^{1}H NMR 8.24 (4 H, AB, J = 8 Hz), 4.55 (2 H, CH_2O, t, J = 7 Hz), 2.37–1.0 (12 H, m); ^{19}F NMR −159.47 (heptet, $J_{FH(exo)}$ = 43 Hz, J_{FH} = 21 Hz); ^{13}C NMR 101.7 (C4[α], d, J = 183 Hz, $\Delta\delta$ = +62.84), 45.95 (C7[β], d, J = 21 Hz, $\Delta\delta$ = +10.53), 43.28 (C3[β], d, J = 24 Hz, $\Delta\delta$ = +7.66), 38.47 (C5[β], d, J = 27 Hz, $\Delta\delta$ = +9.68), 38.50 (C1[γ], d, J = 4.4 Hz, $\Delta\delta$ = −2.77), 28.00 (C2[γ], $\Delta\delta$ = −8.65), 21.4 (C6[γ], d, J = 13 Hz, $\Delta\delta$ = −8.69), 36.59 (C8[δ], $\Delta\delta$ = −1.76), 61.9 (C9, $\Delta\delta$ = −3.09), 150.5, 136.4, 130.6, 123.4 (C_{arom}), 164.5 (CO); MS, m/e 307 (M^+), 287 [$(M - HF)^+$]. Anal. Calcd for $C_{16}H_{18}FNO_4$: C, 62.54; H, 5.86. Found: C, 62.60; H, 5.46. The more polar compound was found to be (2-fluoro-2-norbornyl)ethyl p-nitrobenzoate (**23**): 20% yield; mp 40 °C (hexane); ^{1}H NMR 8.25 (4 H, AB, J = 8 Hz), 4.39 (2 H, CH_2O, t, J = 6.8 Hz, $^4J_{HF}$ = 1.7 Hz), 2.33–1.0 (12 H, m); ^{19}F NMR −162.57 (d quintet, $J_{FH(endo)}$ = 57 Hz, J_{FH} = 28 Hz, $J_{FH(exo)}$ = 9 Hz); ^{13}C NMR 95.64 (C2[α], d, J = 184 Hz, $\Delta\delta$ = +58.99), 47.10 (C1[β], d, J = 19 Hz, $\Delta\delta$ = +5.83), 39.2 (C8[β], d, J = 20 Hz, $\Delta\delta$ = +0.85), 35.90 (C3[β], d, J = 29 Hz, $\Delta\delta$ = +0.28), 64.54 (C9[γ], $\Delta\delta$ = −0.45), 34.87 (C7[γ], d, J = 13 Hz, $\Delta\delta$ = −0.55), 32.3 (C4[γ], $\Delta\delta$ = −6.56), 29.30 (C6[γ], $\Delta\delta$ = −0.79), 32.11 (C5[δ], $\Delta\delta$ = +3. 32), 150.5, 136.4, 130.7, 123.4 (C_{arom}), 164.5 (CO); MS, m/e 307 (M^+), 287 [$(M - HF)^+$]. Anal. Calcd for $C_{16}H_{18}FNO_4$: C, 62.54; H, 5.86. Found: C, 61.82; H, 5.73. Similarly the acetate of 2-norbornylethanol (**25**) was fluorinated, and after chromatography, two fractions were isolated. The less polar one proved to be the 4-fluoro derivative **27**: 15% yield; ^{1}H NMR 4.24 (2 H, CH_2O, t, J = 7 Hz), 2.04 (3 H, Ac, s), 2.40–1.0 (12 H, m); ^{19}F NMR −159.6 (heptet, $J_{FH(exo)}$ = 44 Hz, J_{FH} = 22 Hz); MS, m/e 200 (M^+), 180 [$(M - HF)^+$], 157 [$(M - Ac)^+$], 137 [$(M - Ac - HF)^+$]. Anal. Calcd for $C_{11}H_{17}FO_2$: C, 66.00; H, 8.50. Found: C, 65.87; H, 8.26. The more polar compound was the corresponding 2-fluoro isomer **26**: 30% yield; ^{1}H NMR 4.06 (2 H, CH_2O, dt, J = 6.5 Hz, $^4J_{FH}$ = 1.5 Hz), 2.05 (3 H, Ac, s), 2.40–0.9 (12 H, m); ^{19}F NMR −162.6 (d, quintet, $J_{FH(endo)}$ = 56 Hz, J_{FH} = 27 Hz, $J_{FH(exo)}$ = 9 Hz); MS, m/e 200 (M^+), 180 [$(M - HF)^+$], 157 [$(M - Ac)^+$], 137 [$(M - Ac - HF)^+$]. Anal. Calcd for $C_{11}H_{17}FO_2$: C, 66.00; H, 8.50. Found: C, 66.21; H, 8.36.

Fluorination of tricyclo[5.2.1.0^{2,6}]decane (28) was performed on 1.0 g (7.35 mmol) by using 1.5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with pe followed by HPLC using cyclohexane as eluent. A single compound was thus isolated in 75% yield and identified as 2-fluorotricyclo[5.2.1.0^{2,6}]decane (**29**), a white solid that sublimes at room temperature: ^{1}H NMR 2.4 (1 H, C_6-H, m), 2.2 (1 H, C_1-H, m), 2.10–1.20 (13 H, m); ^{19}F NMR −126.76 (m, $W_{h/2}$ = 75 Hz); ^{13}C NMR 114.1 (C2[α], d, J = 188 Hz, $\Delta\delta$ = +67.60), 54.20 (C6[β], d, J = 18 Hz, $\Delta\delta$ = +7.70), 45.90 (C1[β], d, J = 26 Hz, $\Delta\delta$ = +3.40), 32.70 (C3[β], d, J = 26 Hz, $\Delta\delta$ = +8.77), 40.5 (C10[γ], $\Delta\delta$ = −3.71), 40.47 (C7[γ], $\Delta\delta$ = −2.03), 28.2 (C4[γ], $\Delta\delta$ = −1.50), 25.26 (C9[γ], d, J = 3.1 Hz, $\Delta\delta$ = −2.56), 23.20 (C5[γ], d, J = 8.9 Hz, $\Delta\delta$ = −0.72), 21.49 (C_8[δ], $\Delta\delta$ = −6.33); MS, m/e 154 (M^+). Anal. Calcd for $C_{10}H_{15}F$: C, 77.92; H, 9.74. Found: C, 77.56; H, 9.44.

