The Pseudomonic Acids

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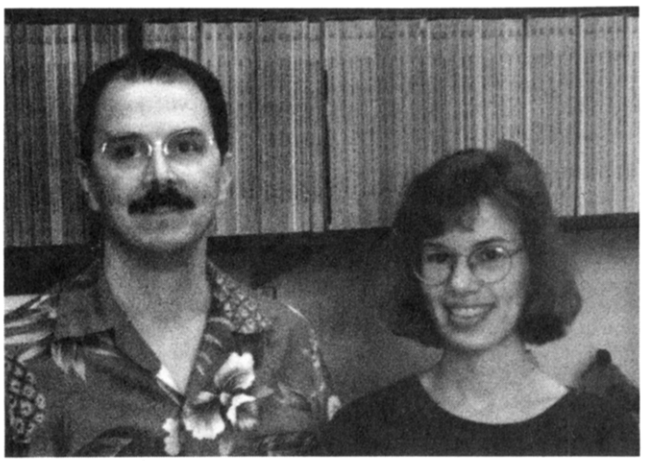
I. Introduction

The pseudomonic acids are a family of *C*-glycopyranoside antibiotics produced by *Pseudomonas fluorescens* (a soil isolate, NCIB 10586), and are potent inhibitors of Gram-positive aerobic bacteria.[1] The antibiotic extract of *P. fluorescens* is a mixture of compounds comprised 90% of pseudomonic acid A (**1**), 8% of pseudomonic acid B (**2**), and <2% of pseudomonic acids C (**3**) and D (**4**) (Figure 1).[2] Although the major metabolite of NCIB 10586 is commonly referred to as pseudomonic acid A, the British Pharmacopoeia and World Health Organization use the generic name "mupirocin", because the name "pseudomonic acid" misleadingly implies activity *against* the *Pseudomonas* species.[3]

All four pseudomonic acids are structurally related, containing a central pyran ring flanked by α-*cis* side chains at C-5 and C-8, as well as β-*cis*-hydroxyl groups at C-6 and C-7 (pseudomonic acid numbering). The major structural difference between these compounds lies in the functionalization of the C-5 and C-8 side chains. Pseudomonic acids A, B, and D contain a C-10/C-11 epoxide, while a C-10/C-11 (*E*)-alkene is incorporated in pseudomonic acid C. Additionally, a C-4′/C-5′ (*E*)-alkene is present only in pseudomonic acid D (**4**). A subset of the title compounds is "monic acids" (**5**–**7**). These compounds correspond to the C-1 carboxylic acid derivatives of the parent compounds and represent the major metabolites observed in vivo. Note that monic acid **5** is derived from both pseudomonic acids A and D. Alkyl esters of **1**–**4** and **5**–**7**, termed "pseudomonates"



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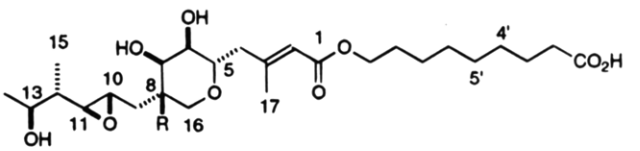
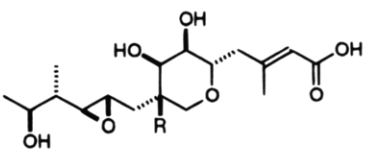
Philip DeShong (left) was born in Texas in 1949 and received his undergraduate education at the College of William and Mary and the University of Texas at Austin (B.Sc. in 1971). While at Texas, Royston M. Roberts and Philip Stotter supervised his research training. He obtained his Sc.D. from the Massachusetts Institute of Technology in 1976 studying with George H. Büchi. After postdoctoral studies with Duilio Arigoni at the Eidgenössische Technische Hochschule, Zürich (1976–1979) and Chris Walsh at MIT (1979), he accepted a faculty position at The Pennsylvania State University. In 1986, he moved to the University of Maryland where he is Professor of Chemistry.



(a) **1** Pseudomonic Acid A: R=H
2 Pseudomonic Acid B: R=OH
3 Pseudomonic Acid C: R=H, C-10/C-11 *E*-alkene
4 Pseudomonic Acid D: R=H, C-4′/C-5′ *E*-alkene



(b) **5** Monic Acid A: R=H
6 Monic Acid B: R=OH
7 Monic Acid C: R=H, C-10/C-11 *E*-alkene

Figure 1. (a) The pseudomonic acids and (b) the monic acids.

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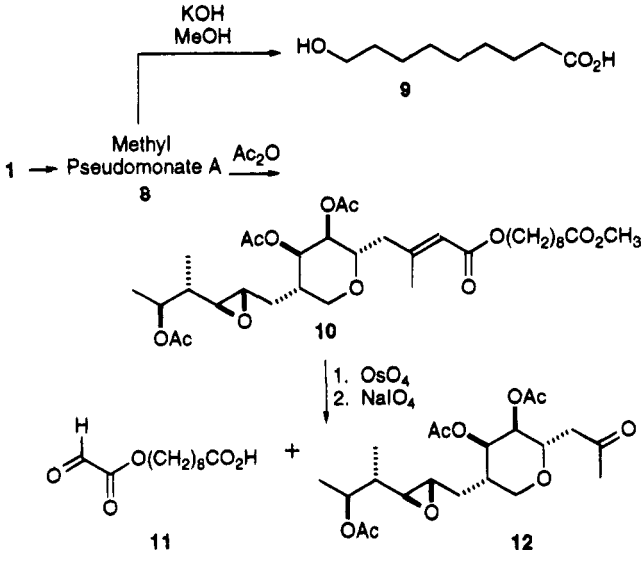
and "monates", respectively, will be referred to frequently in this manuscript, as they represent key targets for those investigating the synthesis and biological activity of the natural products.

II. Characterization

The structure of pseudomonic acid A (**1**) was determined by IR, UV, NMR, and mass spectral analysis of the products of its chemical degradation (Scheme 1). Treatment of pseudomonic acid A with diazomethane gave the corresponding methyl ester **8** that gave 9-hydroxynonanoic acid (**9**) upon hydrolysis with KOH–MeOH.[4]

Scheme 1



When the methyl ester **8** was allowed to react with acetic anhydride and pyridine, triacetate **10** was formed.[5] Oxidative cleavage of the triacetate with osmium tetraoxide/sodium periodate gave α-formyl ester **11** and pyran **12**.

The relative stereochemistry of the pyran ring was determined by analysis of the coupling patterns for the pyran ring protons (Figure 2).[6] The large coupling for H-5/H-6 (10 Hz), indicated that the protons are diaxially disposed. Small coupling constants for H-8/H-16$_a$ (1.5 Hz) and H-8/H-16$_b$ (3 Hz) showed that H-8 is equatorial. H-7 was assigned as equatorial on the basis of the coupling constants ($J_{6,7}$ = 3 Hz; $J_{7,8}$ = 3 Hz). The assignment of a *trans*-C-10/C-11 epoxide was also based on ^{1}H NMR spin-coupling experiments.

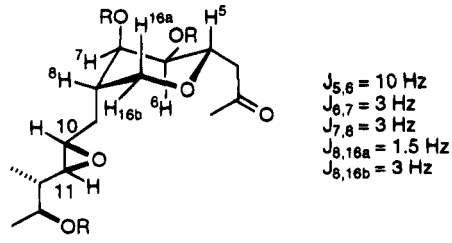


Figure 2. Proton coupling about the pseudomonic acid pyran nucleus.

With relative stereochemistry having been established, the absolute stereochemistry of the molecule was assigned. This was accomplished by X-ray analysis of the *o*-bromophenylhydrazone derivative of **12**, which gave the unambiguous assignment of 5*S*,6*R*,7*R*,8*S*,10*S*,11*S*,12*S*,13*S* as the absolute configuration of pseudomonic acid A.[7]

Mass spectral analysis of pseudomonic acid B (**2**) revealed a molecular ion 16 atomic mass units higher than that of pseudomonic acid A, consistent with an additional hydroxyl moiety.[8] The ^{1}H NMR of pseudomonic acid B is very similar to that of pseudomonic acid A. Acylation of pseudomonic acid B with acetic anhydride and pyridine at room temperature yielded a triacetate that showed an IR absorbance at 3690 cm^{-1}. The presence of a tertiary hydroxyl group was suspected and confirmed by ^{13}C NMR spectroscopy. The signal at δ 39.5, assigned to the C-8 methine of pseudomonic acid A, was absent from the spectrum of pseudomonic acid B; however, a signal at δ 72.0 was observed. It was concluded from these data that a tertiary hydroxyl group was present at C-8. To further substantiate this assignment, it was noted that the H-7/H-8 coupling observed in the ^{1}H NMR spectrum of pseudomonic acid A was absent in the ^{1}H NMR spectrum of pseudomonic acid B, consistent with the lack of a methine hydrogen at C-8.

The spectral data for pseudomonic acid C (**3**) is similar to that of pseudomonic acids A and B, except for an absence of epoxide signals in the ^{1}H NMR spectrum.[9] The C-10 and C-11 epoxide proton signals at δ 2.65 and δ 2.69 are replaced by vinyl signals at δ 5.40. The signals for these two vinyl protons are coincident, making it difficult to determine coupling constants and assign alkene geometry. Complexation of the C-13 hydroxyl group to Eu(fod)$_3$ resulted in separation of the vinyl signals.[10] A coupling value for H-10/H-11 of 15.1 Hz was consistent with *trans*-geometry of the olefin. Unequivocal proof for olefin geometry resulted from the conversion of *trans*-epoxide of pseudomonic acid A to the *trans*-alkene of pseudomonic acid C. Upon treatment with aqueous potassium selenocyanate in refluxing methanol, pseudomonic acid A (**1**) was converted to *trans*-deoxypseudomonic acid A, which was identical in all respects to pseudomonic acid C (**3**).

Pseudomonic acid D (**4**) possesses the same general structural features as pseudomonic acid A; however, ^{1}H and ^{13}C NMR spectroscopy also revealed the presence of a C-4′/C-5′ double bond.[2] The H-4′/H-5′ coupling constant of 15.0 Hz is consistent with *trans*-geometry for this alkene. Proof of this structure was confirmed upon partial synthesis of pseudomonic acid D by esterification of the sodium salt of monic acid A (**5**) with methyl (*E*)-9-chlorononon-4-enoate.

