Tetrahedron 70 (2014) 2982–2991

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of reblastatin: convenient preparation of coupling partners and scaled assembly

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ARTICLE INFO

Article history:
Received 8 January 2014
Received in revised form 25 February 2014
Accepted 6 March 2014
Available online 14 March 2014

Keywords:
Benzenoid/benzoquinone ansamycin
Reblastatin
Total synthesis
Hsp90 inhibitor

ABSTRACT

Potentially scalable total synthesis of reblastatin was achieved based on Panek's previous study. Novel and convenient synthetic routes were developed for the known C8–C20 and C1–C7 coupling partners. The challenging C8–C20 fragment was prepared from TBS protected (*S*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (**6**) in nine steps (20% overall yield), and the C1–C7 fragment was synthesized from commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**9**) in eight steps (35% overall yield). On a larger scale, Panek's eight-step assembly of the target molecule from the two partners was also slightly modified, giving 45 mg reblastatin (19% overall yield) in the first batch synthesis. Notable feature of our study is the settlement of the C14 chirality through a diastereoselective α-alkylation of **6** followed by a three-step full reduction of the lactone carboxyl, making vastly available **6** a universally applicable C11–C14 synthon for benzenoid/benzoquinone ansamycins.

1. Introduction

Benzenoid ansamycin reblastatin (**1**, Fig. 1) was first isolated from the culture of *Streptomyces hygroscopicus* sub sp. *hygroscopicus SANK 61995* by Takatsu,[1] and then by Stead from that of *Streptomyces* sp. S6699.[2] This compound showed considerable anti-proliferative activity against human histiocytic lymphoma U-937 cells (IC_{50} 0.43 μg/mL or 0.78 μM)[1] and inhibitory effect against Oncostatin M (OSM) mediated pathways in HepG2 B6 cells (IC_{50} 0.16 μM),[2] indicating its potential for treatment of cancer and rheumatoid arthritis. The closely related natural product geldanamycin (**2**, Fig. 1) is a well-known heat shock protein 90 (Hsp90) inhibitor, and several of its semisynthetic derivatives are now clinically investigated as cancer chemotherapeutics.[3] Similar to compound **2**, reblastatin **1** is also an ATPase inhibitor of Hsp90,[4b] but the structural difference between the two molecules are of great pharmaceutical significance. For example, reblastatin **1** should have lower hepatotoxicity because of the embedment of a redox-inactive phenolic aromatic core. And secondly, the saturated C4 and C5 in **1**, which may account for its higher molecular affinity to Hsp90,[5] also make the compound more stable. For these reasons, we became interested in a scalable synthesis of **1** to support in vivo studies on its toxicological profiles and therapeutic effects, and to this end a sub-gram (0.1–1 g) sample is usually required.

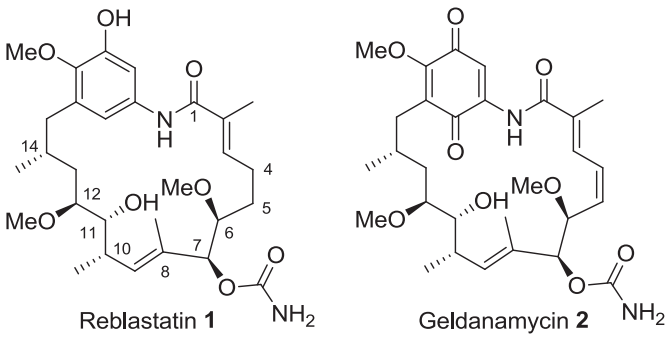

Fig. 1. Structures of reblastatin **1** and geldanamycin **2**.

Panek and co-workers accomplished so far the only total synthesis of reblastatin (Scheme 1),[4] which also stands for the first example of convergent synthesis within the benzenoid/benzoquinone ansamycin family.[6] Their synthesis started with an enantioselective formal [4+2] cycloaddition of benzaldehyde **3** and a chiral crotylsilane developed in the authors' own laboratory.[4b] This robust method helped address the challenging C14 configuration with high efficiency and enabled construction of the four-chiral-centered C8–C20 fragment **4** in 12 steps. More remarkable to us, however, is the late stage assembly of the target molecule. Two key steps, namely a ZrH/Zn mediated highly diastereoselective reductive

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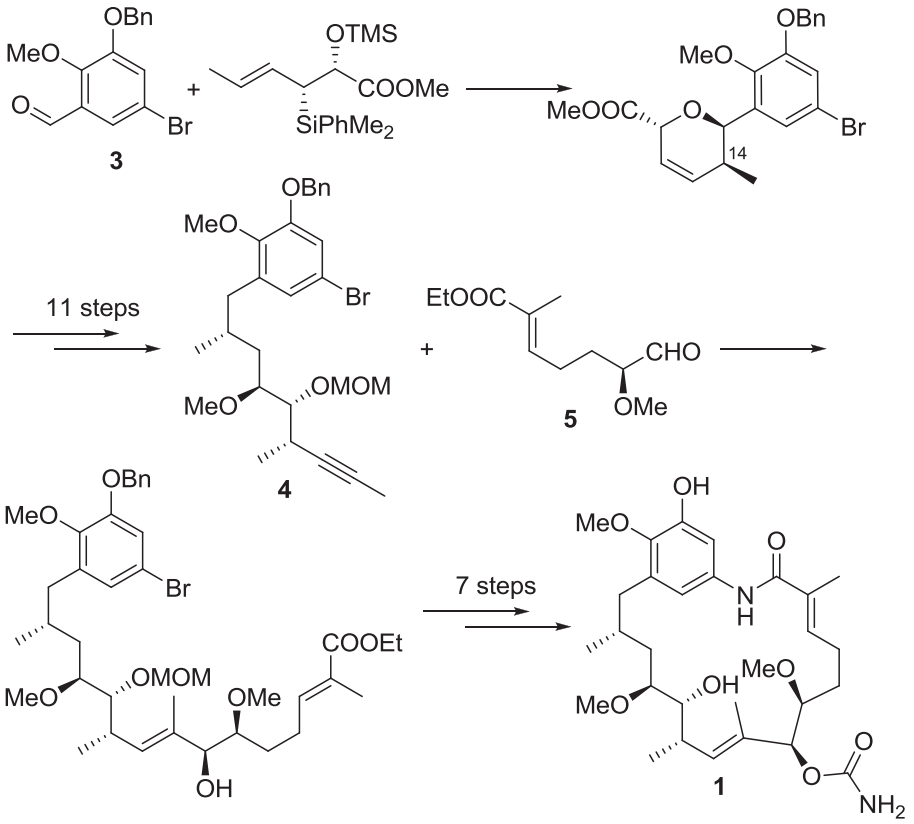
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.03.020

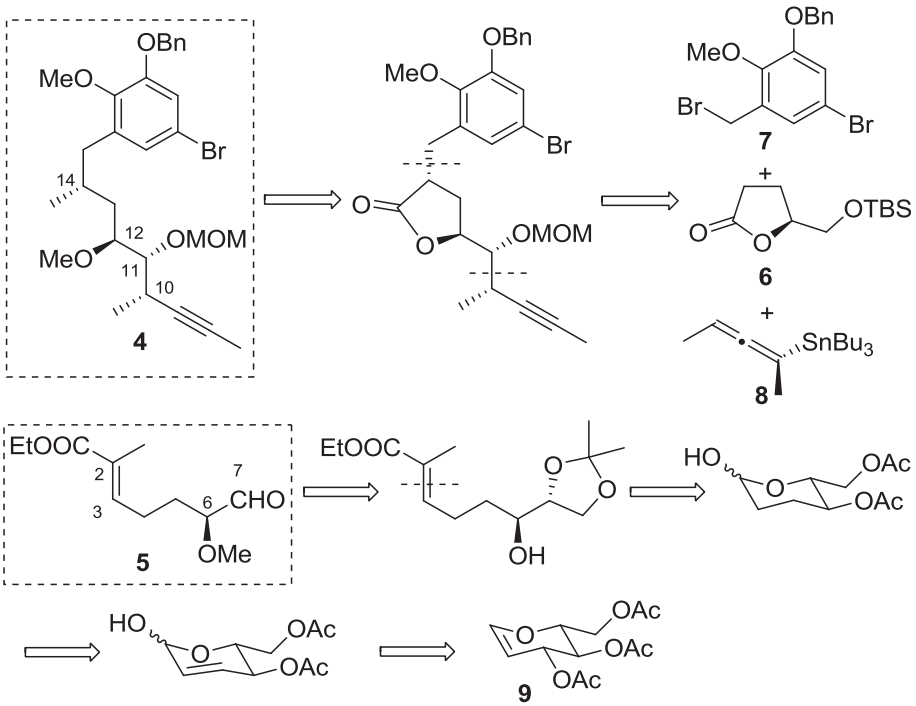


Scheme 1. Panek's total synthesis of reblasatin.

coupling of alkyne **4** and aldehyde **5**, and an unprecedented Hartwig–Buchwald type macrolactam ring-closure, were included in the eight-step sequence that finally delivered reblastatin **1** in 13% overall yield. These excellent achievements undoubtedly formed solid foundation for a scalable synthesis, but we were in short of the supply of Panek's crotylsilane. We therefore developed an alternative approach to **4** and **5** that may feature the easy availability of starting material. In addition, the reported method for assembly **4** and **5** to reblastatin **1** was also slightly modified.

