Supporting Online Material

Efficient Asymmetric Organocatalytic Formation of Erythrose and Threose under Aqueous Conditions

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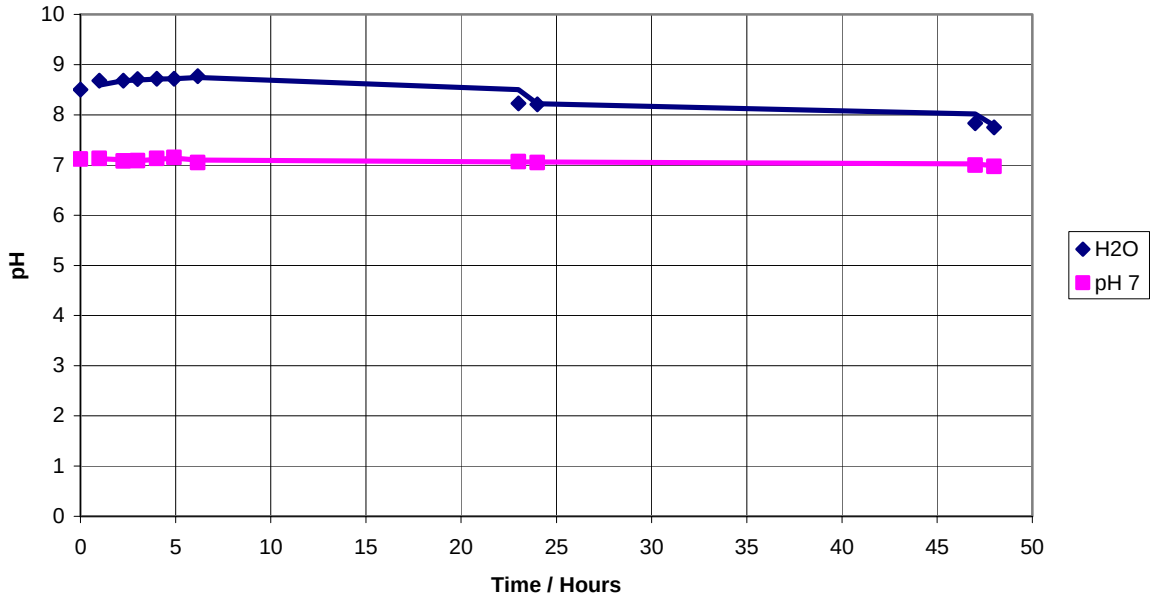
Figure. pH of aldol reaction of TIPS-glycoaldehyde catalysed by (*L*)-proline benzyl ester



Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Jeol EX270 (270 MHz), Jeol ECX400 (400 MHz) or Bruker AV500 (500 MHz) as noted. Data for ^{1}H NMR are reported as follows:

chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p= pentet, m = multiplet), integration, coupling constant *J* (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. Flash column chromatography was performed using silica gel 60 supplied by Fluka except where noted; preparative thin-layer chromatography was performed using Machery-Nagel pre-coated plates with concentration layer. Dichloromethane was used distilled from calcium hydride, methanol was used distilled from magnesium turnings/iodine and tetrahydrofuran was used distilled from sodium/benzophenone unless otherwise stated. Buffer solutions were made up to the desired pH using mixtures of 0.1 mol dm^{-3} potassium dihydrogen orthophosphate and 0.1 mol dm^{-3} sodium hydroxide. All other reagents and solvents were used as supplied by Sigma-Aldrich, Acros or Fluka except where noted.

2-(Triisopropylsilyloxy)acetaldehyde 1 (*1*)

2- Butene-1,4-diol (2.13 mL, 25.9 mmol) was added to a solution of imidazole (8.83 g, 130 mmol) and 4-(dimethylamino)pyridine (0.697 g, 5.71 mmol) in dichloromethane (60 mL) at 0 ^{o}C under nitrogen. Triisopropylsilyl chloride (11.1 ml, 51.8 mmol) was then added dropwise to the solution over a period of 15 minutes. After 1 hour the reaction was allowed to warm to room temperature. After 8 hours the reaction mixture was washed with saturated sodium bicarbonate solution (50 mL) and extracted with diethyl ether (3 × 25 mL). The organic layers were then combined and dried with magnesium sulfate, filtered and concentrated *in vacuo*. Distillation of the crude extract afforded 4-bis-triisopropylsilyloxy

but-2-ene 18 (8.31 g, 20.7 mmol). This was then dissolved in dichloromethane (150 mL) at -78 ^{o}C under nitrogen. Ozone was then bubbled through the solution until a pale blue colour developed (2 hours). Powdered zinc metal (2.13 g, 32.6 mmol) was then added to the solution in one portion followed by 50 % aqueous acetic acid solution (65 mL), and allowed to warm

slowly to room temperature over a period of 5 hours. The reaction mixture was then washed with water (2 × 100 mL) and extracted with dichloromethane (3 × 50 mL). The organic extracts were combined then washed with saturated sodium bicarbonate solution (100 mL) and extracted with dichloromethane (3× 50 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude title compound. This was then distilled to give the pure title compound (8.24 g, 38.0 mmol) in 92 % yield as a clear, colourless liquid. The data was found to be in accordance with the literature (*1*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93-1.06 (m, 21H, $SiCH(CH_3)_2$); 4.24 (d, 1.0 Hz, 2H, CH_2); 9.72 (t, 1.0 Hz, 1H, CHO). ^{13}C NMR (270 MHz, $CDCl_3$): δ 11.8, 17.8, 69.7, 203.0.

