Supplementary Material

S1. Stereospecific syntheses of (2R,3R)- and (2S,3S)-hexanediols from (L)- and (D)-threonine
(Supplementary Figure 1)

Unless otherwise specified, worked up reaction mixtures were dried over anhydrous Na₂SO₄ and concentrated by rotary evaporation with a vacuum of 40-200 Torr, depending on the solvent being removed. THF was distilled from sodium-benzophenone ketyl, and reactions with air- or water-sensitive reagents were carried out under argon in oven-dried glassware.

S1.1 Synthesis of (4S,5R)-2,2,5-trimethyl-4-(methoxycarbonyl)-1,3-dioxolane (4)

(L)-Threonine 1 (59.5 g, 500 mmol; Alfa Aesar, Ward Hill MA) was dissolved in 595 ml water in a 3-neck flask fitted with a bubbler to allow release of gas, and the solution was cooled in an ice-bath. Five ml aliquots of NaNO₂ solution (38 g, 550 mmol in 80 ml water) and 3.5 ml aliquots of 5M H₂SO₄ solution (280 mmol, 56 ml) were added sequentially to the cooled mixture at ~20 min intervals. After the additions were complete, the solution was allowed to warm to room temperature overnight, by which time gas evolution had ceased. The mixture was concentrated by rotary evaporation. The residue was taken up in 500 ml EtOH, and the mixture was filtered through a pad of Celite® (Fisher Scientific, Fairlawn, New Jersey), rinsing twice with 100 ml EtOH. The filtrate was concentrated by rotary evaporation, then pumped under vacuum to yield 69 g of the diol acid 2 as a viscous yellow oil.

Crude diol acid 2 was dissolved in a mixture of THF (150 ml) and MeOH (150 ml), and chlorotrimethylsilane (32 ml) was added dropwise over ~30 min. The slightly cloudy solution was stirred overnight, then filtered through a pad of Celite, and the filtrate was concentrated at 40 Torr to yield the diol methyl ester 3 as a viscous yellow oil, which was used without further
purification. $^1$H NMR (CDCl$_3$): $\delta$ 4.11 (qd, 1H, $J = 6.4, 2.8$ Hz), 4.04 (d, 1H, $J = 2.8$ Hz), 3.84 (s, 3H), 3.63 (br s, 2 x OH), 1.32 (d, 3H, $J = 6.4$ Hz).

Crude diol methyl ester 3 was dissolved in a mixture of acetone (300 ml) and 2,2,-dimethoxypropane (67 ml), and 1 g of p-toluenesulphonic acid was added. The mixture was stirred overnight at room temperature, then concentrated by rotary evaporation. The residue was taken up in ether (200 ml), washed twice with 75 ml saturated aqueous NaHCO$_3$ (foams!) and once with brine, then concentrated to a yellow oil. Kugelrohr distillation (oven temp to 60ºC, 0.5 Torr) gave 34.8 g of the protected diol ester 4 (40% from threonine). $^1$H NMR (CDCl$_3$): $\delta$ 4.21 (qd, 1H, $J = 8.0, 6.0$ Hz), 4.07 (d, 1H, $J = 8.0$ Hz), 3.79 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.44 (d, 3H, $J = 6.0$ Hz). $^{13}$C NMR (CDCl$_3$): $\delta$ 18.7, 25.9, 27.3, 52.5, 75.3, 80.6, 110.8, 171.1 ppm.
The proton NMR was in accord with that previously reported (Servi, 1985).

S1.2. Synthesis of (4R,5R)-5-Hydroxymethyl-2,2,4-trimethyl-1,3-dioxolane (5)

