In Wittig reactions where ethyltriphenylphosphonium bromide was allowed to react with *n*-butyllithium at −78 °C, none of the desired product **4** was formed.The main products indicated by GLC and mass spectrometry were **6** (10–20%) and a ketal alcohol (70–80%). The latter component had a retention time of 12 min (column B, 120 °C) and was assigned structure **5** on the basis of fragment ions occurring at *m/e* 187 (M − 15, 5), 169 (4), 145 (10), 101 (6), 99 (5), 97 (4), 88 (6), 87 (100), 83 (13), 82 (4), 73 (7), 71 (6), 59 (6), 55 (11), 45 (4), 43 (36), and 41 (6). In reactions at 0 °C (as described), formation of **5** was avoided completely, whereas **6** was present in the crude reaction mixture to the extent of 6–8%.

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Registry No.—**1**, 3695-38-3; **2**, 21488-96-0; **3**, 24108-29-0; **4**, 68965-53-7; **5**, 68965-54-8; **6**, 6539-85-1; 6-methyl-5-hepten-2-one, 110-93-0; *trans*-2-methyl-6-oxo-2-hepten-1-al ethylene ketal, 31925-20-9.

References and Notes

(1) K. A. Pittman, D. Rosi, R. Cherniak, A. J. Merola, and W. D. Conway, *Biochem. Pharmacol.*, **18**, 1673 (1969).
(2) K. Ueda, L. C. Gaughan, and J. E. Casida, *J. Agric. Food Chem.*, **23**, 106 (1975).
(3) W. G. Taylor and R. T. Coutts, *Drug Metab. Dispos.*, **5**, 564 (1977).
(4) U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971).
(5) M. Matsui and Y. Yamada, *Agric. Biol. Chem.*, **29**, 956 (1965).
(6) M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977).
(7) E. J. Corey, J. I. Shulman, and H. Yamamoto, *Tetrahedron Lett.*, 447 (1970).
(8) E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 226 (1970).
(9) M. Schlosser, F. K. Christmann, A. Piskala, and D. Coffinet, *Synthesis*, 29 (1971).
(10) M. Schlosser and D. Coffinet, *Synthesis*, 380 (1971).
(11) M. Schlosser and D. Coffinet, *Synthesis*, 575 (1972).
(12) Valeraldehye,[4] hexanal,[10] and heptanal[8] had previously been cis hydroxyisopropenylated by this procedure. In the present work, *cis*-2-methyl-2-hepten-1-ol was obtained (45% distilled yield) from valeraldehyde (under conditions described for the preparation of **4**), and the NMR spectrum was identical with the reported spectrum.[4]
(13) By removing aliquots from the reaction of **1** with 0.5–1.5 mol equiv of selenium dioxide and determining cis–trans isomer distributions by GLC peak area ratios, less than 2% of **4** and greater than 98% of **2** were found. Trans selectivity could thus be improved by stopping the oxidation at the alcohol stage. However, this would be cumbersome because in dioxane the aldehyde represented a major product before **1** was consumed.
(14) W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 790 (1978).
(15) M. Beroza and B. A. Bierl, *Anal. Chem.*, **39**, 1131 (1967).
(16) Yields of **3** from ozonolyses varied from 25 to 77%. Flushing the cold solution with nitrogen gas before adding triphenylphosphine was essential. Decomposition occurred on storing distilled samples of **3** for more than a week.
(17) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).

Synthesis of 4,5,6,7-Tetrahydro-1(3*H*)-isobenzofuranones by Reaction of *N,N*-Dimethyl-2-lithio-1-cyclohexenecarboxamide with Aldehydes and Ketones

