stirred for 5 min at −5 °C. The reaction mixture was poured into 300 mL of ice–water and stirred for 2 h. The solution was then washed with ether (50 mL), acidified to pH 1 with 1 N HCl, and extracted with ethyl acetate (3 × 150 mL). The organic phase was washed with water and brine and dried over $MgSO_4$. Removal of solvent in vacuo and washing of the solid with ether afforded 1.224 g (66%) of compound 11: ^1H NMR (CD_3COCD_3) δ 1.65 (s, 3 H), 1.82 (s, 3 H), 2.65 (m, 3 H) 4.88 (q, 1 H), 6.10 (s, 1 H); IR (1705) cm^{-1}; mp 183–184 °C. Anal. Calcd for $C_9H_{11}ClO_3$: C, 53.39; H, 5.47; Cl, 17.50. Found: C, 53.42; H, 5.64; Cl, 17.44.

Costatolide (1). To a solution of 11 (0.25 g, 1.25 mmol) in dry ether (25 mL) at room temperature under N_2 was added oxalyl chloride (1.1 mL, 12.5 mmol). After the mixture was stirred for 5 h, dimethyl formamide (0.97 mL, 12.5 mmol) was added dropwise over 5 min at 0 °C. Stirring was continued for 10 min, and then tetrabutylammonium chloride (1.74 g, 6.3 mmol) followed by boron trifluoride etherate (0.15 mL, 1.2 mmol) was added at room temperature. The mixture was then stirred 60 h under N_2. The reaction mixture was poured into ice-cooled (0 °C) 10% $NaHCO_3$. The aqueous layer was extracted with ether (3 × 15 mL), and the organic layers were combined, washed with water and brine, and dried over magnesium sulfate. Removal of solvent in vacuo followed by column chromatography (20% ethyl acetate–petroleum ether) on silica gel afforded 0.193 (70%) of costatolide (1): ^1H NMR ($CDCl_3$, 60 MHz) δ 1.88 (m, 3 H), 2.07 (m, 3 H), 2.80 (m, 2 H), 5.60 (q, 1 H), 6.01 (s, 1 H); IR 3018, 1720, 1643, 1120, 825 cm^{-1}; ^{13}C NMR ($CDCl_3$, 250 MHz) δ 13.8, 16.1, 35.1, 220, 222, 224; mass spectrum, *m/e* 187 (M^+ − Cl), 85.

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Registry No. (±)-1, 84926-48-7; 4, 84895-35-2; 5, 1067-09-0; 6, 37428-54-9; 7, 37428-47-0; 8, 84895-36-3; 9, 84895-37-4; (±)-10, 84895-38-5; (±)-11, 84895-39-6; (±)-12, 84895-40-9; methyl 2-methylacetoacetate, 17094-21-2; oxalyl chloride, 79-37-8.

Oxidative Cyclization of Dicarboxylate Dienolates as a New Cyclization Method

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On consideration of the abundance of rings in organic compounds, synthetic methods leading to cyclic structures are of obvious importance in organic synthesis.[1] In principle, the cyclic structures may be constructed either by cyclization of acyclic precursors, whereby one bond is formed, or by cycloaddition reactions in which two or more bonds are simultaneously formed. The Dieckmann[2] and the acyloin cyclizations[3] are most commonly used for the cyclization of dicarboxylic esters into the carbocyclic or heterocyclic ketone systems. The Dieckmann cyclization has been found to be useful for the preparation of cyclic ketones of a ring size of five or larger, although it is almost ineffective for the cyclic systems in the range of 9–12-membered rings. The acyloin cyclization appears to be the method of choice for the preparation of the medium- to large-sized ring systems.

Scheme I

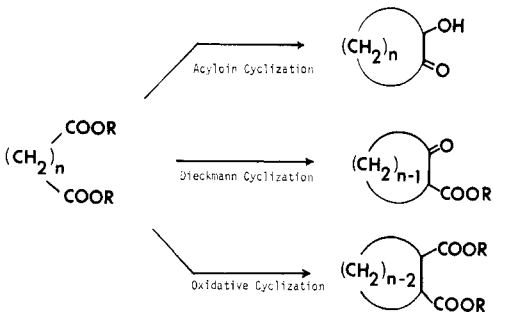

Table I. Oxidative Cyclization of Dimethyl Glutarate to Dimethyl Cyclopropanedicarboxylate

run	metal salt (molar equiv)	% yield (cis/trans ratio[a])
1	Ag_2O (2.5)	0
2	$AgClO_4$ (2.5)	7 (1.0)
3	$FeCl_3$ (2.5)	0
4	$NiCl_2$ (2.5)	0
5	$CuBr_2$ (2.5)	99 (1.2)
6	$CuCl_2$ (2.5)	99 (3.3)
7	$Cu(OAc)_2$ (2.5)	24 (1.4)
8	$CuSO_4$ (2.5)	0
9	CuI	0
10	CuI (1.1), $CuBr_2$ (2.5)	78 (1.7)
11	CuCl (1.1), $CuBr_2$ (2.5)	81 (1.9)

[a] Determined by GC analysis on a 15-ft column of 10% FFAP on Anakrom 60/70 mesh.

