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Biomimetic Synthesis of Resorcylate Natural Products Utilizing Late Stage Aromatization: Concise Total Syntheses of the Marine Antifungal Agents 15G256# and 15G256#

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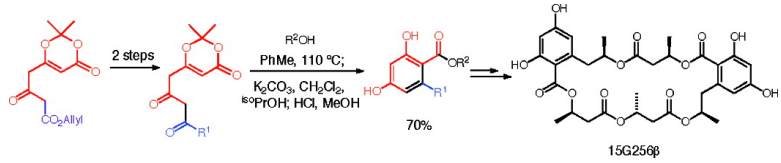

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Biomimetic Synthesis of Resorcylate Natural Products Utilizing Late Stage Aromatization: Concise Total Syntheses of the Marine Antifungal Agents 15G256ι and 15G256β

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Abstract: Diketo-1,3-dioxin-2-ones underwent retro-Diels−Alder reaction on heating in toluene at 110 °C to generate α,γ,ϵ-triketo-ketenes. These were trapped with alcohols to provide 2,4,6-triketocarboxylates, which were smoothly aromatized by sequential reaction with potassium carbonate and methanolic hydrogen chloride to give resorcylate esters. The reaction was applied in the total synthesis of the marine antifungal agents 15G256β (**1**), 15G256ι (**2**), and 15G256π (**3**) and the mycotoxin *S*-(−)-zearalenone (**4**).

Introduction

The 6-alkyl-2,4-dihydroxybenzoic acid unit occurs widely in numerous macrocyclic bioactive natural products[1] isolated from the marine fungus *Hypoxylon oceanicum* LL-15G256,[2] including the antifungal agent 15G256β (**1**) and the related resorcylates 15G256ι (**2**) and 15G256π (**3**), the mycotoxin *S*-(−)-zearalenone (**4**),[3] and the protein tyrosine kinase inhibitor radicicol (**5**)[4] (Figure 1). This class of natural products has been the subject of considerable synthetic studies. Most reported total syntheses employ 6-alkyl-2,4-hydroxybenzoic acids as intermediates and proceed via stepwise derivatization of these key building blocks.[1] Such strategies are often limited by moderate yields in the macrolactonization step and/or the need for multiple protecting group manipulations. A noteworthy strategic exception is shown in the total synthesis of radicicol (**5**) reported by Danishefsky, which uses a Diels−Alder reaction for the construction of the aromatic ring.[5]

Inspired by the polyketide biosynthesis of resorcylate natural products[6] and the biomimetic syntheses of simple resorcylates by Harris and others,[7] we sought to establish a strategy for the synthesis of lactones **6** containing these units utilizing tandem late stage aromatization, from 2,4,6-triketo-ester precursors **7**, and macrocyclization. In addition, we sought mild, highly selective C-acylation conditions to prepare the requisite triketo-esters **7** that avoid the strongly Brønsted basic or Lewis acidic reaction conditions that have hitherto significantly limited the scope of resorcylate biomimetic synthesis. Herein we report the

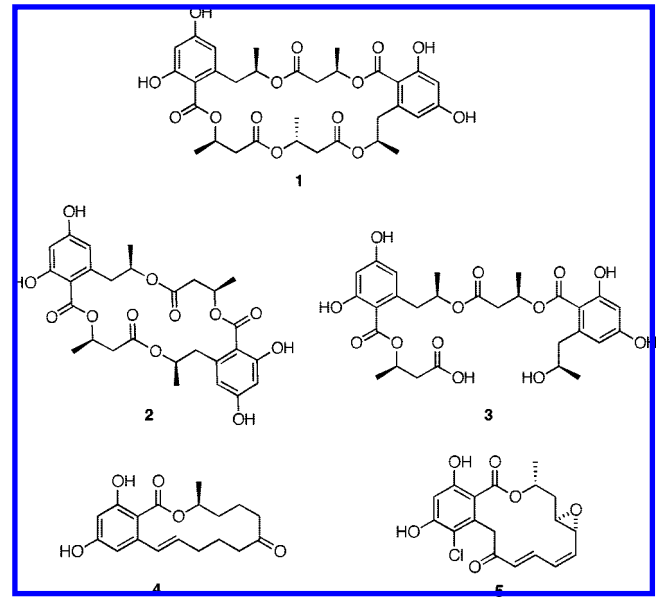


Figure 1. Bioactive resorcylate lactones.

synthesis of dioxinones **9** under mild conditions, their thermolysis and efficient trapping of the resultant novel triketo-ketenes **8** with alcohols[8] X^1-OH to afford the triketo-esters **7** and macrocyclization as key steps in the total synthesis of the marine antifungal agents 15G256β (**1**), 15G256ι (**2**), and 15G256π (**3**), and the mycotoxin *S*-(−)-zearalenone (**4**).[9] Most noteworthy is the fact that delicate functionality such as esters including derivatives of 3-hydroxy-butanoic acid survive the

(1) Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22.
(2) Schlingmann, G.; Milne, L.; Carter, G. T *Tetrahedron* **2002**, *58*, 6825, and references therein.
(3) (a) Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443. (b) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature* **1962**, *196*, 1318.
(4) (a) Delmotte, P.; Delmotte-Plaquee, J. *Nature* **1953**, *171*, 344. (b) Nozawa, K.; Nakajima, S. *J. Nat. Prod.* **1979**, *42*, 374.
(5) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903, and references therein.
(6) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380.
(7) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
(8) For other studies on the generation of acyl-ketenes from dioxinone derivatives see (a) Rodríguez, H.; Reyes, O.; Suarez, M.; Garay, H. E.; Ṕ; erez, R.; Cruz, L. J.; Verdecia, Y.; Martín, N.; Seoane, C. *Tetrahedron Lett.* **2002**, *43*, 439. (b) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105. (c) Clemens, R. J.; Witzeman, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186.
(9) For the total synthesis of zearalenone using RCM and earlier references see (a) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990.

