1-1-2016

A chemoenzymatic route to chiral siloxanes

Ravi Naoum
Brock University

Jacqueline P. Séguin
Brock University

John F. Trant
Brock University

Mark B. Frampton
Brock University

Tomáš Hudlický
Brock University

See next page for additional authors

A Chemoenzymatic Route to Chiral Siloxanes: A Step Towards the Enzymatic Synthesis of Chiral Silicone Polymers

Ravi Naoum, Jacqueline P. Séguin, John F. Trant, Mark B. Frampton, Tomas Hudlicky, and Paul M. Zelisko*

Department of Chemistry and Centre for Biotechology, Brock University
500 Glenridge Avenue, St. Catharines, ON L2S 3A1 Canada
*Tel: +1-905-688-5550 ext. 4389, E-mail: pzelisko@brocku.ca

Keywords

siloxane, chemoenzymatic, silicone, transesterification, chiral, N435, lipase, toluene dioxygenase

Abstract

Immobilized lipase B from *Candida antarctica* (N435) was explored as a potential biocatalyst for the efficient generation of disiloxane-containing chiral polymers from chiral cyclic diol species and siloxane monomeric units. ^{1}H NMR analysis of reaction mixtures suggested that up to 66% consumption of the siloxane starting materials occured. Oligomeric species were observed and chiral products from the coupling of a cyclic diol with a siloxane molecule were isolated and characterized by MALDI-ToF MS and GPC. Immobilized lipases from *Rhizomucor miehei* and *Thermomyces lanuginosus* were also explored as potential catalysts for the polymerization reactions, however, their use did not generate oligomeric products.

Introduction

Synthetic chiral polymers find applications in molecular recognition, catalytic activity, and asymmetric reactions.[1] One of the most common methods for preparing chiral polymers involves the polymerization of optically active monomers. One such example includes the tin-catalyzed ring-opening polymerization of diesters. In 2001

Yasuda *et al.* reported the synthesis of biodegradable chiral polymers from chiral depsipeptide and L-lactide monomers using Sn(2-ethylhexanoate)$_2$ as initiator.[2]

However, the synthesis of the optically active monomers is not always trivial. Biocatalysis is quickly gaining strength as a technique for transforming achiral or racemic compounds into optically pure monomers, and ultimately, polymers.[3,4] One notable application of biocatalysis has been in the use of toluene dioxygenase to synthesize arene *cis*-dihydrodiols as chiral building blocks for further chemical elaboration.[5] In 2004 Bui and Hudlicky reported the synthesis of some polyhydroxylated chiral polymers using this strategy.[6] The synthesis of these polymers began with the whole-cell fermentation of bromobenzene with the recombinant organism *E. coli* JM109(pDTG601A) that overexpresses toluene dioxygenase (TDO) and produces *cis*-dihydrodiols from arenes.[7] The diol derived from bromobenzene was further functionalized and used in acyclic diene metathesis (ADMET) polymerization to afford chiral materials. Similarly *cis*-dihydrodiol-derived materials have also proven amenable monomers for a variety of other polymerization techniques including Lewis-acid catalyzed epoxide-ring opening and head-to-tail Diels-Alder polymerizations. REF: Trant, J. F.; Ho, H.; Hudlicky, T. *Synlett* **2014**, *25*, 2360. The proven versatility and structural diversity of these materials makes them ideal candidates for enzyme-catalyzed polymerizations.

O'Hagan and Parker reported the use of *Candida rugosa* as a catalyst in the polymerization of racemic 10-hydroxyundecanoic acid.[8] ^{1}H-NMR analysis of Mosher's esters derived from the products showed that the *S*-monomer was preferentially incorporated into the polymer over the *R*-monomer.[8]

Siloxane-based materials are used in the manufacturing of a number of products such as semiconductors, glasses, ceramics, plastics, elastomers, resins, optical fibres, coatings, insulators, and cosmetics [9] The thermal stability, low glass transition temperatures, low surface energies, high gas permeability, resistance to oxidation, and biocompatibility of siloxane-based polymers have in large part been the impetus for the use of silicones in these applications.[9]

Various reagents, including the use of compounds such as Karstedt's catalyst, Speier's catalyst, alkoxytitanium complexes, tin carboxylates and strong acids and bases are commonly employed in the synthesis of organosilicon polymers or their modification/functionalization.[9] However, the modification of silicone polymers by strong acids or bases is not always conducive to siloxane bond stability as redistribution or scission of the siloxane backbone may occur, which can greatly alter the molecular weight of the polymeric system and ultimately the physical properties of the silicone.[10] As a result researchers have begun to explore the use of biotechnology as a means of replacing some of the harsher reagents that are typically employed in the modification of silicone polymers.[11]

Gross *et al.* reported one of the first syntheses of silicone polyesteramides with *Candida antarctica* lipase B immobilized on acrylic beads (Novozym-435®, N435) as the polymerization catalyst.[12] Subsequent to this report Clarson and Gross reported the synthesis of organosiloxane-polyester copolymers using N435 to catalyze a polyesterification reaction.[13] Poojari investigated various reaction conditions and their effects on the ultimate molecular weights of the polymers.[13] Performing reactions at 70

°C was found to be optimal for attaining higher molecular weights of the polymers and this was further improved by performing the reactions at reduced pressure.[13]

More recently our group reported the synthesis of disiloxane-containing polyesters catalyzed by N435.[10] These polyesters were fully characterized and the reusability, as well as the thermal tolerance, of N435 was explored. N435 was found to retain at least 90% of its activity up to 130 °C, after which point catastrophic enzyme denaturation appeared to occur. Furthermore, N435 could be reused for at least 10 reactions at 100 °C while maintaining consistent overall monomer conversions; however, the apparent initial rate constant decreased with each subsequent reaction.10

Given the successes that have been reported in the literature with respect to lipase-mediated reactions with achiral silicone systems, it was of interest to examine the capacity of N435 to perform transesterification reactions with siloxane-containing esters and a series of chiral diol species.

Experimental

Materials

Lipase B from *Candida antarctica* (immobilized on acrylic resin, recombinant expressed in *Aspergillus niger*, L119K1582, E.C.3.1.1.3) (Novozym-435, N435), platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (Karstedt's catalyst, Pt^0(dvs)), 9-decenoic acid, and chloroform were purchased from Sigma-Aldrich (Oakville, Ontario, Canada). 1,1,3,3-Tetramethyldisiloxane was purchased from Gelest, Inc. (Morrisville, Pennsylvania, USA). *p*-Toluene sulfonic acid was purchased from Eastman Kodak Company (Rochester, New York, USA). Pentane, methanol, acetone, ethyl acetate, and diethyl ether were purchased from Fisher Scientific (Fair Lawn, New Jersey, USA).

Chloroform-*d* (99.8% deuterated) was purchased from Cambridge Isotope Laboratories, Inc. (Landover, Maryland, USA). Chromium (III) 2,4-pentanedionate was purchased from Alfa Aesar (Ward Hill, Massachusetts, USA). Toluene was purchased from ACP Chemicals (Montréal, Québec, Canada). Distilled water was used for all preparations. All reagents were used as received without further modification or purification unless otherwise stated.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Spectra were acquired using either a Bruker Avance 300, 400, or 600 MHz spectrometer. ^{1}H NMR spectra were referenced to $CDCl_3$ at 7.26 ppm or acetone-d_6 at 2.05 ppm as the internal standard. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.0 ppm as the internal standard. ^{29}Si NMR spectra were referenced to TMS at 0.0 ppm as the internal standard. Spectra were analyzed by the Bruker TopSpin v2.0 software platform.

Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR spectra were acquired on a Mattson Research Series scanning infrared spectrometer in transmittance mode. Samples were prepared as thin films on KBr windows. All spectra were acquired with either 32 or64 scans at 2 cm^{-1} resolution. Spectra were analyzed by the WinFirst software platform.

Mass Spectrometry (Electron Impact [EI] and Matrix Assisted Laser Desorption Time of Flight [MALDI-ToF])

Electron impact mass spectrometry (EI-MS) was carried out on a Kratos/MSI Concept 1S high resolution mass spectrometer in positive ion mode.

MALDI-ToF MS spectra were acquired on a Bruker Autoflex MALDI-ToF mass spectrometer in the positive ion mode. Samples were dissolved into HPLC grade THF or

acetone, sonicated, and combined with a NaCl/THF (acetone) mixture and sonicated a second time. A small sample was transferred to a stainless steel plate that was preloaded with a dried dithranol spot deposited from a THF solution.

Gel Permeation Chromatography (GPC)

Polymer molecular weights and polydispersity indices (relative to polystyrene standards) were analyzed via GPC on a Waters 2695 Separations Module equipped with a Waters 2414 refractive index detector, a Waters 2996 photodiode array detector, and three Jordi Fluorinated DVB mixed bed columns connected in series. THF was used as the eluent at a flow rate of 1.0 mL/min.

Optical Rotations

Optical rotations for isolated compounds were acquired on a Rudolph Research Analytical Autopol IV polarimeter. A 50 mm sample cell was used with a wavelength of 589 nm.

Synthesis of (3a*S*,4R,5*R*,7a*S*)-7-Bromo-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole- 4,5-diol (1)

This compound was prepared according to published protocols.[14] The spectral data are consistent with published data.[15]

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 (d, *J* = 3.1 Hz, 1H), 4.67 (d, *J* = 5.4 Hz, 1H), 4.45 (dd, *J* = 5.4, 4.5 Hz, 1H), 4.36 (dd, *J* = 3.2, 4.5 Hz, 1H), 4.18 (dd, *J* = 4.5, 4.5 Hz 1H), 3.19 (bs, 2H), 1.45 (s, 3H), 1.42 (s, 3H).

(3a*S*,4*R*,5*R*,7a*R*)-2,2-Dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diol (2)

This compound was prepared according to published protocols.[15] The spectral data were consistent with published information.[15]

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95 (m, 2H), 4.68 (dd, *J* = 5.9, 2.5 Hz, 1H), 4.39 (dd, *J* = 6.5, 6.1 Hz, 1H), 4.36 – 4.31 (m, 1H), 4.05 – 3.97 (m, 1H), 2.46 – 2.37 (m, 1H), 2.34 – 2.30 (m, 1H), 1.47 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.8, 127.6, 75.7, 71.8, 71.2, 65.9, 27.9, 25.9.

(3a*S*,4*R*,5*R*,7a*R*)-2,2-Dimethylhexahydrobenzo*[d]*[1,3]dioxole-4,5-diol (3)

Alkene **2** (1.0 g, 5.4 mmol) was dissolved in methanol (20 mL) in a flask equipped with a magnetic stirring bar. The flask was then evacuated, and charged with nitrogen. Palladium on carbon (10 wt %, 100 mg) was added, and the flask was evacuated and charged a balloon filled with hydrogen. The flask was alternately evacuated and recharged four times to establish a hydrogen atmosphere. The reaction mixture was stirred for 16 h at ambient temperature and pressure until thin layer chromatography (TLC) analysis indicated complete consumption of the starting material. The reaction mixture was then filtered through a Celite pad, and the filtrate was subsequently concentrated under reduced pressure to provide 956 mg of **3** in 94 % yield as a clear oil that solidified upon standing. No further purification was required. The product was isolated as a white amorphous solid. R_f = 0.58 [MeOH/EtOAc (10:90)]; mp 101-102^{o}C (hexanes/EtOAc), $[\alpha]_D^{20}$ = – 90.6 (*c* = 0.5, $CHCl_3$); IR (ATR) *v* 3450, 3398, 3274, 2982, 2944, 2877, 1415, 1378, 1333, 1241, 1222, 1051, 874 cm^{-1}; ^{1}H NMR (300 MHZ, $CDCl_3$) δ 4.31 – 4.29 (m, 1H), 4.07 (dd, *J* = 7.0, 5.3 Hz, 1H), 4.04 – 4.01 (m, 1H), 3.65 (dd, *J* = 7.0, 2.6 Hz, 1H), 3.05 (s, 1H), 2.61 (s, 1H), 2.12 – 2.05 (m, 1H), 1.90 – 1.86 (m, 1H), 1.79 – 1.70 (m, 2H), 1.49 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.5, 78.7, 73.9, 73.7, 69.8, 28.3, 26.2, 25.0, 21.1; MS (EI) *m/z* (%) 57 (42), 67 (80), 95 (41), 173

(100); HRMS (EI) calculated for $C_9H_{16}O_4$ (M^+ - CH_3) species 173.0814. Found 173.0807; Anal. Calculated for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.46; H, 8.61.

