2.4 (s, 3 H), 3.8 (dd, 1 H, J = 3.02, 9.28 Hz), 4.3 (m, 1 H, J = 3.0, 6.33 Hz), 6.4 (d, 1 H, J = 9.30 Hz), 7.3 (d, 2 H, J = 8.1 Hz), 7.7 (d, 2 H, J = 8.25 Hz). Anal. Calcd for $C_{11}H_{15}NO_5S \cdot {}^1/_2H_2O$: C, 46.8; H, 5.7; N, 5.0. Found: C, 46.9; H, 5.6; N, 4.9.

General Procedure for *N*-(Arylsulfonyl)threonine Formation. This process is suitable for [(4-isopropylphenyl)-, [(2,5-dimethylphenyl)-, [(2,4-dimethylphenyl)-, [(2,4,6-trimethylphenyl)-, and [(4-methoxyphenyl)sulfonyl]threonine. To 500 mg (4.2 mmol) of L-threonine in 40 mL of THF/H_2O, 1/1, were added 1.3 g (10.5 mmol) of Na_2CO_3 and 5.40 mmol of the appropriate arenesulfonyl chloride. The reaction mixture was stirred at room temperature for 18 h, after which it was washed with benzene (1 × 30 mL). The aqueous phase was then acidified to pH 1 (concentrated H_3PO_4) 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:** 800 mg, 2.65 mmol, 63% yield; mp 128 °C dec; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H, J = 6.35 Hz), 1.2 (d, 6 H, J = 6.91 Hz), 3.0 (m, 1 H), 3.8 (d, 1 H, J = 3.05 Hz), 4.1 (m, 1 H), 7.4 (d, 2 H, J = 8.36 Hz), 7.8 (d, 2 H, J = 8.44 Hz). Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.8; H, 6.3; N, 4.6. Found: C, 51.8; H, 6.3; N, 4.6.

***N*-[(2,5-Dimethylphenyl)sulfonyl]threonine:** clear oil, 804 mg, 2.9 mmol, 69% yield; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.8 (d, 1 H), 4.1 (m, 1 H), 6.4 (d, 1 H), 6.6 (s, 1 H, br), 7.2 (m, 2 H), 7.9 (s, 1 H); mass spectrum calcd for $C_{12}H_{17}NO_5S$ m/e 287.3280, found 243.0564 ($M^+ - C_2H_4O$), 242.0845 ($M^+ - CHO_2$).

***N*-[(2,4-Dimethylphenyl)sulfonyl]threonine:** 880 mg, 3.06 mmol, 73% yield; mp 132–133 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.2 (s, 1 H, br), 3.8 (d, 1 H, J = 3.07 Hz), 4.1 (m, 1 H), 7.1 (d, 1 H, J = 8.3 Hz), 7.2 (s, 1 H), 7.8 (d, 1 H, J = 7.98 Hz). Anal. Calcd for $C_{12}H_{17}NO_5S$: C, 50.2; H, 6.0; N, 4.9. Found: C, 50.0; H, 6.0; N, 4.9.

***N*-[(2,4,6-Trimethylphenyl)sulfonyl]threonine:** 684 mg, 2.27 mmol, 54% yield; mp 165–167 °C dec; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H, J = 6.35 Hz), 2.3 (s, 3 H), 2.6 (s, 6 H), 3.7 (d, 1 H), 4.2 (m, 1 H), 6.2 (d, 1 H, J = 9.37 Hz), 7.0 (s, 2 H). Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.8; H, 6.4; N, 4.6. Found: C, 51.8; H, 6.5; N, 4.4.

***N*-[(4-Methoxyphenyl)sulfonyl]threonine:** 600 mg, 2.07 mmol, 50% yield; mp 139–141 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H, J = 6.33 Hz), 3.9 (s, 3 H), 3.9 (d, 1 H), 4.2 (m, 1 H), 5.3 (s, 1 H, br), 6.2 (d, 1 H, J = 9.41 Hz), 7.1 (d, 2 H, J = 8.79 Hz), 7.9 (d, 2 H, J = 8.78 Hz). Anal. Calcd for $C_{11}H_{15}NO_6S$: C, 45.7; H, 5.2; N, 4.8. Found: C, 45.7; H, 5.3; N, 4.8.

