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Condensation Oligomers with Sequence Control but without Coupling Reagents and Protecting Groups via Asymmetric Hydroformylation and Hydroacyloxylation

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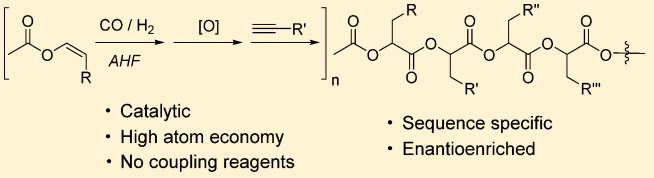
Supporting Information

ABSTRACT: A novel strategy, free of coupling reagents and protection/deprotection steps, for the synthesis of oligo(2-hydroxyacid)s containing up to four monomer units with atom economy, sequence specificity, and control of stereocenter configuration is described. The strategy comprises an iterative application of the sequence asymmetric hydroformylation/oxidation/alkyne hydroacyloxylation that features catalytic, atom-economical C−C and C−O bond forming reactions. Asymmetric hydroformylation with Rh-bisdiazaphospholane catalyst introduces each stereocenter with high enantio- (ca. 93% e.e.), diastereo- (up to 25:1 d.r.), and regioselectivity (>50:1) at low catalyst loadings and mild pressures. The side chain in each monomer is tailored by choosing from a variety of readily available alkynes.



INTRODUCTION

A fundamental challenge in synthesizing sequence-specific oligomers, such as α- and β-peptides or oligoesters, is the waste generated by coupling reagents and protecting groups. Is it possible to devise a scheme by which achiral starting materials are transformed into sequence-specific oligomers with catalytic introduction of all stereogenic centers and near 100% atom economy?

Consider oligoesters, which are important model compounds for the analysis and design of high molecular weight polyester materials or as model foldamers that lack hydrogen bonding capability along the backbone and are readily degradable by hydrolysis.[1] Considerable effort has been placed on generating structurally diverse oligoesters with reliable control of monomer sequence, molecular weight, and tacticity.[2] Current strategies to access sequence defined oligoesters rely on stoichiometric coupling reagents and orthogonal protecting group strategies[3] that are inspired by the solid phase synthesis of oligopeptides.[4] Obvious drawbacks of such methods include low atom economy, limited compatibility with other functional groups, or challenging stereoselective syntheses of monomers. Alternative strategies to generate oligoesters via efficient, low-waste, and scalable processes are highly desirable. Asymmetric hydroformylation (AHF) has emerged as a powerful catalytic and atom-efficient process that can address these challenges. Herein we describe an alternative approach to the synthesis of oligo(2-hydroxyacid)s that employs AHF methodology and two other transformations, aldehyde oxidation and alkyne hydroacyloxylation, in an iterative fashion. The resulting oligoesters, oligo(2-hydroxyacid)s, share the same backbone as poly(lactic acid), a biodegradable and biocompatible polyester with numerous industrial and biomedical applications.[5]

AHF is a catalytic stereoselective carbon−carbon bond forming reaction that generates chiral aldehydes from alkenes, CO and H_2.[6] Several chiral ligands enable this transformation efficiently.[7] We previously have reported that the chiral BisDiazaphos[8] ligand (Figure 1) shows remarkable activity,

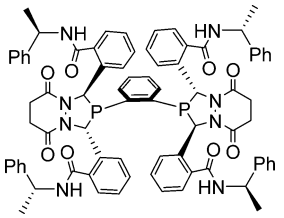


Figure 1. (*S*,*S*,*S*)-BisDiazaphos ligand used in AHF.

enantio- and regioselectivity in the AHF of a variety of alkenes under mild conditions.[9] The high level of synthetic versatility accessible at the aldehyde stage makes AHF an attractive disconnection strategy in organic synthesis. Notable recent syntheses of Patulolide C,[10] Garner's aldehyde,[11] the Prelog-Djerassi lactone,[12] the macrolide dictyostatin,[13] γ-chiral α,β-unsaturated carbonyl compounds, and vinylogous ester oligomers[14] demonstrate the utility of AHF.

We recently reported the regio- and enantioselective Rh-BisDiazaphos catalyzed AHF of 1,2-disubstituted alkenes, specifically *Z*-enamides and *Z*-enol esters.[15] AHF of these substrates generates the corresponding α-functionalized chiral aldehydes with high conversion (53−100%), regioselectivity (5.7:1 to 99:1 α:β), enantioselectivity (84−99% *ee*), and

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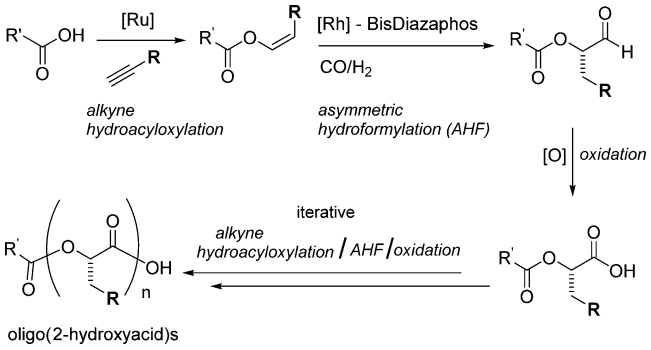
functional group compatibility. Ru-catalyzed alkyne hydroamidation[16] and hydroacyloxylation[17] provide catalytic, economical access to *Z*-enamides and *Z*-enol esters, respectively.