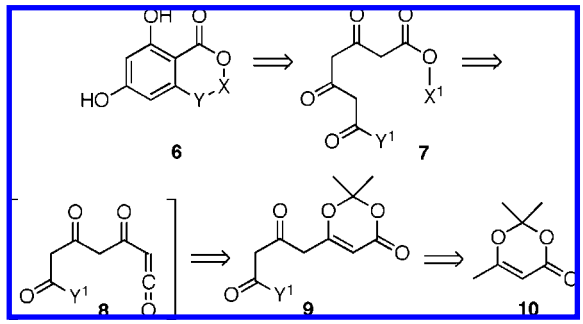
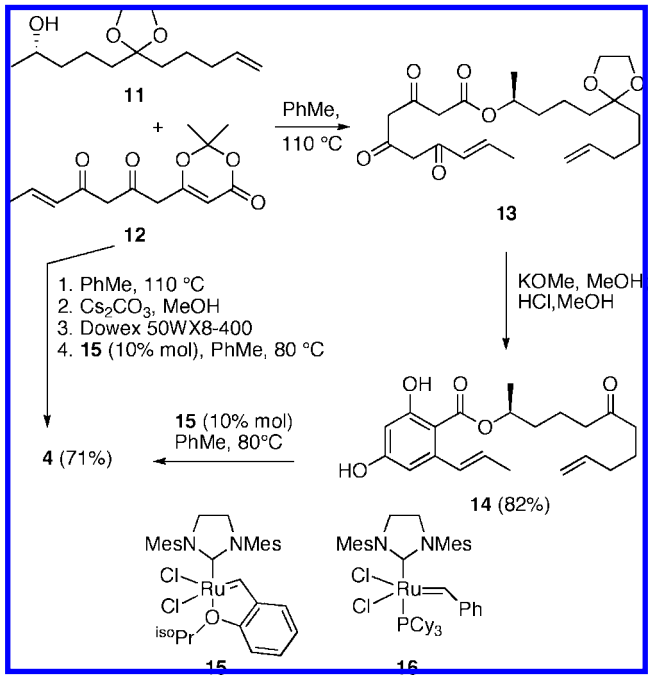


Figure 2. Late stage aromatization−macrocyclization strategy.

Scheme 1. Synthesis of *S*-(−)-Zearalenone (**4**)



C-acylation, thermolysis, alcohol trapping, and aromatization reaction (Figure 2).

Results and Discussion

As an initial approach to this chemistry, we investigated the late stage aromatization with the model substrate *S*-(−)-zearalenone (**4**) as a target (Scheme 1). The key *S*-(+)-alcohol **11**[10] (99% > ee) was prepared in four steps from (±)-5-hexanolide using lipase-mediated kinetic resolution.[11] The second building block **12** was prepared[12] from dioxinone **10** using a Mukaiyama aldol reaction[13,14] as the key step.

Thermolysis of the dioxinone **12** and *in situ* trapping of the triketo-ketene with alcohol **11** gave triketo-ester **13**. This was smoothly aromatized and ketal deprotected to provide the resorcylate **14**. The application of reaction conditions previously described for the aromatization of simple triketo-esters[7] proved unsuccessful, in that the use of a pH = 9.2 buffer[15] or treatment under strongly basic conditions with potassium methoxide only gave a small amount of the desired aromatic product **14**. However, using base-catalyzed aldol condensation with subsequent addition of a strong acid to promote dehydration and aromatization provided resorcylate **14** (87%). Subsequent ring-closing metathesis using the second generation Hoveyda−Grubbs catalyst **15** gave the corresponding macrocyclic lactones (*E*:*Z* 86:14) from which *S*-(−)-zearalenone (**4**) (71%) was isolated. Attempted macrocyclization using catalyst **16** or by the ring closing metathesis of the side chain ketal of ketone **14** or of **13** gave intractable mixtures containing *S*-(−)-zearalenone (**4**). By simple modification of the reaction conditions, we found that the four-step reaction sequence from alcohol **11** and dioxinone **12** to *S*-(−)-zearalenone (**4**) could be carried out without isolation of any intermediates in a single vessel.[16]

Having established the biomimetic aromatization on this model system, we turned our attention to the more complex 15G256 marine antifungal agents, and to facilitate this synthesis, we developed a mild new method for the synthesis of the dioxinones **9**. Sequential double C-acylation of dioxine **17** (Scheme 2) with acyl chloride **18**[17,18] and chloride **20** gave diketo-ester **21**.[19] Subsequent palladium-catalyzed deallylation−decarboxylation provided the key triketo-ester **22**. Thermal decomposition of dioxinone **22** in the presence of alcohol **23** gave triketo-ester **24**, which was aromatized by sequential reaction with potassium carbonate and methanolic hydrogen chloride to provide the 15G256 monomer unit **25** (75%). We have found this mild catalyzed double Claisen condensation strategy and the use of allyl ester **19** to be especially valuable for the synthesis of polyfunctional resorcylates.

The synthesis of the 15G256 diester **25** was extended to the corresponding triester **27** (Scheme 3). Thus thermolysis of dioxinone **26**[20] in the presence of alcohol **23** and aromatization gave the resorcylate triester **27**. It is noteworthy that ester hydrolysis also did not occur in this example at a significant rate during aromatization.

We subsequently applied the resorcylate methods to the total syntheses of the macrocyclic natural products 15G256ι (**2**) and 15G256π (**3**). Thermal decomposition of dioxinone **22** in the presence of alcohol **28** (Scheme 4) afforded the intermediate triketo-ester **29**, which was aromatized as in Scheme 3 to provide resorcylate **30** (70%). Protection of the phenols in **30** by benzylation gave **31** (92%), which was selectively desilylated

(10) (±)-5-Hexanolide was allowed to react sequentially with 4-penten-1-ylmagnesium bromide, Ac_2O, $HOCH_2CH_2OH$−PPTS, and KOH−MeOH (60% over three steps) and the resultant (±)-**11** resolved with CAL-B lipase and CH_2=CHOAc (48%). See Supporting Information.

(11) (a) Cordova, A.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 1906. (b) Nanda, S.; Scott, A. I. *J. Mol. Catal. B: Enzym.* **2004**, *30*, 1.

(12) Sequential BF_3·OEt_2-catalyzed Mukaiyama aldol reaction of the silyl enol ether derived from dioxinone **10** with (*E*)-MeCH=CHCH(OTBS)CH_2CHO. (See Collins, I.; Nadin, A.; Holmes, A. B.; Long, M. E.; Man, J.; Baker, R. *J. Chem. Soc., Perkin Trans.* **1994**, *1*, 2205.) (61%); Dess Martin oxidation; desilylation using HF in H_2O and further Dess Martin oxidation gave **12** (45%, three steps). See Supporting Information.

(13) Giovanni, C.; Zanadi, F.; Appendino, G.; Rassu, G. *Chem. Rev* **2000**, *100*, 1929.

(14) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800.

(15) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, *10*, 2272.

(16) The yield of *S*-(−)-zearalenone (**4**) using a one-vessel reaction without isolation of any intermediates was 43%. This yield was increased to 63% when the Dowex resin was filtered off before the addition of catalyst **15**.

