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A Formal Synthesis of (−)-Cyanolide A Featuring a Stereoselective Mukaiyama Aldol Reaction and Oxocarbenium Reduction

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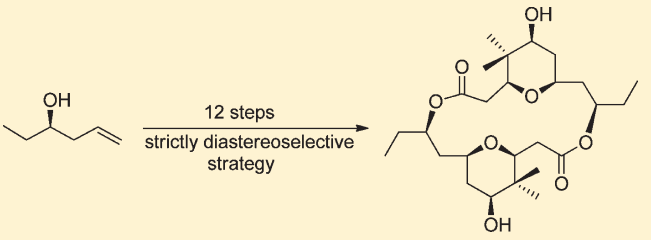
Supporting Information

ABSTRACT: The formal synthesis of the marine natural product (−)-cyanolide A is presented. The synthetic strategy is centered on two acyclic diastereoselective reactions and a single cyclic reaction with modest to excellent dr based on an initial stereocenter. Most notable is a highly stereoselective oxocarbenium reduction based on a "mismatched" reactive conformer to afford the β-*C*-glycoside subunit leading to an efficient synthesis of the diolide aglycon in 12 overall steps.

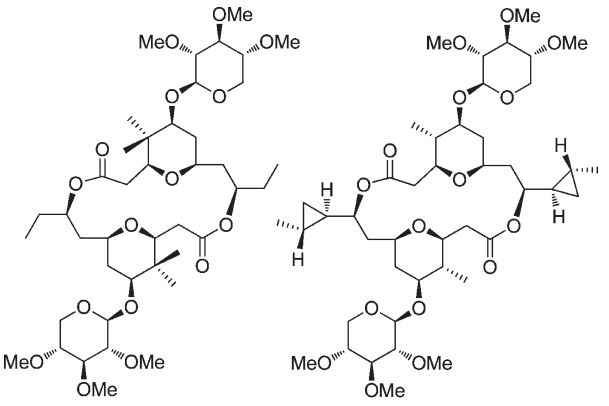


Marine-based organisms continue to provide synthetic organic chemists challenging, intriguing, and biologically relevant natural product targets. As disclosed in 2010 by Gerwick and co-workers, cyanolide A (**1**) is a dimeric 16-membered macrolide that was isolated from the extracts of a Papua New Guinea collection of *Lyngbya bouillonii*.[1] Cyanolide A has been shown to be a highly potent molluscicidal agent against the snail vector *Biomphalaria glabrata* with an $LC_{50} = 1.2\ \mu M$. Regrettably, nearly 1 billion people worldwide are either infected with or at risk of infection of schistosomiasis.[2] This prevalent parasitic infection can cause a host of health problems ranging from bladder cancer to kidney malfunction and ultimately death.[3] One of the major challenges of eradicating schistosomiasis lies in the complex lifecycle of the flatworm and its symbiotic nature with the mammalian and aquatic snail host. Thus, one leading theory on controlling the rate of schistosomiasis is to arrest the cell cycle of the host snail with an antimolluscicidal compound. Fortunately, **1** has great potential to combat this type of infection because of its high potency as an antimolluscicidal agent.

This highly functionalized 16-membered dimeric macrocycle has attracted moderate interest within the synthetic community because of its biological activity and similarity to the clavosolide family of natural products as highlighted in Scheme 1.[4] The efforts of the Hong group confirmed the relative and absolute stereochemistry of **1** through total synthesis by featuring an elegant sequential allylic oxidation followed by intramolecular oxy-Michael addition to the corresponding α,β-unsaturated aldehyde intermediate as the key step.[5] Ensuing dimerization and bis-glycosylation afforded the natural cyanolide A (**1**). In addition to the biological relevance, the polyfunctionality of the monomeric subunit resident in **1** and its close structural relationship to clavosolide A made it an attractive target to further investigate a "mismatched" oxocarbenium cation formation/reduction protocol.[6]

As isolated natural products become more structurally complex, the further development and understanding of known reaction processes is essential for the stereoselective construction

Scheme 1. Structural Similarity between Cyanolide A and Clavosolide A



of such compounds. Generally, the leading strategy for the synthesis of natural products centers on a single asymmetric induction followed by a series of diastereoselective reactions until the desired target is attained. While this tactic is a laudable goal, diastereoselective control of acyclic reactions tends to lag behind their cyclic counterparts. In this paper, we underscore the above-mentioned strategy by highlighting two acyclic and a single cyclic diastereoselective reaction with modest to excellent dr based on an initial stereocenter en route to the formal synthesis of **1**.