2. Results and discussion

As shown in Scheme 2, we planned to start our synthesis of **4** with a substrate-induced trans-selective α-alkylation of chiral γ-lactone

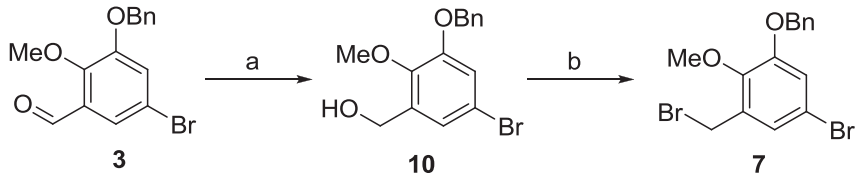


Scheme 2. The retro-synthetic analysis of **4** and **5**.

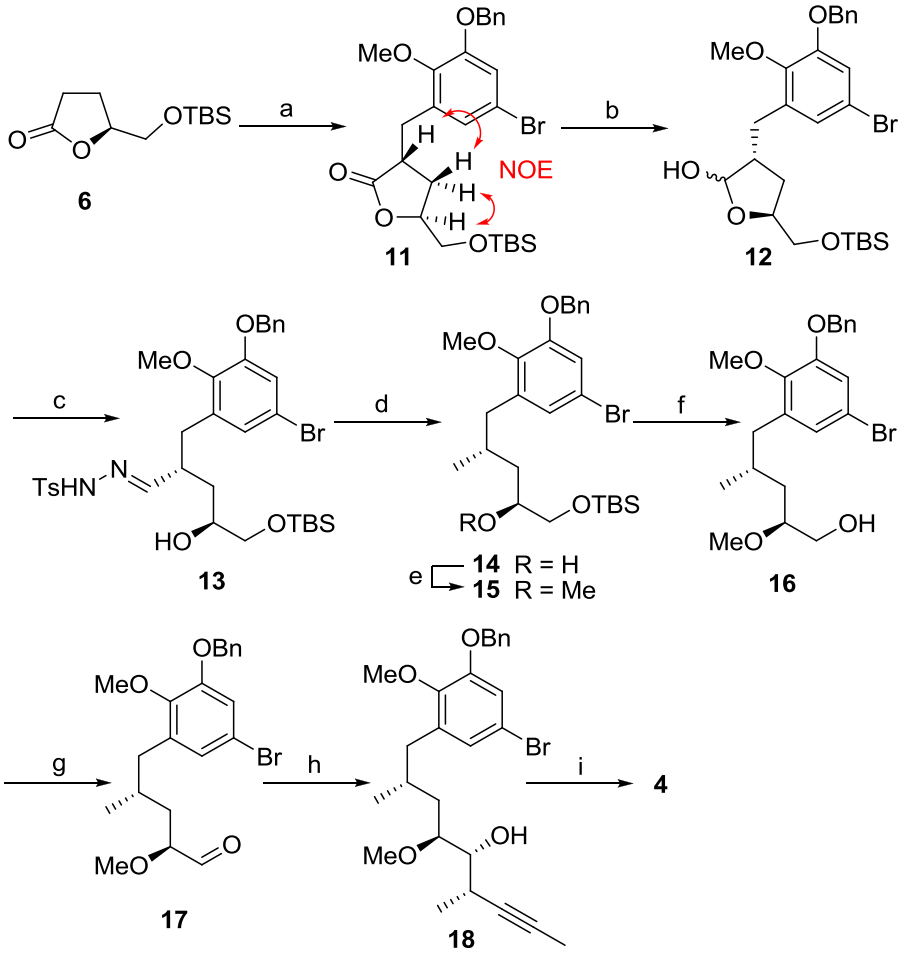
6,[7] a compound that is readily prepared from cheap L-glutamic acid. Provided full reduction of the lactone carboxyl could be realized with ease, such design would be advantageous in its convenience of settling the C14 chirality. Further establishment of the C10–C11 chirality and introduction of the C8–C9 alkyne tail in **4** was expected to be achieved by making use of chiral allenylstannane (*S*)-**8**,[6n] a reagent that is easy to prepare in multi-gram-scale and fairly stable on storage. The C1–C7 fragment **5** (Scheme 2), on the other hand, had been synthesized with ease,[4] but our retro-synthetic analysis suggested that commercially available 3,4,6-tri-*O*-acetyl-D-glucal **9** could also be a suitable starting material, and as such a low temperature reduction using DIBAL-H could be circumvented.

According to the synthetic plan, we first prepared benzyl bromide **7**[8] from aldehyde **3**[4] (Scheme 3). Interestingly, both **7** and **10** readily form crystals in ethanol, and therefore could be obtained in large quantity without chromatography. The anticipated trans-selective alkylation of **6** with **7** was then carried out using LDA as base (Scheme 4) in THF at −78 °C. When the reaction was quenched at −78 °C, *trans*-substituted lactone **11** could be isolated in 82% yield. The relative stereochemistry of **11** was confirmed by NOE.

In order to realize a short transformation of the lactone carboxyl in **11** into the expected C14 methyl group through Caglioti reduction,[9] the compound was firstly reduced into hemiketal **12** (90% yield) using DIBAL-H, and then heated with tosylhydrazine (Scheme 4) to form tosylhydrazone **13** (85% yield). Due to its tautomerism and potential cyclization from the neighboring hydroxyl group, this compound (a single spot by TLC) was applied to next step without full characterization. Upon treatment with catecholborane at room temperature and heating the resulting mixture in THF with $NaOAc\cdot 3H_2O$, the hydrazone functionality was fully reduced to a methyl group, giving the key intermediate **14** in a delightful 67% yield. In comparison to a regular transformation through a 1,4-diol intermediate, this new protocol is advantageous in terms of step-economy since no hydroxyl protection is needed. More significantly in this case is that it enabled the utilization of vastly available lactone **6** as the C11–C14 synthon, so that the structurally complex



Scheme 3. Preparation of benzyl bromide **7**. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt, 91%; (b) PBr_3, DCM, 0 °C to rt, 80%.



Scheme 4. Preparation of the C8–C20 fragment **4**. Reagents and conditions: (a) LDA, **7**, THF, −78 °C, 82%; (b) Dibal–H, toluene, −78 °C, 90%; (c) H_2N–HNTs, 4 Å MS, MeOH, 55 °C, 85%; (d) catecholborane, THF, 0 °C to rt, then $NaOAc\cdot 3H_2O$, reflux, 67%; (e) $Me_3O^+\cdot BF_4^-$, proton sponge, DCM, 0 °C to rt, 88%; (f) hydrogen fluoride–pyridine, pyridine, CH_3CN, 0 °C to rt, 90%; (g) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 95%; (h) **8**, $BF_3\cdot OEt_2$, DCM, −78 °C, 78%, dr 10:1; (i) DIPEA, TBAI, DMAP, MOMCl, DCM, 0 °C to rt, then refluxing, 87%.

building block **4** could be produced at low cost. In sense of the growing number of newly discovered benzenoid/benzoquinone ansamycins that share a common C8–C14 structural feature,[3] this expedient strategy will find its extended application.

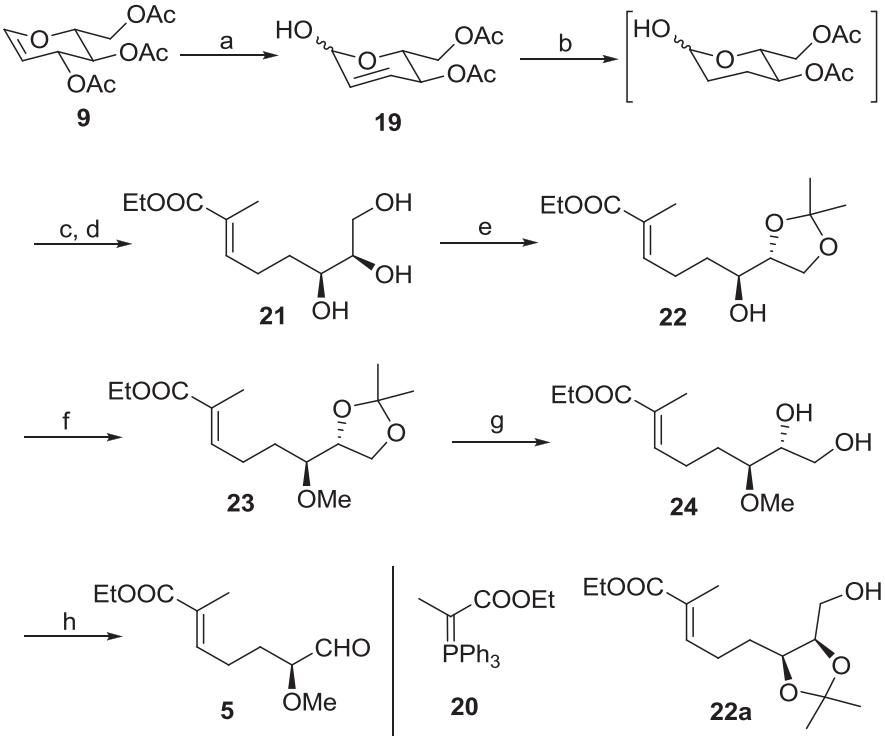
Further elaboration of aldehyde **17** from mono-protected diol **14** was straightforward. Upon O-methylation using Meerwein's salt (**15**), TBS removal using pyridinium hydrogen fluoride (**16**) and subsequent Swern oxidation, **17** was obtained in 73% yield over three steps with the spectra data well matching the previous report[4a] (Scheme 4).

Similar to that reported by Micalizio,[6n] the carbon chain elongation from aldehyde **17** was achieved by asymmetric propargylation using *S*-configured allenylstannane **8** (Scheme 4). A gram-scale reaction of **17** and **8** was carried out in the presence of boron trifluorideetherate, affording an approximate 10:1 mixture of the expected homopropargyl alcohol **18** and its stereoisomer in 78% total yield. Unfortunately, the two isomers were inseparable by silica gel chromatography, even after protection of the C10 hydroxyl with a MOM. However, this minor isomer coexisting with **4** may not affect the assembly of the target molecule and could be possibly removed during the following sequence. In a word, we were satisfied with the cost efficiency and scalability of this synthetic route to produce the key intermediate **4**, as the yield over the nine steps (from **6** to **4**) was up to 20%.

