propionate by reaction of **3h** with methanol and ethanol, respectively, and subsequent tretment with 1 N HCl, to give the N^{α}-hydrochloride salts (Scheme II).

Because of our special interest in the NCA's of β-haloalanines, which have not been made previously, we prepared **3b** both by direct phosgenation of β-chloro-L-alanine and by the route **1** → **3**, using *N*-BOC-β-Cl-L-alanine as the starting material. Both methods afforded a crystalline NCA of β-Cl-L-alanine, identical with one another with reference to elution behavior on thin-layer chromatograms, infrared absorbance, and ^{1}H NMR spectrometry. But the phosgene method was more tedious, especially in workup, and the product yield was only 72%. Reaction of β-chloroalanine with trichloromethyl chloroformate did not give, in our hands, the corresponding NCA.

Experimental Section

Melting points were obtained on a Hoover Uni-melt apparatus and are uncorrected. Proton NMR spectra were obtained on a 500-MHz instrument with an internal reference of tetramethylsilane in acetone-d_6. Thin-layer chromatograms were made on Polygram Sil G silica gel. Eluting solvents were ethyl acetate (A); ethyl acetate/benzene, 1:4 (B) or 1:1 (C); acetone/benzene, 1:1 (D); or acetone (E); visualization was with iodine vapor.

All of the *N*-carboxy α-amino acid anhydrides were prepared as described below for the NCA of β-chloro-L-alanine (**3b**).[12] Analytical data are give in Table I. *N*-BOC-amino acids were either purchased from Sigma Chemical Co. or prepared by standard methods; *N*-BOC-β-Cl-L-alanine was synthesized as described previously.[9] All reagents were of the best grade commercially available.

(12) The NCA of ornithine was prepared by slight modification of our standard procedure. The reaction was carried out in 10 mL of CH_2Cl_2 and 2 equiv of oxalyl chloride were used.

***N*-Carboxy-β-chloro-L-alanine Anhydride (3b).** To a solution of *N*-BOC-β-chloro-L-alanine (400 mg, 1.8 mmol) and *tert*-butyldimethylsilyl chloride (283 mg, 1.9 mmol) in ethyl acetate (2 mL) was added triethylamine (244 μL, 1.8 mmol) at 0 °C, which gave immediate precipitation of the triethylamine hydrochloride; after 30 min of stirring at 0 °C, the triethylamine·HCl was filtered (244 mg, 100%). The filtrate was then evaporated in vacuo, giving an oil which was redissolved in 3.0 mL of CH_2Cl_2. After chilling to 0 °C, oxalyl chloride was added (195 μL, 2.25 mmol), followed by 2–3 drops of DMF. Once gas evolution subsided (approximately 2 min), additional DMF (2 drops) was added and the reaction was allowed to warm to room temperature. Additional DMF was added dropwise until no further gas evolved (approximately 10 min). The solution was then diluted with THF (~10 mL) and evaporated in vacuo; additional THF was added and the solution was evaporated once again. This routine ensures removal of any unreacted oxalyl chloride. The resulting oil was placed on a vacuum line and evaporation of DMF (over about 2 h) afforded white needles. Recrystallization from CH_2Cl_2/hexane gave the desired **3b** in 100% yield (270 mg).

Compounds were prepared for elemental analyses and melting point determination by a second recrystallization from ether/hexane (1:1) at −20 °C.

Acknowledgment. This research was supported by grants from Dow Chemical Company and from USPHS GM 29660. We also gratefully acknowledge the NSF (CHE 8206978), the NIH (University of Chicago Cancer Center Grant CA 14599), and the Louis Block Fund for grants allowing for the purchase of NMR equipment used in this work.

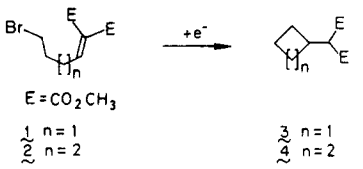
Registry No. **1a**, 15761-38-3; **1b**, 71404-98-3; **1c**, 13734-41-3; **1d**, 13734-34-4; **1e**, 7536-58-5; **1f**, 5068-28-0; **1g**, 57133-29-6; **1h**, 96165-56-9; **3a**, 2224-52-4; **3b**, 96165-57-0; **3c**, 24601-74-9; **3d**, 14825-82-2; **3e**, 13590-42-6; **3f**, 22911-82-6; **3g**, 96165-58-1; **3h**, 96165-59-2; oxalyl chloride, 79-37-8.

Communications

Intramolecular Electroreductive Cyclization[1]

Summary: Unsaturated esters, linked to a carbonyl unit by a chain of variable length, served as substrates for an investigation of intramolecular electroreductive cyclization; an efficient and reliable method for the preparation of γ-hydroxy esters has been devised.

