Stereocontrolled Synthesis of (±)-Asperlin and Related Stereoisomers Using Organotitanium Reagent

Hiroaki HIRAOKA, Kyoji FURUTA, Nobuo IKEDA, and Hisashi YAMAMOTO*
Department of Applied Chemistry, Nagoya University, Chikusa, Nagoya 464
(Received December 26, 1983)

The naturally occurring antibiotics asperlin and related fungal metabolites containing a 5,6-dihydro-2-pyrone moiety have been synthesized stereoselectively. The propargyltitanium reagent derived from 1-trimethylsilyl-3-(tetrahydropyranyloxy)propyne condensed with crotonaldehyde affords the corresponding *erythro* alcohol as the major product, which is converted to (±)-asperlin and the related three stereoisomers in seven steps.

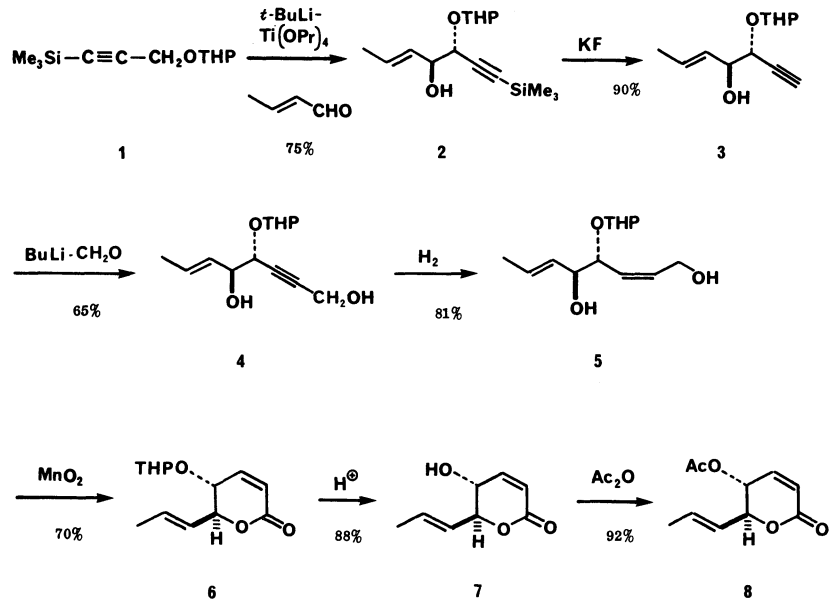
The recent discovery of the regio- and stereoselective synthesis of β-acetylenic alcohols[1] using titanium reagents[2] has substantially simplified the task of stereoselective construction of 3-alkene-1,2-diols and the related structures. We now report the use of this process as a key step in a simple, stereoselective synthesis of (±)-asperlin and related fungal metabolites containing a 5,6-dihydro-2-pyrone moiety, isolated from growing cultures of *Aspergillus nidulans*.[3]

The acetylenic tetrahydropyranyl ether **1** was prepared from propargyl alcohol by reaction with 3,4-dihydro-2*H*-pyran in ether containing a catalytic amount of *p*-toluenesulfonic acid (94%), and then with butyllithium–chlorotrimethylsilane in ether at ambient temperature for 1 h (98%). Successive treatment of acetylene **1** at −78 °C with *t*-butyllithium, titanium tetraisopropoxide, and finally crotonaldehyde effected smooth, stereoselective alkylation to the alcohol **2** in 75% yield (*erythro*: *threo*=95:5). The similar high degree of stereoselectivity has been found previously when the carbon α to acetylene is functionalized, for example, the tetrahydropyranyl ether of propargyl alcohol.[1,2] Exposure of the resulting trimethylsilylacetylene to potassium fluoride in methanol at room temperature for an overnight produced **3** in 90% yield.