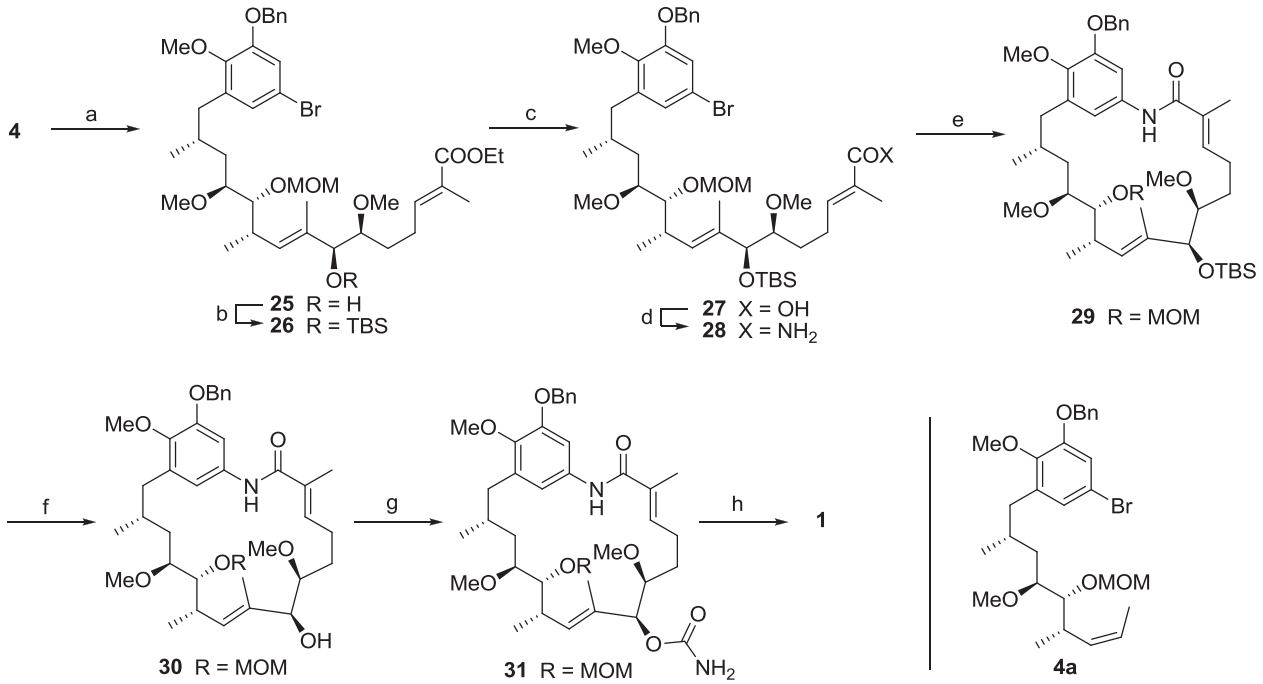
To prepare the C1–C7 fragment **5** (Scheme 5), commercially available tri-*O*-acetyl-D-glucal **9** was heated in water as it was described,[10] giving hemiketal **19** in 81% yield. Compound **19** was hydrogenated and the saturated hemiketal was subjected without purification to a Wittig reaction with phosphorus ylide **20**. The resulting α,β-unsaturated ester from the Wittig reaction was then directly hydrolyzed with K_2CO_3/EtOH to provide triol **21** in 71% yield over three steps. Acetonide protection of **21** with 2,2-dimethoxypropane in the presence of catalytic amount of PPTS produced a 5:1 mixture of **22** and **22a**, with the isolation of the former in 71% yield. After methylation of **22** with Meerwein's salt and subsequent acidic hydrolysis, diol **24** was obtained in good yield and then oxidized with $NaIO_4$ to give the aldehyde **5**. The spectra data and optical rotation of this compound well matched the previous report.[4]

With the above accomplishment in developing the synthesis of alkyne **4** and aldehyde **5**, we literally finished a formal total synthesis of reblastatin. However, we were concerned firstly for the purity issue of our sample of **4**, and secondly the reproducibility of Panek's assembly of the target molecule, in particular the yield, as their late stage synthesis was described on the basis of a series of 10-mg reactions.[4] Hence, the one-pot hydrozirconation/transmetalation of **4** and its subsequent addition to **5** was performed according to their procedure, but on a much larger scale (400 mg of **4**). As we had expected, the impurity in **4** did not cause problem at this moment, and pure **25** was obtained in 66% yield. The medium yield could be attributed to incomplete conversion of **4** since 25% of *cis*-olefin **4a** (contaminated by its isomers, Scheme 6) was formed in the reaction. Optimization was attempted by adding extra dimethylzinc or prolonging the time for Zr/Zn exchange, but the ratio of isolated **25**/**4a** kept unchanged, indicating that incomplete Zr/Zn exchange was not the reason.

With enough quantity of **25** in hand, our journey to **1** was continued following Panek's route (Scheme 6).[4] After smooth TBS protection of the C7–OH (**26**) and hydrolysis of the ethyl ester (**27**), we were facing the same problem as it was previously noted.[4a] The reported amidation method failed to give complete conversion of acid **27** into **28**, and the latter was isolated in <50% yield with recovery of >30% of **27**. To avoid the tedious recovery and retreatment procedure, better conditions were sought and finally led to the isolation of **28** in 80% yield by treating **27** with Boc_2O/NH_4HCO_3 in dioxane and pyridine.[11] More delightfully, the copper(I)-mediated macrolactam ring-closure of **28** proved well reproducible. Although in our case the use of excessive cuprous iodide seemed necessary to drive the reaction into completion, the yield of **29** was nearly identical to that reported by Panek. The remaining steps from **29** to **1** were straightforward using the known protocols, giving the target molecule in ca. 60% yield over three steps. These



Scheme 5. Preparation of the C1–C7 fragment **5**. Reagents and conditions: (a) H_2O, 80 °C, 81%; (b) 10% Pd/C, EtOAc, rt; (c) **20**, THF, reflux; (d) K_2CO_3, EtOH, H_2O, 71% over three steps; (e) 2,2-dimethoxypropane, PPTS, acetone, 71% **22** and 14% **22a**; (f) $Me_3O^+ \cdot BF_4^-$, proton sponge, DCM, 0 °C to rt, 90%; (g) 1 N HCl, CH_3CN, 96%; (h) $NaIO_4$, acetone/H_2O (1/1), 98%.



Scheme 6. The assembly of reblastatin. Reagents and conditions: (a) Cp_2ZrHCl, 50 °C, $ZnMe_2$ at −78 °C, then **5** at 0 °C, toluene, 66% for **25** and 25% for **4a**; (b) TBSOTf, 2,6-lutidine, DCM, 0 °C, 80%; (c) $LiOH·H_2O$, THF/MeOH/H_2O (2/2/1), 94%; (d) Boc_2O, 1,4-dioxane/pyridine (50/1), then NH_4HCO_3, 80%; (e) *N*,*N*′-dimethyl-1,2-ethanediamine, K_2CO_3, CuI, toluene, 100 °C, 82%; (f) pyridine hydrofluoride/pyridine/THF=1:1:2.5, 90%; (g) trichloroacetyl isocyanate, DCM, then MeOH, K_2CO_3, 76%; (h) $AlCl_3$, anisole, DCM, −78 °C to rt, 86%.

results provided solid experimental evidence that the previous report was well reproducible, and by modifying the synthesis of amide **28**, the overall yield of the assembly was significantly elevated (from 13% to 19%).

3. Conclusion

Convenient approaches to the two known coupling partners of reblastatin, i.e., the C8–C20 fragment **4** and C1–C7 fragment **5**, were described. Notably, our synthesis of **4** features the settlement of the challenging C-14 stereochemistry through a simple substrate-induced asymmetric alkylation of inexpensive chiral γ-lactone **6**. By taking advantage of the Caglioti reduction of hemiketal intermediate **12**, we successfully realized a fast transformation of the lactone carboxyl into the expected C-14 methyl. These results suggested that this lactone strategy could be applicable to the synthesis of other benzenoid/benzoquinone ansamycins. In addition, we were able to reproduce the late stage assembly of reblastatin previously reported by Panek, with one of the steps improved and on a >20 fold larger scale. Our first run of the eight-step synthetic sequence from **4** and **5** delivered 45 mg of the final product in 19% overall yield, indicating sub-gram supply of reblastatin by chemical synthesis is possible.

4. Experimental section

4.1. General methods and materials

Unless otherwise indicated, ^1H NMR data were recorded in $CDCl_3$ at 300 and 400 MHz with calibration of spectra to residual $CDCl_3$ (7.26 ppm), and ^{13}C NMR data were recorded at 75 and 100 MHz with calibration to the central line of $CDCl_3$ (77.00 ppm). All reactions were conducted in oven-dried glassware under an argon atmosphere with dry solvents, unless otherwise noted. DCM, pyridine, and 1,4-dioxane were dried by passing through activated alumina column. Anhydrous toluene, Et_2O, and THF were dried by distillation over sodium and benzophenone. Aldehyde **3**,[4] γ-lactone **6**,[12] and chiral allenylstannane (*S*)-**8**[13] were prepared as previously reported.