Synthesis of 9-decenoic acid methyl ester (5)

9-Decenoic acid **4** (4.59g, 27.0 mmol) and *p*-toluene sulfonic acid (0.29 g, 1.53 mmol) were added to a 250 mL round bottomed flask and dissolved into 30 mL of methanol. The reaction mixture was refluxed for 4 h with molecular sieves (4Å). Methanol was removed using a rotary evaporator and the remaining crude mixture was extracted into 30 mL of diethyl ether and washed with 3 x 5.0 mL of 1M $KHCO_3$ and 2 x 5.0 mL of saturated NaCl. The combined aqueous fractions were extracted with 15 mL of diethyl ether. The combined ethereal fractions were washed with 10 mL of saturated NaCl and dried over Na_2SO_4, filtered through a medium porosity glass filter, and solvent removed on the rotary evaporator. The product was a clear and colourless liquid obtained in 96% yield (4.00 g, 23.90 mmol): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.79 (m, 1H), 4.95 (m, 2H), 3.65 (s, 3H), 2.30 (t, *J*=7.41Hz, 2H), 2.04 (m, 2H), 1.62 (m, 2H), 1.31 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 139.1, 114.2, 51.4, 34.1, 33.7, 28.9, 24.92. The spectral data were consistent with literature values.[16]

Synthesis of 1,3-bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane (6)

9-Decenoic methyl ester **5** (4.40g, 23.9 mmol) was added to a 250 mL round bottomed flask, followed by 20μL of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (Karstedt's catalyst, Pt^0(dvs). Toluene (20 mL) and 1,1,3,3-tetramethyldisiloxane (1.60 g, 11.9 mmol) were added to the reaction mixture, which was subsequently heated at reflux for 4 h. Progress of the reaction was monitored by FTIR by following the disappearance of the Si-H peak (2100 cm^{-1}). The reaction was terminated by cooling the

mixture to room temperature and removing toluene using a rotary evaporator. A crude mixture consisting of a straw-coloured oil was obtained. The crude mixture was purified on SiO_2 using flash column chromatography with a mixture of 9:1 pentane:ethyl acetate as the elution solvent. The product was clear and colourless and was isolated with a 21% purified yield (1.25 g, 2.47 mmol): ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.66 (s, 6H), 2.30 (t, *J*=7.44 Hz, 4H), 1.61 (m, 4H), 1.27 (s, 24H), 0.49 (m, 4H), 0.023 (s, 12H); ^{13}C NMR (77.5 MHz, $CDCl_3$): δ 174.3, 51.4, 34.1, 33.4, 29.4, 29.3, 29.3, 29.2, 25.0, 23.3, 18.4, 0.37; ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ 7.25; MS (EI): (M^+ - CH_3 species): 487 m/z. FTIR (KBr, cm^{-1}): 796, 841, 1059, 1173, 1198, 1252, 1437, 1743, 2854, 2924. The spectral data were consistent with literature values.[17]

Synthesis of (3a*S*,4*R*,5*R*,7a*S*)-7-bromo-4-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (7)

1,3-Bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** was added to a stirred solution of diol **1** (45 mg, 0.17 mmol) and stirred for 5 min in toluene (0.85 mL) maintained at 100 °C. The resulting mixture was charged with N435 (14 mg). The reaction mixture was heated 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The unfractionated reaction mixture was subjected to GPC and MALDI-ToF analysis. The light yellow oil produced by the reaction was subjected to flash chromatography with hexanes/EtOAc (97:3) and deactivated silica (10 wt% H_2O) to give 5 mg (4%) of **7** as colorless oil.

R_f = 0.32 [hexanes/EtOAc (80:20)]; $[\alpha]_D^{20}$ = 15.1 (*c* = 0.35, $CHCl_3$); IR (ATR) *v* 3466, 2922, 2853, 1741,1437, 1372, 1250, 1163, 1051, 838, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, *J* = 2.4 Hz, 1H), 5.42 – 5.40 (m, 1H), 4.69 (d, *J* = 5.3 Hz, 1H), 4.45 – 4.42 (m, 1H), 4.29 – 4.26 (m, 1H), 3.67 (s, 3H), 2.40 – 2.28 (m, 4H), 1.75 – 1.57 (m, 4H), 1.46 (s, 3H), 1.41 (s, 3H), 1.28 (bs, 24H), 0.49 (bs, 4H), 0.02 (bs, 12H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 172.7, 127.5, 125.2, 110.5, 76.3, 76.1, 69.6, 68.3, 51.4, 34.2, 34.1, 33.4, 29.4, 29.34, 29.31, 29.2, 29.18, 29.12, 27.7, 26.1, 25.0, 24.9, 23.3, 18.4, 0.4; ^{29}Si NMR (80 MHz, $CDCl_3$) 7.3; MS (EI) *m/z* (%); 133 (34), 287 (60), 317 (100); HRMS (EI) calcd for $C_{34}H_{63}BrO_8Si_2$ (^{81}Br, M^+ - CH_3 species): 721.2991. Found 721.2973.

Synthesis of (3a*S*,4*R*,5*R*,7a*S*)-7-bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (8)

1,3-Bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** (85 mg, 0.17 mmol) was added to a stirred solution of diol **1** (45 mg, 0.17 mmol) and stirred for 5 min in toluene (0.85 mL) maintained at 100 °C. The resulting mixture was charged with N435 (14 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases concentrated under reduced pressure. The unfractionated reaction mixture was subjected to GPC and MALDI-ToF analysis. The light yellow oil produced by the reaction was subjected to flash chromatography with hexanes/EtOAc (97:3) and deactivated silica (10 wt% H_2O) to give 2 mg (1.6%) of **8** as colorless oil.

R_f = 0.37 [hexanes/EtOAc (80:20)]; $[\alpha]_D^{20}$ = -9.8 (*c* = 0.30, $CHCl_3$); IR (ATR) *v* 3431,

2920, 2852, 2323, 2041, 1994, 1904, 1740, 1655, 1459, 1438, 1371, 1250, 1163, 1047, 840, 792 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, *J* = 2.7 Hz, 1H), 5.42 – 5.39 (m, 1H), 4.60 (d, *J* = 5.1 Hz, 1H), 4.49 – 4.44 (m, 2H), 3.66 (s, 3H), 2.40 – 2.28 (m, 4H), 1.63 – 1.57 (m, 4H), 1.44 (s, 3H), 1.39 (s, 3H), 1.27 (bs, 24H), 0.49 (bs, 4H), 0.02 (bs, 12H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 173.4, 131.4, 123.4, 110.7, 76.3, 74.0, 70.9, 66.1, 51.5, 34.2, 34.1, 33.4, 29.4, 29.34, 29.32, 29.2, 29.1, 27.5, 26.2, 24.99, 25.95, 23.3, 18.4, 0.4; ^{29}Si NMR (80 MHz, $CDCl_3$) 7.3; MS (EI) *m/z* (%); 133 (33), 287 (64), 317 (100); HRMS (EI) calcd for $C_{34}H_{63}BrO_8Si_2$ (^{81}Br, M^+ - CH_3 species):721.2991. Found 721.2991.

Synthesis of (3a*S*,4*R*,5*R*,7a*R*)-4-Hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (9)

1,3-Bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** 85 mg, 0.17 mmol) was added to a stirred solution of diol **2** (33 mg, 0.18 mmol) and stirred for 5 min in toluene (0.9 mL) maintained at 100 °C. The resulting mixture was charged with N435 (12 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The unfractionated reaction mixture was subjected to GPC and MALDI-ToF analysis. The light yellow oil produced by the reaction was subjected to flash chromatography with hexanes/EtOAc (90:10) and deactivated silica (10 wt% H_2O) to give 9 mg (8%) of **9** as colorless oil.

R_f = 0.46 [hexanes/EtOAc (70:30)]; $[\alpha]_D^{20}$ = -69.1 (*c* = 0.75, MeOH); IR (ATR) *v* 3460, 2922, 2853, 1739, 1459, 1437, 1371, 1250, 1214, 1165, 1050, 920, 838, 789, 518 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.97 (m, 1H), 5.89 (dd, *J* = 10.2, 4.2 Hz, 1H), 5.40 – 5.38 (m, 1H), 4.70 – 4.67 (m, 1H), 4.35 (dd, *J* = 7.0, 6.1 Hz, 1H), 4.09 (dd, *J* = 7.0, 3.6 Hz, 1H), 3.66 (s, 3H), 2.37 – 2.28 (m, 4H), 1.64 – 1.59 (m, 4H), 1.46 (s, 3H), 1.39 (s, 3H), 1.27 (bs, 24H), 0.49 (t, *J* = 7.5 Hz, 4H), 0.02 (bs, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 173.2, 129.1, 126.6, 109.7, 75.6, 71.8, 69.9, 68.5, 51.5, 34.3, 34.1, 33.4, 29.43, 29.41, 29.35, 29.34, 29.31, 29.2, 29.1, 27.9, 25.8, 25.0, 23.3, 18.4, 0.4. ^{29}Si NMR (80 MHz, $CDCl_3$) δ 7.28; MS (EI) *m/z* (%) 57 (100), 69 (48), 71 (65), 85 (48), 97 (35), 149 (31), 317 (14); HRMS (EI) calcd for $C_{34}H_{64}O_8Si_2$ (M^+ - CH_3 species): 641.3906. Found 641.3894.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-5-Hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (10)

1,3-Bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** (85 mg, 0.17 mmol) was added to a stirred solution of diol **2** (33 mg, 0.18 mmol) and stirred for five min in toluene (0.9 mL) maintained at 100 °C. The resulting mixture was charged with N435 (12 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The unfractionated reaction mixture was subjected to GPC and MALDI-ToF analysis. The light yellow oil produced by the reaction was subjected to flash chromatography with hexanes/EtOAc (90:10) and deactivated silica (10 wt% H_2O) to give 3 mg (3%) of **10** as colorless oil.