The construction of the structure of δ-lactone was carried out by three steps. The acetylene **3** was converted to the dilithio derivative by reaction with butyllithium in dry tetrahydrofuran and then allowed to react with excess paraformaldehyde at room temperature. The resulting propargylic alcohol **4** was reduced with hydrogen using Pd–$CaCO_3$ as catalyst in benzene to afford the (*Z*)-allylic alcohol **5** (81%). Oxidation with activated manganese dioxide in dichloromethane gave the δ-lactone **6** directly.[4]

Tetrahydropyranyl group in **6** was cleaved using *p*-toluenesulfonic acid in methanol at room temperature for 30 min to afford the corresponding alcohol **7** (88%). Acetylation of **7** with acetic anhydride–pyridine produced the acetate **8** which was treated with *m*-chloroperbenzoic acid in dichloromethane at room temperature to give *erythro*-5,6-dihydro-5-acetoxy-6-(*trans*-1,2-epoxypropyl)-2*H*-pyran-2-one (**9**) in 83% yield. Chromatographic separation of **9A** and **9B**, using silica gel and ether–hexane (1:1) as the eluent, gave the pure **9A** and **9B** (3:5).[3f,5]

The *threo*-isomer **11** was obtained by Mitsunobu reaction.[6] Thus, the alcohol **7** was treated with diethyl azodicarboxylate and triphenylphosphine in acetic acid and tetrahydrofuran at room temperature for 30 min to give the isomerically pure 5β-acetate **10**.[3f] Exposure of **10** to *m*-chloroperbenzoic acid in dichloromethane at room temperature yielded after chromatography on silica gel (±)-asperlin and its stereoisomer (47% from **7**). The less polar epoxide **11A** was shown to be spectroscopically identical with naturally derived asperlin.[3]



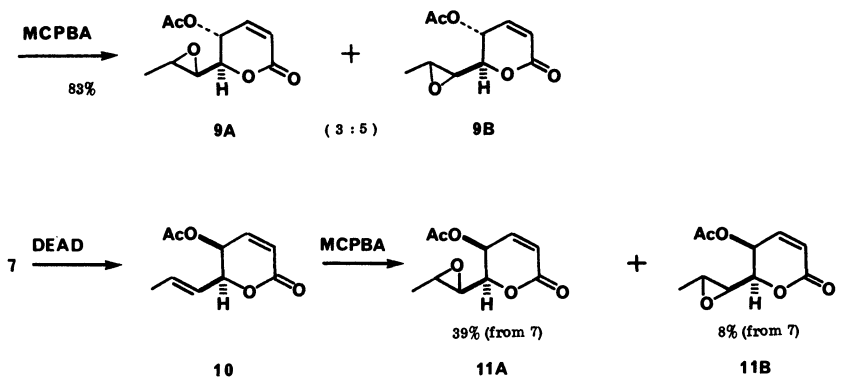


TABLE 1. INHIBITORY EFFECTS OF (±)-ASPERLIN AND STEREOISOMERS ON THE GROWTH OF KB-CELLS *in vitro*

Compound	IC_{50}(μg/ml)
9A	>10
9B	6.1
11A((±)-Asperlin)	6.2
11B	7.2

Preliminary inhibitory test of **9A**, **9B**, **11A**, and **11B** on the growth of KB-cells *in vitro* was shown in Table 1.[7]

Experimental

General. ^{1}H NMR spectra were taken on a JNM-PMX 60 spectrometer. The chemical shifts are reported as parts per million relative to TMS as the internal standard. The infrared spectra were recorded on a Hitachi 260—10 spectrometer in CCl_4 solution unless otherwise stated. The isomeric ratio of the products was determined by gas-liquid phase chromatography (GLC) using Hitachi Model 163 and 164 instruments equipped with a flame ionization detector using nitrogen as carrier gas. For TLC analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm, or silica gel 60 HF_{254} silanized, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck Art. 9385, or silanized silica gel E. Merck Art. 7719. Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone. Benzene was dried over sodium metal. Dichloromethane was dried over **4A** molecular sieves. Pyridine was stored over potassium hydroxide pellets. Other commercially supplied materials were used as received.

