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Phosphate Tether-Mediated Approach to the Formal Total Synthesis of (-)-Salicylihalamides A and B

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Abstract

A concise formal synthesis of the cytotoxic macrolides (-)-salicylihalamides A and B is reported. Key features of the synthetic strategy include a chemoselective hydroboration, highly regio- and diastereoselective methyl cuprate addition, Pd-catalyzed formate reduction, and an E-selective ring-closing metathesis to construct the 12-membered macrocycle subunit. Overall, two routes have been developed from a readily prepared bicyclic phosphate (4-steps), a 13-step route and a more efficient 9-step sequence relying on regioselective esterification of a key diol.

I. Introduction

The cytotoxic macrolides salicylihalamides A (**1a**) and B (**1b**) were isolated from the Australian marine sponge *Halicona* sp. in 1997 by Boyd, Erickson, and co-workers (Figure 1).[1] The structure and relative stereochemistry of the salicylihalamides (**1a** and **1b**) were determined by NMR spectroscopic methods and Mosher ester analysis. These natural products possess a 12-membered unsaturated benzolactone core and an unusual enamide side chain with differing geometry about the C_{17}-C_{18} double bond. In 2000, De Brabander and co-workers reassigned the absolute stereochemistry in the first total synthesis of **1a**.[2]

When screened against the NCI's 60 human tumor cell lines salicylihalamide A (**1a**) exhibited potent cytotoxicity with an average GI_{50} of 15 nM. In comparison to related benzolactone enamide natural products, e.g., apicularen A (**2**), salicylihalamide A (**1a**) exhibited the highest average sensitivity (GI_{50} = 7 nM) against melanoma cell lines.[1] Furthermore, salicylihalamide A (**1a**) possesses selective inhibition of mammalian vacuolar type H^+-ATPase (V-ATPase), with an IC_{50} value <1.0 nM against bovine brain V-ATPase.[3] Salicilyhalamide A has attracted significant attention from the synthetic community due to its potent antitumor properties, structural features, and the limited availability of the material from natural sources.[4]

Previously, we have reported the synthesis of polyol synthons utilizing the concept of multivalent activation with temporary phosphate tethers whereby a number of chemo-,

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Supporting Information Available. Spectroscopic data of new compounds is available free of charge via the Internet at http://pubs.acs.org.

regio- and stereoselective transformations were realized.[5] Herein, we disclose the formal total synthesis of salicylihalamide A in 13 steps from bicyclic phosphate **7** featuring the orthogonal protecting property of chiral aliphatic subunit **6** (overall, 17-step longest linear sequence (LLS)). A more efficient 9-step synthesis from **7** using regioselective esterification of diol **6** is also reported (overall, 13-step LLS), and is on par with the most efficient syntheses reported to date.[4]

Retrosynthetic analysis reveals the construction of the macrolactone (**3** or **4**) from the functionalized benzoic acid derivative **5**[6] and the chiral, non-racemic subunit **6** *via* an *E*-selective ring-closing metathesis (RCM) using Grubbs catalyst $(PCy_3)_2(Cl)_2Ru$=CHPh (cat-**A**)[7] in both routes (Scheme 1). The key intermediate **6** can be derived from enantiomerically pure bicyclic phosphate (*R*,*R*,R_P)-**7**[5a] (derived via desymmetrization with Grubbs catalyst $(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh (cat-**B**))[8] involving a chemoselective hydroboration, highly regio- and diastereoselective cuprate addition, cross metathesis (CM) with the Hoveyda-Grubbs second generation catalyst (cat-**C**),[9] and a Pd-catalyzed reductive allylic transposition using ammonium formate.[5f]

Results and Discussion

II. Construction of *P*-chiral, nonracemic bicyclo[4.3.1]phosphate 7

1,3-*anti*-diol **8**[10] was desymmetrized using a phosphate tether-mediated RCM reaction to construct the *P*-chiral bicyclo[4.3.1]phosphate **7** (Scheme 2).[5] In this strategy, pseudo-*C2*-symmetric phosphate triester **9** was synthesized from a 2-step sequential tripodal coupling[5c] of diol **8** and allyl alcohol with $POCl_3$ or via a one-pot diol coupling with allyl tetraisopropylphosphorodiamidite followed by oxidation.[5g] The method is predicated on facile RCM occurring via the chair conformer bearing a *cis*-diaxial relationship in the reacting olefin pairs (allylphosphate ester *cis* to the terminal olefin) to yield the *P*-chiral, non-racemic bicyclo[4.3.1]-phosphate (*R*,*R*,R_p)-**7**.

III. Synthesis of chiral subunit 6

Scheme 3 details the construction of advanced intermediate **6**, which is the required intermediate in both routes from the bicycle (*R*,*R*,R_P)-**7**. The primary alcohol **10** was obtained via a chemoselective hydroboration of the exocyclic olefin of (*R*,*R*,R_P)-**7,** followed by oxidation under mild conditions ($NaBO_3$•$4H_2O$) developed by Burke and co-workers.[11] Subsequent PMB-ether formation using the *p*-methoxybenzyl trichloroacetimidate derived from *p*-MeOPhCH_2OH produced **11** in 92% yield. A regio- and diastereoselective S_N2' cuprate addition (CuCN•2LiCl, Me_2Zn, *dr* = >95:5) to **11**, followed by methylation ($TMSCHN_2$ and MeOH) afforded monocyclic phosphate ester **12** in excellent overall yield (85%). The orthogonal alignment of the π* arbital (C=C) to the σ* orbital (C-O-PO) and concave nature of the bicycle **11** explains the regio and diastereoselectivity of the S_N2' reaction.[5e,f] Monocyclic phosphate **12** was subjected to cross metathesis with (*Z*)-diacetate **13** using 10 mol% of Hoveyda-Grubbs catalyst cat-**C** to generate CM adduct **14** in 83% yield.[12] Pd-catalyzed, reductive allylic transposition [$Pd(OAc)_2$, PPh_3, $HCOONH_4$] on CM adduct **14** occurred with excellent regioselectivity to afford the terminal olefin **15** in 94% yield.[13] Removal of the phosphate ester in the presence of $LiAlH_4$ provided diol **6** as a single diastereomer in excellent yield (98%).