R_f = 0.41 [hexanes/EtOAc (70:30)]; $[\alpha]_D^{20}$ = - 41.8 (*c* = 0.15, MeOH); IR (ATR) *v* 3429,

2920, 2852, 1739, 1461, 1438, 1374, 1250, 1216, 1163, 1057, 920, 839, 790, 515, 425 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (d, *J* = 2.3 Hz, 2H), 5.23 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.65 (dd, *J* = 5.8, 1.8 Hz, 1H), 4.45 (dd, *J* = 7.1, 5.9 Hz, 1H), 4.42 (bs, 1H)., 3.67 (s, 3H), 2.41 – 2.28 (m, 4H), 1.99 (bs, 1H) 1.68 – 1.60 (m, 4H), 1.44 (s, 3H), 1.37 (s, 3H), 1.27 (bs, 24H), 0.49 (t, *J* = 6.4 Hz, 4H), 0.03 (s, 12H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 173.5, 129.9, 127.6, 109.8, 73.1, 72.9, 72.0, 64.9, 51.5, 34.3, 34.1, 33.4, 29.4, 29.41, 29.36, 29.32, 29.2, 29.1, 27.7, 26.0, 25.0, 23.3, 18.4, 0.4; ^{29}Si NMR (80 MHz, $CDCl_3$) δ 7.29; MS (EI) *m/z* (%) 57 (100), 69 (52), 71 (67), 83 (46), 111 (27), 149 (62), 287 (36), 317 (56); HRMS (EI) calcd for $C_{34}H_{64}O_8Si_2$ (M^+ - CH_3 species): 641.3906. Found 641.3942.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-5-Hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (11)

1,3-Bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** (87 mg, 0.17 mmol) was added to a stirred solution of diol **3** (33 mg, 0.175 mmol) and stirred for 5 min in toluene (0.87 mL) maintained at 100 °C. The resulting mixture was charged with N435 (12 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The unfractionated reaction mixture was subjected to GPC and MALDI-ToF analysis. The light yellow oil produced by the reaction was subjected to flash chromatography with hexanes/EtOAc (90:10) and deactivated silica (10 wt% H_2O) to give 14 mg (12%) of **11** as colorless oil.

R_f = 0.44 [hexanes/EtOAc (70:30)]; $[\alpha]_D^{20}$ = - 35.3 (*c* = 0.7, MeOH); IR (ATR) *v* 3468, 2922, 2853, 1737, 1437, 1369, 1249, 1369, 1249, 1215, 1163, 1055, 1036, 838, 789, 703, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 – 5.16 (m, 1H), 4.35 – 4.31 (m, 1H)., 4.06 (dd, *J* = 6.9, 5.4 Hz, 1H), 3.81 – 3.77 (m, 1H), 3.66 (s, 3H), 2.35 – 2.28 (m, 4H), 2.20 (d, *J* = 4.3 Hz, 1H), 1.96 – 1.91 (m, 2H), 1.83 – 1.79 (m, 2H), 1.63 – 1.50 (m, 4H), 1.50 (s, 3H), 1.37 (s, 3H), 1.27 (bs, 24H), 0.48 (t, *J* = 7.4 Hz, 4H), 0.02 (bs, 12H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 173.5, 108.7, 78.7, 73.5, 72.3, 72.1, 51.4, 34.5, 34.1, 33.4, 29.44, 29.40, 29.33, 29.31, 29.2, 29.1, 28.4, 26.2, 25.1, 25.0, 23.3, 23.0, 22.0, 18.4, 0.7, 0.4, 0.1; ^{29}Si NMR (80 MHz, $CDCl_3$) δ 7.27; MS (EI) *m/z* (%) 55 (55), 67 (66), 95 (60), 155 (65), 325 (100); HRMS (EI) calcd for $C_{34}H_{66}O_8Si_2$ (M^+ - CH_3 species): 643.4062. Found 643.4039; Anal. Calcd for $C_{34}H_{66}O_8Si_2$: C, 61.96; H, 10.09 Found C, 61.77; H, 10.09.

Synthesis of (3a*S*,4*R*,5*R*,7a*R*)-4-Hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (12)

1,3-Bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** (87 mg, 0.17 mmol) was added to a stirred solution of diol **3** (33 mg, 0.175 mmol) and stirred for 5 min in toluene (0.87 mL) maintained at 100 °C. The resulting mixture was charged with N435 (12 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The unfractionated reaction mixture was subjected to GPC and MALDI-ToF analysis. The light yellow oil produced by the reaction was subjected to flash chromatography with hexanes/EtOAc (90:10) and

deactivated silica (10 wt% H_2O) to give 19 mg (16%) of **12** as colorless oil. R_f = 0.48 [hexanes/EtOAc (70:30)]; $[\alpha]_D^{20}$ = -30.7 (*c* = 0.9, MeOH); IR (ATR) *v* 3467, 2922, 2853, 1738, 1437, 1380, 1249, 1216, 1162, 1058, 838, 788, 704, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (dd, *J* = 7.8, 2.6 Hz, 1H), 4.36 – 4.33 (m, 1H), 4.21 (dd, *J* = 7.8, 5.1 Hz, 1H), 4.11 – 4.08 (m, 1H), 3.66 (s, 3H), 2.42 – 2.28 (m, 4H), 2.17 – 2.08 (m, 1H), 1.99 – 1.73 (m, 3H), 1.69 – 1.58 (m, 4H), 1.51 (s, 3H), 1.36 (s, 3H), 1.27 (bs, 24H), 0.49 (t, *J* = 7.5 Hz, 4H), 0.02 (bs, 12H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 173.3, 108.7, 75.7, 75.7, 74.1, 68.3, 51.5, 34.4, 34.1, 33.44, 33.41, 29.45, 29.41, 29.33, 29.31, 29.2, 29.1, 28.1, 26.4, 25.0, 25.0, 24.8, 23.3, 20.6, 18.4, 0.7, 0.4, 0.1; ^{29}Si NMR (80 MHz, $CDCl_3$) δ 7.29; MS (EI) *m/z* (%) 55 (100), 57 (66), 67 (50), 95 (53), 317 (82), 325 (48); HRMS (EI) calcd for $C_{34}H_{66}O_8Si_2$ (M^+ - CH_3 species): 643.4062 Found 643.4046; Anal. Calcd for $C_{34}H_{66}O_8Si_2$: C, 61.96; H, 10.09 Found C, 61.76; H, 9.98.

Synthesis of (3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-2,2-dimethyl-5-((triisopropylsilyl)oxy)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (13)

Triisopropylsilyl trifluoromethanesulfonate (7.2 mL, 27 mmol) was added drop-wise to a stirred solution of diol **1** (6.0 g, 22.6 mmol) and 2,6-lutidine (5.3 mL, 45 mmol) in CH_2Cl_2 (115 mL) maintained at −78 °C under a argon atmosphere.[17] The resulting mixture was allowed to warm to rt over 3 h, then treated with NH_4Cl (60 mL of a saturated aqueous solution).[17] The separated aqueous phase was extracted with CH_2Cl_2 (3× 40 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography hexanes/EtOAc (97:3) to give 5.8 g (61%) of **13** as yellow oil.

R_f = 0.35 [hexanes/EtOAc (90:10)]; $[\alpha]_D^{20}$ = -25.5 (*c* = 0.33, $CHCl_3$); IR ($CHCl_3$) *v* 3560, 2941, 2866, 1644, 1461, 1370, 1339, 1230, 1146, 1077, 1053, 879, 679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 – 5.98 (m, 1H), 4.63 – 4.61 (m, 1H), 4.50 – 4.47 (m, 2H), 4.24 (t, *J* = 3.9 Hz, 1H), 2.67 (d, *J* = 1.4 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.12 – 1.01 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.8, 123.5, 110.0, 75.9, 75.7, 69.3, 68.3, 27.5, 26.2, 18.0, 12.1; MS (EI) *m/z* (%) 376 (16), 322 (21), 321 (100), 319 (98), 303 (32), 301 (31), 240 (52), 159 (62); HRMS (EI) calcd for $C_{18}H_{33}BrO_4Si$ (M^+ - CH_3 species): 405.1091. Found 405.1096.

Synthesis of (((3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl)oxy)triisopropylsilane (14)

Sodium hydride (0.58 g, 24 mmol) was added to a stirred solution of alcohol **13** (8.5 g, 20.1 mmol) and iodomethane (1.6 mL, 26 mmol) in dry THF (70 mL) maintained at 0 °C under an argon atmosphere. Stirring was continued for 4 h at 0 °C then the reaction mixture was treated with ice−water (10 mL). The separated aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography hexanes/EtOAc (90:10) to give 5.5 g (63%) of **14** as a white crystalline solid.

R_f = 0.34 [hexanes/EtOAc (90:10)]; mp 62-63 ˚C (EtOAc); $[\alpha]_D^{20}$ = -55.8 (*c* = 1.5, $CHCl_3$); IR (ATR) *v* 2940, 2889, 2865, 1650, 1462, 1040, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (s, 1H), 4.63 (d, *J* = 5.2 Hz, 1H), 4.57 (s, 1H), 4.50 – 4.38 (m, 1H), 3.71 (s, 1H), 3.55 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.09 (bs, 21H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 122.2, 109.9, 80.3, 75.1, 68.1, 59.7, 27.5, 26.0, 18.0, 12.3; MS (EI) *m/z* (%) 75

(50), 89 (43), 145 (100), 254 (49), 393 (36); HRMS (EI) calcd for $C_{19}H_{35}BrO_4Si$(M-CH_3): 421.1234. Found 421.1229; Anal. Calcd for $C_{19}H_{35}BrO_4Si$: C, 52.40; H, 8.10. Found C, 52.68; H, 8.09.

Synthesis of (3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (15).

To a solution of **14** (3.4 g, 7.8 mmol) in THF (30 mL) stirred under argon atmosphere, was added 5 ml of tetrabutylammonium fluoride solution (1.0 M in THF). After 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography hexanes/EtOAc (50:50) to yield 2.1 g (96%) of **15** as a white crystalline solid.

R_f = 0.56 [hexanes/EtOAc (50:50)]; mp 65-67 ˚C (EtOAc); $[\alpha]_D^{20}$ = -7.5 (*c* = 1.1, $CHCl_3$); IR ($CHCl_3$) *v* 3613, 3025, 2991, 2936, 1646, 1454, 1383, 1375, 1229, 1212, 1077, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.9 Hz, 1H), 4.61 – 4.59 (m, 1H), 4.53 (t, *J* = 5.1 Hz, 1H), 4.35 – 4.30 (m, 1H), 3.76 (t, *J* = 4.2 Hz, 1H), 3.54 (s, 3H), 2.66 (d, *J* = 9.6 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 123.3, 110.3, 78.7, 76.2, 73.9, 66.3, 59.2, 27.6, 26.2; MS (EI) *m/z* (%) 124 (15), 115 (100), 59 (10), 55, (11), 43 (26); HRMS (EI) calcd for $C_{10}H_{15}BrO_4$: 278.0149. Found 278.0153; Anal. Calcd for $C_{10}H_{15}BrO_4$: C, 43.03; H, 5.42. Found C, 44.17; H, 5.44.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-4-Methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (16).

To a flame-dried argon purged round-bottom with attached reflux condenser was charged a suspension of **15** (2.0 g, 7.1 mmol) and tributyltin hydride (2.5 g, 8.5 mmol) in THF (50 mL). Argon was bubbled through the mixture for 30 min. AIBN (0.16 g, 1 mmol) was

added to the mixture before it was immersed in a pre-heated oil bath at 90 ˚C. After 8 h, the reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel hexanes/EtOAc (50:50) to give 1.1 g (76%) of **16** as yellow oil.

R_f = 0.29 [hexanes/EtOAc (50:50)]; $[\alpha]_D^{20}$ = -96.28 (*c* = 1.0, $CHCl_3$); IR (ATR) *v* 3448, 2983, 1736.7, 1457, 1215, 1160, 1055, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 – 5.85 (m, 2H), 4.62 – 4.59 (m, 1H), 4.41 (t, *J* = 6.1 Hz, 1H), 4.30 (bs, 1H), 3.51 (bs, 4H), 2.65 (d, *J* = 6.1 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1, 127.6, 109.2, 80.5, 73.8, 71.9, 64.1, 58.7, 27.8, 25.8; MS (EI) *m/z* (%) 185 (10), 127 (12), 115 (100), 97 (20), 81 (14), 55 (13), 43(32); HRMS (EI) calcd for $C_{10}H_{16}O_4$: 200.1049. Found 200.1048.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-4-Methoxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-5-ol (17).

