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ARTICLE TYPE

Enantioselective Synthesis of Mosquito Oviposition Pheromone and its Epimer from a Naturally Occurring Fatty Acid

David Hurem[a] and Travis Dudding*[a]

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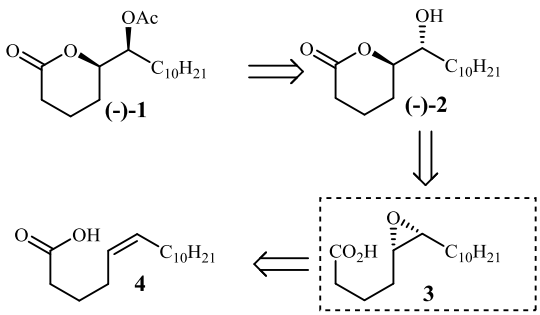
The synthesis of Mosquito Oviposition Pheromones (MOP) (5*R*, 6*S*)-5-acetoxy-6-hexadecanolide and its unnatural (5*R*, 6*R*)-diastereomer in 68 % and 54 % overall yield by a route involving an organocatalyzed epoxidation of naturally occurring *cis*-5-hexadecenoic acid and diastereodivergent esterification is reported. The investigation of a dynamic kinetic asymmetric transformation (DYKAT) as an alternate strategy for preparing the target MOPs is also discussed, however this approach was unsuccessful due to the formation of a ketone by-product that inhibited the lipase mediated acetylation step of the DYKAT process.

Introduction



Scheme 1 Retrosynthetic Analysis

Culex genus mosquitos have been identified as the predominant vectors responsible for the spread of encephalitic diseases including West-Nile virus and dengue fever,[1] leading to the incorporation of *Culex* mosquito control and monitoring programs as major components in global health initiatives. From the control aspect, spraying of commonly used insecticides such as neonicotinoids and pyrethroids has been shown to have negative impacts on ecology,[2] human health,[3] and a high potential for creating resistance in target populations.[4] Accordingly, the necessity of implementing environmentally friendly and sustainable integrated pest management strategies, to combat the associated problems with spraying insecticides alone, has been expressed in the World Health Organization 2012 handbook for integrated vector management.[5] As a possible solution to this pressing need the use of an oviposition attractant, such as mosquito oviposition pheromone (MOP **(-)-1**, Scheme 1), in conjunction with larvacides, has been shown to be a selective control method.[6] Meanwhile similar attract-and-kill principles for pest insect control have been demonstrated as effective methods for controlling western corn rootworm,[7] codling moth,[8] and Mediterranean fruit fly populations.[9] All the same perhaps having been of even greater importance have been applications of MOP in mosquito surveillance programs, due to their selectivity for gravid *Culex* mosquitos. In this respect, the use of oviposition attractants possess a number of benefits over the use of conventional CO_2 based traps because mosquitos are generally not primary hosts of encephalitic diseases and must become infected by taking in blood to transfer the disease to mammals; thus, the ability to attract gravid mosquitos creates a bias for the attraction of infected mosquitos.[10]

Notwithstanding, efforts to implement the widespread use of MOP, especially enantioenriched materials, have been hindered by the shortage of facile synthetic methodology, which in turn has had a direct impact on the ability to acquire data from field studies using individual MOP stereoisomers.[11] Accordingly, to gain access to enantioenriched samples of **(-)-1** and its stereoisomers, and at the same to improve upon a previous racemic synthesis we envisioned the use of a reaction sequence involving a catalytic asymmetric epoxidation of naturally available *cis*-5-hexadecenoic acid **4** to afford **3** and subsequent dynamic kinetic asymmetric transformation (DYKAT) of hydroxylactone **(-)-2** as key steps to the *erythro*-**(-)-1** and *threo*-**(-)-9** isomers (Scheme 1).[12] The results of this approach are reported herein.

With respect to asymmetric epoxidation, it was foreseen that **4** would be a challenging substrate, due to the lack of functionality near the alkene.[13] Nevertheless, Shi and co-workers have recently reported a class of chiral ketone catalysts (**5a-c**) that were able to mediate the asymmetric epoxidation of internal *cis*-olefins,[14a, b] lacking proximal functionality, with moderate to high enantioselectivity. More specifically, it was demonstrated that chiral ketone **5c** catalyzed the epoxidation and subsequent lactonization of aliphatic acids, such as *cis*-Δ^4-C_{12} and *cis*-Δ^5-C_{12} fatty acids with moderate to high levels of stereoselection.[14c] The

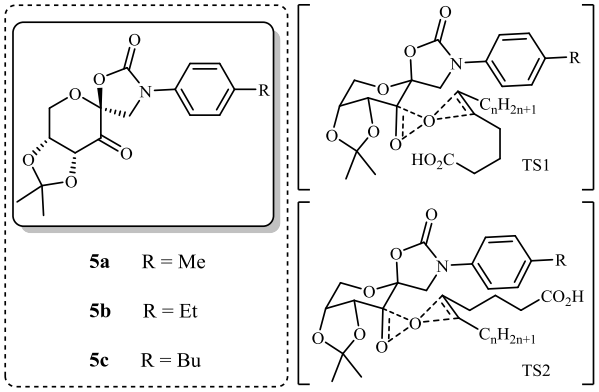
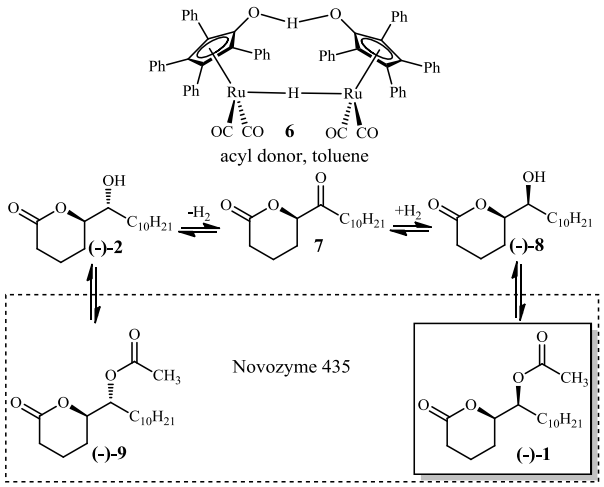


