The residue was dissolved in with HBr/HOAc. These conditions are maximized derivative only, but can be used as a general procedure. To 1 g Threonine. This process was applied to entries 1-4, Table I. To 500 mg of l-threonine: 1H NMR (250 MHz, D2O) 6 1.1 (d, 3 H, 9.41 Hz), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.8 (d, 1 H, J = 3.05 Hz), 4.1 (m, 1 H), 7.1 (d, 1 H, J = 8.35 Hz), 7.2 (d, 1 H, J = 8.44 Hz). Anal. Calcd for C12H18NO5S: C, 51.8; H, 6.3; N, 4.6. Found C, 51.8; H, 6.3; N, 4.6.

General Procedure for N-(Arylsulfonyl)threonine Formation. This process is suitable for (4-isopropylphenyl)-, (2,5-dimethylphenyl)-, (2,4,6-trimethylyphenyl)-, and (4-methoxyphenyl)sulfonyl]threonine. To 500 mg of l-threonine in 40 mL of THF/H2O, 1/1, were added 1.3 g (10.5 mmol) of Na2CO3 and 5.40 mmol of the appropriate aminesulfonil chloride. The reaction mixture was stirred at room temperature for 18 h, after which it was washed with saturated NaHCO3 (2×10 mL). The aqueous phase was then acidified to pH 1 (concentrated H3PO4) and extracted with EtOAc (3×30 mL), which was dried and evaporated to yield the product. Samples for elemental analysis were recrystallized from EtOAc/hexanes.

N-(4-Isopropylphenyl)sulfonyl]threonine: 880 mg, 2.85 mmol, 83% yield; mp 128-133 °C; 1H NMR (250 MHz, acetone-d6) 6 1.1 (d, 3 H, J = 6.35 Hz), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.8 (d, 1 H, J = 3.07 Hz), 4.1 (m, 1 H), 7.1 (d, 1 H, J = 8.35 Hz), 7.2 (s, 1 H), 7.8 (d, 1 H, J = 7.98 Hz). Anal. Calcd for C12H18NO5S: C, 50.2; H, 6.0; N, 4.9. Found: C, 50.0; H, 6.0; N, 4.9.

N-(2,5-Dimethylphenyl)sulfonyl]threonine: 684 mg, 2.27 mmol, 54% yield; mp 165-167 °C; 1H NMR (250 MHz, acetone-d6) 6 1.1 (d, 3 H, J = 6.35 Hz), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.7 (d, 1 H, J = 4.2 Hz), 6.2 (m, 2 H), 7.0 (s, 2 H), 7.2 (d, 1 H, J = 3.97 Hz). Anal. Calcd for C12H18NO5S: C, 51.8; H, 6.4; N, 4.6. Found: C, 51.8; H, 6.5; N, 4.4.

N-(4-Methoxyphenyl)sulfonyl]threonine: 880 mg, 2.85 mmol, 73% yield; mp 128-133 °C; 1H NMR (250 MHz, acetone-d6) 6 1.1 (d, 3 H, J = 6.35 Hz), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.8 (d, 1 H, J = 3.07 Hz), 4.1 (m, 1 H), 7.1 (d, 1 H, J = 8.35 Hz), 7.2 (s, 1 H), 7.8 (d, 1 H, J = 7.98 Hz). Anal. Calcd for C12H18NO5S: C, 50.2; H, 6.0; N, 4.9. Found: C, 50.0; H, 6.0; N, 4.9.

