was purified by prep. TLC on silica gel (1:2 ether–*n*-hexane) to give a 71% yield (14 mg) of pure **11** as colorless crystals: mp 50–53 °C (ether–*n*-hexane) (lit.[19] mp 55–56 °C); IR 1750, 1620 $cm^{-1}$; $^1H$ NMR $\delta$ 1.55 (d, 3 H, $J$ = 7 Hz), 5.54 (qd, 1 H, $J$ = 7, 1.5 Hz), 6.24 (d, 1 H, $J$ = 1.5 Hz), 7.44 (s, 5 H); MS $m/e$ 174 ($M^+$).

**(b) By Using NaH**: Similarly as described in method a, **3a** (50 mg, 0.19 mmol) was treated with NaH (60% oil suspension, 9 mg, 0.23 mmol) in dry DMF (2 mL) at 0 °C for 1 h to give **11** in 82% yield (27 mg), which was identical with **11** prepared by method a.

**Acknowledgment**. We thank Yasunori Tsuzuki for technical assistance.

**Registry No.** **1a**, 5650-40-8; **1b**, 119-53-9; **1c**, 116-09-6; **1d**, 90-02-8; **1e**, 63703-34-4; **1f**, 28203-05-6; **1g**, 124513-25-3; **1h**, 556-52-5; **1i**, 556-82-1; **1j**, 577-85-5; **1k**, 148-53-8; **2**, 4071-85-6; **3a**, 124513-11-7; **3b**, 124513-12-8; **3c**, 124513-13-9; **3d**, 124513-14-0; **3e**, 124513-15-1; **3f**, 124513-16-2; **3g**, 124513-17-3; **3h**, 124513-18-4; **3i**, 124513-19-5; **3j**, 124513-20-8; **4**, 19060-98-1; **5a**, 124513-21-9; **5b**, 124513-22-0; **6**, 104992-44-1; **7a**, 124513-23-1; **7b**, 124513-24-2; **9**, 995-00-6; **10**, 124513-26-4; **11**, 74528-46-4; $ZnCl_2$, 7646-85-7; $ZnI_2$, 10139-47-6; 2-lithio-1,3-dithiane, 36049-90-8; benzoyl chloride, 98-88-4; ethoxyacetylene, 927-80-0; triethylsilyl chloride, 994-30-9; *tert*-butyldimethylsilyl chloride, 18162-48-6.

(19) Metz, G. *Synthesis* **1980**, 394.

## Efficient Syntheses for Optically Pure Stereogenically Labile 4-Substituted-2-hydroxytetronic Acids

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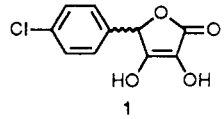
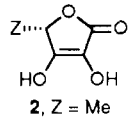
*Received May 15, 1989*

The *aci*-reductone 4-(4-chlorophenyl)-2-hydroxytetronic acid (CHTA, **1**) exhibits antilipidemic and antiaggregatory properties that differ from those of classical phenoxyacetic acids.[1,2] To further explore enzymatic inhibitory mechanisms of action relevant to the treatment and/or prevention of atherosclerosis, we required methods for the synthesis of optically pure 4-alkyl- and 4-aryl-2-hydroxytetronic acids **2** and **3**. The redox functionality present in these species is also found in vitamin C, but outside the scope of vitamin C research this function has received little attention.[3] Although, unsubstituted, 2-alkyl-, and 2-acyltetronic acids are frequently found in nature,[4,5] the 2-hydroxy-substituted redox system, to our knowledge, is only found in vitamin C and the macrolide antibiotic chlorothricin.[6]

Synthesis of 4-monosubstituted-2-hydroxytetronic acids **2** and **3** is complicated by the stereochemical lability of the C-4 stereogenic center. The lability of this center in