Oxidative coupling of metalated organic species has received increasing attention in the recent years for its synthetic utility.[4] For example, the ligand coupling can be effected either thermally or oxidatively in the reactions of organolithiums or Grignard reagents with copper salts. Although copper and silver salts are most extensively used in the oxidative coupling, other metal salts such as Au, Ni, Co, and Pt have also been found useful in certain cases. The coupling may occur via a radical or a nonradical mechanism, perhaps depending on the nature of the metal–carbon bond as well as on the reaction conditions.[4] The ligand coupling may proceed either monocentrically or dicentrically on the metal cluster.[5] The oxidative coupling has been successfully extended to the carbanionic species which are stabilized by a carbonyl,[5,6] alkoxycarbonyl,[7] phosphoryl,[8] or thioamidyl[9] functional group. The cyclization of diketones by intramolecular oxidative coupling has recently been exploited in the syntheses of 1,3-cyclopentanediones[10] and 1,4-cyclohexanediones.[11]

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Table II. Oxidative Cyclization of Dimethyl Glutarate to Dimethyl Cyclopropanedicarboxylate

run	$CuBr_2$[a]	LDA[a]	temp, °C	solvent additive	time	% yield (cis/trans ratio[b])
1	1.5	2.2	−78		overnight	69 (1.5)
2	2.5	2.2	−78		overnight	99 (1.2)
3	5.0	2.2	−78		overnight	94 (1.0)
4	2.5	2.05	−78		overnight	96 (1.5)
5	2.5	2.2	−78		1 h	82 (2.1)
6	2.5	2.2	−22		overnight	64 (3.4)
7	2.5	2.2	−78	10% TMEDA[c]	overnight	80 (2.9)
8	5.0	2.2	−78	10% TMEDA[c]	overnight	99 (2.5)
9	5.0	2.2	−78	10% HMPA[d]	overnight	77 (1.1)
10	5.0	2.2	−78	17% DMF[e]	overnight	77 (3.8)

[a] Molar equivalents with respect to the substrate. Use of $CuBr_2$ was found to give somewhat more reproducible results than than use of $CuCl_2$. [b] Determined by GC analysis. [c] TMEDA was present during the LDA generation. [d] HMPA was added after the LDA generation. [e] DMF was added following the addition of $CuBr_2$.

Table III. Oxidative Cyclization of Dimethyl Dicarboxylates

run	diester	conditions[a]	cyclized product (% yield;[b] cis/trans ratio[c])
1	glutarate (n = 3)	$CuBr_2$	**1a** + **1b** (94; 1.5)
2	glutarate	$CuCl_2$	**1a** + **1b** (88; 3.0)
3	adipate (n = 4)	$CuBr_2$	methyl 2-oxocyclopentanecarboxylate (**3**) (99)
4	adipate	10% TMEDA/THF, −22 °C, $CuBr_2$ or $CuCl_2$[d]	none
5	pimelate (n = 5)	$CuBr_2$	methyl 2-oxocyclohexanecarboxylate (**4**) (99)
6	pimelate	10% TMEDA/THF, −22 °C, $CuBr_2$ or $CuCl_2$[d]	none
7	suberate (n = 6)	$CuBr_2$	**2a** + **2b** (90, 0.8)
8	suberate	$CuCl_2$	**2a** + **2b** (93, 0.6)
9	azelate (n = 7)	$CuBr_2$ or $CuCl_2$	none
10	sebacate (n = 8)	$CuBr_2$ or $CuCl_2$	none
11	dodecanedioate (n = 10)	$CuBr_2$ or $CuCl_2$	none

[a] Run with 2.2 equiv of LDA and 2.0 equiv of Cu salt in THF at −78 °C with a gradual warmup to room temperature, except as noted. [b] Isolated yield. [c] Determined by GC analysis. [d] Run with 5.0 equiv of salt, the temperature being lowered to −78 °C before the salt was added.

