4.97 (s, 1, H_{9b}), 7.58 (s, 1, H_5), 8.10 (s, 1, H_6), 8.66 (s, 1, H_9); mass spectrum, *m/e* 544.

Method B. From 7. A solution of adduct 7 (0.187 g, 0.5 mmol) and DEAC (0.34 g, 2 mmol) in xylene (5 mL) was refluxed under nitrogen for 90 min. After evaporation of the xylene under reduced pressure, the crude product was treated as in method A and gave adducts **8a** and **8b** in the same proportion and with identical yields.

Tetraethyl 1-Methyl-1*H*-pyrrolo[2,3-*f*]isoquinoline-2,3,4,8-tetracarboxylate (9a). Bromine (0.50 g, 3.10 mmol) was added to a suspension of **8a** (0.272 g, 0.5 mmol) in methanol (5 mL) at room temperature. The mixture became a clear solution and was stirred at room temperature for 12 h. The solvent and excess bromine were removed under reduced pressure, and the residue was triturated with aqueous sodium hydroxide (2%, 10 mL) to provide a white precipitate (0.11 g after drying, 47%). Recrystallization from diethyl ether gave an analytical sample of **9a**: mp 135–136 °C; IR (KBr) 1725, 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.25–1.70 (m, 12, 4 CH_2CH_3), 4.25–4.80 (m, 8, 4 CH_2CH_3), 4.55 (s, 3, NCH_3), 8.25 (s, 1, H_5), 9.20 (s, 1, aromatic), 9.40 (s, 1, aromatic).

Anal. Calcd for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.9; H, 5.7; N, 5.8.

Tetraethyl 1-Methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline-2,3,4,7-tetracarboxylate (9b). Bromine (0.50 g, 3.10 mmol) and **8b** (0.27 g, containing about 10% **8a**) in methanol (5 mL) were stirred at room temperature for 12 h. The solution was treated as above to give a white solid (**9b**; 0.13 g, 55% crude product contaminated with 10% **9a**). Recrystallization of this material from diethyl ether (0.104 g) and then purification by high-pressure liquid chromatography (silica gel, Waters, 10-μm packing, eluted with chloroform) gave an analytically pure sample of **9b**: mp 118–122 °C; IR (KBr) 1725, 1715 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.30–1.70 (m, 12, 4 CH_2CH_3), 4.25–4.80 (m, 11, 4 CH_2CH_3 and NCH_3), 8.17 (s, 1, H_5), 8.70 (s, 1, H_6), 10.09 (s, 1, H_9).

Anal. Calcd for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.3; H, 5.8; N, 6.2.

Endo Adduct of Ethyl 2-Methyl-2*H*-pyrrolo[3,4-*c*]-pyridine-6-carboxylate (1) with *N*-Phenylmaleimide. A solution of 0.102 g (0.5 mmol) of 1 and 0.259 g (1.5 mmol) of *N*-phenylmaleimide in 10 mL of chloroform was stirred at room temperature for 4 h. Removal of all solvent under high vacuum left a residue which was washed carefully with diethyl ether to give 0.15 g (79%) of the endo isomer: mp 135–140 °C dec; IR (KBr) 1710, 1765 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.42 (t, 3, J = 7 Hz, CH_2CH_3), 2.14 (s, 3, NCH_3), 3.90–4.05 (m, 2, α to carbonyl), 4.48 (q, 2, J = 7 Hz, CH_2CH_3), 4.65–4.85 (m, 2, bridgehead), 6.30–6.55 (m, 2, H_a and $H_{a'}$), 7.15–7.40 (m, 3, aromatic), 8.12 (s, 1, H_4), 8.75 (s, 1, H_1).

Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.8; H, 5.0; N, 11.4.

Exo Adduct of Ethyl 2-Methyl-2*H*-pyrrolo[3,4-*c*]-pyridine-6-carboxylate (1) with *N*-Phenylmaleimide. A mixture of 0.102 g (0.5 mmol) of 1, 0.174 g (1 mmol) of *N*-phenylmaleimide, and 10 mL of xylene was heated at 120 °C for 20 min. The reaction mixture was evaporated to dryness, and the residue was washed carefully with diethyl ether to give 0.13 g (68%) of exo isomer: mp 190–195 °C dec; IR (KBr) 1710, 1770 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.45 (t, 3, J = 7 Hz, CH_2CH_3), 2.01 (s, 3, NCH_3), 2.91 (s, 2, α to carbonyl), 4.48 (q, 2, J = 7 Hz, CH_2CH_3), 4.63 (s, 1, bridgehead), 4.66 (s, 1, bridgehead), 7.36 (m, 5, aromatic), 8.16 (s, 1, H_4), 8.75 (s, 1, H_1).

Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; N, 5.07; N, 11.13. Found: C, 66.7; H, 5.0; N, 11.4.

Registry No. 1, 51110-69-1; 7, 76190-36-8; **8a**, 76190-37-9; **8b**, 76206-84-3; **9a**, 76190-38-0; **9b**, 76190-39-1; **10a**, 76190-40-4; **10b**, 76248-16-3; 1-methyl-1*H*-pyrrole-3,4-dicarboxaldehyde, 51110-65-7; ethyl aminoacetate, 459-73-4; diethyl acetylenedicarboxylate, 762-21-0; *N*-phenylmaleimide, 941-69-5.

Total Synthesis of *dl*-Ancistrofuran: A Study of Cyclic Ether Formation

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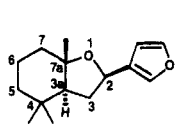
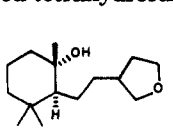
A six-step synthesis of *dl*-ancistrofuran (1) and its C-2 epimer (**31**) which involves a mercuric ion initiated diene cyclization of homogeranic acid to give lactone **16** and the phenylselenenyl chloride induced cyclization of alkylidene lactone **19** has been achieved. Also of interest are the zinc chloride assisted aldol condensation of **17** with α-(phenylthio)-γ-butyrolactone enolate anion to generate **29** and the use of ene adducts of **27** as substrates for cyclization to tetrahydrofurans **25** and **26**.

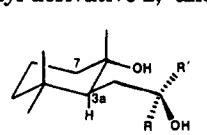
Ancistrofuran (1) is the major component in the defensive secretion of the termite *Ancistrotermes cavithorax* soldier.[1] The compound was assigned its constitution on the basis of spectroscopic analysis;[1] the relative configuration at C_{3a} and C_{7a} was deduced from NMR solvent shift studies on the reduced tetrahydrofuranyl derivative **2**,[2] and the configuration at C_2 was suggested on the basis of chemical studies carried out during the course of the first total synthesis of the molecule.[2] In that work only one of the diastereomeric pair of diols **3a** and **3b** could be cyclized upon treatment with 1 equiv of *p*-toluenesulfonyl chloride in pyridine. The product was identical with natural ancistrofuran. It was argued that "steric compression exists between the furan and ring hydrogens at [C_7] and [C_{3a}] in the conformation required for cyclization of (the monotosylate of) the isomer [**3b**]^2." Therefore, it was concluded that ancistrofuran must have the furan ring cis to the C_{7a} methyl group.



1



2



3a R = H R' = 3-furanyl

3b R' = H R = "

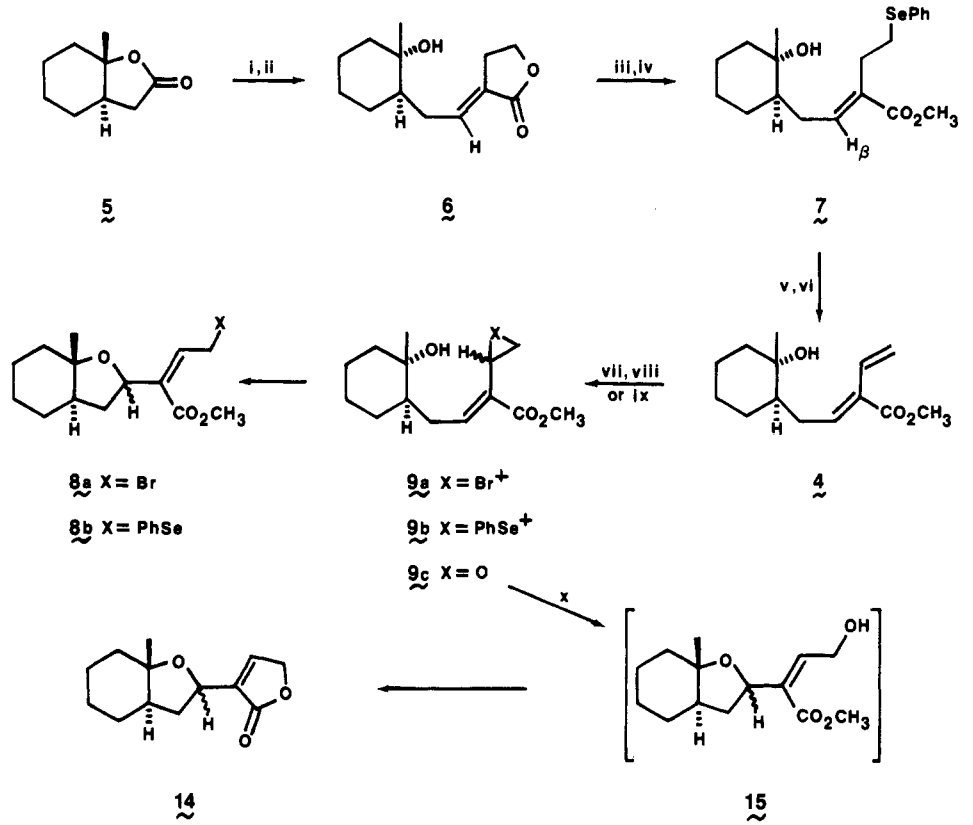
In the course of another synthetic project in our laboratory we had prepared diene **4** by the sequence outlined

(1) Baker, R.; Briner, P. H.; Evans, D. A. *J. Chem. Soc., Chem. Commun.* 1978, 410.

