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Improved Synthesis of the C16−C20 Segment of Resolvin E1 Using Enantioselective Ketone Reduction and Lipase-Catalyzed Resolution

Rasidul Amin,[†] Jian-Xie Chen,[‡] Ian C. Cotterill,[⊥] Daniel Emrich,[‡] Daniel Ganley,[‡] Yuri L. Khmelnitsky,[⊥] Mark D. McLaws,*[,†] Peter C. Michels,[⊥] C. Eric Schwartz,[§,∥] Deb Thomas,[‡] Jun Yan,[†] and Qiang Yang[†]

[†]Chemical Development, AMRI, 21 Corporate Circle, Albany, New York 12203, United States

[‡]Chemical Development, AMRI, 7001 Performance Drive, North Syracuse, New York 13212, United States

[⊥]Fermentation and Biotransformations, AMRI, 21 Corporate Circle, Albany, New York 12203, United States

[§]Resolvyx Pharmaceuticals, 222 Third Street, Cambridge, Massachusetts 02142, United States

Supporting Information

ABSTRACT: A practical synthesis targeting the C16−C20 segment of the endogenous metabolite Resolvin E1 (RvE1) is described. The original route was revised to avoid the use of source-constrained raw materials and chemistries that were problematic on larger scale. The revised route utilizes commercially available (*E*)-1-chloropent-1-en-3-one as the key raw material to replace (*S*)-glycidol. The (*E*)-vinyl iodide functionality was installed by an addition/elimination sequence to prepare the segment required for a subsequent Sonogashira coupling. The chiral secondary hydroxyl group at C18 was established by Corey−Bakshi−Shibata (CBS) reduction followed by lipase-catalyzed acetylation to achieve chiral purity in excess of 98% ee. The revised route offered a viable multikilogram process to support early clinical production of this pro-resolution therapeutic agent.

INTRODUCTION

Resolvin E1 (RvE1, Figure 1), an oxidative metabolite of eicosapentaenoic acid (EPA), is a member of a family of endogenous small molecules that are known to be key mediators in the resolution of inflammation.[1] RvE1 has been shown to promote the resolution of inflammation by decreasing pro-inflammatory pathways such as polymorphonuclear neutrophil migration and production of pro-inflammatory cytokines. Its anti-inflammatory properties have attracted much interest as a potential therapeutic for a wide variety of conditions involving uncontrolled inflammation such as asthma,[2] inflammatory pain,[3] inflammatory bone disorders,[4] and allograft rejection.[5] Advancement of such studies can be hampered by the limited availability of this lipid mediator due to difficulties in its synthesis and purification. Herein, we report our efforts to optimize the synthesis of the C16−C20 segment of RvE1 as part of a larger effort to produce this metabolite in quantities sufficient to support preclinical safety studies and early-phase clinical trials.

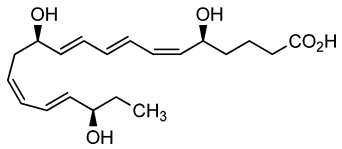


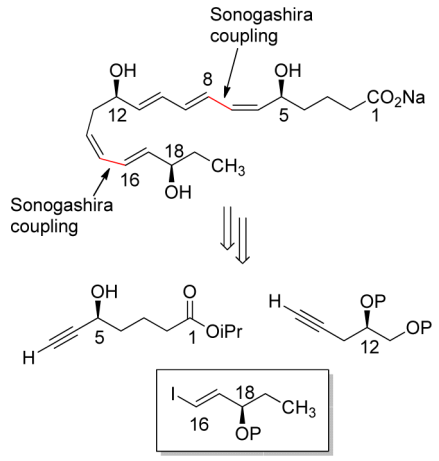
Figure 1. Resolvin E1 (RvE1).

RESULTS AND DISCUSSION

Construction of the polyunsaturated backbone of RvE1 naturally lends itself to disconnection at points of unsaturation that subdivide the molecule into more manageable fragments. Several synthetic routes have been reported for RvE1 utilizing variations on this strategy.[6] As in the approach pioneered by Petasis,[6a] our route[6b] took advantage of the partial and selective reduction of alkynes to establish the C6−C7 and C14−C15 *Z*-olefins. Thus, disconnections at C7−C8 and C15−C16 offer three key segments, thereby providing a modular route to the target molecule (Scheme 1).