To a solution of **16** (1.0 g, 4.99 mmol) in MeOH (10 mL) was added 10 % Pd/C (100 mg, 1.06 mmol). Hydrogen was bubbled through the mixture for 5 min then the mixture was stirred under hydrogen pressure (400 psi). After 8 h, the catalyst was filtered off and the solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel hexanes/EtOAc (50:50) to yield 0.7 g (69%) of **17** as yellow oil.

R_f = 0.26 [hexanes/EtOAc (50:50)]; $[\alpha]_D^{20}$ = -62.16 (*c* = 1.2, $CHCl_3$); IR (ATR) *v* 3465, 2983, 2933, 1442, 1377, 1241, 1213, 1157, 1051, 872 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (bs, 1H), 4.06 – 4.02 (m, 2H), 3.45 (s, 3H), 3.14 – 3.11 (m, 1H), 2.49 (s, 1H), 2.04 - 1.99 (m, 1H), 1.84-1.65 (m, 3H), 1.45 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 108.1, 83.0, 77.5, 74.0, 66.3, 57.7, 28.3, 26.2, 24.3, 20.7; MS (EI) *m/z* (%) 187 (100), 127 (16.3), 100 (17.7), 95 (19.0), 87 (33.2), 84(54.1), 71(42.2), 67(33.5), 59(33.8), 43 (59.5); HRMS (EI) calcd for $C_{10}H_{18}O_4$: 202.1204. Found 202.1205; Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found C, 59.09; H, 8.97.

Synthesis of (((3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl)oxy)triisopropylsilane (18)

Sodium hydride (0.72 g, 30 mmol) was added to a stirred solution of alcohol **13** (11.0 g, 26 mmol) and chloromethyl methyl ether (2.4 mL, 30 mmol) in dry THF (100 mL) maintained at 0 °C under a argon atmosphere. Stirring was continued for 12 h at 0 °C, then the reaction mixture was treated with ice-water (10 mL) and NH_4Cl (10 mL). The separated aqueous phase was extracted with EtOAc (2 × 40 mL) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography hexanes/EtOAc (90:10) to give 6.9 g (56%) of **18** as clear colorless oil.

R_f = 0.58 [hexanes/EtOAc (90:10)]; $[\alpha]_D^{20}$ = -85.65 (*c* = 0.4, MeOH); IR (ATR) *v* 2940, 2889, 2865, 1650, 1462, 1040, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, *J* = 2.3 Hz, 1H), 4.87 (d, *J* = 6.7 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.58 (s, 1H), 4.47 (t, *J* = 5.3 Hz, 1H), 4.16 – 4.14 (m, 1H), 3.39 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.10 – 0.95 (m, 21H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.2, 122.3, 110.1, 97.2, 76.0, 75.9, 68.2, 55.7, 27.5, 26.2, 18.03, 18.0, 12.3; MS (EI) *m/z* 75 (56), 117 (62), 133 (100), 145 (100); HRMS (EI) calcd for $C_{20}H_{37}BrO_5Si$ (M^+ - CH_3 species) 449.1359. Found 449.1357.

(3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (19)

To a solution of **18** (2.9 g, 6.3 mmol) in THF (30 mL) stirred under argon atmosphere, was added 5 mL of tetrabutylammonium fluoride solution (1.0 M in THF). After 1 h, the reaction mixture was treated with ice−water (10 mL). The separated aqueous phase was extracted with EtOAc (2 × 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography hexanes/ EtOAc (50:50) to yield 1.77 g (92%) of **19** as colourless oil.

R_f = 0.52 [Hexanes/ EtOAc (50:50)]; $[\alpha]_D^{20}$ = 4.1 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) *v* 3431, 2935, 1644, 1373, 1227, 1072, 1028, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, *J* = 2.6 Hz, 1H), 4.73 (s, 2H), 4.56 (dd, *J* = 5.2, 0.9 Hz, 1H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.31 (bs, 1H), 4.07 (t, *J* = 4.2 Hz, 1H), 3.37 (s, 3H), 3.31 (d, *J* = 9.0 Hz, 1H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CHCl_3$,75MHz) δ 132.3, 122.8, 110.3, 97.6, 77.6, 76.5, 75.3, 66.5, 56.0, 27.5, 26.3; MS (EI) *m/z* (%) 205 (14), 191 (14), 161 (13), 146 (32), 145 (100), 110 (21), 97 (16), 59 (50), 45 (9), 43 (53) ; HRMS (EI) calcd for $C_{11}H_{17}BrO_5$: 308.0259. Found 308.0259; Anal. Calcd for $C_{11}H_{17}BrO_5$: C, 42.74; H, 5.54. Found C, 42.91; H, 5.44.

Synthesis of (3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-5-methoxy-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole (20).

Sodium hydride (0.18 g, 7.5 mmol) was added to a stirred solution of alcohol **19** (1.7 g, 5.5 mmol) and iodomethane (0.44 mL, 7.01 mmol) in dry THF (55 mL) maintained at 0 °C under an argon atmosphere. Stirring was continued for 6 h at 0 °C, then the reaction

mixture was diluted with ice−water (10 mL). The separated aqueous phase was extracted with EtOAc (2 × 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography on silica gel hexanes/EtOAc (50:50) to give 1.45 g (79%) of **20** as colourless oil.

R_f = 0.68 [hexanes/EtOAc (1:1)]; $[\alpha]_D^{20}$ = -67.3 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) *v* 2985, 2932, 1643, 1454, 1372, 1340, 1216, 1149, 1035, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, *J* = 3.1 Hz, 1H), 4.79 – 4.72 (m, 2H), 4.65 (d, *J* = 5.3 Hz, 1H), 4.47 (t, *J* = 5.7 Hz, 1H), 4.19 – 4.16 (m, 1H), 3.96 – 3.94 (m, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.8, 123.5, 110.1, 96.9, 77.0, 75.4, 75.9, 73.6, 57.4, 55.7, 27.6, 26.0; MS (EI) *m/z* (%) 145 (74), 87 (5), 73 (6), 45 (100), 43 (15); HRMS (EI) calcd for $C_{12}H_{19}BrO_5$: 322.0416. Found 322.04159; Anal. Calcd for $C_{12}H_{19}BrO_5$: C, 44.60; H, 5.93. Found C, 44.61; H, 5.84.

Synthesis of (3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (21)

Concentrated Hydrochloric acid (2 mL) was added to a stirred solution of **20** (1.4 g, 4.3 mmol) in dry MeOH (50 mL) maintained at 0 °C under a argon atmosphere. Stirring was continued for 4 h at 0 °C then the reaction mixture was treated with ice−water (10 mL). The aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was dissolved in 2,2-dimethoxypropane (30 ml) and catalytic amount of *p*-toluenesulfonic acid (20 mg) was added, stirring was continued for 6 h, then reaction mixture was treated with concentrated solution of $NaHCO_3$ (2 × 1 mL). The reaction

mixture was concentrated under reduced pressure The resulting aqueous phase was extracted with EtOAc (2 × 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography hexanes/EtOAc (50:50) to yield 0.5 g (40%) of **21** as a white crystalline solid.

R_f = 0.56 [hexanes/EtOAc (1:1)]; mp 68-69 ˚C (EtOAc); $[\alpha]_D^{20}$ = -52.9 (*c* = 0.85, $CHCl_3$); IR (ATR) *v* 3512, 2995, 2935, 2899, 2829, 1640, 1342, 1198, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 2.5, 0.9 Hz, 1H), 4.64 (dd, *J* = 5.4, 1.3 Hz, 1H), 4.47 (t, *J* = 5.1 Hz, 1H), 4.33 (t, *J* = 3.9 Hz, 1H), 3.98 (t, *J* = 3.9 Hz, 1H), 3.47 (s, 3H), 2.44 (s, 1H), 1.42 (s, 3H), 1.40 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.2, 124.2, 110.0, 76.1, 67.1, 57.1, 27.6, 26.1; MS (EI) *m/z* (%) 115 (100), 124 (11), 15); HRMS (EI) calcd for $C_{10}H_{15}BrO_4$ (M^+ - CH_3 species) 263.9997. Found 263.9951; Anal. Calcd for $C_{10}H_{15}BrO_4$: C, 43.03; H, 5.42. Found C, 43.33; H, 5.39.

Synthesis of (3a*S*,4*R*,5*R*,7a*R*)-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (22).

To a flame-dried argon purged round-bottom with attached reflux condenser was charged a suspension of **21** (0.5 g, 2.5 mmol) and tributyltin hydride (0.87 g, 3 mmol) in THF (50 mL). Argon was bubbled through the mixture for 30 min. AIBN (0.16 g, 1 mmol) was added to the mixture before it was immersed in pre-heated oil bath at 90 ˚C. After 8 h, the reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel hexanes/EtOAc (25:75) to give 0.34 g (67%) of **22** as colorless oil.

R_f = 0.26 [hexanes/EtOAc (1:1)]; $[\alpha]_D^{20}$ = -162.5 (*c* = 3.0, MeOH); IR (ATR) *v* 3439, 2985, 2931, 2825, 1643, 1457, 1375, 1218, 1159, 1098, 1045, 928, 865, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (d, *J* = 1.2 Hz, 2H), 4.49 (d, *J* = 6.0 Hz, 2H), 4.24 (t, *J* = 5.8 Hz, 1H), 4.02 – 4.00 (m, 1H), 3.73 – 3.72 (m, 1H), 3.30 (s, 3H), 2.98 (s, 1H), 1.25 (s, 3H), 1.21 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 127.8, 127.3, 109.0, 75.4, 74.7, 71.6, 68.6, 56.8, 27.6, 25.8; MS (EI) *m/z* (%) 53 (10), 55 (17), 81 (19), 97 (25), 115 (100); HRMS (EI) calcd for $C_{10}H_{16}O_4$ (M^+ - CH3 species): 185.0814. Found 185.0810.

Synthesis of (3a*S*,4*R*,5*R*,7a*R*)-5-Methoxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-ol (23).

To a solution of **22** (1.4 g, 7 mmol) in MeOH (10 mL) was added 10 % Pd/C (100 mg, 1.06 mmol). Hydrogen was bubbled through the mixture for 5 min then the reaction mixture was stirred under hydrogen pressure (400 psi). After 8 h, the catalyst was filtered off and the solution was concentrated under reduced pressure. The residue was purified by flash column chromatography hexanes/EtOAc (50:50) to yield 1.2 g (84%) of **23** as colorless oil.

R_f = 0.23 [hexanes/EtOAc (1:1)]; $[\alpha]_D^{20}$ = -116.5 (*c* = 0.87, MeOH); IR (ATR) *v* 3450, 2984, 2934, 2879, 2827, 1634, 1456, 1373, 1336, 1243, 1214, 1160, 1054, 1011, 909, 875, 857, 825, 788, 720; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 – 4.14 (m, 1H), 3.95 – 3.92 (m, 1H), 3.58 (bs, 1H), 3.47 – 3.45 (m, 1H), 3.23 (s, 3H), 2.93 (d, *J* = 5.7 Hz, 1H), 1.84 – 1.67 (m, 3H), 1.55 – 1.45 (m, 1H), 1.36 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 108.2, 79.0, 78.4, 73.6, 72.45, 56.4, 28.3, 26.1, 21.7, 21.2. MS (EI) *m/z* (%) 67 (36), 84 (34), 127 (18), 187 (100); HRMS (EI) calcd for $C_{10}H_{18}O_4$: (M^+ - CH_3 species)

187.0970. Found 187.0974; Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found C, 59.10; H, 9.00.

Enzymatic Alcohol Preference

Synthesis of (3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (24)

Diester **6** (88 mg, 0.17 mmol) was added to a stirred solution of **21** (47 mg, 0.17 mmol) and stirred for 5 min in toluene (0.7 mL) maintained at 100 °C. The resulting mixture was charged with N435 (13 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography with hexanes/EtOAc (90:10) to give 11 mg (9%) of **24** as colorless oil.