(*L*)-*N*-methyl alanine ethyl ester 6

Sodium bicarbonate (3.13 g, 195 mmol) was added to (*L*)-alanine ethyl ester hydrochloride (2.00 g, 13.0 mmol) in tetrahydrofuran (30 mL, not distilled) and water (30 mL) at 0 ^{o}C. Di-*tert*-butyl dicarbonate (2.84 g, 13.0 mmol) was then added in one portion to the reaction mixture. After 1 hour the reaction was allowed to warm to room temperature. After a further 23 hours the mixture was acidified to pH 4-5 with citric acid and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate, filtered and concentrated *in vacuo* to give (*L*)-*N*-BOC alanine ethyl ester (1.91 g, 8.81 mmol) as a colourless oil which was used without further purification. Potassium bis(trimethylsilyl)amide 0.5 M in toluene (13.3 mL, 6.65 mmol) was then added to the *N*-BOC L-alanine ethyl ester (1.44 g, 6.65 mmol) in tetrahydrofuran (35 mL) under argon at -78 ^{o}C. After 0.5 hours iodomethane (0.455 mL, 7.32 mmol) was added to the solution. The reaction mixture was then allowed to warm to room temperature overnight. After 18 hours the solution was washed with saturated potassium carbonate solution (30 mL), then brine (30 mL) followed by 1 M

sodium hydroxide solution (30 mL). The aqueous washes were each extracted with ethyl acetate (3 × 10 mL). The organic fractions were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to give (*L*)-*N*-BOC *N*-methyl alanine ethyl ester (1.19 g, 5.15 mmol) as an orange oil which was used without further purification. Trifluoroacetic acid (7.64 mL, 103 mmol) was then added to the (*L*)-*N*-BOC *N*-methyl alanine ethyl ester (1.19 g, 5.15 mmol) in dichloromethane (20 mL) at 0 ^{o}C and stirred for 4 hours. The solution was then concentrated *in vacuo*, washed with 25 mL saturated sodium bicarbonate solution and extracted with ethyl acetate (3 × 10 mL). The organic extracts were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. The crude amino acid derivative was then purified by flash column chromatography (9:1 40-60 pentane:acetone) to give the title compound (0.664 g, 5.06 mmol) in 39 % overall yield as a colourless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.30 (t, 2.0 Hz, 3H, CH_2CH_3); 1.48 (d, 7.0 Hz, 3H, $CHCH_3$); 2.60 (s, 3H, $NHCH_3$); 3.59 (q, 7.0 Hz, 1H, $CHCH_3$); 4.23 (q, 2.0 Hz, 2H, CH_2CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.2, 18.8, 34.5, 58.3, 60.6, 175.6.

(*L*)-*N*-methyl leucine ethyl ester 7

Sodium bicarbonate (2.46 g, 153 mmol) was added to (*L*)-leucine ethyl ester hydrochloride (2.00 g, 10.2 mmol) in tetrahydrofuran (25 mL, not distilled) and water (25 mL) at 0 ^{o}C. Di-*tert*-butyl dicarbonate (2.23 g, 10.2 mmol) was then added to the reaction mixture, which after 1 hour was allowed to warm to room temperature. After a further 23 hours the mixture was acidified to pH 4-5 with citric acid and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate, filtered and concentrated *in vacuo* to give (*L*)-*N*-BOC leucine ethyl ester (2.23 g, 8.65 mmol) as a colourless oil which was used without further purification. Potassium bis(trimethylsilyl)amide 0.5 M in toluene (15.9 mL, 7.95 mmol) was then added to the (*L*)-*N*-BOC leucine ethyl ester (2.23 g, 8.60