The retrosynthetic analysis of **1** followed the previous disconnection of Hong in that the carbohydrate moiety would be attached at the last step as shown in Scheme 2.[5] Completion of the dimerized diol **2** would be obtained via a tandem Yamaguchi esterification−macrolactonization reaction process of the hydroxyl

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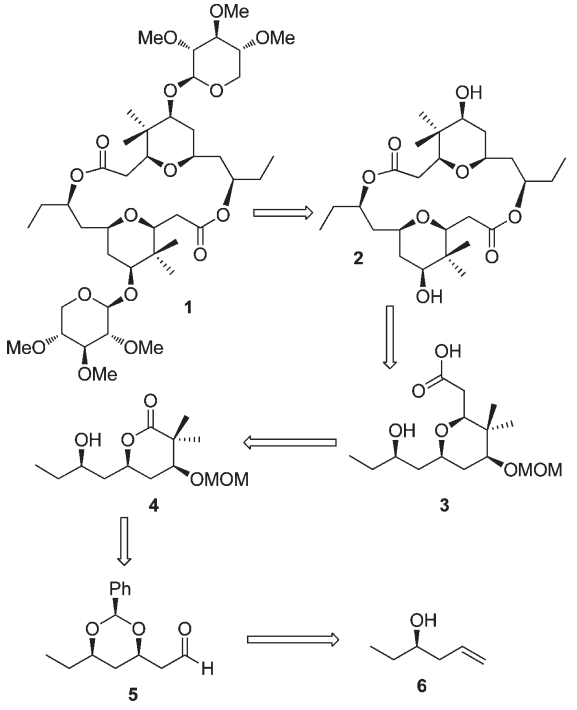
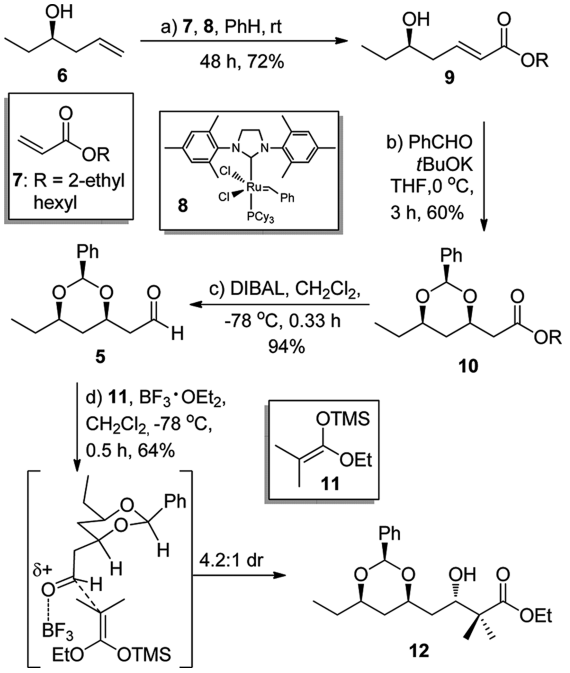
Scheme 2. Retrosynthetic Analysis of (−)-Cyanolide A



Scheme 3. Synthesis of the β-Hydroxy Ester 12



acid monomer **3**. Thus, *seco* acid **3** would be derived from a functionalization of the alkylation product of lactone **4** followed by a stereoselective mismatched oxocarbenium cation formation/reduction sequence to afford the necessary β-*C*-glycoside precursor. We envisaged the generation of lactone **4** from a sequential acetal deprotection/acid catalyzed cyclization event in which, in turn, the requisite stereocenter would be produced from a 1,3-directed Mukaiyama aldol reaction between the appropriate silyl ketene acetal and aldehyde **5**. Thus, the required aldehyde **5** could, in principle, be derived in three steps from **6** by means of a Ru-catalyzed cross-metathesis with an appropriate acrylate followed by an intramolecular oxy-Michael addition to set the second stereocenter and final partial DIBAL reduction of the ester moiety.

With this retrosynthetic plan in mind, the initial focus was placed on the synthesis of the β-hydroxy ester **12**. As shown in Scheme 3, treatment of the previously reported homoallylic alcohol **6** (prepared in one step via the asymmetric allylboration of propanal)[7] with 2-ethylhexyl acrylate (**7**) in the presence of Grubbs' second-generation catalyst (**8**) under the conditions as described by O'Doherty diastereoselectively provided the δ-hydroxy-(*E*)-α,β-unsaturated ester **9** in 72% yield.[8] It is worth noting that methyl acrylate in place of **7** worked equally well by TLC analysis; however, isolation and purification were troublesome due to the low molecular weight of the desired product. An ensuing tandem hemiketal formation/intramolecular hetero-Michael addition utilizing PhCHO and KO-*t*-Bu to **9** over 3 h at 0 °C afforded the *syn*-benzylidine acetal **10** in 60% yield and as a single diastereomer as assessed by ^{1}H NMR analysis.[9] Partial reduction of the ester moiety resident in **10** with DIBAL to the requisite aldehyde proceeded at −78 °C and was complete within 20 min by TLC analysis to furnish **5** in 94% yield and set the stage for the directed Mukaiyama aldol reaction with the *gem*-dimethyl silyl ketene acetal **11**. Thus, we initially attempted the union of **11** and **5** utilizing $TiCl_4$ as the Lewis acid promoter based on the 1,3-*anti*-chelation control model, but unfortunately, only starting material decomposition was observed.[10] Although $BF_3 \cdot OEt_2$ will only allow for chelation to the aldehyde carbonyl via an open transition state, we were encouraged by Evans' report based on their electrostatic model of modest to high levels of dr for 1,3-*anti*-products during a Mukaiyama aldol reaction with silyl enol ether nucleophiles.[11] In accordance with their model, the addition of **11** to aldehyde **5** readily proceeded with $BF_3 \cdot OEt_2$, via the presumed transition state shown in Scheme 3 to provide aldol adduct **12** in 64% with a modest dr of 4.2:1 for the desired 1,3-*anti*-product.