R_f = 0.50 [hexanes/EtOAc (80:20)]; $[\alpha]_D^{20}$ = -43.5 (*c* = 0.65, MeOH); IR (ATR) *v* 2940, 2889, 2865, 1650, 1462, 1040, 880 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.24 (d, *J* = 3.2 Hz, 1H), 5.51 (dd, *J* = 5.5, 3.6 Hz, 1H), 4.64 (d, *J* = 5.3 Hz, 1H), 4.43 (t, *J* = 5.7 Hz, 1H), 4.04 – 3.91 (m, 1H), 3.66 (s, 3H), 3.39 (s, 3H), 2.37 – 2.34 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.62 – 1.59 (m, 4H), 1.44 (s, 3H), 1.39 (s, 3H), 1.28 – 1.26 (m, 24H), 0.49 (t, *J* = 7.4 Hz, 4H), 0.02 (s, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 173.2, 130.2, 123.3, 110.5, 76.7, 74.6, 74.1, 68.4, 57.7, 51.5, 34.2, 34.1, 33.46, 33.43, 29.47, 29.42, 29.37, 29.34, 29.32, 29.2, 29.0, 27.5, 26.1, 24.99, 24.97, 23.3, 18.4, 0.4. ^{29}Si NMR (80 MHz, $CDCl_3$) δ

7.24; MS (EI) *m/z* (%) 57 (45), 91 (32), 115 (61), 124 (25), 133 (30), 203 (30), 317 (100); HRMS (EI) calcd for $C_{35}H_{65}BrO_8Si_2$ (M^+ - CH_3 species): 733.3167. Found 733.3169.

Synthesis of (3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (25)

Diester **6** (87 mg, 0.17 mmol) was added to a stirred solution of **15** (47 mg, 0.17 mmol) and stirred for 5 min in toluene (0.8 mL) maintained at 100 °C. The resulting mixture was charged with N435 (13 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography with hexanes/EtOAc (90:10) to give 13 mg (10%) of **25** as colorless oil.

R_f = 0.48 [hexanes/EtOAc (80:20)]; $[\alpha]_D^{19}$ = -44.1 (*c* = 0.69, $CHCl_3$); IR (ATR) *v* 2921, 2853, 1739, 1648, 1437, 1371, 1250, 1165, 1115, 1043, 841, 794 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (d, *J* = 4.2 Hz, 1H), 5.48 (t, *J* = 3.7 Hz, 1H), 4.69 (d, *J* = 5.8 Hz, 1H), 4.44 (t, *J* = 6.2 Hz, 1H), 3.72 (dd, *J* = 6.4, 3.5 Hz, 1H), 3.66 (s, 3H), 3.48 (s, 3H), 2.37 – 2.28 (m, 4H), 1.65 – 1.59 (m, 4H), 1.41 (s, 3H), 1.39 (s, 3H), 1.27 (bs, 24H), 0.49 (t, *J* = 7.3 Hz, 4H), 0.02 (s, 12H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.3, 173.0, 128.3, 125.3, 110.3, 77.8, 76.7, 74.9, 67.6, 59.2, 51.4, 34.2, 34.1, 33.42, 33.40, 29.43, 29.40, 29.35, 29.32, 29.30, 29.2, 29.1, 27.7, 25.9, 25.0, 23.3, 18.4, 0.40; ^{29}Si NMR (120 MHz, $CDCl_3$) δ 7.29; MS (EI) *m/z* (%) 57 (35), 85 (15), 115 (14), 149 (100), 317 (45); HRMS (EI) calcd for $C_{35}H_{65}BrO_8Si_2$ (M^+ - CH_3 species): 733.3167. Found 733.3159.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-5-Methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (26)

Diester **6** (79 mg, 0.16 mmol) was added to a stirred solution of **22** (34 mg, 0.17 mmol) and stirred for 5 min in toluene (0.85 mL) maintained at 100 °C. The resulting mixture was charged with N435 (12 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography with hexanes/EtOAc (90:10) to give 4 mg (3.5%) of **26** as colorless oil.

R_f = 0.40 [(Hex/EtOAc (80:20)]; $[\alpha]_D^{18}$ = -58.2 (*c* = 0.95, $CHCl_3$); IR (ATR) *v* 2922, 2854, 1740, 1460, 1372, 1251, 1162, 1101, 1041, 840, 788, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.92 (m, 2H), 5.27 (dd, *J* = 7.2, 3.4 Hz, 1H), 4.68 – 4.66 (m, 1H), 4.44 (t, *J* = 6.7 Hz, 1H), 3.97 (t, *J* = 3.5 Hz, 1H), 3.66 (s, 3H), 3.38 (s, 3H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.70 – 1.59 (m, 4H), 1.42 (s, 3H), 1.37 (s, 3H), 1.27 (s, 24H), 0.48 (t, *J* = 7.0 Hz, 4H), 0.02 (s, 12H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.3, 173.5, 128.7, 127.9, 109.7, 73.3, 73.2, 72.2, 71.3, 57.7, 51.4, 34.4, 34.1, 33.4, 33.4, 29.5, 29.4, 29.3, 29.3, 29.3, 29.2, 29.1, 27.6, 25.8, 25.0, 23.3, 18.4, 0.4; ^{29}Si NMR (80 MHz, $CDCl_3$) δ 7.28; MS (EI) *m/z* (%) 45 (91), 57 (39), 69 (46), 71 (42), 115 (57), 125 (54), 149 (55), 163 (36), 317(100), 318 (48); HRMS (EI) calcd for $C_{35}H_{66}O_8Si_2$(M^+ - CH3 species): 655.4062. Found 655.4054.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-4-Methoxy-2,2-dimethyl-3a,4,5,7a-

tetrahydrobenzo[*d*][1,3]dioxol-5-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-tetramethyldisiloxanyl)decanoate (27)

Diester **6** (160 mg, 0.32 mmol) was added to a stirred solution of **16** (65 mg, 0.32 mmol) and stirred for 5 min in toluene (1.5 mL) maintained at 100 °C. The resulting mixture was charged with N435 (22 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography with hexanes/EtOAc (90:10) to give 21 mg (9.6%) of **27** as colorless oil.

R_f = 0.38 [(hexanes/EtOAc (80:20)]; $[\alpha]_D^{20}$ = -38.4 (*c* = 1.15, MeOH); IR (ATR) *v* 2922, 2853, 1738, 1460, 1372, 1250, 1197, 1164, 1120, 1054, 839, 789, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 – 5.93 (m, 2H), 5.51 (t, *J* = 4.0 Hz, 1H), 4.70 (dd, *J* = 6.3, 3.2 Hz, 1H), 4.37 (t, *J* = 6.8 Hz, 1H), 3.66 (s, 3H), 3.51 (dd, *J* = 7.6, 3.4 Hz, 1H), 3.47 (s, 3H), 2.34 – 2.27 (m, 4H), 1.63 – 1.59 (m, 4H), 1.47 (s, 3H), 1.38 (s, 3H), 1.27 (bs, 24H), 0.48 (t, *J* = 7.3 Hz, 4H), 0.02 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 173.3, 129.6, 126.7, 109.4, 79.3, 74.4, 72.3, 65.3, 58.5, 51.4, 34.3, 34.1, 33.43, 33.41, 29.45, 29.40, 29.36, 29.31, 29.2, 29.1, 27.8, 25.4, 25.0, 24.98, 23.29, 23.28, 18.4, 0.4; ^{29}Si NMR (80 MHz, $CDCl_3$) δ 7.28; MS (EI) *m/z* (%) 59 (22), 81 (24), 97 (27), 115 (24), 125 (41), 149 (39), 317(100); HRMS (EI) calcd for $C_{35}H_{66}O_8Si_2$ (M^+ - CH3 species): 655.4062. Found 655.4034.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-5-Methoxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-

tetramethyldisiloxanyl)decanoate (28)

Diester **6** (135 mg, 0.27 mmol) was added to a stirred solution of **23** (56 mg, 0.28 mmol) and stirred for 5 min in toluene (1.35 mL) maintained at 100 °C . The resulting mixture was charged with N435 (22 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography with hexanes/EtOAc (90:10) to give 11 mg (6%) of **28** as colorless oil.

R_f = 0.25 [hexane/EtOAc (80:20)]; $[\alpha]_D^{20}$ = - 41.4 (*c* = 0.55, EtOAc); IR (ATR) *v* 2923, 2853, 1739, 1437, 1369, 1249, 1215, 1164, 1109, 1056, 923, 836, 786, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (dd, *J* = 8.1, 2.6 Hz, 1H), 4.33 – 4.31 (m, 1H), 4.21 (dd, *J* = 8.1, 5.2 Hz, 1H), 3.66 (bs, 4H), 3.31 (s, 3H), 2.41 – 2.37 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.01 – 1.81 (m, 3H), 1.78 – 1.69 (m, 1H), 1.68 – 1.61 (m, 4H), 1.49 (s, 3H), 1.35 (s, 3H), 1.27 (bs, 24H), 0.48 (t, *J* = 7.3 Hz, 4H), 0.02 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 173.7, 108.6, 76.9, 75.8, 75.1, 74.1, 56.9, 51.4, 34.5, 34.1, 33.44, 33.41, 29.5, 29.4, 29.35, 29.31, 29.2, 29.08, 28.15, 26.4, 25.0, 24.98, 23.3, 21.9, 20.9, 18.4, 0.4; ^{29}Si NMR (80 MHz, $CDCl_3$) δ 7.29; MS (EI) *m/z* (%) 55 (93), 57 (100), 67 (58), 71 (96), 83 (54),127 (43), 163 (48), 187 (29), 243 (32), 317 (83); HRMS (EI) calcd for $C_{35}H_{68}O_8Si_2$ (M^+ - CH_3): 657.4212. Found 657.4205; Anal. Calcd for $C_{35}H_{68}O_8Si_2$: C, 62.46; H, 10.18. Found C, 62.64; H, 10.28.

Synthesis of (3a*R*,4*R*,5*R*,7a*R*)-4-methoxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl 10-(3-(10-methoxy-10-oxodecyl)-1,1,3,3-

tetramethyldisiloxanyl)decanoate (29)

Diester **6** (370 mg, 0.74 mmol) was added to a stirred solution of **17** (150 mg, 0.74 mmol) and stirred for 5 min in toluene (3.5 mL) maintained at 100 °C. The resulting mixture was charged with N435 (52 mg). The reaction mixture was heated at 100 °C for 7 d. After 7 d the reaction mixture was cooled down to room temperature, then treated with Et_2O (3 mL). The reaction mixture was filtered through medium porosity Büchner funnel and the organic phases were concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography with hexanes/EtOAc (90:10) to give 31 mg (6%) of **29** as colorless oil.

R_f = 0.23 [hexane/EtOAc (80:20)]; $[\alpha]_D^{19}$ = -36.1 (*c* = 1.52, EtOAc); IR (ATR) *v* 2924, 2854, 2430, 1789, 1739, 1250, 1216, 1168, 1117, 1057, 923, 833, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 – 5.36 (m, 1H), 4.32 (dd, *J* = 8.3, 3.5 Hz, 1H), 4.07 (dd, *J* = 7.3, 5.4 Hz, 1H), 3.65 (s, 3H), 3.42 (s, 3H), 3.23 (dd, *J* = 7.4, 2.7 Hz, 1H), 2.33 – 2.27 (m, 4H), 1.97 – 1.71 (m, 4H), 1.65 – 1.54 (m, 4H), 1.51 (s, 3H), 1.36 (s, 3H), 1.27 (bs, 24H), 0.48 (t, *J* = 7.3 Hz, 4H), 0.02 (s, 12H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 173.2, 108.4, 81.3, 77.4, 73.7, 67.8, 57.7, 51.4, 34.5, 34.1, 33.43, 33.40, 29.4, 29.39, 29.33, 29.32, 29.30, 29.2, 29.1, 28.4, 26.2, 25.1, 25.0, 23.3, 23.0, 21.6, 18.4, 0.4; ^{29}Si NMR (120 MHz, $CDCl_3$) δ 7.23; MS (EI) *m/z* (%) 55 (90), 57 (100), 67 (48), 71 (80), 83 (50), 127 (26), 149 (52), 243 (25), 317 (52); HRMS (EI) calcd for $C_{35}H_{68}O_8Si_2$ (M^+ - CH_3): 657.4212. Found 657.4205; Anal. Calcd for $C_{35}H_{68}O_8Si_2$: C, 62.46; H, 10.18. Found C, 62.61; H, 10.40.