(2) Baker, R; Briner, P. H.; Evans, D. A. *J. Chem. Soc., Chem. Commun.* 1978, 981.

0022-3263/81/1946-1198$01.25/0

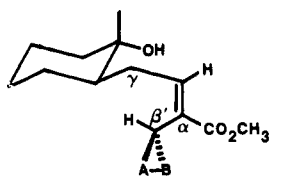
Scheme I[a]



[a] (i) DIBALH, −78 °C, $PhCH_3$; (ii) α-(γ-butyrolactonylidene)triphenylphosphorane, THF, room temperature or α-(diethylphosphono)-γ-butyrolactone, NaH, THF, room temperature; (iii) PhSeNa, THF, HMPA, 80 °C; (iv) CH_2N_2; (v) CH_3CO_3H, $CHCl_3$, room temperature; (vi) CH_2Cl_2, 50 °C; (vii) NBS, $CDCl_3$, room temperature; (viii) PhSeCl, $CDCl_3$, room temperature; (ix) *m*-CPBA, $CDCl_3$ or $PhCONHCO_3H$, THF; (x) TFA, $CDCl_3$ or SiO_2.

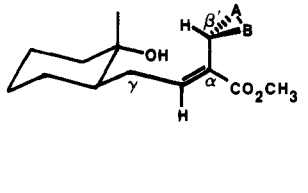
in Scheme I[3] in order to study its cyclization by electrophiles. Thus, condensation of the hemiacetal derived from the trans-fused lactone **5**[4] with α-(γ-butyrolactonylidene)triphenylphosphorane[5a] or the sodium salt of α-(diethylphosphono)-γ-butyrolactone[5b] gave olefin **6** in 64 and 69% yields, respectively. Opening of this lactone with sodium phenylselenoate under aprotic conditions[6] led to a single isomer of selenide **7** (assigned the *E* configuration on the basis of the appearance of H_β at δ 6.80 in the ^1H NMR spectrum[7a] and subsequent chemical transformations) via S_N2 cleavage of the lactone ring.[3] Peracetic acid oxidation of **7** and thermolysis of the resulting selenoxide at 50 °C provided diene **4** in 45% overall yield from **5**.

Exposure of diene ester **4** to *N*-bromosuccinimide or phenylselenenyl chloride in deuteriochloroform at room temperature led to 1:1 mixtures of diastereomeric tetrahydrofurans assigned structures **8a** and **8b** in 85 and 31% yields, respectively. These presumably arose via the intermediacy of onium ions **9a** and **9b** which must suffer attack by the internal tertiary hydroxyl group only in the S_N2' sense since no seven-membered cyclic ethers were discernible. It is noteworthy that only the *Z* olefin geometry was generated in products **8a** and **8b** (H_β δ 6.57 and 6.43; $(CH_2X)_\gamma$, δ 4.32 and ~4.2, respectively).[7b] We cannot determine whether these S_N2' cyclizations occurred in a selective syn or anti sense because the onium ions **9a** and **9b** were presumably generated as epimeric mixtures (cf. epoxide **9c** discussed below). That is, closure through epimeric rotamers (**10**/**11** and **12**/**13**) in varying amounts



10 A = X, B = $H_2C_{\gamma'}$

12 A = $H_2C_{\gamma'}$, B = X



11 A = X, B = $H_2C_{\gamma'}$

13 A = $H_2C_{\gamma'}$, B = X

would account for the formation of C_2 epimeric mixtures of **8a** and **8b**. What is clear from the analysis of molecular models is that preferential generation of the *Z* olefin in **8a** and **8b** is a result of the minimized steric interaction of H_β' with the C_γ methylene group in conformers **10**/**11** and **12**/**13** as opposed to rotamers arising from rotation about C_α–C_β' in **10**–**13** in which severe $C_\gamma H_2$–$C_\gamma' H_2X$ congestion is present.

(3) This reaction of α-alkylidene γ-lactones with $PhSe^-$ has been communicated: Hoye, T. R.; Caruso, A. J. *Tetrahedron Lett.* **1978**, 4611.
(4) Ficini, J.; Maujean, A. *Bull. Soc. Chim. Fr.* 1971, 219.
(5) (a) Fliszár, S.; Hudson, R. F.; Salvadori, G. *Helv. Chim. Acta* **1963**, *46*, 1580. (b) Howie, G. A.; Marini, P. E.; Cassaday, J. M. *J. Med. Chem.* **1974**, *17*, 840. Minami, T.; Niki, I.; Agawa, T. *J. Org. Chem.* **1974**, *39*, 3236.
(6) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365. Liotta, D.; Santiesteban, H. *Ibid.* **1977**, 4369. Scarborough, R. M., Jr.; Smith, A. B., III *Ibid.* **1977**, 4361.
(7) (a) α-[(*E*)- and (*Z*)-ethylidene]-γ-butyrolactone vinyl protons resonate at δ 6.82 and 6.36, respectively: Casey, C. P.; Brunsvold, W. R. *J. Organomet. Chem.* **1975**, *102*, 175. (b) Chemical shifts calculated from additivity coefficients in Table 3-3-1 of Jackman and Sternhell ("Applications of Nuclear Press: New York, 1969; p 185) are δ 6.54 and 6.35 for the vinyl protons in **8a** and **8b** as opposed to δ 7.08 and 6.89 for those of the corresponding *E* isomers. Moreover, the C-4 methylenes of methyl (*E*)- and (*Z*)-4-bromo-2-butenoate resonate at δ 3.94 and 4.40, respectively: Gedye, R. N.; Westaway, K. C.; Arora, P.; Bisson, R.; Khalil, H. *Can. J. Chem.* **1977**, *55*, 1218.

Treatment of diene **4** with *m*-chloroperbenzoic acid in methylene chloride at room temperature for 3 days provided the butenolides **14** again as an inseparable 3:1 mixture of epimers. When benzoylperoxycarbamic acid (BPCA) was used instead as the oxidant[8] the fragile epoxides **9c** could be isolated in 57% yield if quickly chromatographed on silica gel. Some (~5%) conversion to the butenolides **14** had already occurred during purification, and this process, which presumably proceeds via the alcohols **15**, could be hastened by the addition of a catalytic amount of trifluoroacetic acid to a deuteriochloroform solution of **9c**. The *m*-chlorobenzoic acid generated during the MCPBA oxidation was sufficiently acidic to promote the same transformation. Exposure of epoxides **9c** to a bicarbonate wash during workup of the BPCA reaction also led directly to **14**.

This facile generation of lactones **14** suggested an obvious entry into the ancistrofuran skeleton. To achieve this we required ready access to the trimethylated transfused **16**.[9] This was accomplished in 88% yield by mercuric trifluoroacetate induced cyclization of homogeranic acid and sodium borohydride reduction of the derived organomercury bromide. Reduction of **16** with DIBALH led to the crude hemiacetal **17**. It is noteworthy that this trimethylated material exists predominantly in the cyclic hemiacetal form in deuteriochloroform whereas the normethyl analogue **18** prefers the open hydroxy aldehyde tautomer. We attribute this preference in the latter case to the ring strain present in the trans-fused cyclic hemiacetal. The presence of the bulky *gem*-dimethyl groups in **17**, however, apparently disfavors the free aldehyde by a buttressing interaction. In retrospect this observation was an omen of chemistry to come, some of which will now be presented.

The Wittig reaction of **17** with α-(γ-butyrolactonylidene)triphenylphosphorane led to the (*E*)-alkylidene lactone **19** (56% from **16**). However, use of the analogous phosphonate anion led to isolation of not **19** but two tetrahydrofurans **20** resulting from internal Michael reaction. The precise stereochemistry of these two isomers was not determined. It was no surprise to learn that isolated **19** could be cyclized to a mixture of **20** by exposure to a catalytic amount of DBN in $CDCl_3$ at 60 °C (77%). In contrast, the monomethyl analogue **6** could not be induced to undergo this conjugate addition under several sets of basic or acidic conditions. The *gem*-dimethyl groups again were exhibiting a marked effect on the chemistry.