4.2. (3-(Benzyloxy)-5-bromo-2-methoxyphenyl)methanol (10)[8]

To a stirred solution of **3** (9.00 g, 28.0 mmol) in MeOH (95 mL) was added $NaBH_4$ (2.13 g, 56.0 mmol) in portions at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, and then at room temperature overnight. The solution was adjusted to pH 7 using AcOH and concentrated under reduced pressure. The residue was dissolved in DCM (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous phase was extracted with DCM (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was recrystallized from ethanol to afford the title compound as a white solid in 91% yield (8.25 g, 24.8 mmol). Mp: 83–85 °C. ^1H NMR (400 MHz, $CDCl_3$) δ=7.47–7.30 (m, 5H), 7.11 (d, J=1.5 Hz, 1H), 7.06 (d, J=1.5 Hz, 1H), 5.07 (s, 2H), 4.66 (s, 2H), 3.88 (s, 3H), 2.10 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.4, 146.6, 136.5, 136.4, 128.9, 128.4, 127.6, 123.9, 117.3, 116.5, 71.3, 61.2, 61.1; IR (neat) 3320, 1476, 1291, 1218, 1028, 748, 699 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{15}BrO_3$ M^+ 322.0205, found 322.0185.

4.3. 1-(Benzyloxy)-5-bromo-3-(bromomethyl)-2-methoxybenzene (7)

To a stirred solution of **10** (8.25 g, 24.8 mmol) in anhydrous DCM (60 mL) was added PBr_3 (2.17 mL, 22.9 mmol) dropwisely at 0 °C. Once addition completed, the solution was warmed to room temperature and stirred for 4 h before it was quenched with water (30 mL). The layers were separated and the aqueous layer was extracted further with DCM (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and

concentrated under reduced pressure. The residue was recrystallized from ethanol to afford the title compound as a white solid in 80% yield (7.87 g, 20.4 mmol). Mp: 73–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.50–7.31 (m, 5H), 7.11 (s, 1H), 7.06 (s, 1H), 5.07 (s, 2H), 4.47 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.7, 147.3, 136.3, 133.7, 128.9, 128.5, 127.6, 125.7, 118.1, 116.1, 71.3, 61.2, 27.2; IR (neat) 2942, 1481, 1304, 1233, 1058, 748, 698 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{15}Br_2O_2$ $(M+H)^+$ 384.9439, found 384.9457.

4.4. (3*R*,5*S*)-3-(3-(Benzyloxy)-5-bromo-2-methoxybenzyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one (11)

An oven-dried three-neck flask was purged with argon and charged with LDA (15.2 mL, 2.0 M solution in THF, 30.4 mmol) and anhydrous THF (65 mL) at −78 °C. A solution of **6** (5.14 g, 22.4 mmol) in THF (15 mL) was added slowly through a syringe under stirring. The resulting mixture was stirred for 1 h at −78 °C, and then **7** (7.87 g, 20.4 mmol) in THF (10 mL) was added dropwisely. After stirring was continued at −78 °C for additional 0.5 h, the reaction was quenched by slow addition of saturated aqueous NH_4Cl at −78 °C and gradually warmed to room temperature. The resulting mixture was extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:100 to 1:20, EtOAc/hexanes) to yield a light yellow oil in 82% yield (8.97 g, 16.7 mmol). $[\alpha]_D^{20}$ +6.15 (*c* 1.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.46–7.30 (m, 5H), 7.01 (d, *J*=1.9 Hz, 1H), 6.93 (d, *J*=1.9 Hz, 1H), 5.05 (s, 2H), 4.48 (m, 1H), 3.83 (s, 3H), 3.81 (d, *J*=2.9 Hz, 1H), 3.60 (dd, *J*=11.3, 2.8 Hz, 1H), 3.21 (dd, *J*=13.6, 4.6 Hz, 1H), 3.12 (m, 1H), 2.66 (dd, *J*=10.3, 13.5 Hz, 1H), 2.14 (m, 1H), 2.01 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=179.1, 152.7, 147.3, 136.5, 134.6, 128.9, 128.4, 127.6, 125.4, 116.4, 116.3, 78.4, 71.2, 65.3, 60.9, 40.6, 31.3, 29.9, 26.0, 18.5, −5.3, −5.4; IR (neat) 3034, 2931, 1771, 1573, 1479, 1258, 839 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{35}BrNaO_5Si$ $(M+Na)^+$ 557.1335, found 557.1329.

4.5. (3*R*,5*S*)-3-(3-(Benzyloxy)-5-bromo-2-methoxybenzyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-furan-2-ol (12)

To a stirred solution of **11** (7.80 g,14.6 mmol) in dry toluene (50 mL) was dropwisely added diisobutylaluminum hydride (14.6 mL, 1.2 M in toluene, 17.5 mmol) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 2 h and quenched by slow addition of MeOH (10 mL). The solution was allowed to warm to room temperature, diluted with EtOAc (50 mL), and stirred with saturated aqueous sodium/potassium tartrate (100 mL) for 2 h. The resulting clear biphasic solution was separated, and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:100 to 1:20, EtOAc/hexanes) to yield a clear oil in 90% yield (6.99 g, 13.0 mmol). $[\alpha]_D^{20}$ −2.16 (*c* 1.20, $CHCl_3$). The spectra of the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.52–7.31 (m, 5H), 6.99 (d, *J*=2.2 Hz, 1H), 6.92 (d, *J*=2.0 Hz, 1H), 5.11 (s, 1H), 5.06 (s, 2H), 4.42 (t, *J*=7.6 Hz, 1H), 3.94–3.75 (m, 4H), 3.52 (m, 1H), 2.72 (m, 1H), 2.58–2.41 (m, 2H), 2.14 (m, 1H), 1.65 (dd, *J*=12.7, 7.9 Hz, 1H), 0.89 (m, 9H), 0.22 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.8, 147.4, 136.7, 135.6, 128.9, 128.4, 127.6, 125.7, 116.2, 115.9, 102.4, 79.6, 71.2, 65.0, 60.9, 48.7, 32.3, 28.2, 26.1, 18.6, −5.2, −5.4; IR (neat) 3415, 3036, 2929, 1573, 1476, 1256, 839 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{37}BrNaO_5Si$ $(M+Na)^+$ 559.1491, found 559.1484.

4.6. *N*′-((2*R*,4*S*)-2-(3-(Benzyloxy)-5-bromo-2-methoxybenzyl)-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxypentylidene)-4-methylbenzenesulfonohydrazide (13)

To a stirred solution of **12** (6.99 g, 13.0 mmol) in anhydrous MeOH (120 mL) was added *p*-tosylhydrazine (4.83 g, 26.0 mmol) and powdered 4 Å molecular sieve (2.60 g). The suspension was heated at 55 °C under stirring for 16 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (1:30 to 1:10, EtOAc/hexanes) to give a pale yellow foam in 85% yield (7.76 g, 11.0 mmol). $[\alpha]_D^{20}$ −15.4 (*c* 1.45, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{33}H_{46}BrN_2O_6Si$ $(M+H)^+$ 705.2029, found 705.1983.

4.7. (2*S*,4*R*)-5-(3-(Benzyloxy)-5-bromo-2-methoxyphenyl)-1-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-2-ol (14)

Compound **13** (7.30 g, 10.3 mmol) obtained from last step was dissolved in anhydrous THF (60 mL) under argon and cooled to 0 °C. Catecholborane (31.0 mL, 31.0 mmol, 1.0 M in THF) was added dropwisely through a syringe. The solution was stirred for 15 min at 0 °C, and then 2 h at room temperature. $NaOAc\cdot 3H_2O$ (12.7 g, 93.0 mmol) was then added in one portion and the reaction mixture was heated at reflux for 12 h. After that, the solution was cooled to room temperature, diluted with Et_2O (70 mL), and washed with 1M NaOH (2×50 mL). The aqueous washes were extracted with Et_2O (2×50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:30, EtOAc/hexanes) to afford the desired compound as a colorless oil in 67% yield (3.65 g, 6.96 mmol). $[\alpha]_D^{20}$ −4.95 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.49–7.29 (m, 5H), 6.96 (d, *J*=2.0 Hz, 1H), 6.93 (d, *J*=1.9 Hz, 1H), 5.06 (s, 2H), 3.81(s, 3H), 3.77(m, 1H), 3.62 (dd, *J*=9.9, 3.2 Hz, 1H), 3.38 (dd, *J*=9.5, 7.7 Hz, 1H), 2.61 (dd, *J*=6.3, 13.2 Hz, 1H), 2.47 (dd, *J*=8.2, 13.2 Hz, 1H), 2.02 (m, 1H), 1.50 (m, 1H), 1.14 (m, 1H), 0.91 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.7, 147.4, 137.1, 136.7, 128.8, 128.3, 127.6, 126.0, 115.9, 115.5, 71.1, 69.9, 68.0, 60.8, 39.9, 38.0, 30.8, 26.1, 19.6, 18.5, −5.1, −5.2; IR (neat) 3472, 3033, 2929, 1573, 1475, 1255, 1092, 837 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{39}BrNaO_4Si$ $(M+Na)^+$ 545.1699, found 545.1711.

