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ENANTIOSPECIFIC TOTAL SYNTHESIS OF PSEUDOMONIC ACIDS FROM ARABINOSE

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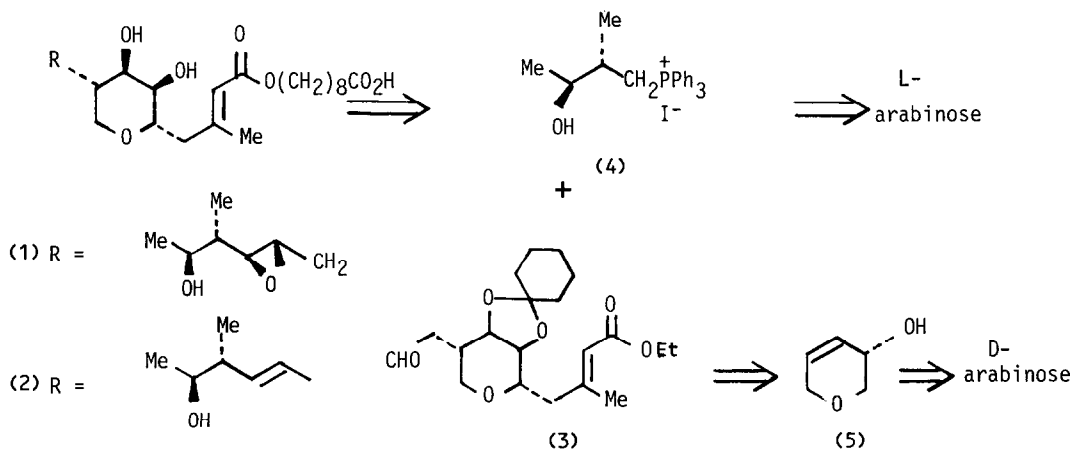
Abstract: The enantiospecific synthesis of pseudomonic acids from arabinose is described.

Pseudomonic acids A (1) and C (2) are members of a novel class of compounds with antibacterial and antimycoplasmal activity.[1] The first reported synthesis of racemic pseudomonic acid C involved a key step of coupling the racemic form of the pyranose aldehyde (3) with the ylid derived from the racemic form of the phosphonium salt (4) (Scheme 1).[2] Subsequent approaches to racemic[3] pseudomonic acids have been directed towards alternative synthesis of racemic aldehyde (3); also, several preliminary publications[4,5] have indicated strategies for the enantiospecific synthesis of the optically active form of aldehyde (3) or a close equivalent of (3). Very recently, an enantiospecific synthesis of pseudomonic acid C, based on the ring opening of a pyranose epoxide, has appeared.[6] This paper describes the enantiospecific synthesis of the chiral aldehyde (3) from D-arabinose, and the coupling of (3) with the ylid derived from the chiral phosphonium salt (4), the enantiospecific synthesis of which from L-arabinose was described in the preceding letter.[7]

The principle of the enantiospecific synthesis of (3) relies on the introduction of the

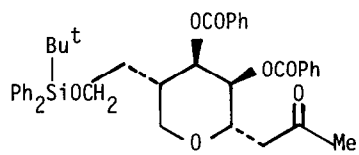


Scheme 1

two cis carbon side chains by sequential Claisen rearrangements[4,8] on the chiral allylic alcohol (5).

The allylic alcohol (5), in which the chirality is derived from C-2 of D-arabinose, may be prepared (Scheme 2) in batches of 10 g by pyrolysis of the orthoformates of triol (6) in an overall yield of 30% from D-arabinose.[4] Treatment of (5) with N,N-dimethylacetamide dimethyl acetal in refluxing xylene formed the Claisen rearrangement[9] product, the γ,δ-unsaturated amide (7) (82%) which, with iodine in aqueous tetrahydrofuran at 0°, gave the iodolactone (8) (81%). 1,5-Diazabicyclo[5,4,0]undec-5-ene caused the only possible regiospecific anti elimination of HI to form 1S,6S-3,7-dioxabicyclo[4,5,0]non-4-en-8-one (9),[10] m.p. 58°, b.p. 86-88°, 0.07 mm Hg, $[\alpha]_D^{20}$-63.9° (c, 1.0 in $CHCl_3$) in 98% yield. Subsequent reduction of (9) with sodium borohydride in ethanol gave the diol (10), m.p. 80-81°(ethyl acetate, hexane) $[\alpha]_D^{20}$-272° (c, 1.0 in acetone) (86%) in which the primary hydroxyl group was selectively protected as the diphenyl-tert-butylsilyl ether (11), $[\alpha]_D^{20}$-83.2° (c, 1.0 in $CHCl_3$) (93%).

