Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 24 Sep 2006.

To cite this article: Leo A. Paquette & Matthew R. Sivik (1991) Preparation of Annulated 2,4-Dioxygenated-5-Methylfurans, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:3, 467-479, DOI: 10.1080/00397919108016771

To link to this article: http://dx.doi.org/10.1080/00397919108016771

SYNTHETIC COMMUNICATIONS, 21(3), 467-479 (1991)

PREPARATION OF ANNULATED 2,4-DIOXYGENATED-5-METHYLFURANS

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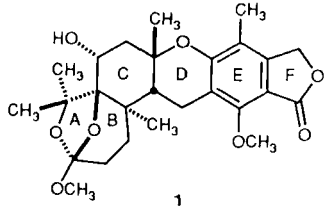
Abstract: A concise route from dihydropyran to the furans **12** and **13** has been developed that takes advantage of the regioselective Baeyer-Villiger oxidation of bicyclic ketone **6**.

The austalides, a family of mycotoxins produced by whole maize cultures of *Aspergillus ustus*,[2] arise biogenetically[3] via 6-farnesyl-5,7-dihydroxy-4-methylphthalide, a confirmed intermediate in the biogenesis of mycophenolic acid.[4] The molecular architecture of these structurally unique meroterpenoids, as exemplified by austalide B (**1**), is endowed with functional group diversity



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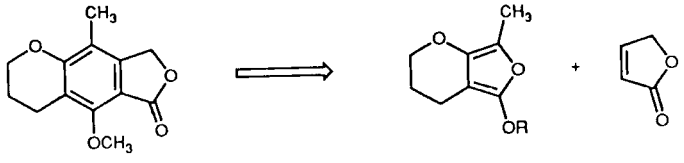
sufficient to make them a useful forum for the development of new multiple annulation methods. Despite the obvious synthetic challenge offered by this class of compounds, no attempt to prepare any member of the group has yet been reported.

As part of our interest in developing concise strategies for the rapid assembly of polycyclic natural products, we initiated a model investigation directed toward construction of the DEF subunit of **1**. As illustrated in Scheme 1, the key focus of the retrosynthetic plan was the elaboration of a furan of type **3** for the purpose of involving this heterocycle in Diels-Alder condensation with butenolide **4** or its equivalent under high-pressure or catalyzed conditions,[5] as necessary, with subsequent aromatization.[6] Our interest in this approach was piqued by the realization that 2,4-dioxygenated-5-methyl furans related to **3** are not presently known,[7] with resultant lack of information concerning their ability to engage in (4+2)π cycloaddition reactions. In this note, we detail a serviceable route to the parent of **3** (R=H) as well as an O-silylated derivative, and point out the remarkable inertness of the latter compound as a dienophile.