N-(4-Methylphenyl)sulfonyl]threonine: 500 mg of l-threonine in 40 mL of CH3CN/H2O, 1/1, were added 1.3 g (10.5 mmol) of Na2CO3 and 5.40 mmol of 4-biphenylsulfonil chloride. The reaction mixture was stirred at room temperature for 48 h, the CH3CN was evaporated, and 10 mL of 2 N NaOH was added. After being washed with benzene (1×30 mL), the aqueous phase was acidified to pH 1 (concentrated H2PO4) and extracted with EtOAc (3×30 mL) which was dried and evaporated to yield 500 mg, 1.48 mmol, 36% of product: mp 184-185 °C; 1H NMR (250 MHz, acetone-d6) 6 1.2 (d, 3 H, J = 3.9 Hz), 3.9 (d, 1 H, J = 8.1 Hz), 4.1 (m, 1 H), 6.6 (m, 1 H), 8.7 (s, 1 H), 7.5 (m, 3 H), 7.7 (d, 1 H, J = 7.9 Hz) and 7.8 (d, 2 H, J = 8.0 Hz). Anal. Calcd for C12H18NO5S: C, 57.3; H, 5.1; N, 4.2. Found: C, 57.6; H, 4.9; N, 4.5.

Na/NH3 Removal of N-Arylsulfonyl Groups from Threonine. This process was applied to entries 1-4, Table I. To 100 mg of N-(arylsulfonyl)threonine in 10 mL of refluxing NH3 was added Na till a persistent blue color was observed for 10 min. Ammonium chloride was then added to the reaction mixture until the blue color disappeared; the NH3 was then allowed to evaporate. The residue was dissolved in 5 mL of H2O and evaporated to dryness in vacuo to yield threonine hydrochloride. This was then added to the reaction mixture until it was cooled to 0 °C, and H2O (10 mL) was added. The aqueous phase was washed with EtOAc (2×15 mL) before being evaporated to dryness in vacuo to yield threonine hydrobromide quantitatively: 1H NMR (250 MHz, D2O) 6 1.2 (d, 3 H, J = 6.57 Hz), 3.8 (d, 1 H, J = 8.89 Hz), 4.2 (m, 1 H).

Improved, Stereospecific Synthesis of Highly Substituted Butyrolactones via Dyotropic Rearrangement

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Butyrolactones (dihydropyran-2(3H)-furanes) comprise a very important and ubiquitous structural moiety throughout all of organic chemistry, being well-represented in both natural and unnatural molecular families. Many of these substances exhibit important and potentially very useful pharmacological activity, often as a direct result
of the incorporation of the lactone structure into the molecule. Moreover, butyrolactones serve as versatile synthetic intermediates in their own right, being easily convertible to other important compound classes such as furs, cyclopenentones, etc. This combination of factors has stimulated a great amount of research into methods for the construction of functionalized butyrolactone rings. Although the lactones incorporated into most natural products bear substituents in stereochemically defined configurations, stereospecific approaches for the synthesis of highly substituted butyrolactones are quite unusual.

Many approaches to substituted butyrolactones are available, usually involving the dehydroxylation of the corresponding 3-hydroxy acids with the desired substituent groups already in place. Some substituents can be affixed via alkylation of lactone enolates but both of these general procedures are quite difficult. Additionally, the placement of substituents such as phenyl, phenoxy, naphthyl, etc. which cannot be introduced via an enolate protocol is quite difficult.

We recently reported a new synthetic method for the preparation of spiro butyrolactones from cyclohexane-carboxaldehyde and substituted acetic acid derivatives, based upon an observation that 3-lactones underwent a stereospecific dyotropic rearrangement in the presence of magnesium cation. We have recently extended the utility of this approach to the synthesis of 3-substituted 5-alkylbutyrolactones. As part of a project whose ultimate aim is the application of dyotropic rearrangements to the construction of natural products, it seemed advisable to subject the rearrangement to a detailed examination of its stereochemical course, including a search for other Lewis acid catalysts, with an eye toward confirming the stereospecificity and increasing the overall efficiency of the approach. We now report the results of this model study, which features methyl group migration (as opposed to hydrogen), including experimental details for the preparation of a number of new, highly substituted, stereochemically pure butyrolactones.

