SUPPORTING INFORMATION

Syn-Anti Isomerization of Aldols by Enolization

Dale E. Ward,* Marcelo Sales, and Pradip K. Sasmal

*Department of Chemistry, University of Saskatchewan, 110 Science Place,
Saskatoon, SK S7N 5C9, Canada.*

E-mail: Dale.Ward@usask.ca

Table of Contents

Experimental procedures.....			S2
12a	S4	12s	S4
19ac	S6	19st	S7
20at	S8	20ac	S9
20st	S10	23aa	S10
23sa	S12	23ss	S13
24as	S14	24ss	S15
Assignment of Relative Stereochemical Configurations			S15
Determination of Isomerization Rate Constants.....			S20
¹ H NMR Spectra			S31-S50
11a	S31	12a	S32
19ac	S34	19at	S35
19st	S37	20ac	S38
20sc	S40	20st	S41
22ss	S43	23aa	S44
23sa	S46	23ss	S47
24as	S49	24ss	S50
		12s	S33
		19sc	S36
		20at	S39
		21as	S42
		23as	S45
		24aa	S48

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.

² Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

³ Harwood, L. M. *Aldrichimica Acta* **1985**, *18*, 25.

500 MHz for ^1H and 75, 100, or 125 MHz for ^{13}C . Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^1H NMR) served as the internal standard: CDCl_3 (7.26 δ_{H} , 77.23 δ_{C}); CD_3OD (3.31 δ_{H} , 49.15 δ_{C}); C_6D_6 (7.16 δ_{H} , 128.39 δ_{C}). The ^1H 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 ^1H 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 multiplicity⁴ (as determined by J -modulation⁵ or HSQC⁶) and were confirmed, where necessary, by two dimensional $^1\text{H}/^{13}\text{C}$ correlation experiments (HSQC and/or HMBC⁷).

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-2*H*-thiopyran;⁸ **18s**;⁹ **21aa**, **21ss**, **22aa**, and **22as**¹⁰; tetrahydro-3-methyl-4*H*-thiopyran-4-one.¹¹ All other reagents were commercially available and unless otherwise noted, were used as received.

⁴ The multiplicity of ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t = CH₂, q = CH₃)

⁵ Brown, D. W.; Nakashima, T. T.; Rabenstein, D. L. *J. Mag. Reson.* **1981**, *45*, 302.

⁶ Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Magn. Reson. Chem.* **1993**, *31*, 287-292.

⁷ Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093-2094.

⁸ Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618-1629.

⁹ Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027-3037.

¹⁰ Ward, D. E.; Guo, C.; Sasmal, P. K.; Man, C. C.; Sales, M. *Org. Lett.* **2000**, *2*, 1325-1328.

¹¹ (a) Spears, G. W.; Caufield, C. E.; Still, W. C. *J. Org. Chem.* **1987**, *52*, 1226-1231. (b) Unruh, G. R.; Birney, D. M. *J. Am. Chem. Soc.* **2003**, *125*, 8529-8533