***N*-[(4-Phenylphenyl)sulfonyl]threonine.** To 500 mg (4.2 mmol) of L-threonine in 40 mL of CH_3CN/H_2O, 1/1, were added 1.3 g (10.5 mmol) of Na_2CO_3 and 1.24 g (5.0 mmol) of 4-biphenylsulfonyl chloride. The reaction mixture was stirred at room temperature for 48 h, the CH_3CN 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 H_3PO_4) 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; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.2 (d, 3 H), 3.9 (d, 1 H), 4.1 (m, 1 H), 6.6 (m, 1 H), 6.7 (s, 1 H), 7.5 (m, 3 H), 7.7 (d, 2 H), 7.9 (d, 2 H), 8.0 (m, 2 H). Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.3; H, 5.1; N, 4.2. Found: C, 57.6; H, 4.9; N, 4.5.

Na/NH_3 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 NH_3 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 NH_3 then was allowed to evaporate. The residue was dissolved in 5 mL of 1 M H_3PO_4 and washed with EtOAc (1 × 5 mL) before being applied to an ion-exchange column (Dowex 50W-X8, 200–400 mesh, hydrogen form). Salts were eluted with H_2O, and threonine was eluted with 2% NH_3/H_2O, with ninhydrin monitoring of the elution. Evaporation gave pure threonine: ^{1}H NMR (250 MHz, D_2O) δ 1.2 (d, 3 H, J = 6.57 Hz), 3.5 (d, 1 H, J = 4.89 Hz), 4.2 (m, 1 H).

Cleavage of *N*-[(2,4-Dimethylphenyl)sulfonyl]threonine with HBr/HOAc. These conditions are maximized for this derivative only, but can be used as a general procedure. To 1 g (10.6 mmol) of phenol in 10 mL of 32% HBr/HOAc in a flask with a glass stopper was added in three portions over 3 h a solution of 100 mg (0.35 mmol) of *N*-[(2,4-dimethylphenyl)sulfonyl]-threonine in 3 mL of EtOAc. After addition was complete, the reaction mixture was stirred for an additional 15 h at room temperature, then it was cooled to 0 °C, and H_2O (10 mL) was added. The aqueous phas was washed with EtOAc (2 × 15 mL) before being evaporated to dryness in vacuo to yield threonine hydrobromide quantitatively: ^{1}H NMR (250 MHz, D_2O) δ 1.2 (d, 3 H), 3.9 (d, 1 H), 4.3 (m, 1 H). When EtOAc and incremental addition were not used, a mixture of threonine and 2-amino-3-bromobutyric acid hydrobromide was obtained: ^{1}H NMR (250 MHz, D_2O) δ 1.3 (d, 3 H), 4.2 (d, 1 H), 5.4 (m, 1 H).

Sample Preparation for Cyclic Voltammograms.[4a] In general a sample was prepared in 20 mL of CH_3CN that was 0.1 M in $Et_4N^+Br^-$ and 0.01 M in *N*-(arylsulfonyl)threonine. This was transferred to a PAR cyclic voltammogram cell equipped with Pt microelectrodes as cathode and anode and a Ag/Ag^+, $AgNO_3$ reference electrode. Standard conditions used a sweep rate of 100 mV/s at 100 mA and 50 s/in. and swept from 0 to −3 or 3.3 V, depending on the compound. A sample voltammogram is shown in Figure 1.