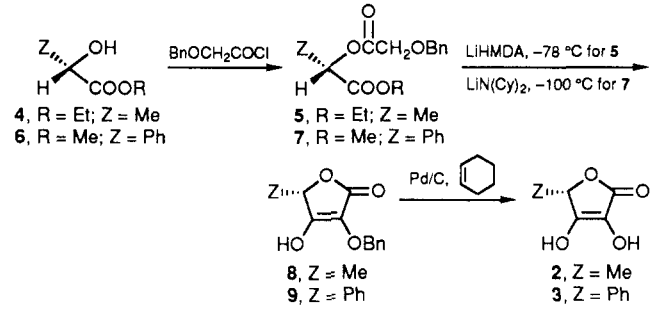
**1**



**2**, Z = Me
**3**, Z = Ph

(1) Witiak, D. T.; Kim, S. K.; Tehim, A. K.; Sternitzke, F. D.; McCreery, R. L.; Kim, S. U.; Feller, D. R.; Romstedt, K. J.; Kamanna, V. S.; Newman, H. A. I. *J. Med. Chem.* **1988**, *31*, 1437–1445.
(2) Kamanna, V. S.; Newman, H. A. I.; Patel, S. T.; Tehim, A. K.; Witiak, D. T.; Feller, D. R. *Lipids* **1989**, *24* 25–32.
(3) Haynes, L. J.; Plimmer, J. R. *Q. Rev. Chem. Soc.* **1960**, 292–315.
(4) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625–694.
(5) Pattenden, G., *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133–198.
(6) Berdy, J. In *Handbook of Antibiotic Compds.*; CRC: Boca Raton, FL, 1980; Vol. II, p 415.

**Scheme I**




tetronic acid **3** can be compared to the lability of the asymmetric center of mandelic acid[7,8] and phenylglycine.[9,10] Phenylglycine undergoes extensive racemization during peptide synthesis.[9]

Older synthetic methods[11] involving benzoin and intermolecular Claisen condensations employed in the synthesis of L-ascorbic acid would likely produce racemic 4-aryl-2-hydroxytetronic acids. Elegant syntheses published for the naturally occuring chiral tetronic acids such as (−)-vertinolide,[12] (*S*)-carlosic acid,[13] chlorothricin,[14] related 2-acylated[15] or 2-unsubstituted[16] tetronic acids, and chiral tetronic acid intermediates useful for the synthesis of the seco acid of erythronolide B[17] were not applicable for the synthesis of optically pure enantiomers of 4-aryl-2-hydroxytetronic acids. Some targets contain quaternary chiral centers not expected to undergo racemization during their preparation.[12,14] Other syntheses are dependent upon intramolecular Claisen condensations facilitated by a second carbonyl function, thereby affording 2-acyltetronic acids.[13,15] In some cases the 4-substituent at the chiral center is alkyl[16,17] and, therefore, racemization under reaction conditions employed is more easily prevented.

### Results and Discussion

The intramolecular Claisen condensation involving use of a nonnucleophilic sterically hindered base was anticipated to be a useful approach for the synthesis of optically pure 4-alkyl- and 4-aryl-2-hydroxytetronic acids of known absolute configuration [(*S*)-**2** and (*S*)-**3**] from accessible asymmetric $\alpha$-hydroxy esters **4** and **6**, respectively (Scheme I). Such a Claisen condensation is a particularly facile intramolecular process suitable for the construction of tetronic acids via C2–C3 bond connection. Thus (phenylmethoxy)acetyl derivative **5**, prepared from ester **4** and (phenylmethoxy)acetyl chloride in 86% yield, underwent intramolecular Claisen condensation with lithium hexamethyldisilazide (LiHMDA) (−78 °C) to afford 2-(phenylmethoxy)tetronic acid (**8**) in 82% yield without detectable epimerization. The enantiomeric purity of the protected tetronic acid (*S*)-(+)-**8** (>98% ee) was determined by using high resolution NMR (500 MHz) analysis

(7) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548–3551.
(8) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700–3704.
(9) Bodansky, M. In *Principles of Peptide Syn.*; Springer-Verlag: Berlin, New York, 1984; p 160.
(10) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525–5540.
(11) Helferich, B.; Peters, O. *Ber.* **1937**, *70*, 465–468.
(12) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761–3764.
(13) Bloomer, J. L.; Kappler, F. E. *J. Chem. Soc., Perkin Trans. I* **1976**, 1485–1491.
(14) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635–648.
(15) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans 1* **1987**, 121–129.
(16) Brandänge, S.; Flodman, L.; Norberg, A. *J. Org. Chem.* **1984**, *49*, 927–928.
(17) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565.

