Syn-Anti Isomerization of Aldols by Enolization

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Experimental Procedures

General Methods. All solvents were distilled prior to use. Et₃N and TiCl₄ were distilled from CaH₂. Anhydrous solvents were distilled under argon atmosphere as follows: Tetrahydrofuran (THF) from benzophenone potassium ketyl; ether from benzophenone sodium ketyl; CH₂Cl₂ and toluene from CaH₂; MeOH from Mg(OMe)₂. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were ice/water (0 °C) and CO₂(s)/acetone (-78 °C). Reaction temperatures refer to that of the bath.

Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) precoated (0.25 mm) with silica gel 60 F₂₅₄. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR.

Flash column chromatography (FCC) was performed according to Still et al.¹ with Merck Silica Gel 60 (40-63 μm). Medium pressure chromatography (MPC) was performed essentially as reported by Taber.² Dry flash column chromatography was performed according to Harwood.³ All mixed solvent eluents are reported as v/v solutions.

Spectral Data. High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focussing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in CDCl₃ solution at 300, 400, or

¹ Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923.
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³ Harwood, L. M. Aldrichimica Acta 1985, 18, 25.
500 MHz for $^1$H and 75, 100, or 125 MHz for $^{13}$C. Signals due to the solvent ($^{13}$C NMR) or residual protonated solvent ($^1$H NMR) served as the internal standard: CDCl$_3$ (7.26 δ$_H$, 77.23 δ$_C$); CD$_3$OD (3.31 δ$_H$, 49.15 δ$_C$); C$_6$D$_6$ (7.16 δ$_H$, 128.39 δ$_C$). The $^1$H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of couplings constants ($J$) corresponds to the order of the multiplicity assignment. Couplings constants ($J$) are reported to the nearest 0.5 Hz. The $^1$H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or NOE experiments. The $^{13}$C NMR assignments were made on the basis of chemical shift and multiplicity$^4$ (as determined by $J$-modulation$^5$ or HSQC$^6$) and were confirmed, where necessary, by two dimensional $^1$H/$^{13}$C correlation experiments (HSQC and/or HMBC$^7$).

**Materials:** The preparations of the following compounds were described previously: 3a, 7a, 7s, 8, 10, 11a, 11s, 13a, 13s, 14a, 14s, 15a, 15s, 16a, 16s, 17a, and 3,6-Dihydro-4-trimethylsilyloxy-2H-thiopyran$^8$, 18s,$^9$ 21aa, 21ss, 22aa, and 22as$^{10}$; tetrahydro-3-methyl-4H-thiopyran-4-one.$^{11}$ All other reagents were commercially available and unless otherwise noted, were used as received.

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4 The multiplicity of $^{13}$C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t = CH$_2$, q = CH$_3$)

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(3S)-rel-3-[(R)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (12a). Bu$_4$NI (11 mg, 0.03 mmol), i-Pr$_2$EtN (0.90 mL, 0.67 g, 5.2 mmol) and MOMCl (0.23 mL, 0.24 g, 3.0 mmol) were sequentially added to a solution of 11a (311 mg, 1.02 mmol) in CH$_2$Cl$_2$ (3 mL). After 3 days, dilute HCl as added and mixture was extracted with CH$_2$Cl$_2$ (x3). The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and fractionated by MPC (35% ethyl acetate in hexane) to give the titled compound as a white solid (343 mg, 96%): IR (DRIFT) $\nu_{\text{max}}$ 2909, 1708, 1428, 1264, 1153, 1032, 916, 730 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.78 (1H, d, $J = 7$ Hz, HCO$_2$), 4.58 (1H, d, $J = 7$ Hz, HCO$_2$), 4.57 (1H, dd, $J = 2, 8$ Hz, HC-1'), 4.12-4.02 (3H, m, H$_2$CO), 3.91 (1H, m, H$_2$CO), 3.13 (1H, ddd, $J = 1.5, 5.5, 13.5$ Hz, HC-2), 3.03 (1H, ddd, $J = 4, 5.5, 8$ Hz, HC-3), 2.98 (1H, dd, $J = 4$, 13.5 Hz, HC-2), 2.95-2.89 (1H, m, HC-5), 2.93-2.91 (2H, br s, H$_2$C-6), 2.89-2.76 (3H, m, H$_2$C-7', HC-9'), 2.62 (1H, m, HC-5), 2.53 (1H, br d, $J = 13.5$ Hz, HC-9'), 2.38 (1H, ddd, $J = 2, 3.5, 11$ Hz, HC-6'), 2.14 (1H, ddd, $J = 3, 5, 13.5$ Hz, HC-10'), 1.75 (1H, ddd, $J = 3.5, 12, 13.5$ Hz, HC-10'); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.4 (s, C-4), 108.3 (s, C-5'), 96.7 (t, OCH$_2$O), 76.4 (d, C-1'), 64.6 (t, CH$_2$O), 64.3 (t, CH$_2$O), 56.5 (q, CH$_3$O), 54.8 (d, C-3), 50.7 (d, C-6'), 43.0 (t, C-5), 36.6 (t, C-10'), 33.7 (t, C-2), 31.1 (t, C-6), 28.9 (t, C-7'), 26.9 (t, C-9'); LRMS (EI), $m/z$ (relative intensity): 348 ([M]$^+$, 3), 286 (18), 159 (14), 133 (25), 132 (66), 99 (100), 86 (12), 55 (19); HRMS $m/z$ calcd for C$_{15}$H$_{24}$O$_5$S$_2$ 348.1065, found 348.1067.

(3R)-rel-3-[(R)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (12s).
Following the procedure describe above for 12a, 11s (1.043 g, 3.426 mmol) upon workup gave a light yellow solid (1.342 g) that was crystallized from ethyl acetate (10 mL) to give the titled compound as needle-like crystals (1.150 g, 95%): IR (DRIFT) \( \nu_{\max} \) 2957, 1707, 1164, 1149, 1097, 1055, 1034, 894 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.88 (1H, dd, \( J = 3, 3 \) Hz, HC-1'), 4.69 (1H, d, \( J = 6.5 \) Hz, HCO2), 4.63 (1H, d, \( J = 6.5 \) Hz, HCO2), 3.97 (1H, m, H\(_2\)CO), 3.90-3.82 (2H, m, H\(_2\)CO), 3.77 (1H, m, H\(_2\)CO), 3.36 (3H, s, H\(_3\)CO), 3.30 (1H, ddd, \( J = 3, 5.5, 10.5 \) Hz, HC-3), 3.02-2.87 (5H, m, H\(_2\)C-2, H\(_2\)C-6, HC-7'), 2.86 (1H, ddd, \( J = 2.5, 13, 13 \) Hz, HC-9'), 2.83 (1H, ddd, \( J = 3, 3, 13 \) Hz, HC-7'), 2.77 (1H, ddd, \( J = 4, 4, 13.5 \) Hz, HC-5), 2.68 (1H, ddd, \( J = 5.5, 11.5, 13.5 \) Hz, HC-5), 2.51 (1H, ddd, \( J = 3, 3.5, 4, 13.5 \) Hz, HC-9'), 2.43 (1H, ddd, \( J = 3, 3, 12 \) Hz, HC-6'), 2.07 (1H, ddd, \( J = 2.5, 4, 13.5 \) Hz, HC-10'), 1.73 (1H, ddd, \( J = 3.5, 13, 13.5 \) Hz, HC-10'); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 208.9 (s, C-4), 108.9 (s, C-5'), 97.5 (t, OCH\(_2\)O), 71.8 (d, C-1'), 64.5 (t, CH\(_2\)O), 64.2 (t, CH\(_2\)O), 56.2 (q, CH\(_3\)O), 55.8 (d, C-3), 50.9 (t, C-6'), 44.5 (t, C-5), 37.1 (t, C-10'), 32.1 (t, C-2), 30.3 (t, C-6), 28.1 (t, C-7'), 27.0 (t, C-9'); LRMS (EI), \( m/z \) (relative intensity): 348 ([M]+, 2), 286 (18), 224 (10), 159 (13), 133 (24), 132 (65), 99 (100), 55 (14); HRMS \( m/z \) calcd for C\(_{15}\)H\(_{24}\)O\(_5\)S\(_2\) 348.1065, found 348.1062.