We report herein that Rh-BisDiazaphos catalyzed AHF of (*Z*)-enol esters provides sequence specific chiral oligo(2-hydroxyacid)s as part of an iterative sequence comprising enol ester formation, AHF, and aldehyde oxidation. This catalytic and atom-economical approach to oligoester synthesis avoids drawbacks of common methods, such as in high amounts of waste, tedious separations, and difficult scale-up that result from coupling reagents and protection/deprotection strategies.

Our synthetic strategy to generate oligo(2-hydroxyacid)s is depicted in Scheme 1. The reaction sequence involves Ru-

Scheme 1. Synthetic Strategy for Coupling Reagent and Protecting Group Free Synthesis of Sequence Specific Oligoesters

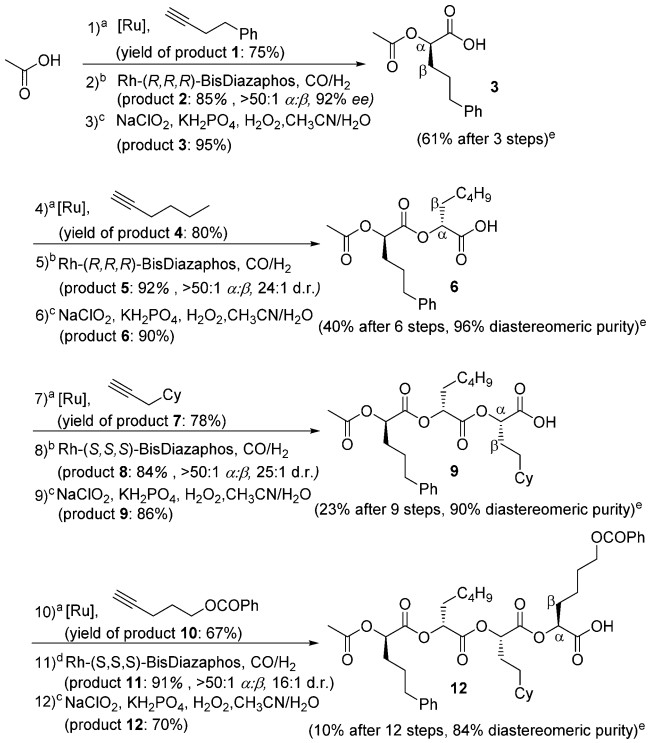


catalyzed addition of carboxylic acids to alkynes to yield (*Z*)-enol esters, Rh-BisDiazaphos catalyzed AHF of the (*Z*)-enol esters to give α-functionalized chiral aldehydes, and oxidation of the aldehydes to produce new chiral α-functionalized chiral carboxylic acids. Oligo(2-hydroxyacid)s can be formed via multiple iterations of this three-step reaction sequence, with each iteration adding one new monomer unit. The side chain of each monomer is tailored by choosing from a variety of readily available alkynes. The stereochemistry of each monomer is determined by the chirality of the AHF catalyst. All organic starting materials are achiral and readily available. The methodology is demonstrated for four iterations to generate a tetramer of four unique monomer units in a single sequence (Scheme 2).

RESULTS AND DISCUSSION

The alkyne hydroacyloxylation reaction[17a] in the presence of 5% Ru(methallyl)$_2$dppb (dppb =1,4-bis(diphenylphosphino)-butane) affords, after 16 h at 45 °C in THF, the corresponding (*Z*)-enol ester products **1**, **4**, **7**, and **10** (Scheme 2) with conversion greater than 90%, isolated yields between 67 and 80%, and *Z* selectivity higher than 90% (commonly observed byproducts are the *E* isomer and the 1,1-disubstituted alkene regioisomer). We note that not all alkynes undergo successful hydroacyloxylation; replacing 3-cyclohexyl propyne with phenylacetylene in step 7 led to less than 10% formation of the desired *Z* product. Signals in the 6–8 ppm region of ^{1}H NMR spectrum suggest alkyne oligomerization as major pathway. Replacing 5-benzoyloxy-1-pentyne in step 10 with 5-methoxypent-1-yne gave, however, comparable high conversion.

Scheme 2. Synthesis of a Tetramer via the Proposed Iterative Alkyne Hydroacyloxylation/AHF/Oxidation Sequence



[a]Conditions: Ru(methallyl)$_2$dppb (5 mol%), carboxylic acid (1 equiv), alkyne (1.5 equiv), THF, 45 °C, 16–24 h. Reported yields represent isolated yields. [b]Conditions: Rh(acac) (CO)$_2$ (0.3 mol%), (*S,S,S*)- or (*R,R,R*)-BisDiazaphos (0.36 mol%), 150 psig 1:1 CO/H$_2$, 65 °C, 12 h, THF, [enol ester] = 1.5 M. Reported yields represent isolated yields. Regioselectivity was determined by crude ^{1}H NMR integrations. Enantiomeric excess (for **2**) was determined by NaBH$_4$ reduction of the aldehyde, followed by chiral HPLC analysis. Diastereomeric ratios (for **5**, **8**, **11**) were determined by ^{1}H NMR and quantitative ^{13}C integrations of the aldehyde signals. [c]Conditions: aldehyde (1 equiv), KH$_2$PO$_4$ (4 equiv), H$_2$O$_2$ (4.1 equiv), NaClO$_2$ (4 equiv), CH$_3$CN, H$_2$O, 10 °C to room temperature, 3 h. Reported yields represent isolated yields. [d]0.5 mol% Rh(acac) (CO)$_2$, 0.6 mol% (*S,S,S*)-BisDiazaphos. [e]Reported yields represent isolated yields. Diastereomeric purity was determined by ^{13}C integrations of the aldehyde signals. dppb = 1,4-bis(diphenylphosphino)butane, acac = acetylacetonate

The (*Z*)-enol esters undergo successful AHF. At 0.3–0.5% Rh(acac) (CO)$_2$ (acac = acetylacetonate) and 0.36–0.6% (1.2 equiv) of (*S,S,S*) or (*R,R,R*)-BisDiazaphos and 150 psig of 1:1 CO/H$_2$ at 65 °C in THF for 12 h, the corresponding α-functionalized chiral aldehydes **2**, **5**, **8**, and **11** are generated with excellent regioselectivity (>50:1 α:β), diastereoselectivity (between 16:1 and 25:1) and conversion (95–100%). AHF studies performed with both enantiomers of BisDiazaphos in steps 5 and 8 indicate that stereoinduction is predominantly catalyst controlled.

