NMR Facility at Yale University, which was supported by NSF Chemistry Grant CHE 7916210.

Supplementary Material Available: All experimental procedures and full spectral characterizations of the material described herein (3 pages). Ordering information is given on any current masthead page.

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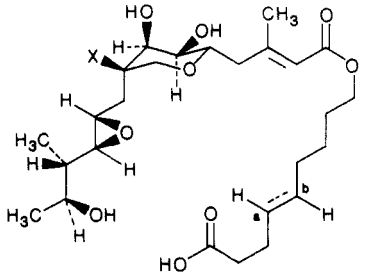
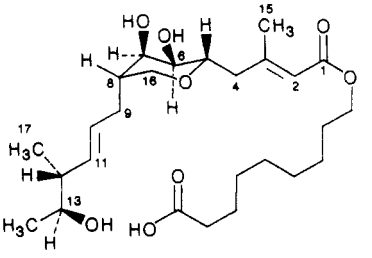
Total Synthesis of (+)-Pseudomonic Acid C†

Summary: The convergent enantiospecific total synthesis of (+)-pseudomonic acid C (**1c**) has been completed from D-glucose.

Sir: The pseudomonic acids consist of a small group of four related metabolites, originally isolated from submerged cultures of *Pseudomonic fluorescens* NCIB 10586.[2] Detailed studies of structural and chemical characterizations of the major component pseudomonic acid A (**1a**) and the lesser components B, C, and D have been reported in a series of papers.[3] In 1982, X-ray crystallography established the absolute configuration of the monate skeleton of pseudomonic acid C (**1c**).[4] The therapeutic value of



1a, X = H; C_a-C_b = C_2H_4
1b, X = OH; C_a-C_b = C_2H_4
1d, X = H; C_a-C_b = *E*-CH=CH

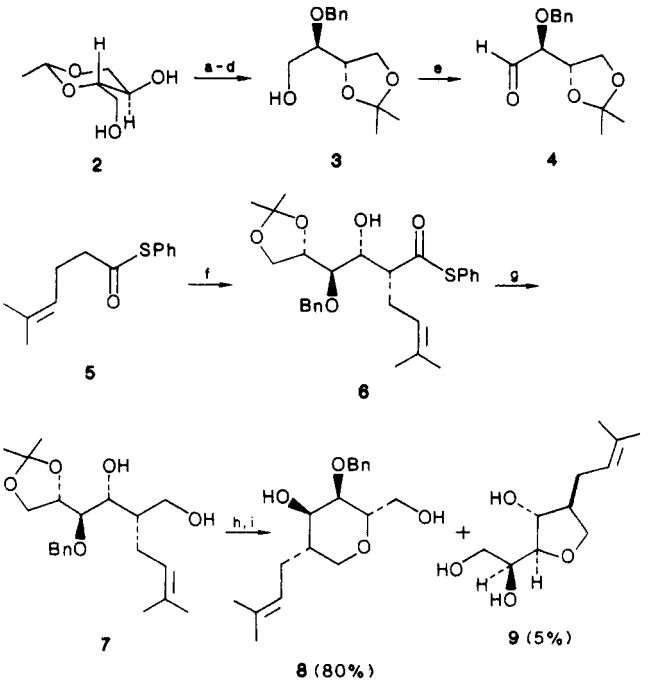


1c (pseudomonic acid C)

these antibiotics has been clinically developed in the Beecham Laboratories.[5] Several chemical investigations have documented strategies for the total synthesis of pseudomonic acid C, and numerous approaches have been published. The conversion of pseudomonic acid C (**1c**) to the major metabolite **1a** has also been reported.[7] Herein, we communicate our recent efforts affording a convergent total synthesis of (+)-pseudomonic acid C.

Construction of a chiral tetrahydropyran, bearing four contiguous asymmetric centers (C_5 through C_8; **1c** numbering), suggested use of a reduced (at C_{16}) carbohydrate precursor. However, the necessary absolute configuration at C_5 was directly apparent only in the series of L-hexoses.

