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Synthesis of Two Subunits of the Macrolide Domain of the Immunosuppressive Agent Sanglifehrin A and Assembly of a Macrolactone Precursor. Application of Masamune *anti*-Aldol Condensation

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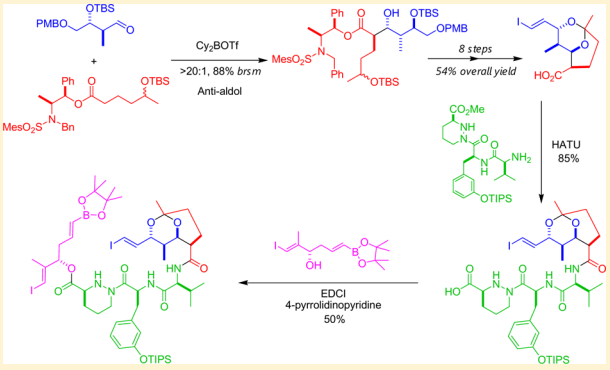
Supporting Information

ABSTRACT: Asymmetric *anti*-aldol coupling of a norephedrine-derived ester with an α-chiral aldehyde was used to synthesize a carboxylic acid representing the C13−C19 segment of the macrocyclic domain present in the immunosuppressive agent sanglifehrin A. Felkin addition set configuration at the C14−C17 stereotetrad in this unit in which hydroxyl functions at C15 and C17 were masked as an internal ketal. The carboxyl group of this segment was coupled to the *N*-terminus of the tripeptide portion (C1−N12) of sanglifehrin A macrolactone to assemble the C1−C19 domain. Synthesis of the C20−C25 subunit of sanglifehrin A containing a (23*S*) alcohol was completed via asymmetric allylation of (*E*)-3-iodo-2-methylprop-2-enal followed by oxidative cleavage of the terminal vinyl appendage and a Takai olefination with pinacol dichloromethylboronate. Esterification of this alcohol with a C1−C19 carboxylic acid furnished an open C1−C25 macrolactone precursor, but this substance failed to undergo macrocyclization via intramolecular Suzuki−Miyaura coupling.



INTRODUCTION

Naturally occurring substances that display immunosuppressive properties provide an opportunity for studying the immune response and for developing medicinal agents to treat host versus graft disease such as organ and tissue rejection that can occur after surgical transplantation.[1] The cyclic peptide cyclosporin A[2] and the macrolide rapamycin[3] are two natural products that have found widespread use as drugs for modifying the immune system by suppressing the formation of antibodies against cell surface antigens of transplanted tissue. Side effects of these drugs, such as nephrotoxicity associated with prolonged use of cyclosporin A,[4] remain a problem and have continued to drive the search for new, improved immunosuppressive agents. Sanglifehrins emerged from research conducted by scientists at Novartis on metabolites produced by a species of *Streptomyces* (sp A92-308110),[5] studies which led to the discovery that sanglifehrin A (SFA, **1**) inhibits T cell proliferation induced by IL-2 with an IC_{50} of 200 nM. Although SFA, like cyclosporin A, shows strong affinity for binding to the protein cyclophilin A, other data suggest that SFA has a novel mode of action and that its use as a molecular probe may lead to the discovery of a novel target involved in T cell activation.[6] These promising indications have stimulated efforts directed toward synthesis of **1**, resulting in total syntheses by Nicolaou[7] and Paquette[8] as well as numerous contributions from the Novartis group[9] and others[10] (Scheme 1).

The structure of SFA is characterized by two principal domains, a [5,5]-spirolactam segment and a 22-membered macrolide connected by a substituted nine-carbon chain.[11] The macrolide portion, for which **2** is an internally masked progenitor, contains a tripeptide (C1−N12) consisting of linked (*S*)-valine, (*S*)-*m*-hydroxyphenylalanine, and (*S*)-piperazic acid residues embedded within the ring. We recently reported a synthesis of tripeptide **3** using catalytic asymmetric phase-transfer to set absolute configuration in the *m*-hydroxyphenylalanine unit,[12] and our continuing program directed toward synthesis of the SFA macrolide has now focused on subunits **4** and **5**. A vinyl boronate at C20 of **4** and a disubstituted iodoalkene at C19 of **5** are incorporated into the synthesis plan for potential closure of the macrocycle at the C19−C20 bond via a Suzuki−Miyaura coupling[13] patterned on a successful application of the reaction in our synthesis of the macrolide rutamycin B.[14] Subunit **4** also carries functionality at its distal C25 terminus in the form of a trisubstituted iodoalkene for eventual linkage of the macrolactone domain **2** to the spirolactam portion of SFA via Stille coupling. A key strategic element of this synthesis plan is that Suzuki−Miyaura

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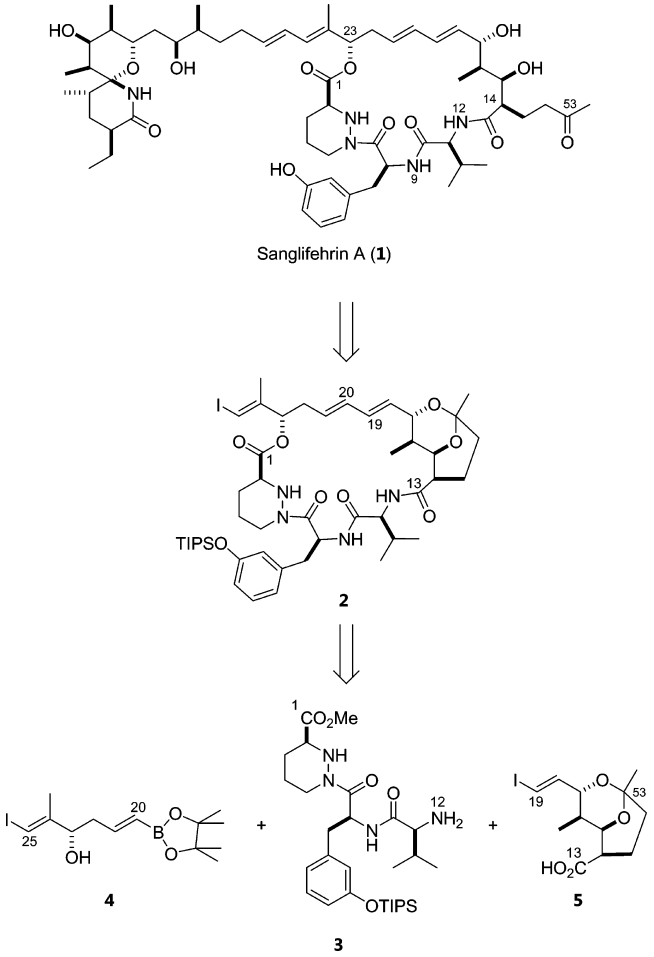
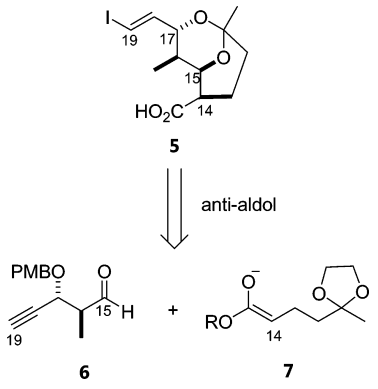
Scheme 1. Retrosynthetic Analysis of the Macrolactone Domain of Sanglifehrin A



Scheme 2. *anti*-Aldol Approach to the C13−C19 Segment of the SFA Macrolactone



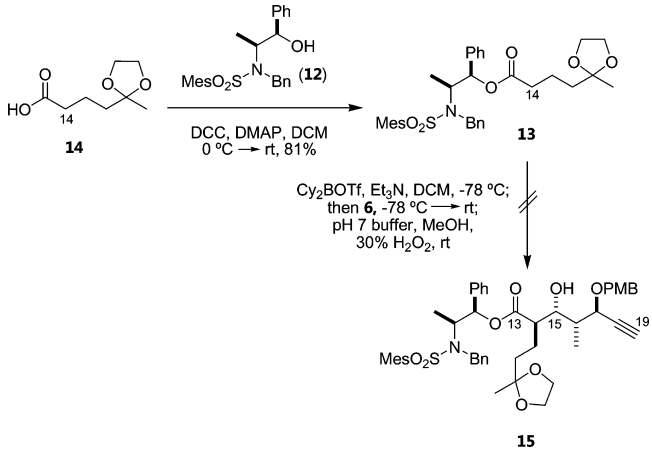
coupling of C19 with C20 will take precedence over a Stille reaction at the more sterically hindered terminus C25.

RESULTS AND DISCUSSION

First-Generation Synthesis of C13−C19 Fragment 5. A significant challenge associated with the synthesis of **5** involves setting the four contiguous stereogenic centers at C14−C17, and our first approach to this stereotetrad employed a strategy that merges chiral aldehyde **6** with a chiral ester enolate **7** to forge the C14−C15 bond via a matched stereoselective *anti*-aldol reaction (Scheme 2). Synthesis of **6** began from known propargylic alcohol **8**,[15] prepared in eight steps from (*R*)-methyl 3-hydroxy-2-methylpropionate (**9**, Scheme 3). After protection of the secondary alcohol of **8** as its PMB ether **10** by treatment with *p*-methoxybenzyl trichloroacetimidate, cleavage of the silyl ether followed by oxidation of the resulting primary alcohol **11** with Dess−Martin periodinane (DMP) afforded substituted 4-alkynal **6**.

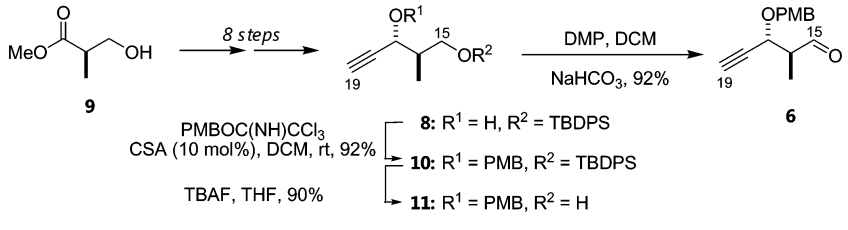
The partner **7** envisioned for aldol condensation with **6** (Scheme 2) contains a chiral adjuvant (R*) at the ester site that is programmed to steer bond formation toward an anti relationship of substituents at C14 and C15 while ensuring Felkin addition to the *re* face of the aldehyde carbonyl. Masamune has shown that enol dicyclohexylborinates generated from esters prepared from the norephedrine-derived alcohol **12** undergo aldol addition to aldehydes to give a high proportion of the anti product (Scheme 4).[16] Ketal ester **13** was

Scheme 4. Synthesis of Norephedrine-Derived Ester 13 and Attempted *anti*-Aldol Condensation with 6



therefore prepared from known carboxylic acid **14**[17] by esterification with **12** in the presence of DCC and DMAP, and its enol dicyclohexylborinate was reacted with **6**. Oxidative workup with hydrogen peroxide was expected to produce *anti*-aldol adduct **15**, but no more than a trace of this substance

Scheme 3. Synthesis of Aldehyde 6 for *anti*-Aldol Coupling



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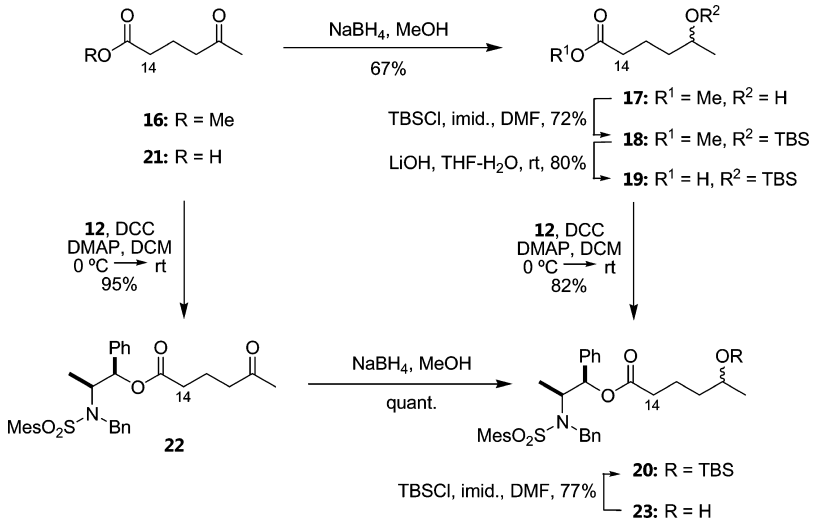
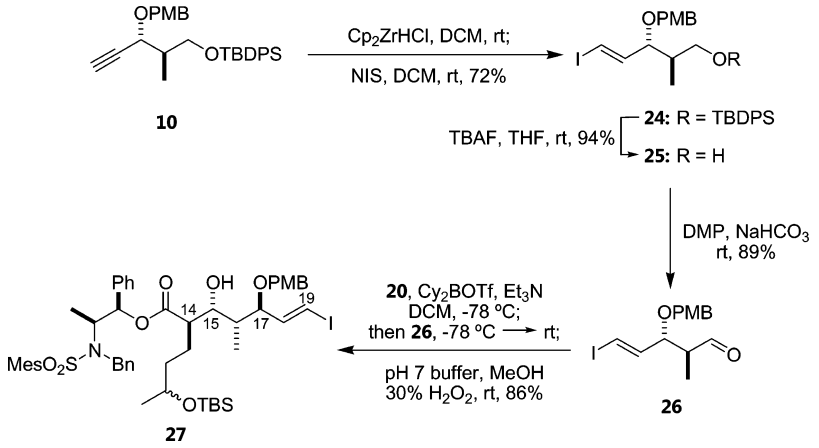
Scheme 5. Synthesis of Modified Norephedrine-Derived Ester 20



Scheme 6. Synthesis of C15−C19 Aldehyde 26 and Its *anti*-Aldol Coupling with 20



could be detected in the reaction mixture. Careful examination of the mixture revealed two explanations for this failure. First, it was apparent that the ketal moiety had been lost and that subsequent processes, probably catalyzed by triflic acid, had ensued. A second, more worrisome, problem was that the terminal alkyne of **6** had been compromised in spite of the fact that the reaction with **13** had been conducted under buffered conditions at low temperature. These observations mandated structural changes to both **6** and **13** if a successful *anti*-aldol coupling between these partners was to be realized, and a revised plan was developed that replaced the ketal of **13** and the alkyne of **6** with functionality compatible with our reaction conditions.

Modification of **13** was accomplished by replacing the ketal with a protected secondary alcohol in anticipation that subsequent oxidation would furnish the ketone needed for creating the internal ketal of **5**. For this realignment, two routes were pursued (Scheme 5). First, methyl 5-oxohexanoate (**16**) was reduced with sodium borohydride, and the resultant hydroxy ester **17** was protected as silyl ether **18**.[18] Saponification of **18** led to carboxylic acid **19**, which was esterified with **12** in the presence of DCC and DMAP to afford **20** as a 1:1 mixture of diastereomers. Altenatively, 5-oxohexanoic acid (**21**) was esterified with **12**, and the resultant keto ester **22** was reduced to alcohol **23** before silylation to **20**.

