as to achieve a continuous peptide synthesis whereby the growing peptide is the only component in solution.

The polymeric alcohol II is recyclable. A sample was subjected to three cycles of benzoylation, followed by a reaction with benzylamine for determining the amount of available OH groups, as previously described. The loading of the polymer was found to be virtually the same at each cycle.

Experimental Section

Preparation of the Polymers Ia-c. To a mixture of 50 g of macroreticular polystyrene (XE-305, Rohm & Haas) and 100 g of 4-chloro-3-nitrobenzoyl chloride was added a solution of 25 g of aluminum trichloride in 300 mL of dry nitrobenzene. The mixture was stirred mechanically at 60 °C for 5 h and poured into a mixture of 150 mL of DMF, 100 mL of concentrated HCl, and 150 g of ice. The beads slowly turned white. They were washed with 300-mL portions of DMF–water (3:1) until the washings were colorless, then with warm (60 °C) DMF, and finally with 6 portions of 300 mL of methylene chloride–methanol (2:1). The dried polymer Ib weighed 82 g (1.88 mmol/g). Anal. Calcd: N, 2.54 (1.81 mmol/g); Cl, 7.90 (2.21 mmol/g). Similarly prepared from the corresponding substituted benzoic acid chlorides were the polymers Ia and Ic, with respective loadings of 1.45 and 1.65 mmol/g.

Preparation of the Polymer II. Most experiments were carried out with polymer II prepared from Ib, due to its higher loading. Hydrolysis was carried out with a mixture of 130 mL of 40% benzyltrimethylammonium hydroxide in water, 130 mL of water, and 260 mL of dioxane, for 8 h at 90 °C. The polymer was filtered, and the process was repeated. The beads were then washed with 4 portions of warm (60 °C) dioxane. Acetic acid (30 mL) was added with stirring for 15 min. The polymer was washed with dioxane until the washings were neutral, followed by 6 portions of 300 mL of methylene chloride–methanol (2:1). Anal. Calcd: Cl, <0.1; N, 2.38 (1.7 mmol/g). The amount of available OH groups was determined by esterifing with a threefold excess of benzoyl chloride and pyridine in dry chloroform at 0–10 °C for 30 min, washing with chloroform, and reacting with excess benzylamine. The polymer was washed with chloroform, and excess benzylamine was extracted with hydrochloric acid. The organic phase afforded pure *N*-benzylbenzamide, and from its weight the loading on the polymer was determined to be 1.7-1.8 mmol/g, assuming quantitative reactions at each stage.

Preparation of Polymeric Active Esters III. Esters of simple acids were prepared from the acid chloride and pyridine as just described. Active esters of Boc-protected amino acids were prepared by the symmetric anhydride method as follows: 4 mmol of the Boc-protected amino acid was dissolved in 6 mL of methylene chloride (THF was added in cases of poor solubility). The solution was cooled to −10 to 0 °C and 2 mmol DCC was added. After 30 min at 0 °C, the mixture was filtered directly into a vessel containing 1 g of the polymer II. Pyridine (0.5 mL) was added, and the mixture was shaken for 1 h at room temperature. The polymer was washed with six to eight 10-mL portions of chloroform. Active esters of Boc-glycine, Boc-phenylalanine, and Boc-(*O*-benzyl)tyrosine were thus prepared. Determination of the loading by reacting the polymers with an excess of benzylamine and weighing the resulting amide showed that 70–80% of the available OH groups underwent esterification.

Relative Reactivity of Active Esters. *o*-Nitrophenyl benzoate, 4-(benzoyloxy)-3-nitrobenzophenone, and *N*¹-(benzoyloxy)benzotriazole (1 mmol each) were dissolved in 50 mL of chloroform at room temperature, and 4 mL of *tert*-butylamine was added. Disappearance times for the starting esters determined by TLC, were 11 days, 7 h, and 2 min, respectively.