0022-3263/90/1955-1112$02.50/0 

of the chiral amine [(S)-methylbenzylamine] salt compared to the salt derived from racemic 8. For the (S)-(+)-8 salt a single quartet ($J$ = 7.1 Hz) was observed at $\delta$ 4.88 for the proton bonded to the chiral center. Two overlapping quartets were observed for the salt of racemic 8. Transfer hydrogenation[18] produced the target *aci*-reductone 2 in 79% yield.

Owing to the increased acidity of the C-4 proton, methods employed for the synthesis of optically pure 4-alkyl species failed to produce optically pure (S)-4-phenyl-2-(phenylmethoxy)tetronic acid (9) under several experimental conditions. Whereas protected ester 7 was easily generated from methyl (S)-(+)-mandelate (6) in 84% yield, conversion of 7 to optically pure 2-(phenylmethoxy)tetronic acid 9 required experimentation. Unsuccessful conditions using several bulky nonnucleophilic bases included LiHMDA (2.1 equiv, −78 °C, 5% yield), lithium diisopropylamide [LDA (2.1 equiv), −78 °C, 11% yield], LDA (2.4 equiv, HMPA, −78 °C, no desired product), *t*-BuLi (2.1 equiv, HMPA, −78 °C, no desired product), lithium isopropylcyclohexylamide [LiICA (2.4 equiv), −78 °C, 30% yield, 17% ee]. Since LiICA proved more effective than either LiHMDA or LDA, we investigated use of lithium dicyclohexylamide [$LiN(Cy)_2$] under kinetically controlled conditions. Use of 2.1 equiv of $LiN(Cy)_2$ (−78 °C, 10 min) provided 2-(phenylmethoxy)tetronic acid 9 (35% yield, 88–92% ee), but at −100 °C, 10 min the ee was >98% (250-MHz NMR).

Debenzylation under transfer hydrogenation conditions afforded enantiomerically pure target (S)-3 in 40% yield. The enantiomeric excess was determined by observing the 4-H proton resonance signal of optically pure (S)-9 and deprotected species (S)-3 as their (S)-methylbenzylamine salts.

The successful use of relatively unexplored[19] $LiN(Cy)_2$ vs LiICA, LDA, or LiHMDA to provide 2-hydroxytetronic acid redox compounds of high enantiomeric purity is unprecedented. Furthermore, these intramolecular Claisen condensations are expected to be applicable for construction of a wide range of optically pure 4-substituted-2-hydroxytetronic acids of known absolute configuration. Such a chiron approach[20] becomes all the more practical since methodologies for the preparation of α-hydroxy acid precursors of known absolute configuration are available.[21]

## Experimental Section

**General.** Melting points were determined in open capillaries and are uncorrected.

**Ethyl (S)-(−)-2-[(Phenylmethoxy)acetoxy]propanoate (5).** To a stirred solution (0 °C) of 1.0 g (8.47 mmol) of ethyl (S)-lactate (4) in 8.0 mL of dry $CH_2Cl_2$ containing 2.0 mL (12.7 mmol) of (phenylmethoxy)acetyl chloride was added 1.0 mL (12.4 mmol) of dry pyridine. The resulting mixture was stirred for 0.5 h, warmed to room temperature, and stirred for an additional 1 h. The mixture was poured into ice-cold $H_2O$ (25 mL) containing 10 mL of $CH_2Cl_2$. After being allowed to stand overnight in order to ensure complete hydrolysis of the acid chloride, the organic layer was separated, washed with $H_2O$ (2 × 15 mL), 10% aqueous HCl (2 × 10 mL), saturated $NaHCO_3$ solution (2 × 10 mL), and brine (2 × 10 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The residual oil was purified over silica gel–$CH_2Cl_2$ and distilled (Vigreux column), affording 1.93 g (86%) of colorless oil bp 150–151 °C (1.25 Torr). 5: $[\alpha]^{22}_D$ −35.3° (*c* 1.10, MeOH); IR $\nu_{max}^{neat}$ 2980, 1750, 1450, 1370 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 1.28 (t, 3 H, $J$ = 7.1 Hz), 1.51 (d, 3 H, $J$ = 7.1 Hz), 4.20 (s, 2 H), 4.24 (q, 2 H, $J$ = 7.1 Hz), 4.66 (s, 2 H), 5.18 (q, 1 H, $J$ = 7.1 Hz), 7.28–7.40 (m, 5 H). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.86; H, 6.62.