Attempts to convert lactone **19** to a diene analogous to **4** were unsuccessful. The product obtained from its reaction with sodium phenylselenoate was proved to be the cyclic ether **21** again of unknown stereochemistry (60% of a purified single diastereomer). Apparently even the mildly basic $PhSe^-$ was capable of causing an internal Michael reaction (Scheme II).

We next examined electrophile induced ether formation. Reaction of the electron-deficient olefin in alkylidene lactone **19** with *N*-bromosuccinimide in either deuteriochloroform or acetonitrile provided a 3:1 mixture of two diastereomeric bromo ethers **22** (83%).[10] These presumably arose from trans addition of Br and OH to the *E* olefin in **19**, but precise stereochemistry was not assigned. Cyclization of **19** with phenylselenenyl chloride[11] in acetonitrile or chloroform rapidly led to a 1:1 mixture of separable selenides **23** and **24** (90–97% of mixture, 67% of separated diastereomers). The stereochemistry in these was assigned by again assuming a trans addition to the olefin and by the subsequent finding that **23** ultimately led to ancistrofuran and **24** to the C_2-epimer of the natural material. Interestingly, the monomethyl alkylidene lactone **6** showed no sign of reaction with PhSeCl under the same conditions even after 3 days. Once again the *gem*-dimethyl substituents were enforcing proximity of the hydroxy and side-chain functionality, thereby leading to reaction pathways not observed in their absence.

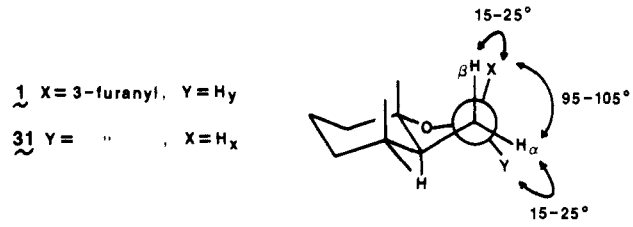


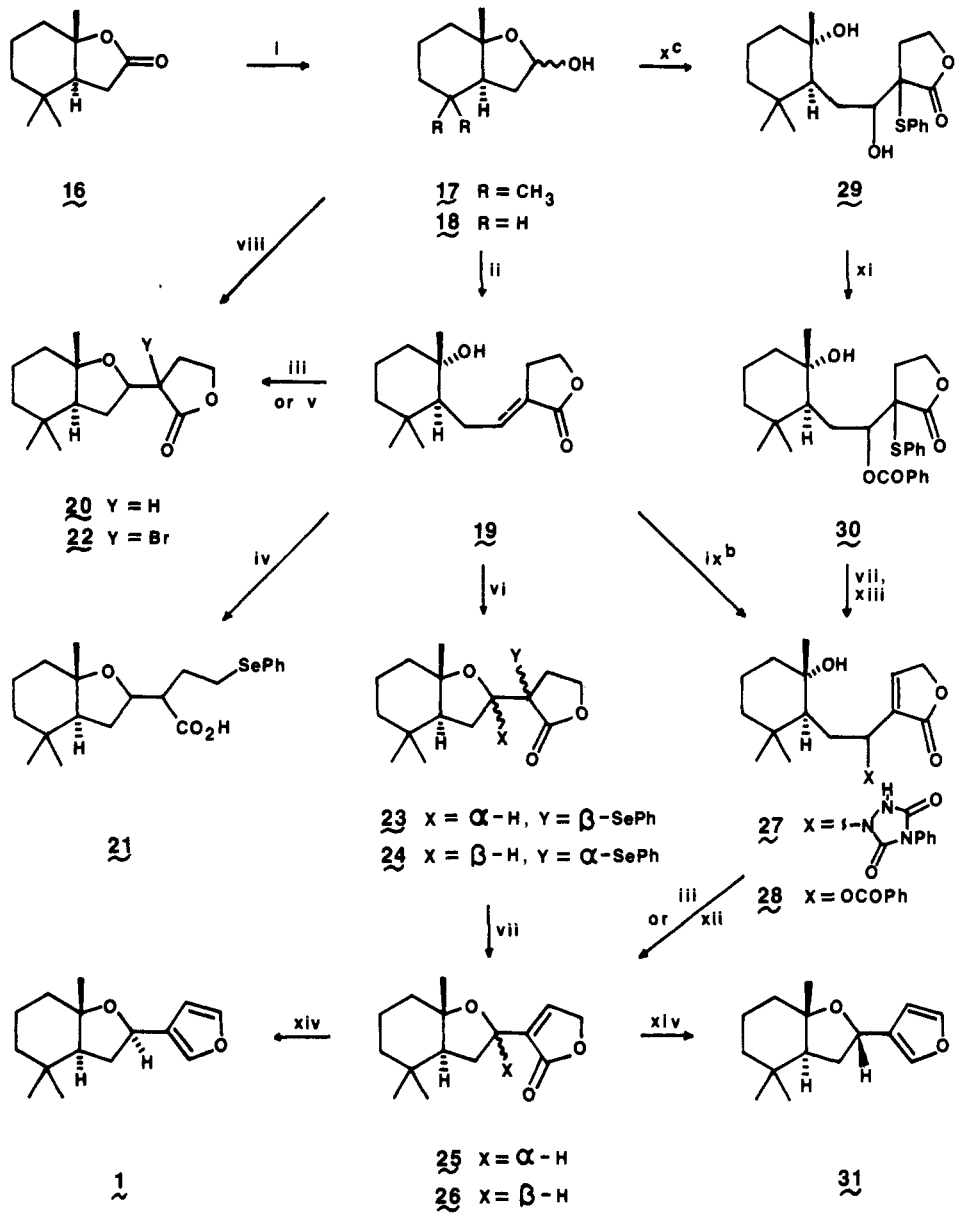
Figure 1.

Further transformation of selenides **23** and **24** involved treatment of each with 40% peracetic acid in methylene chloride at room temperature which smoothly gave the corresponding butenolides **25** and **26** (93% and 90% yield). These butenolides were also available from the triazolidinediones **27** which in turn were produced as a 2:1 mixture of diastereomers when **19** was reacted in an ene fashion with *N*-phenyltriazolinedione.[12] Attempted acetylation of the free NH in **27** (Et_3N, Ac_2O, CH_2Cl, room temperature) gave instead the cyclized ethers **25** and **26** (2:1, 54% from **19**). Thus, the heterocyclic moiety was a sufficiently good leaving group to be displayed by the tertiary alcohol under mildly basic conditions. Another substrate that underwent an intramolecular S_N2 reaction of this type was the monobenzoate ester **28**. This was prepared by a zinc chloride mediated aldol condensation of excess 2-(phenylthio)-γ-butyrolactone enolate anion[13] with the hemiacetal **17** to give **29**. The derived benzoate **30** could be oxidized (CH_3CO_3H) and eliminated (74 °C) to the butenolides **28**. In the presence of a catalytic amount of diazabicyclononane, **28** (2:1 mixture of epimers) generated the butenolides **25** and **26** (2:1) in 72% yield. These facile cyclization reactions of both diastereomeric triazolidinediones (**27**) and benzoates (**28**) stand in sharp contrast to the reported failure of furan diol **3b** to undergo a similar reaction.[2] It should also be noted that in no instance was any seven-membered cyclic ether containing product—potentially available via an S_N2' reaction—observed.

With several routes of access to the butenolides **25** and **26** available, we studied the reduction of each with diisobutylaluminum hydride (1 equiv) in order to complete the construction of furans **1** and **31**.[14] In many instances over reduction to the corresponding diols competed with consumption of all starting lactone. The best results were obtained by carrying out the reduction in methylene chloride (1.0 equiv of DIBALH, −78 °C, 1.25 h) where ancistrofuran (**1**) was isolated from **2k** in 35% yield (72% based upon consumed **25**) and 2-epiancistrofuran (**31**) was obtained in 71% yield (75% based upon unrecovered **26**).

(8) Rebek, J.; Wolf, S. F; Mossman, A. B. *J. Chem. Soc., Chem. Commun.* **1974**, 711.
(9) For an alternate preparation of **16** and a discussion of complications associated with its isomerization to the cis-fused isomer under the reaction conditions, see: Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978**, *43*, 3693.
(10) For a similar cyclization see: Tomoskozi, I.; Galambos, G.; Kovács, G.; Gruber, L. *Tetrahedron Lett.* **1979**, 1927.
(11) Nicolaou, K. C.; Lysenko, Z. *Tetrahedron Lett.* **1977**, 1257.
(12) Hoye, T. R.; Bottorff, K. J.; Caruso, A. J.; Dellaria, J. F. *J. Org. Chem.* **1980**, *45*, 4287.
(13) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1980** *45*, 3549.
(14) Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542. Minato, H.; Nagasaki, T. *Chem. Ind. (London)* **1965**, 899.