A multikilogram-scale synthesis of the C16−C20 segment was required to support production of API for preclinical and future cGMP production. A previously developed route[6a,b] (Scheme 2) used (*S*)-glycidol as a starting point, and due to timeline constraints, was successfully practiced without further

Scheme 1. Retrosynthetic approach to RvE1



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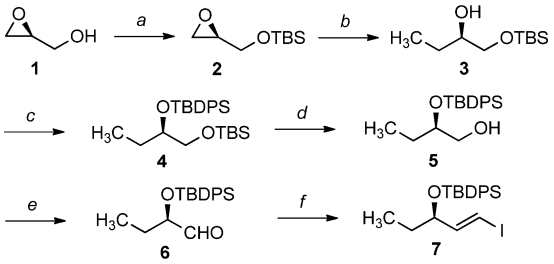
Scheme 2. Synthetic route to the C16−C20 segment used for early scale-up[a]



[a]Reagents and conditions: (a) TBSCl, imidazole, DMAP, CH_2Cl_2, 10 °C, 30 min. (b) CH_3MgBr, CuI, THF, −30 °C, 2.5 h. (c) TBDPSCl, DMAP, imidazole, CH_2Cl_2, 10−20 °C, 17 h. (d) CSA, MeOH, CH_2Cl_2, 0 °C, 3.5 h; 63% yield overall from **1**. (e) Pyr-SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C, 2 h; 64% yield. (f) $CrCl_2$, CHI_3, THF, 5−15 °C, 1.5 h; 70% yield.

modification to provide 3 kg of this fragment to support production of RvE1 for early toxicological studies. Several aspects of the synthesis proved difficult, indicating that a modified process was needed to support future production. In particular, the chiral epoxide (*S*)-glycidol was becoming increasingly difficult to procure on kilo scale and had a propensity to polymerize over time. The quality of (*S*)-glycidol varied greatly, depending on its source and even between lots from the same supplier. Additionally, half of the synthetic steps to produce the C16−C20 fragment were designed to affect a protecting group strategy to isolate and manipulate two hydroxyl groups in turn. While this strategy provided significant flexibility for analogue preparation early in discovery, a more atom-efficient process was considered highly desirable going forward.

Takai olefination to append the C16 carbon (**6** to **7**, Scheme 2) and provide the requisite *E*-vinyl iodide, while successfully practiced at 400-g scale, could not be advanced further due to rapidly decreasing yields as the scale increased. All attempts to optimize the Takai reaction in order to maintain yield proved unsuccessful, and it became clear we had reached the limits of its utility in this process. The sourcing and cost of chromium chloride, which was used in 6-fold excess, and management of the resulting chromium waste were also considered undesirable going forward.

The route to the C16−C20 segment of RvE1 was completely revisited in order to meet the key objectives of replacing (*S*)-glycidol with a more suitable raw material and to find an alternative to the Takai olefination chemistry. After an extensive literature investigation, the route outlined in Scheme 3 was chosen for further consideration. The route takes advantage of a well-known procedure[7] that condenses acetylene and acid chlorides to provide β-chlorovinyl ketones such as compound **8**. While this procedure was practiced in-house early in our investigation, several commercial suppliers were quickly identified which would satisfy our projected needs. The iodide was then introduced by addition/elimination reaction using sodium iodide.[8] Ketone reduction to provide the C18 hydroxyl group was envisioned taking place in an asymmetric fashion,[9] or chirality could be achieved through resolution of a racemic mixture.[10] The proposed route benefits from the absence of protecting group involvement until the final step, allowing for complete flexibility in the choice of protecting group one may wish to install to render the fragment ready for downstream chemistries.

The investigation began with introduction of the vinyl iodide. A typical reaction was run in acetone (8−15 volumes) with 1.9 equiv of sodium iodide and a catalytic amount of aluminum trichloride at reflux for several hours. A light-orange oil was initially obtained after an aqueous extractive workup and concentration, which could be crystallized in heptane at cryogenic temperatures to give an off-white solid in yields up to 88%. The solid was unstable at ambient temperature but could be stored for at least several weeks at −20 °C. A sample of the product in solution was shown to be stable over three days at ambient temperature. Consequently, the process was telescoped, and the β-iodovinyl ketone was not isolated as a solid, but rather stored as a solution and was used directly in the next step.

The chiral reduction of **9** was initially evaluated under a variety of reducing conditions (Table 1). While a superior enantioinduction was achieved using $(-)Ipc_2BCl$, the undesired enantiomer was produced (entry 3). Presumably, the desired

Table 1. Evaluation of chiral reduction conditions for 9 to (*R*)-10

entry	reduction conditions	er (*R*):(*S*)
1	(*S*)-methyl-CBS-oxazaborolidine, catecholborane[11]	86:14
2	Ru[(*S*,*S*)-TsDPEN(*p*-cymene)][12]	no product
3	$(-)Ipc_2BCl$[13]	7:93
4	$[RuCl_2(p\text{-cymene})]_2$, (1*R*,2*S*)-aminoindan-2-ol[14]	52:48
5	4,2,5,6-di-*O*-cylcohexylidene-α-D-glucofurnaose, $NaBH_4$[15]	50:50

