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Diastereodivergent Total Synthesis of Mosquito Oviposition Pheromone

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The unnatural *threo*-6-acetoxy-5-hexadecanolide and the natural mosquito oviposition pheromone *erythro*-6-acetoxy-5-hexadecanolide were synthesized in a diastereodivergent fashion in 44 % and 33 % overall yield respectively from 5-bromovaleric acid and undecanal. The synthesis proceeds through a rare but naturally occurring fatty acid intermediate and utilizes a mild chemoenzymatic domino epoxidation-lactonization as a key step to form the 6-hydroxy-5-hexadecanolide core.

Introduction

A series of experiments initiated in 1983 by Pickett and coworkers led to the identification of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**1**) as the major chemical component of *Culex* sp. egg rafts responsible for the potent and selective attraction of gravid *Culex* mosquitos (Figure 1).[1]

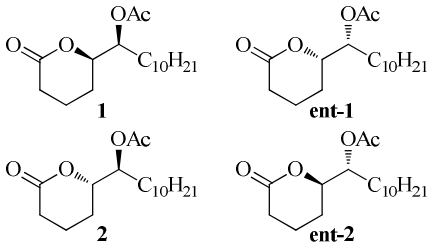
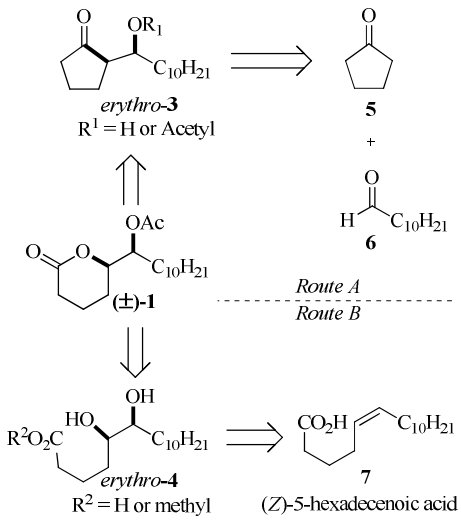


Figure 1. Stereoisomers of Mosquito Oviposition Pheromone **1**

Mosquito species of the *Culex* genus comprise the majority of vectors responsible for the transmission of encephalitic arboviruses, such as West Nile virus.[2] In order to monitor these diseases, Mosquito Oviposition Pheromone (MOP) **1** has become a sought after attractant for the surveillance of arbovirus occurrence within mosquito populations, due to its selectivity for gravid mosquitos that have had a chance to become laterally infected.[3] Apart from its use in mosquito surveillance, **1** has also been used in conjunction with larvacides as an alternative method of pest control.[4] Accordingly, the existing demand for this natural product has generated over twenty total syntheses of **1** and its corresponding stereoisomers since Mori's total synthesis in 1983.[5, 6, 7, 8, 9a, c] Although various enantioselective syntheses have afforded sufficient quantities of **1** and its corresponding stereoisomers to allow for the elucidation of their specific biological activities, these methods are of limited practicality for the large scale production and use of optically enriched **1** in control or surveillance applications. Notwithstanding, biological activity assays indicated that the non-natural stereoisomers (**ent-1**, **2** and **ent-2**, Figure 1) were inactive, but not repulsive,[1c, e] allowing for the use of racemic mixtures of **1** and **ent-1** as attractants in oviposition traps.[9] In view of this fact, it is important to note that bioactive plant oil containing a racemic mixture of **1** and **ent-1** can be produced from *Kochia scoparia* seed extract that initially contained ~25 % (*Z*)-5-hexadecenoic acid, thus offering a renewable source for the production of oviposition attractant.[9a, b]

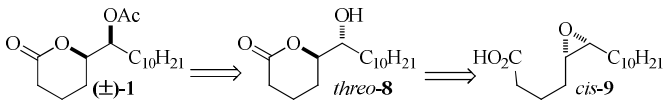
The most successful strategies for the synthesis of racemate **(±)-1** have involved either aldol addition of cyclopentanone to undecylaldehyde followed by Bayer-Villiger oxidation and acetylation (Route A, Scheme 1),[6] or dihydroxylation of (*Z*)-5-hexadecenoic acid (**7**) or the methyl ester of **7** followed by intramolecular cyclization to form the *erythro*-hydroxyalkanolide precursor to **(±)-1** (Route B, Scheme 1).[9a, c]