Preparative Electrochemical Deprotection.[4a] Using the electrode placement indicated in Figure 2, a Hg pool as cathode, and Pt foil as anode, we electrolyzed 40 mL of 0.1 M $Et_4N^+Br^-$ in CH_3CN at −3 V until the background current was less than 2 mA. Phenol (300 mol %) was added to the cathodic chamber, and the system was again electrolyzed to a background of less than 2 mA. *N*-(Arylsulfonyl)threonine (100 mg) was next added to the cathodic chamber and the electrolysis carried out at the appropriate $E^2_{1/2}$. Typically current would increase to 18–20 mA and remain there until reaction was nearly complete. A slow return to 2 mA was then observed. About 120% of the necessary number of coulombs was used. The cathodic solution was then evaporated to dryness in vacuo, and the solid residue was dissolved in 3 mL of 1 M H_3PO_4 and washed with $CHCl_3$. The aqueous phase was then loaded onto an ion-exchange column (Dowex 50W-X8, 20–50 mesh, hydrogen form), salts were eluted with H_2O, and threonine was eluted with 2% NH_3/H_2O, with ninhydrin monitoring of the elution. Yields are given in Table I.

Registry No. *i*-PrPh, 98-82-8; *p*-$Me_2C_6H_4$, 106-42-3; PhOMe, 100-66-3; *m*-$Me_2C_6H_4$, 108-38-3; Ph_2, 92-52-4; *p*-(*i*-Pr)$C_6H_4SO_2Cl$, 54997-90-9; 2,5-$Me_2C_6H_3SO_2Cl$, 19040-62-1; *p*-$MeOC_6H_4SO_2Cl$, 98-68-0; 2,4-$Me_2C_6H_3SO_2Cl$, 609-60-9; *p*-$PhC_6H_4SO_3H$, 2113-68-0; *p*-$PhC_6H_4SO_2Cl$, 1623-93-4; $PhSO_2Cl$, 98-09-9; *p*-$MeC_6H_4SO_2Cl$, 98-59-9; $PhSO_2$-Thr-OH, 93474-55-6; *p*-$MeC_6H_4SO_2$-Thr-OH, 34235-88-6; *p*-(*i*-Pr)$C_6H_4SO_2$-Thr-OH, 113793-27-4; 2,5-$Me_2C_6H_3SO_2$-Thr-OH, 113793-28-5; 2,4-$Me_2C_6H_3SO_2$-Thr-OH, 113793-29-6; 2,4,6-$Me_3C_6H_2SO_2$-Thr-OH, 113793-30-9; *p*-$MeOC_6H_4SO_2$-Thr-OH, 113793-31-0; *p*-$PhC_6H_4SO_2$-Thr-OH, 113793-32-1; 2,4,6-$Me_3C_6H_2SO_2Cl$, 773-64-8; H-Thr-OH, 72-19-5.

Improved, Stereospecific Synthesis of Highly Substituted Butyrolactones via Dyotropic Rearrangement

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Butyrolactones (dihydro-2(3*H*)-furanones) comprise a very important and ubiquitous structural moiety throughout all of organic chemistry, being well-represented in both natural and unnatural molecular families.[1] Many of these substances exhibit important and potentially very useful pharmacological activity,[2] often as a direct result

(1) Nakanishi, K.; Goto, T.; Ito, S.; Nozoe, S. *Natural Products Chemistry*; Kodansha: Tokyo, 1974.

0022-3263/88/1953-2371$01.50/0

Table I. Yield Data[a] for the Transformation of Substituted Acetic Acid Derivatives to 3-Substituted 4,5,5-Trimethylbutyrolactones

suffix	acid (1)	yield of 2[b]	yield of 3[c]	yield of 4[d]
a	$PhCH_2CO_2H$	74	94	86
b	$PhOCH_2CO_2H$	89	93	91
c	$PhSCH_2CO_2H$	69	91	81
d[e]	$C_4H_3SCH_2CO_2H$	44	80	41
e[f]	$C_{10}H_7CH_2CO_2H$	32	75	62