William R. Baker and R. M. Coates*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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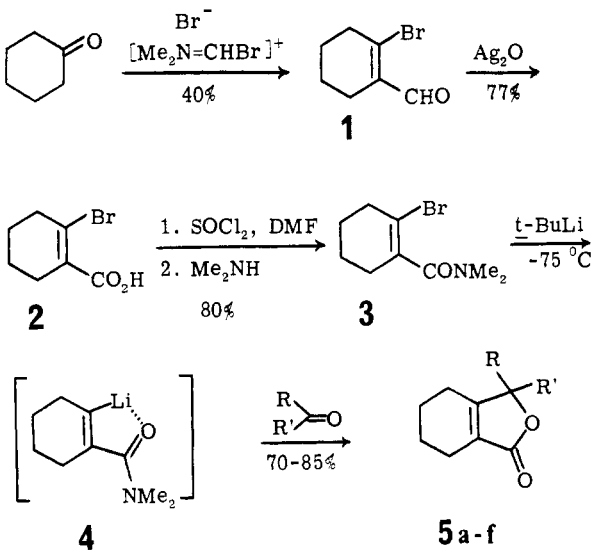
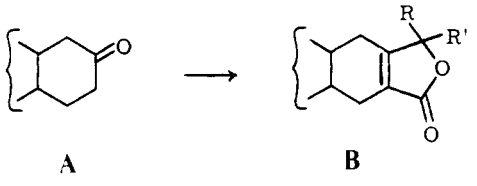
The frequent occurrence of α,β-unsaturated γ-lactones in many types of natural products has stimulated considerable interest in the synthesis of $\Delta^{\alpha,\beta}$-butenolides.[1] Although a great variety of synthetic routes to these compounds may be found in the literature, there appear to be few reports of syntheses of bicyclic $\Delta^{\alpha,\beta}$-butenolides with a carbocycle fused across the α and β positions, such as 4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranones (**5**).[1-3] The necessity of preparing fused bicyclic butenolides from cyclohexanone and related compounds (A → B) has prompted us to develop a new synthetic route to

Scheme I





these compounds. The key reaction in the synthesis (Scheme I) involves the generation of the lithio derivative of *N,N*-dimethyl-2-bromo-1-cyclohexenecarboxamide (**3**) by bromine-lithium exchange with *tert*-butyllithium in tetrahydrofuran (THF)–pentane at −75 °C and subsequent reaction of the vinyllithium reagent (**4**) with aldehydes and ketones.

2-Bromo-1-cyclohexenecarboxaldehyde (**1**), prepared by condensation of cyclohexanone with the bromo Vilsmeier reagent as described by Arnold and Holy,[4] was oxidized with silver oxide to the crystalline bromo acid (**2**) in 77% yield. The dimethylamide was obtained by reaction of the corresponding acid chloride with dimethylamine in pentane at −78 °C.

Parham and co-workers have demonstrated that *o*-bromobenzoic acid and its esters undergo bromine–lithium exchange to produce ortho-lithiated benzoates upon reaction with *n*-butyllithium in THF–hexane at −100 °C.[5] For example, metalation of *o*-bromobenzoic acid followed by addition of valerophenone provided 3-*n*-butyl-3-phenylphthalide in 67% yield.[5a] Recently, this procedure has been utilized to effect the lithiation of 2-bromo-3-methyl-2-butenoic acid.[6] Tertiary benzamides have been metalated regiospecifically in the ortho position by deprotonation with *sec*-butyllithium–tetramethylethylenediamine in THF and the resulting lithium reagent trapped by reaction with benzophenone to give 3,3-diphenylphthalide.[7] These findings provided precedent and guidance in a search for suitable procedures for the preparation of butenolides **5** from bromo acid **2** and bromo amide **3**.

Reaction of bromo acid **2** with 2 equiv of *n*-butyllithium or bromo amide **3** with 1 equiv of *n*-butyllithium in a mixture of THF–hexane at −80 to −85 °C for 15–30 min and subsequent addition of 2.1 equiv of benzaldehyde gave rise to phenyl-substituted lactone **5a** in 45–50% yield after hydrolysis with 25% aqueous acetic acid and column chromatography to separate unidentified polar byproducts. In order to improve the yield of lactone, we carried out a series of experiments in which the conditions and reactants were varied and the yield

Table I. Lactones Prepared from the Reaction of *N,N*-Dimethyl-2-lithio-1-cyclohexenecarboxamide (4) with Aldehydes and Ketones

RR′C=O	registry no.	lactone	registry no.	isolated yield, %
R = Ph, R′ = H	100-52-7	**5a**	68965-56-0	85
R = CH_3, R′ = H	75-07-0	**5b**	68965-57-1	70
R = *trans*-PhCH=CH, R′ = H	14371-10-9	**5c**	68965-58-2	83
R = R′ = Ph	119-61-9	**5d**	68965-59-3	81
R = R′ = CH_3	67-64-1	**5e**	68965-60-6	70
R = R′ = $-CH=CH(CH_2)_3-$	930-68-7	**5f**	68965-61-7	73

was determined by integration of the NMR spectrum of the unpurified product.[8] Although a thorough systematic study was not done, changes in solvent (ether and proportion of hydrocarbon), temperature (−95 to −70 °C), and time (15–60 min) resulted in similar or, in cases of low conversion, reduced yields. However, the yield of **5a** from bromo amide **3** was increased to 60% by use of *sec*-butyllithium in THF–hexane (−80 to −85 °C, 30 min) and ultimately to 90% with 2.1 equiv[9] of *tert*-butyllithium in THF–pentane (−70 to −75 °C, 60 min). The yield of purified lactone dropped to 57% when this last procedure was performed on bromo acid **2**.