4.8. (((2*S*,4*R*)-5-(3-(Benzyloxy)-5-bromo-2-methoxyphenyl)-2-methoxy-4-methylpentyl)oxy)(*tert*-butyl)dimethylsilane (15)

To a stirred solution of **14** (3.20 g, 6.1 mmol) in DCM (70 mL) was added powdered 4 Å molecular sieves (1.93 g), proton sponge (3.92 g, 18.3 mmol), and $Me_3O^+\cdot BF_4^-$ (2.71 g, 18.3 mmol) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and 8 h at room temperature (monitored by TLC until total consumption of the starting material). The resulting mixture was filtered over Celite, and the filtrate was washed with 1 M aqueous $CuSO_4$ (70 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:100 to 1:50, EtOAc/hexanes) to afford a colorless oil in 88% yield (2.91 g, 5.43 mmol). $[\alpha]_D^{20}$ −8.61 (*c* 1.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.48–7.32 (m, 5H), 6.97 (s, 1H), 6.93 (s, 1H), 5.06 (s, 2H), 3.84 (s, 3H), 3.66 (dd, *J*=10.6, 5.6 Hz, 1H), 3.56 (dd, *J*=10.5, 4.7 Hz, 1H), 3.45 (s, 3H), 3.34 (m, 1H), 2.62 (dd, *J*=13.2, 6.1 Hz, 1H), 2.45 (dd, *J*=13.2, 8.6 Hz, 1H), 2.01 (m, 1H), 1.53 (m, 1H), 1.30 (m, 1H), 0.97–0.87 (m, 12H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.7, 147.4, 137.2, 136.8, 128.9, 128.3, 127.6, 126.1, 115.9, 115.5, 80.1, 71.1, 66.0, 60.8, 58.3, 39.4, 38.1, 30.9, 26.2, 19.7, 18.6, −5.0, −5.1; IR (neat) 3033, 2930, 1573, 1475, 1255, 1101, 838 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{41}BrNaO_4Si$ $(M+Na)^+$ 559.1855, found 559.1844.

4.9. (2*S*,4*R*)-5-(3-(Benzyloxy)-5-bromo-2-methoxyphenyl)-2-methoxy-4-methylpentan-1-ol (16)

To a stirred solution of **15** (2.70 g, 5.04 mmol) in MeCN (108 mL) in a nalgene vial was added premixed solution of [pyridine hydrofluoride/pyridine/CH_3CN (1:1:3) by volume] (75 mL) at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and 2 h at room temperature before 1 M aqueous HCl (170 mL) and Et_2O (170 mL) were added under stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3×170 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (1:10 to 1:3, EtOAc/hexanes) to afford a colorless oil in 90% yield (1.94 g, 4.55 mmol). $[\alpha]_D^{20}$ +6.88 (*c* 0.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ=7.38 (m, 5H), 6.97 (d, *J*=1.9 Hz, 1H), 6.90 (d, *J*=1.9 Hz, 1H), 5.06 (s, 2H), 3.82 (s, 3H), 3.72 (dd, *J*=11.5, 3.4 Hz, 1H), 3.48 (dd, *J*=11.5, 5.7 Hz, 1H), 3.40 (m, 1H), 3.40 (s, 3H),2.64 (dd, *J*=13.2, 5.8 Hz, 1H), 2.37 (dd, *J*=13.1, 8.8 Hz, 1H), 1.92 (m, 1H), 1.66 (m, 1H), 1.24 (m, 1H), 0.89 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.7, 147.3, 136.9, 136.6, 128.8, 128.3, 127.6, 126.0, 115.9, 115.6, 79.8, 71.1, 64.3, 60.8, 57.3, 38.4, 37.8, 31.0, 20.0; IR (neat) 3426, 3032, 2931, 1573, 1477, 1221, 1094, 739 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{27}BrNaO_4$ $(M+Na)^+$ 445.0990, found 445.0984.

4.10. (2*S*,4*R*)-5-(3-(Benzyloxy)-5-bromo-2-methoxyphenyl)-2-methoxy-4-methylpentanal (17)

To a stirred solution of oxalyl chloride (1.32 mL, 9.19 mmol) in DCM (11 mL) at −78 °C was added dimethyl sulfoxide (1.30 μL, 18.3 mmol) in DCM (11 mL) under argon. The reaction mixture was stirred for 15 min before **16** (1.94 g, 4.55 mmol) in DCM (11 mL) was added dropwisely. After stirring was continued for 1 h, a solution of triethylamine (2.55 mL, 18.3 mmol) in DCM (11 mL) was added over a period of 0.5 h. After the solution was stirred at −78 °C for additional 0.5 h, it was allowed to warm to room temperature and saturated aqueous $NaHCO_3$ (40 mL) was added. The layers were separated and the aqueous phase was extracted with DCM (3×40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:20, EtOAc/hexanes) to afford light yellow oil in 95% yield (1.84 g, 4.37 mmol). $[\alpha]_D^{20}$ −42.6 (*c* 1.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ=9.64 (d, *J*=5.1 Hz, 1H), 7.49−7.30 (m, 5H), 6.98 (d, *J*=2.3 Hz, 1H), 6.90 (d, *J*=2.2 Hz, 1H), 5.07 (s, 2H), 3.82 (s, 3H), 3.66 (m, 1H), 3.43 (s, 3H), 2.60 (dd, *J*=13.2, 6.5 Hz, 1H), 2.47 (dd, *J*=13.2, 8.2 Hz, 1H), 2.05 (m, 1H), 1.67 (m, 1H), 1.41 (m, 1H), 0.92 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=204.2, 152.7, 147.3, 136.6, 136.4, 128.8, 128.3, 127.6, 125.9, 116.0, 115.7, 84.3, 71.1, 60.8, 58.6, 37.7, 36.7, 30.5, 19.3; IR (neat) 3031, 2932, 2713, 1733, 1573, 1477, 1096, 858, 740 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}BrNaO_4$ $(M+Na)^+$ 443.0834, found 443.0821.

4.11. (4*S*,5*R*,6*S*,8*R*)-9-(3-(Benzyloxy)-5-bromo-2-methoxyphenyl)-6-methoxy-4,8-dimethylnon-2-yn-5-ol (18)

An oven-dried 10 mL flask was charged with (*S*)-allenylstannane **8** (2.04 g, 5.70 mmol) and DCM (7 mL) at −78 °C under argon. A solution of **17** (1.20 g, 2.85 mmol) in DCM (7 mL) was added, followed by slow addition of $BF_3{\cdot}OEt_2$ (0.72 mL, 5.7 mmol) through a syringe. The resulting solution was stirred for 0.5 h at −78 °C before saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was warmed up to room temperature. The two layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:15 to 1:10, EtOAc/hexanes) to afford a light yellow oil in 78% yield (1.08 g, 2.21 mmol). $[\alpha]_D^{20}$ −24.4 (*c* 1.10, $CHCl_3$); spectra for the major component: ^1H NMR (500 MHz, $CDCl_3$) δ=7.46−7.30 (m, 5H), 6.95 (d, *J*=2.0 Hz, 1H), 6.94 (d, *J*=2.0 Hz, 1H), 5.05 (s, 2H), 3.81 (s, 3H), 3.69 (dd, *J*=9.1, 3.1 Hz, 1H), 3.60 (m, 1H), 3.38 (s, 3H), 2.60 (dd, *J*=13.3, 5.9 Hz, 1H), 2.46 (dd, *J*=13.3, 8.9 Hz, 1H), 2.39 (m, 1H), 2.01 (m, 1H), 1.78 (d, *J*=2.3 Hz, 3H), 1.62 (m, 1H), 1.25 (m, 1H), 1.25 (d, *J*=6.6 Hz, 3H), 0.89 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.4, 147.1, 137.0, 136.4, 128.5, 128.0, 127.3, 125.7, 115.6, 115.1, 80.1, 79.8, 77.8, 73.3, 70.8, 60.5, 56.9, 37.9, 34.8, 30.3, 28.7, 18.8, 18.4, 3.4; IR (neat) 3452, 3033, 2933, 2245, 1573, 1477, 1091, 859, 736 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{33}BrNaO_4$ $(M+Na)^+$ 511.1460, found 511.1447.

4.12. 1-(Benzyloxy)-5-bromo-2-methoxy-3-((2*R*,4*S*,5*R*,6*S*)-4-methoxy-5-(methoxymethoxy)-2,6-dimethylnon-7-yn-1-yl) benzene (4)

MOMCl (1.34 mL, 17.7 mmol) was added to the stirred solution of **18** (1.08 g, 2.21 mmol), DIPEA (4.62 mL, 26.5 mmol), TBAI (163 mg, 0.44 mmol), and DMAP (81 mg, 0.66 mmol) in DCM (18 mL) at 0 °C under argon. The reaction mixture was warmed to room temperature, stirred for 0.5 h, and then heated at reflux for 8 h. After that, the mixture was cooled to room temperature and saturated aqueous $NaHCO_3$ (20 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:30 to 1:20, EtOAc/hexanes) to afford a light yellow oil in 87% yield (1.02 g, 1.92 mmol). $[\alpha]_D^{20}$+8.35 (*c* 1.03, $CHCl_3$); spectra for the major component: ^1H NMR (500 MHz, $CDCl_3$) δ=7.46−7.30 (m, 5H), 6.96 (d, *J*=2.0 Hz, 1H), 6.95 (d, *J*=2.0 Hz, 1H), 5.05 (s, 2H), 4.83 (d, *J*=6.6 Hz, 1H), 4.66 (d, *J*=6.6 Hz, 1H), 3.81 (s, 3H), 3.68 (d, *J*=8.7 Hz, 2H), 3.40 (s, 3H), 3.37 (s, 3H), 2.63 (dd, *J*=13.4, 5.6 Hz, 1H), 2.47 (m, 2H), 2.01 (m, 1H), 1.77 (d, *J*=3.1 Hz, 3H), 1.70 (m, 1H), 1.33 (m, 1H), 1.27 (d, *J*=5.2 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=152.7, 147.4, 137.4, 136.7, 128.8, 128.3, 127.6, 126.0, 115.9, 115.4, 97.5, 81.3, 80.9, 79.7, 78.2, 71.1, 60.8, 57.2, 56.3, 38.0, 37.0, 30.9, 28.8, 19.1, 18.8, 3.7; IR (neat) 3033, 2930, 2824,1573, 1477, 1099, 1034,739 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{37}BrNaO_5$ $(M+Na)^+$ 555.1722, found 555.1730.