A logical tactic for avoiding complications with the alkyne function of **6** during its aldol-coupling sequence with **20** would be its conversion to the terminal (*E*)-iodoalkene of **5** at a stage earlier than originally planned. To this end, alkyne **10** was subjected to hydrozirconation−iodination[19] to give iodoalkene **24** (Scheme 6); after cleavage of the TBS ether, oxidation of alcohol **25** with Dess−Martin periodinane provided aldehyde **26**. Pleasingly, reaction of **26** with the dicyclohexylboron enolate of **20** delivered *anti*-aldol product **27** in excellent yield with a diastereomeric ratio favoring the (14*R*,15*R*) isomer in excess of 20:1.[20]

At this point, our blueprint for **27** specified conversion of the side-chain secondary silyl ether to a ketone and subsequent internal ketal formation with C15 and C17 hydroxyl functions. In order to advance this plan, it was first necessary to mask the C15 hydroxyl group, and this was accomplished by reacting PMB ether **27** with DDQ to give acetal **28** (Scheme 7).[21] The sulfonamido ester of **28** which hitherto had served as our chiral adjuvant was now requisitioned as a protecting group to avoid δ-lactone formation, while the side chain alcohol was liberated. Cleavage of the silyl ether of **28** with conventional reagents was more troublesome than expected, but the fluoride source tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F)[22] proved equal to the task and the resulting alcohol **29** was smoothly oxidized to ketone **30**. Exposure of **30** to *p*-

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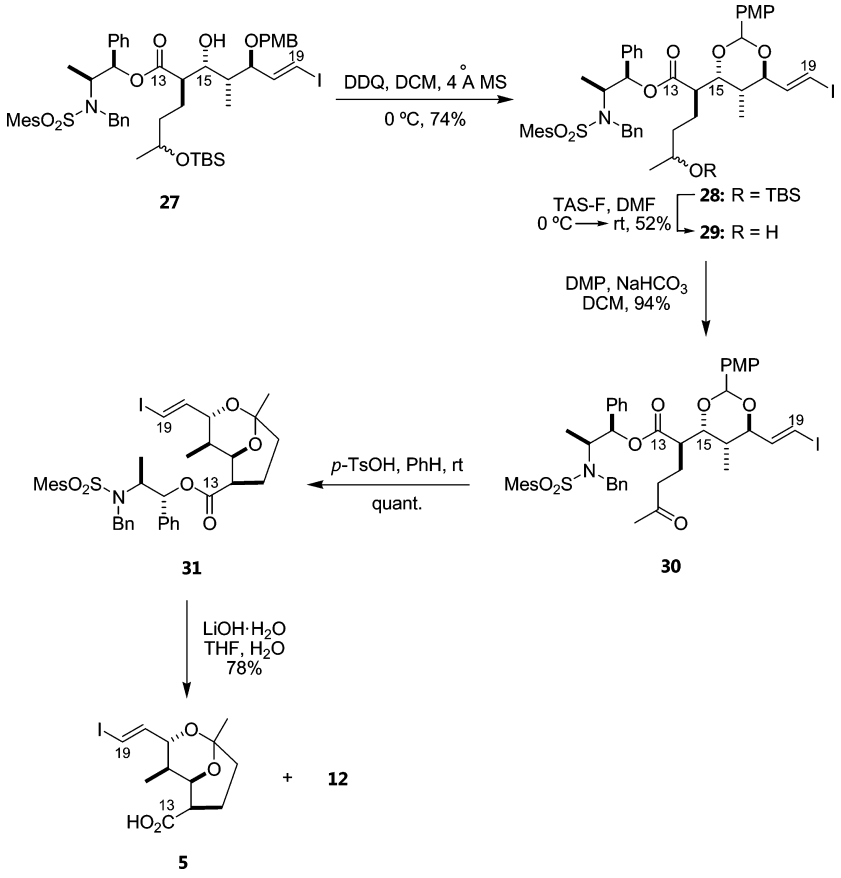
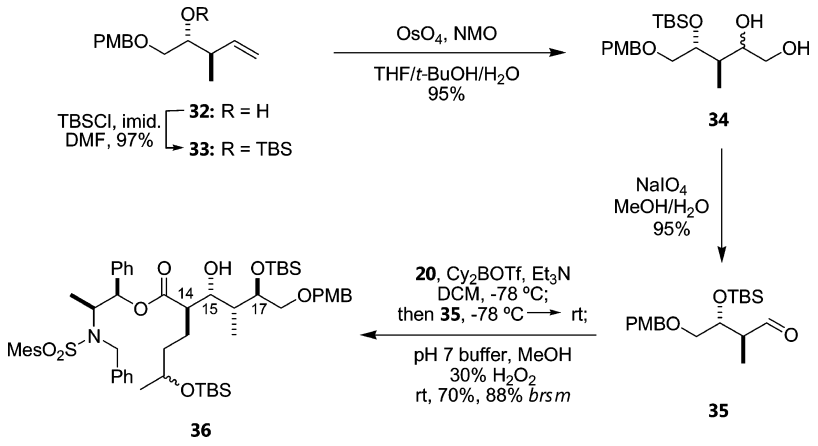
Scheme 7. Synthesis of the C13−C19 Segment of SFA Macrolactone as Internal Ketal 5



Scheme 8. Synthesis of Aldehyde 35 and Its *anti*-Aldol Coupling with 20



toluenesulfonic acid in benzene first unmasked the benzylidene acetal and then catalyzed internal ketal formation to furnish **31**. Saponification of ester **31** with lithium hydroxide afforded carboxylic acid **5** and also permitted recovery of alcohol **12**.

The lengthy sequence to **5** (17 steps from **9**) resulting in a 13% overall yield from **8** made a shorter, more efficient synthesis of this portion of the SFA macrolactone obligatory, and a second route to **5** was therefore explored which bypassed aldehyde **26** but retained our successful *anti*-aldol approach to the C14−C17 stereotetrad.

Second-Generation Route to 5. The new aldehyde partner deployed for *anti*-aldol coupling with **20** in our second pathway was obtained from alcohol **32**, prepared by asymmetric crotylation of [(*p*-methoxybenzyl)oxy]acetaldehyde[23] with (*E*)-crotyldiisopinylcampheylborane[24] (Scheme 8). Protection of **32** as silyl ether **33** was followed by dihydroxylation of the vinyl appendage and oxidative cleavage of the resultant diol **34** with sodium periodate. This afforded aldehyde **35** in excellent overall yield, whereas ozonolytic cleavage of **33** was complicated by reaction of ozone with the PMB ether and gave only a modest yield of **35**. Treatment of **35** with the enol dicyclohexylborinate of **20** under the double stereodifferentiating conditions used with **27** led to *anti*-aldol product **36** in good yield with a C14/C15 anti/syn ratio (>20:1) similar to that observed in **27**.

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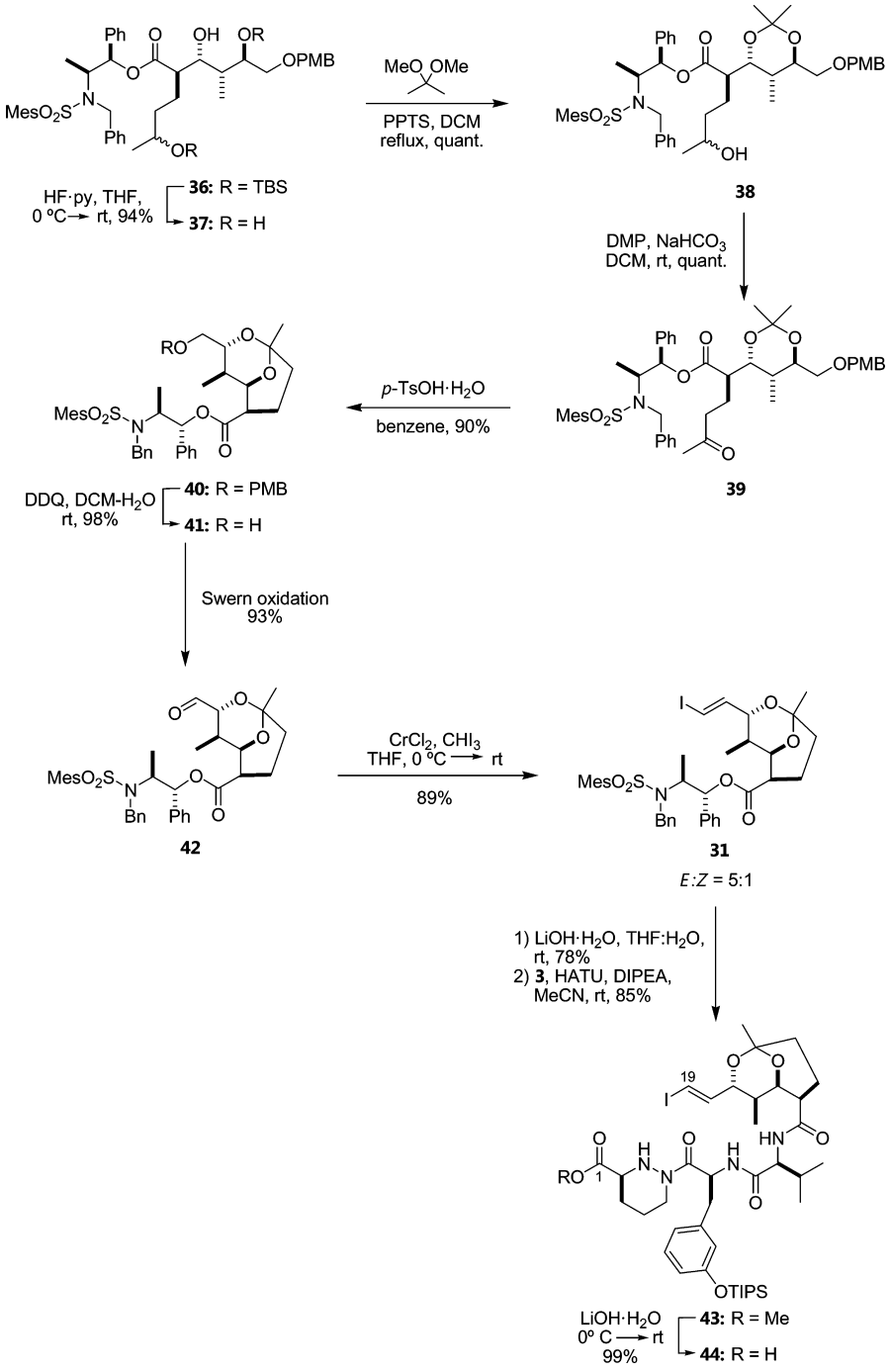
Scheme 9. Second-Generation Synthesis of the C13−C19 Segment 5 of SFA Macrolactone and Its Coupling with Tripeptide 3



Although selective deprotection of the C17 silyl ether of **36** could be achieved with TAS-F,[22] it proved more convenient to remove both silyl ethers from **36** with HF−pyridine and then protect triol **37** as acetonide **38** (Scheme 9). Oxidation of the remaining side chain alcohol gave C53 ketone **39** and exposure of this substance to *p*-toluenesulfonic acid resulted in benzene-catalyzed internal transketalization to **40**. Removal of PMB protection from **40** was carried out with DDQ, and oxidation of the resulting primary alcohol **41** furnished aldehyde **42**. A Takai reaction[25] of **42** with iodoform in the presence of chromium(II) chloride led to iodoalkene **31** as a separable 5:1 mixture of *E*:*Z* isomers; final saponification of this ester afforded **5** in an overall yield of 34% from **32**.

In addition to its more direct access to **5** (12 steps from *cis*-2-butene-1,4-diol), this second-generation route claims the advantage of an inexpensive starting material that enables practical scale-up of the synthesis. With carboxylic acid **5** in hand, its linkage to the *N*-terminus of previously synthesized tripeptide **3**[12] was tested as a first step in assembling a precursor to SFA macrolactone **2**. The reaction was carried out using *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU) as activating agent[26] in the presence of Hunig's base and gave coupled product **43** in good yield. Saponification of ester **43** with lithium hydroxide produced carboxylic acid **44** representing C1−C19 of the SFA macrolactone.

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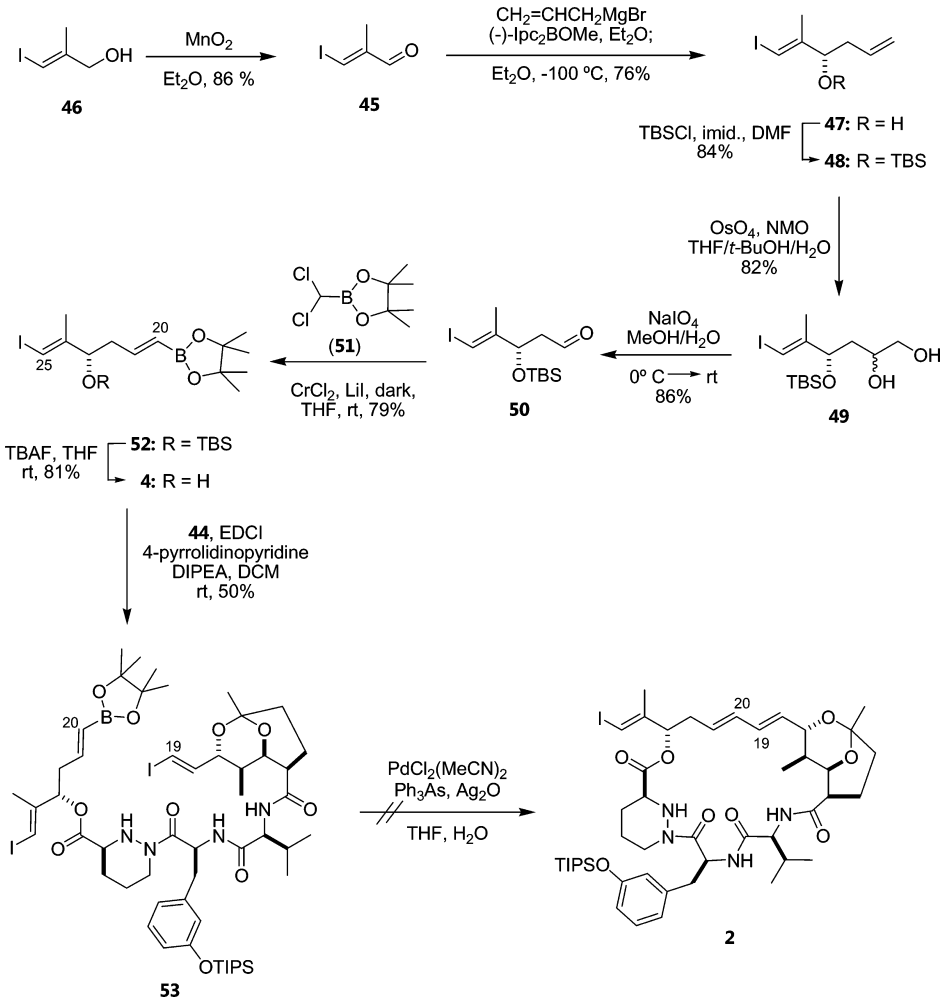
Scheme 10. Synthesis of the C20−C25 Portion 4 of SFA Macrolactone



Synthesis of C20−C25 Subunit 4 of SFA Macrolactone. The third subunit **4** (Scheme 1) comprising C20−C25 of SFA macrolactone required for esterification of C1−C19 carboxylic acid **44** bears a (23*S*) hydroxyl substituent as well as functional groups at each terminus for sequential connections at C19 and C25. Our route to **4** programmed asymmetric chain extension of 3-iodo-2-methylprop-2-enal (**45**) and commenced from known iodo alcohol **46**, the latter prepared by Negishi zirconation−methylation−iodination[27] of propargyl alcohol (Scheme 10). Oxidation of **46** with manganese dioxide led to aldehyde **45** which underwent asymmetric allylation in the presence of (−)-diisopinylcampheylmethoxyborane[28] to yield (*S*)-dienol **47**. Protection of **47** as silyl ether **48** followed by regioselective dihydroxylation of the terminal vinyl function afforded diol **49**, and oxidative cleavage of this diol with sodium periodate furnished aldehyde **50**. Takai olefination[25] of **50** with pinacol dichloromethylboronate **51**[29] in the presence of chromium(II) chloride and lithium iodide led to vinyl boronate **52**, and final cleavage of this silyl ether provided **4**. The sequence to **4** from propargyl alcohol required eight steps and resulted in a 25% overall yield from **45**.

