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Stereoselective Synthesis of Baulamycin A

Jonathan R. Thielman,[†] David H. Sherman,[‡*] and Robert M. Williams[†°*]

[†]Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA;

[°] University of Colorado Cancer Center, Aurora, CO 80045, USA

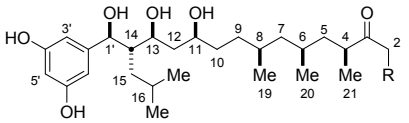
[‡] Life Sciences Institute, University of Michigan, Ann Arbor, Michigan 48109, USA; [3]University of Colorado Cancer Center, Aurora, CO 80045, USA

KEYWORDS GO HERE

ABSTRACT: New structural classes of antibiotics are rare, structurally-novel broad-spectrum antibiotics exceptionally so. The recently discovered baulamycins constitute a remarkable example of these highly-prized compounds and, as such, have attracted considerable attention in the form of both synthetic efforts and biological studies. For the first time, we report a gram-scale preparation of the common carbon framework of the baulamycin family, as well as the total synthesis of its most potent member, baulamycin A. Our approach employs highly-stereoselective, catalyst-controlled asymmetric conjugate additions to thioesters to set key stereocenters, as well as the first reported use of "dry ozonolysis" to reveal a masked carboxylic acid in the total synthesis of a natural product.

INTRODUCTION

The worldwide appearance of drug- and multidrug-resistant pathogens is widely recognized as a serious threat to public health.[1-4] Thus, our interest was strongly piqued when Sherman and coworkers published a report detailing unusual broad-spectrum antibiotic activity in the newly-identified natural products baulamycins A (**1**) and B (**2**) (Fig. 1).[5] These natural products represent an entirely new molecular scaffold of natural antibiotics and present a compelling opportunity to identify new biochemical targets for the development of new antimicrobial agents.



1: baulamycin A, R = Me
2: baulamycin B, R = H

Figure 1. Structure of baulamycins A and B.

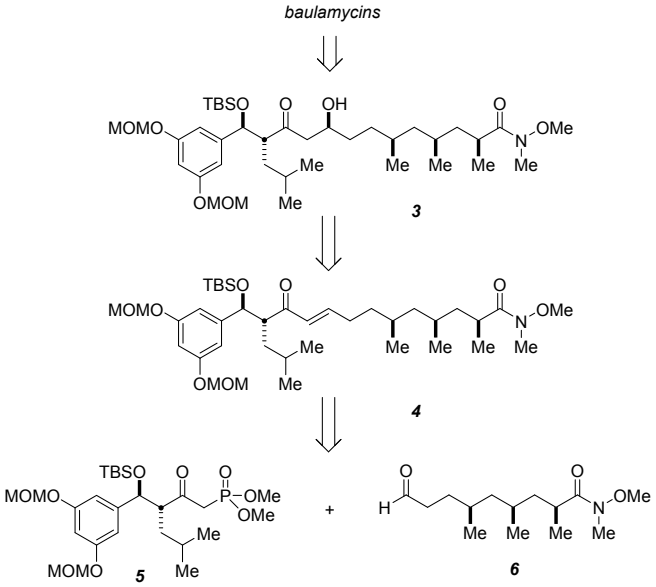
These partially-deoxygenated polyketides were isolated in low yield with substantial difficulty from *Streptomyces tempisquensis*, making them ideal targets for total synthesis. At the time of their isolation, intriguing questions about the baulamycins' biological mode of action drew our attention. Identified during a high-throughput screen for inhibitors of enzymes involved in siderophore biosynthesis, the baulamycins were initially proposed to target microbial iron acquisition, a validated but under-exploited target.[6] At the same time, lack of potentiation by iron deprivation in whole-cell assays suggested the possibility of other cellular targets.[5] Our interest in these questions was only amplified when, during the course of our own investigations, elegant work by Wuest and coworkers raised the possibility of membrane disruption as an alternate or additional mode of action.[7] Finally, the unusual structure of the baulamycin scaffold holds promise, as it remains distinct from all previously-reported classes of antimicrobials. In the face of ever-growing resistance to known structural manifolds, this characteristic was particularly alluring.

With the above in mind, we set about designing a scalable synthetic route to the baulamycins that would give access to both the natural products as well as designed derivatives, with the hope of further interrogating the underlying biological mode of action. In the course of our initial synthetic investigations, the relative stereochemistry of the natural products was revised and their absolute stereochemistry assigned in Aggarwal and co-workers' seminal total synthesis of **1** and **2**[8], an achievement paralleled by the concurrent work of Sengupta *et al* in their synthesis of the antipode of the natural product[9], and of Guchhait *et al* in their synthesis of the proposed structure.[10]

Our strategic synthetic analysis partitioned the baulamycin scaffold into left-hand side (LHS) and right-hand side (RHS) moieties, disconnecting at the C11 – C12 carbon-carbon bond (Scheme 1). Initial work in our group toward the proposed structure of the baulamycins envisioned a coupling of the LHS and RHS fragments by way of a diastereoselective aldol reaction. When extensive optimization of these efforts failed to produce the required diastereoselectivity, our attention turned to alternate methods of accessing late-stage key intermediate **3**. We imagined obtaining this β-hydroxy ketone from a diastereoselective formal hydration of enone **4**, which in turn would be accessed by Horner-Wadsworth-Emmons coupling of key RHS intermediate **6** with β-keto phosphonate **5**.

Finally, we envisioned **5** arising from a diastereoselective aldol reaction between known[11] thiazolidinethione **23** and protected 3,5-dihydroxybenzaldehyde **22**. The optimal approach to **6** appeared – at first glance – less obvious. A number of reports detail the construction of polydeoxypropionates, employing both iterative and non-

iterative strategies with varying degrees of generality and target-specificity.[12-14] We ruled out approaches relying upon the purchase of expensive chiral, non-racemic starting materials as infeasible; methods requiring the synthesis of complex catalysts were also deemed undesirable. Ultimately, we settled upon the asymmetric conjugate addition of Grignard reagents to α,β-unsaturated thioesters developed by Feringa and coworkers as the most tractable path toward **6** and similar structures.[15]



Scheme 1. Retrosynthetic analysis based on Horner-Wadsworth-Emmons coupling of left- and right-hand sides.

RESULTS

Wittig coupling of known[16] phosphonium ylide **7** (Scheme 2, prepared on >100 g scale in three steps from bromoacetic acid) with inexpensive ($0.02/mol) hydrocinnamaldehyde gave unsaturated thioester **9**. Pleasingly, when treated with methylmagnesium bromide in the presence of catalytic CuBr and (*R*,*S*)-Josiphos, **9** smoothly gave β-methyl thioester **10** in good yield and with excellent enantioselectivity. Reduction of the thioester with DIBAL-H at -65 °C proceeded rapidly and quantitatively[17], and Wittig olefination of the resulting aldehyde gave homologated thioester **11** in excellent overall yield and diastereoselectivity. A second asymmetric conjugate addition under Feringa's conditions gave **12** with excellent diastereoselectivity; subsequent reduction and Wittig olefination yielded hydrocarbon **13**, which was easily purified by elution from silica with neat pentane. Our attempts at hydroboration-oxidation reminded us of the subtleties of apparently-simple reaction manifolds. Initial attempts to employ 9-BBN as the borylating agent were foiled by incomplete separation of 1,5-cyclooctanediol from our alcohol product. The reaction with borane-THF, while surprisingly regioselective and free of reagent-derived impurities, was hindered by competing protodeboronation of the generated trialkylboranes during the oxidative workup, giving up to 32% yield of the alkane. In the end, disiamylborane proved most effective, giving the desired alcohol in quantitative yields with complete regioselectivity. Protection of the alcohol as the methyl carbonate proceeded accordingly, setting the stage for the oxidation of the terminal arene to unveil carboxylic acid **15**.

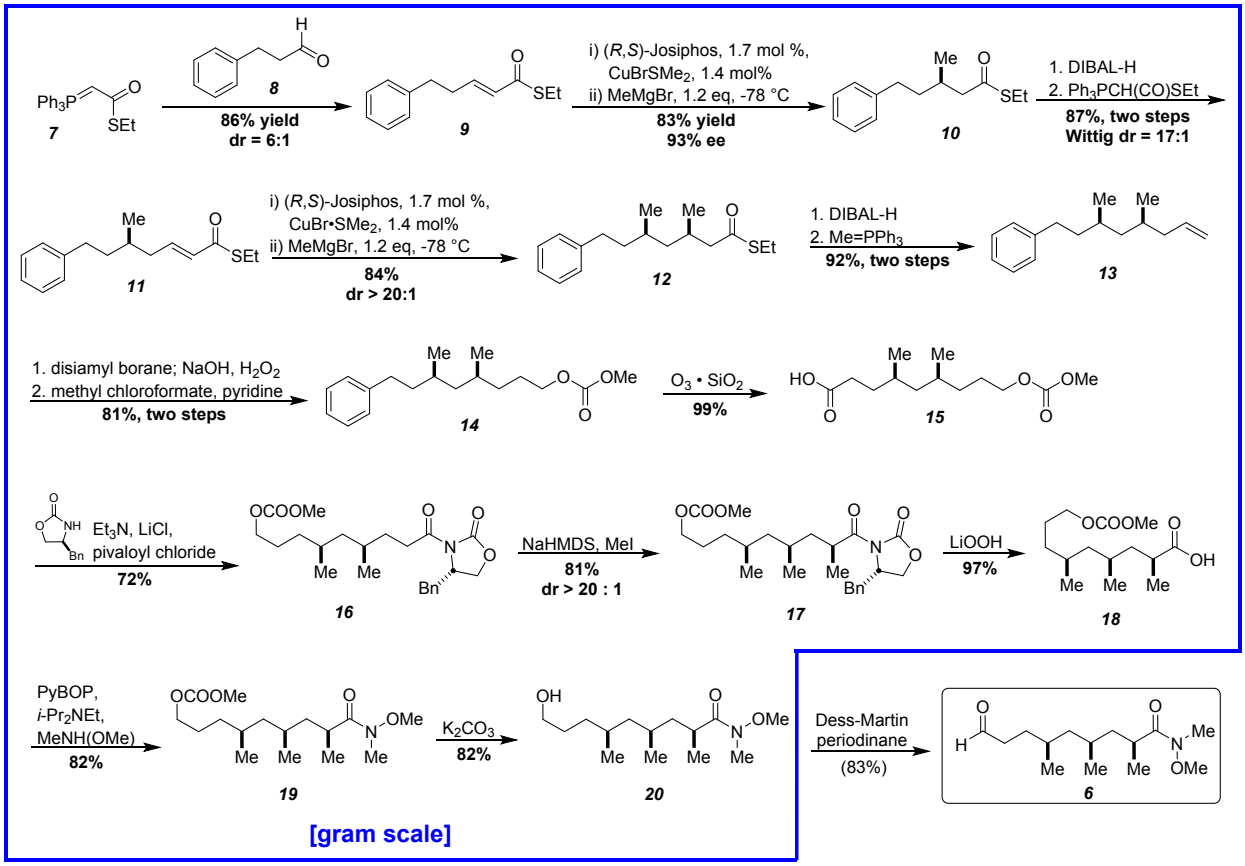
Our initial work toward the proposed structure of the baulamycins relied upon Sharpless' well-known adaption of the ruthenium tetroxide oxidation of arenes to access compounds like **15** from aromatic precursors.[18] This approach, while indeed successful, nonetheless suffered from a variety of drawbacks including complicated purifications and modest yields (~50%, despite optimization). In pursuit of alternate conditions that would alleviate what, at the time, was a major supply problem in our sequence, we noted with interest the application of so-called "dry ozonolysis" in the oxidation of arenes to carboxylic acids and other oxygenated species.[19-20] Once a topic of active research, these conditions – consisting in the adsorption of substrate onto silica followed by exposure to gaseous O_3 at cryogenic temperatures – have seen little use in the last twenty years, despite extensive prior documentation.[21] Pleasingly, application of these conditions to **14** gave **15** as the sole product in quantitative yield on a multi-gram scale, re-emphasizing the synthetic utility of this neglected reaction.