Peptide Synthesis Cycle. A TFA salt of the growing peptide was dissolved in chloroform (10 mL/mmol). The polymeric active ester of the next amino acid to be coupled, in 40% excess, was added, and 2 equiv of dry triethylamine was added. Shaking was continued until complete disappearance of the spot of the starting amino peptide, determined by TLC with ninhydrin spraying. The polymer was washed with chloroform, and the combined washings were extracted with 10% sodium bicarbonate and then with cold, 10% sodium bisulfate solution. Evaporation of the solvent and Boc deblocking with trifluoroacetic acid completed the cycle. Thus, we prepared the pentapeptide Boc-Tyr(OBzl)-Gly-Gly-Phe-Leu-Obzl in an overall crude yield of 92%, starting from leucine benzyl ester hydrochloride. The peptide was hydrolyzed in 6 N HCl for 24 h and submitted to amino acid analysis. Amino acid ratios were as follows: Gly, 2.0; Phe, 0.92; Leu, 1.14; Tyr, 0.78.

Racemization Test. Starting from optically pure L-leucine methyl ester and L-phenylalanine, we prepared the dipeptide Boc-L-Phe-L-Leu-OMe as described above. Boc deblocking and reaction with benzoyl chloride resulted in formation of Bz-L-Phe-L-Leu-OMe. Any racemization in the phenylalanine during the preparation of the polymeric active ester and the coupling step would result in formation of some of the DL stereoisomer of the latter dipeptide. The diastereoisomer ratio was determined by analytical HPLC (silica column, 3% 2-propanol in hexane as eluent, UV detector set at 250 nm). The DL stereoisomer accounted for only 0.3% of the mixture.[13]

Registry No. Boc-Tyr(OBzl)-Gly-Gly-Phe-Leu-OBzl, 66831-30-9; polystyrene, 9003-53-6; 4-chloro-3-nitrobenzoyl chloride, 38818-50-7; 4-fluoro-3-nitrobenzoyl chloride, 400-94-2; 4-methoxy-3-nitrobenzoyl chloride, 10397-28-1; *N-tert*-butoxycarbonylglycine, 4530-20-5; *N-tert*-butoxycarbonylphenylalanine, 13734-34-4; *N-tert*-butoxycarbonyl-*O*-benzyltyrosine, 2130-96-3; *o*-nitrophenyl benzoate, 1523-12-2; 4-(benzoyloxy)-3-nitrobenzophenone, 82469-49-6; *N*-(benzoyloxy)benzotriazole, 54769-36-7; *tert*-butylamine, 75-64-9.

(13) This test was carried out at the Department of Chemistry, University of Massachusetts, Amherst, in collaboration with Dr. L. A. Carpino.

Cyclodextrin-Mediated Chiral Sulfoxidations

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Sulfoxides chiral at sulfur have been used successfully to direct carbon–carbon bond formation in asymmetric syntheses;[1] furthermore, sulfoxidations mediated by flavin adenine dinucleotide monooxygenases[2a] and rat liver cytochrome P-450 isozymes[2b] occur with a stereochemical preference. While the synthesis of optically active sulfoxides is most commonly accomplished by the reaction of *O*-menthyl arene- or alkanesulfinates with Grignard reagents (Andersen synthesis),[3] the enantioselective oxidation of aryl alkyl sulfides to sulfoxides by chemical[4] and biochemical[5] methods continues to stimulate interest. Initial chemical routes using chiral oxidants (peracids, hydroperoxides) resulted in a relatively low transfer of chirality, about 8% ee at best.[6] Recently, Davis and

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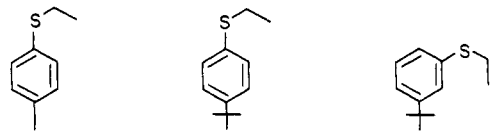
Table I. Chiral Induction in Cyclodextrin-Mediated Sulfoxidations

entry[a]	substrate[b]	CD[c]	oxidant[d]	ee,[e,f] %
1	1a	α	H_2O_2	0.4
2	2a	β	H_2O_2	0.4
3	3a	β	H_2O_2	6.7
4	3a	α	H_2O_2	4.6
5	3a	γ	H_2O_2	−4.1
6	3a	β	*m*-ClPBA	20.7
7	3a	β	*m*-ClPBA (4 °C)	33.7
8	3a	β	*t*-BuOOH	19.7
9	3a	β	$PhI(OAc)_2$	−25.9
10	1a	α	*m*-ClPBA	−7.5
11	3a	β (0 mM)	*m*-ClPBA	<0.3
12	3a	β (0.2 mM)	*m*-ClPBA	<0.3
13	3a	β (0.4 mM)	*m*-ClPBA	1.5
14	3a	β (0.9 mM)	*m*-ClPBA	4.0
15	3a	β (2.2 mM)	*m*-ClPBA	12.4
16	3a	β (4.4 mM)	*m*-ClPBA	15.8
17	3a	β (8.8 mM)	*m*-ClPBA	19.4