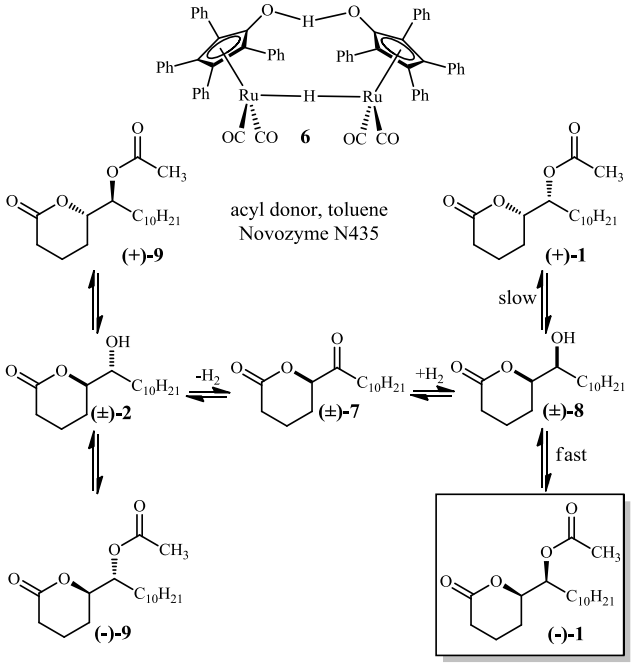
Fig. 1 Shi's Epoxidation Catalysts and Proposed Competing *Spiro*-Transition States



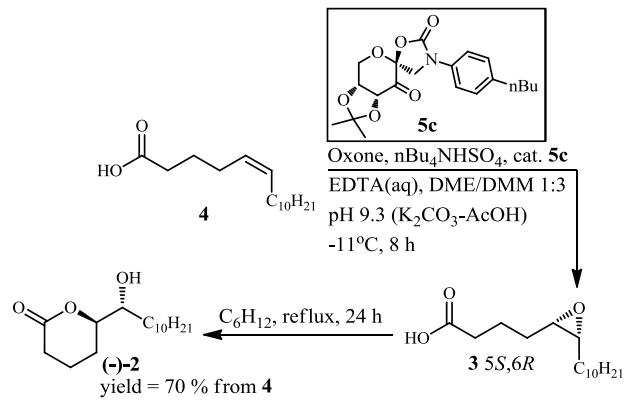
Scheme 2 DYKAT Strategy for Enantioenriched (5*R*, 6*R*)-Hydroxylactone **(-)-2**

origin of stereoinduction in these epoxidations was thought to derive from two competing *spiro*-transition states (Figure 1, TS1 and TS2), however only TS1 allows for favourable van der Waals contacts between the aniline *para*-substituent of the catalyst and the *n*-alkyl chain of the substrate in the transition state, as well as, stabilization resulting from aqueous solvation of the substrate carboxylate group.[15] Given this precedent, it was reasoned that **4** would be an ideal substrate for asymmetric epoxidation with catalysts **5a-c**. Although it was expected that **5c** would generate the highest level of stereoinduction as a result of the longer hydrophobic *n*-alkyl chain of the catalyst as it could form a larger number of favourable van der Waals contacts which in turn would allow for greater transition state stabilization, respectively.

At the same time, it was envisioned that a DYKAT of enantioenriched secondary alcohol **(-)-2**, mediated by Shvo's catalyst (**6**),[16] under the established conditions of Bäckvall *et al*. would afford **(-)-1** (Scheme 2).[17] A key question regarding this step, however, was the lipase selectivity for lactones **(-)-2** and **(+)-2** which was without precedent. Albeit based on previous reports, it was projected that immobilized *Candida antarctica* lipase A (CALA) would selectively acetylate **(-)-8** over **(+)-8**.[18] Consequently, it was anticipated a separate set of DYKAT experiments using racemate **(±)-2** could be carried out as an alternative route to **(-)-1**, provided that selectivity for acetylation



Scheme 3 DYKAT Strategy for Racemic *threo*-Hydroxylactone **(±)-2**



Scheme 4 Chiral Epoxidation and Lactonization

of **(-)-8** was observed using enantioenriched material (Scheme 3, See ESI for experimental details regarding **(±)-2** synthesis).

Results and Discussion

Mindful of the above design plan our initial efforts focused on identifying a suitable method for converting unsaturated fatty acid **4** to optically enriched oxirane **3** and/or hydroxylactone **(-)-2** by a domino reaction sequence proceeding through epoxide **3** (See ESI for fatty acid synthesis). As noted, the use of a Shi epoxidation appeared ideal in this context given the known robustness of this method towards alkenes lacking proximal directing groups, thus catalysts **5a-c** were prepared using a modified synthetic approach based on two previously reported routes.

Employing **5c**, an initial experiment carried out under standard Shi epoxidation conditions, encouragingly provided desired epoxide **3** and hydroxylactone **(-)-2** in an approximate 60:40 ratio with respectable optical activity (Scheme 4).[14c] It is perhaps worth noting that in a previous reported involving racemic epoxidation that afforded racemate **(±)-2**,[12] it was revealed that

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Table 1 Yield and Enantioselectivity of Asymmetric Epoxidation/Lactonization using Varying Epoxidation Catalyst Derivatives.