With scalable access to **15** in hand, we proceeded with the installation of the third methyl-bearing stereogenic center. Construction of *N*-acyloxazolidinone **16** followed by alkylation under Evans' conditions[22] gave trimethylated oxazolidinone **17** as a single diastereomer. With the last stereogenic center of the right-hand side of the baulamycins in place, hydrolysis[23], Weinreb amide formation, and deprotection[24] gave alcohol **20** in good overall yield. Finally, it was determined that the oxidation of **20** with Dess-Martin periodinane provided **6** in optimal yields; however, **6**, being relatively unstable, was not isolated but rather used immediately in the next step.

Turning to the left-hand side of the baulamycin scaffold, we first developed a scalable route to aldehyde **22** from 3,5-dihydroxybenzoic acid, giving decagram quantities of **22** in three steps (Scheme 3). As we had hoped, coupling with thiazolidinethione **23** under Evans' conditions gave the TMS-protected aldol, which was immediately deprotected without purification in excellent yield giving **24** as a single diastereomer. TBS-protection followed by half-reduction with DIBAL-H[25] gave the aldehyde, which could be transformed to the β-ketophosphonate in excellent yield over two steps, giving **5** in an overall yield of 40% from commercial material.

With efficient access to both left- and right-hand sides of the baulamycin scaffold in hand, we turned our attention to the coupling of **5** and **6** to give key enone intermediate **26**. Pleasingly, application of Paterson's barium hydroxide-mediated Horner-Wadsworth-Emmons conditions[26] to equimolar quantities of **5** and freshly-prepared **6** gave **26** in good yield on a gram scale. With access to ample quantities of the common carbon skeleton of the baulamycins effectively secured, we turned our attention to the task of developing conditions for the diastereoselective formal hydration of **26** to give β-hydroxy ketone **27**.

Our intuitions that this transformation might prove challenging were validated over the course of an extended

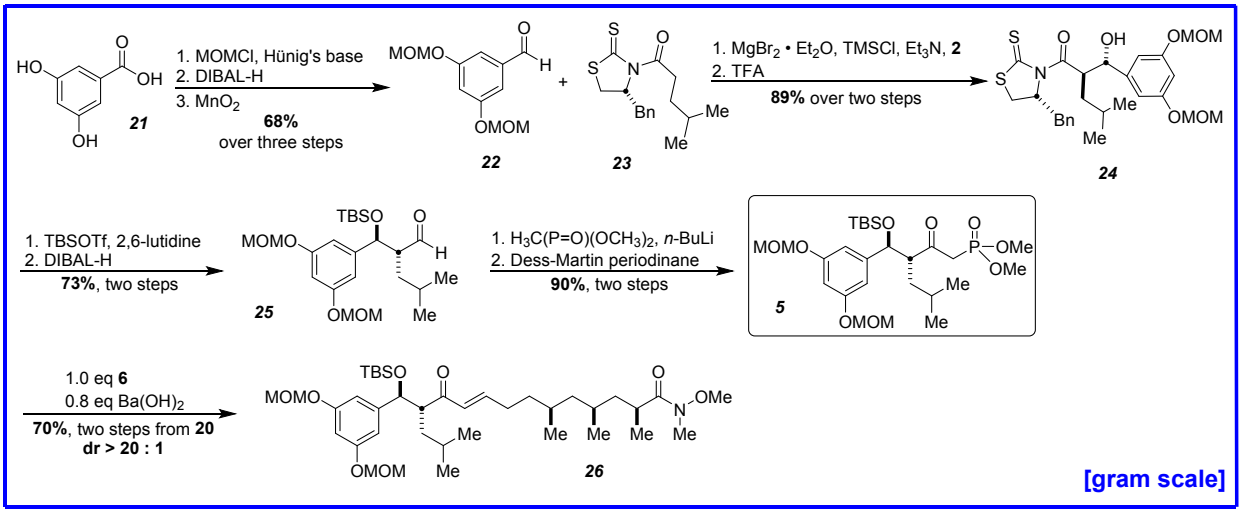


Scheme 2. Synthesis of key RHS intermediate **6**.

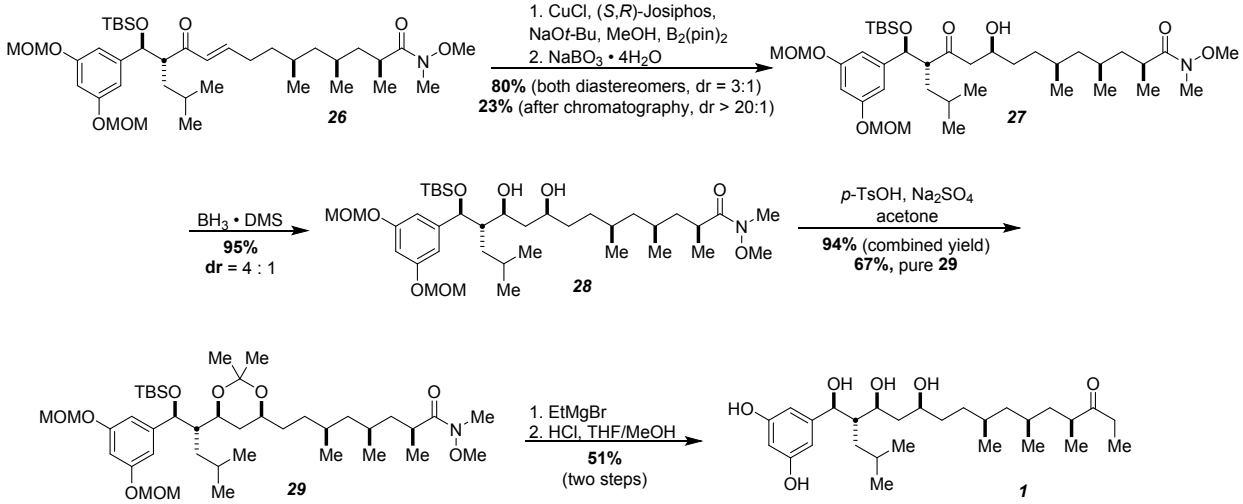
campaign to identify conditions for the diastereoselective formation of **27**. A long list of seemingly-promising transformations, including catalyst-directed epoxidations, hydroperoxidations, dihydroxylations and borylations, as well as a variety of substrate-controlled conditions, were surveyed with little initial success.

Finally, it was discovered that conditions[27] employing Cu(I)-catalyzed β-borylation with $B_2(pin)_2$ in the presence of (*R*,*S*)-Josiphos followed by oxidation with sodium perborate gave 11-*epi*-**27** in excellent yield and 17:1 d.r. Invigorated, we attempted the β-borylation of **26** with (*S*,*R*)-Josiphos, which indeed gave **27** as the major diastereomer in reasonable yield and with modest selectivity after oxidation (Scheme 4). At this juncture, exhaustive efforts to identify conditions leading to improved diastereoselectivity were not undertaken; purification of **27** by flash chromatography provided the required amounts of diastereomerically pure material.

With appreciable quantities of **27** in hand, we now turned our attention the final stereocenter in the baulamycin scaffold, the C13 hydroxyl. Ultimately, it was found that *syn*-reduction of **27** was best effected by BH_3•DMS at -20 °C, giving diol **28** in near-quantitative yields as a 4:1 mixture with its C13-epimer.



Scheme 3. Synthesis of key LHS intermediate **5** and coupling with LHS aldehyde **6.**



Scheme 4. Completion of the synthesis of baulamycin A.

These isomers could be readily separated by protection as the acetonides followed by selective hydrolysis of the *anti*-acetonide with *p*-TsOH in dry DCM at 0 °C.[28] Subsequent Weinreb ketone synthesis proceeded uneventfully, and global deprotection furnished baulamycin A in good overall yield.

CONCLUSION

In summary, we report here a gram-scale preparation of the common carbon scaffold of the baulamycins, as well as the total synthesis of the archetypal member of this family of natural products. Further investigations into the biological activity and additional direct biochemical targets of the baulamycins in human pathogenic bacterial will be reported in due course.

EXPERIMENTAL

General Considerations. The use of flame- or oven-dried glassware, inert atmosphere and other specific elements of air-free technique are explicitly noted and described in detail for each experimental procedure in which they were used. The use of dried glassware or inert atmosphere should not be assumed for reactions which do not explicitly describe their use.

Where used below, the term *high vacuum* refers to a vacuum measured at approximately 0.10 – 0.05 mm Hg. The term *purge* is used to refer to the evacuation of an experimental apparatus by high vacuum and subsequent back-filling with a specified inert gas at least three times. The term *sparge* indicates that a gas was vigorously bubbled through a solvent, typically from a stainless steel needle positioned with its tip at the lowest point of the vessel. The term *oven-dried* refers to an apparatus which has been kept at a temperature of 120 °C overnight; the term *flame-dried* refers to glassware placed under high vacuum and heated with a propane torch until frosting of glass components was no longer observed, then cooled under positive pressure of a dry inert gas. *Freeze-pump-thaw degassed* denotes that the material thus described has been placed in a Schlenk flask sealed with a fresh rubber septum, connected to high vacuum by a sidearm equipped with a closed stopcock, magnetically stirred at -196 °C until frozen, exposed to high vacuum by opening of the stopcock for at least 3 minutes, resealed by closing of the stopcock, thawed, and thus treated a total of three times.

Reactions conducted in flame- or oven-dried glassware were conducted with anhydrous solvents and reagents. In these cases, toluene, THF, DMF, diethyl ether, dichloromethane, acetonitrile, DMSO, pyridine, benzene, methanol, triethylamine and diisopropylamine were sparged with argon then dried by passage through a Glass Contour solvent purification system. Anhydrous *n*-pentane, hexanes and *tert*-butyl methyl ether were obtained by drying over 4 Å molecular sieves (20% w/w) for at least 12 hours prior to use. Acetone was dried over 3 Å molecular sieves (20 % w/w) overnight then used immediately to prevent re-equilibration to a higher water content through self-condensation[29]. Concentrations of acids, bases, and hydrogen peroxide refer to aqueous solutions except where otherwise noted.

Except when stated otherwise, reactants and reagents were obtained commercially and used without further purification. The terms *freshly distilled* and *freshly purified*, when used without citing an alternative reference, refer to purification according to the procedures described in standard reference works[30,31] or references contained therein.

Flash chromatography was performed on "Standard Grade" 60 Å porosity, 230-400 mesh silica gel from Sorbent Technologies. Analytical and preparative TLC were conducted on glass-backed plates precoated (0.21 – 0.27 mm) with Merck Silica Gel 60 F254. Preparative TLC was conducted by loading 10 mgs or less of sample onto 20 cm x 20 cm plates. In the case of analytical TLC, unless otherwise noted, compounds were visualized by 254 nm UV light or by immersion in Seebach's stain[32] followed by heating in a stream of hot air until the plate evolved a uniform blue color.

^{1}H and ^{13}C NMR spectra were acquired at various field strengths as indicated using Varian and Bruker spectrometers. ^{1}H NMR spectra were referenced internally to residual undeuterated solvents ($CHCl_3$ σ = 7.26 ppm, CH_3OH σ = 3.31 ppm, DMSO, σ = 2.50 ppm, CH_3CN σ = 1.94 ppm, H_2O σ = 4.79 ppm, C_6H_6 σ = 2.50 ppm, acetone σ = 2.05 ppm). ^{13}C NMR spectra were referenced internally to the solvent ($CHCl_3$ σ = 77.0 ppm, CH_3OH σ = 49.0 ppm).

