229. Enantioselective Synthesis of Pseudomonic Acids. I. Synthesis of Key Intermediates

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Summary

An enantioselective synthesis of key intermediates for the synthesis of the antimicrobially active pseudomonic acids A (**1**), B (**2**) and C (**3**) is described. D-Ribose (**4**) was used as starting material.

In 1971, *Chain & Mellows* first isolated and purified antimicrobially active substances produced by fermentation of a strain of *Pseudomonas fluorescens* [1]. Meanwhile the structures of pseudomonic acids A (**1**), B (**2**) and C (**3**) have been elucidated [2–6]. In spite of considerably growing interest in the synthesis of these antibiotic substances, as reflected by several recent reports on **1** and **3** [7–12], no approach to optically active compounds has been described so far. In addition, it should be noted that pseudomonic acid B (**2**) has not yet been the target molecule for synthetic studies at all.

In the present communication we report an enantioselective synthesis[1]) of the intermediate **24** and its derivatives **25–29** *(Scheme 2)*, most suitable precursors to the pseudomonic acids A–C (**1–3**). On the basis of our retrosynthetic analysis *(Scheme 1)*, we have chosen the readily available D-ribose (**4**) rather than the more expensive L-lyxose (**5**), as starting material from the pool of chiral building blocks. To assemble the molecular framework, the following main problems had to be solved: a) introduction of an alkyl chain at C(1) of the pentose **4** to form a C-glycoside, b) selective protection of the hydroxyl groups at C(2) and C(3), c) introduction of the second side-chain at C(4).

The known acetal **6** (prepared from D-ribose (**4**) under kinetic control [14][2])) on *Wittig* reaction with (acetylmethylidene)triphenylphosphorane in acetonitrile

[1]) The term *EPC*-synthesis (synthesis of Enantiomerically Pure Compounds) has been proposed by *Seebach & Hungerbühler* [13] for all syntheses that finally lead to enantiomerically pure products.

[2]) The more stable furanose acetonides formed as by-products can easily be cleaved to the starting material **4**.

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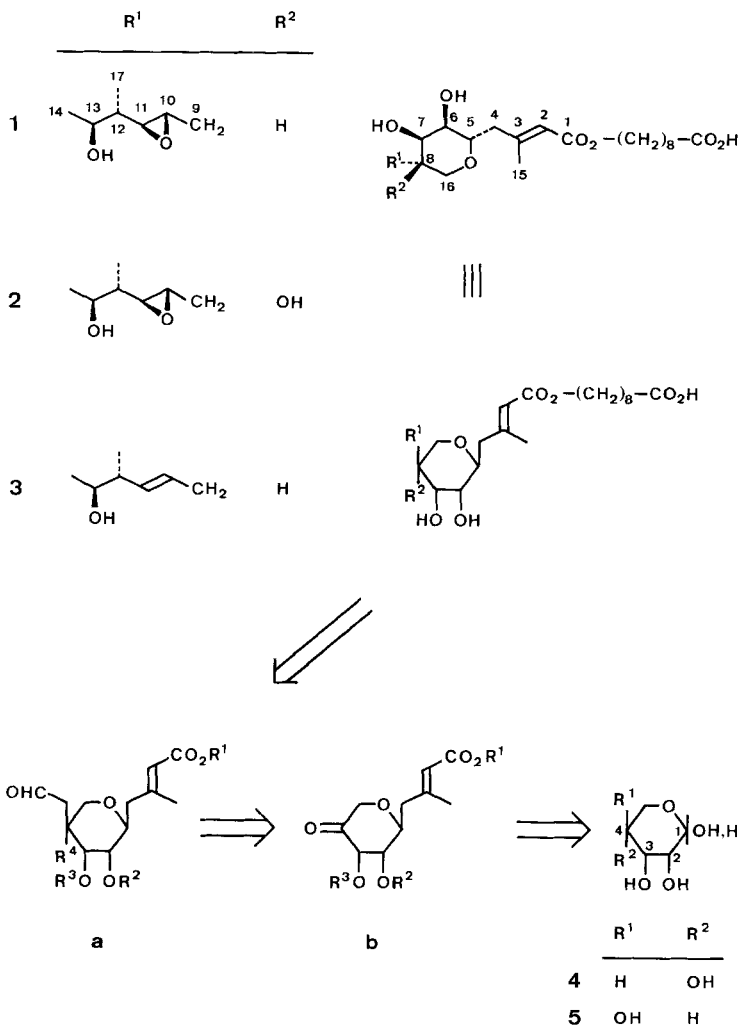
Scheme 1