(3S,5S)-rel-Tetrahydro-3-[(R)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (19at). A solution of BuLi in hexane (2.5 M, 1.2 mL, 3.0 mmol) was added dropwise over 5 minutes to a stirred solution of \( i \)-Pr\(_2\)NH (0.46 mL, 3.3 mmol) in THF (3 mL) at 0 °C under argon. After 5 minutes, the mixture was cooled to −78 °C and a solution of 2-methylthiopyranone (196 mg, 1.51 mmol) in THF (0.2 mL) was added dropwise over 30 seconds. After 30 minutes, benzaldehyde (0.230 mL, 2.26 mmol) was added over 10 seconds and, after 3 minutes, the reaction mixture was poured onto ice-cold NH\(_4\)Cl (10 mL, 0.1 M) with vigorous stirring. The mixture was diluted with H\(_2\)O and extracted with CH\(_2\)Cl\(_2\) (3×). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated to give a light yellow oil (401 mg) which contained a 2.6:1.5:1 mixture of 19at, 19ac, and 19st, respectively, as determined by \(^1\)H NMR. Fractionation of the crude product by FCC (25% ethyl acetate in hexane) gave two fractions: a 1:7.2:4.4
mixture of 19at, 19ac, and 19st, respectively, as an oil (106 mg, 30%); a 10:1:1 mixture of 19at, 19ac, and 19st, respectively, as a solid (143 mg, 40%). A portion of the latter fraction (57 mg) was crystallized from CH₂Cl₂/hexane (1:2, 1.5 mL) to give the titled compound (43 mg): \textbf{IR} (DRIFT) νmax 3445, 2912, 1706, 1454, 1039, 1024, 768, 701 cm⁻¹; \textbf{1H NMR} (500 MHz, CDCl₃) δ 7.43-7.32 (5H, m, ArH), 5.30 (1H, dd, J = 3.5, 9.5 Hz, HC-1'), 3.09 (1H, ddq, J = 4.5, 9, 6.5 Hz, HC-5), 3.01 (1H, ddd, J = 4, 6.5, 9.5 Hz, HC-3), 3.01 (1H, ddd, J = 2, 4.5, 13 Hz, HC-6), 2.73 (1H, d, J = 3.5 Hz, HO), 2.72 (1H, dd, J = 4, 14 Hz, HC-2), 2.70 (1H, dd, J = 9, 13 Hz, HC-6), 2.46 (1H, ddd, J = 2, 6.5, 14 Hz, HC-2), 1.27 (3H, d, J = 6.5 Hz, H₃C); \textbf{13C NMR} (125 MHz, CDCl₃) δ 213.0 (s, C-4), 141.2 (s, Ar), 129.0 (d ×2, Ar), 128.7 (d, Ar), 127.0 (d ×2, Ar), 74.3 (d, C-1'), 58.0 (d, C-3), 45.5 (d, C-5), 37.7 (t, C-6), 32.9 (t, C-2), 15.5 (q, CH₃); \textbf{LRMS} (EI), m/z (relative intensity): 236 ([M⁺], 1), 130 (100), 129 (26), 107 (36), 97 (39), 87 (33), 79 (27), 77 (30); \textbf{HRMS} m/z calcd for C₁₃H₁₆O₂S 236.0871, found 236.0869 (EI).

(3S,5R)-rel-Tetrahydro-3-[(R)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (19ac). Fractionation of a 1:7.2:4.4 mixture of 19at, 19ac, and 19st (30 mg), respectively (see above), by preparative TLC (3% MeOH in CH₂Cl₂) gave 19ac (12 mg) and 19st (8 mg).

\textbf{IR} (DRIFT) νmax 3524, 2974, 2904, 1695, 1453, 1290, 1050, 701 cm⁻¹; \textbf{1H NMR} (500 MHz, CDCl₃) δ 7.40-7.30 (5H, m, ArH), 4.86 (1H, dd, J = 3.5, 8.5 Hz, HC-1'), 3.54 (1H, d, J = 3.5 Hz, HO), 3.09 (1H, ddd, J = 4.5, 8.5, 12.5 Hz, HC-3), 2.91 (1H, ddq, J = 4.5, 13, 6.5 Hz, HC-5), 2.90 (1H, ddd, J = 3, 4.5, 14.5 Hz, HC-6), 2.73 (1H, dd, J = 13, 14.5 Hz, HC-6), 2.66 (1H, dd, J = 12.5, 13.5 Hz, HC-2), 2.44 (1H, ddd, J = 3, 4.5, 13.5 Hz, HC-2), 1.15 (3H, d, J = 6.5 Hz, H₃C); \textbf{13C NMR} (125 MHz, CDCl₃) δ 214.2 (s, C-4), 140.5 (s, Ar), 128.9 (d ×2, Ar), 128.5 (d, Ar), 127.2 (d ×2, Ar), 74.1 (d, C-1'), 60.6 (d, C-3), 49.4 (d, C-5), 39.0 (t, C-6), 34.3 (t, C-2), 14.7 (q, CH₃); \textbf{LRMS} (EI), m/z (relative intensity): 236 ([M⁺], 4), 189 (23), 130 (100), 107 (45), 97 (46), 88 (37), 79 (30), 77 (28); \textbf{HRMS} m/z calcd for C₁₃H₁₆O₂S 236.0871, found 236.0874 (EI).
(3R,5R)-rel-Tetrahydro-3-[(R)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (19st). Fractionation of a 1:7.2:4.4 mixture of 19at, 19ac, and 19st (30 mg), respectively (see above), by preparative TLC (3% MeOH in CH₂Cl₂) gave 19ac (12 mg) and 19st (8 mg).

IR (DRIFT) νₘₐₓ 3389, 2920, 1701, 1452, 1036, 1025, 766, 701 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.41-7.27 (5H, m, ArH), 5.43 (1H, dd, J = 4, 4 Hz, HC-1'), 3.13 (1H, ddd, J = 1, 9.5, 13 Hz, HC-2), 3.07 (1H, ddd, J = 1, 4.5, 13.5 Hz, HC-6), 3.07 (1H, ddd, J = 4, 4, 9.5 Hz, HC-3), 2.89 (1H, ddq, J = 4.5, 7, 7 Hz, HC-5), 2.72 (1H, d, J = 4 Hz, HO), 2.71 (1H, ddd, J = 2, 4, 13 Hz, HC-2), 2.67 (1H, ddd, J = 2, 7, 13.5 Hz, HC-6), 1.26 (3H, d, J = 7 Hz, H₃C); ¹³C NMR (125 MHz, CDCl₃) δ 213.7 (s, C-4), 141.0 (s, Ar), 128.8 (d × 2, Ar), 128.0 (d, Ar), 126.2 (d × 2, Ar), 71.9 (d, C-1'), 56.6 (d, C-3), 46.6 (d, C-5), 36.6 (t, C-6), 29.6 (t, C-2), 16.0 (q, CH₃); LRMS (EI), m/z (relative intensity): 236 ([M]+, 3), 130 (100), 107 (40), 97 (33), 88 (38), 79 (60), 77 (57), 55 (33); HRMS m/z calcd for C₁₃H₁₆O₂S 236.0871, found 236.0871 (EI).

(3R,5S)-rel-Tetrahydro-3-[(R)-hydroxyphenylmethyl]-5-methyl-4H-thiopyran-4-one (19sc). A 1:7.2:4.4 mixture of 19at, 19ac, and 19st (37 mg), obtained as above, was added to a solution of imidazole (109 mg, 1.6 mmol) in CH₂Cl₂ (2 mL). After 4 days, the mixture was diluted with aqueous citric acid (0.1 M) and extracted with CH₂Cl₂ (3 × mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give a 3.5:3:2.5:1 mixture of 19at, 19ac, 19sc, and 19st, respectively (35 mg, 94%), as determined by ¹H NMR. Fractionation of the mixture by PTLC (2% MeOH in CH₂Cl₂) gave a pure sample of 19sc (9 mg): IR (DRIFT) νₘₐₓ 3532, 2971, 2929, 1706, 1451, 1070, 1016, 703 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.25 (5H, m, ArH), 5.38 (1H, br dd, J = 1.5, 3 Hz, HC-1'), 3.12 (1H, d, J = 1.5 Hz, HO), 3.07 (1H, dd, J = 12, 12.5 Hz, HC-2), 3.01 (1H, ddd, J = 3, 3.5, 12 Hz, HC-3), 2.92 (1H, ddq, J = 5, 12, 6.5 Hz, HC-5), 2.88 (1H, ddd, J = 3, 5, 13 Hz, HC-6), 2.73 (1H, dd, J = 12, 13 Hz, HC-6), 2.68 (1H, ddd,
J = 3, 3.5, 12.5 Hz, HC-2), 1.14 (3H, d, J = 6.5 Hz, H3C); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 214.1 (s, C-4), 141.0 (s, Ar), 128.6 (d ×2, Ar), 127.6 (d, Ar), 125.9 (d ×2, Ar), 71.2 (d, C-1’), 60.1 (d, C-3), 49.3 (d, C-5), 39.1 (t, C-6), 30.8 (t, C-2), 14.7 (q, CH$_3$); LRMS (EI), m/z (relative intensity): 236 ([M]$^+$, 5), 189 (35), 130 (100), 107 (52), 105 (30), 97 (41), 79 (53), 77 (54); HRMS m/z calc'd for C$_{13}$H$_{16}$O$_2$S 236.0871, found 236.0875 (EI).