IV. Formal Total Synthesis of (–)-Salicylihalamide A & B in 13 steps from (*R*,*R*,R_p)-7

Initial efforts focused on the synthesis of benzolactone **3** from the key diol intermediate **6** utilizing protection with TIPSCl to differentiate the hydroxyl groups (Scheme 4). Diol **6** was selectively protected as a TIPS-ether **16** (86% yield),[14] followed by MOM protection to furnish the fully protected triol **17** in 92% yield. Compound **17** was desilylated in 95% yield

to afford the key subunit **18**, which was ready for coupling with benzodioxinone **5**. Alcohol **18** was treated with NaH, followed by addition of benzodioxinone **5**, to provide ester **19** in 66% yield. Subsequent methylation resulted in the production of the known RCM precursor **20** in 90% yield.[2a,4e] To complete the formal synthesis, RCM reaction of **20** was carried out using condition developed by De Brabander and coworkers[4e] (10 mol% of cat-**A**)[7] to furnish the known salicylihalamide macrolide **3** in 82% yield and with excellent *E*-selectivity (*E/Z* = 10:1). The physical and spectroscopic data of the synthetic sample (^{1}H, ^{13}C, IR, HRMS), as well as specific rotation, were all in full agreement with those reported in the literature.[2a,4d,e]

V. Regioselective Esterification Studies on Key Fragment 6

To further streamline the process, we next explored the feasibility of a regioselective esterification of diol **6** in order to avoid the aforementioned orthogonal protection pathway. Scheme 5 highlights the key regioselective esterification studies on diol **6**. As shown in entry one, use of NaH as the base yielded a readily separable mixture (1:1) of both isomers **21a** (known) and **21b** in 85% yield, while implementation of LiHMDS gave modest improvement of selectivity (2:1). However, implementation of NaHMDS as base resulted in a 3.6:1 mixture of the desired benzolactone **21a** and its regioisomer **21b**, which could be readily converted back to starting diol **6** (K_2CO_3, MeOH) for recycling.

VI. Formal Total Synthesis of (–)-Salicylihalamides A and B in 9 steps from (*R,R,R*$_p$)-7

Compound **21a** was protected as the di-MOM ether **22** (86% yield), and subjected to RCM condition developed by De Brabander and coworkers[4e] (cat-**A**) to afford salicylihalamide macrolide **4** in 84% yield and with excellent *E* selectivity (*E/Z* = 9:1) (Scheme 6). The spectral data (^{1}H, ^{13}C, IR, HRMS) of **4** was in complete agreement with those reported in the literature along with specific rotation {$[\alpha]_D = -29.6$ (*c* 0.65, $CHCl_3$)}.[4e]

Conclusion

In conclusion, the synthesis of key macrolactones **3** and **4** are reported representing formal syntheses of salicylihalamides A and B. Overall, a 13-step route (17-LLS) and a 9-step route (13-LLS) have been developed, from a common, readily prepared, chiral, nonracemic bicyclic phosphate (*R,R,R*$_P$)-**7,** with an overall yield of 17.5% and 22.5%, respectively. Each route proceeds through the common diol subunit **6**. The 13-step route requires differential protection of diol **6**, while the more efficient 9-step sequence relies on a regioselective esterification of diol **6**. The latter route has 13 steps in its longest linear sequence (LLS), which is on par with the most efficient syntheses of this key late stage subunit reported to date.

Experimental Section

General Methods

All reactions were carried out in oven- or flame-dried glassware, under argon atmosphere, using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, THF and CH_2Cl_2 were passed through a purification system employing activated Al_2O_3. Et_3N was eluted through basic alumina and stored over KOH. Butyl lithium was titrated prior to use. All olefin metathesis catalysts were obtained commercially and used without further purification. All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz, and 126 MHz instruments, respectively, and calibrated to the solvent peak. All mass spectra were obtained using electrospray ionization (ESI) (MeOH) coupled to high-resolution mass spectrometry (HRMS). Observed rotations at 589 nm were measured using an automatic polarimeter. Infrared spectra were obtained using a Fourier transform infrared (FTIR) spectrometer.

(1*R*,6*R*,8*S*)-8-(2-Hydroxyethyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (10)

Bicyclic phosphate (R,R,R_p)-**7** (1.50 g, 7.41 mmol) was dissolved in anhydrous THF (20 mL), followed by slow addition of 9-BBN (2.71 g, 22.2 mmol) in anhydrous THF (45 mL) under argon atmosphere. The solution was stirred at rt for 3 h. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to 0 °C, and H_2O (3.5 mL) was added dropwise, followed by addition of $NaBO_3$•$4H_2O$ (10.26 g, 66.69 mmol) in one portion. After removing the ice bath, additional H_2O (7 mL) was added, and the reaction mixture stirred at rt for 1 h. After complete oxidation as monitored by TLC, the crude solution was added dried (Na_2SO_4), filtered through pad of Celite® and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified via flash column chromatography (10:1 EtOAc/MeOH) to provide alcohol **10** (1.30 g, 80%) as a white solid; $[\alpha]_D = -96.0$ (*c* = 1.82, $CHCl_3$); FTIR (neat) 3454, 3072, 2962, 2935, 2887, 1288, 1066, 975 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.01 (dddd, *J* = 11.9, 6.7, 3.0, 2.2 Hz, 1H), 5.59 (ddd, *J* = 11.9, 3.9, 2.6 Hz, 1H), 5.18 (ddd, *J* = 24.6, 3.7, 1.9 Hz, 1H), 4.95 (dtd, *J* = 14.1, 5.6, 2.7 Hz, 1H), 4.86-4.74 (m, 1H), 4.35 (ddd, *J* = 27.9, 14.7, 6.7 Hz, 1H), 3.84-3.64 (m, 2H), 3.00 (s, 1H), 2.20 (ddd, *J* = 14.7, 12.0, 6.2 Hz, 1H), 1.97-1.89 (m, 1H), 1.86-1.77 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.7, 127.6, 77.4 (d, *J* = 6.6 Hz), 74.5 (d, *J* = 6.5 Hz), 63.0 (d, *J* = 6.4 Hz), 57.4, 38.1 (d, *J* = 9.2 Hz), 34.8; HRMS calcd. for $C_8H_{13}O_5PK$ $(M+K)^+$ 259.0138; found 259.0138 (TOF MS ES+).