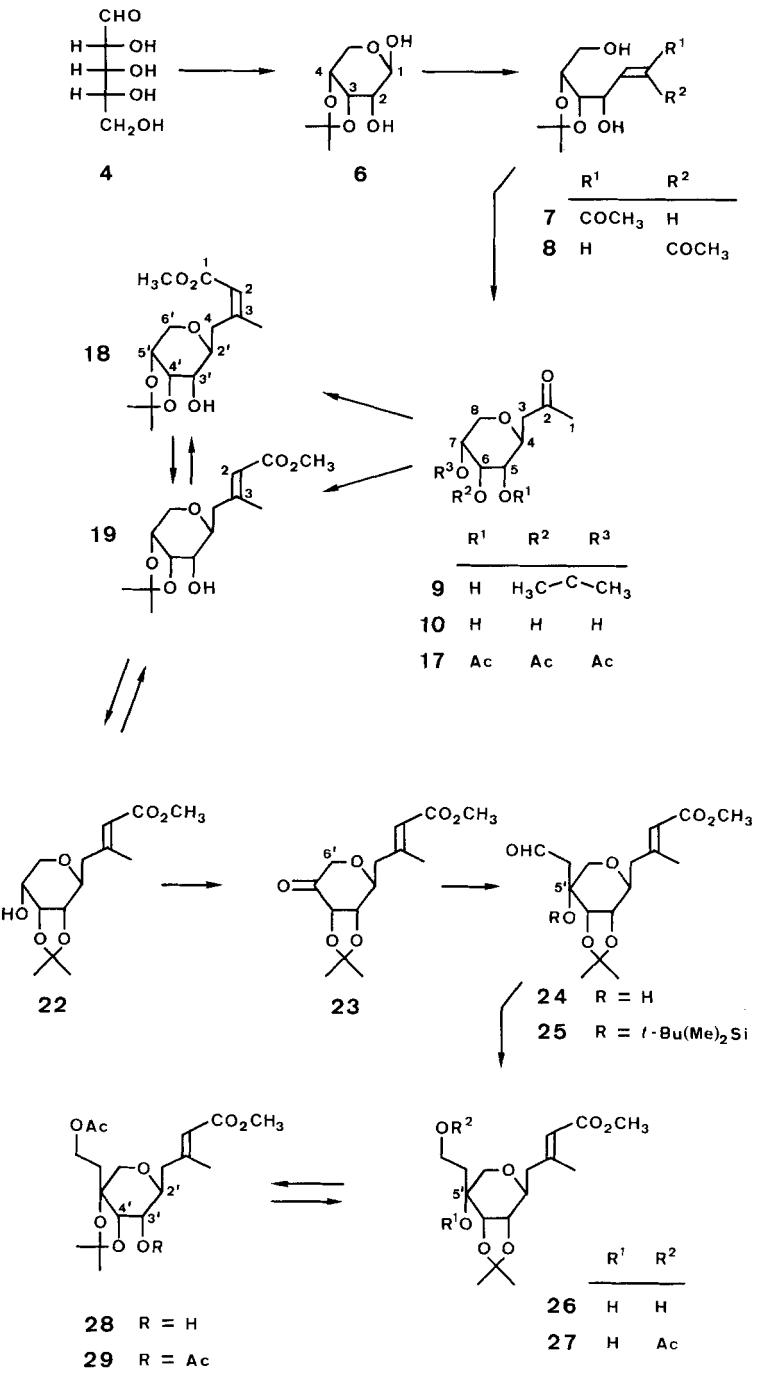


under reflux was transformed to a mixture of the unsaturated ketones **7**[3]) ((*E*)-isomer) and **8** ((*Z*)-isomer), which was treated without workup with a catalytic amount of sodium methoxide at 0° to yield the crystalline C-glycoside **9** (70% after chromatography; m.p. 113.5–114°; $[\alpha]_D = +13.8°$ ($c = 1.45$)). The latter was also

[3]) All the compounds described have been characterized analytically and spectroscopically: IR. ($CHCl_3$): $\tilde{\nu}_{max}$ in cm^{-1}; ^1H-NMR. ($CDCl_3$): chemical shifts in ppm relative to TMS; $[\alpha]_D$($CHCl_3$)-values at r.t.; m.p. are uncorrected.

The numbering of the C-atoms in compounds **7**–**10** and **17** follows the octulose nomenclature, the one in **18**–**27** the methyl 4-(tetrahydro-2*H*-pyran-2-yl)butenoate nomenclature.

Scheme 2


4
6
7 COCH3 H
8 H COCH3
18
19
9 H H3C–C–CH3
10 H H H
17 Ac Ac Ac
22
23
24 R = H
25 R = t-Bu(Me)2Si
28 R = H
29 R = Ac
26 H H
27 H Ac

characterized as its triol **10**[4]) and triacetate **17**. The large coupling constants of 10 Hz in the ^{1}H-NMR. spectra of **9**, **10** and **17** between H–C(4) and H–C(5) proofs the β-configuration of the newly introduced C_3-side chain at C(4). By a further *Wittig* reaction of **9** with (methoxycarbonylmethylidene)triphenylphosphorane in acetonitrile under reflux followed by chromatography, a 3:2 mixture of the diastereomeric α,β-unsaturated esters **18** and **19** was obtained[5]).