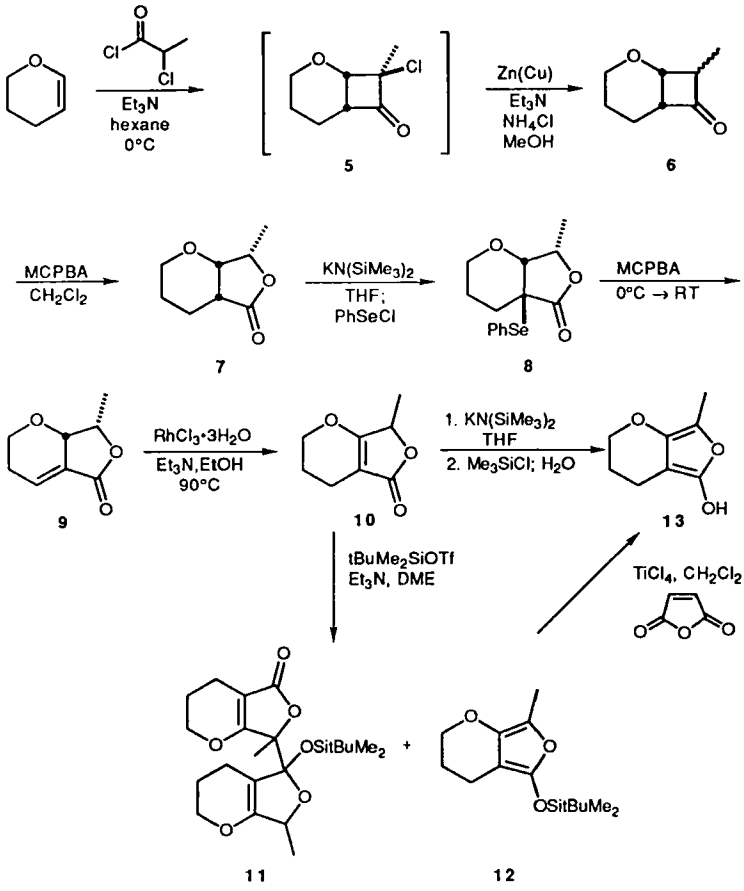
Scheme I



2 **3** **4**

The task of constructing bicyclic lactone **7**, an intermediate that incorporates all of the necessary carbon and oxygen atoms of the target heterocycle, was the first subgoal of the undertaking. Toward this objective, dihydropyran was brought into reaction with methylchloroketene as generated in situ from α-chloropropionyl chloride and triethylamine[8] (Scheme II). As is customary,[9,10] the resulting cycloaddition proved to be fully regioselective, since direct reduction of **5** with zinc-copper couple afforded cyclobutanone **6** as a 5:1 mixture of α- and β-methyl diastereomers (^{1}H NMR analysis). Baeyer-Villiger oxidation of **6** with *m*-chloroperbenzoic acid generated the structurally related lactones, with a strong

Scheme II



preference being shown for 1,2-migration of the methyl-substituted carbon to oxygen. At this point, the α-stereoisomer **7** could be conveniently separated by silica gel chromatography.

While phenylselenenylation of the enolate anion of **7** proceeded smoothly to give **8**, subsequent oxidative elimination of the selenoxide resulted in unique positioning of the double bond as in **9**. Thus, the inductive effect of the tetrahydropyranyl ether oxygen kinetically retards the alternative cis-hydrogen

abstraction process that would have given rise to **10**. However, the desired butenolide was secured upon heating **9** with rhodium trichloride trihydrate and triethylamine in methanol.[11]

The conversion of butenolides to their anions for the purpose of O-alkylation and the like has long been recognized to be problematical.[7b] Intermediate **10** proved not to be an exception to this trend. For example, stirring **10** with *tert*-butyldimethylsilyl triflate and triethylamine in dry 1,2-dimethoxyethane at room temperature for 2 h gave the "dimeric" product **11** in greatest amount (40%), alongside siloxyfuran **12** (10%) and unreacted lactone (40%). Although considerable experimentation did not result in yield improvement or enhancement in the extent of conversion,[12] the means was found for producing the hydroxy furan **13** directly from **10** (15% isolated) or less directly via the desilylation of **12** (71%). Once formed, **13** exhibited no obvious tendency for reversion to **10**.

With the availability of **12** in modest amounts, attention was next paid to its reactivity as a diene in Diels-Alder reactions. The illustrative examples that have been compiled in Table I show **12** to be notably unreactive toward a representative selection of good to excellent dienophiles. The furan is inert toward neat dimethyl acetylenedicarboxylate, fumaryl chloride, and crotonolactone at 90°C, fails to condense with maleic anhydride or crotonolactone when compressed with these reagents under 160,000 psi of pressure for several days, and resists cycloaddition to maleic anhydride when stirred together in diethyl ether that is 5 M in lithium perchlorate.[13]

The striking lack of reactivity of **12** (as well as the O-methyl ether of **13**[14]) renders Scheme I unworkable and necessitates that the eastern sector of the austalides be assembled differently. Suitable alternatives are the subject of continuing effort in these laboratories.