Oxidation of the aldehydes afforded the corresponding carboxylic acids **3**, **6**, **9**, and **12** in 70 to 95% yield under Pinnick[18] oxidation conditions without epimerization. Although Pinnick oxidation uses stoichiometric reagents, emerging catalytic aldehyde oxidation methods have the potential to improve the efficiency of this step.[19]

Tetramer **12** was obtained in 10% overall isolated yield and 84% diastereomeric purity after 4 iterations (12 steps total) and

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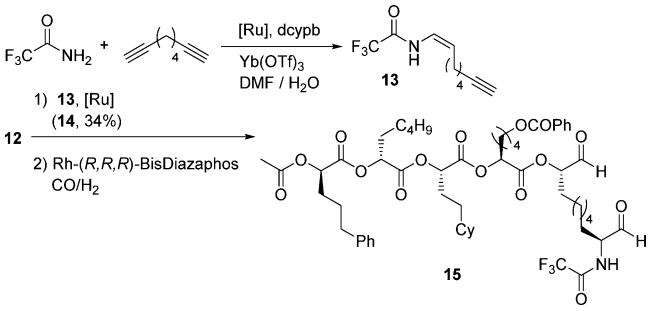
was characterized by NMR spectroscopy (^{1}H, quantitative and nonquantitative ^{13}C, Tocsy1D, Cosy, HSQC, HMBC) and ESI-MS. The absolute configuration of each stereocenter in the major diastereomer was monitored by optical rotation after each AHF step. The observed preference for Rh to insert at the Re face of the alkene when the (*S*,*S*,*S*) enantiomer of BisDiazaphos is used is consistent with previous observations.[8b,9c]

Hydroacyloxylation/AHF enables novel ligations. For example, connection of tetramer carboxylic acid **12** to a carboxamide can be effected via a diyne linker.[20] This ligation began with hydroamidation[16a] of one end of 1,7-octadiyne with trifluoroacetamide to generate the (*Z*)-enamide **13** (Scheme 3).[21,22] The pendant alkyne of **13** was then joined to tetramer

Scheme 3. Demonstration of Coupling between the Synthesized Tetramer and a Carboxamide Using a Diyne Linker[a]



[a]dcypb = 1,4-bis(dicyclohexylphosphino)butane; [Ru] = bis(2-methallyl)cycloocta-1,5-diene-ruthenium(II).

12 by hydroacyloxylation to generate the diunsaturated enol ester/enamide **14**. AHF of (*Z*)-enol ester and the (*Z*)-enamide functionalities yielded the dialdehyde **15** with greater than 95% conversion. The two aldehyde groups provide sites for further transformations.

This work establishes, as a proof-of-concept, that short oligoesters can be synthesized with sequence-specificity and stereocontrol in the absence of coupling agents or protection/deprotection steps. The main limitation at this stage is low overall yield, a result of unoptimized isolation and purification procedures after the Pinnick oxidation and hydroacyloxylation[23] steps. As in the development of chemical syntheses of peptides, it is likely that growth of oligomers on solid-phase supports[24] partially can mitigate these problems. Improved efficiency of the catalytic hydroacyloxylation and the enantioselectivity of the AHF also would enable higher yields and diastereomeric purity. At the current stage of development, the AHF/oxidation/hydroacyloxylation sequence may be most effective for making fragments for convergent syntheses rather than long, linear sequences.

In summary, this paper demonstrates the novel generation of oligo(2-hydroxyacid)s via iterative AHF/oxidation/alkyne hydroacyloxylation reaction sequence. Significantly this approach begins with achiral starting materials, avoids coupling reagents, and features sequence specificity and catalytic C−C and C−O bond forming reactions, with introduction of all stereocenters by enantioselective catalysis. Key to this sequence is efficient AHF which provides high stereo- (up to 25:1 d.r.) and regiocontrol (>50:1) at low catalyst loadings (0.3−0.5%) and mild pressures (150 psi CO/H_2). This strategy represents an attractive method for making 2-hydroxyacid esters. A similar strategy can, in principle, be applied to the synthesis of peptides and other sequence specific oligomers. However, α-peptide synthesis via hydroamidation-AHF currently is limited by a lack of atom-efficient methods for converting α-chiral aldehydes to the corresponding α-chiral carboxamides.