III. Biosynthesis

Using ^{13}C-labeled precursors, Mellows and Phillips have shown that pseudomonic acid A is derived primarily from acetate. The exceptions are C-15, C-16, and C-7′.[11] C-15 and C-16 are derived from methionine (Figure 3). C-7′ was shown to arise from C-1 of propionate; this observation prompted Mellows and Phillips to postulate that a propionate "primer" was involved in the mechanism of formation of the 9-hydroxynonanoic acid moiety. The investigators

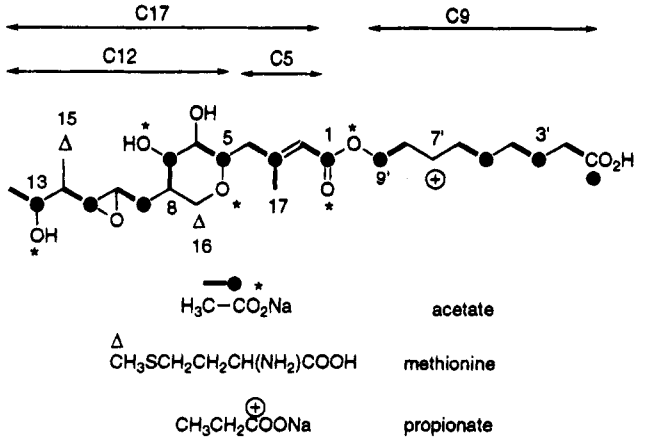
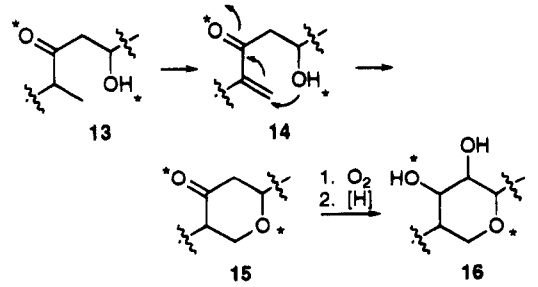


Figure 3. Biosynthesis of pseudomonic acid A.

demonstrated that C-17 of pseudomonic acid A is derived from the C-2 of acetate; however, the intact acetate unit is not incorporated. Surprisingly, it was also found that radiolabeled C-3 of propionate can be incorporated into the sites that had been previously derived from C-2 of acetate. Presumably, this occurs by degradation of C-3 labeled propionate to C-2 labeled acetate, via C-3 labeled pyruvate, prior to incorporation.

Using ^{17}O-labeled acetate, Simpson and Martin found that the oxygen atoms attached to C-1, C-5, C-7, C-13, and C-9′ are acetate derived.[12] On the basis of these ^{17}O labeling studies, two important conclusions regarding the biosynthesis of the antibiotic were drawn. First, it appeared that the C-1 ester linkage was formed by the condensation of two separate 17-carbon and 9-carbon units, rather than a Baeyer–Villiger-type oxidation of an intermediate ketone. Second, the mechanism of the formation of the pyran ring could occur as shown in Scheme 2. Dehydrogenation of the acyclic polyketide **13** at C-8/C-16 affords an α,β-unsaturated ketone **14**. Intramolecular Michael addition by the C-5 hydroxyl group gives the corresponding 3-ketopyran **15**. Subsequent oxidation state adjustment yields the pseudomonic acid nucleus **16**.

Scheme 2



While it is generally accepted that pseudomonic acid is biologically synthesized by assembling C_{12}, C_5, and C_9 units, the pathway has not been completely characterized. 3-Hydroxy-3-methylglutarate has also been implicated as a carbon source for the molecule; however, this hypothesis has been difficult to prove.[13] In order to gain more knowledge about the biosynthetic pathway leading to pseudomonic acid, Whatling et al. have studied the chromosome of *P. fluorescens*.[14] They have found a 60 kb region that is required for the synthesis of the antibiotic and are currently attempting DNA sequence analysis throughout that region.

IV. Bioactivity

Antimicrobial activity of the fermentation broth of *P. fluorescens* was first reported in 1887 by Garre, but it was not until the late 1960s that Fuller et al. determined that the pseudomonic acids were responsible for the bioactivity.[1,4] Since pseudomonic acid A is the major component of the antibiotic extracts, emphasis was placed on the development of this compound as a pharmaceutical agent. Studies have shown that pseudomonic acids B, C, and D exhibit similar antimicrobial activity to that of pseudomonic acid A.

Pseudomonic acid A is a potent inhibitor of Gram-positive aerobic bacteria.[15] In particular, it shows excellent activity against *Staphylococcus aureus*, the primary cause of many skin infections. Most strains of *S. aureus* are inhibited at MIC ≈ 0.12 mg/L of pseudomonic acid A or lower. Other antibiotic-resistant strains of *S. aureus* require larger, but still relatively small, doses of pseudomonic acid A (MIC ≤1 mg/L) to inhibit bacterial growth. Most Gram-negative bacteria are unaffected by pseudomonic acid A, with the exception of *Heamophilus influenzae*, *Neisseria meningitidis* and *N. gonorrhoea*, *Branhamella catarrhalis*, *Bordetella pertussis*, and *Pastureila multicoda*. While pseudomonic acid A is generally used to treat skin infections such as impetigo, it is also used to treat cutaneous candidiasis and burn wound infections.[16–22]

Pseudomonic acid A is used clinically under the trade name "Bactroban" and is currently marketed by Beecham Pharmaceutical Company. Unfortunately, it exhibits poor bioavailability; it has been found that pseudomonic acid A is rapidly hydrolyzed at the C-1 ester upon entering the blood stream.[23] Furthermore, it undergoes intramolecular epoxide opening under acidic or basic conditions to give cyclized polyethers, with subsequent loss of activity (Figure 4). Thus, the antibiotic must be used topically, and has been formulated as 2% ointment in polyethylene glycol.

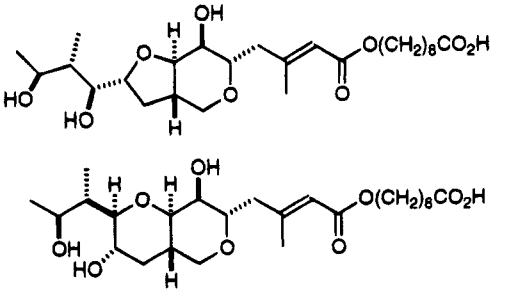


Figure 4. Rearranged adducts of pseudomonic acid A.

Pseudomonic acid A strongly inhibits both bacterial protein and RNA synthesis.[24] Upon studying the effect of pseudomonic acid A on *Staphylococcus* and *E. coli*, Pederson[25] and Haseltine[26] suggested that the compound acts by depriving the bacteria of one or more amino acids. Later it was shown by Hughes and Mellows that bactereostasis can be alleviated by

addition of isoleucine into the culture medium and that pseudomonic acid A acts by competitively inhibiting bacterial isoleucyl tRNA synthetase.[27] The tRNA synthetase enzyme is known to contain two hydrophobic domains which interact with the methyl and ethyl groups of isoleucine.[28,29] The C-8 side chain of the antibiotic appears to interact with the enzyme in an analogous manner (Figure 5). It has been shown that the epoxide of the side chain is not covalently bound to the tRNA synthetase, even though there are activated thiol moieties close to the binding site of the substrate.

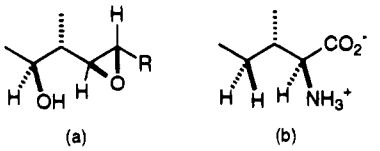


Figure 5. (a) Pseudomonic acid A C-8 side chain and (b) isoleucine.

Pseudomonic acid A specifically inhibits formation of the enzyme/isoleucine/AMP complex that is responsible for transfer of the amino acid to tRNA.[30] The antibiotic does not inhibit the transfer of isoleucine from the complex to tRNA, since tRNA is still smoothly aminoacylated when a purified complex of enzyme/isoleucine/AMP is combined with tRNA in the presence of pseudomonic acid A. While pseudomonic acid A has the ability to inhibit bacterial RNA synthesis, it has a low affinity for the mammalian synthetase enzyme.[31] Thus, the material does not produce any mutagenic or teratogenic side effects and is generally not irritating to humans. In addition, pseudomonic acid does not seem to be harmful to its producing organism during fermentation; *Pseudomonas fluorescens* has a pseudomonic acid-resistant isoleucyl tRNA synthetase.

Pseudomonic acid A is 95% bound to human serum protein.[32] Structure–activity relationship studies were performed in attempt to find pseudomonic acid analogues that would be less serum bound and exhibit greater biological activity. Clayton et al. found that methyl monate A, the methyl ester of **5**, is only bound to human serum by 30% yet possesses the same bioactivity as the natural product. Analogues with unnatural C-2/C-3 (*Z*)-olefin geometry exhibit activities that are 100 times less than that of pseudomonic acid A. Finally, these studies showed that monic acid A (**5**) is not biologically active. The data obtained from these experiments suggests that there are actually two important binding sites for the molecule in the enzyme; one on the C-8 side chain as well as one on the C-5 substituent. These results are supported by the work of Yanagisawa et al.,[33] who have studied a variety of amino acid sequences of isoleucyl tRNA synthestase. They have located the ATP binding site with respect to the isoleucine binding site, and have postulated that while the C-8 side chain of pseudomonic acid is interacting with the isoleucine binding site, the C-5 substituent is bound at the ATP binding site.

In order to further understand the binding between pseudomonic acid A and tRNA synthetase, other pseudomonic acid analogues have been prepared and their biological activities surveyed. Modification of the C-12 to C-14 portion of the molecule led to reduction or complete loss of activity.[34,35] On the other hand, some heterocyclic C-1 analogues are more stable in vivo than pseudomonic acid A, and exhibit good antimicrobial activity.[36–42]

V. Synthesis of the Pseudomonic Acids

Due to their unusual structures and potent biological activity, the pseudomonic acids have attracted significant synthetic interest. Two important structural features govern the strategies utilized to prepare this family of compounds: the α-*cis*-pyran side chains at C-5 and C-8, and the C-10/C-11 (*E*)-olefin present in pseudomonic acid C (**3**). The syntheses of pseudomonic acids and their derivatives have been accomplished by condensation of the side chain (C-10 through C-14) with the pyran nucleus having the proper absolute configuration.

Establishment of the relative stereochemistry between C-5 and C-8 (pseudomonic acid numbering) is critical to a successful synthesis of pseudomonic acids. A *cis* relationship between the substituents directs subsequent hydroxylation to the β-face of the dihydropyran. This results exclusively in formation of the β-*cis*-diol. Therefore, by preparing a dihydropyran possessing α-*cis* side chains at C-5 and C-8, the formation of all four contiguous stereogenic centers in the pseudomonic acid nucleus can be controlled. A variety of methods have been utilized to prepare the requisite α-*cis*-pyran intermediates, including elaboration of carbohydrates, modification of Diels–Alder adducts, and regioselective functionalization of dihydropyrans (*vide infra*).

The other structural feature that must be considered is the C-10/C-11 (*E*)-alkene present in pseudomonic acid C. This functionality is utilized in the syntheses of other members of this family, since stereoselective epoxidation of that olefin provides access to pseudomonic acids A, B, and D. Wittig and other alkene-forming processes have been employed for homologation of the C-8 side chain (*vide infra*).