Table I. Attempted Diels-Alder Reactions of **12**.

dienophile	solvent	concentrations	conditions	result
maleic anhydride	CH_2Cl_2	0.13 M in each reactant	160,000 psi 4 days	no reaction
	CH_2Cl_2	0.19 M in **12**, 2.0 M in MA	160,000 psi, 4 days	no reaction
	CH_2Cl_2, $TiCl_4$	0.55 M in **12**, 1.1 M in MA	-78°C, 30 m → RT, 3 h	isolation of **10**
fumaryl chloride	neat		90°C, 8 h	no reaction
dimethyl acetylenedicarboxylate	neat		90°C, 3 h 100°C, 1 d	no reaction
crotonolactone	neat		90°C, 6 h	no reaction
maleic anhydride	ether	0.2 M in **12**, 1.0 M in MA 5 M in $LiClO_4$	RT, 2 days 60°C, 4 h (sealed tube)	no reaction

Experimental Section

(1*R,6*R**)-8-Methyl-2-oxabicyclo[4.2.0]octan-7-one (6).** To a chilled (0°C), mechanically stirred solution of triethylamine (7.37 mL, 55 mmol) and dihydropyran (4.55 mL, 50 mmol) in freshly distilled hexane (200 mL) was added dropwise via syringe pump a solution of 2-chloropropionyl chloride (4.85 mL, 50 mmol) in pentane (20 mL) during 3 h. After completion of the addition, the reaction mixture was stored at 0°C for an additional hour and used directly in the next step.

To a suspension of zinc dust (9.80 g, 150 mmol) in glacial acetic acid (60 mL) was added copper(II) acetate dihydrate (700 mg, 3.50 mmol) After 30 min of stirring, the solvent was decanted and washed with ether (3 x 60 mL) and methanol (3 x 60 mL). At this point, methanol (100 mL) was added, followed by ammonium chloride (12.30 g, 230 mmol) and triethylamine (14 mL, 100 mmol). After vigorous stirring for 15 min, the suspension was transferred to the chilled (0°C) chlorocyclobutanone mixture. This slurry was stirred for 3 h, the suspension was allowed to settle, and the supernatant fluid was decanted and diluted with ether (200 mL). This organic solution was washed with brine (100 mL), dried, and concentrated in vacuo. The residue was purified by chromatography through a column of silica gel (elution with 20% ethyl acetate in petroleum ether) to give 4.25 g (39%) of **6** as a faint yellow oil. The isomer distribution determined by ^{1}H NMR indicated the α,β methyl ratio to be 5:1. For the α-methyl isomer: IR (neat, cm^{-1}) 2940, 2850, 1750, 1730; ^{1}H NMR (300 MHz, C_6D_6) δ 3.80 (t, J = 5.6 Hz, 1 H), 3.51 (dpent, J = 11.2, 2.0 Hz, 1 H), 2.84 (td, J = 11.2, 1.6 Hz, 1 H), 2.73 (dpent, J = 7.1, 3.5 Hz, 1 H), 2.51-2.46 (br m, 1 H), 1.86 (dm, J = 14 Hz, 1 H), 1.33 (qt, J = 12.5, 5.0 Hz, 1 H), 1.2-1.0 (m, 1 H), 1.09 (d, J = 7.1 Hz, 3 H), 0.98-0.88 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm

207.46, 65.90, 64.66, 57.61, 54.75, 22.36, 18.62, 6.24; MS *m/z* (M^+) calcd 140.0383, obsd 140.0818.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.65; H, 8.69.

The β isomer was distinguished from its epimer on the basis of the appearance of its CH-O- proton as only a doublet (J = 7.2 Hz) at δ 3.91 and of its methyl doublet (J = 7.9 Hz) at a more shielded position (δ 0.84).