Infrared spectra were recorded on a Nicolet iS5 or Nicolet iS50 FT-IR spectrometer. Mass spectra were obtained on

various TOF or QTOF spectrometers. Optical rotations were measured using a Rudolf Research Autopol III polarimeter operating at 589 nm at room temperature, typically 25 °C.

***S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate (7).** Following the previously described procedure[34], a 2-L round-bottom flask containing a magnetically-stirred solution of bromoacetic acid (50.0 g, 360 mmol, 1.00 eq) in DCM (700 mL) was charged with ethanethiol (34.6 mL, 468 mmol, 1.3 eq) and 4-dimethylaminopyridine (4.40 g, 36.0 mmol, 0.10 eq) at 0 °C. *N*,*N*-dicyclohexylcarbodiimide (77.94 g, 378 mmol, 1.05 eq) was then added portionwise, and the addition funnel rinsed with DCM (50 mL). The resulting thick white slurry was stirred 20 hrs, at which point the reaction mixture was filtered through Celite® and the filter cake washed with DCM (4 x 200 mL). The filtrate was concentrated under reduced pressure to give the crude thioester as a tan oil with particulate inclusions. This material was taken up in benzene (500 mL) and charged to a 1-L Erlenmeyer flask, to which triphenylphosphine (99.15 g, 378 mmol, 1.05 eq) was added. The reaction mixture was allowed to sit for four days with periodic agitation, at which point the mixture was filtered to reveal a white solid which was washed with toluene (2 x 100 mL) to give the triphenylphosphonium bromide salt as free-flowing crystalline powder. This solid was taken up in DCM (500 mL) and charged to a 3-L round-bottom flask containing a 10% w/w solution of Na_2CO_3 (500 mL). The reaction vessel was then equipped with a mechanical stirring apparatus and the biphasic mixture stirred for 6 hrs, evolving a yellow color. The layers were separated and the aqueous phase extracted with DCM (3 x 500 mL); the combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to give a light yellow solid. Precipitation from DCM with pentane (2:1 pentane / DCM) and filtration, followed by repeated concentration and precipitation of the mother liquor as above, afforded **7** (108 g, 82% over three steps) as a free-flowing, white crystalline powder. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 – 7.51 (m, 9H), 7.51 – 7.41 (m, 6H), 3.66 (d, J = 22.5 Hz, 1H), 2.84 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 180.5, 133.0 (d, J = 10.3 Hz), 132.2 (d, J = 2.9 Hz), 128.9 (d, J = 12.5 Hz), 126.8 (d, J = 90.9 Hz), 46.9 (d, J = 109.7 Hz), 23.1 (d, J = 2.4 Hz), 16.3. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 13.5. **IR** (neat) 1578, 1336, 1085, 871, 691, 501 cm^{-1}. **HRMS** (ESI): calc'd for $C_{22}H_{21}OPS$ $[M + H]^+$ 365.1124, found 365.1122. Characterization was in accordance with that previously reported[35].

***S*-ethyl (*E*)-5-phenylpent-2-enethioate (9).** The procedure described in the literature[36] was adapted as follows: to a 1-L round-bottom flask containing a magnetically-stirred solution of hydrocinnamaldehyde (5.56 mL, 42 mmol, 1.0 eq) in DCM (200 mL) was added **7** (20.00 g, 55 mmol, 1.3 eq). The resulting solution was stirred 22 hrs at room temperature, at which time TLC showed complete consumption of starting material. The reaction mixture was concentrated under reduced pressure and the residue repeatedly extracted under sonication with pentane (4 x 100 mL). The combined washings were then purified by flash chromatography on silica gel (300 g) eluting with 49:1 pentane / Et_2O to give **9** (7.93 g, 86%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (apparent t, J = 7.4 Hz, 2H), 7.24 – 7.15 (m, 3H), 6.92 (dt, J = 15.5, 6.8 Hz, 1H), 6.12 (dt, J = 15.5, 1.5 Hz, 1H), 2.94 (q, J = 7.4 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.56 – 2.47 (m, 2H), 1.28 (t, J = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 190.0, 143.9 140.6, 129.1, 128.5, 128.3, 126.2, 34.3, 33.9, 23.1, 14.8. Characterization agreed with that previously reported in the literature[36].

***S*-ethyl (*R*)-3-methyl-5-phenylpentanethioate (10)**. An argon-purged, 250-mL round-bottom flask equipped with a magnetic stir bar as charged with $CuBr{\cdot}Me_2S$ (0.065 g, 0.32 mmol, 0.014 eq) and (R,S_P)-Josiphos ethanol adduct (0.247 g, 0.390 mmol, 0.017 eq), followed by *tert*-butyl methyl ether (125 mL). The resulting orange solution was stirred at r.t. for 30 min, then cooled to -78 °C. To this solution was added methylmagnesium bromide (9.1 mL of a 3.0 M solution in Et_2O, 27.0 mmol, 1.2 eq); **9** (5.00 g, 23 mmol, 1.00 eq) was then added as a solution in *tert*-butyl methyl ether (33 mL) over 1.5 hrs via syringe pump. The reaction mixture was allowed to stir for 14 hrs at -78 °C, at which time TLC showed complete consumption of starting material. MeOH (8 mL) was added at -78 °C and the mixture allowed to warm to room temperature; saturated aqueous NH_4Cl was then added and the biphasic mixture stirred 30 min. The layers were separated and the aqueous layer extracted with a 1:1 mixture of DCM / Et_2O (3 x 100 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography on silica gel (250 g) eluting with 49:1 pentane / Et_2O gave **10** (4.49 g, 83%, 93% e.e.) as a colorless oil. Enantiomeric excess was determined by reduction to the alcohol with LAH (3.00 eq) followed by HPLC analysis on a chiral column using the following conditions: column = Chiralpak IB, eluent = 97:3 hexanes/*iso*-propanol, flow = 1.0 mL/min; t_R = 12.55 min (*R*), 13.51 min (*S*). Absolute configuration was established by conversion to the known[37] aldehyde **30** in the next step. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 – 7.25 (m, 3H), 7.21 – 7.15 (m, 3H), 2.88 (q, J = 7.4 Hz, 2H), 2.72 – 2.54 (m, 3H), 2.41 (dd, J = 14.5, 8.0 Hz, 1H), 2.16 – 2.02 (m, 1H), 1.74 – 1.62 (m, 1H), 1.57 – 1.46 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 199.0, 142.3, 128.3, 128.3, 125.7, 51.2, 38.4, 33.2, 30.8, 23.3, 19.5, 14.8. **IR** (neat): 3026, 2930, 1685, 1454 cm^{-1}. **[α]$^{25}_D$** = +6.5° (*c* 0.83, CH_2Cl_2). **HRMS** (ESI): calc'd for $C_{14}H_{21}OS$ $[M + H]^+$ 237.1308, found 237.1310.

(*R*)-3-methyl-5-phenylpentanal (30). A 1-L flame-dried round bottom containing **10** (8.05 g, 34.1 mmol, 1.00 eq) and equipped with a magnetic stir bar was capped with a rubber septum, purged with argon and charged with DCM (340 mL) to give a colorless, magnetically-stirred solution which was then cooled to -65 °C. DIBAL-H (35.8 mL of a 1.0 M solution in hexanes) was added slowly, and the resulting colorless solution stirred 50 minutes, at which time TLC showed complete consumption of starting material. MeOH (3 mL) was added at -65 °C and the solution stirred 10 min; the solution was then allowed to warm to rt. Saturated aqueous Rochelle's salt was added and the resulting biphasic mixture stirred until two clear phases were obtained; layers were then separated and the aqueous phase extracted with DCM. The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal **30** (6.01 g, 100%) as a colorless oil. Characterization agreed with that previously reported[37]: $[\alpha]^{25}_D$ = +22.8° (*c* 1.0, CH_2Cl_2); lit. $[\alpha]^{25}_D$ = +22.9°(*c* 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.75 (t, J = 2.4 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.21 - 7.15 (m, 3H), 2.73 – 2.55 (m, 2H), 2.45 (ddd, J = 16.1, 5.7, 2.0 Hz, 1H), 2.28 (ddd, J = 16.1, 7.9, 2.6 Hz, 1H), 2.18 – 2.04 (m, 1H), 1.74 – 1.62 (m, 1H), 1.62 – 1.50 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 202.7, 142.1, 128.4, 128.3, 125.8, 51.0, 38.6, 33.3, 27.8, 19.8.

***S*-ethyl (*R*,*E*)-5-methyl-7-phenylhept-2-enethioate (11).** To a 1-L round bottom flask containing a colorless, magnetically-stirred solution of **30** (6.01 g, 34.1 mmol, 1.00 eq) in $CHCl_3$ (340 mL) was added **7** (24.84 g, 68.2 mmol, 2.00 eq), giving a pale gold solution which was brought to reflux and stirred 12 hrs, at which time ^{1}H NMR of a reaction aliquot showed no aldehyde signal. The reaction solution was allowed to cool to r.t., then concentrated onto silica (50 g) and purified by flash chromatography on silica gel (400 g) eluting with 98:2 pentane / ether to give **11** (6.41 g, 72%) as a colorless oil. The *Z*-isomer of **11** was also isolated as a colorless oil; integration of the corresponding signals in the ^{1}H NMR spectrum of the crude reaction mixture indicate a d.r. of 17:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 6.86 (dt, J = 15.2, 7.5 Hz, 1H), 6.10 (apparent d, J = 15.4 Hz, 1H), 2.94 (q, J = 7.4 Hz, 2H), 2.72 – 2.53 (m, 2H), 2.31 – 2.19 (m, 1H), 2.13 – 2.01 (m, 1H), 1.76 – 1.60 (m, 2H), 1.57 – 1.41 (m, 1H), 1.28 (d, J = 7.5 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 190.0, 143.8, 142.3, 129.9, 128.34, 128.30, 125.7, 39.5, 38.4, 33.4, 32.2, 23.0, 19.5, 14.8. **IR** (neat): 3026, 2927, 1668, 1631, 1453 cm^{-1}. **$[\alpha]^{25}_D$** = +6.6° (*c* 0.37, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{16}H_{23}OS$ $[M + H]^+$ 263.1464, found 263.1470.