**(S)-(+)-4-Hydroxy-5-methyl-3-(phenylmethoxy)-2(5*H*)-furanone (8).** To a stirred solution (−78 °C) of 3.95 mmol of LiHMDA in 20.0 mL of dry THF (2.47 mL of 1.6 M *n*-butyllithium in hexane and 0.83 mL of hexamethyldisilazane) under an argon atmosphere was added dropwise a solution of 0.5 g (1.88 mmol) of 5 in 5.0 mL of THF. The resulting mixture was allowed to stir at −78 °C for 1 h. Following quenching with 10% HCl solution (10 mL), $Et_2O$ was added, and the mixture was warmed to room temperature. The organic layer was removed and washed with brine (2 × 10 mL), dried ($Na_2SO_4$), and concentrated in vacuo. Crystallization of the residue from $Et_2O$/petroleum ether afforded 0.34 g (82%) of colorless prisms, mp 114–115 °C. 8: $[\alpha]^{22}_D$ +21° (*c* 1.00, MeOH); IR $\nu_{max}^{neat}$ 2990, 2710, 1740, 1660, 1500, 1455, 1440, 1400, 1350 cm$^{-1}$; $^1$H NMR ($CD_3COCD_3$, 250 MHz) $\delta$ 1.35 (d, 3 H, $J$ = 6.6 Hz), 4.75 (q, 1 H, $J$ = 6.6 Hz), 5.03 (s, 2 H), 7.28–7.43 (m, 5 H). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.57; H, 5.58.

**(S)-(−)-α-Methylbenzylamine Salt of (S)-(+)-8.** (S)-(−)-Methylbenzylamine (0.03 mL, 0.23 mmol) was added dropwise to 0.05 g (0.03 mmol) of (S)-(+)-8 dissolved in MeOH (1 mL). Concentration in vacuo afforded a residue that was subjected to $^1$H NMR analysis (270 and 500 MHz).

**(S)-(+)-3,4-Dihydroxy-5-methyl-2(5*H*)-furanone (2).** To a solution of (S)-(+)-8 (0.05 g, 0.23 mmol) in EtOH (10 mL) were added 10% Pd/C (0.05 g) and cyclohexene (0.58 mL, 5.68 mmol). The mixture was refluxed for 1 h under argon, filtered, and concentrated in vacuo. Recrystallization of the residue from acetone/hexane afforded 0.024 g (79%) of colorless prisms, mp 178–179 °C (lit.[22] mp for racemic 2 174.5–176.5 °C). 2: $[\alpha]^{22}_D$ +4.7° (*c* 1.00, MeOH); IR $\nu_{max}^{neat}$ 3350, 3040, 1760, 1640, 1440, 1340, 1290, 1210, 1160 cm$^{-1}$; $^1$H NMR ($CD_3COCD_3$, 250 MHz) $\delta$ 1.38 (d, 3 H, $J$ = 6.6 Hz), 4.74 (q, 1 H, $J$ = 6.6 Hz). Anal. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65. Found: C, 46.02; H, 4.69.