Scheme 1. Previous Routes to Racemic Mosquito Oviposition Pheromone

Both strategies lead to a concise synthesis of racemic *erythro*-6-acetoxy-5-hexadecanolide **(±)-1** with high overall yields (~ 65 %). Utilizing route B, product **(±)-1** was obtained from the naturally available acid **7** *via* the dihydroxylation route; unfortunately this transformation required the use of stoichiometric heavy metal reagents. Alternatively, route A was recently employed to access enantioenriched **1** and **2** using the Hajos-Parish asymmetric aldol reaction,[7, 8] however the large excess of *m*-CPBA (~ 5 eq) for Bayer-Villiger oxidation detracted from this procedure. Apart from the hazardous reagents required for these oxidations, the necessity for purification by column chromatography at each step of the synthesis greatly limited the scalability of these reactions.

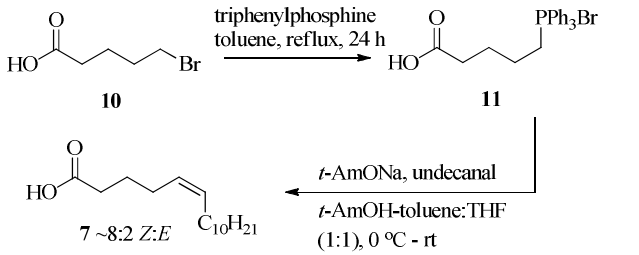
To overcome the limitations associated with the above oxidations and at the same time incorporate salient features of routes A and B in Scheme 1, it was reasoned that a more ideal synthesis would intersect naturally available acid **7** and proceed through a benign, metal-free oxidation. Epoxidations of olefins, mediated by the *in situ* lipase catalyzed generation of peroxyacids using aqueous hydrogen peroxide as a primary oxidant have been reported in the literature and would offer one means to this end.[10] It was also understood that this very mild oxidation procedure would yield the hydroxylactone *threo*-**8**, after which the relative geometry at C(6) could be inverted by esterification to afford **(±)-1** (Scheme 2). Accordingly, the total synthesis of **(±)-1** *via* an environmentally benign lipase mediated epoxidation of (*Z*)-5-hexadecenoic acid **7** is reported. Marked features of this synthesis include the minimization of column purification by using urea inclusion crystallization and favourable 'Green' metrics.



Scheme 2. Retrosynthetic Analysis

Results and Discussion

At the outset, fatty acid **7** was synthesized by Wittig olefination under kinetic conditions to favour the (*Z*)-isomer (Scheme 3), as determined by characteristic signals from ^{1}H and ^{13}C NMR.[11] Although Wittig olefination can not be considered green, the reaction was chosen as a facile route to pure 5-hexadecenoic acid 7, as a proof of principle for the synthesis of (±)-1 from the naturally available fatty acid.



Scheme 3. Synthesis of Fatty Acid Precursor using a Conia-Dauben Modified Wittig Reaction under Kinetic Conditions

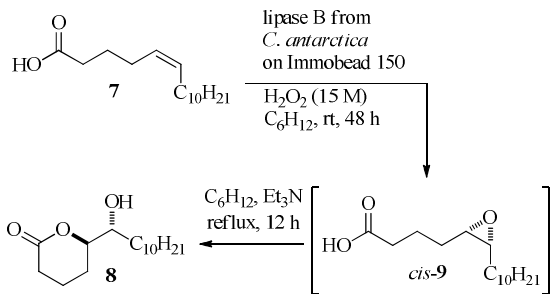
While investigating choice of base, it was found that the use of sodium *t*-amyloxide, in a similar manner to that described by Dauben *et al*.,[12] resulted in higher yields and cleaner workup than analogous reactions with potassium *t*-butoxide in THF (see SI for detailed experimental procedure)(Table 1). Purification methods for the removal of triphenylphosphine oxide (TPPO) were then investigated. The majority of TPPO remained in the organic reaction medium, however ~25 % of TPPO was carried over in the acid/base extraction resulting in a significant TPPO impurity in the crude oil extract. The use of column purification proved challenging, requiring a gradient mobile phase starting with hexanes, then hexanes-ethyl acetate (1:1) to produce colourless fatty acid in 61 % yield at a maximum 100 mg scale. To overcome difficulties with large scale column purification, the gram scale (1 – 5 g) purification of extract was achieved using urea inclusion crystallization.[13] This technique allowed for the isolation of up to 3 g of clear colourless fatty acid material that was free of TPPO and analytically pure in 48 % overall yield and retention of the (*Z*)-stereochemistry, while producing only aqueous urea solution and a small volume of TPPO in methanol as waste.