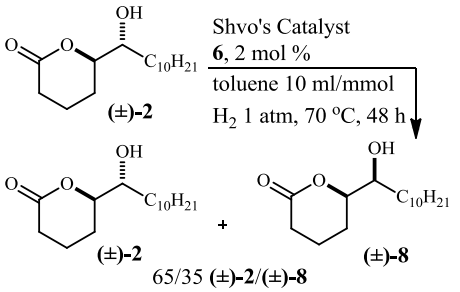
Entry	Catalyst (Figure 2)	Yield (%)[a)]	α° (conc.)[b)]	Absolute Configuration[c)]
1	**5a**	65	-6.5(1.01)	(-)-*R*,*R*
2	**5b**	68	-8.3(1.04)	(-)-*R*,*R*
3	**5c**	70	-9.3(0.95)	(-)-*R*,*R*

[a)] Represents the isolated yield of **(-)-2** and the corresponding enantiomer. [b)] Optical rotation was obtained at 21°C, in $CHCl_3$ and concentrations are expressed in parenthesis in units of g/100ml, lit.[19] -10.2 (c = 0.87 g/100ml) in $CHCl_3$. [c)] The absolute configuration was inferred from the sign of optical rotation, while the relative configuration was inferred from comparison of hydroxylactone **(-)-2** spectra with those in literature.[19]

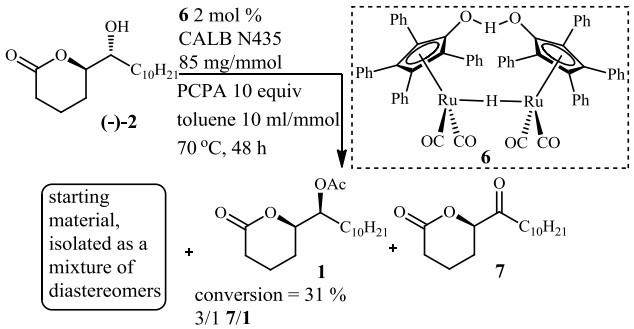
the use of a proton shuttle, such as a catalytic amount of triethylamine facilitated the lactonization of epoxide **3** in the absence of catalyst **5c**. Notwithstanding, for the case at hand it was interestingly found that no such proton shuttle was necessary to facilitate the lactonization of a crude isolate consisting of a mixture of epoxide **3**, lactone **(-)-2** and catalyst **5c**. Conversely, purification of this mixture to remove residual catalyst resulted in a slow lactonization, requiring the addition of triethylamine to complete the lactonization in 24 h, suggesting that catalyst by-products generated under the epoxidation reaction conditions had an advantageous role in promoting intramolecular 6-exo-*trig* cyclization in the lactonization step.

Having an operationally simple one-pot route from **4** to **(-)-2** the use of catalysts **5a-b** was then investigated, which provided the key lactol intermediate, **(-)-2**, with lower optical activity, albeit similar overall yields (65 % - 70 %, Table 1). These results may be easily understood by invoking the abovementioned mechanistic proposal of Shi and theoretical studies by Houk and others.[15] More specifically, the superior selectivity of **5c** relative to **5a-b** can be traced to transition state stabilization as stacking of the 4-butylaniline group of **5c** atop the hydrocarbon chain of **4** in epoxidation TS1 would generate a larger number of favourable (induced dipole – induced dipole) van der Waals contacts than those present in the related epoxidation transition states for **5a-b** (Figure 1). This last conclusion necessarily followed from the larger size of the 4-butylaniline group of **5c** relative to the smaller 4-methyl and 4-ethylaniline groups of **5a-b**.

Next with a viable synthesis to chiral *threo*-hydroxylactone **(-)-2** established, a one-step method for the inversion of the C(6) stereocenter was needed to afford *erythro*-diastereomer **(-)-8**. As such, a preliminary model system using Shvo's catalyst (**6**)[19a-b] and racemic **(±)-2** was considered, which ultimately provided a 65/35 ratio of **(±)-2**/**(±)-8**, thus demonstrating there was a



Scheme 5 Epimerization of *threo*-Hydroxylactone **(±)-2** using Shvo's Catalyst



Scheme 6 Attempted DYKAT of Enantioenriched Hydroxylactone

thermodynamic bias for the *threo*-hydroxylactone under the catalytic epimerization conditions (Scheme 5).[20] While this result was promising as a significant portion of the substrate was successfully epimerized to afford a mixture of both *threo*- and *erythro*-diastereomers it was foreseen that a subsequent acetylation would not be economic in mass transfer so a more desirable one-pot C(6)-inversion/acetylation approach with complete mass transfer to a single stereoisomer was alternatively investigated. This rationale prompted an examination of a DYKAT methodology using a *p*-chlorophenyl acetate donor (PCPA) and Novozyme N435 *Candida antarctica* lipase B (N435, CALB) immobilized enzyme as a potential route affording **(-)-1** selectively, starting from **(-)-2** (Scheme 6).[21] The initial result from this enzyme mediated processes unfortunately were not encouraging, as the reaction halted at ~30% conversion and a persistently co-eluting by-product was isolated along with the desired *erythro*-**1** *via* silica gel chromatography, despite the use of several different normal mobile phases. Consequently, the absolute configuration and enantiomeric ratio of the acetylated product could not be determined, however ^{1}H NMR analysis revealed *erythro*-**1** had formed preferentially under these reaction conditions, as judged from the characteristic ^{13}C NMR chemical shifts of C(5) and C(6) observed in the spectrum obtained from the product isolate (80.5 ppm and 74.4 ppm). Meanwhile the co-eluting by-product was suspected to be ketone **7**, formed by the oxidation of alcohols **8** and **2**, supported by the appearance of a characteristic multiplet for C(5) at 4.78-4.73 ppm observed in the ^{1}H NMR spectrum of the product isolate and the appearance of a

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Table 2 Investigation of DYKAT Reaction Parameters

Entry	Time (days)	Atmosphere	Temperature (°C)	Donor	Lipase	Conversion (%)[d)]	Ratio **7**/**1**[e)]
1	2	N_2	70	VA (10 equiv.)	CALB[a)]	52	10
2	2	N_2	70	PCPA (10 equiv.)	CALB[a)]	32	3
3	2	N_2	50	PCPA (10 equiv.)	CALB[a)]	31	3
4	2	H_2	70	PCPA (10 equiv.)	CALB[a)]	32	3
5	5	N_2	70	PCPA (10 equiv.)	CALB[b)]	32	3
6	7	N_2	70	PCPA (15 equiv.)	CALA[b)]	32	3
7	17	N_2	70	PCPA (15 equiv.)	CALB[c)]	33	3
8	24	N_2	70	PCPA (15 equiv.)	CALA[b)]	33	3