[a] All reactions were carried out in H_2O (10 mL) for 1 h; temperature is ambient (25 °C) unless otherwise specified. [b] [1a] = 0.65 mM; [2a] = [3a] = 0.50 mM. [c] [αCD] = 10.3 mM; [βCD] = 8.8 mM unless otherwise specified; [γCD] = 7.7 mM. [d] $[H_2O_2]$ = 220 mM; [*m*-ClPBA] = 0.12 mM; [*t*-BuOOH] = 55 mM; $[PhI(OAc)_2]$ = 0.08 mM. [e] Percent enantiomeric excess of the sulfoxide that elutes first from the HPLC column; -ee indicates an excess of the sulfoxide that elutes second. [f] The ee's for entries 1-10 have been adjusted to account for enantioselective extraction from aqueous cyclodextrin solution. Entries 11-16 have not been thusly adjusted; however, under the conditions described in entry 17, a -1.3% ee is obtained in the extraction, and other entries would have smaller adjustments proportional to the cyclodextrin concentration. Entries are based on at least two independent trials for each set of oxidation conditions.

co-workers[7] have demonstrated that chiral 2-sulfonyloxaziridines can be used to improve significantly on this induction, providing a 35% ee in the oxidation of methyl *p*-tolyl sulfide to the sulfoxide. To date, this represents the maximal induction obtained in a chemical sulfoxidation. It occurred to us that the binding of an aromatic substrate to cyclodextrin might induce asymmetry in the oxidation (Figure 1) inasmuch as differences in the stabilities of diastereomeric sulfoxide/cyclodextrin complexes have been previously observed.[8] Such "template-directed" chiral sulfoxidations have already been demonstrated with bovine serum albumin as the chiral binding site,[9] although in this instance chiral material (up to 93% ee) is obtained as a result of both enantioselective sulfoxidation and enantiospecific binding of one sulfoxide that inhibits its further oxidation to the achiral sulfone. It is obviously desirable to show that an inexpensive and readily available chiral template can also be used to induce chirality in an otherwise achiral reaction.

We now report that cyclodextrin mediates chiral sulf-



1 2 3

a, SULFIDE (−S−)
b, SULFOXIDE (−S(=O)−)
c, SULFONE (−S(=O)(=O)−)

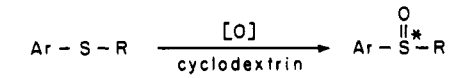
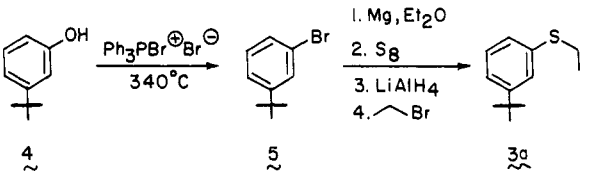


Figure 1.

Scheme I



oxidations involving achiral reagents and that the best example provides optical induction comparable to the best chemical method examined to date.

Substrate sulfides **1a** and **2a** were prepared by alkylation of the corresponding thiophenol, and meta sulfide **3a**[10] was prepared via the meta bromide as shown in Scheme I.[7] Sulfoxidations were carried out in aqueous solution for 1 h, and then the reactions were extracted with hexane, concentrated, and analyzed on a chiral (dinitrobenzoyl)-phenylglycinate HPLC column described by Pirkle.[11] In each case, unreacted sulfide eluted within 1.8 min at a flow rate of 2.0 mL/min, while the enantiomeric sulfoxides **1b**, **2b**, and **3b** eluted at 12.7–13.8, 10.4–11.1, and 8.3–8.9 min, respectively. While no attempt was made to assign the *S* and *R* isomers of sulfoxides **2b** and **3b**, the isomers of **1b** are known to elute in the order (1) *S* and (2) *R* in this HPLC system.[2a] Each oxidation was performed under conditions such that at least half of the starting sulfide remained unreacted; the kinetic preference for sulfoxide formation thereby assured minimal contamination by the corresponding sulfone. As reported by Walsh for 1,[2a] authentic samples of sulfones **1c**, **2c**, and **3c** coeluted with the slower eluting enantiomer of the corresponding sulf-

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(8) (a) Mikolajczyk, M.; Drabowicz, J.; Cramer, F. *J. Chem. Soc. D.* **1971**, 317. (b) Mikolaczyk, M.; Drabowicz, J. *Tetrahedron Lett.* **1972**, 2379. (c) Mikolaczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510.