With aldol adduct **12** in hand, the focus was shifted to completion of the monomeric subunit via a stereoselective oxocarbenium reduction to forge the β-*C*-glycoside moiety as delineated in Scheme 4. Hence, treatment of hydroxy ester **12** with MOMCl and DIPEA afforded acetal **13** in 78% yield, analogous to our previous efforts with clavosolide A.[6] Conversion of the Mukayiama aldol adduct **13** into the desired lactone **4** was initiated by transforming **13** to the diol by means of hydrogenolysis of the benzylidene acetal followed by acid catalyzed lactonization. Along this line, treatment of **13** with H_2 and Pearlman's catalyst [$Pd(OH)_2$] at rt in MeOH led to the formation of the corresponding diol, which was used immediately without purification. Subsequent lactonization was accomplished under standard ester hydrolysis conditions by treating the crude diol with aqueous trifluoroacetic acid (TFA) in THF. The hydroxy lactone **4** was obtained in 73% yield from **13**.

With the synthesis of lactone **4** complete, our attention shifted toward the construction of the β-*C*-glycoside subunit. Thus, alkylation of lactone **4** with allylmagnesium bromide afforded the intermediate hemiketal **14**, which underwent tandem stereoselective oxocarbenium cation formation/reduction with TFA and Et_3SiH to afford the β-*C*-glycoside (as determined by NOE) **17**

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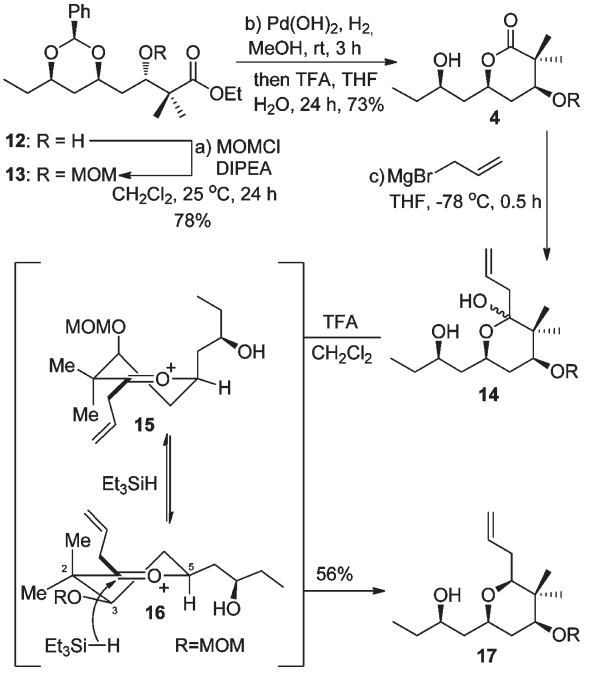
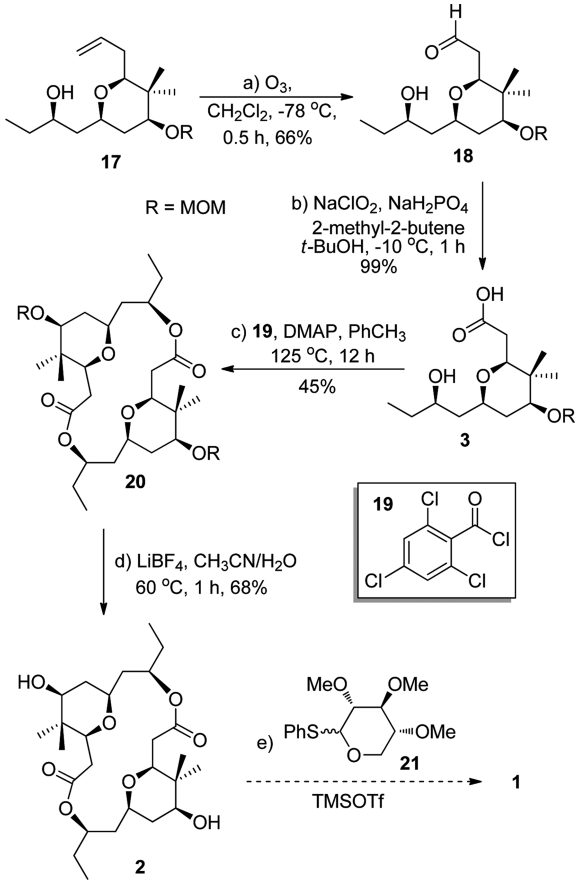
Scheme 4. Synthesis of the β-*C*-Glycoside 17