4.13. (6*S*,7*R*,*E*)-Ethyl 6,7,8-trihydroxy-2-methyloct-2-enoate (21)

Tri-*O*-acetyl-D-glucal **9** (4.4 g, 16.2 mmol) was added into water (200 mL) under vigorous stirring at 80 °C. The solid melted at once to give an oil, and then dissolved within minutes. After 1.5 h at 80 °C, the solution was cooled to room temperature, and extracted with DCM (3×200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:5 EtOAc/hexanes) to afford **19** as a colorless oil in 81% yield (3.0 g, 13.04 mmol). The H NMR data matched that in the previously report.[10]

Product from the above step (3.0 g, 13.04 mmol) was dissolved in EtOAc (50 mL) and stirred under an atmosphere of H_2 (1 atm) overnight in the presence of 10% Pd on charcoal (0.3 g). The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude product was then mixed with ylide **20** (7.02 g, 19.4 mmol) in THF (100 ml). The resulting yellow solution was heated at reflux overnight and concentrated under reduced pressure. Upon dissolving the residue (10 g, mixed with triphenylphosphine oxide) in EtOH (50 mL) and H_2O (5 mL), K_2CO_3 (8.92 g, 64.6 mmol) was added. The mixture was stirred at

room temperature for 1.5 h, diluted with H_2O (20 mL), and extracted with DCM (5××80 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:30 MeOH/DCM) to afford a white solid (2.67 g, 71% over three steps). $[\alpha]_D^{20}$ −13.7 (*c* 2.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.76 (t, *J*=7.5 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.86–3.72 (m, 3H), 3.60 (m, 1H), 2.45 (s, 1H), 2.35 (m, 1H), 1.86 (s, 3H), 1.70–1.60 (m, 2H), 1.30 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=168.2, 141.0, 128.7, 73.7, 73.1, 63.3, 60.6, 31.7, 25.1, 14.3, 12.4; IR (neat) 3354, 3179, 1709, 1453, 1282, 1110 cm^{-1}; HRMS (ESI) (*m*/*z*) calcd for $C_{11}H_{21}O_5$ $[M+H]^+$ 233.1384, found 233.1381.

4.14. (*S*,*E*)-Ethyl-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2-methylhex-2-enoate (22)

2,2-Dimethoxypropane (13.2 mL) and pyridinium *p*-toluenesulfonate (135 mg, 0.54 mmol) were added to a solution of the triol **21** (2.5 g, 10.8 mmol) in acetone (80 mL). The reaction mixture was stirred for 2.5 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (1/12 EtOAc/hexanes) to afford **22** as a colorless oil in 71% yield (2.08 g, 7.65 mmol). A small amount of another regioisomer **22a** was also isolated in 14% yield (0.42 g, 1.54 mmol). $[\alpha]_D^{20}$ +5.7 (*c* 1.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.74 (t, *J*=7.5 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 4.03 (m, 1H), 3.97 (m, 1H), 3.90 (m, 1H), 3.78 (m, 1H), 2.36 (m, 2H), 1.86 (s, 3H), 1.59 (m, 1H), 1.50 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.29 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=168.1, 140.9, 128.7, 109.1, 78.6, 70.1, 64.5, 60.5, 31.4, 26.5, 25.3, 24.9, 14.3, 12.4; IR (neat) 3485, 2985, 1709, 1649, 1370, 1264, 1067 cm^{-1}; HRMS (ESI) (*m*/*zm*/*z*) calcd for $C_{14}H_{25}O_5$ $[M+H]^+$ 273.1697, found 273.1691.

4.15. (*S*,*E*)-Ethyl-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-methoxy-2-methylhex-2-enoate (23)

To a stirred solution of alcohol **22** (1.65 g, 6.07 mmol) in DCM (60 mL) was added powdered 4 Å molecular sieves (3.9 g), proton sponge (3.9 g, 18.2 mmol) and $Me_3O^+ \cdot BF_4^-$ (2.69 g, 18.2 mmol) under an argon atmosphere. The mixture was stirred at room temperature overnight, filter over Celite and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with 1 N aqueous $CuSO_4$ (40 mL), saturated aqueous NH_4Cl (40 mL), and brine (40 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:20, EtOAc/hexanes) to afford a colorless oil in 90% yield (1.52 g, 5.31 mmol). $[\alpha]_D^{20}$ +3.3 (*c* 2.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.75 (t, *J*=7.4 Hz, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 4.03 (m, 2H), 3.85 (m, 1H), 3.41 (s, 3H), 3.25 (m, 1H), 2.29 (m, 2H), 1.84 (s, 3H), 1.66 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.28 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=168.2, 141.6, 128.2, 109.1, 80.8, 77.2, 66.5, 60.4, 58.5, 29.4, 26.5, 25.3, 24.0, 14.3, 12.4; IR (neat) 2985, 2935, 1712, 1650, 1456, 1369, 1263, 1080 cm^{-1}; HRMS (ESI) (*m*/*z*) calcd for $C_{15}H_{27}O_5$ $[M+H]^+$ 287.1853, found 287.1848.

4.16. (6*S*,7*R*,*E*)-Ethyl 7,8-dihydroxy-6-methoxy-2-methyloct-2-enoate (24)

A solution of **23** (1.34 g, 4.70 mmol) in 1 M HCl (12 mL) and CH_3CN (25 mL) was stirred at room temperature for 1 h. The reaction mixture was neutralized with solid $NaHCO_3$, diluted with H_2O, and extracted with DCM (3×80 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:100, MeOH/DCM) to afford a colorless oil in 96% yield (1.11 g, 4.51 mmol). $[\alpha]_D^{20}$ +10.35 (*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.75 (t, *J*=7.4 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.74 (m, 3H), 3.42 (s, 3H), 3.29 (m, 1H), 2.30 (m, 2H), 1.85 (s, 3H), 1.76 (m, 1H), 1.64 (m, 1H), 1.30 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=168.2, 141.2, 128.4, 82.3, 72.2, 63.5, 60.5, 58.5, 28.9, 24.4, 14.3, 12.4; IR (neat) 3425, 2934, 1709, 1648, 1275, 1098 cm^{-1}; HRMS (ESI) (*m*/*z*) calcd for $C_{12}H_{23}O_5$ $[M+H]^+$ 247.1540, found 247.1539.

4.17. (*S*,*E*)-Ethyl 6-methoxy-2-methyl-7-oxohept-2-enoate (5)

Solid $NaIO_4$ (874 mg, 4.06 mmol) was added to a solution of diol **24** (500 mg, 2.03 mmol) in acetone (10 mL) and H_2O (10.0 mL). The reaction mixture was stirred at room temperature for 2 h before it was diluted with H_2O (20 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1:12, EtOAc/hexanes) to afford aldehyde **5** as a colorless oil in 98% yield (425 mg, 1.99 mmol). $[\alpha]_D^{20}$ −60.4 (*c* 1.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.68 (d, *J*=1.5 Hz, 1H), 6.71 (t, *J*=7.5 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.56 (m, 1H), 3.46 (s, 3H), 2.31 (m, 2H), 1.84 (s, 3H), 1.80 (m, 2H), 1.30 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ=203.7, 168.0, 140.1, 129.3, 85.1, 60.6, 58.4, 28.7, 23.9, 14.4, 12.5; IR (neat) 2935, 2829, 2723, 1733, 1710, 1650, 1447, 1267, 1132, 1092 cm^{-1}; HRMS (ESI) (*m*/*z*) calcd for $C_{11}H_{19}O_4$ $[M+H]^+$ 215.1278, found 215.1278.

4.18. (2*E*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*R*)-Ethyl-15-(3-(benzyloxy)-5-bromo-2-methoxyphenyl)-7-hydroxy-6,12-dimethoxy-11-(methoxymethoxy)-2,8,10,14-tetramethylpentadeca-2,8-dienoate (25)

To a stirred solution of **4** (420 mg, 0.787 mmol) in toluene (7 mL) under argon was added Cp_2ZrHCl (425 mg, 1.65 mmol). The reaction mixture was heated at 50 °C for 6 h, and then cooled to −78 °C. A solution of dimethylzinc (0.98 mL, 1.20 M in toluene) was added dropwisely and the solution was warmed to 0 °C. Aldehyde **5** (253 mg, 1.18 mmol) in toluene (1 mL) was added dropwisely and the resulting mixture was stirred for an additional hour at 0 °C before it was quenched with saturated aqueous NH_4Cl (5 mL). The two layers were separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:10 to 1:2, EtOAc/hexanes) to yield firstly *Z*-alkene **4a** as a clear oil (105 mg, 0.197 mmol, 25%) and then the title compound **4** as a yellow glass (390 mg, 0.521 mmol, 66%). $[\alpha]_D^{20}$ +10.3 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.49–7.30 (m, 5H), 6.94 (m, 2H), 6.68 (t, *J*=6.8 Hz, 1H), 5.33 (d, *J*=10.0 Hz, 1H), 5.06 (s, 2H), 4.83 (d, *J*=6.5 Hz, 1H), 4.62 (d, *J*=6.6 Hz, 1H), 4.16 (q, *J*=7.1 Hz, 2H), 3.87 (d, *J*=6.6 Hz, 1H), 3.80 (s, 3H), 3.60 (d, *J*=8.6 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.29 (s, 3H), 3.23 (m, 2H), 2.57 (m, 2H), 2.43 (m, 1H), 2.25 (m, 2H), 1.97 (m, 1H), 1.83 (s, 3H), 1.74 (m, 1H), 1.65 (s, 3H), 1.57 (m, 1H), 1.32–1.15 (m, 5H), 1.08 (d, *J*=6.6 Hz, 3H), 0.78 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=168.1, 152.6, 147.4, 141.3, 137.2, 136.7, 134.1, 131.8, 128.8, 128.5, 128.3, 127.6, 125.9, 115.9, 115.4, 97.7, 81.6, 81.5, 80.1, 78.8, 71.1, 60.8, 60.7, 58.7, 57.2, 56.3, 37.9, 37.0, 34.7, 30.7, 29.6, 24.2, 19.3, 17.9, 14.5, 12.8, 12.6; HRMS (ESI) *m*/*z* calcd for $C_{39}H_{57}BrNaO_9$ $(M+Na)^+$ 773.3063, found 773.3056.