***S*-ethyl (*3R*,*5R*)-3,5-dimethyl-7-phenylheptanethioate (12).** To a flame-dried, argon-purged 500-mL round bottom flask were added CuBr•DMS (0.070 g, 0.341 mmol, 1.4 mol %) and (R,S_P)-Josiphos (0.266 g, 0.415 mmol, 1.7 mol %); the flask sealed with a rubber septum and *tert*-butyl methyl ether (100 mL) was added to give an orange solution. This solution was stirred 10 min, then cooled to -78 °C and stirred a further 15 min. Methylmagnesium bromide (9.8 mL of a 3.0 M solution in Et_2O, 29.3 mmol, 1.20 eq) was then added dropwise, giving a yellow solution. **11** (6.39 g, 24.4 mmol, 1.00 eq) was then added dropwise via syringe pump as a solution in *tert*-butyl methyl ether (25 mL) over 2 hrs. The resulting solution was stirred 16 hrs, at which time TLC showed complete consumption of starting material. The reaction was quenched with methanol (~3 mL) at -78 °C to give an opaque yellow-white suspension which was stirred 5 min, then allowed to come to r.t. Et_2O and saturated aqueous NH_4Cl were added, the mixture stirred, water added and the layers separated. The aqueous phase was then extracted with Et_2O (2 x 200 mL), the organics combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal an orange oil (6.80 g). This crude material was adsorbed onto silica, loaded onto a column containing silica gel (170 g), and purified by flash chromatography eluting with 98:2 pentane/ether to reveal the product as a colorless oil (5.73 g, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 2.87 (q, J = 7.4 Hz, 2H), 2.73 – 2.61 (m, 1H), 2.61 – 2.46 (m, 2H), 2.29 (dd, J = 14.4, 8.3 Hz, 1H), 2.21 – 2.06 (m, 1H), 1.74 – 1.59 (m, 1H), 1.59 – 1.48 (m, 1H), 1.45 – 1.36 (m, 1H), 1.36 – 1.28 (m, 1H), 1.24 (t, J = 7.4 Hz, 3H), 1.06 (dt, J = 13.6, 7.3 Hz, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 199.3, 142.9, 128.3, 128.3, 125.6, 51.3, 44.3, 38.4, 33.2, 29.7, 28.6, 23.3, 20.1, 20.0, 14.8. . **$[\alpha]^{25}_D$** = +4.56° (*c* 1.54, $CHCl_3$). **IR** (neat): 2928 (alkane C-H stretch), 1686 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{17}H_{27}OS$ $[M + H]^+$ 279.1777, found 279.1777.

***(3R,5R)*-3,5-dimethyl-7-phenylheptanal (31)**. To a 2000-mL, flame-dried, argon-purged round bottom flask containing a magnetically stirred, colorless solution of **12** (6.21 g, 22.3 mmol, 1.00 eq) was added DIBAL-H (33.4 mL of a 1.0 M solution in toluene, 33.4 mmol, 1.50 eq) dropwise over 15 min at -65 °C. The resulting colorless solution was stirred an additional 10 min, after which time TLC showed no starting material remaining. Methanol (4 mL) was added at -65 °C and the solution stirred until gas evolution ceased. The reaction solution was then allowed to warm to r.t. and saturated aqueous Rochelle's salt was added; the resulting mixture was then stirred until two clear phases were obtained. Layers were separated and the aqueous phase extracted with DCM (2 x 150 mL). The organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the pure product (4.68 g, 96%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.31 – 7.25 (m, 2H), 7.21 – 7.14 (m, 3H), 2.68 (ddd, J = 13.6, 10.3, 5.5 Hz, 1H), 2.55 (ddd, J = 13.7, 10.1, 6.1 Hz, 1H), 2.44 – 2.31 (m, 1H), 2.23 – 2.09 (m, 2H), 1.73 – 1.61 (m, 1H), 1.60 – 1.48 (m, 1H), 1.47 – 1.37 (m, 1H), 1.37 – 1.23 (m, 1H), 1.11 (dt, J = 13.7, 7.0 Hz, 1H), 1.00 – 0.89 (m, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 202.9, 142.8, 128.3, 125.6, 50.9, 44.6, 38.5, 33.2, 29.7, 25.6, 20.5, 19.9. **$[\alpha]^{25}_D$** = +15.3° (*c* 1.17, $CHCl_3$). **IR** (neat): 2914 (alkane C-H stretch), 1722 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{15}H_{22}NaO$ $[M + Na]^+$ 241.1563, found 241.1552.

((*3R*,*5S*)-3,5-dimethyloct-7-en-1-yl)benzene (13). To a 500-mL, flame-dried, argon-purged round bottom flask containing a magnetically stirred suspension of freshly-dried methyltriphenylphosphonium bromide (9.17 g, 25.7 mmol, 1.20 eq, dried by heating at 100 °C under high vacuum for 2 hrs) in THF (105 mL) was added *n*-butyllithium (9.4 mL of a 2.5 M solution in hexanes, 23.5 mmol, 1.10 eq) at 0 °C; an orange color evolved and most of the solid dissolved. The reaction mixture was brought to r.t. and stirred for 1 hr, at which time **31** (4.68 g, 21.4 mmol, 1.00 eq) was added as a solution in THF (40 mL + 3 x 10 mL washes). The resulting cloudy orange reaction suspension was stirred 40 min, at which time TLC showed complete consumption of starting material. Saturated aqueous NH_4Cl, Et_2O and water were added and stirred to give a colorless, biphasic mixture. The aqueous phase was separated, extracted with Et_2O (2 x 200 mL); the organics were then combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a colorless oil. Passage of this crude material through a plug of SiO_2 eluting with pentane gave pure **13** (4.30 g, 93%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.12 (m, 3H), 5.85 – 5.68 (m, 1H), 5.05 – 4.91 (m, 2H), 2.66 (ddd, J = 13.6, 10.4, 5.4 Hz, 1H), 2.54 (ddd, J = 13.6, 10.4, 5.8 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.88 – 1.78 (m, 1H), 1.70 – 1.49 (m, 3H), 1.45 – 1.21 (m, 3H), 1.00 (dd, J = 13.8, 6.9 Hz, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 143.1, 137.5, 128.3, 128.3, 125.5, 115.6, 44.3, 41.2, 38.7, 33.3, 30.1, 29.8, 20.2, 20.0. **$[\alpha]^{25}_D$** = +9.86° (*c* 0.77, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{16}H_{25}$ $[M + H]^+$ 217.1951, found 217.1964.

***(4S,6R)*-4,6-dimethyl-8-phenyloctan-1-ol (32).** A 2-necked, 250-mL round bottom flask was outfitted with a pressure-equalized dropping funnel and magnetic stir bar, then sealed with rubber septa. The entire apparatus was then flame dried under high vacuum and purged with argon. The round bottom flask was charged with BH_3•THF (40.4 mL of a 1.0 M solution in THF, 40.4 mmol, 1.10 eq), and 2-methyl-2-butene (9.40 mL, 88.8 mmol, 2.42 eq) was added via the dropping funnel as a solution in THF (20 mL) over 30 min at 0 °C. The colorless reaction solution was then stirred 2.5 hrs, at which time **13** (7.94 g, 36.7 mmol, 1.00 eq) was added as a solution in THF (20 mL + 2 x 5 mL washes). The resulting solution was allowed to gradually come to r.t. over 1 hr, then stirred an additional 1 hr.

TLC indicated complete consumption of starting material. The reaction vessel was cooled to 0 °C and aqueous sodium hydroxide (13.93 mL of a 3 M solution, 41.8 mmol, 1.14 eq) was added portionwise, with an initial evolution of gas. The reaction mixture evolved a cloudy, opaque appearance. The reaction vessel was then equipped with an internal thermometer and 30% aqueous hydrogen peroxide (w/w) (13.93 mL) was then added very slowly, keeping the reaction temperature below 20 °C. The resulting cloudy mixture was stirred 2 hrs, then water and Et_2O were added and the resulting layers separated. The pH of the aqueous phase was adjusted to 7.5 with saturated aqueous NH_4Cl, then the aqueous phase was extracted with Et_2O (3 x 120 mL) and the organics combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal **32** (8.63 g, 100%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 3.69 – 3.56 (m, 2H), 2.67 (ddd, J = 13.6, 10.5, 5.4 Hz, 1H), 2.54 (ddd, J = 13.6, 10.4, 5.9 Hz, 1H), 1.72 – 1.45 (m, 4H), 1.45 – 1.23 (m, 3H), 1.23 – 1.04 (m, 2H), 1.00 (dt, J = 13.9, 7.2 Hz, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 143.1, 128.3, 128.3, 125.5, 63.4, 44.8, 38.7, 33.3, 32.7, 30.2, 29.9, 29.8, 20.2, 20.1. **$[\alpha]^{25}_D$** = +10.6° (*c* 1.45, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{16}H_{30}NO$ $[M + NH_4]^+$ 252.2322, found 252.2317.

(*4S*,*6R*)-4,6-dimethyl-8-phenyloctyl methyl carbonate (14). To a 500-mL round bottom flask purged with argon, sealed with a rubber septum, and containing a magnetically stirred, colorless solution of **32** (8.60 g, 36.7 mmol, 1.00 eq), pyridine (3.84 mL, 47.7 mmol, 1.30 eq) and 4-dimethylaminopyridine (0.090 g, 0.734 mmol, 2 mol %) in DCM (75 mL) was added methyl chloroformate (3.69 mL, 47.7 mmol, 1.30 eq) dropwise over 5 min. A pale pink color evolved, and the reaction solution was stirred 3 hrs, at which time ^{1}H NMR of a reaction aliquot confirms the absence of starting material. Saturated aqueous NH_4Cl and water were added and the biphasic mixture stirred until two clear, distinct phases were obtained. The layers were separated and the aqueous phase extracted with DCM (2 x 120 mL); the organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal 9.85 g colorless oil. This crude material was adsorbed onto SiO_2 and loaded onto a column of silica gel (300 g). Flash chromatography eluting with 95:5 hexanes / ethyl acetate gave **14** (8.60 g, 80%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H), 7.18 (m, 3H), 4.11 (t, J = 6.8, 2H), 3.78 (s, 3H), 2.66 (ddd, J = 13.6, 10.5, 5.4 Hz, 1H), 2.54 (ddd, J = 13.6, 10.4, 5.9 Hz, 1H), 1.77 – 1.46 (m, 5H), 1.44 – 1.22 (m, 3H), 1.12 (m, 1H), 1.00 (dt, J = 13.9, 7.2 Hz, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 155.9, 143.1, 128.3, 128.2, 125.5, 68.6, 54.6, 44.8, 38.6, 33.3, 32.6, 29.8, 29.8, 26.1, 20.2, 20.0. **$[\alpha]^{25}_D$** = +5.6° (*c* 0.34, $CHCl_3$). **IR** (neat): 2955 (alkane C-H stretch), 1747 (carbonate C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{18}H_{32}NO_3$ $[M + NH_4]^+$ 310.2377, found 310.2383.

(*4R*,*6S*)-9-((methoxycarbonyl)oxy)-4,6-dimethylnonanoic acid (15). Carbonate **14** (7.00 g, 23.9 mmol) was dissolved in DCM; silica (175 g, 7.3 g/mmol **14**) was then added and the DCM removed under reduced pressure to give a free-flowing white powder. This powder was charged to a 1000-mL round bottom flask equipped with a magnetic stir bar. The flask was sealed with a plastic cap and a stainless steel needle was introduced through the cap in such a way that the tip of the needle rested at the bottom of the flask below the surface of the silica. A second needle of slightly-narrower gauge was introduced through the cap such that its tip was positioned in the headspace of the flask; this needle would serve as a point of efflux. A stream of ozone in oxygen (OREC ozone generator, high-purity oxygen as input) was introduced into the flask through the longer needle and the flask cooled to -78 °C with magnetic stirring. After approximately 2 hrs, the silica obtained a pale blue coloration; the flask was uncapped and allowed to warm to r.t. The reaction was monitored by TLC on aliquots of the silica extracted with ethyl acetate; after three cycles of ozone saturation at -78 °C followed by warming to r.t., TLC indicated the complete consumption of starting material. The room-temperature silica was loaded into a glass column and eluted with two column volumes of ethyl acetate; the combined ethyl acetate washings were then concentrated under reduced pressure to give pure **15** (6.22 g, 100%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.38 (br. s, 1H), 4.12 (t, J = 6.7, 2H), 3.78 (s, 3H), 2.45 – 2.25 (m, 2H), 1.79 – 1.46 (m, 5H), 1.45 – 1.30 (m, 2H), 1.29 – 1.18 (m, 1H), 1.18 – 1.05 (m, 1H), 1.05 – 0.93 (m, 1H), 0.92 – 0.80 (m, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 179.8, 155.9, 68.5, 54.6, 44.5, 32.6, 31.5, 31.2, 29.7, 29.5, 26.1, 19.9, 19.8. **$[\alpha]^{25}_D$** = +1.6° (*c* 4.2, $CHCl_3$). **HRMS** (ESI): calc'd for $C_{13}H_{24}NaO_5^+$ $[M + Na]^+$ 283.1516, found 283.1523.