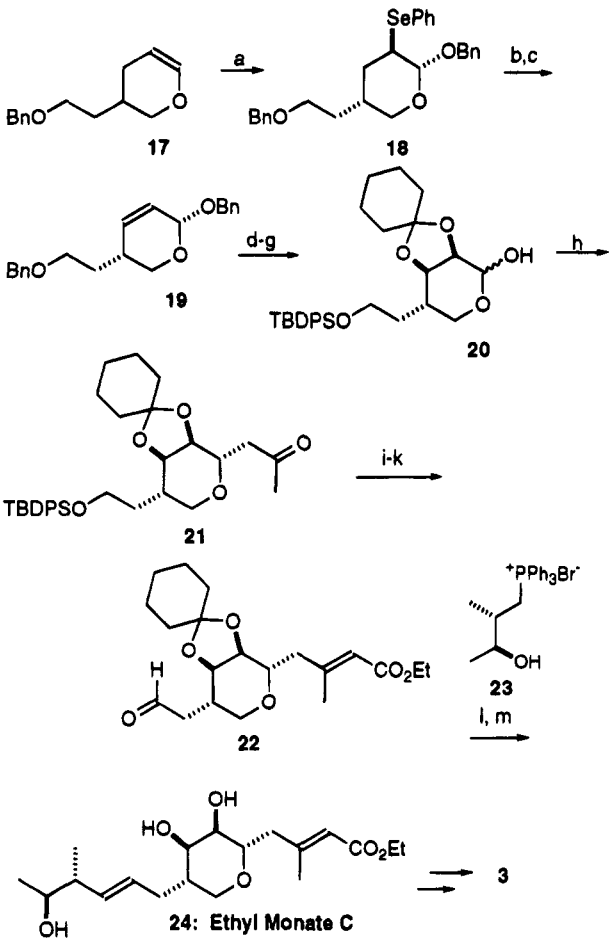
The partial and total syntheses that have been reported are reviewed here; semisynthetic preparation of analogues, however, will not be covered.[34–42] Methods for preparation of the pseudomonic acid nucleus and attachment of the C-8 side chain with correct C-10/C-11 alkene geometry are highlighted. From hereon, atom numbering of all compounds utilizes the pseudomonic acid numbering system, regardless of the IUPAC nomenclature for a particular compound.

A. The Kozikowski Synthesis

Kozikowski's preparation of pseudomonic acid C was the first reported synthesis of the NCIB 10586 metabolite (Scheme 3). A key transformation of this approach involved a benzyloxyselenation to prepare the precursor of an α-*cis*-substituted dihydropyran.[43] Later in the synthesis, Kozikowski used Wittig olefination to lengthen the C-8 side chain and provide the C-10/C-11 (*E*)-alkene.

Dihydropyran **17** was reacted with phenylselenium chloride and benzyl alcohol to give a 2.5:1 mixture of diastereomeric selenides. The major selenide

Scheme 3



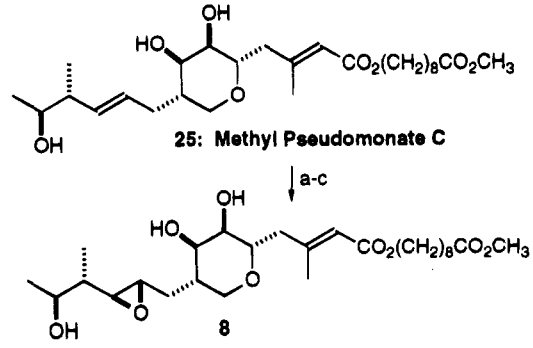
(a) PhSeCl, BnOH, Et_3N; then separation (b) $NaIO_4$, $NaHCO_3$, CH_3OH/H_2O; (c) $CaCO_3$, CCl_4, reflux; (d) OsO_4, NMO, aq. acetone; (e) cyclohexanone, H^+; (f) H_2, 10% Pd/C, EtOH; (g) TBDPSCl, imidazole; (h) $Ph_3PCHCOCH_3$, CH_3CN, 170 °C; (i) $(EtO)_2P(O)CHCO_2Et$; (j) TBAF; (k) PCC; (l) **23**, 2 equiv. *n*-BuLi; (m) 50% aq. HOAc

isomer **18** was oxidized then eliminated to give Δ^6-alkene **19**. As expected, subsequent dihydroxylation occurred exclusively from the β-face of the molecule. Protection of the hydroxyl groups was followed by debenzylation and conversion of the resulting primary alcohol to the TBDPS ether **20**. The mixture of anomeric pyrans was allowed to react with (acetylmethylene)triphenylphosphorane to provide the methyl ketones as a 2.5:1 mixture of *cis/trans* diastereomers at C-5. The major isomer, **21**, was shown to be the kinetic product, as it could be converted to the epimer after being resubjected to the reaction conditions. This is one of the first applications of Wittig chemistry in the formation of *C*-glycopyranosides, and this approach has been used extensively by others in the synthesis of the pseudomonic acids for C-5 side chain introduction (*vide infra*).

Having established the relative stereochemistry on the pyran, the side chains were introduced sequentially. Cyclohexylidene **21** was converted to aldehyde **22**, the precursor for C-8 side chain extension, via a series of standard transformations. Ester **22** is an important intermediate in the synthesis of the pseudomonic acids. This material will be referred to frequently, as several synthetic strategies have culminated in the preparation of **22**. Wittig reaction of ylide **23** with **22** was expected to produce the *E*-olefin, on the basis of several preliminary experiments as well as the reported behavior of other γ-oxido ylides.[44] When racemic substrates **22** and **23** were stirred together at room temperature for 3 h, a mixture of four diastereomers was produced. The two major isomers were separated and identified as a 3:2 (*E/Z*) mixture of Δ^{10}-alkene isomers. This result was somewhat disappointing in light of earlier model studies that had indicated high selectivity for the *E*-isomer. Subsequent removal of the cyclohexylidene ketal provided ethyl monate C (**24**), which was finally converted to pseudomonic acid C (**3**) by saponification of the ethyl ester, esterification with methyl iodononanoate, and subsequent hydrolysis of C-1′.

Kozikowski also examined epoxidation protocols for the conversion of methyl pseudomonate C (**25**) to methyl pseudomonate A (**8**) (Scheme 4).[45] Rogers et al. had previously reported that silylation of hydroxyl groups of **25**, followed by *m*-CPBA oxidation and deprotection provided the synthetic target **8** and its isomer, in a 1:2 ratio.[9] Kozikowski found that selective protection of the vicinal diol as the benzylidine acetal, oxidation of the hydroxy alkene with VO(acac)$_2$/TBHP, and hydrogenolysis of the protecting group, provided the epoxide **8** as a 3:1 mixture with its undesired isomer. To date, this is the most efficient method for conversion of pseudomonic acid C to pseudomonic acid A derivatives.

Scheme 4



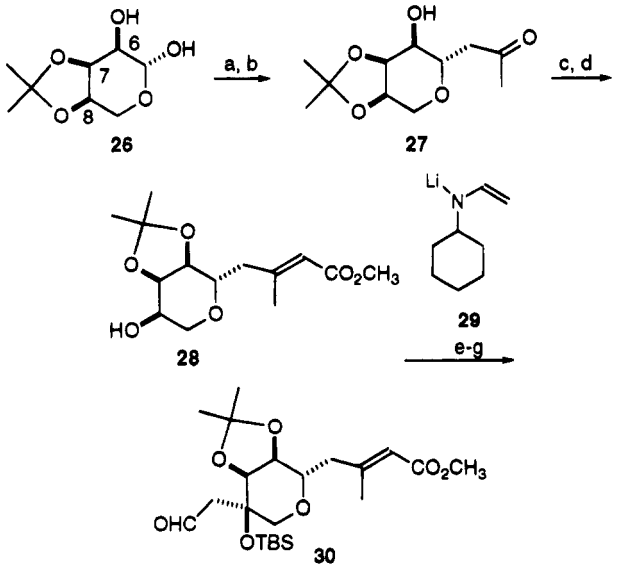
(a) PhCHO, TsOH, $CuSO_4$; (b) $VO(acac)_2$, TBHP; (c) H_2, 10% Pd/C, EtOH

B. The Schönenberger Synthesis

Schönenberger reported the first enantioselective synthesis of pseudomonic acid precursors from carbohydrate starting materials (Scheme 5).[46] The elaboration of D-ribose is particularly useful in the synthesis of pseudomonic acid B (**2**) and its derivatives since the chiral intermediates in this strategy contain a hydroxyl group at C-8 of the pyran. Because D-ribose already contains the requisite C-6 and C-7 hydroxyl groups, Schönenberger's primary concern was introduction of the C-5 and C-8 side chains.

Ribose was converted to pyran ketal **26** by a published procedure.[47] The anomeric center was converted to what would be the C-5 stereocenter of pseudomonic acid by the Wittig protocol described by Kozikowski.[43] Subsequent treatment with sodium

Scheme 5



(a) $Ph_3PCHCOCH_3$; (b) $NaOCH_3$; (c) $Ph_3PCHCO_2CH_3$, CH_3CN, reflux; (d) 2,2-dimethoxypropane, TsOH; (e) DMSO, Ac_2O; (f) **29**; (g) 2 equiv. TBSOTf

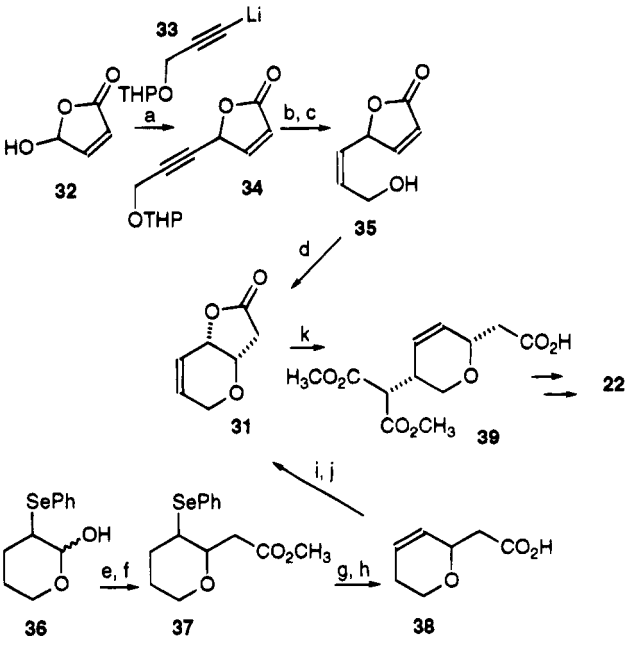
methoxide effected ring closure to afford ketone **27**. A second Wittig reaction was used to homologate the C-5 side chain of **27**, resulting in a 3:2 mixture of *E/Z* geometric isomers.