Table 1. Choice of Base and Purification Technique in Wittig Olefination

Entry	Base	Solvent	Urea Yield [a] (%)	Column Yield [b] (%)	*Z*:*E* [c]
1	*t*-BuOK	THF	32	45	8:2
2	*t*-AmONa	THF: toluene (1:1)	74	-	8:2

(a) Yield of reactions purified using two serial urea inclusion crystallizations at 5 g scale. (b) Yields of reactions purified by column chromatography at 100 mg scale. (c) Ratios were estimated using ^{1}H NMR.[11]

With the requisite fatty acid in hand, the lipase mediated Prylazhaev oxidation of the olefin was investigated (Scheme 4).



Scheme 4.Chemoenzymatic Epoxidation and Lactonization

Initially the incremental addition of hydrogen peroxide to a 100 mM solution of fatty acid **7** in cyclohexane over immobilized lipase resulted in a poor combined yield (30 %) of hydroxylactone and epoxyacid (Table 2, Entry 1). Previously, it was reported that the epoxyacid **9** undergoes oxidation to the peracid at a much slower rate than the unsaturated acid **7**, while the formation of peracid is much faster than the epoxidation.[10a] Accordingly, it was reasoned that an incremental addition of the fatty acid would maintain higher concentrations of the unsaturated fatty acid **7** during the progress of the reaction, which ultimately resulted in complete consumption of fatty acid as observed by TLC after 48 hours with minimal formation of by-products (Table 2, Entry 2).

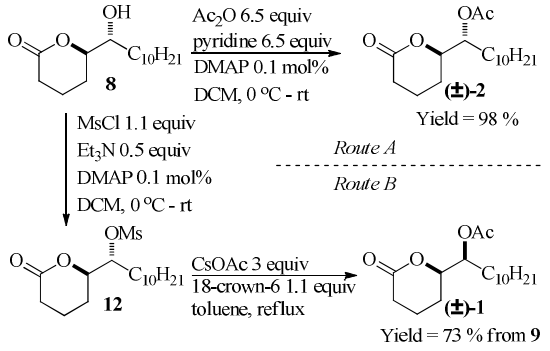
Under the room temperature oxidation conditions as described above, the epoxy acid **9** was formed along with ~10 % hydroxylactone **8** as observed by crude ^{1}H NMR. Complete lactonization was then achieved by heating the cyclohexane solution of **8** and **9** under reflux. Further optimization revealed that the addition of 0.04 % (v/v) Et_3N significantly reduced the time required for lactonization from 72 h to 12 h, likely due to the base acting as a proton shuttle. The diastereomerically pure *threo*-hydroxylactone **8** was isolated in 40 % yield by crystallization from hexanes, and the remaining hydroxylactone **8** was obtained from flash chromatography of the mother liquor and subsequent crystallization for a combined yield of 65 %. With these working experimental conditions, the ability to reuse the immobilized lipase was investigated, which revealed that the procedure could be repeated up to three times with no apparent loss of activity, so long as reaction runs were repeated immediately after filtration (Table 2, Entry 2-4). Whereas storage of the used immobilized lipase for one week at 7 °C unfortunately resulted in complete loss of activity.

Table 2. Oxidation Conditions and Catalyst Recycling

Entry	Addition time of H_2O_2 (h)[a]	Aliquots of fatty acid 8[b]	No. of lipase reuses[c]	Yield (%)[d]
1	24	1	0	30
2	24	4	0	69
3	24	4	1	68
4	24	4	2	69

(a) Aqueous H_2O_2 (15 M) was added over 24 h via syringe pump. (b) Aliquots of a solution of **8** (0.21 M) in cyclohexane were added to the reaction in 6 h increments. (c) Fatty acid **8** (1.5 mmol) was epoxidized over 48 h using the same 126 mg of lipase (CALB Immobead 150) for each reuse. (d) Represents yield of hydroxylactone **9**.