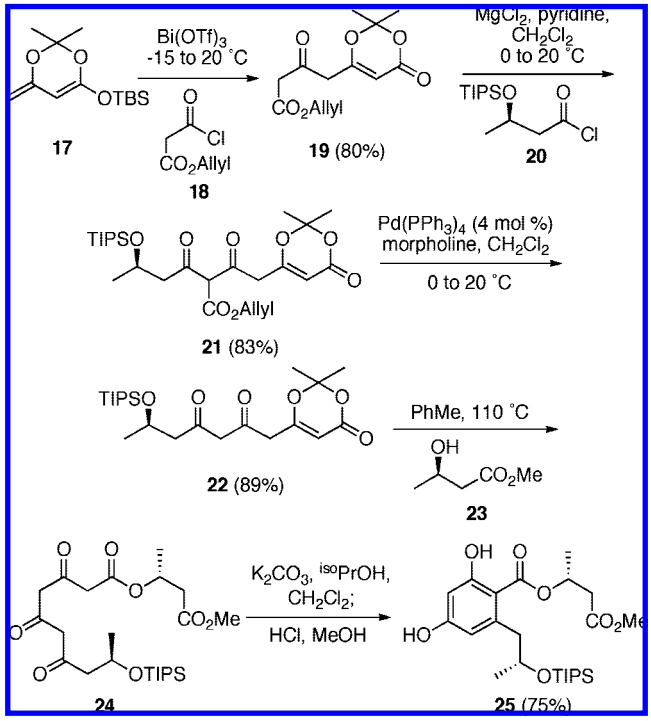
(17) (a) Lida, A.; Osada, J.; Nagase, R.; Misaki, T.; Tanabe, Y. *Org. Lett.* **2007**, *9*, 1859. (b) Ollevier, T.; Desyroy, V.; Catrinescu, C.; Wischert, R. *Tetrahedron Lett.* **2006**, *47*, 9089.

(18) (a) Alternatively to ref 17, compound **19** can be synthesized *via* alkylation of the enolate of dioxinone **10** with 1-(CH_2=$CHCH_2OCOCH_2CO$)-benzotriazole. See Supporting Information. (b) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854.

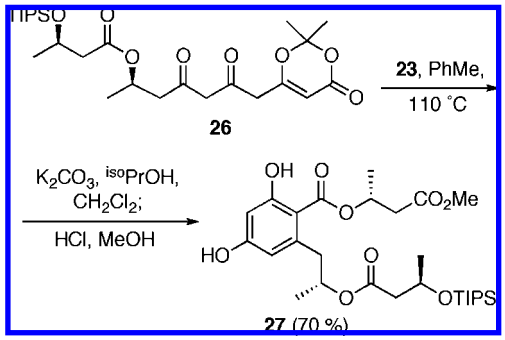
(19) All the di- and tri-keto-esters exist as mixtures of keto and enol tautomers. However, for convenience, they are drawn as single entities.

(20) The synthesis of the dioxinone **26** closely follows the methods in Scheme 2; see the Supporting Information.

Scheme 2. Synthesis of 15G256 Monomer Unit **25**



Scheme 3. Synthesis of the Resorcylate Triester **27**

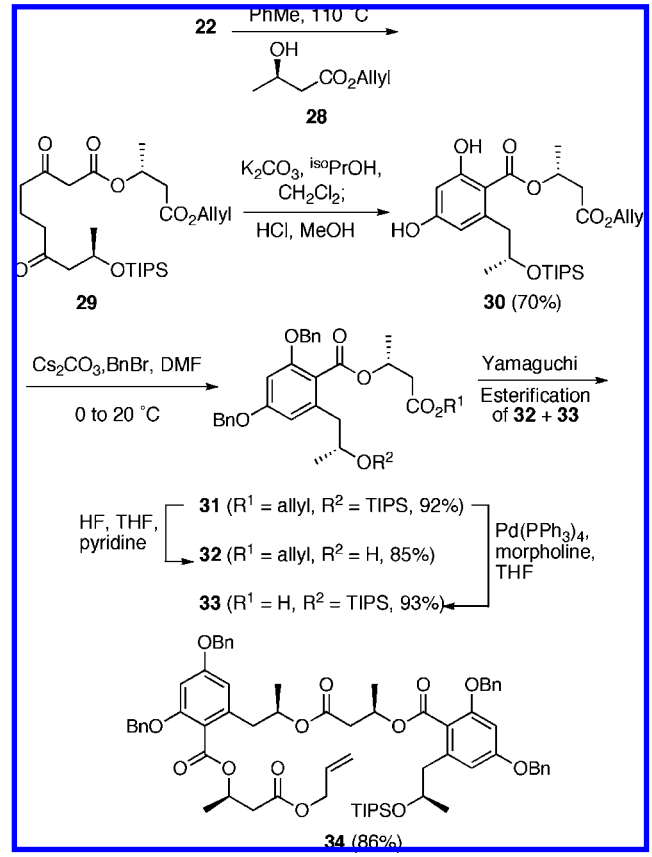


or deallylated giving alcohol **32** (85%) and carboxylic acid **33** (93%), respectively. Yamaguchi esterification[21] of both units **32** and **33** gave the corresponding tetraester **34** (86%). Finally selective deallylation of ester **34** (Scheme 5) gave acid **35** (87%), which was subsequently debenzylated by hydrogenolysis and desilylated to give the hydroxy acid natural product 15G256π (**3**) (86%). Alternatively, desilylation of **35** and Yamaguchi macrolactonization gave lactone **36** (76%). Debenzylation gave the resorcylate natural product 15G256ι (**2**) (75%), the structure of which was confirmed by X-ray crystallography and by comparison with authentic material (see Supporting Information).[2]

This synthetic methodology was extended to the unsymmetrical macrolactone 15G256β (**1**). Acid **35** and alcohol **28** were esterified under Yamaguchi conditions to give the pentaester **37** (71%) (Scheme 6). Subsequent deallylation, desilylation, and intramolecular macrolactonization gave lactone **38**

(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Scheme 4. Synthesis of Tetraester **34**



(65% from **37**). Finally, debenzylation by hydrogenolysis gave the antifungal resorcylate 15G256β (**1**) (85%).