Scheme II[a]



[a] (i) DIBALH, −78 °C, $PhCH_3$; (ii) α-(γ-butyrolactonylidene)triphenylphosphorane, THF, room temperature; (iii) DBN, room temperature, $CDCl_3$; (iv) PhSeNa, THF, HMPA, 80 °C; (v) NBS, CH_3CN, room temperature; (vi) PhSeCl, CH_3CN, room temperature; (vii) CH_3CO_3H, CH_2Cl_2, room temperature; (viii) α-(diethylphosphono)-γ-butyrolactone, NaH, THF, room temperature; (ix) *N*-phenyl-1,2,4-triazoline-3,5-dione, CH_2Cl_2, room temperature; (x) α-(phenylthio)-γ-butyrolactone, LDA, −78 °C and $ZnCl_2$, Et_2O, 0 °C; (xi) PhCOCl, Et_3N, CH_2Cl_2, room temperature; (xii) Ac_2O, Et_3N, CH_2Cl_2, room temperature; (xiii) $CDCl_3$, 74 °C; (xiv) DIBALH, −78 °C, CH_2Cl_2 and then 10% H_2SO_4 quench. [b] See ref 12. [c] See ref 13.

The synthetic ancistrofuran exhibited proton NMR properties identical with those shown by the natural material.[1,2] Comparison of such data from **1** with that of 2-epiancistrofuran (**31**) supported the stereochemical assignment at C-2 originally proposed by Baker et al.[2] Thus, although the C-2 methine proton in **1** and **31** gave rise to a non-first-order signal at 80 or 100 MHz, analysis at 270 MHz indicated coupling constants of 8 and 6 Hz for that proton in **1** and 10 and <2 Hz for the signal in **31**. Figure 1 shows the range of dihedral angles between that methine and the adjacent methylene protons that can be readily attained by a Dreiding model of the rather rigid, trans-fused bicyclic ether skeleton. The coupling constants can then be assigned in **1** as $J_{y\alpha} = 8$ and $J_{y\beta} = 6$ Hz and in **31** as $J_{x\beta} = 10$ and $J_{x\alpha} < 2$ Hz.

In summary, ancistrofuran (**1**) has been synthesized in six steps and an effective overall yield of 10% from homogeranic acid via the lactone **16**, alkylidene lactone **19**, selenide **23**, and butenolide **25**.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot stage and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotomer; proton nuclear magnetic resonance spectra were obtained on a Varian HFT-80 instrument in the Fourier transform mode; mass spectra were determined on AEI MS-30 (electron impact, EI, at 70 eV) and Finnigan 4000 (chemical ionization, CI) instruments. Chromatographic purifications were performed under pressure, using a modification of the short column chromatography method[15] on silica gel H for TLC (EM 7736, type 60).

(15) Hunt, B. J.; Rigley, W. *Chem. Ind. (London)* **1967**, 1868.

(±)-*trans*-(2-Hydroxy-2-methylcyclohexane)acetaldehyde (18). To a solution of lactone **5**[4] (3.91 g, 25.4 mmol) in dry toluene (220 mL) under nitrogen at −78 °C was added a 1 M solution of diisobutylaluminum hydride (26.6 mL) in hexane over a 6-min period. The reaction mixture was stirred at −78 °C for 1 h, quenched with methanol (5 mL), and allowed to warm to room temperature. Brine addition, followed by the dropwise addition of 5% $KHSO_4$ solution, dissolved the gelatinous aluminum salts. The layers were separated and the aqueous layer was back extracted with ether (50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford crude hydroxy aldehyde **18** in quantitative yield as a viscous oil: IR (CCl_4) 3390 (s), 2930 (s), 2860 (s), 1725 (s), 1445 (s), 1375 (s), 1325 (m), 1100 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.71 (t, J = 1 Hz, CH_2CHO), 1.12 (s, CH_3); mass spectrum (EI), m/e (relative intensity) 156 (8), 141 (16), 139 (100), 121 (36), 113 (21), 95 (78), 81 (34); exact mass calcd for $C_9H_{16}O_2$ 156.1149, found 156.1137.

(±)-[1α(*E*),2β]-3-[2-(2-Hydroxy-2-methylcyclohexyl)-ethylidene]dihydro-2(3*H*)-furanone (6). A. To a solution of hydroxy aldehyde **18** (3.96 g, 25.4 mmol) in dry tetrahydrofuran (100 mL) was added α-(γ-butyrolactonylidene)triphenylphosphorane[5] (10.84 g, 31.32 mmol) as a crystalline solid. The resultant heterogenous reaction mixture was stirred under nitrogen at room temperature for 27.5 h. The mixture was then filtered, concentrated, and subjected to silica gel chromatography (1:1 hexanes–ethyl acetate) to afford olefin **6** (3.65 g, 16.29 mmol, 64.1%) as a white solid. Recrystallization from hexanes–ethyl acetate (3×) gave an analytical sample: mp 90.5–91.0 °C; IR (KBr) 3390 (s), 2980 (m), 2930 (s), 2855 (m), 1750 (s), 1682 (m), 1440 (m), 1382 (m), 1230 (s), 1200 (m), 1110 (s), 1030 (s), 910 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75 (m, CH_2CH=C), 4.32 (t, J = 7 Hz, CH_2CH_2—O), 2.84 (br t, J = 7 Hz, CH_2CH_2—O), 1.13 (s, CH_3); mass spectrum (EI), m/e (relative intensity) 224 (11), 209 (5), 206 (13), 191 (7), 181 (15), 139 (31), 125 (100), 115 (60). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.76; H, 9.05.

B. To a magnetically stirred solution of sodium hydride (67 mg, 2.80 mmol) in dry tetrahydrofuran (4 mL) under nitrogen was added α-(diethylphosphono)-γ-butyrolactone (623 mg, 2.80 mmol) as a neat liquid, and this mixture was stirred at room temperature for 15 min. Hydroxy aldehyde **18** (398 mg, 2.50 mmol) in dry tetrahydrofuran (2 mL) solution was then rapidly added, and the mixture was stirred at room temperature for 13 h. To the reaction mixture were added saturated NH_4Cl solution and ether. The layers were separated and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield lactone **6** (389 mg, 1.74 mmol, 69%).

(±)-[1α(*E*),2β]-Methyl 4-(2-Hydroxy-2-methylcyclohexyl)-2-[2-(phenylseleno)ethyl]-2-butenoate (7). To a magnetically stirred solution of diphenyl diselenide (1.270 g, 4.07 mmol) in dry tetrahydrofuran (15 mL) contained in a resealable tube was added sodium metal (179 mg, 7.78 mmol). The tube was sealed under nitrogen and the mixture was stirred at 80 °C for 22 h during which time a cream-colored precipitate appeared. The reaction mixture was allowed to cool and lactone **6** (1.578 g, 7.04 mmol) and hexamethylphosphoric triamide (HMPA) (2 mL) were added. The tube was resealed under nitrogen and heated at 80 °C for 17 h. The reaction mixture was poured into 100 mL of 10% KH_2PO_4 solution, acidified to pH 2 with 10% H_2SO_4 solution, and extracted with ethyl acetate (3×). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude product as a dark brown oil. This material was dissolved in ethyl acetate and esterified with excess diazomethane at room temperature. Unreacted diazomethane was destroyed with 10% acetic acid and the reaction mixture was washed with saturated $NaHCO_3$ solution, water, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Silica gel chromatography (3:1 hexane–ethyl acetate) afforded **7** (1.95 g, 4.93 mmol, 70%) as a light brown oil: IR (CCl_4) 3620 (w), 2930 (s), 2860 (m), 1720 (s), 1650 (m), 1585 (m), 1480 (m), 1440 (s), 1300 (m), 1250 (s), 1200 (m), 1160 (m), 980 (m), 910 (m), 720 (m), 690 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 and 7.2 (m, PhSe), 6.80 (br t, J = 7 Hz, CH=C), 3.70 (s, OCH_3), 2.82 (m, CH_2CH_2Se), 1.05 (s, CH_3); mass spectrum (EI), m/e (relative intensity) 396 (3), 381 (3), 378 (2), 239 (82), 221 (78), 189 (100); exact mass calcd for $C_{20}H_{28}O_3{}^{80}Se$ 396.1201, found 396.1180.