Fluorination of 2-ethyl-1-methoxybicyclo[2.2.2]octane (30) was performed on 0.5 g (2.97 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in pe followed by HPLC using 5% EtOAc in cyclohexane as eluent. A single compound was thus isolated in 25% yield and identified as 2-ethyl-2-fluoro-1-methoxybicyclo[2.2.2]octane (**31**): ^{1}H NMR 3.29 (3 H, OMe, d, J_{FH} = 1 Hz), 2.20–1.0 (13 H, m), 0.99 (CH_3CH_2, t, J = 7 Hz); ^{19}F NMR −146.18 (q, J_{FH} = 32 Hz); ^{13}C NMR 101.45 (C2[α], d, J = 180 Hz, $\Delta\delta$ = +61.94), 76.91 (C1[β], d, J = 33 Hz, $\Delta\delta$ = +2.13), 40.40 (C3[β], d, J = 23 Hz, $\Delta\delta$ = +6.34), 26.45 (C10[β], d, J = 26 Hz, $\Delta\delta$ = +2.73), 50.78 (C9[γ], $\Delta\delta$ = +2.40), 27.11 (C7[γ], d, J = 6.9 Hz, $\Delta\delta$ = +0.40), 26.45 (C6[γ], $\Delta\delta$ = −2.55), 22.77 (C4[γ], d, J = 7.5 Hz, $\Delta\delta$ = −2.09), 6.26 (C11[γ], d, J = 4.4 Hz, $\Delta\delta$ = −5.42), 25.90 (C5[δ], $\Delta\delta$ = −1.01), 25.08 (C8[δ], $\Delta\delta$ = −0.67); MS, m/e 186 (M^+), 166 [$(M - HF)^+$]. Anal. Calcd for $C_{11}H_{19}FO$: C, 70.97; H, 10.21. Found: C, 70.99; H, 10.18.

Fluorination of bicyclo[2.2.2]octane (35) was performed on 1 g (9.09 mmol) by using 2% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with pe followed by HPLC using cyclohexane as eluent. Two compounds were isolated. The less polar one was proved to be 2-fluorobicyclo[3.2.1]octane (**37**): 40% yield; mp 131 °C (from pentane–methanol); ^{1}H NMR 4.77 (1 H, CHF, br dd, J_{FH} = 53 Hz, J = 9 Hz), 2.05–1.2 (12 H, m); ^{19}F NMR −169.68 (m, $W_{h/2}$ = 140 Hz); ^{13}C NMR 91.08 (C2[α], d, J = 175 Hz, $\Delta\delta$ = +58.28), 35.50 (C1[β], d, J = 20 Hz, $\Delta\delta$ = +0.30), 29.25 (C3[β], d, J = 19 Hz, $\Delta\delta$ = +10.15), 26.89 (C8[γ], d, J = 7 Hz, $\Delta\delta$ = −12.8), 25.90 (C4[γ], $\Delta\delta$ = −6.90), 22.03 (C7[γ], d, J = 8 Hz, $\Delta\delta$ = −6.87), 24.29 (C5[δ], $\Delta\delta$ = −10.9), 18.39 (C4[δ], d, J = 5 Hz, $\Delta\delta$ = −10.5); MS, m/e 128 (M^+). Anal. Calcd for $C_8H_{13}F$: C, 75.00; H, 10.16. Found: C, 74.60; H, 9.85. The more polar compound was the expected known 1-fluorobicyclo[2.2.2]octane (**36**), obtained in 50% yield; mp (sealed tube) 174 °C, identical in all respects with the one reported in the literature.[2a]

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Reaction of Glyoxal with Acetoacetic Esters: Formation of Furo[3,2-*b*]furan Derivatives†

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The reaction of glyoxal with ethyl or methyl esters of acetoacetic acid in aqueous solution at pH 7 yields furo[3,2-*b*]furan derivatives **6a** and **6b**, respectively. The structures were based on ^{1}H and ^{13}C NMR and mass spectra and confirmed by X-ray analysis of **6b**. Dehydration of **6a** under acidic conditions afforded a mixture of furan **2a** and diethyl *cis*-3a,6a-dihydro-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (**7a**). The corresponding methyl esters were obtained by using **6b**. These results require revision of structures reported by earlier workers for some of these products.

The reaction between glyoxal and β-keto esters has been the subject of several studies. From the reaction of glyoxal with ethyl acetoacetate in concentrated aqueous zinc chloride, Polonowsky[1] obtained a crystalline product, mp 207 °C, identified as 2-methyl-3-carboxyfuran-5-acetic acid, and two isomers, one a crystalline product, mp 139 °C, and

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(1) Polonowsky, M. *Justus Liebigs Ann. Chem.* **1888**, *246*, 1.