(1*R*,6*R*,8*S*)-8-(2-((4-Methoxybenzyl)oxy)ethyl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide (11)

To a stirring solution of NaH (142 mg, 5.91 mmol) in anhydrous Et_2O (10 mL), under argon atmosphere, was slowly cannulated a solution of PMBOH (8.17 g, 59.09 mmol) in dry Et_2O (30 mL) at rt. After stirring for 40 min, the solution was cooled to 0 °C, and Cl_3CCN (8.54 g, 59.1 mmol) was slowly added via dropwise addition. After 5-10 min., the solution was removed from the ice bath and stirred for an additional hour. The reaction was quenched with saturated $NaHCO_3$ (20 mL), and the layers separated. The aqueous layer was further extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude mixture was dissolved in dry CH_2Cl_2 (118 mL) and cannulated into a flask containing the phosphate-**10** (2.6 g, 11.82 mmol), followed by the addition of PPTS (300 mg, 1.18 mmol) at rt under argon atmosphere. After stirring for 16 h, the reaction was quenched with saturated $NaHCO_3$ (40 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (EtOAc) afforded PMB ether-**11** (3.71 g, 92%) as a viscous, light yellow oil; $[\alpha]_D = -64.66$ (*c* = 2.40, $CHCl_3$); FTIR (neat): 3055, 2933, 2866, 1612, 1512, 1298, 1093, 975, 738, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.02 (dddd, *J* = 11.9, 6.7, 3.1, 2.2 Hz, 1H), 5.57 (ddd, *J* = 11.9, 3.9, 2.6 Hz, 1H), 5.22-5.13 (m, 1H), 5.00 (ddt, *J* = 14.8, 8.9, 3.0 Hz, 1H), 4.81 (dddd, *J* = 10.5, 8.5, 4.1, 2.1 Hz, 1H), 4.43 (d, *J* = 2.9 Hz, 2H), 4.46-4.32 (m, 1H), 3.81 (s, 3H), 3.65-3.52 (m, 2H), 2.19 (ddd, *J* = 14.6, 12.0, 6.2 Hz, 1H), 2.02-1.84 (m, 2H), 1.74 (ddd, *J* = 14.6, 3.4, 2.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 130.1, 129.8, 129.3, 127.8, 113.8, 77.2 (d, J_{CP} = 6.3 Hz), 74.1 (d, J_{CP} = 6.6 Hz), 72.8, 64.7, 62.9 (d, J_{CP} = 6.4 Hz), 55.2, 35.9 (d, J_{CP} = 9.4 Hz), 34.9 (d, J_{CP} = 5.9 Hz); HRMS calcd. for $C_{16}H_{21}O_6PK$ $(M+K)^+$ 379.0713; found 379.0706 (TOF MS ES+).

(4*R*,6*S*)-4-((*S*)-But-3-en-2-yl)-2-methoxy-6-(2-((4-methoxybenzyl)oxy)ethyl)-1,3,2-dioxaphosphinane 2-oxide (12)

Within a glovebox, CuCN (1.75 g, 19.51 mmol, dried overnight in a vacuum oven at 60 °C/0.3 mmHg and stored in a glovebox) and LiCl (1.65 g, 39.02 mmol, dried overnight in a vacuum oven at 60 °C/0.3 mmHg and stored in a glovebox) were added to a round bottom

flask and sealed with a septa. The flask was removed from the glovebox and placed under a balloon of argon. Anhydrous THF (20 mL) was added to the mixture that was stirred for 20 min at rt then cooled to −30 °C. A solution of Me_2Zn (16.2 mL, 1.2 M in toluene) was added rapidly via dropwise addition, and the solution was stirred for 30 min at −30 °C (solution turns deep green). After 30 min, phosphate **11** (1.32 g, 3.90 mmol) in anhydrous THF (6 mL) was cannulated dropwise (1 mL rinse) into the stirring reaction mixture, and the solution was immediately removed from the bath and stirred at rt for 2 h. Upon completion (monitored by TLC, baseline spot in EtOAc), the reaction was cooled to 0 °C and slowly quenched with 10% aqueous HCl (2 mL), followed by water (4 mL), and stirred at rt for 10 min, where pepper-colored salts formed. The solution was filtered through a pad of Celite and rinsed thoroughly with EtOAc. To the resulting biphasic solution was added 10% aqueous HCl (3 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 25 mL), and the combined organic layers were concentrated under reduced pressure. The resulting oil was dissolved in MeOH (~10 mL), where $TMSCHN_2$ (2 M in Et_2O, ~5 mL) was added dropwise, resulting in a deep yellow solution. Excess $TMSCHN_2$ was quenched via slow dropwise addition of glacial acetic acid (3-4 drops), and the solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash column chromatography (2:1 EtOAc/hexane) provided title compound **12** (1.23 g, 85%) as a clear oil, and as a ~1:1 mixture of diastereomers at phosphorus; FTIR (neat) 2925, 2852, 1265, 1093, 1033, 972, 749, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.85-5.74 (m, 1H), 5.15-5.05 (m, 2H), 4.82-4.63 (m, 1H), 4.44 (s, 2H), 4.49-4.30 (m, 1H), 3.81 (s, 3H), 3.78 (d, *J* = 6.6 Hz, 1.5H), 3.76 (d, *J* = 6.6 Hz, 1.5H), 3.69-3.52 (m, 2H), 2.57-2.36 (m, 1H), 2.23-2.05 (m, 2H), 1.92-1.80 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 1.5 H), 1.06 (d, *J* = 6.9 Hz, 1.5 H); HRMS calcd. for $C_{18}H_{27}O_6PK$ $(M+K)^+$ 409.1182; found 409.1188 (TOF MS ES+).

(4*S*,*E*)-4-((4*R*,6*S*)-2-Methoxy-6-(2-((4-methoxybenzyl)oxy)ethyl)-2-oxido-1,3,2-dioxaphosphinan-4-yl)pent-2-en-1-yl acetate (14)

The monocyclic phosphate **12** (1.0 g, 2.70 mmol) was weighed into a round bottom flask and dissolved in CH_2Cl_2 (degassed 10 min. with Ar, 27.0 mL), followed by the addition of diacetate **13** (0.56 g, 3.24 mmol) and cat-**C** (168 mg, 0.27 mmol) under argon at rt. The reaction mixture was heated at 45 °C for 1 h under continuous argon flow and, upon completion, as monitored by TLC, was concentrated under reduced pressure. Flash column chromatography (1:1 EtOAc/hexane) provided title compound **14** (0.99 g, 83%) as a clear oil, and as a ~1:1 mixture of diastereomers at phosphorus; FTIR (neat) 3053, 2954, 2927, 2852, 1737, 1265, 1247, 1093, 1031, 972, 1031, 972, 749, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.79-5.72 (m, 1H), 5.67-5.60 (m, 1H), 4.80-4.62 (m, 1H), 4.53 (t, *J* = 5.3 Hz, 2H), 4.47-4.29 (m, 3H), 3.81 (s, 3H), 3.77 (d, *J* = 7.4 Hz, 1.5 H), 3.75 (d, *J* = 7.4 Hz, 1.5 H), 3.68-3.53 (m, 2H), 2.59-3.38 (m, 1H), 2.23-2.04 (m, 2H), 2.07 (2s, 3H), 1.93-1.81 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 1.5 H), 1.05 (d, *J* = 6.9 Hz, 1.5 H); HRMS calcd. for $C_{21}H_{31}O_8PK$ $(M+K)^+$ 481.1394; found 481.1390 (TOF MS ES+).