in 56% yield over the two-step sequence from **4**. Of the two possible reactive conformers (**15** versus **16**), and based on the isolated β-*C*-glycoside, the proposed conformer **16** places all of the substituents at C_3 and C_5 in the pseudoequatorial positions. In a variety of past projects from our laboratory, stereoselective endocyclic oxocarbenium reductions have placed the C_3 hydroxyl moiety in the axial position and the C_5 substituent in the pseudoequatorial geometry.[12] Typically, these oxocarbenium formation/reduction reactions are complete at $-78 \rightarrow -40$ °C within 0.25−0.5 h and provide the desired β-*C*-glycoside with >20:1 dr. On the basis of Woerpel's observations and our prior investigations, these C_3 axial and C_5 pseudoequatorial oxocarbenium conformations represent a "matched" geometry from a reactive conformer perspective. However, the reactive oxocarbenium conformer **16** places the C_3 and C_5 substituents in the pseudoequatorial positions.[13] Interestingly, the stereoselective oxocarbenium formation/reduction reaction required >12 h for completion at −20 °C as also seen in the synthesis of clavosolide A. Hence, it is once again suggested that **16** represents a "mismatched" reactive conformer that nonetheless allowed for a highly stereoselective oxocarbenium reduction, albeit with extended reaction time. It is worth noting that the yield is ∼10% lower over the three steps from lactone **4** than it was for an identical sequence during the synthesis of clavosolide A. We speculate that this is due to the *gem*-dimethyl substituent α to the lactone carbonyl of **4**, thus providing more steric hindrance for nucleophilic attack of the Grignard reagent.

With the functionalized β-*C*-glycoside **17** in hand, our focus turned toward completion of the formal synthesis of **1** as described in Scheme 5. Consequently, standard ozonolysis of the olefin moiety resident in **17** followed by a PPh_3 reductive workup provided aldehyde **18** in 66% yield. Subsequently, a Lindgren−Kraus−Pinnick oxidation provided the necessary *seco* acid **3** in virtually quantitative yield which was then used without further purification.[14] Dimerization of the monomeric acid **3** was

Scheme 5. Synthesis of 2 via a Yamaguchi Dimerization



accomplished under the previously reported Yamaguchi macrolactonization conditions to afford the MOM-protected aglycon **20** in a modest 45% yield.[6,15] Final deprotection of the two MOM acetals was accomplished utilizing $LiBF_4$ in aq MeCN furnishing aglycon **2** in a 68% yield, thus constituting a formal synthesis of **1**. The spectral data (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz), optical rotation, and HRMS data of synthetic **2** were in complete agreement with those previously reported.[4c−e,5] The final diastereoselective glycosylation of **2** with thioacetal **21** and TMSOTf could be carried out in accordance with the Hong report for the total synthesis of **1**.[5]

In summary, an extremely efficient formal synthesis of **1** has been successfully achieved in 12 steps. The described tactic underscores a strictly diastereoselective strategy which incorporates two acyclic and a single cyclic reaction with modest to excellent dr based on the initial stereocenter of alcohol **6**. Additionally, we have observed a highly stereoselective oxocarbenium reduction based on a "mismatched" reactive conformer to afford the β-*C*-glycoside subunit leading to an efficient synthesis of **2**.

EXPERIMENTAL SECTION

(5*R*,*E*)-2-Ethylhexyl 5-hydroxyhept-2-enoate (9). To a stirred solution of **6** (3.00 g, 29.9 mmol, 1.00 equiv) in anhydrous benzene (150 mL) under an atmosphere of Ar at rt was added 2-ethylhexyl acrylate (11.0 g, 59.9 mmol, 2.00 equiv) dropwise. To the resulting solution was added Grubbs' second-generation catalyst (0.509 g 0.599 mmol, 0.020 equiv), and the solution was allowed to stir for 48 h at rt.

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The reaction was then concentrated under reduced pressure. Subsequent flash chromatography (silica, 7% EtOAc/hexanes) afforded **9** as a brown, viscous oil (5.52 g, 72%): TLC R_f = 0.77 in 35% EtOAc/hexanes; $[\alpha]^{23}_D$ = −5.6 (*c* 0.055, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (m, 1H), 5.92 (dt, *J* = 15.8, 1.3 Hz, 1H), 4.05 (m, 2H), 3.70 (m, 1H), 2.42 (m, 1H), 2.33 (m, 1H), 1.55 (m, 4H), 1.37 (m, 2H), 1.30 (m, 6H), 0.97 (t, *J* = 7.6 Hz, 3H), 0.90 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 145.3, 124.3, 72.3, 67.2, 40.1, 39.2, 30.8, 30.3, 29.3, 24.2, 23.3, 14.4, 11.4, 10.2; IR (neat) cm^{-1} 3443, 2934, 1713, 1457, 737; HRMS (EI) calcd for $C_{15}H_{28}O_3$ [M − OH] 239.2011, found 239.2019.