3-(Tetrahydro-2-pyranyloxy)-1-(trimethylsilyl)propyne (1). To a mixture of propargyl alcohol (5.82 ml, 100 mmol) and 3,4-dihydro-2*H*-pyran(11.0 ml, 120 mmol) in dry ether (100 ml) was added a catalytic amount of *p*-toluenesulfonic acid (0.2 g) at 0 °C. After the mixture was stirred for 30 min at room temperature, the solution was poured into aqueous sodium hydrogencarbonate and the product was extracted with ether. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel using ether–hexane (1:12) as eluent to give the propargyl ether as a colorless oil (13.2 g, 94%). A solution of the resulting acetylene (12.6 g, 90 mmol) in dry ether (100 ml) was treated with butyllithium in hexane (1.6 mol dm^{-3} solution, 61.8 ml, 98.9 mmol) dropwise at 0 °C. After the resulting white suspension was stirred for 30 min at 0 °C, chlorotrimethylsilane (12.6 ml, 98.9 mmol) was added at 0 °C. After being stirred for 1 h, the solution was poured into diluted hydrochloric acid and the product was extracted with ether repeatedly. The combined ether layers were washed with water, dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel using ether–hexane (1:30) as eluent to afford the ether **1** as a colorless liquid (18.9 g, 99%). ^{1}H NMR (CCl_4) δ=0.17 (s, 9H, Me_3Si), 1.63 (m, 6H, CH_2), 3.21—3.88 (m, 2H, C(6′)H_2), 4.10 (s, 2H, ≡C–CH_2), 4.69 (m, 1H, C(2′)H); IR 2970, 2205, 1260, 1135, 1040, 860 cm^{-1}; Found: C, 62.38; H, 9.22%. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21, H, 9.49%. TLC analysis showed a single spot (R_f=0.61; 1:2, ether–hexane).

(5E)-erythro-3-(Tetrahydro-2-pyranyloxy)-1-trimethylsilyl-5-hepten-1-yn-4-ol (2). To a solution of the acetylene **1** (3.18 g, 15 mmol) in dry tetrahydrofuran (15 ml) at −78 °C was added *t*-butyllithium in pentane (1.96 mol dm^{-3} solution, 7.65 ml, 15.0 mmol) dropwise over 5 min. The resulting red solution was stirred for 1 h at −78 °C and treated with titanium tetraisopropoxide (4.47 ml, 15.0 mmol). After stirring 10 min at −78 °C, the orange solution was treated with crotonaldehyde (1.14 ml, 14.0 mmol), and was then stirred 10 min at −78 °C, allowed to reach room temperature over 1 h. The yellow solution was diluted with ether and washed with diluted hydrochloric acid. The dried (magnesium sulfate) ether layers were concentrated and the residue was subjected to chromatography on silica gel using ether–hexane (1:7) as eluent to give the alcohol **2** as a colorless oil (2.96 g, 75%). ^{1}H NMR (CCl_4) δ=0.15 (s, 9H, Me_3Si), 1.4—2.0 (m, 9H), 2.6 (s, 1H, OH), 3.27—4.30 (m, 4H), 4.78 (m, 1H), 5.33—5.77 (m, 2H, CH=CH); IR 3600, 3450, 2960, 2880, 2200, 1685, 1260, 1025, 850 cm^{-1}; Found: C, 63.59; H, 9.41%. Calcd for $C_{15}H_{26}O_3Si$: C, 63.78; H, 9.28%. TLC analysis showed a single spot (R_f=0.30; 1:2, ether–hexane). GLC analysis of the hydrolized diol showed that the product was 95% pure *erythro* isomer and contained 5% of *threo* isomer.

(5E)-erythro-3-(Tetrahydro-2-pyranyloxy)-5-hepten-1-yn-4-ol (3). A mixture of **2** (2.91 g, 10.3 mmol), potassium fluoride (2.99 g, 51.5 mmol), and methanol (20 ml) was stirred overnight at ambient temperature, then diluted with ether, washed with water, dried (magnesium sulfate), and concentrated to a light yellow oil which was subjected to chromatography on silica gel using ether–hexane (2:5) as eluent to give the acetylene **3** as an oil (1.95 g, 90%). ^{1}H NMR (CCl_4) δ=1.7 (m, 9H), 2.33 (t, *J*=2 Hz, 1H, ≡CH), 2.62 (m, 1H), 3.27—4.40 (m, 4H), 4.87 (m, 1H), 5.52—5.77 (m, 2H, CH=CH); IR 3600, 3450, 3320, 2950, 1685, 1130, 1030, 970 cm^{-1}; Found: C, 68.51; H, 8.69%. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%. TLC analysis showed a single spot (R_f=0.32; 1:2, ether–hexane).