The desired (*E*)-isomer **19** [m.p. 110.5–111.5°; $[\alpha]_D = +22.1°$ ($c = 0.89$). – IR.: 1711, 1648. – ^{1}H-NMR.: 2.22 (*d*, $J(2, H_3C–C(3)) = 1.3$, $H_3C–C(3)$); 5.76 (*m*, H–C(2))] could easily be isolated from the mixture by crystallization. The mother liquor which contained mainly the (*Z*)-isomer **18** [$[\alpha]_D = +0.9°$ ($c = 1.3$). – IR.: 1697, 1643. – ^{1}H-NMR.: 1.96 (*d*, $J(2, H_3C–C(3)) = 1.5$, $H_3C–C(3)$); 5.78 (*m*, H–C(2))] was evaporated to dryness. The residue was dissolved in acetonitrile/acetone and the solution irradiated in a pyrex vessel with the light of a Hg medium-pressure

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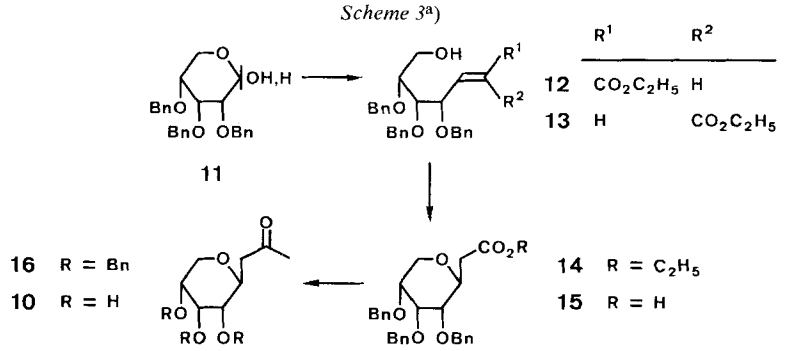
[4]) The triol **10** can also be prepared in good yields from D-ribose (**4**) by the sequence shown in *Scheme 3*. *Wittig* reaction of the tri-*O*-benzyl-ribose **11** with (ethoxycarbonylmethylidene)triphenylphosphorane led quantitatively to an approximately 1:1 mixture of **12** ((*E*)-isomer) and **13** ((*Z*)-isomer), which on treatment with NaOEt/EtOH cyclized to the C-glycoside **14** (85%). Basic hydrolysis (→ **15**, 90%), reaction with MeLi (→ **16**, 50%) and finally hydrogenolysis gave the triol **10**.