(4*S*,6*R*)-2-Methoxy-4-(2-((4-methoxybenzyl)oxy)ethyl)-6-((*S*)-pent-4-en-2-yl)-1,3,2-dioxaphosphinane 2-oxide (15)

To a stirring solution of HCO_2NH_4 (63 mg, 1.00 mmol) in degassed DCE (4 mL) was added $Pd(OAc)_2$ (12 mg, 0.05 mmol) and Ph_3P (66 mg, 0.25 mmol) at rt, and the mixture was stirred for 15 min at rt under argon, at which point a solution of acetate **14** (220 mg, 0.50 mmol) in degassed DCE (2 mL) was added dropwise via cannula. The stirring solution was equipped with a reflux condenser and placed into an oil bath at 90 °C for 1 h. The reaction mixture was cooled to rt, washed with sat. $NaHCO_3$ (6 mL) solution, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were rinsed with

brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (1:1 EtOAc/hexane) afforded the desired compound **15** (180 mg, 94 %) as a clear oil, and as a ~1:1 mixture of diastereomers at phosphorus; FTIR (neat): 3053, 2956, 2927, 2854, 12654, 1093, 1035, 970, 749, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.81-5.70 (m, 1H), 5.10-5.02 (m, 2H), 4.82-4.63 (m, 1H), 4.48-4.38 (m, 2H), 4.37-4.21 (m, 1H), 3.81 (s, 3H), 3.78 (d, *J* = 7.4, Hz, 1.5H), 3.76 (d, *J* = 7.7 Hz, 1.5 H), 3.69-3.54 (m, 2H), 2.42-2.27 (m, 1H), 2.22-1.76 (m, 6H), 0.90 (d, *J* = 6.8 Hz, 1.5H), 0.86 (d, *J* = 6.8 Hz, 1.5H); HRMS calcd. for $C_{19}H_{29}O_6PNa$ $(M+Na)^+$ 407.1599; found 407.1612 (TOF MS ES+).

(3*S*,5*R*,6*S*)-1-((4-Methoxybenzyl)oxy)-6-methylnon-8-ene-3,5-diol (6)

To a suspension of $LiAlH_4$ (53 mg, 1.10 mmol) in anhydrous Et_2O (3 mL) was added dropwise a solution of 1:1 diastereomeric phosphate mixture **15** (170 mg, 0.45 mmol) in Et_2O (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, quenched via slow sequential addition of H_2O (60 μL), 15% NaOH (60 μL), H_2O (180 μL), and removed from the ice bath. After stirring for 30 minutes, 10% aqueous HCl (5 mL) was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were rinsed with brine (1 × 10 mL)), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash column chromatography (1:1 EtOAc/Hexane) afforded diol **6** (125 mg, 98% yield) as a viscous oil; $[\alpha]_D$ = +15.16 (*c* = 1.20, $CHCl_3$); FTIR (neat) 3412, 2921, 2866,1298, 1093, 975, 740, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.82 (dddd, *J* = 16.9, 10.2, 7.6, 6.6 Hz, 1H), 5.07-4.99 (m, 2H), 4.46 (s, 2H), 4.20-4.12 (m, 1H), 3.81 (s, 3H), 3.77-3.71 (m, 1H), 3.72 (td, *J* = 9.3, 4.7 Hz, 1H), 3.65 (td, *J* = 9.2, 3.8 Hz, 1H), 3.59 (br. s, 1H), 2.97 (br. s, 1H), 2.35-2.28 (m, 1H), 1.97-1.88 (m, 2H), 1.71-1.55 (m, 4H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 137.5, 129.7, 129.3, 115.9, 113.8, 73.0, 72.3, 69.9, 69.2, 55.2, 39.0, 38.6, 37.2, 36.1, 15.1; HRMS calcd. for $C_{18}H_{28}O_4Na$ $(M+Na)^+$ 331.1885; found 331.1877 (TOF MS ES+).

(4*S*,5*R*,7*S*)-9-((4-Methoxybenzyl)oxy)-4-methyl-7-((triisopropylsilyl)oxy)non-1-en-5-ol (16)

To a stirring solution of diol **6** (50 mg, 0.16 mmol) in CH_2Cl_2 (4 mL) was added 2,6-lutidine (70 mg, 0.65 mmol), and the mixture was cooled to −78 °C. TIPSOTf (100 mg, 0.32 mmol) was added dropwise, and the reaction mixture was stirred for 2 h and then allowed to slowly warm to 0 °C. After completion of the reaction, as monitored by TLC, it was quenched with sat. NH_4Cl, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (1:10 EtOAc/Hexane) afforded the desired silyl ether **16** (64 mg, 86%) as a viscous oil; $[\alpha]_D$ = +12.88 (*c* = 1.35, $CHCl_3$); FTIR (neat) 3406, 2923, 2850, 1265, 1095, 740, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.78 (dddd, *J* = 16.9, 10.3, 7.5, 6.8 Hz, 1H), 5.06-4.95 (m, 2H), 4.41 (dd, *J* = 39.1, 11.6 Hz, 2H), 4.36-4.31 (m, 1H), 3.83 (d, *J* = 0.9 Hz, 1H), 3.81 (s, 3H), 3.80-3.76 (m, 1H), 3.50-3.39 (m, 2H), 2.25-2.17 (m, 1H), 2.10-1.93 (m, 2H), 1.89-1.80 (m, 1H), 1.76-1.65 (m, 1H), 1.64-1.50 (m, 2H), 1.08 (s, 12H), 1.06 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 137.7, 130.3, 129.3, 129.2, 115.6, 113.7, 72.6, 71.6, 70.2, 66.3, 55.2, 38.9, 36.8, 36.3, 35.5, 18.1, 18.1, 17.7, 14.7, 12.3, 12.3; HRMS calcd. for $C_{27}H_{48}O_4SiNa$ $(M+Na)^+$ 487.3220; found 487.3210 (TOF MS ES+).