The synthesis was completed by way of a late diastereodivergent acetylation strategy. To this end, the *threo*-**12** was synthesized by *O*-acetylation of **8** using standard conditions (Scheme 5a).[8] Conversely, the **(±)-1** was synthesized by mesylation of the C(6) hydroxyl, followed by substitution of the resulting mesylate with acetate (Scheme 5b).[5h]



Scheme 5. Diasteredivergent Acetylation Strategy

At this stage the reaction metrics of the key oxidation steps and the overall synthesis, including several commonly used green metrics were determined for this synthesis and compared with two of the more successful racemic syntheses.[14] Due to the fact that current 'Green' metrics fail to account for every possible parameter that influences the environmental impact of a process, no one metric can be applied to assess the sustainability of a given process. As such, a series of green metrics were selected, along with standard reaction metrics like yield and steps, to compare the presented racemic synthesis with successful syntheses from the literature. Two metrics relating to mass efficiency were selected; (1) Sheldon's E-factor was selected as an easy measure of relative waste and (2) Glaxo-Smith-Klein's (GSK) metric was used to gauge reaction mass efficiency. Carbon efficiency (CE) was also calculated to gauge the efficiency of the transfer of organic material this synthesis. E-Factors and RME were calculated for each step of the synthesis by Equation 1 and 2 respectively, such that m_{sm} is the mass of starting materials and m_p is the mass products.[14]

Equation 1. $$E = \frac{m_{sm} - m_p}{m_p}$$

Equation 2. $$RME = \frac{m_p}{m_{sm}} \times 100\%$$

The mass of all consumable starting reagents and catalysts were incorporated, while solvents were considered recoverable and aqueous solutions were considered benign, and therefore excluded from the calculation. These assumptions were made for the sake of comparing syntheses at the bench scale, where solvent choices, quantities and lifecycles can be expected to change significantly during scale up to an industrial process. Silica and urea were considered recoverable and were not factored into the equation as well. CE was determined according to Equation 3, such that n_p is the moles of product,

n_{sm} is the moles of each reagent, C_{sm} is the number of carbons of that reagent and C_p is the number of carbons in the product.

Equation 3. $$CE = \frac{n_p \times C_p}{\sum C_{sm} \times n_{sm}} \times 100\%$$

The reaction and green metrics of this reaction were then compared with those of the previous successful conventional syntheses.[6, 9c] The reaction metrics for the key oxidation step reveal that the lipase mediated reaction is far more efficient in terms of mass efficiency despite its lower yield compared to oxidation with osmium tetroxide. (Table 3) Although the dihydroxylation proceeded with high carbon efficiency, the use of excess inorganic salts lowered its RME and increased its E-factor significantly. Meanwhile, Bayer-Villiger oxidation was more 'Green' than that of dihydroxylation, while the lipase epoxidation was more mass and carbon efficient. Notwithstanding, apart from its moderate yield, the lipase oxidation appeared quite desirable in comparison to the other known techniques, especially since toxic osmium reagents and *m*-CPBA were replaced with aqueous hydrogen peroxide. Although cyclohexane was used as a solvent, it was successfully recovered by distillation (~ 95 % recovery), and reused in subsequent reaction runs.

Table 3. Comparison of Oxidation Reaction Metrics and Primary Oxidants

Metric	Dawson *et al.*[6]	Michaelakis *et al.*[9c]	This Work
Yield of **8**	82 %	90 %	69 %
Oxidant	*m*-CPBA	$K_3Fe(CN)_6$	H_2O_2
E-Factor	1.3	15.1	0.4
RME	44 %	6.2 %	66 %
CE	55 %	92 %	69 %

Finally, the E-factor for the overall process was determined as a sum of E-Factors at each step, while the overall RME and CE was calculated as the product of each RME and CE in the linear sequence. The overall synthesis scored lower in comparison to the oxidation alone (Table 4). Although the overall synthesis was more mass and carbon efficient than that proposed by Michaelakis *et al*., yields were half that of either synthesis. The synthesis of Dawson *et al*. was the most mass and carbon efficient between the three. However, the nature of reagents and reaction conditions cannot be accounted for by the available green metrics. As such, metrics can only serve to aid in a qualitative assessment of the relative sustainability of different processes or reactions when placed into the context of what is known about the environmental impact of the different reagents used in the respective processes or reactions.

Table 4. Comparison of Overall Synthesis Metrics

Metric	Dawson et al.[6]	Michaelakis et al.[9c]	This Work
Yield[a]	22 %	23 %	16 %
Steps	3	5	4
E-Factor	6	106	9
RME[b]	5.2 %	0.0020 %	2.1 %
CE[c]	12 %	0.047 %	3.5 %

(a) Represents the overall yield of the active (5*R*,6*S*)-**1** in a mixture of stereoisomers.

Experimental

Materials and Methods

Reagents and solvents were purchased from Sigma-Aldrich at the highest available reagent grade purity, and used without further purification unless otherwise stated. Oven-dried glassware was used in all experiments unless otherwise stated.