Conclusion

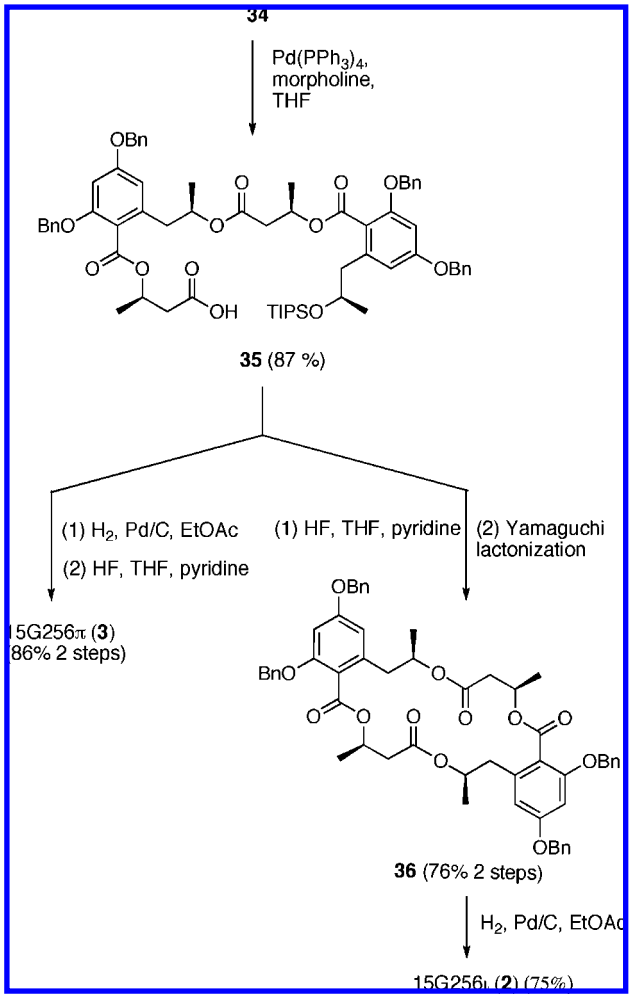
In summary, we report a new strategy for the synthesis of resorcylate natural products using a biomimetic highly selective late-stage aromatization reaction and its application to concise total syntheses of the antifungal natural products 15G256β (**1**), 15G256ι (**2**), and 15G256π (**3**), and the mycotoxin *S*-(−)-zearalenone (**4**). The stability of delicate functionality to the generation of the resorcylate units by cyclization and aromatization is especially noteworthy. Further applications of this strategy toward more complex biologically active targets are currently under investigation.

Experimental Section

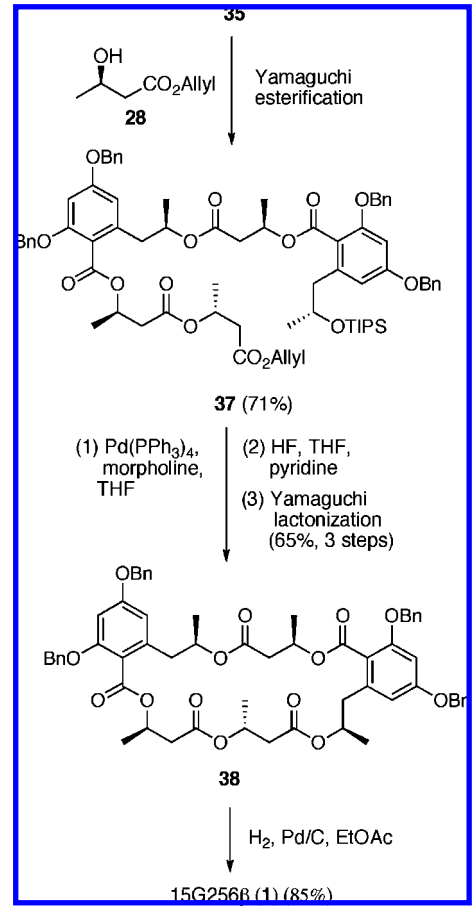
(*S*,*E*)-6-Oxoundec-10-en-2-yl 2,4-Dihydroxy-6-(prop-1-enyl)-benzoate (14). Alcohol **11** (33.8 mg, 0.15 mmol), dioxinone **12** (37.3 mg, 0.15 mmol), and PhMe (0.4 mL) were heated to reflux for 1.5 h. After rotary evaporation, the residue containing triketo-ester **13**[22] was dissolved in MeOH (2.0 mL), KOH (39.8 mg, 0.71 mmol) was added, and the mixture was vigorously stirred at room temperature for 12 h. Subsequently, the pH was reduced to 1 with HCl in MeOH (1.25 M; 2.5 mL, 3.1 mmol) and the mixture stirred for 20 min. The mixture was poured into H_2O (2.0 mL) and extracted with EtOAc (3 × 2 mL), and the combined organic layers were washed with brine and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes:EtOAc 1:3) gave resorcylate **14** (43.5

(22) The triketo-esters **13** or **29** were used directly as a crude material as indicated in the experimental procedure. All attempts to purify the product by chromatography were unsuccessful. The consumption of the starting material was monitored by TLC and ^{1}H NMR.

Scheme 5. Synthesis of 15G256π (**3**) and 15G256ι (**2**)



Scheme 6. Synthesis of 15G256β (**1**)



mg, 82%) as a colorless oil: R_f 0.43 (EtOAc:hexanes 1:3); $[\alpha]_D^{25}$ +16.1 (c 15.3 CH_2Cl_2); IR (film) 3371 (br), 1644, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.71 (s, 1H), 6.93 (dd, J = 1.6, 15.4 Hz, 1H), 6.31 (d, J = 2.6 Hz, 1H), 6.33 (d, J = 2.6 Hz, 1H), 5.91−5.70 (m, 3H), 5.19−5.12 (m, 1H), 5.00 (d, J = 17.2 Hz, 1H), 4.81 (d, J = 10.3 Hz, 1H), 2.47−2.41 (m, 4H), 2.04 (q, J = 7.2 Hz, 2H), 1.83 (dd, J = 6.6, 1.6 Hz, 3H), 1.71−1.65 (m, 6H), 1.38 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 170.8, 164.7, 160.5, 144.4, 137.8, 132.4, 127.0, 115.3, 108.4, 104.2, 102.1, 72.2, 42.3, 41.9, 35.3, 33.0, 22.8, 19.9, 19.3, 18.4; MS (CI) m/z 361 $[M + H]^+$; HRMS (CI) calcd for $C_{21}H_{29}O_5$: $[M + H]^+$, 361.1937; found: $[M + H]^+$, 361.1956. Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.96; H, 7.92.

