Synthesis of Enantiomerically Pure Stereogenically Labile 4-Aryl-2-hydroxytetronic Acids from Enantiomerically Pure Silyl-Protected Mandelaldehydes: *aci*-Reductone Analogues of Propionic Acid Nonsteroidal Anti-inflammatory Agents

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Enantiomerically pure 4-aryl-2-hydroxytetronic acids (**3**) are expected to be useful tools for determining the mechanism by which corresponding racemic *aci*-reductones produce their multiple biological effects. Our published synthetic methods for the construction of the title compounds were only useful for the preparation of 4-alkyl analogues owing to facile racemization of the chiral benzylic proton with 4-aryl systems. The synthesis of these enantiomerically pure 4-aryl *aci*-reductones has now been accomplished in four steps by condensing enantiomerically pure *tert*-butyldimethylsilyl protected mandelaldehydes **16a–c** with the anion of ethyl 1,3-dithiane-2-carboxylate in the presence of pivaloyl chloride to yield protected β,γ-dihydroxy-α-ketobutanoates **22a–c** after dithiane hydrolysis. Reaction of **22a–c** with tetrabutylammonium fluoride resulted in silyl deprotection, cyclization, and pivaloyl migration to afford 2-(pivaloyloxy)tetronic acids **25a–c**. Pivaloate deprotection by either acid hydrolysis or selective hydride reduction produced enantiopure targets **3a–c**.

Introduction

4-Aryl-2-hydroxytetronic acids are proposed[1,2] as functional mimics of arylacetic and 2-arylpropanoic acid (**1**) nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and ibuprofen. The tetronic acid moiety in **2** may be viewed as a new nonclassical bioisostere for the carboxylic acid[3] functional group; both possess p*K*a's of approximately 5. Additionally, substitution of a hydroxyl group on the 2-position of the tetronic acid provides *aci*-reductones **3** with biologically relevant redox potentials (E_1 = 0.112–0.157 at pH 7.4) in the range of ascorbic acid (E_1 = 0.162 at pH 7.4).[4] Two-electron oxidation of **3** produces dehydro species **4**, which in the case of ascorbic acid exists in hydrated forms.[5] The 2-hydroxytetronic acid functionality is found in vitamin C, closely related relatives such as isoascorbic acid, erythroascorbic acid, and various derivatives, and is incorporated into the macrolide antibiotic chlorothricin.[6] A series of racemic 4-aryl-2-hydroxytetronic acids, prepared according to Dahn,[7] exhibit a wide array of biological activities[1,2,4,8] potentially related to both reactive oxygen species (ROS) scavenging and/or enzyme inhibitory mechanisms.[1,2] Comparison of eudismic ratios for optically pure enantiomeric pairs is expected to aid in differentiation of nonstereoselective radical scavenging and stereoselective enzyme inhibitory processes.

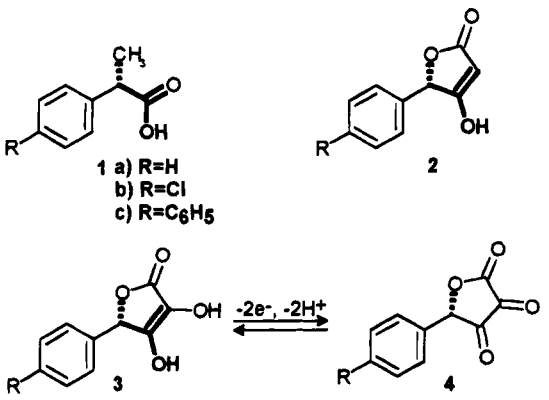

Figure 1.

Procedures for the preparation of ascorbic acid[9] and other 2-hydroxytetronic acids[10] generally utilize three

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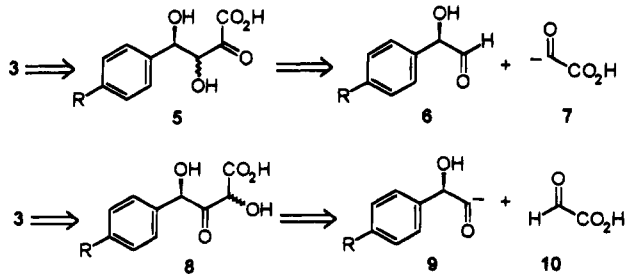
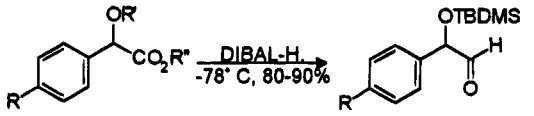
Scheme 1



Scheme 2



11a R'=$COCH_2OBn$; R"=CH_3
12a-c R'=H; R"=H
13a-c R'=H; R"=CH_3
14a-c R'=(+)-MPTA; R"=CH_3
15a-c R'=TBDMS; R"=CH_3

16a-c

different routes: (1) hydroxyl group insertion[11] at the 2 position of corresponding tetronic acids;[10a,12] (2) intramolecular Claisen cyclization[6,11b,13] of (α-oxy substituted)acetyloxymandelate esters; and (3) base-promoted cyclization of 2,4-dihydroxy-3-ketobutanoates.[14] These methods are not generally applicable for the production of enantiomerically pure 4-aryl-2-hydroxytetronic acids owing to the lability of the chiral benzylic proton. The lability of this stereocenter is similar to that of mandelate esters (pK_a 16) which undergo racemization during either KCN-catalyzed or LiOH-promoted ester hydrolysis at pH < 12.5,[15,16] and phenylglycine, which undergoes extensive racemization during peptide synthesis.[17]

The only published method for the synthesis of stereogenically labile 4-aryl-2-hydroxytetronic acids involves intramolecular Claisen cyclization of methyl (*S*)-(+)-(α-benzyloxy)acetyloxymandelate using the sterically hindered base lithium dicyclohexylamide under kinetic conditions.[13b] Benzyl group cleavage by catalytic hydrogenation yields optically pure (*S*)-(+)-4-phenyl-2-hydroxytetronic acid (**3a**), but in less than 8% yield from starting optically pure mandelic acid. Cyclizations of precursor mandelates containing electron-withdrawing substituents have been unsuccessful using this protocol. The aldol condensation approach discussed in this article is useful for the preparation of enantiomerically pure stereogenically labile 2-hydroxytetronic acids from easily produced enantiomerically pure mandelaldehydes **16a–c** and commercially available ethyl 1,3-dithiane-2-carboxylate.

Fundamentally, keto ester intermediates **5** and **8** (Scheme 1) are available from acyl anions **7** or **9** and either mandelaldehyde **6** or glyoxylate **10**, respectively. α-Ketobutanoate **5** is expected to be relatively more stable toward racemization than β-keto regioisomer **8**. Additionally, acid-catalyzed decarboxylation is not problematic with α-keto acids. For these reasons, our synthetic strategy relies upon the construction of protected α-keto-β,γ-dihydroxybutanoates **5** and their conversion to target *aci*-reductones **3a–c**.

Results and Discussion

Enantiomerically pure mandelaldehydes[18] **16a–c** (Scheme 2) were prepared by DIBAL-H reduction of silyl protected methyl mandelates **15a–c**. Production of the optically pure precursor mandelic acids[20a] **12b,c** was best accomplished by resolution[20] using methylbenzylamine and recrystallization of the diastereomeric salts from absolute EtOH. Optically pure mandelic acids, determined by observing the benzyl proton signal of the corresponding methyl mandelate (+)-MPTA[21] esters **14a–c** in the ^1H NMR spectrum, were methylated using diazomethane and protected as their TBDMS ethers **15a–c**.

Alternatively, optically active (*S*)-(+)- or (*R*)-(−)-methyl mandelates[22] **13b,c** were available by Fischer esterification of racemic mandelic acids[23] **12b,c**, PCC oxidation to methyl benzoylformates, and asymmetric reduction with Alpine borane.[24] Enantiomeric excess was 82% based upon ^1H NMR analysis of the corresponding (+)-MTPA[21] esters **14b,c**.