(2S,6R)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (20at). Using the procedure described above for the synthesis of 19, aldol reaction of 2-methylcyclohexanone (557 mg, 4.97 mmol) with benzaldehyde (0.60 mL, 6.00 mmol) gave, after workup, a crude product containing a 46:24:21:9 mixture 20at, 20ac, 20st, and 20sc, respectively, as determined by $^1$H NMR. The mixture was fractionated by MPC (10-30% ethyl acetate in hexane; gradient elution) to give (in order of elution): 20sc (65 mg, 6%; 95% diastereomeric purity by $^1$H NMR), 20ac (173 mg, 16%; 98% diastereomeric purity by $^1$H NMR), 20at (336 mg, 31%; 95% diastereomeric purity by $^1$H NMR) and a 5:1 mixture of 20st and 20at, respectively (130 mg, 12%). A sample of enriched 20at (10 mg) was further fractionated by PTLC (2% MeOH in CH$_2$Cl$_2$) to give a sample of >98% diastereomeric purity by $^1$H NMR. Spectral data was similar to that previously reported.$^{12}$ $^1$H NMR (500 MHz, CDCl$_3$) δ 7.39-7.28 (5H, m, ArH), 4.86 (1H, dd, J = 3, 9.5 Hz, HC-1’), 3.42 (1H, d, J = 3 Hz, HO), 2.76 (1H, ddd, J = 5.5, 9.5, 9.5 Hz, HC-2), 2.70 (1H, ddq, J = 5, 5.5, 7 Hz, HC-6), 1.96 (1H, m, HC-5), 1.74-1.63 (3H, m, HC-4, HC-4, HC-5), 1.55 (1H, m, HC-3), 1.37 (1H, m, HC-3), 1.21 (3H, d, J = 7 Hz, H$_3$C); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 218.2 (s, C-1), 141.5 (s, Ar), 128. (d ×2, Ar), 128.32 (d, Ar), 127.2 (d ×2, Ar), 75.0 (d, C-1’), 54.9 (d, C-2), 44.5 (d, C-6), 34.2 (t, C-5), 30.1 (t, C-3), 20.3 (t, C-4), 16.5 (q, CH$_3$).

$^{12}$ See the section on Assignment of Relative Stereochemical Configurations for additional discussion.
(2S,6S)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (20ac). A sample of enriched 20at (10 mg), obtained as above, was further fractionated by PTLC (2% MeOH in CH$_2$Cl$_2$) to give a sample of >98% diastereomeric purity by $^1$H NMR. Spectral data was similar to that previously reported.$^{12}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38-7.26 (5H, m, ArH), 4.80 (1H, dd, $J = 3, 8.5$ Hz, HC-1'), 3.91 (1H, d, $J = 3$ Hz, HO), 2.64 (1H, dddd, $J = 1, 5.5, 8.5, 13$ Hz, HC-2), 2.47 (1H, dddd, $J = 1, 6, 13, 6.5$ Hz, HC-6), 2.12 (1H, dddd, $J = 3, 3, 3, 6, 13$ Hz, HC-5), 1.77 (1H, m, HC-4), 1.69-1.56 (2H, m, HC-3, HC-4), 1.39 (1H, dddd, $J = 4, 13, 13, 13$ Hz, HC-5), 1.33 (1H, dddd, $J = 4, 13, 13, 13$ Hz, HC-3), 1.07 (3H, d, $J = 6.5$ Hz, H$_3$C);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 217.0 (s, C-1), 141.3 (s, Ar), 128.6 (d $\times$2, Ar), 128.0 (d, Ar), 127.2 (d $\times$2, Ar), 74.9 (d, C-1'), 57.9 (d, C-2), 46.4 (d, C-6), 37.4 (t, C-5), 32.1 (t, C-3), 25.2 (t, C-4), 14.4 (q, CH$_3$).

(2R,6R)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylene cyclohexanone (20sc). A sample of enriched 20sc (10 mg), obtained as above, was further fractionated by PTLC (2% MeOH in CH$_2$Cl$_2$) to give a sample of >98% diastereomeric purity by $^1$H NMR. Spectral data was similar to that previously reported; however, the relative stereochemical configuration for this diastereomer was incorrectly assigned in the literature.$^{12}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37-7.23 (5H, m, ArH), 5.38 (1H, dd, $J = 2.5, 3$ Hz, HC-1'), 3.15 (1H, d, $J = 3$ Hz, HO), 2.61 (1H, dddd, $J = 1.5, 2.5, 6.5, 12.5$ Hz, HC-2), 2.50 (1H, dddd, $J = 1.5, 5.5, 12.5, 6.5$ Hz, HC-6), 2.12 (1H, dddd, $J = 2.5, 2.5, 3.5, 5.5, 13$ Hz, HC-5), 1.86-1.75 (2H, m, HC-3, HC-4), 1.74 (1H, dddd, $J = 3.5, 12.5, 12.5, 13$ Hz, HC-3), 1.60 (1H, dddd, $J = 3.5, 4.5, 12.5, 12.5, 13$ Hz, HC-4), 1.40 (1H, dddd, $J = 3.5, 12.5, 12.5, 13$ Hz, HC-5), 1.06 (3H, d, $J = 6.5$ Hz, H$_3$C);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 216.8 (s, C-1), 141.8 (s, Ar), 128.4 (d $\times$2, Ar), 127.1 (d, Ar), 126.0 (d $\times$2, Ar), 71.0 (d, C-1'), 57.4 (d, C-2), 46.3 (d, C-6), 37.6 (t, C-5), 27.0 (t, C-3), 25.1 (t, C-4), 14.5 (q, CH$_3$).
(2R,6S)-rel-2-[(R)-Hydroxyphenylmethyl]-6-methylcyclohexanone (20st). A sample of enriched 20st (10 mg), obtained as above, was further fractionated by PTLC (2% MeOH in CH₂Cl₂) to give a sample of >98% diastereomeric purity by ¹H NMR. Spectral data was similar to that previously reported; however, the relative stereochemical configuration for this diastereomer was incorrectly assigned in the literature.¹² ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.24 (5H, m, ArH), 5.32 (1H, br d, J = 3 Hz, HC-1'), 2.84 (1H, br s, HO), 2.77 (1H, ddd, J = 3, 5.5, 10 Hz, HC-2), 2.60 (1H, ddq, J = 5, 5.5, 7 Hz, HC-6), 1.92 (1H, m, HC-5), 1.83 (1H, m, HC-3), 1.74-1.65 (2H, m, HC-4, HC-4), 1.71 (1H, m, HC-5), 1.69 (1H, m, HC-3), 1.18 (3H, d, J = 7 Hz, H₃C);¹³ C NMR (125 MHz, CDCl₃) δ 218.0 (s, C-1), 141.8 (d, Ar), 128.4 (d ×2, Ar), 127.4 (d, Ar), 126.1 (d ×2, Ar), 71.6 (d, C-1''), 53.9 (d, C-2), 45.2 (d, C-6), 33.7 (t, C-5), 25.9 (t, C-3), 20.0 (t, C-4), 16.7 (q, CH₃).

