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A versatile approach to the total synthesis of the pseudomonic acids

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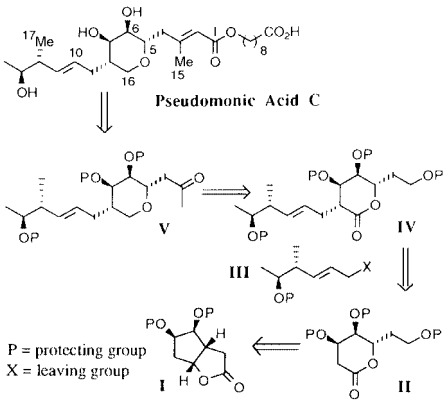
The total synthesis of pseudomonic acid C is described using an approach which gives access to analogues and putative biosynthetic precursors; the key step is installation of the C_7 side-chain *via* alkylation of a trisubstituted δ-lactone with complete stereocontrol and in 85% yield under conditions which avoid the possible competing elimination of a protected hydroxy group β to the carbonyl.

Pseudomonic acid C is one of a family of *C*-glycopyranosides produced by *Pseudomonas fluorescens*.[1] These compounds are potent inhibitors of Gram positive bacterial and mycoplasmal pathogens[2] and pseudomonic acid A (with a 10,11-epoxide) is used clinically for the treatment of bacterial skin infections. More recently new pseudomonic acid derivatives such as thiomarinol have been isolated from marine organisms.[3]

Despite their biological importance, the biosynthesis of these polyketide derived secondary metabolites[4] has not been established. Results of feeding studies with oxygen-18 precursors indicate that the oxygens attached to C-1, C-5, C-7 and C-13 are all derived from acetate whereas the oxygen at C-6 must originate from either the atmosphere or water.[5] These results are in accord with the proposal that the tetrahydropyran ring is formed either *via* an intramolecular conjugate addition of 5-OH to an enone or *via* an intramolecular S_N2 type attack of the 5-OH onto an activated 16-hydroxy group. However, the mechanism of cyclisation has not been established and its timing relative to other steps such as hydroxylation at C-6 or esterification at C-1 is not known. Therefore our goal was to develop a new and flexible approach to the synthesis of pseudomonic acid which would give access to acyclic compounds to examine these processes as well as to analogues for biological assessment. Previous routes have involved either elaboration of carbohydrates or the modification of dihydropyrans.[6] These approaches do not give access to the required putative biosynthetic intermediates and hence a new strategy was required.

The key features of this strategy (Scheme 1) are: (i) the enantioselective synthesis of a suitably protected functionalised δ-lactone **II** from the bicyclic lactone **I**; (ii) preparation of the C_7 side-chain **III** with a good leaving group to act as the electrophile for reaction with the enolate of **II**; (iii) installation of the C_7 side-chain with complete stereocontrol under conditions which avoid the possible competing elimination of a protected hydroxy group β to the carbonyl in **II** to give **IV**; (iv) reduction of the lactone **IV** to a tetrahydropyran followed by further manipulation of the side chain to methyl ketone **V** and chain extension with a known phosphonate[7] to the target compound. Lactone **IV** would be the precursor of the acyclic compounds required to examine the ring closure reactions.