4.19. (2*E*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*R*)-Ethyl-15-(3-(benzyloxy)-5-bromo-2-methoxyphenyl)-7-((*tert*-butyldimethylsilyl)oxy)-6,12-dimethoxy-11-(methoxymethoxy)-2,8,10,14-tetramethylpentadeca-2,8-dienoate (26)

An oven-dried flask was charged with **25** (390 mg, 0.521 mol) and DCM (5.9 mL) at 0 °C. The reaction was protected under argon and 2,6-lutidine (0.24 mL, 2.09 mmol) was added, followed by

TBSOTf (0.24 mL, 1.04 mmol) dropwisely. The reaction mixture was stirred for 2 h at 0 °C before it was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The two layers were separated and the aqueous layer was extracted with DCM (3×5 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:30 to 1:10, EtOAc/hexanes) to yield a yellow glass (360 mg, 0.417 mmol, 80%). $[\alpha]_D^{20}$ +20.7 (*c* 1.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ=7.50–7.29 (m, 5H), 6.94 (s, 2H), 6.67 (t, *J*=7.0 Hz, 1H), 5.16 (d, *J*=9.8 Hz, 1H), 5.05 (s, 2H), 4.84 (d, *J*=6.6 Hz, 1H), 4.62 (d, *J*=6.4 Hz, 1H), 4.14 (q, *J*=7.1 Hz, 2H), 3.96 (d, *J*=6.6 Hz, 1H), 3.80 (s, 3H), 3.60 (d, *J*=9.4 Hz, 1H), 3.46 (s, 3H), 3.40 (s, 3H), 3.28 (s, 3H), 3.20 (d, *J*=10.4 Hz, 1H), 3.08 (m, 1H), 2.60 (dd, *J*=13.4, 5.4 Hz, 1H), 2.47 (m, 2H), 2.24 (m, 2H), 1.98 (m, 1H), 1.81 (s, 3H), 1.78 (m, 1H), 1.60 (s, 3H), 1.47 (m, *J*=7.0 Hz, 1H), 1.37–1.11 (m, 5H), 1.05 (d, *J*=6.4 Hz, 3H), 0.89 (s, 9H), 0.77 (d, *J*=6.4 Hz, 3H), 0.07 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=167.6, 152.1, 146.8, 141.2, 136.7, 136.1, 134.6, 130.4, 128.2, 128.1, 127.7, 127.0, 125.3, 115.3, 114.8, 97.1, 83.2, 80.8, 80.4, 79.2, 70.5, 60.2, 60.0, 59.5, 56.4, 55.7, 37.4, 36.2, 34.0, 30.0, 29.8, 25.5, 24.6, 18.7, 17.8, 17.3, 13.9, 12.2, 12.0, −5.0, −5.2; HRMS (ESI) *m*/*z* calcd for $C_{45}H_{71}BrNaO_9Si$ $(M+Na)^+$ 885.3948, found 885.3895.

4.20. (2*E*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*R*)-15-(3-(Benzyloxy)-5-bromo-2-methoxyphenyl)-7-((*tert*-butyldimethylsilyl)oxy)-6,12-dimethoxy-11-(methoxymethoxy)-2,8,10,14-tetramethylpentadeca-2,8-dienoic acid (27)

Ester **26** (350 mg, 0.405 mmol) was dissolved in a mixture of THF/MeOH/H_2O (2:2:1 by volume, 29 mL). Then $LiOH\cdot H_2O$ (338 mg, 8.10 mmol) was added and the stirring was continued for 48 h at room temperature before it was concentrated under reduced pressure. The residue was diluted with a buffer of NaH_2PO_4 (30 mL, pH 4.5) and extracted with DCM (3×30 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude acid was essentially pure and used in the next step without further purification (318 mg, 0.381 mmol, 94%). $[\alpha]_D^{20}$ +15.9 (*c* 1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ=7.50–7.30 (m, 5H), 6.94 (s, 2H), 6.81 (t, *J*=7.2 Hz, 1H), 5.16 (d, *J*=9.7 Hz, 1H), 5.05 (s, 2H), 4.84 (d, *J*=6.6 Hz, 1H), 4.61 (d, *J*=6.5 Hz, 1H), 3.96 (d, *J*=6.5 Hz, 1H), 3.80 (s, 3H), 3.59 (d, *J*=9.4 Hz, 1H), 3.46 (s, 3H), 3.40 (s, 3H), 3.28 (s, 3H), 3.20 (d, *J*=10.5 Hz, 1H), 3.08 (m, 1H), 2.60 (dd, *J*=13.5, 5.7 Hz, 1H), 2.54–2.35 (m, 2H), 2.35–2.15 (m, 2H), 1.98 (m, 1H), 1.81 (s, 3H), 1.72 (m, 1H), 1.60 (s, 3H), 1.49 (m, 1H), 1.39–1.12 (m, 2H), 1.05 (d, *J*=6.6 Hz, 3H), 0.89 (s, 9H), 0.76 (d, *J*=6.5 Hz, 3H), 0.07 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.0, 152.6, 147.4, 144.7, 137.2, 136.7, 135.1, 130.9, 128.8, 128.3, 127.6, 127.5, 125.9, 115.9, 115.4, 97.6, 83.8, 81.4, 80.8, 79.9, 71.1, 60.8, 60.0, 57.1, 56.3, 38.0, 36.8, 34.6, 30.6, 30.2, 26.1, 25.4, 19.3, 18.4, 17.9, 12.8, 12.3, −4.4, −4.6; HRMS (ESI) *m*/*z* calcd for $C_{43}H_{67}BrNaO_9Si$ $(M+Na)^+$ 857.3635, found 857.3627.

4.21. (2*E*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*R*)-15-(3-(Benzyloxy)-5-bromo-2-methoxyphenyl)-7-((*tert*-butyldimethylsilyl)oxy)-6,12-dimethoxy-11-(methoxymethoxy)-2,8,10,14-tetramethylpentadeca-2,8-dienamide (28)

To a stirred solution of acid **27** (250 mg, 0.299 mmol) in a mixture of 1,4-dioxane (10 mL) and pyridine (0.2 mL) was added Boc_2O (1.10 g, 5.05 mmol). The reaction mixture was stirred for 15 min before addition of NH_4HCO_3 (400 mg, 5.06 mmol). The stirring was continued for 18 h at room temperature (monitor by TLC). After complete consumption of the mixed anhydride, the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:5 to 1:0, EtOAc/hexanes) to yield a light yellow glass (200 mg, 0.239 mmol, 80%). $[\alpha]_D^{20}$ +13.6 (*c* 1.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ=7.50–7.30 (m, 5H), 6.94 (dd, *J*=6.8, 2.2 Hz, 2H), 6.31 (t, *J*=7.2 Hz, 1H), 5.30 (br, 1H), 5.15 (d, *J*=9.7, 1H), 5.06 (s, 2H), 4.83 (d, *J*=6.6 Hz, 1H), 4.62 (d, *J*=6.6 Hz, 1H), 3.95 (d, *J*=6.7 Hz, 1H), 3.79 (s, 3H), 3.59 (d, *J*=9.3 Hz, 1H), 3.45 (s, 3H), 3.42 (d, *J*=3.8 Hz, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 3.20 (d, *J*=10.5 Hz, 1H), 3.09 (m, 1H), 2.60 (dd, *J*=5.3, 13.4 Hz, 1H), 2.50 (m, 1H), 2.41 (m, 1H), 2.31–2.10 (m, 2H), 1.96 (m, 1H), 1.81 (s, 3H), 1.73 (m, 1H), 1.59 (s, 3H), 1.46 (m, 1H), 1.37–1.13 (m, 2H), 1.05 (d, *J*=6.6 Hz, 3H), 0.89 (s, 9H), 0.75 (d, *J*=6.6 Hz, 3H), 0.07 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=171.7, 152.6, 147.3, 137.4, 137.3, 136.6, 135.1, 131.0, 130.4, 128.8, 128.3, 127.6, 125.9, 115.9, 115.3, 97.6, 83.9, 81.4, 80.9, 79.9, 71.1, 60.8, 60.0, 57.1, 56.3, 38.0, 36.9, 34.6, 30.7, 30.5, 26.0, 25.1, 19.3, 18.3, 17.8, 12.9, 12.7, −4.4, −4.7; HRMS (ESI) *m*/*z* calcd for $C_{43}H_{68}BrNNaO_8Si$ $(M+Na)^+$ 856.3795, found 856.3764.