Scheme I



[a] (a) Trityl chloride (1.1 equiv), DMAP (1.1 equiv), DMF (80%); (b) NaH dispersion, THF, benzyl bromide (83%); (c) 40% concentrated HCl in methanol, 22 °C, 14 h (84%): (d) PPTs (0.1 equiv), acetone, 18 h (78%); (e) ClCOCOCl (1.5 equiv), Me_2SO (2.4 equiv), CH_2Cl_2, -78 °C; then Et_3N (2.4 equiv), -78 °C → 0 °C (87%); (f) 9-BBN triflate, Et_2O, thio ester **5** (1 equiv), diisopropylethylamine (1.4 equiv); add **4** at -78 °C → 0 °C (79%); (g) $LiAlH_4$, ether, 0 °C → 22 °C, 1 h (85%); (h) TsCl (1.4 equiv), CH_2Cl_2, DMAP (1.1 equiv), Et_3N (2.5 equiv), 22 °C, 4 h; (i) TsOH (1.1 equiv), MeOH, 16 h, 22 °C; add $NaOCH_3$ in methanol (80% yield of **8**).

Our introduction of the desired absolute stereochemistry at C_5, as well as C_6, was accomplished by D-glucose, as illustrated in Scheme I. A classical three-step sequence provided the known diol **2**,[8] and arrangement of appropriate protection gave the optically pure primary alcohol **3**. Swern oxidation provided aldehyde **4**, which was used immediately for condensation at -78 °C in anhydrous ether with the preformed *Z*(O)-boron enolate derived from thio ester **5**.[9,10] High stereocontrol was observed with formation

† Dedicated to Professor George Büchi on the occasion of his 65th birthday.

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(6) (a) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. (b) Bean, J.-M.; Aburaki, S.; Pougny, J.-R.; Sinay, P. *J. Am. Chem. Soc.* **1983**, *105*, 621. (c) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3661. (d) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 4317. See ref 6d for additional citations of synthetic approaches.
(7) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *Tetrahedron Lett.* **1981**, *22*, 2059.
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(9) The enolate was prepared by addition of 9-BBN triflate (0.5 M solution in hexane) to the thio ester **5** in anhydrous ether containing diisopropylethylamine (0.5 equiv) at 0 °C. After stirring for 1.5 h at room temperature, the enolate was cooled to -78 °C for reaction with **4**.
(10) Masamune, S. *Heterocycles* **1984**, *21*, 107.

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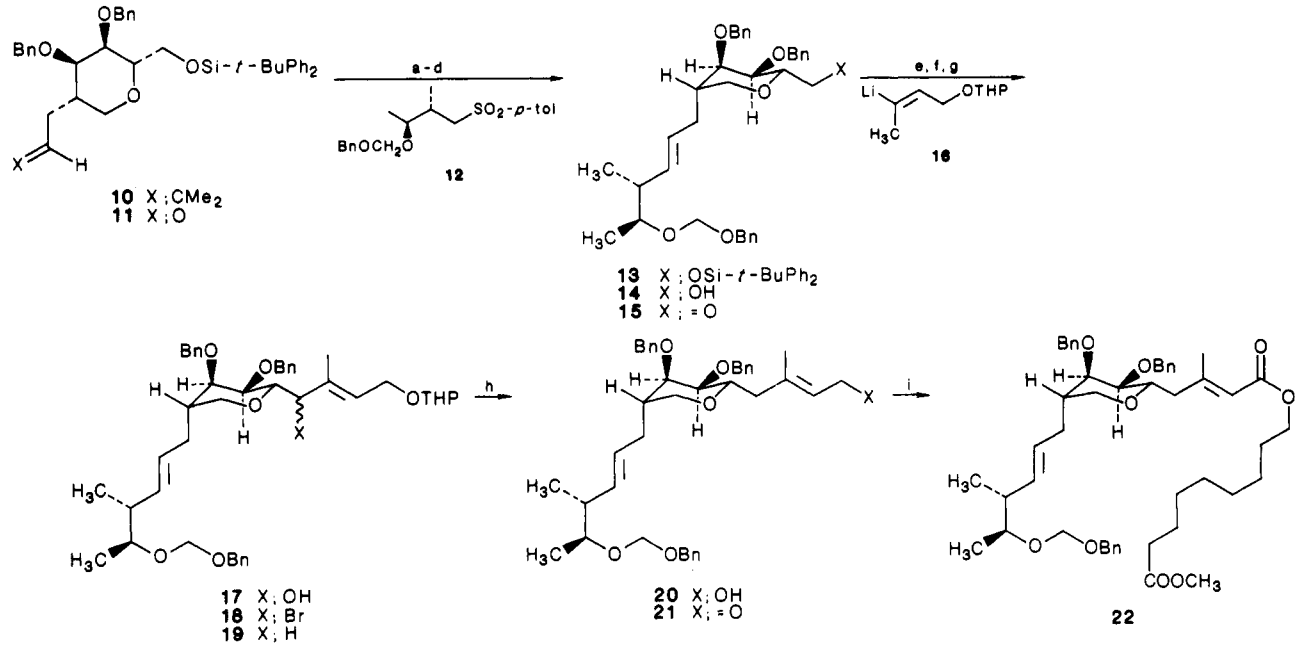
Scheme II[a]