(3S,5R)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (23aa). Bu₄NI (12 mg, 0.33 mmol), i-Pr₂EtN (0.86 mL, 64 mg, 0.50 mmol) and MOMCl (0.25 mL, 27 mg, 0.33 mmol) were sequentially added to a stirred solution of 22aa (16 mg, 0.33 mmol) in CH₂Cl₂ (2 mL) under argon. After 16 h, the reaction mixture was diluted with aqueous citric acid (0.1M) and extracted with CH₂Cl₂ (3×20 mL). The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by preparative TLC (50% ethyl acetate in hexane; multiple elution) to give recovered 22aa (7 mg, 43%) and 23aa (8 mg, 46%): IR (DRIFT) νmax 3520, 2917, 1701, 1427, 1100, 1034, 891, 735 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.72 (1H, d, J = 6.5 Hz, HCO₂), 4.59 (1H, d, J = 6.5 Hz, HCO₂), 4.18 (1H, ddd, J = 4.5, 6.5, 8 Hz, HC-1''), 4.07-3.90 (8H, m, H₂CO ×4), 4.00 (1H, dd, J = 5, 5 Hz, HC-1''), 3.38 (3H, s, H₂CO),
(3R,5R)-rel-3-[(R)-(6S)-1,4-Dioxo-8-thiaspiro[4.5]deca-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]deca-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (23as). Using the same procedure as described for 23aa but using 20 equiv of MOMCl and 30 equiv of i-Pr₂EtN, reaction of 22as (32 mg, 0.065 mmol) for 20 h gave 24as (16 mg, 42%), 23sa (12 mg, 35%), and 23as (5 mg 14 %): ¹H NMR (500 MHz, CDCl₃) δ 4.72 (1H, ddd, J = 2.5, 3, 8 Hz, HC-1”), 4.70 (1H, d, J = 5.5 Hz, HCO2), 4.58 (1H, d, J = 5.5 Hz, HCO2), 4.39 (1H, dd, J = 4, 6 Hz, HC-1”), 4.12-3.94 (8H, m, H₂C₂ O ×4), 3.35 (3H, s, H₃CO), 3.20 (1H, ddd, J = 1, 5, 13 Hz, HC-5), 3.15 (1H, d, J = 2.5 Hz, HOC-1”), 3.13 (1H, ddd, J = 5, 8, 8.5 Hz, HC-5), 3.03 (1H, m, HC-2), 2.97 (1H, ddd, J = 10, 14 Hz, HC-7”), 2.92 (1H, ddd, J = 5, 5.5, 6.0 Hz, HC-3), 2.92 (1H, dd, J = 8.5, 13 Hz, HC-6), 2.92-2.87 (1H, m, HC-2), 2.84 (1H, ddd, J = 2, 3, 14 Hz, HC-7”), 2.82-2.73 (4H, m, H₂C₂”)’, HC-9”, HC-10”), 2.61-2.52 (2H, m, HC-9”, HC-9”), 2.18 (1H, ddd, J = 4, 5.5, 9 Hz, HC-6), 2.18-2.11 (2H, m, HC-10”, HC-10”), 2.06 (1H, ddd, J = 3, 3, 10 Hz, HC-6”), 1.73 (1H, ddd, J = 3.5, 10.5, 13 Hz, HC-10”), 1.70 (1H, ddd, J = 3.5, 10.5, 13 Hz, HC-10”); ¹³C NMR (125 MHz, CDCl₃) δ 210.7 (s, C-4), 110.2 (s, C-5”), 108.7 (s, C-5”), 97.4 (t, OCH₃O), 74.0
(d, C-1'), 67.1 (d, C-1''), 64.9 (t, CH₂O), 64.8 (t, CH₂O), 64.7 (t, CH₂O), 64.4 (t, CH₂O), 58.5 (d, C-3), 56.2 (q, CH₃O), 53.8 (d, C-5), 50.0 (d, C-6'), 46.4 (d, C-6''), 36.2 (t, OCH₂O), 35.8 (t, OCH₂O), 35.7 (t, OCH₂O), 35.6 (t, OCH₂O), 35.5 (t, OCH₂O), 32.0 (t, C-2), 31.4 (t, C-6), 28.4 (t, C-7), 26.9 (t, C-9' or C-9''), 26.8 (t, C-9' or C-9''), 26.7 (t, C-7''); LRMS (EI), m/z (relative intensity): 536 ([M⁺], 1), 188 (8), 133 (15), 132 (50), 100 (10), 99 (100), 86 (18), 55 (11); HRMS m/z calcd for C₂₃H₃₆O₈S₃ 536.1572, found 536.1561 (EI).

![Chemical Structure](image)

(3S,5S)-rel-3-[(R)-(6S)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(S)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (23sa). See procedure for 23as. IR (DRIFT) νₓ max 3518, 2913, 1711, 1427, 1153, 1133, 1108, 1034 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.69 (1H, ddd, J = 2.5, 3, 3.5 Hz, HC-1'), 4.68 (1H, d, J = 6 Hz, HCO₂), 4.65 (1H, d, J = 6 Hz, HCO₂), 4.47 (1H, dd, J = 4.5, 5 Hz, HC-1''), 4.14-3.91 (8H, m, H₂CO ×4), 3.37 (3H, s, H₃CO), 3.21 (1H, ddd, J = 4.5, 5, 9.5 Hz, HC-5), 3.07 (1H, dd, J = 9.5, 13.5 Hz, HC-6), 3.04-2.92 (5H, m, HOC-1', HC-2, HC-3, HC-6, HC-7'), 2.88-2.69 (5H, m, HC-2, H₂C-7'', HC-9', HC-9''), 2.66 (1H, ddd, J = 2, 3, 13.5 Hz, HC-7'), 2.53 (1H, m, HC-9'), 2.50 (1H, m, HC-9''), 2.16 (1H, ddd, J = 3, 4, 13.5 Hz, HC-10'), 2.10 (1H, ddd, J = 3.5, 4.5, 11 Hz, HC-6''), 2.07 (1H, ddd, J = 3, 4, 13.5 Hz, HC-10''), 2.01 (1H, ddd, J = 2.5, 3, 11.5 Hz, HC-6'), 1.74 (1H, ddd, J = 3.5, 13, 13 Hz, HC-10'), 1.69 (1H, ddd, J = 3.5, 13, 13 Hz, HC-10''); ¹³C NMR (125 MHz, CDCl₃) δ 211.0 (s, C-4), 110.1 (s, C-5'), 109.0 (s, C-5''), 98.6 (t, OCH₂O), 72.8 (d, C-1''), 68.5 (d, C-1'), 65.1 (t, CH₂O), 64.64 (t, CH₂O), 64.61 (t, CH₂O), 64.60 (t, CH₂O), 57.3 (d, C-5), 56.8 (q, CH₃O), 54.7 (d, C-3), 49.1 (d, C-6''), 47.5 (d, C-6'), 36.7 (t, C-10''), 36.3 (t, C-10'), 32.7 (t, C-2), 31.4 (t, C-6), 28.3 (t, C-7''), 26.8 (t, C-9' or C-9''), 26.7 (t, C-9' or C-9''), 26.3 (t, C-7'); LRMS (EI), m/z (relative intensity): 536 ([M⁺], 1), 188 (8), 133 (11), 132 (44), 100 (10), 99 (100), 86 (20), 55 (13); HRMS m/z calcd for C₂₃H₃₆O₈S₃ 536.1572, found 536.1578 (EI).
(3R,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yloxymethyl]-5-[(S)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (23ss). Using the same procedure as described for 23as, reaction of 22ss (13 mg, 0.026 mmol) for 6 h gave recovered 22ss (3 mg, 23%) and a 2:1 mixture of 23ss and 24ss, respectively (12 mg, 80%). Further fractionation by preparative TLC (2% MeOH in CH₂Cl₂; multiple elution) gave 23ss (3 mg, 18%): $^1$H NMR (500 MHz, CDCl₃) δ 4.69 (1H, d, $J$ = 6 Hz, HCO₂), 4.66 (1H, d, $J$ = 6 Hz, HCO₂), 4.65-4.63 (1H, m, HC-1'), 4.56-4.54 (1H, m, HC-1''), 4.10-3.86 (8H, m, H₂CO ×₄), 3.36 (3H, s, H₃CO), 3.24-3.18 (2H, m), 3.05 (1H, d, $J$ = 2 Hz, HOC-1'), 3.05-2.70 (11H, m), 2.69-2.56 (2H, m), 2.14 (1H, ddd, $J$ = 4, 4, 10 Hz, HC-6'/HC-6''), 2.11-2.03 (3H, m, HC-6'/HC-6'', HC-10', HC-10''), 1.73 (1H, ddd, $J$ = 3.5, 10.5, 14 Hz, HC-10'/HC-10''). $^{13}$C NMR (125 MHz, CDCl₃) δ 211.1 (s, C-4), 110.0 (s), 109.2 (s), 100.0 (t), 73.0 (d), 67.1 (d), 64.8 (t), 64.6 (t), 64.5 (t), 64.4 (t), 60.2 (d), 57.4 (d), 56.9 (q), 49.7 (d), 46.4 (d), 35.6 (t), 35.4 (t), 33.0 (t), 32.8 (t), 29.2 (t), 27.5 (t), 27.1 (t), 26.8 (t).