(9) Sugimoto, T.; Kokubo, T.; Miyazaki, J.; Tanimoto, S.; Okano, M. *Bioorg. Chem.* **1981**, *10*, 311.

(10) This material contains 3% of the para isomer, a result of a 6% impurity of *p-tert*-butylphenol present in commercially available **4**; however, the meta and para sulfoxides are easily resolved under the HPLC conditions used.

(11) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964.

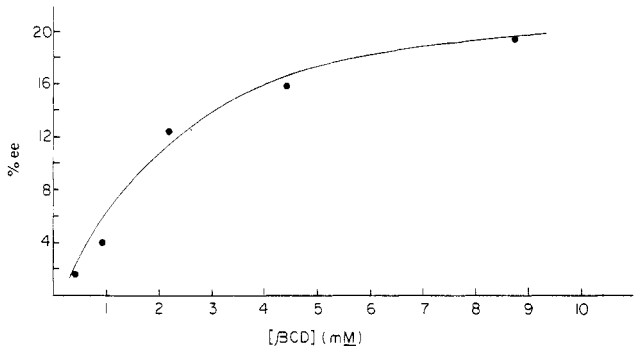

Figure 2. Effect of β-cyclodextrin on the oxidation of **3a** by *m*-ClPBA.

oxide on the Pirkle HPLC column, and it was therefore important to minimize this potential source of error. It should be noted, however, that sulfone contamination would afford an apparent ee opposite to that observed in most entries in Table I.

The results of the cyclodextrin-mediated sulfoxidation reactions are tabulated in Table I, and the findings are summarized as follows: (1) the substrate that "feels" the chiral environment of cyclodextrin most (**3a**) is that which is nearest the rim of the cyclodextrin torus[19] (entries 1–3); (2) the optical induction using β-cyclodextrin (βCD) is somewhat larger than that with either α- or γCD (entries 3–5); (3) oxidants that can themselves bind to βCD[20] give larger inductions than H_2O_2, which cannot (entries 3 and 6–9); (4) an oxidant capable of binding to CD can give significant induction even when the induction attributable to the substrate/CD complex is negligible (entries 1 and 10); and (5) the effect of βCD on the oxidation of **3a** by *m*-chloroperoxybenzoic acid (*m*-ClPBA) shows saturation (Figure 2), as expected for a process involving equilibrium binding of one or both of the reactants (entries 11–17).

Of particular interest is the reaction of sulfide **3a** with *m*-ClPBA at 4 °C in the presence of βCD (entry 7). *m*-Chlorobenzene derivatives structurally related to *m*-ClPBA ((*m*-chlorophenyl)acetate,[12] (*m*-chlorobenzoyl)acetic acid[13]) have been shown to form inclusion complexes with βCD (K_d = 3.5 (25 °C) and 6.0 (50 °C) × 10^{-3} M, respectively), and it is reasonable to assume that *m*-ClPBA does as well. The 33.7% ee (slightly better than a 2:1 ratio of isomers) obtained in this oxidation is nearly the same as that reported for the best chemical method of enantioselective sulfoxidation to date,[7] 35.1%. Furthermore, the actual difference in transition-state energies which characterizes the two possible oxidation pathways is probably greater in the βCD-mediated reaction (done at 4 °C) than in the chiral oxidant reaction (done at −78 °C). This is quite remarkable when put in the proper context—βCD is available for about $0.35/g,[14] requires no preparation or resolution before use, and is completely recyclable inasmuch as it is not consumed during the reaction.

