Table II. Positional Parameters and Their Estimated Standard Deviations[a]

atom	x	y	z	B(A2)
Ag	0.90981 (2)	0.29118 (4)	0.79232 (1)	5.536 (7)
S	1.08600 (7)	0.5724 (1)	0.84826 (5)	5.50 (2)
F1	1.2444 (2)	0.4880 (6)	0.8261 (2)	11.9 (1)
F2	1.2643 (3)	0.5364 (6)	0.9324 (2)	13.6 (1)
F3	1.1999 (4)	0.3299 (5)	0.8873 (2)	13.3 (2)
O1	1.0283 (2)	0.4791 (5)	0.7908 (1)	7.22 (8)
O2	1.1067 (3)	0.7222 (4)	0.8270 (2)	7.8 (1)
O3	1.0573 (3)	0.5644 (5)	0.9092 (2)	9.6 (1)
C1	0.6862 (3)	0.0438 (6)	1.0238 (2)	6.7 (1)
C2	0.6651 (2)	-0.0028 (4)	0.9490 (2)	4.46 (7)
C3	0.6895 (2)	0.1340 (4)	0.9061 (1)	3.34 (6)
C4	0.6377 (2)	0.2597 (4)	0.8743 (2)	3.25 (6)
C5	0.5352 (2)	0.3270 (4)	0.8700 (2)	3.99 (7)
C6	0.4533 (3)	0.2518 (7)	0.8113 (3)	7.2 (1)
C7	0.7301 (3)	-0.1459 (5)	0.9491 (2)	6.4 (1)
C8	0.5596 (3)	-0.0658 (5)	0.9141 (2)	6.4 (1)
C9	0.5332 (3)	0.5027 (6)	0.8586 (3)	8.1 (1)
C10	0.5138 (3)	0.3146 (6)	0.9379 (2)	6.4 (1)
C11	0.7915 (2)	0.1197 (4)	0.9025 (1)	3.60 (6)
C12	0.8095 (3)	0.0389 (5)	0.8500 (2)	4.90 (8)
C13	0.9043 (3)	0.0295 (6)	0.8469 (2)	6.47 (9)
C14	0.9811 (3)	0.1044 (6)	0.8971 (2)	8.1 (1)
C15	0.9635 (3)	0.1876 (6)	0.9519 (3)	7.2 (1)
C16	0.8699 (3)	0.1910 (5)	0.9534 (2)	5.13 (9)
C17	0.6849 (2)	0.3539 (4)	0.8314 (2)	3.75 (6)
C18	0.6641 (3)	0.3180 (5)	0.7613 (2)	5.26 (9)
C19	0.7122 (3)	0.3937 (6)	0.7215 (2)	7.0 (1)
C20	0.7794 (3)	0.5091 (6)	0.7509 (2)	7.6 (1)
C21	0.7986 (3)	0.5484 (5)	0.8203 (3)	7.2 (1)
C22	0.7520 (2)	0.4721 (5)	0.8611 (2)	5.37 (9)
C23	1.2037 (4)	0.4765 (7)	0.8744 (2)	7.7 (1)

[a] Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter.

Summary and Conclusions

The combination of a nearly optimal complexing cleft and steric hindrance to alternative complexation sites in (*Z*)-2,2,5,5-tetramethyl-3,4-diphenylhex-3-ene (1) provides the opportunity for formation of unusually stable metal complexes with predictable structures. Complex 3, in the solid phase, is shown to be a 1:1 complex. The silver ion is located between the cleft formed by the phenyl rings. Individual units are connected in a polymeric chain. Further work is in progress to establish the extent of the series of metal complexes of 1.

