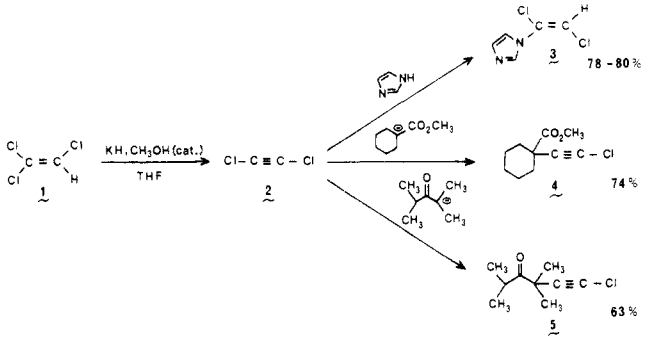
exception of that recently disclosed by Kende and Fludzinski,[2] all suffer from serious drawbacks such as operational difficulty, irreproducibility, or product contamination. Although the procedure developed by Kende and Fludzinski is a notable improvement over the previous methods, it is nevertheless time-consuming and requires a potentially eventful distillation for the separation of the dichloroacetylene from hexamethyldisilazane.

We have found that dichloroacetylene is rapidly and cleanly generated in high yield from a mixture of trichloroethylene and potassium hydride (1.2–1.3 equiv) in tetrahydrofuran at room temperature on the addition of a catalytic amount of methanol (1–2 μL/mmol of Cl_2CCHCl). The reaction is over in less than 1 h (VPC,[3]



cessation of H_2 evolution). The dichloroacetylene-containing supernatant is virtually free of potassium chloride and residual potassium hydride, which are insoluble in tetrahydrofuran, and hence no distillation is required.

The dichloroacetylene so formed has been unambiguously identified by IR (strong absorption at 983 cm^{-1})[2] and through known[2] chemical transformations: on reaction with imidazole, it produces *N*-(1,2-dichlorovinyl)imidazole (**3**) in 78–80% yield (three runs);[4,5] chloroethynylation of methyl cyclohexanecarboxylate and 2,4-dimethyl-3-pentanone with **2** affords the expected adducts **4** and **5** in yields of 74% and 63%, respectively.

This highly convenient preparation of dichloroacetylene should enhance the attractiveness of much of its unique chemistry.[1]

Experimental Section

Preparation of Dichloroacetylene (2). *Warning*—although we have used the following procedure repeatedly without the slightest incident, it is strongly recommended that all work with dichloroacetylene be conducted in a good hood and behind a safety shield. To a stirred suspension of oil-free potassium hydride (from 1.24 g of a ca. 42% dispersion, ca. 13 mmol) in 9.1 mL of dry tetrahydrofuran under argon at 25 °C are added 900 μL (1.32 g, 10.0 mmol) of trichloroethylene and then 10 μL (7.9 mg, 0.25 mmol) of methanol. The hydrogen evolution ceases after ca. 1 h, at which time VPC analysis[3] indicates a complete reaction. The supernatant (ca. 1 M[6]), which is employed in all subsequent work, is either used immediately or stored at −25 °C.

The reactions of dichloroacetylene with imidazole,[2,4] methyl cyclohexanecarboxylate,[2] and 2,4-dimethyl-3-pentanone[2] were performed essentially as described in the literature.

Acknowledgment. We thank Dr. Luche for his interest in our work and the CNRS (UA 332) for financial support. A.M. is grateful to NATO for a postdoctoral fellowship.

Registry No. **2**, 7572-29-4; trichloroethylene, 79-01-6.

(2) Kende, A. S.; Fludzinski, P. *Synthesis* **1982**, 455–456 and references cited therein. See also: Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551–3562. Pielichowski, J.; Popielarz, R. *Synthesis* **1984**, 433–434.

(3) Conditions: 10% SE 30 on Chromosorb W, 2.5 m × 2 mm, column temperature 50 °C, injection temperature 150 °C, N_2 flow rate 33 mL/min. No significant amount of any byproduct was detected.

(4) One equivalent of dichloroacetylene, based on a quantitative conversion of **1** to **2**, was used. It has been reported[2] that this reaction, when run in the presence of an excess of **2**, affords **3** in 76% yield.