We became interested in the possible intramolecular oxidative coupling of the dicarboxylate dienolate as a potential cyclization method. If successful, this cyclization constitutes a complementary method to the Dieckmann and the acyloin cyclizations in terms of the ring size of the cyclized product (Scheme I). In addition, it was envisioned that the complexation of the terminal enolates to the oxidizing metal salts was such that the unfavorable entropy factor normally associated with the medium to large ring closure might be favorably compensated. We report herein a partial realization of this goal.

The dienolate of dimethyl glutarate (n = 3), generated by the deprotonation of dimethyl glutarate with 2.2 molar equiv of lithium diisopropylamide (LDA) in THF at −78 °C, was treated with 2.5 molar equiv of $CuBr_2$ or $CuCl_2$ at −78 °C and allowed to warm to room temperature overnight. After quenching and an extractive workup (see Experimental Section), two products were isolated and identified as dimethyl *cis*- (**1a**) and *trans*-1,2-cyclopropanedicarboxylate (**1b**).[12] A number of other readily available transition-metal salts were also examined as oxidants in this cyclization in terms of the reaction yield and the cis/trans isomer ratio (Table I).

Several features are noteworthy in the results shown in Table I. Among the various salts examined, $CuBr_2$ and $CuCl_2$ were found to be most satisfactory in terms of the cyclization yield. It is also interesting to note that the cis isomer is obtained in a greater amount than the trans isomer in almost all of the successful experiments. This is perhaps due to the chelation effect of the transition-metal cation on maintaining the particular conformations which lead to the cyclized products. The observation that $CuCl_2$ gives a higher cis/trans isomer ratio than $CuBr_2$ is also in accord with the view that complexation is important, and the effect is greater with the more electrophilic cupric ion ($CuCl_2 > CuBr_2$). It is also clear from our results that Cu^+ alone is not a strong enough oxidant for this cyclization.[13]

Other possible variations of the reaction conditions such as the amounts of base and Cu^{2+} salt, temperature, and solvent modification have also been examined (Table II). It was found that at least 2.0 molar equiv of Cu^{2+} salt was needed for the optimum yield of the cyclization. The use of a smaller excess of LDA (2.05 vs. 2.20) improved the cis/trans isomer ratio to a minor degree. A shorter reaction time also improved the cis/trans isomer ratio, but at the expense of the cyclization yield. It seems likely that the product was initially formed with a higher cis/trans isomer ratio and that the cis isomer slowly isomerized to the trans isomer under the basic reaction conditions. The change of temperature or the use of the solvent additives such as TMEDA, HMPA, or DMF actually lowered the cyclization yield, while increasing the cis/trans isomer ratio, although these changes were expected to enhance the solubility of both the dienolate and $CuBr_2$. The reasons for the lower cyclization yields under these conditions are not clear. The possible enhanced deprotonation of the cyclized product

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by the dienolate under these conditions is not consistent with the enhanced cis/trans ratio observed, because the enhanced deprotonation process is expected to decrease the cis/trans ratio.

The possible extension of this oxidative cyclization to longer chain diesters has also been studied (Table III). The same procedures which were most successful for dimethyl glutarate ($CuBr_2$ and $CuCl_2$) were used, especially the same concentration of the dienolate to be cyclized. Earlier experiments with dimethyl glutarate indicated that concentrations lower than 0.06 M reduced the amount of cyclization. Only dimethyl suberate ($n = 6$) has been found to cyclize in high yield to dimethyl *cis*- and *trans*-1,2-cyclohexanedicarboxylate.[14] It is interesting that formation of the trans isomer is favored over the cis isomer in this case. It is presumably because of the fact that the complexation between Cu^{2+} and the dicarboxylate favors the conformation (diequatorial-like) which leads to the trans isomer over the conformation (axial–equatorial-like) leading to the cis isomer.

The attempted oxidative cyclizations of dimethyl adipate ($n = 4$) and dimethyl pimelate ($n = 5$) led to quantitative yields of Dieckmann cyclization products **3** and **4**.[15] Evidently, the Dieckmann cyclization of their monoenolates is much faster than a second deprotonation to form their dienolates. The use of 10% TMEDA/THF as a solvent at −22 °C sufficiently increased the rate of deprotonation in both cases to completely suppress the Dieckmann cyclization, but subsequent treatment of the respective dienolates with excess $CuBr_2$ or $CuCl_2$ failed to produce any oxidative cyclization. It remains unexplained why neither the oxidative cyclization nor the Dieckmann cyclization could be observed for the diesters with $n = 7$, 8, and 10 under the standard conditions successfully used for the diesters with $n = 3$ and 6.

In summary, the oxidative cyclization of dicarboxylate dianion appears to be quite effective in preparation of the three and six-membered-ring systems, although its generality to other ring sizes is lacking.