(*R*)-4-Methoxy-4-oxobutan-2-yl 2,4-Dihydroxy-6-((*R*)-2-methyl-4-oxo-4-((*R*)-1-(triisopropylsilyloxy)ethoxy)butyl)benzoate (27). Dioxinone **26** (20 mg, 0.040 mmol) and alcohol **23** (5.6 mg, 0.048 mmol) in PhMe (2.4 mL) were heated at reflux for 1.5 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and *iso*-PrOH (1.5:1; 6.4 mL). K_2CO_3 (120 mg, 0.87 mmol) was added, and the mixture was vigorously stirred at room temperature for 1 h. The solution was acidified to pH 2 with HCl in MeOH (1.25 M; 2.5 mL, 3.1 mmol) and stirred for an additional 45 min. The reaction mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes:EtOAc 4:1) gave resorcylate **27** (15.0 mg, 70%) as a yellow oil: R_f 0.83 (hexanes:EtOAc 7:3); $[\alpha]_D$ −31.1 (c 1.33 $CHCl_3$); IR (KBr) 3385, 1736, 1469, 1620, 1450, 1312, 1257, 1194, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 11.65 (s, 1H), 6.28 (d, J = 2.6 Hz, 1H), 6.21 (d, J = 2.6 Hz, 1H), 5.68 (br s, 1H), 5.67−5.51 (m, 1H), 5.18−5.07 (m, 1H), 4.30−4.18 (m, 1H), 3.69 (s, 3H), 3.26 (dd, J = 13.5, 4.2 Hz, 1H), 2.91 (dd, J = 13.5, 9.1 Hz, 1H), 2.81 (dd, J = 15.5, 7.1 Hz, 1H), 2.68 (dd, J = 15.5, 5.7 Hz, 1H), 2.48 (dd, J = 14.6, 5.0 Hz, 1H), 2.30 (dd, J = 14.6, 7.9 Hz, 1H), 1.47 (d, J = 6.1 Hz, 3H), 1.27 (d, J = 6.1 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H), 1.02 (m, 21H);^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 170.1, 165.5, 160.3, 142.8, 112.4, 105.2, 102.3, 71.1, 68.9, 65.6, 51.9, 45.2, 42.3, 40.4, 23.6, 20.2, 19.8, 18.0 (6 C), 12.2 (3C); MS (ESI) m/z 555 $[M + H]^+$; HRMS (ESI) calcd $C_{28}H_{47}O_9Si$: $[M + H]^+$, 555.2989; found: $[M + H]^+$, 555.2991. Anal. Calcd for $C_{28}H_{46}O_9Si$: C, 60.62; H, 8.36. Found: C, 60.58; H, 8.41.

(*R*)-4-(Allyloxy)-4-oxobutan-2-yl 2,4-Dihydroxy-6-((*R*)-2-(triisopropylsilyloxy)propyl)benzoate (30). Dione **22** (1000 mg, 2.34 mmol) and alcohol **28** (360 mg, 2.5 mmol) in PhMe (15 mL) were heated at reflux for 1.5 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and *iso*-PrOH (1.5:1; 400 mL).[22] K_2CO_3 (5 g, 36 mmol) was added, and the mixture was stirred at room temperature for 3 h. The solution was acidified to pH 2 with HCl in MeOH (1.25 M; 100 mL, 125 mmol) and stirred for an additional 1 h. The reaction mixture was filtered, diluted with CH_2Cl_2 (250 mL), and washed with H_2O and brine, and the organic layer was dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes:EtOAc 4:1) gave resorcylate **30** (811 mg, 70%):[23] R_f 0.83 (hexanes:EtOAc 7:3); $[\alpha]_D$ −84.1 (c 0.6 $CHCl_3$); IR (KBr) 3403, 1741, 1648,

(23) In some experiments, traces of the transesterification product with methanol were detected. To circumvent this problem, trifluoroacetic acid was used instead of methanolic HCl. Alternatively, filtration and evaporation of the solvent after the K_2CO_3 treatment of **29** gave a crude aldol product, which was aromatized using TFA (1 equiv) in chloroform.

1619, 1450, 1311, 1257, 1189 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.62 (s, 1H), 6.29 (d, J = 2.6 Hz, 1H), 6.27 (d, J = 2.6 Hz, 1H), 5.95−5.80 (m, 1H), 5.65−5.55 (m, 1H), 5.29 (d, J = 15.9 Hz, 1H), 5.21 (d, J = 9.8 Hz, 1H), 5.11 (s, 1H), 4.58 (d, J = 6.0 Hz, 2H), 4.24−4.14 (m, 1H), 3.34 (dd, J = 13.2, 3.2 Hz, 1H), 2.80 (dd, J = 15.6, 7.3 Hz, 1H), 2.68 (dd, J = 15.6, 5.6 Hz, 1H), 2.57 (dd, J = 13.2, 9.0 Hz, 1H), 1.44 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 0.92 (m, 21H);^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.7, 165.4, 159.9, 145.0, 131.5, 118.9, 113.5, 105.2, 101.7, 69.5, 68.5, 65.6, 46.5, 40.8, 24.6, 19.9, 18.0 (3C), 17.9 (3C), 12.5 (3C). MS (ESI) m/z 495 $[M + H]^+$; HRMS (ESI) calcd $C_{26}H_{43}O_7Si$: $[M + H]^+$, 495.2778; found: $[M + H]^+$, 495.2776. Anal. Calcd for $C_{26}H_{42}O_7Si$: C, 61.13; H, 8.56. Found: C, 61.23; H, 8.66.

(*R*)-4-(Allyloxy)-4-oxobutan-2-yl 2,4-Bis(benzyloxy)-6-((*R*)-2-(triisopropylsilyloxy)propyl)benzoate (31). Cs_2CO_3 (140 mg, 0.43 mmol) and BnBr (86 μL, 0.69 mmol) were added to diphenol **30** (85 mg, 0.172 mmol in DMF (1.5 mL) at 0 °C, the mixture was allowed to warm up to room temperature, and, after 1 h, saturated aqueous NH_4Cl (4 mL) was added. The mixture was diluted with Et_2O (25 mL), subsequently washed with aqueous HCl (1 M; 2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine, and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes:EtOAc 9:1) gave diether **31** (106 mg, 92%) as a pale yellow oil: $[\alpha]_D$ −21.0 (*c* 0.53 $CHCl_3$); IR (KBr) 1739, 1602, 1454, 1380, 1268, 1160, 1093, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.26 (m, 10H), 6.50 (s, 1H), 6.44 (s, 1H), 5.92−5.80 (m, 1H), 5.52−5.41 (m, 1H), 5.28 (d, J = 15.9 Hz, 1H), 5.21 (d, J = 9.8 Hz, 1H), 5.01 (bs, 4H), 4.56 (d, J = 6.0 Hz, 2H), 4.22−4.12 (m, 1H), 2.81 (dd, J = 13.5, 6.1 Hz, 1H), 2.73 (dd, J = 15.8, 6.2 Hz, 1H), 2.66 (dd, J = 13.5, 6.7 Hz, 1H), 2.44 (dd, J = 15.8, 7.2 Hz, 1H), 1.27 (d, J = 6.1 Hz, 3H), 1.09 (d, J = 6.1 Hz, 3H), 1.03 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 167.3, 159.9, 156.9, 139.1, 136.5, 136.4, 131.9, [128.6, 128.4, 128.0, 127.9, 127.4] (10C), 118.3, 117.8, 108.4, 98.6, 70.4, 70.0, 69.2, 68.0, 65.2, 43.5, 40.5, 23.4, 19.6, 18.1 (3C), 18.0 (3C), 12.4 (3C). MS (ESI) m/z 675 $[M + H]^+$; HRMS (ESI) calcd $C_{40}H_{55}O_7Si$: $[M + H]^+$, 675.3708; found: $[M + H]^+$, 675.3717. Anal. Calcd for $C_{40}H_{54}O_7Si$: C, 71.18; H, 8.06. Found: C, 71.24; H, 7.97.