Protected diol ester 4 (34.45 g, 198 mmol) was added dropwise to a slurry of LiAlH$_4$ in ether cooled in an ice-bath and under Ar atmosphere. When the addition was complete, the mixture was allowed to warm to room temperature and stirred overnight. The mixture was again cooled in an ice-bath, and water (5 ml; vigorous H$_2$ evolution!), 20% aq. NaOH (3.75 ml), and water (17.5 ml) were sequentially added dropwise. The resulting mixture was stirred vigorously for 30 min to allow the white precipitate to granulate, and was then filtered through a pad of Celite, rinsing with ether. The filtrate was dried, concentrated, and Kugelrohr distilled (over temp to 70ºC, 8 Torr), yielding alcohol 5 (25.7 g, 89%) as a colorless oil. $^1$H NMR (CDCl$_3$): $\delta$ 4.02 (dq, 1H, $J = 8.4, 6$ Hz), 3.81 (ddd, 1H, $J = 12, 5.2, 4.8$ Hz), 3.66 (m, 1H), 3.62 (ddd, 1H, $J = 12, 7.2, 4.4$ Hz), 2.05 (dd,1H, $J = 7.2, 5.2$ Hz, OH), 1.43 (s, 3H), 1.41 (s, 3H), 1.30 (d, 3H, $J =$
6.0 Hz. $^{13}$C NMR (CDCl$_3$): $\delta$ 17.8, 27.1, 27.6, 61.6, 72.9, 82.9, 108.7 Hz. The proton NMR was in accord with that previously published (Nagashima and Ohno, 1991).

**S1.3. Synthesis of (2R,3R)-hexanediol (8)**

Trifluoromethanesulphonic anhydride (33.6 ml, 200 mmol) was added dropwise over ~30 min to a solution of alcohol 5 (25.5 g, 175 mmol), CH$_2$Cl$_2$ (300 ml), and pyridine (14.2 ml, 200 mmol) cooled in an ice-acetone bath to ~10°C. When the addition was complete, the mixture was warmed to 0°C, and was stirred until all the starting alcohol had been consumed. The mixture was washed successively with ice-water, saturated aqueous NaHCO$_3$, and brine, and the organic phase was dried and filtered through a 2 cm plug of silica gel with suction, rinsing well with CH$_2$Cl$_2$. The filtrate was concentrated without heating, and pumped under vacuum for 5 min. The resulting brown oil was immediately taken up in 100 ml dry ether and kept at 0°C until used in the coupling step below.

A dried flask under Ar was charged with CuI (3.8 g, 20 mmol) and dry ether (500 ml), and after cooling to ~10°C in an ice-acetone bath, EtMgBr (2M in THF, 110 ml, 220 mmol) was added slowly, keeping the temperature <0°C. The mixture was stirred for 15 min at <0°C, then the ether solution of triflate was added dropwise over ~90 min, keeping the temperature <0°C. When the addition was complete, the mixture was allowed to slowly warm to room temperature overnight. The mixture was then poured into 500 ml saturated aqueous NH$_4$Cl. The organic layer was separated and washed with saturated aqueous NH$_4$Cl and brine, dried, and concentrated. The residue was taken up in a mixture of THF (150 ml) and 3M HCl (150 ml) and stirred at room temperature for 16 hr. The mixture was cooled to 0°C and quenched by addition of cold 5M NaOH in portions. The mixture was then saturated with salt and extracted with
EtOAc (2 x 100 ml). The combined extracts were washed with brine, dried, and concentrated by rotary evaporation followed by partial Kugelrohr distillation (room temperature, 6.5 Torr). The residue was taken up in 10% ether in pentane (50 ml) and purified by vacuum flash chromatography on silica gel in a 150 ml Buchner funnel, eluting with 10% ether in pentane (3 x 100 ml), then ether (5 x 100 ml). The first two fractions contained a small amount of the ketal starting material, and the diol eluted in fractions 5-8, which were combined, concentrated, and Kugelrohr distilled, giving 9.43 g of the diol (46% from alcohol 5; 53% based on recovered ketal; 97.5% chemically pure by GC). The diol was 97% enantiomerically pure, and contaminated with 0.9% of the (R,S)-diastereomer, as determined by GC on a chiral stationary phase Cyclodex B column (30 m × 0.25 mm × 0.25 micron film thickness, J&W Scientific, Folsom CA), programmed from 50 ºC/1 min, then 3ºC/min to 200ºC. Under these conditions, the four stereoisomers elute in the following order: (2S,3S) 21.89 min, (2R,3R) 22.25 min, (2R,3S) 23.06 min, (2S,3R) 23.25 min. 1H NMR (CDCl₃): δ 3.58 (quint, 1H, J = 6.4 Hz), 3.36-3.31 (m, 1H), 2.44 (br s, 2 × OH), 1.56-1.32 (m, 4H), 1.18 (d, 3H, J = 6.4 Hz), 0.94 (t, 3H, J = 6.8 Hz). 13C NMR (CDCl₃): δ 14.3, 19.0, 19.7, 35.7, 71.1, 76.1 ppm. The spectra matched those of the racemic compound prepared as described in Lacey et al. (2004).