EXPERIMENTAL SECTION

All steps involving enol ester synthesis and AHF were carried out under moisture and oxygen free conditions using standard Schlenk and glovebox techniques. The oxidation step and all workup procedures were performed in air. Dry and oxygen-free THF solvent was collected from a solvent column system that uses activated alumina. Anhydrous DMF solvent was sparged with N_2 and stored in a N_2 filled glovebox. Acetic acid was distilled before use. All chemicals were purchased and used without further purification. BisDiazaphos ligands were prepared as reported in literature.[8a] All alkynes were degassed by sparging with N_2 before use. Reactors were assembled as previously reported.[25]

Regiomeric ratios, diastereomeric ratios, and conversion were determined by proton ^{1}H NMR spectroscopy on crude reaction mixtures. ^{1}H chemical shifts are referenced to tetramethylsilane in $CDCl_3$. ^{13}C chemical shifts are referenced to residual solvent peak. ^{19}F chemical shifts are referenced to tetramethylsilane in the proton spectrum using the unified scale. Splitting patterns in ^{1}H NMR spectra are reported as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), broad (br), and multiplet (m). Mass spectra were collected using electrospray ionization or atmospheric solids analysis probe-mass spectrometry (for **13** only), and a TOF analyzer. Flash column chromatography was performed on Silicycle Siliaflash P60 silica gel 40−63 μm and 230−400 mesh and TLC spots were visualized using a UV lamp at 254 nm. Absolute configuration of the chiral centers was determined by monitoring optical rotation at each aldehyde stage for all monomers and by $LiAlH_4$ reduction of the aldehyde at the monomer and dimer stages.

General Procedure for Enol Ester Synthesis.[17a] Ru(methallyl)$_2$dppb (5 mol%) and dry and degassed THF (1.5 mL) were combined in an oven-dried Schlenk flask equipped with a stir bar inside a N_2 glovebox. Inside a fume hood, the carboxylic acid (1 eq, 2 mmol) was added to the reaction flask via syringe as a solution in dry and degassed THF (0.5 mL), followed by neat alkyne (1.5 eq, 3 mmol). The solution was immersed in an oil bath and allowed to stir at 45 °C for 24 h under N_2. After reaction is complete, the reaction mixture is passed through a pad of silica in a fritted glass funnel, the silica washed with 20% EtOAc/hexanes (200 mL) and the dark yellow oil residue is purified via silica gel flash column chromatography with 10% EtOAc/hexanes as eluent.

(Z)-4-Phenylbut-1-en-1-yl Acetate ***(1)***. All characterization data is in accordance with previously reported data.[15]

(Z)-Hex-1-en-1-yl (R)-2-Acetoxy-5-phenylpentanoate ***(4)***. Started with 1.47 mmol **3**. 80%, 0.37 g colorless oil, 20:1 *Z*/*E*. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.28 (m, 2H), 7.22−7.15 (m, 3H), 6.97 (dt, *J* = 6.3, 1.6 Hz, 1H), 5.10 (dd, *J* = 6.9, 5.7 Hz, 1H), 4.94 (td, *J* = 7.5, 6.3 Hz, 1H), 2.74−2.55 (m, 2H), 2.14 (s, 3H), 2.10 (qd, *J* = 7.3, 1.4 Hz, 2H), 1.96−1.88 (m, 2H), 1.83−1.72 (m, 2H), 1.40−1.22 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 167.4, 141.4, 133.6, 128.4, 128.35, 126.0, 115.5, 71.7, 35.2, 31.1, 30.5, 26.8, 24.1, 22.2, 20.6, 13.9. HRMS-(ESI) for $C_{19}H_{26}O_4$ $[M+NH_4]^+$: calculated 336.2170, found 336.2170

(Z)-3-Cyclohexylprop-1-en-1-yl (R)-2-(((R)-2-Acetoxy-5-phenylpentanoyl)oxy)heptanoate ***(7)***. started with 0.96 mmol **6**. 78%, 0.36 g colorless oil, 22:1 *Z*/*E* ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.30−7.24 (m, 2H), 7.21−7.16 (m, 3H), 6.99 (dt, *J* = 6.3, 1.5 Hz, 1H), 5.15 (t, *J* = 6.2 Hz, 1H), 5.07 (dd, *J* = 8.1, 4.6 Hz, 1H), 4.97 (q, *J* = 7.5 Hz, 1H), 2.73−2.60 (m, 2H), 2.13 (s, 3H), 2.05−1.87 (m, 6H), 1.86−1.76 (m, 2H), 1.74−1.58 (m, 5H), 1.51−1.38 (m, 2H), 1.37−1.27 (m, 5H), 1.27−1.08 (m, 3H), 0.96−0.87 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 169.8, 167.1, 141.6, 134.1, 128.38, 128.35, 125.9, 114.2, 72.4, 71.8, 37.7, 35.4, 33.0, 32.98, 32.1, 31.3, 31.0, 30.6, 26.8,

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26.5, 26.3, 24.5, 22.4, 20.6, 14.0. HRMS-(ESI) for $C_{29}H_{42}O_6$ [M +NH_4]$^+$: calculated 504.3320, found 504.3317

(4R,7R,10S, Z)-10-(2-Cyclohexylethyl)-2,5,8,11-tetraoxo-7-pentyl-4-(3-phenylpropyl)-3,6,9,12-tetraoxaheptadec-13-en-17-yl Benzoate ***(10)***. The alkyne for step 10 was synthesized according to a known procedure starting from the alcohol precursor 4-pentyn-1-ol. All characterization data is in accordance with previous report.[26] Started with 0.36 mmol **9**. Purification of **10** via silica gel chromatography using 20% EtOAc/hexanes. 67%, 0.173 g yellow oil, 20:1 *Z*/*E*. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.07−7.98 (m, 2H), 7.58−7.51 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.30−7.23 (m, 2H), 7.20−7.14 (m, 3H), 7.03 (dt, *J* = 6.3, 1.6 Hz, 1H), 5.18 (t, *J* = 6.2 Hz, 1H), 5.12−5.05 (m, 2H), 5.01 (td, *J* = 7.4, 6.2 Hz, 1H), 4.34 (t, *J* = 6.5 Hz, 2H), 2.73−2.58 (m, 2H), 2.31 (qd, *J* = 7.5, 1.6 Hz, 2H), 2.11 (s, 3H), 2.05−1.74 (m, 10H), 1.71−1.59 (m, 5H), 1.47−1.38 (m, 2H), 1.36−1.08 (m, 10H), 0.95−0.81 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 169.5, 169.2, 166.7, 166.5, 141.6, 134.4, 132.9, 130.4, 129.6, 128.4, 125.9, 114.0, 72.8, 72.5, 71.8, 64.3, 37.1, 35.4, 33.2, 32.9, 32.5, 31.3, 31.0, 30.6, 28.5, 28.2, 26.9, 26.5, 26.21, 26.18, 24.5, 22.4, 21.2, 20.6, 14.0. HRMS-(ESI) for $C_{42}H_{56}O_{10}$ [M+NH_4]$^+$: calculated 738.4212, found 738.4214