(3S)-rel-3-[(R)-(6R)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4H-thiopyran-4-one (12a). Bu₄NI (11 mg, 0.03 mmol), *i*-Pr₂EtN (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 CH₂Cl₂ (3 mL). After 3 days, dilute HCl as added and mixture was extracted with CH₂Cl₂ (×3). The combined organic layers were dried over Na₂SO₄, concentrated, and fractionated by MPC (35% ethyl acetate in hexane) to give the titled compound as a white solid (343 mg, 96%): **IR** (DRIFT) $\nu_{\max}$ 2909, 1708, 1428, 1264, 1153, 1032, 916, 730 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 4.78 (1H, d, *J* = 7 Hz, HCO₂), 4.58 (1H, d, *J* = 7 Hz, HCO₂), 4.57 (1H, dd, *J* = 2, 8 Hz, HC-1'), 4.12-4.02 (3H, m, H₂CO), 3.91 (1H, m, H₂CO), 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, H₂C-6), 2.89-2.76 (3H, m, H₂C-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'); **¹³C NMR** (125 MHz, CDCl₃) δ 209.4 (s, C-4), 108.3 (s, C-5'), 96.7 (t, OCH₂O), 76.4 (d, C-1'), 64.6 (t, CH₂O), 64.3 (t, CH₂O), 56.5 (q, CH₃O), 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 C₁₅H₂₄O₅S₂ 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 (1.150g, 95%): **IR** (DRIFT) ν_{max} 2957, 1707, 1164, 1149, 1097, 1055, 1034, 894 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ 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_2CO), 3.90-3.82 (2H, m, H_2CO), 3.77 (1H, m, H_2CO), 3.36 (3H, s, H_3CO), 3.30 (1H, ddd, $J = 3, 5.5, 10.5$ Hz, HC-3), 3.02-2.87 (5H, m, H_2C -2, H_2C -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) δ 208.9 (s, C-4), 108.9 (s, C-5'), 97.5 (t, OCH_2O), 71.8 (d, C-1'), 64.5 (t, CH_2O), 64.2 (t, CH_2O), 56.2 (q, CH_3O), 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 ($[\text{M}]^+$, 2), 286 (18), 224 (10), 159 (13), 133 (24), 132 (65), 99 (100), 55 (14); **HRMS** m/z calcd for $\text{C}_{15}\text{H}_{24}\text{O}_5\text{S}_2$ 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*-Pr₂NH (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_4Cl (10 mL, 0.1 M) with vigorous stirring. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 $\times$). The combined organic layers were dried over Na_2SO_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 ^1H 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): **IR** (DRIFT) ν_{max} 3445, 2912, 1706, 1454, 1039, 1024, 768, 701 cm⁻¹; **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); **¹³C NMR** (125 MHz, CDCl₃) δ 213.0 (s, C-4), 141.2 (s, Ar), 129.0 (d $\times$ 2, Ar), 128.7 (d, Ar), 127.0 (d $\times$ 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); **LRMS** (EI), m/z (relative intensity): 236 ([M]⁺, 1), 130 (100), 129 (26), 107 (36), 97 (39), 87 (33), 79 (27), 77 (30); **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).

IR (DRIFT) ν_{max} 3524, 2974, 2904, 1695, 1453, 1290, 1050, 701 cm⁻¹; **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); **¹³C NMR** (125 MHz, CDCl₃) δ 214.2 (s, C-4), 140.5 (s, Ar), 128.9 (d $\times$ 2, Ar), 128.5 (d, Ar), 127.2 (d $\times$ 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); **LRMS** (EI), m/z (relative intensity): 236 ([M]⁺, 4), 189 (23), 130 (100), 107 (45), 97 (46), 88 (37), 79 (30), 77 (28); **HRMS** m/z calcd for C₁₃H₁₆O₂S 236.0871, found 236.0874 (EI).

(3*R*,5*R*)-rel-Tetrahydro-3-[(*R*)-hydroxyphenylmethyl]-5-methyl-4*H*-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) ν_{max} 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 $\times$ 2, Ar), 128.0 (d, Ar), 126.2 (d $\times$ 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).

(3*R*,5*S*)-rel-Tetrahydro-3-[(*R*)-hydroxyphenylmethyl]-5-methyl-4*H*-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 $\times$ 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) ν_{max} 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, H_3C); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1 (s, C-4), 141.0 (s, Ar), 128.6 (d $\times 2$, Ar), 127.6 (d, Ar), 125.9 (d $\times 2$, 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 calcd for $C_{13}H_{16}O_2S$ 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 1H 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 1H NMR), **20ac** (173 mg, 16%; 98% diastereomeric purity by 1H NMR), **20at** (336 mg, 31%; 95% diastereomeric purity by 1H 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_2Cl_2) to give a sample of >98% diastereomeric purity by 1H NMR. Spectral data was similar to that previously reported.¹² 1H 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_3C); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.2 (s, C-1), 141.5 (s, Ar), 128. (d $\times 2$, Ar), 128.32 (d, Ar), 127.2 (d $\times 2$, 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

