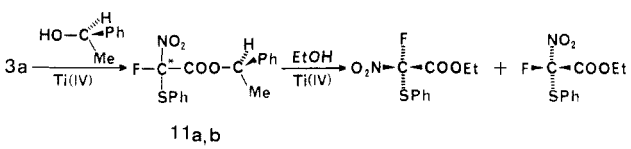
Scheme I



11a,b

96%), EtSH (NaOEt/THF, 0 °C/1 h, 93%), PhOH (NaH/THF, 20 °C/0.5 h, 98%), KOCOPh (DMF, 20 °C/3 h, 86%), potassium phthalimide (DMF, 100 °C/5 h, 89%), di-*tert*-butyl iminodicarboxylate potassium salt (DMF, 120 °C/1 h, 66%), and NaN_3 ($Et_2O/EtOH/H_2O$, 20 °C/10 h, 67%), produced the geminally functionalized fluoroacetates, **4a–d** and **7a–c**, respectively. Although **4d** and **7a–c** could not be brominated, **4a–c** produced rather unstable bromides **5a,b** (NBS/BPO/CCl_4, reflux/1.5–10 h, 43–60%) and **5c** (Br_2/CCl_4, reflux/4 h, 21%). The sulfur functionalized bromides **5a,b** were immediately treated with NaN_3 (AcOEt/EtOH/H_2O, 20 °C/16–28 h, 32–40%) to afford the tetrafunctional carbon compounds **6a,b**.

We also examined possible synthesis of the title compounds starting with ethyl dibromofluoro- and dibromonitroacetates **10a,b**. When **10a,b** were treated carefully with 1 equiv of NaN_3 under the conditions mentioned above, the azido derivatives **8a,b** were obtained in 47% and 15% yields, respectively. An attempt to introduce the amino group by treating **10a,b** with $HNEt_2$ yielded only $Et_2NCOCOOEt$, probably formed by hydrolysis during workup. Attempts to introduce the S or O functionality into **10a** by treatment with NaSPh, NaSEt, or $NaOCH_2Ph$ gave mainly the unexpected reduced products **4a**, **9a**, and **9b**, respectively. The tetrafunctional compounds described here[9] have not been reported previously, despite their structural simplicity.[10,11]

We have also succeeded in resolving this unique structure (Scheme I). The ester **3a** was transesterified ((+)-α-phenethyl alcohol/$Ti(OPr^i)_4$, 110 °C/2 h, 85%)[12] to give a mixture of diastereomeric phenethyl esters (in a ratio of 1:1) and two isomers were separated: **11a** (less polar isomer), $[\alpha]_D$ +136.3°;[13] **11b** (more polar one), $[\alpha]_D$ −93.4°. Each isomer was successfully transformed (EtOH/$Ti(OEt)_4$, 90 °C/2.5 h, 83%)[12] into the optically active ethyl ester: (+)-**3a**, $[\alpha]_D$ +134.2°; (−)-**3a**, $[\alpha]_D$ −132.6°.[14] The racemic α-fluoroglycine derivative **7a** could be also resolved in the same manner: (+)-**7a**, $[\alpha]_D$ +12.7°; (−)-**7a**, $[\alpha]_D$ −13.1°. To our knowledge, this work describes the first synthesis of optically active compounds having four distinctly different labile functional groups.[15] Studies on the broad usefulness of optically active multifunctional carbon compounds are now in progress.[16]

(8) (a) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647. (b) Hudlicky, M. "Organic Fluorine Chemistry"; Plenum Press: New York, London, 1971. (c) Chambers, R. D. "Fluorine in Organic Chemistry"; John Wiley: New York, 1973.

(9) Yields are not optimized. The spectral and analytical data for all new compounds were in accord with the structures proposed.

(10) Even the trifunctionalized carbon structures **1a–c** and **7a–c** are not known. As for the ester of α-fluoro alcohol **4d**, see: Ortiz de Montellano, P. R.; Vinson, W. A. *J. Am. Chem. Soc.* **1979**, *101*, 2222.

(11) Spectral analyses of these unusual structures should also be noted. In their ^{13}C NMR spectra, the central carbon shift positions of **3a–c** (δ 119.0–119.6) are unexpectedly low, probably the lowest of the reported data for ethyl acetate derivatives. The most interesting data must be those of ^{19}F NMR and mass spectra for the compounds bearing four labile groups on a carbon atom. All of these data will be reported elswhere.

(12) (a) Schnurrenberger, P.; Züger, M. F.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1197. (b) Seebach, D.; Hungerbühler, E.; Naef, R. *Synthesis* **1982**, 138. (c) Rehwinkel, H.; Steglich, W. *Ibid.* **1982**, 826.