General Procedure for Asymmetric Hydroformylation. *Caution! Carbon monoxide is a toxic gas and manipulations should be conducted in a well-ventilated fume hood close to a carbon monoxide detector. Hydrogen is a highly flammable and explosive gas. Precautions should be taken when using CO/H_2 mixtures.*

An oven-dried glass pressure bottle equipped with a stir bar is charged with THF 20 mM stock solutions of Rh(acac) $(CO)_2$ (0.3% catalyst loading, 150.37 μL) and BisDiazaphos ligand (0.36%, 180.44 μL) inside an N_2 glovebox and then attached to a reactor. Inside a fume hood, the reactor is subjected to three pressurizing (150 psig)−depressurizing (20 psig) cycles, then pressurized to 150 psig and immersed in an oil bath set to 65 °C. After at least 30 min of catalyst preactivation, the reactor is removed from the oil bath, allowed to cool down for 5 min and depressurized down to 10−20 psig. The alkene (1.00 mmol) is injected into the reactor as a solution in THF (amount of THF adjusted so that alkene concentration in the reactor is 1.5 M) via a gastight syringe and the reactor is then pressurized to 150 psig and immersed in the oil bath. Good gas−liquid mixing is ensured by vigorous stirring with the stir bar constantly breaking the gas−liquid interface. After the reaction is complete, the reactor is allowed to cool down for 30 min and then depressurized. Crude ^{1}H NMR spectra are obtained by adding $CDCl_3$ directly to the crude THF solution. Reaction mixture is passed through a pad of silica gel and washed with 20% EtOAc in hexanes (200 mL) to remove residual catalyst.

(R)-(+)-1-Oxo-5-phenylpentan-2-yl Acetate ***(2)***. All characterization data is in accordance with previously reported data.[15] $[\alpha]_D^{20}$ + 18.8 (c 1.00, $CHCl_3$). For determination of absolute configuration: the aldehyde was reduced with $LiAlH_4$ in dry THF at 0 °C warming to room temperature for 24 h total reaction time, followed by slow addition of MeOH, sat aq. NH_4Cl and extraction with ethyl acetate of the resulting 5-phenyl-1,2-pentanediol $[\alpha]_D^{20}$ + 0.8 (c 1.00, $CHCl_3$). Lit. $[\alpha]_D^{20}$ − 13.6 (*c* 1.00, $CHCl_3$) for (*S*)-4-phenyl-1,2-butanediol[27]

(R)-1-Oxoheptan-2-yl (R)-2-Acetoxy-5-phenylpentanoate ***(5)***. Started with 1.17 mmol **4**, 92%, 0.38 g colorless oil. ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.45 (s, 1H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.22−7.15 (m, 3H), 5.07 (dd, *J* = 7.8, 4.9 Hz, 2H), 2.74−2.61 (m, 2H), 2.12 (s, 3H), 2.03−1.92 (m, 2H), 1.90−1.67 (m, 4H), 1.45−1.36 (m, 2H), 1.36−1.24 (m, 4H), 0.93−0.85 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 170.6, 169.9, 141.5, 128.41, 128.40, 126.0, 78.8, 72.0, 35.3, 31.3, 30.7, 28.5, 26.8, 24.4, 22.3, 20.6, 13.9. HRMS-(ESI) for $C_{20}H_{28}O_5$ [M+NH_4]$^+$: calculated 366.2275, found 366.2278. $[\alpha]_D^{20}$ + 25.8 (*c* 1.00, $CHCl_3$). For determination of absolute configuration (*R*,*R*): the aldehyde was reduced with $LiAlH_4$ in dry THF at 0 °C warming to room temperature for 30 h total reaction time, followed by slow addition of MeOH, sat aq. NH_4Cl and extraction with ethyl acetate of the resulting mixture of 5-phenyl-1,2-pentanediol and 1,2-heptanediol. Optical rotation of this mixture of diols was compared with a prepared mixture of the same two diols of (*R*) configuration and known optical rotation value.

(S)-4-Cyclohexyl-1-oxobutan-2-yl (R)-2-(((R)-2-Acetoxy-5-phenylpentanoyl)oxy)heptanoate ***(8)***. Started with 0.5 mmol **7**, 84%, 0.217 g colorless oil. ^{1}H NMR ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.48 (s, 1H), 7.27 (dd, *J* = 8.6, 6.5 Hz, 2H), 7.18 (t, *J* = 6.9 Hz, 3H), 5.14 (t, *J* = 6.2 Hz, 1H), 5.07 (dd, *J* = 8.1, 4.5 Hz, 1H), 4.97 (dd, *J* = 8.8, 4.5 Hz, 1H), 2.72−2.61 (m, 2H), 2.12 (s, 3H), 2.02−1.60 (m, 13H), 1.48−1.11 (m, 12H), 0.94−0.84 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 170.5, 169.9, 169.6, 141.6, 128.39, 128.38, 126.0, 79.3, 72.7, 71.8, 37.3, 35.3, 33.2, 33.0, 32.3, 31.3, 31.0, 30.5, 26.8, 26.5, 26.3, 26.22, 26.20, 24.5, 22.4, 20.6, 14.0. HRMS-(ESI) for $C_{30}H_{44}O_7$ [M +NH_4]$^+$: calculated 534.3425, found 534.3427. $[\alpha]_D^{20}$ + 6.6 (*c* 1.00, $CHCl_3$).