The lithium salt of the ethyl glyoxylate anion equivalent,[19] ethyl 1,3-dithiane-2-carboxylate,[25] was condensed[26] with optically pure aldehyde **16b** at −78 °C in THF to yield 30% of hydroxy dithiane **17b** in a diastereomeric ratio of 1.7:8.3 (Scheme 3). Dithiane **17b** was not amenable to oxidative hydrolysis[27] under several condi-

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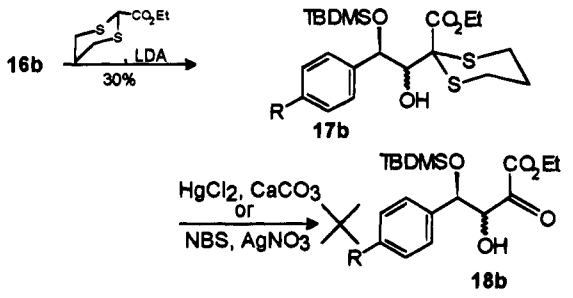
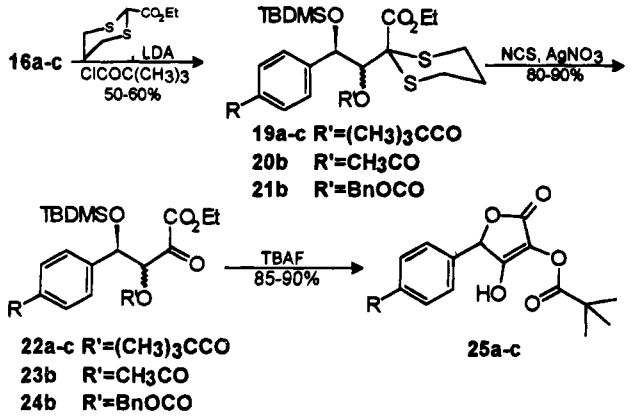
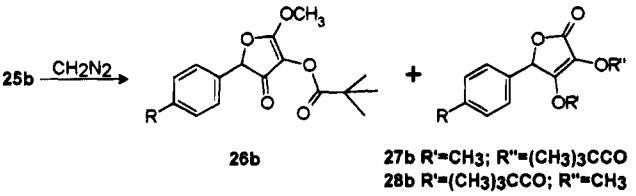
Scheme 3



Scheme 4



Scheme 5



tions. Reaction with $HgCl_2$ buffered with $CaCO_3$ in 80% aqueous CH_3CN resulted in no reaction, and treatment with NBS, $AgNO_3$, and 2,4,6-collidine provided an inseparable mixture of products.

Trapping alkoxide anion intermediates during aldol condensations (Scheme 4) both improved reaction yields and provided intermediates with increased stability to dithiane hydrolysis conditions. Following the method of Belletire[26b] the lithium salt of ethyl 1,3-dithiane-2-carboxylate was treated at −78 °C with a mixture of aldehydes **16a−c** and pivaloyl chloride (1.0:1.1) to furnish a 1.7:8.3 ratio of pivaloyl dithiane diastereomers **19a−c** in 60% yield. Dithiane hydrolysis[27] effected with NCS and $AgNO_3$ in aqueous CH_3CN furnished protected β-hydroxy-α-keto ester intermediates **22a−c** in 80% yield.

Silyl deprotection and cyclization induced with TBAF provided α-(pivaloyloxy)tetronic acids **25a−c** in 80−85% yields. Interestingly, the pivaloyl group underwent O → O acyl migration during the cyclization. Evidence for the assigned structure included (1) broad OH stretching absorbance signals in the infrared; (2) high solubility in $NaHCO_3$ solution; and (3) reaction of tetronic acid **25b** with diazomethane in ether produced a 2:1 ratio of regioisomers **26b** and **27b** in the absence of 2-methoxytetronate **28b** (Scheme 5). This is unlike the 2:3 mixture of regioisomers generated during reaction of 5,5-dimethyltetronic acid with CH_2N_2.[28] The methoxy proton resonance signals at δ 4.05 (major) and 3.72 (minor) were assigned to the methyl tetronate and 4-furanone, respectively. The pivaloyloxy regioisomers exhibit ^1H NMR signals for the methoxy groups at δ 4.05 (minor) and 3.89 (major) corresponding to tetronate **27b** and 4-furanone **26b**, respectively.

The enantiomeric excess of the 2-(pivaloyloxy)tetronate was determined by ^1H NMR analysis of corresponding (*R*)-(+)-methylbenzylamine salts. The salt of racemic 2-(pivaloyloxy)tetronic acid in $CDCl_3$ clearly demonstrated a 1:1 mixture of diastereomers. The resonance signals corresponding to the enantiomeric furanone protons at δ 5.20 (*R*-tetronic acid) and 5.11 (*S*-tetronic acid) were easily visible. A single resonance peak was observed for optically pure salts.

Racemic 2-(pivaloyloxy)tetronic acids **25a−c** were synthesized by treating racemic 2-hydroxytetronic acids[7] with excess pivaloyl chloride in a 1:1 solution of pyridine and CH_2Cl_2. Both steric and electronic effects favor formation of the 2-pivaloyloxy intermediates. Numerous examples exist demonstrating regioselectivity for pivaloyl chloride.[29] Furthermore, bonding of the pivaloyl group to the 3-hydroxyl function generates an anhydride equivalent (i.e. vinylogous anhydride) expected to undergo rapid hydrolysis.

General methods for the cleavage of pivaloyl esters[29] involve hydroxide anion hydrolysis or hydride reduction. Reductive cleavage was not initially attempted since simultaneous destruction of the furanone ring was anticipated. Alkaline hydrolysis was unsatisfactory resulting either in no reaction or decomposition. No reaction took place upon treatment of tetronic acid **25b** with bis(tributyl)tin oxide[30] in refluxing benzene. Attempted cleavage with a *Pseudomonas* species enzyme[31] in 1.0 M phosphate buffer at pH 7 resulted in isolation of starting material after 7 days. Stirring in a mixture of Et_3N and 15% aqueous EtOH (1:1) resulted in no reaction after 24 h.

Successful hydrolysis was effected by warming a solution of pivaloate ester **25b** in MeOH:H_2O:concentrated HCl (8:1:1) to reflux for 24 h. The 2-hydroxytetronic acid target **3b** was isolated with approximately 84% ee, as observed by ^1H NMR analysis of the diastereomeric (*R*)-(+)-methylbenzylamine salts. Acidic pivaloate hydrolysis using a variety of conditions (Table 1) resulted in *aci*-reductone target **3b** with varying degrees of enantiomeric purity. Enantiomerically pure compounds **3a−c**, as observed by ^1H NMR analysis of corresponding (*R*)-(+)-methylbenzylamine salts, were formed in 50−60% yield by warming the pivaloate intermediates **25a−c** in AcOH:H_2O (9.8:0.2) at a gentle reflux for 24 h. Owing to detection limits of the method used to determine enantiomeric purity, compounds **3a−c** are reported to be not less than 96% ee, but may approach 100% ee.

The difficulty experienced with the hydrolysis of the pivaloyl ester prompted studies utilizing different protecting groups at the C-3 hydroxyl. Thus, aldol condensation in the presence of either acetyl chloride or

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Table 1

starting material[a]	reaction conditions[b]	time, h	% ee[c]	% yield
25b	MeOH:H_2O:HCl (8:1:1)	24	84%	ND
22b	MeOH:H_2O:HCl (8:1:1)	24	84%	ND
18b	THF:HCl (9:1)	1.5	54%	ND
25b	AcOH:THF:H_2O (6:2:2)	24	70%[d]	ND
25b	AcOH:H_2O (8:2)	6	93%	80
25b	AcOH:H_2O (9:1)	12	ND	ND
25b	AcOH:H_2O (9.5:0:5)	12	95%	ND
25b	AcOH:H_2O (9.8:0.2)	24	100%	60
25c	TFA:H_2O (9.8:0.2)	12	dec	0

[a] Starting materials, unless noted, were enantiomerically pure. [b] All reactions were warmed for the given time at a gentle reflux at a dilution of approximately 0.1 M. [c] The percent ee was determined by ^{1}H NMR analysis of the corresponding diastereomeric (*R*)-(+)-methylbenzylamine salts. [d] The starting material for this reaction was 86% ee.

benzylchloroformate produced dithianes **20b** and **21b**, respectively, in approximately 60% yield and in similar ratios of diastereomers. Both derivatives **20b** and **21b**, like derivatives **22a–c**, underwent hydrolysis affording α-keto esters **23b** and **24b** in near 80% yield. However, attempted silyl deprotection and cyclization using TBAF resulted in decomposition mixtures. Decomposition likely occurs by TBAF-induced intramolecular transacetylation and subsequent retroaldol reaction. The pivaloyl ester, which does not easily undergo such migration, is essential in directing cyclization to form desired tetronic acids.