(5) We have performed this transformation with dichloroacetylene–THF taken from a reaction mixture that had been stored at −25 °C for 3 days and obtained essentially the same result (75% yield).

(6) This is based on VPC and on the conversion of **2** to **3**. Similar concentrations were obtained in 50- and 100-mmol preparations (2 μL of CH_3OH/mmol of Cl_2CCHCl was used).

Preparation of Small Ring Carbocycles via Intramolecular Oxidative Coupling of Bisenolates Derived from α,ω-Diesters[1]

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Recently, a method for the preparation of carbocycles of general structure **4** was reported[2] that involved oxidative coupling of bisenolates derived from certain α,ω-diesters **2**. Unfortunately, this oxidative cyclization of dicarboxylate dienolates was reported[2] to be lacking in generality and appeared to be effective only in preparation of three- and six-membered ring systems. For example, attempts to generate cyclobutanoid **4a** by applying this methodology to dimethyl adipate (**2a**) led instead to a quantitative yield of the Dieckmann condensation product **7a**. Although addition of *N,N,N′,N′*-tetramethylethylenediamine was reported[2] to suppress completely the unwanted Dieckmann cyclization, subsequent treatment of the dienolate derived from dimethyl adipate (**2a**) with excess cupric bromide or chloride failed to produce any oxidative cyclization product.

Despite the fact that the above results would seem to preclude any success in such a venture, we decided to examine whether this intramolecular oxidative coupling reaction could be applied to di-*tert*-butyl adipate (**3a**), for which the competitive Dieckmann reaction would be somewhat sterically impeded (Scheme I). To our amazement, by use of cupric chloride as an oxidant at a reaction temperature of −78 °C, cyclobutanoid **5a** was obtained in approximately 20% isolated yield, accompanied by unreacted starting material (17%) and the corresponding Dieckmann condensation product (**8a**, approximately 30% yield[3])! Consistent with the previous studies[2] involving dimethyl adipate (**2a**), attempts to effect this oxidative coupling at higher temperatures (e.g., −20 or 0 °C) resulted in low yields (≤5%) of cyclobutanoid **5a** and a substantial amount of nondistillable product.

In order to confirm formation of the four-membered carbocycle in the above process, diester **5a** was saponified with potassium hydroxide in refluxing ethylene glycol, affording the corresponding diacid (**6a**), whose melting

(1) Abstracted from: Sarussi, S. J. M.S. Thesis, Loyola University of Chicago, Jan 1986.

(2) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125.

(3) In a series of experiments designed to optimize production of cyclobutanoid **5a**, the yield of the undesired Dieckmann condensation product **8a** was found to be remarkably constant (30 ± 5%) both when the reaction temperature was varied from −78 to 0 °C and when the reaction time subsequent to the addition of the metallic oxidant was increased from 0.5 to 3.0 h. Such results indicate that the Dieckmann condensation is probably occurring during the formation of the bisenolate, prior to the addition of cupric chloride. At a reaction temperature of −78 °C, however, the isolated yield of **5a** did increase significantly with time (5% at 0.5 h after addition of cupric chloride vs. 21% after a reaction time of 3.0 h).

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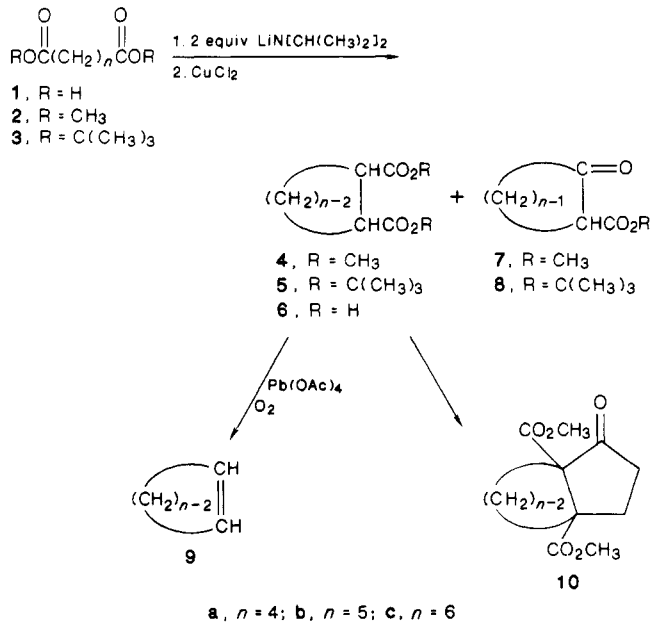
Scheme I



point was in agreement with that reported[4] for *trans*-1,2-cyclobutanedicarboxylic acid.