(4R,7R,10S,13S)-10-(2-Cyclohexylethyl)-13-formyl-2,5,8,11-tetraoxo-7-pentyl-4-(3-phenylpropyl)-3,6,9,12-tetraoxaheptadecan-17-yl Benzoate ***(11)***. 0.5% Rh(acac) $(CO)_2$, 0.6% (*S*,*S*,*S*)-BisDiazaphos. Started with 0.24 mmol **10**. 92%, 0.17 g yellow oil. ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.45 (s, 1H), 8.08−7.98 (m, 2H), 7.54 (dt, *J* = 7.0, 1.7 Hz, 1H), 7.47−7.38 (m, 2H), 7.32−7.22 (m, 2H), 7.22−7.08 (m, 3H), 5.14 (t, *J* = 6.3 Hz, 1H), 5.11−5.03 (m, 3H), 4.32 (t, *J* = 6.5 Hz, 2H), 2.71−2.59 (m, 2H), 2.11 (s, 3H), 2.02−1.55 (m, 16H), 1.49−1.38 (m, 2H), 1.37−1.08 (m, 13H), 0.94−0.80 (m, 5H).^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 170.5, 169.6, 169.5, 169.3, 166.5, 141.6, 132.9, 130.3, 129.6, 128.4, 125.9, 78.7, 73.2, 72.6, 71.8, 64.4, 37.2, 35.3, 33.3, 33.0, 32.6, 31.3, 31.0, 30.5, 29.7, 28.6, 28.3, 28.2, 26.9, 26.5, 26.2, 26.2, 24.5, 22.4, 21.5, 20.6, 14.0. HRMS-(ESI) for $C_{43}H_{58}O_{11}$ [M+Na]$^+$: calculated 773.3872, found 773.3870. $[\alpha]_D^{20}$ −2.8 (*c* 1.00, $CHCl_3$).

General Procedure for Aldehyde Oxidation. The aldehyde (1 equiv, 3.1 mmol), CH_3CN (7.64 mL), H_2O (7.43 mL), KH_2PO_4 (4 eq, 12.4 mmol, 1.67 g), and 30% H_2O_2 (4.1 eq, 12.71 mmol, 1.44 g 30% solution) were combined in a round-bottom flask in this order. The reaction flask was cooled to 10 °C and $NaClO_2$ (4 equiv, 12.4 mmol, 1.11 g) was added dropwise as a solution in H_2O (7.64 mL). The solution was stirred vigorously for 3 h, while allowing it to warm up to room temperature. After reaction is complete, sodium sulfite is added for quenching, followed by 1 M HCl (20 mL), and the aqueous mixture is extracted with dichloromethane (30 mL × 5). Two additional extractions of the aqueous mixture with EtOAc were performed after synthesis of **9** and **12**. The organic layers are combined, dried over $MgSO_4$ and solvent removed in vacuo to afford the carboxylic acid product as a yellow oil. Note: All acetonitrile needs to be removed before the enol ester formation step to avoid catalyst poisoning.

(R)-2-Acetoxy-5-phenylpentanoic Acid ***(3)***. Started with 3.1 mmol **2**, 95%, 0.7 g colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34−7.24 (m, 2H), 7.24−7.15 (m, 3H), 5.03 (dd, *J* = 7.1, 5.4 Hz, 1H), 2.66 (dd, *J* = 8.5, 6.7 Hz, 2H), 2.14 (s, 3H), 1.96−1.87 (m, 2H), 1.78 (p, *J* = 7.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 170.9, 141.5, 128.5, 128.4, 126.1, 71.8, 35.3, 30.5, 26.9, 20.6. HRMS-(ESI) for $C_{13}H_{16}O_4$ [M−H]$^-$: calculated 235.0975, found 235.0978. Separation by HPLC (supports no epimerization of the chiral center during oxidation): CHIRALPAK 1A (AD-H), 5% iPrOH/hexanes, 0.5 mL/min, ambient temperature, 220 nm, t_R 8.8 min (minor, (*S*)), 10.1 min (major, (*R*))

(R)-2-(((R)-2-Acetoxy-5-phenylpentanoyl)oxy)heptanoic Acid ***(6)***. Started with 0.54 mmol **5**, 90%, 0.175 g yellow oil. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.82 (br, 1H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.22−7.14 (m, 3H), 5.16−4.96 (m, 2H), 2.67−2.60 (m, 2H), 2.12 (s, 3H), 2.01−1.84 (m, 4H), 1.79 (p, *J* = 7.3, 6.7 Hz, 2H), 1.48−1.40 (m, 2H), 1.34−1.27 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 170.8, 169.9, 141.6, 128.37, 128.35, 125.9, 72.3, 71.9, 35.3, 31.2, 30.8, 30.5, 26.7, 24.6, 22.3, 20.6, 14.0. HRMS-(ESI) for $C_{20}H_{28}O_6$ [M+NH_4]$^+$: calculated 382.2225, found 382.2224