mmol) in tetrahydrofuran (50 mL) under argon at -78 ^{o}C. After 0.5 hours iodomethane (0.592 mL, 9.52 mmol) was added to the solution. The reaction mixture was then allowed to warm to room temperature overnight. After 18 hours the solution was washed with saturated potassium carbonate solution (40 mL), then brine (40 mL) followed by 1 M sodium hydroxide solution (40 mL). The aqueous washes were each extracted with ethyl acetate (3 × 15 mL). The organic fractions were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to give (*L*)-*N*-BOC *N*-methyl leucine ethyl ester (1.32 g, 4.83 mmol) as an yellow oil which was used without further purification. Trifluoroacetic acid (8.47 mL, 114 mmol) was then added to the (*L*)-*N*-BOC *N*-methyl leucine ethyl ester (1.32 g, 4.83 mmol) in dichloromethane (20 mL) at 0 ^{o}C and stirred for 4 hours. The solution was then concentrated *in vacuo*, washed with saturated sodium bicarbonate solution (25 mL) and extracted with ethyl acetate (3 × 10 mL). The organic extracts were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. The crude amino acid derivative was then purified by flash column chromatography (9:1 40-60 pentane:acetone) to give the title compound (0.492 g, 2.84 mmol) in 28 % overall yield as a colourless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 (m, 6H, $CH(CH_3)_2$); 1.30 (t, 7.0 Hz, 3H, CH_2CH_3); 1.42-1.61 (m, 2H, $CH_2CH(CH_3)_2$); 1.75 (m, 1H, $CH(CH_3)_2$); 2.38 (s, 3H, $NHCH_3$) 3.47 (dd, 5.5 Hz, 1H, CHNH); 4.20 (p, 7.0 Hz, 2H, CH_2CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.2, 21.4, 24.9, 34.7, 42.7, 60.5, 61.8, 175.9.

(*D*/*L*)-Proline benzyl ester hydrochloride (*2*)

Benzyl alcohol (9.8 mL) was cooled to 0 ^{o}C under nitrogen. Thionyl chloride (0.98 mL, 13.5 mmol) was then added, followed by racemic (*D*/*L*)-proline (0.690 g, 6.00 mmol). After 2 hours the solution was allowed to warm to room temperature. After a further 48 hours diethyl ether (42 mL) was added to the reaction mixture, which was then placed in to the freezer at -20 ^{o}C for one week. The crystallised hydrochloride salt was then separated by vacuum

filtration and washed with diethyl ether (5 × 20 mL) to provide the pure title compound (0.870 g, 1.00 mmol) in 60 % yield as a white crystalline solid. The data was found to be in accordance with the literature (*2*). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.69-1.93 (m, 4H, CHC_2H_2); 2.12 (m, 1H, NHCH); 2.84-3.10 (m, 2H, $NHCH_2$); 3.78 (dd, 5.5 Hz, 3.0 Hz, 1H, CHNH); 5.1 (s, 2H, CH_2Ar); 7.34 (m, 5H, C_6H_5); ^{13}C NMR (400 MHz, $CDCl_3$): δ 23.3, 28.2, 46.4, 59.7, 68.9, 128.7, 129.1, 129.2, 134.8, 169.9; mp: 142-144 ^{o}C.

(*L*)-Proline heneicosan-11-yl ester 9

N-Methylmorpholine (0.22 mL, 2.0 mmol) was added to a stirred solution of heneicosan-11-ol (156 mg, 0.50 mmol), (*L*)-*N*-BOC proline (215 mg, 1.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (192 mg, 1.0 mmol) and 4-dimethylamino pyridine (6.1 mg, 0.050 mmol) in dichloromethane (3 mL) under nitrogen. The reaction mixture was stirred for 24 hours, after which ethyl acetate (50 mL) was added. The organic mixture was then washed with citric acid (1 mol dm^{-3}, 50 mL) followed by saturated aqueous potassium carbonate solution (50 mL). The separated organic layer was dried with magnesium sulfate, filtered and solvent removed *in vacuo* to provide the crude (*L*)-*N*-BOC proline heneicosan-11-yl ester. This was then purified by flash column chromatography (9:1 pentane:diethyl ether) to give (*L*)-*N*-BOC proline heneicosan-11-yl ester (290 mg, 0.57 mmol) as a clear, colourless oil. This was then dissolved in dichloromethane (3 mL) under nitrogen at 0 ^{o}C, and trifluoroacetic acid (0.53 mL, 6.87 mmol) added to the stirred solution. After 13 hours the reaction mixture was washed with saturated aqueous potassium carbonate solution (10 mL) and extracted with dichloromethane (3 × 3 mL). The combined organics were dried with magnesium sulfate and concentrated *in vacuo* to give the title compound (177 mg, 0.43 mmol) in 43 % overall yield as an off-white solid. IR (film) 3434.6, 2924.3, 2854.1, 1731.0, 1688.0, 1465.5, 1377.7, 1332.9, 1204.1, 1125.7, 721.1 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t,

6H, 9.0 Hz, CH_3); 1.11-1.30 (m, 32H, $(CH_2)_{16}$); 1.47-1.53 (m, 4H, $CH_2(CH_2)_{16}$); 1.67-1.88 (m, 3H, CH_2CH_2); 2.07-2.20 (m, 1H, CH_2CH_2); 2.08-2.17 (m, 1H, CH_2CH); 2.87-3.11 (m, 3H, CH_2NH); 3.75 (dd, 1H, 7.5 Hz, 12.5 Hz, CHC(O)O); 4.88 (p, 1H, 9.0 Hz, $CH(CH_2)CH_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.1, 22.7, 25.3, 25.6, 29.3, 29.4, 29.5, 29.6, 29.6, 31.9, 34.0, 37.5, 46.9, 59.8, 72.0, 75.5, 174.6; $[\alpha]_D$ = - 15.3 (c = 2.6, $CHCl_3$). mp: 38.2-39.9 ^oC.