To begin the sequence, we treated 2,2-dimethylpropanal with a substituted acetic acid diion, and the resulting 3-hydroxy acid was purified via recrystallization to remove the unwanted erythro diastereomer. Even extended reaction times did not completely suppress the formation of this kinetically favored isomer, which, if not removed at this stage, damaged the stereochemical integrity of the product. The acid was cyclized to the corresponding trans 3-lactone by using benzenesulfonyl chloride in pyridine at 0 °C, whereupon treatment with magnesium bromide etherate resulted in dyotropic rearrangement to the butyrolactone. The overall reaction sequence is outlined in Scheme I, and the yield data are arranged in Table I. Yields for the overall transformation were good to excellent and the products thus produced often analytically pure. In contrast to the initial report, we found the rearrangement step to be quite slow, requiring at least 6 h to achieve completion. Although this time could be shortened somewhat by increasing the reaction temperature, we sought a catalyst that might enhance the reaction rate as well as provide more insight into the nature of this intriguing reaction. Specifically, we wished to confirm the concerted nature of the rearrangement to rule out the possibility of a carbocationic intermediate, and we reasoned that catalyst variation might aid in this endeavor. To this end, several other acidic potential catalysts known to initiate certain rearrangement reactions, some involving carbocations, were examined: p-toluenesulfonyl acid, zinc isopropoxide. All were employed in stoichiometric quantities to enhance the rate of any reaction, and the trans phenyl-substituted lactone 3a was utilized as the substrate. In the case of the first three catalysts, the 3-lactone was recovered unchanged after a 48-h exposure at ambient temperature. We found such inactivity rather surprising, especially for boron trifluoride, in view of the catalytic efficacy of these agents observed in other contexts involving oxygen migration. Titanium tetraisopropoxide

<table>
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*All yields, while unoptimized, pertain to material purified as specified. Recrystallized from chloroform or ethyl acetate. Filtered through silica gel. Recrystallized from hexane (if crystalline) or distilled (if oil). \( \text{CH}_3\text{H}_2\text{S} = 2\text{-thienyl.} \) \( \text{CH}_3\text{H}_2 = \text{1-naphthyl.} \)

induced a transesterification reaction, opening the lactone ring to produce the corresponding isopropyl β-keto ester. This point, magnesium bromide appears to be the catalyst of choice.

The stereospecificity of the rearrangement was surmised primarily from proton NMR data. The H-3,4 coupling constants for vicinal hydrogens in the 3- and 4-positions (IUPAC numbering; see Scheme I) have been shown to be larger for trans than for cis configurations. In all cases, the proton on C-3 in compounds 4 appeared as a doublet split by 10–12 Hz. Additionally, the 4-methyl group (the one that has undergone migration) absorbs farther upfield in cis than in trans cases. Finally, the physical constants for phenyl-substituted butyrolactone 4a agreed with those reported for the trans isomer and are markedly different for the cis compound. The close similarity of the H-3,4 coupling constant value for this compound to those for the other butyrolactone derivatives strengthens the support for a trans configuration.

Diastereomeric purity hinges upon rigorous purification of the β-hydroxy acid precursor, since an erythro isomer is converted to the cis β-lactone, which in turn rearranges to the butyrolactone in which the 4- and 3-substituents bear a cis relationship (this was confirmed experimentally). This is graphically depicted in Scheme II. The dependence of product configuration upon β-lactone stereochemistry provides additional evidence for the concerted nature of the rearrangement, since the existence of a carbocyclic intermediate species is inconsistent with the observed stereospecificity.

The most attractive features of this sequence, aside from its stereospecificity, are the ready availability of appropriate starting materials and the overall ease of execution. Thus, we feel optimistic that dyotropic chemistry will find increased application to problems of organic synthesis.