Sir: In 1982 we reported that electroreduction of (ω-bromoalkylidene)malonates **1** and **2** led to the reasonably efficient production of cycloalkanes **3** and **4**.[3] This result suggests, as is characteristic of electroreduced olefins bearing one or more electron-withdrawing groups, that the β-carbon behaves as though it possesses nucleophilic character.[4]



(1) Dedicated to the memory of Mary Baizer.
(2) Alfred P. Sloan Foundation Fellow, 1980–1984.
(3) Nugent, S. T.; Baizer, M. M.; Little, R. D. *Tetrahedron Lett.* **1982**, *23*, 1339.

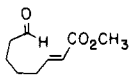
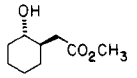
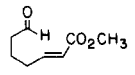
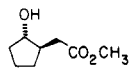
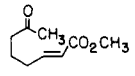
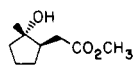
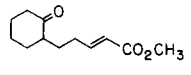
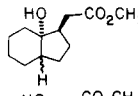
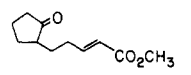
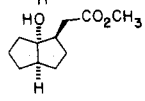
Armed with this information, we considered that a reasonable way to synthesize γ-hydroxy esters and their corresponding lactones would be to construct molecules wherein the halogen-bearing carbon in **1** and **2** was replaced by a ketone or an aldehyde.[5] Of the many structural variations which can be envisioned, two of the more interesting and potentially more useful involve the selection of both cyclic and acyclic substrates bearing a monoactivated rather than a geminal doubly activated electrophore.

We are pleased to report that an efficient and reliable

(4) This suggestion is in accord with numerous electrochemical experiments and with the results of ESR measurements which have been conducted on the radical anions of both cyclic and acyclic enones. See, for example: "Organic Electrochemistry: An Introduction and a Guide", 2nd ed.; Baizer, M. M., Lund, H., Eds.; Marcel Dekker, Inc.: New York, 1983. See also: Russell, G. A.; Stevenson, G. R. *J. Am. Chem. Soc.* **1971**, *93*, 2432. Bowers, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Kolodny, N. H.; Kronberger, K.; Roe, D. K. *Ibid.* **1970**, *92*, 2783.
(5) For an intermolecular variant of the present reaction, see: Shono, T.; Ohmizu, H.; Kawakami, S.; Sugiyama, H. *Tetrahedron Lett.* **1980**, *21*, 5029. Corey and Pyne have developed a nonelectrochemically based method for five-membered ring annulation which involves free radical generation from ketones using zinc–trimethylchlorosilane, followed by internal addition to a π bond. See: Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. For other examples of free radical cyclizations, refer to the review of Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883.

0022-3263/85/1950-2202$01.50/0

Table I

substrate	cyclized products[a]	trans/cis[a,b]	yield,[c] %
		1.8 : 1	72
		1.4 : 1	70 (84)
		5.1 : 1	76 (85)
		(2.5 : 1)[a]	74
		11.4 : 1	79

[a] The major trans product is illustrated. Cis products (i.e., cis-OH and ester groups) are also produced. The trans/cis ratio reflects the ratio of these two types of products. [b] Values were obtained from duplicate runs and reflect the fact that the range of values/2 ≤ 0.1. [c] The numbers refer to isolated yields of pure compounds. For comparison, the values listed in parentheses represent yield obtained by proton NMR.

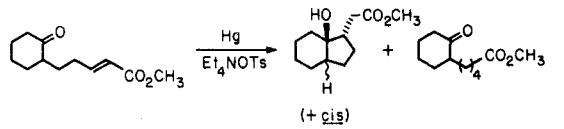
electrochemical procedure for the electroreductive coupling has been devised. Our results are summarized in Table I.[6] Notice first that the isolated yields of cyclized products are uniformly good, ranging from 70% to 80%. Note too that both aldehydes and ketones function well as substrates. With cyclic ketones, bi- and tricyclic products are obtained.[7]

In general, there exists a preference for the formation of products wherein the ester and hydroxyl groups are trans to one another on the vicinal carbons of the newly formed ring. Of the substrates examined, ketones show a greater preference than aldehydes, and of the ketones, the greatest preference (11.4:1) is manifest in the formation of the bicyclo[3.3.0]octane ring system.[8]

While the methodology which was used to achieve the results illustrated in Table I is reliable and efficient, there remains a drawback which could prevent its adoption and general use. That is, the pH of the solution must be carefully controlled by the dropwise addition of acetic acid. Otherwise, the solution would become basic and saponification could occur. On the other hand, if too much acetic acid is added or if it is added too rapidly, then the amount of carbon–carbon π bond reduction increases at the expense of the desired ring closure.

Attempts to alleviate this problem by carrying out the reaction under anhydrous conditions in acetonitrile or DMF met with failure. However, we have recently discovered a simple solution to the problem, *a solution which makes the procedure much simpler to conduct, increases the yield of the cyclized product relative to reduction of the carbon–carbon π bond, significantly reduces the possibility of saponification, and still maintains the reliability inherent to the original procedure.* One merely needs to substitute a carbon acid, in this case, 2 equiv of diethyl malonate, in place of water as the proton source.[9] The equations shown below vividly illustrate these points.