**Methyl (S)-(+)-2-Phenyl-2-[(phenylmethoxy)acetoxy]-ethanote (7).** To a stirred solution (0 °C) of 1.0 g (6.02 mmol) of methyl (S)-(+)-mandelate (6) in 15.0 mL of dry $CH_2Cl_2$ containing 1.4 mL (9.03 mmol) of (phenylmethoxy)acetyl chloride was added 0.7 mL (8.65 mmol) of dry pyridine. The resulting mixture was stirred for 1 h, warmed to room temperature, and stirred for an additional 3 h. The mixture was poured into ice-cold $H_2O$ (30 mL) and $CH_2Cl_2$ (10 mL). After being allowed to stand overnight to ensure complete hydrolysis of acid chloride, the organic layer was separated and washed with $H_2O$ (2 × 15 mL), 10% aqueous HCl (2 × 10 mL), saturated $NaHCO_3$ solution (2 × 10 mL), and brine (2 × 10 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The residual oil was purified over silica gel–petroleum ether/$Et_2O$ (90:10), affording 1.5 g (84%) of colorless needles, mp 50–51 °C. 7: $[\alpha]^{22}_D$ +97.0° (*c* 1.00, $CHCl_3$); IR $\nu_{max}^{neat}$ 2890, 1750, 1440, 1430, 1390, 1340, 1200 1125 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 3.73 (s, 3 H), 4.23 (d, 1 H, $J$ = 16.8 Hz), 4.29 (d, 1 H, $J$ = 16.8 Hz), 4.67 (s, 2 H), 6.04 (s, 1 H), 7.29–7.49 (m, 10 H). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.86; H, 5.84.

**(S)-(+)-4-Hydroxy-5-phenyl-3-(phenylmethoxy)-2(5*H*)-furanone (9).** To a stirred solution (−100 °C) of 2.67 mmol of $LiN(Cy)_2$ in 20.0 mL of dry THF (1.67 mL of 1.6 M *n*-butyllithium

(18) Ananthanamaiah, G. M.; Sivanandoiah, K. M. *J. Chem. Soc., Perkin Trans. I* **1977**, 490–491.

(19) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582–584.

(20) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983.

(21) Optically pure, but commercially unavailable α-hydroxy ester precursors are available using Evan's chiral oxazolidinone auxiliaries.[24] For example, we have prepared methyl (S)-α-hydroxy-α-biphenylylacetate in high optical yield (94% ee) from 4-biphenylylacetyl chloride[25] and (S)-4-isopropyloxazolidin-2-one. Treatment of the resulting oxazolidinone carboxamide (76%) with LiHMDA and dibenzylperoxy dicarbonate yielded the intermediate carbonate as a single diastereomer (71%, de > 98%). Lithium hydroperoxide[26] hydrolysis afforded the protected hydroxy acid[27] (78%), transfer hydrogenation generated the (S)-α-hydroxyacetic acid (83%), and esterification (diazomethane) yielded the methyl acetate (91%), the enantiomeric purity of which was determined by conversion of the corresponding α-hydroxy acid to the α-methoxy-α-(trifluoromethyl)phenylacetic acid (MPTA) ester with (+)-MPTA-Cl[28] and observing the benzylic proton signal [$^1$H NMR ($CDCl_3$), 250 MHZ] at $\delta$ 6.15 (s, 1 H), in comparison to the ester derived from racemic acid.[29]

(22) Tomita, Y.; Eto, M.; Lio, M.; Murakami, H.; Omura, H. *Sci. Bull. Fac. Agr. Kyushu Univ.* **1974**, 28, 131–137.

in hexane and 0.53 mL of dicyclohexylamine) under an argon atmosphere was added dropwise a solution of 0.4 g (1.27 mmol) of (*S*)-(+)-**7** in 2.5 mL of THF. The mixture was stirred at −100 °C for 10 min and quenched with a cooled solution of 10% aqueous HCl (5 mL). $Et_2O$ (15 mL) was added, the mixture warmed to room temperaure, and the organic layer separated, washed with brine (5 mL), and extracted with 10% $NaHCO_3$ solution (2 × 5 mL). The aqueous extract was acidified (cold 10% aqueous HCl) and extracted with $Et_2O$ (2 × 10 mL). The $Et_2O$ layer was washed with brine (2 × 4 mL), dried ($Na_2SO_4$), and concentrated in vacuo. Recrystallization of the residue from hexane/$Et_2O$ afforded 0.11 g (30%) of colorless prisms, mp 124–125 °C. **9**: $[\alpha]^{22}_D$ +39.7° (*c* 1.00, MeOH); IR $\nu_{max}^{neat}$ 2920, 2680, 1735, 1650, 1390, 1340, 1140; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 5.14 (d, 1 H, *J* = 11.4 Hz), 5.18 (d, 1 H, *J* = 11.4 Hz), 5.51 (s, 1 H), 7.08–7.12 (m, 2 H), 7.26–7.43 (m, 8 H). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.54; H, 5.08.

