+), (vii) NaOME in CH_2Cl_2

Scheme 4

with triphenylphosphine gave the required chiral phosphonium salt (1), m.p. 183-184°, $[\alpha]_D^{20}$+5.2° (c, 0.4 in $CHCl_3$) in 89% yield.

The properties of methyl 2,3-anhydro-5-deoxy-α-L-lyxofuranoside (2) prepared as in Scheme 2 are markedly different from those previously reported for this compound (2).[10] Although the above sequence ensures that the C-5 methyl and the anomeric methoxyl groups in (2) are trans to each other, some ambiguity may arise in the stereochemical relationship of the epoxide ring to the methyl group. Accordingly, another synthesis of epoxide (2) was devised in which the cis relationship of the epoxide ring and of the C-methyl group could be guaranteed (Scheme 4). L-Arabinose on treatment with ethanethiol in concentrated hydrochloric acid formed the dithioacetal[11] (12); selective tosylation of the primary hydroxyl group in (12), followed by immediate demercaptalisation with mercury (II) chloride in acetone produced the crystalline acetonide[4] (13) in 56% yield from (12). The acetonide (13) with lithium aluminium hydride gave 5-deoxy-1,2-O-isopropylidene-β-L-arabinofuranose[12] (14) (87% yield). Mesylation of the free hydroxyl group in (14) produced the syrupy mesylate (15), $[\alpha]_D^{20}$+2.0 (c, 0.6 in $CHCl_3$); methanolysis of (15) led to an anomeric mixture of methyl furanosides, (16) and (17), which was exposed to methanolic sodium methoxide to produce a mixture of the two epoxides (2) and (18), easily separated by flash chromatography. This synthesis of the mixture of the anomeric epoxides requires that the



(i) pyridinium chlorochromate, CH_2Cl_2 molecular sieve (ii) $NaBH_4$, EtOH, 0° (iii) TsCl, pyridine, 0°

Scheme 5

C-5 methyl and the oxirane ring be cis to each other. One of these epoxides was shown to be identical to (2) produced in Scheme 2, and underwent regiospecific ring opening to (3), as described above; as before there was no indication of the formation of (19).

An alternative approach to the construction of the required relative stereochemistry of the two methyl groups on a furanose is shown in Scheme 5. The alcohol (14) on treatment with pyridinium chlorochromate yielded the ketone (20)[13] which was reduced by sodium borohydride to the L-lyxoalcohol (21)[14] and esterified with tosyl chloride to produce the tosylate (22), m.p. 97-98°, $[\alpha]_D^{20}$+35.5° (c, 1.1 in $CHCl_3$) in an overall yield of 61% from (14). Although displacement of cyclopentyl tosylates by dimethyl copper lithium reagents has been successfully achieved in several cases, coupling reactions of tosylate (22) with lithium dimethyl cuprate[15] or with higher order mixed cuprates[7] gave no product corresponding to (23).

The accompanying paper[1] describes the Wittig reaction between the chiral phosphonium salt (1) and a suitable aldehyde in the total synthesis of pseudomonic acid C.[16]

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