(S)-2-(((R)-2-(((R)-2-Acetoxy-5-phenylpentanoyl)oxy)heptanoyl)oxy)-4-cyclohexylbutanoic Acid ***(9)***. Started with 0.42 mmol **8**, 86%, 0.19 g, colorless oil. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.31−7.23 (m, 2H), 7.18 (dd, *J* = 8.2, 6.5 Hz, 3H), 5.17 (t, *J* = 6.2 Hz, 1H), 5.06 (ddd, *J* = 8.3, 5.6, 4.3 Hz, 2H), 2.73−2.59 (m, 2H), 2.12 (s, 3H), 2.04−1.75 (m, 8H), 1.74−1.60 (m, 6H), 1.47−1.37 (m, 2H), 1.36−1.09 (m, 9H), 0.93−0.84 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

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174.9, 170.6, 169.7, 169.2, 141.6, 128.4, 126.0, 72.7, 72.6, 71.9, 37.2, 35.3, 33.2, 33.0, 32.5, 31.3, 31.0, 30.6, 28.5, 27.0, 26.5, 26.24, 26.21, 24.5, 22.4, 20.6, 14.0. HRMS-(ESI) for $C_{30}H_{44}O_8$ $[M+NH_4]^+$: calculated 550.3375, found 550.3369

(2S,5S,8R,11R)-2-(4-(Benzoyloxy)butyl)-5-(2-cyclohexylethyl)-4,7,10,13-tetraoxo-8-pentyl-11-(3-phenylpropyl)-3,6,9,12-tetraoxatetradecanoic Acid ***(12)*****.** Started with 0.22 mmol **11**, 70% yield, 120 mg yellow oil. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.05−8.02 (m, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.29−7.23 (m, 2H), 7.19−7.14 (m, 3H), 5.18−5.10 (m, 2H), 5.09−5.05 (m, 2H), 4.33 (t, J = 6.4 Hz, 2H), 2.64 (td, J = 9.1, 6.3 Hz, 2H), 2.11 (s, 3H), 2.02−1.75 (m, 10H), 1.72−1.58 (m, 6H), 1.47−1.36 (m, 2H), 1.36−1.05 (m, 13H), 0.93−0.81 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 169.6, 168.6, 168.3, 168.0, 165.6, 140.6, 131.9, 129.2, 128.5, 127.3, 124.9, 71.8, 71.6, 71.1, 70.8, 63.4, 36.1, 34.3, 32.2, 31.9, 31.3, 30.2, 30.0, 29.49, 29.45, 28.7, 27.3, 27.1, 25.9, 25.5, 25.2, 23.4, 21.3, 20.6, 19.5, 12.9. HRMS-(ESI) for $C_{43}H_{58}O_{12}$ $[M+NH_4]^+$: calculated 784.4267, found 784.4269

Procedures and Characterization Data for Enamide Synthesis and AHF (Scheme 3). *(4R,7R,10S,13S)-10-(2-Cyclohexylethyl)-2,5,8,11-tetraoxo-7-pentyl-4-(3-phenylpropyl)-13-(((((1Z,7Z)-8-(2,2,2-trifluoroacetamido)octa-1,7-dien-1-yl)oxy)carbonyl)-3,6,9,12-tetraoxaheptadecan-17-yl Benzoate* ***(14)*****.** Ru(methallyl)$_2$dppb (6 mol%, 6 mg) and 0.5 mL dry and degassed THF were combined in an oven-dried Schlenk flask equipped with a stir bar inside a N_2 glovebox. Inside a fume hood, the tetramer carboxylic acid **12** (1 eq, 120 mg, 0.16 mmol) was added to the reaction flask via syringe as a solution in 0.5 mL dry and degassed THF, followed by neat alkyne **13** (1.5 eq, 0.0623 mL, 0.24 mmol). The solution was immersed in an oil bath and allowed to stir at 45 °C for 48 h under N_2. After reaction is complete, the reaction mixture is passed through a pad of silica in a fritted glass funnel, washed with 20% EtOAc in hexanes (450 mL) and solvent removed in vacuo. The yellow oil residue is purified via silica gel flash column chromatography with 20% EtOAc/hexanes as eluent to give the product as a viscous yellow oil in 34% yield (54 mg) in 7:1 Z/E ratio. ^{1}H NMR ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.07−7.95 (m, 2H), 7.56 (td, J = 7.4, 1.6 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.31−7.23 (m, 2H), 7.18 (dd, J = 7.9, 6.1 Hz, 3H), 6.95 (dd, J = 6.4, 1.7 Hz, 1H), 6.63 (t, J = 10.8, 8.9 Hz, 1H), 5.19−5.11 (m, 1H), 5.11−4.99 (m, 4H), 4.92 (q, J = 7.2 Hz, 1H), 4.36−4.29 (m, 2H), 2.72−2.52 (m, 2H), 2.11 (s, 3H), 2.08−1.74 (m, 15H), 1.73−1.55 (m, 8H), 1.48−1.36 (m, 6H), 1.35−1.08 (m, 10H), 0.95−0.82 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 169.6, 169.3, 169.1, 167.8, 166.7, 166.6, 154.5, 141.6, 134.0, 133.0, 132.97, 130.2, 129.5, 128.4, 128.35, 125.9, 118.8, 117.0, 115.2, 72.8, 72.6, 72.2, 71.8, 64.4, 37.2, 35.3, 33.3, 32.9, 32.5, 31.3, 31.0, 30.54, 30.46, 28.44, 28.42, 28.1, 27.0, 26.5, 26.2, 25.5, 24.5, 24.1, 22.4, 21.5, 20.6, 14.00. HRMS-(ESI) for $C_{53}H_{70}F_3NO_{13}$ $[M+NH_4]^+$: calculated 1003.5138, found 1003.5144