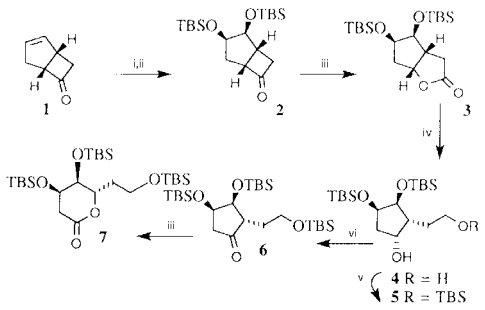
Scheme 1

The first step was introduction of a *cis*-vicinal diol which was achieved *via* treatment of *cis*-bicyclo[3.2.0]hept-7-en-2-one **1** with catalytic osmium tetroxide giving a 9:1 mixture of *exo*:*endo* vicinal diols.[8] (−)-(1*S*,5*R*)-Bicyclic ketone **1** required as the starting material was prepared with 95% ee *via* resolution of the bisulfite adduct.[9] The *syn* diols could be protected as either the acetonide or benzyl ethers but, for ease of manipulation at later stages of the synthesis, the *tert*-butyldimethylsilyl (TBS) ether **2** was preferred (Scheme 2) Baeyer–Villiger oxidation proceeded as expected[10] with complete regiocontrol giving the required lactone **3** in 68% yield over the three steps from **1**.

Elaboration of bicyclic lactone **3** to the required δ-lactone **7** was accomplished by a straightforward sequence involving initial reduction of **3** with $LiAlH_4$ to diol **4**. Selective protection of the primary alcohol of **4** as either the benzoate, trityl ether or TBDPS ether proceeded in excellent yields (> 90%), but the best protecting group for later stages of the synthesis proved to be the TBS ether. Oxidation of alcohol **5** with TPAP[11] followed by treatment of the resultant cyclopentanone **6** with MCPBA gave δ-lactone **7** possessing the stereogenic centres which would become C-5, C-6 and C-7 of pseudomonic acid.

The key stage of the total synthesis was the alkylation to introduce selectively the C_7 side chain of pseudomonic acid. Examples of alkylation of δ-lactones have been reported,[12] and Seebach *et al.*[13] showed that stereocontrol of the methylation of a δ-lactone possessing a free hydroxy group β to the carbonyl could be achieved using chelation control with the alkoxide. However, we found no literature precedents for alkylation of a δ-lactone possessing a β-silyl ether and it was anticipated that β-elimination to give the α,β-unsaturated lactone may be a competing process.

Allylic bromides have been used as electrophiles in the alkylation of simple δ-lactones in natural product synthesis[14]



Scheme 2 *Reagents and conditions*: i, OsO_4, NMO (*N*-methylmorpholine *N*-oxide), Me_2CO; ii, TBSOTf, CH_2Cl_2, pyridine; iii, *m*-CPBA, $NaHCO_3$, CH_2Cl_2; iv, $LiAlH_4$, THF; v, TBSCl, imidazole, CH_2Cl_2; vi, TPAP (tetrapropylammonium perruthenate), NMO, CH_2Cl_2.

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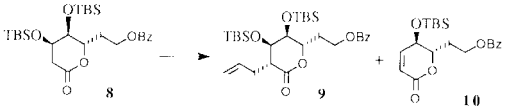
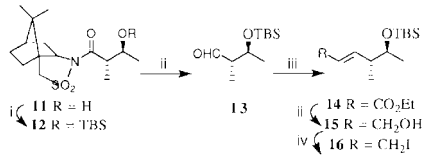


Scheme 3

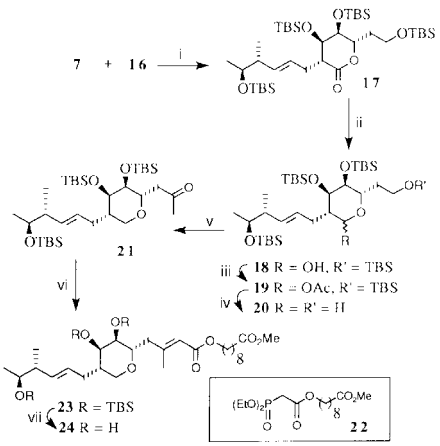


Scheme 4 *Reagents and conditions*: i, TBSOTf, pyridine, CH_2Cl_2; ii, DIBAL-H, CH_2Cl_2, −78 °C; iii, $(EtO)_2POCHCO_2Et$, BuLi, THF; iv, DIPHOS (1,2-bis(diphenylphosphino)ethane), I_2, 0 °C.