(±)-[1α(*E*),2β]-Methyl 2-Ethenyl-4-(2-hydroxy-2-methylcyclohexyl)-2-butenoate (4). To a solution of selenide **7** (407 mg, 1.03 mmol) in chloroform (9.5 mL) was added 40% peracetic acid (296 mg, 1.56 mmol). The mixture was stirred at room temperature for 15 min and poured into saturated $NaHCO_3$ solution (50 mL). The layers were separated and the aqueous phase was back extracted with chloroform (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and transferred to a 250-mL round-bottomed flask equipped with a reflux condenser and nitrogen inlet. Pyridine (83 μL, 1.03 mmol) was added and the resultant solution was warmed in an oil bath at 55 °C for 1.2 h. The bright yellow solution was then concentrated under reduced pressure to yield the crude product as an oil which, when subjected to silica gel chromatography (5:1 hexanes–ethyl acetate), afforded diene **4** (178 mg, 0.75 mmol, 73%) as a colorless oil: IR (CCl_4) 3600 (w), 3070 (w), 2930 (m), 2850 (w), 1720 (s), 1670 (m), 1620 (w), 1425 (m), 975 (w), 915 (w); ^1H NMR ($CDCl_3$) δ 6.74 (br t, J = 7 Hz, CH_2CH=C), 6.47 (dd, J = 18, 11 Hz, H_tH_cC=CHC), 5.55 (br d, J = 18 Hz, H_tH_cC=CHC), 5.32 (br d, J = 11 Hz, H_tH_cC=CHC), 3.74 (s, OCH_3), 2.68 (ddd, J = 15, 7, 3 Hz, CHHCH=C), 2.10 (br dd, J = 15, 7 Hz, CHHCH=C), 1.15 (s, CH_3); mass spectrum (EI), m/e (relative intensity) 238 (2), 223 (1), 220 (18), 205 (17), 161 (36), 138 (28), 128 (70), 43 (100); exact mass calcd for $C_{14}H_{22}O_3$ 238.1568, found 238.1561.

(±)-[2α(*Z*),3aβ,7aα]- and -[2α(*Z*),3aα,7aβ]-Methyl β-(2-Bromoethylidene)octahydro-7a-methyl-2-benzo[*b*]furanethanoates (8a). To a solution of diene **4** (29.1 mg, 0.122 mmol) in deuteriochloroform (350 μL) at room temperature was added crystalline *N*-bromosuccinimide (NBS 24 mg, 0.134 mmol). The reaction was monitored by NMR and appeared to be complete within 5 min during which time all of the NBS went into solution. The reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield a 3:1 ratio (NMR analysis) of bromo esters **8a** (36 mg, 0.11 mmol, 93% crude, 88% after preparative layer chromatography, SiO_2, 3:1 hexanes–ethyl acetate) as a slightly yellow oil: IR (CCl_4) 2980 (w), 2940 (s), 2865 (m), 1720 (s), 1650 (m), 1620 (w), 1460 (m), 1435 (s), 1320 (m), 1200 s), 1155 (m), 1020 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.57 and 6.52 (ddd, J = 8, 8, 2 Hz, $CHCH_2Br$, major and minor isomers), 4.75 and 4.58, (br d, J = 7 Hz, CH–O, major and minor), 4.32 (complex 8-line m, CH_2Br, major), 3.65 (s, OCH_3), 1.00 and 1.10 (s, CH_3, major and minor); mass spectrum (EI), m/e relative intensity) 303 (8), 301 (9), 271 (9), 269 (10), 189 (12), 137 (27), 110 (30), 95 (100), 81 (54), 79 (34); exact mass calcd for $C_{13}H_{18}O_3{}^{79}Br$ (M^+–CH_3) 301.0439, found 301.0461.

(±)-[2α(*Z*),3aβ,7aα]- and -[2α(*Z*),3aα,7aβ]-Methyl β-[2-(Phenylseleno)ethylidene]octahydro-7α-methyl-2-benzo-[*b*]furanethanoates (8b). To a solution of diene **4** (9.6 mg, 0.0403 mmol) in deuteriochloroform (300 μL) at room temperature in an NMR tube was added crystalline benzeneselenenyl chloride (7.8 mg, 0.0407 mmol). The reaction was monitored by NMR and appeared to be complete within 5 min, during which time the deep red color of benzeneselenenyl chloride disappeared. The reaction mixture was subjected directly to preparative layer chromatography (6:1 hexanes–ethyl acetate) to provide a 3:1 mixture (NMR analysis) of selenides **8b** (5.0 mg, 0.0127 mmol, 31%) as a colorless oil: IR (CCl_4) 3015 (m), 2980 (m), 2960 (m), 2940 (s), 2860 (m), 1720 (s), 1640 (m), 1580 (m), 1480 (m), 1455 (m), 1435 (s), 1375 (m), 1325 (m), 1220 (s), 1155 (m), 1020 (s), 850 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 and 7.23 (m, PhSe), 6.48 (br t, J = 8 Hz, CH=C), 4.67 (br d, J = 7 Hz, CH–O), 4.65–3.71 (m, CH_2Se), 3.61 (s, OCH_3), 1.01 and 0.90 (s, CH_3, major and minor isomers); mass spectrum (EI), m/e (relative intensity) 396 (1), 394 (2), 392 (1), 237 (32), 219 (38), 157 (14), 155 (9), 127 (23), 109 (35), 95 (100), 59 (14); exact mass calcd for $C_{20}H_{28}O_3{}^{78}Se$ 392.1054, found 392.1067.

(±)-(2α,3aα,7aβ)- and -(2α,3aβ,7aα)-Octahydro-7a-methyl-2-(4-oxa-5-oxocyclopentenyl)benzo[*b*]furans (14). A. To a magnetically stirred solution of diene **4** (12.1 mg, 0.051 mmol) in dichloromethane (0.5 mL) was added 85% *m*-chloroperbenzoic acid (9.2 mg, 0.053 mmol). This was followed by the addition of another portion of dichloromethane (0.5 mL). The solution was tightly capped and stirred at room temperature for 72 h. The reaction mixture was then diluted with dichloromethane (10 mL),

washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford butenolide **14** in quantitative crude yield as a 3:1 mixture of diastereomers: IR (CCl_4) 2940 (s), 2860 (m), 1765 (s), 1670 (m), 1450 (m), 1370 (w), 1340 (m), 1200 (m), 1150 (m), 1070 (s), 1005 (s), 900 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (br t, J = 1.5 Hz, $CHCH_2$–O), 4.76 (m, 1 H, CH–O), 4.76 (d, J = 1.5 Hz, CH_2O), 1.02 and 1.01 (s, CH_3, major and minor isomers); mass spectrum (EI), m/e (relative intensity) 222 (1), 208 (12), 207 (100), 172 (18), 161 (12), 95 (44), 81 (40), 67 (39), 43 (72); exact mass calcd for $C_{13}H_{18}O_3$ 222.1255, found 222.1269.

B. To a solution of diene **4** (28.7 mg, 0.121 mmol) in chloroform (2 mL) was added solid benzoylperoxycarbamic acid (BPCA; 34 mg, 0.188 mmol) followed by the addition of another portion of chloroform (1.5 mL). The reaction mixture was stirred at room temperature for 5 days, filtered, concentrated under reduced pressure, and subjected to preparative layer chromatography (1:1 hexanes–ethyl acetate) to afford a 3:1 ratio (NMR analysis) of epoxy esters **9c** (17.5 mg, 0.0689 mmol, 57%) contaminated by a few percent of the butenolides **14** as a colorless oil: IR (CCl_4) 3550 (w), 2950 (s), 2890 (m), 1730 (s), 1685 (m), 1460 (m), 1220 (m), 1160 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.96 ddd, J = 8, 8, 3 Hz, CH=C), 3.74 (s, OCH_3), 3.58 (m, $H_cH_t\overline{CCHRO}$), 2.97 (dd, J = 6, 4.5 Hz, $H_cH_t\overline{CCHRO}$, major) and 2.86 (dd, J = 6, 3.5 Hz, $H_cH_t\overline{CCHRO}$, major), 2.5–2.9 (m, $H_2\overline{CCHRO}$, minor), 1.15 and 1.25 (s, CH_3, major and minor isomers); mass spectrum (EI), m/e (relative intensity) 245 (1), 239 (3), 236 (2), 222 (15), 189 (16), 161 (24), 146 (33), 95 (74), 81 (49), 67 (34), 43 (100); exact mass calcd for $C_{13}H_{19}O_4$ ($M^+ - CH_3$) 239.1283, found 239.1290.

To a solution of epoxides **9c** (12.3 mg, 0.0484 mmol) in deuteriochloroform (300–350 μL) at room temperature in an NMR tube was added trifluoroacetic acid-*d* (1 μL, 0.0129 mmol). The reaction was monitored by NMR and appeared to be complete after 1 h. The solution was then concentrated under reduced pressure and subjected to preparative layer chromatography (1:1 hexanes–ethyl acetate) to afford butenolides **14** (9.5 mg, 0.0428 mmol, 88%) as a mixture of diastereomers identical with that obtained from *m*-chloroperbenzoic acid oxidation of diene **4**.