With the C-5 side chain in place, all that was required was to incorporate the C-8 side chain. Ketal transposition upon treatment of the C-6/C-7 acetonide with 2,2-dimethoxypropane gave C-8 alcohol **28**. Oxidation of the hydroxyl group permitted the introduction of the C-8 side chain via a stereo- and regioselective aldol condensation with the lithium salt of ethylidenecyclohexylamine (**29**). The resulting imine was then hydrolyzed to the corresponding aldehyde. Silylation of the tertiary alcohol provided **30**. Schönenberger expected that this optically active intermediate could be converted to pseudomonic acid B (**2**) by the homologation protocol described by Kozikowski (*vide supra*), although this conversion has not been reported. Schönenberger's technology is one of only two syntheses that has addressed incorporation of the C-8 hydroxyl group for the preparation of pseudomonic acid B.[48]

C. The Raphael Synthesis

Raphael completed a formal total synthesis of pseudomonic acid A utilizing a palladium-catalyzed ring opening of a racemic bicyclic lactone **31** that contained the C-5 side chain (Scheme 6).[49,50] Exploiting the high diastereofacial control in the alkylation of π-allylpalladium intermediates, the C-8 side chain was introduced *cis* to the C-5 side chain. The key bicyclic lactone intermediate **31**, as well as its regioisomer, has been utilized by others to prepare the pseudomonic acids (*vide infra*). Raphael reported two strategies for the preparation of this 5,6-fused bicyclic system. The first strategy involved Michael addition of an alkoxide onto a γ-lactone to provide bicyclic intermediate **31**, while the second involved iodolactonization onto a pyran to produce the 5,6-fused system.

Scheme 6



(a) **33**; (b) H_2, Lindlar; (c) Amberlite IR-120, CH_3OH; (d) methanesulphonic acid; (e) $Ph_3PCHCOCH_3$; (f) $NaOCH_3$, CH_3OH; (g) O_3; then elimination; (h) KOH, CH_3OH, H_2O (i) $PhSePF_6$; (j) H_2O_2; then elimination; (k) dimethyl sodiomalonate, $Pd(Ph_3)_4$.

Condensation of hydroxybutenolide **32** with alkynyllithium **33**, and concomitant relactonization of the intermediate hydroxy acid, afforded butenolide **34**. Alkyne reduction, followed by THP removal provided allylic alcohol **35**. The key *cis*-fused lactone intermediate **31** was obtained by acid-catalyzed cyclization of alcohol **35**.

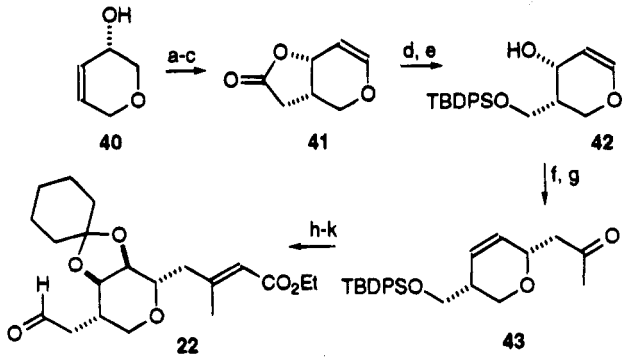
An alternative synthesis of lactone **31**, starting from tetrahydropyranol selenide **36**, was accomplished by Wittig reaction at the anomeric center, followed by base-catalyzed ring closure to provide ester **37**. Oxidation of the selenide, followed by elimination, gave the dihydropyran skeleton. Hydrolysis of the ester provided carboxylic acid **38**. Phenylselenolactonization of dihydropyran **38** produced *cis*-fused lactone **31**.

Palladium-catalyzed alkylations of bicyclic allylic systems have been shown to occur in an S_N2' fashion with overall retention of configuration.[51-53] When **31** was treated with dimethyl sodiomalonate in the presence of tetrakis(triphenylphosphine)palladium-(0), such a transformation occurred to give diester **39**. By utilizing a palladium-catalyzed alkylation strategy, Raphael prepared a pseudomonic acid nucleus with *cis* substituents. Finally, conversion of the carboxylic acid to a methyl ketone and decarboxylation of the diester provided a derivative that was converted to pyran **22**, the key intermediate in the Kozikowski synthesis of pseudomonic acid A.

D. The Fleet Synthesis

Like Schönenberger, Fleet utilized a carbohydrate template in his enantiospecific synthesis of the pseudomonic acid nucleus. From the single stereocenter of dihydropyranol **40**, derived from D-arabinose, a series of Claisen rearrangements permitted stereoselective introduction of the α-*cis* side chains

Scheme 7



(a) $CH_3C(OCH_3)_2N(CH_3)_2$, reflux; (b) I_2, THF, H_2O; (c) DBU, benzene; (d) $NaBH_4$, EtOH; (e) TBDPSCl, imidazole; (f) $CH_3CC(OCH_3)_2N(CH_3)_2$, xylene, reflux; (g) CH_3Li; (h) OsO_4, NMO; (i) cyclohexanone, $CuSO_4$, TsOH; (j) NaH, $(EtO)_2P(O)CH_2CO_2Et$; (k) TBAF; then PCC.

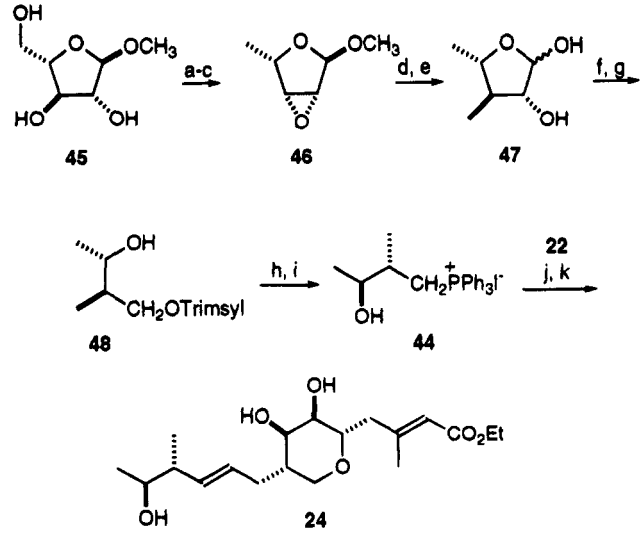
at C-5 and C-8 (Scheme 7).[54,55] In addition to preparing the chiral pseudomonic acid nucleus, Fleet also investigated the C-10/C-11 alkene formation as a means of completing the C-8 side chain.[56] The study culminated in the enantiospecific syntheses of pseudomonic acids A and C.

D-Arabinose was converted to allylic alcohol **40** in four steps by standard methods.[57] An Eschenmoser variant of the Claisen rearrangement provided a γ,δ-unsaturated amide. Iodolactonization and subsequent elimination of HI from this material gave *cis*-fused bicyclic lactone **41**, an isomer of Raphael's intermediate **31**. Reduction of lactone **41** with $NaBH_4$ and silylation of the resulting primary alcohol gave dihydropyran **42** with the desired α-configuration at C-8. At this point, the newly generated secondary allylic alcohol provided a convenient handle for stereoselective introduction of the C-5 side chain. A second Eschenmoser–Claisen rearrangement transferred the C-7 hydroxyl, via an intermediate amine ketene acetal, to the C-5 amide with retention of configuration. Methyllithium addition to the resulting amide provided dihydropyran **43**, which was converted in four steps to Kozikowski's aldehyde **22** as a single enantiomer. Ethyl monate C (**24**) was ultimately prepared by condensing this aldehyde with chiral phosphonium salt **44**, derived from L-arabinose (Scheme 8).

The preparation of phosphonium salt **44** began with methyl α-arabinoside (**45**) that was converted to epoxide **46**, via the 5-deoxyarabinoside, by treatment under Mitsunobu conditions. Regio- and stereospecific epoxide ring opening with methyl cuprate provided 3-deoxyarabinoside **47**. Periodate oxidation, followed by reduction of the resulting aldehyde, gave a diol. The primary alcohol was then selectively activated as its trimyslate **48**. Iodide displacement of the trimyslate, followed by treatment with triphenylphosphine, afforded chiral phosphonium salt **44**.

Reaction of chiral aldehyde **22** and chiral phosphonium salt **44** gave a complex mixture of products, comprised of 25% protected ethyl monate C, with the desired (*E*)-alkene geometry. These results were in accordance with Kozikowski's findings for this Wittig reaction. Removal of the cyclohexylidine protecting group gave ethyl monate C (**24**). This work constituted a formal synthesis of pseudomonic acids A (**1**)

Scheme 8



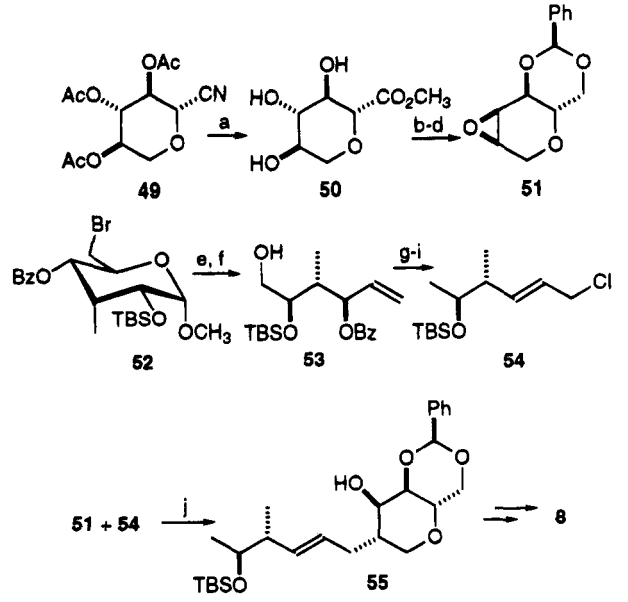
(a) trimsyl chloride, pyridine; (b) NaI, refluxing butanone; then H_2, Pd/C, CH_3OH, Et_3N; (c) PPh_3, DEAD; (d) $(CH_3)_2Cu(CN)Li_2$; (e) Dowex 50W-8x resin, 60 °C; (f) $NaIO_4$; followed by $NaBH_4$; (g) trimsyl chloride, pyridine; (h) NaI, refluxing butanone; (i) PPh_3, refluxing toluene; (j) 2 equiv. *n*-BuLi, then **22**; (k) HOAc.

and C (**3**), since ethyl monate C had been converted to those compounds.

E. The Sinäy Synthesis

Sinäy's enantioselective synthesis of methyl pseudomonate C also involved intermediates derived from carbohydrate precursors (Scheme 9).[58] The tetrasubstituted pyran nucleus, with the appropriate stereochemistry about C-5 through C-8, was prepared by elaboration of D-xylose. The C-8 side chain, representing carbons C-9 through C-15 and containing the *anti* configuration between C-12 and C-13,

Scheme 9



(a) $NaOCH_3$; then NaOH; then CH_3OH, HCl; (b) $LiAlH_4$; then $PhCH(OCH_3)_2$, TsOH; (c) TsCl, pyridine; (d) $NaOCH_3$, $CHCl_3$; (e) Zn, propanol, H_2O; (f) $NaBH_4$, EtOH; (g) TsCl, pyridine; then NaI, butanone; then $NaBH_4$, DMSO; (h) $NaOCH_3$, CH_3OH; (i) $SOCl_2$, pyridine; (j) Mg; then CuI, THF.

was formed via the ring opening of a D-glucose derivative. The key step in this convergent synthesis was linking the two carbohydrate-derived pieces by a nucleophilic epoxide opening. Using this strategy, Sinäy was able to avoid the C-10/C-11 alkene geometry problem.