(13) All optical rotations were measured in chloroform at 24–25 °C (*c* 0.9–4.0).

(14) Absolute configuration of the enantiomers has not yet been determined. No racemization[12] at the tetrafunctionalized asymmetric center was observed as checked by Chiralcel OB chromatography.

(15) Hirschmann, H.; Hanson, K. R. *Top. Stereochem.* **1983**, *14*, 183.

(16) Considering that the conventional direct fluorination methods often lack selectivity, the fluorinated compounds obtained here can be useful synthon molecules bearing both fluorine and an asymmetric carbon atom. These compounds are excellent precursors of α-fluoro-α-amino acid derivatives and, further, candidates for models to study steric aspects of reaction mechanisms.

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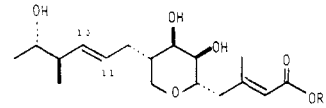
An Enantiospecific Synthesis of Monic Acid C

Summary: Monic acid C (**2**) has been prepared in optically pure form from dihydropyran, thus affording a route to the naturally occurring pseudomonic acids A and C.

Sir: The pseudomonic acids are naturally occurring pyrans from *Pseudomonas fluorescens* that have been found to possess significant antibacterial and antimycoplasmal activity.[1] Upon saponification, pseudomonic acid C (**1**) gives monic acid C (**2**),[2] from which both **1** and its more abundant congener pseudomonic acid A (**3**) have been reconstituted. Several pathways to these materials in racemic



1, R = $(CH_2)_8CO_2H$
2, R = H
3, R = $(CH_2)_8CO_2H$, 10,11-epoxide

form have been published[3] and three enantioselective syntheses, all from carbohydrate precursors, have been described.[4] We now report a synthesis of **2** from dihydropyran in which the incorporation of absolute stereochemistry as well as deployment of the cis-oriented side chains is effected by conceptually novel methods.

The reaction of dihydropyran with bromine and (−)-borneol in the presence of *N*,*N*-dimethylaniline (CH_2Cl_2, −78 °C) gave the bromo acetal **4** together with its diastereoisomer (1:1) in 84% yield.[5] Without separation, this mixture was treated with 1,8-diazabicyclo[5.4.0]undec-7-

(1) O'Hanlon, P. J.; Rogers, N. H.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2655 and reference cited.

(2) Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2827.

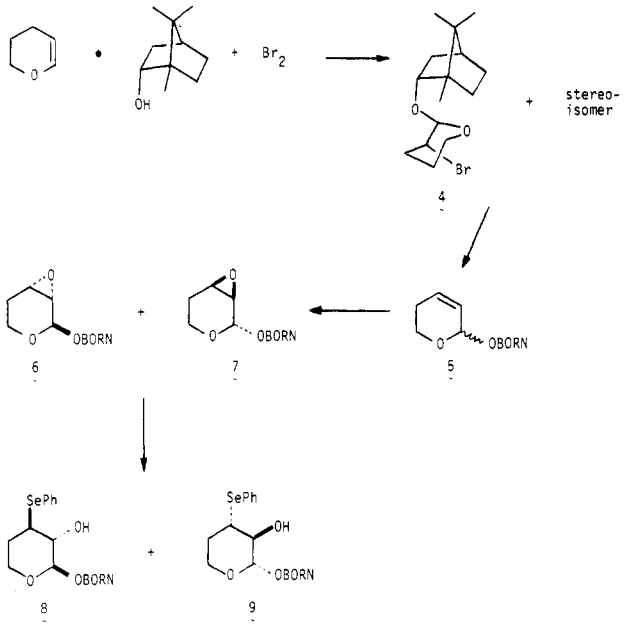
(3) (a) Jackson, R. F. W.; Raphael, R. A.; Stibbard, J. H. A.; Tidbury, R. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2159. (b) Snider, B. B.; Phillips, G. B.; Cordova, R. *J. Org. Chem.* **1983**, *48*, 3003. (c) Schönenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333. (d) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. (e) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *Tetrahedron Lett.* **1981**, *22*, 2059.

(4) (a) Beau, J.-M.; Aburaki, S.; Pougny, J.-R.; Sinaÿ, P. *J. Am. Chem. Soc.* **1983**, *105*, 621. (b) Fleet, G. W. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3657. Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3661. (c) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1984**, *49*, 1462. (d) Curran, D. P.; Suh, Y.-G. *Tetrahedron Lett.* **1984**, *25*, 4179. Curran, D. P. *Tetrahedron Lett.* 1982, *23*, 4309.