Synthetic Procedures

Synthesis of (4-carboxybutyl)triphenylphosphonium bromide (11). A solution of triphenylphosphine (16.3 g, 62.3 mmol), and 5-bromovaleric acid (10.2 g, 56.1 mmol) in dry toluene (85 ml) were heated under reflux for 24 h. Toluene was removed *in vacuo* at 70 °C. Ether (20 ml) was added to the resulting amorphous solid and shaken vigorously. The white precipitate was filtered, washed with ether (3 x 15 ml) and dried *in vacuo* for 4 h at 35 °C to yield the title compound as a white solid that was used in subsequent reactions without further purification (21.6 g, 86 %, E = 0.2). m.p.: 191-193 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.5 (s, 1H), 7.82 (m, 15H), 3.64 (m, 2H), 2.30 (t, J = 7.2 Hz, 2H), 1.68 (m, 4H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 174.5, 135.38, 135.35, 134.1, 134.0, 130.8, 130.6, 118.6, 118.4, 33.06, 25.8, 25.6, 21.7, 20.8, 20.14.

Synthesis of (*Z*)-5-hexadecenoic acid (7). To a flame-dried flask containing 4-(carboxybutyl)triphenylphosphonium bromide (6.01 g, 13.6 mmol), was added an 0.8 M solution of sodium *t*-amylate in *t*-amyl alcohol and 1:1 toluene:THF (38 ml), at 0 °C, under a nitrogen atmosphere and with moderate to fast stirring with magnetic stir bar. To the resulting viscous orange suspension was added undecanal (2.54 g, 14.9 mmol) over 10 minutes with vigorous stirring under the conditions described above. The reaction was allowed to warm to room temperature overnight. The cream coloured mixture was extracted with H_2O (4 x 10 ml). The combined aqueous phase was cooled in an ice bath and slowly brought to pH ~2 by dropwise addition of aqueous 2% H_2SO_4 solution, extracted with ether (3 x 10 ml), combined organic layers were dried ($MgSO_4$) and concentrated to a clear yellow oil (3.62 g). The crude oil was dissolved in methanol (6.6 ml) and transferred hot to a boiling solution of urea in methanol (16.5 g in 26 ml). The

solution was allowed to crystallize overnight then filtered. The collected urea crystals were dissolved in 2% H_2SO_4, extracted with ether (3 x 10 ml), dried ($MgSO_4$), and ether was removed *in vacuo* to yeild **7** as clear, nearly colourless oil containing about 10 % aromatic impurities by ^{1}H NMR (2.78 g). The analytically pure fatty acid was obtained by repeating the above process to yield **7** as a clear, colourless oil (2.56 g, 74 %, *Z*:*E* = 8:2, E = 3.6). ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.5 (s, 1H), 5.46-5.32 (m, 2H), 2.36 (t, *J* = 6.7 Hz, 2H), 2.14-2.01 (m, 4H), 1.74-1.70 (m, 2H), 1.35-1.10 (m, 18 H), 0.92-0.87 (t, *J* = 6.7 Hz, 3H) ; ^{13}C NMR (600 MHz, $CDCl_3$): δ 180.5, 131.3, 128.1, 33.4, 31.9, 29.8-29.2, 27.3, 26.5, 24.5, 22.6, 14.1; IR (KBr pellet): ν 3500-2500, 2920, 2856, 1710, 1460, 1410, 935 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{30}O_2$ $[M + H]^+$, 255.2324; found, 255.2304.

SYNTHESIS OF *THREO*-6-HYDROXY-5-HEXADECANOLIDE (8). A solution of fatty acid **7** (376 mg, 1.48 mmol) in cyclohexane (7 ml) was added in aliquots (2 ml) to a vial containing lipase B from *C. Antarctica* on Immobead 150^{TM} (126 mg) with gentle stirring over 24 h. At the same time, to the above mixture was added 15 M aqueous H_2O_2 at a rate of 0.04 ml/h *via* syringe pump and PTFE tubing (0.8 ml). Reaction mixture was stirred for an additional 24 h upon addition of all reagents, then filtered, phases were separated, the combined organic layer was dried ($MgSO_4$), adjusted to 27 ml with cyclohexane with 0.04 % (v/v) Et_3N then heated under reflux for 12 h. The resulting solution was concentrated and **8** was crystallized from hot hexane as a white solid containing only the *threo*-diastereomer **8** (196 mg, 48 %). The mother liquor was concentrated and purified by flash chromatography (1:1 hexane/EtOAc 0.02 % Et_3N) to yield **8** as a white solid (79 mg, 21 %). The two were combined to yield **8** as a white powder (275 mg, 69 %, E = 0.4) m.p.: 65-67 ^{o}C; ^{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 (300 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 pellet): ν 3554(br), 2955, 1706 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{30}O_3$ $[M + H]^+$ 271.2273, found 271.2258.