(6E)-erythro-4-(Tetrahydro-2-pyranyloxy)-6-octen-2-yn-1,5-diol (4). A solution of the acetylene **3** (8.60 g, 41.0 mmol) in dry tetrahydrofuran (90 ml) at 0 °C was treated with

butyllithium in hexane (1.60 mol dm^{-3} solution, 51.2 ml, 82.0 mmol). The pale yellow solution was stirred 1 h at 0 °C and treated with paraformaldehyde (6.14 g, 205 mmol). After stirring 10 min at 0 °C and 30 min at room temperature, the mixture was poured into diluted hydrochloric acid and the product was extracted with ether. The combined extracts were washed with water, dried (magnesium sulfate), and concentrated. Purification of the residue by chromatography on silica gel using ethyl acetate–hexane (1:1) as eluent to furnish the alcohol **4** as a colorless liquid (6.36 g, 65%). ^{1}H NMR (CCl_4) δ=1.7 (m, 9H), 3.61 (m, 4H), 4.12 (m, 2H), 4.20 (br s, 2H, CH_2OH), 4.90 (m, 1H), 5.47—5.77 (m, 2H, CH=CH); IR 3410, 2970, 1260, 1130, 1030, 870 cm^{-1}; Found: C, 64.77; H, 8.53%. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39%. TLC analysis showed a single spot (R_f=0.28; ether).

*(2Z,6*E*)-erythro-4-(Tetrahydro-2-pyranyloxy)-2,6-octadien-1,5-diol (5).* A mixture of the alcohol **4** (4.94 g, 20.6 mmol), Lindlar catalyst (5 g) and quinoline (0.655 ml) in benzene (80 ml) was stirred 12 h at room temperature under hydrogen (1 atm). The mixture was filtered, and the filter cake was washed with ether repeatedly. The filtrates were combined and concentrated *in vacuo*. The residue was subjected to chromatography on silica gel using ethyl acetate–hexane (2:3) as eluent to yield the (*Z*)-allylic alcohol **5** as a colorless oil (4.05 g, 81%). ^{1}H NMR (CCl_4) δ=1.7 (br s, 6H), 1.73 (d, J=6 Hz, 3H, CH_3), 3.50 (m, 2H), 3.83—4.47 (m, 6H), 4.60 (m, 1H), 5.13—6.13 (m, 4H, olefinic protons); IR 3410, 2955, 1250, 865 cm^{-1}; Found: C, 64.73; H, 8.87%. Calcd for $C_{13}H_{22}O_4$: C, 64.43; H, 9.15%; R_f=0.23 (ether).

*5,6-Dihydro-6-[(*E*)-1-propenyl]-5-(Tetrahydro-2-pyranyloxy) 2*H*-pyran-2-one (6).* Activated manganese (IV) oxide (25.7 g, 296 mmol) was added portionwise to a stirred solution of the diol **5** (3.89 g, 16.1 mmol) in dichloromethane (120 ml) at room temperature. After stirring 12 h at room temperature, the reaction mixture was filtered, and the filter cake was washed well with ether. The solvent was removed *in vacuo*, leaving a pale yellow oil which was submitted to chromatography on silica gel using ethyl acetate–hexane (1:5) as eluent to afford the lactone **6** as a colorless liquid (2.67 g, 70%). ^{1}H NMR (CCl_4) δ=1.63 (br m, 6H), 1.76 (d, J=7 Hz, 3H, =CCH_3), 3.27—4.33 (m, 4H), 4.77 (m, 1H), 5.57—6.10 (m, 3H), 6.73 (dd, J=9 and 3 Hz, C(4)H); IR 2955, 1740, 1125, 1030 cm^{-1}; Found: C, 65.33; H, 7.77%. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%. TLC analysis showed a single spot (R_f=0.64; ether).