(5*R*,7*S*)-9,9-Diisopropyl-7-(2-((4-methoxybenzyl)oxy)ethyl)-10-methyl-5-((*S*)-pent-4-en-2-yl)-2,4,8-trioxa-9-silaundecane (17)

To a stirring solution of silyl ether **16** (60 mg, 0.129 mmol) in anhydrous CH_2Cl_2 (5 mL), under argon, was added $^iPr_2NEt$ (167 mg, 1.292 mmol) and MOMCl (52 mg, 0.646 mmol) at 0 °C. The reaction was stirred at rt for 3-4 h. Upon completion (monitored by TLC), the

reaction was diluted with CH_2Cl_2 (5 mL) followed by sat. NH_4Cl solution (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were washed with brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude reaction mixture was purified through flash column chromatography (1:10 EtOAc/hexane) to afford MOM-ether **17** (60 mg, 92%) as a clear oil; $[\alpha]_D$ = +9.12 (*c* = 1.08, $CHCl_3$); FTIR (neat): 2923, 2850, 1460, 1265, 1097, 1039, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 5.78 (dddd, *J* = 17.1, 10.2, 6.9, 6.4 Hz, 1H), 5.07-4.96 (m, 2H), 4.66 (dd, *J* = 10.4, 6.8 Hz, 2H), 4.43 (dd, *J* = 14.8, 11.5 Hz, 2H), 4.12-4.06 (m, 1H), 3.81 (s, 3H), 3.64 (ddd, *J* = 9.8, 6.6, 2.6 Hz, 1H), 3.57-3.52 (m, 2H), 3.36 (s, 3H), 2.15-2.08 (m, 1H), 1.94-1.80 (m, 3H), 1.67-1.60 (m, 2H), 1.52 (ddd, *J* = 14.2, 7.4, 3.4 Hz, 1H), 1.06 (br. s, 18H), 1.06-1.04 (m, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 137.5, 130.7, 129.2, 115.7, 113.7, 96.6, 79.9, 72.6, 68.1, 66.5, 55.7, 55.3, 38.3, 38.1, 37.1, 36.5, 18.3, 18.3, 14.2, 12.9; HRMS: calcd. for $C_{29}H_{52}O_5SiNa$ $(M+Na)^+$ 531.3482; found 531.3502 (TOF MS ES +).

(3*S*,5*R*,6*S*)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-6-methylnon-8-en-3-ol (18)

A solution of protected triol **17** (52 mg, 0.110 mmol) in anhydrous THF (2 mL) was treated with TBAF (1 M in THF, 0.3 mL) at 0 °C and stirred for 2 h at rt. After completion of the reaction, as monitored by TLC, the reaction mixture was concentrated under reduced pressure. The crude product was purified through flash column chromatography (1:6 EtOAc/hexane) to afford alcohol **18** (34 mg, 95%) as a viscous oil; $[\alpha]_D$ = +38.6 (*c* = 1.00, $CHCl_3$); FTIR (neat) 3412, 2921, 2856,1298, 1093, 975, 749, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.92-6.87 (d, *J* = 8.6 Hz, 2H), 5.78 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H), 5.05-4.99 (m, 2H), 4.69 (dd, *J* = 10.1, 6.6 Hz, 2H), 4.45 (s, 2H), 4.05-3.96 (m, 1H), 3.81 (s, 3H), 3.75-3.60 (m, 3H), 3.41 (s, 3H), 3.31 (d, *J* = 3.4 Hz, 1H), 2.19-2.12 (m, 1H), 1.89-1.81 (m, 2H), 1.81-1.68 (m, 2H), 1.52 (dddd, *J* = 32.1, 14.2, 9.6, 2.8 Hz, 2H), 0.88 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 137.2, 130.2, 129.3, 115.9, 113.8, 96.9, 79.0, 72.8, 68.3, 66.8, 55.9, 55.2, 37.6, 37.4, 37.0, 36.5, 14.2; HRMS calcd. for $C_{20}H_{32}O_5Na$ $(M+Na)^+$ 375.2147; found 375.2146 (TOF MS ES+).

(3*S*,5*R*,6*S*)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-6-methylnon-8-en-3-yl 2-allyl-6-hydroxybenzoate (19)

To a suspension of NaH (24 mg, 0.852 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (2 mL), under argon, was added, dropwise, a solution of alcohol **18** (30 mg, 0.085) in anhydrous THF (1 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. A solution of benzodioxinone **5** (37 mg, 0.170 mmol) in THF (1 mL) was added dropwise via cannula to the mixture, and the reaction was warmed to rt and stirred for 6 h. The reaction was quenched with saturated NH_4Cl (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were rinsed with brine (1×10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash column chromatography (1:4 EtOAc/Hexane) afforded ester **19** (29 mg, 66%) as a viscous oil, along with recovered starting material (9 mg); $[\alpha]_D$ = +12.3 (*c* = 1.00, $CHCl_3$) FTIR (neat) 3435, 3053, 2956, 2925, 2854, 1646, 1265, 1033, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.17 (s, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.72 (dd, *J* = 7.4, 1.1 Hz, 1H), 5.97 (dddd, *J* = 16.9, 10.2, 6.1, 6.1 Hz, 1H), 5.72 (dddd, *J* = 17.0, 10.1, 7.0, 7.0 Hz, 1H), 5.62-5.56 (m, 1H), 5.03-4.90 (m, 4H), 4.63 (dd, *J* = 41.5, 6.9 Hz, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.64 (ddd, *J* = 39.4, 15.7, 6.1 Hz, 2H), 3.58-3.51 (m, 3H), 3.37 (s, 3H), 2.11-1.98 (m, 3H), 1.97-1.88 (m, 1H), 1.88-1.70 (m, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 162.3, 159.1, 142.4, 137.7, 136.9, 134.0, 130.1, 129.3, 122.3, 116.12, 116.0, 115.5, 113.7, 112.7, 112.6, 96.5, 78.0, 72.8, 71.8, 66.4, 55.9, 55.2, 39.9, 37.5, 36.0,

35.2, 34.8, 13.5; HRMS calcd. for $C_{30}H_{40}O_7Na$ $(M+Na)^+$ 535.2672; found 535.2627 (TOF MS ES+).

(3*S*,5*R*,6*S*)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-6-methylnon-8-en-3-yl 2-allyl-6-methoxybenzoate (20)