General procedure for enzyme-free control reactions

A 5 mL round bottomed flask was charged with approximately 50 mg of chiral diol (**1**, **2**, or **3**) and combined with dimethyl ester **6** in a 1:1 mole ratio. Toluene (1 mL) was then added to the reaction flask the flask outfitted with a water-jacketed condenser. The reaction mixture was heated to either 70 or 100°C with stirring (60 rpm) for 24 h. The reaction was terminated by cooling the mixture to room temperature and removing the solvent on a rotary evaporator.

General procedure for examining the enzyme-mediated hydrolysis of the dimethyl ester

A 10 mL round bottomed flask was charged with 150 µL of dimethyl ester **6**. N435 was added to the reaction flask at 10 wt% of the dimethyl ester. Toluene (1 mL) was then added to the reaction flask and a condenser was fitted to the neck of the round bottom flask. Each reaction mixture was heated to either 70 or 100°C with stirring (60 rpm) for 24 h. The reaction was terminated by cooling it to room temperature, adding 3.0 mL of diethyl ether, filtrating the reaction through a medium porosity fritted glass Buchner funnel to remove the N435 and then washing the N435 beads with 3x 2.0 mL of diethyl ether. The ether layers were combined and the solvents were subsequently removed using a rotary evaporator.

Results and Discussion

1,3-Bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** was selected as the model siloxane for lipase-mediated reactions with chiral diol molecules (

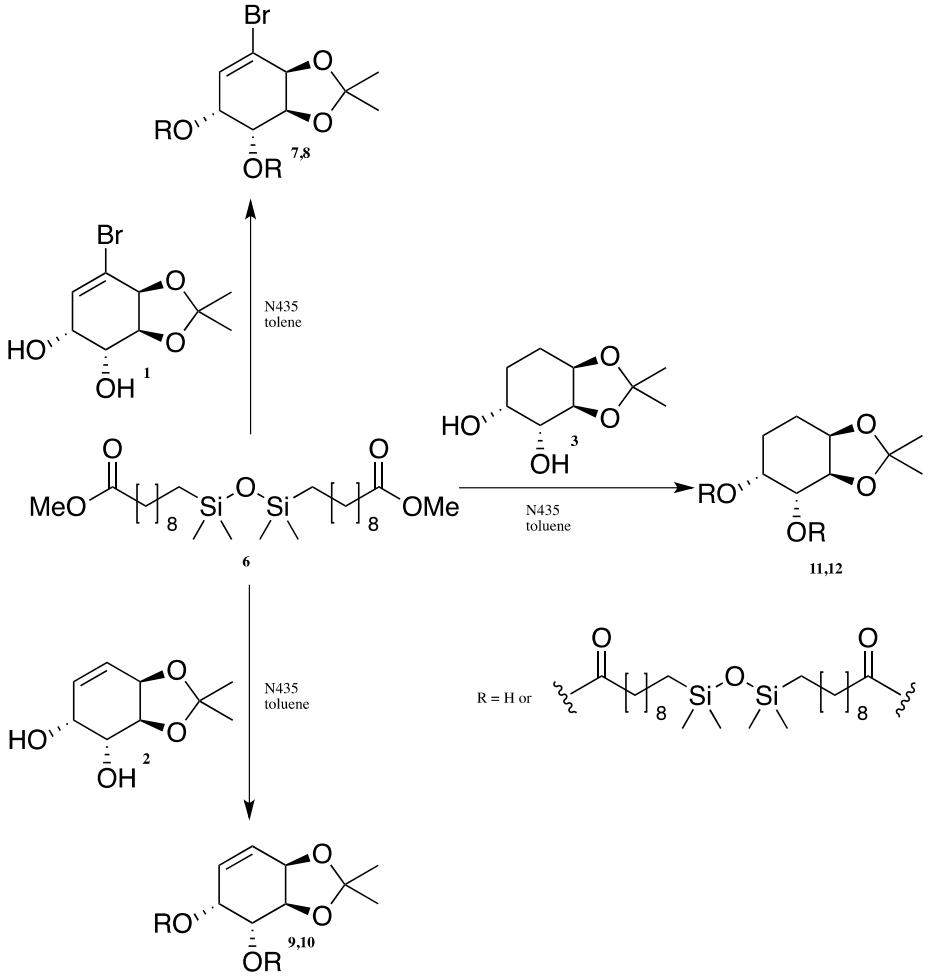


Figure 1 The reacion of 1,3-bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** with chiral diols at 100°C.

). Based on previous research it was known that the distance between the ester moiety and the siloxane portion of the diester was sufficient to be tolerated by N435 and should not be a complicating factor in the experiments.[17] For the acyl acceptor partner, three

different chiral diol species (

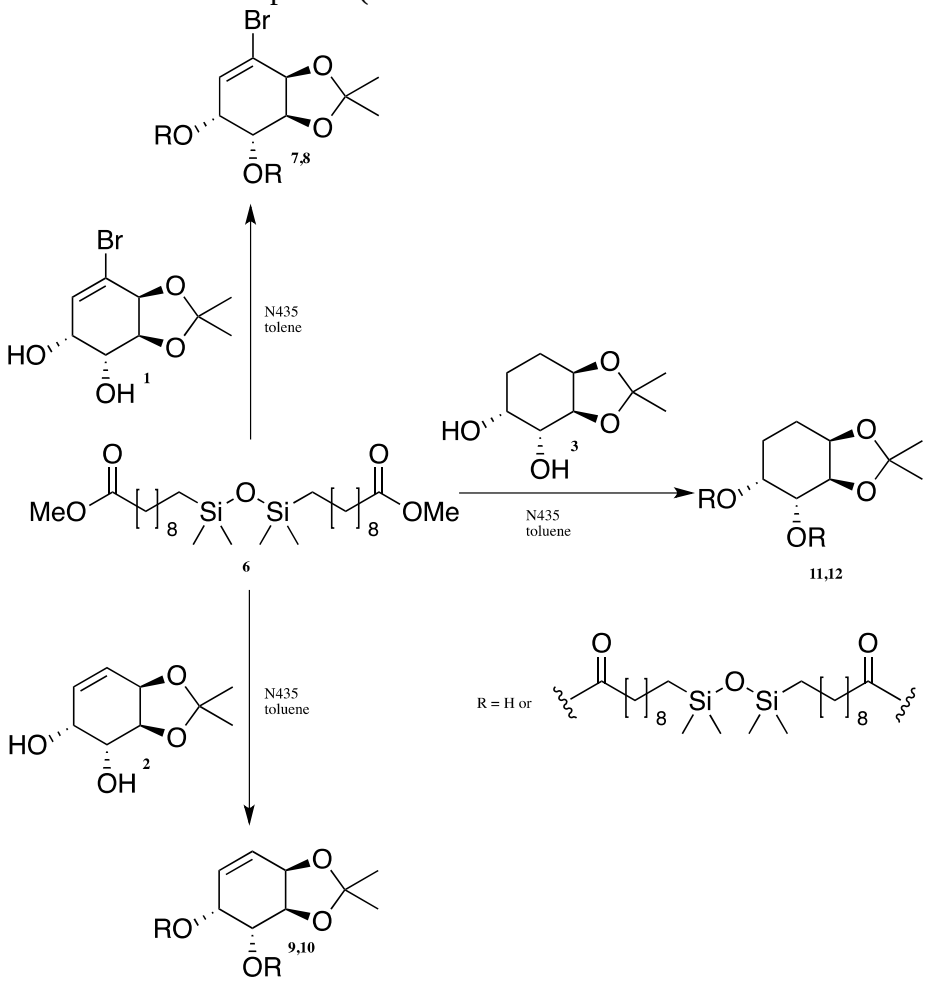


Figure 1 The reacion of 1,3-bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** with chiral diols at 100°C.

) with different steric constraints and unsaturation-states were examined. We wished to evaluate the diol substrate toleranceof the immobilized *Candida antarctica* lipase B (CalB, N435) for the synthesis of chiral siloxane polymers. N435 was selected as the biocatalyst because it possesses a broad substrate scope, a high degree of efficiency in chemical reactions, and remarkable thermal stability. Moreover, there is substantial literature precedence concerning the use of N435 for the synthesis of siloxane-based polyester systems.[10,12,24]

The bioacatalytic reactions were monitored by ^{1}H NMR through comparing the integrations of the resonances of the α-protons of the diester carbonyl to those of the pendent methyl ester fucntionality. The ratio of these integrals was used to determine the % consumption of the starting diester. As the reaction progressed, the methoxy group of the esters was liberated and subsequently removed from the reaction as methanol. The resonance corresponding to the methylene, which is a triplet, shifts slightly downfield in the ^{1}H NMR spectrum of the product. Therefore, the ratio of the integration of the signal resulting from the methylene in the starting material to the signal derived from the methylene in the product was used in the estimating reaction conversion. The chiral diols for this study were synthesized with *R* stereochemistry at both diol positions as CalB has a preference for alcohols with *R* stereochemistry.[18-22] To further demonstrate the enzyme's selectivity, identical transesterfication control reactions were performed with siloxane diester **6** and chiral diols **1**, **2**, and **3** using lipases from *Rhizomucor miehei* and *Thermomyces lanuginosus*. In all cases, these experiments only yielded starting materials, which was consistent with previous reports in the literature.[23]

Background Hydrolysis

One of the physiological roles of a lipase is to hydrolyse esters to the corresponding alcohols and acids. In the event that some water molecules were trapped within the enzyme active site during the immobilization process, control experiments were performed in order to determine the amount of ester hydrolysis that could be catalyzed by the enzyme under the reaction conditions. This background hydrolysis, rather than the deisred transesterification of the ester moieties, would also result in a

decrease in the integration of the peak of the protons from the methyl group, therefore producing a false indication that esterification or polymerization had occurred.

These reactions were carried out by incubating the diester at 100°C in toluene in the absence of the chiral diols for 24 h, and they were catalyzed using a 10 wt% of the N435 relative to the diester. The reactions were terminated after 24 h by cooling the reaction mixture to room temperature, adding 2.0 mL of diethyl ether, and removing the N435 beads by filtration using a fritted Buchner filter. Following filtration, the beads were washed with 3 x 2.0 mL of diethyl ether to recover any remaining starting materials or products, and the solvents were removed using a rotary evaporator. These reactions were carried out in triplicate.

On average, 7 % hydrolysis of the diester was observed with N435 at 100°C. This amount of hydrolysis was considered during analysis of spectral data for the polymerization reactions and all the data reported below represents consumption rates above that of this background.

Consumption of Siloxane Diester

In the absence of the enzyme, transesterification reactions were not observed between **6** and any of the chiral diols as evidenced by ^{1}H NMR.