0022-3263/88/1953-2807$01.50/0

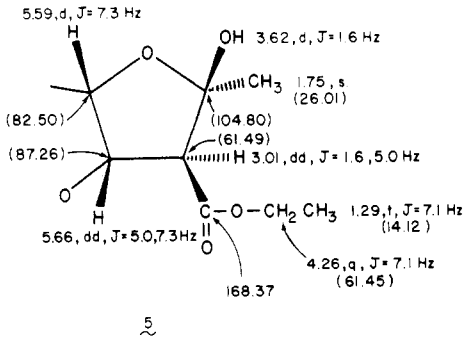

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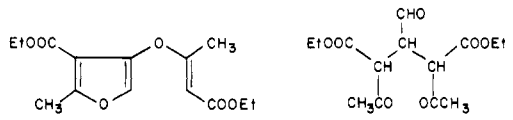
Figure 1. Partial structure of **6a** proposed by APT and ^1H–^{13}C correlation. The attached numbers are ^1H chemical shifts, multiplicities, and coupling constants (^{13}C chemical shifts).

the other a heavy yellow oil, assigned the furan structures **1** and **2a**, respectively. In a later study by West[2] in which



1

3

Et = CH_2CH_3

condensation was carried out at pH 7.0 and in the absence of zinc chloride, the two isomers isolated by Polonowsky were obtained along with a new compound, mp 109–110 °C, which was claimed to be diethyl 3-formyl-2,4-diacetylglutarate (**3**). This work was repeated and extended by Gault et al.[3–7] who revised the structure of the latter product to the dihydrofuran **4a**[3,8] and converted it to **2a** by dehydration in 50% sulfuric acid.[4]

The reaction of glyoxal with dimethyl 3-oxoglutarate in acidic media has been the subject of extensive investigations, initially by Weiss et al., which resulted in the characterization of carbocyclic products which include esters of *cis*-bicyclo[3.3.0]octane-3,7-dione[9a] and *endo*- and *exo*-tetracyclo[5.5.1.$0^{2,6}$.$0^{10,13}$]tridecane triketone.[9b–d]

In connection with some other work, we have reinvestigated the reaction of glyoxal with ethyl and methyl acetoacetates and now report revised structures for some of the products.

Prolonged reaction of glyoxal and ethyl acetoacetate in water at pH 7.0 and 5–10 °C led to a crystalline solid and an oil, which contained at least five other compounds. The solid, after careful purification, gave a compound $C_{14}H_{20}O_7$, mp 112–113 °C, which is presumably identical with that obtained by West and by Gault and co-workers and assigned structures **3**[2] and **4**[3,8] respectively. The 300-MHz ^1H NMR spectrum of this compound lacked a signal due to an aldehyde proton, thus eliminating structure **3**, but instead showed two *C*-methyl singlets, signals due to two nonequivalent ethyl ester groups,[10] an hydroxyl group, indicated by the presence of a doublet exchangeable by D_2O, at δ 3.62 (J = 1.6 Hz), and, in addition, a doublet of doublets at δ 3.01 (J = 1.6 Hz and 5.0 Hz) and 5.66 (J = 5.0 Hz and 7.3 Hz) and a doublet at δ 5.59 (J = 7.3 Hz). Assignment of the latter multiplets to the -CH(OH)CHCH- system of **4a** would require the acetoacetate side chain to be present in the keto form, a situation denied by the absence of a signal below 175 ppm for a ketone carbonyl[11] in the ^{13}C NMR spectrum of this compound.[12] Moreover, the 1.6-Hz coupling is small for CHOH[13,14] but is more appropriate to a 4-bond coupling[15,16] and could be accommodated by the cyclic hemiacetal part structure **5** (Figure 1). The preference for four-bond coupling via W geometry[15,16] of the HO–C–C–H system requires trans stereochemistry for H and OH, while the remaining coupling constants of 5.0 Hz and 7.3 Hz are best accommodated by successive trans and cis disposition of hydrogens. The ^{13}C resonance assignments in **5** were based on chemical shift values, APT and ^1H–^{13}C correlation experiments. The similarity in shift of C-4 and C-5 requires attachment of oxygen at C-4 in **5**. Consideration of remaining features of the ^1H NMR and ^{13}C NMR spectra and subsequent degradative experiments are consistent with conversion of part structure **5** into structure **6a**, the cyclic hemiacetal of Gault's structure **4a**.[3,8]

Treatment of **6a** with acidified aqueous acetone for 2.5 h afforded two $C_{14}H_{18}O_6$ isomers separable by chromatography into an oil (major product) and a crystalline solid, mp 135–136.5 °C.[17] The spectroscopic properties of the oil were fully consistent with structure **2a** suggested by earlier workers[1–7] although the compound exists (in $CDCl_3$) almost entirely in the enol form. The mass spectrum showed the sequential loss of ketene, ethylene, and water characteristic of β-keto esters,[18] a feature missing from the spectra of compounds possessing the furofuran skeleton, e.g. **6a**, **7a**.

The ^1H NMR spectrum of the crystalline compound required the presence of two equivalent ethyl esters, two equivalent uncoupled methyl groups at δ 2.30 and two equivalent uncoupled single protons at δ 5.96 implying a high degree of symmetry, a situation confirmed by the ^{13}C NMR spectrum which showed only seven carbon resonances. Interestingly, the methylene protons of the ethyl esters were nonequivalent and appeared as part of an ABX_3 pattern. Such diastereotopic behavior exhibited by ethyl groups is well-known[19,20] and may be explained by