Esterification of allylic alcohol **4** with carboxylic acid **44** afforded our macrolactone precursor **53** in modest yield, setting the stage for intramolecular Suzuki−Miyaura cross-coupling that would lead to **2**. Unfortunately, all attempts to close the macrocycle at C19−C20 using a variety of palladium species, including one that had demonstrated success with a somewhat similar substrate,[14] were unsuccessful. The outcome in every case was fragmentation of **53** that regenerated **44**. This result suggests that formation of a π-allylpalladium intermediate at the allylic ester connection in this structure supersedes oxidative addition needed to initiate Suzuki−Miyaura coupling and implies that a different order of subunit assembly will be required for reaching **2**. Investigations along this line will be reported in due course.

■ CONCLUSION

Two subunits representing C13−C19 and C20−C25 portions of sanglifehrin A macrolactone were synthesized in stereoselective fashion from readily available starting materials. An efficient method for constructing the C14−C17 stereotetrad of SFA macrolactone via asymmetric Masamune *anti*-aldol condensation was devised, and the intact C13−C19 segment was coupled to the *N*-terminus of the C1−N12 tripeptide moiety to complete a stereoselective synthesis of the C1−C19 domain of the lactone. Esterification this C1−C19 carboxylic acid with a C20−C25 alcohol produced an open, fully functionalized C1−C25 segment of SFA macrolactone, but attempts to close the macrocycle via intramolecular Suzuki−Miyaura cross-coupling were unsuccessful.

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EXPERIMENTAL SECTION

General Techniques. All reactions requiring anhydrous conditions were conducted in a flame-dried glass apparatus under an atmosphere of argon. THF, Et_2O, DCM, DMF, benzene, and MeCN were dried by passage through an activated alumina column under argon. DMSO was distilled from CaH_2 at 15 mmHg and stored over activated 4 Å molecular sieves. Anhydrous MeOH was freshly distilled from CaH_2. Preparative chromatographic separations were performed on silica gel (35−75 μm); reactions were followed by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with a UV lamp or phosphomolybdic acid. All commercially available reagents were used as received unless stated otherwise. Optical rotations were measured with a polarimeter at ambient temperature using a 1 mL capacity cell with 1 dm path length. Infrared (IR) spectra were recorded using a thin film supported on KBr disks or dispersed in a KBr pellet. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified on either a 300, 400, or 700 MHz spectrometer. Spectra were obtained on $CDCl_3$ solutions in a 5 mm diameter tube, and chemical shifts (δ) are quoted in parts per million (ppm) relative to the residual signals of chloroform (δH 7.26 ppm or δC 77.0 ppm). Multiplicities in the ^{1}H NMR spectra are described as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (J) are reported in hertz. High-resolution mass spectra (HRMS) were measured at 70 eV using a quadrupole analyzer and are reported with ion mass/charge (m/z) ratios as values in atomic mass units.

*(3R,4R)-3-[(tert-Butyldiphenylsilyl)oxy]-5-(4-methoxybenzyloxy)-4-methyl-1-pentyne (**10**).* To a solution of **8** (1.00 g, 2.83 mmol) and freshly prepared 4-methoxybenzyl trichloroacetimidate[30] (3.20 g, 11.32 mmol) in DCM (20 mL) at room temperature was added camphorsulfonic acid (65.8 mg, 0.283 mmol), and the mixture was stirred for 48 h. The mixture was filtered through a pad of Celite which was washed with a 1:2 DCM/hexane mixture (40 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (25 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (10% EtOAc/hexanes) to give **10** (1.23 g, 92%) as a colorless oil: $[\alpha]^{25}_D$ +28.8 (c 1.00, $CHCl_3$); IR (neat) 3287, 3070, 2958, 2930, 2857, 1612, 1513, 1428, 1248, 1112, 1036, 824, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H), 2.05−2.15 (m, 1H), 2.46 (d, J = 2.0 Hz, 1H), 3.64−3.71 (m, 2H), 3.82 (s, 3H), 4.38 (dd, J = 6.4 and 2.0 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.36−7.46 (m, 6H), 7.64−7.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.3, 19.3, 26.8, 40.4, 55.3, 65.0, 69.7, 70.4, 74.9, 81.4, 113.9, 127.6, 129.6, 130.0, 133.6, 133.7, 135.6, 135.7, 159.2; HRMS calcd for $C_{30}H_{36}NaO_3Si$ $[M + Na]^+$ m/z 495.2331, found m/z 495.2294.

*(2R,3R)-3-[(4-Methoxybenzyl)oxy]-2-methylpent-4-yn-1-ol (**11**).* To a solution of **10** (974 mg, 2.06 mmol) in THF (20 mL) at room temperature was added TBAF (2.47 mL of a 1 M solution in THF, 2.47 mmol), and the mixture was stirred for 14 h, after which it was diluted with Et_2O (80 mL) and washed with water (60 mL) and brine (60 mL). The solution was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the resultant oil via flash chromatography (10% EtOAc/hexanes) afforded **11** (433 mg, 90%) as a colorless oil: $[\alpha]^{21}_D$ +123.3 (c 1.00, $CHCl_3$); IR (neat) 3427 (br), 3292, 2931, 2867, 1613, 1586, 1514, 1464, 1303, 1247, 1174, 1033, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (d, J = 7.2 Hz, 3H), 2.06−2.14 (m, 1H), 2.55 (d, J = 2.4 Hz, 1H), 3.60 (dd, J = 11.2, 7.2 Hz, 1H), 3.72 (dd, J = 11.2, 3.6 Hz, 1H), 3.83 (s, 3H), 4.07 (dd, J = 7.2, 2.4 Hz, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.3, 40.5, 55.3, 66.1, 70.6, 72.5, 75.1, 81.4, 113.9, 129.3, 129.8, 159.4; HRMS calcd for $C_{14}H_{18}O_3$ $[M]^+$ m/z 234.1256, found m/z 234.1258.

*(2S,3R)-3-[(4-Methoxybenzyl)oxy]-2-methylpent-4-ynal (**6**).* To a mixture of **11** (25.5 mg, 0.109 mmol) and $NaHCO_3$ (27.4 mg, 0.327 mmol) in DCM (5.0 mL) at room temperature was added Dess−Martin periodinane (69.2 mg, 0.163 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM (3 × 5.0 mL). The combined extract was washed with water (5.0 mL) and brine (5.0 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification of the crude product by flash chromatography (10% EtOAc/hexanes) furnished **6** (23.2 mg, 92%) as a yellow oil: $[\alpha]^{22}_D$ +133.8 (c 1.00, $CHCl_3$); IR(neat) 3280, 2921, 2850, 2720, 2113, 1733, 1613, 1515, 1457, 1248, 1174, 1033, 818, 708, 517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (d, J = 7.2 Hz, 3H), 2.61 (d, J = 1.6 Hz, 1H), 2.71−2.78 (m, 1H), 3.83 (s, 3H), 4.32 (dd, J = 6.4, 1.6 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.79 (d, J = 11.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 10.5, 50.7, 55.3, 68.3, 70.5, 76.2, 80.2, 113.9, 129.1, 129.8, 159.5, 202.3; HRMS calcd for $C_{14}H_{16}NaO_3$ $[M + Na]^+$ m/z 255.0997, found m/z 255.0979.

*(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 5-(1,3-dioxalanyl)hexanoate (**13**).* DCC (1 M solution in DCM, 3.3 mL, 3.30 mmol) and DMAP (20.1 mg, 0.164 mmol) were added to a stirred solution of **14** (287 mg. 1.65 mmol) in DCM (5.0 mL), and the mixture was cooled to 0 °C. The solution was stirred for 5 min, **12** (698 mg, 1.65 mmol) was added in one portion, and stirring was continued at 0 °C for 45 min. The mixture was allowed to warm to room temperature, and was kept at that temperature for 19.5 h, at which point all of the carboxylic acid **14** had been consumed. The mixture was filtered, the filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography (10% EtOAc/hexanes) to give **13** (772 mg, 81%) as a colorless solid: mp 90−92 °C; $[\alpha]^{21}_D$ +14.5 (c 1.00, $CHCl_3$); IR(neat) 3063, 3031, 2981, 2940, 2880, 1744, 1604, 1496, 1454, 1379, 1328, 1205, 1149, 1055, 1061, 932, 859, 764, 731, 700, 659, 568, 537 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.15 (d, J = 6.8 Hz, 3H), 1.29 (s, 3H), 1.68−1.57 (m, 4H), 2.27−2.09 (m, 2H), 2.30 (s, 3H), 2.53 (s, 6H), 3.96−3.87 (m, 4H), 4.07 (dq, J = 6.8 and 4.0 Hz, 1H), 4.62 (d, J = 16.8 Hz, 1H), 4.76 (d, J = 16.8 Hz, 1H), 5.85 (d, J = 4.0 Hz, 1H), 6.90 (s, 2H), 6.94−6.92 (m, 2H), 7.37−7.18 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.9, 19.2, 20.9, 23.0, 23.8, 34.0, 38.2, 48.2, 56.7, 64.6, 78.0, 109.7, 126.0, 127.1, 127.4, 127.8, 128.3, 128.4, 132.2, 133.4, 138.6, 138.7, 140.2, 142.5, 171.7; HRMS calcd for $C_{33}H_{42}NO_6S$ $[M + H]^+$ m/z 580.2733, found m/z 580.2720.

*(1R,2S)-2-(N-Benzyl-2,4,6-trimethylsulfonamido)-1-phenylpropyl 5-(tert-Butyldimethylsilyloxy)hexanoate (**20**). Method A.* To a solution of **16** (178.9 mg, 1.24 mmol) in MeOH (6.2 mL) at room temperature was added $NaBH_4$ (51.6 mg, 1.37 mmol), and the mixture was stirred for 30 min. The reaction was quenched with water (3.0 mL), MeOH was removed under reduced pressure, and the residue was partitioned between Et_2O (6.0 mL) and water (6.0 mL). The aqueous phase was extracted with Et_2O (4 × 10 mL), and the combined organic extract was washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to afford **17** (121.0 mg, 67%) as a colorless oil: IR (neat) 3422 (br), 2963, 2926, 1739, 1437, 1373, 1250, 1201, 1168, 1129, 1018, 986, 943 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (d, J = 8.4 Hz, 3H), 1.45−1.52 (m, 2H), 1.65−1.80 (m, 3H), 2.36 (t, J = 9.6 Hz, 2H), 3.69 (s, 3H), 3.78−3.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.1, 23.5, 33.8, 38.6, 51.6, 67.5, 174.2. In order to avoid δ-lactone formation, this compound was used promptly for the next reaction.

To a solution of **17** (106.4 mg, 0.728 mmol) and imidazole (198.2 mg, 2.91 mmol) in DMF (7.3 mL) at room temperature was added TBSCl (219.5 mg, 1.46 mmol), and the mixture was stirred for 26 h. The mixture was diluted with Et_2O (8.0 mL) and was washed with 5% HCl (8 mL). The aqueous washing was extracted with Et_2O (3 × 8.0 mL), and the combined organic extract was washed with water (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL). The solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, and the crude product was purified by flash chromatography (15% EtOAc/hexanes) to give **18** (135.8 mg, 72%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.07 (s, 6H), 0.90 (s, 9H), 1.14 (d, J = 6.0 Hz, 3H) 1.41−1.48 (m, 2H), 1.60−1.75

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(m, 2H), 2.33 (t, J = 7.6 Hz, 2H), 3.69 (s, 3H), 3.80−3.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.8, −4.4, 21.2, 23.7, 25.7, 25.9, 34.1, 39.0, 51.5, 68.2, 174.2. This compound was used immediately for the next reaction.

To a solution of **18** (111.0 mg, 0.426 mmol) in THF (1.4 mL) and water (1.4 mL) at room temperature was added $LiOH·H_2O$ (26.8 mg, 0.639 mmol), and the mixture was stirred for 6 h. The solution was acidified with 1 M HCl, the aqueous phase was extracted with Et_2O (2 × 2.0 mL), and the combined organic extract was concentrated under reduced pressure to give **19** (84.2 mg, 80%) as a colorless oil: IR (neat) 3200−2600, 2957, 2930, 2858, 1712, 1473, 1463, 1414, 1374, 1361, 1255, 1137, 1096, 1042, 1005, 920, 836, 808, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.13 (s, 6H), 0.91 (s, 9H), 1.15 (d, J = 6.0 Hz, 3H), 1.45−1.53 (m, 2H), 1.62−1.79 (m, 2H), 2.39 (t, J = 7.2 Hz, 2H), 3.81−3.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.8, −4.4, 21.0, 23.7, 25.7, 25.9, 33.9, 38.8, 68.2. This compound was unstable and was used promptly for the next reaction.

DCC (1 M solution in DCM, 0.68 mL, 0.68 mmol) was added to a stirred solution of DMAP (4.2 mg, 0.034 mmol) and **12** (173.2 mg, 0.409 mmol) in DCM (1.7 mL), and the mixture was cooled to −5 °C. After 5 min, **19** (84.0 mg, 0.341 mmol) was added in one portion, and stirring was continued at −5 °C for 45 min. The mixture was allowed to warm to room temperature and was stirred for 21 h, after which all of **19** had been consumed. The mixture was filtered, the filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography (10% EtOAc/hexanes) to provide **20** (181.6 mg, 82%) as a colorless oil.