D-Xylose was converted to cyanide **49** by the method of Helferich and Ost.[59] After deacylation and hydrolysis, the resulting carboxylic acid was esterified to give triol **50**. Reduction of the ester and selective protection of the 1,3-diol as the benzylidene acetal was followed by tosylation of the least hindered C-8 hydroxyl group. Base-catalyzed epoxide closure afforded **51**, with no trace of the isomeric epoxide. Thus, the C-5, C-6, and C-7 centers of the pseudomonic acid nucleus were in place, with the correct relative and absolute stereochemistry. Regio- and stereoselective epoxide ring opening with the appropriate Grignard reagent would yield the pseudomonic acid precursor with an intact C-8 side chain.

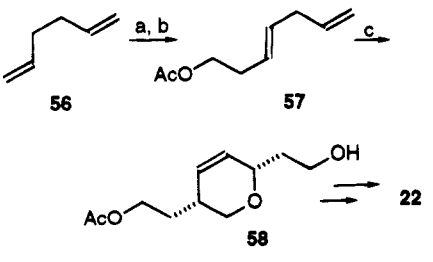
The allylic anion used by Sinäy was prepared in enantiomerically pure form from D-glucose. Zinc-promoted ring opening of glucose derivative **52** gave an aldehyde that was reduced to alcohol **53**. Reduction of the primary alcohol, via the tosylate, to the corresponding alkane was followed by debenzoylation. The resulting allylic alcohol was treated with thionyl chloride to yield allylic chloride **54**.

Copper-catalyzed ring opening of epoxide **51** was successfully effected upon reaction with the Grignard reagent of chloride **54**, to afford alcohol **55**. The epoxide cleavage was both regio- and stereoselective, and surprisingly the (*E*)-alkene was not isomerized during the reaction. This strategy represents the first example of introduction of the C-9 to C-15 side chain onto the pyran nucleus. Sinäy completed the enantioselective synthesis of methyl pseudomonate C (**8**) by removal of the benzylidene protecting group of **55** and homologation of the C-5 side chain by Wittig technology.

F. The Snider Synthesis

Snider has shown that the dihydropyran nucleus of pseudomonic acid can be prepared by Diels–Alder reaction between formaldehyde and a 1,3-diene (Scheme 10).[60,61] The use of this electrocyclic process allowed for the formation of the *cis* diastereomer, with respect to the C-5 and C-8 substituents, of the dihydropyran.

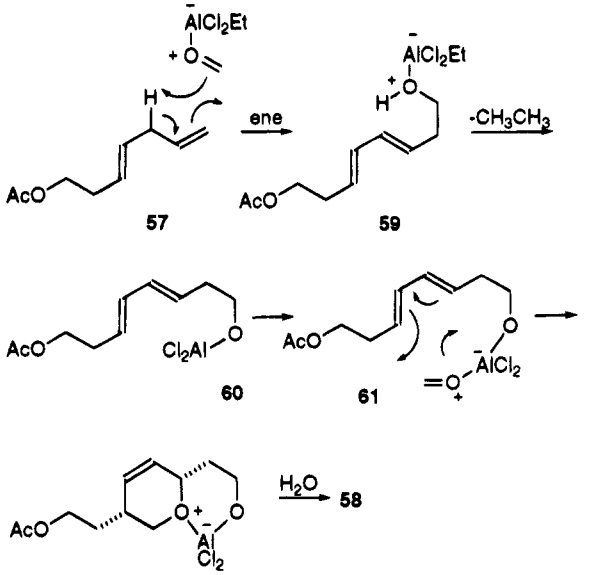
Scheme 10



(a) $(CH_2O)_n$, $(CH_3)_2AlCl$; (b) Ac_2O, pyridine; (c) $(CH_2O)_n$, $EtAlCl_2$.

Ene reaction of 1,5-hexadiene (**56**) with formaldehyde–dimethylaluminum chloride complex gave 3,6-heptadienol. Subsequent acylation provided non conjugated **57**. Reaction of **57** with formaldehyde–ethylaluminum dichloride gave dihydropyran **58**, with *cis* side chains at positions C-5 and C-8. The mechanism for this transformation involves a second ene reaction followed by a "quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction" (Scheme 11). The ene reaction between the terminal double bond of **57** and the CH_2O–$AlEtCl_2$ complex resulted in conjugated (*E,E*)-diene **59**. Loss of ethane from this intermediate gave **60**. Complexation of aluminum alkoxide **60** to an additional molecule of formaldehyde produced Diels–Alder substrate **61**. Only (*E,E*) substrate **61** underwent cycloaddition, whereupon decomplexation of the aluminum alkoxide yielded dihydropyran **58**. The *cis* arrangement of the side chains was confirmed by ^1H NMR spectroscopy. Snider's preparation of the pseudomonic acid dihydropyran with *cis* side chains is one of the few synthetic strategies that does not utilize a preexisting pyran nucleus. Dihydropyran **58** was converted to Kozikowski's intermediate **22** by a series of standard transformations, and therefore constituted a formal total synthesis of pseudomonic acids A (**1**) and C (**3**).

Scheme 11

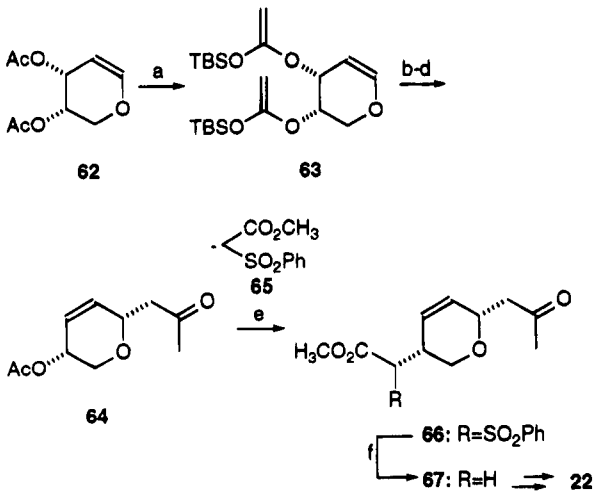


G. The Curran Synthesis

Curran synthesized Kozikowski's advanced pseudomonic acid intermediate **22** in chiral form by modification of L-arabinose (Scheme 12).[62] The key steps in this strategy involved an Ireland ester–Claisen rearrangement to provide an α-*cis*-dihydropyran, followed by palladium-catalyzed allylic alkylation.

L-Arabinose was converted in two steps to bis-acetate **62**, the precursor for the Claisen rearrangement. Acetate deprotonation, followed by a *tert*-butyldimethylsilyl chloride quench, gave the corresponding bis-silyl ketene acetal **63**. Mono-Claisen rearrangement transposed the chiral center from C-7 to C-5 with retention of configuration. While a tandem bis-Claisen of **63** was possible, Curran has demonstrated that the first sigmatropic rearrangement is much more facile, due to a "vinylogous anomeric" effect.[63] Subsequent transposition of the second silyl ketene acetal is less favored than the

Scheme 12



(a) LDA; then TBSCl; (b) 60 °C; then KF; (c) $SOCl_2$; then o-$CH_3C_6H_4COOH$, NEt_3; (d) CH_3MgBr; (e) $Pd(dppe)_2$, **65**; (f) Na(Hg), CH_3OH, NaH_2PO_4.

first, due to the absence of that accelerating effect. The carboxylic acid resulting from the Claisen rearrangement was converted to methyl ketone **64** by esterification followed by treatment with methylmagnesium bromide.

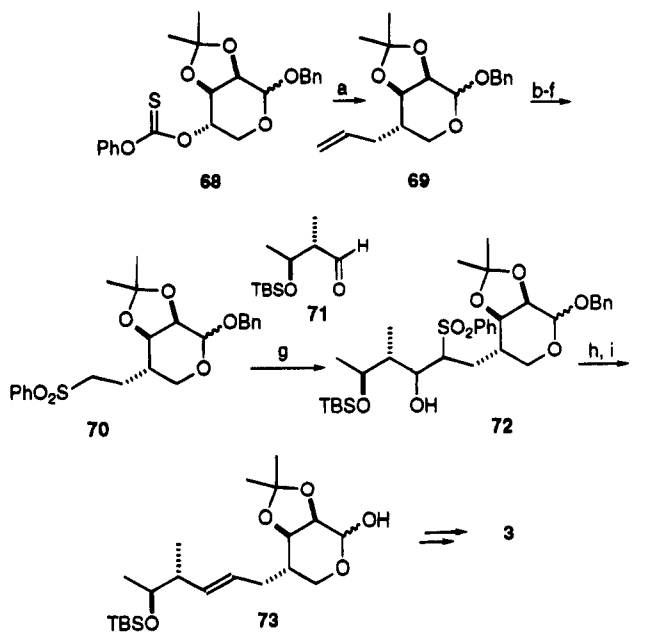
The stage was now set for the other key step of Curran's strategy, a palladium-catalyzed allylic alkylation of pyran **64**. An unsymmetrical π-allylpalladium intermediate is presumably involved. Upon the basis of steric considerations, Curran anticipated that alkylation would occur regioselectively at the site of the acetate leaving group. Indeed, when allylic acetate **64** was reacted with the sodium anion of methyl (phenylsulfonyl)acetate (**65**) in the presence of $Pd(dppe)_2$, *cis*-dihydropyran **66** was the only regioisomer formed. The 1:1 mixture of sulfone diastereomers was reduced with sodium amalgam to give *cis* keto ester **67**. Subsequent transformations provided Kozikowski's pseudomonic acid precursor **22** in chiral form.

H. The Keck Synthesis

Since Wittig methodology for C-8 side chain extension does not selectively afford the E-Δ^{10}-isomer, Keck's approach to the synthesis of pseudomonic acid C focused on the extension of the C-8 side chain by a Julia coupling.[64,65] This protocol involves the coupling of an aldehyde with a sulfoxide anion, followed by reductive elimination of the resulting β-hydroxy sulfone. This technology generally results in the formation of a *trans* double bond.[66] The pyran sulfoxide Keck planned to utilize for Julia coupling was obtained by a radical coupling of a thioacyl pyran and an allylstannane (Scheme 13). The intermediates used in this synthesis were obtained in optically active form.

L-Lyxose was converted by a series of steps to thioacyl glycoside **68**. Photolysis of **68** in the presence of allyltributylstannane provided exclusively pyran **69**. The stereochemical outcome of this condensation was a consequence of attack by allylstannane on the least hindered α-face of the intermediate

Scheme 13



(a) allyl tributylstannane, hv; (b) OsO_4, $NaIO_4$; (c) $NaBH_4$; (d) MsCl, pyridine; (e) KSPh; (f) CH_3CO_3H; (g) $LiN(TMS)_2$, then **71**; (h) MsCl, pyridine; (i) Li, NH_3.

pyran radical. Oxidative cleavage of the alkene provided an aldehyde that was immediately reduced. The resulting alcohol was converted to the corresponding phenyl sulfide via a mesylate, and the sulfide was oxidized with peracetic acid to sulfone **70**.