Experimental Section

All reactions were carried out under an atmosphere of nitrogen, unless otherwise specified. Glassware was routinely oven-dried at 120 °C for a minimum of 4 h and then was assembled under a nitrogen stream. Anhydrous solvents were obtained by distillation, immediately prior to use, from sodium benzenophenone ketyl (tetrahydrofuran), barium oxide (diisopropylamine), or sodium (toluene). Infrared spectra were obtained by using either a Nicolet Model 20-DXB Fourier transform or a Perkin-Elmer Model 700 spectrophotometer; absorption maxima are reported in wavenumbers (cm⁻¹) and, in the case of the latter instrument, are standardized by reference to the 1801-cm⁻¹ peak of polystyrene. Proton nuclear magnetic resonance spectra were recorded on either a Varian T-60 or Nicolet NT-360 instrument; carbon-13 spectra were obtained on the latter. All samples were measured as solutions in deuteriochloroform (CDCl₃) or dimethyl sulfoxide-d₆ (DMSO-d₆). Chemical shifts are reported downfield from tetramethylsilane (TMS) in parts per million of the applied field. Peak multiplicities are abbreviated as follows: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; envelope, e. Coupling constants (J) are reported in hertz (Hz). Thin-layer chromatographic analyses were carried out on Analtech silica gel "G" (250 μm) plates with the specified solvent as eluent; visualization was effected either by ultraviolet light or by charring with phosphomolybdic acid. Preparative column chromatography employed Merck silica gel 60 (230–400 ASTM mesh). Combustion microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

General Procedure for the Preparation of β-Hydroxy Acids. An oven-dried, three-necked flask, equipped with a low-temperature thermometer, nitrogen inlet, rubber septum, and magnetic stirring bar, was charged with 30 mL of tetrahydrofuran (THF) followed by 4.05 g (5.61 mL, 40 mmol) of diisopropylamine. The solution was stirred and cooled to −78 °C in an ice bath to 0 °C (7.5 mL of dry ice-acetone bath, and 25.0 mL of a 1.6 M solution (40 mmol) of n-butyllithium in hexanes was added over a 15-min period. The resulting yellow solution of lithium diisopropylamide was stirred at −40 °C for 15 min, whereupon 20 mL of a 1.0 M solution (20 mmol) of the acetic acid derivative in THF was added dropwise via syringe over a 10-min period. The resulting solution was stirred for 1 h, returning to room temperature. An 8-mL portion of a 2.5 M solution (20 mmol) of 2,2-dimethylpropanol was then added via syringe, causing an exotherm to ca. 35 °C and a lessening of the yellow color. Stirring at an elevated temperature was continued for 16 h, at which point the mixture was poured onto ca. 50 g of ice, the layers were separated, and the aqueous phase was extracted with 20 mL of ether. The ether was discarded, and the aqueous phase was extracted with another 20 mL of ether. The ether was discarded, and the aqueous phase was acidified with 6 N hydrochloric acid, and the resulting mixture was extracted with three 20-mL portions of ether. The consolidated extracts were washed with brine and dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to afford the crude product. A single recrystallization from ethyl acetate or chloroform rendered the material sufficiently pure to proceed to the next step.

General Procedure for the Preparation of β-Lactones. An oven-dried 25-mL Erlenmeyer flask was fitted with a rubber septum and magnetic stirring bar and was charged with 10 mL of anhydrous ether. A 500-mg portion of β-hydroxy acid 2 was added, and the stirred solution was cooled in an ice bath to 0 °C. Benzene sulfonfonyl chloride (2 equiv) was added dropwise via syringe with stirring, and the resulting solution was stored at 35 °C for 16 h. The resulting orange/red solution was poured onto ca. 50 g of ice, and the mixture was extracted with three 15-mL portions of ether. The consolidated extracts were sequentially washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, water, and finally brine. After the extracts were dried over anhydrous magnesium sulfate and filtered, the solvents were removed under reduced pressure to afford the crude product. Filtration through silica gel, employing dichloromethane as the eluent, afforded material of sufficient purity to proceed to the next step.