(2*S*,6*S*)-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 CH₂Cl₂) to give a sample of >98% diastereomeric purity by ¹H NMR. Spectral data was similar to that previously reported.¹² **¹H NMR** (500 MHz, CDCl₃) δ 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, dddq, *J* = 1, 6, 13, 6.5 Hz, HC-6), 2.12 (1H, ddddd, *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, H₃C); **¹³C NMR** (125 MHz, CDCl₃) δ 217.0 (s, C-1), 141.3 (s, Ar), 128.6 (d ×2, Ar), 128.0 (d, Ar), 127.2 (d ×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, CH₃).

(2*R*,6*R*)-rel-2-[(*R*)-Hydroxyphenylmethyl]-6-methylcyclohexanone (20sc). A sample of enriched **20sc** (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 7.37-7.23 (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, dddq, *J* = 1.5, 5.5, 12.5, 6.5 Hz, HC-6), 2.12 (1H, ddddd, *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, ddddd, *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, H₃C); **¹³C NMR** (125 MHz, CDCl₃) δ 216.8 (s, C-1), 141.8 (s, Ar), 128.4 (d ×2, Ar), 127.1 (d, Ar), 126.0 (d ×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, CH₃).

(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); ¹³C 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-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 (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) ν_{max} 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, H₃CO),

3.23 (1H, ddd, $J = 4.5, 4.5, 12$ Hz, HC-5), 3.22 (1H, ddd, $J = 4.5, 5, 12$ Hz, HC-3), 3.17-2.91 (6H, m, H₂C-2, HC-6, HC-7', H₂C-7''), 2.87 (1H, ddd, $J = 3.5, 3.5, 13$ Hz, HC-6), 2.79 (1H, dd, $J = 10, 14$ Hz, HC-7'), 2.78-2.65 (3H, m, HC-9', H₂C-9''), 2.59 (1H, br d, $J = 13.5$ Hz, HC-9'), 2.30 (1H, ddd, $J = 3.5, 5, 10$ Hz, HC-6'), 2.17 (1H, ddd, $J = 3.5, 6.5, 7.5$ Hz, HC-6''), 2.07 (1H, ddd, $J = 3, 5.5, 13.5$ Hz, HC-10'), 1.93 (1H, ddd, $J = 4, 7, 13$ Hz, HC-10''), 1.73 (1H, ddd, $J = 4.5, 8, 13$ Hz, HC-10''), 1.65 (1H, ddd, $J = 3.5, 11, 13.5$ Hz, HC-10''); ¹³C NMR (125 MHz, CDCl₃) δ 213.3 (s, C-4), 109.1 (s, C-5''), 109.0 (s, C-5'), 98.2 (t, OCH₂O), 74.9 (d, C-1'), 70.3 (d, C-1''), 65.0 (t, CH₂O), 64.9 (t, CH₂O), 64.6 (t, CH₂O), 64.4 (t, CH₂O), 60.2 (d, C-3), 57.5 (d, C-5), 56.8 (q, CH₃O), 48.9 (d, C-6'), 47.8 (d, C-6''), 36.1 (t, C-6), 35.9 (t, C-10'), 35.7 (t, C-2), 35.6 (t, C-10''), 29.0 (t, C-7'), 28.7 (t, C-7''), 26.9 (t, C-9' or C-9''), 26.8 (t, C-9'' or C-9'); LRMS (EI), m/z (relative intensity): 536 ([M]⁺, 1), 188 (6), 133 (12), 132 (41), 100 (11), 99 (100), 86 (12), 55 (8); HRMS m/z calcd for C₂₃H₃₆O₈S₃ 536.1572, found 536.1571 (EI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-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, H₂CO ×4), 3.35 (3H, s, H₃CO), 3.20 (1H, ddd, $J = 1, 5, 13$ Hz, HC-6), 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, dd, $J = 10, 14$ 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, H₂C-7', HC-9', HC-9''), 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, OCH₂O), 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, C-10'), 35.8 (t, C-10''), 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).