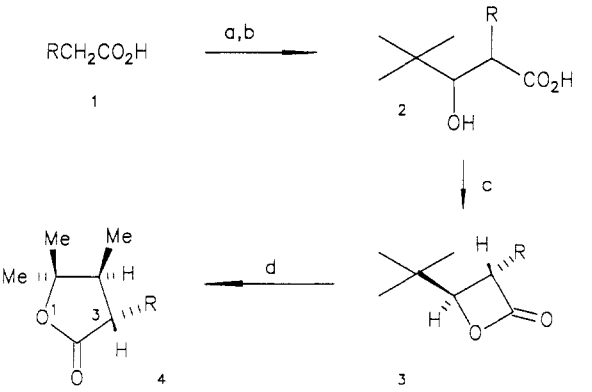
[a] All yields, while unoptimized, pertain to material purified as specified. [b] Recrystallized from chloroform or ethyl acetate. [c] Filtered through silica gel. [d] Recrystallized from hexane (if crystalline) or distilled (if oil). [e] C_4H_3S = 2-thienyl. [f] $C_{10}H_7$ = 1-naphthyl.

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 furans, cyclopentenones, etc.[3] 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,[4] usually involving the dehydration of the corresponding 3-hydroxy acids with the desired substituent groups already in place. Some substituents can be affixed via alkylation of lactone enolates,[5] but both of these general routes suffer from low, if any, diastereoselectivity. 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 cyclohexanecarboxaldehyde and substituted acetic acid derivatives,[6] based upon an observation that β-lactones underwent a stereospecific dyotropic rearrangement in the presence of magnesium cation.[7] We have recently extended the utility of this approach to the synthesis of 3-substituted 5-alkylbutyrolactones.[8] 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

Scheme I[a]



[a] a = 2LDA, THF; b = Me_3CCHO; c = $PhSO_2Cl$, pyr; d = $MgBr_2$.

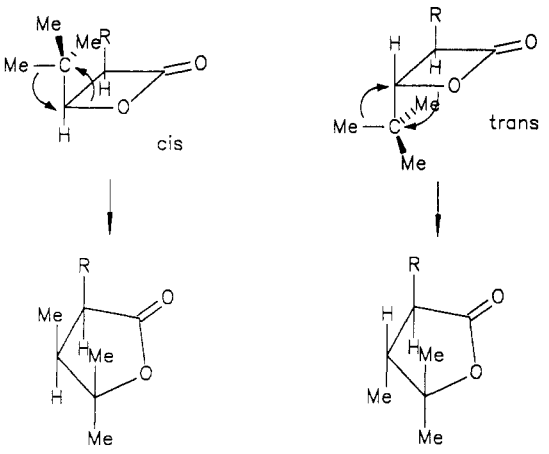
acid catalysts, with an eye toward confirming the stereospecificity and increasing the overall efficiency of the approach. We now report the results of this model study, which features methyl group migration (as opposed to hydrogen), including experimental details for the preparation of a number of new, highly substituted, stereochemically pure butyrolactones.

To begin the sequence, we treated 2,2-dimethylpropanal with a substituted acetic acid dianion, and the resulting β-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,[9] which, if not removed at this stage, damaged the stereochemical integrity of the product. The acid was cyclized to the corresponding trans β-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,[7] 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*-toluenesulfonic acid, zinc chloride, boron trifluoride etherate, and titanium tetraisopropoxide. 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 β-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.[10] Titanium tetraisopropoxide

(2) Levine, J. A.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1986**, *29*, 1996 and references cited therein.
(3) Grimm, E. L.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 242 and references cited therein.
(4) Reviews: (a) Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1980**, *14*, 661. (b) Boyd, G. V.; Wolfe, J. F.; Ogliaruso, M. A. *The Chemistry of Acid Derivatives*; Patai, S., Ed.; Wiley: New York, 1979. For some recent approaches, see: (c) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (d) Giese, B.; Hasskerl, T.; Lunig, U. *Chem. Ber.* **1984**, *117*, 859. (e) Hoppe, D.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 241. (f) Costisella, B.; Gross, H.; Schick, H. *Tetrahedron* **1984**, *40*, 733. (g) Tamaru, Y.; Mitzutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (h) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. (i) Takano, S.; Morimoto, M.; Ogasawara, K. *Synthesis* **1984**, 834. (j) Simpson, J. H.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 1759. (k) Beckwith, A. L.; Pigou, P. E. *J. Chem. Soc., Chem. Commun.* **1986**, 85. (l) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 475, 624. (m) Clerici, A.; Porta, O.; Zago, P. *Tetrahedron* **1986**, *42*, 561. (n) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.
(5) Zenk, P. C.; Wiley, R. A. *Synthesis* **1984**, 695.
(6) Black, T. H.; DuBay, W. J. *Tetrahedron Lett.* **1987**, *28*, 4787.
(7) Mulzer, J.; Bruntrup, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 793.
(8) Black, T. H.; Fields, J. D. *Synth. Commun.* **1988**, *18*, 125.
(9) Mulzer, J.; Bruntrup, G.; Chuchoilowski, A.; Pointner, G. *J. Chem. Soc. C* **1979**, 52.
(10) For instance, see: Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961.