Advantageously, silyl deprotection, cyclization, and pivaloyl group hydrolysis were performed in one step by warming α-keto-β-pivaloyl ester **22b** to reflux in a solution of concentrated HCl:H_2O:MeOH (1:1:8) for 24 h. Target 2-hydroxytetronic acid **3b** was produced with 84% ee. The reaction was monitored by TLC, which revealed that cyclization to 2-pivaloyloxytetronic acid **25b** was complete within 1 h. The subsequent 23 h of reaction time was necessary for pivaloyl ester hydrolysis. Deprotection of the 3-hydroxyl group prior to acid-catalyzed cyclization was rationalized to produce compounds of high enantiomeric purity, because of the decreased exposure time to acid-catalyzed racemizing conditions. Hydrogenation of benzyl carbonate **24b** provided acyloin **18b**, which was not isolated; heating to reflux in a solution of concentrated HCl:THF (1.0:9.0) for 1.5 h afforded *aci*-reductone **3b** with only 55% ee. The unexpected increased rate of racemization most likely resulted from acid-catalyzed tautomerization to the β-keto ester and subsequent acid-induced racemization. The pivaloyl esterification (intermediates **22a–c**) protects against such tautomerization/racemization processes.

Reductive removal of the pivaloyl protecting group in tetronates **25a–c** was successful using a hydride reducing agent.[6b] Reaction of the lithium anion of pivaloate ester **25c** with 3.0 equiv of DIBAL-H in THF at −78 °C produced optically pure 2-hydroxytetronic acid **3c** in 50% isolated yield with starting material as the major impurity. Advantages of hydride reduction include (1) decreased racemization; (2) fewer reaction byproducts; and (3) shorter reaction times when compared to acid hydrolysis conditions.

In summary, a method for the production of optically pure 4-aryl-2-hydroxytetronic acids **3a–c** has been developed. The reaction scheme affords target *aci*-reductones in 20–25% overall yield starting from enantiomerically pure methylbenzylamine salts of mandelic acid precursors. The methodology was utilized for the synthesis of both enantiomers of 4-phenyl-2-hydroxytetronic acid [(*S*)-(+)-**3a**] and [(*R*)-(−)-**3a**], 4-(4-chlorophenyl)-2-hydroxytetronic acid [(*S*)-(+)-**3b**] and [(*R*)-(−)-**3b**] and 4-(1,1′-biphenyl-4-yl)-2-hydroxytetronic acid [(*S*)-(+)-**3c**] and [(*R*)-(−)-**3c**]. Early biological evaluation of biphenyl *aci*-reductones **3c** indicates the (*S*)-(+)-enantiomer to be approximately 30 times more potent than the (*R*)-(−)-enantiomer in inhibiting arachidonic acid-induced platelet aggregation at IC_{50} values less than 10 μM. This early data is in agreement with the expected activity of these compounds based upon their stereochemical relationship to NSAIDs wherein (*S*)-(+)-enantiomers also are most potent. Other protecting group strategies may result in an improved synthetic sequence, but investigations thus far have not led to such improvements.

Experimental Section

General Methods. Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt Apparatus and are uncorrected. Infrared spectra were recorded by a Laser Precision Analytical RFX-FTIR spectrometer (Model TSI-400). Nuclear magnetic resonance spectra were obtained with either an IBM-Bruker model NR/250 or NR/270 FT NMR spectrometer. TMS ($CDCl_3$, DMSO-d_6, acetone-d_6, CD_3OD, or D_2O) was used as internal standard. THF was distilled from Na/benzophenone ketyl, CH_2Cl_2 was dried over P_2O_5, and DMF was distilled and stored over molecular sieves. Optical rotations were taken on a Perkin-Elmer Model 241 polarimeter using a 10 cm, 1 mL cell. Mass spectra were acquired with either a VG 70-250S or a Nicolet FTMS-2000 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Starting materials were purchased from either Aldrich or Sigma chemical companies.

Methyl (*R*)-(−)-α-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-phenylacetate (*R*15a): α-Hydroxy acetate ***R*13a** (1.65 g; 10.0 mmol), 2.26 g (15.0 mmol) of TBDMSCl, 1.16 g (17.0 mmol) of imidazole, and 12 mL of DMF were combined in a 100 mL round bottom flask and stirred under argon for 18 h. The reaction mixture was diluted with 150 mL of Et_2O, washed with 3 × 25 mL of H_2O and 1 × 25 mL of brine, dried (Na_2SO_4), and concentrated. The compound was dried under reduced pressure (0.3 mmHg, 60 °C) for 1.5 h to yield 2.8 g (99%) of [(*tert*-butyldimethylsilyl)oxy]acetate ***R*15a** as a colorless oil: $[\alpha]^{22}_D$ −53.6° (*c* 1.25, EtOH); [lit.[18d] $[\alpha]^{20}_D$ −50.0 (*c* 1.04, $CHCl_3$)]; ^{1}H-NMR ($CDCl_3$) δ 7.47–7.27 (m, 5 H), 5.22 (s, 1 H), 3.67 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.02 (s, 3 H).

Methyl (*S*)-(+)-α-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-phenylacetate (*S*15a): Prepared as described for (*R*)-(−)-enantiomer ***R*15a** starting with hydroxyacetate ***S*13a**: $[\alpha]^{22}_D$ +57.4° (*c* 0.592, EtOH), [lit.[18d] $[\alpha]^{20}_D$ +51.3° (*c* 1.03, $CHCl_3$)].

Methyl (*R*)-(−)-α-(4-Chlorophenyl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetate (*R*15b): Methyl mandelate ***R*13b** (2.05 g; 10.0 mmol) was protected as described for ***R*15a** leaving 3.03 g (97%) of a colorless oil, $[\alpha]^{22}_D$ −60° (*c* 0.616, EtOH); ^{1}H-NMR ($CDCl_3$) δ 7.41–7.37 (m, 2 H), 7.32–7.27 (m, 2 H), 5.18 (s, 1 H), 3.66 (s, 3 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.02 (s, 3 H).

Methyl (*S*)-(+)-α-(4-Chlorophenyl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetate (*S*15b): Prepared as described for (*R*)-(−)-enantiomer ***R*15b** starting with methyl mandelate ***S*13b**: $[\alpha]^{22}_D$ +59° (*c* 0.652, EtOH).

Methyl (*R*)-(−)-α-(1,1′-Biphenyl-4-yl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetate (*R*15c): Prepared in an analogous manner as described for ***R*15a** using 1.8 g (7.5 mmol) of methyl mandelate ***R*13c** as starting material to produce 2.6 g (98%) of ***R*15c** as a colorless oil: $[\alpha]^{22}_D$ −71.9° (*c* 0.914, EtOH); ^{1}H-NMR ($CDCl_3$) δ 7.59–7.33 (m, 9 H), 5.28 (s, 1 H), 3.70 (s, 3 H), 0.92 (s, 9 H), 0.12 (s, 3 H), 0.05 (s, 3 H).

Methyl (*S*)-(+)-α-(1,1′-Biphenyl-4-yl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetate (*S*15c): Prepared as described for (*R*)-(−)-enantiomer ***R*15c** starting with methyl mandelate ***S*13c**: $[\alpha]^{22}_D$ +68.8° (*c* 0.780, EtOH).

(*R*)-(−)-α-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-phenylacetaldehyde (*R*16a): To a 100 mL 2-necked round bottom flask equipped with a septum and nitrogen inlet was added 2.8 g (10 mmol) of (*R*)-(−)-methyl acetate ***R*15a** dissolved in 55 mL of dry toluene. The solution was cooled to −78 °C (CO_2/acetone), and 12 mL (12 mmol) of a 1.0 M solution of DIBAL-H in toluene was added slowly (5 min) with stirring. The reaction mixture was stirred for 1 h at −78 °C and poured into a mixture of 100 g of ice and 100 mL of $CHCl_3$. The reaction flask was rinsed with 100 mL of $CHCl_3$, and the mixture was stirred vigorously for 30 min. After separation of the $CHCl_3$ layer, the aqueous phase was washed with 100 mL of $CHCl_3$ (emulsion) and the combined $CHCl_3$ extracts were washed with brine 1 × 80 mL, dried (Na_2SO_4), and concentrated leaving 2.2 g (88%) of aldehyde ***R*16a** as a clear colorless oil of greater than 90% purity (^{1}H-NMR). The unstable aldehyde was not further purified and was immediately utilized in the next transformation: $[\alpha]^{22}_D$ −39.5° (*c* = 0.612, EtOH); [lit.[18d] $[\alpha]^{22}_D$ +3.1° (*c* = 1.22, $CHCl_3$)]; ^{1}H-NMR ($CDCl_3$) δ 9.51 (d, *J* = 2.2 Hz, 1 H), 7.40−7.29 (m, 5 H), 5.00 (d, *J* = 2.2 Hz, 1 H), 0.95 (s, 9 H), 0.12 (s, 3 H) 0.04 (s, 3 H).