(*R*)-4-(Allyloxy)-4-oxobutan-2-yl 2,4-Bis(benzyloxy)-6-((*R*)-2-hydroxypropyl)benzoate (32). HF·pyridine (0.2 mL) was added with stirring to ether **31** (20 mg, 0.03 mmol) in THF and pyridine (4:1; 2 mL) at 0 °C. The mixture was allowed to warm up to room temperature and, after 12 h stirring, poured into H_2O and EtOAc (1:1; 30 mL), and the solution was basified to pH 6 with K_2CO_3. The organic layer was washed with H_2O and brine and dried ($MgSO_4$). Rotary evaporation gave alcohol **32** (13 mg, 85%) as an oil, which was used in the next step without further purification.[24] Chromatography (hexanes:AcOEt 9:1) gave a sample of **32**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.29 (m, 10H), 6.47 (s, 1H), 6.45 (s, 1H), 5.94−5.82 (m, 1H), 5.55−5.45 (m, 1H), 5.29 (d, J = 15.9 Hz, 1H), 5.22 (d, J = 9.8 Hz, 1H), 5.02 (d, J = 11.7 Hz, 4H), 4.56 (d, J = 5.8 Hz, 2H), 3.92−4.02 (m, 1H), 2.76−2.62 (m, 6H), 2.50 (dd, J = 15.8, 7.2 Hz, 1H), 1.24 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.1 Hz, 3H).

(*R*)-3-(2,4-Bis(benzyloxy)-6-(()-2-(triisopropylsilyloxy)propyl)-benzoyloxy)butanoic Acid (33). Morpholine (7 μL, 0.08 mmol) and $Pd(PPh_3)_4$ (4.5 mg, 0.004 mmol) in THF (0.1 mL) were added with stirring to diester **31** (26 mg, 0.04 mmol) in THF (0.8 mL) at 0 °C. The mixture was allowed to warm up to room temperature, and, after 30 min stirring, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.8 mL). The mixture was poured into H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Rotary evaporation and chromatography (CH_2Cl_2:MeOH 19:1) gave acid **33** (23 mg, 93%) as an amorphous solid: R_f 0.30 (hexanes:EtOAc 7:3); $[\alpha]_D$ −17.5 (*c* 1.0 $CHCl_3$); IR (KBr) 1716, 1602, 1456, 1270, 1160, 1093, 1058 cm^{-1};^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.28 (m, 10H), 6.49 (s, 1H), 6.44 (s, 1H), 5.48−5.36 (m, 1H), 5.01 (d, J = 4.3 Hz, 4H), 4.22−4.12 (m, 1H), 2.81 (dd, J = 13.5, 6.1 Hz, 1H), 2.69 (dd, J = 15.8, 6.2 Hz, 1H), 2.66 (dd, J = 13.5, 6.7 Hz, 1H), 2.44 (dd, J = 15.8, 7.2 Hz, 1H), 1.28 (d, J = 6.1 Hz, 3H), 1.10 (d, J = 6.1 Hz, 3H), 1.02 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 167.3, 159.9, 156.9, 139.2, 136.5, 136.3, 128.6 (2C), 128.4 (2C), 128.0 (2C), 127.9 (2C), 127.4 (2C), 117.6, 108.5, 98.6, 70.4, 70.0, 69.2, 67.7, 43.5, 40.1, 23.4, 19.5, 18.1(3C), 18.0 (3C), 12.4 (3C); MS (ESI) m/z 635 $[M + H]^+$; HRMS (ESI) calcd $C_{37}H_{51}O_7Si$: $[M + H]^+$, 635.3419; found: $[M + H]^+$, 635.3404. Anal. Calcd for $C_{37}H_{50}O_7Si$: C, 70.00; H, 7.94. Found: C, 69.98; H, 8.03.

(*R*)-4-(Allyloxy)-4-oxobutan-2-yl 2,4-Bis(benzyloxy)-6-((*R*)-2-((*R*)-3-(2,4-bis(benzyloxy)-6-((*R*)-2-(triisopropylsilyloxy)propyl)-benzoyloxy)butanoyloxy)propyl)benzoate (34). 2,4,6-Trichlorobenzoyl chloride (8 μL, 0.054 mmol) was added with stirring to acid **33** (15 mg, 0.024 mmol) and *iso*-Pr_2NEt (24 μL, 0.14 mmol) in PhMe (0.9 mL) at 0 °C. After 30 min, alcohol **32** (15 mg, 0.029 mmol) and DMAP (6 mg, 0.054 mmol) in PhMe (0.5 mL) were added, giving a white precipitate. The mixture was allowed to warm up to room temperature, after 30 min stirring, poured into EtOAc (15 mL), washed with 1 M HCl and brine, and dried ($MgSO_4$). Rotary evaporation and chromatography (CH_2Cl_2:MeOH 19:1) gave tetraester **34** (24 mg, 86%) as a yellow oil: R_f 0.75 (hexanes:EtOAc 7:3); $[\alpha]_D$ −21.4 (*c* 4.80 $CHCl_3$); IR (KBr) 1731, 1602, 1456, 1378, 1270, 1160, 1093, 1054, 736 cm^{-1};^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.26 (m, 20H), 6.50 (s, 1H), 6.44 (m, 2H), 6.41 (s, 1H), 5.92−5.80 (m, 1H), 5.52−5.42 (m, 1H), 5.44−5.34 (m, 1H), 5.28 (d, J = 15.9 Hz, 1H), 5.20 (d, J = 9.8 Hz, 1H), 5.13−5.03 (m, 1H), 5.01 (bs, 8H), 4.55 (d, J = 6.0 Hz, 2H), 4.22−4.12 (m, 1H), 2.90 (dd, J = 13.8, 6.7 Hz, 1H), 2.86−2.52 (m, 5H), 2.45 (dd, J = 15.9, 6.7 Hz, 1H), 2.35 (dd, J = 15.3, 8.3 Hz, 1H), 1.27 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H), 1.09 (d, J = 6.1 Hz, 3H), 1.03 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 169.3, 167.2, 167.0, 160.2, 159.8, 157.1, 156.9, 139.1, 137.6, 136.5, 136.4 (2C), 136.3, 131.9, [128.5, 128.4, 128.0, 127.9, 127.9, 127.5, 127.4, 127.3] (20C), 118.3, 117.8, 117.6, 108.5, 107.7, 99.1, 98.6, 71.4, 70.4, 70.3, 70.1, 69.9, 69.2, 68.2, 68.1, 65.2, 43.6, 40.9, 40.4, 39.2, 23.4, 19.6, 19.4 (2C), 18.1 (3C), 18.0 (3C), 12.4 (3C). MS (ESI) m/z 1135 $[M + H]^+$; HRMS (ESI) calcd $C_{68}H_{83}O_{13}Si$: $[M + H]^+$, 1135.5613; found: $[M + H]^+$, 1135.5603. Anal. Calcd for $C_{68}H_{82}O_{13}Si$: C, 71.93; H, 7.28. Found: C, 71.87; H, 7.27.