Experimental Section

Ethyl Tolyl Sulfide (1a). To a solution of sodium methoxide formed from Na metal (6.5 g, 0.28 mol) and methanol (150 mL) were added with stirring *p*-methylthiophenol[15] (30 g, 0.24 mol) and then ethyl bromide (26.3 g, 0.24 mol). The reaction was heated at gentle reflux for 1 h and then neutralized with NH_4Cl and the solvent removed in vacuo. The mixture was partitioned between H_2O and Et_2O, and then the organic layer was dried over $MgSO_4$, concentrated, and distilled to give the product as a colorless liquid (27 g, 75%): bp 103–108 °C (6 torr) (lit.[21] bp 101–103 °C at 2 torr); ^1H NMR ($CDCl_3$) δ 1.3 (t, 3, CH_2CH_3), 2.3 (s, 3, Ar CH_3), 2.9 (q, 2, CH_2), 7.2 (s, 4, Ar H); chemical ionization mass spectrum, *m/e* 153 $(M + 1)^+$.

Anal. Calcd for $C_9H_{12}S$: C, 70.99; H, 7.96; S, 21.05. Found: C, 71.03; H, 7.99; S, 20.92.

Ethyl 4-*tert*-Butylphenyl Sulfide (2a). Prepared as above, except that *p*-*tert*-butylthiophenol[15] was used. The product was isolated by distillation to afford a colorless liquid (80%): bp 75–76 °C (0.2 torr); ^1H NMR ($CDCl_3$) δ 1.3 (t and sharp s, 12, CH_3), 2.9 (q, 2, CH_2), 7.3 (s, 4, Ar H); chemical ionization mass spectrum, *m/e* 195 $(M^+ + 1)^+$.

Anal. Calcd for $C_{12}H_{18}S$: C, 74.15; H, 9.36; S, 16.50. Found: C, 74.40; H, 9.21; S, 16.22.

***m*-Bromo-*tert*-butylbenzene (5).** This was carried out analogously to and on the time scale as the preparation previously described for 2-bromonaphthalene,[16] with *m*-*tert*-butylphenol[15] and $Ph_3PBr^+Br^-$ as the starting materials. After distillation, the product was obtained as a colorless liquid (30%): bp 94–98 °C (6 torr) (lit.[22] bp 95–97 °C at 10 torr); ^1H NMR ($CDCl_3$) δ 1.3 (s, 9, CH_3), 7.1–7.6 (m, 4, Ar H); chemical ionization mass spectrum, *m/e* 212/214 $(M)^+$.

Anal. Calcd for $C_{10}H_{13}Br$: C, 56.35; H, 6.16; Br, 37.49. Found: C, 56.62; H, 6.23; Br, 37.58.

Ethyl 3-*tert*-Butylphenyl Sulfide (3a). To a solution of *m*-bromo-*tert*-butylbenzene (10.0 g, 47 mmol) in dry THF (80 mL) was added Mg turnings (1.2 g, 48 mmol); then a small I_2 crystal was added, and the mixture was heated to reflux under anhydrous conditions for 3 h. To the dark green solution of the Grignard reagent was added sulfur (1.5 g, 47 mmol) portionwise, and the yellow reaction was refluxed for 45 min. LAH (1.0 g) was added portionwise, and the mixture was refluxed for 30 min. The excess LAH was decomposed by careful addition of MeOH (100 mL), then a solution of ethyl bromide (5.1 g, 47 mmol) in MeOH (100 mL) was added all at once, and the resulting mixture was refluxed for 30 min. The mixture was filtered, then the solvent was removed in vacuo, and the residue was partitioned between H_2O and Et_2O. The organic layer was dried over $MgSO_4$, and the product was isolated by two distillations to afford a colorless liquid (2.6 g, 29%): bp 94–96 °C (4 torr); ^1H NMR ($CDCl_3$) δ 1.3 (t and sharp s, 12, CH_3), 2.9 (q, 2, CH_2), 7.1–7.4 (m, 4, Ar H); chemical ionization mass spectrum, *m/e* 195 $(M + 1)^+$.

Anal. Calcd for $C_{12}H_{18}S$: C, 74.15; H, 9.36; S, 16.50. Found: C, 74.31; H, 9.11; S, 16.30.

Achiral Sulfoxidations (1b, 2b, 3b). Each of the sulfoxides was prepared from the corresponding sulfides in the following way.[17] A mixture of the sulfide (3.1 mmol) and $NaIO_4$ (3.1 mmol) in H_2O/MeOH (1 mL:7 mL) was stirred at 0 °C for 15 min and then at room temperature for 12 h. The white paste was partitioned between H_2O and CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and evaporated. Purification on a preparative silica gel TLC plate eluted with Et_2O gave the unreacted sulfide at R_f 1.0 and the product sulfoxide at R_f 0.3; elution from the silica gel with CH_2Cl_2/MeOH (95:5) and drying in vacuo at room temperature in each case gave the desired sulfoxide as a yellow oil (60–70%). ^1H NMR ($CDCl_3$) demonstrates that the ethyl CH_2 signal has changed from a quartet to a multiplet, as expected for diastereotopic hydrogens.