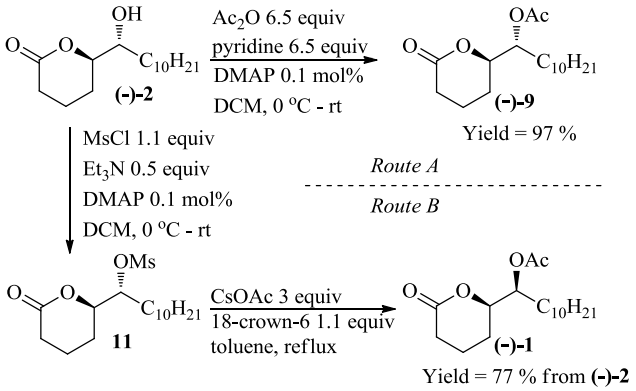
All reactions were conducted as described in the representative DYKAT method outlined in the experimental section using **(±)-2** as starting material. The acyl donors used were *p*-chlorophenylacetate (PCPA) or vinyl acetate (VA). [a)] Reaction was conducted using 85mg/mmol of immobilized lipase. [b)] Reaction was conducted using 270 mg/mmol of immobilized lipase. [c)] Reaction was initially conducted using 270 mg/mmol of immobilized lipase (86 mg), then 71 mg of lipase was added on days 9, 13, 15, 16. [d)] Conversion was determined from the percentage of recovered starting material. [e)] Estimated from ^{1}H NMR spectrum of the product co-eluting **7** and **1**.

new carbonyl signal at 207.8 ppm in the ^{13}C NMR spectrum. In an attempt to further elucidate the identity of this unknown by-product, a subsequent reaction was performed using vinyl acetate (VA) and **(±)-2**, which is known to favour the formation of oxidized products in these types of transformations.[16] To this end, a marked increase in the consumption of the starting material was observed with VA, and as expected, the isolated materials from the reaction consisted almost exclusively of the ketone by-product (Entry 1, Table 2) as supported by ^{1}H NMR, ^{13}C NMR, and comparison with the product isolated using PCPA as a donor, thus further corroborating the tentative structural assignment of this by-product as the ketone **7**. Moreover, oxidation of **(±)-2** with Cornforth's reagent afforded material that was spectrometrically identical with that of by-product ketone **7** when compared with ^{1}H NMR and ^{13}C NMR spectra of product spot isolates from DYKAT trails.

Having established the identity of the co-eluting by-product as **7** a systematic examination of reaction parameters was conducted using racemic *threo*-hydroxylactone **(±)-2** in an attempt to improve the efficiency of the DYKAT approach (Entry 2-8, Table 2). It was initially thought that conversion was ceasing due to a thermal deactivation of the enzyme, however lowering the reaction temperature had no effect on the outcome of the reaction (Entry 3, Table 2). Similarly, running the reaction under a hydrogen atmosphere (1 atm) in order to reduce the steady state concentration of the suspected oxidized product, likewise met with no success (Entry 4, Table 2). At that stage, reasoning that the low conversion was an artefact of an unfavourable equilibrium, a series of additional conditions were then examined employing greater lipase loadings, acyl donor equivalents and reaction times, none of which had an effect on overall conversion or reduced by-product formation (Entries 5-7, Table 2). Given these failures, the N435, CALB immobilized enzyme was subsequently exchanged for a CALA enzyme immobilized on Immobead150 to probe the effect of enzyme and immobilization medium, yet disappointingly no improvement was observed (Entry 8, Table 2). Moreover, even the successive additions of fresh immobilized lipase after conversion had ceased did not result in additional conversion of starting material (Entry 7, Table 2).

Based on these results equilibrium considerations and the thermal or otherwise slow decay of enzyme could be ruled out as a cause for the observed conversion limit. Instead, it was clear from ^{13}C NMR spectra that the by-product contained a highly deshielded carbon (207.8 ppm) that could compete with electrophilic acyl donor (~169 ppm) for the nucleophilic serine in the active site of the lipase to form a hemiacetal complex with the enzyme. The competitive reversible inhibition of lipases by methyl-*n*-alkyl ketones and aldehydes has been known for some time.[23] Furthermore, trifluoroketones are known to form inhibitory hemiacetal complexes in serine proteases with serine-containing catalytic triads at the active site, similar to that of CALA and CALB.[24] It was therefore, suspected that **7** may play a role in the inactivation of the lipase in this reaction.

In order to determine if ketone **7** did in fact have an inhibitory effect on the lipase-mediated acetylation of alcohols **2** and **8**, two parallel DYKAT reactions were then conducted under the conditions outlined in Scheme 6, with and without the addition of **7** at the beginning of the reaction. Notably, in the presence of **7** no acetylated products were formed after 12 hours, while conversely in the absence of **7** a mixture of ketone **7** and *erythro*-acetate **1** (4:1) was obtained, while the *syn*:*anti* ratio of recovered starting materials remained the same in both cases. Overall it would seem based on these trends and previous reports of lipase and protease inhibition by electron poor ketones that the observed inhibitory action of ketone **7**, likely results from the formation of



Scheme 7 Diastereodivergent acetylation

a hemiacetal between **7** and serine in the active-site of the lipases N435 and CALB. In this context, it was reasoned that the lactone moiety of **7** was capable of acting as a strong hydrogen acceptor, forming a hydrogen bonding network within the active site pocket of the enzyme, which further stabilized the inhibitor-enzyme complex, contributing to the observed drastic reduction in reaction rate at an apparently low threshold concentration of **7**. Irrespective, although the reasons for the accumulation of the oxidized intermediate **7** remains unclear, as it was difficult to identify a source of stoichiometric oxidant that would allow for the accumulation of ketone **7**, it is hypothesized that quinonic impurities formed by the auto or ambient oxidation of *p*-chlorophenol may have led to increased steady-state concentrations of **7**.