(3*S*,5*S*)-rel-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-thiopyran-4-one (23sa). See procedure for **23as**. **IR** (DRIFT) ν_{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).

(3*R*,5*S*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*R*)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-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%): ¹H 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''), 1.68 (1H, ddd, *J* = 3.5, 9.5, 13 Hz, HC-10'/HC-10''); ¹³C 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).

(3*S*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*R*)-1,4-dioxo-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-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) ν_{max} 2913, 1716, 1427, 1152, 1098, 1033, 890, 734 cm⁻¹; ¹H 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, dd, *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''), 2.59 (2H, br d, $J = 13.5$ 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 $\times 2$, C-5', C-5''), 98.3 (t $\times 2$, OCH_2O), 75.1 (d $\times 2$, C-1', C-1''), 64.9 (t $\times 2$, CH_2O), 64.5 (t $\times 2$, CH_2O), 59.7 (d $\times 2$, C-3, C-5), 56.7 (q $\times 2$, CH_3O), 48.4 (d $\times 2$, C-6', C-6''), 35.7 (t $\times 2$, C-10', C-10''), 34.3 (t $\times 2$, C-2, C-6), 29.1 (t $\times 2$, C-7', C-7''), 26.9 (t $\times 2$, C-9', C-9''); **LRMS** (EI), m/z (relative intensity): 580 ($[\text{M}]^+$, 1), 518 (4), 456 (10), 133 (20), 132 (60), 100 (9), 99 (100), 86 (22); **HRMS** m/z calcd for $\text{C}_{25}\text{H}_{40}\text{O}_9\text{S}_3$ 580.1834, found 580.1839 (EI).

(3*R*,5*R*)-rel-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-thiopyran-4-one (24as). See procedure for **23as**. **IR** (DRIFT) ν_{max} 2914, 1708, 1428, 1261, 1153, 1097, 1032, 890 cm^{-1} ; ^1H 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, $\text{H}_3\text{COCOC-1''}$), 3.36 (3H, s, $\text{H}_3\text{COCOC-1'}$), 3.00 (1H, ddd, $J = 4.5, 5.5, 6$ Hz, HC-5), 3.13-2.95 (5H, , $\text{H}_2\text{C-2}$, HC-3 , HC-6 , HC-7), 2.91-2.69 (6H, , HC-6 , HC-7' , $\text{H}_2\text{C-7''}$, 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, $\text{CH}_2\text{OC-1''}$), 97.3 (t, $\text{CH}_2\text{OC-1'}$), 74.5 (d, C-1'), 72.3 (d, C-1''), 64.8 (t, CH_2O), 64.6 (t, CH_2O), 64.6 (t, CH_2O), 64.6 (t, CH_2O), 57.5 (d, C-3), 57.0 (d, C-5), 56.8 (q, $\text{CH}_3\text{OCOC-1''}$), 56.4 (q, $\text{CH}_3\text{OCOC-1'}$), 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 ($[\text{M}]^+$, 1), 456 (10), 133 (25), 132 (65), 100 (8), 99 (100), 86 (14), 55 (8); **HRMS** m/z calcd for $\text{C}_{25}\text{H}_{40}\text{O}_9\text{S}_3$ 580.1834, found 580.1828 (EI).