Experimental Section

((*Z*)-2,2,5,5-Tetramethyl-3,4-diphenylhex-3-ene)silver(I) Triflate (3). In Ethanol. A solution was prepared containing 15.1 mg (0.052 mmol) of 1 and 9.5 mg (0.055 mmol) of silver nitrate in 0.625 mL of absolute ethanol by being heated at 80 °C in a water bath. ^{1}H NMR analysis showed a 0.03 ppm downfield shift of the aromatic resonances in 1. **In THF.** Solid 1 (17.0 mg, 0.058 mmol) and silver triflate (16.7 mg, 0.065 mmol) were sealed in a flask under argon with a rubber septum. Freshly distilled (sodium benzophenone ketyl) THF (4 mL) was added via syringe. After stirring for 1 h, the solvent was removed under vacuum, giving a white solid. Trituration with $CDCl_3$ and removal of solvent under vacuum gave colorless crystals of 3, which displayed the same ^{1}H NMR spectrum after melting, mp = 195–196 °C, as before melting. In the presence of ethanolic HCl, 3 gave a white precipitate. 3: ^{13}C NMR[1] (see Table I); ^{1}H NMR (see Table I). Anal. Calcd: C, 50.28; H, 5.14. Found: C, 49.56; H, 5.28. Since decreasing the concentration to obtain a UV spectrum also decreased the fraction of complexed ligand, it was not possible to obtain a satisfactory spectrum even with short pathlength cells. More concentrated solutions showed tailing of the UV absorption out to 300 nm.

Determination of K. A stock solution of 3 in $CDCl_3$ (0.018 M) was diluted to give six samples over the concentration range 0.018 to 0.0007 M. ^{1}H NMR spectra were measured at 400 MHz (VXR-400). The chemical shift of the most downfield signal in the most downfield triplet (δ = 6.870 in 1) was recorded. The data was fitted to the following equation:

$$\delta_{obs} = (\delta_1[1] + \delta_3[3])/([1] + [3])$$

$$= (\delta_1[1] + \delta_3(S - [1]))/S \qquad S = [1] + [3]$$

The chemical shifts for pure 1, pure 3, and the equilibrating mixture are δ_1, δ_3, and δ_{obs}, respectively.

X-ray Analysis of 3. A colorless crystal of $C_{23}H_{28}AgF_3O_3S$ crystallized from dichloromethane having approximate dimensions of 0.20 × 0.16 × 0.06 mm was mounted on a glass fiber in a random orientation. Data collection was performed with Mo Kα radiation (λ = 0.71073 Å) on an Enraf-Nonius CAD4 diffractometer. The monoclinic cell parameters and calculated volume are a = 14.469 (5), b = 8.541 (2), and c = 20.386 (4) Å, β = 109.96 (2)°, V = 2368.1 Å^3. For Z = 4 and M_r = 549.41 the calculated density is 1.54 g/cm^3. The space group was determined to be $P2_1/c$. The data were collected at a temperature of 21 ± 1° using the ω-2θ scan technique. Data were collected to a maximum 2θ of 52.0°. A total of 5186 reflections were collected, of which 4984 were unique. A total loss in intensity of 4.1% was measured. An anisotropic decay correction was applied ranging from 0.990 to 1.063 with an average value of 1.022. The linear absorption coefficient is 9.7 cm^{-1} for Mo Kα radiation. Relative transmission coefficients ranged from 0.916 to 0.999 with an average value of 0.969. The structure was solved by direct methods and refined by full matrix least squares. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. Only the 3479 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 280 variable parameters and converged (largest parameter shift was 0.02 times its esd) with unweighted and weighted agreement factors of $R_1 = \sum|F_o - F_c|/\sum F_o = 0.040$, $R_2 = (\sum w(F_o - F_c)^2/\sum wF_o^2)^{1/2} = 0.062$. The standard deviation of an observation of unit weight was 2.17. All calculations were performed on a VAX11/750 computer using SDP/VAX.[9] Final atomic positions are given in Table II.

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Supplementary Material Available: Experimental details, table of bond distances, table of bond angles, and table of dihedral angles for X-ray structure 3 (13 pages). Ordering information is given on any current masthead page.