Accordingly, given the synthetic shortcomings of the DYKAT approach and the successful asymmetric induction *via* Shi epoxidation, the asymmetric syntheses of the target compounds, **(-)-9** and **(-)-1**, was ultimately realized by subjecting **(-)-2** to a diastereodivergent esterification strategy which afforded (5*R*, 6*R*)-**(-)-9** and (5*R*, 6*S*)-**(-)-1** in 68 % and 54 % overall yield starting from fatty acid **4** (Scheme 7).[12]

Experimental

Materials were obtained from commercial suppliers (Sigma-Aldrich) and were used without further purification unless otherwise stated. For use in PCPA synthesis *p*-chlorophenol was purified by vacuum distillation. Dry solvents were obtained by distillation under N_2 from CaH_2 (DCM) or Na (toluene and THF). Reactions were monitored by thin layer chromatography (TLC) using TLC silica gel 60 F254, EMD Merck. Flash column chromatography was performed over Silicycle ultrapure silica gel (230-400 mesh). NMR spectra were obtained with a Bruker DPX-300 (^{1}H 300 MHz, ^{13}C 75.5 MHz) in $CDCl_3$. The chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane. Mass spectra were obtained on an MSI/Kratosconcept IS Mass spectrometer. Optical rotations were meassured using a Perkin Elmer 341 with sodium lamp polarimeter. FTIR spectra were obtained on an ATI Mattson Research Series spectrometer. Melting points were obtained using Indosati scientific melting point apparatus and were uncorrected.

Catalysts **5a-c** were synthesized according to previously outlined synthetic procedures.[14a, b] Shi epoxidation conditions were based on published epoxidation procedures.[14c] Characterization data for catalysts were in good agreement with literature. [14a, b]

Representative synthesis hydroxylactone [(-)-2] using catalyst (5c):

To a solution of fatty acid **4** (200 mg, 0.786 mmol) and catalyst **5c** (76 mg, 0.196 mmol) in DME-DMM (dimethoxyethane-dimetheoxymethane) 3:1 (12 ml) was added an aqueous buffer (7.9 ml, 0.1 M AcOH-K_2CO_3 pH 9.3 in 0.4 mM aqueous EDTA) and Bu_4NHSO_4 (10 mg, 0.031 mmol) with vigorous stirring. The solution was cooled in a -11 °C ice-salt bath for 15 minutes then solutions of Oxone (6.3 ml, 0.20 M in 0.4 mM aqueous EDTA) and K_2CO_3 (6.3 ml, 0.84 M in 0.4 mM aqueous EDTA) were delivered simultaneously over 6 hours. The solution was adjusted to pH ~2 by slow addition of 10% HCl (3.5 ml), extracted with EtOAc (3 x 10ml), dried ($MgSO_4$), filtered and concentrated. The crude oil was dissolved in cyclohexane (14 ml) and heated under reflux for 24 hours. The resulting yellow solution was concentrated and purified by flash chromatography (Et_2O) then recrystallized from hexanes to afford the target compound **(-)-2** as a white solid (149 mg, 70 %). m.p 65-66 °C (hexanes); lit 68-70 °C (hexanes-EtOAc)[19]; α^D -9.3° (c = 0.95, $CHCl_3$); lit. -10.2 ° (c = 0.87)[19]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.2 (m, 1H), 3.6 (m, 1 H), 2.6-2.5 (m, 2H), 2.0-1.2 (m, 22H), 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.6, 83.2, 73.3, 32.6, 31.9, 29.5, 25.4, 24.2, 22.7, 18.4, 14.1; IR (KBr): ν 3554(br), 2955, 1706 cm^{-1};HRMS (FAB): m/z calcd for $C_{16}H_{30}O_3$ $[M + H]^+$ 271.2273, found 271.2262.

Hydroxylactone [(-)-2] using catalyst (5a):

Starting with fatty acid **4** (254 mg, 1.00 mmol) the representative epoxidation procedure using catalyst **5a** was followed to synthesise **(-)-2** as a white solid (175 mg, 65 %). m.p. 65-67 °C (hexanes); lit 68-70 °C (hexanes-EtOAc)[19]; α^D -6.5° (c = 1.04, $CHCl_3$); lit. -10.2 ° (c = 0.87, $CHCl_3$)[19]; ^{1}H and ^{13}C NMR were in agreement with those reported using catalyst **5c**.

Hydroxylactone [(-)-2] using catalyst (5b):

Starting with fatty acid **4** (255 mg, 1.00 mmol) the representative epoxidation procedure using catalyst **5b** was followed to synthesis **(-)-2** as a white solid (183 mg, 68 %). m.p. 65-67 °C; lit 68-70 °C (hexanes-EtOAc)[19]; α^D -8.6°(c = 1.01, $CHCl_3$), lit. -10.2 ° (c = 0.87, $CHCl_3$)[19]; ^{1}H and ^{13}C NMR were in agreement with those reported using catalyst **5c**.

Characterization data were in good agreement with literature for all asymmetric epoxidation products.[19]

(5*R*, 6*R*)-6-Acetoxy-5-hexadecanolide [(-)-9] with chirality from catalyst (5c):

To a solution of lactone **(-)-2** (50 mg, 0.18 mmol) in CH_2Cl_2 (1.2 ml) was added Ac_2O (0.11 ml, 1.2 mmol), pyridine (0.10 ml, 1.2 mmol) and DMAP (1.4 mg, 0.012 mmol) at 0 °C under nitrogen. The reaction was allowed to slowly warm to room temperature. Upon stirring for 0.5 h the reaction was quenched by addition of brine (3 ml) and stirred vigorously for an additional 30 minutes. The mixture was extracted with CH_2Cl_2 (3 x 10 ml), the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (1:1 hexane-EtOAc 0.01 % Et_3N) to yield **(-)-9** as a clear colourless oil (54 mg, 97 %).; α^D: -

13.0° (c = 2.0, $CHCl_3$), -14.4° (c = 2.2, $CHCl_3$)[26]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.97(m, 1H), 4.34 (dt, *J* = 4.5, 3.6 Hz, 1 H), 2.60-2.47 (m, 2H), 2.08 (s, 3H), 2.01-1.50 (m, 6H), 1.27 (s, 16H) 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.9, 170.7, 79.8, 73.9, 31.9, 29.9-29.3, 25.3, 24.1, 22.7, 21.0, 18.4, 14.1. Characterization data were in good agreement with literature.[26]

