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# Tuning Diketodioxinone Reactivity: Biomimetic Synthesis of the Resorcylate Antibiotic Fungal Metabolites *ent*-W1278A, -B, and -C, Using Iterative Aromatization Reactions

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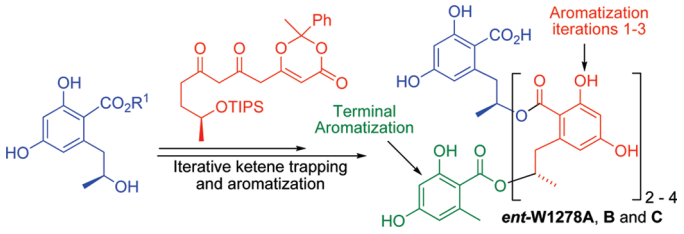


The onset temperature of the retro-Diels−Alder reactions of diketo-1,3-dioxin-2-ones to generate α,γ,ε-triketo-ketenes was found to be significantly reduced with 2-phenyl substitution. These ketenes, generated at 78 °C, were trapped with alcohols to provide resorcylate esters following aromatization by sequential reaction with cesium acetate and trifluoroacetic acid. The methodology was applied iteratively to the total synthesis of the resorcylate antibiotics W1278A, -B, and -C. It is noteworthy that in this process the linking of the monomer units occurs during construction of the aromatic ring.

## Introduction

A distinguishing feature of numerous bioactive natural products is the 6-alkyl-2,4-dihydroxybenzoic acid unit.[1] This unit also serves as the backbone of the oligo-esters W1278A (**1a**, $n$ = 2), -B (**1b**, $n$ = 3), and -C (**1c**, $n$ = 4) (Figure 1), isolated from *Ascomycete sp*. LL-W1278 and determined by hydrolytic degradation to contain (*S*)-building blocks.[2] These compounds possess antibiotic activity, are potent inhibitors in many enzyme-based assays, and are reported to have antiviral activity against the influenza A virus. In consequence of these activities, we sought to undertake the total synthesis of the reported structures of these unique oligomers.

Although a classical synthetic approach could be used to assemble the W1278 antibiotics employing stepwise esterification reactions of suitably protected 6-alkyl-2,4-hydroxybenzoic acid, we considered this approach problematic. Such a strategy would be severely hampered by the need for multiple/selective protecting group manipulations and probable formation of the undesired benzopyranone **6**.[1] Following our previous report on the biomimetic synthesis of resorcylate natural products including 15G256$\beta$ (**2**) and 15G256$\iota$ (**3**),[3] we intended to apply a similar late stage aromatization strategy to the synthesis of the homologues W1278A (**1a**), W1278B (**1b**), and W1278C (**1c**) (Figure 2). Further, we sought to find a more general route to synthesize the diketo-dioxinone derivatives **7** by using milder thermolytic conditions in order to suppress conversion of the delicate hydroxyl-ester intermediates **5** into the benzopyranone **6**. Herein we report a novel synthesis of the dioxinones **7**, a study of the influence of the substituents $R^3$ and $R^4$ on the rate of ketene generation and the application of the methodology to the total synthesis of the oligo-esters

(1) Winssinger, N.; Barluenga, S. *Chem. Commun*. **2007**, 22.
(2) Roll, D. M.; Schlingmann, G. *Chirality* **2005**, *17*, S48. Roll, D. M.; Schlingmann, G. *J. Chromatogr. A* **2007**, *1156*, 256. Nishihara, Y.; Tsujii, E.; Takase, S.; Tsurumi, Y.; Kino, T.; Hino, M.; Yamashita, M.; Hashimoto, S. *J. Antibiot*. **2000**, *53*, 1123. Nishihara, Y.; Tsujii, E.; Takase, S.; Tsurumi, Y.; Kino, T.; Hino, M.; Yamashita, M.; Hashimoto, S. *J. Antibiot*. **2000**, *53*, 1341.
(3) Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, J.; Barrett, A. G. M. *J. Am. Chem. Soc*. **2008**, *130*, 10293.