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Regioselective Reductions of Diacids: Aspartic Acid to Homoserine

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Intermediary metabolism centers on the controlled interconvertion of low-molecular weight, heavily functionalized carbon compounds, many containing repetitive functionalities. Examples include the polyhydroxylated compounds of glycolysis and the Calvin cycle, the di- and tricarboxylic acids of the Krebs cycle, and the diamino and

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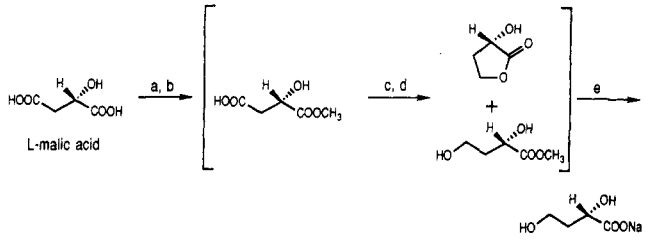
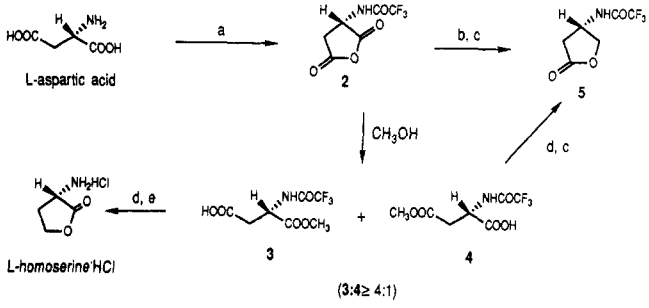
Scheme I[a]



[a] (a) $(CF_3CO)_2O$; (b) CH_3OH; (c) BH_3–THF, 0 °C; (d) CH_3OH; (e) Na_2CO_3/H_2O.

Scheme II[a]



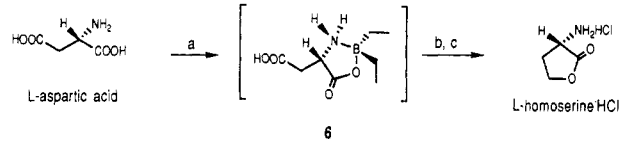
[a] (a) $(CF_3CO)_2O$; (b) $NaBH_4$/THF, 0 °C; (c) HCl/H_2O; (d) BH_3-THF, 0 °C; (e) $HCl/C_2H_5OH/H_2O$, Δ.

dicarboxylic amino acids. Chemical transformations capable of such regioselective differentiation of these repeating functional groups could be useful in the laboratory. Here we describe simple methods which allow for the regioselective reduction of dicarboxylic acids.

Homoserine, an amino acid not found in proteins but central to the biosynthesis of a diverse array of metabolites including threonine, methionine, isoleucine, homocysteine, and cystathionine, has been shown to arise biosynthetically from the reduction of the γ-carboxylate of aspartic acid.[1] Direct reduction of the C-1 carboxyl of hydroxy 1,4-dicarboxylic acids has been achieved from the anhydride,[2,3] and more recently some degree of C-4 selective reduction has been demonstrated with specific diesters of aspartic acid.[4] However, the increased reactivity of the C-1 carbonyl was sufficient in the *o*-TFA derivative of malic anhydride to allow for clean regioselective opening with MeOH to the C-1 ester. The resulting C-4 monoacid was set for direct reduction with borane to give **1**. Trifluoroacetic anhydride treatment of malic acid made it possible to carry out the anhydride formation, regioselective opening, reduction, and deprotection all in a single vessel with no requirement for chromatographic purification (Scheme I).

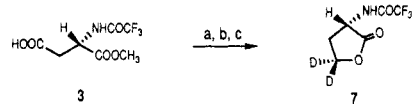
Aspartic acid reacted under the same conditions was not quite so clean and gave a 4:1 mixture of the monoacids **3** and **4** (Scheme II). In this case the two products were easily separated by trituration of the monoacid mixture with diethyl ether/petroleum ether (2:1) to afford either of the amino alcohols cleanly on reduction. The trituration

Scheme III[a]



[a] (a) $B(C_2H_5)_3$–THF, reflux; (b) BH_3–THF, 0 °C; (c) HCl/H_2O.