An analogous coupling using cupric chloride as the oxidant was attempted starting with di-*tert*-butyl pimelate (**3b**) but was found to proceed too slowly at −78 °C. However, increasing the reaction temperature to 0 °C after addition of the oxidant resulted in an efficient transformation (>50% isolated yield) to the desired cyclopentanoid (**5b**)[5] and only low (≤2%) yields of the undesirable Dieckmann condensation product (**8b**). To verify the obtention of cyclopentanoid **5b** in this oxidative coupling process, it was converted to the corresponding diacid **6b** under conditions favoring cis → trans isomerization. The IR spectrum and melting point of the latter (**6b**) were identical with those exhibited by an authentic sample[6] of *trans*-1,2-cyclopentanedicarboxylic acid.

By using reaction conditions that were essentially the same as those employed for the preparation of cyclopentanoid **5b**, di-*tert*-butyl suberate (**3c**)[7] was converted to di-*tert*-butyl 1,2-cyclohexanedicarboxylate (**5c**) in approximately 75% yield. However, since the corresponding methyl ester (**4c**) had previously been obtained[2] in 93% yield from dimethyl suberate (**2c**), there is no advantage in the use of the corresponding *tert*-butyl ester **3c** for this oxidative cyclization. Attempts to extend the methodology to di-*tert*-butyl azelate and di-*tert*-butyl sebacate led to no observable cyclization products under our standard reaction conditions (treatment of the bisenolate in THF with cupric chloride at 0 °C).

In conclusion, oxidative cyclization of dicarboxylate dienolates offers a route to three–six-membered carbocycles possessing functionality that can undergo a variety of subsequent transformations [e.g., bisdecarboxylation[8] (**6** → **9**)], thereby enhancing their synthetic utility. One of the most recent examples illustrating the potential of cyclic vicinal dicarboxylic esters such as **4** and **5** as synthetic intermediates involves a cyclopentannulation process[9] (e.g., **4** → **10**).

Experimental Section

General Methods. All organic reagents were purchased from Aldrich Chemical Co., and Florisil (60–100 mesh) was obtained from Fisher Scientific Co. Tetrahydrofuran was purified prior to use by distillation from lithium aluminum hydride. Anhydrous cupric chloride was obtained by drying the commercially available salt for 10 h at 125 °C prior to use. All reactions were carried out under a nitrogen atmosphere. Products were recovered from the ether extracts after drying the organic layer over anhydrous magnesium sulfate and removal of the solvent with a rotary evaporator under reduced pressure. Melting points were determined on a Fisher-Johns block and are uncorrected. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. ^{1}H NMR spectra were obtained on a Varian EM-360A or Varian FT-80 spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. Infrared spectra were recorded with a Beckman Acculab 1 spectrophotometer, and vapor-phase chromatography (VPC) was performed on a Hewlett-Packard 5750 chromatograph using a 6 ft × $^1/_8$ in. column packed with 5% OV-17 on 100–120-mesh Gas Chrom Q. Peak areas were determined by use of a Hewlett-Packard Model 3392A integrator and are uncorrected for response factors relative to an internal standard. TLC analyses were conducted on precoated silica gel sheets (E. M. Merck, Catalog No. 5775). The microanalysis was performed by Micro-Tech Laboratories, Skokie, IL.