(5*R*, 6*S*)-6-Acetoxy-5-hexadecanolide [(-)-1] with chirality from catalyst (5c):

A flame-dried two neck flask equipped with a magnetic stir bar, rubber septum and a vacuum adapter connected to a two-line Schlenk manifold was charged with a solution of (5*R*, 6*R*)-hydroxylactone **(-)-2** (52 mg, 0.19 mmol) in CH_2Cl_2 (5 ml), under N_2. The above solution was cooled in an ice bath then MsCl (0.02 ml, 0.2 mmol) and Et_3N (0.02 ml, 0.1 mmol) were added dropwise at 0 ^{o}C under N_2. The reaction flask was allowed to warm to room temperature over 0.5 h, then the reaction mixture was washed with water (3 ml), sat. $NaHCO_3$ (3 ml) and brine (3 ml), then dried ($MgSO_4$) and concentrated. The crude mesylate was dried under vacuum (0.1 mmHg, 40 ^{o}C, 2 h), then dissolved in dry toluene (5 ml) under N_2. To a flame-dried two neck flask equipped with a magnetic stir bar, septum and condenser attached to a two-line Schlenk manifold was added CsOAc (92 mg, 0.48 mmol) and 18-crown-6 (56 mg, 0.21mmol) under a rapid flow of nitrogen. The contents of the reaction flask were further dried by vacuum purging and backfilling with N_2 three times at 100 ^{o}C. The mesylate solution was transferred to the reaction flask via cannula with rapid stirring under N_2. The reaction mixture was heated under reflux for 16 h. The mixture was then cooled to room temperature, poured into Et_2O (10 ml) and washed with water (3 ml), sat. $NaHCO_3$ (3 ml) and brine (3 ml), then dried ($MgSO_4$), concentrated and purified by flash chromatography (2:1 hexane-EtOAc 0.02 % Et_3N) to afford **(-)-1** as a clear colourless oil (46 mg, 77 %). α^D: -34.1° (c = 2.0, $CHCl_3$); lit -38.1° (c = 1.02 $CHCl_3$)[19]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.98 (m, 1H), 4.36 (m, 1H), 2.56-2.39 (m, 2H), 2.08 (s, 3H), 2.01-1.70 (m, 3H), 1.62 (m, 3H) 1.22 (s, 16H) 0.84 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.8, 170.4, 80.5, 74.3, 31.8, 29.6-29.3, 25.2, 23.4, 22.6, 21.0, 18.3, 14.1. Characterization data were in good agreement with literature.[19]

Epimerization of [(±)-2] to [(±)-8] using Shvo`s Catalyst (6):

A flame-dried flask was charged with **(±)-2** (48 mg, 0.179 mmol), Shvo`s catalyst **6** (2 mg, 0.002 mmol) and toluene (0.85 ml) under H_2 (1 atm) and heated at 70 °C for 24 h. The solution was isolated by filtration, concentrated and purified by flash chromatography (1:1 hexanes:EtOAc) and subsequently prepared for analysis by NMR in $CDCl_3$. See SI for NMR spectra.

Attempted DYKAT of [(±)-2] using VA donor:

A flame dried two-neck flask, equipped with stir-bar was charged with **(±)-2** (45 mg, 0.166 mmol), **6** (2 mg, 0.002 mmol) and CALB (N435, 18 mg) and dried by evacuating and flushing with N_2 three times. A second flame dried flask was charged with VA (0.16 ml, 1.73 mmol) and dry toluene (0.83 ml) under N_2. The solution of vinyl acetate was dried by passing dry N_2 through the solution *via* syringe needle for 1 h and then transferred via cannula to the two neck flask using a positive pressure of N_2. The reaction mixture was heated under N_2 for 48 h, the solution was isolated by filtration, concentrated under reduced pressure and purified by flash chromatography (2:1 then 1:1 hexane-EtOAc 0.02 % Et_3N). Starting material was recovered as a mixture of diastereomers (22 mg, 48 %). The product suspected to be **7** was isolated with trace (~10 %) acetylated starting materials as clear oil. (28 mg) ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (m, 1H), 2.67-2.57 (m, 4H), 2.18-2.10 (m, 4H), 1.59 (m, 2H), 1.25 (s, 14H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.8, 169.7, 83.3, 38.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 24.3, 22.9, 22.7, 19.9, 14.1.

Representative DYKAT of chiral hydroxylactone [(-)-2] using PCPA:

A flame dried two-neck flask, equipped with stir-bar was charged with **(±)-2** (86 mg, 0.325 mmol), **6** (7 mg, 0.006 mmol) and CALB (N435, 94 mg) and dried by evacuating and flushing with N_2 three times. A second flame dried flask was charged with PCPA (547 mg, 3.21 mmol) and dry toluene (2.0 ml) under N_2. The solution of phenyl acetate was dried by passing dry N_2 through the solution *via* syringe needle for 1 h and then transferred via cannula to the two neck flask using a positive pressure of N_2. The reaction mixture was heated under N_2 for 48 h, the solution was isolated by filtration, concentrated under reduced pressure and purified by flash chromatography (2:1 then 1:1 hexane-EtOAc 0.02 % Et_3N). Starting material was recovered as a mixture of diastereomers (59 mg, 69 %). The product suspected to be **7** was isolated with ~25 % acetylated starting materials as clear oil. (28 mg, see SI for NMR spectra)

Synthesis of (±)-6-oxy-5-hexadecanolide [(±)-7]:

To a screw cap vial equipped with a magnetic stir bar and a rubber septum was added hydroxylactone **(±)-2** (186 mg, 0.688mmol), PDC (388 mg, 1.03 mmol), 3 Å molecular sieves (412 mg), AcOH (1 drop) and DCM (0.7 ml). The mixture was stirred under N_2 for 24 h then to the dark residue was added hexanes-EtOAc (5:1, 2 ml) and the mixture was filtered through a pad of silica (d = 0.5 cm, h = 2 cm). The clear solution was concentrated and purified by flash chromatography (5:1 hexanes-EtOAc). The solution was concentrated and a white solid was obtained by crystallization from cold hexanes (21 mg, 11 %). m.p 26-27 ^{o}C (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.76 (m, 1H), 2.71-2.56 (m, 4H), 2.20-2.14 (m, 1H), 1.90 (m, 3H), 1.60 (t, *J* = 6.7 Hz, 2H), 1.27 (s, 14 H), 0.89 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 207.8, 169.7, 83.3, 38.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 24.4, 22.9, 22.7, 17.9 14.1; IR (KBr): ν 2923, 1725, 1745 cm^{-1};HRMS (FAB): m/z calcd for $C_{16}H_{28}O_3$ $[M+H]^+$ 268.2039, found 268.2044.