(3S,5R)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yloxymethyl]-5-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (24aa). Following the procedure described for 23aa but at 2.5 times higher concentration, reaction of 22aa (24 mg, 0.049 mmol) for 20 h gave the titled compound (24 mg, 83%): IR (DRIFT) νmax 2913, 1716, 1427, 1152, 1098, 1033, 890, 734 cm⁻¹; $^1$H NMR (500 MHz, CDCl₃) δ 4.70 (2H, d, $J$ = 6.5 Hz, HCO₂ ×₂), 4.60 (2H, d, $J$ = 6.5 Hz, HCO₂ ×₂), 4.12 (2H, ddd, $J$ = 4.5, 5 Hz, HC-1', HC-1''), 4.05-3.91 (8H, m, H₂CO ×₄), 3.37 (6H, s, H₃CO ×₂), 3.12 (2H, ddd, $J$ = 4, 4.5, 12.5 Hz, HC-3, HC-5), 3.04 (2H, dd, $J$ = 12.5, 13 Hz, HC-2, HC-6), 3.00 (2H, br d, $J$ = 14 Hz, HC-7', HC-7''), 2.90 (2H, br d, $J$ = 13 Hz, HC-2, HC-6), 2.81 (2H, dd, $J$ =
9.5, 14 Hz, HC-7', HC-7''), 2.74 (2H, ddd, J = 3, 10.5, 13.5 Hz, HC-9', HC-9''), 2.30 (2H, ddd, J = 3.5, 5, 9.5 Hz, HC-6', HC-6''), 2.07 (2H, ddd, J = 3, 6, 13.5 Hz, HC-10', HC-10''), 1.64 (2H, ddd, J = 3.5, 10.5, 13.5 Hz, HC-10', HC-10''); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.2 (s, C-4), 109.1 (s × 2, C-5', C-5''), 98.3 (t × 2, OCH$_2$O), 75.1 (d × 2, C-1', C-1''), 64.9 (t × 2, CH$_3$O), 64.5 (t × 2, CH$_2$O), 59.7 (d × 2, C-3, C-5), 56.7 (q × 2, CH$_3$O), 48.4 (d × 2, C-6', C-6''), 35.7 (t × 2, C-2, C-6), 34.3 (t × 2, C-2, C-6), 29.1 (t × 2, C-7', C-7''), 26.9 (t × 2, C-9', C-9''); LRMS (EI), m/z (relative intensity): 580 ([M]+, 1), 518 (4), 456 (10), 133 (20), 132 (60), 100 (9), 99 (100), 86 (22); HRMS m/z calcd for C$_{25}$H$_{40}$O$_9$S$_3$ 580.1834, found 580.1839 (EI).

(3R,5R)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (24as). See procedure for 23as. IR (DRIFT) ν$_{max}$ 2914, 1708, 1428, 1261, 1153, 1097, 1032, 890 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 4.72 (1H, d, J = 5.5 Hz, HCOC-1''), 4.71 (1H, d, J = 6 Hz, HCOC-1'), 4.63 (1H, d, J = 5.5 Hz, HCOC-1''), 4.56 (1H, d, J = 6 Hz, HCOC-1'), 4.53 (1H, d, J = 4, 6 Hz, HC-1''), 4.16 (1H, dd, J = 3.5, 4 Hz, HC-1''), 4.08-3.92 (8H, , HC-2', HC-2'', HC-3', HC-3''), 3.37 (3H, s, H$_3$COCOC-1''), 3.36 (3H, s, H$_3$COCOC-1'), 3.00 (1H, ddd, J = 4.5, 5.5, 6 Hz, HC-5), 3.13-2.95 (5H, , H$_2$C-2', HC-3, HC-6,HC-7'), 2.91-2.69 (6H, , HC-6, HC-7', H$_2$C-7'', HC-9', HC-9''), 2.56-2.48 (2H, , HC-9', HC-9''), 2.28 (1H, ddd, J = 3.5, 4, 11 Hz, HC-6'), 2.15-2.09 (1H, , HC-10'), 2.11 (1H, ddd, J = 4, 4, 11 Hz, HC-6''), 1.69 (1H, ddd, J = 3.5, 12.5, 13.5 Hz, HC-10''), 1.65 (1H, ddd, J = 3.5, 12, 13 Hz, HC-10'); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 208.7 (s, C-4), 109.1 (s, C-5'), 108.8 (s, C-5''), 98.4 (t, CH$_2$OC-1''), 97.3 (t, CH$_2$OC-1''), 74.5 (d, C-1'), 72.3 (d, C-1''), 64.8 (t, CH$_2$O), 64.6 (t, CH$_2$O), 64.6 (t, CH$_2$O), 64.6 (t, CH$_2$O), 57.5 (d, C-3), 57.0 (d, C-5), 56.8 (q, CH$_3$OCOC-1''), 56.4 (q, CH$_3$OCOC-1''), 49.7 (d, C-6'), 49.0 (d, C-6''), 36.1 (t, C-10''), 36.0 (t, C-10'), 31.1 (t, C-6), 29.4 (t, C-2), 28.6 (t, C-7), 28.3 (t, C-7''), 26.84 (t, C-9' or C-9''), 26.76 (t, C-9'' or C-9''); LRMS (EI), m/z (relative intensity): 580 ([M]+, 1), 456 (10), 133 (25), 132 (65), 100 (8), 99 (100), 86 (14), 55 (8); HRMS m/z calcd for C$_{25}$H$_{40}$O$_9$S$_3$ 580.1834, found 580.1828 (EI).
(3R,5S)-rel-3-[(R)-(6S)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-
[(S)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-
thiopyran-4-one (24ss). Following the procedure described for 23aa, reaction of 22ss (15 mg, 0.031 mmol) for 4 days gave after fractionation by PTLC (2% MeOH in CH₂Cl₂), a 2.5:1 mixture
of 24ss and 23ss, respectively (12 mg) and 24ss (5 mg, 27%): IR (DRIFT) ν_max 2915, 1708, 1427, 1261, 1155, 1032, 892 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.66 (2H, d, J = 6 Hz, HCO₂ × 2), 4.63 (2H, d, J = 6 Hz, HCO₂ × 2), 4.55 (2H, dd, J = 3, 6.5 Hz, HC-1', HC-1''), 4.07-3.84 (8H, m, H₂CO × 4), 3.35 (6H, s, H₂CO × 2), 3.08 (2H, ddd, J = 3, 5.5, 9 Hz, HC-3, HC-5), 3.01-2.94 (4H, m, H₂C-2, H₂C-6), 2.91-2.82 (4H, m, H₂C-7', H₂C-7''), 2.77 (2H, ddd, J = 3, 11, 13.5 Hz, HC-9', HC-9''), 2.58 (2H, ddd, J = 3.5, 5.5, 13.5 Hz, HC-9', HC-9''), 2.11 (2H, ddd, J = 4.5, 6.5, 9 Hz, HC-6', HC-6''), 2.05 (2H, ddd, J = 3, 5.5, 13.5 Hz, HC-10', HC-10''), 1.67 (2H, ddd, J = 3.5, 11, 13.5 Hz, HC-10', HC-10''); ¹³C NMR (125 MHz, CDCl₃) δ 208.3 (s, C-4), 109.2 (s × 2, C-5', C-5''), 98.6 (t × 2, OCH₃O), 72.3 (d × 2, C-1', C-1''), 64.8 (t × 2, CH₂O), 64.5 (t × 2, CH₂O), 59.8 (d × 2, C-3, C-5), 56.8 (q × 2, CH₃O), 49.4 (d × 2, C-6', C-6''), 36.0 (t × 2, C-10', C-10''), 31.2 (t × 2, C-2, C-6), 29.1 (t × 2, C-7', C-7''), 26.8 (t × 2, C-9', C-9''); LRMS (EI), m/z (relative intensity): 580 ([M⁺], 1), 518 (9), 133 (30), 132 (69), 100 (9), 99 (100), 86 (13), 55 (12); HRMS m/z calcd for C₂₅H₄₀O₉S₃ 580.1834, found 580.1831 (EI).