(2S,3S)-hexanediol was synthesized in identical fashion from (D)-threonine (Chem-Impex International, Wooddale IL), ee 94.2 %, and 0.6% (2S,3R)-diastereomer.

S2. Kinetic resolution of (2R,3S)- and (2S,3R)-hexanediols from racemic (2R*,3S*)-hexanediol

Racemic (2R*,3S*)-hexanediol (10 g, 85 mmol, prepared by OsO₄-catalyzed dihydroxylation of (Z)-2-hexene as described in Lacey et al. (2004) was added to a slurry of vinyl acetate (24 ml, 260 mmol), t-butyl methyl ether (350 ml), and Amano lipase PS (5 g), and
the mixture was stirred at room temperature for 10 d. The mixture was then filtered, concentrated, and fractionated by vacuum flash chromatography on 300 g silica gel, eluting with 40% EtOAc (5 x 200 ml), then 100% EtOAc (3 x 300 ml). The combined mono- and diacetates eluted in the first two fractions, whereas the unreacted diols eluted in fractions 5-7. The unreacted diols (3.65 g) were an 86:14 mixture of (2S,3R): (2R,3S)-diols.

After concentration, the combined acetates were hydrolyzed in 1.25 M NaOH overnight, and the diols were recovered by saturating the solution with salt and extracting twice with EtOAc. The resulting crude diols consisted of a 14:86 mixture of (2S,3R): (2R,3S) diols.

The two scalemic mixtures, each enriched in a different enantiomer of hexanediol (3.5 g of each), were again stirred in two separate reactions in mixtures of vinyl acetate (8 ml) and Amano lipase PS (3.5 g) in t-butyl methyl ether (100 ml) for 3 d, then worked up as described above. After vacuum flash chromatography, the hexanediols were Kugelrohr distilled (oven temperature to 85°C at 5 Torr), yielding 2.4 g of the less reactive (2S,3R)-hexanediol (91.4% e.e., 2.8% (2R,3R)-diastereomer) and 2.68 g of the more readily acetylated (2R,3S)-diol (93.4% ee, 1.1% (2R,3R)-diastereomer).

S3. Synthesis of (R)-2-methyl-1-butanol

(S)-(+-)3-bromo-2-methyl-1-propanol (7 g, 46 mmol; Aldrich Chemical Co.), 3,4-dihydro-2H-pyran (4.2 g, 50 mmol), and 100 mg of p-toluenesulfonic acid were stirred 2 h at room temperature in diethyl ether (100 mL). The mixture was washed with saturated aqueous NaHCO₃ and brine, and the organic layer was dried and concentrated. Kugelrohr distillation (oven temp to 90°C, 9 mm Hg) yielded 9.2 g (85%) of the protected alcohol [(S)-3-bromo-2-
methylpropoxy]-2-tetrahydro-2H-pyran. MS (m/z rel. intensity): 235, 237 (M⁺-1, 4), 135, 137 (6), 115 (6), 101 (6), 85 (100), 67 (9), 55 (54), 41 (45).

Methyl magnesium chloride (3 M in THF, 36 ml, 108 mmol) was added dropwise to a mixture of the protected alcohol (8.5 g, 36 mmol) and Li₂CuCl₄ (0.1 M in THF, 18 ml, 1.8 mmol) in THF (20 mL) at −30°C. The mixture was warmed to room temperature and stirred overnight. After quenching the reaction mixture with dilute HCl, added slowly at 0°C with vigorous stirring, the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 x 100 ml) and the combined organic extracts were washed with saturated aqueous NaHCO₃, water, and brine, yielding 5.0 g (80 %) of [(R)-2-methylbutoxy]-2-tetrahydro-2H-pyran as a yellow liquid. MS (m/z rel. intensity): 171 (M⁺, 4), 142 (4), 115 (14), 101 (10), 85 (100), 71 (30), 56 (40), 43 (64).