(*L*)-Proline icosyl ester 10

N-Methylmorpholine (0.15 mL, 1.40 mmol) was added to a stirred solution of icosanol (105 mg, 0.35 mmol), (*L*)-*N*-BOC proline (151 mg, 0.70 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (134 mg, 0.70 mmol) and 4-dimethylamino pyridine (5.0 mg, 0.035 mmol) in dichloromethane (3 mL) under nitrogen. The reaction mixture was stirred for 24 hours, after which ethyl acetate (50 mL) was added. The organic mixture was then washed with citric acid (1 mol dm^{-3}, 50 mL) followed by saturated aqueous potassium carbonate solution (50 mL). The separated organic layer was dried with magnesium sulfate, filtered and solvent removed *in vacuo* to provide the crude (*L*)-*N*-BOC proline icosyl ester. This was then purified by flash column chromatography (7:3 pentane:diethyl ether) to give (*L*)-*N*-BOC proline icosyl ester (177 mg, 0.36 mmol) as a clear, colourless oil. This was then dissolved in dichloromethane (3 mL) under nitrogen at 0 ^oC, and trifluoroacetic acid (0.53 mL, 6.87 mmol) added to the stirred solution. After 13 hours the reaction mixture was washed with saturated aqueous potassium carbonate solution (10 mL) and extracted with dichloromethane (3 × 3 mL). The combined organics were dried with magnesium sulfate and concentrated *in vacuo* to give the title compound (110 mg, 0.28 mmol) in 40 % overall yield as an off-white solid. IR (film) 3345.1, 2920.3, 2852.2, 1734.1, 1677.8, 1466.8, 1338.5, 1204.3, 1180.8, 1117.7, 908.7, 734.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3H, 7.0 Hz, CH_3); 1.23-1.31 (m, 36H, $(CH_2)_{18}$); 1.61 (tt, 2H, 7.0 Hz, 7.0 Hz, $CH_2(CH_2)_{18}$); 1.71-1.77 (m,

2H, CH_2CH_2); 1.80-1.87 (m, 1H, CH_2CH); 2.08-2.17 (m, 1H, CH_2CH); 2.88-2.94 (m, 1H, CH_2NH); 2.99 (br s, 1H, NH); 3.05-3.11 (m, 1H, CH_2NH); 3.77 (dd, 1H, 5.5 Hz, 8.0 Hz, CH); 4.05-4.14 (m, 2H, $CH_2C(O)O$); ^{13}C NMR (270 MHz, $CDCl_3$): δ 14.1, 22.6, 25.8, 28.6, 29.2, 29.3, 29.5, 29.6, 31.9, 46.9, 29.7, 65.1, 175.2; $[\alpha]_D$ = - 16.7 (c = 2.3, $CHCl_3$). mp: 40.4-41.7 ^oC.

General procedure for 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-proline benzyl ester 5 (*1*)

(*L*)-Proline benzyl ester hydrochloride (31.2 mg, 0.129 mmol) was shaken with saturated sodium bicarbonate solution (6 mL), then extracted with chloroform (3 × 3 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the free ester. This was then immediately added to 2-(triisopropylsilyloxy)acetaldehyde **1** (280 mg, 1.29 mmol) in water (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (15:1 pentane:diethyl ether) to provide the aldol product 3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*syn*/2-*anti*** (215 mg, 0.497 mmol) in 77 % yield, 18 % *e.e.*, 1.5:1 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] after conversion of the isolated *anti* isomer **6-*anti*** to the 1-hydroxy-3-*p*-nitrobenzoate-derivative**.** The data was found to be in accordance with the literature (*1*). ^1H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, $SiCH(CH_3)_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, $CHOHCH_2$); 4.19 (dd, 2.0 Hz, 2.0 Hz, 1H,

CHO SiCH(CH_3)$_2$); 9.62 (d, 2.0 Hz, 1H, CHO (*anti*)); 9.67 (d, 2.0 Hz, 1H, CHO (*syn*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1

General procedure for buffered 2-(triisopropylsilyloxy)acetaldehyde aldol 1 reactions, catalysed by (*L*)-proline benzyl ester 5 (*1*)

(*L*)-Proline benzyl ester hydrochloride (31.2 mg, 0.129 mmol) was shaken with saturated sodium bicarbonate solution (6 mL), then extracted with chloroform (3 × 3 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the free ester. This was then immediately added to 2-(triisopropylsilyloxy)acetaldehyde **5** (280 mg, 1.29 mmol) in pH 7 phosphate buffer (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (15:1 pentane:diethyl ether) to provide the aldol product 3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*syn*/2-*anti*** (195 mg, 0.452 mmol) in 70 % yield, 47 % *e.e.*, 1.5:1 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] after conversion of the isolated *anti* isomer **6-*anti*** to the 1-hydroxy-3-*p*-nitrobenzoate-derivative. The data was found to be in accordance with the literature (*1*). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, SiCH(CH_3)$_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, CHOHCH_2); 4.19 (dd, 2.0 Hz, 2.0 Hz, 1H, CHO SiCH(CH_3)$_2$); 9.62 (d, 2.0 Hz, 1H, CHO (*anti*)); 9.67 (d, 2.0 Hz, 1H, CHO (*syn*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1; $[\alpha]_D$ = - 1.5 (c = 2.0, $CHCl_3$)