According to previous reports,[10,13,17,24] reactions were carried out a 70°C or 100°C over a period of 24 h to ascertain the extent to which the transesterification reactions would occur between the siloxane diester and the chiral diol molecules. With all three diol systems the higher temperature resulted in the greatest consumption of the siloxane diester (Table 1) as determined by ^{1}H NMR analysis. At both reaction temperatures chiral diol **3** resulted in the greatest consumption of the siloxane diester **6**, with the

maximum being approximately 60%. Of the three chiral diols **3** is fully saturated and the least sterically hindered. This likely facilitated the incorporation of diol **3** into the enzymes' active site relative to the other diol species, ultimately resulting in a more efficient transesterification reaction.

MALDI-ToF and GPC Analysis

MALDI-ToF analysis of the unfractionated reaction systems suggested that the reaction products were simply dimers of the chiral diols and the siloxane diester (Table 2). However, not all analytes respond to MALDI-ToF analysis, raising the possibility that this technique may not provide a complete picture of the reaction products.[25] To corroborate the MALDI-ToF MS data, GPC analysis of the (Table 2) unfractionated reaction systems was also performed. Data from the GPC revealed that although the reaction products were not limited to dimers, that any higher molecular weight molecules that were synthesized were at best oligomers rather than the desired polymers. Of the three chiral diols, the fully saturated diol **11, 12** displayed the greatest potential for forming polymeric species, reaching molecular weight values of M_w = 1,432 g/mol and M_n = 1,124 g/mol as evidenced by GPC; it was not possible to obtain reliable molecular weight data for these reaction products utilizing MALDI-ToF MS. Although the GPC data suggested that tetrameric species were present in both the **11** and **12** reaction mixtures it was unclear whether both hydroxyl groups of the chiral diol reacted or if only a single transesterification event was occurring per diol functionality.

Isolation and Identification of Individual Molecules

Attempts were made to fractionate the reactions in an effort to isolate and characterize individual molecules and to determine the substitution pattern with respect to

the diol molecules. Although it was not possible to isolate all of the components of the reactions, as higher oligomeric species did not elute from the column, the "dimer" species for the reactions between the siloxane diester **6** and each of the chiral diol molecules were successfully isolated. The isolated compounds were fully characterized using ^{1}H NMR, ^{13}C NMR, ^{29}Si NMR, FT-IR, and MS. Spectral analysis revealed that both of the chiral hydroxyl moieties in the diol species were accessible to the N435 and could participate in transesterification reactions (Table 3). With unsaturated diols **1** and **2** the transesterification at the hydroxyl group distal to the acetonide group predominated in the isolated products while the proximal hydroxyl group relative to the acetonide was the dominant species isolated from the transesterification reaction with saturated diol **3**. All of the six isolated products **7**, **8**, **9**, **10**, **11**, **12** from the enzyme-mediated transesterification reactions were optically active (Table 3), strongly suggesting that the oligomeric products also possessed optical activity. However, given that an accurate concentration of the individual components from the reaction could not be obtained, optical activity measurements were not performed on the unfractionated reaction products as the results would be meaningless.

Hyrdoxyl Selectivity by N435

Gotor reported the selective acetylation of the secondary alcohols found in shikimic acid using lipases. He noted that *Candida antarctica* lipase A exhibited greater selectivity for shorter chain acyl donors while *Candida antarctica* lipase B demonstrated a preference for acyl donors with longer chains.[26] With these results in mind, the substrate preference of N435 for the two hydroxyl moieties in chiral diols **1**, **2**, and **3** was examined. Based upon the isolated dimer species obtained from the transesterification of

chiral diols **1**, **2**, and **3** with **6**, the analysis would suggest that, to varying degrees, N435 demonstrates a preference for the secondary alcohol distal to the acetonide group (Table 4) in each of the three cases. In an effort to further probe the selectivity of N435 for the two free hydroxyl groups in the chiral diols, analogues of diols **1**, **2**, and **3** were synthesized based on a procedure reported by Banwell, where the hydroxyl groups were selectively protected (Figure 2). This afforded the opportunity to study the capacity of the lipase to mediate transesterification reactions when one of the chiral hydroxyl groups was already blocked.

When compounds **6**, **15**, and **21** were reacted in a 1:1:1 ratio in toluene at 100°C in the presence of 10 wt% (based on the total mass of the starting materials) of N435, the formation of products was only observed by ^{1}H NMR after 7 days. This suggested that the N435 had difficulty processing the brominated chiral substrate once the steric bulk was increased at one of the hydroxyl groups. The transesterified products were formed in a 0.9±0.1:1 ratio indicating that any preference by the enzyme for either of the hydroxyl groups in the brominated chiral diol was likely negligible.

Chiral substrates **16** and **22** were tested in a similar manner as the protected brominated substrates. Unsaturated substrates **16** and **22** were reacted in a 1:1:1 ratio with siloxane **6** in toluene at 100°C with 10 wt% N435. In a similar trend to that observed for the unprotected substrates, N435 processed the unsaturated substrates more efficiently than the corresponding brominated species with product formation being observed after 6 days. With substrates **16** and **22** the N435 demonstrated a clear preference for the hydroxyl moiety distal to the acetonide with the transesterification product at this location forming in a 0.1±0.1 (proximal):1 (distal) ratio versus the proximal hydroxyl group.

Surprisingly, when substrates **17** and **23** were reacted in a 1:1:1 ratio with siloxane **6** at 100°C in toluene with 10 wt% N435, transesterification of the hydroxyl group proximal to the acetonide was preferred over that of the distal hydroxyl moiety (1.8±0.3:1). The exact reason for this striking inversion of selectivity due to a relatively distal structural change is currently being explored.

Conclusions

A two-enzyme chemoenzymatic route for the synthesis of siloxane ester oligomers (~1,400 g/mol) has been described. The CalB was challenged with three chiral diols (two unsaturated **1, 2** and one saturated **3**) with the fully saturated diol species **3** leading to the most efficient transesterification reactions (~60%). Fractionating the reactions via column chromatography resulted in the isolation of dimeric species of the chiral diols and siloxane diester. The isolated species revealed that both of the free alcohols on each chiral diol are enzymatically accessible and the products of the biocatalytic transesterification reactions retain their optical activity. The N435 demonstrated no selectivity for the diols in the brominated substrates while the hydroxyl group distal to the acetonide was preferred in the unsaturated substrate and the hydroxyl group proximal to the acetonide was preferred in the fully saturated chiral substrate. Although the reactions reported herein tended to favour the formation of oligomeric species, the data suggest that a chemoenzymatic approach to chiral siloxane polymers should be possible, opening a possible avenue for an environmentally benign synthesis of chiral silicones.

Acknowledgements

The authors would like to thank the Natural Sciences and Engineering Research Council (NSERC) of Canada and Brock's Advanced Biomanufacturing Centre for funding this research and Prof. Alex Adronov (McMaster University) for his assistance with the GPC.

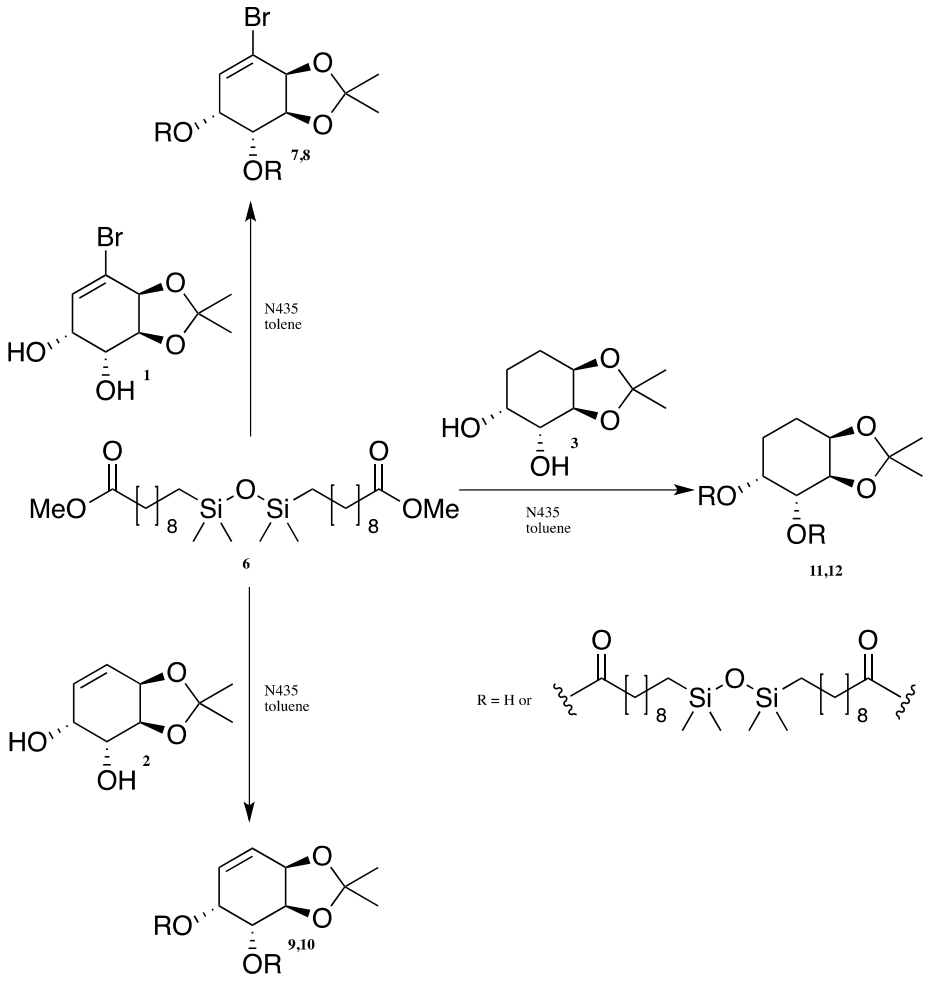


Figure 1 The reacion of 1,3-bis(9-carboxynonylmethylester)-1,1,3,3-tetramethyldisiloxane **6** with chiral diols at 100°C.

Table 1 The % conversion of polymerization reactions of diester **6** with chiral diols **1**, **2**, and **3** at 100°C over 24 h and 7 days. All reactions were carried out in 1 mL of toluene, stirred at 60 rpm, and catalyzed by 10 wt% of N435 relative to the combined mass of the monomers.

	% Consumption of Siloxane Diester 6	
Chiral Diol	**24 h**	**7 days**
1	15 ± 2	28 ± 7
2	12 ± 2	23 ± 1
3	33 ± 3	58 ± 6

Table 2 Molecular weights of the unfractionated reaction products as determined by MALDI-ToF MS and GPC after 7 days.

Reaction Products	Molecular Weights (g/mol)			
	MALDI-ToF MS		*GPC*	
	M_n	M_w	M_n	M_w
7,8	598±38	625±45	803	826
9,10	757±50	897±35	801	823
11,12	850±51	940±72	1,124	1,432

Table 3 Summary of isolated yields and optical properties of N435-catalyzed transesterification products of siloxane diester **6** and saturated and unsaturated chiral diols.