Assignment of Relative Stereochemical Configurations

3a

3s

17a

17s
Mukaiyama used the Stiles-House rule to assign the relative configurations of 3a and 3s according to their $^3J_{HH_1\cdot HH_2}$ vicinal coupling constants of 9 Hz and 2 Hz, respectively. This assignment has been verified by X-ray crystallographic analysis of structures of 3a and 3b demonstrating that the Stiles-House rule can be applied to these substrates. Similarly, the relative configurations for the related aldols 17a and 17s were assigned according to their $^3J_{HH_1\cdot HH_3}$ vicinal coupling constants of 9 Hz and 2 Hz, respectively.

Mukaiyama et al. was the first to assign the relative configurations of the aldols 20. The assignment of the syn/anti aldol relative configuration was based on the Stiles-House rule; i.e. the magnitude of the $^3J_{HH_a\cdot HH_b}$ coupling constant (Table S1). However, the approach used to assign the 2,6-cis/trans relative configuration of aldols 20 was not reported. Subsequent reports on aldols 20 all refer to Mukaiyama’s earlier assignment without mention of the method used to assign the 2,6-cis/trans relative configuration. Only the report by Duhamel et al. provides both $^1H$ and $^{13}C$ NMR data for aldols 20. Our NMR data for the four aldols 20 correspond

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closely to that reported in the literature (Table S1): $\delta_H$ within $\pm0.2$; $J_{Ha-Hb}$ within $\pm0.1$ Hz; $\delta_C$ within $+0.4 \pm0.3$ ppm).\(^{18}\)

Mukaiyama’s assignments of the syn/anti relative configurations in the four aldols 20, which were based on the Stiles-House rule, are further supported by $^{13}$C NMR. The chemical shifts for the CHOH carbons in the anti aldols 20at and 20ac (75.0 and 74.9 ppm, respectively) are more downfield the in the syn aldols 20st and 20sc (71.6 and 71.0 ppm, respectively), as expected.\(^{19}\) However, upon closer examination of the accumulated data it became evident that the literature assignment of the relative configurations of 20sc and 20st should be reversed (Table S1).

**Table S1.** Comparison of literature and corrected relative configurations for aldols 20.

| $\delta_C$ CHOH | $\delta_H$ CHOH | $J_{Ha-Hb}$ | Literature$^{13, 16, 17}$ | Corrected |
|----------------|----------------|-------------|---------------------------|-----------|
| 75.0           | 4.86           | 9.5         | 20at                      | 20at      |
| 74.9           | 4.80           | 8.5         | 20ac                      | 20ac      |
| 71.6           | 5.32           | 3.0         | 20sc                      | 20st      |
| 71.0           | 5.38           | 2.5         | 20st                      | 20sc      |

A thorough analysis of the $^1$H-$^1$H coupling constants of aldols 210 has not been reported in the literature (Table S2). For aldol 20ac, the vicinal coupling constants between $H_a$ and the adjacent $H_2C$ group (5.5 and 13 Hz) and between $H_c$ and the adjacent $H_2C$ group (6 and 13 Hz) suggest a 2,6-cis relative configuration where both $H_a$ and $H_c$ are in the axial orientation. Similarly, the vicinal coupling constants for aldol 20sc between $H_a$ and the adjacent $H_2C$ group (6.5 and 12.5 Hz) and between $H_c$ and the adjacent $H_2C$ group (5.5 and 12.5 Hz) also suggest a 2,6-cis relative configuration. By contrast, the vicinal coupling constants for aldol 20at between $H_a$ and the adjacent $H_2C$ group (5.5 and 9.5 Hz) and between $H_c$ and the adjacent $H_2C$ group (5 and 5.5 Hz) suggest a 2,6-trans relative configuration where the chair conformation with the methyl substituent in the axial orientation is predominant. For aldol 20st, the vicinal coupling constants between $H_a$ and the adjacent $H_2C$ group (5.5 and 10 Hz) and between $H_c$ and the adjacent $H_2C$ group (5 and 5.5 Hz) suggest a 2,6-trans relative configuration where the chair conformation with the methyl substituent in the axial orientation is predominant.

\(^{18}\) The consistent +0.4 ppm difference in carbon shift is most likely due to a different reference calibration.

\(^{19}\) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* 1979, 44, 4294-4299.
group (5 and 5.5 Hz) also suggest a 2,6-trans relative configuration where the chair conformation with the methyl substituent in the axial orientation is predominant.

**Table S2.** $^1$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) data for 19 and 20 in CDCl$_3$.

|          | 20at | 20ac | 20st | 20sc |
|----------|------|------|------|------|
| $^3$J$_{Ha-Hb}$ | 9.5  | 8.5  | 3    | 2.5  |
| $^3$J$_{Ha-CH2}$ | 9.5  | 13   | 10   | 12.5 |
| $^3$J$_{Ha-CH2}$ | 5.5  | 5.5  | 5.5  | 6.5  |
| $^3$J$_{Hc-CH2}$ | 5.5  | 13   | 5.5  | 12.5 |
| $^3$J$_{Hc-CH2}$ | 5    | 6    | 5    | 5.5  |
| $\delta$$_{H}$ H$_a$ | 4.86 | 4.80 | 5.32 | 5.38 |
| $\delta$$_{H}$ CH$_3$ | 1.21 | 1.07 | 1.18 | 1.06 |
| $\delta$$_{C}$ CHO$OH$ | 75.0 | 74.9 | 71.6 | 71.0 |
| $\delta$$_{C}$ CH$_3$ | 16.5 | 14.4 | 16.7 | 14.5 |

|          | 19at | 19ac | 19st | 19sc |
|----------|------|------|------|------|
| $^3$J$_{Ha-Hb}$ | 9.5  | 8.5  | 4    | 3    |
| $^3$J$_{Ha-CH2}$ | 6.5  | 12.5 | 9.5  | 12   |
| $^3$J$_{Ha-CH2}$ | 4    | 4.5  | 4    | 3.5  |
| $^3$J$_{Hc-CH2}$ | 9    | 13   | 7    | 12   |
| $^3$J$_{Hc-CH2}$ | 4.5  | 4.5  | 4.5  | 5    |
| $\delta$$_{H}$ H$_a$ | 5.30 | 4.86 | 5.43 | 5.38 |
| $\delta$$_{H}$ CH$_3$ | 1.27 | 1.15 | 1.26 | 1.14 |
| $\delta$$_{C}$ CHO$OH$ | 74.3 | 74.1 | 71.9 | 71.2 |
| $\delta$$_{C}$ CH$_3$ | 15.5 | 14.7 | 16.0 | 14.7 |

Further support for the assignment of the 2,6-*cis/trans* relative configurations in 20 can be found from a comparison of the $^1$H and $^{13}$C NMR shifts of the methyl substituent. The analysis of the vicinal H-H coupling constants above suggests that aldols 20ac and 20sc have methyl groups with an equatorial orientations but the major conformations for aldols 20at and 20st have methyl groups with an axial orientation. The similar $^1$H and $^{13}$C NMR shifts for the methyl groups in
**20ac** and **20sc** and for those in **20at** and **20st** (Table S2) confirms the expected similar environments.

Thus, the syn/anti aldol relative configurations for the four aldols **20** can be assigned by the Stiles-House rule and corroborated by the $^{13}$C chemical shifts for the carbinol carbon; the 2,6-cis/trans relative configuration of all four aldols **20** can be assigned from $^1$H-$^1$H coupling constant analysis and corroborated by the proton and carbon chemical shifts for the methyl groups. Finally, our assignment is fully consistent with the isomerization relationships and rate constants illustrated in Scheme 3. The assignment of the relative configurations for the aldols **19** was based on an analysis similar to that described above for **20** (Table S2).