2-Ethylhexyl 2-((4*R*,6*R*)-6-Ethyl-2-phenyl-1,3-dioxan-4-yl)-acetate (10). Ester **9** (1.93 g, 7.53 mmol, 1.00 equiv) was dissolved in anhydrous THF (75.0 mL) under Ar and cooled to 0 °C. To this solution were added benzaldehyde (0.890 g, 8.28 mmol, 1.10 equiv) and KO-*t*-Bu (0.0840 g, 0.753 mmol, 0.100 equiv) sequentially. This addition was repeated three times for benzaldehyde and 11 times for KO-*t*-Bu in 15 min intervals upon which the reaction was quenched via the addition of a pH 7.00 phosphate buffer solution (30.0 mL). The resulting mixture was warmed to rt and stirred vigorously until a distinct separation of layers was observed. The layers were partitioned with H_2O and Et_2O in a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the crude product. Subsequent flash chromatography (silica, 1% EtOAc/Hexanes) afforded **10** as a yellow, viscous oil (1.63 g, 60%): TLC R_f = 0.74 in 15% EtOAc/hexanes; $[\alpha]^{23}_D$ = −2.6 (*c* 0.057, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.55 (d, *J* = 6.4 Hz, 2H), 7.39 (m, 3H), 5.61 (s, 1H), 4.36 (m, 1H), 4.09 (m, 2H), 3.83 (m, 1H), 2.69 (dq, *J* = 7.3, 5.9 Hz, 2H), 1.77 (m, 2H), 1.63 (m, 2H), 1.45 (m, 3H), 1.34 (s, 6H), 1.06 (t, *J* = 7.5 Hz, 3H), 0.93 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 139.0, 128.9, 128.5, 126.5, 101.0, 78.3, 73.7, 67.4, 41.6, 39.1, 36.5, 30.8, 29.3, 29.2, 24.1, 23.0, 14.4, 11.3, 9.8; IR (neat) cm^{-1} 2941, 2869, 1731, 1458, 754, 700; HRMS (EI) calcd for $C_{22}H_{34}O_4$ 362.2457, found 362.2471.

2-((4*R*,6*R*)-6-Ethyl-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (5). To stirred solution of **10** (1.97 g, 5.44 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (27.2 mL) at −78 °C under Ar was added DIBAL-H as a 1.0 M solution in toluene (5.63 mL, 5.63 mmol, 1.20 equiv), dropwise. The mixture was allowed to stir at −78 °C until the starting material was consumed as indicated by TLC analysis (∼20 min) upon which the reaction was quenched via the addition of chilled acetone (48.0 mL). The resulting mixture was allowed to stir for 10 min, at which time the mixture was warmed to rt. To the mixture was added a 20% aqueous solution of sodium potassium tartrate (45.0 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated. Subsequent flash chromatography (silica, 7% EtOAc/hexanes) afforded **5** as a clear, viscous oil (1.19 g, 94%): TLC R_f = 0.30 in 10% EtOAc/hexanes; $[\alpha]^{23}_D$ = +1.2 (*c* 0.049, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.86 (t, *J* = 1.8 Hz, 1H), 7.49 (m, 2H), 7.35 (m, 3H), 5.58 (s, 1H), 4.40 (m, 1H), 3.79 (m, 1H), 2.87 (ddd, *J* = 16.8, 7.3, 2.0 Hz, 1H), 2.68 (ddd, *J* = 16.8, 5.2, 1.6 Hz, 1H), 1.71 (m, 2H), 1.60 (m, 1H), 1.47 (m, 1H), 1.00 (t, *J* = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 138.8, 129.0, 128.5, 126.4, 101.0, 78.3, 72.3, 49.8, 36.6, 29.1, 9.8; IR (neat) cm^{-1} 2962, 2873, 2729, 1723, 1345, 760, 697; HRMS (EI) calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1253.

(3*S*)-Ethyl 4-((4*S*,6*R*)-6-Ethyl-2-phenyl-1,3-dioxan-4-yl)-3-hydroxy-2,2-dimethylbutanoate (12). To a solution of **5** (1.13 g, 4.82 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (28.4 mL) at −78 °C was added silyl ketene acetal **11** (1.13 g, 5.98 mmol, 1.24 equiv) followed by $BF_3 \cdot OEt_2$ (0.85 g, 5.98 mmol, 1.24 equiv) dropwise. The resulting mixture was allowed to stir until the starting material was consumed as indicated by TLC analysis (∼30 min) and was subsequently quenched via addition of saturated aqueous $NaHCO_3$ (15.0 mL). The reaction was warmed to rt and partitioned between $CHCl_3$ and H_2O, and the aqueous layer was extracted with $CHCl_3$ (3 × 25 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated to yield the crude *β*-hydroxy ester. Subsequent flash chromatography (silica, 10% EtOAc/hexanes) afforded **12** as a clear viscous oil as a separable 4.2:1 mixture of diastereomers (1.08 g, 64%): TLC R_f = 0.81 in 37% EtOAc/hexanes; $[\alpha]^{23}_D$ = −11.3 (*c* 0.026, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$ δ 7.50 (m, 2H), 7.34 (m, 3H), 5.54 (s, 1H), 4.18 (m, 1H) 4.16 (q, *J* = 6.6 Hz, 2H), 4.07 (m, 1H), 3.71 (m, 1H), 2.93 (d, *J* = 5.9 Hz, 1H), 1.71 (m, 2H), 1.56 (m, 4H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 178.0, 139.3, 128.8, 128.4, 126.4, 100.8, 78.5, 74.3, 72.7, 61.0, 47.0, 38.3, 37.0, 29.2, 22.5, 20.7, 14.5, 9.8; IR (CH_2Cl_2) cm^{-1} 2972, 2875, 1723, 754, 703; HRMS (EI) calcd for $C_{20}H_{30}O_5$ 350.2093, found 350.2094.