General procedure for 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-*N*-methyl leucine ethyl ester 7 (*1*)

(*L*)-*N*-Methyl leucine ethyl ester **7** (22.3 mg, 0.129 mmol) was added to 2-(triisopropylsilyloxy)acetaldehyde **1** (280 mg, 1.29 mmol) in water (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude reaction mixture. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (15:1 pentane:diethyl ether) to provide the aldol product 3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*syn*/2-*anti*** (223 mg, 0.516 mmol) in 80 % yield, 15 % *e.e*., 1.5:1 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] after conversion of the isolated *anti* isomer ***ent*-2-*anti*** to the 1-hydroxy-3-*p*-nitrobenzoate-derivative. The data was found to be in accordance with the literature (*1*). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, $SiCH(CH_3)_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, $CHOHCH_2$); 4.9 (dd, 2.0 Hz, 2.0 Hz, 1H, CHOHCHO); 9.62 (d, 2.0 Hz, 1H, CHO (*anti*)); 9.67 (d, 2.0 Hz, 1H, CHO (*syn*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1

General procedure for buffered 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-*N*-methyl leucine ethyl ester 7 (*1*)

(*L*)-*N*-Methyl leucine ethyl ester **7** (22.3 mg, 0.129 mmol) was added to 2-(triisopropylsilyloxy)acetaldehyde **1** (280 mg, 1.29 mmol) in pH 7 phosphate buffer (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude reaction mixture. This was then purified by flash column chromatography

using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (15:1 pentane:diethyl ether) to provide the aldol product 3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*syn*/2-*anti*** (220 mg, 0.510 mmol) in 79 % yield, 57 % *e.e*., 1.5:1 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] after conversion of the isolated *anti* isomer ***ent*-2-*anti*** to the 1-hydroxy-3-*p*-nitrobenzoate-derivative. The data was found to be in accordance with the literature (*1*). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, $SiCH(CH_3)_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, $CHOHCH_2$); 4.9 (dd, 2.0 Hz, 2.0 Hz, 1H, CHOHCHO); 9.62 (d, 2.0 Hz, 1H, CHO (*anti*)); 9.67 (d, 2.0 Hz, 1H, CHO (*syn*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1; $[\alpha]_D$ = +1.7 (c = 2.0, $CHCl_3$)

General procedure for 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-*N*-methyl alanine ethyl ester 6 (*1*)

(*L*)-*N*-Methyl alanine ethyl ester **6** (16.9 mg, 0.129 mmol) was added to 2-(triisopropylsilyloxy)acetaldehyde **1** (280 mg, 1.29 mmol) in water (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude reaction mixture. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (15:1 pentane:diethyl ether) to provide the aldol product 3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*syn*/2-*anti*** (195 mg, 0.452 mmol) in 70 % yield, 7 % *e.e*., 3.0:1 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] after conversion of the isolated *anti* isomer ***ent*-2-*anti*** to the 1-hydroxy-3-*p*-nitrobenzoate-derivative. The data was found to be in

accordance with the literature (*1*). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, $SiCH(CH_3)_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, $CHOHCH_2$); 4.9 (dd, 2.0 Hz, 2.0 Hz, 1H, CHOHCHO); 9.62 (d, 2.0 Hz, 1H, CHO (*anti*)); 9.67 (d, 2.0 Hz, 1H, CHO (*syn*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1

General procedure for 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-proline heneicosan-11-yl ester 9 (*1*)

2-(Triisopropylsilyloxy)acetaldehyde **1** (280 mg, 1.29 mmol) was added to (*L*)-proline heneicosan-11-yl ester **9** (51.0 mg, 0.129 mmol) in water (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (15:1 pentane:diethyl ether) to provide the aldol product 3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*syn*/2-*anti*** (137 mg, 0.316 mmol) in 49 % yield, 10 % *e.e*., 2.0:1 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] after conversion of the isolated *anti* isomer **2-*anti*** to the 1-hydroxy-3-*p*-nitrobenzoate-derivative. The data was found to be in accordance with the literature (*1*). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, $SiCH(CH_3)_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, $CHOHCH_2$); 4.19 (dd, 2.0 Hz, 2.0 Hz, 1H, CHO $SiCH(CH_3)_2$); 9.62 (d, 2.0 Hz, 1H, CHO (*anti*)); 9.67 (d, 2.0 Hz, 1H, CHO (*syn*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1

General procedure for buffered 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-proline heneicosan-11-yl ester 9 (*1*)