*5,6-Dihydro-5-hydroxy-6-[(*E*)-1-propenyl]-2*H*-pyran-2-one (7).* The lactone **6** (1.72 g, 7.20 mmol) was dissolved in dry methanol (20 ml) and treated with a catalytic amount of *p*-toluenesulfonic acid (150 mg) at room temperature. After stirring 30 min at room temperature, the reaction mixture was poured into aqueous sodium hydrogencarbonate and the product was extracted with ethyl acetate three times. The combined organic layers were washed with water, dried over magnesium sulfate, and concentrated. The residue was submitted to chromatography on silica gel using ether–hexane (3:1) as eluent to give the alcohol **7** as a colorless liquid (978 mg, 88%). ^{1}H NMR ($CDCl_3$) δ=1.75 (d, J=6 Hz, 3H, CH_3), 3.1 (s, 1H, OH), 4.03—4.82 (m, 2H), 5.43—6.07 (m, 3H), 6.83 (dd, J=2 and 10 Hz); IR 3410, 2960, 2930, 2860, 1720, 1260, 1080, 1020 cm^{-1}; Found: C, 62.06; H, 6.74%. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54%. TLC analysis showed a single spot (R_f=0.46; ether).

*5,6-Dihydro-5-acetoxy-6-[(*E*)-1-propenyl]-2*H*-pyran-2-one (8).* A mixture of the alcohol **7** (154 mg, 1.00 mmol), pyridine (1 ml) and acetic anhydride (1 ml) was allowed to stand at room temperature for 1 h. The resulting solution was poured into aqueous sodium hydrogencarbonate and the product was extracted with ethyl acetate repeatedly. The combined organic layers were washed with brine and dried over magnesium sulfate. Concentration yielded the acetate **8** as an oil (181 mg, 92%). ^{1}H NMR (CCl_4) δ=1.73 (d, J=6 Hz, 3H, CH_3), 2.05 (s, 3H, Ac), 4.77 (t, J=6 Hz, 1H, C(6)H), 5.23 (m, 1H, C(5)H), 5.4—5.9 (m, 2H, propenyl), 6.03 (br d, J=10 Hz, 1H, C(3)H), 6.68 (dd, J=4 and 10 Hz); IR 1745, 1375, 1225, 1025 cm^{-1}. TLC analysis showed a single spot (R_f=0.62; ether). This product was used for the next reaction without further purification.

(±)-Asperlin (11A) and Related Stereoisomers (9A, 9B, and 11B). The crude acetate **8** (165 mg, 0.842 mmol) was dissolved in dichloromethane (3 ml) at 0 °C and the solution was treated with *m*-chloroperbenzoic acid (415 mg, 1.68 mmol). After stirring overnight at ambient temperature, the mixture was poured into aqueous sodium sulfite and the product was extracted with ethyl acetate several times. The combined organic layers were washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was subjected on silica-gel chromatography using ether–hexane (1:1) as eluent to afford two isomeric epoxides **9A** (less polar fraction, 57 mg, 32%) and **9B** (more polar fraction, 91 mg, 51%).

9A: ^{1}H NMR (CCl_4) δ=1.33 (d, J=5 Hz, 3H, CH_3), 2.07 (s, 3H, Ac), 2.63—3.13 (m, 2H, epoxide), 4.07 (t, J=6 Hz, 1H, C(6)H), 5.35 (t, J=4 Hz, 1H, C(5)H), 6.03 (d, J=10 Hz, 1H, C(3)H), 6.77 (dd, J=4 and 10 Hz, 1H, C(4)H); IR 3000, 2940, 1750, 1375, 1230 cm^{-1}; Found: C, 56.88; H, 5.86%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%. TLC analysis showed a single spot (R_f=0.60; ether).

9B: ^{1}H NMR (CCl_4) δ=1.30 (d, J=5 Hz, 3H, CH_3), 2.10 (s, 3H, Ac), 2.73—3.15 (m, 2H), 4.47 (t, J=4 Hz, 1H, C(6)H), 5.37 (t, J=4 Hz, 1H, C(5)H), 6.00 (d, J=10 Hz, 1H, C(3)H), 6.67 (dd, J=4 and 10 Hz, 1H, C(4)H); IR 2990, 2950, 1750, 1380, 1230, 1120, 1030 cm^{-1}; Found: C, 56.47; H, 5.83%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%. TLC analysis showed a single spot (R_f=0.46; ether).