[a] (a) Formation of carbanion **12**; LDA (1.1 equiv), THF, −60 °C; addition of **11**, −60 °C, 20 min; addition of CS_2 (excess), −60 °C → +5 °C, 20 min; add CH_3I (10 equiv), 22 °C, 1 h (96%); (b) n-Bu_3SnH (1.5 equiv), toluene, cat. AIBN, 95 °C (86%); (c) 1.0 M n-$Bu_4N^+F^-$ in THF (85%); (d) PDC (1.7 equiv), CH_2Cl_2, 3 Å powdered molecular sieves (76%); (e) preparation of **16** at −100 °C; add anhydrous CeI_3 (1 equiv) in THF, 30 min; add **15**, −100 °C → 0 °C; quench aq. NH_4Cl (65%); (f) CBr_4, CH_2Cl_2, $BaCO_3$ (1.7 equiv), Ph_3P (1.7 equiv), 45 min (75%); (g) n-Bu_3SnH (1.5 equiv), toluene, AIBN, 65 °C, 1 h (82%); (h) PPTs (0.5 equiv), MeOH, 22 °C, 14 h (98%); (i) MnO_2 (excess), THF, 5 h; then methyl 9-hydroxynonanoate, NaCN, HOAc, 16 h (98%).

of the pure 2,3-syn,3,4-anti isomer **6** in 79% yield after preparative thin-layer or flash chromatography.[11] The aldol reaction exhibits diastereofacial selectivity with attack from the re-face of the aldehyde through the general chair-like cyclic transition state, which affords a Felkin model for establishing the observed C_3 and C_4 geometries.[12,13] Hydride reduction of **6** gave the 1,3-diol **7**. Selective conversion to the primary tosylate followed by acid cleavage of the acetonide, and base treatment yielded the tetrahydropyran **8** (80%) along with small amounts of tetrahydrofuran **9** (17%), resulting from nucleophilic participation of the benzyl ether at C-4.[14]