(2) West, E. *J. Am. Chem. Soc.* **1925**, *47*, 2780; *J. Biol. Chem.* **1925**, *66*, 63.
(3) Gault, H.; Selim, M.; Selim-Dorgans, M. *C.R. Hebd. Seances Acad. Sci.* **1956**, *243*, 1125.
(4) Selim-Dorgans, M.; Selim, M.; Gault, H. *C.R. Hebd. Seances Acad. Sci.* **1957**, *244*, 1047.
(5) Gault, H.; Gordon-Fischhof, E.; Selim-Dorgans, M. *Bull. Soc. Chim. Fr.* **1959**, 1167.
(6) Gault, H.; Selim-Dorgans, M.; Selim, M. Fr. Pat. 1 185 403 *Chem. Abstr.* **1961**, *55*, 19948c.
(7) Gault, H.; Gordon-Fischhof, E.; Selim-Dorgans, M. *Bull. Soc. Chim. Fr.* **1960**, 1667.
(8) No stereochemistry was reported; that depicted in **4a** results from this study.
(9) (a) Edwards, J. M.; Weiss, U. *Tetrahedron Lett.* **1968**, 4885. (b) Edwards, J. M.; Qureshi, I. H.; Weiss, U.; Akiyama, T.; Silverton, J. H. *J. Org. Chem.* **1973**, *38*, 2919. (c) Akiyama, T.; Silverton, J. V. *Acta Crystallogr., Sect. B* **1975**, *B31*, 2336. (d) Rice, K. C.; Sharpless, N. E.; Weiss, U.; Highet, R. J. *Tetrahedron Lett.* **1975**, 3763.
(10) The signals due to the methylene hydrogens of the ethyl groups appear as overlapping A_2X_3 and ABX_3 patterns.
(11) Matusch, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 260.
(12) A further feature which argues against the assignment of structure **4a** to this compound is the following. Based on the above reasoning and ^{13}C–^1H correlation experiments, ^{13}C resonances at δ 61.49, 87.26, and 82.50 would be assigned to C-4 and C-5 of the dihydrofuran **4a** and CH(Ac)-COOEt, respectively. Using the carbon spectrum of **7a** (see Experimental Section) as a model, one would expect δ values of 80–90 ppm for C-4 and C-5 in the ^{13}C NMR spectrum of a compound possessing structure **4a**. Thus the C-4 resonance is too high field for structure **4a**.
(13) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance in Organic Chemistry*, 2nd Ed.; Pergammon Press: Oxford, 1969; p 298, 334.
(14) Sohár, P. *Nuclear Magnetic Resonance Spectroscopy*; CRC Press: Boca Raton, FL, 1983, Vol. II, p 100.
(15) Reference 13, p 334, 341 and references therein.
(16) Reference 14, Vol. I, p 62, 67 and references therein.
(17) This compound is believed to be identical with that obtained by Polonowsky[1] and West[2] who assigned structure **1**.
(18) Bowie, J. H.; Lawesson, S.-O.; Schroll, G.; Williams, D. H. *J. Am. Chem. Soc.* **1965**, *87*, 5742.

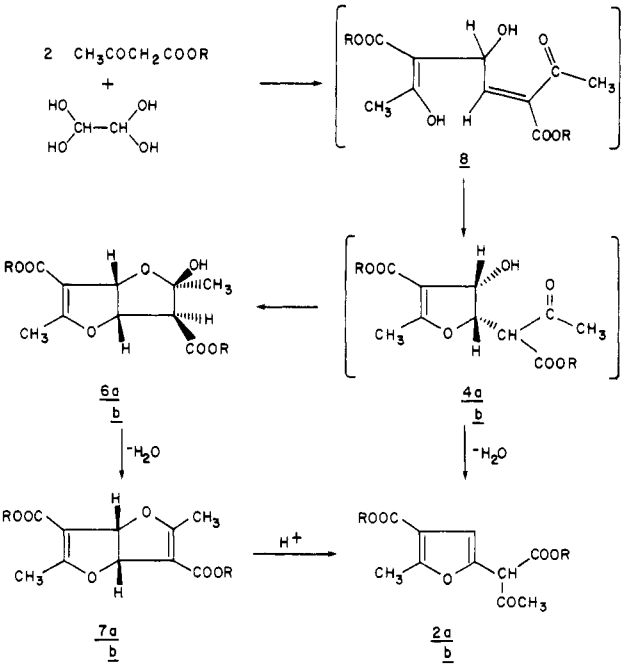
the presence of a proximal chiral center. Consideration of the ^1H and ^{13}C chemical shifts and the simplicity of the spectrum leads to the dihydrofuro[3,2-*b*]furan structure **7a** for this isomer. The formation of **7a** and **2a** could involve trans-1,2-dehydration of the cyclic hemiacetal **6a** or its ring-opened isomer **4a**, respectively. That the situation is more complex than this became clear during experiments to determine whether **7a** and **2a** resulted from consecutive or competitive reactions which were carried out during attempts to increase the yield of **7a**. When **6a** is dissolved in chloroform containing trifluoroacetic acid, the ratio of **2a**:**7a** was 3:2 after 1 min, while after 52 h compound **2a** was the sole product. This suggests that **2a** can be formed from **7a** and this was confirmed in a separate experiment. The conversion **7a** → **2a** might proceed by a mechanism involving protonation at O(4) and heterolytic cleavage between C(3a)–O(4) followed by proton loss from C(6a) to generate the furan ring of the trans enol of **2a** and subsequent conversion to the cis enol form. This acid lability of **7a** provides an explanation for the formation of **2a** as the sole product during prolonged dehydration of **6a** using 50% sulfuric acid.[4]

A parallel investigation of the corresponding methyl esters, to help with spectral interpretation, has been carried out and yielded similar results. Thus, glyoxal and methyl acetoacetate afforded a crystalline compound, $C_{12}H_{16}O_7$, whose mass spectrum and ^1H and ^{13}C NMR spectra were in accord with structure **6b**. This structure and, in particular, the stereochemical assignments have been confirmed by single-crystal X-ray analysis.

Acid-catalyzed dehydration of **6b**, using trifluoroacetic acid in chloroform, afforded the furan **2b** and the furo[3,2-*b*]furan **7b** in the ratio 7:1. The assignment of structure **7b** was based upon its origin and particularly its remarkably simple NMR spectra which showed three singlets at δ 2.31, 3.78, and 5.98 (ratio 3:3:1) in the proton spectrum and six singlets in the proton-decoupled carbon spectrum (see Experimental Section).

The mechanism of the Weiss condensation of glyoxal[21-23] or malondialdehyde[22] with dimethyl 3-ketoglutarate has recently been discussed and it is interesting to compare these examples with the reaction between glyoxal and acetoacetic esters. In the former examples, Bertz makes a compelling case for the initial steps in the reaction being aldolization, dehydration, and subsequent Michael addition. Such a sequence with ethyl acetoacetate and glyoxal would yield **3** via ethyl 2-acetyl-4-oxo-2-butenoate, and loss of water from **3** would lead to derivatives of furo[2,3-*b*]furan which have not been observed in the present study. A more plausible pathway (Scheme I) would involve two successive aldol condensations and dehydration to give **8**, 5-Exo-Trig cyclization via an intramolecular Michael addition of enolic hydroxyl to give **4a**, and, finally, cyclic hemiacetal formation, although the order of the last two steps could be reversed. Loss of water from **4a** and **6a** would generate **2a** and **7a**, respectively; **2a**, **6a**, and **7a** were all detected (TLC) in the crude oily byproduct formed in the preparation of **6a**.