Scheme IV[a]



[a] (a) $NaBD_4$/THF; (b) BF_3–$O(C_2H_5)_2$, 0 °C; (c) HCl/H_2O.

step meant that an overall two-pot procedure was required, and even though the overall yield of homoserine was ≥70%, this proved not to be the preferred procedure for the synthesis of homoserine. In fact, the regioselectivity of the methanolysis step was found to be limited to the TFA protected 5-membered ring anhydrides. *N*-*p*-TSA aspartic acid anhydride opened to a 3:1 mixture, and in the 6-membered case, *N*-TFA-pyroglutamic acid, a 1:1 mixture of the two possible acids was recovered.

The observation that >1 equiv of BH_3 was required for the reduction of the aspartate monoacids **3** and **4** (see Experimental Section) suggested that 1 equiv might be complexing with the amino acid and only the additional equivalents undergoing reaction. Such complexation has been observed in related systems.[5] In attempts to utilize such a complex, 1 equiv of triethylborane was allowed to react directly with aspartic acid.[6] The THF-soluble product contained two distinct ethyl groups bound to boron (^{11}B, ^{13}C coupling) and two nonequivalent N-H protons in the ^1H NMR spectrum. The assignment of the C-1 carboxyl, amino complex[6,7] was supported by the preparation of similar complexes with glycine and β-alanine. A previously formed complex was found to equilibrate with added amino acids allowing for the estimation of equilibrium constants from the ^{13}C NMR spectrum. With glycine and β-alanine, K_{eq} = 13, favoring the glycine complex; with glycine and aspartic acid, K_{eq} = 47, again favoring the complex with the unsubstituted 5-membered ring of glycine; and with aspartic acid alone, the ratio of the 5- to the 6-membered ring complex was found to be 27:1. The direct reduction of this in situ formed complex with BH_3 (Scheme III) avoided the previous separation of the two isomeric esters described above and provided a convenient one-vessel conversion of aspartic acid into homoserine.

This reductive procedure provides a particularly facile method for the regiochemical reduction of **1**, **4**, and longer α-amino diacids (works equally well for glutamic acid); however, the same conditions were not suitable for the related α-hydroxy acids. The Cu(II) complex of the amino acids were not stable under the same reductive conditions,[8] and the oxazolindinone derivatives[9] are more difficult to prepare than these boron complexes.

Intermediates **2**, **3**, **4**, and **6** proved useful in the selective reduction of aspartic acid. The regiochemical control

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produces either optical antipode of homoserine or β-amino-γ-hydroxybutanoic acid. Using the method described previously,[3] anhydride **2** was reduced with $NaBH_4$ in THF at 0 °C to give lactone **5** in 92% yield. Both of these compounds have proven to be useful chiral synthons[10-12] and are both important biological compounds in their own right.[1,13-15] Furthermore, all of these procedures are readily modified for isotopic enrichments (e.g., see Scheme IV).

Experimental Section

Sodium 2(*S*),4-Dihydroxybutyrate (1). L-Malic acid (1.34 g, 0.01 mol) was dissolved in trifluoroacetic anhydride (6 mL), and the the excess anhydride and acid were removed in vacuo. The remaining solid, *O*-TFA-L-malic anhydride, was opened by methanolysis to the monoacid, dried, and lyophilized from H_2O. The resulting powder was dissolved in THF (10 mL) and cooled to 0 °C, and a BH_3–THF solution (20 mL, 1 M) was added dropwise. After 2 h the reaction was quenched with methanol (10 mL), the THF and methanol were removed in vacuo, and the product was evaporated from MeOH several times to remove the methyl borate. The remaining oil, a mixture of 2,4-dihydroxybutyric acid lactone and the corresponding methyl ester, was treated with aqueous sodium carbonate (0.011 mol). Evaporation of the water gave the spectroscopically clean sodium salt of 2,4-dihydroxybutyrate: ^1H NMR (D_2O, 500 MHz) δ 1.62 (m, 1 H, β-H), 1.81 (m, 1 H, β′-H), 3.50 (br t, J = 7.5 Hz, 2 H, γ,γ′-H), 3.96 (q, J = 4.5 Hz, 1 H, α-H); ^{13}C NMR (D_2O, 100.6 MHz) δ 37.3 (t, J = 127.4 Hz, C-3), 59.4 (t, J = 143.5 Hz, C-4), 70.6 (d, J = 145.6 Hz, C-2), 182.1 (br s, C-1).