(3*S*)-Ethyl 4-((4*R*,6*R*)-6-Ethyl-2-phenyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)-2,2-dimethylbutanoate (13). To a stirred solution of **12** (0.720 g, 2.06 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (7.00 mL) under Ar at 0 °C was added diisopropylethylamine (0.090 g, 0.720 mmol, 5.00 equiv). To the resulting solution was added MOMCl (0.030 g, 0.357 mmol, 2.50 equiv) dropwise, and the reaction was allowed to warm to rt and stirred until the starting material was consumed as indicated by TLC analysis (∼36 h). The reaction was then quenched via the dropwise addition of saturated aqueous $NaHCO_3$ and partitioned between CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude protected alcohol. Subsequent flash chromatography (silica, 7% EtOAc/hexanes) afforded **13** as a yellow viscous oil (0.630 g, 78%): TLC R_f = 0.92 in 37% EtOAc/hexanes; $[\alpha]^{23}_D$ = −13.9 (*c* 0.034, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.35 (m, 3H), 5.52 (s, 1H), 4.69 (d, *J* = 1.1 Hz, 2H), 4.11 (m, 4H), 3.38 (s, 3H), 1.64 (m, 6H), 1.40 (m, 1H), 1.22 (m, 6H), 1.13 (s, 3H), 1.00 (t, *J* = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 139.4, 128.6, 128.3, 126.3, 100.5, 99.1, 81.0, 78.5, 73.3, 60.7, 56.3, 47.5, 38.3, 37.4, 29.1, 21.5, 21.1, 14.3, 9.8; IR (CH_2Cl_2) cm^{-1} 2947, 1729, 1467, 922, 700; HRMS (EI) calcd for $C_{22}H_{34}O_6$ 394.2355, found 394.2360.

(4*S*,6*R*)-6-((*R*)-2-Hydroxybutyl)-4-(methoxymethoxy)-3,3-dimethyltetrahydro-2*H*-pyran-2-one (4). To a solution of **13** (0.530 g, 1.34 mmol, 1.00 equiv) in MeOH (20.0 mL) at rt was added $Pd(OH)_2$ (0.530 g). The mixture was then subjected to an atmosphere of H_2 until the starting material was consumed as indicated by TLC analysis (∼3 h). The mixture was subsequently filtered over Celite and concentrated in vacuo to afford the crude *syn*-diol, which was used without further purification.

To a solution of the crude diol (0.411 g, 1.34 mmol, 1.00 equiv) in a solution of THF (6.10 mL) and H_2O (0.620 mL) was added TFA (15.0 *μ*L, 0.201 mmol, 0.150 equiv), and the resulting mixture was refluxed for 24 h at 60 °C. The reaction was cooled to rt and quenched via the dropwise addition of saturated aqueous $NaHCO_3$. The mixture was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3 × 12 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude lactone. Subsequent flash chromatography (silica, 47% EtOAc/hexanes) afforded **4** as a clear, viscous oil (0.260 g, 73%): TLC R_f = 0.14 in 37% EtOAc/hexanes; $[\alpha]^{23}_D$ = +7.0 (*c* 0.030, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.74 (d, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.44 (m, 1H), 3.73 (m, 2H), 3.38 (s, 3H), 2.19 (m, 2H), 1.88 (m, 2H), 1.74 (m, 1H), 1.46 (m, 2H), 1.35 (s, 3H), 1.25 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 96.2, 76.0, 70.7, 56.1, 44.4, 43.2, 32.1, 30.7, 23.9, 21.5, 10.0. IR (CH_2Cl_2) cm^{-1} 2938, 1729, 1264, 1145, 1039, 737; HRMS (EI) calcd for $C_{13}H_{24}O_5$ [M − H] 259.1545, found 259.1554.