Di-*tert*-butyl Adipate (3a). A mixture of 4.76 g (32.6 mmol) of adipic acid (**1a**) and 10.0 mL (137.5 mmol) of thionyl chloride in 15 mL of 2:1 (v/v) benzene–cyclohexane was heated at gentle reflux for 2.5 h, after which the reaction mixture was concentrated to a volume of approximately 10 mL by distillative removal of the solvent at atmospheric pressure. At this point, the heat source was removed, and 15 mL of cyclohexane was added to the reaction flask. The mixture was once again concentrated to a volume of 5–10 mL by distillation of cyclohexane and any residual thionyl chloride at atmospheric pressure. After the mixture was cooled to room temperature, the bis(acid chloride) was transferred, using 5.0 mL of anhydrous ether, to an addition funnel, and this latter solution was subsequently added dropwise over 5 min to a stirred mixture of 13.0 mL (102.5 mmol) of *N,N*-dimethylaniline and 10.0 mL (106 mmol) of *tert*-butyl alcohol in 5.0 mL of anhydrous ether. This mixture was stirred vigorously for an additional 20 h at room temperature, after which it was diluted with 100 mL of 10% (w/v) aqueous sodium chloride and the product isolated by extraction with ether. The organic layer was washed with 3:1 (v/v) 2 M aqueous hydrochloric acid–saturated brine (3 × 100 mL), 3:1 (v/v) 1 M aqueous sodium hydroxide–saturated brine (2 × 100 mL), and saturated brine (1 × 100 mL) in successive order. The product was isolated from the organic extract in the usual manner and purified by evaporative distillation [bp 115–130 °C (bath temperature) (0.20 mm)], affording 7.23 g (86%) of diester **3a** as a low-melting solid: mp 29–31 °C (lit.[7] mp 32 °C); ^{1}H NMR δ 2.25 (br t, J = 6 Hz, 2 CH_2C=O), 1.2–1.9 (complex m, 4 H), 1.48 (s, 2 $C(CH_3)_3$). VPC analysis (oven temperature 200 °C, flow 15 mL/min) indicated the distilled product (retention time, 5.1 min) to be >99% pure.

Di-*tert*-butyl 1,2-Cyclobutanedicarboxylate (5a). To a solution of diisopropylamine (0.75 mL, 5.33 mmol) in 8.0 mL of anhydrous tetrahydrofuran (THF) cooled to −10 °C (ice–acetone bath) was added dropwise via syringe 4.0 mL of a 1.35 M solution of *n*-butyllithium in hexane. The resulting solution of lithium diisopropylamide (LDA) in THF was stirred for an additional 10 min at −10 °C prior to cooling the mixture to −78 °C (dry ice–acetone bath). At this point, a solution of 2.31 mmol of diester **3a** in 4.0 mL of anhydrous THF was added dropwise over 3 min, and the mixture was allowed to stir at −78 °C for an additional 15 min prior to addition of 792 mg (5.89 mmol) of anhydrous cupric chloride. This mixture was subsequently stirred at −78 °C (external bath temperature) for an additional 3 h, after which the bath was removed and 10 mL of 2 M aqueous hydrochloric

(4) Perkin, A. G. *J. Chem. Soc., Trans.* **1894**, *65*, 572.
(5) VPC analysis of this product (**5b**) indicated the presence of a mixture of cis:trans stereoisomers, the cis:trans ratio decreasing (from 1:1 to 1:3) with increasing time (1.0 vs. 2.0 h at 0 °C). As expected, isomerization of the cyclic diesters **5b** occurred under the strongly basic reaction conditions.
(6) Available from Aldrich Chemical Co., Inc., Milwaukee, WI.
(7) Backer, H. J.; Homan, J. D. H. *Recl. Trav. Chim. Pays-Bas* **1939**, *58*, 1048.
(8) For a review, see: Sheldon, R. A.; Kochi, J. K. *Org. React. (N.Y.)* **1972**, *19*, 279–421.
(9) Corey, E. J.; Su, W.; Houpis, I. N. *Tetrahedron Lett.* **1986**, *27*, 5951.