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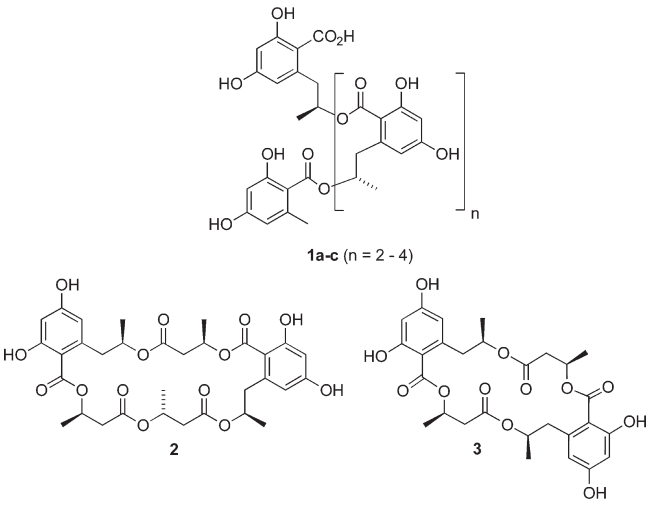



**FIGURE 1.** Biooligomers W1278A (**1a**, $n = 2$), W1278B (**1b**, $n = 3$), and W1278C (**1c**, $n = 4$) and the structurally related antifungal resorcylates 15G256$\beta$ (**2**) and 15G256$\iota$ (**3**).

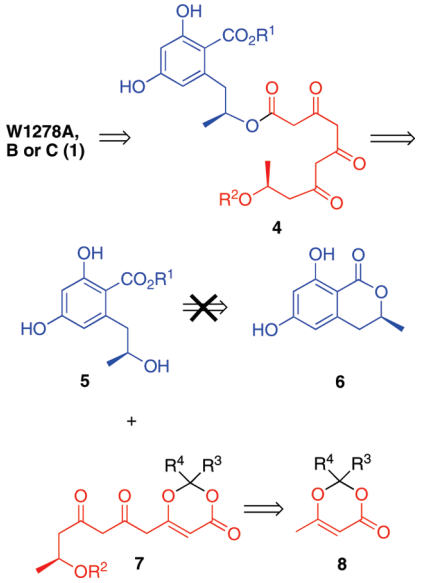


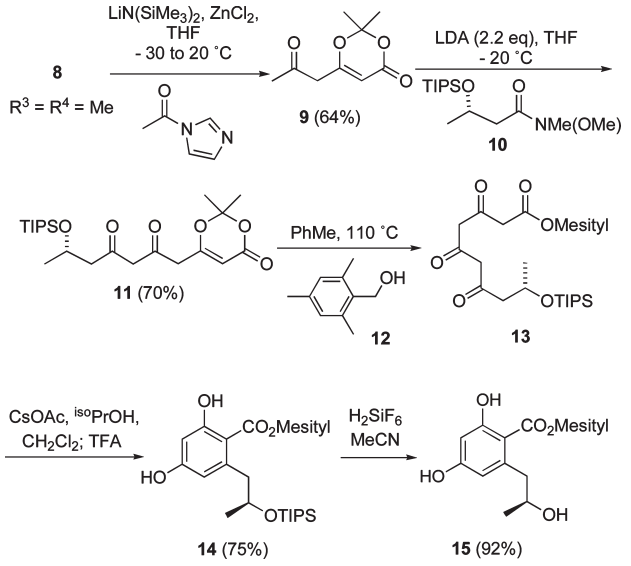

**FIGURE 2.** Retrosynthesis of the W1278 antibiotics, using a sequential late stage aromatization−macrocyclization strategy.

W1278A (**1a**, $n = 2$), -B (**1b**, $n = 3$), and -C (**1c**, $n = 4$) with minimum protecting group manipulations.