Sulfone **70** was then deprotonated and condensed with aldehyde **71**, available in three steps from (*S*)-ethyl 3-hydroxybutyrate. The diastereomeric mixture of β-hydroxy sulfones **72** was mesylated and then treated with lithium in ammonia, providing only the (*E*)-alkene **73**. The Julia protocol was the first method to produce exclusively the desired olefin geometry on the C-8 side chain via coupling of C-10 and C-11. Keck completed the synthesis of pseudomonic acid C (**3**) by attaching the remainder of the C-5 side chain with a series of Wittig reactions that had been described previously by Kozikowski.

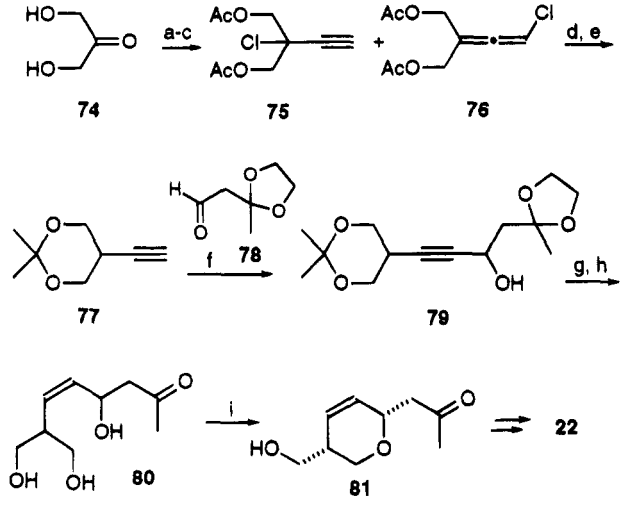
Utilizing the stereoselective free radical allylation of C-8 described here, Keck later performed a "second-generation" synthesis of pseudomonic acid C.[67] In this approach, the C-8 iodo analogue of thioacyl glycoside **68** was coupled to the functionalized C-9 to C-14 fragment. Thus, Keck eventually employed a free radical allylation to append the entire C-8 side chain in a single step.

I. The Bates Synthesis

Bates' synthesis of the pseudomonic acid nucleus involved a cyclodehydration of a functionalized triol (Scheme 14).[68] The high degree of stereocontrol observed for this cyclization resulted predominantly in formation of the C-5/C-8 *cis*-dihydropyran.

The key triol precursor was prepared in eight steps, starting from dihydroxyacetone (**74**). Lithium acetylide was added to the bis-acetate of **74**. Treatment of the resulting propargyl alcohol with phosphorous oxychloride gave a mixture of propargyl chloride **75** and allene **76**. This isomeric mixture was reduced

Scheme 14



(a) Ac_2O, pyridine; (b) lithium acetylide; (c) $POCl_3$; (d) LAH; (e) 2,2-dimethoxypropane; (f) EtMgBr; then **78**; (g) H_2, Lindlar; (h) dilute HCl; (i) distillation.

with $LiAlH_4$, and the resulting diol protected as the acetonide. The magnesium salt of acetonide **77** was condensed with aldehyde **78**, providing a mixture of diastereomeric propargylic alcohols **79**. Catalytic hydrogenation of the alkyne using Lindlar's catalyst afforded the corresponding (*Z*)-alkene. Treatment of this material with dilute acid removed the acetonide and produced triol **80**. Distillation was required to affect cyclization of **80** to dihydropyran **81**, as a 6:1 *cis/trans* ratio of diastereomers. Presumably, this cyclization occurred via β-elimination of water from **80** to give the corresponding $\alpha,\beta,\gamma,\delta$-dienone intermediate, followed by Michael addition of the alcohol.

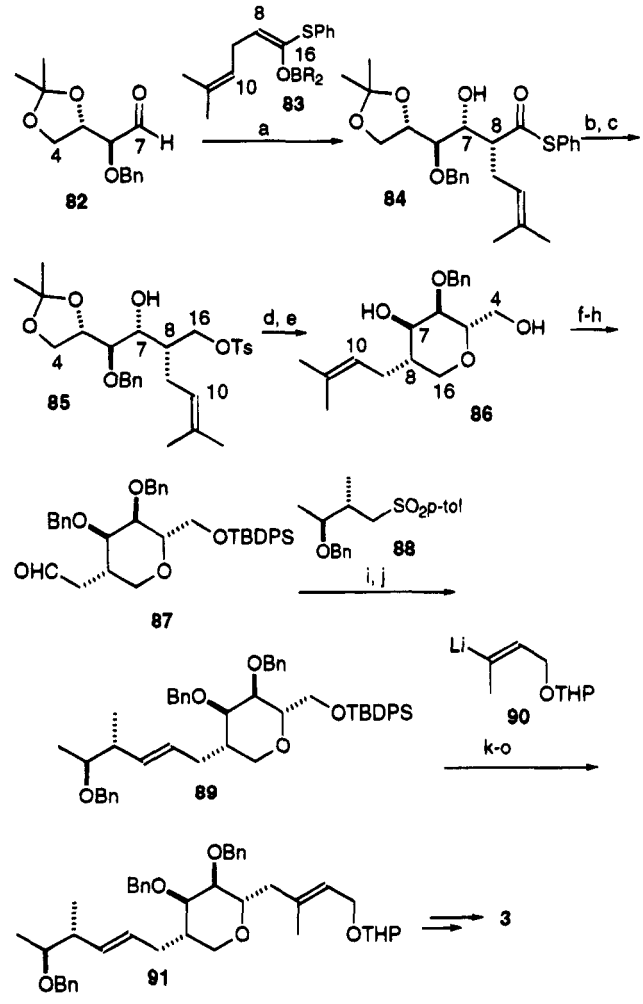
This cyclodehydration adduct is virtually identical to intermediate **43** of Fleet's synthesis. Conversion of alcohol **81** to pyran **22** was accomplished by standard procedures involving *cis* hydroxylation of the olefin and side chain homologation.

J. The Williams Synthesis

Williams also took advantage of the absolute stereochemistry of a carbohydrate derivative in order to prepare pseudomonic acid C.[69] His strategy was unique in that, unlike the other syntheses, the pyran ring system was assembled relatively late in the synthesis (Scheme 15). The key step in this strategy involved nucleophilic ring closure of an acyclic precursor possessing four contiguous stereocenters of the pyran nucleus. The C-8 side chain was homologated by a Julia coupling. This coupling approach differed from Keck's in that the pyran now served as the aldehydic component while C-11 through C-14 portion served as the source of the α-sulfonyl carbanion.

Aldehyde **82**, containing what would ultimately become C-4 through C-7 of the pyran nucleus, was prepared in eight steps from D-glucose. Addition of the (*Z*)-9-BBN-boron enolate **83** gave alcohol **84** with predominantly *anti* stereoselectivity between the C-7 hydroxyl and C-8 thioester moiety.[70] Conversion of thioester **84** to tosylate **85** and acid-catalyzed acetonide removal produced the corresponding triol. Base-catalyzed cyclization afforded tetrahydropyran

Scheme 15



(a) **83**; (b) $LiAlH_4$; (c) TsCl, Et_3N; (d) TsOH, CH_3OH; (e) $NaOCH_3$, CH_3OH; (f) TBDPSCl, Et_3N, DMAP; (g) NaH, benzyl bromide; (h) O_3; (i) LDA, **88**; then CS_2; then CH_3I; (j) Bu_3SnH, AIBN; (k) TBAF; (l) PDC; (m) **90**, CeI_3; (n) CBr_4, $BaCO_3$, Ph_3P; (o) Bu_3SnH, AIBN.

86 in which the four contiguous stereocenters of the pyran ring are established. Homologation of the C-8 side chain was accomplished by hydroxyl group protection and ozonolysis of the olefin to give aldehyde **87**. Condensation of **87** with the α-sulfonyl anion of **88** resulted in a mixture of β-hydroxy sulfone diastereomers that were not separated. Sulfonyl **88** was prepared by the method of Still starting from (+)-(2*R*,3*S*)-2-methyl-3-[(benzyloxy)methoxy]-1-butanol.[71]

After repeated attempts at β-hydroxy sulfone elimination, Williams found that quenching the Julia adduct with CS_2/CH_3I provided a mixture of xanthates that could be subjected to reductive elimination with tri-*n*-butyltin hydride. This modification of Julia's protocol, first reported by Lythgoe and Waterhouse,[72] gave alkene **89** as a 4:1 mixture of *E/Z*-isomers.

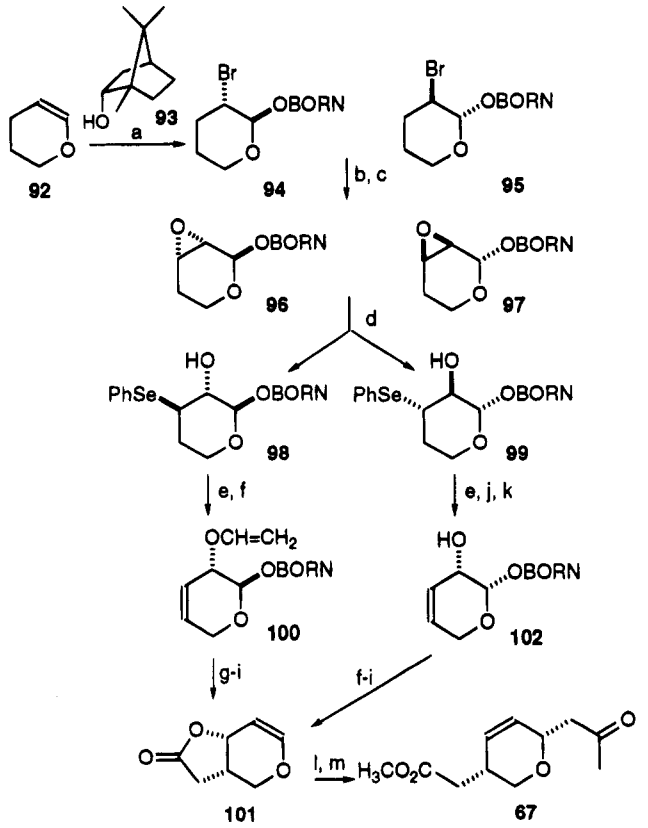
The synthesis of pseudomonic acid C was ultimately completed by C-5 side chain extension. Removal of the silyl protecting group from **89** and oxidation of the resulting alcohol gave an aldehyde, which was subsequently condensed with vinyllithium **90**. Conversion of the resulting alcohol to a bromide was followed by tin hydride reduction to give **91** with

complete retention of C-2 (*E*)-alkene geometry. Deprotection, oxidation of the primary alcohol, and esterification provided pseudomonic acid C in its enantiomerically pure form.