acid was quickly added to the reaction mixture. The product was subsequently isolated by dilution of this mixture with 100 mL of 15% (w/v) aqueous sodium chloride and extraction with 4:1 (v/v) ether–dichloromethane. The organic layer was washed in succession with 1:1 (v/v) 2 M aqueous hydrochloric acid–saturated brine (2 × 100 mL) and saturated brine (1 × 100 mL). The product was then isolated from the organic extract in the usual manner and purified by evaporative distillation [bp 80–100 °C (bath temperature) (0.20 mm)], affording 408 mg of a colorless oil shown by ^{1}H NMR and VPC analyses (retention times: **3a** > **5a** > **8a**) to contain diester **5a**, Dieckmann cyclization product **8a**, and unreacted starting material in a ratio of 3.0:4.5:2.5. Chromatography of this distillate on Florisil (20 mL, elution with hexane–2% ether) afforded 124 mg (21%, uncorrected for recovered starting material) of purified diester **5a** as an undetermined mixture of stereoisomers: ^{1}H NMR δ 3.10–3.40 (m, 2 CHC=O), 2.05–2.45 (m, 4 H), 1.47 (s, 2 C(CH$_3$)$_3$). Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.45; H, 9.03. The structural identity of **5a** was further confirmed by its saponification using 3:1 (v/v) ethylene glycol–20% aqueous potassium hydroxide at reflux for 2.5 h. Acidification of the cooled reaction mixture, followed by extraction with 4:1 (v/v) ether–ethyl acetate, afforded a white, crystalline solid (mp 110–125 °C), which was subsequently purified by recrystallization from benzene: mp of *trans*-diacid **6a** (57% overall yield based on diester **5a**) 128–130 °C (lit.[4] mp 127–129 °C).

Oxidative Cyclization of Di-*tert*-butyl Pimelate (3b).[10] A procedure identical with that described above for the preparation of diester **5a** was used with the following modifications: (a) The quantities of diisopropylamine (1.00 mL, 7.13 mmol), *n*-butyllithium (7.0 mmol), and anhydrous cupric chloride (1.01 g, 7.5 mmol) were increased relative to the starting diester (644 mg, 2.36 mmol). (b) After addition of cupric chloride to the reaction mixture, it was allowed to warm to 0 °C over a period of 30 min and stirred for an additional 60 min at 0 °C. Evaporative distillation [bp 80–90 °C (bath temperature) (0.30 mm)] of the crude product afforded 495 mg (78%, if solely diester **5b**) of a colorless oil shown by ^{1}H NMR and VPC analyses (oven temperature 200 °C, flow 15 mL/min) to be a mixture consisting of >70% diester **5b** (1:1 mixture of cis:trans stereoisomers; retention times 4.68 and 4.42 min, respectively), <2% Dieckmann cyclization product (**8b**; retention time 3.57 min), and 28% starting diester (**3b**; retention time 5.34 min). Since the chromatographic separation of this mixture proved to be troublesome, verification of the obtention of a cyclopentanoid product (**5b**) was achieved by the transesterification process described below to afford the known[11] dimethyl ester **4b**.

Dimethyl 1,2-Cyclopentanedicarboxylate (4b). The distilled mixture (495 mg) of products obtained in the cyclization described above was heated for 40 h in 4.0 mL of a 1:1 (v/v) mixture of refluxing glacial acetic acid–2 M aqueous hydrochloric acid to effect hydrolysis of the *tert*-butyl ester moiety. At this point, the heat source was removed, and 5 mL of toluene was added to the reaction flask. The mixture was then concentrated to a volume of approximately 2 mL by distillation at atmospheric pressure. This latter procedure (i.e., addition of toluene and subsequent distillation) was repeated two additional times, leaving behind a suspension of the solid diacid (**6b** contaminated with **1b**) in toluene. After addition of 0.25 mL (6.13 mmol) of methyl alcohol, 1.00 mL (8.13 mmol) of 2,2-dimethoxypropane, and a catalytic amount (17 mg) of *p*-toluenesulfonic acid monohydrate, the mixture was stirred at room temperature for 20 h. Dilution of the mixture with 20 mL of 15% (w/v) aqueous sodium chloride and extraction with 3:1 (v/v) ether–dichloromethane, followed by washing the organic layer with 3:1 (v/v) brine–1 M aqueous sodium hydroxide (2 × 20 mL), afforded 406 mg of a yellow oil after the usual isolation procedure. Evaporative distillation [bp 90–110 °C (bath temperature) (0.35 mm) [lit.[11] bp 119–120 °C (bath temperature) (16 mm)]], followed by chromatography on silica gel (Baker Analyzed, 40–140 mesh, 15 mL, elution with hexane–3% ether), afforded 215 mg (1.15 mmol, 49% overall yield based on acyclic diester **3b**) of diester **4b**,[12] homogeneous by TLC and VPC analyses: ^{1}H NMR δ 3.73 (s, 6 H, 2 OCH$_3$), 2.95–3.38 (complex m, 2 H, 2 CHC=O), 1.55–2.40 (complex m, 6 H).