(*4S*,*6R*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4,6-dimethyl-9-oxononyl methyl carbonate (16). To a 50-mL flame-dried, argon-purged round bottom flask equipped with a magnetic stir bar and capped with a rubber septum was added **15** (0.250 g, 0.96 mmol, 1.00 eq) as a solution in THF (1.5 mL, including washes) followed by triethylamine (0.33 mL, 2.40 mmol, 2.50 eq) and pivaloyl chloride (0.12 mL, 0.960 mmol, 1.00 eq) at 0 °C. A white precipitant formed and the resulting suspension was stirred 1 hr, then (*S*)-4-benzyl-2-oxazolidinone (0.170 g, 0.96 mmol, 1.00 eq) and lithium chloride (0.061 g, 1.44 mmol, 1.50 eq). The resulting mixture was stirred 24 hrs, then saturated aqueous ammonium chloride was added, the resulting mixture stirred, layers separated and the aqueous layer extracted with Et_2O. The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a brown oil. This crude material was purified by flash chromatography on silica gel (25 g) eluting first with 9:1 hexanes/ethyl acetate followed by 3:2 hexanes/ethyl acetate gave **16** (0.30 g, 72%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 3H), 7.23 – 7.17 (m, 2H), 4.66 (ddt, J = 10.3, 6.8, 3.2 Hz, 1H), 4.23 – 4.14 (m, 2H), 4.11 (t, J = 6.8 Hz, 2H), 3.76 (s, 3H), 3.29 (dd, J = 13.3, 3.4 Hz, 1H), 2.98 (ddd, J = 15.8, 9.9, 5.5 Hz, 1H), 2.87 (ddd, J = 16.4, 9.8, 5.9 Hz, 1H), 2.74 (dd, J = 13.3, 9.7 Hz, 1H), 1.78 – 1.49 (m, 5H), 1.48 – 1.32 (m, 2H), 1.26 (dt, J = 13.6, 6.9 Hz, 1H), 1.18 – 1.07 (m, 1H), 1.01 (dt, J = 14.0, 7.2 Hz, 1H), 0.94 – 0.83 (m, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 173.6, 155.9, 153.4, 135.3, 129.4, 128.9, 127.3, 68.5, 66.1, 55.2, 54.6, 44.7, 37.9, 33.2, 32.6, 30.9, 29.7, 29.6, 26.1, 19.9. **$[\alpha]^{25}_D$** = +39.5° (*c* 0.24, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1779 (C=O stretch), 1745 (C=O stretch), 1698 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{23}H_{34}NO_6$ $[M + H]^+$ 420.2381, found 420.2383.

(*4S*,*6S*,*8S*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4,6,8-trimethyl-9-oxononyl methyl carbonate (17). To a 500-mL argon-purged round bottom flask capped with a rubber septum and containing a magnetically-stirred colorless solution of **16** (5.00 g, 11.9 mmol, 1.00 eq) in THF (90 mL) was added sodium hexamethyldisilazide (14.3 mL of a 1.0 M solution in THF, 14.3 mmol, 1.20 eq) dropwise at -78°C. The resulting pale brown solution was stirred 1 hr, at which time methyl iodide (1.85 mL,

29.8 mmol, 2.50 eq) was added dropwise. The resulting solution was then stirred 4.5 hrs, at which time TLC indicated complete consumption of starting material. Saturated aqueous NH_4Cl, water, Et_2O and saturated aqueous $Na_2S_2O_3$ were added and the mixture allowed to warm to r.t. with stirring overnight. The layers were separated and the aqueous phase extracted with Et_2O (2 x 100 mL); the organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a dark yellow oil. Flash chromatography on silica gel (250 g) eluting first with 9:1 hexanes / ethyl acetate followed by 3:1 hexanes / ethyl acetate gave **17** (4.66 g, 81%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 3H), 7.22 (d, J = 6.7, 2H), 4.69 (ddt, J = 10.3, 7.4, 3.1 Hz, 1H), 4.25 – 4.15 (m, 2H), 4.13 (t, J = 6.7 Hz, 2H), 3.94 – 3.83 (m, 1H), 3.77 (s, 3H), 3.25 (dd, J = 13.4, 3.3 Hz, 1H), 2.77 (dd, J = 13.4, 9.6 Hz, 1H), 1.90 (ddd, J = 13.7, 9.3, 4.7 Hz, 1H), 1.80 – 1.67 (m, 1H), 1.67 – 1.52 (m, 2H), 1.52 – 1.41 (m, 1H), 1.41 – 1.31 (m, 1H), 1.30 – 1.18 (m, 4H), 1.18 – 1.01 (m, 2H), 1.01 – 0.92 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 177.2, 155.8, 152.9, 68.5, 65.9, 55.1, 54.5, 45.0, 40.5, 37.7, 35.2, 32.5, 29.6, 28.0, 26.0, 20.4, 19.9, 18.6. **$[\alpha]^{25}_D$** = +46.1° (*c* 0.20, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1778 (C=O stretch), 1746 (C=O stretch), 1695 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{24}H_{36}NO_6$ $[M + H]^+$ 434.2537, found 434.2532.

(2S,4S,6S)-9-((methoxycarbonyl)oxy)-2,4,6-trimethylnonanoic acid (18). To a 500-mL round bottom flask containing a magnetically stirred colorless solution of **17** (4.19 g, 9.67 mmol, 1.00 eq) in THF (100 mL) was added a solution of lithium hydroxide monohydrate (0.811 g, 19.3 mmol, 2.00 eq) and 30% (w/w) hydrogen peroxide (7.83 mL, 77.3 mmol, 8.00 eq) in water (25 mL + 25 mL of washings) at 0 °C. Gas evolution was noted; the walls of the flask were then rinsed with an additional 50 mL THF and the resulting cloudy, colorless mixture was stirred 45 min, at which time TLC indicated the complete consumption of starting material. $Na_2S_2O_3$ (8.00 eq) dissolved in water was added, followed by saturated aqueous NH_4Cl as well as solid NH_4Cl to give a biphasic mixture of approximately neutral pH. Et_2O was added, layers were separated and the aqueous phase extracted with ethyl acetate (3 x 300 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil. Flash chromatography on silica gel (250 g) eluting with 13:5 hexanes / ethyl acetate + 1% (v/v) AcOH gave **18** (2.58 g, 97%) colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 4.12 (t, J = 6.8 Hz, 2H), 3.78 (s, 3H), 2.67 – 2.49 (m, 1H), 1.79 – 1.46 (m, 5H), 1.41 – 1.29 (m, 1H), 1.24 – 1.02 (m, 6H), 0.97 (dt, J = 14.0, 7.2 Hz, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 182.8, 155.9, 68.5, 54.6, 45.0, 40.9, 37.2, 32.7, 29.6, 28.1, 26.1, 20.3, 19.7, 18.1. **$[\alpha]^{25}_D$** = +12.9° (*c* 0.57, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1747 (C=O stretch), 1704 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{14}H_{27}O_6$ $[M + H]^+$ 275.1853, found 275.1858.

(*4S*,*6S*,*8S*)-9-(methoxy(methyl)amino)-4,6,8-trimethyl-9-oxononyl methyl carbonate (19). To an argon-flushed, 500-mL round bottom flask containing a magnetically stirred colorless solution of **18** (2.48 g, 9.04 mmol, 1.00 eq) in DCM (20 mL) was added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (4.94 g, 9.49 mmol, 1.05 eq) and diisopropylethylamine (3.85 mL, 22.1 mmol, 2.45 eq). The resulting near-colorless solution was stirred 10 min, at which time *N*,*O*-dimethylhydroxylamine hydrochloride (1.19 g, 12.2 mmol, 1.35 eq) was added and the reaction solution stirred an additional 1.5 hrs. At this time, TLC indicated complete consumption of starting material. The reaction solution was charged to a separatory funnel and rinsed with 1N HCl (1 x 30 mL), water (1 x 30 mL), saturated aqueous $NaHCO_3$ (1 x 30 mL), dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a glassy solid. This crude material was dissolved in DCM, adsorbed onto SiO_2 (35 g); subsequent purification by flash chromatography on silica gel (250 g) eluting with 3:1 hexanes / ethyl acetate gave **19** (2.24 g, 82%) as a colorless, low-viscosity oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (t, J = 6.8 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 3.18 (s, 3H), 3.01 (s, 1H), 1.79 (ddd, J = 13.9, 9.6, 4.7 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.66 – 1.50 (m, 2H), 1.50 – 1.40 (m, 1H), 1.40 – 1.29 (m, 1H), 1.24 – 1.15 (m, 1H), 1.15 – 1.06 (m, 4H), 1.04 – 0.89 (m, 2H), 0.87 (d, J = 4.2 Hz, 3H), 0.85 (d, J = 4.2 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 155.9, 68.6, 61.4, 54.6, 45.2, 41.1, 32.7, 32.6, 29.6, 28.1, 26.2, 20.6, 19.9, 18.5. **$[\alpha]^{25}_D$** = +16.1° (*c* 0.27, $CHCl_3$). **IR** (neat): 2956 (alkane C-H stretch), 1747 (C=O stretch), 1662 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{16}H_{32}NO_5$ $[M + H]^+$ 318.2275, found 318.2272.

(*2S*,*4S*,*6S*)-9-hydroxy-*N*-methoxy-*N*,2,4,6-tetramethylnonanamide (20). To an argon-purged 500-mL round bottom flask equipped with a magnetic stir bar, sealed with a rubber septum and containing **19** (2.17 g, 6.84 mmol, 1.00 eq) was added 1% (w/w) K_2CO_3 in methanol (60 mL). The resulting colorless solution was stirred 1 hr, at which time ^{1}H NMR of a reaction aliquot appeared to indicate the complete consumption of starting material. The reaction solution was diluted with Et_2O and washed with water. These washings were then back-extracted twice with Et_2O and the combined organics dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil with included water. This material was dissolved in DCM, re-dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a colorless oil. Despite the apparent lack of starting material in the reaction mixture, flash chromatography on silica gel (150 g) gave both starting material (0.52 g) and product (1.22 g, 69%) as colorless oils. The recovered starting material was re-subjected to the conditions described above (13 mL 1% (w/w) K_2CO_3 in methanol for 2 hrs); workup without chromatography gave additional pure product (0.22 g) which was combined with the previously-obtained material to give **20** (1.46 g, 82%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.68 – 3.56 (m, 2H), 3.18 (s, 3H), 3.02 (s, 1H), 1.80 (ddd, J = 13.8, 9.6, 4.4 Hz, 1H), 1.67 – 1.40 (m, 4H), 1.40 – 1.29 (m, 2H), 1.26 – 1.16 (m, 1H), 1.16 – 1.06 (m, 4H), 1.06 – 0.90 (m, 2H), 0.87 (d, J = 4.1 Hz, 3H), 0.86 (d, J = 4.1 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 63.4, 61.5, 45.3, 41.3, 32.7, 32.5, 32.4, 30.0, 29.8, 28.3, 20.5, 20.1, 18.5. **$[\alpha]^{25}_D$** = +28.5° (*c* 0.22, $CHCl_3$). **IR** (neat): 2931 (alkane C-H stretch), 1643 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{14}H_{30}NO_3$ $[M + H]^+$ 260.2220, found 260.2193.