(*R*)-3-(2,4-Bis(benzyloxy)-6-((*R*)-2-((*R*)-3-(2,4-bis(benzyloxy)-6-((*R*)-2-(triisopropylsilyloxy)propyl)benzoyloxy)butanoyloxy)propyl)benzoyloxy)butanoic Acid (35). Morpholine (4 μL, 0.044 mmol) and $Pd(PPh_3)_4$ (3 mg, 0.002 mmol) in THF (0.1 mL) were added with stirring to tetraester **34** (25 mg, 0.022 mmol) in THF (0.8 mL) at 0 °C. The mixture was allowed to warm up to room temperature, and, after 30 min stirring, the reaction was quenched with saturated aqueous NH_4Cl (0.8 mL). The mixture was poured into H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Rotary evaporation and chromatography (CH_2Cl_2:MeOH 9:1) gave acid **35** (21 mg, 87%) as an amorphous solid: R_f 0.30 (hexanes:EtOAc 7:3); $[\alpha]_D$ −19.8 (*c* 7.5 $CHCl_3$); IR (KBr) 3100, 1725, 1602, 1545, 1434, 1378, 1272, 1162, 1093, 1054 cm^{-1};^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.26 (m, 20H), 6.50 (d, J = 1 Hz, 1H), 6.45 (d, J = 1 Hz, 1H), 6.42 (d, J = 1 Hz, 1H), 6.41 (d, J = 1 Hz, 1H), 5.54−5.40 (m, 2H), 5.12−5.05 (m, 1H), 5.05−4.94 (bs, 8H), 4.24−4.14 (m, 1H), 2.92 (dd, J = 13.8, 7.2 Hz, 1H), 2.84−2.74 (m, 2H), 2.73−2.62 (m, 3H), 2.48 (dd, J = 16.1, 5.3 Hz, 1H), 2.36 (dd, J = 15.2, 8.0 Hz, 1H), 1.26 (d, J = 6.1 Hz, 3H), 1.20 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H), 1.10 (d, J = 6.1 Hz, 3H), 1.03 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 169.6, 167.5, 167.0, 160.2, 159.9, 157.2, 157.0, 139.2, 137.6, 136.5, 136.4 (2C), 136.2, [128.5, 128.4, 128.0, 128.0, 127.9, 127.4,

(24) All attempts to purify the product by chromatography were unsuccessful, giving a less pure material as a result of lactonization to provide the corresponding isocumarin.

127.3] (20C), 117.5 (2C), 108.5, 107.8, 99.1, 98.7, 71.7, 70.4, 70.3, 70.0, 69.9, 69.2, 68.3, 68.1, 43.6, 41.1, 40.1, 39.1, 23.4, 19.6, 19.5, 19.4, 18.1 (3C), 18.0 (3C), 12.4 (3C). MS (ESI) *m/z* 1095 $[M + H]^+$; HRMS (ESI) calcd $C_{65}H_{79}O_{13}Si$: $[M + H]^+$, 1095.5290; found: $[M + H]^+$, 1095.5305. Anal. Calcd for $C_{65}H_{78}O_{13}Si$: C, 71.27; H, 7.18. Found: C, 71.31; H, 7.10.

(*R*)-4-((*R*)-4-(Allyloxy)-4-oxobutan-2-yloxy)-4-oxobutan-2-yl 2,4-Bis(benzyloxy)-6-((*R*)-2-((*R*)-3-(2,4-bis(benzyloxy)-6-((*R*)-2-(triisopropylsilyloxy)propyl)benzoyloxy)butanoyloxy)propyl)benzoate (37). 2,4,6-Trichlorobenzoyl chloride (16 μL, 0.108 mmol) was added with stirring to acid **35** (60 mg, 0.055 mmol) and *iso*-Pr_2NEt (56 μL, 0.33 mmol) in PhMe (1.9 mL) at 0 °C. After 30 min, alcohol **28** (13 mg, 0.090 mmol) and DMAP (12 mg, 0.108 mmol) in PhMe (0.9 mL) was added, giving a white precipitate. The mixture was allowed to warm up to room temperature, after 30 min stirring, poured into EtOAc (20 mL), washed with HCl 1 M and brine, and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes:AcOEt 4:1) gave pentaester **37** (48 mg, 71%) as a yellow oil: R_f 0.70 (hexanes:EtOAc 7:3); $[\alpha]_D$ −20.0 (*c* 3.25, $CHCl_3$); IR (KBr) 1737, 1602, 1454, 1380, 1272, 1162, 1093, 1054, 738 cm^{-1};^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.26 (m, 20H), 6.49 (d, J = 1.0 Hz 1H), 6.44 (s, 2H), 6.41 (s, 1H), 5.92−5.81 (m, 1H), 5.49−5.34 (m, 2H), 5.32−5.18 (m, 3H), 5.13−5.05 (m, 1H), 5.00 (d, J = 3.0 Hz, 4H), 4.97 (d, J = 3.0 Hz, 4H), 4.54 (d, J = 6.0 Hz, 2H), 4.23−4.14 (m, 1H), 2.90 (dd, J = 13.9, 6.9 Hz, 1H), 2.83−2.60 (m, 6H), 2.48 (dd, J = 15.6, 6.0 Hz, 1H), 2.38 (dd, J = 11.9, 7.9 Hz, 1H), 2.34 (dd, J = 11.9, 7.9 Hz, 1H), 1.27 (d, J = 6.1 Hz, 3H), 1.26 (d, J = 6.1 Hz, 3H), 1.20 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H), 1.09 (d, J = 6.1 Hz, 3H), 1.03 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 169.3, 169.2, 167.2, 166.9, 160.2, 159.8, 157.1, 156.9, 139.1, 137.6, 136.5, 136.3(2C), 136.2, 131.8, [128.5, 128.4, 128.0, 127.9, 127.8, 127.5, 127.4, 127.3] (20C), 118.5, 117.7, 117.5, 108.5, 107.6, 99.0, 98.6, 71.4, 70.4, 70.3, 70.0, 69.9, 69.2, 68.1 (2C), 67.5, 65.2, 43.6, 40.9, 40.7, 40.5, 39.2, 23.4, 19.7, 19.4 (3C), 18.1 (3C), 18.0 (3C), 12.4 (3C); MS (ESI) *m/z* 1221 $[M + H]^+$; HRMS (ESI) calcd $C_{72}H_{89}O_{15}Si$: $[M + H]^+$, 1221.5971; found: $[M + H]^+$, 1221.5968. Anal. Calcd for $C_{72}H_{88}O_{15}Si$: C, 70.79; H, 7.26. Found: C, 70.90; H, 7.16.