The second carbon chain was now introduced by a second Claisen amide acetal rearrangement to form the tertiary amide (12), $[\alpha]_D^{20}$-26.0° (c, 1.0 in $CHCl_3$) in 94% yield; the cis stereochemistry of the two carbon chains is guaranteed by the combination of the Claisen rearrangements, and the iodolactonization which ensures that the hydroxyl group of the allylic alcohol in (11) is cis to the first carbon side chain introduced. Treatment of (12)

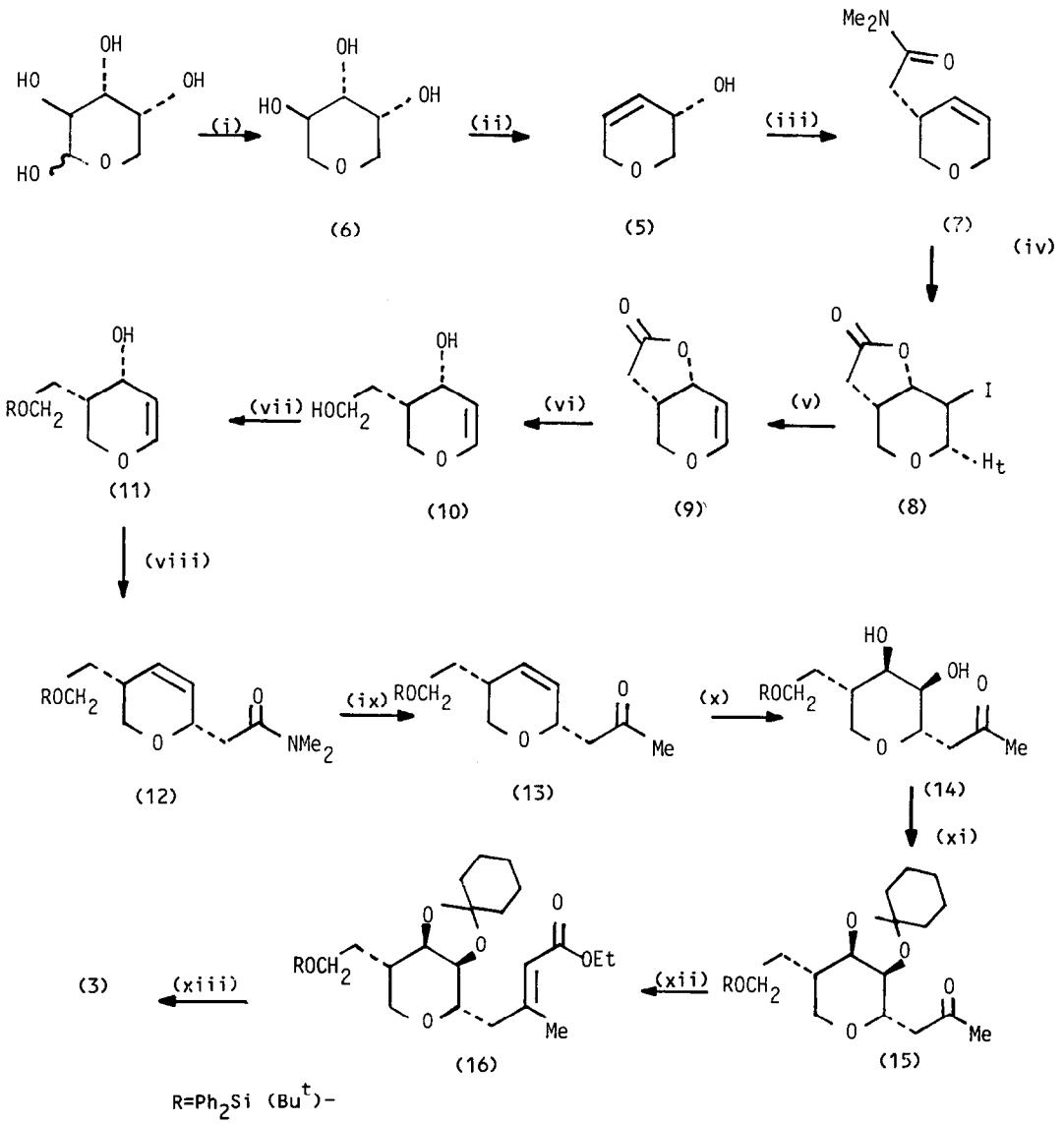


(18)

with a small excess of methyl lithium led to the formation of the methyl ketone (13) $[\alpha]_D^{20}$-33.3° (c, 2.0 in $CHCl_3$) (81% yield) which was hydroxylated from the least hindered side by osmium tetroxide/N-methylmorpholine-N-oxide to give the diol (14), $[\alpha]_D^{20}$+18.6° (2.0 in $CHCl_3$) in 85% yield; a small amount of the all cis diastereomer of (14) was also formed in this reaction.