(3*R*,5*S*)-rel-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]tetrahydro-4*H*-thiopyran-4-one (24ss). Following the procedure described for **23aa**, reaction of **22ss** (15 mg, 0.031mmol) 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, 1103, 1032, 892 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 4.66 (2H, d, J = 6 Hz, HCO2 $\times$ 2), 4.63 (2H, d, J = 6 Hz, HCO2 $\times$ 2), 4.55 (2H, dd, J = 3, 6.5 Hz, HC-1', HC-1''), 4.07-3.84 (8H, m, H₂CO $\times$ 4), 3.35 (6H, s, H₃CO $\times$ 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 $\times$ 2, C-5', C-5''), 98.6 (t $\times$ 2, OCH₂O), 72.3 (d $\times$ 2, C-1', C-1''), 64.8 (t $\times$ 2, CH₂O), 64.5 (t $\times$ 2, CH₂O), 59.8 (d $\times$ 2, C-3, C-5), 56.8 (q $\times$ 2, CH₃O), 49.4 (d $\times$ 2, C-6', C-6''), 36.0 (t $\times$ 2, C-10', C-10''), 31.2 (t $\times$ 2, C-2, C-6), 29.1 (t $\times$ 2, C-7', C-7''), 26.8 (t $\times$ 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

Mukaiyama used the Stiles-House rule to assigned the relative configurations of **3a** and **3s** according to their $^3J_{H1'-H2}$ vicinal coupling constants of 9 Hz and 2 Hz, respectively.¹³ 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.¹⁴ Similarly, the relative configurations for the related aldols **17a** and **17s** were assigned according to their $^3J_{H1'-H3}$ vicinal coupling constants of 9 Hz and 2 Hz, respectively.¹⁵

Mukaiyama et al. was the first to assign the relative configurations of the aldols **20**.¹³ The assignment of the *syn/anti* aldol relative configuration was based on the Stiles-House rule; i.e. the magnitude of the $^3J_{Ha-Hb}$ 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.^{16,17} Only the report by Duhamel et al. provides both 1H and ^{13}C NMR data for aldols **20**.¹⁷ Our NMR data for the four aldols **20** correspond

¹³ Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.

¹⁴ Kitamura, M.; Nakano, K.; Miki, T.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* **2001**, *123*, 8939-8950.

¹⁵ Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 5369-5372.

¹⁶ (a) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265-1267. (b) Sugasawa, T.; Toyoda, T.; Sasakura, K. *Synth. Commun.* **1979**, *9*, 583-602. (c) Nozaki, H.; Oshima, K.; Takai, K.; Ozawa, S. *Chem. Lett.* **1979**, 379-380. (d) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932-945. (e) Tsuboniwa, N.; Matsubara, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 2569-2572. (f) Fujisawa, H.; Sasaki, Y.; Mukaiyama, T. *Chem. Lett.* **2001**, 190-191. (g) Koreeda, M.; Koo, S. *Tetrahedron Lett.* **1990**, *31*, 831-834.

¹⁷ Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232-2235.

closely to that reported in the literature (Table S1): δ_{H} within ± 0.2 ; $^3J_{\text{Ha-Hb}}$ within ± 0.1 Hz; δ_{C} within $+0.4 \pm 0.3$ 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 than 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**.

δ_{C} CHOH	δ_{H} CHOH	$J_{\text{Ha-Hb}}$	Literature ^{13, 16d,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 ^1H - ^1H 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

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. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) data for **19** and **20** in CDCl_3 .