K. The White Synthesis

While most enantioselective syntheses of pseudomonic acid rely on carbohydrates as the origin of chirality, White chose achiral dihydropyran as the starting material to prepare Fleet's chiral lactone.[73,74] White then utilized a carbosulfenylation protocol to introduce the desired α-*cis* side chains. A variation of Julia's methodology was used to append the C-8 side chain and create the C-10/C-11 (*E*)-alkene (Scheme 16).

Scheme 16



(a) Br_2, **93**, $C_6H_5N(CH_3)_2$; (b) DBU, 95 °C; (c) *m*-CPBA; (d) PhSeSePh, $NaBH_4$, LiBr; (e) 30% H_2O_2, $NaHCO_3$, EtOH, H_2O; (f) ethyl vinylether, $Hg(OCOCF_3)_2$, reflux; (g) 250 °C; (h) $AgNO_3$, KOH, EtOH, H_2O; (i) $SnCl_4$; (j) MnO_2; (k) DIBALH; (l) Ph_3CSCl, $CH_2C(CH_3)OTMS$ (2 equiv.), $ZnBr_2$; (m) CH_2N_2.

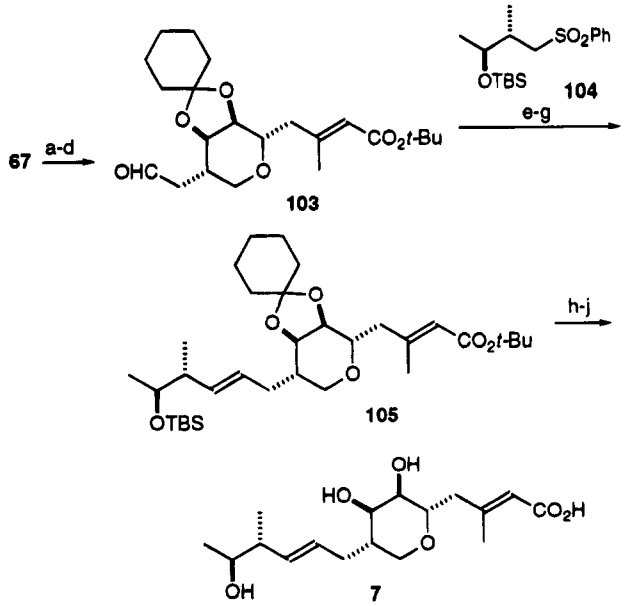
Treatment of dihydropyran (**92**) with bromine and (−)-borneol (**93**) gave a 1:1 mixture of diastereomeric bromoacetals **94** and **95**. Elimination of HBr and epoxidation afforded *trans*-epoxides **96** and **97** as the major products, along with the corresponding *cis* diastereomers. It was subsequently found that **96** would lead to pseudomonic acid with the correct absolute stereochemistry, while **97** gave the diastereomer.

Diastereomeric epoxides **96** and **97** were opened regioselectively by nucleophilic addition of phenyl selenide. The resulting β-hydroxy selenides **98** and **99** were separated chromatographically. Diastereomer **98** was converted to allyl vinyl ether **100** by selenide oxidation/elimination, followed by mercury-catalyzed vinylation. A Claisen rearrangement transposed the stereocenter at C-6 to C-8 with retention of configuration. Oxidation of the intermediate aldehyde gave a carboxylic acid which, upon brief treatment with stannic chloride, eliminated the chiral auxiliary and produced lactone **101**.

With the C-8 stereocenter in place, an S_N2' lactone opening, with overall retention of configuration, was required to incorporate the C-5 side chain. White used a carbosulfenylation approach,[75] in which tritylsulfenyl chloride attacked the pyran olefin from the less hindered β-face. The intermediate sulfonium ion was regioselectively opened at C-5 by addition of the silyl enol ether of acetone. Sulfide elimination, and concomitant opening of the lactone, gave the dihydropyran with *cis* substituents. Reaction of the resulting carboxylic acid with diazomethane provided ester **67**, which had also been prepared by Curran (*vide supra*). Selenide **99**, the diastereomer of **98**, required inversion of configuration at C-6 in order to be transformed to ester **67**. This was achieved in three steps via the intermediate allylic alcohol **102**. Subjection of allyl vinyl ether of **96** to the Claisen/carbosulfenylation protocol resulted in formation of ester **67**.

White investigated both the Wittig and Julia technologies as C-8 chain-lengthening strategies. As previously observed, White found that Wittig condensation of the phosphonium salt **48**, comprising C-11 through C-15, and the C-10 aldehydic dihydropyran did not result in high stereoselectivity for the (*E*)-alkene. A suitable alternative came from the Julia protocol (Scheme 17). White's intermediate **67** was converted in four steps to aldehyde **103**. Condensation of **103** with the anion of sulfone **104**, prepared by the method of Keck, followed by acylation gave a mixture of β-acetoxy sulfones. Reduction of these sulfones with sodium amalgam yielded a 17:3

Scheme 17



(a) OsO_4, NMO, *t*-BuOH, THF, H_2O; (b) 1,1-dimethoxycyclohexane, TsOH; (c) $(CH_3)_2P(O)CH_2CO_2t$-Bu, NaH, LiBr; (d) Li(*n*-Bu)(*i*-Bu)$_2$AlH; (e) *n*-BuLi, **104**; (f) Ac_2O, pyridine; (g) Na(Hg), Na_2PO_4, EtOAc, CH_3OH; (h) TBAF; (i) CF_3CO_2H; (j) 50% aq. CF_3CO_2H.

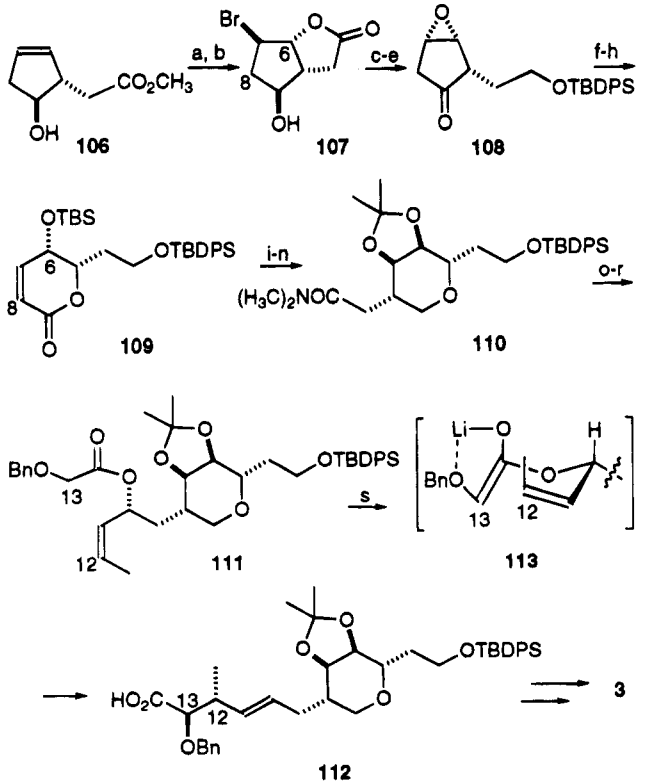
E/Z ratio of alkenes **105**. The synthesis of monic acid C (**7**) was completed in three additional steps by a series of deprotections.

L. The Barrish Synthesis

In the Barrish total synthesis of pseudomonic acid C, the C-5 side chain of a chiral cyclopentene derivative was used as a platform for construction of the remaining three contiguous stereocenters of the tetrahydropyran nucleus (Scheme 18).[76,77] This was achieved by a stepwise transfer of stereochemical information from C-5 to C-8, via C-6. The stereocenter at C-6 was formed by a C-5 side chain lactonization/reduction sequence. Transposition of this stereocenter to C-8 was accomplished via a Claisen rearrangement. Homologation of the C-8 side chain, and creation of the stereocenters at C-12 and C-13, was accomplished by Ireland–ester–Claisen technology.

Cyclopentadiene was transformed to chiral ester **106** by the method of Partridge.[78,79] Hydrolysis of the ester and bromolactonization gave lactone **107** and established the stereocenter at C-6. Lactone reduction and base-catalyzed epoxidation gave the corresponding epoxy diol. Protection of the primary hydroxyl group and oxidation of the secondary hydroxyl provided epoxy ketone **108**. Baeyer–Villiger oxidation of ketone **108** resulted in regioselective ring expansion to the lactone. Base-catalyzed enolization and concomitant epoxide opening afforded a hydroxy dihydropyranone that was protected as its TBS ether (**109**). Reduction of the carbonyl to a methylene group followed by a selective desilylation set the stage for introduction of the C-8 side chain. Using the Eschenmoser variant of the Claisen rearrangement, the allylic alcohol was transposed from the C-6 to C-8 with retention of configuration. Osmylation of the resulting dihydropyran established the *cis*-C-6/C-7 diol. This diol was protected as its acetonide to afford pyran **110**.

Scheme 18



(a) NaOH, H_2O; (b) NBS; (c) $LiBH_4$; (d) 15% NaOH; (e) TBDPSCl, pyridine; (f) *m*-CPBA; (g) Et_3N; (h) TBSOTf; (i) DIBALH; (j) Et_3SiH, BF_3; (k) aq. HOAc; (l) $CH_3C(OCH_3)_2N(CH_3)_2$, xylene, 140 °C; (m) OsO_4, NMO; (n) acetone, TsOH; (o) propynyllithium, BF_3OEt_2; (p) R-Alpine-borane; (q) benzyloxy acetic acid, DCC, DMAP; (r) H_2, Lindlar; (s) LDA; then TMSCl; then H_3O^+.

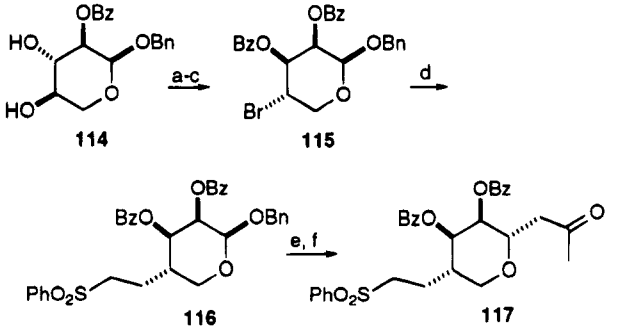
Barrish envisioned that an Ireland–ester–Claisen rearrangement of the appropriate allylic acetate would provide a pseudomonic acid side chain with correct C-10/C-11 geometry, as well as the desired relative stereochemistry between C-12 and C-13. Several Claisen strategies were attempted. The method that afforded the best stereoselectivity is presented here.

Propynyllithium was added to amide **110**, and the resulting propargyl ketone was reduced with (*R*)-alpine–borane, with nearly complete stereoselectivity for the (*R*)-alcohol. Coupling of the alcohol to benzyloxy acetic acid, followed by careful reduction of the alkyne, gave (*Z*)-alkene **111**. This material was treated under standard Ireland–Claisen conditions to give ester **112**. The rearrangement proceeded with high stereocontrol via the (*E*)-enolate and chelated transition state **113**. The C-5 side chain was homologated in a manner similar to those described previously, to complete an enantioselective synthesis of pseudomonic acid C (**3**).