(±)-[1α(*E*),2β]-3-[2-(2-Hydroxy-2,6,6-trimethylcyclohexyl)ethylidene]dihydro-2(3*H*)-furanone (19). Lactone **16** (2.08 g, 11.4 mmol) was reduced in toluene (40 mL) with DIBALH (1.1 equiv) by a procedure identical with that used to prepare **18**. Crude hemiacetal **17** (1.88 g, 10.2 mmol, 89%) was obtained as a viscous oil, solutions of which contained detectable quantities of free aldehyde: IR (CCl_4) 3595 (w), 3365 (s), 2935 (s), 2860 (m), 1725 (m), 1460 (s), 1375 (m), 1240 (m), 1150 (m), 1080 (m), 965 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.74 (0.2 H, t, J = 3 Hz, CHO, free aldehyde), 5.5 (0.8 H, br t, J = 7 Hz, CHO, lactol), 1.28, 1.15, 1.07, 0.95, 0.92, 0.87, 0.82 (s, CH_3's); mass spectrum (EI), m/e (relative intensity) 169 (59, $M^+ - CH_3$), 166 (7), 151 (24), 141 (22), 95 (60), 82 (73), 81 (57), 71 (100), 43 (72).

The hemiacetal **17** (1.88 g, 10.2 mmol) was converted to lactone **19** with α-(γ-butyrolactonylidene)triphenylphosphorane by the procedure outlined for the preparation of **6**. Compound **19** was obtained as a white solid in 56% yield after short-column chromatography (1:1 hexanes–ethyl acetate). Recrystallization (3×, hexanes–ethyl acetate) afforded an analytical sample: mp 104–105 °C; IR (KBr) 3460 (m), 2930 (m), 1740 (s), 1665 (m), 1430 (w), 1380 (w), 1225 (s), 1200 (m), 1272 (m), 1085 (m), 1035 (s), 955 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (tt, J = 7, 3 Hz, CH=C), 4.34 (t, J = 7 Hz, CH_2—O), 2.88 (br t, J = 7 Hz, CH_2CH_2—O), 2.30 (m, CH_2CH=C), 1.17, 0.94, and 0.86 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 252 (3), 237 (3), 234 (4), 138 (16), 126 (11), 125 (100), 115 (54), 81 (14), 43 (21). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.05; H, 9.85.

(±)-*trans*-Octahydro-4,4,7a-trimethyl-2-(3-oxa-2-oxocyclopentyl)benzo[*b*]furan (20). Reaction of hemiacetal **17** (463 mg, 2.52 mmol) with the sodium salt of α-(diethylphosphono)-γ-butyrolactone in THF was performed by the procedure described for the preparation of **6** except that the reaction was quenched after 1 h. A 2.5:1 ratio of two diastereomeric lactones was obtained in 53% yield. Separation by preparative gas chromatography (10% SE-30, 190 °C) gave each pure diastereomer. Major isomer: IR (CCl_4) 2950 (s), 2870 (s), 1780 (s), 1460 (m), 1380 (s), 1160 (s), 1030 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0–4.3 (m, 3 H, CH_2O, CHOC), 1.1–2.7 (m, 11 H), 1.12, 0.93, 0.84 (3 s, CH_3's); mass spectrum (CI, NH_3, pos), m/e 270 ($M + NH_4^+$), 253 ($M + H^+$), 237, 209 ($M + H^+ - CO_2$), 167 ($M + H^+ - C_4H_6O_2$); mass spectrum (CI, NH_3, neg), m/e 269, 251 ($M - H^+$), 207 ($M - H^+ - CO_2$). Minor isomer: IR (CCl_4) 2950 (s), 2870 (s), 1775 (s), 1455 (m), 1375 (m), 1160 (m), 1030 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0–4.4 (m, 3 H, CH_2O, CHOC), 2.88 (ddd, J = 9, 9, 4 Hz, 1 H), 1.1–2.4 (m, 10 H), 1.14, 0.99, 0.83 (3 s, CH_3's); mass spectrum, (CI, NH_3, pos), m/e 270 ($M + NH_4^+$), 253 ($M + H^+$), 237; mass spectrum (CI, NH_3, neg), m/e 269, 251 ($M - H^+$).

(±)-*trans*-β-[2-(Phenylseleno)ethyl]octahydro-4,4,7a-trimethylbenzo[*b*]furanacetic Acid (21). Lactone **19** (454 mg, 1.80 mmol) was subjected to the conditions reported above for the conversion of **6** to **7** except that 1 N HCl was used to acidify the reaction mixture. Purification by short-column chromatography on SiO_2 (2:1 hexanes–ethyl acetate) afforded **21** (510 mg, 1.25 mmol, 69%) as a mixture of two diastereomers. Careful screening of chromatographic fractions allowed isolation of a single isomer as a colorless oil: IR (CCl_4) 3050 (w), 2980 (m), 2940 (s), 2850 (m), 1725 (w), 1705 (s), 1540 (s), 1480 (m), 1450 (m), 1430 (m), 1370 (m), 1240 (m), 1100 (m), 980 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 and 7.22 (m, PhSe), 4.15 (br t, J = 7 Hz, CH–O), 2.90 (br m, CH_2Se), 1.10, 0.81, 0.81 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 412 (1), 410 (6), 408 (3), 253 (13), 167 (22), 153 (20), 148 (99), 129 (40), 123 (37), 115 (41), 85 (34), 81 (24), 69 (75), 57 (100), 43 (54); exact mass calcd for $C_{21}H_{30}O_3{}^{80}Se$ 410.1360, found 410.1390. This sample was treated with excess ethereal diazomethane and further characterized as its methyl ester: IR (thin film) 3080 (w), 2960 (s), 2880 (m), 1740 (s), 1580 (m), 1480 (m), 1460 (m), 1440 (m), 1370 (m), 1250 (m), 1200 (m), 1150 (m), 1020 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 and 7.23 (m, PhSe), 4.15 (ddd, J = 7, 7, 3 Hz, CH–O), 3.65 (s, OCH_3), 2.75 (m, CH_2Se), 1.06, 0.89, and 0.78 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 426 (3), 424 (11), 422 (5), 267 (68), 235 (12), 184 (19), 167 (46), 149 (35), 129 (85), 123 (99), 101 (51), 95 (33), 69 (100), 59 (12); exact mass calcd for $C_{22}H_{32}O_3{}^{80}Se$ 424.1516, found 424.1490.

(±)-*trans*-2-(1-Bromo-3-oxa-2-oxocyclopentyl)octahydro-4,4,7a-trimethylbenzo[*b*]furan (22). To a magnetically stirred solution of unsaturated lactone **19** (362 mg, 1.43 mmol) in dry acetonitrile (2.5 mL) at room temperature was added crystalline *N*-bromosuccinimide (NBS, 280 mg, 1.57 mmol). The solution was stirred at room temperature for 2 h, concentrated under reduced pressure, and subjected to silica gel chromatography (9:1 hexanes–ethyl acetate) to afford bromo lactone **22** (392 mg, 1.18 mmol, 83%) as a 3:1 mixture of diastereomers. Careful screening of the chromatographic fractions allowed isolation of pure samples of each of the two diastereomers. The major (more polar) crystalline isomer was recrystallized from hexanes (2×) to provide an analytical sample, mp 125–127 °C. Major diastereomer: IR (thin film) 3000 (w), 2975 (w), 2970 (s), 2860 (m), 1780 (s), 1455 (m), 1365 (m), 1210 (m), 1170 (m), 1150 (m), 1025 (m), 995 (m), 950 (m), 910 (m), 870 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25–4.50 (m, 3H, CH_2O, CHOC), 2.86 (ddd, J = 8, 9, 14 Hz, BrCCHH), 2.39 (ddd, J = 3, 3, 14, BrCCHH), 1.19, 1.00, 0.88, (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 332 (1), 330 (1), 317 (97), 315 (100), 289 (61), 287 (64), 251 (49), 167 (18), 165 (7), 151 (21), 123 (70), 109 (22), 85 (14), 81 (21), 69 (92). Anal. Calcd for $C_{15}H_{23}BrO_3$: C, 54.39; H, 7.00; Br, 24.12. Found: C, 54.42; H, 6.97; Br, 24.21. Minor diastereomer: IR (thin film) 3000 (w), 2940 (s), 2860 (m), 1785 (s), 1460 (m), 1375 (m), 1210 (m), 1170 (s), 1025 (m), 995 (m), 950 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.3–4.5 (m, 3 H, CH_2O, CHOC), 2.81 (ddd, J = 8, 9, 14 Hz, BrCHH), 2.43 (ddd, J = 3, 3, 14 Hz, BrCHH), 1.16, 0.96, 0.86 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 332 (2), 330 (2), 317 (96), 315 (100), 251 (15), 167 (33), 165 (4), 163 (2), 123 (67), 109 (20), 95 (18), 81 (16), 69 (77); exact mass calcd for $C_{15}H_{23}{}^{79}BrO_3$ 330.0831, found 330.0822.