Transformations for attachment of the $C_{11} \rightarrow C_{14}$ carbon chain of pseudomonic acid C, and subsequent completion of the total synthesis are described in Scheme II. Formation of the silyl ether **10** proceeded in two steps (Ph_2-t-BuSiCl, 1 equiv; CH_2Cl_2; Et_3N, DMAP, 1 equiv; 22 °C: then benzyl bromide, THF, NaH, 12 h) with 84% overall yield. Ozonolysis in methylene chloride containing pyridine selectively gave the desired aldehyde **11** without competing oxidation of the benzyloxy units to their corresponding benzoates. Introduction of the trans C_{10}–C_{11} unsaturation was explored by using Julia methodology[15] for coupling the chiral α-sulfonyl carbanion **12**[16] with aldehyde **11**. Although the usual protocol for reductive eliminations of a variety of β-hydroxy sulfone derivatives failed to produce olefinic materials,[17] we were able to adapt an alternative procedure reported by Lythgoe and Waterhouse.[18] Thus addition of sulfone **12** was followed by a carbon disulfide–methyl iodide quench, leading to a mixture of diastereomeric β-sulfonyl xanthates which were purified by flash chromatography. Reductive elimination with tri-n-butyltin hydride in toluene at 100 °C gave 86% yield of the desired olefin **13** (E/Z ratio is 85:15).[19] This process afforded an excellent 83% overall yield and should prove generally useful for connective constructions in functionally complex molecules.

Deprotection and oxidation gave aldehyde **15** for incorporation of the α,β-unsaturated ester of pseudomonic acid C.[20] Addition of the vinyllithium **16** in the presence of anhydrous cerium(III) iodide (1 equiv) at −100 °C afforded a 65% yield of alcohols **17** as a mixture (3:1) of C-4 epimers.[21] Without cerium iodide,[22] our products **17** were accompanied by substantial amounts of β-elimination of the C_6-benzyloxy substituent. The unwanted C-4 hydroxyl

(11) Small amounts (~5%) of a second pure diastereoisomer were also obtained; however, stereoassignments have not been feasible.

(12) Although stereoselectivities for the Masamune aldol procedure using similar α,β-dialkoxysubstituted aldehydes have not been published, the β-alkoxy substituent appears to confer increased stereocontrol, whereas the α-benzyloxy unit does not provoke a chelation-controlled (anti-Cram) addition. Related discussions are presented in ref 10 and 13 and Gennari, C.; Bernardi, A.; Poli, G.; Scolastico, C. *Tetrahedron Lett.* **1985**, *26*, 2372.

(13) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.

(14) Possible ring closure to the isomeric oxetane was never observed.

(15) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833.

(16) The optically active sulfone **12** was prepared from (+)-(2*R*,3*S*)-2-methyl-3-(benzyloxymethoxy)-1-butanol via established procedures. Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(17) An efficient and high yielding procedure for introduction of the C_{10}–C_{11} alkene of pseudomonic acid C has been a recurring problem. Coincident with our investigations, Keck and co-workers had extensively explored the Julia methodology with similar difficulties. We thank Gary Keck for private communications (see also ref 6a–d).

(18) Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1977**, 4223.

(19) The more polar *E*-olefin was cleanly separated by preparative TLC on silica.

(20) Oxidation (PDC) led to a mixture (4:1) of **15**, and the thermodynamically more stable epimeric aldehyde (at C-5), which was subsequently separated by preparative TLC. Swern conditions at −78 °C gave a 1:3 ratio.

(21) Lithium reagent **16** was prepared from the corresponding vinyl bromide using *tert*-butyllithium (2 equiv, THF, −100 °C). See: Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V. *Tetrahedron Lett.* **1978**, 1051. All attempts for C_3–C_4 bond formation via alkylations using various organometallic reagents of **1b** failed.

(22) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1042. No epimerization at C-5 was observed in the products **17**.

of **17** was excised by transformation to the bromides **18**, follow d by tin hydride reduction at 60 °C providing only **19**.[23] Fortunately each step of this reduction process occurred without loss of regio- or stereochemical integrity of the adjacent trisubstituted alkene.[24]

Finally the total synthesis was completed upon removal of the tetrahydropyranyl ether yielding **20** and manganese dioxide oxidation. After the conjugated aldehyde **21** was formed, a second allylic oxidation was initiated by in situ addition of 9-hydroxynonanoate methyl ester (1 equiv) with sodium cyanide and glacial acetic acid, affording nearly quantitative conversion to the methyl pseudomonate **22**.[25] Deprotection with boron chloride at −90 °C in methylene chloride (2 min) followed by treatment of the residue with 1 M lithium hydroxide in aqueous methanol (10 min for saponification of the methyl ester) and reacidification (HOAc) gave a 97% yield of synthetic (+)-pseudomonic acid C (**1c**), $[\alpha]^{24}_D$ +8.7° (*c* 0.3, $CHCl_3$), as confirmed by direct comparisons with the authentic natural metabolite.[26,27]