USE OF A CARBON ACID



	YIELD OF HYDROXYESTERS	RATIO OF CYCLIZED TO UNCYCLIZED PRODUCT
10% AQUEOUS CH_3CN	65 – 74	3.2 : 1
$CH_2(CO_2Et)_2$, CH_3CN	88	ca. 99 : 1

Research designed to gain some understanding of the factors which govern, among other things, the stereochemical outcome of these reactions is ongoing at the present time.

A typical procedure follows.[10] A degassed solution of 0.74 M Et_4NOTs in a 9:1 mixture of CH_3CN and water was introduced into anode (15 mL) and cathode (10 mL) chambers of an H-cell. The substrate (0.2 mmol) was added and reduced at −2.1 to −2.2 V. The pH of the solution was maintained between the starting value (pH meter) and 0.6 unit higher through the periodic addition of glacial acetic acid. After the passage of 2.7 F/mol of electricity, the reaction was complete. The colorless catholyte was withdrawn and, following a standard water workup, was subjected to capillary GC analysis and product isolation using gravity flow chromatography (E. Merck or Baker silica gel, 15–40% ether in Skellysolve F).

Reactions employing diethyl malonate as the proton source were conducted in a similar fashion with the following differences. Both the cathode and anode chambers were charged with 0.74 M Et_4NOTs in dry acetonitrile. Diethyl malonate (0.8 mmol) and 0.2 mmol of the substrate were added to the catholyte and the reduction was carried out at −2.25 V; pH control was not required. Following completion of the reaction as evidenced by the uptake of at least 2 F/mol of electricity, the reaction mixture was treated with 0.4 mmol of glacial acetic acid prior to a standard water workup.

Acknowledgment. We are pleased to acknowledge the support of this research by the National Science Foundation. R.D.L. is grateful to the Alfred P. Sloan Foundation for a research fellowship.

Registry No. $CH_2(CH_2)_3COCH(CH_2)_2CH{=}CHCO_2Me$, 96293-26-4; $CHO(CH_2)_4CH{=}CHCO_2Me$, 96293-27-5; $CHO(CH_2)_3CH{=}CHCO_2Me$, 2018-86-2; $CH_3CO(CH_2)_3CH{=}CHCO_2Me$,

(6) Details regarding the preparation of starting materials will appear in a full account of this work. Satisfactory analytical data was obtained for all compounds.

(7) The minor products, viz. those where the ester and hydroxyl groups are cis to one another, undergo lactonization both upon capillary GC analysis and upon mild acid treatment (column chromatography on silica gel or treatment with PPTS) to give bi- and tricyclic products. The lactones were not normally formed in the electrochemical reactions conducted in 10% aqueous acetonitrile.

(8) Bicyclo[3.3.0]octanes serve as useful intermediates in the construction of a wide variety of natural products. See, for example: Paquette, L. A., *Tetrahedron* **1981**, *37*, 4359–4559. Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; **1984**, *119*. Ramaiah, M. *Synthesis* **1984**, 529.

(9) Other researchers have also taken advantage of dialkyl malonates as proton sources in electrochemical transformations. See, for example: Powell, L. A.; Wightman, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 4412 and references therein. Interestingly, the ratio of trans to cis oriented hydroxyl and ester groups decreases when the reaction medium is changed from 10% aqueous acetonitrile to acetonitrile/dialkyl malonate. We are exploring this result in greater detail.

(10) Reactions were carried out in a standard H-cell equipped with a Pt foil anode, a mercury pool cathode, and a medium porosity sintered-glass frit. The cathodic chamber also contained a reference electrode (SCE with agar junction) and a combination pH electrode. Solutions were degassed by using nitrogen prior to each run; reactions were run under a nitrogen atmosphere. Each run called for the use of an Electrosynthesis Model 410 potentiostatic controller equipped with a Model 420 power unit and a Model 640 digital coulometer (all available from The Electrosynthesis Company, East Amherst, NY).

96293-28-6; $CO(CH_2)_3CH(CH_2)_2CH{=}CHCO_2Me$, 96293-29-7; $CO(CH_2)_4CH(CH_2)_4CO_2Me$, 13672-67-8; $CH_2(CO_2Et)_2$, 105-53-3; *trans*-$CH_2(CH_2)_3CH(OH)CHCH_2CO_2Me$, 78844-18-5; *cis*-$CH_2(CH_2)_3CH(OH)CHCH_2CO_2Me$, 78002-67-2; *trans*-$CH_2(CH_2)_2CH(OH)CHCH_2CO_2Me$, 96293-31-1; *cis*-$CH_2(CH_2)_2CH(OH)CHCH_2CO_2Me$, 96293-32-2; *trans*-$CH_2(CH_2)_2C(CH_3)(OH)CHCH_2CO_2Me$, 96293-33-3; *cis*-$CH_2(CH_2)_2C(CH_3)(OH)CHCH_2CO_2Me$, 96293-34-4; methyl α-(7α-hydroxyoctahydroindene-1-yl)acetate, 96293-30-0; methyl α-(7a-hydroxyoctahydropentalene-1-yl)acetate, 96293-35-5.

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