The scope of the lactone synthesis was investigated by reaction of lithio amide **3** with a series of saturated and unsaturated aldehydes and ketones (Table I). The lactones **5a–f** were obtained in 70–85% yield after purification by either medium pressure liquid chromatography or direct crystallization. The availability of a variety of β-bromo-α,β-unsaturated aldehydes via the Vilsmeier reaction[4] indicates that the reaction sequence in Scheme I may be useful for the synthesis of other cyclic and acyclic $\Delta^{\alpha,\beta}$-butenolides.

Experimental Section

General. All melting points were determined on a Reichert melting stage. All melting and boiling points are uncorrected. Proton nuclear magnetic resonance spectra were measured on a Varian Associates Model EM-390 spectrometer in the solvent indicated. Chemical shifts are reported as δ values with tetramethylsilane as an internal standard. Infrared spectra were recorded on either Perkin-Elmer Model 137, 237B, or 337 grating infrared spectrophotometers or a Beckman Model 12 grating infrared spectrophotometer. Microanalyses were performed by J. Nemeth and associates at the University of Illinois microanalytical laboratory.

THF was freshly distilled from sodium benzophenone ketyl immediately before use in all reactions. Pentane was stored over sodium wire and utilized directly. Dimethylformamide was distilled from calcium oxide and stored over molecular sieves. *n*-Butyllithium in hexane, *sec*-butyllithium in cyclohexane, and *tert*-butyllithium in pentane were obtained from Ventron Corp. and titrated before use.[10] All lithiation reactions were performed under an atmosphere of dry nitrogen in flame-dried apparatus.

2-Bromo-1-cyclohexenecarboxaldehyde (1) was prepared in 40% yield from cyclohexanone by the method of Arnold and Holy.[4] The bromo aldehyde is unstable at room temperature and was stored in a freezer at −20 °C. The distillation of large quantities was performed using a wiped-film molecular still with the heating jacket at 60 °C (0.001 mm): bp 75 °C (0.4 mm) [lit. 51 °C (0.7 mm)]; IR (film) 1681 (C=O), 1621 C=C) cm^{-1}; ^1H NMR (neat) δ 1.43–1.90 (m, 4 H, CH_2CH_2), 1.96–2.33 (m, 2 H, allylic CH_2), 2.56–2.83 (m, 2 H, allylic CH_2), 9.93 (s, 1 H, CHO).

2-Bromo-1-cyclohexenecarboxylic Acid (2). An aqueous suspension of silver oxide was prepared by vigorously stirring a mixture of 30 g (0.17 mol) of silver nitrate in 60 mL of deionized water and 14 g (0.35 mol) of sodium hydroxide in 60 mL of deionized water in a 1-L Morton flask.[11] The brown suspension was stirred vigorously and cooled in an ice bath, while 16 g (0.08 mol) of freshly distilled aldehyde 1 was added. The resulting mixture was warmed to room temperature over a 30-min period. The black silver precipitate was filtered with suction and washed repeatedly with hot water. The filtrate was washed with diethyl ether, cooled in an ice bath, and acidified with concentrated hydrochloric acid. The crude bromo acid was collected by filtration, combined with material similarly prepared from another 8.0 g of bromo aldehyde 1, and recrystallized from aqueous ethanol: yield 77%; mp 103–104 °C; IR (KBr) 2400–3600 (OH), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–1.93 (m, 4 H, CH_2CH_2), 2.23–2.80 (m, 4 H, allylic CH_2), 9.80 (br s, 1 H, $-CO_2H$).

Anal. Calcd for $C_7H_9BrO_2$: C, 41.00; H, 4.39; Br, 39.01. Found: C, 41.30; H, 4.42; Br, 38.98.

***N,N*-Dimethyl-2-bromo-1-cyclohexenecarboxamide (3).** To a stirred suspension of 11 g (0.05 mol) of bromo acid **2** in 75 mL of dry pentane was added 9.6 g (0.07 mol) of thionyl chloride and 1.2 mL (1.13 g, 0.015 mol) of dry dimethylformamide at room temperature. Evolution of sulfur dioxide began immediately and continued for ~30 min as the solid dissolved. After 45 min, the reaction mixture was filtered, concentrated to a volume of ~25 mL under reduced pressure at room temperature, and added dropwise with stirring to 40 mL (0.60 mol) of dimethylamine cooled in a dry ice–acetone bath. The resulting mixture was stirred at room temperature for 18 h, diluted with 20 mL of water, and extracted with diethyl ether. The organic extracts were combined, washed with 10% hydrochloric acid and saturated sodium bicarbonate, dried ($MgSO_4$) and concentrated under reduced pressure. Distillation of the residue afforded 9.9 g (80%) of carboxamide **3**: bp 100–103 °C (0.2 mm); IR (film) 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.50–1.93 (m, 4 H, CH_2CH_2), 2.23–2.80 (m, 4 H, allylic CH_2), 2.96 (s, 3 H, NCH_3), 3.00 (s, 3 H, NCH_3).