General Procedure for the Preparation of Butyrolactones. An oven-dried 25-mL three-necked flask was equipped with a nitrogen inlet and stirring bar and was charged with 10 mL of a 1.0 M solution (10 mmol) of β-lactone 3 in anhydrous ether. Stirring was begun, and 2.58 g (10 mmol) of magnesium bromide etherate was added in one portion. The light yellow mixture was stirred under nitrogen for 6 h, whereupon the reaction was terminated by the cautious addition of 10 mL of water. The layers were separated, the ether layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure to afford the product. Recrystallization from
hexane (or, in the case of 4c, distillation under reduced pressure) afforded material of analytical purity. Using this protocol, we prepared and characterized butyrolactones 4a-c, displaying the following analytical data.

**trans-4,5-Dihydro-3-(phenyl-4,5,5-trimethyl-2(3H))-furanone (4a):** mp 90–92 °C (lit. 75-24-5); IR (KBr) 1765, 1413, 1241, 855, 788, 708 cm⁻¹; NMR (CDCl₃) 7.33 (s, 5 H, Ar H), 3.5 (d, J = 12 Hz, 1 H, CHO = O), 2.72-2.08 (m, 1 H, CH₂CH₃), 1.55 (s, 3 H, CH₃CO), 1.38 (s, 3 H, CH₂CO), 1.06 (d, 3 H, CH₃CH₂); TLC (CH₂Cl₂): Rf 0.55.

**trans-4,5-Dihydro-3-(phenyl-4,5,5-trimethyl-2(3H))-furanone (4b):** mp 74–75 °C (lit. 74-75 °C); IR (KBr) 2895, 1772 (li2, 1757, 1241, 1140 cm⁻¹; NMR (CDCl₃) 7.32–6.91 (m, 5 H, Ar H), 4.60 (d, J = 11 Hz, 1 H, CH₃CO), 2.91–2.08 (br m, 1 H, CH₂CH₃), 1.52 (s, 3 H, CH₃), 1.36 (s, 3 H, CH₂), 1.11 (d, 3 H, CH₃CH₂); TLC (CH₂Cl₂): Rf 0.64.

**trans-4,5-Dihydro-3-(phenylthio)-4,5,5-trimethyl-2(3H)-furanone (4c):** bp 125-130 °C (0.05 mm) (lit. 150–160 °C (0.1 mm)); IR (neat) 2975, 1767 (li2, 1765), 1377, 1268, 1246, 1133, 1122 cm⁻¹; NMR (CDCl₃) 7.56-6.95 (m, 5 H, Ar H), 3.41 (d, J = 11 Hz, 1 H, CHO = O), 2.90–1.56 (br m, 1 H, CH₂CH₃), 1.40 (s, 3 H, CH₃), 1.31 (s, 3 H, CH₂), 1.10 (d, 3 H, CH₃CH₂); TLC (CH₂Cl₂): Rf 0.71.

**trans-4,5-Dihydro-3-(2-thienyl)-4,5,5-trimethyl-2(3H)-furanone (4d):** mp 92–95 °C; IR (KBr) 1766, 1397, 1383, 1378, 1241, 1129 cm⁻¹; NMR (CDCl₃) 7.29 (d, 2 H, =CH₂), 7.00 (m, 2 H, other Ar H), 5.00 (s, 1 H, CH₃CO), 4.55 (s, 3 H, CH₃CO), 1.38 (s, 3 H, CH₂), 1.14 (d, 4 H, CH₂CH₂), TLC (ethyl acetate): Rf 0.77. Anal. Caled for C₁₅H₁₈O₂S: C, 62.83; H, 6.71. Found: C, 63.18; H, 6.90.

**trans-4,5-Dihydro-3-(1-naphthyl)-4,5,5-trimethyl-2(3H)-furanone (4e):** mp 164–165 °C; IR (KBr) 1760, 1396, 1390, 1242, 1075, 961 cm⁻¹; NMR (CDCl₃) 8.10–7.20 (m, 7 H, Ar H), 4.23 (d, J = 10 Hz, 1 H, CHO = O), 1.60 (s, 3 H, CH₃CO), 1.44 (4 s, 3 H, CH₃CO), 1.04 (d, 4 H, CH₂CH₂), TLC (ethyl acetate): Rf 0.75. Anal. Caled for C₁₉H₁₈O₂: C, 69.80; H, 7.13. Found: C, 79.98; H, 7.18.