M. The Nagarajan Synthesis

Nagarajan formulated an approach to the pseudomonic acid nucleus that involved the radical coupling of a xylose derivative with phenyl vinyl sulfoxide (Scheme 19).[80] In order for D-xylose to be used as a suitable pseudomonic acid precursor, inversion at C-7 was required.

Scheme 19



(a) Ph_3P, CHI_3, imidazole, toluene, reflux; (b) NBS, H_2O, DMSO; (c) PhCOCl, pyridine; (d) phenyl vinyl sulfoxide, Bu_3SnH, AIBN; (e) cyclohexene, Pd/C, CH_3OH, reflux; (e) $Ph_3PCHCOCH_3$, CH_3CN; then DBU.

Protected D-xylopyranose analogue **114** was dehydroxylated by reaction with triphenylphosphine, iodoform, and imidazole. The resulting dihydropyran was treated with aqueous NBS to give a bromohydrin and then converted to bis-benzoate **115**. Reaction of bromide **115** with phenyl vinyl sulfone in the presence of Bu_3SnH gave sulfone **116** with retention of

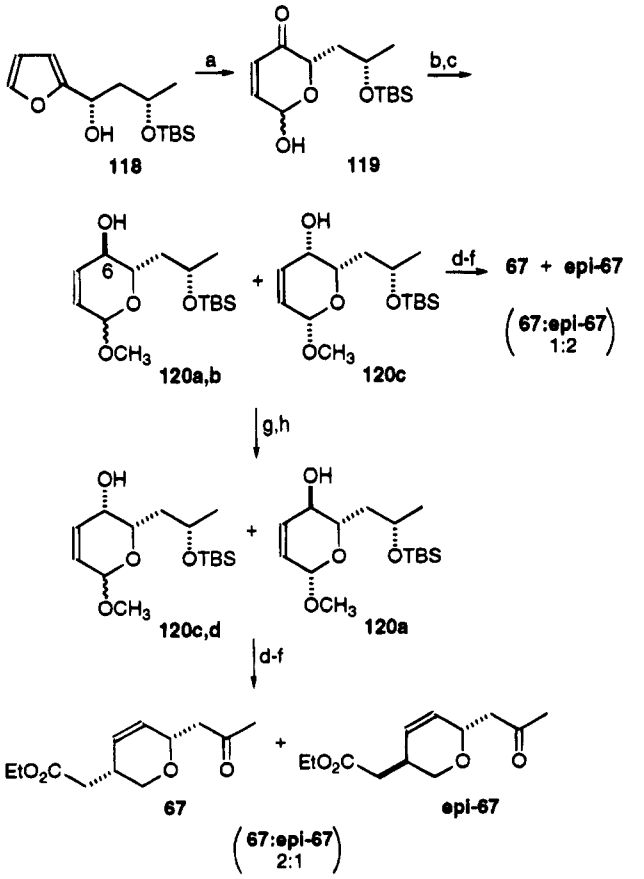
configuration at C-8. The stereoselectivity of this process was a consequence of attack on the least hindered α-face of the intermediate pyran radical. Debenzylation of **116** and subsequent Wittig reaction at the anomeric center as developed by Kozikowski (*vide supra*), completed the synthesis of pseudomonic acid precursor **117** in chiral form. This material was converted to an intermediate previously described by Keck and utilized in the synthesis of **3**.

N. The DeShong Synthesis

DeShong and Class have prepared the dihydropyran nucleus of pseudomonic acid A via a furan oxidation strategy.[81-83] Pyranones resulting from furan oxidation were reduced to afford diastereomeric allylic alcohols. A subsequent Claisen rearrangement was utilized to transfer the stereocenter at C-6 to C-8. DeShong also investigated palladium-catalyzed alkylation of pyran derivatives for introduction of the C-8 side chain of pseudomonic acid A. This work culminated in two formal syntheses of pseudomonic acid A.

The first phase of this synthesis involved construction of dihydropyran **67** with *cis* side chains at C-5 and C-8 (Scheme 20). White and Curran had shown that dihydropyran **67** can be converted to pseudomonic acids A and C by *cis*-hydroxylation of the double bond and side chain extension (*vide supra*).[62,63,73,74,84] Furfuryl alcohol **118** was prepared by the condensation of furyllithium and 3-(silyloxy)butanal to give a mixture of *syn*- and *anti*-furfuryl alcohols. While each furfuryl alcohol was eventually converted to dihydropyran **67**, the results of experiments with the *syn* series will be described in detail. Oxidation of furfuryl alcohol **118** with *m*-CPBA[85] provided a mixture of *syn*-pyranones **119** that were subsequently methylated. The resulting methoxypyranones were reduced with $LiAlH_4$ to give three of the four possible allylic alcohols **120a–c** in ~1:1:1 ratio. A detailed ^1H NMR analysis was utilized to identify the relative configurations of allylic alcohols **120a–c**.

Scheme 20



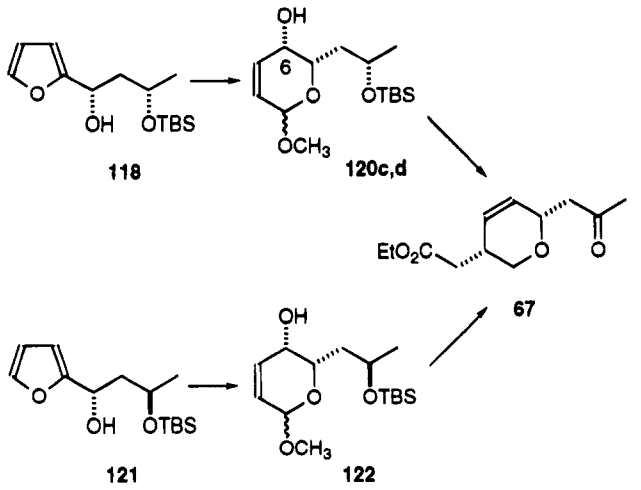
(a) *m*-CPBA; (b) CH_3I, Ag_2O; (c) $LiAlH_4$; (d) $CH_3C(OEt)_3$, CH_3CO_2H; (e) Et_3SiH, $TiCl_4$; (f) PCC; (g) DEAD, PPh_3, $PhCO_2H$; (h) $NaOCH_3$, CH_3OH.

The mixture of allylic alcohols **120a–c** was converted to dihydropyran **67** in three steps. A Johnson–Claisen rearrangement smoothly transferred the stereocenter from C-6 to C-8 on the pyran.[86] The resulting ester was simultaneously desilylated and reduced at the anomeric center. Oxidation of the hydroxyl group provided predominantly *epi*-**67**, the dihydropyran with a *trans* relationship between C-5 and C-8. The formation of *epi*-**67** preferentially from this mixture indicated that the major diastereomers of the allylic alcohols produced by the reduction of **119** bore a *trans* relationship between the hydroxyl group at C-6 and the alkyl substituent at C-5. To prepare the *cis*-pyran **67** as the major product, it would be necessary to invert the stereocenter at C-6. Accordingly, alcohols **120a–c** were subjected to standard Mitsunobu conditions that resulted in the isolation of the corresponding allylic benzoates.[87] No products from S_N2' displacement with benzoic acid were observed. Saponification of the benzoate esters gave a new mixture of allylic alcohols **120a,c,d** that by comparison of the ^1H NMR spectra was *different* from the alcohol mixture **120a,b,c** prior to Mitsunobu inversion. Confirmation that C-6 inversion had occurred came from conversion of the Mitsunobu mixture to *cis*-dihydropyran **67**. Subjection of **120a,c,d** to the Claisen, reduction, and oxidation sequence now afforded the desired pyran derivative as the major product.

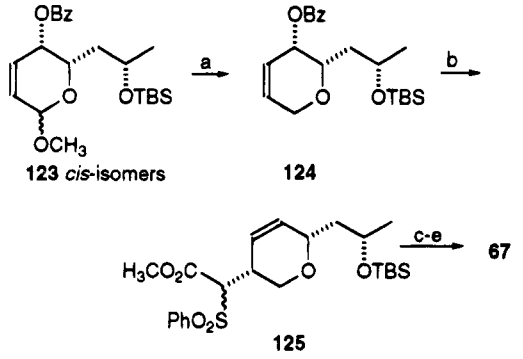
In a manner similar to that described for the *syn*-furfuryl alcohol **118**, the *anti*-furfuryl alcohol **121** was also converted to dihydropyran **67**. The results of these experiments demonstrated that separation of furfuryl alcohols **118** and **121** is unnecessary since their corresponding pyranones require the same reactions in order to provide the pseudomonic acid nucleus with *cis* side chains at C-5 and C-8 (Scheme 21).

In addition to the Claisen strategy for the preparation of pseudomonic acid precursors, DeShong and Class utilized a palladium-catalyzed alkylation[51-53] of pyranone intermediates to prepare pyran **67**. An anomeric mixture of *cis-syn*-allylic benzoates **123**, derived from *syn*-pyranone, was treated with $Et_3SiH/TiCl_4$ (Scheme 22).[88,89] The resulting ether **124** was then reacted with the anion of methyl (phenylsulfonyl)acetate in the presence of $Pd(dppe)_2$ to afford a 1:1 mixture of diastereomeric sulfones **125**. The degree of regio- and stereoselectivity of this reaction was determined by conversion of the sulfone mixture to dihydropyran **67**. Sulfone reduction, silyl ether cleavage, and oxidation of the resulting alcohol afforded **67** as a single isomer. While the results of

Scheme 21



Scheme 22



(a) Et_3SiH, $TiCl_4$; (b) $PhSO_2CH_2CO_2CH_3$, NaH, $Pd(dppe)_2$; (c) Na(Hg); (d) HF/ H_2SiF_6; (e) PCC.

this study culminated only in the synthesis of the nucleus of pseudomonic acids A and C, it appears that a palladium-catalyzed allylic alkylation strategy can be employed for introducing the intact C-8 side chain onto **124** in a single step.

VI. Abbreviations

acac	acetylacetonate
AIBN	azobisisobutyronitrile
AMP	adenosine monophosphate
Cp	cyclopentadienyl
m-CPBA	*m*-chloroperoxybenzoic acid
DCC	dicyclohexylcarbodiimide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
dba	dibenzylacetone
DMAP	4-(dimethylamino)pyridine
dppe	(diphenylphosphino)ethane
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato
LDA	lithium diisopropylamide
MIC	minimum inhibitory concentration
Ms	methanesulfonyl (or methylsulfonyl)
NBS	*N*-bromosuccinimide
PCC	pyridinium chlorochromate
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethane sulfonyl [or (trifluoromethyl)sulfonyl]
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
trimsyl	2,4,6-trimethylbenzenesulfonyl [or (2,4,6-trimethylphenyl)sulfonyl]
Ts	*p*-toluenesulfonyl (or *p*-tolylsulfonyl)

VII. Acknowledgments

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