Methoxymethyl 3,5-bis(methoxymethoxy)benzoate (21). To a 500-mL, flame-dried three neck round bottom flask equipped with a magnetic stir bar and pressure-equalized dropping funnel was added 3,5-dihydroxybenzoic acid (10.63 g, 69.0 mmol, 1.00 eq); the flask was then sealed with rubber septa and purged with argon. DCM (80 mL) was added, followed by Hünig's base (72.11 mL, 414 mmol, 6.00 eq). The resulting off-white suspension was then cooled to 0 °C with stirring and methoxymethyl chloride (25.00 g, 311 mmol, 4.5

eq) was added dropwise (dropping funnel) over 1.5 hrs with some evolution of white gas. The resulting opaque, dark brown solution was allowed to come to r.t. and stirred 23 hrs, at which time TLC appeared to show complete consumption of starting material. Saturated aqueous $NaHCO_3$ was added and the biphasic mixture stirred until color had lightened considerably. Layers were then separated and the aqueous phase extracted with DCM (2 x 150 mL). Organics were combined and back-extracted with aqueous KOH (1 N, 2 x 250 mL), washed with brine, and dried over Na_2SO_4, then decanted and concentrated under reduced pressure to reveal the product as a brown oil (17.84 g) which was used directly in the next step without further purification. Pure **21** could be obtained as a colorless oil by purification by flash chromatography on silica gel eluting with 3:1 hexanes / ethyl acetate. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 (d, J = 2.3 Hz, 2H), 6.95 (t, J = 2.3 Hz, 1H), 5.47 (s, 2H), 5.20 (s, 4H), 3.54 (s, 3H), 3.49 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 165.5, 158.1, 131.9, 110.9, 109.9, 94.5, 91.1, 57.8, 56.1. **IR** (neat): 2956 (C-H stretch), 1723 (C=O stretch), 1595 (C=C stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{13}H_{19}O_7$ $[M+H]^+$ 287.1125, found 287.1116.

(3,5-bis(methoxymethoxy)phenyl)methanol (33). A flame-dried 1000-mL round bottom flask equipped with a magnetic stir bar, purged with argon and containing crude **21** (14.53 g, 50.8 mmol, 1.00 eq) was sealed with a rubber septum and charged with DCM (100 mL) to give a pale yellow stirred solution. The reaction vessel was cooled to -78 °C and DIBAL-H (100 mL of a 1.0 M solution in hexanes, 100 mmol, 1.97 eq) was added over 15 minutes via cannula. The yellow reaction solution was stirred an additional 5 minutes, at which time TLC showed complete consumption of starting material. Excess MeOH was added at -78 °C; once gas evolution had ceased, the reaction mixture was allowed to warm somewhat and saturated aqueous Rochelle's salt was added. The biphasic mixture was allowed to warm to r.t. and stirred overnight, at which time layers were separated. The aqueous phase was extracted with diethyl ether (3 x 150 mL); organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the crude product (12.04 g) as a viscous, yellow oil which was used directly in the next step without further purification. Pure **33** could be obtained as a colorless oil after purification by flash chromatography on silica gel eluting with 98:2 DCM/MeOH. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.72 (d, J = 2.3 Hz, 2H), 6.66 (t, J = 2.3 Hz, 1H), 5.16 (s, 4H), 4.64 (s, 2H), 3.48 (s, 6H), 1.68 (s, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.4, 143.5, 107.9, 104.0, 94.4, 65.1, 56.0. **IR** (neat): 3401 (br, O-H stretch), 2902 (C-H stretch), 1596 cm^{-1}. **HRMS** (ESI): calc'd for $C_{13}H_{19}O_7$ $[M+H]^+$ 287.1125, found 287.1116.

3,5-bis(methoxymethoxy)benzaldehyde (22). To a 1000-mL round bottom flask containing a magnetically-stirred solution of crude **33** (12.04 g) in DCM (200 mL) was added activated manganese dioxide (88.33 g, 1.02 mol). The walls of the flask were rinsed with DCM (2 x 25 mL) and the black suspension cooled with an ice bath until the reaction was no longer exothermic. The reaction was then brought to r.t. and stirred 21 hrs, at which time TLC showed complete consumption of starting material. The reaction mixture was filtered through Celite and the filter cake thoroughly washed with DCM and the combined filtrates concentrated under reduced pressure to reveal 9.40 g yellow oil. Flash chromatography on silica gel (330 g) eluting with 85:15 hexanes/ethyl acetate gave **22** (9.16 g, 59% over three steps) as a colorless oil that solidified on standing at -30 °C over a period of months. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.21 (d, J = 2.3 Hz, 2H), 6.98 (t, J = 2.3 Hz, 1H), 5.21 (s, 4H), 3.49 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 191.6, 158.7, 138.5, 111.1, 110.4, 94.5, 56.2. **IR** (neat): 2904 (C-H stretch), 2827 (aldehyde C-H stretch), 1700 (C=O stretch), 1593 cm^{-1}. **HRMS** (ESI): calc'd for $C_{11}H_{15}O_5$ $[M+H]^+$ 227.0910, found 227.0912.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-2-((*S*)-(3,5-bis(methoxymethoxy)phenyl)(hydroxy)methyl)-4-methylpentan-1-one (24). To a 500-mL round bottom flask containing freshly-prepared[38] (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)-4-methylpentan-1-one (3.43 g, 11.2 mmol, 1.00 eq) was added $MgBr_2$•Et_2O (0.434 g, 1.68 mmol, 15 mol %). The flask was equipped with a magnetic stir bar, sealed with a rubber septum and purged with argon. Ethyl acetate (10 mL) was then added, followed by **22** (2.53 g, 11.2 mmol, 1.00 eq) as a solution in ethyl acetate (5 mL + 3 mL washings). Triethylamine (3.12 mL, 22.4 mmol, 2.00 eq) and trimethylsilyl chloride (2.13 mL, 16.8 mmol, 1.50 eq) were then added to give a pale yellow opaque suspension. The reaction mixture was stirred 43 hrs, at which time TLC indicated complete consumption of starting material. The reaction mixture was filtered through a plug of silica gel, eluting with Et_2O. The filtrate was then concentrated under reduced pressure into a 500-mL round bottom flask to give the crude trimethylsilyl ether as a viscous, yellow oil. This material was dried under high vacuum overnight; the flask was then charged with a magnetic stir bar, sealed with a rubber septum and purged with argon. DCM (100 mL) was added to give a yellow solution, then trifluoroacetic acid (1.72 mL, 22.4 mmol, 2.00 eq) was added dropwise over 5 min. The resulting solution was stirred 1.5 hrs; saturated aqueous $NaHCO_3$ was then added and the resulting biphasic mixture stirred until gas evolution had ceased. The layers were separated and the aqueous phase extracted with DCM (2 x 100 mL); the organics were then combined, dried over Na_2SO_4, decanted, and concentrated under reduced pressure onto SiO_2 (25 g). This silica-adsorbed material was then loaded onto a silica gel (250 g) column and purified by flash chromatography eluting with 9:1 hexanes / ethyl acetate followed by 7:3 hexanes / ethyl acetate to give **24** (5.31 g, 89%) as a light yellow amorphous solid after azeotropic drying with heptane and drying on high vacuum. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.18 (m, 3H), 6.65 (d, J = 2.2 Hz, 2H), 6.56 (t, J = 2.3 Hz, 1H), 5.22 – 5.14 (m, 3H), 5.06 (d, J = 6.8 Hz, 2H), 4.86 (dt, J = 8.3, 4.1 Hz, 1H), 4.80 (td, J = 6.7, 3.3 Hz, 1H), 3.34 (s, 6H), 3.27 (d, J = 9.1 Hz, 1H), 3.10 (dd, J = 13.2, 3.8 Hz, 1H), 2.89 (dd, J = 13.2, 10.7 Hz, 1H), 2.70 (dd, J = 11.3, 6.8 Hz, 1H), 2.61 (d, J = 11.3 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.79 (t, J = 7.1 Hz, 2H), 1.00 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 202.0, 177.1, 158.3, 145.5, 136.4, 129.4, 128.8, 127.2, 106.0, 103.9, 94.3, 74.2, 68.8, 56.0, 48.1, 37.8, 36.5, 31.9, 25.7, 23.7, 22.2. **$[\alpha]^{25}_D$** = -200° (*c* 0.24, $CHCl_3$). **IR** (neat): 3491 (O-H stretch), 2952 (alkane C-H stretch), 1667 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{27}H_{35}NNaO_6S_2$ $[M+Na]^+$ 556.1798, found 556.1821.

(*R*)-2-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylpentanal (25). A 500-mL flame-dried round bottom flask charged with **24** (5.31 g, 9.95 mmol, 1.00 eq) was equipped with a magnetic stir bar, sealed with a rubber septum and purged with argon. DCM (80 mL) was added to give a yellow solution, then 2,6-lutidine (2.32 mL, 19.9 mmol, 2.00 eq) was added at 0 °C, followed by *tert*-butyldimethylsilyl triflate (3.43 mL, 14.9 mmol, 1.50 eq)

dropwise. The cooling bath was then removed and the yellow reaction solution allowed to warm towards ambient temperature over 20 min, at which time TLC indicated the complete consumption of starting material. Saturated aqueous $NaHCO_3$ and water were added and the biphasic mixture stirred; the layers were then separated and the aqueous phase extracted with Et_2O (2 x 100 mL). The combined organics were then rinsed with 1 N HCl (1 x 200 mL), water (1 x 200 mL), saturated aqueous $NaHCO_3$ (1 x 200 mL) and dried over Na_2SO_4. The organics were then decanted and concentrated under reduced pressure to reveal a viscous yellow oil that contained residual 2,6-lutidine. This crude material was then redissolved in Et_2O (200 mL), re-washed with 1 N HCl (2 x 100 mL), rinsed with water (1 x 150 mL) and saturated aqueous $NaHCO_3$ (1 x 150 mL), then dried over $MgSO_4$. Filtration and concentration under reduced pressure followed by stirring under high vacuum overnight gave the crude TBS ether as a viscous yellow oil. This material was then charged to a flame-dried 500-mL round bottom flask equipped with a magnetic stir bar; the flask was sealed with a rubber septum and purged with argon. DCM (100 mL) was added to give a stirred rich yellow solution. DIBAL-H (19.5 mL of a 1.0 M solution in hexanes, 19.5 mmol, 2.00 eq) was then added dropwise at -78 °C over 30 min to give a near-colorless solution. This solution was then immediately quenched with saturated aqueous Rochelle's salt at -78 °C; the resulting heterogeneous mixture was then allowed to warm to r.t. with stirring and stirred an additional 2 hrs to give two clear phases. The layers were separated and the aqueous phase extracted with DCM (2 x 100 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a yellow oil. Flash chromatography on silica gel (250 g) eluting with 9:1 hexanes / ethyl acetate gave **25** (3.18 g, 73%) as a colorless oil. Characterization agreed with that recently reported[39]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (d, J = 3.8 Hz, 1H), 6.65 (d, J = 2.3 Hz, 2H), 6.63 (d, J = 2.2 Hz, 1H), 5.14 (s, 4H), 4.73 (d, J = 6.7 Hz, 1H), 3.46 (s, 6H), 2.69 – 2.58 (m, 1H), 1.62 – 1.51 (m, 1H), 1.46 (dt, J = 13.5, 6.5 Hz, 1H), 1.04 (ddd, J = 13.6, 8.7, 4.7 Hz, 1H), 0.85 (s, 9H), 0.83 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.5 Hz, 3H), 0.01 (s, 3H), -0.20 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 204.3, 158.1, 145.0, 108.1, 104.1, 94.5, 75.8, 58.1, 55.9, 35.1, 25.7, 25.6, 23.1, 21.8, 18.0, -4.6, -5.2.