(4a*R,7*S**,7a*S**)-Hexahydro-7-methyl-5*H*-furo[3,4-*b*]pyran-5-one (7).** *m*-Chloroperbenzoic acid (0.70 g, 3.57 mmol) was added as a solution in dichloromethane (10 mL) to a stirred and cooled (-25°C) mixture of **6** (0.50 g, 3.57 mmol) and sodium bicarbonate (0.60 g, 7.13 mmol) in the same solvent (35 mL). After 2 h, the cooling bath was removed and the mixture was allowed to warm to room temperature, then stirred for 1 h. Following dilution with ether (125 mL), the organic phase was washed with saturated aqueous K_2CO_3 solution (3 x 50 mL) and brine (50 mL) prior to drying. The concentrate was chromatographed on TLC grade silica gel to give 0.217 g (39%) of isomerically pure **7** as a colorless oil; IR (neat, cm^{-1}) 2970, 2927, 1775; ^1H NMR (300 MHz, C_6D_6) δ 3.83 (qd, J = 6.5, 2.9 Hz, 1 H), 3.57-3.52 (m, 1 H), 3.32 (t, J = 3.2 Hz, 1 H), 2.81-2.76 (m, 1 H), 2.12-2.10 (m, 1 H), 2.08-1.97 (m, 1 H), 1.38 (qt, J = 13.0, 4.1 Hz, 1 H), 1.25-1.17 (m, 1 H), 1.22 (d, J = 6.5 Hz, 1 H), 0.95 (d, J = 7.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 175.88, 77.77, 75.05, 65.03, 41.60, 22.47, 20.29, 13.47; MS *m/z* (M^+) calcd 156.0786, obsd 156.0786.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.15; H, 7.79.

(4a*S,7*S**,7a*R**)-Hexahydro-7-methyl-4a-(phenylselenyl)-5*H*-furo[3,4-*b*]-pyran-5-one (8).** A solution of **7** (1.00 g, 6.4 mmol) in dry tetrahydrofuran (10 mL) was added via a syringe pump to a cold (-78°C) solution of potassium bis(trimethylsilyl)amide in toluene (15.3 mL of 0.5 M) and dry THF (30 mL) over

1 h. Upon completion of the addition, the mixture was stirred at -78°C for another 15 min, at which point a solution of phenylselenyl chloride (1.47 g, 7.68 mmol) and HMPA (1.22 mL, 7.0 mmol) in dry THF (20 mL) was introduced. After 1 h at -78°C, the reaction mixture was allowed to come to room temperature, stirred for 3 h, diluted with ether (120 mL), washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with petroleum ether followed by 20% ethyl acetate in petroleum ether) gave 1.16 g (58%) of **8** as an orange oil; IR (neat, cm^{-1}) 2920, 2850, 1762; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2 H), 7.06-6.95 (m, 3 H), 4.55 (qd, J = 6.5, 2.9 Hz, 1 H), 3.55 (d, J = 2.8 Hz, 1 H), 3.47-3.41 (m, 1 H), 2.73 (td, J = 11.8, 1.8 Hz, 1 H), 2.31-2.23 (m, 1 H), 1.64 (td, J = 13.2, 5.0 Hz, 1 H), 1.33 (qt, J = 13.7, 4.1 Hz, 1 H), 1.20 (d, J = 6.5 Hz, 3 H), 0.95-0.78 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.16, 138.27, 129.87, 129.27, 125.02. 79.99, 76.57, 65.65, 49.54, 30.25, 24.86, 23.43; MS *m/z* (M^+) calcd 310.0272, obsd 310.0257.