![DIBAL-H](image)

The bisaldol **22ss** is symmetric as shown by the presence of only 11 resonances in the $^{13}$C NMR spectrum. Bisaldol **22ss** was a very minor product (ca 1% yield; but never isolated in pure form) obtained from the aldol reaction of **7s** with **10**. Reduction of **22ss** with DIBAL-H as previously described gave the symmetric triol (71%) shown above whose structure determination has been previously described.

![Bisaldol 21as](image)

Bisaldol **21as** is asymmetric on the basis of 21 signals in the $^{13}$C NMR spectrum. A 3,5-syn relative configuration for **21as** was assigned on the basis of the coupling constants between HC-3 and H$_2$C-2 (3.5, 11.5 Hz) and between HC-5 and H$_2$C-6 (3.5, 12 Hz) indicative of cis equatorial substituents on a six-membered ring in a chair conformation. Structure **21as** is firmly established as keto-enol tautomerism of **21aa** (structure determination previously described) can produce only one asymmetric diastereomer.
Determination of Isomerization Rate Constants

Two-Component Equilibrations

The 1st order reversible isomerization of two aldols (A and B) via their common unstable enol (C) is shown in Scheme S1. The kinetic model assumes that each reaction is 1st order with respect to the particular ‘reactant’ at a fixed concentration of imidazole. The forward and reverse reactions each comprise two steps, enolization ($k_e$ and $k'_e$; slow) and ketonization ($k_k$ and $k'_k$; fast). The overall rate constants for the forward and reverse reactions are given by the product of the rate constant for enolization and the partition for ketonization; for example, in the isomerization of A to B via C, $k_1 = (k_ek'_k)/(k_k+k'_k)$. The ‘composite’ rate constants $k_1$ and $k_1^{-1}$ can be easily obtained by simply monitoring the rate of appearance or disappearance of the aldol substrates A and/or B. By contrast, determination of the four individual rate constants requires a more sophisticated approach that must involve direct or indirect detection of the enol intermediate C.

Scheme S1

For a kinetically first order reversible reaction:

\[
A \xleftrightarrow{k_1} B
\]

It can be easily shown that for a system not at equilibrium (i.e., $[A] \neq [A]_e$):\(^\text{20}\)

\[
(k_1 + k_1^{-1})t = -\ln \left( \frac{[A]_0 - [A]_t}{[A]_0 - [A]_e} \right) = -\ln \left( \frac{R_t - R_e}{R_t + 1} \right)
\]

where $[A]_0$ is the initial concentration of A, $[A]_e$ is the concentration of A at equilibrium, $[A]_t$ is the concentration of A at time $t$, $R_t$ is the ratio of [A]/[B] at time $t$ and $R_e$ is the equilibrium ratio

\(^{20}\) Zuman, P.; Patel, R. C. *Techniques in Organic Reaction Kinetics*; John Wiley and Sons: New York, 1984, 68-120.
of [A]/[B]. In this form, the equation resembles that for an irreversible first order reaction of A with a rate constant \( k_{\text{obs}} (= k_1 + k_{-1}) \) but with the analytical concentration of A (i.e. [A]_t) replaced by the ‘active’ concentration of A (i.e. [A]_t-[A]_e) which is that fraction of A undergoing transformation. Thus, \( k_{\text{obs}} (= k_1 + k_{-1}) \) is the first order rate constant for equilibration of a non-equilibrium system.

Starting from ‘pure’ (or nearly pure) A or B, the ratio of [A]/[B] was determined by \(^1\text{H} \) NMR as a function of time. The rate constant for equilibration (\( k_{\text{obs}} \)) is given by the slope of line obtained from a plot of \(-\ln[(R_t-R_e)/(R_t+1)]\) versus \( t \) using at least eight data points obtained within the first two half-lives (\( R^2 > 0.99 \)). The equilibrium ratio of [A]/[B] was determined after at least 10 half-lives. Prolonged isomerizations (>15 days) in CDCl_3 or acetone-\( d_6 \) began to show non-negligible amounts of deuterated products that interfered with the determination of the equilibrium ratios. In these cases, equilibrium ratios were determined by \(^1\text{H} \) NMR after workup of similar reactions conducted in non-deuterated solvent. Because \( k_{\text{obs}} = k_1 + k_{-1} \) and \( K_{\text{eq}} = k_1/k_{-1} \) the constants \( k_1 \) and \( k_{-1} \) are readily derived.

To illustrate the procedure, isomerization of 7a to 7s is described in detail. A 0.3 M solution of imidazole in CDCl_3 was prepared by weighing imidazole (21 mg, 0.031 mmol) into a 1 mL volumetric flask and diluting to 1.00 mL with CDCl_3 (previously filtered through a column of basic Al_2O_3). A solution of 7a (6 mg, 0.02 mmol) in the above solution (0.65 mL) was transferred into a well-stoppered 5 mm NMR tube. The ratio of 7a to 7s was measured periodically by \(^1\text{H} \) NMR (Table S3) by integrating the signals at \( \delta 4.50 \) (7a) and \( \delta 4.79 \) (7s). After one week the ratio of 7a to 7s was 0.67 and this ratio was unchanged after 15 days.

A plot of \(-\ln[(R_t-R_e)/(R_t+1)]\) versus time using the data in entries 1-13 of Table S3 is shown in Figure S1. Regression analysis of this data yields a slope of 0.0214 with a standard deviation of 0.0003 (1.5%) or 0.0214±0.0007 (95% confidence limit). However, \( k_{\text{obs}} \) is a pseudo 1\(^{st}\) order rate constant that includes the concentration of imidazole and the order of reaction in imidazole. Thus, assuming no more than a 5% relative error in the concentration of imidazole (in this case 0.30±0.015 M) and an order of 1.3, gives a cumulative relative error in \( k_{\text{obs}} \) of ca. 7%. Similar analysis of other isomerizations gave similar results and we conclude that a relative error of <10% is a reasonable estimate of the accuracy of the \( k_{\text{obs}} \) listed in Tables 1, 2, and 3 (entries 8-12). The rate constants determined from only 2-3 intermediate data points (Table 1, entry 7; Table 3, entries 1-6) are less accurate though the relative error is probably <20%.
Table S3. Isomerization of 7a to 7s with 0.3 M imidazole in CDCl₃

| Entry | Ratio of 7a to 7s | Time (h) | -ln[(Rₜ₋Rₑ)/(Rₜ₊1)] |
|-------|------------------|----------|---------------------|
| 1     | 50               | 0.00     | 0.033               |
| 2     | 22               | 2.4      | 0.075               |
| 3     | 17               | 3.4      | 0.097               |
| 4     | 12               | 5.4      | 0.14                |
| 5     | 8.5              | 7.4      | 0.19                |
| 6     | 6.8              | 9.4      | 0.24                |
| 7     | 5.8              | 11.4     | 0.28                |
| 8     | 4.9              | 13.4     | 0.34                |
| 9     | 4.1              | 15.5     | 0.39                |
| 10    | 3.6              | 17.5     | 0.45                |
| 11    | 1.6              | 44       | 1.03                |
| 12    | 1.5              | 48       | 1.10                |
| 13    | 1.3              | 60       | 1.29                |
| 14    | 0.67             | 162      |                     |
| 15    | 0.66             | 351      |                     |

Figure S1. Plot of $-\ln[(R_t-R_e)/(R_t+1)]$ versus time for the isomerization of 7a to 7s with 0.3 M imidazole in CDCl₃.
Four-Component Equilibrations