(±)-[2*R*-[2α(*R),3aβ,7aα]]- and -[2*R*-[2α(*R**),3aα,7aβ]]-[1-(Phenylseleno)-3-oxa-2-oxocyclopentyl]octahydro-4,4,7a-trimethylbenzo[*b*]furans (23 and 24).** To a magnetically stirred solution of lactone **19** (416 mg, 1.65 mmol) in dry acetonitrile (29 mL) at room temperature was added crystalline benzeneselenenyl chloride (347 mg, 1.81 mmol). This solution was stirred at room temperature over a 40-min period during which time the deep red color of the benzeneselenenyl chloride disap-

peared. The reaction mixture was then diluted with ether, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield the crude product as a gold oil. Careful silica gel chromatography (9:1 hexanes–ethyl acetate) afforded pure selenides **23** (230 mg, 0.565 mmol, 34%) and **24** (220 mg, 0.548 mmol, 33%).

23: IR (thin film) 3125 (w), 2930 (s), 2850 (m), 1765 (s), 1640 (w), 1560 (w), 1440 (s), 1370 (s), 1200 (m), 1170 (s), 1145 (m), 1020 (m), 985 (m), 900 (m), 730 (m), 680 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6 and 7.3 (m, SePh), 4.0–4.4 (m, 3 H, CH_2O, CHOC), 2.77 (ddd, J = 9, 9, 14 Hz, PhSeCC**H**H), 1.1–2.2 (m, 10 H), 1.10, 0.96, 0.86 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 410 (1), 408 (2), 406 (1), 242 (99), 161 (100), 123 (78), 95 (18), 85 (21), 69 (90), 57 (85).

24: IR (thin film) 2940 (s), 2850 (m), 1770 (s), 1580 (w), 1450 (s), 1370 (m), 1200 (m), 1170 (s), 1030 (s), 985 (m), 860 (w), 735 (m), 680 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6, 7.3 (m, SePh), 4.0–4.4 (m, 3 H, CH_2O, CHOC), 2.87 (ddd, J = 9, 9, 14 Hz, PhSeCC**H**H), 1.1–2.35 (m, 10 H), 1.16, 1.01, 0.87 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 410 (1), 408 (1), 401 (1), 244 (99), 167 (13), 161 (100), 123 (58), 95 (10), 81 (15), 69 (54); exact mass calcd for $C_{21}H_{28}O_3{}^{80}Se$ 409.1203, found 408.1225.

(±)-(2α,3aβ,7aα)- and -(2α,3aα,7aβ)-Octahydro-4,4,7a-trimethyl-2-(4-oxa-5-oxocyclopentenyl)benzo[*b*]furans (25 and 26). To a magnetically stirred solution of selenide **23** (230 mg, 0.564 mmol) or **24** (223 mg, 0.547 mmol) in dichloromethane (15 mL) at room temperature was added 40% peracetic acid (214 mg, 1.13 mmol) in two portions of equal volume. Upon the addition of the first equivalent of oxidant the solution turned bright yellow and was rendered colorless again by the addition of the second equivalent. The reaction mixture was stirred for 1 h at room temperature, diluted with dichloromethane, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield butenolides **25** (131 mg, 0.524 mmol, 93%) and **26** (214 mg, 0.496 mmol, 91%) as white crystalline solids. One recrystallization from hexanes–ethyl acetate and sublimation (0.5 mmHg, 80 °C) provided analytical samples, mp 120–121 °C (**25**) and 133–135 °C (**26**).

25: IR (CCl_4) 3000 (m), 2945 (s), 2875 (m), 1760 (s), 1660 (w), 1455 (m), 1370 (m), 1340 (m), 1200 (m), 1070 (s), 1050 (m), 990 (m), 925 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (br t, J = 2 Hz, C**H**CH_2–O), 4.74 (br d, J = 2 Hz, CH_2–O), 4.66 (m, CHOC), 1.06, 0.93, 0.78 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 250 (1), 235 (100), 207 (33), 179 (28), 167 (12), 123 (12), 109 (10), 95 (11), 81 (12), 69 (44). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.17; H, 8.66.

26: IR (CCl_4) 3000 (m), 2940 (s), 2875 (m), 1765 (s), 1655 (w), 1455 (m), 1380 (m), 1340 (m), 1205 (m), 1155 (m), 1070 (s), 1055 (s), 1020 (m), 990 (s), cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (br t, J = 2 Hz, C**H**CH_2O), 4.79 (m, 3 H, CHOC and CH_2O), 1.16, 0.90, 0.86 (3 s, CH_3's); mass spectrum (CI, NH_3, pos ion), 268 ($M + NH_4^+$), 251 ($M + H^+$), 233 ($M + H^+ - H_2O$); mass spectrum (CI, NH_3, neg ion), 266 ($M + NH_2^-$), 249 ($M - H^+$). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.78.

***dl*-Ancistrofuran (1) and *dl*-2-Epiancistrofuran (31).** To a magnetically stirred solution of butenolide **25** (82 mg, 0.328 mmol) or **26** (127 mg, 0.508 mmol) in dichloromethane (1.3 mL or 2 mL) under nitrogen at −78 °C was added a 1 M solution of diisobutylaluminum hydride (350 μL or 533 μL) in hexane protionwise over a 30-min period. The resulting solution was stirred for 40 min −78 °C and then quenched with 10% H_2SO_4 solution (2 mL). The layers were separated, and the aqueous layer was back extracted with dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude product. Preparative layer chromatography (9:1 hexanes–ethyl acetate) gave recovered starting butenolide **25** (30 mg, 0.12 mmol, 37%) and ancistrofuran (**1**, 27 mg, 0.115 mmol, 35%) or recovered **26** (5 mg, 0.020 mmol, 4%) and 2-epiancisrofuran (**31**, 84 mg, 0.359 mmol, 71%) as a colorless oil. Analytical samples of **1** and **31** were obtained by preparative gas chromatography (10% SE-30, 190 °C).

1: IR (CCl_4) 3010 (m), 2950 (s), 2875 (s), 1500 (m), 1480 (s), 1375 (m), 1160 (s), 1135 (m), 1090 (m), 1050 (m), 1030 (s), 990 (s), 910 (s), 875 (s), 845 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.37 (br s, 2 furan α-H's), 6.39 (br s, furan β-H), 4.92 (dd, J = 6, 8 Hz, 3-furanyl-CHOC), 2.20 (ddd, J = 11, 6, 6 Hz, C$H_\beta H_\alpha$C(H)(O)-3-furanyl), 1.1–2.0 (m, 8 H), 1.14, 0.99, 0.87 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 234 (24), 219 (76), 191 (27), 138 (55), 123 (56), 109 (46), 95 (54), 82 (100), 69 (68), 43 (60). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.88; H, 9.33.

31: IR (CCl_4) 3000 (m), 2950 (s), 2880 (m), 1500 (m), 1475 (m), 1460 (s), 1445 (m), 1390 (m), 1380 (s), 1325 (m), 1210 (m), 1160 (s), 1100 (s), 1085 (s), 1025 (s), 990 (s), 955 (m), 930 (m), 875 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.37 (br s, 2 furan α-H's), 6.34 (br s, furan β-H), 504 (br d, J = 10 Hz, 3-furanyl-C**H**OC), 2.16 (ddd, J = 11, 11, 10 Hz, $CH_\alpha H_\beta$C(H)(O)-3-furanyl), 1.92 (br d, J = 11 Hz, C**H**(C)(C)(C)), 1.73 (m, 2 H), 1.3–1.6 (m, 5 H), 1.19, 0.93, 0.87 (3 s, CH_3's); mass spectrum (EI), m/e (relative intensity) 234 (31), 219 (34), 191 (12), 138 (100), 123 (63), 109 (32), 95 (92), 82 (94), 69 (59). Anal. Calcd for $C_{15}H_{22}O_3$: C, 76.88; H, 9.46. Found: C, 77.01; H, 9.17.

Butenolides 25 and 26 via Diols 29 and Benzoate Esters 30 and 28. To a magnetically stirred solution of α-(phenylthio)-γ-butyrolactone (3.49 g, 18.0 mmol) in dry tetrahydrofuran (20 mL) at −78 °C under nitrogen was added lithium diisopropylamide (1 M, 18 mL) in tetrahydrofuran. The mixture was stirred at −78 °C for 1 h and a 0.69 M solution of freshly fused zinc chloride in ether (26.1 mL) was added via syringe. The mixture was allowed to warm to 0 °C over a 30-min period and a solution of hemiacetal **17** (1.03 g, 5.63 mmol) in dry tetrahydrofuran (6 mL) was added. The reaction mixture was diluted with ether, washed with 10% H_2SO_4 solution, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield the crude product as a gold oil. Silica gel chromatography (3:1 hexanes–ethyl acetate) afforded diol **29** (1.34 g, 3.54 mmol, 63%) as a mixture of diastereomers: IR ($CHCl_3$) 3595 (w), 3380 (s), 2940 (s), 1760 (s), 1580 (w), 1460 (m), 1375 (m), 1170 (s), 1050 (m), 1025 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.6 (m, PhS), 3.5–4.5 (m, CC**H**O**H**, CH_2O), 2.83 (br ddd, J = 9, 9, 13 Hz, CH_cH$_t$SPh), 1.44, 1.21, 1.04, 0.82, 0.77 (s, CH_3's); mass spectrum (CI, NH_3, pos ion), 378 ($M + NH_4^+ - H_2O$), 361 ($M + H^+ - H_2O$), 343 ($M + H^+ - H_2O$), 270 ($M + H^+ - PhS$), 212; mass spectrum (CI, NH_3, neg ion), 378 ($M + e^-$), 268, 193, 183.