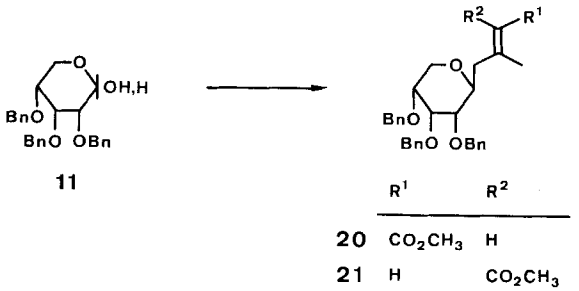
Scheme 3[a])



[a]) Bn = benzyl.

[5]) The full side-chain can also be introduced by a single *Wittig* reaction. Hence, treatment of **11** with the ylide from (*E*)-3-methoxycarbonyl-(2-methylallyl)triphenylphosphonium bromide [15] followed by cyclization under basic conditions gave a mixture of the two isomeric C-glycosides **20** and **21**.

Scheme 4



lamp. From the equilibrium mixture a further crop of **19** was collected by crystallization (total yield after these two operations: 80%). Treatment of **19** in 2,2-dimethoxypropane with a catalytic amount of *p*-toluenesulfonic acid [16] quantitatively gave a separable mixture (approx. 1:1) of the two acetonides **19** and **22**. The isomer **22** was oxidized applying the method of *Pfitzner & Moffat* [17] using DMSO/Ac_2O to the corresponding ketone **23** [95%; $[\alpha]_D = +16.8°$ ($c = 0.86$). – IR.: 1742, 1712, 1650. – ^{1}H-NMR.: 4.03 and 4.30 (*AB*-system, J(gem) = 18, 2 H–C(6′))]. Subsequent regio- and stereoselective aldol condensation with the Li-salt of ethylidenecyclohexylamine [18] [19] in THF led to the target intermediate **24** [IR.: 3700–3250, 3570, 2740, 1717, 1648. – ^{1}H-NMR.: 9.85 ($d \times d$, $J = 3.5$, $J = 2.5$, H–C=O)], which either could be chromatographed (60%) or be trapped as the *O*-silylated compound **25** by directly adding 2 equiv. of *t*-butyldimethylsilyl trifluoromethanesulfonate. Reduction of **24** with $NaBH_4$ (→ diol **26**) followed by selective monoacetylation of the primary hydroxyl group yielded **27** with a free tertiary hydroxyl group at C(5′). To confirm the assigned configuration of the C-side chain at C(5′), **27** was subjected to equilibration. Indeed the isomeric acetonide **28** was formed and characterized as its diacetate **29** [$[\alpha]_D = +12.0°$ ($c = 0.55$). – ^{1}H-NMR.: 4.35 (*d*, J(3′,4′) = 3.5, H–C(4′)); 4.80 ($d \times d$, J(2′,3′) = 10, J(3′,4′) = 3.5, H–C(3′))].

The compounds **23–29** offer most attractive opportunities for the synthesis of the pseudomonic acids A (**1**), B (**2**) and C (**3**) in their optically active forms, particularly of B (**2**) with an additional hydroxyl group at C(8). Furthermore the described compounds open the possibility for the synthesis of modified analogues.

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