To a suspension of NaH (~2 mg, 0.078 mmol, 60% w/v dispersion in mineral oil) in anhydrous THF (1 mL) was added, dropwise, a solution of ester **19** (20 mg, 0.039) in anhydrous THF (2 mL). To this reaction mixture MeI (22 mg, 0.156 mmol) was added, and stirring was continued for 1 h at rt. The reaction mixture was quenched with cold water (2 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were rinsed with brine (1 × 8 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash column chromatography (1:3 EtOAc/Hexane) afforded the methyl ether **20** (19 mg, 90%) as a viscous oil; $[\alpha]_D = -1.6$ (*c* = 0.50, $CHCl_3$); FTIR (neat) 2952, 2925, 2852, 1641, 1265, 1069, 1033, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 3H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.93 (dddd, *J* = 16.7, 10.2, 6.5, 6.5 Hz, 1H), 5.75 (dddd, *J* = 16.8, 10.2, 7.4, 6.5 Hz, 1H), 5.51-5.42 (m, 1H), 5.10-5.03 (m, 2H), 5.00-4.90 (m, 2H), 4.73 (dd, *J* = 11.4, 6.8 Hz, 2H), 4.46 (dd, *J* = 25.3, 11.3 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.73-3.69 (m, 1H), 3.66-3.56 (m, 2H), 3.41 (s, 3H), 3.36 (d, *J* = 6.4 Hz, 2H), 2.11-1.98 (m, 3H), 1.97-1.89 (m, 1H), 1.88-1.79 (m, 1H), 1.77-1.67 (m, 2H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 159.1, 156.2, 138.1, 137.1, 136.4, 130.5, 130.2, 129.2, 124.1, 121.6, 116.4, 115.8, 113.7, 108.7, 97.0, 78.3, 72.7, 70.7, 55.8, 55.5, 55.3, 37.6, 37.2, 36.5, 35.3, 35.2, 13.7; HRMS calcd. for $C_{31}H_{42}O_7Na$ $(M+Na)^+$ 549.2833; found 549.28631(TOF MS ES+).

(3*S*,5*R*,6*S*,*E*)-14-Methoxy-3-(2-((4-methoxybenzyl)oxy)ethyl)-5-(methoxymethoxy)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3)

Grubbs catalyst $(Cy_3P)_2Cl_2Ru$=CHPh (~3 mg, 10 mol%, cat-**A**) was added to a solution of methyl ether **20** (14 mg, 0.026 mmol) in degassed, anhydrous CH_2Cl_2 (5 mL) at rt under argon. The stirring solution was equipped with a reflux condenser and placed into an oil bath at 40 °C for 1 h. After completion of the reaction, as monitored by TLC, the reaction mixture was concentrated under reduced pressure. Flash column chromatography (1:4 EtOAc/Hexane) afforded the major *E*-isomer **3** (11 mg, 82%) as a viscous oil (containing a small amount of *Z*-isomer, the *E/Z* ratio was 10:1 as determined by ^1H NMR of the crude reaction); $[\alpha]_D = -41.7$ (*c* = 0.35, $CHCl_3$); FTIR (neat) 2942, 2911, 2850, 1649, 1266, 1239, 1064, 1033, 908, 748, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.8 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 5.53-5.45 (m, 2H), 5.35 (ddt, *J* = 15.2, 9.5, 2.1 Hz, 1H), 4.85 (dd, *J* = 46.3, 6.7 Hz, 2H), 4.48 (s, 2H), 4.16 (dd, *J* = 9.3, 3.6 Hz, 1H), 3.81 (s, 3H), 3.76-3.70 (m, 1H), 3.72 (s, 3H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.44 (s, 3H), 3.33 (ddd, *J* = 14.0, 4.1, 2.1 Hz, 1H), 2.31 (d, *J* = 13.3 Hz, 1H), 2.13 (ddd, *J* = 18.8, 12.2, 6.2 Hz, 1H), 2.08-1.98 (m, 1H), 1.91 (dtd, *J* = 11.6, 7.4, 4.1 Hz, 1H), 1.82-1.65 (m, 2H), 1.46 (dd, *J* = 15.5, 9.4 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 159.1, 156.4, 139.1, 131.4, 130.7, 129.9, 129.0, 128.5, 124.5, 122.8, 113.7, 109.8, 96.8, 79.2, 72.6, 72.2, 66.6, 55.6, 55.3, 55.3, 37.7, 37.7, 36.4, 35.7, 34.0, 13.4; HRMS calcd. for $C_{29}H_{38}O_7Na$ $(M+Na)^+$ 521.2515; found 521.2525 (TOF MS ES+).

(3*S*,5*R*,6*S*)-5-Hydroxy-1-((4-methoxybenzyl)oxy)-6-methylnon-8-en-3-yl 2-allyl-6-hydroxybenzoate (21a)

To a solution of diol **6** (50 mg, 0.16 mmol) in anhydrous THF (2 mL) was added, dropwise, NaHMDS (1 M in THF, 1.3 mL) at −20 °C, and the reaction mixture was stirred for 15 min at −20 °C. A solution of benzodioxinone **5** (42 mg, 0.14 mmol) in THF (1 mL) was added

dropwise via cannula to the reaction mixture, and the combined mixture was warmed to 0 °C and stirred for 6 h. The reaction was quenched with saturated NH_4Cl, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were rinsed with brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash column chromatography (1:5 EtOAc/Hexane) yielded the both isomers **21a** (32.8 mg) and **21b** (9.2 mg) as viscous oils (65% overall yield); $[\alpha]_D = -10.0$ (*c* = 0.25, CHCl); FTIR (neat) 3435, 3053, 2956, 2925, 2854, 1656, 1265, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.05 (s, 1H), 7.31(dd, *J* = 8.2, 7.6 Hz, 1H), 7.17 (d, *J* = 8.6, Hz, 2H), 6.87 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.71(dd, *J* = 7.5, 1.1 Hz, 1H), 5.95 (dddd, *J* = 16.9, 10.2, 6.0, 6.0 Hz, 1H), 5.76 (dddd, *J* = 16.9, 10.2, 7.6, 6.6 Hz, 1H), 5.66-5.60 (m, 1H), 5.01-4.93 (m, 3H), 4.89-4.83 (m, 1H), 4.38 (dd, *J* = 23.2, 11.5 Hz, 2H), 3.75 (s, 3H), 3.66 (dd, *J* = 15.7, 5.9 Hz, 1H), 3.55 (dd, *J* = 15.7, 5.9 Hz, 1H), 3.53-3.47 (m, 2H), 3.41-3.34 (m, 1H), 2.66 (d, *J* = 4.4 Hz, 1H), 2.27-2.21 (m, 1H), 2.10-1.94 (m, 2H), 1.91-1.78 (m, 2H), 1.71-1.64 (m, 1H), 1.62-1.57 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 162.6, 159.8, 142.6, 137.7, 137.2, 134.4, 129.9, 129.4, 122.7, 116.4, 116.8, 115.4, 113.7, 112.2, 72.8, 71.8, 70.7, 66.7, 55.2, 40.0, 39.1, 38.6, 37.0, 35.1, 15.6; HRMS calcd. for $C_{28}H_{36}O_6Na$ $(M+Na)^+$ 491.2410; found 491.2420 (TOF MS ES+).