To a solution of diol **29** (106 mg, 0.279 mmol) in dichloromethane (0.56 mL) was added triethylamine (56 mg, 0.558 mmol) and benzoyl chloride (43 mg, 0.306 mmol), and the mixture was stirred at room temperature for 120 h. The reaction mixture was diluted with ether, washed with 10% H_2SO_4 solution, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), concentrated under reduced pressure, $NH_4^+ - H_2O$), subjected to silica gel chromatography to afford a mixture of two diasteromeric benzoate esters **30** (62 mg, 0.129 mmol, 46%): IR (CCl_4) 3600 (m), 3500 (m), 3070 (m), 2935 (s), 2870 (m), 1780 (s), 1725 (s), 1600 (m), 1460 (s), 1380 (s), 1260 (s), 1170 (s), 1100 (s), 1025 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–8.1 (m, SPh, OCOPh), 5.82 (m, C**H**OCOPh), 3.9–4.4 (m, CH_2O), 2.94 (ddd, J = 9, 9, 13 Hz, CH_cH$_t$SPh), 1.17, 1.10, 1.01, 0.95, 0.77 (s, CH_3's); mass spectrum (CI, NH_3, pos ion), 500 ($M + NH_4^+$), 482 ($M + NH_4^+ - H_2O$), 465, 391, 378, 374, 270, 252, 235.

To a solution of benzoate ester **30** (62 mg, 0.129 mmol) in dichloromethane (1 mL) was added 40% peracetic acid (27 mg, 0.141 mmol). The reaction mixture was stirred at room temperature for 20 min, diluted with dichloromethane, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resultant mixture of sulfoxides was dissolved in deuteriochloroform and warmed in an oil bath at 74 °C. The elimination reaction was monitored by NMR and appeared to be complete after 15 min. The reaction mixture was subjected to preparative layer chromatography (1:1 hexanes–ethyl acetate) to afford butenolide **28** (34 mg, 0.091 mmol, 71%) as a colorless oil: IR (CCl_4) 3600 (w), 3500 (w), 2940 (s), 2870 (s), 1770 (s), 1725 (s), 1600 (w), 1450 (m) 1385 (w), 1270 (s), 1100 (m), 1060 (m) cm^{-1}; ^1H NMR ($CDCl_3$) 8.07 (ddd, J = 8, 2 Hz, 2 H, *o*-ArH), 7.37 (m, 4 H, *m,p*-ArH, C=CH), 6.0. (br t, J = 7 Hz, CHO), 4.82 (br s, CH_2O), 1.23, 1.00, 0.85 (3 s, CH_3's); mass spectrum (CI, NH_3, pos ion), 390 ($M + NH_4^+$), 373, 372, 268, 252.

To a solution of butenolide **2**, (3.1 mg, 0.0083 mmol) in benzene-d_6 (300 μL) was added neat diazabicyclononene (0.5 mg, 0.0042 mmol) and the mixture was allowed to stand at room temperature. The reaction was monitored by NMR and appeared to be complete after 72 h. The reaction mixture was diluted with

ether, washed with 10% H_2SO_4 solution, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield a 2:1 mixture of butenolides **26** and **25** (1.5 mg, 0.006 mmol, 72% crude).

Butenolides 25 and 26 via Triazolidinediones 27. To a solution of ene adducts **27**[12] (84 mg, 0.198 mmol) in dichloromethane (0.8 mL) was added triethylamine (40 mg, 0.396 mmol) and acetic anhydride (40 mg, 0.396 mmol). The resultant bright yellow solution was stirred at room temperature for 6 h, diluted with ether, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product when subjected to preparative layer chromatography (1:1 hexanes–ethyl acetate) afforded a 2:1 mixture of butenolides **25** and **26** (29 mg, 0.116 mmol, 59%).

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Registry No. 1, 70003-96-2; 4, 76248-72-1; 5, 76215-55-9; 6, 76248-73-2; 7, 76248-74-3; 8a (isomer 1), 76215-56-0; 8a (isomer 2), 76215-57-1; 8b (isomer 1), 76215-58-2; 8b (isomer 2), 76215-59-3; 9c (isomer 1), 76215-60-6; 9c (isomer 2), 76248-75-4; 16, 71075-17-7; 17, 76215-61-7; 18, 76215-62-8; 19, 76248-76-5; 20, 76215-63-9; 21, 76215-64-0; 21 methyl ester, 76215-65-1; 22, 76215-66-2; 23, 76215-67-3; 24, 76232-17-2; 25, 76215-68-4; 26, 76215-69-5; 27 (isomer 1), 74561-77-6; 27 (isomer 2), 74542-30-6; 28 (isomer 1), 76215-70-8; 28 (isomer 2), 76248-77-6; 29, 76232-18-3; 30, 76215-71-9; 31, 76248-78-7; α-(γ-butyrolactonylidene)triphenylphosphorane, 34932-07-5; α-(diethylphosphono)-γ-butyrolactone, 2907-85-9; diphenyl diselenide, 1666-13-3; benzeneselenenyl chloride, 5707-04-0; 14 (isomer 1), 76215-72-0; 14 (isomer 2), 76215-73-1; α-(phenylthio)-γ-butyrolactone, 35998-30-2.

Notes

2,4-Dinitrophenyl Dihydrogen Phosphate: A New Synthesis of Its Mono-2,6-lutidinium Salt

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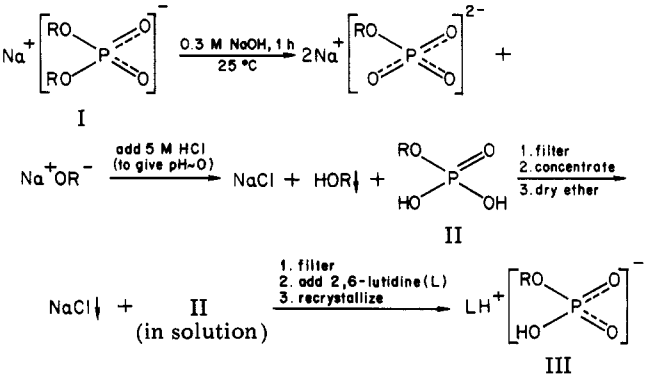
2,4-Dinitrophenyl phosphate[1] (2,4-DNPP) has been the focus of attention in both nonenzymatic[2-14] and enzymatic[15-20] studies of phosphate esters, the latter studies relating in particular to *E. coli* alkaline phosphatase. In consequence there has been active interest in suitable methods for its preparation. Of the several methods reported,[2-7] not all are satisfactory, as has been described.[4,6,8]

Scheme I



R = 2,4-dinitrophenyl

Two well worked out procedures[4,6] are relatively time consuming.

In connection with our studies on phosphate ester hydrolysis we have had need for 2,4-DNPP and for this purpose have developed a simple preparative procedure which we believe will be of general use. The method starts from the easily prepared[10] bis(2,4-dinitrophenyl) phosphate[21] and is based on the observation that in highly alkaline aqueous solution the diester hydrolyzes much more rapidly than the monoester, with a rate difference of about 80-fold at pH 13.5 and 25 °C. For the latter conditions we allow the diester to hydrolyze for ~6 half-lives ($k = 1.2 \times 10^{-3}$ s^{-1}; $6t_{1/2} = 62$ min); this relatively rapid hydrolysis is then quenched by addition of acid. Separation of the monoester from the other components is readily achieved. The overall procedure is summarized by Scheme I; details are in the Experimental Section.

Experimental Section

The method of Bunton and Farber[10] is used to prepare bis(2,4-dinitrophenyl) phosphate as the pyridinium salt (yield ~ 75%). The pyridinium ion is exchanged for Na^+ with use of cation-exchange resin (Dowex 50W X8) in the Na^+ form. For

(1) A complete name for the free acid is 2,4-dinitrophenyl dihydrogen phosphate; the term "2,4-dinitrophenyl phosphate" is commonly used, as here, to include the free acid as well as the monoanion and dianion.
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(21) The free acid is more properly called bis(2,4-dinitrophenyl) hydrogen phosphate.

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