Scheme 3. Proposed new route to the C16−C20 segment of RvE1

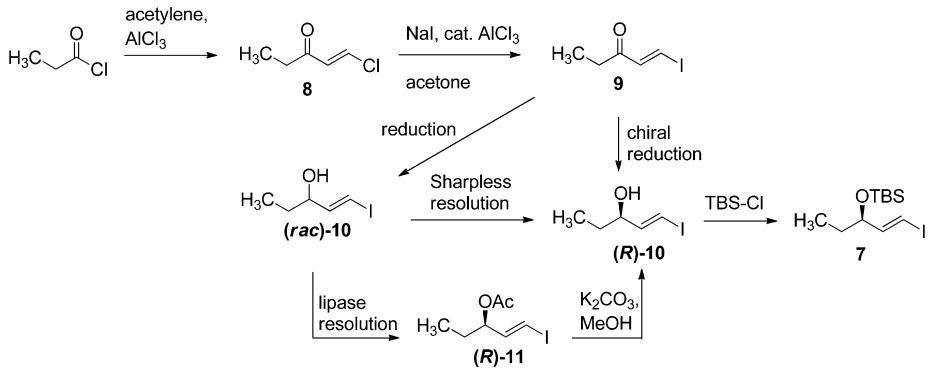


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Table 2. CBS reduction of ketone 9

entry	catalyst loading (equiv)	H donor	borane (equiv)	temp (°C)	addition time (min)	er (*R*):(*S*)
1	0.1	*N*,*N*-diethylaniline borane	1.0	20	30	86:14
2	0.1	*N*,*N*-diethylaniline borane	1.0	20	60	91:9
3	0.1	*N*,*N*-diethylaniline borane	1.0	20	90	92:8
4	0.1	borane methyl sulfide	1.0	20	90	94:6
5	0.1	borane methyl sulfide	0.6	0	90	96:4
6	0.05	borane methyl sulfide	0.6	0	90	93:7
7	0.05	borane methyl sulfide	0.6	0	120	95:5
8	0.05	borane methyl sulfide	0.6	0	420	92:8

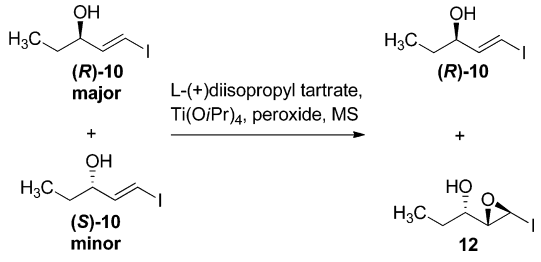
enantiomer could be produced in comparable selectivity by using (+)Ipc_2BCl, but this was not tried since we found a more superior reaction. Of the conditions screened, the Corey–Bakshi–Shibata (CBS) reduction[11] using (*S*)-(−)-2-methyl-CBS-oxazaborolidine and catecholborane held some advantages for scale-up considerations (entry 1). Unlike (+)Ipc_2BCl, the CBS reagent is used catalytically which greatly reduces material costs and, based on initial model analysis, was also more cost-effective when compared with hypothetical biocatalytic options for the manufacture of supplies needed to support early clinical evaluation. Consequently, continued investigation focused on optimization of the CBS protocol.

The reduction was carried out by adding a solution of ketone **9** to a solution of catalyst and catechol borane at ambient temperature. Conversion was quantitative by GC analysis in each case. Residual catechol from the hydrogen donor proved difficult to remove, and alternative hydrogen donors were investigated (Table 2). The two alternate hydrogen donors evaluated performed equally well. Borane methyl sulfide complex was chosen for further evaluation due to some difficulties in purging associated aniline byproducts when using *N*,*N*-diethylaniline borane. Variations in addition time showed some influence on the er, reaching a maximum at a 2-h dosing time frame (entry 7), and then degraded enantioselectivity was observed as the addition time became overly protracted (entry 8). Although modest improvements in enantioselectivity were made by lowering the reaction temperature and extending the addition time of ketone, the required >98% ee specification was not achieved. Efforts to enrich the mixture to achieve high enantiopurity were, therefore, undertaken.

Procedures designed to resolve a racemic or enriched enantiomeric mixture were also investigated concurrent with the chiral reduction investigation. Two distinct approaches were evaluated. One route involved the kinetic epoxidation of γ-iodo allylic alcohols using a Sharpless epoxidation reaction reported by Kitano and co-workers[10a] as outlined in Scheme 4.