Conclusions

The asymmetric synthesis of MOPs (5*R*, 6*R*)-**(-)-9** and natural (5*R*, 6*S*)-**(-)-1** was completed in two steps from a naturally occurring fatty acid **4** with overall yields of 54 % and 68 %, respectively. A key step in this synthesis involved a Shi epoxidation of **4** which afforded enantioenriched hydroxylactone **(-)-2**, which subsequently was subjected to a diastereodivergent esterification that provided the targeted MOPs **(-)-1** and **(-)-9**. Notably, it was found that the chain length of the Shi epoxidation

catalyst used had a dramatic effect on stereoinduction, with shorter chain lengths providing lactone products of lower optical activity. Moreover, a DYKAT approach to **(-)-1** and **(-)-9** was also investigated that proved unsuccessful, due to the formation of a ketone intermediate, **7**, which acted as a lipase inhibitor. While the scope of this work focused on the synthesis of MOPs **(-)-1** and **(-)-9**, it is noteworthy that many of the mechanistic facets of this study garner considerable attention. More to the point, studying the correlation between er and the formation of catalyst-substrate aggregates in the biphasic conditions of Shi's epoxidation may help to rationalize the role of amphilicity in other aggregate forming asymmetric organocatlysts.[25] Meanwhile, the investigation of ketones structurally related to **7** as inhibitors of medicinally relevant lipases is warranted.

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Notes and references

[a] *Department of Chemistry, Brock University, 500 Glenridge Ave., St. Catharines, Canada.Tel: 905-688-5550 x340; E-mail: tdudding@brocku.ca*