2-(Triisopropylsilyloxy)acetaldehyde **5** (280 mg, 1.29 mmol) was added to (*L*)-proline heneicosan-11-yl ester **9** (51.0 mg, 0.129 mmol) in pH 7 phosphate buffer (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (15:1 pentane:diethyl ether) to provide the aldol product 3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*syn*/2-*anti*** (145 mg, 0.335 mmol) in 52 % yield, 46 % *e.e.*, 5.5:1 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] after conversion of the isolated *anti* isomer **2-*anti*** to the 1-hydroxy-3-*p*-nitrobenzoate-derivative. The data was found to be in accordance with the literature (*1*). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, $SiCH(CH_3)_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, $CHOHCH_2$); 4.19 (dd, 2.0 Hz, 2.0 Hz, 1H, CHO $SiCH(CH_3)_2$); 9.62 (d, 2.0 Hz, 1H, CHO (*anti*)); 9.67 (d, 2.0 Hz, 1H, CHO (*syn*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1

General procedure for 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-proline icosyl ester 10 (*1*)

(*L*)-Proline icosyl ester **10** (50.1 mg, 0.127 mmol) was added to 2-(triisopropylsilyloxy)acetaldehyde **1** (275 mg, 1.27 mmol) in water (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude reaction mixture. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (30:1:1:0.32 pentane:diethyl ether:dichloromethane:acetic acid) to provide the acetal product 5-

triisopropylsilanyloxy-2,6-bis-triisopropylsilanyloxymethyl-[1,3]dioxan-4-ol **8** (110 mg, 0.172 mmol) in 40 % yield, 17 % *e.e*., as a mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]. IR (film) 2945, 2892, 2868, 2360, 1734, 1684, 1653, 1635, 1576, 1559, 1540, 1521, 1506, 1464, 1386, 1368, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09-1.12 (m, 63H, $SiCH(CH_3)_2$); 3.09-3.12 (m, 1H, OH); 3.67 (dd, 1H, 16.5 Hz, 7.5 Hz, $CHOSiCH(CH_3)_2$); 3.74-3.85 (m, 3H, $CHCHCH_2OSiCH(CH_3)_2$); 3.99-4.06 (m, 2H, $CH_2CH(OO)$); 5.25 (t, 4.5 Hz, 1H, $CH_2CH(OO)$ (*major diastereomer*)); 5.33 (br s, 1H, $CH_2CH(OO)$ (*minor diastereomer*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 12.0, 17.9, 62.8, 65.3, 69.1, 81.4, 93.6, 98.2; $[\alpha]_D$ = + 4.6 (c = 0.5, $CHCl_3$); HRMS (ESI) exact mass calcd for $[M+NH_4]^+$ ($C_{33}H_{76}NO_6Si_3$) requires *m/z* 666.4975, found *m/z* 666.4961

General procedure for buffered 2-(triisopropylsilyloxy)acetaldehyde 1 aldol reactions, catalysed by (*L*)-proline icosyl ester 10 (*1*)

(*L*)-Proline icosyl ester **10** (50.1 mg, 0.127 mmol) was added to 2-(triisopropylsilyloxy)acetaldehyde **1** (275 mg, 1.27 mmol) in pH 7 phosphate buffer (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude reaction mixture. This was then purified by flash column chromatography using Merck TLC grade silica gel with silica/alumina binder supplied by Aldrich (30:1:1:0.32 pentane:diethyl ether:dichloromethane:acetic acid) to provide the acetal product 5-triisopropylsilanyloxy-2,6-bis-triisopropylsilanyloxymethyl-[1,3]dioxan-4-ol **8** (88.1 mg, 0.138 mmol) in 32 % yield, 23 % *e.e*., as a mixture of diastereomers as a clear, colourless oil. The enantiomeric excess was determined using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]. IR (film) 2945, 2892, 2868, 2360, 1734,

1684, 1653, 1635, 1576, 1559, 1540, 1521, 1506, 1464, 1386, 1368, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09-1.12 (m, 63H, $SiCH(CH_3)_2$); 3.09-3.12 (m, 1H, OH); 3.67 (dd, 1H, 16.5 Hz, 7.5 Hz, $CHOSiCH(CH_3)_2$); 3.74-3.85 (m, 3H, $CHCHCH_2OSiCH(CH_3)_2$); 3.99-4.06 (m, 2H, $CH_2CH(OO)$); 5.25 (t, 4.5 Hz, 1H, $CH_2CH(OO)$ (*major diastereomer*)); 5.33 (br s, 1H, $CH_2CH(OO)$ (*minor diastereomer*)); ^{13}C NMR (400 MHz, $CDCl_3$): δ 12.0, 17.9, 62.8, 65.3, 69.1, 81.4, 93.6, 98.2; HRMS (ESI) exact mass calcd for $[M+NH_4]^+$ ($C_{33}H_{76}NO_6Si_3$) requires *m/z* 666.4975, found *m/z* 666.4961

General procedure for determination of stereochemistry of (*anti*)-3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal 2-*anti* (*1*)