A solution of the alcohol **7** (0.33 g, 2.14 mmol), triphenylphosphine (2.81 g, 10.7 mmol), and acetic acid (0.613 ml, 10.7 mmol) in dry tetrahydrofuran (10 ml) was combined with a solution of diethyl azodicarboxylate (1.68 ml, 10.7 mmol) in tetrahydrofuran (4.3 ml) at room temperature. After 30 min, the reaction mixture was poured into aqueous sodium hydrogencarbonate and the product was extracted with ethyl acetate several times. The combined extracts was washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. The residual oil was subjected to simple short-path chromatography (ether–hexane, 2:1) and the crude product was used for the next reaction without further purification.

The oxidation was carried out in an analogous manner from the above acetate to produce the two isomeric epoxides **11A** (less polar fraction, 177 mg, 39% from the alcohol **7**) and **11B** (more polar fraction, 37 mg, 8% from the alcohol **7**).

(±)-Asperlin (11A):[3] ^{1}H NMR ($CDCl_3$) δ=1.37 (d, J=5 Hz, 3H, CH_3), 2.13 (s, 3H, Ac), 2.90—3.28 (m, 2H, epoxide), 4.17 (dd, J=3 and 7 Hz, 1H, C(6)H), 5.32 (dd, J=3 and 6 Hz, 1H, C(5)H), 6.17 (d, J=10 Hz, 1H, C(3)H), 7.03 (dd, J=6 and 10 Hz, 1H, C(4)H); IR 3000, 2960, 1750, 1380, 1230, 1040, 760 cm^{-1}; Found: C, 56.76; H, 6.04%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%. TLC analysis showed a single spot (R_f=0.51; ether).

11B: ^{1}H NMR (CCl_4) δ=1.32 (d, J=5 Hz, 3H, CH_3), 2.12 (s, 3H, Ac), 2.75—3.15 (m, 2H, epoxide), 4.28 (t, J=4 Hz, 1H, C(6)H), 5.47 (dt, J=4 and 6 Hz, 1H, C(5)H), 6.07 (d, J=10 Hz, C(3)H), 6.73 (dd, J=6 and 10 Hz, 1H, C(4)H); IR 2990, 2950, 1750, 1380, 1230, 1050 cm^{-1}; Found: C, 56.77; H, 6.20%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%. TLC analysis showed a single spot (R_f= 0.37; ether).

We acknowledge Professor T. Nishiguchi for helpful discussions.

References

1) M. Ishiguro, N. Ikeda, and H. Yamamoto, *J. Org. Chem.*, **47**, 2225 (1982); **48**, 142 (1983); K. Furuta, M. Ishiguro, R. Haruta, N. Ikeda, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **57**, 2768 (1984).

2) For recent reviews of the synthetic reactions using organotitanium reagents, see: M. T. Reetz, in "Topics in Current Chemistry," Springer, Berlin (1982), pp. 1—54; B. Weidmann and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **22**, 31 (1983); D. Seebach, B. Weidmann, and L. Widler, in "Modern Synthetic Methods 1983," ed by R. Scheffold, Wiley, New York and Salle/Sauerländer, Aarau (1983), pp. 217—353.

3) a) A. D. Argoudelis and J. F. Zieserl, *Tetrahedron Lett.*, **1966**, 1969; b) R. H. Evans, Jr., G. A. Ellestad, and M. P. Kunstmann, *Tetrahedron Lett.*, **1969**, 1791; c) W. Rosenbrook, Jr. and R. E. Carney, *Tetrahedron Lett.*, **1970**, 1867; d) M. Tanabe, T. Hamasaki, D. Thomas, and L. Johnson, *J. Am. Chem. Soc.*, **93**, 273 (1971); e) S. Lesage and A. S. Perlin, *Can. J. Chem.*, **56**, 2889 (1978); f) Jiu, Kraychy, Mizuba, U. S. Patent, 3909362 (1975).

4) J. S. Pizey, "Synthetic Reagents," Wiley, New York (1974), Vol. 2, p. 164.

5) By analogy to the TLC behavior of natural asperlin and its isomer, the less polar isomer has tentatively been assigned to **9A**.

6) O. Mitsunobu, *Synthesis*, **1981**, 1.

7) We thank Ono Pharamaceutical Company, Inc. for the biological tests.