**Improved Procedure for Preparation of Optically Active 3-Hydroxyglutarate Monoesters and 3-Hydroxy-5-oxoalkanoic Acids**

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We have recently reported the reaction of 1-phenylethanol with the prochiral anhydride 1, leading to acids 2 and 3 in ratios of up to 15:1. The chiral glutarate monoester 2 is useful for conversion into the Wadsworth-Emmons reagents 6 and 7, useful synths for the synthesis of mevinic acid analogues (Scheme I).

The previous synthesis had two disadvantages. First, the prochiral recognition in the reaction of 1-phenylethanol with 1, although good, still gives a 9:4:6 mixture of 2 and 3, at best. In order to remove the minor isomer, it is necessary to convert the mixture of 2 and 3 into methyl esters 4 and 5, which are separable by preparative HPLC. The second problem comes in the protocol for conversion of 2 into the phosphonates 6 and 7. For example, the conversion of 4 to reagent 7 involves reaction with dimethyl (lithiomethyl)phosphonate. Although the methyl ester reacts faster than the phenethyl ester, this reaction is accompanied by much β elimination of the (tert-butyldimethyl)silylxylo group. Consequently, it is necessary to desilylate, carry out the (lithiomethyl)phosphonate reaction, and then reinstall the silyl protecting group. Similar problems are encountered in the preparation of 6. In this Note, we report a modification of our original synthesis that solves these two problems.

The solution arrived at involves replacement of the 1-phenylethanol used in our original work with 1-(1‘-naphthyl)ethanol (8). The racemic 1-(1‘-naphthyl)ethanol (8) is obtained in 95% yield on a 0.5 M scale by treatment of commercially available 1-naphthaldehyde with methyllithium in ether. The alcohol is separated into its two enantiomers by an enzyme-mediated transesterification procedure developed by Klibanov and co-workers (Scheme II). The racemic alcohol, 2,2,2-trichloroethanol butyrate, a crude preparation of porcine pancreatic lipase (Sigma, E.C. 3.1.1.3), and heptane are stirred at 60 °C. On a large scale the reaction takes several days. Because the enzyme gradually loses its activity with time, the procedure we have developed calls for the periodic addition of fresh enzyme. A total of 100 g of crude enzyme resolves 60 g of alcohol in 14 days. After the enzyme is filtered from the reaction mixture, the resulting liquid is fractionally distilled to remove the excess 2,2,2-trichloroethanol butyrate and the 2,2,2-trichloroethanol byproduct from the reaction mixture. The (S)-8 and (R)-9 remaining in the reaction mixture can also be separated by distillation (bp 125 and 145 °C, respectively), though in practice it has proven easier to distill the two as a mixture and then separate by chromatography. The process converts 95–98% of the R isomer present in the mixture. Further reaction time does not increase the percentage of conversion. The R alcohol is isolated as its butyrate ester. Saponification of the ester affords optically pure R alcohol in 91% yield from the racemic mixture. The S alcohol isolated from the reaction mixture contains 2–5% of the R isomer. Optically pure (>99.5% ee) material is obtained in 90–95% yield (from the racemic mixture) after two recrystallizations.

Anhydride 1 is obtained from commercially available diethyl 3-hydroxypentanediode by a slight modification of the previously reported procedure. Silylation of the alcohol with tert-butyldimethylchlorosilane and imidazole, saponification of the diester to the diacid by NaOH in ethanol, and finally, closure of the anhydride utilizing acetic anhydride in benzene afford anhydride 1 in 80% yield for the three-step sequence. The only purification required is a recrystallization of the final product.

The protocol developed for utilization of the R alcohol is shown in Scheme III. Reaction of anhydride 1 with (R)-1-(1‘-naphthyl)ethanol in the presence of (dimethylamino)pyridine (DMAP) with CH₂Cl₂ as solvent gives acid...