(Z)-2,2,2-Trifluoro-N-(oct-1-en-7-yn-1-yl)acetamide ***(13)*****.** Synthesized according to a modified known procedure:[16a] In an oven-dried 50 mL Schlenk flask equipped with a magnetic stir bar inside a nitrogen-filled glovebox, bis(2-methallyl) (COD)ruthenium(II) (5%, 240 mg), 1,4-bis(dicyclohexylphosphino)butane (6%, 405 mg), ytterbium triflate (4%, 372 mg), and trifluoroacetamide (1 equiv, 15 mmol, 1.7 g) were combined, and anhydrous DMF (22 mL) was added. In a fume hood on a Schlenk line, degassed 1,7-octadiyne (2 equiv, 30.0 mmol, 4.1 mL) was added via syringe, followed by degassed H_2O (1.62 mL). The dark red solution was stirred for 24 h at 60 °C in an oil bath. The mixture was then poured into saturated aqueous sodium bicarbonate solution (100 mL). This mixture was extracted with ethyl acetate (3 × 50 mL), the combined organic layers were washed with water (5 × 50 mL) and brine (1 × 50 mL), dried over magnesium sulfate, filtered, and the volatiles were removed in vacuo. The dark brown oil was purified twice by flash column chromatography on silica gel with 10% EtOAc in hexanes for the first column and 5% EtOAc in hexanes for the second column. The product was obtained as a bright yellow oil in 20% yield, 0.53 g. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.62 (s, 1H), 6.66 (dd, J = 10.8, 9.0 Hz, 1H), 5.08 (q, J = 7.9 Hz, 1H), 2.26−2.19 (m, 2H), 2.15−2.04 (m, 2H), 1.97 (t, J = 2.7 Hz, 1H), 1.59 (h, J = 3.6, 2.8 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 118.9, 116.8, 114.6, 84.0, 68.8, 28.0, 27.6, 25.3, 18.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ −75.66. HRMS-(ASAP-MS) for $C_{10}H_{12}F_3NO$ $[M+H]^+$: calculated 220.0944, found 220.0944

(4R,7R,10S,13S)-10-(2-Cyclohexylethyl)-13-((((2S)-1,10-dioxo-9-(2,2,2-trifluoroacetamido)decan-2-yl)oxy)carbonyl)-2,5,8,11-tetraoxo-7-pentyl-4-(3-phenylpropyl)-3,6,9,12-tetraoxaheptadecan-17-yl Benzoate ***(15)*****.** Procedure modified from the general hydroformylation procedure due to the small amount of sample: Two oven-dried glass pressure bottles each equipped with a stir bar and two reactors are brought into a N_2 filled glovebox. One pressure bottle is charged with THF 100 mM stock solution of Rh(acac) (CO)$_2$ (25.35 μL stock solution, 5% catalyst loading) and 20 mM stock solution of (*S*,*S*,*S*)-BisDiazaphos (152.11 μL stock solution, 6% ligand loading) and then attached to a reactor. The second pressure bottle is charged with the viscous enol ester/enamide substrate (50 mg) as a mixture in 0.5 mL dry THF. After all the THF is removed (under vacuo inside the glovebox), the pressure bottle is attached to a reactor. Inside a fume hood, the reactor containing the catalyst mixture is subjected to three pressurizing (150 psig)−depressurizing (20 psig) cycles, then pressurized to 150 psig and immersed in an oil bath set to 65 °C. After 30 min of catalyst preactivation, the reactor is removed from the oil bath, allowed to cool down for 5 min, and depressurized down to 10−20 psig. The catalyst solution is then transferred to the second reactor containing the substrate using a syringe. The reactor containing now the substrate and the catalyst solution is then pressurized to 150 psig and immersed in the oil bath. Good gas−liquid mixing is ensured by vigorous stirring with the stir bar constantly breaking the gas−liquid interface. After 3 h at 65 °C, the reactor is allowed to cool down for 30 min and then depressurized. Crude ^{1}H NMR spectra are obtained by adding $CDCl_3$ directly to the crude THF solution. Reaction mixture is passed through a pad of silica gel and washed with 20% EtOAc in hexanes to remove residual catalyst. Recovered after silica pad: 30 mg combined weight, yellow oil, higher than 95% conversion of the starting material to a dialdehyde (determined by ^{1}H and ^{13}C NMR). Due to the small amount of sample, **15** could not be isolated and its diastereomeric purity could not be unambiguously determined. ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.58 (s, 1H), 9.46 (s, 1H), 8.04 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.27 (t, J = 7.6 Hz, 2H), 7.17 (d, J = 7.5 Hz, 3H), 5.19−4.98 (m, 5H), 4.64−4.53 (m, 1H), 4.38−4.30 (m, 2H), 2.73−2.58 (m, 2H), 2.11 (s, 3H), 2.09−1.57 (m, 20H), 1.52−1.07 (m, 20H), 0.93−0.81 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 195.6, 169.5, 168.6, 168.3, 168.2, 168.0, 156.3, 140.6, 131.9, 129.2, 128.5, 127.3, 124.9, 115.8, 77.7, 71.8, 71.53, 71.48, 70.8, 63.5, 57.9, 36.1, 34.3, 32.3, 31.9, 31.5, 30.6, 30.2, 30.0, 29.5, 27.7, 27.5, 27.4, 27.3, 27.2, 27.1, 25.9, 25.5, 25.2, 25.17, 23.6, 23.5, 21.6, 21.4, 20.6, 19.5, 12.9. HRMS-(ESI) for $C_{55}H_{74}F_3NO_{15}$ $[M+NH_4]^+$: calculated 1063.5349, found 1063.5334

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02210.

^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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