The crude THP-protected alcohol (4 g, ~23 mmol), 1-tetradecanol (10 g, 46 mmol), and 100 mg of p-toluenesulfonic acid were stirred for 5 h at room temperature under vacuum (~5 Torr), collecting the liberated (R)-2-methyl-1-butanol in a trap cooled to −78°C. (R)-2-methyl-1-butanol was recovered as a colorless liquid as a single enantiomer, as determined by analysis on the Cyclodex B chiral GC column (oven temperature 35° isothermal; [R]-enantiomer 12.00 min; [S]-enantiomer 12.30 min). The retention times and spectra matched those of a racemic standard (Aldrich Chem. Co.).

S4. Results of chemical syntheses

Synthesis of (2R,3R)- and (2S,3S)-hexanediols in high enantiomeric purity and in multigram scale was made possible by the ready availability of the two enantiomers of the starting material, threonine, with some modification of the route described by Bianchi et al.
Thus, the amino group of \((L)\)-threonine (1, Supplementary Fig. 1) was converted to a hydroxyl group with retention of configuration, followed by conversion of the carboxylic acid function to the corresponding methyl ester by treatment with methanol and chlorotrimethylsilane (Nakao et al., 1981) and then protection of the vicinal diol as a ketal, giving ester 4. It proved advantageous to carry out these three successive steps before purification of ester 4 because the intermediates 2 and 3 were viscous, highly polar, and rather intractable oils. Purified ester 4 was reduced with LiAlH\(_4\) to give alcohol 5, which was then converted to the unstable triflate 6. After rapid purification by passage through a pad of silica gel, the triflate 6 was immediately alkylated with ethylmagnesium bromide in ether/THF, with CuI catalysis. Removal of the ketal protecting group with aqueous acid then gave (2\(R\),3\(R\))-hexanediol 8 in high chemical and enantiomeric purity. The analogous series of reactions beginning with \((D)\)-threonine provided ready access to the (2\(S\),3\(S\))-enantiomer.

Although it would have been possible to prepare the (2\(R\),3\(S\))- and (2\(S\),3\(R\))-stereoisomers from the threonine enantiomers by a somewhat longer and less efficient route than that described above (Ibuka et al., 1988), we opted instead to prepare the enantiomers by kinetic resolution of the racemate with vinyl acetate and Amano PS lipase in t-butyl methyl ether. After two reaction cycles, the less reactive (2\(S\),3\(R\))-hexanediol was obtained in 86% enantiomeric excess, whereas the more reactive (2\(R\),3\(S\))-enantiomer was obtained in ~96% ee. Thus, kinetic resolution did not result in enantiomeric purities as high as those of the (2\(R\),3\(R\))- and (2\(S\),3\(S\))-stereoisomers obtained from the threonine chiral synthons, but it did involve fewer steps overall.

References


Supplementary Figures

Supplementary Fig. 1. Schematic for synthesis of (2R,3R)-hexanediol from (L)-threonine.

L-threonine, 1

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\begin{align*}
\text{NaNO}_2 \quad \text{H}_3\text{O}^+ & \quad \text{MeCH/THF} \quad \text{Me}_3\text{SiCl} \quad \text{H}^+ \\
\text{MeO} & \quad \text{MeO} \\
\text{OH} & \quad \text{OH} \\
\text{COOH} & \quad \text{COOH} \\
\text{COO}^- & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

\( \text{MeO} \quad \text{OMe} \)

\( (2R,3R)\)-hexanediol, 8

\( \text{LiAlH}_4 \quad \text{EtCl} \quad \text{Pyridine} \quad \text{EtMgBr, other} \quad \text{Li}_2\text{CuCl}_4 \quad \text{H}_3\text{O}^+ \)