dimethyl ((*R*)-3-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-2-oxohexyl)phosphonate (5). To a 500-mL flame-dried, argon-purged round bottom flask containing a colorless, magnetically stirred solution of dimethyl methylphosphonate (2.39 mL, 22.0 mmol, 3.05 eq) in THF (35 mL) was added *n*-BuLi (8.64 mL of a 2.5 M solution in hexanes, 21.6 mmol, 3.00 eq) dropwise over 8 min at -78 °C; approximately halfway through this addition the reaction solution became opaque as a fine white suspension appeared to form. This suspension was stirred 1.5 hrs, at which time **25** (3.18 g, 7.22 mmol, 1.00 eq) was added dropwise over 25 min as a solution in THF (20 mL + 25 mL washings). The reaction mixture was then stirred an additional 10 min, at which time TLC showed complete consumption of **25**. The reaction was quenched via the addition of saturated aqueous NH_4Cl and Et_2O at -78 °C; the biphasic mixture was stirred as it was allowed to come to r.t. gradually. Water and additional Et_2O were added to obtain two clear phases; the layers were then separated and the aqueous phase extracted with Et_2O (2 x 150 mL). The organics were then combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to reveal the crude β-hydroxyphosphonate as a yellow oil. ^{1}H NMR indicated an inconsequential 1:1 mixture of diastereomers at C-13. This crude material was then charged to a 2000-mL round bottom flask equipped with a magnetic stir bar; the flask was charged with DCM (65 mL) to give a pale yellow solution. Dess-Martin periodinane (4.60 g, 10.8 mmol, 1.50 eq) was then added to the reaction flask against a stream of argon; the reaction vessel was capped with a rubber septum and the opaque white reaction suspension stirred 30 min, at which time TLC indicated complete consumption of starting material. The reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ and the resulting the biphasic mixture stirred. Water and solid $Na_2S_2O_3$ were then added portionwise with shaking until two clear phases were obtained. Layers were then separated and the aqueous phase extracted twice with Et_2O. The organics were combined, rinsed with water (1x) and brine (1x), then dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a milky, off-white oil. This crude material was then purified by flash chromatography on silica gel (250 g) eluting with ethyl acetate to give **5** (3.65 g, 90%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.65 (d, J = 2.2 Hz, 2H), 6.62 (t, J = 2.2 Hz, 1H), 5.15 (s, 4H), 4.50 (d, J = 8.5 Hz, 1H), 3.79 (dd, J = 11.2, 9.4 Hz, 6H), 3.46 (s, 6H), 3.35 (dd, J = 20.9, 15.1 Hz, 1H), 3.21 – 3.05 (m, 2H), 1.65 – 1.54 (m, 1H), 1.34 – 1.21 (m, 1H), 0.81 (s, 9H), 0.77 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.5 Hz, 3H), -0.05 (s, 3H), -0.25 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 205.1, 158.0, 145.1, 108.5, 104.3, 94.4, 78.5, 58.7, 55.9, 52.8 (d, J = 6.4 Hz), 52.7 (d, J = 6.3 Hz), 43.6 (d, J = 133 Hz), 37.7, 25.7, 25.4, 23.5, 21.6, 18.0, -4.8, -5.3. **$[\alpha]^{25}_D$** = -79.5° (*c* 0.38, $CDCl_3$). **IR** (neat): 2954 (alkane C-H stretch), 1712 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{26}H_{47}NaO_9PSi$ $[M + Na]^+$ 585.2619, found 585.2601.

(*2S*,*4S*,*6S*,*12R*,*E*)-12-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-methoxy-*N*,2,4,6,14-pentamethyl-11-oxopentadec-9-enamide (26). To a 500-mL flame-dried, argon-purged round bottom flask containing a magnetically stirred colorless solution of **20** (0.620 g, 2.39 mmol, 1.00 eq) in DCM (24 mL) was added Dess-Martin periodinane (1.52 g, 3.59 mmol, 1.50 eq). The flask was sealed with a rubber septum and the reaction mixture stirred; most of the solid dissolved to give a slightly cloudy, colorless mixture which was stirred 18 min, at which time TLC showed no starting material. Ethanol (0.07 mL, 1.20 mmol, 0.50 eq) was added to quench any excess periodinane, and the resulting mixture was stirred an additional 30 min. All volatiles were then evaporated under reduced pressure to leave a white residue which was sonicated with 1:1 hexanes / ethyl acetate. The resulting suspension was then passed through a plug of silica gel, eluting with 1:1 hexanes / ethyl acetate. The combined eluent was concentrated under reduced pressure into a 100-mL round bottom flask to reveal the crude aldehyde as a colorless oil. This flask was then charged with a magnetic stir bar and THF (12 mL) to give a colorless stirred solution. Barium hydroxide octahydrate (0.603 g, 1.91 mmol, 0.80 eq) which had been pre-treated at 120 °C for 2 hrs was added at room temperature. The reaction flask was sealed with a rubber septum and a wide-bore stainless steel needle inserted through the septum such that the needle reached the bottom of the flask. A vigorous stream of argon was bubbled through the white reaction suspension, vented by way of a second needle piercing the rubber septum which in turn was exhausted through a mineral oil bubbler. The reaction was thus stirred 25 min, at

which time **5** (1.34 g, 2.39 mmol, 1.00 eq) was added as a solution in THF (12 mL), followed by water (0.3 mL). The opaque white reaction mixture was stirred 1.5 hrs, during which time the reaction mixture obtained a gel-like consistency and TLC indicated complete consumption of the aldehyde starting material. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and Et_2O; the aqueous phase was then diluted with water, the layers separated, and the aqueous phase extracted with additional Et_2O (3 x 25 mL). The organics were then combined, rinsed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to reveal 1.51 g pale yellow oil. Flash chromatography on silica gel eluting with 1:1 hexanes/ethyl acetate gave a viscous, colorless oil. Azeotropic drying with DCM followed by heptane gave **26** (1.17 g, 70% over two steps) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89 (dt, J = 15.6, 6.9 Hz, 1H), 6.67 (d, J = 2.3 Hz, 2H), 6.62 (t, J = 2.2 Hz, 1H), 6.28 (d, J = 15.6 Hz, 1H), 5.15 (s, 4H), 4.58 (d, J = 9.2 Hz, 1H), 3.71 (s, 3H), 3.47 (s, 6H), 3.19 (s, 3H), 3.18 – 3.10 (m, 1H), 3.02 (s, 1H), 2.35 – 2.11 (m, 2H), 1.80 (ddd, J = 13.8, 9.4, 4.7 Hz, 1H), 1.66 – 1.41 (m, 4H), 1.35 – 1.17 (m, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.07 – 0.93 (m, 2H), 0.90 (d, J = 3.0 Hz, 3H), 0.88 (d, J = 2.9 Hz, 3H), 0.75 (s, 9H), 0.72 (app. d, J = 6.6 Hz, 4H), 0.69 (d, J = 6.6 Hz, 3H), -0.11 (s, 3H), -0.31 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 203.7, 157.9, 147.5, 145.8, 131.9, 108.7, 104.0, 94.5, 78.4 61.4, 55.9, 55.6, 45.1, 41.1, 38.4, 35.3, 32.6, 30.1, 29.7, 28.1, 25.7, 25.6, 23.7, 21.5, 20.5, 19.9, 18.5, 18.0, -4.8, -5.5. **$[\alpha]^{25}_D$** = -40.2° (c 0.84, $CHCl_3$). **IR** (neat): 2926 (alkane C-H stretch), 1665 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{38}H_{68}NO_8Si$ $[M + H]^+$ 694.4709, found 694.4701.

(*2S*,*4S*,*6S*,*9S*,*12R*)-12-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-9-hydroxy-*N*-methoxy-*N*,2,4,6,14-pentamethyl-11-oxopentadecanamide (27). A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with copper(I) chloride (6.8 mgs, 0.0687 mmol, 12 mol %) and (S,R_P)-Josiphos ethanol adduct (0.132 g, 0.173 mmol, 36 mol %), sealed with a rubber septum, and purged with argon. To this vial was then added dry, degassed toluene (1 mL) to give a dark orange, homogenous solution (henceforth "Solution A"). Solution A was stirred 30 min, then sodium *tert*-butoxide (0.05 mL of a 2.0 M solution in degassed THF, 0.0864 mmol, 18 mol %) was added. Meanwhile, a flame-dried 25-mL round bottom flask was charged with **26** (0.400 g, 0.576 mmol, 1.00 eq), bis(pinacolato)diboron (0.249 g, 0.979 mmol, 1.70 eq) and a magnetic stir bar, then sealed with a rubber septum and purged with argon. Dry, degassed toluene (3 mL) was then added to this flask, yielding a colorless, homogenous solution. To this solution was then added 0.83 mL of Solution A (a volume such that the reaction vessel contained 10 mol % CuCl and 30 mol % (S,R)-Josiphos), yielding a bright orange homogenous reaction solution which was stirred 19 hrs, at which time ^{1}H NMR of an aliquot indicated complete consumption of starting material. The reaction was quenched by the addition of saturated aqueous NH_4Cl and water. The layers were then separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to give a viscous orange oil. This crude material was then purified by flash chromatography on silica gel (50 g) eluting with 4:1 hexanes/ethyl acetate to give the boronate ester as a pale yellow oil; ^{1}H NMR analysis showed a 3:1 mixture of C-11 epimers which were carried on to the next step without further purification.

The mixed boronate ester isomers were charged to a 20-mL glass vial equipped with a magnetic stir bar, and THF (3 mL) was added to give a colorless solution. Sodium perborate tetrahydrate (0.412 g, 2.68 mmol, 5.00 eq) was added, followed by water (3 mL). The resulting brown mixture was stirred 13 hrs, at which time the reaction mixture was partitioned between water and EtOAc to obtain two phases. The layers were separated and the aqueous phase extracted with Et_2O (3 x 7 mL). The organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a yellow oil. This crude material was then purified by flash chromatography on silica (50 g) gel eluting with 4:1 hexanes / ethyl acetate to give recovered starting material (0.113 g) and pure **27** (0.077 g) as colorless oils; additional product contaminated with 11-*epi*-**27** was also isolated as a colorless oil. The recovered starting material was then oxidized as follows: to a colorless, magnetically stirred solution of recovered starting material in THF (5 mL) was added a freshly-prepared homogenous solution of sodium perborate tetrahydrate (0.105 g, 0.687 mmol, 5.00 eq) in water (5 mL). The resulting opaque colorless mixture was then stirred 15 hrs, at which time TLC indicated complete consumption of starting material. The reaction was then worked up in a manner directly analogous to that described above, giving a colorless oil which was then combined with the impure product obtained above to give a colorless oil (0.250 g). A second round of flash chromatography on silica (25 g) gel again eluting with 4:1 hexanes / ethyl acetate yielded further pure product (0.027 g), which was combined with that obtained above, giving pure **27** (0.094 g, 23% over two steps) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 – 6.62 (m, 3H), 5.18 (s, 4H), 4.61 (d, J = 9.0 Hz, 1H), 4.09 – 3.98 (m, 1H), 3.73 (s, 3H), 3.49 (s, 6H), 3.40 (s, 1H), 3.21 (s, 3H), 3.04 (s, 1H), 2.96 (ddd, J = 10.5, 8.9, 3.7 Hz, 1H), 2.75 – 2.68 (m, 2H), 1.82 (ddd, J = 13.7, 9.1, 4.9 Hz, 1H), 1.65 – 1.44 (m, 5H), 1.44 – 1.32 (m, 2H), 1.32 – 1.19 (m, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.09 – 0.94 (m, 2H), 0.91 (d, J = 7.4 Hz, 3H), 0.89 (d, J = 7.4 Hz, 3H), 0.83 (s, 9H), 0.78 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H), -0.02 (s, 3H), -0.24 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 216.2, 158.0, 145.1, 108.6, 104.2, 94.4, 78.1, 67.7, 61.4, 58.8, 55.9, 51.9, 45.3, 41.1, 38.2, 33.8, 32.6, 32.4, 29.8, 28.1, 25.8, 25.8, 23.7, 21.5, 20.7, 20.0, 18.4, 18.0, -4.8, -5.2. **$[\alpha]^{25}_D$** = -13.2 ° (c 1.1, $CHCl_3$). **IR** (neat): 3447 (alcohol O-H stretch), 1701 (ketone C=O stretch), 1663 (amide C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{38}H_{69}ClNO_9Si$ $[M + Cl]^-$ 746.4436, found 746.4421.