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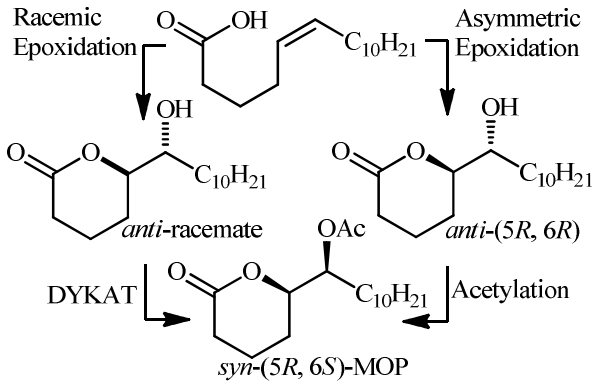
1. (a) L. D. Kramer, J. Li and P.-Y. Shi, *Lancet Neurol*., 2007, **6**, 171; (b) S. L. Rossi, T. M. Ross and J. D. Evans, *Clin. Lab Med.*, 2010, **30**, 47.
2. (a) J. R. Clark, L. R. Goodman, P. W. Borthwick, J. M. Patrick, G.M. Cripe, P. M. Moody, J. C. Moore and E. M. Lores, *Environ. Toxicol. Chem*., 1989, **8**, 393; (b) R. J. Gill, O. Ramos-Rodriguez and N. E. Raine, *Nature*, 2012, **491**, 105; (c) G. Di Prisco, V. Cavaliere, D. Annoscia, P. Varricchio, E. Caprio, F. Nazzi, G. Gargiulo and F. Pennacchio, *Proc. Natl. Acad. Sci*., 2013, **110**, 18466; (d) C. Lu, K. M. Warchol, R. A. Callahan, *B. Insectol*., 2014, **67**, 125.
3. M. Koureas, A. Tsakalof, A. Tsatsakis and C. Hadjichristodoulou, *Toxicol. Lett*., 2012, **210**, 155.
4. (a) F. Darriet and F. Chandre, *Pest Manag. Sci*., 2012, **69**, 905; (b) M. A. Riaz, A. Chandor-Proust, C. Dauphin-Villemant, R. Poupardin, C. M. Jones, C. Strode, M. Régent-Kloeckner, J.-P. David and S. Reynaud, *Aquat. Toxicol*., 2013, **126**, 326.
5. *WHO Handbook for Integrated Vector Management*; World Health Organization: Geneva, Switzerland, 2012.
6. (a) S. M. Cook, Z. R. Khan and J. A. Pickett, *Ann. Rev. Entomol*., 2007, **52**, 375; (b) W. A. Otieno, T. O. Onyango, M. M. Pile, B. R. Laurence, G. W. Dawson, L. J. Wadhams and J. A. Pickett, A. *Bull. Entomol. Res*., 1988, **78**, 463.
7. M. Schumann, A. Patel and S. Vidal, *Appl. Soil Ecol*., 2013, **64**, 178.
8. (a) M. Mansour, *J. Appl. Entomol*., 2010, **134**, 234; (b) J. Huang, L. J. Gut and J. R. Miller, *J. Econ. Entomol*., 2013, **106**, 2144.
9. V. Navarro-Llopis, J. Primo and S. Vacas, *Pest Manag. Sci*., 2013, **69**, 478.
10. (a) W. K. Reisen and A. R. Pfuntner, *J. Am. Mosq. Contr. Assoc*., 1987, **3**, 601; (b) S. A. Allan and D. Kline, *J. Vector Ecol*., 2004, **29**, 285; (c) J. L. Hardy, E. J. Houk, L. D. Kramer and W. C. Reeves, *Ann. Rev. Entomol*., 1983, **28**, 229.
11. (a) S. L. Rossi, T. M. Ross and J. D. Evans, *Clin. Lab. Med*., 2010, **30**, 47; (b) J. F. Anderson, T. G. Andreadis, C. R. Vossbrinck, S. Tirrell, E. M. Wakem, R. A. French, A. E. Garmendia and H. J. Van Kruiningen, *Science*, 1999, **286**, 2331; (c) A. Michaelakis, A. P. Mihou, E. A. Couladouros, A. K. Zounos and G. Koliopoulos, *J. Agric. Food Chem*., 2005, **53**, 5225; For a recent synthesis of MOP stereoisomers see: (d) H.-B. Dong, M.-Y. Yang, X.-T. Zhang and M.-A. Wang, *Tetrahedron Asymmetry*, 2014, **25**, 610.
12. Although **4** is known to be available from the seed oil extract of Kochia scoparia, the fatty acid was synthesized using the previously reported Wittig methodology as a proof of principal for the purpose of this investigation; D. Hurem and T. Dudding, *RSC Adv*., 2014, **4**, 15552.
13. Methods for asymmetric epoxidation of unfunctionalized olefins have been limited to date. For *in vivo* P450 epoxidation see: (a) T. Kubo, M. W. Peters, P. Meinhold and F. H. Arnold, *Chem. Eur. J*., 2006, **12**, 1216; for chloroperoxidase epoxidation see: (b) S. Hu and L. P. Hager, *Tetrahedron Lett*., 1992, **40**, 1641; for a review of organocatalyzed epoxidations see: (c) Y. Zhu, Q. Wang, R. G. Cornwall and Y. Shi, *Chem. Rev*., 2014, **114**, 8199; for a review of enantioselective olefin oxidations see: (c) C. Bonini and G. Righi, *Tetrahedron*, 2002, **58**, 4981.
14. (a) D. Goeddel, L. Shu, Y. Yuan, O. A. Wong, B. Wang and Y. Shi, *J. Org. Chem*., 2006, **71**, 1715; (b) M.-X. Zhao, D. Goeddel, K. Li and Y. Shi, *Tetrahedron*, 2006, **62**, 8064; (c) C. P. Burke and Y. Shi, *Org. Lett*., 2009, **11**, 5150.
15. (a) K. N. Houk, J. Liu, N. C. DeMello and K. R. Condroski,. *J. Am. Chem. Soc*., 1997, **119**, 10147; (b) C. Jenson, J. Liu, K. N. Houk and W. L. Jorgensen, *J. Am. Chem. Soc*., 1997, **119**, 12982. (c) L. Shu, P. Wang, Y. Gan and Y. Shi, *Org. Lett*., 2003, **5**, 293; (d) D. A. Singleton and Z. Wang, *J. Am. Chem. Soc*., 2005, **127**, 6679; (e) S. T. Schneebeli, M. L. Hall, R. Breslow and R. Friesner, *J. Am. Chem. Soc*., 2009, **131**, 3965.
16. (a) Y. Shvo, D. Czarkie and Y. Rahamim, *J. Am. Chem. Soc*., 1986, **108**, 7400; (b) M. J. Mays, M. J. Morris, P. R. Raithby, Y. Shvo and D. Czarkie, *Organometallics*, 1989, **8**, 1162.
17. B. A. Persson, A. L. Larsson, M. Le Ray and J.-E. Bäckvall, *J. Am. Chem. Soc*., 1999, **121**, 1645.
18. B. Henkel, A. Kunath and H. Schick, *J. prakt. Chem*., 1997, **339**, 434.
19. C. Gravier-Pelletier, Y. Le Merrer and J. C. Depezay, *Tetrahedron*, 1995, **51**, 1663.
20. The ratio of diastereomers was estimated using the relative integrals of C(6) protons by ^{1}H NMR using an authentic sample of *erythro*-hydroxylactone **(-)-8** produced using a proline-catalyzed aldol/Bayer-Villiger route.: B. Sun, L. Peng, X. Chen, Y. Li, Y. Li and K. Yamasaki, *Tetrahedron: Asymmetry*, 2005, **16**, 1305.
21. The synthesis of PCPA acyl donor was accomplished using a modified solvent-free acetylation of *p*-chlorophenol under microwave conditions. The literature procedure was successfully scaled to produce adequate quantities of PCPA needed to conduct DYKAT experiments. (see ESI for detailed experimental procedure for PCPA synthesis): H. Veisi, R. Ghorbani-Vaghei, H. Eskandari, S. Hemmati, A. Rezaei, S. Hajinazari, M. Raoof, H. Far and A. Entezari, *Phosphorus, Sulfur, and Silicon*, 2011, **186**, 213.
22. The ratio of the suspected ketone by-product, 7, to the combined MOP diastereomers was 3:1 as inferred from the relative intensities of the ^{1}H NMR (C5) proton signals.
23. M. Graber, R. Irague, E. Rosenfeld, S. Lamare, L. Franson and K. Hult, *Biochim. Biophys. Acta*, 2007, **1774**, 1052.
24. L. Dzhekieva, S. A. Adediran, R. Herman, F. Kerff, C. Duez, P. Charlier, E. Sauvage, R. F. Pratt, *Biochemistry*, 2013, **52**, 2128.
25. (a) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, and C. F. Barbas III, *J. Am. Chem. Soc*., 2006, **128**, 734; (b) F. Rodriguez-Llansola, J. F. Miravet and B. Escuder, *Chem. Commun*., 2009, 7303; (c) B. Lipshutz and S. Ghorai, *Org. Lett*., 2009, **11**, 705; (d) B. Lipshutz and S. Ghorai, *Org. Lett*., 2012, **14**, 422.
26. L. Guo-qiang, X. Hai-jian, W. Bi-chi, G. Guong-zhong and Z. Wei-shan, *Tetrahedron Lett*., 1985, **26**, 1233



Direct epoxidation of *cis*-5-hexadecenoic acid towards the synthesis of Mosquito Oviposition Pheromone (MOP) and evaluation of Dynamic Kinetic Asymmetric Transformation (DYKAT) for late-stage asymmetric induction are presented.