(*R*)-1-((2*R*,4*S*,6*S*)-6-Allyl-4-(methoxymethoxy)-5,5-dimethyltetrahydro-2*H*-pyran-2-yl)butan-2-ol (17). To a solution of **4** (0.160 g, 1.00 mmol, 1.00 equiv) in anhydrous THF (10.0 mL) at

−78 °C under Ar was added allylmagnesium bromide (0.640 mL, 1.0 M in Et_2O, 0.640 mmol, 2.80 equiv) dropwise over a period of 30 min. The resulting solution was allowed to stir at −78 °C until the starting material was consumed as indicated by TLC analysis (∼5 min), at which time the reaction was quenched via saturated aqueous NH_4Cl (5.00 mL). The layers were partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude hemiketal as a clear viscous oil, which was carried forward without further purification.

The crude hemiketal (0.302 g, 1.00 mmol, 1.00 equiv) was subsequently dissolved in CH_2Cl_2 under Ar and cooled to −50 °C, at which time TFA (0.456 g, 4.00 mmol, 4.00 equiv) was added dropwise followed immediately by Et_3SiH (1.05 g, 9.00 mmol, 9.00 equiv) dropwise. The resulting mixture was warmed to −15 °C over the course of ∼1 h and stirred until the reaction was complete as indicated by TLC analysis (∼14 h.). The reaction was then quenched via addition of saturated aqueous $NaHCO_3$ (3 mL), and the mixture was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude β-*C*-glycoside as a pale yellow, viscous, oil. Subsequent flash chromatography (silica, 12% EtOAc/hexanes) afforded **17** as a clear, viscous oil (0.160 g, 56%): TLC R_f = 0.45 in 27% EtOAc/hexanes; $[\alpha]^{23}_D$ = +2.5 (*c* 0.004, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.09 (m, 2H), 4.72 (d, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 3.87 (s, 1H), 3.72 (m, 1H), 3.57 (m, 1H), 3.37 (s, 3H), 3.28 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.09 (dd, *J* = 10.4, 2.3 Hz, 1H), 2.27 (m, 2H), 1.78 (m, 1H), 1.50 (m, 5H), 0.91 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 117.6, 96.2, 84.2, 81.4, 78.2, 73.9, 55.9, 41.9, 38.8, 35.4, 34.0, 30.5, 22.9, 13.7, 10.1; IR (CH_2Cl_2) cm^{-1} 2936, 2879, 1150, 1091, 1032, 913; HRMS (EI) calcd for $C_{16}H_{30}O_4$ [M − $C_2H_5O_2$] 225.1855, found 225.1858.

2-((2*S*,4*S*,6*R*)-6-((*R*)-2-Hydroxybutyl)-4-(methoxymethoxy)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (18). To a solution of **17** (0.100 g, 0.35 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (7.00 mL) and MeOH (0.160 mL) was added 5 drops of anhydrous pyridine. The resulting mixture was cooled to −78 °C, and O_3 was bubbled through the solution until the starting material was consumed as indicated by TLC analysis (∼30 min.). The solution was then sparged with O_2, and the reaction was quenched via portionwise addition of PPh_3 (0.121 g, 0.46 mmol, 3.00 equiv) and stirred at rt for 4 h. The resulting mixture was concentrated in vacuo to yield the crude aldehyde as a clear, viscous oil. Subsequent flash chromatography (silica, 32% EtOAc/hexanes) afforded **18** as a clear viscous oil (0.067 g, 66%): TLC R_f = 0.22 in 32% EtOAc/hexanes; $[\alpha]^{23}_D$ = −1.6 (*c* 0.018, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.6 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.59 (d, *J* = 7.0 Hz, 1H), 3.69 (m, 3H), 3.36 (s, 3H), 3.32 (m, 1H), 3.04 (s, 1H), 2.54 (m, 2H), 1.83 (m, 1H), 1.52 (m, 5H), 0.90 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 96.2, 81.0, 79.1, 73.2, 55.9, 44.0, 42.4, 38.4, 35.1, 30.5, 22.9, 13.8, 10.1; IR (CH_2Cl_2) cm^{-1} 2933, 1727, 1600, 1147, 1093, 1035; HRMS (EI) calcd for $C_{15}H_{28}O_5$ [M − C_2H_5] 259.1545, found 259.1541.