Method B. To a solution of **23** (275 mg, 0.511 mmol) and imidazole (139 mg, 2.046 mmol) in DMF (5.0 mL) was added TBSCl (154 mg, 1.023 mmol), and the mixture was stirred at room temperature for 24 h. The solution was diluted with Et_2O (10 mL) and was washed with 5% HCl (10 mL), water (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL). The solution was dried over anhydrous $MgSO_4$ and concentrated, and the crude product was purified by flash chromatography (10% EtOAc/hexanes) to give **20** (256 mg, 77%) as a colorless oil: IR (neat) 3069, 3032, 2949, 2928, 2856, 1745, 1604, 1496, 1471, 1455, 1379, 1327, 1207, 1155, 1096, 1017, 932, 858, 836, 808, 774, 729, 699, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.04, 0.05, and 0.06 (s, 6H), 0.90 and 0.90 (s, 9H), 1.09−1.16 (m, 3H), 1.14 and 1.16 (s, 3H), 1.30−1.39 (m, 2H), 1.48−1.53 (m, 1H), 1.57−1.68 (m, 1H), 2.05−2.24 (m, 2H), 2.31 (s, 3H), 2.54 (s, 6H), 3.74−3.78 (m, 1H), 4.05−4.09 (m, 1H), 4.63 (d, J = 16.8 Hz, 1H), 4.76 (d, J = 16.8 Hz, 1H), 5.86 (d, J = 3.6 Hz, 1H), 6.90 (s, 2H), 6.93−6.94 (m, 2H), 7.20−7.37 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.7, −4.4, 12.8, 12.9, 18.1, 20.9, 21.2, 23.0, 23.8, 25.9, 34.3, 34.3, 38.9, 39.0, 48.2, 56.7, 68.2, 68.2, 78.0 126.0, 127.1, 127.4, 127.4, 127.8, 128.4, 128.4, 132.2, 133.4, 138.6, 138.7, 138.7, 140.2, 142.5, 171.9; HRMS (ES) calcd for $C_{37}H_{54}NO_5SSi$ $[M + H]^+$ m/z 652.3492, found m/z 652.3511. This material was identical spectroscopically with the compound prepared by method A.

*(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 5-Oxohexanoate (**22**).* DCC (1 M solution in DCM, 10.0 mL, 10 mmol) was added to a stirred solution of DMAP (94.0 mg, 0.768 mmol) and **12** (3.26 g, 7.68 mmol) in DCM (50 mL), and the mixture was cooled to −5 °C. After the solution had been stirred for 5 min, **21** (1.00 g, 7.68 mmol) was added in one portion and stirring was continued at −5 °C for 45 min. The mixture was allowed to warm to room temperature and was stirred for 34 h, after which all of **21** had been consumed. The mixture was filtered, the filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography (30% EtOAc/hexanes) to give **22** (3.91 g, 95%) as a colorless amorphous solid: mp 105−107 °C; $[\alpha]^{25}_D$ +6.7 (c 2.22, $CHCl_3$); IR (neat) 3088, 3064, 3029, 2982, 2940, 1743, 1715, 1604, 1565, 1496, 1454, 1418, 1381, 1322, 1205, 1151, 1073, 1056, 1016, 931, 860, 763, 731, 700, 660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (d, J = 6.8 Hz, 3H), 1.72−1.80 (m, 2H), 2.06−2.14 (m, 1H), 2.09 (s, 3H), 2.19−2.27 (m, 1H), 2.30 (s, 3H), 2.38 (t, J = 7.2 Hz, 2H), 2.54 (s, 6H), 4.04−4.10 (m, 1H), 4.67 (q, J = 16.4 Hz, 2H), 5.88 (d, J = 4 Hz, 1H), 6.89 (s, 2H), 6.94−6.96 (m, 2H), 7.20−7.35 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.7, 18.5, 20.9, 23.0, 29.9, 32.9, 42.2, 48.1, 56.7, 78.2, 126.0, 127.1, 127.3, 127.9, 128.4, 132.2, 133.3, 138.5, 138.6, 140.2, 142.5, 171.5, 207.9; HRMS (ES) calcd for $C_{31}H_{37}NNaO_5S$ $[M + Na]^+$ m/z 558.2290, found m/z 558.2288.

*(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 5-Hydroxyhexanoate (**23**).* To a solution of **22** (300 mg, 0.560 mmol) in MeOH (22 mL) was added $NaBH_4$ (21.2 mg, 0.560 mmol), and the suspension was stirred at room temperature for 10 min. The reaction was quenched with saturated aqueous NH_4Cl (11 mL), and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic extract was dried over anhydrous $NaSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to provide **23** (301 mg, quant) as a colorless oil: IR (neat) 3560, 3412, 3064, 3032, 2935, 2857, 1743, 1604, 1496, 1454, 1324, 1152, 1016, 859, 765, 732, 701, 659, 567; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.12 (s, 3H), 1.13 (s, 3H), 1.33−1.40 (m, 2H), 1.50−1.69 (m, 3H), 2.09−2.26 (m, 2H), 2.30 (s, 3H), 2.53 (s, 6H), 3.73 (br s, 1H), 4.06−4.14 (m, 1H), 4.61 (d, J = 16.8 Hz, 1H) 4.73 (d, J = 16.8 Hz, 1H), 5.88 (d, J = 4.0 Hz, 1H), 6.89 (s, 2H), 6.94−6.96 (m, 2H), 7.21−7.38 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.9, 20.7, 20.9, 23.0, 23.5, 33.9, 38.4, 48.1, 56.7, 67.5, 78.1, 126.0, 127.4, 127.9, 128.4, 132.2, 133.3, 138.5, 138.6, 140.2, 142.5, 172.0; HRMS (ES) calcd for $C_{31}H_{40}NO_5S$ $[M + H]^+$ m/z 538.2627, found m/z 538.2623.

*((3R,4S,E)-5-[(tert-Butyldiphenylsilyl)oxy]-1-iodo-3-[(4-methoxybenzyl)oxy]-1-pentene (**24**).* To a solution of **10** (25.0 mg, 0.0635 mmol) in THF (0.80 mL) at room temperature was added bis(cyclopentadienyl)zirconium(IV) chlorohydride (65.5 mg, 0.254 mmol), and the suspension was stirred for 30 min. A solution of *N*-iodosuccinimide (57.1 mg, 0.254 mmol) in THF was added dropwise, and the dark brown suspension was stirred for 1 h. The resulting mixture was concentrated in vacuo to leave a brown solid which was purified by flash chromatography (5% Et_2O/hexanes) to yield **24** (22.9 mg, 72%) as a pale yellow oil: $[\alpha]^{26}_D$ +16.8 (c 1.00, $CHCl_3$); IR (neat) 3070, 2958, 2930, 2857, 1612, 1587, 1513, 1471, 1427, 1389, 1360, 1302, 1248, 1174, 1152, 1112, 1036, 952, 823, 740, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.92 (d, 3H, 6.8 Hz), 1.06 (s, 9H), 1.93−2.01 (m, 1H), 3.60 (dd, J = 6.0, 9.6 Hz, 1H), 3.72 (dd, J = 4.8, 9.6 Hz, 1H), 3.82 (s, 3H), 3.90 (t, J = 7.6 Hz, 1H), 4.26 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 11.2, 1H), 6.27 (d, J = 14.4 Hz, 1H), 6.49 (dd, J = 8.0, 14.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 1H), 7.33−7.46 (m, 6H), 7.66 (d, J = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.6, 19.3, 26.9, 39.9, 55.3, 65.1, 70.4, 78.6, 82.2, 113.8, 114.3, 127.7, 129.2, 129.6, 130.0, 130.3, 133.7, 133.8, 135.6, 145.2, 159.1; HRMS (ES) calcd for $C_{30}H_{37}INaO_3Si$ $[M + Na]^+$ m/z 623.1454, found m/z 623.1465.

*(2R,3R,E)-5-Iodo-3-[(4-methoxybenzyl)oxy]-2-methylpent-4-en-1-ol (**25**).* To a solution of **24** (13.9 mg, 0.0371 mmol) in THF (0.40 mL) at room temperature was added TBAF (1 M solution in THF, 50 μL, 0.0446 mmol), and the mixture was stirred for 6 h. The solution was diluted with Et_2O (1.6 mL) and was washed with H_2O (1.2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (10−30% EtOAc/hexanes) gave **25** (7.9 mg, 94%) as a pale yellow oil: $[\alpha]^{25}_D$ +89.2 (c 1.00, $CHCl_3$); IR (neat) 3421, 3039, 2953, 2924, 2844, 1717, 1611, 1586, 1559, 1514, 1464, 1387, 1302, 1248, 1173, 1108, 1062, 1035, 952, 820, 758, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.86 (d, J = 6.8 Hz, 3H), 1.84−1.92 (m, 1H), 2.63 (br s, 1H), 3.54−3.69 (m, 3H), 3.83 (s, 3H), 4.29 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 6.36 (d, J = 14.8 Hz, 1H), 6.50 (dd, J = 8.0, 14.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.5, 29.7, 39.5, 55.3, 66.6, 70.5, 79.5, 86.1, 114.0, 129.5, 145.4, 159.4; HRMS (CI) calcd for $C_{14}H_{19}IO_3$ $[M]^+$ m/z 362.0379, found m/z 362.0371.

*(2S,3R,E)-5-Iodo-3-[(4-methoxybenzyl)oxy]-2-methylpent-4-enal (**26**).* To a suspension of **25** (128 mg, 0.353 mmol) and $NaHCO_3$ (97 mg, 1.153 mmol) in DCM (8.8 mL) at room temperature was added DMP (245 mg, 0.577 mmol), and the mixture was stirred for 75 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (8.0 mL), and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic extract was washed with water (20 mL) and

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brine (20 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo left crude product which was purified by flash chromatography (10% EtOAc/hexanes) to afford **26** (113 mg, 89%) as a colorless oil: $[\alpha]^{20}_D$ +90.0 (*c* 1.00, $CHCl_3$); IR (neat) 3036, 2954, 2934, 2862, 2836, 2718, 1727, 1611, 1586, 1514, 1456, 1389, 1340, 1302, 1248, 1175, 1113, 1061, 1035, 953, 820, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (d, *J* = 6.8 Hz, 3H), 2.56−2.64 (m, 1H), 3.83 (s, 3H), 3.96 (t, *J* = 7.6 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 6.43−6.53 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 9.68 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 10.5, 50.0, 55.3, 70.5, 80.4, 81.7, 114.0, 129.5, 143.9, 159.4, 202.8; HRMS (EI) calcd for $C_{14}H_{17}IO_3$ $[M]^+$ *m*/*z* 360.0222, found *m*/*z* 360.0208.

*(2R,3R,4R,5R,E)-((1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 7-Iodo-5-[(4-methoxybenzyl)oxy]-2-[3-[(tert-butyldimethylsilyl)oxy]butyl]-3-hydroxy-4-methylhept-6-enoate (**27**).* To a solution of **20** (199 mg, 0.305 mmol) in DCM (1.4 mL) at room temperature was added triethylamine (0.1 mL, 0.666 mmol), and the mixture was cooled to −78 °C. A solution of freshly prepared dicyclohexylboron triflate (1 M solution in hexane, 0.67 mL, 0.67 mmol) was added dropwise over 2 min, and the resulting cloudy mixture was stirred at −78 °C for 2.5 h. A solution of **26** (100 mg, 0.278 mmol) in DCM (1.4 mL) was added dropwise, and the mixture was stirred for a further 8.5 h at −78 °C. The mixture was allowed to warm to room temperature over 1 h and the reaction was quenched by addition of pH 7 buffer solution (1.1 mL). After diluting the mixture with MeOH (5.6 mL), 30% aqueous H_2O_2 (0.6 mL) was added carefully and the mixture was stirred vigorously overnight. The mixture was concentrated under reduced pressure, the oily residue was partitioned between water (3.0 mL) and DCM (6.0 mL), and the aqueous layer was extracted with DCM (3 × 6.0 mL). The combined organic extract was washed with water (6.0 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (5% EtOAc/hexanes) yielded **27** (242 mg, 86%) as a colorless oil: IR (neat) 3461 (br), 3063, 3025, 2960, 2926, 2853, 1740, 1653, 1607, 1558, 1514, 1497, 1456, 1379, 1323, 1250, 1207, 1153, 1048, 1034, 953, 909, 836, 775, 730, 699, 661; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) −0.02 and −0.00 (s, 6H), 0.85 and 0.86 (s, 9H), 0.89−0.94 (m, 6H), 1.10−1.13 (m, 2H), 1.16−1.20 (m, 3H), 1.21−1.23 (m, 2H), 1.70−1.72 (m, 1H), 2.05 (br s, 1H), 2.33 (s, 3H), 2.40−2.43 (m, 1H), 2.49 (s, 3H), 2.51 (s, 3H), 3.48−3.55 and 3.56−3.62 (m, 1H), 3.69−3.75 (m, 1H), 3.79 and 3.79 (s, 3H), 4.02−4.11 (m, 1H), 4.18−4.23 (m, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.59−4.66 (m, 1H), 4.81−4.88 (m, 1H), 5.74−5.78 (m, 1H), 6.37 (dd, *J* = 3.2, 14.4 Hz, 1H), 6.53 (dd, *J* = 8.0, 14.4 Hz, 1H), 6.75−6.79 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 6.0 Hz, 2H), 7.12−7.26 (m, 8H), 7.36 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.4, −4.3, 9.6, 13.8, 14.1, 18.0, 20.9, 22.9, 25.8, 36.0 and 36.7, 38.5 and 38.7, 48.2, 49.3 and 49.6, 55.3, 56.7, 68.0 and 68.3, 70.6, 70.9, 77.9 and 78.2, 79.1, 83.7, 114.0, 126.5, 127.0, 127.9, 128.0, 128.1, 128.2, 129.4, 129.5, 132.1, 133.7, 138.4, 139.0 and 139.2, 140.4, 142.4, 145.5, 159.4, 174.5; HRMS (ES) calcd for $C_{51}H_{70}INNaO_8SSi$ $[M + Na]^+$ *m*/*z* 1034.3534, found *m*/*z* 1034.3481.

*(R)-((1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 5-[(tert-Butyldimethylsilyl)oxy]-2-((4R,5R,6R)-6-((E)-2-iodovinyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-hexanoate (**28**).* To a mixture of **27** (17.0 mg, 16.8 μmol) and 4 Å molecular sieves in DCM (0.4 mL) at 0 °C was added DDQ (6.2 mg, 20.2 μmol), and the resulting mixture was stirred at 0 °C for 2 h. The mixture was allowed to warm to room temperature and was stirred for 30 min, after which the reaction was quenched with saturated aqueous $NaHCO_3$ (0.4 mL). The aqueous layer was extracted with DCM (3 × 0.5 mL), and the combined organic extract was washed with brine (2.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Chromatography of the crude product (10% EtOAc/hexanes) gave **28** (12.6 mg, 74%) as a colorless oil: IR (neat) 3063, 3031, 2956, 2929, 2855, 1741, 1614, 1516, 1496, 1456, 1382, 1322, 1250, 1205, 1153, 1033, 1010, 910, 834, 775, 731, 698, 660, 566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) −0.03 and 0.00 (s, 6H), 0.84 and 0.85 (s, 9H), 0.88−0.93 (m, 6H), 1.07−1.28 (m, 5H), 1.98−2.09 (m, 1H), 2.31 (s, 9H), 2.31−2.40 (m, 1H), 2.68−2.79 (m, 1H), 3.45−3.51 and 3.58−3.67 (m, 2H), 3.72−3.80 (m, 1H), 3.83 (s, 3H), 3.90−3.94 (m, 2H), 4.33−4.37 (m, 2H), 4.55−4.59 (m, 1H), 5.63 (d, *J* = 4.8 Hz, 1H), 5.74 (d, *J* = 2.4 Hz, 1H), 6.46−6.51 (m, 1H), 6.60−6.65 (m, 3H), 6.88−6.89 (m, 2H), 7.03−7.07 (m, 2H), 7.13−7.14 (m, 1H), 7.24−7.30 (m, 6H), 7.36−7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.8 and −4.7, −4.4 and −4.3, 12.7 and 12.7, 14.1 and 14.3, 15.3, 18.0 and 18.1, 20.9, 22.8, 22.9 and 23.1, 23.9, 24.1 and 25.6, 25.8 and 25.9, 36.3, 36.5 and 37.2, 47.0, 47.4, 47.7, 55.3, 56.6, 65.9, 67.7, 68.1, 71.6, 76.7, 77.0, 77.4, 78.2, 78.4, 78.9, 82.2, 98.2, 113.7, 126.5 and 126.6, 127.2, 127.7, 127.8, 128.0, 128.3, 128.4, 131.2, 132.1, 133.2, 138.3, 139.3, 140.5, 142.4, 143.9, 160.0, 173.2 and 173.5; HRMS (ES) calcd for $C_{51}H_{68}INNaO_8SSi$ $[M + Na]^+$ *m*/*z* 1032.3377, found *m*/*z* 1032.3325.