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(23) Reductions with *n*-Bu_3SnH at 100 °C also led to ring opening and further reduction of the THP ether.
(24) The high degree of stereocontrol for this two-step procedure is not general.
(25) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(26) Experimental details and all data for complete chemical characterizations will be forthcoming in the full account of this work.
(27) We wish to thank Professor Gary Keck (University of Utah) for generously providing samples of natural pseudomonic acids A and C.

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The Effect of Preorganization of Macrocyclic Hosts on the Complexation of Neutral Molecules

Summary: The contribution of preorganization to recognizing and binding *neutral* guest species is described. We found that hemispherands form relatively stable complexes with malononitrile. A substantial contribution to the free energy of complexation originates from the relief of electrostatic O···O repulsion which is present in the uncomplexed ligand.

Sir: Hemispherands[1] represent a class of ligands in which at least half of the binding sites are preorganized. In this paper we describe the contribution of preorganization to recognizing and binding *neutral* guest species. We found that hemispherands form relatively stable complexes with malononitrile. A substantial contribution to the free energy of complexation originates from the relief of electrostatic O···O repulsion which is present in the uncomplexed ligand.

(1) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43–106.

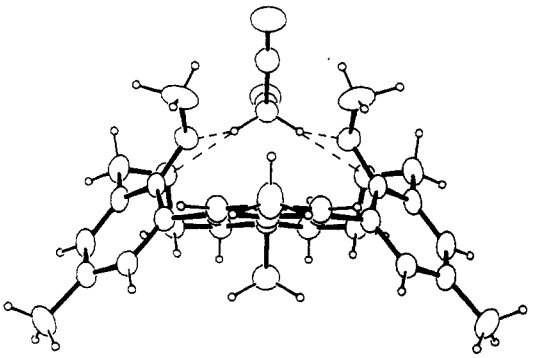
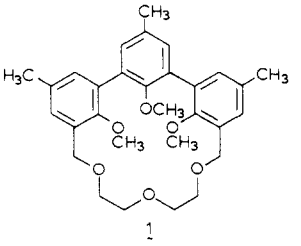


Figure 1. Front view of the structure of 1–malononitrile. Hydrogen bonds indicated by dashed lines: C···O distance range, 3.09–3.15 Å; C–H···O angle range, 129–149°.

Cram and co-workers have studied the complexation of a variety of hemispherands with alkali and substituted ammonium cations.[2] They found that hemispherand **1** exhibits a strong binding capacity toward a number of cations.[2]

We are currently interested in the selective complexation of neutral guests, e.g., urea,[3] nitromethane,[4a] and malononitrile,[4b] by macrocyclic hosts. In such complexes the guest is hydrogen-bonded to the receptor molecule. So far the investigations carried out in solution, using malononitrile as a probe for studying conformational properties of flexible ligands, have stressed the importance of a proper relative orientation of binding sites.[4b] Therefore, we studied ligands **1** and **2**, both designed according to the preorganization principle.[5] Hemispherand **1** was prepared according to Cram,[2a] and **2** was prepared from a highly prefunctionalized pyrylium salt,[6] in order to study the effect of different H-bond acceptor sites.



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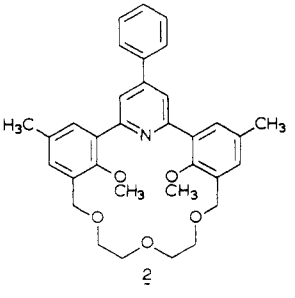

2

(2) (a) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566. (b) Lein, G. M.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *107*, 448–455.
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