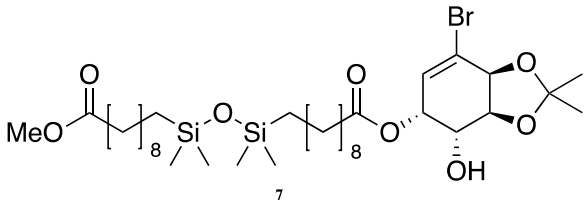
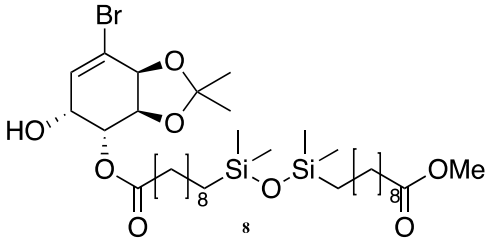
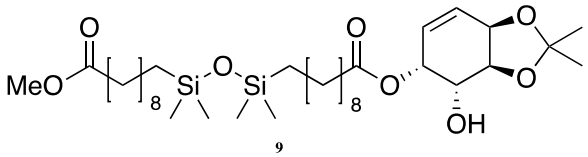
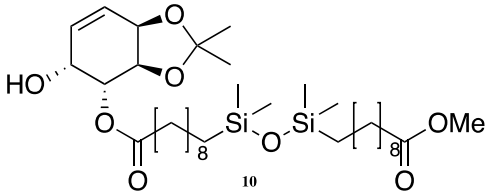
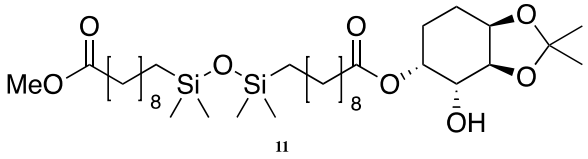
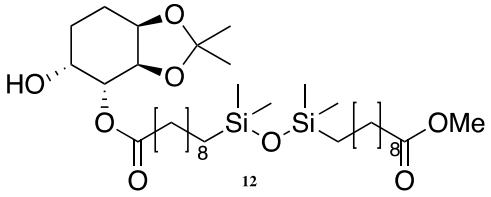
Isolated Compound	Isolated Yield (%)	Optical Rotation
 **7**	4	$[\alpha]_D^{20}$ = 15.1 (*c* = 0.35, $CHCl_3$)
 **8**	2	$[\alpha]_D^{20}$ = -9.8 (*c* = 0.30, $CHCl_3$)
 **9**	8	$[\alpha]_D^{20}$ = -69.1 (*c* = 0.75, MeOH)
 **10**	3	$[\alpha]_D^{20}$ = - 41.8 (*c* = 0.15, MeOH)
 **11**	16	$[\alpha]_D^{20}$ = -35.3 (*c* = 0.9, MeOH)
 **12**	12	$[\alpha]_D^{20}$ = - 30.7 (*c* = 0.7, MeOH)

Table 4 The apparent selectivity of N435 for the alcohols of the chiral diols in transesterification reactions with siloxane **6**.

Chiral Diol	Ratio of Distal to Proximal Ester Relative to the Position of the Acetonide
1	1.86±0.17 : 1
2	2.3±0.3 : 1
3	1.28±0.02 : 1

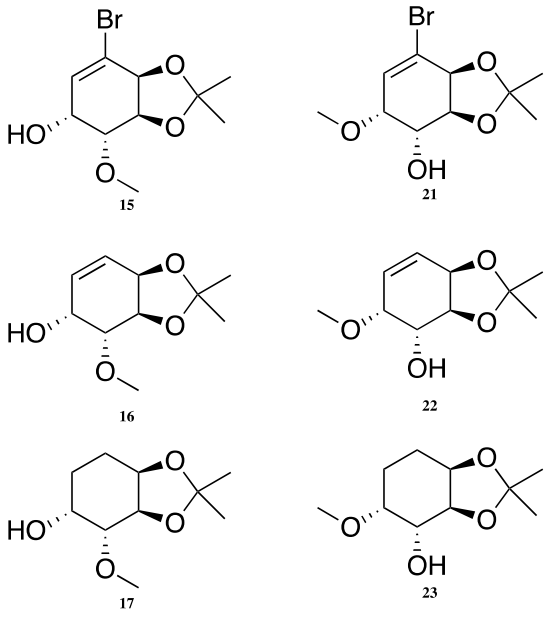


Figure 2 Chiral, monoprotected analogues of the diols to probe the substrate preference of N435.

AUTHOR INFORMATION

Corresponding Author

*Paul M. Zelisko
Brock University
Department of Chemistry and Centre for Biotechnology
500 Glenridge Avenue
St. Catharines, Ontario
Canada L2S 3A1
Tel: +1-905-688-5550 ext. 4389
E-mail: pzelisko@brock.ca

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

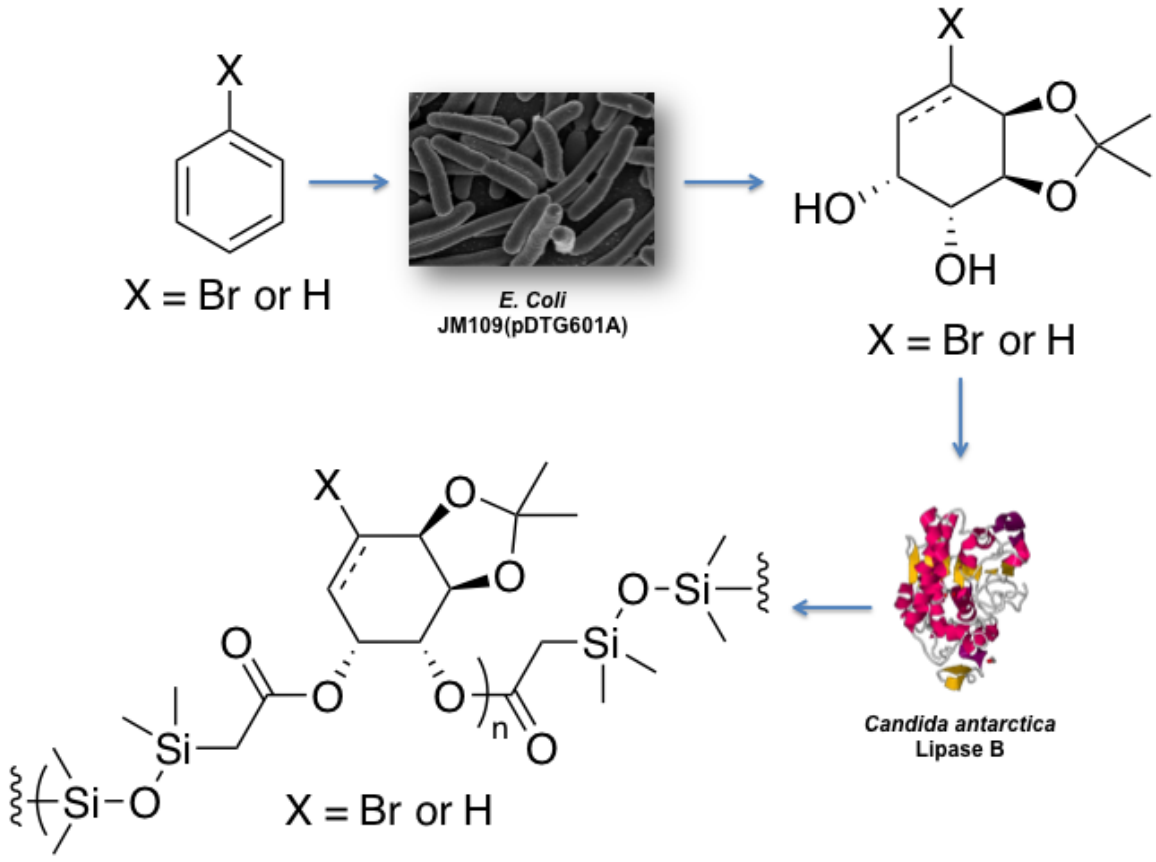
Funding Sources

Natural Sciences and Engineering Research Council (NSERC) of Canada and the Brock University Advanced Biomanufacturing Centre.

ABBREVIATIONS

ADMET, acyclic diene metathesis; AIBN, azoisobutyronitrile; EI, electron impact; FTIR, Fourier transform infrared; GPC, gel permeation chromatography; HRMS, high resolution mass spectroscopy; MALDI-ToF, matrix-assisted laser desorption time-of-flight; N435, lipase B from *Candida antarctica* immobilized on acrylic beads; NMR, nuclear magnetic resonance; TDO, toluene dioxygenase; THF, tetrahydrofuran; TLC, thin layer chromatography

Graphical Abstract



1

2 **References**

[1] Itsuno, S. An Overview of polymer-immobilized chiral catalysts and synthetic chiral polymers. In *Polymeric chiral catalysts design and chiral polymer synthesis*; Itsuno, S. Ed.; John Wiley & Sons: Hoboken, 2011; p 1.

[2] Shirahama, H.; Tanaka, A.; Yasuda, H. *J. Polym. Sci. A1*, **2002**, *40*, 302-316.

[3] Hudlicky, T.; Reed, J.W. *Chem. Soc. Rev.*, **2009**, *38*, 3117-3132.

[4] Clouthier, C.M.; Pelletier, J.N. *Chem. Soc. Rev.*, **2012**, *41*, 1585-1605.

[5] Hudlicky, T.; Reed, J.W. *Synlett*, **2009**, *5*, 685-703.

[6] Bui, V. P.; Hudlicky, T. *Tetrahedron*, **2004**, *60*, 641-646.

[7] Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.*, **1989**, *264*, 14940-14946.

[8] O'Hagan, D.; Parker, A. H. *Polym. Bull.*, **1998**, *41*, 519-524.

[9] Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*, John Wiley & Sons, New York, **2000**.

[10] Frampton, M. B.; Séguin, J. P.; Marquardt, D.; Harroun, T. A. *J. Mol. Catal. B: Enzym.*, **2013**, *85-86*, 149-155.

[11] Zelisko, P.M. (Ed.). *Bio-Inspired Silicon-Based Materials*, Advances in Silicon Science Series, Matisons, J. (Ed.), **2014**, Springer: Dordrecht.

[12] Sharma, B.; Azim, A.; Azim, H.; Gross, R. A. *Macromolecules*, **2007**, *40*¸7919-7927.

[13] Poojari, Y.; Palsule, A. S.; Cai, M.; Clarson, S. J.; Gross, R. A. *Eur. Polym. J.*, **2008**, *44*, 4139-4145.

[14] Hudlicky, T.; Price, J. D.; Olivo, H. F., *Synlett* **1991,** *1991* (09), 645-646.

[15] Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T., *J. Am. Chem. Soc.*, **1990,** *112* (25), 9439-9440.

[16] Ranganathan, D.; Ranganathan, S.; Mehrotra, M. M. *Tetrahedron*, **1980**, *36*, 1869-1875.

[17] Frampton, M.B.; Zelisko, P.M. *Enzyme Microb. Technol.*, **2014**, *58-59*, 87-92.

[18] Ottosson, J.; Fransson, L.; Hult, K. *Protein Sci.*, **2002**, *11*, 1462-1471.

[19] Gedey, S.; Liljeblad, A.; Lázár, L.; Fülöp, F.; Kanerva, L.T. *Can. J. Chem.*, **2002**, *80*, 565-570.

[20] Yazbeck, D.; Derrick, A.; Panesar, M.; Deese, A.; Gujral, A.; Tao, J. *Org. Proc. Res. Dev.*, **2006**, *10*, 656-660.

[21] Yang, B.; Lihammar, R.; Bäckvall, J-E. *Chem. Eur. J.*, **2014**, *20*, 13517-13521.

[22] Juhl, P.B.; Trodler, P.; Yagi, S.; Pleiss, J. *BMC Struct. Biol.*, **2009**, *9*, doi:10.1186/1472-6807-9-39.

[23] Séguin, J.P. *Enzyme-Mediated Synthesis of Disiloxane-Containing Chiral Polymers*, Hons. B.Sc. Thesis, Brock University, April 2013.

[24] Frampton, M.B.; Zelisko, P.M. *Chem. Commun.*, **2013**, *49*, 9269-9271.

[25] Byrd, H.C.M.; McEwen, C.N. *Anal. Chem.*, **2000**, *72*, 4568-4576.

[26] Armesto, N.; Ferrero, M.; Fernández, S. ; Gotor, V. *J. Org. Chem.*, **2002**, *67*, 4978-4981.