(4*S*,5*R*,7*S*)-7-Hydroxy-9-((4-methoxybenzyl)oxy)-4-methylnon-1-en-5-yl 2-allyl-6-hydroxybenzoate (21b)

$[\alpha]_D = +2.0$ (*c* = 0.25, $CHCl_3$); FTIR (neat): 3439, 3046, 2950, 2931, 2867, 1661, 1243, 742, 729, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.35 (dd, *J* = 8.1, 7.6 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.91 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.76 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.03-5.84 (m, 1H), 5.84-5.71 (m, 1H), 5.51-5.43 (m, 1H), 5.08-4.95 (m, 3H), 4.93-4.86 (m, 1H), 4.38 (dd, *J* = 21.1, 12.2 Hz, 2H), 3.79 (s, 3H), 3.78-3.76 (m, 1H), 3.68-3.50 (m, 3H), 3.31-3.27 (m, 1H), 2.31-2.23 (m, 1H), 2.04-1.90 (m, 2H), 1.87-1.65 (m, 4H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 162.9, 159.2, 142.4, 137.6, 136.1, 134.3, 132.5, 129.3, 122.6, 116.8, 116.3, 115.5, 113.8, 112.1, 76.6, 73.0, 68.0, 66.5, 55.6, 39.9, 38.5, 37.1, 36.9, 36.7, 15.2; HRMS calcd. for $C_{28}H_{36}O_6Na$ $(M+Na)^+$ 491.2410; found 491.2415 (TOF MS ES+).

(3*S*,5*R*,6*S*)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-6-methylnon-8-en-3-yl 2-allyl-6-(methoxymethoxy)benzoate (22)

To a solution of ester **21a** (25 mg, 0.053 mmol) in anhydrous DCE (5 mL), under argon, was added $^iPr_2NEt$ (69 mg, 0.53 mmol) and MOMCl (43 mg g, 0.53 mmol) at rt. The stirring solution was equipped with a reflux condenser and placed into an oil bath at 90 °C for 3-4 h. Upon completion (monitored by TLC), the reaction was diluted with CH_2Cl_2 (5 mL), followed by saturated NH_4Cl solution (6 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were washed with brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude reaction mixture was purified through flash column chromatography (1:4 EtOAc/hexane) to afford title compound **22** (25 mg, 86%) as a clear oil; $[\alpha]_D = +5.27$ (*c* = 0.55, $CHCl_3$); FTIR (neat): 2952, 2925, 2852, 1641, 1265, 1033, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.24 (m, 3H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.90-6.86 (m, 3H), 5.94 (dddd, *J* = 16.7, 10.2, 6.6, 6.6 Hz, 1H), 5.73 (dddd, *J* = 16.9, 10.2, 7.5, 6.6 Hz, 1H), 5.49-5.42 (m, 1H), 5.16 (dd, *J* = 26.3, 6.9 Hz, 2H), 5.10-5.03 (m, 2H), 4.99-4.90 (m, 2H), 4.72 (dd, *J* = 12.8, 6.9 Hz, 2H), 4.46 (dd, *J* = 21.6, 11.3 Hz, 2H), 3.81 (s, 3H), 3.70-3.57 (m, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 3.37 (d, *J* = 6.5 Hz, 2H), 2.13-1.97 (m, 3H), 1.95-1.77 (m, 2H), 1.76-1.71 (m, 2H), 0.90 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 159.1, 153.8, 138.1, 137.1, 136.3, 130.45, 130.2, 129.2, 124.9, 122.6, 116.5, 115.9, 113.7, 112.2, 96.8,

94.4, 78.2, 72.7, 70.8, 66.5, 56.0, 55.8, 55.7, 37.6, 37.2, 36.5, 35.4, 35.1, 13.7; HRMS calcd. for $C_{32}H_{44}O_8K$ $(M+K)^+$ 595.2673; found 595.2653 (TOF MS ES+).

(3*S*,5*R*,6*S*,*E*)-3-(2-((4-Methoxybenzyl)oxy)ethyl)-5,14-bis(methoxymethoxy)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (4)

Grubbs catalyst $(Cy_3P)_2Cl_2Ru$=CHPh (~3 mg, 10 mol%, cat-**A**) was added to a solution of compound **22** (15 mg, 0.027 mmol) in degassed, anhydrous CH_2Cl_2 (5 mL) at rt under argon. The stirring solution was equipped with a reflux condenser and placed into an oil bath at 40 °C for 1 h. After completion of the reaction, as monitored by TLC, the reaction mixture was concentrated under reduced pressure. Flash column chromatography (1:5 EtOAc/Hexane) afforded macrolide **4** (12 mg, 84%) as a viscous oil (a small amount of *Z*-isomer was observed, the *E/Z* ratio was 9:1 as determined by ^{1}H NMR of crude reaction); $[\alpha]_D = -29.6$ (*c* = 0.65, $CHCl_3$); FTIR (neat): 2952, 2921, 2850, 1639, 1263, 1249, 1064, 908, 736, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 7.21 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 7.6 Hz, 1H), 5.53-5.46 (m, 2H), 5.39-5.31 (m, 1H), 5.07 (s, 2H), 4.85 (dd, *J* = 44.1, 6.8 Hz, 2H), 4.47 (s, 2H), 4.14 (dd, *J* = 9.3, 3.6 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, *J* = 16.4, 9.5 Hz, 1H), 3.69-3.64 (m, 2H), 3.44 (s, 3H), 3.40 (s, 3H), 3.34 (ddt, *J* = 16.4, 4.5, 2.3 Hz, 1H), 2.35-2.28 (m, 1H), 2.19-2.09 (m, 1H), 2.07-1.99 (m, 1H), 1.96-1.89 (m, 1H), 1.80-1.67 (m, 2H), 1.48 (dd, *J* = 15.4, 9.4 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 159.1, 154.2, 139.1, 131.3, 130.6, 129.9, 129.0, 128.5, 125.3, 123.9, 113.7, 112.8, 96.9, 94.4, 79.4, 72.6, 72.2, 66.5, 56.0, 55.6, 55.3., 37.7, 37.7, 36.4, 35.5, 34.0, 13.4; HRMS calcd. for $C_{30}H_{40}O_8Na$ $(M+Na)^+$ 551.2621; found 551.2605 (TOF MS ES+).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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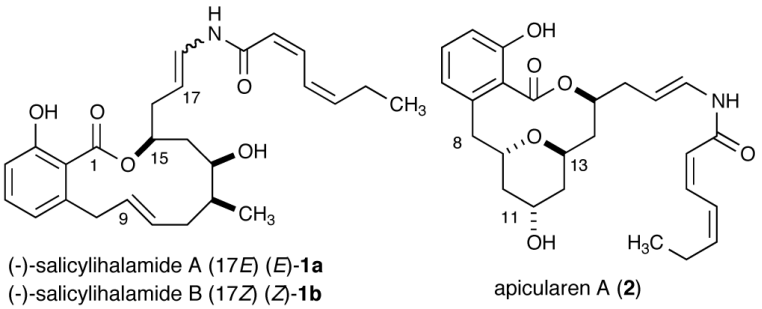
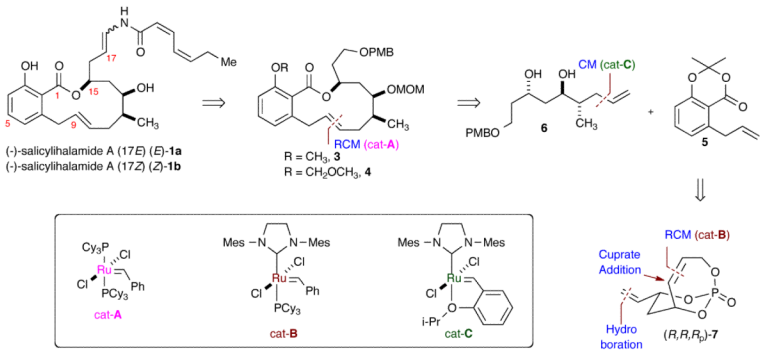
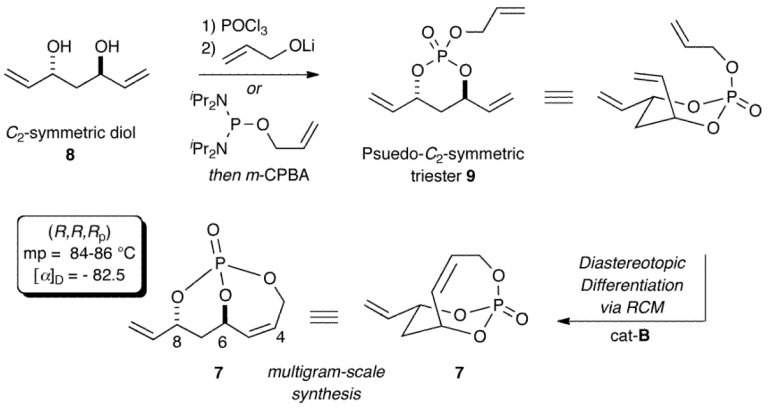