1-Methyl *N*-(Trifluoroacetyl)-L-aspartate (3). L-Aspartic acid (3.99 g, 0.03 mol) and trifluoroacetic anhydride (20 mL) were reacted as above. Following the MeOH addition, the dried residue was carefully triturated several times with ether/petroleum ether (1:2), and the resulting fine suspension was filtered to remove **4**: 6.0 g, 82%; mp 115-116 °C; $[\alpha]^{20}_D$ −40° (2.0 g/100 mL CH_3OH) (D isomer, $[\alpha]^{20}_D$ +40.5° (2.0 g/100 mL CH_3OH); IR ($CHCl_3$) 3410 (w), 3035 (w), 2957 (w), 1750 (shoulder), 1729 (s), 1234 (m), 1172 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.97 (dd, J = 18, 4.5 Hz, 1 H, β-H), 3.17 (dd, J = 18, 4 Hz, 1 H, β′-H), 3.80 (s, 3 H, methoxy), 4.84 (m, 1 H, α-H), 7.39 (br s, 1 H, NH); ^{13}C NMR (D_2O, 100.6 MHz) δ 35.7 (td, J = 132.2, 4.8 Hz, β-C), 50.3 (d, J = 142.6 Hz, α-C), 54.3 (q, J = 149.1 Hz, OCH_3), 116.5 (q, J = 285.8 Hz, CF_3), 159.5 (qd, J = 37.6, 3.6 Hz, CF_3CO), 172.1 (m, C-1), 174.5 (m, γ-C); Cl^+ MS m/z 244 $(M + H)^+$, 256 $(M - OH)^+$, 212 $(M - OCH_3)^+$, 198 $(M - COOH)^+$, 184 $(M - CH_2COOH)^+$, 114 $(M - C_4H_7O_4)^+$. Anal. Calcd for $C_7H_8NO_4F_3$: C, 34.54; H, 3.32; N, 5.76. Found: C, 34.27, H, 3.09; N, 5.85.

(*S*)-α-Amino-γ-butyrolactone Hydrochloride. **2** (2.43 g, 0.01 mol) and BH_3–THF (22 mL, 1.0 M) were reacted as above except that dilute HCl/C_2H_5OH (2:1) at reflux for 12 h was required to hydrolyze the methyl ester and the *N*-TFA. The product was crystallized from H_2O/acetone: 1.26 g (92%); mp 219-220 °C; $[\alpha]^{20}_D$ −25.4° (2 g/100 mL H_2O) (D isomer, $[\alpha]^{20}_D$ +25.0°, (2 g/100 mL H_2O); ^1H NMR (D_2O, 500 MHz) δ 2.23 (m, 1 H, β-H), 2.59 (m, 1 H, β′-H), 4.24 (m, 2 H, α-H′, γ-H), 4.40 (td, 1 H, J = 9, 1 Hz, γ-H); ^{13}C NMR (D_2O, 100.6 MHz) δ 27.56 (β-C), 49.41 (α-C), 68.26 (γ-C), 178.29 (C-1).

(*S*)-*N*-(Trifluoroacetyl)-α-amino-γ-butyrolactone-γ,γ′-d_2 (7). **2** (1.22 g, 5.0 mmol) was added to a suspension of $NaBD_4$ (0.42 g, 10 mmol, 98% D) in THF (10 mL). BF_3–$O(C_2H_5)_2$ (2 mL) was added at 0 °C, and after 2 h the reaction mixture was filtered and quenched with dilute HCl (5%, 10 mL). The solvent was removed in vacuo, and the residue was dried several times with CH_3OH to remove the borate formed. The solid was treated with 5% HCl and lyophilized to a pure white powder, 0.95 g (96%, 98% d_2): ^1H NMR ($CDCl_3$, 500 MHz) δ 2.23 (t, J = 12 Hz, 1 H, β-H), 2.92 (dd, J = 8.5, 12.5 Hz, 1 H, β′-H), 4.57 (m, 1 H, α-H), 6.98 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 27.2 (ddd, J = 139.5, 133.6, 3.8 Hz, B-C), 48.7 (br d, J = 141.8 Hz, α-C), 65.1 (br m, γ-C), 115.9 (q, J = 287.9 Hz, CF_3), 156.6 (qt, J = 36.9, 4.7 Hz, CF_3CO), 174.1 (br t, J = 73o.6 Hz, C-1).