A series of test reactions were conducted in an attempt to generate pure (***R***)**-10** using Sharpless epoxidation to consume the unwanted (*S*)-enantiomer. An initial reaction was conducted using **10** (90:10 enantiomeric ratio (er), >99.9 area %) with 0.15 equiv of L-(+)-diisopropyl tartrate, molecular sieves, 0.1 equiv of titanium(IV) isopropoxide, and 0.7 equiv of 6 M *tert*-butyl hydrogen peroxide in decane at −20 to −30 °C. The progress of the reaction was monitored by GC-FID to an er of 98:2. Unfortunately, chromatographic purification to remove the undesired epoxide and reaction byproducts afforded no pure product due to poor separation. Several improvements were made in an effort to reduce byproduct burden and facilitate isolation. An improved resolution (>99.8:0.2) was achieved using 80% cumene hydroperoxide instead of *tert*-butyl hydrogen peroxide, and the amount of this reductant was also lowered to 0.25 equiv. Despite these improvements, isolation of pure material was not achieved, and cumyl alcohol persisted at elevated levels after chromatographic purification. Additionally, repeated attempts to purify **10** by normal phase chromatography showed it to be unstable to the column conditions which further eroded recoveries.

Scheme 4. Attempted resolution by sharpless epoxidation



A final attempt to purify material contaminated with cumyl alcohol was made by taking forward and protecting the hydroxyl group as the triethylsilyl (TES) ether. As expected, the reaction generated two products, the desired TES-protected (***R***)**-10** and the undesired TES-protected cumyl alcohol. Unfortunately, these two products proved to be inseparable by column chromatography, and this approach was abandoned in favor of an enzymatic resolution process.[10b]

An abbreviated evaluation of supported biocatalysts known to be suited to the kinetic resolution of secondary alcohols[16] identified five supported lipase enzymes as the most promising candidates for resolution of (*E*)-1-iodopent-1-en-3-ol. Initially all reactions were screened at milligram scale using a 85:15 enantiomeric mixture favoring the (*R*)-enantiomer with 100 wt % enzyme loading and 3 equiv of vinyl acetate in methyl *tert*-butylether (MTBE) at ambient temperature. The reactions were terminated by the addition of methanol at approximately 6 h. The reaction mixtures were analyzed by chiral GC, and the results for the most promising biocatalysts are summarized in Table 3.

Each of the candidate lipase enzymes preferentially acetylated the (*R*)-enantiomer of the alcohol. *Candida antarctica* Lipase B (CALB)[17] was judged to be best suited for this reaction due to the superior reaction kinetics and excellent enantiomeric excess obtained for (***R***)**-11** (>99%) with nearly complete depletion of (***R***)**-10**. Consequently, within the short time frame for parallel comparison with the best chemical alternatives, method development was prioritized using this enzyme.

Other combinations of reaction solvents and acyl donors were tested with CALB under conditions comparable to the initial screen, and the results are shown in Table 4. All conditions investigated led to preferential acylation of the (*R*)-enantiomer with high ee.

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Table 3. Lipase-catalyzed resolution of 10

entry	lipase	% (*R*)-**10** remaining	% (*S*)-**10** remaining	% (*R*)-**11** remaining	% (*S*)-**11** remaining
1	*Candida antarctica B* (CALB)	0.82	11.5	87.4	0.30
2	*Mucor miehei* (MML)	69.9	14.5	15.4	0
3	*Pseudomonas cepacia* (PS)	69.6	14.5	15.9	0
4	*Pseudomonas fluorescens* (PS AK-20)	29.2	12.8	57.9	0
5	*Candida rugosa* (OF)	76.6	14.0	8.7	0.69

Further evaluation on a larger scale (1 g input) using CALB in either CH_2Cl_2 or MTBE and vinyl acetate was conducted to verify the results of the initial evaluation. Both solvents again performed well. A slightly reduced reaction rate observed in otherwise identical conditions using CH_2Cl_2 suggested a reduced enzymatic activity relative to that observed in MTBE. Considering favorable process solvents for scale-up, and limited time frame, further evaluations were focused on MTBE as reaction medium.

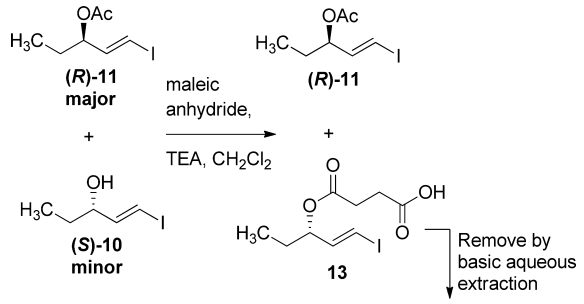
To further assess performance and robustness for scale-up, a series of reactions were then conducted using reduced amounts of CALB to optimize loading and to establish the impact of biocatalyst loading on reaction rate. Two experiments were conducted using 5 wt % and 2.5 wt % catalyst loading. Samples were pulled periodically and analyzed by chiral GC to assess relative reaction rates. The results are shown in Table 5. As expected, reaction rate diminished noticeably as the catalyst loading was reduced from 5 wt % to 2.5 wt %. However, reaction completion was achieved in each case (compare entry 6 at 5 wt % loading and entry 9 at 2.5 wt % loading) resulting in a comparable ratio of acetylated (*R*)-**11** and unmodified (*S*)-**10**. Further evaluation concluded an optimal loading of 6.5 wt % provided a good balance of reaction rate and enzyme loading on kilo scale.