Figure 1.
Structures of two important benzolactone enamide class compounds

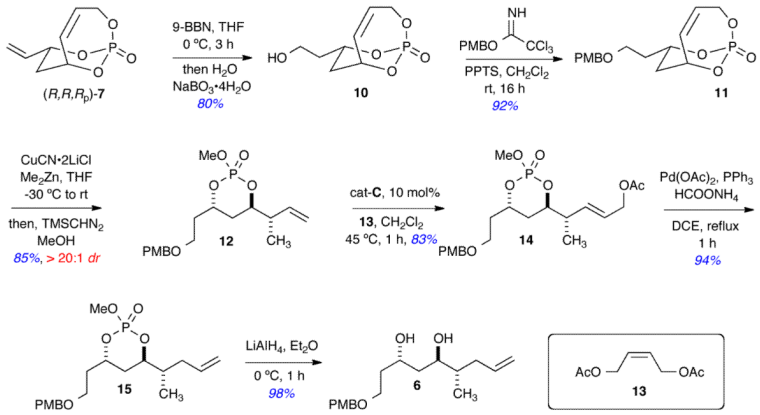


Scheme 1.
Retrosynthetic Analysis of (–)-Salicylihalamides

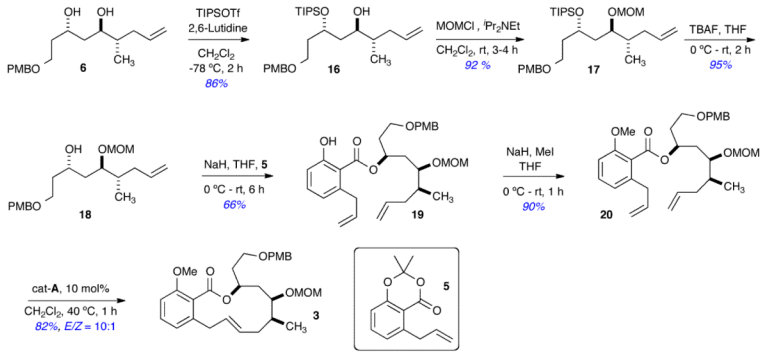


Scheme 2.

Construction of *P*-chiral, nonracemic bicyclo[4.3.1]phosphate (*R*,*R*,R_p)-**7**

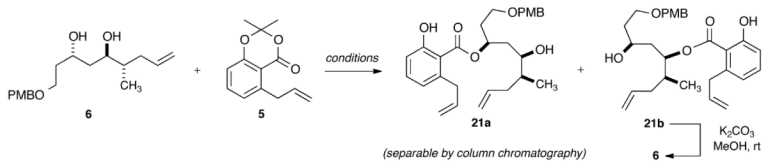


Scheme 3.
Synthesis of Key Fragment **6**



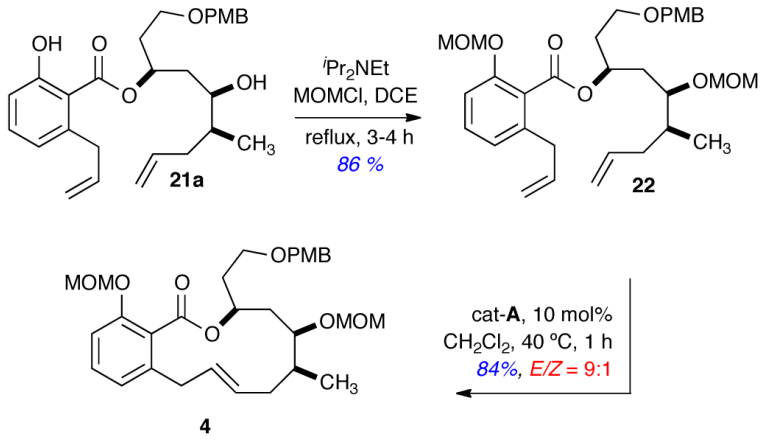
Scheme 4.

Formal Total Synthesis of (–)-Salicylihalamides in 13 steps from (R,R,R_p)-**7** (17-LLS).



Entry	Conditions	Yield	*regioselectivity* **21a**:**21b**
1.	NaH, THF, 0 °C	85%	1:1
2.	LiHMDS, THF, -78 °C to 0 °C	ND	2:1
3.	NaHMDS, THF, -20 °C to 0 °C	65%	3.6:1

Scheme 5.
Regioselective Esterification Studies on Key Fragment **6**



Scheme 6.

Formal Total Synthesis of (–)-Salicylihalamides A and B in 9 steps from (R,R,R_p)-**7**