**(*S*)-(+)-3,4-Dihydroxy-5-phenyl-2(5*H*)-furanone (3).** To a solution of (*S*)-(+)-**9** (0.04 g, 0.14 mmol) in EtOH (5 mL) were added 10% Pd/C (0.04 g) and cyclohexene (0.36 mL, 3.56 mmol). The mixture was refluxed for 1 h under argon, filtered, and concentrated in vacuo. Recrystallization of the residue from acetone/hexane afforded 0.01 g (40%) of colorless needles, mp 142–143 °C (lit.[23] mp for racemic **3** 150.5–152 °C dec). **3**: $[\alpha]^{22}_D$ +109.4° (*c* 0.80, MeOH); IR $\nu_{max}^{neat}$ 3300, 1740, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + $d_6$-DMSO, 250 MHz) δ 4.98 (s, 1 H), 7.23–7.41 (m, 5 H). Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.69; H, 4.25.

**Acknowledgment.** We are grateful to the U.S. Public Health Service National Heart, Lung and Blood Institute for support of this work through grant no. R01 HL-12740.

**Registry No.** (±)-**1**, 124400-07-3; (*S*)-**2**, 119006-88-1; (*S*)-**3**, 124400-08-4; (*S*)-**4**, 687-47-8; (*S*)-**5**, 124400-09-5; (*S*)-**6**, 21210-43-5; (*S*)-**7**, 124400-10-8; (*S*)-**8**, 124400-11-9; (*S*)-**8**·(*S*)-$PhCH(CH_3)NH_2$, 124400-13-1; (*S*)-**9**, 124400-12-0; $PhCH_2OCH_2C(O)Cl$, 19810-31-2.

(23) Dahn, H.; Lawendel, J. S. *Helv. Chim. Acta* **1954**, *37*, 1318–1327.
(24) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348.
(25) Logemann, W. *Hoppe*-Seylers *Z. Physiol. Chem.* **1952**, *290*, 61–66.
(26) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
(27) Removal of the chiral auxilliary with $Mg(OCH_3)_2$[24] (0.02 M; 1.1 equiv) at −15 °C to −20 °C followed by deprotection via transfer hydrogenation yielded partially racemized α-hydroxy ester [(35% ee, $[\alpha]^{22}_D$ +49.1° (*c* 1.00, MeOH)] in 61% overall yield from the oxazolidinone carboximide.
(28) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
(29) The racemic methyl α-hydroxyacetate, mp 104–105 °C, was prepared by $CH_2N_2$ esterification of the racemic acid, which was synthesized as follows: in situ cyanosilylation[30] [$Me_3SiCl$, KCN, $Zn(CN)_2$] of 4-biphenylcarboxaldehyde furnished trimethylsilyl cyanohydrin ether, which was hydrolyzed with HCl[31] to the hydroxy amide (mp 226–227 °C) and finally to racemic α-hydroxy acid (mp 201–202 °C, lit.[32] mp 201–203 °C) with KOH/MeOH in 56% overall yield.
(30) Rasmussen, J. K.; Heilmann, S. M. *Org. Synth.* **1984**, *62*, 196–201.
(31) Grunewald, G. L.; Brouillette, W. J.; Finney, J. A. *Tetrahedron Lett.* **1980**, *21*, 1219–1220.
(32) Blicke, F. F.; Grier, N. *J. Am. Chem. Soc.* **1943**, *65*, 1725–1728.