Having quickly identified suitable conditions for enzymatic resolution to upgrade the enantiopurity of the C18 stereocenter, our attention turned to identifying a convenient and scalable procedure for removal of the unmodified minor enantiomer from the crude reaction product. Within the target time frame, two approaches were prioritized. The first approach investigated chemical modification. Thus, the crude reaction product of (*R*)-**11**/(*S*)-**10** (88:12 ratio) obtained after enzymatic resolution was diluted with CH_2Cl_2 and treated with maleic anhydride and triethylamine (TEA) to modify the (*S*)-enantiomer, thus rendering it water extractable (Scheme 5).[18] The reaction mixture was washed with 20% sodium carbonate solution several times followed by a brine wash. The resulting organic phase was then passed through a pad of SiO_2 to remove polar impurities. The filtrate was concentrated to

Table 5. CALB-catalyzed acylation at different biocatalyst loadings as a function of reaction time

entry	CALB amount (wt %)	reaction time (h)	% (*R*)-**10** remaining	% (*S*)-**10** remaining	% (*R*)-**11** produced	% (*S*)-**11** produced
1	2.5	1	58.0	13.6	28.4	0
2	5.0	1	38.8	13.5	47.7	0
3	2.5	3.5	21.7	13.0	65.3	0
4	5.0	3.5	2.4	11.6	85.5	0
5	2.5	5	11.1	12.6	76.3	0
6	5.0	5	0.5	11.8	87.3	0
7	2.5	8	1.5	12.1	86.4	0
8	5.0	8	0	11.3	88.7	0
9	2.5	24	0.2	11.7	88.1	0
10	5.0	24	0	11.3	88.5	0.2

Scheme 5. Attempted route to remove (*S*)-10 from (*R*)-11



give a light-yellow oil in a yield approaching theoretical and a high chiral purity of 99.7% area % by chiral GC. The reaction was repeated on a 10-fold scale and gave favorable results, although the chiral purity was slightly degraded to 98.6% area % by chiral GC. Under further investigation, reaction completion suffered further upon scale-up, giving product with increasingly diminished chiral purity.

The second, more conservative approach leveraged the considerable differences in polarity between the acetylated and unacetylated hydroxyl group. A mixture of (*R*)-**11** and (*S*)-**10** obtained from the enzymatic resolution was easily purified by silica gel plug purification to obtain (*R*)-**11** in an essentially enantiopure form. While plug purification was reasonably straightforward and successfully implemented to purify multikilogram quantities, future work to purify the mixture obtained from lipase resolution could evaluate nonchromatographic approaches such as distillation.

The compatibility of the acetate group in downstream chemistries was evaluated and ultimately proved too labile. Therefore, deacetylation was conducted to provide (*R*)-**10** for further manipulation. Removal of the acetate group was easily achieved using a standard acetate methanolysis procedure consisting of potassium carbonate in methanol to afford (*R*)-**10** with yields routinely in the 85−90% range. (*R*)-**10** proved to be

Table 4. CALB-catalyzed resolution of 10

entry	solvent	acyl donor	% (*R*)-**10** remaining	% (*S*)-**10** remaining	% (*R*)-**11** remaining	% (*S*)-**11** remaining
1	MTBE	vinyl butyrate	1.6	8.7	88.4	0.48
2	iPr_2O	vinyl acetate	3.9	10.8	79.4	0.46
3	iPr_2O	vinyl butyrate	2.9	8.4	86.2	0.69
4	CH_2Cl_2	vinyl acetate	1.2	11.1	87.7	0
5	CH_2Cl_2	vinyl butyrate	0	9.0	91.0	0

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reasonably stable, once isolated, and could be stored for long periods of time at −20 °C.

After further investigations were completed, the *tert*-butyl dimethyl silyl (TBS) group was identified as the most suitable protecting group for downstream processing. Silylation using standard conditions afforded the target compound **7** in quantitative yield after workup and silica gel plug purification.

■ CONCLUSIONS

A novel route was developed for the synthesis of the C16−C20 segment of RvE1 in which the two main objectives of removing (*S*)-glycidol and the Takai olefination reaction from the previous sequence were accomplished. The new route utilizes readily available *β*-chlorovinyl ketone **9** as the key starting material, allowing for introduction of the requisite vinyl iodide functionality by treatment with sodium iodide. The C18 chiral secondary hydroxyl group is introduced using a sequence involving CBS-mediated asymmetric reduction followed by lipase-catalyzed acetylation and enantiomeric enrichment. The process was successfully implemented multiple times on 4−9 kg scale to produce a total of 27 kg of TBS-protected vinyl iodide **7** in an average overall yield of 66% within an aggressive timeline to support ongoing API production. A portion of compound **7** was used to support the production of a total of 585 g of RvE1 in two comparably sized batches for nonclinical safety studies and early-phase clinical testing.