Chiral Sulfoxidations. A stock solution of the sulfide was made by dissolving it in CH_3CN. For each oxidation, two reactions were run consecutively: reaction A, 10 mL of H_2O, 140 μL of sulfide solution; reaction B, 10 mL of H_2O, 100 mg of cyclodextrin, 140 μL of sulfide solution. To each was added the described amount of oxidant, and each was stirred at room temperature for 1 h. Cyclodextrin (100 mg) was then dissolved in reaction A, and both A and B were extracted with hexane (2 × 20 mL). The organic extracts were evaporated to a small volume (ca. 50 μL by using a pear-shaped flask) and the enantiomeric ratio was determined on a 10-μL aliquot by HPLC using a Pirkle type-I ionic (dinitrobenzoyl)phenylglycinate column[18] and eluted with

(12) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
(13) Straub, T. S.; Bender, M. L. *J. Am. Chem. Soc.* **1972**, *94*, 8881.
(14) Chemical Dynamics Corp., South Plainfield, NJ 07080.
(15) Obtained from Aldrich Chemical Co., Milwaukee, WI.
(16) Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **1967**, *32*, 1607.
(17) Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282.
(18) Obtained from Regis Chemical Co., Morton Grove, IL 60053.

hexane/2-propanol (95:5) at a flow rate of 2.0 mL/min, back pressure <1000 psi. The ratio could be determined directly by integration of the peak areas of interest.

Sulfones (1c–3c). To a solution of sulfides **1a–3a** (30 mg) in *tert*-butyl alcohol/saturated aqueous $MgSO_4$ (500 μL:500 μL) was added an excess of $KMnO_4$, and the purple reactions were stirred at room temperature for 4 h. The sulfones were isolated by preparative TLC on silica plates, which, when eluted with Et_2O, gave R_fs of ca. 0.9, and were easily separable from both contaminating sulfide and sulfoxide.

Acknowledgment. We thank Mr. David O'Krongly and Dr. Robert Corcoran for assistance in obtaining ^1H NMR data. The support and shared interest of Professor Ronald Breslow is gratefully acknowledged. This work was performed at Columbia University while the author held an NIH Postdoctoral Fellowship.

Registry No. **1a**, 622-63-9; (±)-**1b**, 67529-34-4; (*R*)-**1b**, 1519-40-0; (*S*)-**1b**, 62961-00-6; **1c**, 7569-34-8; **2a**, 30506-33-3; (±)-**2b**, 88315-70-2; (*R*)-**2b**, 88336-00-9; (*S*)-**2b**, 88336-01-0; **2c**, 34545-14-7; **3a**, 88315-69-9; (±)-**3b**, 88315-71-3; (*R*)-**3b**, 88336-02-1; (*S*)-**3b**, 88336-03-2; **3c**, 88315-72-4; **4**, 585-34-2; **5**, 3972-64-3; cyclodextrin, 1269-70-4; *p*-methylthiophenol, 106-45-6; *p*-*tert*-butylthiophenol, 2396-68-1.

(19) Based on both an examination of CPK molecular models and the results of Bender and co-workers (*J. Am. Chem. Soc.* **1967**, *89*, 3242), which indicate a greatly enhanced rate of hydrolysis for *m*-*tert*-butylphenyl acetate as compared to the para isomer.
(20) The binding of *tert*-butylhydroperoxide (Matsui and co-workers, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1909) and of aromatics to cyclodextrins is well documented.
(21) Gilman, H.; Beaber, N. J. *J. Am. Chem. Soc.* **1925**, *47*, 1449.
(22) Ruechardt, C.; Eichler, S. *Chem. Ber.* **1962**, *95*, 1921.