Anal. Calcd for $C_9H_{14}BrNO$: C, 46.57; H, 6.03; Br, 34.46; N, 6.03. Found: C, 46.39; H, 6.06; Br, 34.47; N, 6.02.

General Method for the Metalation of *N,N*-Dimethyl-2-bromo-1-cyclohexenecarboxamide (3) with *tert*-Butyllithium. 3-Phenyl-4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranone (5a). A 5.1-mL (9.05-mmol) aliquot of a 1.77 M solution of *tert*-butyllithium in pentane was added dropwise to a stirred solution of 1.0 g (4.31 mmol) of bromo amide **3** in 15 mL of THF cooled to −75 °C in a liquid nitrogen-diethyl ether bath. The rate of addition was adjusted so as to maintain an internal temperature of −70 to −75 °C. After 1 h, 0.95 g (9.05 mmol) of freshly distilled benzaldehyde was added rapidly by means of a syringe, causing the reaction mixture to warm to −50 °C. The reaction mixture was kept at −50 °C for 15 min and then hydrolyzed by adding 10 mL of a 2:3 mixture of 20–25% aqueous acetic acid–THF. The solution was concentrated under reduced pressure at room temperature, diluted with 15 mL of water, and saturated with sodium chloride. The aqueous layer was extracted several times with ether, and the combined organic extracts were washed with 10% hydrochloric acid, 5% sodium bicarbonate, and water. Drying ($MgSO_4$) and evaporation under reduced pressure afforded the crude lactone, which was purified by medium pressure liquid chromatography[12] to give 786 mg (85%) of **5a**. An analytical sample was obtained by distillation in a Kugelrohr apparatus (oven temperature 210–230 °C, 0.6 mm): mp 43–44 °C; IR (film) 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.50–1.86 (m, 4 H, CH_2CH_2), 1.8–2.4 (m, 4 H, allylic CH_2), 5.63 (s, 1 H, H at C-3), 7.26 (m, 5 H, aromatic).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.53. Found: C, 78.22; H, 6.63.

The following five lactones were prepared in the same manner from 0.6–1.02 g (2.6–4.38 mmol) of bromo amide **3**, 3.1–5.2 mL (5.48–9.20 mmol) of *tert*-butyllithium solution, 15–20 mL of THF, and 5.4–9.0 mmol of the nonvolatile carbonyl compounds. When the electrophile was acetaldehyde and acetone, 2 mL (35 mmol and 27 mmol, respectively) was used.

3-Methyl-4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranone (5b). The yield of lactone **5b** amounted to 460 mg (70%) after purification by medium pressure liquid chromatography. An analytical specimen was prepared by Kugelrohr distillation (oven temperature 140–160 °C, 0.6 mm): IR (film) 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.36 (d, J = 7 Hz, 3 H, CH_3), 1.53–2.00 (m, 4 H, CH_2CH_2), 2.0–2.4 (m, 4 H, allylic CH_2), 4.83 (br q, 1 H, H at C-3).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.07; H, 7.89. Found: C, 70.70; H, 8.06.

(*E*)-3-(2-Phenylethenyl)-4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranone (5c). The product was recrystallized from diethyl ether–pentane at −25 °C: yield 506 mg (81%); mp 82–83 °C; IR (KBr) 1770

cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.50–1.90 (m, 4 H, CH_2CH_2), 2.0–2.4 (m, 4 H, allylic CH_2), 5.26 (br d, J = 8 Hz, 1 H, H at C-3), 5.86 (2d, J = 8 and 16 Hz, 1 H, C**H**=CHPh), 6.73 (d, J = 16 Hz, 1 H, CH=C**H**Ph), 7.30 (m, 5 H, aromatic).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 80.01; H, 6.67. Found: C, 79.70; H, 6.36.

3,3-Diphenyl-4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranone (5d). The lactone was purified by recrystallization from diethyl ether–pentane at −25 °C: yield 1.05 g (83%); mp 143–145 °C; IR (KBr) 1770 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.56–1.86 (m, 4 H, CH_2CH_2), 2.16–2.46 (m, 4 H, allylic CH_2), 7.26 (m, 10 H, aromatic).