	20at	20ac	20st	20sc
$^3J_{\text{Ha-Hb}}$	9.5	8.5	3	2.5
$^3J_{\text{Ha-CH}_2}$	9.5	13	10	12.5
$^3J_{\text{Ha-CH}_2}$	5.5	5.5	5.5	6.5
$^3J_{\text{Hc-CH}_2}$	5.5	13	5.5	12.5
$^3J_{\text{Hc-CH}_2}$	5	6	5	5.5
$\delta_{\text{H}} \text{H}_a$	4.86	4.80	5.32	5.38
$\delta_{\text{H}} \text{CH}_3$	1.21	1.07	1.18	1.06
$\delta_{\text{C}} \text{CHOH}$	75.0	74.9	71.6	71.0
$\delta_{\text{C}} \text{CH}_3$	16.5	14.4	16.7	14.5
	19at	19ac	19st	19sc
$^3J_{\text{Ha-Hb}}$	9.5	8.5	4	3
$^3J_{\text{Ha-CH}_2}$	6.5	12.5	9.5	12
$^3J_{\text{Ha-CH}_2}$	4	4.5	4	3.5
$^3J_{\text{Hc-CH}_2}$	9	13	7	12
$^3J_{\text{Hc-CH}_2}$	4.5	4.5	4.5	5
$\delta_{\text{H}} \text{H}_a$	5.30	4.86	5.43	5.38
$\delta_{\text{H}} \text{CH}_3$	1.27	1.15	1.26	1.14
$\delta_{\text{C}} \text{CHOH}$	74.3	74.1	71.9	71.2
$\delta_{\text{C}} \text{CH}_3$	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 ^1H 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 ^1H 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 ^1H - ^1H 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).

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**.¹⁰ Reduction of **22ss** with DIBAL-H as previously described gave the symmetric triol (71%) shown above whose structure determination has been previously described.¹⁰

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_2C -2 (3.5, 11.5 Hz) and between HC-5 and H_2C -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)¹⁰ 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**, $k_1 = (k_e k_{k'})/(k_k + k_{k'})$. The ‘composite’ rate constants k_1 and k_{-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:

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

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

where $[\mathbf{A}]_0$ is the initial concentration of **A**, $[\mathbf{A}]_e$ is the concentration of **A** at equilibrium, $[\mathbf{A}]_t$ is the concentration of **A** at time t , R_t is the ratio of $[\mathbf{A}]/[\mathbf{B}]$ 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 ^1H NMR as a function of time. The rate constant for equilibration (k_{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 ^1H 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 ^1H 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_{obs} is a pseudo 1st 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_{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_{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)	$-\ln[(R_t - R_e) \div (R_t + 1)]$
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 $-\ln[(R_t - R_e) \div (R_t + 1)]$ 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), $k_1 = (k_e k_k)/(k_k + k_{k'})$.

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^{-2}h^{-1}) for isomerization of **19**, **20**, and **22-24** in CDCl_3 with 0.4 M imidazole at room temperature.^a

aldol	k_1	k_{-1}	k_2	k_{-2}	k_3	k_{-3}	k_4	k_{-4}	k_n+k_{-n} (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

^a 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_{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_{obs}). For example, comparing the k_{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_4+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 ($[k_2+k_{-2} + k_4+k_{-4}]\div 2$) to the average rate of isomerization via an enol distal to the hydroxyl group ($[k_1+k_{-1} + k_3+k_{-3}]\div 2$) 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_{-1} 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 ($k_4+k_{-4}=0.74\times 10^{-2}\text{h}^{-1}$) is twice as fast as the isomerization between **23aa** and **23sa** via the enol proximal to the MOM group ($k_1+k_{-1}=0.36\times 10^{-2}\text{h}^{-1}$).²³ By contrast, isomerization of **23ss** to **23sa** via the enol proximal to the hydroxy group ($k_4+k_{-4}=0.16\times 10^{-2}\text{h}^{-1}$) is ca. 25% slower than the isomerization of **23ss** to **23as** via the enol proximal to the MOM group ($k_1+k_{-1}=0.21\times 10^{-2}\text{h}^{-1}$).²³ 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 CDCl_3 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 CDCl_3 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 CDCl_3 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 CDCl_3 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 CDCl_3 with 0.4 M imidazole: a) starting with **24aa**; b) starting with $(\pm)\text{-24as}$; 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.

11a

12s

12a

19ac

19at

^{19}S C

19st

20at

20sc

20st

21as

22ss

23aa

23as

24aa

(±)-24as

24ss