and so we carried out model studies using allyl bromide. Treatment of trisubstituted δ-lactone **8** with LDA followed by addition of allyl bromide gave, at best, 20% yield of the alkylated product **9** (Scheme 3). HMPA has been used to improve yields in the alkylation of δ-valerolactone,[15] but on addition of HMPA to our reaction, β-elimination occurred giving the α,β-unsaturated lactone **10** as the major product. However, when the reaction was repeated with the more reactive allyl iodide as the electrophile, **9** was obtained in 84% yield. From NMR studies it was evident that a single product had been isolated and the X-ray crystal structure confirmed that the allyl group in **9** was indeed on the opposite face to the protected vicinal diol as required for the synthesis of pseudomonic acid.

The next stage was the preparation of the C_7 side chain **III** with iodide as the leaving group. The enantioselective synthesis of the analogous alcohol **15** (92% de) has been described by Keck and Tafesh.[16] We adopted a similar approach to **15** (Scheme 4) but used the known alcohol **11**[17] to establish the two asymmetric centres. Protection as the TBS ether **12** and reductive cleavage of the auxiliary using DIBAL-H at −78 °C gave aldehyde **13** in 93% yield over the two steps. Chain extension of **13** to **14** followed by reduction with DIBAL-H gave the required allylic alcohol **15** (> 99% de). Reaction of **15** with DIPHOS and I_2 at 0 °C[18] gave allylic iodide **16** in quantitative yield. The key alkylation of the lithium enolate of δ-lactone **7** with allylic iodide **16** in the presence of HMPA led to the required tetrasubstituted δ-lactone **17** in 85% yield after purification (Scheme 5).

Having created all the necessary asymmetric centres around the central δ-lactone core, the next goal was reduction to the analogous tetrahydropyran using a modification of the procedure described by Kraus *et al.*[19] Treatment of lactone **17** with



Scheme 5 *Reagents and conditions*: i, LDA, HMPA, −78 to 5 °C; ii, DIBAL-H, CH_2Cl_2, −78 °C; iii, Ac_2O, pyridine; iv, Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C; v, PDC, CH_2Cl_2 then MeMgBr, Et_2O, −5 °C then TPAP, NMO, CH_2Cl_2; vi, **22**, KHMDS, THF; viii, TBAF, THF.

DIBAL-H in CH_2Cl_2 at −78 °C gave lactol **18** which could be reduced directly to the tetrahydropyran with triethylsilane in the presence of $BF_3{\cdot}Et_2O$. However, an improved yield was obtained by acetylation to **19** prior to the triethylsilane reduction. The reaction conditions led to the concommitant selective removal of the TBS ether to unmask the primary alcohol **20** required for the next stage of the synthesis. Oxidation of **20** with PDC to the corresponding aldehyde, introduction of C-17 using MeMgBr and a second oxidation with TPAP then gave methyl ketone **21** in 74% yield from **20**.

The final carbon–carbon bond forming reaction was the Horner–Emmons coupling of ketone **21** with phosphonate **22** (prepared in 75% yield by the DCC/DMAP mediated coupling methyl 9-hydroxynonanoic acid with diethyl phosphonoacetic acid) giving the *E*-unsaturated ester **23**. Deprotection of the TBS ethers with TBAF gave methyl pseudomonate C **24**, with spectroscopic data in accord with those previously reported[7,20] and with $[\alpha]_D$ +10.0 (*c* 0.15, $CHCl_3$). Interestingly our literature search revealed no $[\alpha]_D$ value for methyl pseudomonate C derived from natural sources and only that for material prepared by total synthesis.[20] Hence a sample of pseudomonic acid C isolated from *Ps. fluorescens* was methylated giving ester **24** with $[\alpha]_D$ +10.7 (*c* 0.3, $CHCl_3$), in good agreement with the value obtained for our synthetic sample. The methyl ester may be hydrolysed[20] to pseudomonic acid C.

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