(7*S,7a*S**)-2,3,7,7a-Tetrahydro-7-methyl-5*H*-furo[3,4-*b*]pyran-5-one (9).** A solution of **8** (1.10 g, 3.50 mmol) in dichloromethane (50 mL) was treated with sodium bicarbonate (0.65 g, 7.7 mmol) and *m*-choroperbenzoic acid (1.21 g, 7.00 mmol) at 0°C. This mixture was stirred at 0°C for 1 h and at room temperature for 4 h before being diluted with ether (100 mL), washed with brine (2 x 50 mL), dried, and concentrated. The residue was chromatographed on silica gel (elution with petroleum ether followed by 20% ethyl acetate in petroleum ether) to give 0.30 g (56%) of **9** as a colorless crystalline solid, mp 81-82°C (from ether); IR ($CHCl_3$, cm^{-1}) 3010, 2995, 2925, 2865, 1762, 1689; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (d, J = 3.2 Hz, 1 H), 4.32-4.23 (m, 1 H), 3.94-3.88 (m, 1 H), 3.45 (dd, J = 11.7, 6.8 Hz, 1 H), 2.95 (td, J = 11.2, 4.6 Hz, 1 H), 1.76-1.63 (m, 1 H), 1.29-1.18 (m, 1 H), 0.98 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$)

ppm 166.06, 134.00, 129.88, 76.29, 73.41, 63.59, 24.96, 15.23; MS *m/z* (M^+-C_2H_4O) calcd 110.0367, obsd 110.0410.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.36; H, 6.56.

2,3,4,7-Tetrahydro-7-methyl-5*H*-furo[3,4-*b*]pyran-5-one (10). A solution of **9** (0.200 g, 1.30 mmol) in ethanol (4 mL) was treated with rhodium trichloride trihydrate (10 mg) followed by triethylamine (1 mL) and placed in a screw-cap pressure vial. The reaction mixture was heated in a 90°C oil bath for 6 h, cooled, diluted with ether (30 mL), and washed with brine (15 mL). The aqueous layer was extracted with ether (15 mL) and the combined organic phases were dried, concentrated, and purified by chromatography on TLC grade silica gel (elution with 20% ethyl acetate in petroleum ether). There was isolated 0.175 g (88%) of **10** as a colorless oil that slowly crystallized, mp 48-50°C; IR (neat, cm^{-1}) 2935, 1755, 1675; ^1H NMR (300 MHz, C_6D_6) δ 4.24 (qt, J = 6.7, 1.6 Hz, 1 H), 3.34 (t, J = 5.1 Hz, 2 H), 1.86-1.79 (m, 2 H), 1.03 (d, J = 6.7 Hz, 3 H), 1.03-0.90 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 176.38, 171.24, 99.46, 73.42, 69.17, 20.90, 17.55, 16.33; MS *m/z* (M^+) calcd 154.0630, obsd 154.0655.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.20; H, 6.69.

3,4-Dihydro-5-(*tert*-butyldimethylsilyloxy)-7-methyl-5*H*-furo[3,4-*b*]pyran-5-one (12). To a cold (0°C), magnetically stirred solution of **10** (181 mg, 1.17 mmol) and triethylamine (0.22 mL, 1.53 mmol) in dry 1,2-dimethoxyethane (4 mL) was added *tert*-butyldimethylsilyl triflate (300 μL, 1.29 mmol). This mixture was stirred at 0°C for 1 h and at room temperature for 12 h prior to dilution with ether (10 mL) and washing with brine. The organic phase was dried and concentrated to leave a residue that was purified by column chromatography (silica gel, elution with 30% ethyl acetate in petroleum ether). There was obtained 30 mg (10%) of **12**, 100 mg (40%) of **11**, and 72 mg (40%) of unreacted

10.

For **11**: colorless solid, mp 136-137°C (from ether); IR ($CHCl_3$, cm^{-1}) 1740, 1705, 1670; ^1H NMR (300 MHz, C_6D_6) δ 4.63 (qt, J = 6.5, 2.0 Hz, 1 H), 3.74 (dt, J = 10.8, 4.0 Hz, 1 H), 3.64-3.48 (m, 3 H), 2.00-1.95 (m, 4 H), 1.52 (s, 3 H), 1.50-1.30 (m, 2 H), 1.26 (d, J = 6.5 Hz, 3 H), 1.23-1.05 (m, 2 H), 1.00 (s, 9 H), 0.26 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 176.68, 170.86, 156.65, 110.49, 104.54, 100.08, 87.16, 76.69, 68.76, 67.57, 25.84, 22.08, 20.93, 19.33, 18.43, 18.37, 17.88, 16.80, -2.38, -3.62; MS *m/z* (M^+-C_4H_9) calcd 365.1420, obsd 365.1465.