Scheme I[a]



[a] **a**, R = CH_2CH_3; **b**, R = CH_3.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Evaporation under reduced pressure was carried out on a Büchi rotary evaporator. Chemicals were reagent grade; solvents were spectroscopic grade and distilled prior to use. Thin layer separations were carried out on a Chromatotron Model 7924T (Harrison Research, Palo Alto, CA) and Merck silica gel 60 PF_{254} containing gypsum. BDH silica (chromatographic grade) (60–120 mesh) was used in column chromatographic separations. Mass spectra were determined on a VG 7070HS mass spectrometer equipped with a VG2035 data system. Electron impact spectra were obtained at 70 eV with a source temperature of 200 °C; samples were introduced via a direct probe inlet. ^1H and ^{13}C NMR (proton-decoupled) spectra were determined on a General Electric GN300NB 300-MHz NMR spectrometer using solutions in deuteriochloroform. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. ^{13}C chemical shift assignments were aided by APT and ^{13}C–^1H shift correlation experiments.[24] Compounds were analyzed for C and H by Alfred Bernhardt, West Germany, or Guelph Chemical Laboratories, Ontario, Canada.

General Method for Glyoxal Condensations. The following is a modification of the procedure used by West. Glyoxal (500 mL of approximately 5.75% aqueous solution adjusted to pH 7.0 using 20% aqueous sodium carbonate) and the β-keto ester (0.977 mol) were mixed, diluted to 1.25 L with water, stirred until homogeneous (ca. 1–5 min), readjusted to pH 7.0, and then refrigerated. The oil which was formed within a few days gradually deposited crystals, which were collected by filtration after a period of 2–3 weeks, depending on the dicarbonyl compound. The crude product was freed from oily contaminants by being washed with cold (−70 °C) ether and purified by two recrystallizations from 95% ethanol.

(a) From Ethyl Acetoacetate. Colorless crystals (19.5 g, 13.3%) of diethyl 3a,5,6,6a-tetrahydro-5-hydroxy-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (**6a**): mp 112–113 °C (lit. mp 109–110 °C;[2] 121 °C[3]); ^1H NMR δ 1.29 (t, J = 7.1 Hz, CH_3 of ethyl ester at C-6), 1.32 (t, J = 7.1 Hz, CH_3 of ethyl ester at C-3), 1.75 (s, CH_3 at C-5), 2.25 (s, CH_3 at C-2), 3.01 (dd, $J_{6,5\text{-OH}}$ = 1.6 Hz, $J_{6,6a}$ = 5.0 Hz, H at C-6), 3.62 (d, $J_{6,5\text{-OH}}$ = 1.6 Hz, hydroxyl at C-5), 4.18 and 4.25 (qq, $J_{CH_2CH_3}$ = 7.1 Hz, J_{AB} = 10.9 Hz, H_B and

(19) (a) Shafer, P. R.; Davis, D. R.; Vogel, M.; Nagarajan, K.; Roberts, J. D. *Proc. Nat. Acad. Sci. U.S.A.* **1961**, *47*, 49. (b) Coyle, T. D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1961**, *83*, 4138. (c) Pritchard, J. G.; Lauterbur, P. C. *J. Am. Chem. Soc.* **1961**, *83*, 2105. (d) Waugh, J. S.; Cotton, F. A. *J. Phys. Chem.* **1961**, *65*, 562. (e) Sohár, P.; Kosáry, J.; Kasztreiner, E. *Acta Chim. Acad. Sci. Hung.* **1975**, *84*, 201.

(20) For a review, see: Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307.

(21) Yang-Lan, S.; Mueller-Johnson, M.; Oehldrich, J.; Wichman, D.; Cook, J. M.; Weiss, U. *J. Org. Chem.* **1976**, *41*, 4053.

(22) Bertz, S. H. *J. Org. Chem.* **1985**, *50*, 3585 and references therein.

(23) Bertz, S. H.; Adams, W. O.; Silverton, J. V. *J. Org. Chem.* **1981**, *46*, 2828.

(24) (a) Freeman, R.; Morris, G. A. *J. Chem. Soc., Chem. Commun.* **1978**, 684. (b) Bodenhausen, G.; Freeman, R. *J. Am. Chem. Soc.* **1978**, *100*, 320. (c) Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 501.

H_A of ethyl ester CH_2, ABX_3 system), 4.26 (q, J = 7.1 Hz, ethyl ester CH_2, A_2X_3 system), 5.59 (d, $J_{6a,3a}$ = 7.3 Hz, H_B of AB pattern, H at C-3a), 5.66 (dd, $J_{6a,3a}$ = 7.3 Hz, $J_{6a,6}$ = 5.0 Hz, H_A of AB pattern with additional splitting, H at C-6a); ^{13}C NMR δ 14.12 (CH_3 of ethyl ester at C-6), 14.44 (CH_3 of ethyl ester at C-3), 14.59 (CH_3 at C-2), 26.01 (CH_3 at C-5), 59.89 (CH_2 of ethyl ester at C-3), 61.45 (CH_2 of ethyl ester at C-6), 61.49 (C-6), 82.50 (C-3a), 87.26 (C-6a), 104.43 (C-3), 104.80 (C-5), 165.02 (ester carbonyl at C-3), 168.37 (ester carbonyl at C-6), 171.91 (C-2); MS, m/z (relative intensity) 300 (M^+, 2), 255 (4), 240 (12), 239 (5), 212 (5), 211 (13), 195 (8), 194 (9), 170 (8), 167 (27), 165 (9), 139 (19), 125 (5), 124 (7), 123 (8), 121 (7), 97 (6), 43 (100), 39 (5), 31 (5), 29 (26). Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 56.19; H, 6.55.