2-((2*S*,4*S*,6*R*)-6-((*R*)-2-Hydroxybutyl)-4-(methoxymethoxy)-3,3-dimethyltetrahydro-2*H*-pyran-2-yl)acetic Acid (3). To a stirred solution of **18** (0.067 g, 0.232 mmol, 1.00 equiv) in *t*-BuOH (3.05 mL) and H_2O (1.02 mL) was added 2-methyl-2-butene (1.63 g, 23.23 mmol, 100.00 equiv) followed by NaH_2PO_4 (0.278 g, 2.32 mmol, 10.0 equiv), and the mixture was cooled to −5 °C. To this mixture was added $NaClO_2$ (0.047 g, 0.87 mmol, 6.00 equiv) as a 1.40 M solution of 3:1 *t*-BuOH/H_2O (0.370 mL), and the reaction was allowed to stir until the starting material was consumed as indicated by TLC analysis (∼30 min). The reaction was subsequently quenched via the addition of saturated aqueous NH_4Cl (1.0 mL). The resulting mixture was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield **3** as a clear viscous oil, which was judged pure via without further purification. (0.071 g, 99%): TLC R_f = 0.35 in 60% EtOAc/hexanes; $[\alpha]^{23}_D$ = −8.1 (*c* 0.026, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) 4.71 (d, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 3.90 (m, 1H), 3.67 (m, 1H), 3.56 (s, 1H), 3.35 (m, 3H), 2.46 (m, 2H), 1.81 (m, 1H), 1.54 (m, 5H), 1.25 (m, 3H), 0.90 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 96.2, 81.4, 81.0, 78.0, 74.2, 55.9, 41.2, 38.5, 35.2, 29.9, 22.8, 13.6, 9.7; IR (CH_2Cl_2) cm^{-1} 2939, 1730, 1150, 1099, 1038; HRMS (EI) calcd for $C_{15}H_{28}O_6$ [M − HOH] 286.1780, found 286.1775.

(1*S*,5*R*,7*R*,9*S*,11*S*,15*R*,17*R*,19*S*)-5,15-Diethyl-9,19-bis(methoxymethoxy)-10,10,20,20-tetramethyl-4,14,21,22-tetraoxatricyclo[15.3.1^{17,11}]docosane-3,13-dione (20). To a stirred solution of **3** (0.071 g, 0.233 mmol, 1.00 equiv) in anhydrous THF (1.60 mL) under Ar was added Et_3N (0.033 g, 0.330 mmol, 1.40 equiv) followed by 2,4,6-trichlorobenzoyl chloride (0.0680 g, 0.280 mmol, 1.20 equiv) dropwise, and then the mixture was allowed to stir at room temperature for 2.5 h. The resulting mixture was diluted with anhydrous toluene (12.2 mL) and added dropwise over 5 h to a refluxing solution of DMAP (0.043 g, 0.350 mmol, 5.00 equiv) in toluene (46.0 mL) at 120 °C. After the addition was complete, the auxiliary flask was washed with toluene (2.00 mL), and the resulting rinse was added dropwise to the reaction mixture over the course of 0.5 h. The resulting mixture was refluxed for 14 h, cooled to rt, and concentrated in vacuo to yield the crude diolide and as a pale yellow, viscous oil. Subsequent flash chromatography (silica, 20% EtOAc/hexanes) afforded **20** as a clear, viscous oil (0.030 g, 45%): TLC R_f = 0.26 in 20% EtOAc/hexanes; $[\alpha]^{23}_D$ = −6.3 (*c* 0.011, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.90 (m, 2H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.38 (m, 9H), 2.34 (m, 4H), 1.88 (m, 3H), 1.59 (m, 6H), 1.25 (m, 6H), 0.90 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 96.2, 81.5, 80.9, 75.4, 74.2, 55.9, 40.9, 38.5, 35.6, 35.2, 28.5, 22.8, 13.7, 9.8; IR (CH_2Cl_2) cm^{-1} 2962, 2879, 2362, 1736, 1150, 1096, 1040; HRMS (EI) calcd for $C_{30}H_{52}O_{10}$ 572.3560, found 572.3548.

Aglycon Dimer 2. To a stirred solution of **20** (0.030 g, 0.052 mmol, 1.00 equiv) in CH_3CN (1.02 mL) and H_2O (5.00 μL) was added $LiBF_4$ (1.04 mL, 1.0 M in CH_3CN, 1.04 mmol, 20.0 equiv), and the resulting mixture was refluxed at 70 °C until the starting material was consumed as observed by TLC analysis (∼40 min). The reaction was cooled to rt and subsequently quenched via addition of saturated aqueous $NaHCO_3$ (1.0 mL). The mixture was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated to yield the crude diol as a clear, viscous oil. Subsequent flash chromatography (silica, 50% EtOAc/hexanes) afforded **2** as a clear, viscous oil (0.017 g, 68%): TLC R_f = 0.28 in 60% EtOAc/hexanes; $[\alpha]^{23}_D$ = −13.6 (*c* 0.009, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (dd, 14.6, 6.7 Hz, 2H), 3.46 (m, 4H), 3.39 (m, 2H), 2.41 (dd, *J* = 15.6, 1.1, 2H), 2.28 (dd, *J* = 15.7, 9.1, 2H), 1.86 (m, 4H), 1.58 (m, 8H), 1.34 (dd, *J* = 12.3, 11.4 Hz, 2H), 0.93 (s, 6H), 0.87 (t, *J* = 7.3 Hz, 6H), 0.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 81.0, 75.7, 75.3, 74.0, 41.3, 39.0, 37.6, 35.7, 28.5, 22.6, 12.9, 9.9; IR (CH_2Cl_2) cm^{-1} 2965, 2873, 1733, 1200, 741; HRMS (EI) calcd for $C_{26}H_{44}O_8$ 484.3036, found 484.3048.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Spectroscopic data for all the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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