The rate constants in these systems cannot be obtained directly from concentration vs. time profiles. One method to obtain these rate constants involves comparing the observed concentration vs. time profiles to simulated profiles from a kinetic model and adjusting the rate constants to find the best ‘fit’. The kinetic model used (Scheme 3 or 5) assumes each isomerization reaction is 1st order with respect to the particular ‘starting’ aldol concentration at a fixed concentration of imidazole. As in the two-component equilibrations, the forward and reverse reactions each comprise two steps, enolization (slow) and ketonization (fast). Because the enols are unstable and don’t accumulate (i.e. ketonization is much faster than enolization) their presence can be ignored by using the corresponding ‘composite’ rate constants $k_n$, $k_{-n}$ (n=1-4). These pseudo 1st order rate constants are given by the product of the rate constant for enolization and the partition for ketonization. For example, in the isomerization of 19at to 19ac via 19e (Scheme 3), $k_1 = (k_ek_c)/(k_ek_c+k_c-k_e)$. To fit the experimental data to the kinetic model we used the software program developed by F. J. Wiegert and R. J. McKinney.21 This program uses the Gear integration algorithm22 to adjust the rate constants for the best ‘fit’. Input data include experimental concentration versus time profiles, initial guesses of the rate constants, and equilibrium ratios. The ratios $k_n/k_{-n}$ (n=1-4) are fixed by the corresponding equilibrium ratios for the component pair of aldols. Reasonable initial guesses for the rate constants are required to obtain a reliable fit; we estimated the rate constants from the initial (10-20%) rate of isomerization starting with highly enriched individual components. Thus, individual isomerization experiments were conducted with each of the possible diastereomers of 20 (4), 22 (3), 23 (4), and 24 (3), and 3 of the 4 diastereomers of 19. The initial rate data and the final equilibrium ratios allowed all eight rate constants to be estimated. It must be noted that the experimental concentration versus time profiles from all isomerization experiments were simultaneously analyzed by the program to find the ‘best’ set of

21 Program number QCMP022 from the Quantum Chemistry Program Exchange: QCPE, Department of Chemistry, Indiana University, 800 East Kirkwood Ave, Bloomington, IN 47405-7102 (http://qcpe.chem.indiana.edu ).

22 (a) Gear, C. W. Numerical Value Problems in Ordinary Differential Equations; Prentice-Hall: Englewood Cliffs, New Jersey, 1971. (b) Stabler, R. N.; Chesick, J. P. Int. J. Chem. Kinet. 1978, 10, 461-469.
rate constants for isomerization (Table S4). Plots of the experimental and calculated concentration vs. time profiles are given in Figures S2-S6. In general, there is excellent agreement between experimental and calculated isomerization. Very prolonged experiments (e.g. 24) result in non-negligible deuterium incorporation that introduces error in the determination of the component ratios and associated rate constants.

**Table S4.** Rate constants (10^{-3} h^{-1}) for isomerization of 19, 20, and 22-24 in CDCl3 with 0.4 M imidazole at room temperature.

| Aldol | k_1  | k_1  | k_2  | k_2  | k_3  | k_3  | k_4  | k_4  | k_n+k_n\text{(ave.)} |
|-------|------|------|------|------|------|------|------|------|------------------|
| 19    | 1.7  | 2.8  | 1.1  | 0.80 | 0.15 | 0.43 | 2.8  | 0.86 | 2.7              |
| 20    | 0.14 | 1.2  | 0.15 | 0.040| 0.023| 0.25 | 0.56 | 0.022| 0.60             |
| 22    | 2.0  | 1.2  | 0.42 | 0.60 | 0.60 | 0.42 | 1.2  | 2.0  | 2.1              |
| 23    | 0.23 | 0.13 | 0.10 | 0.060| 0.078| 0.13 | 0.26 | 0.48 | 0.37             |
| 24    | 0.051| 0.015| 0.026| 0.013| 0.013| 0.026| 0.015| 0.051| 0.052            |

*Rate constants for 19 and 20 refer to the kinetic model in Scheme 3; rate constants for 22-24 refer to the kinetic model in Scheme 5.*

The sums $k_n+k_n$ (n=1-4) can be used to compare the ease of the isomerization between two components within a four-component equilibration or to compare with the rate of isomerization in a two-component equilibration (i.e., $k_{\text{obs}}$). In contrast to a two-component system, the rate that equilibrium is achieved in a four-component system depends on the initial distribution of the components. The average of $k_n+k_n$ (n=1-4) can be used as an overall indication of the facility of equilibration in a four-component system and can be compared to the rate of isomerization in a two-component equilibration (i.e., $k_{\text{obs}}$). For example, comparing the $k_{\text{obs}}$ measured for 17a (Table 3, entry 5) with the average of $k_n+k_n$ for 19 (Table 5, entry 1) suggests that these aldols isomerize with similar facility. The same conclusion applies to 3a and 20 indicating that the methyl group in 19 and 20 does not affect the process significantly. Similarly, isomerizations of 7 (Table 1, entry 8) and 22 (Table 5, entry 3) occur at comparable rates.

The data in Table S4 suggests that enolizations of 19, 20, or 23 occur with low regioselectivity. If the rate for reversible isomerization of two aldols via their common unstable enol is characterized by $k_n+k_n$, then the fastest isomerizations for 19 and 20 ($k_1+k_1$) proceed via an enol
proximal to the methyl group whereas the fastest isomerization for 23 \((k_3+k_4)\) proceeds via an enol proximal to the hydroxy group. In each case the magnitude of the preference is modest (< 2.5:1). Moreover, the ratios of the average rate of isomerization via an enol proximate to the hydroxyl group \([\frac{(k_2+k_2 + k_3+k_4)}{2}]\) to the average rate of isomerization via an enol distal to the hydroxyl group \([\frac{(k_1+k_1 + k_3+k_3)}{2}]\) for 19, 20, and 23 vary by less than a factor of 2.1. Comparison of the isomerization rate constants for the individual components of 22 and 23 also indicates a modest regioselectivity of enolization. The ratios of analogous rate constants between 22 and 23 show much less variation (3.2-10:1) compared to those of 19 and 20. Because the equilibrium ratios of 22as:22aa:22sa (30:18:30, respectively) are very similar to those of 23as:23aa:23sa (24:13:23, respectively), comparison of the rates of isomerization of among these sets of isomers is meaningful. Comparing the ratios for \(k_1, k_1, k_4,\) and \(k_4\) between 22 and 23 reveals that \(k_1\) and \(k_4\) are ca. about eight times larger but \(k_4\) and \(k_4\) are ca. four times larger. This implies that the presence of the MOM group in 23 has a greater negative effect on the isomerization via the enol proximate to the MOM group (i.e. 23aa – 23sa) compared to the isomerization via the enol proximate to the hydroxy group (i.e. 23as – 23aa). Thus, reversible isomerization between 23aa and 23as via the enol proximal to the hydroxy group \((k_4+k_4=0.74\times10^{-2}\text{h}^{-1})\) is twice as fast as the isomerization between 23aa and 23sa via the enol proximal to the MOM group \((k_1+k_1=0.36\times10^{-2}\text{h}^{-1})\). By contrast, isomerization of 23ss to 23sa via the enol proximal to the hydroxy group \((k_4+k_4=0.16\times10^{-2}\text{h}^{-1})\) is ca. 25% slower than the isomerization of 23ss to 23as via the enol proximal to the MOM group \((k_1+k_1=0.21\times10^{-2}\text{h}^{-1})\). The structural origins for these rather small rate differences are not obvious but relative stereochemical configuration is clearly a factor.

\(^{23}\) The equilibrium ratios for these two isomerizations are nearly identical.
Figure S2. Concentration versus time profiles for isomerization of 19 in CDCl₃ with 0.4 M imidazole: a) starting with 19ac; b) starting with 19at; c) starting with 19st. Points are experimental data and lines are calculated using the kinetic model in Scheme 3 with the rate constants in Table S4.
Figure S3. Concentration versus time profiles for isomerization of 20 in CDCl₃ with 0.4 M imidazole: a) starting with 20at; b) starting with 20st; c) starting with 20sc; d) starting with 20ac. Points are experimental data and lines are calculated using the kinetic model in Scheme 3 with the rate constants in Table S4.
Figure S4. Concentration versus time profiles for isomerization of 22 in CDCl₃ with 0.4 M imidazole: a) starting with 22aa; b) starting with 22ss; c) starting with (±)-22as. Points are experimental data and lines are calculated using the kinetic model in Scheme 5 with the rate constants in Table S4.
Figure S5. Concentration versus time profiles for isomerization of 23 in CDCl₃ with 0.4 M imidazole: a) starting with 23ss; b) starting with 23sa; c) starting with 23as; d) starting with 23aa. Points are experimental data and lines are calculated using the kinetic model in Scheme 5 with the rate constants in Table S4.
Figure S6. Concentration versus time profiles for isomerization of 24 in CDCl₃ with 0.4 M imidazole: a) starting with 24aa; b) starting with (±)-24as; c) starting with 24ss. Points are experimental data and lines are calculated using the kinetic model in Scheme 5 with the rate constants in Table S4.