SYNTHESIS OF *THREO*-6-ACETOXY-5-HEXADECANOLIDE ((±)-2). To a solution of lactone **8** (342 mg, 1.27 mmol) in CH_2Cl_2 (7.6 ml) was added Ac_2O (0.72 ml, 7.56 mmol) and pyridine (0.61 ml, 7.56 mmol) at 0 ^{o}C under nitrogen. The reaction was allowed to slowly warm to room temperature. Upon stirring for 40 h the reaction was quenched by addition of brine (18 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 **(±)-2** as a clear colourless oil (392 mg, 98 %, E = 0.3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (m, 1H), 4.37 (dt, *J* = 4.5, 3.6, 1 H), 2.60-2.47 (m, 2H), 2.11 (s, 3H), 2.01-1.50 (m, 6H), 1.27 (s, 16H) 0.9 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 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; IR (KBr): cm^{-1}; HRMS (EI): m/z calcd for $C_{18}H_{32}O_4$ $[M]^+$ 312.2301, found 312.2313.

SYNTHESIS OF *ERYTHRO*-6-ACETOXY-5-HEXADECANOLIDE ((±)-1). 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 *threo*-hydroxylactone **8** (164.7 mg, 0.609 mmol) in CH_2Cl_2 (15 ml) under N_2. The above solution was cooled in an ice bath then MsCl (0.05 ml, 0.646 mmol) and Et_3N (0.05 ml, 0.358 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 (10 ml), sat. $NaHCO_3$ (10 ml) and brine (10 ml), then dried ($MgSO_4$) and concentrated. The crude mesylate was further dried under vacuum (0.1 mmHg, 40 ^{o}C, 2 h), then dissolved in dry toluene (15 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 (311.8 mg, 1.628 mmol) and 18-crown-6 (180.3 mg, 0.682 mmol) 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 (30 ml) and washed with water (10 ml), sat. $NaHCO_3$ (10 ml) and brine (10 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 (139.8 mg, 73 %, E = 4.5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (m, 1H), 4.32 (m, 1 H), 2.56-2.39 (m, 2H), 2.04 (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 (300 MHz, $CDCl_3$): δ 170.8, 170.4, 80.5, 74.2, 31.8, 29.6-29.3, 25.2, 23.4, 22.6, 21.0, 18.3, 14.1; HRMS (EI): m/z calcd for $C_{18}H_{32}O_4$ $[M]^+$ 312.2301, found 312.2303.

Conclusions

The diastereoselective synthesis of the biologically active *erythro*-6-acetoxy-5-hexadecanolide was achieved in 33 % overall yield using a benign chemoenzymatic domino epoxidation-lactonization procedure. The E-factor for this oxidation/cyclization process was ~0.4, while the E-factor for the overall synthesis starting from 5-bromovaleric acid and undecanal was ~9, whereas E-factors in pharmaceutical production range between 25 and 100.[14a, b] A technique used in industrial purification of plant oils was demonstrated as a practical means of purifying a fatty acid from Wittig reactions on a gram scale. The *threo*-diastereomer was synthesized in 44 % overall yield.

At this stage the reliance on conventional means for the synthesis of fatty acid **7**, and acetylation to afford **(±)-1** has, as illustrated by E-factors provided in the experimental, introduced the largest volume of waste, and required the use of non-benign solvents. The benign oxidation procedure utilized in this work has never-the-less significantly improved upon the 'greeness' of the synthesis from previous attempts that also relied on such non-benign solvents as DCM and toluene.

Ongoing work is focussed on applying asymmetric methodologies to add to the overall utility of this approach. Moreover, in keeping within the tenets of green chemistry,[15] catalytic methods for the stereoinversion of the C(6) center are being investigated. At the same time, starting fatty acid sources from biological avenues are being explored. The overall long term aims of this research effort are to further improve the synthesis of **1** with reduced overall waste output to render its use in mosquito control applications more feasible.

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Notes and references

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Electronic Supplementary Information (ESI) available: [Supporting Experimental Procedures, Determination of *Z*:*E* Ratios, NMR Spectra of Isolated Products and Synthetic Intermediates]. See DOI: 10.1039/b000000x/

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