*(R)-((1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 5-Hydroxy-2-((4R,5R,6R)-6-((E)-2-iodovinyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)hexanoate (**29**).* To a solution of **28** (9.4 mg, 9.9 μmol) in DMF (0.4 mL) at 0 °C was added TAS-F (6.8 mg, 24.7 μmol), and the mixture was stirred at 0 °C for 1.5 h. The solution was allowed to warm to room temperature, during which time progress of the reaction was monitored by TLC and further quantities (6.8 mg, 24.7 μmol) of TAS-F were added at 8 and 24 h intervals. After 47 h, the mixture was diluted with EtOAc (1.0 mL), and the solution was washed with pH 7 buffer (1.0 mL). The aqueous phase was extracted with EtOAc (3 × 2.0 mL), and the combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (40% EtOAc/hexanes) to provide **29** (4.3 mg, 52%) as a colorless oil: IR (neat) 3522 (br), 3063, 3025, 2960, 2923, 2851, 1738, 1615, 1602, 1518, 1496, 1455, 1402, 1379, 1317, 1250, 1172, 1152, 1118, 1055, 1032, 1010, 991, 910, 861, 831, 774, 731, 699, 660, 597, 566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.91−1.02 (m, 6H), 1.12−1.61 (m, 6H), 1.75−1.83 (m, 1H), 2.34 (s, 9H), 2.35−2.40 (m, 1H), 2.65−2.78 (m, 1H), 3.45−3.65 (m, 1H), 3.76 (s, 3H), 3.80−3.91 (m, 2H), 4.05−4.35 (m, 4H), 4.45−4.46 (m, 1H), 5.57−5.58 (m, 1H), 5.69 (s, 1H), 6.48−6.52 (m, 1H), 6.58−6.63 (m, 2H), 6.70−6.72 (m, 2H), 6.85−6.95 (m, 4H), 7.00−7.05 (m, 2H), 7.10−7.15 (m, 1H), 7.25−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.2 and 12.3, 14.3 and 14.3, 20.9, 22.9, 23.4 and 24.1, 23.7 and 23.7, 31.9, 35.6 and 36.2, 47.6 and 48.1, 47.9, 55.4, 56.2 and 56.3, 60.4, 67.0 and 67.6, 78.0, 80.4, 81.4, 96.6 and 96.6, 113.6, 126.8, 126.9, 127.2, 127.7, 128.1, 128.2, 128.6, 128.6, 130.3, 132.1, 133.3, 138.0, 139.1 and 139.3, 140.5, 142.4, 144.3, 160.2, 173.5 and 173.8; HRMS (ES) calcd for $C_{45}H_{54}INNaO_8S$ $[M + Na]^+$ *m*/*z* 918.2513, found *m*/*z* 918.2494.

*(R)-((1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 2-((4R,5R,6R)-6-((E)-2-Iodovinyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-5-oxohexanoate (**30**).* To a mixture of **29** (17.7 mg, 26.5 μmol) and $NaHCO_3$ (6.7 mg, 79.4 μmol) in DCM (1.3 mL) at room temperature was added DMP (16.8 mg, 39.7 μmol), and the mixture was stirred for 2 h. The reaction was quenched with water (1.0 mL), and the aqueous layer was extracted with DCM (3 × 1.0 mL). The combined organic extract was washed with brine (2.0 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (30% EtOAc/hexanes) gave **30** (16.6 mg, 94%) as a colorless oil: $[\alpha]^{20}_D$ +5.8 (*c* 1.00, $CHCl_3$); IR (neat) 3058, 3028, 2824, 2853, 1742, 1718, 1615, 1518, 1496, 1456, 1379, 1320, 1250, 1152, 1120, 1032, 1010, 860, 830, 760, 731, 700, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.89 (d, *J* = 4 Hz, 3H), 1.21−1.32 (m, 3H), 1.69−1.85 (m, 4H), 1.83 (s, 3H), 1.96−2.01 (m, 1H), 2.33 (s, 9H), 2.67−2.71 (m, 1H), 3.76 (s, 3H), 3.91−3.95 (m, 1H), 4.20−4.34 (m, 4H), 4.47 (d, *J* = 4 Hz, 1H), 5.61 (d, *J* = 6.4 Hz, 1H), 5.68 (s, 1H), 6.48−6.52 (m, 1H), 6.64−6.66 (m, 2H), 6.72−6.74 (m, 2H), 6.85−6.89 (m, 4H), 7.04−7.08 (m, 2H), 7.17−7.18 (m, 1H), 7.20−7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.2, 14.4, 20.9, 22.9, 29.7, 31.9, 39.6, 47.1, 47.7, 55.4, 56.0, 77.9, 80.3, 81.3, 96.5, 113.6, 127.0, 127.3, 127.7, 128.2, 128.3, 128.7, 130.2, 130.9, 132.1, 133.1, 138.0, 140.5, 142.5, 144.3, 160.2, 173.5, 207.0; HRMS (ES) calcd for $C_{45}H_{52}INNaO_8S$ $[M + Na]^+$ *m*/*z* 916.2356, found *m*/*z* 916.2391.

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*(4R,5R,6R,7R)-((1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 7-((E)-1,6-Dimethyl-8,9-dioxabicyclo[3.3.1]nonan-((E)-2-iodovinyl)-4-carboxylate (**31**). Method A.* To a solution of **30** (5.0 mg, 5.6 μmol) in benzene (0.6 mL) at room temperature was added *p*-TsOH·H_2O (0.1 mg, 0.6 μmol), and the mixture was stirred for 8 h. The solution was diluted with benzene (1.0 mL), and the reaction was quenched with saturated aqueous $NaHCO_3$ (1.0 mL). The separated organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash chromatography (30% EtOAc/hexanes) afforded **31** (4.6 mg, quant) as a yellow solid.

Method B. To a stirred suspension of $CrCl_2$ (163 mg, 1.326 mmol) in THF (2.7 mL) at 0 °C was added dropwise a solution of **42** (16.8 mg, 0.027 mmol) and CHI_3 (209 mg, 0.530 mmol) in THF (2.7 mL). The mixture was allowed to warm to room temperature and then was stirred vigorously for 1.5 h and diluted with Et_2O (3 mL). The reaction was quenched with half-saturated aqueous $Na_2S_2O_3$ (6.0 mL), the aqueous phase was extracted with Et_2O (6.0 mL), and the combined organic extract was washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification of the crude product by flash chromatography (10% EtOAc/hexanes) furnished **31** (18 mg, 89%, *E*:*Z* mixture 5:1) as a yellow oil: $[\alpha]^{20}_D$ +11.2 (*c* 0.50, $CHCl_3$); IR (neat) 3058, 3025, 2924, 2854, 1732, 1604, 1496, 1456, 1381, 1322, 1261, 1204, 1154, 1120, 1075, 1052, 1014, 932, 910, 880, 854, 763, 731, 699, 659 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ (ppm) 0.43 (d, *J* = 7.7 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.34 (s, 3H), 1.77−1.83 (m, 1H), 1.93−1.97 (m, 1H), 2.03−2.09 (m, 2H), 2.13−2.20 (m, 1H), 2.30 (s, 3H), 2.42 (s, 6H), 2.82 (dt, *J* = 13.3, 4.2 Hz, 1H), 4.21−4.23 (m, 1H), 4.38 (dd, *J* = 11.2, 6.3 Hz, 1H), 4.41−4.42 (m, 1H), 4.45 (d, *J* = 16.1 Hz, 1H), 4.67 (d, *J* = 16.1 Hz, 1H), 5.79 (d, *J* = 6.3 Hz, 1H), 6.34 (dd, *J* = 14.0, 6.3 Hz, 1H), 6.38 (d, 14.0 Hz, 1H), 6.85 (s, 2H), 6.93 (d, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.0 Hz, 1H), 7.27−7.29 (m, 5H); ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 12.1, 14.9, 20.9, 22.2, 22.9, 29.2, 33.8, 36.5, 43.7, 48.1, 56.4, 71.9, 78.2, 79.6, 80.0, 95.4, 127.0, 127.5, 127.9, 128.2, 128.3, 128.5, 132.1, 132.9, 137.4, 138.0, 140.3, 142.6, 145.7, 170.5; HRMS (ES) calcd for $C_{37}H_{44}INNaO_6S$ $[M + Na]^+$ *m*/*z* 780.1832, found *m*/*z* 780.1871. This material was identical spectroscopically with the compound prepared by method A.

*(4R,5R,6R,7R,E)-1,6-Dimethyl-8,9-dioxabicyclo[3.3.1]nonan-7-(2-iodovinyl)-4-carboxylic Acid (**5**).* To a solution of **31** (17.0 mg, 0.022 mmol) in THF (1.5 mL) and water (0.75 mL) at room temperature was added LiOH·H_2O (4.7 mg, 0.112 mmol), and the mixture was stirred for 4 d. Water (1.0 mL) was added, and the mixture was acidified to pH 5 with 1 M HCl. The aqueous solution was extracted with EtOAc (2.0 mL), and the extract was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to give **5** (6.2 mg, 78%, 83% brsm) as a white foam: $[\alpha]^{22}_D$ +14.1 (*c* 1.00, $CHCl_3$); IR (neat) 3500−2500 (br), 2954, 2923, 2845, 1722, 1604, 1423, 1381, 1114, 956, 792, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.91 (d, *J* = 6.8 Hz, 3H), 1.37 (s, 3H), 1.86−1.89 (m, 1H), 2.06−2.21 (m, 4H), 2.71 (br s, 1H), 4.40 (dd, *J* = 4.0, 10.8 Hz, 1H), 4.48 (d, *J* = 5.6 Hz, 1H), 6.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.6, 20.6, 29.5, 30.9, 35.9, 37.7, 72.3, 78.1, 79.9, 95.9, 145.2, 179.3; HRMS (CI) calcd for $C_{12}H_{17}IO_4$ $[M]^+$ *m*/*z* 352.0172, found *m*/*z* 352.0162.

*(2R,3R)-1-[(4-Methoxybenzyl)oxy]-3-methylpent-4-en-2-ol (**32**).* To a stirred suspension of potassium *tert*-butoxide (8.50 g, 69.55 mmol) in dry THF (90 mL) at −78 °C was added *trans*-2-butene (12.0 mL, 133.74 mmol) followed by *n*-BuLi (1.6 M in hexanes, 46.8 mL, 74.90 mmol). The resulting yellow solution was stirred at −45 °C for 0.5 h and then cooled to −78 °C, and a solution of (+)-*B*-methoxydiisopinocampheylborane (22.0 g, 69.55 mmol) in THF (90 mL) was added. The mixture was stirred for 1 h, BF_3·OEt_2 (9.24 mL, 74.90 mmol) was introduced slowly, and the solution was stirred for 0.5 h. A solution of [(*p*-methoxybenzyl)oxy]acetaldehyde (9.64 g, 53.50 mmol) in THF (90 mL) was added, and the mixture was stirred at −78 °C for 4 h. The reaction was quenched at −78 °C with NaOH (3N, 90 mL) and a 30% aqueous solution of H_2O_2 (90 mL), and the mixture was warmed slowly to room temperature and was stirred for 3 h. The aqueous layer was separated and extracted with Et_2O (3 × 250 mL), and the combined organic extract was washed with brine (250 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (4:1 DCM/Et_2O) to afford **32** (9.00 g, 71%) as a colorless oil: $[\alpha]^{20}_D$ +5.6 (*c* 3.33, $CHCl_3$); IR (neat) 3465 (br), 3073, 2954, 2906, 2856, 2829, 1612, 1586, 1514, 1464, 1302, 1248, 1174, 1098, 1035, 999, 917, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.06 (d, *J* = 6.8 Hz, 3H), 2.35−2.40 (m, 1H), 2.46 (br s, 1H), 3.41 (dd, *J* = 7.6, 9.6 Hz, 1H), 3.53 (dd, *J* = 3.2, 9.6 Hz, 1H), 3.68 (br s, 1H), 3.83 (s, 3H), 4.50 (s, 2H), 5.08 (s, 1H), 5.12 (d, *J* = 4.0 Hz, 1H), 5.81−5.90 (m, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 16.2, 40.8, 55.3, 72.3, 73.1, 73.5, 113.9, 115.4, 129.4, 130.2, 140.2, 159.3; HRMS (EI) calcd for $C_{14}H_{20}O_3$ $[M]^+$ *m*/*z* 236.1412, found *m*/*z* 236.1403.

*(3R,4R)-4-[(tert-Butyldimethylsilyl)oxy]-5-[(4-methoxybenzyl)-oxy]-3-methylpent-1-ene (**33**).* To a solution of **32** (1.60 g, 6.771 mmol) and imidazole (922 mg, 13.542 mmol) in DMF (13.5 mL) at room temperature was added TBSCl (1.33 g, 8.80 mmol), and the mixture was stirred at room temperature for 18 h. The reaction was quenched with water (15 mL), and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extract was washed with water (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography (10% EtOAc/hexanes) of the crude product gave **33** (2.29 g, 97%) as a colorless oil: $[\alpha]^{20}_D$ +3.5 (*c* 1.00, $CHCl_3$); IR (neat) 3073, 2956, 2929, 2897, 2857, 1613, 1587, 1514, 1471, 1463, 1361, 1302, 1249, 1173, 1120, 1038, 1005, 914, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.07 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.05 (d, *J* = 7.2 Hz, 3H), 2.42−2.45 (m, 1H), 3.33−3.42 (m, 2H), 3.74−3.78 (m, 1H), 3.84 (s, 3H), 4.41−4.48 (m, 2H), 5.00 (s, 1H), 5.04 (d, *J* = 3.2 Hz, 1H), 5.80−5.88 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.9, −4.2, 17.0, 18.2, 25.9, 41.6, 55.3, 72.9, 73.0, 74.8, 113.7, 114.7, 129.2, 130.6, 140.2, 159.1; HRMS (EI) calcd for $C_{20}H_{34}NaO_3Si$ $[M + Na]^+$ *m*/*z* 373.2175, found *m*/*z* 373.2163.