(*S*)-(+)-α-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-phenylacetaldehyde (*S*16a) was prepared as described for (*R*)-(−)-enantiomer ***R*16a** starting with (*S*)-(+)-acetate ***S*15a**: $[\alpha]^{22}_D$ +39.6° (*c* = 0.442, EtOH).

(*R*)-(−)-α-(4-Chlorophenyl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetaldehyde (*R*16b): (*R*)-(−)-Methyl acetate ***R*15b** (3.0 g; 9.5 mmol) was reduced as described for aldehyde ***R*16a** leaving 2.5 g (93%) of ***R*16b** as a clear colorless oil of better than 95% purity (^{1}H-NMR). The aldehyde was not further purified owing to it's instability to temperatures above 60 °C and to silica gel and was utilized immediately in the next transformation: $[\alpha]^{22}_D$ −33.71° (*c* 0.330, EtOH); ^{1}H-NMR ($CDCl_3$) δ 9.47 (d, *J* = 2.0 Hz, 1 H), 7.33−7.32 (m, 4 H), 4.95 (d, *J* = 2.0 Hz, 1 H), 0.92 (s, 9 H), 0.10 (s, 3 H), 0.02 (s, 3 H).

(*S*)-(+)-α-(4-Chlorophenyl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetaldehyde (*S*16b) was prepared as described for (*R*)-(−)-enantiomer ***R*16b** starting with (*S*)-(+)-acetate ***S*15b**: $[\alpha]^{22}_D$ +46.5° (*c* 0.316, EtOH).

(*R*)-(−)-α-(1,1′-Biphenyl-4-yl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetaldehyde (*R*16c): (*R*)-(−)-methyl acetate (***R*15c**) (2.6 g, 7.4 mmol) was reduced as described for ***R*16a** leaving 2.3 g (95%) of unstable aldehyde ***R*16c** as a colorless oil which was not further purified, but immediately utilized in the next synthetic transformation: ^{1}H-NMR ($CDCl_3$) δ 9.54 (d, *J* = 2.1 Hz, 1 H), 7.63−7.35 (m, 9 H), 5.05 (d, *J* = 2.1 Hz, 1 H), 0.97 (s, 9 H), 0.14 (s, 3 H), 0.07 (s, 3 H).

(*S*)-(+)-α-(1,1′-Biphenyl-4-yl)-α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetaldehyde (*S*16c) was prepared as described for (*R*)-(−)-enantiomer ***R*16c** starting with (*S*)-(+)-methyl α-(silyloxy)mandelate ***S*15c**: $[\alpha]^{22}_D$ +36.6° (*c* 1.01, EtOH).

(2β*R*)-(−)-2-Carbethoxy-2-[β-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-α-hydroxy-β-phenylethyl]-1,3-dithiane (*R*17a): To a dry 25 mL flask under inert atmosphere containing 0.47 mL (3.0 mmol) of ethyl 1,3-dithiane-2-carboxylate in 8 mL of THF at −78 °C was added 2.2 mL (3.3 mmol) of 1.5 M LDA. The solution was stirred at this temperature for 15 min and then allowed to warm at room temperature for 10 min and subsequently cooled to −78 °C. A solution of 0.75 g (3.0 mmol) of aldehyde **R16a** in 2 mL of THF was slowly added to the dithiane anion. The reaction mixture was quenched at −78 °C after 1 h by the addition of 0.5 mL of glacial acetic acid. The mixture was diluted with 40 mL of Et_2O and washed successively with 1 × 10 mL of H_2O, 2 × 10 mL of $NaHCO_3$, 1 × 10 mL of H_2O and 1 × 10 mL of brine, dried over Na_2SO_4, and concentrated. Purification over silica gel using EtOAc:hexanes (8:2) as eluant provided 360 mg (28% yield) of hydroxy dithiane ***R*17a** as a colorless oil and as a single diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.35−7.20 (m, 5 H), 4.84 (d, *J* = 6.4 Hz, 1 H), 4.32 (dd, *J* = 7.0, 7.2 Hz, 1 H), 4.08−3.90 [m, 2 H (OCH_2CH_3)], 3.32−3.09 (m, 2 H), 2.76−2.63 (m, 3H), 2.07−1.87 (m, 2 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 0.73 (s, 9 H), 0.02 (s, 3 H), −0.24 (s, 3 H); Anal. Calcd for $C_{21}H_{34}O_4SiS_2$; C, 56.98; H, 7.74. Found: C, 56.71; H, 7.81.

(2β*R*)-(−)-2-Carbethoxy-2-[α-[(2,2-dimethyl-1-propanoyl)oxy]-β-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-β-phenylethyl]-1,3-dithiane (*R*19a): A solution of 1.58 mL (10.0 mmol) of ethyl 1,3-dithiane-2-carboxylate in 25 mL of THF under argon was cooled to −78 °C (CO_2/acetone), and 6.7 mL (10.0 mmol) of 1.5 M LDA (solution in cyclohexanes) was added with stirring. The reaction mixture was removed from the dry ice bath for 10 min, cooled to −78 °C, and stirred for 1 h. A solution consisting of 2.26 g (9.0 mmol) of (*R*)-(−)-acetaldehyde ***R*16a**, 6 mL of THF, and 1.25 mL (10 mmol) of pivaloyl chloride was added dropwise with stirring.[26b] Stirring was continued for 2 h at −78 °C and for 1 h at rt. The reaction mixture was diluted with 200 mL of Et_2O and washed with 1 × 20 mL of H_2O, 2 × 20 mL of 5% aqueous HCl, 1 × 20 mL of H_2O, and 1 × 20 mL of brine. The organic layer was dried (Na_2SO_4) and concentrated. Chromatography over silica gel (70−230 mesh) using EtOAc:hexanes (0.5:9.5) and distillation (0.3 mmHg, 110 °C) to remove excess ethyl 1,3-dithiane-2-carboxylate provided 3 g (63%) of dithiane ***R*19a** as an 8.3:1.7 mixture of diastereomers [integration of the benzylic protons at δ 5.92 (major) and 5.67 (minor)]: IR (NaCl plates) 2960, 2929, 2904, 1729, 1279, 1250, 1215, 1140, 1113, 1093, 1057, 1030, 847, 838 cm^{-1}; ^{1}H NMR of the major isomer ($CDCl_3$) δ 7.35−7.18 (m, 5 H), 5.92 (d, *J* = 7.7 Hz, 1 H), 5.11 (d, *J* = 7.7 Hz, 1 H), 4.22-4.08 [m, 2 H, (OCH_2CH_3)], 3.33 (ddd, *J* = 3.5, 10.5, 14.0 Hz, 1 H), 3.09 (ddd, *J* = 3.2, 10.8, 14.0 Hz, 1 H), 2.86−2.71 (m, 2 H), 2.10−1.86 (m, 2 H), 1.32 (t, *J* = 7.1 Hz, 3 H), 0.96 (s, 9 H), 0.73 (s, 9 H), 0.06 (s, 3 H), −0.24 (s, 3 H); Anal. Calcd for $C_{26}H_{42}O_5SiS_2$; C, 59.29; H, 8.04. Found: C, 59.01; H, 7.28.

(2β*S*)-(+)-2-Carbethoxy-2-[α-[(2,2-dimethyl-1-propanoyl)oxy]-β-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-β-phenylethyl]-1,3-dithiane (*S*19a) was prepared by a procedure identical to that described for (*R*)-(−)-enantiomer ***R*19a** starting with (*S*)-(+)-aldehyde ***S*16a**. The mixture of diastereomers that formed (8.3:1.7) was not separated.