(b) From Methyl Acetoacetate. Colorless crystals (13.35 g, 10%) of dimethyl 3a,5,6,6a-tetrahydro-5-hydroxy-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (**6b**): mp 120–122 °C; ^1H NMR δ 1.74 (s, CH_3 at C-5), 2.26 (s, CH_3 at C-2), 3.04 (dd, $J_{6,5\text{-OH}}$ = 1.7 Hz, $J_{6,6a}$ = 5.0 Hz, H at C-6), 3.64 (d, $J_{6,5\text{-OH}}$ = 1.7 Hz, hydroxyl at C-5), 3.74 (s, C-6 ester methyl), 3.81 (s, C-3 ester methyl), 5.58 (d, $J_{6a,3a}$ = 7.2 Hz, H_B of AB pattern, H at C-3a), 5.67 (dd, $J_{6a,3a}$ = 7.2 Hz, $J_{6a,6}$ = 5.0 Hz, H_A of AB pattern with additional splitting, H at C-6a); ^{13}C NMR δ 14.51 (CH_3 at C-2), (CH_3 at C-2), 25.90 (CH_3 at C-5) 51.13 (C-6 ester methyl), 52.49 (C-3 ester methyl), 61.41 (C-6), 82.46 (C-3a), 87.37 (C-6a), 104.44 (C-3 and C-5), 165.37 (C-3 ester carbonyl), 168.81 (C-6 ester carbonyl), 172.40 (C-2); MS, m/z (relative intensity) 272 (M^+, 2.3), 223 (6), 222 (19), 212 (16), 211 (8), 197 (8), 195 (5), 181 (7), 180 (32), 165 (7), 153 (30), 152 (7), 137 (8), 121 (9), 79 (5), 59 (7), 43 (100), 42 (11), 39 (6). Anal. Calcd for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 52.95; H, 5.96.

Dehydration of Diethyl 3a,5,6,6a-Tetrahydro-5-hydroxy-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (6a). (a) To a stirred solution of the diethyl ester **6a** (1.1 g) in acetone (6 mL) was added 1.1 mL of 4 M sulfuric acid over 2 h. After stirring for a further 0.5 h, the reaction mixture was diluted with water (10 mL) and the product extracted with ether (3 × 10 mL). The ether extracts were dried ($MgSO_4$), filtered, and evaporated to give a two-component mixture (0.92 g, 88%) containing a crystalline material and a pale yellow oil. Chromatography of the mixture on a column of silica gel (50 g) using benzene, 9:1 benzene/acetone, and then 4:1 benzene/acetone as eluting solvent afforded a pale yellow oil (0.779 g, 74%), a fraction containing both components (0.041 g, 4%), and a colorless crystalline material (0.091 g, 9%).

The pale yellow oil was purified for analysis by Chromatatron elution (2-mm silica disk, 5% ethyl acetate in hexane) to give colorless ethyl 2-methyl-5-(1-(ethoxycarbonyl)-2-oxopropyl)-furan-3-carboxylate (**2a**): bp 100 °C at 0.1 mm (lit. bp 290–300 °C;[1] 130–140 °C at 0.5–0.8 mm;[2] 145 °C at 0.1 mm[4]); ^1H NMR δ 1.25 (t, J = 7.1 Hz, CH_3 of acetoacetate ethyl ester), 1.36 (t, J = 7.1 Hz, CH_3 of furan ethyl ester), 2.00 (s, CH_3 of acetoacetate side chain, enol form), 2.26 (very small s, CH_3 of acetoacetate side chain, keto form), 2.58 (s, CH_3 at C-2), 4.22 (q, J = 7.1 Hz, CH_2 of acetoacetate ethyl ester), 4.30 (q, J = 7.1 Hz, CH_2 of furan ethyl ester), 4.74 (very small s, CH of acetoacetate, keto form), 6.46 (s, proton at C-3), 6.70 (very small s, proton at C-3, keto form) 13.39 (s, enolic proton); ^{13}C NMR δ 13.88 (furan C-2 methyl), 14.12 (CH_3 of furan ethyl ester), 14.36 (CH_3 of acetoacetate ethyl), 20.08 (CH_3 of acetoacetate, enol form), 60.03 (CH_2 of acetoacetate ethyl), 61.00 (CH_2 of furan ethyl ester) 94.75 (C-1′ of acetoacetate side chain, enol form), 112.25 (furan C-4), 114.40 (furan C-3), 146.00 (furan C-5), 158.44 (furan C-2), 164.13 (furan ester C=O), 172.02 (acetoacetate ester C=O), 178.54 (C-2′ of acetoacetate side chain, enol form); MS, m/z (relative intensity) 282 (M^+, 9), 240 (43), 239 (6), 237 (22), 236 (53), 212 (20), 211 (40), 209 (7), 195 (9), 194 (78), 191 (8), 183 (11), 167 (9), 166 (11), 165 (41), 151 (7), 139 (7), 93 (6), 79 (10), 43 (10). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.80; H, 6.12.

The solid component was recrystallized from 95% ethanol to give colorless crystals of diethyl *cis*-3a,6a-dihydro-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (**7a**): mp 135–136.5 °C (lit. mp 139 °C;[1] 138–139.5 °C[2]); ^1H NMR δ 1.32 (t, J = 7.1 Hz, CH_3s of ethyl esters at C-3, C-6), 2.30 (s, methyls at C-2, C-5), 4.23 and 4.28 (qq, $J_{CH_2\text{-}CH_3}$ = 7.1 Hz, J_{AB} = 11.10 Hz, H_B and H_A of ethyl ester methylene ABX_3 system), 5.96 (s, C_{3a} and C_{6a} protons); ^{13}C NMR δ 14.44 (CH_3s of ethyl esters), 14.63 (methyls at C-2, C-5), 59.94 (CH_2s of ethyl esters), 88.34 (C-3a, C-6a), 103.34 (C-3, C-6), 164.83 (ester carbonyl), 174.33 (C-2, C-5); MS, m/z (relative intensity) 282 (M^+, 3), 240 (7), 237 (13), 236 (36), 211 (8), 209 (5), 195 (7), 194 (62), 191 (6), 183 (8), 166 (11), 165 (34), 163 (7), 151 (5), 137 (5), 121 (10), 43 (100), 29 (23). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.74; H, 6.51.