Anal. Calcd for $C_{22}H_{34}O_6Si$: C, 62.53; H, 8.11. Found: C, 62.44; H, 8.10.

For **12**: colorless oil; IR (neat, cm^{-1}) 1750, 1680; ^1H NMR (300 MHz, C_6D_6) δ 3.46-3.42 (m, 2 H), 1.80 (t, J = 6.2 Hz, 2 H), 1.51 (s, 3 H), 1.00 (qt, J = 6.4, 2.1 Hz, 2 H), 0.94 (s, 9 H), 0.23 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 174.58, 168.66, 101.14, 99.56, 69.19, 25.77, 24.95, 20.76, 18.02, 16.11, -3.14, -3.50; MS *m/z* (M^+-*t*-BuSiMe$_2$) calcd 153.0552, obsd 153.0602.

3,4-Dihydro-7-methyl-2*H*-furo[3,4-*b*]pyran-5-ol (13). A. From 10. To a stirred solution of potassium bis(trimethylsilyl)amide (0.60 mL of 0.5 M in toluene) in dry tetrahydrofuran (0.60 mL) at -25°C was added dropwise during 1 h a solution of **10** (38 mg, 250 μmol) in THF (0.6 mL). The mixture was stirred for 1 h, trimethylsilyl chloride (38 μL, 300 μmol) was introduced, and stirring was maintained for 1 h at -25°C and 12 h at room temperature. The mixture was diluted with water and extracted with ether (2 x 4 mL). The combined extracts were washed with brine, dried, and concentrated to give after silica gel chromatography 6 mg (15%) of **13** and 30 mg (79%) of unreacted **10**.

For **13**: colorless solid, mp 128-130°C (from ether); IR ($CHCl_3$, cm^{-1})

3350, 1750, 1680; ^{1}H NMR (300 MHz, $CHCl_3$) δ 4.33 (t, J = 5.2 Hz, 2 H), 2.26 (t, J = 6.7 Hz, 2 H), 2.19-1.90 (m, 2 H), 1.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.17, 170.72, 101.19, 99.84, 69.96, 22.78, 20.81, 15.89; MS *m/z* (M^+) calcd 154.0630, obsd 154.0617.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.21; H, 6.65.

B. From 12. A cold (-78°C), magnetically stirred solution of maleic anhydride (22 mg, 220 μmol) in dry dichloromethane (0.10 mL) was treated with 0.12 mL of a 1.0 M solution of titanium tetrachloride in CH_2Cl_2. Ten minutes later, a solution of **12** (30 mg, 110 μmol) in CH_2Cl_2 (0.10 mL) was added and stirring at -78°C was maintained for 30 min. The reaction mixture was warmed to room temperature, treated with triethylamine (0.25 mL), stirred for 3 h, and placed atop a column of silica gel. Elution with 20% ethyl acetate in petroleum ether furnished 12 mg (71%) of **13**.

Acknowledgment. We are grateful to the National Institutes of Health for their financial support of this work (Grant GM-30827).

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12. A telling observation was the failure realized when the procedure was developed by Asaoka, Miyake, and Takei for the synthesis of 7-hydroxyphthalides from unsaturated lactones via 2-(trialkylsilyloxy)-furans was appied to **10** [Asaoka, M., Miyake, K. and Takei, H., Chem. Lett., **1977**, 167].

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14. Prepared by reaction of **13** with trimethyloxonium tetrafluoroborate in dichloromethane at 0°C: Sivik, M. R. unpublished results.

(Received in USA 22 December, 1990)