(2β*R*)-(−)-2-Carbethoxy-2-[β-(4-chlorophenyl)-α-[(2,2-dimethyl-1-propanoyl)oxy]-β-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3-dithiane (*R*19b): (*R*)-(−)-Acetaldehyde ***R*16b** (0.85 g; 3.0 mmol) underwent aldol reaction as described for ***R*19a**. Chromatography over silica gel (70−230 mesh) using EtOAc:hexanes (0.5:9.5) provided 1.1 g (62%) of dithiane ***R*19b** as a diastereomeric mixture in the ratio of (8.4:1.6) [integration of the benzyl protons at δ 5.92 (major) and 5.83 (minor)]. The major diastereomer crystallized from the oil upon standing 4−8 days: mp 88−89 °C; IR (KBr, pellet) 2978, 2967, 2929, 2858, 1741, 1724, 1225, 1144, 1101, 1022, 858, 838 cm^{-1}; ^{1}H-NMR (major diastereomer) ($CDCl_3$) δ 7.32−7.15 (m, 4 H), 5.83 (d, *J* = 7.3 Hz, 1 H), 5.11 (d, *J* = 7.3 Hz), 4.18−4.04 (m, 2 H OCH_2CH_3), 3.26 (ddd, *J* = 3.4, 10.5, 14.0 Hz, 1 H), 3.08 (ddd, *J* = 3.2, 10.8, 14.0 Hz, 1 H), 2.83−2.69 (m, 2 H), 2.07−1.83 (m, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 0.97 (s, 9 H), 0.73 (s, 9 H), 0.05 (s, 3 H), −0.26 (s, 3 H). Anal. Calcd for $C_{26}H_{41}O_5SiS_2Cl$; C, 55.64, H, 7.36. Found: C, 55.37; H, 7.63.

(2β*S*)-(+)-2-Carbethoxy-2-[β-(4-chlorophenyl)-α-[(2,2-dimethyl-1-propanoyl)oxy]-β-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3-dithiane (*S*19b) was prepared by a procedure identical to that described for the synthesis of (*R*)-(−)-enantiomer ***R*19b** starting with aldehyde ***S*16b**. The mixture of diastereomers that formed (8.4:1.6) was not separated.

(2β*R*)-(−)-2-[β-(1,1′-Biphenyl-4-yl)-α-[(2,2-dimethyl-1-propanoyl)oxy]-β-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-ethyl]-2-carbethoxy-1,3-dithiane (*R*19c): (*R*)-(−)-Acetaldehyde ***R*16c** (0.98 g; 3.0 mmol) underwent aldol reaction as described for dithiane ***R*19a**. Chromatography over silica gel (70−230 mesh) using EtOAc:hex (0.5:9.5) provided 1.1 g (62%) of dithiane ***R*19c** as a diastereomeric mixture in the ratio of (8.5:1.5) [integration of the benzyl protons at δ 5.92 (major) and 5.65 (minor)]. The diastereomers were separated by chromatography (major was slightly less polar) for analytical purposes: ^{1}H-NMR (major diastereomer) ($CDCl_3$) δ 7.57−7.30 (m, 9 H), 5.92 (d, *J* = 7.4 Hz, 1 H), 5.18 (d, *J* = 7.4 Hz, 1 H), 4.20-4.04 (m, 2 H, OCH_2CH_3), 3.27 (ddd, *J* = 3.5, 10.4, 13.9 Hz, 1 H), 3.09 (ddd, *J* = 3.2, 10.7, 14.0 Hz, 1 H), 2.83−2.72 (m, 2 H), 2.07−1.83 (m, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 0.95 (s,

9 H), 0.75 (s, 9 H), 0.07 (s, 3 H), −0.22 (s, 3 H). Anal. Calcd for $C_{32}H_{46}O_5SiS_2 \cdot {}^1/_4H_2O$; C, 63.30, H, 7.72. Found: C, 63.25; H, 7.64.

(2βS)-(+)-2-[β-(1,1′-Biphenyl-4-yl)-α-[(2,2-dimethyl-1-propanoyl)oxy]-β-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-ethyl]-2-carbethoxy-1,3-dithiane (S19c) was prepared by a procedure identical to that described for the synthesis of (*R*)-(−)-enantiomer ***R*19c**. The mixture of diastereomers that formed (8.5:1.5) was not separated.

Ethyl (4*R*)-(−)-3-[(2,2-Dimethyl-1-propanoyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-oxo-4-phenylbutanoate (*R*22a): A solution of 0.54 g (4.0 mmol) of NCS and 0.77 g (4.5 mmol) of $AgNO_3$ in 20 mL of CH_3CN:H_2O (8:2)[27] was added to a solution of 0.53 g (1.0 mmol) of pivaloyl dithiane diastereomers ***R*19a** in 2 mL of acetone. The reaction mixture was stirred at rt for 25 min and quenched by the addition of 1 mL of saturated Na_2SO_3 solution, 1.0 mL of saturated Na_2CO_3 solution, 1.0 mL of brine, and 70 mL of CH_2Cl_2:hexanes (1:1) at 1 min intervals. The organic layer was separated, washed with 1 × 15 mL of brine, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The crude product was diluted with EtOAc:hexanes (1:9) and filtered through silica gel using EtOAc:hexanes (9.5:0.5) as elutant to provide 0.30 g (70%) of α-keto ester ***R*22a** as an 8.3:1.7 mixture of diastereomers [^{1}H NMR integration of the benzylic protons at δ 5.72 (minor) and 5.65 (major)] in the form of a colorless oil: IR (NaCl plates) 2960, 2931, 2860, 1736, 1271, 1259, 1153, 838 cm^{-1}; ^{1}H-NMR ($CDCl_3$) for mixture δ 7.41−7.25 [m, 6 H (major and minor)], 5.71 [d, *J* = 5.4 Hz, 0.2 H (minor)], 5.66 [d, *J* = 8.0 Hz, 1 H (major)], 5.23 [d, *J* = 5.4 Hz, 0.2 H (minor)], 4.98 [d, *J* = 8.0 Hz, 1 H (major)], 4.28 [q, *J* = 7.2 Hz, 2 H (major)], 4.14 [q, *J* = 7.2 Hz, 0.4 H (minor)], 1.34 (t, *J* = 7.2 Hz, 3 H), 1.24 [t, *J* = 7.2 Hz, 0.6 H (minor)], 1.16 [s, 1.8 H (minor)], 1.05 [s, 9 H (major)], 0.84 [s, 1.8 H (minor)], 0.78 [s, 9 H (major)], 0.02 [s, 0.6 H (minor)], 0.01 [s, 3 H (major)], −0.02 [s, 0.6 H (minor)], −0.04 [s, 3 H (major)]. Anal. Calcd for $C_{23}H_{36}O_6Si$: C, 63.27; H, 8.31: Found; C, 63.17; H, 8.41.

Ethyl (4*S*)-(+)-3-[(2,2-Dimethyl-1-propanoyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-oxo-4-phenylbutanoate (*S*22a): Dithiane ***S*19a** was hydrolyzed to ***S*22a** as described for synthesis of (4*R*)-(−)-enantiomer ***R*22a**.

Ethyl (4*R*)-(−)-4-(4-Chlorophenyl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-oxobutanoate (*R*22b): A solution of 2.9 g (5.17 mmol) of pivaloyl dithiane diastereomers ***R*19b** in 10 mL of acetone was hydrolyzed as described for the synthesis of α-keto ester ***R*22a**. Filtration through silica gel using EtOAc:hexanes (9.5:0.5) as eluant provided 2.0 g (82%) of α-keto ester ***R*22b** as an 8.4:1.6 mixture of diastereomers [integration of ^{1}H NMR for the benzylic protons at δ 5.82 (minor) and 5.59 (major)] in the form of a colorless oil: IR (NaCl plates) 2960, 2933, 2860, 1738, 1274, 1261, 1151, 1092 cm^{-1}; ^{1}H-NMR ($CDCl_3$) for major diastereomer δ 7.40−7.30 (m, 4 H), 5.59 (d, *J* = 8.0 Hz, 1 H), 4.96 (d, *J* = 8.0 Hz, 1 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.06 (s, 9 H), 0.78 (s, 9 H), −0.06 (s, 3 H), −0.26 (s, 3 H). Anal. Calcd for $C_{23}H_{35}O_6SiCl$: C, 58.64; H, 7.49: Found: C, 58.39; H, 7.55.