4.22. (4*E*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-20-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-13-(methoxymethoxy)-4,10,12,16-tetramethyl-,14,19-trimethoxy-2-azabicyclo[16.3.1]docosa-1(21),4,10,18(22),19-pentaen-3-one (29)

An oven-dried sealed tube was charged with amide **28** (150 mg, 0.180 mmol), K_2CO_3 (371 mg, 2.69 mmol), and anhydrous toluene (12 mL). The mixture was fully degassed by ultrasonic under argon. Then cuprous iodide (174 mg, 0.916 mmol) and *N*,*N*′-dimethyl-1,2-ethanediamine (191 μL, 1.79 mmol) were added successively and the suspension turned to deep green. The sealed tube was closed and the mixture was heated at 100 °C for 36 h. The suspension was filtered through a plug of silica gel and the filter cake was washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography (1:5 to 1:1, EtOAc/hexanes) to yield a clear glass (111 mg, 0.147 mmol, 82%). $[\alpha]_D^{20}$ +82.6 (*c* 1.48, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ=7.51–7.28 (m, 6H), 6.92 (br, 1H), 6.43 (d, *J*=1.9 Hz, 1H), 6.01 (t, *J*=6.4 Hz, 1H), 5.11 (m, 1H), 5.09 (s, 2H), 4.81 (d, *J*=6.7 Hz, 1H), 4.67 (d, *J*=6.7 Hz, 1H), 3.83 (m, 1H), 3.80 (s, 3H), 3.52 (m, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.26 (d, *J*=8.5 Hz, 1H), 3.04 (m, 1H), 2.69 (dd, *J*=13.5, 7.6 Hz, 1H), 2.66–2.49 (m, 2H), 2.35–2.09 (m, 2H), 1.81 (d, *J*=6.4 Hz, 1H), 1.71–1.58 (m, 4H), 1.49 (s, 3H), 1.37–1.14 (m, 3H), 1.08 (d, *J*=6.6 Hz, 3H), 0.88 (s, 9H), 0.83 (d, *J*=6.6 Hz, 3H), 0.07 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=172.8, 152.4, 145.5, 137.1, 137.0, 135.4, 134.9, 133.8, 132.6, 132.2, 128.8, 128.2, 127.6, 117.8, 106.0, 97.7, 83.8, 83.7, 82.7, 80.7, 70.8, 61.1, 61.0, 57.6, 56.3, 35.9, 35.5, 34.4, 33.2, 31.5, 26.1, 24.7, 20.2, 18.4, 17.2, 13.7, 11.4, −4.4, −4.6; HRMS (ESI) *m*/*z* calcd for $C_{43}H_{67}NNaO_8Si$ $(M+Na)^+$ 776.4534, found 776.4522.

4.23. (4*E*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-20-(Benzyloxy)-9-hydroxy-13-(methoxymethoxy)-4,10,12,16-tetramethyl-14,19-trimethoxy-2-azabicyclo[16.3.1]docosa-1(21),4,10,18(22),19-pentaen-3-one (30)

Compound **29** (110 mg, 0.145 mmol) was placed in a nalgene vial and CH_3CN (11 mL) was added followed by the premixed solution of pyridine hydrofluoride/pyridine/CH_3CN (1:1:2.5 by volume, 5.0 mL). The reaction mixture was stirred at room temperature for 24 h before it was quenched by addition of saturated aqueous $NaHCO_3$ (20 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:3 to 1:0, EtOAc/hexanes) to yield a clear glass (84 mg, 0.131 mmol, 90%). $[\alpha]_D^{20}$ +99.1 (*c* 1.53, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ=8.00 (br, 1H), 7.53–7.28 (m, 6H), 6.42 (s, 1H),

6.06 (t, J=6.4 Hz, 1H), 5.39 (d, J=9.3 Hz, 1H), 5.10 (s, 2H), 4.76 (d, J=6.7 Hz, 1H), 4.67 (d, J=6.7 Hz, 1H), 3.82 (m, 1H), 3.80 (s, 3H), 3.52 (d, J=6.4 Hz, 1H), 3.45 (s, 3H), 3.43 (s, 3H), 3.38 (m, 1H), 3.38 (s, 3H), 3.21 (m, 1H), 2.81–2.59 (m, 3H), 2.49 (m, 1H), 2.32 (m, 1H), 2.22 (m, 1H), 1.74 (s, 3H), 1.69–1.60 (m, 3H), 1.57 (s, 3H), 1.34 (m, 1H), 1.10 (d, J=6.6 Hz, 3H), 0.92 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=171.2, 152.3, 144.9, 137.1, 135.9, 135.4, 134.2, 133.8, 133.3, 132.7, 128.7, 128.1, 127.6, 116.0, 104.9, 97.5, 83.3, 83.2, 81.1, 79.7, 70.7, 61.0, 59.2, 58.0, 56.2, 36.8, 35.9, 34.2, 33.7, 30.9, 24.5, 20.9, 17.3, 13.5, 12.2; HRMS (ESI) m/z calcd for $C_{37}H_{53}NNaO_8$ $(M+Na)^+$ 662.3669, found 662.3664.

4.24. (4*E*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-Carbamicacid-20-(benzyloxy)-13-(methoxymethoxy)-4,10,12,16-tetramethyl-8,14,19-trimethoxy-3-oxo-2-azabicyclo[16.3.1]docosa-1(21),4,10,18(22),19-pentaen-9-yl ester (31)

Trichloroacetyl isocyanate (32 μL, 0.263 mmol) was added to a stirred solution of **30** (84 mg, 0.131 mmol) in DCM (16.8 mL) and the reaction mixture was stirred for 15 min. MeOH (21 mL) was added followed by K_2CO_3 (84 mg, 0.604 mmol), and stirring was continued for 0.5 h (monitor by TLC). The solvent was evaporated under reduced pressure, and the residue was diluted with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:1 to 2:1, EtOAc/hexanes) to yield a clear glass (68 mg, 0.100 mmol, 76%). $[\alpha]_D^{20}$ +66.9 (c 1.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.29 (br, 1H), 7.53–7.27 (m, 5H), 6.42 (s, J=2.0 Hz, 1H), 6.09 (t, J=7.5 Hz, 1H), 5.41 (d, J=9.7 Hz, 1H), 5.23 (s, 1H), 5.11 (m, 2H), 4.86 (d, J=6.7 Hz, 1H), 4.64 (d, J=6.7 Hz, 1H), 3.79 (s, 3H), 3.60 (d, J=8.7 Hz, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 3.39 (m, 2H), 3.32 (s, 3H), 3.26 (d, J=5.3 Hz, 1H), 2.71–2.51 (m, 2H), 2.44 (m, 2H), 2.26 (m, 1H), 1.84 (s, 3H), 1.77 (m, 1H), 1.67 (m, 2H), 1.59 (s, 3H), 1.55 (m, 1H), 1.46 (m, 1H), 1.09 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=170.5, 156.8, 152.1, 144.7, 137.3, 136.1, 134.9, 134.6, 133.5, 130.1, 128.7, 128.0, 127.6, 115.0, 110.0, 104.5, 97.4, 84.3, 80.5, 80.2, 77.5, 70.7, 61.1, 59.0, 56.9, 56.3, 37.0, 34.9, 34.5, 30.0, 29.4, 25.9, 20.9, 17.8, 13.7, 13.3; HRMS (ESI) m/z calcd for $C_{38}H_{54}N_2NaO_9$ $(M+Na)^+$ 705.3727, found 705.3721.

4.25. Reblastatin (1)

Anisole (31 mL) was added to a suspension of aluminum trichloride (360 mg, 2.71 mmol) in DCM (24 mL) at −78 °C and the resulting light yellow solution was stirred for additional 5 min. Then **29** (65 mg, 0.0952 mmol) in DCM (7.5 mL) was added dropwisely. The solution was allowed to gradually warm up to 0 °C over 3 h and the stirring was continued for additional 1 h at room temperature. Aqueous HCl (0.5 M, 15 mL) was added slowly and the mixture was diluted with saturated aqueous NH_4Cl (15 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1:100 to 1:10, MeOH/DCM) to yield reblastatin as a white solid (45 mg, 0.0819 mmol, 86%). $[\alpha]_D^{20}$ +59.2 (c 1.13, $CHCl_3$); ^{1}H NMR (600 MHz, DMSO) δ=9.23 (s, 1H), 9.21 (s, 1H), 6.86 (br, 1H), 6.50 (br, 2H), 6.29 (s, 1H), 5.85 (s, 1H), 5.30 (d, J=9.1 Hz, 1H), 4.87 (d, J=7.4 Hz, 1H), 4.31 (d, J=5.2 Hz, 1H), 3.63 (s, 3H), 3.33 (s, 3H), 3.33 (m, 1H), 3.27 (m, 1H), 3.21 (s, 3H), 3.01 (m, 1H), 2.57 (dd, J=13.3, 6.2 Hz, 1H), 2.38 (m, 2H), 2.22 (m, 1H), 2.11 (m, 1H), 1.75 (m, 1H), 1.68 (s, 3H), 1.55 (m, 1H), 1.43 (s, 3H), 1.36 (m, 1H), 1.26 (m, 1H), 1.15 (m, 1H), 0.90 (d, J=6.6 Hz, 3H), 0.80 (d, J=5.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO) δ=170.3, 156.2, 149.9, 142.5, 134.6, 133.5, 133.4, 132.2, 129.7, 114.7, 107.2, 81.1, 80.7, 79.5, 73.7, 59.8, 58.3, 56.5, 35.8, 34.3, 33.7, 31.2, 29.8, 23.6, 19.7, 16.2, 13.1, 11.7; HRMS (ESI) m/z calcd for $C_{29}H_{44}N_2NaO_8$ $(M+Na)^+$ 571.2995, found 571.3001.

Acknowledgements

This project received financial support from National Natural Science Foundation of China (_501100001809) (21272279). The authors received valuable advice from Dr. Hanqing Dong (Arvinas Inc.) during the preparation of the manuscript.

Supplementary data

^{1}H and C NMR spectra for all new and important known compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.020.

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