*(3R,4R)-4-[(tert-Butyldimethylsilyl)oxy]-5-[(4-methoxybenzyl)-oxy]-3-methylpentane-1,2-diol (**34**).* To a solution of **33** (7.00 g, 19.97 mmol) in THF (91 mL), *t*-BuOH (91 mL), and water (18 mL) at 0 °C was added NMO (3.51 g, 29.96 mmol). The mixture was stirred for 3 min, at which point a solution of OsO_4 (0.05 M in *t*-BuOH, 20.0 mL, 1.00 mmol) was added. The mixture was stirred for 47 h at room temperature, the reaction was quenched with saturated aqueous Na_2SO_3 (55 mL), and EtOAc (100 mL) and water (100 mL) were added. The separated aqueous phase was extracted with EtOAc (2 × 200 mL), and the extract was combined with the organic phase which was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (50% EtOAc/hexanes) gave **34** (7.31 g, 95%) as a colorless oil: IR (neat) 3406 (br), 2954, 2929, 2856, 1613, 1587, 1514, 1463, 1361, 1303, 1249, 1173, 1101, 1037, 1005, 953, 836, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.10 (s, 6H), 0.90 (s, 9H), 0.91 (d, *J* = 12.6 Hz, 3H), 1.86−1.93 (m, 1H), 2.40 (br s, 1H), 3.40−3.57 (m, 3H), 3.65−3.72 (m, 3H), 3.83 (s, 3H), 3.96−4.02 (m, 1H), 4.47 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −5.0, −4.5, 10.9 and 12.6, 18.0 and 18.1, 25.8, 30.3, 37.1 and 39.9, 55.3, 65.0 and 65.4, 71.6 and 72.5, 73.1 and 73.2, 73.8 and 74.0, 113.9, 129.4, 129.7, 159.4; HRMS (CI) calcd for $C_{20}H_{37}O_5Si$ $[M + H]^+$ *m*/*z* 385.2410, found *m*/*z* 385.2418.

*(2S,3R)-3-[(tert-Butyldimethylsilyl)oxy]-4-[(4-methoxybenzyl)-oxy]-2-methylbutanal (**35**).* To a solution of **34** (426.1 mg, 1.11 mmol) in MeOH (7.4 mL) and water (3.7 mL) at 0 °C was added $NaIO_4$ (1.42 g, 6.65 mmol), and the mixture was allowed to warm to room temperature with stirring over 1.5 h. The mixture was partitioned between DCM (13 mL) and water (13 mL), and the aqueous phase was extracted with DCM (20 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/hexanes) to give **35** (372.7 mg, 95%) as a colorless oil: $[\alpha]^{20}_D$ +39.5 (*c* 1.00, $CHCl_3$); IR (neat) 2955, 2931, 2857, 2709, 1725, 1613, 1586, 1514,

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1464, 1361, 1302, 1250, 1174, 1103, 1038, 1006, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.12 (d, J = 7.0 Hz, 3H), 2.58−2.65 (m, 1H), 3.47−3.49 (m, 2H), 3.83 (s, 3H), 4.11−4.15 (m, 1H), 4.45 (s, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 9.76 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −5.1, −4.4, 10.0, 18.0, 25.7, 50.0, 55.3, 71.7, 72.7, 73.1, 113.8, 129.3, 130.0, 159.3, 203.8; HRMS (ES) calcd for $C_{19}H_{32}NaO_4Si$ $[M + Na]^+$ m/z 375.1968, found m/z 375.1976.

*(2R,3R,4R,5R)-(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 5-[(tert-Butyldimethylsilyl)oxy]-3-hydroxy-6-[(4-methoxybenzyl)oxy]-4-methylhexanoate (**36**).* To a solution of **20** (1.06 g, 1.63 mmol) in DCM (8.0 mL) at room temperature was added Et_3N (0.54 mL, 3.90 mmol), and the mixture was cooled to −78 °C. A solution of dicyclohexylboron triflate (1 M solution in hexane, 3.58 mL, 3.58 mmol) was added dropwise over 5 min, and the resulting cloudy mixture was stirred at −78 °C for 2 h. A solution of **35** (0.57 g, 1.63 mmol) in DCM (4.0 mL) was added dropwise, and the mixture was stirred for a further 15.5 h at −78 °C. The mixture was allowed to warm to room temperature over 1 h, and the reaction was quenched by addition of pH 7 buffer solution (8.0 mL). The mixture was diluted with MeOH (40 mL), 30% aqueous H_2O_2 (4.0 mL) was added carefully, and the mixture was stirred vigorously overnight. The mixture was concentrated under reduced pressure, the residue was partitioned between water (20 mL) and DCM (40 mL), and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic extract was washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (5−10% EtOAc/hexanes) to provide **36** (1.14 g, 70%, 88% brsm) as a colorless foam: IR (neat) 3474 (br),3065, 3033, 2954, 2930, 2857, 1741, 1607, 1587, 1514, 1497, 1471, 1463, 1372, 1325, 1251, 1206, 1155, 1094, 1005, 910, 838, 776, 731, 699, 660, 597, 567 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ (ppm) −0.06 and −0.03 (s, 3H), −0.02 and −0.02 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.84 and 0.85 (s, 9H), 0.85 and 0.86 (s, 9H), 0.91−0.92 (m, 3H), 0.93−0.98 (m, 2H), 1.06−1.20 (m, 8H), 1.91−1.95 (m, 1H), 2.35 (s, 3H), 2.54 and 2.56 (s, 6H), 2.57−2.65 (m, 1H), 3.45−3.51 (m, 1H), 3.45−3.56, 3.56−3.59 and 3.60−3.62 (m, 2H), 3.81 (s, 3H), 3.88−3.95 (m, 1H), 3.88−4.00 (m, 1H), 4.15−4.20 (m, 1H), 4.44−4.46 (m, 2H), 4.80−4.85 (m, 1H), 5.02−5.08 (m, 1H), 5.61 (m, 1H), 6.66−6.68 (m, 2H), 6.86−6.89 (m, 2H), 6.95−7.00 (m, 2H), 7.01−7.03 (m, 2H), 7.03−7.05 (m, 1H), 7.20−7.27 (m, 5H), 7.48−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.8, −4.7, −4.4, −4.3, 9.8, 9.9, 13.4, 13.6, 14.1, 18.0, 20.9, 22.7, 22.9, 23.4, 24.0, 24.5, 25.8, 25.9, 31.6, 34.7, 35.6, 36.4, 37.2, 48.3, 49.6, 50.1, 55.2, 56.8, 67.9, 68.4, 71.7, 72.8, 73.0, 73.2, 74.9, 76.7, 77.1, 77.4, 78.1, 78.4, 126.2, 126.3, 126.7, 127.7, 127.9, 128.0, 128.1, 128.2, 129.4, 129.7, 132.2, 134.0, 134.1, 138.8, 140.0, 140.1, 140.5, 142.4, 159.3, 174.6, 175.1; HRMS (ES) calcd for $C_{56}H_{86}NO_9SSi_2$ $[M + H]^+$ m/z 1004.5562, found m/z 1004.5648.

*(2R,3R,4R,5R)-(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 3,5-Dihydroxy-2-(3-hydroxybutyl)-6-[(4-methoxybenzyl)oxy]-4-methylhexanoate (**37**).* To a solution of **36** (126 mg, 0.125 mmol) in THF (2.5 mL) at 0 °C was added dropwise HF·py complex (1.40 mL), and the mixture was stirred at 0 °C for 30 min. The solution was allowed to warm to room temperature over 30 min, cooled to 0 °C, and diluted with Et_2O (2.5 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (4.0 mL), and the aqueous phase was extracted with Et_2O (4.0 mL). The combined organic phase was washed with brine (5.0 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (50% EtOAc/hexanes) of the residue yielded **37** (91 mg, 94%) as a colorless foam: IR (neat) 3453 (br), 3063, 3025, 2954, 2924, 2854, 1738, 1610, 1514, 1455, 1378, 1318, 1249, 1152, 1034, 1011, 910, 853, 731, 699, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.95−0.96 (m, 3H), 1.00−1.02 (m, 3H), 1.21−1.23 (m, 3H), 1.35−1.50 (m, 2H), 1.50−1.63 (m, 2H), 1.72−1.79 (m, 1H), 2.33 (s, 3H), 2.49 (s, 6H), 2.61−2.69 (m, 1H), 3.50−3.56 (m, 3H), 3.79−3.85 (m, 1H), 3.83 (s, 3H), 4.09−4.20 (m, 2H), 4.50 (s, 2H), 4.60−4.69 (m, 1H), 4.80−4.87 (m, 1H), 5.80−5.82 (m, 1H), 6.80−6.83 (m, 2H), 6.89−6.91 (m, 4H), 7.14−7.17 (m, 2H), 7.20−7.29 (m, 6H), 7.36−7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 9.7, 14.0, 20.9, 22.9, 23.4, 24.9, 25.4, 35.7 and 36.2, 35.8, 48.1, 48.9, 49.4, 55.3, 56.6, 67.3 and 67.6, 71.9 and 72.1, 72.2, 73.1, 73.7, 78.2, 113.9, 126.6, 126.7, 127.1, 128.0, 128.2, 128.3, 129.5, 129.8, 132.1, 133.0, 138.3, 139.0, 140.4, 142.5, 159.4, 174.6 and 174.8; HRMS (ES) calcd for $C_{44}H_{57}NNaO_9S$ $[M + Na]^+$ m/z 798.3652, found m/z 798.3690.

*(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl (5R,S)-5-Hydroxy-2-((2R,3R,4R)-6-[(4-methoxybenzyl)-oxy]-2,2,5-trimethyl-1,3-dioxan-4-yl)hexanoate (**38**).* To a solution of **37** (218 mg, 0.281 mmol) and 2,2-dimethoxypropane (0.10 mL, 0.844 mmol) in DCM (7.0 mL) at room temperature was added PPTS (9.9 mg, 0.0394 mmol), and the mixture was heated at reflux for 3 h. The solution was cooled, and the reaction was quenched with saturated aqueous $NaHCO_3$ (7.0 mL). The aqueous phase was extracted with DCM (2 × 10.0 mL), and the combined organic extract was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to furnish **38** (245 mg, quant) as a colorless foam: IR (neat) 3470 (br), 3063, 3031, 2965, 2924, 2853, 1741, 1610, 1513, 1458, 1379, 1320, 1247, 1224, 1153, 1034, 1011, 930, 910, 854, 821, 732, 699, 660, 598, 567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.94−0.97 (m, 6H), 1.10−1.13 (m, 3H), 1.28−1.32 (m, 6H), 1.30−1.52 (m, 4H), 1.65 (br s, 1H) 1.75−1.85 (m, 1H), 2.36 (s, 3H), 2.49 and 2.50 (s, 6H), 2.57−2.70 (m, 1H), 3.40−3.52 (m, 4H), 3.82 (s, 3H), 3.90−4.02 (m, 2H), 4.01−4.55 (m, 2H), 4.56−4.61 and 4.91−4.97 (m, 2H), 5.74−5.75 (m, 1H), 6.67−6.71 (m, 2H), 6.89−6.91 (m, 2H), 6.95−6.96 (m, 2H), 7.09−7.12 (m, 2H), 7.18−7.19 (m, 1H), 7.26−7.32 (m, 5H), 7.46−7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 11.9 and 12.0, 14.1 and 14.2, 21.0, 22.9, 23.5 and 23.6, 23.7, 24.3 and 25.1, 24.7, 34.1, 36.1 and 36.7, 46.3 and 46.9, 48.1, 55.3, 46.5, 66.8 and 67.5, 70.7 and 70.8, 71.4, 73.1, 74.5, 78.1 and 78.2, 101.3, 113.8, 126.6 and 126.7, 127.3, 128.0, 128.1, 128.3, 128.4, 129.3, 130.3, 132.2, 133.4, 138.4, 139.2 and 139.3, 140.4, 142.5, 159.2, 173.9 and 174.2; HRMS (ES) calcd for $C_{47}H_{62}NO_9S$ $[M + H]^+$ m/z 816.4145, found m/z 816.4174.

*(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 2-((4R,5R,6R)-6-[(4-Methoxybenzyl)oxy]-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-oxohexanoate (**39**).* To a mixture of **38** (300 mg, 0.368 mmol) and $NaHCO_3$ (93 mg, 1.103 mmol) in DCM (18 mL) at room temperature was added DMP (234 mg, 0.551 mmol), and the mixture was stirred for 30 min. The reaction was quenched with water (18 mL), and the aqueous phase was extracted with DCM (2 × 25 mL). The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (30% EtOAc/hexanes) of the crude product gave **39** (302 mg, quant) as a colorless solid: mp 153−155 °C; $[\alpha]^{20}_D$ +35.2 (c 1.00, $CHCl_3$); IR (neat) 3058, 3025, 2924, 2854, 1740, 1718, 1610, 1513, 1456, 1380, 1322, 1247, 1153, 1035, 1011, 909, 854, 731, 699, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.99 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.40−1.51 (m, 1H), 1.67−1.76 (m, 1H), 1.81−1.83 (m, 1H), 1.82 (s, 3H), 2.03 (t, J = 7.6 Hz, 2H), 2.36 (s, 3H), 2.47 (s, 6H), 2.65 (dt, J = 3.6, 11.2 Hz, 1H), 3.46−3.55 (m, 3H), 3.83 (s, 3H), 3.97−4.01 (m, 2H), 4.51−4.56 (m, 2H), 4.58 (d, J = 16.4 Hz, 1H), 4.90 (d, J = 16.4 Hz, 1H), 5.78 (d, J = 5.6 Hz, 1H), 6.73 (d, J = 7.2 Hz, 2H), 6.89 (d, J = 7.2 Hz, 2H), 6.94 (s, 2H), 7.12−7.16 (m, 2H), 7.23−7.31 (m, 6H), 7.41−7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 11.8, 14.4, 20.9, 22.1, 22.9, 23.7, 24.7, 29.6, 34.1, 40.0, 45.8, 48.0, 55.3, 56.3, 70.7, 71.5, 73.0, 74.6, 77.8, 101.3, 113.8, 126.9, 127.3, 128.1, 128.2, 128.3, 128.6, 129.3, 130.4, 132.2, 133.3, 138.4, 138.9, 140.5, 142.6, 159.2, 173.7, 206.9; HRMS (ES) calcd for $C_{47}H_{59}NNaO_9S$ $[M + Na]^+$ m/z 836.3808, found m/z 836.3759.