■ EXPERIMENTAL SECTION

Reaction progress, chemical purity, and chiral purity were evaluated by GC-FID or HPLC analysis under the conditions described below:

GC Method A: HP-1 (25 m × 30 mm, 0.25 μm); Carrier Gas = Helium; Flow = 1.0 mL/min; Injector Temp. = 150 °C; Split/Flow = 100 mL/min; MS Detector; Initial Oven Temp. = 100 °C; Initial Time = 2 min; Ramp Rate = 20 °C/min; Final Oven Temp. = 300 °C; Final Time = 17 min.

Chiral GC Method B: Supelco Chiraldex G-TA (30 m × 0.25 mm, 0.12 μm); Carrier Gas = Helium; Flow =1.0 mL/min; Injector Temp. = 225 °C; Split/Flow = 100 mL/min; MS Detector; Oven Temp. = 100 °C isothermal; Analysis Time = 25 min.

HPLC Method C: Waters Symmetry Shield RP18, (5 μm, 4.6 mm × 150 mm) with a mobile phase 30% acetonitrile in water and detection at 220 nm; Flow: 1.0 mL/min; Temp. 25 °C; Analysis Time 18 min.

(*E*)-1-Iodopent-1-en-3-one (9). A mixture of (*E*)-1-chloropent-1-en-3-one **8** (1.99 kg, 16.7 mol), NaI (4.80 kg, 32.0 mol), and $AlCl_3$ (5.10 g, 38.4 mmol) in acetone (16 L) was heated at 55−57 °C for 3.5 h, at which point the reaction was judged complete (<1% of (*E*)-1-chloropent-1-en-3-one) by GC−MS analysis (Method A). The reaction mixture was cooled to ambient temperature and diluted with DI water (16 L) and MTBE (16 L), and the phases were separated. The MTBE phase was washed with 10% aqueous $Na_2S_2O_3$ (2 × 8 L) and dried over $MgSO_4$. The filter cake was washed with MTBE (2 × 2 L), and the resulting MTBE-rich filtrate was taken forward to the formation of (*E*)-1-iodopent-1-en-3-ol **10** without further manipulation: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.72 (d, *J* = 15.0 Hz, 1 H), 7.07 (d, *J* = 14.7 Hz, 1 H), 2.45 (q, *J* = 7.5 Hz, 2 H), 1.02 (t, *J* = 7.5 Hz, 3 H).

(*E*)-1-Iodopent-1-en-3-ol (10). A solution of (*E*)-1-iodopent-1-en-3-one **9** in MTBE (16.7 mol theoretical) was added over a period of 7 h at 0−10 °C to a solution of boranemethyl sulfide complex (953 mL, 10.0 mol) and (*S*)-methyl-CBS-oxazaborolidine (232 g, 835 mmol) in MTBE (400 mL). TLC analysis (9:1 heptane/EtOAc) after 30 min at 0−5 °C indicated complete consumption of compound **9**. The reaction mixture was quenched with MeOH (2 L) and DI water (6 L), maintaining the temperature between 0 and 15 °C. The phases were separated, and the organic phase was washed with 1:1 0.5 M HCl/brine (2 × 2 L), $NaHCO_3$ (2 L), and brine (2 L). The MTBE phase was treated with $MgSO_4$, filtered over SiO_2 (3.5 kg), washed with MTBE (2 × 2 L), concentrated to dryness, and azeotropically dried with MTBE (2 × 3.5 L) to afford 3.10 kg of (*E*)-1-iodopent-1-en-3-ol **10** (87%, uncorrected over two steps) with residual MTBE and a ratio of (***R***)-**10** to (***S***)-**10** of 94:6 by GC-FID (Method B). This crude oil was taken forward without further manipulation. ^{1}H NMR spectra are consistent with data reported for the pure enantiomer (***R***)-**10**.[6b]

(*R*,*E*)-1-Iodopent-1-en-3-yl acetate ((*R*)-11). A solution of (*E*)-1-iodopent-1-en-3-ol **10** (3.10 kg, 14.6 mol) in MTBE (12.4 L) was treated with vinyl acetate (1.2 L, 13.1 mol) and CALB enzyme (201 g, 6.7 wt %). GC-FID (Method B) analysis after 15 h at 20−25 °C indicated a complete conversion. The reaction mixture was filtered, and the enzyme was washed with MTBE (2 × 1.9 L). The MTBE-rich filtrate was concentrated to dryness and azeotropically dried with heptane (2 × 3 L) to afford 4.61 kg (>100%) of a mixture of (***R***)-**11** and the minor alcohol isomer (***S***)-**10**. The crude material was purified using approximately 14 kg silica gel, eluting with 69 L of heptanes, 21 L of 5% EtOAc/heptanes, and 21 L 10% EtOAc/heptanes to afford 2.77 kg of (*R*,*E*)-1-iodopent-1-en-3-yl acetate (***R***)-**11** with trace residual heptane after concentration to an oil (75% yield, uncorrected); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.38−6.52 (m, 2 H), 5.12 (ddd, *J* = 6.6 Hz, 1 H), 2.07 (s, 3 H), 1.59−1.69 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.2, 143.9, 80.0, 76.9, 26.9, 21.2, 9.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_7H_{11}INaO_2$ 276.9701, found 276.9701; GC-FID 99.9 area % (Method B).