(*2S*,*4S*,*6S*,*9S*,*11S*,*12S*)-12-((*S*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-9,11-dihydroxy-*N*-methoxy-*N*,2,4,6,14-pentamethylpentadecanamide (28). To a 20-mL glass scintillation vial containing **28** (0.093 g, 0.131 mol, 1.00 eq) and equipped with a magnetic stir bar was added anhydrous THF (1.5 mL) to give a colorless solution. The vial was blown out with argon, capped with a rubber septum and cooled to -30 °C. BH_3•DMS (27 µL, 0.287 mmol, 2.20 eq) was then added via syringe through the rubber septum and the resulting solution stirred 14 hrs, at which time TLC indicated complete consumption of starting material. Saturated aqueous $NaHCO_3$ (0.75 mL) and 30% (w/w) H_2O_2 (0.70 mL) were added sequentially, with gas evolution observed upon the initial addition of base. The resulting mixture was stirred 15 min, then Et_2O and water were added and the biphasic mixture sonicated to give two clear phases. The layers were separated and the aqueous phase extracted with Et_2O (2 x 10 mL); the organics

were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the product (0.090 g, 96%) as a colorless oil was used in the subsequent step without further purification. ^{1}H NMR showed a 3:1 mixture of **28** and 13-*epi*-**28**; epimers were separated in the subsequent step. **^{1}H NMR** (400 MHz, $CDCl_3$) Major (*syn*) isomer: δ 6.66 (d, J = 2.3 Hz, 2H), 6.61 – 6.57 (m, 1H), 5.14 (s, 4H), 4.63 (d, J = 5.6 Hz, 1H), 3.97 (dd, J = 9.5, 5.1 Hz, 1H), 3.75 (br s, 1H), 3.70 (s, 3H), 3.46 (s, 6H), 3.18 (s, 3H), 3.01 (br s, 1H), 1.83 – 1.71 (m, 4H), 1.59 – 1.14 (m, 12H), 1.10 (d, J = 6.7 Hz, 3H), 1.07 – 0.95 (m, 1H), 0.90 (s, 9H), 0.89 – 0.82 (m, 9H), 0.75 (d, J = 6.5 Hz, 3H), 0.04 (s, 3H), -0.20 (s, 3H). Minor (*anti*) isomer: δ 6.74 – 6.52 (m, 3H), 5.14 (s, 4H), 4.82 (d, J = 3.5 Hz, 1H), 4.24 (d, J = 10.3 Hz, 1H), 3.76 (br s, 1H), 3.69 (s, 3H), 3.47 (s, 6H), 3.17 (s, 3H), 3.00 (br s, 1H), 1.85 – 1.10 (m, 16H), 1.09 (d, J = 6.7 Hz, 3H), 1.00 (m, 2H), 0.92 (s, 9H), 0.91 – 0.82 (m, 9H), 0.80 (d, J = 6.5 Hz, 3H), 0.08 (s, 3H), -0.17 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) Major (*syn*) isomer: δ 157.9, 146.5, 108.3, 103.6, 94.4, 74.6, 73.6, 61.4, 55.9, 49.5, 45.2, 41.2, 39.7, 36.1, 35.3, 32.7, 32.2, 29.9, 28.2, 25.8, 23.0, 22.3, 20.7, 20.0, 18.4, 18.1, -4.5, -5.2. Minor (*anti*) isomer: δ 158.0, 145.9, 107.9, 103.7, 94.5, 78.0, 69.3, 67.3, 61.4, 56.0, 55.9, 47.7, 45.1, 41.2, 40.4, 34.5, 34.3, 32.7, 29.8, 28.2, 25.9, 25.7, 23.4, 22.0, 20.6, 20.0, 18.4, 18.0, -4.5, -5.3. **HRMS** (ESI): calc'd for $C_{38}H_{71}NNaO_9Si$ $[M + Na]^+$ 736.4790, found 736.4848.

(*2S*,*4S*,*6S*)-8-((*4S*,*6S*)-6-((*1S*,*2S*)-1-(3,5-bis(methoxymethoxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-*N*-methoxy-*N*,2,4,6-tetramethyloctanamide (29). To a 20-mL glass scintillation vial equipped with a magnetic stir bar and containing **28** and 13-*epi*-**28** (0.051 g, 0.0714 mmol, 1.00 eq, 3:1 ratio of epimers) was added dry acetone (2 mL) to give a colorless solution. Sodium sulfate (0.101 g, 0.714 mmol, 10.0 eq) was added, followed by *p*-TsOH (1.2 mgs, delivered as 0.1 mL of a freshly-prepared solution of 12 mgs *p*-TsOH in 1 mL dry acetone, 0.00714 mmol, 10 mol %) to give a colorless suspension. This reaction mixture was then stirred 1 hr, at which time TLC indicated complete consumption of starting material. The reaction was quenched with saturated aqueous $NaHCO_3$ (12 drops) to obtain a near-neutral mixture which was then partitioned between EtOAc (7 mL) and water (5 mL). The resulting layers were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The organics were then combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil (0.051 g, 94%). This crude residue was then dissolved in anhydrous DCM (3.5 mL) and transferred to a 20-mL glass scintillation vial containing a magnetic stir bar. The vial was blown out with argon, capped with a rubber septum and cooled to 0 °C, at which time *p*-TsOH (0.6 mgs, delivered as 0.1 mL of a freshly-prepared solution of 5.8 mgs *p*-TsOH in 1 mL dry DCM, 0.00338 mmol, 5 mol %) was added. This colorless solution was then stirred 4 hr 15 min, at which time the solution was quenched with Et_3N (5 drops) and concentrated under reduced pressure to give **29** together with 13-*epi*-**28** as a pale yellow oil. This crude material was then dissolved in DCM and loaded directly onto a silica gel (2.5 g) plug, which was eluted with several plug volumes of 7:3 hexanes / ethyl acetate, giving pure **29** (0.036 g, 67%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.3 Hz, 2H), 6.58 (t, J = 2.2 Hz, 1H), 5.18 – 5.09 (m, 4H), 4.73 (d, J = 5.5 Hz, 1H), 3.96 – 3.83 (m, 1H), 3.70 (apparent s, 4H), 3.46 (s, 6H), 3.18 (s, 3H), 3.01 (s, 1H), 1.89 – 1.82 (m, 1H), 1.78 (ddd, J = 13.7, 9.0, 4.9 Hz, 1H), 1.59 – 1.42 (m, 5H), 1.38 (s, 3H), 1.34 (s, 3H), 1.34 – 1.15 (m, 5H), 1.10 (apparent d, J = 6.8 Hz, 5H), 1.01 (ddd, J = 13.6, 8.4, 5.2 Hz, 1H), 0.98 – 0.89 (m, 1H), 0.88 (s, 9H), 0.87 – 0.82 (m, 6H), 0.81 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H), 0.01 (s, 3H), -0.21 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 157.6, 146.3, 108.7, 103.3, 98.1, 94.5, 74.7, 69.2, 69.0, 61.4, 55.9, 48.4, 45.1, 41.1, 34.9, 34.0, 33.6, 32.6, 32.5, 31.9, 30.2, 28.1, 26.1, 25.8, 23.2, 22.5, 20.7, 20.0, 19.8, 18.4, 18.1, -4.7, -5.1. **$[\alpha]^{25}_D$** = -12.8° (*c* 0.95, $CHCl_3$). **IR** (neat): 2952 (alkane C-H stretch), 1669 (C=O stretch) cm^{-1}. **HRMS** (ESI): calc'd for $C_{41}H_{79}N_2O_9Si$ $[M + NH_4]^+$ 771.5549, found 771.5594.

Baulamcyin A (1). A 2-dram vial equipped with a magnetic stir bar and containing **29** (29.9 mgs, 0.0396 mmol, 1.00 eq) was sealed with a rubber septum, purged with argon and charged with Et_2O (2 mL) to give a colorless solution. Ethyl magnesium bromide (0.13 mL of a 3.0 M solution in diethyl ether, 0.396 mmol, 10.0 eq) was added dropwise at room temperature, and the resulting solution was stirred 19 hrs, at which time the reaction mixture was cooled to 0 °C and saturated aqueous NH_4Cl was added dropwise until gas evolution ceased. Water and additional diethyl ether were added and the resulting biphasic mixture stirred until two clear phases were obtained. The layers were then separated and the aqueous phase extracted with diethyl ether (3 x 10 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal the ethyl ketone (23.1 mg) as a colorless oil. A portion of this material was then deprotected as follows: a 20-mL glass vial equipped with a magnetic stir bar crude was charged with crude ethyl ketone (20.4 mg, 0.0282 mmol, 1.00 eq) followed by THF (1 mL) and methanol (1 mL) to give a colorless solution. 2 N HCl (1 mL) was then added dropwise to give an opaque white mixture which clarified upon stirring. The reaction solution was stirred 36 hrs, then quenched by the slow, portionwise addition of solid $NaHCO_3$ until gas evolution ceased and the pH of the reaction approached neutrality. EtOAc and water were added to give two clear phases, which were then separated. The aqueous phase was then extracted with EtOAc (4 x 10 mL). The organics were combined, dried over Na_2SO_4, decanted and concentrated under reduced pressure to reveal a colorless oil. This crude residue was dissolved in EtOAc and purified by PTLC eluting with 1:1 heptane / ethyl acetate to reveal baulamcyin A (8.9 mgs, 51% over two steps) as a colorless oil. Characterization matched that previously reported in the literature in all respects. **^{1}H NMR** (400 MHz, methanol-d4) δ 6.33 (d, J = 2.2 Hz, 2H), 6.15 (t, J = 2.2 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.00 (dt, J = 10.0, 3.4 Hz, 1H), 3.74 – 3.64 (m, 1H), 2.75 (dqd, J = 9.1, 6.9, 5.0 Hz, 1H), 2.64 – 2.242 (m, 2H), 1.88 (m, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.61 – 1.46 (m, 2H), 1.46 – 1.27 (m, 5H), 1.27 – 1.13 (m, 4H), 1.06 (d, J = 6.9 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H), 0.99 – 0.90 (m, 2H), 0.89 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, methanol-d4) δ 218.6, 159.3, 148.3, 106.3, 102.2, 76.9, 73.7, 72.9, 48.8, 46.6, 45.0, 42.0, 41.0, 37.6, 35.7, 35.4, 33.4, 31.2, 29.5, 26.9, 23.6, 22.8, 20.9, 20.6, 18.2, 8.1. **$[\alpha]^{25}_D$** = -15.3° (*c* 0.65, CH_3OH). **HRMS** (ESI): calc'd for $C_{28}H_{49}O_6$ $[M + H]^+$ 481.3524, found 481.3529.

ASSOCIATED CONTENT

Supporting Information.

Copies of ^{1}H and ^{13}C NMR spectra for newly-reported compounds.

This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*Robert M. Williams: robert.williams@colostate.edu
*David H. Sherman: davidhs@umich.edu

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