Ethyl (4*S*)-(+)-4-(4-Chlorophenyl)-3-[(2,2-dimethyl)-1-propanoyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-oxobutanoate (*S*22b): Dithiane ***S*19b** was hydrolyzed to α-keto ester ***S*22b** by the method described for the synthesis of α-keto acid enantiomer ***R*22b**.

Ethyl (4*R*)-(−)-4-(1,1′-Biphenyl-4-yl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-2-oxobutanoate (*R*22c): A solution of 0.6 g (1.0 mmol) of pivaloyl dithiane diastereomers ***R*19c** in 2 mL of acetone was hydrolyzed by the method described for production of α-keto ester ***R*22a**. Filtration through silica gel using EtOAc:hexanes (9.5:0.5) as eluant provided 0.36 g (70%) of α-keto ester ***R*22c** as an 8.5:1.5 mixture of diastereomers [integration of ^{1}H NMR for the benzylic protons at δ 5.78 (minor) and 5.71 (major)] in the form of a colorless oil: ^{1}H-NMR ($CDCl_3$) for major diastereomer δ 7.63−7.35 (m, 9 H), 5.71 (d, *J* = 7.9 Hz, 1H), 5.06 (d, *J* = 7.9 Hz, 1 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.10 (s, 9 H), 0.82 (s, 9 H), −0.01 (s, 3 H), −0.20 (s, 3 H). Anal. Calcd for $C_{29}H_{40}O_6Si$: C, 67.94; H, 7.86: Found: C, 67.67; H, 7.81.

Ethyl (4*S*)-(+)-4-(1,1′-Biphenyl-4-yl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-oxobutanoate (*S*22c): Dithiane ***S*19c** was hydrolyzed to α-keto ester ***S*22c** by the method described for the synthesis of α-keto ester enantiomer ***R*22c**.

(*R*)-(−)-3-[(2,2-Dimethyl)-1-propanoyl)oxy]-4-hydroxy-5-phenyl-2(5*H*)-furanone (*R*25a): (4*R*)-(−)-α-Keto ester ***R*22a** (0.28 g; 0.64 mmol) was dissolved in 20 mL of THF and 0.7 mL (0.7 mmol) of a 1.0 M solution of tetrabutylammonium flouride in THF was added dropwise with stirring. The reaction solution turned yellow, and after 10 min 5 mL of 10% aqueous HCl and 75 mL of Et_2O were added. The Et_2O layer was separated and washed with 1 × 10 mL of 5% aqueous HCl solution, 2 × 10 mL of H_2O, and 1 × 10 mL of brine, dried (Na_2SO_4), and concentrated *in vacuo* leaving 170 mg (95%) of tetronic acid ***R*25a**. An analytical sample was recrystallized from $CHCl_3$ and hexanes: mp 135−138 °C; $[\alpha]^{22}_D$ −80.4° (*c* 0.734, EtOH); IR (KBr pellet) 3037, 2989, 2976, 2937, 2875, 2717, 1762, 1651, 1481, 1456, 1367, 1340, 1290, 1265, 1128, 1018, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42−7.39 (m, 5 H), 5.69, (s, 1 H), 1.35 (s, 9 H); Anal. Calcd for $C_{15}H_{16}O_5 \cdot {}^1/_8H_2O$: C, 64.68; H, 5.88: Found: C, 64.76; H, 5.62.

(*S*)-(+)-3-[(2,2-Dimethyl-1-propanoyl)oxy]-4-hydroxy-5-phenyl-2(5*H*)-furanone (*S*25a): Cyclization of α-keto ester ***S*22a** to tetronic acid ***S*25a** was performed as described for the synthesis of *R*-tetronic acid enantiomer ***R*25a**: mp 136−139 °C, $[\alpha]^{22}_D$ +81.9° (*c* 0.804, EtOH).

(*R*)-(−)-5-(4-Chlorophenyl)-3-[(2,2-dimethyl)-1-propanoyl]oxy-4-hydroxy-2(5*H*)-furanone (*R*25b): (4*R*)-(−)-α-Keto ester ***R*22b** (0.38 g; 0.8 mmol) was cyclized as described for the production of tetronic acid ***R*25a** leaving 235 mg (94%) of tetronic acid ***R*25b**: mp 93−95 °C; $[\alpha]^{22}_D$ −70.34° (*c* 0.118, EtOH); IR (KBr, pellet) 3700−2600 (broad, vinylogous acid), 1770, 1749, 1660, 1495, 1323, 1302, 1130, 1091, 1007 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45−7.30 (m, 4 H), 5.65 (s, 1 H), 1.35 (s, 9 H). Anal. Calcd for $C_{15}H_{15}O_5Cl \cdot {}^1/_4H_2O$: C, 57.15; H, 4.96: Found: C, 56.88; H, 5.08.

(*S*)-(+)-5-(4-Chlorophenyl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-hydroxy-2(5*H*)-furanone (*S*25b): Cyclization of α-keto ester ***S*22b** was performed as described for the production of (*R*)-(−)-enantiomer ***R*25b**. Recrystallization from Et_2O and hexanes provided a white powder: mp 104−110 °C; $[\alpha]^{22}_D$ +85° (*c* 1.312, EtOH).

(*R*)-(−)-5-(1,1′-Biphenyl-4-yl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-hydroxy-2(5*H*)-furanone (*R*25c): (4*R*)-(−)-α-Keto ester ***R*22c** (0.35 g; 0.7 mmol) was cyclized as described for the production of tetronic acid ***R*25a** leaving 235 mg (94%) of ***R*25c**. A sample was recrystallized as white plates from acetone and hexanes: mp 213−220 °C dec; $[\alpha]^{22}_D$ −82.3° (*c* 0.164, EtOH); IR (KBr, pellet) 2983, 2934, 1774, 1752, 1676, 1130, 1122, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65−7.36 (m, 9 H), 5.74 (s, 1 H), 1.36 (s, 9 H). Anal. Calcd for $C_{21}H_{20}O_5$ C, 71.58; H, 5.72: Found: C, 71.10; H, 5.76.

(*S*)-(+)-5-(1,1′-Biphenyl-4-yl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-hydroxy-2(5*H*)-furanone (*S*25c): Cyclization of α-keto ester ***S*22c** was performed as described for the production of (*R*)-(−)-enantiomer ***R*25c** to yield ***S*25c**: mp 210−215°C dec; $[\alpha]^{22}_D$ +84.8° (*c* 0.466, EtOH).

(*R*)-(−)-3,4-Dihydroxy-5-phenyl-2(5*H*)-furanone (*R*3a): Pivaloyl tetronic acid ***R*25a** (0.17 g, 0.62 mmol) and 10 mL of AcOH:H_2O (9.8:0.2) were combined with stirring and warmed to ca. 100 °C for 24 h. The stir bar was removed and rinsed with 2 mL of iPrOH, and the yellow solution was concentrated leaving an oil that was crystallized by warming on a steam bath and adding 2 mL of $CHCl_3$ and 1 mL of hexanes. The flask was allowed to cool slowly to rt and subsequently at 0 °C for 3 h. The crystalline solid was filtered and washed with small portions of $CHCl_3$:hexanes (1:1) to yield 50 mg of optically pure 2-hydroxytetronic acid. The mother liqueur was concentrated on a steam bath and diluted with hexanes until the solution became slightly turbid. Upon cooling, an additional 15 mg of product was isolated to yield a total of 65 mg (55%) of tetronic acid ***R*3a**: mp 164−170 °C dec; $[\alpha]^{22}_D$ −140° (*c* 0.546, EtOH); ^{1}H NMR ($CDCl_3$ + d_6-DMSO) δ 7.24−

7.45 (m, 5H), 5.70 (s, 1H). Anal. Calcd for $C_{10}H_8O_4$: C, 62.5; H 4.2. Found: C, 62.29; H, 4.25.

(*S*)-(+)-3,4-Dihydroxy-5-phenyl-2(5*H*)-furanone (*S*3a) was prepared by a procedure identical to the one described for the preparation of *R*-(−)-enantiomer ***R*3a**: mp 165−170 °C dec lit.[13b] 142−143 °C; $[\alpha]^{22}_D$ +135° (*c* 0.512, EtOH) [lit.[13d] $[\alpha]^{21}_D$ +109.4° (*c* 0.80; MeOH)].