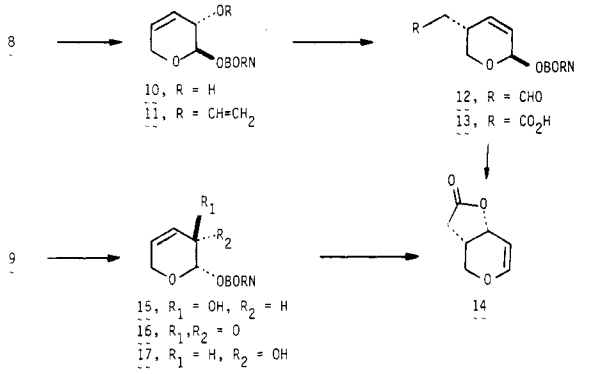
(5) Sweet, F; Brown, R. K. *Can. J. Chem.* **1968**, *46*, 707.

0022-3263/86/1951-0956$01.50/0

ene (95–100 °C, 20 h)[6], affording a pair of diastereomeric olefins (99%), which were epoxidized (*m*-chloroperbenzoic acid, CH_2Cl_2, 25 °C, 48 h) to a mixture of **6** and **7** in 61% yield. These were reacted with sodium phenyl selenide,



prepared from $(C_6H_5Se)_2$ and $NaBH_4$, to give after separation by chromatography optically pure selenides **8** and **9** (1:1) in 96% yield. The tetrahydropyran **8**, which has the desired 3*R* absolute configuration, was first treated with hydrogen peroxide,[7] and the resulting allylic alcohol **10** was converted to the vinyl ether **11** (78%) by transetherification (ethyl vinyl ether, $Hg(OCOCF_3)_2$, reflux, 120 h). Claisen rearrangement of **11** (250 °C) afforded al-

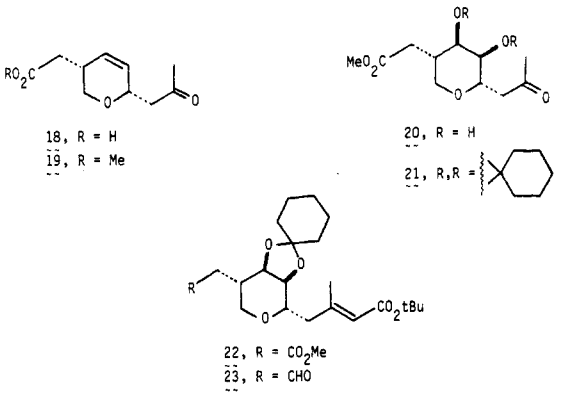


dehyde **12** (94%),[8] which was oxidized ($AgNO_3$, KOH, EtOH, 25 °C, 0.5 h)[9] to the crystalline carboxylic acid **13** (mp 64–66 °C) in 93% yield. Brief treatment of **13** with stannic chloride (CH_2Cl_2, −78 °C) gave (−)-borneol and lactone **14** (84%, mp 51–52 °C, $[\alpha]_D^{22}$ −75.1°); the latter was identical with a substance prepared by Fleet from D-arabinose in the course of his synthesis of **1**.[4b]

γ-Lactone **14** could also be obtained indirectly from **9**, thereby lending the synthesis a high degree of stereochemical convergence. Thus, treatment of **9** with hydrogen peroxide afforded **15** (79%), which was oxidized with manganese dioxide (CH_2Cl_2) to **16** (86%). Reduction of this ketone with diisobutylaluminum hydride (1.5 equiv, toluene, −78 °C, 1 h) cleanly gave **17** (88%), from which **14** was obtained by application of a sequence analogous to that employed with **10**.

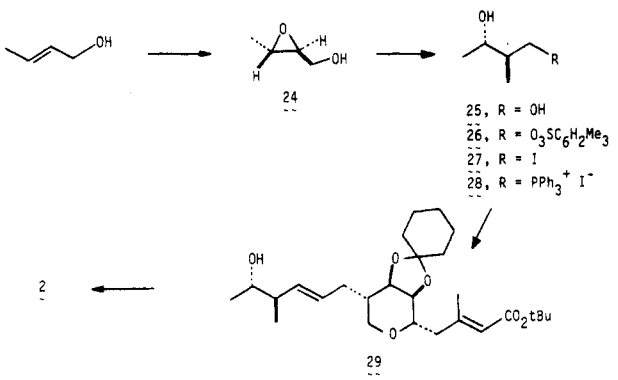
(6) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.
(7) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(8) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1.
(9) Shamma, M.; Rodriguez, H. R. *Tetrahedron* **1968**, *24*, 6583.