Scheme II



induced a transesterification reaction, opening the lactone ring to produce the corresponding isopropyl β-keto ester.[11] Thus, at this point, magnesium bromide appears to be the catalyst of choice.

The stereospecificity of the rearrangement was surmised primarily from proton NMR data. The 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.[7,12] 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) absorbances are farther upfield in cis than in trans cases.[7] 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 carbocationic 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 benzophenone 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 1601-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 ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6). 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 with a 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 10-min period. The resulting clear yellow solution of lithium diisopropylamide was stirred at ca. −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 cooling bath was removed, and the resulting mixture was stirred for 1 h, returning to room temperature. An 8-mL portion of a 2.5 M solution (20 mmol) of 2,2-dimethylpropanal was then added via syringe, causing an exotherm to ca. 35 °C and a lessening of the yellow color. Stirring at ambient 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 twice with 20 mL of ether. The ether was discarded, the aqueous phase acidified with 6 N hydrochloric acid, and the resulting mixture extracted with three 20-mL portions of ether. The consolidated extracts were washed with brine and dried over anhydrous magnesium sulfate and the solvents 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 pyridine. A 500-mg portion of β-hydroxy acid **2** was added, and the stirred solution was cooled in an ice bath to 0 °C. Benzenesulfonyl 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

(11) This behavior is well documented in the patent literature, as titanium is commonly exploited as a transesterification catalyst. See: Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974 and references cited therein.

(12) Jaime, C.; Ortuno, R. M.; Font, J. *J. Org. Chem.* **1986**, *51*, 3946. Although the authors caution against universal application of a coupling constant/configuration correlation, they point out that "...it is worth noting that for all compounds studied so far [i.e., with protons in the 3- and 4-positions] $J_{trans} > J_{cis}$...."

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–e**, displaying the following analytical data.

***trans*-4,5-Dihydro-3-phenyl-4,5,5-trimethyl-2(3*H*)-furanone (4a)**: mp 90–92 °C (lit.[7] mp 92 °C); IR (KBr) 1765 (lit.[7] 1765), 1413, 1241, 1153, 988, 708 cm^{-1}; NMR ($CDCl_3$) 7.33 (s, 5 H, Ar *H*), 3.5 (d, J = 12 Hz, 1 H, C*H*C=O), 2.72–2.08 (m, 1 H, CH_3CH), 1.55 (s, 3 H, CH_3CO), 1.38 (s, 3 H, CH_3CO), 1.06 (d, 3 H, CH_3CH); TLC (CH_2Cl_2) R_f 0.55.

***trans*-4,5-Dihydro-3-phenoxy-4,5,5-trimethyl-2(3*H*)-furanone (4b)**: mp 74–75 °C (lit.[7] mp 74–75 °C); IR (KBr) 2975, 2865, 1772 (lit.[7] 1765), 1284, 1140 cm^{-1}; NMR ($CDCl_3$) 7.32–6.91 (m, 5 H, Ar *H*), 4.60 (d, J = 11 Hz, 1 H, C*H*C=O), 2.91–2.08 (br m, 1 H, CH_3CH), 1.52 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.11 (d, 3 H, $CHCH_3$); TLC (CH_2Cl_2) R_f 0.64.