(*R*)-(−)-5-(4-Chlorophenyl)-3,4-dihydroxy-2(5*H*)-furanone (*R*3b): Pivaloyl tetronic acid ***R*25b** (165 mg, 0.53 mmol) was hydrolyzed as described for ***R*3a** leaving a total of 70 mg (58%) of tetronic acid ***R*3b**: mp 173−176 °C dec; $[\alpha]^{22}_D$ −128° (*c* 0.24, EtOH); ^{1}H NMR (CD_3COCD_3) δ 7.48−7.37 (m, 4 H), 5.69 (s, 1 H).

(*S*)-(+)-5-(4-Chlorophenyl)-3,4-dihydroxy-2(5*H*)-furanone (*S*3b): Pivaloyl tetronic acid ***S*25b** was hydrolyzed to produce target ***S*3b** by the procedure described for the synthesis of *R*-(−)-enantiomer ***R*3b**: mp 165−168 °C dec; $[\alpha]^{22}_D$ +105.4° (*c* 0.242, EtOH).

(*R*)-(−)-5-(1,1′-Biphenyl-4-yl)-3,4-dihydroxy-2(5*H*)-furanone (*R*3c). Method A: Pivaloyl tetronic acid ***R*25c** (180 mg, 0.50 mmol) was hydrolyzed as described for ***R*3a** leaving a total of 70 mg (52%) of tetronic acid ***R*3c**: mp 207−210 °C dec; $[\alpha]^{22}_D$ −154° (*c* 0.13, EtOH) ^{1}H NMR (DMSO-d_6) δ 7.72−7.65 (m, 4 H), 7.50−7.34 (m, 5 H), 5.76 (s, 1 H), 3.35 (br s, 2 H). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51; Found: C, 71.78, H, 4.64. **Method B:** A suspension of 178 mg (0.50 mmol) of pivaloyltetronic acid ***R*25c** in 25 mL of THF was cooled to −78 °C in a dry flask under N_2 atmosphere. To the solution with rapid stirring was added 0.33 mL (0.50 mmol) of 1.5 M LDA. After 5 min, 1.75 mL (1.75 mmol) of 1 M DIBAL-H was added dropwise and the orange solution was stirred at −78 °C for 45 min. The solution was quenched by the addition of 3 mL of 10% aqueous HCl and 50 mL of Et_2O. The organic layer was washed with 1 × 30 mL of H_2O and extracted with 2 × 30 mL of $NaHCO_3$ solution. The $NaHCO_3$ layer was washed with 1 × 30 mL of Et_2O, acidified with 10% aqueous HCl, and extracted with 2 × 40 mL of Et_2O. The Et_2O layer was washed with 1 × 25 mL of H_2O and 25 mL of brine, dried over Na_2SO_4, and concentrated leaving 100 mg of a white solid containing about 75% of the desired 2-hydroxytetronic acid and 25% of the starting 2-pivaloyltetronic acid (^{1}H NMR). Recrystallization of the white solid with EtOH/H_2O (1:1) provided 55 mg (41%) of pure 2-hydroxytetronic acid: mp 194−202 °C dec; $[\alpha]^{21}_D$ −168° (*c* 0.31, EtOH).

(*S*)-(+)-5-(1,1′-Biphenyl-4-yl)-3,4-dihydroxy-2(5*H*)-furanone (*S*3c): Pivaloyl tetronic acid ***S*25c** was hydrolyzed to produce target ***S*3c** by the procedure described for the synthesis of *R*-(−)-enantiomer ***R*3c**: mp 182−187 °C dec; $[\alpha]^{22}_D$ +145° (*c* 0.11, EtOH).

5-(4-Chlorophenyl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-methoxy-2(5*H*)-furanone (27b) and 5-(4-Chlorophenyl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-2-methoxy-4(5*H*)-furanone (26b). A solution of 0.30 g (1 mmol) of 2-pivaloyloxytetronic acid **25b** and 20 mL of ether was cooled to 0 °C and CH_2N_2 was added until the characteristic color of diazomethane persisted. The solution was concentrated and the resultant solid was dried in vacuo leaving a (2:1) mixture of **26b** and **27b**: ^{1}H NMR ($CDCl_3$) δ 7.30−7.25 (m, 6 H), 5.53 (s, 1 H (major)), 5.45 (s, 0.5 H), 4.05 (s, 1.5 H), 3.89 (s, 3 H (major)), 1.28 (s, 9 H (major)), 1.25 (s, 4.5 H).

The (*R*)-(+)-methylbenzylamine salt of racemic 5-(4-chlorophenyl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-hydroxy-2(5*H*)-furanone (25b) was prepared by dissolving 0.23 g (1.0 mmol) of (*p*-chlorophenyl)-2-hydroxytetronic acid in a mixture of 2 mL of pyridine, 2 mL of CH_2Cl_2, and 0.14 mL (1.1 mmol) of pivaloyl chloride under argon. The solution was stirred at rt for 12 h followed by the addition of 1 mL of saturated $NaHCO_3$. After 1 h the mixture was diluted with 20 mL of Et_2O and extracted with 3 × 3 mL of $NaHCO_3$ solution. The aqueous layer was washed with 1 × 5 mL of Et_2O and acidified with 10% HCl solution and extracted with 2 × 20 mL of Et_2O. The organic layer was washed with 1 × 5 mL of 10% HCl solution, 2 × 5 mL of H_2O, and 1 × 5 mL of brine, dried ($MgSO_4$), and concentrated leaving a white waxy solid. Racemic crude tetronic acid **25b** (0.015 g, 0.05 mmol) was dissolved in 0.75 mL of $CDCl_3$ containing 0.01 mL (0.1 mmol) of (*R*)-methylbenzylamine and 1 drop of D_2O: ^{1}H NMR ($CDCl_3$) δ 7.36−7.27 (m, 22 H (note the extra 4 protons are from excess amine)), 5.20 (s, 1 H ((*R,R*)-diastereomeric salt)), 5.11 (s, 1 H ((*S,R*)-diastereomeric salt)), 3.98 (q, *J* = 6.9 Hz, 2.5 H (excess amine), 1.40 (d, *J* = 6.9 Hz, 8 H (excess amine)), 1.28 (s, 18 H).

The (*R*)-(+)-methylbenzylamine salt of (*R*)-(−)-5-(4-chlorophenyl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-hydroxy-2(5*H*)-furanone (*R*25b) was prepared by mixing 0.015 g (0.05 mmol) of tetronic acid ***R*25b** in 0.75 mL of $CDCl_3$, 0.01 mL (0.1 mmol) of (*R*)-methylbenzylamine, and 1 drop of D_2O: ^{1}H NMR ($CDCl_3$) δ 7.36−7.27 (m, 9 H (2 additional protons were from excess amine)), 5.20 (s, 1 H), 3.98 (q, *J* = 6.9 Hz, 1.2 H (excess amine), 1.40 (d, *J* = 6.9 Hz, 4 H (excess amine)), 1.28 (s, 9 H).

The (*R*)-(+)-methylbenzylamine salt of (*S*)-(−)-5-(4-chlorophenyl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-hydroxy-2(5*H*)-furanone (*S*25b) was prepared by mixing 0.018 g (0.06 mmol) of (*S*)-(+)-tetronic acid ***S*25b** in 0.75 mL of $CDCl_3$ and 0.02 mL (0.2 mmol) of (*R*)-methylbenzylamine. ^{1}H NMR ($CDCl_3$) δ 7.33−7.19 (m, 19 H (excess amine)), 5.13 (s, 1 H), 4.30 (s, 7 H (RNH_3 + excess amine)), 3.99 (q, *J* = 6.7, 3 H (excess amine)), 1.34 (d, *J* = 6.7, 9 H (excess amine), 1.24 (s, 9 H).

The (*R*)-(+)-methylbenzylamine salt of (*R*)-(−)-5-(1,1′-biphenyl-4-yl)-3-[(2,2-dimethyl-1-propanoyl)oxy]-4-hydroxy-2(5*H*)-furanone (*R*25c) was prepared by mixing 0.015 g (0.05 mmol) of tetronic acid ***R*25c** in 0.75 mL of $CDCl_3$ and 0.01 mL (0.1 mmol) of (*R*)-methylbenzylamine: ^{1}H NMR ($CDCl_3$) δ 7.46−7.22 (m, 26 H (excess amine)), 5.27 (s, 1 H), 4.02 (q, *J* = 6.7 Hz, 3.4 H (excess amine)), 3.39 (br s, 11.6 H (RNH_3 + excess amine)), 1.35 (d, *J* = 6.7 Hz, 10 H (excess amine)), 1.24 (s, 9 H).