Studies on the Intramolecular Claisen Condensation; Facile Synthesis of Tetronic Acids

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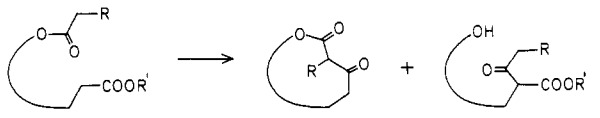
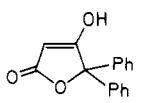
An ester of an acyloxy carboxylic acid can in principle give both a cyclic (**2**) and an acyclic (**3**) product in the intramolecular Claisen condensation. Disregarding re-



1 *2* *3*

actions of compounds that have additional anion-stabilizing groups, e.g., acetoacetates, few examples have however been reported of cyclizations of the type **1** → **2**. In 1956 Haynes and Stanners[1] treated α-acetoxy esters with (diisopropylamino)magnesium bromide and obtained, e.g., γ,γ-dimethyl- and γ,γ-diphenyltetronic acid (**4**) in yields

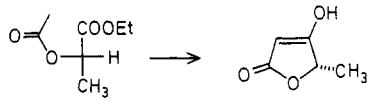


4

of 46% and 85%, respectively. Ireland and Thompson[2] recently improved the former yield to 95% by using lithium diisopropylamide as base.

(1) Haynes, L. J.; Stanners, A. H. *J. Chem. Soc.* **1956**, 4103-4106.
(2) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041-3052.

We now report some attempted intramolecular Claisen diester condensations using lithium bis(trimethylsilyl)-amide as base. Rathke and Lindert[3] found that this base smoothly deprotonates esters of acetic acid in THF at −78 °C but reacts markedly more slowly with esters of the higher carboxylic acids, and we therefore started with esters of acetoxy carboxylic acids in order to optimize the formation of the cyclic product **2**. Thus, when ethyl 2-(*S*)-acetoxypropanoate was added to 2.4 equiv of lithium bis(trimethylsilyl)amide in THF (−78 °C),[4] hydrolytic workup after 1 h gave (+)-γ-methyltetronic acid (**5**)[5] in a

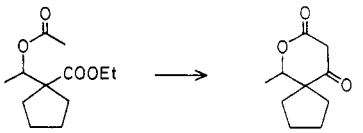


5

yield better than 95%. The analogous reaction using lithium diisopropylamide as base yielded a complex mixture containing only traces of **5**, and much of the starting ester was recovered (VPC, ^1H NMR). It seems reasonable to assume that the cause of the recovery of the starting ester is that it was transformed into its dianion by lithium diisopropylamide.

Similar treatment of ethyl 3-acetoxybutanoate and dimethyl 2-acetoxybutanedioate with lithium bis(trimethylsilyl)amide gave ethyl crotonate and dimethyl fumarate, respetively, as major products. In view of the

steric requirements of this base,[3] we interpret the result as being due to a selective deprotonation of the acetoxy group, followed by a cyclic (internal base) elimination of acetate ion. It is evident that the elimination leading to the α,β-unsaturated ester was faster than the formation of both the five- and the six-membered ring lactone. When elimination is prohibited, as in **6**, ring closure to the lactone **7** occurs. However, while the formation of **5** was essen-



6 *7*

tially complete within 30 min at −78 °C, only ca. 20% of **7** had been formed after 70 min at this temperature (VPC). In another run, the components were mixed at −78 °C (30 min) and the temperature was then raised to ca. −50 °C. It was found (VPC) that a reaction time of 3 h was necessary to complete the formation of **7**.

From an experiment with the γ-acetoxy ester **8**, we conclude that the formation of a seven-membered ring lactone is not a favored process. The use of 2.3 equiv of lithium bis(trimethylsilyl)amide (−78 °C, 2 h) led to a mixture of several compounds. The least polar component (**9**)[6] was obtained in a yield of 15% after chromatography on silica gel.

Application of the tetronic acid synthesis to tartaric acid would give optically pure carbohydrate-like C_6 compounds.

(3) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318-2320.
(4) This order of addition was used in all experiments.
(5) The levorotatory form of this compound, mp 115 °C, $[\alpha]_{546}$ −21° (*c* 0.5, H_2O), is a metabolite of *Penicillium Charlesii* G. Smith[13] and was shown to have the *R* configuration by a synthesis of **5** from ethyl (*S*)-lactate in low yield.[14]
(6) Duus, F.; Lawesson, S.-O. *Tetrahedron* **1971**, *27*, 387-399.

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