Attachment of the β-methylbutenoate side chain of monic acid was accomplished in 90% yield by treatment of **14** with triphenylmethanesulfenyl chloride and isopropenyl trimethylsilyl ether in the presence of zinc bromide (CH_2Cl_2, −78 °C).[10] This reaction gave **18** as the major product accompanied by the corresponding trans keto acid, which were converted to their methyl esters (CH_2N_2, ether) and separated by HPLC (μ-Porasil).



Hydroxylation of **19** (catalytic OsO_4, *N*-methylmorpholine *N*-oxide, *t*-BuOH–THF–H_2O) furnished diol **20**, which was protected as the ketal **21** (1,1-dimethoxycyclohexane, *p*-TsOH).[3d] This ketone was condensed with *tert*-butyl dimethylphosphonoacetate[11] (NaH, THF, 0 °C) to give **22** together with a small amount of its *Z* isomer (83%).[12] Selective reduction of the methyl ester of **22** was accomplished with the "ate" complex from *n*-butyllithium and diisobutylaluminum hydride[13] (THF, −78 °C), which afforded, after oxidation with pyridinium chlorochromate (CH_2Cl_2, 25 °C), aldehyde **23** in 94% yield.

The 2*S*,3*S* phosphonium salt **28** was conveniently prepared from **24**, obtained from *trans*-2-butenol in 95% enantiomeric excess and 58% yield upon epoxidation with



tert-butyl hydroperoxide in the presence of titanium tetraisopropoxide and (+)-diisopropyl L-tartrate.[14] Exposure of **24** to lithium cyanomethylcuprate[15] gave **25** and (2*R*)-3-methylbutane-1,2-diol (1:1, 92%), which were separated as their primary 2,4,6-trimethylbenzenesulfonates (trimsylates). Conversion of **26** via iodide **27** to **28** followed the route previously described for the racemic compound.[3d]

(10) We surmise that this reaction proceeded by sulfenylation of the olefin and nucleophilic attack by the silyl enol ether on an episulfonium intermediate, followed by anti elimination of the resulting trans lactone sulfide (see also: Alexander, R. P.; Paterson, I. *Tetrahedron Lett.* **1983**, *24*, 5911). Mechanistic evidence relating to this interesting process will be presented in a full paper.
(11) Fukuyama, Y.; Kirkemo, C. L.; White, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 646.
(12) Wadsworth, W. S., Jr. *Org. React. (N.Y.)* **1977**, *25*, 73.
(13) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.
(14) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.
(15) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.

A Schlosser-modified Wittig reaction[16] of **23** with **28** (2 equiv of *n*-BuLi, THF, −40 °C to 0 °C) afforded the olefin **29** (37%), from which the two protecting groups were removed (94%) by successive treatment with anhydrous trifluoroacetic acid (CH_2Cl_2, 0 °C to 25 °C, 3 h) and with aqueous trifluoroacetic acid (50%, 25 °C, 0.75 h). The resulting monic acid C (**2**, $[\alpha]^{24}_D$ −5.8°) was identical with the corresponding substance ($[\alpha]^{23}_D$ −6.7°) derived from natural monic acid A[2] by comparison of their IR and NMR spectra.

Acknowledgment. We are grateful to Dr. M. J. Soulal, Beecham Pharmaceuticals, for a sample of natural monic acid A and to Dr. G. W. J. Fleet, Oxford University, for IR and NMR spectra of **14**. Financial support was provided by the National Science Foundation (CHE-8101223) and the National Institutes of Health (AI10964).

(16) Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311.

Supplementary Material Available: Experimental spectroscopic data for **2**, **4–6**, **8–23**, and **29** (6 pages). Ordering information is given on any current masthead page.

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Additions and Corrections

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Stefano Colonna,* Stefano Banfi, Francesca Fontana, and Maurizio Sommaruga. Asymmetric Periodate Oxidation of Functionalized Sulfides Catalyzed by Bovine Serum Albumin.

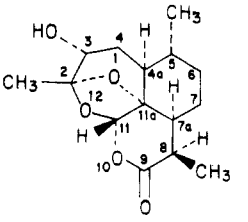
Page 770. Column 2, line 29, "catalytic" should read "stoichiometric".

Louis S. Hegedus* and Michael S. Holden. Synthesis of Carbocycles by the Interaction of Ambiphilic Reagents. Reactions of Cationic Oxyallyl–Iron(II) Complexes with η^1-Allyliron(II) Complexes and with *N*-Tosyl Enamines.

Page 3920. **Acknowledgment**: Support for this research by National Science Foundation Grant No. CHE8200522 is gratefully acknowledged.

Ai Jeng Lin,* Daniel L. Klayman, James M. Hoch, James V. Silverton, and Clifford F. George. Thermal Rearrangement and Decomposition Products of Artemisinin (Qinghaosu).

Page 4505. The correct structure of **4** should appear as follows:



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