The (*R*)-(+)-methylbenzylamine salt of (±)-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone (3a) was prepared by dissolving 12 mg (0.05 mmol) of the racemic 2-hydroxytetronic acid **3a** in 0.8 mL of $CDCl_3$. The initial suspension was taken into solution by the addition of 0.01 mL (0.1 mmol) of (*R*)-(+)-methylbenzylamine. The ^{1}H NMR spectrum was taken immediatly before crystallization took place. Better separation of the diastereomeric benzylic protons was observed after addition of D_2O, but D_2O initiates crystallization: ^{1}H-NMR ($CDCl_3$) δ 7.37−7.19 (m, 24 H (diastereomeric mixture + excess amine)), 4.99 (s, 1 H), 4.96 (s, 1 H), 4.77 (br s, 7 H (RNH_3 + excess amine)), 3.70 (q, *J* = 6.7 Hz, 3 H (diasteromeric mixture + excess amine)), 1.18 (d, *J* = 6.7 Hz, 8 H (diastereomeric mixture + excess amine)).

The (*R*)-(+)-methylbenzylamine salt of (*R*)-(−)-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone (*R*3a) was greater than 98% de by ^{1}H NMR analysis. (*R*)-(−)-2-Hydroxytetronic acid ***R*3a** (12 mg; 0.05 mmol) was dissolved in 0.8 mL of $CDCl_3$ containing 0.01 mL (0.1 mmol) of (*R*)-(+)-methylbenzylamine: ^{1}H NMR ($CDCl_3$) δ 7.32−7.18 (m, 16 H), 6.04 (br s, 6 H (RNH_3 + excess amine)), 4.88 (s, 1 H), 3.84 (q, *J* = 6.7 Hz, 2 H (excess amine)), 1.26 (d, *J* = 6.7 Hz, 6 H (excess amine)).

The (*R*)-(+)-methylbenzylamine salt of (*S*)-(+)-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone (*S*3a) was in greater than 98% de by ^{1}H NMR analysis. (*S*)-(+)-2-Hydroxytetronic acid ***S*3a** (12 mg; 0.05 mmol) was dissolved in 0.8 mL of $CDCl_3$ and 0.02 mL (0.2 mmol) of (*R*)-(+)-methylbenzylamine: ^{1}H NMR ($CDCl_3$) δ 7.30−7.17 (m, 14 H (excess amine)), 6.40 (br s, 6 H (NH_3 + excess amine)), 4.98 (s, 1 H), 3.72 (q, *J* = 6.7 Hz, 1.6 H (excess amine)), 1.22 (d, *J* = 6.7 Hz, 5 H (excess amine)).

The (*R*)-(+)-methylbenzylamine salt of racemic 5-(4-Chlorophenyl)-3,4-dihydroxy-2(5*H*)-furanone (3b) was prepared by dissolving 12 mg (0.05 mmol) of the racemic 2-hydroxytetronic acid **3b** in 0.8 mL of $CDCl_3$. The initial suspension was taken into solution by the addition of 0.01 mL (0.1 mmol) of (*R*)-(+)-methylbenzylamine. The ^{1}H NMR spectrum was taken immediatly prior to sample crystallization. Separation of the diastereomeric benzylic protons was best observed after addition of D_2O, but addition of D_2O also initiates crystallization: ^{1}H-NMR ($CDCl_3$) δ 7.28−7.02 (m, 20 H (excess amine)), 6.23 (br s, 12 H (RNH_3 + excess amine)),

4.96 (s, 1 H), 4.91 (s, 1 H), 3.77 (q, J = 6.8 Hz, 2.5 H (excess amine), 1.22 (d, J = 6.8 Hz, 7 H (excess amine)).

The (*R*)-(+)-methylbenzylamine salt of (*R*)-(−)-5-(4-chlorophenyl)-3,4-dihydroxy-2(5*H*)-furanone (*R*3b) was greater than 98% de by ^{1}H NMR analysis. (*R*)-(−)-2-hydroxytetronic acid ***R*3b** (12 mg; 0.05 mmol) was dissolved in 0.8 mL of $CDCl_3$ containing 0.01 mL (0.1 mmol) of (*R*)-(+)-methylbenzylamine and 1 drop of D_2O: ^{1}H NMR ($CDCl_3$) δ 7.28−7.02 (m, 9 H), 4.93 (s, 1 H), 3.92 (br q, J = 6.8 Hz, 1 H), 1.27 (d, J = 6.8 Hz, 3 H).

The (*R*)-(+)-methylbenzylamine salt of (*S*)-(+)-5-(4-chlorophenyl)-3,4-dihydroxy-2(5*H*)-furanone (S3b) was greater than 98% de by ^{1}H NMR analysis. (*S*)-(+)-2-hydroxytetronic acid ***S*3b** (12 mg; 0.05 mmol) was dissolved in 0.8 mL of $CDCl_3$ containing 0.02 mL (0.2 mmol) of (*R*)-(+)-methylbenzylamine: ^{1}H NMR ($CDCl_3$) δ 7.31−7.07 (m, 26 H (excess amine)), 4.92 (s, 1 H), 4.22 (s, 11 H (RNH_3 + excess amine)), 3.97 (q, J = 6.7 Hz, 4 H (excess amine)), 1.34 (d, J = 6.7 Hz, 12 H (excess amine)).

The (*R*)-(+)-methylbenzylamine salt of racemic 5-(1,1′-biphenyl-4-yl)-3,4-dihydroxy-2(5*H*)-furanone (3c) was prepared by diluting 12 mg (0.05 mmol) of the racemic 2-hydroxytetronic acid **3c** in 0.8 mL of $CDCl_3$. The suspension was taken into solution by the addition of 0.01 mL (0.1 mmol) of (*R*)-(+)-methylbenzylamine. The ^{1}H NMR spectrum was taken immediately and prior to crystallization. Addition of D_2O resulted in sample crystallization within 2−4 min: ^{1}H-NMR ($CDCl_3$) δ 7.61−7.18 (m, (excess amine)), 5.08 (s, 1 H), 5.03 (s, 1 H), 3.97 (q, J = 6.7 Hz, (excess amine)), 3.84 (br s, (RNH_3 + excess amine)), 1.33 (d, J = 6.7 Hz, (excess amine)).

The (*R*)-(+)-methylbenzylamine salt of (*R*)-(−)-5-(1,1′-Biphenyl-4-yl)-3,4-dihydroxy-2(5*H*)-furanone (*R*3c) was determined to be greater than 98% de by ^{1}H NMR analysis. The sample was prepared as described for the preparation of the racemic salt: ^{1}H NMR ($CDCl_3$) δ 7.58−7.25 (m, 22 H (excess amine)), 5.69 (br s, 7 H (RNH_3 + excess amine)), 4.98 (s, 1 H), 3.96 (q, J = 6.7 Hz, 2 H (excess amine)), 1.34 (d, J = 6.7 Hz, 7 H (excess amine)).

The (*R*)-(+)-methylbenzylamine salt of (*S*)-(+)-5-(1,1′-biphenyl-4-yl)-3,4-dihydroxy-2(5*H*)-furanone (*S*3c) was determined to be greater than 98% de by ^{1}H NMR analysis. The sample was prepared as described for the racemic salt: ^{1}H NMR ($CDCl_3$) δ 7.54−7.19 (m, (excess amine)), 5.05 (s, 1 H), 4.03 (q, J = 6.6 Hz,), 3.28 (br s, RNH_3 + excess amine), 1.35 (d, J = 6.6 Hz).

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Supplementary Material Available: ^{1}H NMR spectra of MPTA esters **14b**, (*R*)-**14b**, (*S*)-**14b**, **14c**, (*R*)-**14c**, and (*S*)-**14c**, silyl protected methyl mandelates **15b** and **15c**, aldehydes **16a**, **16b**, **and 16c**, and the (*R*)-methylbenzylamine salts of (±)-**3a**, (*R*)-**3a**, (*S*)-**3a**, (±)-**3b**, (*R*)-**3b**, (*S*)-**3b**, (±)-**3c**, (*R*)-**3c**, (*S*)-**3c**, (±)-**25b**, (*R*)-**25b**, and (*S*)-**25b** (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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