(*R*,*E*)-1-Iodopent-1-en-3-ol ((*R*)-10). A solution of (*R*,*E*)-1-iodopent-1-en-3-yl acetate (***R***)-**11** (2.77 kg, 10.9 mol) in MeOH (11 L) was added to K_2CO_3 (4.51 kg, 32.7 mol) at 20−25 °C. After 1 h, HPLC analysis (Method A) indicated the reaction was complete. DI water (13 L) was added to the reaction mixture maintaining the temperature below 35 °C. The reaction mixture was diluted with CH_2Cl_2 (13 L), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (5.5 L), and the combined organic layers were washed with brine (5.5 L), dried with $MgSO_4$, and concentrated to afford 1.99 kg of (*R*,*E*)-1-iodopent-1-en-3-ol (***R***)-**10** (86% yield, uncorrected) as an oil with a trace amount of residual CH_2Cl_2; GC-FID 99.5 area % (Method B). ^{1}H NMR spectrum is consistent with previously reported data.[6b]

(*R*,*E*)-*tert*-Butyl((1-iodopent-1-en-3-yl)oxy)-dimethylsilane (7). A solution of (***R***)-**10** (1.99 kg, 6.09 mol) in CH_2Cl_2 (7 L) was added to a mixture of DMAP (57.0 g, 305 mmol) and imidazole (949 g, 9.14 mol). The resulting slurry was cooled to 0−5 °C and a solution of *tert*-butyldimethylsilyl chloride (1.82 kg, 7.92 mol) in CH_2Cl_2 (2.4 L) was added dropwise over a period of 20 min, maintaining the temperature below 30 °C. HPLC analysis (Method C) after 16 h at 20−25 °C indicated <1% of (***R***)-**10** remained. The reaction mixture was diluted with DI water (13 L), and the phases were separated. The CH_2Cl_2 phase was washed with brine (5 L),

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dried over $MgSO_4$, and filtered washing with CH_2Cl_2 (2 × 2 L). The filtrate was concentrated to dryness, azeotropically dried with heptane (4 L), and purified using 4 kg silica gel, eluting with 40 L heptane to afford 3.1 kg of (*R*,*E*)-*tert*-butyl((1-iodopent-1-en-3-yl)oxy)dimethylsilane **7** (85% yield, uncorrected) as an oil with trace amounts of residual heptane and CH_2Cl_2; HPLC 99.7 area % (Method C). ^{1}H NMR spectrum is consistent with previously reported data.[19]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra for **7**, **9**, **10**, and (***R***)-**10**. ^{1}H NMR and ^{13}C NMR spectra for (***R***)-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mark.mclaws@amriglobal.com. Telephone: (518) 512-2552.

Present Address

‖(C. E. Schwartz) Avila Therapeutics, Waltham, MA 02453, United States. Tel.: +1 781 891 0086. Fax: +1 781 891 0069. E-mail: eschwartz@avilatx.com.

Notes

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■ REFERENCES

(1) (a) Bannenberg, G. L. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 644−658. (b) Serhan, C. N. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2008**, *79*, 157−163. (c) Serhan, C. N.; Chiang, N.; Van Dyke, T. E. *Nat. Rev. Immunol.* **2008**, *8*, 349−361. (d) Arita, M.; Bianchini, F.; Aliberti, J.; Sher, A.; Chiang, N.; Hong, S.; Yang, R.; Petasis, N. A.; Serhan, C. N. *J. Exp. Med.* **2005**, *201*, 713−722.

(2) (a) Hisada, T.; Ishizuka, T.; Aoki, H.; Mori, M. *Expert Opin. Ther. Targets* **2009**, *13*, 513−522. (b) Haworth, O.; Cernadas, M.; Yang, R.; Serhan, C. N.; Levy, B. D. *Nat. Immunol.* **2008**, *9*, 873−879.

(3) Xu, Z.-Z.; Zhang, L.; Liu, T.; Park, J. Y.; Berta, T.; Yang, R.; Serhan, C. N.; Ji, R.-R. *Nat. Med.* **2010**, *16*, 529−597.

(4) Hasturk, H.; Kantarci, A.; Goguet-Surmenian, E.; Blackwood, A.; Andry, C.; Serhan, C. N.; Van Dyke, T. E. *J. Immunol.* **2007**, *179*, 7021−7029.