***trans*-4,5-Dihydro-3-(phenylthio)-4,5,5-trimethyl-2-(3*H*)-furanone (4c)**: bp 125–130 °C (0.05 mm) [lit.[7] bp 150–160 °C (0.1 mm)]; IR (neat) 2978, 1767 (lit.[7] 1765), 1377, 1268, 1246, 1133, 1122 cm^{-1}; NMR ($CDCl_3$) 7.56–6.95 (m, 5 H, Ar *H*), 3.41 (d, J = 11 Hz, 1 H, C*H*C=O), 2.90–1.56 (br m, 1 H, CH_3CH), 1.40 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.10 (d, 3 H, $CHCH_3$); TLC (CH_2Cl_2) R_f 0.71.

***trans*-4,5-Dihydro-3-(2-thienyl)-4,5,5-trimethyl-2(3*H*)-furanone (4d)**: mp 92–92.5 °C; IR (KBr) 1766, 1397, 1383, 1378, 1241, 1129 cm^{-1}; NMR ($CDCl_3$) 7.29 (d, 2 H, =C*H*S), 7.00 (m, 2 H, other Ar *H*), 3.81 (d, J = 12 Hz, 1 H, C*H*O=O), 1.55 (s, 3 H, CH_3CO), 1.38 (s, 3 H), CH_3CO), 1.14 (d, 4 H, CH_3CH); TLC (ethyl acetate) R_f 0.77. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 63.18; H, 6.99.

***trans*-4,5-Dihydro-3-(1-naphthyl)-4,5,5-trimethyl-2-(3*H*)-furanone (4e)**: mp 164–165 °C; IR (KBr) 1760, 1396, 1260, 1132, 1075, 961 cm^{-1}; NMR ($CDCl_3$) 8.10–7.20 (m, 7 H, Ar *H*), 4.23 (d, J = 10 Hz, 1 H, C*H*C=O), 1.60 (s, 3 H, CH_3CO), 1.44 (s, 3 H, CH_3CO), 1.04 (d, 4 H, CH_3CH); TLC (ethyl acetate) R_f 0.75. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.29; H, 7.13. Found: C, 79.98; H, 7.18.

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Registry No. **1a**, 103-82-2; **1b**, 122-59-8; **1c**, 103-04-8; **1d**, 1918-77-0; **1e**, 86-87-3; *threo*-**2a**, 34296-63-4; *erythro*-**2a**, 33398-52-6; *threo*-**2b**, 114059-23-3; *erythro*-**2b**, 70982-80-8; *threo*-**2c**, 114094-14-3; *erythro*-**2c**, 114094-15-4; *threo*-**2d**, 75245-44-2; *erythro*-**2d**, 75245-45-3; *threo*-**2e**, 114059-24-4; *erythro*-**2e**, 114059-25-5; **3a**, 69974-12-5; **3b**, 70982-91-1; **3c**, 114059-26-6; **3d**, 114059-27-7; **3e**, 114059-28-8; **4a**, 71647-85-3; **4b**, 71647-89-7; **4c**, 71647-88-6; **4d**, 114059-29-9; **4e**, 114059-30-2; $(Me)_3CCHO$, 630-19-3; $(Me)_3CCOCH(Ph)CO_2CH(Me)_2$, 114059-31-3.

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.[1] The chiral glutarate monoester **2** is useful for conversion into the Wadsworth–Emmons reagents **6** and **7**, useful synthons 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 94:6 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*-butyldimethylsilyl)oxy group. Consequently, it is necessary to desilylate **4**, 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. 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.[2] The alcohol is separated into its two enantiomers by an enzyme-mediated transesterification procedure developed by Klibanov and co-workers (Scheme II).[3] The racemic alcohol, 2,2,2-trichloroethyl 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-trichloroethyl 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 commerially available diethyl 3-hydroxypentanedioate by a slight modification of the previously reported procedure.[1,4] 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 CH_2Cl_2 as solvent gives acid

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