A sample of (*anti*)-3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*anti*** (10.7 mg, 0.0247 mmol) was added to a solution of 4-nitrobenzoyl chloride (11.3 mg, 0.0609 mmol) and 4-(dimethylamino)pyridine (0.664 mg, 0.00543 mmol) in dichloromethane (0.5 mL) at 0 ^{o}C under argon. Triethylamine (0.0172 mL, 0.124 mmol) was then added to the reaction mixture. After 3 hours methanol (0.5 mL) was added to the solution, followed by sodium borohydride (9.34 mg, 0.247 mmol). After 1 hour the reaction mixture was allowed to warm to room temperature. After a further 2 hours the solution was diluted with dichloromethane (5 mL) and washed with saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with dichloromethane (3 × 2 mL). The organic extracts were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to give the crude acylated and reduced product. Purification by preparative thin-layer chromatography (4:1 Pentane:diethyl ether) provided the 1-hydroxy-3-*p*-nitrobenzoate-derivative (2.8 mg, 0.0048 mmol) in 19 % yield as a colourless oil. The enantiomeric excess was then determined by chiral shift NMR analysis using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] (0.9 mg, 0.0010 mmol) in deuterated chloroform (0.7 mL). Only HPLC data provided in the literature

(*1*), full data provided below; IR (film) 2945, 2891, 2867, 1724, 1607, 1531, 1462, 1384, 1349, 1320, 1278, 1103, 1059, 1015, cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 (m, 42H, $SiCH(CH_3)_2$); 3.55-3.81 (m, 2H, CH_2OH); 3.90-4.09 (m, 2H, $CH_2OSiCH(CH_3)_2$); 4.21 (q, 4.0 Hz, 1H, $CHCH_2OH$); 5.32 (q, 4.0 Hz, 1H, CHOOCAr); 8.19 (dd, 9.0 Hz, 13.0 Hz, 4H, $C_6H_4NO_2$); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.8, 12.5, 17.9, 18.0, 18.1, 27.0, 30.3, 61.7, 63.4, 72.6, 76.7, 123.5, 130.8,135.6, 150.6, 164.3; HRMS (ESI) exact mass calcd for $[M+H]^+$ ($C_{29}H_{54}NO_7Si_2$) requires *m/z* 584.3433, found *m/z* 584.3436.

General procedure for 2-(triisopropylsilyloxy)acetaldehyde 1 retro-aldol reaction investigation

(*L*)-Proline benzyl ester hydrochloride (11.1 mg, 4.6 μmol) was shaken with saturated sodium bicarbonate solution (2 mL), then extracted with chloroform (3 × 1 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the free ester. This was then immediately added to a sample of (*anti*)-3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal **2-*anti***, 47 % *e.e*., (20.0 mg, 0.0462 mmol) in water (0.5 mL). After 5 hours the reaction mixture was extracted with diethyl ether (3 × 1 mL); the organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to return the *anti*-aldol product (20.0 mg, 0.0462 mmol) in 100 % yield, 50 % *e.e*. as a clear, colourless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (m, 42H, $SiCH(CH_3)_2$); 3.74 (m, 2H, CH_2); 3.91 (m, 1H, $CHOHCH_2$); 4.19 (dd, 2.0 Hz, 2.0 Hz, 1H, CHOHCHO); 9.62 (d, 2.0 Hz, 1H, CHO); ^{13}C NMR (400 MHz, $CDCl_3$): δ 11.9, 12.4, 18.0, 62.7, 74.3, 78.9, 202.1

***meso*-Erythritol tetraacetate** (*3*, *4*)

Pyridine (0.05 mL, 0.618 mmol) was added to *meso*-erythritol **17** (10.0 mg, 0.0819 mmol) in acetic acid anhydride (1 mL) under nitrogen, followed by 4-(dimethylamino)pyridine (0.5 mg,

4.1 μmol). After 5 hours the reaction mixture was diluted with dichloromethane (10 mL), and washed with water (10 mL). The separated organic layer was then washed with saturatred sodium bicarbonate solution (10 mL), 1 mol dm^{-3} hydrochloric acid (10 mL) followed by brine (10 mL). The aqueous layers were each extracted with dichloromethane (3 × 4 mL) and combined with the washed organic layer. The combined organic extracts were then dried with magnesium sulfate, filtered and concentrated *in vacuo* to proivde the crude title compound. This was then purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the pure title compound (23.5 mg, 0.0811 mmol) in 99 % yield as a white, crystalline solid. The data was found to be in accordance with the literature (*16*, *26*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (d, 9.5 Hz, 12H, CH_3CO_2); 4.16 (dd, 5.5 Hz, 12.0 Hz, 2H, CH_2); 4.30 (dd, 2.5 Hz, 12.0 Hz, CH_2); 5.24 (t, 2.5 Hz, 2H, CH); $[\alpha]_D$ = 0.0 (c = 1.0, $CHCl_3$)