## New Stereoselective Propanal/Propanoic Acid Synthons for Aldol Reactions[1]

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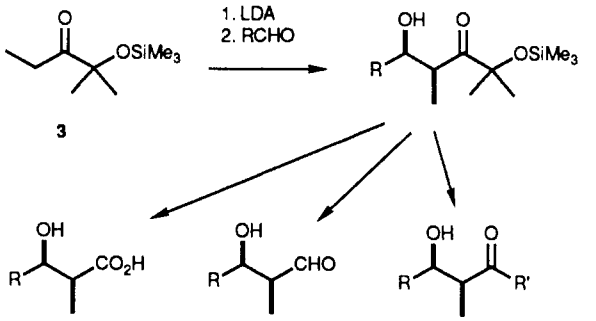
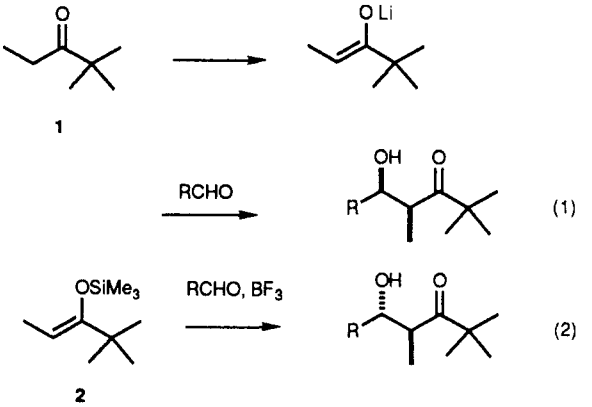
*Received August 1, 1989*

It has been well established that reactions of performed main-group metal enolates with aldehydes show a correlation between enolate geometry and aldol relative configuration if the nonreacting carbonyl ligand is sterically bulky.[2] For example, 2,2-dimethyl-3-pentanone undergoes deprotonation to give a *Z* enolate, which reacts with aldehydes to given syn aldols of high stereochemical purity (eq 1).[3] Conversely, the trimethylsilyl enol ethers of such ketones undergo anti-selective Lewis acid mediated aldol reactions (eq 2).[4]

**Scheme I**




To capitalize on this high aldol stereoeselectivy, we developed aldol reagent **3**.[3,5,6] Like 2,2-dimethyl-3-pentanone, ketone **3** gives a *Z* enolate that reacts with a variety of aldehydes to give syn aldols that can be cleaved by periodic acid to give β-hydroxy acids,[7] reduced and then cleaved by periodate to give β-hydroxy aldehydes,[8] or treated sequentially with an alkyllithium reagent and periodate to provide β-hydroxy ketones (Scheme I).[9]

Reagent **3** and its relatives have been employed in several syntheses as syn-selective propanal or propanoic acid synthons.[10] A structurally related synthon, ethyl trityl

(1) Paper 50 in the series Acyclic Stereoselection. For paper 49, see: Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Carbohyd. Res.*, in press.

(2) (a) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (b) Heathcock, C. H. In *Asymmetric Synthesis, Volume 3*; Morrison, J. D., Ed.; Academic Press: New York, 1984; p 111, and references contained therein.
(3) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
(4) Heathcock, C. H.; Hug, K. T.; Flippin, L. A. *Tetrahedron Lett.* **1984**, *25*, 5793.
(5) Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 2337.
(6) Buse, C. T. Ph.D. Dissertation, University of California, Berkeley, 1978.
(7) (a) Young, S. D.; Buse, C. T.; Heathcock, C. H. *Org. Synth.* **1985**, *63*, 79. (b) Bal, B.; Buse, C. T.; Smith, K.; Heathcock, C. H. *Ibid.* **1983**, *63*, 89.
(8) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095.
(9) White, C. T.; Heathcock, C. H. *J. Org. Chem.* **1981**, *46*, 191.
(10) (a) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118. (b) Dauben, W. G.; Saugier, R. K.; Fleischhauer, I. *J. Org. Chem.* **1985**, *50*, 3767. (c) Heathcock, C. H.; Montgomery, S. H. *Tetrahedron Lett.* **1983**, *24*, 4637. (d) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, *23*, 4991. (e) Heathcock, C. H.; Finkelstein, B. L. *J. Chem. Soc., Chem. Commun.* **1983**, 919. (f) Heathcock, C. H. Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922. (g) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825. (h) Heathcock, C. H.; Radel, P. A. *J. Org. Chem.* **1986**, *51*, 4322.

0022-3263/90/1955-1114$02.50/0 