(7*R*,11*R*,15*R*,23*R*,27*R*)-2,4,18,20-Tetrakis(benzyloxy)-7,11,15,23,27-pentamethyl-7,8,11,12,15,16,23,24,27,28-decahydro-5*H*-dibenzo[*k*,*u*][1,5,9,15,19]pentaoxacyclotetracosine-5,9,13,21,25-pentaone (38). Morpholine (10 μL, 0.051 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) in THF (0.15 mL) were added with stirring to pentaester **37** (60 mg, 0.049 mmol) in THF (1.0 mL) at 0 °C. The mixture was allowed to warm up to room temperature, and, after 30 min stirring, the reaction was quenched with saturated aqueous NH_4Cl (0.9 mL). The mixture was poured into H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Rotary evaporation gave the crude carboxylic acid, which was used in the next step without further purification. HF·pyridine (0.3 mL) was added with stirring to the crude carboxylic acid in THF and pyridine (4:1; 3 mL) at 0 °C. The mixture was allowed to warm up to room temperature and, after 12 h stirring, poured into H_2O and EtOAc (1:1; 30 mL), and the solution was basified to pH 6 with K_2CO_3. The organic layer was washed with H_2O and brine and dried ($MgSO_4$). Rotary evaporation gave crude hydroxy acid as a yellow oil, which was used in the next step without further purification. 2,4,6-Trichlorobenzoyl chloride (9 μL, 0.060 mmol) was added with stirring to crude hydroxy acid and *iso*-Pr_2NEt (47 μL, 0.22 mmol) in PhMe (1.5 mL) at 0 °C. After 30 min, the mixture was diluted with PhMe (2.0 mL) and added dropwise over 1 h to a solution of DMAP (11 mg, 0.092 mmol) in PhMe (1.0 mL), giving a white precipitate. After 30 min stirring, the mixture was poured into EtOAc (15 mL) and washed with 1 M HCl and brine and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes:EtOAc 4:1) gave macrolactone **38** (32.5 mg, 65% from **37**) as a yellow oil: R_f 0.75 (hexanes:EtOAc 7:3); $[\alpha]_D$ −28 (*c* 0.4, $CHCl_3$); IR (KBr) 1733, 1604, 1454, 1380, 1270, 1162, 1095, 1052, 738 cm^{-1};^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.28 (m, 20H), 6.43 (d, J = 1 Hz, 1H), 6.42 (d, J = 1 Hz, 1H), 6.35 (d, J = 1 Hz, 1H), 6.32 (d, J = 1 Hz, 1H), 5.57−5.48 (m, 2H), 5.30−5.21 (m, 1H), 5.05−4.85 (m, 10H), 2.88 (d, J = 7.2 Hz, 2H), 2.72−2.38 (m, 8H), 1.33−1.24 (m, 12 H), 1.22 (d, J = 6.2 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 169.4, 169.3, 167.3, 166.9, 160.0, 159.8, 156.9, 156.8, 137.5, 137.1, 136.5, 136.3, 136.3(2C), [128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.4, 127.4, 127.2] (20C), 118.2, 118.0, 108.2 (2C), 99.0, 98.5, 71.9, 71.2, 70.4, 70.3, 70.1, 70.0, 68.4, 67.9, 67.7, 41.0, 40.9, 40.3, 38.9, 38.8, 19.7, 19.4, 18.8 (3C); MS (ESI) *m/z* 1007 $[M + H]^+$; HRMS (ESI) calcd $C_{60}H_{63}O_{14}$: $[M + H]^+$, 1007.4218; found: $[M + H]^+$, 1007.4247. Anal. Calcd for $C_{60}H_{62}O_{14}$: C, 71.55; H, 6.21. Found: C, 71.48; H, 6.15.

(7*R*,11*R*,15*R*,23*R*,27*R*)-2,4,18,20-Tetrahydroxy-7,11,15,23,27-pentamethyl-7,8,11,12,15,16,23,24,27,28-decahydro-5*H*-dibenzo[*k*,*u*][1,5,9,15,19]pentaoxacyclotetracosine-5,9,13,21,25-pentaone (15G256*β*) (1). Pd/C (10%, 25 mg) was added to macrolactone **38** (20 mg, 0.020 mmol) in EtOAc (4 mL). After 12 h stirring under H_2, the mixture was filtered through celite, rotary evaporated, and chromatographed (hexanes:EtOAc 4:1) to give 15G256*β* (**1**) (11 mg, 85%) as a white amorphous solid whose analytical properties were identical to those described for the natural product: R_f 0.40 (hexanes:EtOAc 7:3); $[\alpha]_D$ −21.0 (*c* 0.23 MeOH); IR (KBr) 3384, 1733, 1648, 1619, 1450, 1384, 1313, 1094, 1189, 1054 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 6.23 (d, J = 5.3 Hz, 2H), 6.20 (s, J = 5.3 Hz, 2H), 5.55−5.45 (m, 2H), 5.30−5.20 (m, 1H), 5.05−4.95 (m, 2H), 3.45 (dd, J = 13.2, 6.2 Hz, 1H), 3.34 (dd, J = 13.3, 6.5 Hz, 1H), 2.89 (d, J = 13.5, 7.7 Hz, 1H), 2.84 (dd, J = 11.2, 7.9 Hz, 1H), 2.80 (dd, J = 11.5, 7.4 Hz, 1H), 2.75 (dd, J = 13.5, 8.3 Hz, 1H), 2.71−2.55 (m, 4H), 1.40 (d, J = 6.2 Hz, 3H), 1.39 (d, J = 6.2 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.1 Hz, 3H), 1.12 (d, J = 6.3 Hz, 3H).^{13}C NMR (75 MHz, CD_3OD) δ 171.4, 171.2, 171.2 (2C), 171.0, 165.5, 165.0, 163.5, 163.3, 143.2, 142.9, 113.2, 112.7, 107.3, 106.5, 102.8, 102.7, 73.8, 73.3, 70.2, 70.1, 69.1, 42.5, 41.9, 41.5, 41.4, 41.1, 20.2, 20.1, 19.9, 19.7, 19.6. MS (ESI) *m/z* 647 $[M + H]^+$; HRMS (ESI): calcd $C_{32}H_{39}O_{14}$: $[M + H]^+$, 647.2340, found: $[M + H]^+$, 647.2341.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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