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.77; H, 6.20. Found: C, 82.78; H, 5.94.

3,3-Dimethyl-4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranone (5e). The yield of lactone **5e** amounted to 410 mg (70%) after recrystallization from diethyl ether–pentane at −25 °C: mp 36–38 °C; IR (KBr) 1770 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.40 (s, 6 H, $C(CH_3)_2$), 1.53–1.86 (m, 4 H, CH_2CH_2), 2.06–2.33 (m, 4 H, allylic CH_2).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.30; H, 8.42. Found: C, 72.09; H, 8.69.

Spiro[2-cyclohexene-1,3′-4′,5′,6′,7′-tetrahydro-1′(3′*H*)-isobenzofuranone] (5f). The product was recrystallized from diethyl ether–pentane at −25 °C: yield 505 mg (73%); mp 75–77 °C; IR (KBr) 1770 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.50–1.93 (m, 8 H, $2CH_2CH_2$), 1.93–2.50 (m, 6 H, allylic CH_2), 5.23 (br d, J = 10 Hz, 1 H, C**H**=CHCH$_2$–), 6.13 (doublet of triplets, J = 2 and 10 Hz, 1 H, CH=C**H**CH$_2$–).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 76.48; H, 7.38. Found: C, 76.23; H, 7.76.

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Registry No.—1, 38127-47-8; **2**, 68965-62-8; **3**, 68965-63-9; **4**, 68965-64-0.

References and Notes

(1) Y. S. Rao, *Chem. Rev.*, **76**, 625 (1976).
(2) Prior to 1972 this family of compounds was named as derivatives of 4,5,6,7-tetrahydrophthalide by *Chem. Abstr.*
(3) 3-Substituted 4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranones have been previously synthesized by condensation of anhydrides with 3,4,5,6-tetrahydrophthalic anhydride,[3a] regioselective Grignard addition to ethyl 2-formyl-1,2,3,4-tetrahydrobenzoate and subsequent double-bond isomerizations,[3b] and electrolytic oxidative decarboxylation of a 3a-carboxy-3a,4,5,6,7,7a-hexahydro-1(3*H*)-isobenzofuranone:[3c] (a) G. Lardelli, G. Dijkstra, P. D. Harkes, and J. Boldingh, *Recl. Trav. Chim. Pays-Bas*, **85**, 43 (1966); E. Gren, A. Strazdyn, and G. Vanag, *J. Gen. Chem. USSR* (*Engl. Transl.*), **32**, 2825 (1962); (b) W. Cocker, T. B. H. McMurry, and D. M. Sainsbury, *J. Chem. Soc. C*, 1152 (1966); (c) S. Torii, T. Okamoto, and H. Tanaka, *J. Org. Chem.*, **39**, 2486 (1974).
(4) Z. Arnold and A. Holy, *Collect. Czech. Chem. Commun.*, **26**, 3059 (1961).
(5) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051, 2053 (1974); (b) W. E. Parham and R. M. Piccirilli, *ibid.*, **41**, 1268 (1976); (c) W. E. Parham and L. D. Jones, *ibid.*, **41**, 2704 (1976).
(6) W. E. Parham and D. W. Bogkin, *J. Org. Chem.*, **42**, 260 (1977).
(7) P. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977).
(8) Diphenylacetic acid was added as an internal standard, and the integration of the singlet at δ 5.63 for the benzylic proton of **5a** was determined.
(9) An extra equivalent of *tert*-butyllithium is required on account of competitive dehydrohalogenation of *tert*-butyl bromide to isobutylene; see D. Seebach and H. Newman, *Chem. Ber.*, **107**, 847 (1974).
(10) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(11) E. Campaign and W. M. LeSeur, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, 1963, p 919.
(12) Preparative medium pressure liquid chromatography was performed using a heavy walled 2.5 × 75 cm glass column. The column was packed dry with 85 g of large pore "58 μm" silica gel manufactured by Alfa Products of Danvers, Mass., that had been fractionated twice through sieves (Sargent Welch Scientific Co.) to give silica gel the average particle size of which was between 45 and 63 μm. Solvent (40% diethyl ether in hexane) was delivered from a Milroyal D controlled-volume pump supplied by the Milton Roy Co. of Ivyland, Pa. The eluent flow was monitored by an SF-770 Spectroflow variable wavelength ultraviolet detector manufactured by Schoeffel Instrument Co. of Westwood, N.J. Anhydrous diethyl ether from Mallinkrodt and distilled hexane were degassed under water aspirator prior to use. Schematic diagrams and a detailed set of directions for the assembly and use of this liquid chromatography apparatus are available upon request to the senior author.