Registry No. **1a**, 124-04-9; **3a**, 20270-53-5; **3b**, 55623-59-1; *trans*-**4b**, 941-75-3; *cis*-**5a**, 108836-33-5; *trans*-**5a**, 108836-34-6; *cis*-**5b**, 108836-35-7; *trans*-**5b**, 108836-36-8; *trans*-**6a**, 1124-13-6; *trans*-**6b**, 1461-97-8; **8a**, 84109-76-2.

(10) Diester **3b**[7] was prepared from pimelic acid by a procedure identical with that described for the preparation of di-*tert*-butyl adipate (**3a**).

(11) Ingold, C. K.; Mohrhenn, H. G. G. *J. Chem. Soc.* **1935**, *138*, 1482.

(12) Diester **4b** can be assumed to possess the trans configuration in view of the vigorous reaction conditions used to hydrolyze diesters **5b** (1:1 cis:trans mixture). Further confirmation of the identity of **4b** was obtained by its saponification to afford diacid **6b**. The IR spectrum and melting point of the latter were identical with those exhibited by an authentic sample[6] of *trans*-1,2-cyclopentanedicarboxylic acid.

Aldehyde-Promoted Decomposition of 1-(Alkylthio)-2-alkylisoindoles

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Primary amines undergo facile condensation with *o*-phthalaldehyde (OPA) in the presence of alkanethiols to generate 1-(alkylthio)-2-alkylisoindoles **1**.[1] This reaction is of considerable analytical importance and is widely used for derivatization of primary amines prior to liquid chromatographic analysis. Thiol coreagents most frequently employed for this purpose are 2-mercaptoethanol (2-ME) or ethanethiol (ET). Both of these thiols lead to formation of products whose stability is highly variable, with in situ half-lives ranging from a few minutes to several hours.[2] Excess OPA in the reaction mixture has been shown to exert a significant destabilizing effect,[2-4] and derivative loss in the presence of excess OPA follows pseudo-first-order kinetics with

$$k_{app} = k_0 + k_{OPA}[OPA]$$

where k_0 is the first-order rate constant for OPA-independent loss and k_{OPA} is the second-order term for the OPA-dependent process. Under typical analytical conditions, the latter term predominates and derivative stability is dictated by the OPA-dependent process. Considerable speculation has arisen concerning the nature of the reactions leading to decomposition of these derivatives and, in particular, apparent differences between those derived from 2-ME and ET.[1,3,4] In our earlier studies we demonstrated strong parallels between the OPA-dependent decomposition of 2-ME and ET-derived isoindoles[2] and suggested at that time that the most probable sequence in both cases was one initiated by electrophilic attact at C(3) of the isoindole. Subsequent findings appear to substantiate this hypothesis.

We have found isoindoles of type **1a** and **1b** to be quite susceptible to decomposition by aldehydes in general, with OPA representing a special case. In a study of reactivity of **1a** and **1b** toward para-substituted benzaldehydes, rate constants for both isoindoles correlated well with Hammett σ_p constants (Figure 1), yielding ρ values of 1.30 (r = 0.9969) and 1.44 (r = 0.9720) for **1a** and **1b**, respectively.

(1) Simons, S. S.; Johnson, D. F. *J. Am. Chem. Soc.* **1976**, *98*, 7098–7099.

(2) Jacobs, W. A.; Leburg, M. W.; Madaj, E. J. *Anal. Biochem.* **1986**, *156*, 334–340.

(3) Nakamura, H.; Matsumoto, A.; Tamura, Z. *Anal. Lett.* **1982**, *15*, 1393–1410.

(4) Stobaugh, J. F.; Repta, A. J.; Sternson, L. A.; Garren, K. W. *Anal. Biochem.* **1983**, *135*, 495–504.

0022-3263/87/1952-3464$01.50/0