***B*,*B*-Diethylboroxazolidone (6).** To a suspension of very finely ground L-aspartic acid (1.33 g, 0.01 (mol) in THF was added triethylborane–THF (10 mL, 1.0 M). The mixture was refluxed under N_2 until the solution cleared. The solvent was removed under house vacuum, and the resulting oil was solidified and treated with petroleum ether. The product was collected by filtration as white powder: yield ~100%; ^1H NMR (acetone-d_6, 500 MHz) δ 0.336 (br q, J = 8 Hz, 2 H, CH_2), 0.382 (br q, J = 8 Hz, 2 H, CH_2), 0.746 (t, J = 8 Hz, 3 H, CH_3), 0.757 (t, J = 8 Hz, 3 H, CH_3), 2.89 (dd, J = 18, 6.5 Hz, 1 H, β-H), 2.95 (dd, J = 18, 4.5 Hz, β′-H), 3.98 (br m, 1 H, α-H), 5.41 (br s, 1 H, NH_2), 5.90 (br s, 1 H, NH_2); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 8.95 (qt, J = 123.6, 4.7 Hz, CH_3), 9.20 (qt, J = 123.6, 4.7 Hz, CH_3), 12.6 (br m, $W_{1/2}$ ~ 500 Hz, CH_2), 13.4 (br m, $W_{1/2}$ ~ 500 Hz, CH_2), 34.0 (tt, J = 130.3, 4.0 Hz, β-C), 52.4 (dm, J = 141.0, 3.6 Hz, α-C), 172.6 (q = J = 7.1 Hz, C-4), 173.2 (br m, J = 5.1 Hz, C-1), minor (6-membered) isomer resolved signals δ 8.48 (CH_3), 9.63 (CH_3), 38.4 (β-C), 60.5 (α-C).

(*S*)-α-Amino-γ-butyrolactone Hydrochloride. L-Aspartic acid (1.33 g, 0.01 mol) was treated with triethylborane–THF (10 mL, 0.01 mol) to prepare the amino acid–borane complex described above. This clear solution was cooled to 0 °C with an ice–water bath, BH_3–THF (12 mL, 1.2 mmol) was added dropwise, and the mixture was stirred for an additional 2 h at 0 °C. Hydrochloric acid (5%, 10 mL) was added, and the solvent was removed under house vacuum at 60 °C. The remaining residue was redissolved in a small amount of HCl (5%, 15 mL), refluxed for 30 min to allow for complete hydrolysis of the boron complex, dried in vacuo, redissolved, and dried with MeOH several times to remove the boric acid. The residue was crystallized from aqueous acetone to give white crystals: 1.18 g (86%); NMR spectra as above; $[\alpha]^{20}_D$ −26.8° (1 g/100 mL H_2O) [lit.[15] $[\alpha]^{26}_D$ −27.0° (*c* = 5)] (D isomer, $[\alpha]^{20}_D$ +27.1° (1 g/100 mL H_3O). Anal. Calcd for $C_4H_8NO_2Cl$: C, 34.92; H, 5.87; N, 10.18. Found: C, 34.99; H, 5.54; N, 10.20.

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An Example of Regioselective Esterification by Intramolecular Acyl Transfer from a Tertiary Amine

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Despite the fact that the famous antimalarial quinine (1) has been known for 170 years, there is still considerable interest in its chemical and biological properties. Much of the most recent attention is due to the utility of quinine as a chiral resolving agent and catalyst.[1] In addition, however, malaria is still a worldwide problem, and quinine is the only antimalarial toward which resistance of the

(1) Dijkstra, G. D. H.; Kellogg, R. M.; Svendson, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069 and references cited therein.

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