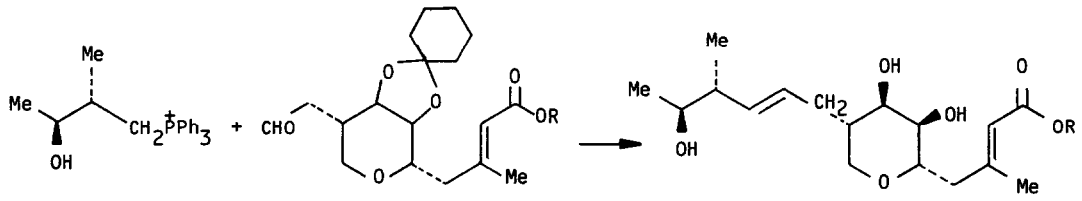
The chiral diol, with 4 contiguous chiral carbons, (14) is thus formed from S-3,6-dihydro-2H-pyran-3-ol (5) in 8 steps in an overall yield of 34% and is readily available in quantities of several gram. The dibenzoate (18) of the diol (14) was prepared (benzoyl chloride in pyridine) and its H^1-NMR spectral parameters were in close agreement with those reported for the racemic modification of the dibenzoate.[2]

Reaction of (14) with cyclohexanone gave the corresponding cyclohexylidene derivative (15) (93% yield) which was subjected to a Wadsworth Emmons olefination[11] with the sodium salt of triethyl phosphonoacetate (3 equiv) to give a mixture of (16) (75%)and the isomeric Z-olefin (19%). The silyl protecting group was removed from (16) by treatment with tetrabutyl ammonium fluoride (87% yield), and the resulting alcohol was oxidised with pyridinium chlorochromate in dichloromethane in the presence of powdered molecular sieve to produce the required chiral aldehyde (3) in 80% yield (aldehyde CHO at δ9.80).



(i) HBr, Ac_2O; $Pd/H_2/Et_3N$; MeONa/MeOH. (ii) $HC(OEt)_3$/AcOH trace in EtOAc followed by pyrolysis at 250°C. (iii) $MeC(OMe)_2NMe_2$, refluxing xylene, 18 h. (iv) I_2, aqueous THF, 0°. (v) DBU, benzene, 18 h. (vi) $NaBH_4$, EtOH. (vii) $Ph_2Si(Bu^t)Cl$, imidazole, DMF (viii) $MeC(OMe)_2NMe_2$, xylene refluxing, 7 h. (ix) MeLi (1.1 equiv), THF, -78° (x) OsO_4, N-methylmorpholine-N-oxide (xi) cyclohexanone, anhydrous $CuSO_4$, 4-Me-$C_6H_4SO_3H$. (xii) NaH, $(EtO)_2P(O)CH_2COOEt$ (3 equiv), 24 h, THF, room temp. (xiii) Bu_4NF (1 M 2 equiv. in THF) room temp, 4 h, then pyridinium chlorochromate (3 equiv), CH_2Cl_2 powdered molecular sieve, 1 h, room temp.

Scheme 2



(4) (3) (17) R = Et (2) R = $O(CH_2)_8COOH$

Scheme 3

The aldehyde (3) (Scheme 3) was added to the ylid (1.5 equiv) derived from the chiral phosphonium salt[7] (4) [by treatment with 2 equiv of butyl lithium per equiv of (4)] in THF at -40°, and kept at -30° for 2 h; the reaction mixture was then warmed to 0° in 30 min, left for a further 30 min at 0° and quenched with acetic acid. The reaction gave a complex mixture of products from which was isolated the cyclohexylidene derivative of ethyl monate C (25% yield) by flash chromatography, identical to authentic material prepared from ethyl monate C (17).[1] The other products of this reaction were not identified and the yield has not yet been optimised. The cyclohexylidene derivative was hydrolysed by aqueous acetic acid (50% v/v, room temp, 3 days) to beautifully crystalline ethyl monate C (17), m.p. and mixed m.p. 98.5-99° (lit[1] m.p. 96.5-97.5°) $[\alpha]_D^{20}$ + 12.1° (c, 0.81 in $CHCl_3$) identical in all respects to an authentic sample prepared from monic acid A.[1]

Since chiral ethyl monate C has been converted to pseudomonic acid C (2) and pseudomonic acid A (1),[1,6] this work constitutes a total enantiospecific synthesis of both pseudomonic acids from arabinose.

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