(b) When **6a** (0.140 g) was dissolved in chloroform (1.5 mL) containing trifluoroacetic acid (0.005 g) allowed to stand for 1 min, and then evaporated, an oily solid (0.133 g) was obtained which was shown by ^1H NMR analysis to contain **2a**, **7a**, and unchanged **6a** in a ratio of 3:2:1. Separation by Chromatotron elution (1-mm silica, 5% ethyl acetate in hexane) gave **2a** (0.070 g, 53%) and **7a** (0.045 g, 34%), identical with compounds described in part a by ^1H NMR, MS, and TLC.

(c) A solution of **6a** (0.061 g) in $CDCl_3$ (0.57 mL) containing trifluoroacetic acid (0.005 g) was allowed to stand for 52 h at room temperature when ^1H NMR analysis showed that furan **2a** was the sole product. Evaporation of the solution yield pure **2a** (0.057 g, 99%).

Dehydration of Dimethyl 3a,5,6,6a-Tetrahydro-5-hydroxy-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (6b). To a stirred solution of **6b** (0.196 g) in chloroform (1.5 mL) was added a catalytic amount of trifluoroacetic acid (0.010 g). After being stirred for 1 min, the solution was evaporated and then placed under high vacuum (0.1 mm) for 2 h to give 0.183 g of colorless oil which was separated on the Chromatotron (1-mm silica, 1:3 ethyl acetate/hexane, 30-mL fractions) to give the following. Fraction 1, colorless crystals (0.143 g, 78%) of methyl 2-methyl-5-(1-(methoxycarbonyl)-2-oxopropyl)furan-3-carboxylate (**2b**): mp 61–62 °C; ^1H NMR δ 2.00 (s, CH_3 of acetoacetate side chain, enol form), 2.59 (s, CH_3 at C-2), 3.74 (s, acetoacetate ester methyl), 3.82 (s, furan ester methyl), 6.46 (s, proton at C-3), 13.28 (s, enolic proton); ^{13}C NMR δ 13.87 (furan C-2 methyl), 20.09 (CH_3 of acetoacetate, enol form), 51.30 (furan ester methyl), 52.08 (acetoacetic ester methyl), 94.48 (C-1′ of acetoacetate side chain, enol form), 111.38 (furan C-4), 114.16 (furan C-3), 145.96 (furan C-5), 158.87 (furan C-2), 164.50 (furan ester C=O), 172.38 (acetoacetate ester C=O), 178.85 (C-2′ of acetoacetate side chain, enol form); MS, m/z (relative intensity) 254 (M^+, 9), 223 (15), 222 (40), 213 (5), 212 (47), 211 (6), 197 (21), 191 (8), 181 (10), 180 (88), 179 (6), 165 (19), 153 (10), 152 (27), 151 (7), 148 (6), 137 (23), 121 (11), 120 (7), 79 (12), 77 (10), 69 (5), 59 (8), 51 (6), 43 (100), 31 (5). Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.58; H, 5.67. Fraction 2: a 1:2 (by ^1H NMR) mixture of **2b** and **7b** (0.21 g, 11.5%). Fraction 3, colorless crystals (0.020 g, 11%) of dimethyl *cis*-3a,6a-dihydro-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (**7b**); mp 150.5–151.5 °C; ^1H NMR δ 2.31 (s, methyls at C-2, C-5), 3.78 (s, ester methyls at C-3, C-6), 5.98 (s, protons at C-3a, C-6a); ^{13}C NMR δ 14.58 (CH_3s at C-2, C-5), 51.26 (ester methyls), 88.39 (C-3a, C-6a), 103.11 (C-3, C-6), 165.18 (ester carbonyl), 174.73 (C-2, C-5); MS, m/z (relative intensity) 254 (M^+, 4), 223 (13), 222 (46), 212 (12), 211 (9), 197 (6), 195 (6), 191 (5), 181 (9), 180 (73), 165 (10), 153 (5), 152 (15), 151 (5), 148 (5), 137 (11), 121 (8), 59 (6), 43 (100). Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.81; H, 5.48.

Crystallographic Study. Dimethyl 3a,5,6,6a-tetrahydro-5-hydroxy-2,5-dimethylfuro[3,2-*b*]furan-3,6-dicarboxylate (**6b**): $C_{12}H_{16}O_7$; M_r, 272.27, monoclinic, $P2_1/C$; a = 7.54025 (14), b = 21.1142 (3), and c = 9.05542 (17) Å, β = 112.739 (2)°, V = 1330.79 Å^3, ρ_c = 1.359 mg m^{-3}, Z = 4, λ = 0.70939 Å, μ = 0.11 mm^{-1} (Mo Kα_1).

Data Collection, Solution, and Refinement of the Structure. Diffraction intensities of a 0.15 × 0.30 × 0.55 mm crystal were collected at 295 K with graphite monochromatized MoKα_1 radiation by means of the $\theta/2\theta$ scan technique with profile analysis[25] to $2\theta_{max}$ = 50° using an Enraf Nonius CAD-4 diffractometer with PDP-8e computer. A total of 3055 reflections were measured, of which 2346 were unique and 1671 were considered significant ($I_{net} > 3.0\sigma(I_{net})$). Lorentz and polarization factors were applied, but no absorption corrections were made because of the small value of μ. The cell parameters were obtained by least-squares refinement of the setting angles of 60 reflections with 60.00 < 2θ < 97.00°.

(25) Grant, D. F.; Gabe, E. J. *J. Appl. Crystallogr.* **1978**, *11*, 114.