*(4R,5R,6R,7R)-(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 1,6-Dimethyl-7-[[4-methoxybenzyl)oxy]-methyl]-8,9-dioxabicyclo[3.3.1]nonane-4-carboxylate (**40**).* To a solution of **39** (280 mg, 0.344 mmol) in benzene (17 mL) was added p-TsOH·H_2O (7 mg, 0.034 mmol), and the mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous phase was extracted with DCM (20 mL). The combined organic extract was

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washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography (10−20% EtOAc/hexanes) of the crude product afforded **40** (234 mg, 90%) as a colorless foam: $[\alpha]^{20}_D$ +8.2 (*c* 1.00, $CHCl_3$); IR (neat) 3058, 3031, 2982, 2938, 2851, 1737, 1610, 1513, 1496, 1455, 1381, 1324, 1248, 1152, 1101, 1055, 1032, 931, 912, 859, 818, 763, 731, 699, 672, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.40 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.35 (s, 3H), 1.71−1.80 (m, 1H), 1.83−1.95 (m, 1H), 2.05−2.25 (m, 3H), 2.30 (s, 3H), 2.42 (s, 6H), 2.79−2.83 (m, 1H), 3.29−3.32 (m, 1H), 3.49−3.43 (m, 1H), 3.82 (s, 3H), 4.10−4.15 (m, 1H), 4.15−4.19 (m, 1H), 4.35−4.39 (m, 1H), 4.46 (d, *J* = 16.4 Hz, 1H), 4.68 (d, *J* = 16.4 Hz, 1H), 4.51 (s, 2H), 5.78 (d, *J* = 6.4 Hz, 1H), 6.85−6.91 (m, 6H), 7.10−7.15 (m, 2H), 7.19−7.29 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 12.5, 14.8, 20.9, 22.2, 22.9, 29.4, 33.3, 34.0, 44.1, 48.1, 55.3, 56.5, 72.0, 72.5, 73.1, 76.4, 78.2, 95.1, 113.8, 127.0, 127.5, 127.9, 128.1, 128.2, 128.4, 129.3, 130.4, 132.1, 133.0, 137.5, 138.1, 140.4, 142.5, 159.2, 170.7; HRMS (ES) calcd for $C_{44}H_{53}NNaO_8S$ $[M + Na]^+$ *m*/*z* 778.3390, found *m*/*z* 778.3414.

*(4R,5R,6R,7R)-(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 1,6-Dimethyl-7-(hydroxymethyl)-8,9-dioxabicyclo[3.3.1]nonane-4-carboxylate (**41**).* To a solution of **40** (14.5 mg, 19.2 μmol) and DDQ (6.6 mg, 28.8 μmol) in DCM (0.95 mL) at room temperature was added water (0.05 mL), and the resulting brown-green solution was stirred for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (3.0 mL), and the aqueous layer was extracted with DCM (3 × 3.0 mL). The combined organic extract was washed with water (6.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to afford **41** (12 mg, 98%) as a colorless oil: $[\alpha]^{26}_D$ +16.2 (*c* 1.00, $CHCl_3$); IR (neat) 3492 (br), 3063, 3025, 2939, 1737, 1604, 1496, 1454, 1382, 1324, 1207, 1152, 1125, 992, 930, 860, 758, 699, 658 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ (ppm) 0.40 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 4.2 Hz, 3H), 1.33 (s, 3H), 1.77−1.82 (m, 1H), 1.91−1.95 (m, 1H), 2.01−2.10 (m, 1H), 2.15−2.27 (m, 2H), 2.30 (s, 3H), 2.42 (s, 6H), 2.80−2.85 (m, 1H), 3.30−3.36 (m, 1H), 3.59−3.62 (m, 1H), 4.04−4.08 (m, 1H), 4.19−4.22 (m, 1H), 4.38−4.41 (m, 1H), 4.45 (d, *J* = 16.4 Hz, 1H), 4.67 (d, *J* = 16.4 Hz, 1H), 5.80 (d, *J* = 6.0 Hz, 1H), 6.85 (s, 2H), 6.91 (d, *J* = 7.2 Hz, 2H), 7.14−7.16 (m, 2H), 7.25−7.29 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 12.3, 14.8, 20.9, 22.0, 22.9, 29.2, 29.7, 32.0, 34.0, 43.8, 48.1, 56.4, 64.3, 71.8, 76.7, 78.2, 95.2, 127.0, 127.5, 127.9, 128.2, 128.3, 128.5, 132.2, 132.9, 137.4, 138.1, 140.4, 142.6, 170.5; HRMS (ES) calcd for $C_{36}H_{45}NNaO_7S$ $[M + Na]^+$ *m*/*z* 658.2814, found *m*/*z* 658.2801.

*(4R,5R,6R,7R)-(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 1,6-Dimethyl-7-formyl-8,9-dioxabicyclo-[3.3.1]nonane-4-carboxylate (**42**).* To a solution of oxalyl chloride (27 μL, 0.301 mmol) in DCM (3.0 mL) at −78 °C was added dropwise a solution of DMSO (43 μL, 0.602 mmol) in DCM (1.2 mL), and the mixture was stirred for 10 min. A solution of **41** (160 mg, 0.252 mmol) in DCM (2.5 mL) was added slowly, the solution was stirred at −78 °C for 20 min, and Et_3N (0.19 mL) was added dropwise. The solution was stirred for 10 min and then was allowed to warm slowly to room temperature before the reaction was quenched with water (6.0 mL). The aqueous phase was extracted with DCM (6.0 mL), and the combined organic phase was washed with brine (6.0 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (25% EtOAc/hexanes) to give **42** (156 mg, 93%) as a colorless viscous oil: $[\alpha]^{26}_D$ +29.8 (*c* 1.00, $CHCl_3$); IR (neat) 3069, 3031, 2940, 2851, 2813, 1738, 1604, 1496, 1454, 1382, 1324, 1206, 1153, 1124, 1012, 930, 910, 860, 763, 731, 699, 658 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ (ppm) 0.44 (d, *J* = 7.7 Hz, 3H), 1.27 (d, *J* = 4.2 Hz, 3H), 1.39 (s, 3H), 1.76−1.82 (m, 1H), 1.95−2.01 (m, 1H), 2.06−2.12 (m, 2H), 2.22−2.27 (m, 1H), 2.30 (s, 3H), 2.45 (s, 6H), 2.75−2.78 (m, 1H), 4.18−4.22 (m, 2H), 4.44−4.45 (m, 1H), 4.47 (d, *J* = 16.1 Hz, 1H), 4.65 (d, *J* = 16.1 Hz, 1H), 5.82 (d, *J* = 5.6 Hz, 1H), 6.85 (s, 2H), 6.94 (d, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 2H), 7.23−7.29 (m, 6H), 9.33 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 11.6, 14.7, 20.9, 21.6, 22.9, 28.9, 30.4, 34.0, 43.6, 48.1, 56.3, 71.2, 78.3, 80.6, 95.1, 127.0, 127.5, 127.8, 128.3, 128.5, 132.2, 132.9, 137.2, 138.1, 140.3, 142.6, 170.1, 200.0; HRMS (ES) calcd for $C_{36}H_{43}NNaO_7S$ $[M + Na]^+$ *m*/*z* 656.2658, found *m*/*z* 656.2634.

*(S)-Methyl 1(S)-[2(S)-2-[(3R,4R,5R,6R)-3-(1,4-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane-6-carboxamido)-(E)-2-(iodovinyl)-3-methylbutanamido]-3-[3-[(triisopropylsilyl)oxy]phenyl]propanoyl]-piperazine-3-carboxylate (**43**).* To a solution of **3** (26.5 mg, 0.0753 mmol), **5** (50.8 mg, 0.0903 mmol), and HATU (30.0 mg, 0.0790 mmol) in MeCN (2.5 mL) at room temperature was added $(i\text{-}Pr)_2NEt$ (14.4 μL, 0.0828 mmol), and the mixture was stirred for 29 h. The reaction was quenched with pH 7 buffer (2.5 mL), the separated aqueous phase was extracted with DCM (3 × 3.0 mL), and the combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (70% EtOAc/hexanes with 1% Et_3N) afforded **43** (57.6 mg, 85%) as a yellow oil: $[\alpha]^{20}_D$ −22.5 (*c* 0.40, $CHCl_3$); IR (neat) 3298, 3216, 3063, 2944, 2867, 1745, 1639, 1604, 1584, 1547, 1485, 1443, 1384, 1277, 1235, 1164, 1128, 1004, 882, 844, 781, 734, 687 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ (ppm) 0.88 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.7 Hz, 18H), 1.23−1.29 (m, 5H), 1.44 (s, 3H), 1.45−1.56 (m, 2H), 1.69 (s, 2H), 1.75−1.85 (m, 2H), 1.94−2.01 (m, 2H), 2.05−2.25 (m, 4H), 2.64−2.66 (m, 2H), 2.83−2.96 (m, 2H), 3.73 (s, 3H), 4.26 (d, *J* = 5.6 Hz, 1H), 4.31 (dd, *J* = 4.9, 8.4 Hz, 1H), 4.45 (dd, *J* = 6.3, 11.2 Hz, 1H), 5.70−5.75 (m, 1H), 6.45−6.48 (m, 2H), 6.70 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 12.7, 12.8, 17.6, 18.0, 19.5, 22.8, 30.8, 31.0, 36.1, 38.7, 39.6, 41.9, 49.7, 52.2, 57.7, 58.1, 71.8, 79.0, 80.4, 95.7, 118.1, 121.4, 122.4, 129.2, 137.9, 145.3, 156.1, 170.1, 171.6, 172.2, 174.5; HRMS (ES) calcd for $C_{41}H_{66}IN_4O_8Si$ $[M + H]^+$ *m*/*z* 897.3695, found *m*/*z* 897.3726.

*(S)-1(S)-[2(S)-2-[(3R,4R,5R,6R)-3-(1,4-Dimethyl-2,9-dioxabicyclo-[3.3.1]nonane-6-carboxamido)-(E)-2-iodovinyl)-3-methylbutanamido]-3-[3-[(triisopropylsilyl)oxy]phenyl]propanoyl]piperazine-3-carboxylic Acid (**44**).* To a solution of **43** (3.7 mg, 4.13 μmol) in THF (0.22 mL) and water (60 μL) at 0 °C was added $LiOH{\cdot}H_2O$ (0.4 mg, 8.25 μmol), and the mixture was stirred at 0 °C for 1 h. The mixture was diluted with EtOAc (3.9 mL) and was washed with 1 M aqueous NaH_2PO_4 (2 × 1.0 mL). The separated organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give virtually pure **44** (3.6 mg, 99%) as a colorless viscous oil: IR (neat) 3300−2560 (br), 3061, 2926, 2864, 1750, 1632, 1601, 1584, 1485, 1443, 1384, 1273, 1231, 1163, 1122, 1007, 879, 836, 779, 732, 685 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ (ppm) 0.87 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.7 Hz, 18H), 1.23−1.29 (m, 5H), 1.42 (s, 3H), 1.57−1.65 (m, 2H), 1.69−2.09 (m, 6H), 2.12−2.25 (m, 2H), 2.66−2.67 (m, 1H), 2.89−2.99 (m, 3H), 3.69 (s, 1H), 4.26−4.30 (m, 2H), 4.45 (dd, *J* = 6.3, 11.2 Hz, 1H), 5.80 (br s, 1H), 6.47−6.51 (m, 2H), 6.68 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 12.7, 12.8, 17.6, 18.0, 19.5, 22.8, 30.8, 32.0, 36.1, 38.6, 39.6, 41.9, 50.1, 57.6, 58.1, 71.8, 79.0, 80.4, 95.7, 118.1, 121.4, 122.4, 129.3, 137.8, 145.2, 156.0, 170.7, 172.1, 173.4, 175.0; HRMS (ES) calcd for $C_{40}H_{64}IN_4O_8Si$ $[M + H]^+$ *m*/*z* 883.3538, found *m*/*z* 883.3541.

*(E)-3-Iodo-2-methylprop-2-en-1-al (**45**).* To a stirred suspension of zirconocene dichloride (652 mg, 2.23 mmol) in DCM (19 mL) at room temperature was added trimethylaluminum (2.57 mL), and the mixture was cooled to 0 °C. A solution of propargyl alcohol (500 mg, 8.92 mmol) in DCM (18 mL) was added via cannula, and the mixture was allowed to warm to room temperature and was stirred for 10 h. The mixture was cooled to −30 °C, a solution of I_2 (3.39 g, 13.38 mmol) in Et_2O (5.2 mL) was added, and the mixture was stirred at −30 °C for 30 min. The solution was allowed to warm to 0 °C and was poured into a mixture of saturated aqueous sodium potassium tartrate (26 mL) and pentane (173 mL), which was stirred vigorously for 10 min. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 43 mL). The combined organic extract was washed with brine (100 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave **46** (615.1 mg, 35%) as a yellow

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oil: IR (neat) 3335, 3074, 3047, 2915, 2864, 1732, 1683, 1621, 1446, 1377, 1276, 1253, 1147, 1069, 1013, 942, 883, 832, 776, 704, 667, 576 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.81 (br, 1H), 1.87 (s, 3H), 4.14 (s, 2H), 6.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.3, 67.2, 77.3, 147.2.

To a solution of **46** (270 mg, 1.52 mmol) in Et_2O (15 mL) at room temperature was added freshly prepared MnO_2 (1.32 g, 15.2 mmol), and the suspension was stirred vigorously for 10 h. The suspension was filtered and the filtrate was concentrated under reduced pressure to give **45** (230 mg, 86%) as a yellow oil: IR (neat) 3527, 3345, 3047, 2954, 2920, 2821, 2722, 1690, 1593, 1375, 1294, 1147, 1013, 831, 799, 695, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.93 (s, 3H), 7.82 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 16.5, 109.5, 150.8, 189.5; HRMS (CI) calcd for C_4H_5IO $[M]^+$ m/z 195.9385, found m/z 195.9381.

*(S,E)-1-Iodo-2-methylhexa-1,5-dien-3-ol (**47**).* Allylmagnesium bromide (3.60 mL, 1 M solution in Et_2O, 3.60 mmol) was added dropwise to a solution of (−)-*B*-methoxydiisopinylcampheylborane (1.13 g, 3.58 mmol) in Et_2O (16.0 mL) at 0 °C, and the pale gray suspension was allowed to warm to 25 °C over 1 h. The solvent was removed under reduced pressure, and pentane (4.0 mL) was added to the residual solid. The resulting slurry was stirred at 25 °C for 10 min, the solids were allowed to settle over 30 min, and the clear supernatant was transferred carefully to a flask via cannula. This process was repeated four times (4.0 mL of pentane each, 16.0 mL total volume), and the resulting solution was added dropwise over 1 h to a solution of **45** (540.0 mg, 2.76 mmol) in Et_2O (10 mL) at −100 °C. The solution was stirred for 1 h at −100 °C, MeOH (0.2 mL) was added, and the mixture was allowed to warm to room temperature over 40 min. Saturated aqueous $NaHCO_3$ (2.4 mL) and H_2O_2 (2.0 mL of a 30% aqueous solution) were added, and the mixture was stirred for 12 h. The layers were separated, the aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic extract was washed with saturated aqueous NH_4Cl (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (20% Et_2O/hexanes) of the residue gave **47** (497.7 mg, 76%) as a colorless oil: $[\alpha]^{20}_D$ −18.7 (*c* 0.9, $CHCl_3$); IR (neat) 3384, 3069, 2922, 1702, 1641, 1478, 1454, 1386, 1368, 1277, 1040, 995, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.85 (s, 3H), 1.86 (br s, 1H), 2.29−2.43 (m, 2H), 4.24 (dd, J = 5.2, 7.6 Hz, 1H), 5.16 (s, 1H), 5.19 (d, J = 3.2 Hz, 1H), 5.71−5.82 (m, 1H), 6.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.2, 39.9, 75.4, 78.4, 118.7, 133.6, 149.0; HRMS (CI) calcd for $C_7H_{11}IO$ $[M]^+$ m/z 237.9855, found m/z 237.9867.