(5) Levy, B. D.; Zhang, Q.-y.; Bonnans, C.; Primo, V.; Reilly, J. J.; Perkins, D. L.; Liang, Y.; Arnaout, M. A.; Nikolic, B.; Serhan, C. N. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2011**, *84*, 43−50.

(6) (a) Petasis, N. A.; , Trihydroxy Polyunsaturated Eicosanoid Derivatives. U.S. Pat. Appl. 2005/0228047, 2005. (b) Petasis, N. A.; , Trihydroxy Polyunsaturated Eicosanoid. U.S. Pat. Appl. 2009/0291916, 2009. (b) Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* **2009**, *50*, 6079−6082. (c) Allard, M.; Barnes, K.; Chen, X.; Cheung, Y.-Y.; Duffy, B.; Heap, C.; Inthavongsay, J.; Johnson, M.; Krishnamoorthy, R.; Liu, X.; Manley, C.; Shan, Z.; Steffke, S.; Varughese, D.; Wang, R.; Wang, Y.; Yang, Q.; Schwartz, C. E. *Tetrahedron Lett.* **2011**, *52*, 2623−2626.

(7) (a) Pohland, A. E.; Benson, W. R. *Chem. Rev.* **1966**, *66*, 161−197. (b) Snelders, D. J. M.; Dyson, P. J. *Org. Lett.* **2011**, *13*, 4048−4051. (c) Li, L.-H.; Tius, M. A. *Org. Lett.* **2002**, *4*, 1637−1640.

(8) Luo, F.-T.; Negishi, E.-I. *J. Org. Chem.* **1985**, *50*, 4762−4766.

(9) (a) Caprio, V.; Williams, J. M. J. *Catalysts in Asymmetric Synthesis*, 2nd ed.; John Wiley & Sons: Chichester, 2009; pp 47−73. (b) Andersson, P. G.; Munslow, I. *Modern Reduction Methods*; Wiley-VCH: Weinheim, 2008.

(10) (a) Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 6351−6354. (b) Bänziger, M.; Griffiths, G. J.; McGarrity, J. F. *Tetrahedron Asymmetry* **1993**, *4*, 723−726. (c) Gueugnot, S.; Alami, M.; Linstrumelle, G.; Mambu, L.; Petit, Y.; Larchevêque, M. *Tetrahedron* **1996**, *52*, 6635−6646.

(11) (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(12) (a) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327−3355. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1993; pp 56−82.

(13) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539−1546.

(14) (a) Palmer, M.; Walsgrove, T.; Wills, M. J. *J. Org. Chem.* **1997**, *62*, 5226−5228. (b) Kenny, J. A.; Palmer, M. J.; Smith, A. R. C.; Walsgrove, T.; Wills, M. *Synlett* **1999**, 1615−1617. (c) Wills, M.; Gamble, M.; Palmer, M.; Smith, A.; Studley, J.; Kenny, J. *J. Mol. Catal. A: Chem.* **1999**, *146*, 139−148. (d) Palmer, M. J.; Kenny, J. A.; Walsgrove, T.; Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans. I* **2002**, 416−427.

(15) (a) Morrison, J. D.; Grandbois, E. R.; Howard, S. I. *J. Org. Chem.* **1980**, *45*, 4229−4231. (b) Hirao, A.; Nakahama, S.; Mochizuki, H.; Itsuno, S.; Yamazaki, N. *J. Org. Chem.* **1980**, *45*, 4231−4233.

(16) (a) Ojima, I., *Catalytic Asymmetric Synthesis*, 3rd ed.; John Wiley & Sons; Hoboken, NJ, 2010; pp 270−279. (b) Kaler, A.; Meena, V. S.; Singh, M.; Pujala, B.; Chakraborti, A. K.; Banerjee, U. C. *Tetrahedron Lett.* **2011**, *52*, 5355−5358. (c) Reigada, J. B.; Tcacenco, C. M.; Andrade, L. H.; Kato, M. J.; Porto, A. L. M.; Lago, J. H. G. *Tetrahedron: Asymmetry* **2007**, *18*, 1054−1058. (d) Gotor, V. *Org. Process. Res. Dev.* **2002**, *6*, 420−426. (e) García-Granados, A.; Melguizo, E.; Parra, A.; Simeó, Y.; Viseras, B.; Dobado, J. A.; Molina, J.; Arias, J. M. *J. Org. Chem.* **2000**, *65*, 8214−8223.

(17) Novozymes lipase B from *Candida antarctica* was obtained from Codexis.

(18) Brossat, M.; Moody, T. S.; de Nanteuil, F.; Taylor, S. J. C.; Vaughan, F. *Org. Process. Res. Dev.* **2009**, *13* (4), 706−709.

(19) Rodriquez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2012**, *53*, 1912−1915.