***D*-Threitol tetraacetate** (*3*, *4*)

Pyridine (0.05 mL, 0.618 mmol) was added to D-threitol (10.0 mg, 0.0819 mmol) in acetic acid anhydride (1 mL) under nitrogen, followed by 4-(dimethylamino)pyridine (0.5 mg, 4.1 μmol). After 5 hours the reaction mixture was diluted with dichloromethane (10 mL), and washed with water (10 mL). The separated organic layer was then washed with saturatred sodium bicarbonate solution (10 mL), 1 mol dm^{-3} hydrochloric acid (10 mL) followed by brine (10 mL). The aqueous layers were each extracted with dichloromethane (3 × 4 mL) and combined with the washed organic layer. The combined organic extracts were then dried with magnesium sulfate, filtered and concentrated *in vacuo* to proivde the crude title compound. This was then purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the pure title compound (23.3 mg, 0.0803 mmol) in 98 % yield as an off-white oil. The data was found to be in accordance with the literature (*3*, *4*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (d,

9.5 Hz, 12H, CH_3CO_2); 4.16 (dd, 5.5 Hz, 12.0 Hz, 2H, CH_2); 4.30 (dd, 2.5 Hz, 12.0 Hz, CH_2); 5.24 (t, 2.5 Hz, 2H, CH); $[\alpha]_D$ = + 22.3 (c = 1.0, $CHCl_3$)

***L*-Threitol tetraacetate** (*3*, *5*)

Pyridine (0.05 mL, 0.618 mmol) was added to L-threitol (10.0 mg, 0.0819 mmol) in acetic acid anhydride (1 mL) under nitrogen, followed by 4-(dimethylamino)pyridine (0.5 mg, 4.1 μmol). After 5 hours the reaction mixture was diluted with dichloromethane (10 mL), and washed with water (10 mL). The separated organic layer was then washed with saturatred sodium bicarbonate solution (10 mL), 1 mol dm^{-3} hydrochloric acid (10 mL) followed by brine (10 mL). The aqueous layers were each extracted with dichloromethane (3 × 4 mL) and combined with the washed organic layer. The combined organic extracts were then dried with magnesium sulfate, filtered and concentrated *in vacuo* to proivde the crude title compound. This was then purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the pure title compound (23.8 mg, 0.0819 mmol) in 100 % yield as an off-white oil. The data was found to be in accordance with the literature (*3*, *5*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (d, 17.0 Hz, 12H, CH_3CO_2); 3.99 (dd, 6.0 Hz, 12.0 Hz, 2H, CH_2); 4.27 (dd, 4.0 Hz, 14.0 Hz, CH_2); 5.26 (t, 4.0 Hz, 2H, CH); $[\alpha]_D$ = - 20.7 (c = 1.0, $CHCl_3$)

General procedure for buffered glycolaldehyde 13 aldol reactions catalysed by (*L*)-*N*-methyl leucine ethyl ester 7 (*3*)

Glycolaldehyde dimer **12** (240 mg, 2.00 mmol) was added to a stirred mixture of (*L*)-*N*-methyl leucine ethyl ester **7** (17.3 mg, 0.10 mmol) in pH 7 phosphate buffer (3 mL). After 5 hours the reaction mixture was concentrated *in vacuo*, and re-dissolved in methanol (3 mL) at 0 ^oC. Sodium borohydride (152 mg, 4.00 mmol) was then added carefully and the reaction kept at 0 ^oC for 3 hours, after which it was allowed to warm to room temperature. After a

further 15 hours, the reaction was cooled to 0 ^{o}C and quenched with 2 mol dm^{-3} hydrochloric acid (3 mL). It was then concentrated *in vacuo* and re-dissolved in dichloromethane (5 mL). Pyridine (1 mL) was then added, followed by 4-dimethylaminopyridine (1.3 mg, 0.01 mmol) then acetic anhydride (3 mL). The reaction mixture was stirred for 7 hours, then washed with water (10 mL) and extracted with dichloromethane (3 × 5 mL). The separated and combined organics were then washed with 1 mol dm^{-3} hydrochloric acid (10 mL), brine (10 mL) and finally water (10 mL). The organic layer was then dried with magnesium sulfate and concentrated *in vacuo* to give the crude reduced and acylated derivatised tetroses (18.2 mg). These products were then dissolved in ethyl acetate and analysed by chiral-phase GC analysis using the conditions provided in the literature (*3*). GC tetra-acetylated erythritol: (CP-Chirasil-Dex CB); T_{inj} = 250 ^{o}C, T_{det} = 275 ^{o}C, flow = 1.5 mL min^{-1}, t_i=100 ^{o}C (10 min), (1.5 ^{o}C min^{-1}) t_f = 180 ^{o}C (10.0 ^{o}C min^{-1}) t_f = 200 ^{o}C (10 min): t_R = 36.71 min; GC tetra-acetylated threitol: (CPChirasil-Dex CB); T_{inj} = 250 ^{o}C, T_{det} = 275 ^{o}C, flow = 1.5 mL min^{-1}, t_i = 100 ^{o}C (10 min), (180 ^{o}C min^{-1}) t_f = 200 ^{o}C (10 min): *L*-isomer: t_R = 38.56 min; *D*-isomer: t_R = 38.70 min. 8:1 *anti*:*syn*; 68 % *e.e.* (*D*-enantiomer).

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