*(S,E)-3-[(tert-Butyldimethylsilyl)oxy]-1-iodo-2-methylhexa-1,5-diene (**48**).* To a solution of **47** (138 mg, 0.581 mmol) in DMF (2.0 mL) at 0 °C was added imidazole (111 mg, 1.63 mmol) followed by TBSCl (149 mg, 0.988 mmol), and the mixture was stirred at room temperature for 7 h. The mixture was diluted with Et_2O (2.5 mL), and the reaction was quenched with saturated aqueous NH_4Cl (2.5 mL). The aqueous phase was extracted with Et_2O (2.5 mL), and the combined organic extract was washed with water (5.0 mL) and brine (5.0 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to leave crude product which was purified by flash chromatography (5% Et_2O/hexanes) to give **48** (172 mg, 84%) as a colorless oil: $[\alpha]^{20}_D$ −16.5 (*c* 1.00, $CHCl_3$); IR (neat) 3078, 2955, 2929, 2900, 2857, 1641, 1615, 1472, 1278, 1253, 1082, 1005, 939, 914, 836, 776, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.01 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.79 (s, 3H), 2.21−2.34 (m, 2H), 4.18 (t, J = 6.4 Hz, 1H), 5.03 (s, 1H), 5.07 (d, J = 5.2 Hz, 1H), 5.67−5.77 (m, 1H), 6.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −5.0, −4.9, 18.2, 19.7, 25.8, 41.0, 77.2, 77.6, 117.1, 134.4, 149.9; HRMS (CI) calcd for $C_{13}H_{25}IOSi$ $[M]^+$ m/z 352.0719, found m/z 352.0745.

*(2R,S,4S,5E)-4-[(tert-Butyldimethylsilyl)oxy]-6-iodo-5-methylhex-5-ene-1,2-diol (**49**).* To a solution of **48** (28.9 mg, 85.2 μmol) in a mixture of THF (0.39 mL), *t*-BuOH (0.39 mL), and water (80 μL) at 0 °C was added NMO (12.7 mg, 93.7 μmol) followed by OsO_4 (0.10 mL, 0.05 M in *t*-BuOH, 4.26 μmol, 0.05 equiv). The solution was stirred vigorously at room temperature for 15 h, and the reaction was quenched with saturated aqueous Na_2SO_3 (1.0 mL). The mixture was stirred for 2 h and partitioned between EtOAc (1.0 mL) and water (1.0 mL). The separated aqueous phase was extracted with EtOAc (2 × 4.0 mL), and the combined organic extract was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (50% Et_2O/hexanes) to give **49** (1:1 mixture, 25.9 mg, 82%) as a colorless oil: IR (neat) 3329 (br), 3063, 2956, 2928, 1638, 1611, 1469, 1274, 1250, 1087, 1001, 928, 914, 836, 776, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.40 and 0.52 (s, 3H), 0.11 and 0.12 (s, 3H), 0.92 (s, 9H), 1.65−1.68 (m, 2H), 1.80 and 1.81 (s, 3H), 3.43−3.52 (m, 1H), 3.60−3.62 (m, 1H), 3.83−3.88 (m, 1H), 4.46−4.52 (m, 1H), 6.30 and 6.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −5.4 and −5.3, −5.0 and −4.7, 18.0 and 18.1, 19.4 and 20.7, 25.8, 38.2 and 38.9, 66.7 and 67.0, 68.7 and 70.7, 74.9, 78.0 and 78.8, 149.2 and 149.7; HRMS (CI) calcd for $C_{13}H_{27}IO_3Si$ $[M]^+$ m/z 386.0774, found m/z 386.0734.

*(3S,4E)-3-[(tert-Butyldimethylsilyl)oxy]-5-iodo-4-methylpent-4-enal (**50**).* To a solution of **49** (20.0 mg, 0.052 mmol) in a mixture of MeOH (0.35 mL) and water (0.17 mL) at 0 °C was added $NaIO_4$ (66.4 mg, 0.311 mmol) portionwise over 5 min. The resulting slurry was stirred vigorously for 40 min at 25 °C and was partitioned between DCM (0.5 mL) and water (0.5 mL). The separated aqueous layer was extracted with DCM (0.5 mL), and the combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (20% Et_2O/hexanes) of the residue provided **50** (15.7 mg, 86%) as a pale yellow oil: $[\alpha]^{20}_D$ −29.8 (*c* 1.00, $CHCl_3$); IR (neat) 2954, 2929, 2857, 2719, 1728, 1618, 1472, 1362, 1279, 1255, 1095, 994, 838, 777, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.03 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.83 (d, J = 0.8 Hz, 3H), 2.47 (ddd, J = 2.0, 4.4, 16.0 Hz, 1H), 2.71 (ddd, J = 2.8, 8.0, 16.0 Hz, 1H), 4.72 (dd, J = 4.0, 8.0 Hz, 1H), 6.37 (d, J = 1.2 Hz, 1H), 9.76 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −5.3, −4.9, 18.1, 19.7, 25.6, 49.7, 72.6, 78.9, 148.8, 200.5; HRMS (CI) calcd for $C_{12}H_{23}IO_2Si$ $[M]^+$ m/z 354.0512, found m/z 354.0546.

*(3S,1E,5E)-3-[(tert-Butyldimethylsilyl)oxy]-1-iodo-2-methyl-6-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)-1,5-hexadiene (**52**).* To a stirred suspension of $CrCl_2$ (27.8 mg, 0.226 mmol) in THF (0.28 mL) at room temperature was added a solution of **50** (8.0 mg, 0.023 mmol) and **51** (11.9 mg, 0.056 mmol) in THF (0.06 mL). To this mixture was added dropwise a solution of LiI (15.2 mg, 0.113 mmol) in THF (0.03 mL), and the mixture was stirred vigorously in the dark for 12 h. The reaction was quenched with ice-cold water (1.0 mL), and the mixture was extracted with Et_2O (3 × 2.0 mL). The combined extract was washed with brine (2.0 mL), dried over anhydrous $MgSO_4$, and filtered. Removal of the solvent under reduced pressure left crude product which was purified by flash chromatography (10% EtOAc/hexanes) to furnish **52** (8.5 mg, 79%) as a colorless oil: $[\alpha]^{20}_D$ −9.6 (*c* 0.50, $CHCl_3$); IR (neat) 2976, 2954, 2928, 2856, 1640, 1363, 1321, 1253, 1146, 1082, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.00 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 1.27 (s, 12H), 1.79 (s, 3H), 2.29−2.42 (m, 2H), 4.22 (t, J = 6.0 Hz, 1H), 5.47 (d, J = 18.0 Hz, 1H), 6.20 (s, 1H), 6.53 (dt, J = 6.8, 18.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −5.1, −4.9, 18.2, 19.6, 24.7, 25.8, 43.2, 77.2, 77.6, 83.0, 149.9, 150.0; HRMS (ES) calcd for $C_{19}H_{37}BIO_3Si$ $[M + H]^+$ m/z 479.1650, found m/z 479.1524.

*(3S,1E,5E)-1-Iodo-2-methyl-6-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)hexa-1,5-dien-3-ol (**4**).* To a solution of **52** (5.7 mg, 0.012 mmol) in THF (0.24 mL) at room temperature was added TBAF (14 μL, 1 M solution in THF, 0.014 mmol), and the solution was stirred at room temperature for 12 h. The mixture was diluted with Et_2O (0.30 mL), washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (20% Et_2O/hexanes) afforded **4** (3.5 mg, 81%) as a colorless oil: $[\alpha]^{20}_D$ −12.1 (*c* 0.19, $CHCl_3$); IR (neat) 3453 (br), 2977, 2920, 2850, 1640, 1362, 1144, 996, 970, 850; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (s, 12H), 1.86 (s, 3H), 2.38−2.51 (m, 2H), 4.30 (br s, 1H), 5.59 (d, J = 10.0 Hz, 1H), 6.36 (s, 1H), 6.57 (dt, J = 4.0, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

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(ppm) 20.2, 24.8, 42.0, 75.1, 78.8, 83.3, 148.7, 149.0; HRMS (ES) calcd for $C_{13}H_{23}BIO_3$ $[M + H]^+$ m/z 365.0785, found m/z 365.0745.

*(S)-[(S,1E,5E)-1-Iodo-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,5-dien-3-yl] 1-[(S)-2-[(S)-2-[(3R,4R,5R,6R)-1,4-Dimethyl-2,9-dioxa-3-((E)-2-iodovinyl)bicyclo[3.3.1]nonane-6-carboxamido]-3-methylbutanamido]-3-[3-[(triisopropylsilyl)oxy]-phenyl]propanoyl]piperazine-3-carboxylate (**53**).* To a solution of **44** (16.2 mg, 18.3 μmol), **4** (13.4 mg, 36.7 μmol), EDC (7.0 mg, 36.7 μmol), and 4-pyrrolidinopyridine (0.3 mg, 36.7 μmol) in DCM (0.2 mL) at room temperature was added $(i\text{-Pr})_2$NEt (3.2 μL, 18.3 μmol), and the mixture was stirred for 23 h. The reaction was quenched with water (0.2 mL), and the separated aqueous layer was extracted with DCM (2 × 1.0 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (40% Et_2O/hexanes to 20% MeOH/DCM) to give **53** (11.2 mg, 50%) as a colorless oil: ^{1}H NMR (700 MHz, $CDCl_3$) δ (ppm) 0.85−0.92 (m, 9H), 1.11 (d, J = 7.0 Hz, 18H), 1.20−1.35 (m, 5H), 1.31 (s, 12H), 1.40−1.45 (m, 2H), 1.56−1.73 (m, 7H), 1.80−2.00 (m, 5H), 2.01−2.21 (m, 4H), 2.23−2.25 (m, 1H), 2.48−2.62 (m, 2H), 2.91−2.99 (m, 1H), 3.60−3.75 (m, 4H), 4.25−4.50 (m, 3H), 5.35−5.60 (m, 3H), 6.35−6.49 (m, 3H), 6.70−6.85 (m, 2H), 7.10−7.13 (m, 1H), 7.36−7.40 (m, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ (ppm) 12.7, 14.2, 17.4, 18.0, 19.5, 19.9, 20.2, 22.7, 23.0, 24.8, 25.6, 27.2, 29.5, 30.8, 31.3, 32.0, 35.9, 36.1, 38.8, 39.0, 42.0, 50.2, 57.8, 58.3, 70.6, 71.9, 78.8, 80.2, 81.9, 83.3, 95.7, 113.7, 118.1, 121.1, 122.2, 127.0, 129.2, 129.8, 130.0, 130.1, 137.8, 144.2, 145.3, 146.5, 146.9, 156.0, 170.1, 170.3, 172.0, 174.4; HRMS (ES) calcd for $C_{53}H_{84}BI_2N_4O_{10}Si$ $[M + H]^+$ m/z 1229.4139, found m/z 1229.4077.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Morris, R. E. In *New Immunosuppressive Modalities and Anti-rejection Approaches in Organ Transplantation*; Kupiec-Weglinski, J. W., Ed.; R. G. Landes: Austin, TX, 1994.

(2) Faulds, D.; Goa, K. L.; Benfield, P. *Drugs* **1993**, *45*, 953.

(3) (a) Vezina, D.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721. (b) Sehgal, S. N.; Baker, H.; Vezina, C. *J. Antibiot.* **1975**, *28*, 727.

(4) Busauschina, A.; Schnuelle, P.; van der Woude, F. J. *Transplant Proc.* **2004**, *36*, 229S.

(5) Sanglier, J. J.; Quesniaux, V.; Fehr, T.; Hofmann, H.; Mahnke, M.; Memmert, K.; Schuler, W.; Zenke, G.; Gschwind, L.; Maurer, C.; Schilling, W. *J. Antibiot.* **1999**, *52*, 466.

(6) Zhang, L.-H.; Liu, J. O. *J. Immunol.* **2001**, *166*, 5611.

(7) (a) Nicolaou, K. C.; Ohshima, T.; Murphy, F.; Barluenga, S.; Xu, J.; Winssinger, N. *Chem. Commun.* **1999**, 809. (b) Nicolaou, K. C.; Xu, J.; Murphy, F.; Barluenga, S.; Baudoin, O.; Wei, H.-X.; Gray, D. L. F.; Ohshima, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2447. (c) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830.

(8) (a) Paquette, L. A.; Konetzki, I.; Duan, M. *Tetrahedron Lett.* **1999**, *40*, 2109. (b) Duan, M.; Paquette, L. A. *Tetrahedron Lett.* **2000**, *41*, 3789. (c) Duan, M.; Paquette, L. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3632. (d) Paquette, L. A.; Duan, M. S.; Konetzki, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257.

(9) (a) Cabrejas, L. M. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2443. (b) Banteli, R.; Brun, L.; Hall, P.; Metternich, R. *Tetrahedron Lett.* **1999**, *40*, 2109. (c) Metternich, R.; Denni, D.; Thai, B.; Sedrani, R. *J. Org. Chem.* **1999**, *64*, 9632. (d) Wagner, J.; Cabrejas, L. M. M.; Grossmith, C. E.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255. (e) Hall, P.; Brun, J.; Denni, D.; Metternich, R. *Synlett* **2000**, 315.

(10) (a) Gurjar, M. K.; Chaudhuri, A. R. *Tetrahedron Lett.* **2002**, *43*, 2435. (b) Dias, L.; Salles, A. G. *Tetrahedron Lett.* **2006**, *47*, 2213.

(11) Fehr, T.; Kallen, J.; Oberer, L.; Sanglier, J. J.; Schilling, W. *J. Antibiot.* **1999**, *52*, 474.

(12) White, J. D.; Suttisintong, K. *J. Org. Chem.* **2013**, *78*, 2757.

(13) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.

(14) (a) White, J. D.; Tiller, T.; Ohba, Y.; Porter, W. J.; Jackson, R. W.; Wang, S.; Hanselmann, R. *Chem. Commun.* **1988**, 79. (b) White, J. D.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Ohba, Y.; Tiller, T.; Wang, S. *J. Org. Chem.* **2001**, *66*, 5217.

(15) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198 and references cited therein.

(16) Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

(17) Bates, H. A. *J. Am. Chem. Soc.* **1982**, *104*, 2490.

(18) Hernandez, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314.

(19) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

(20) The 1:1 mixture of stereoisomers at the side-chain silyl ether of **26** was easily distinguished from the anti:syn mixture at C14,C15 by ^{1}H and ^{13}C NMR.

(21) Toshima, K.; Jyojima, T.; Miyamoto, N.; Katohno, M.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **2001**, *66*, 1708.

(22) (a) Middleton, W. J. U.S. Patent 3,940,402, 1976; *Chem. Abstr.* **1976**, *85*, P6388j. (b) White, J. D.; Carter, R. G. Silyl Ethers. In *Science of Synthesis*; Thieme, Stuttgart, 2002; Vol. *4*, p 371.

(23) Yang, F.; Newsome, J. J.; Curran, D. P. *J. Am. Chem. Soc.* **2006**, *128*, 14200.

(24) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(25) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(26) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

(27) Negishi, E.; Vanhorn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501.

(28) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(29) Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137.

(30) Bernat, V.; Andre-Barres, C.; Baltas, M.; Saffon, N.; Vial, H. *Tetrahedron* **2008**, *64*, 9216.

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J. Org. Chem. 2015, 80, 2249−2262