The structure was solved by direct methods using the NRC VAX crystal structure programs[26] and refined by full-matrix least-squares methods to final residuals of R_f and R_w of 0.052 and 0.032, respectively ($R_f = \Sigma(F_o - F_c)/\Sigma(F_o)$; $R_w = \Sigma(w(F_o - F_c)^2/\Sigma(wF_o)^2)$. The last least-squares cycle was calculated with 35 atoms, 237 parameters, and 1671 reflections. The final difference map showed no peaks greater than 0.250 e A^{-3}. Ten H atoms were found from difference maps, but the positions of the methyl hydrogens were calculated. The molecule shows no unusual features.

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(26) Gabe, E. J.; Lee, F. L.; LePage, Y. In *Crystallographic Computing III*; Sheldrick, G. M.; Kruger, C.; Goddard, R., Eds.; Clarendon Press: Oxford, 1985; p 167 et seq.

Supplementary Material Available: Full final atomic positional parameters (Table I), complete bond lengths and bond angles for **6b** (Table II), thermal parameters (Table III), and an ORTEP-II plot of **6b** (4 pages). Ordering information is given on any current masthead page.

Proton-Ionizable Crown Compounds. 16. Synthesis, Structural Features, and Cation Transport Studies of Crown Ethers Containing the 4-Pyridone *N*-Hydroxide Subcyclic Group

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Pyridino-14-crown-4, two 4-(2-tetrahydropyranoxy)pyridino-14-crown-4 compounds, and the corresponding 4-(2-tetrahydropyranoxy)pyridino-15-crown-5 and -18-crown-6 compounds were oxidized to the *N*-oxide analogues by treatment with *m*-chloroperbenzoic acid. Upon hydrolysis, the tetrahydropyranoxy-substituted compounds became the *N*-hydroxy-4-pyridono-crown compounds in solution. A crystal structure determination of one of the new crowns showed that the 4-hydroxypyridine *N*-oxide was the stable form in the solid state. Of the alkali-metal cations, the *n*-octyl-substituted 1-hydroxy-4-pyridono-14-crown-4 compound transported lithium ions selectively in an aqueous metal hydroxide–methylene chloride–0.01 M aqueous hydrochloric acid bulk liquid membrane system.

We have reported a variety of proton-ionizable crown ligands. The majority of these compounds have the proton-ionizable group as part of the macroring. Examples shown in Figure 1 include crowns containing 4-pyridone (**1**),[1-3] triazolo (**2**),[4,5] and sulfonamido (**3**)[6-8] proton-ionizable units.

These new proton-ionizable crown compounds are effective transport agents for various cations in a water–methylene chloride–water bulk membrane system. Ligand **1** ($n = 1$) was found to be selective for potassium ions,[9] while **1** ($n = 0$) was found to be selective for lithium ions.[10] Ligand **2** proved to be selective for silver ions over all other metal ions tested.[11,12] Sulfonamido ligand **3** is an excellent carrier for all of the alkali metals.[8] In every case, transport of alkali-metal ions by these ligands occurred only when the source phase pH value was 13 or higher, indicating that ionization from the macrocycle was a necessary part of the transport process. Indeed, transport by ligand **3** occurred above pH values of 13.5, indicating that proton ionization of both N-H protons was necessary.[8] In general, the best metal ion transport results were observed where the receiving phase was acidic, showing that these transport systems were proton-driven.

Ligand **4**[3] was prepared with the hope that it would be even more selective for lithium ions than **1** ($n = 0$). The 14-crown-4 ligands have been shown to be selective complexing agents for lithium cations.[13] Compound **4**, how-

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(1) Bradshaw, J. S.; Nakatsuji, Y.; Huszthy, P.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 353.
(2) Bradshaw, J. S.; Huszthy, P.; Koyama, H.; Wood, S. G.; Strobel, S. A.; Davidson, R. B.; Izatt, R. M.; Dalley, N. K.; Lamb, J. D.; Christensen, J. J. *J. Heterocycl. Chem.* **1986**, *23*, 1837.
(3) Bradshaw, J. S.; Guynn, J. M.; Wood, S. G.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1987**, *24*, 415.
(4) Bradshaw, J. S.; Nielsen, R. B.; Tse, P.-K.; Arena, G.; Wilson, B. E.; Dalley, N. K.; Lamb, J. D.; Christensen, J. J.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 361.
(5) Bradshaw, J. S.; McDaniel, C. W.; Skidmore, B. D.; Nielsen, R. B.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1987**, *24*, 1085.
(6) Biernat, J. F.; Bradshaw, J. S.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 1667.
(7) Bradshaw, J. S.; Koyama, H.; Dalley, N. K.; Izatt, R. M.; Biernat, J. F.; Bochenska, M. *J. Heterocycl. Chem.* **1987**, *24*, 1077.
(8) Biernat, J. F.; Bochenska, M.; Bradshaw, J. S.; Koyama, H.; LindH, G. C.; Lamb, J. D.; Christensen, J. J.; Izatt, R. M. *J. Inclusion Phenom.* **1987**, *5*, 729.
(9) Izatt, R. M.; LindH, G. C.; Clark, G. A.; Nakatsuji, Y.; Bradshaw, J. S.; Lamb, J. D.; Christensen, J. J. *J. Membr. Sci.* **1987**, *31*, 1.
(10) Izatt, R. M.; LindH, G. C.; Bruening, R. L.; Huszthy, P.; Lamb, J. D.; Bradshaw, J. S.; Christensen, J. J. *J. Inclusion Phenom.* **1987**, *5*, 739.
(11) Izatt, R. M.; Bruening, R. L.; Bradshaw, J. S.; Lamb, J. D.; Christensen, J. J. *Pure Appl. Chem.*, in press.
(12) Izatt, R. M.; Bruening, R. L.; LindH, G. C.; McDaniel, C. W.; Bradshaw, J. S.; Christensen, J. J. *Anal. Chem.*, in press.
(13) See, for example: Bartsch, R. A.; Czech, B. P.; Kang, S. I.; Stewart, L. E.; Walkowiak, W.; Charewicz, W. A.; Heo, G. S.; Son, B. *J. Am. Chem. Soc.* **1985**, *107*, 4997.

0022-3263/88/1953-2811$01.50/0