Experimental Section

General Information. Dimethyl glutarate and dimethyl adipate were obtained from Aldrich Chemical Co. Other diesters were prepared from their respective diacids (Aldrich) by Fisher esterification. All solvents used were distilled from the appropriate drying agent prior to use: THF (soldium–benzophenone), diisopropylamine (CaH_2), TMEDA (CaH_2), HMPA (CaH_2), and DMF (CaH_2). Transition-metal salts (anhydrous) were dried at 130 °C immediately before use. All reactions were done in flame-dried glassware under N_2 by using standard syringe techniques for all liquid transfers. ^1H NMR spectra were obtained on a Varian EM-390 or Varian FT-80 spectrometer in $CDCl_3$ containing Me_4Si as an internal reference. IR spectra were obtained on a Pye-Unicam 2-300 or a Perkin-Elmer 297 spectrometer. Mass spectra were obtained on a Hewlett-Packard 5980A spectrometer. Gas chromatographic analyses were performed on an Antek Model 300 GC equipped with a flame ionization detector and a Hewlett-Packard 3390A integrator.

Oxidative Cyclization of Dimethyl Glutarate (Representative Procedure). A solution of dimethyl glutarate (338 mg, 2.11 mmol) in THF (30 mL) was added dropwise to a THF (6 mL) solution of LDA (2.2 equiv), prepared from diisopropylamine (491 mg, 4.85 mmol) and *n*-BuLi (3.00 mL of a 1.55 M solution in hexane, 4.64 mmol) at −78 °C over 30 min, to give a viscous, cloudy solution. After an additional 15 min at −78 °C, $CuBr_2$ (943 mg, 4.22 mmol) was added in one portion. The resulting dark brown reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by pouring the mixture into 3 M HCl, and this mixture was extracted with ether. The combined organic extract was washed with brine until neutral, dried over $MgSO_4$, and evaporated. The crude product was purified on a silica gel column (ether/hexane eluent) to give a total of 313 mg (94% yield) of **1a** and **1b**. The same procedure was used for $CuCl_2$. Dimethyl suberate could also be cyclized with both $CuBr_2$ and $CuCl_2$ by the same procedure. Pure isomers could be obtained by using a longer silica gel column (ether/hexane eluent) or by silica gel preparative thin-layer chromatography (10% ether/hexane).

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Registry No. **1a**, 826-34-6; **1b**, 826-35-7; **2a**, 1687-29-2; **2b**, 3205-35-4; **3**, 10472-24-9; **4**, 41302-34-5; dimethyl glutarate, 1119-40-0; dimethyl adipate, 627-93-0; dimethyl pimelate, 1732-08-7; dimethyl suberate, 1732-09-8.

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Formation of Ethers by the Reductive Desulfurization of Thiono Esters

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We have recently reported the conversion of esters to ethers via a thionation–reductive desulfurization process (Scheme I.)[1] The thionation step was that used by Lawesson and his co-workers.[2] The desulfurization process was carried out with Raney nickel under very mild conditions in aprotic solvents.[1] We now report additional ester compounds that have been reduced by using this thionation–desulfurization procedure. The conversion of two dithiono esters to the diethers by the Raney nickel desulfurization process and results of metal hydride reductions of the thiono esters are also reported.

Table I shows the results of the reductive desulfurization of several thiono esters. The thiono esters of runs 1–5 were prepared by using Lawesson's reagent (**1**, see Scheme I). These thiono esters were not isolated but were immediately treated with Raney nickel to form the corresponding ethers. The desulfurization process was also carried out on *O,O'*-dimethyl 2,6-pyridinedicarbothioate (**2**)[3] and *O,O'*-diethyl dithiooxalate (**3**),[4] which were prepared by a different synthetic route. The product ethers were analyzed by VPC using an internal standard. The NMR and/or IR spectra of the isolated ethers were identical with those of authentic samples.

The thionation step appears to be a limiting factor in the overall reduction process. β-Methoxyethyl benzoate did not form the thiono ester when treated with reagent **1**.[1] β-Phenoxyethyl benzoate, on the other hand, readily reacted with **1** and was reduced to the ether in an overall yield of 70% (run 1, Table I). Apparently the phenyl group is deactivating the ether oxygen toward the electrophilic phosphorus atoms of compound **1**. Ethyl γ-chlorobutyrate failed to form a thiono ester because it polymerized in the presence of reagent **1** (run 2).

Methyl picolinate also failed to react with reagent **1**.[1] Compound **2**, a dithiono ester analogue of methyl picolinate was prepared by a different synthetic route.[3] This

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