## Results and Discussion

Initially the synthesis of diketodioxinone **11** (Scheme 1), using a highly selective *C*-alkylation of keto-dioxinone **9**, was undertaken. We found the Weinreb amide **10**[4] to be especially useful in that competitive *O*- and/or double *C*-alkylation was suppressed, and this variant of the Claisen condensation reaction proved to be more convenient to scale up.[5] Retro-Diels−Alder reaction of dioxinone **11**[6] in the presence of alcohol **12**[7] gave triketo-ester **13**,[8] which was aromatized by sequential reaction with cesium acetate and trifluoroacetic acid to provide the protected monomer unit **14** (75%). Selective desilylation with hexafluorosilicic acid gave alcohol **15** in 92% yield.[9]

**SCHEME 1. Synthesis of W1278 Monomer Unit 15**

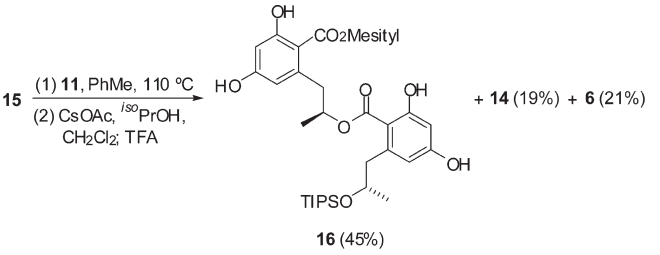



We subsequently applied this biomimetic aromatization strategy to oligomer chain elongation in a process that involved arene ring construction as the monomer units were linked together. Unfortunately, reflux of dioxinone **11** in toluene (Scheme 2) in the presence of alcohol **15** followed by sequential aromatization gave diester **16** in only a moderate 45% yield,[10] together with ester **14** (19%) and benzopyranone **6** (21%).[11] Obviously, competing $\delta$-lactonization was occurring at the thermolysis temperature of 110 °C.

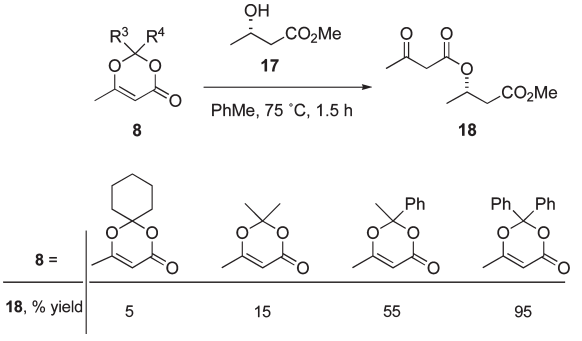
A potential solution to this problem is to enhance the rate of the key retro-Diels−Alder[12] reaction to produce the key $\alpha,\gamma,\varepsilon$-triketo-ketene. We considered that the rate of dioxinone

(4) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3477.
(5) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467. Lygo, B. *Tetrahedron* **1995**, *51*, 12859.
(6) All the di- and triketo-esters exist as mixtures of keto and enol tautomers. However, for convenience, they are drawn as single entities.
(7) For the first use of dioxinones and the derived acyl-ketenes in the total synthesis of macrolactams and macrolactones see: Boeckman, R. K. Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486. Boeckman, R. K. Jr.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. For the use of dioxinones and the derived acyl-ketenes in the total synthesis of macrocyclic natural products see: Boeckman, R. K. Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. Paquette, L. A.; Macdonald, D.; Anderson, L. G.; Wright, J. *J. Am. Chem. Soc.* **1989**, *111*, 8037. Paquette, L. A.; Macdonald, D.; Anderson, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 9292. Boeckman, R. K. Jr.; Shao, P.; Wrobleski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572. Simpson, T. J.; Soulas, F.; Willis, C. L. *Synlett* **2008**, 2196.
(8) The triketo-ester **13** or its analogues were used directly as 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.
(9) Previous experiments with the corresponding benzyl ester afforded mixtures of the desired alcohol and isocoumarin **6**, when desilylation reaction was attempted, showing the tendency of this alcohol to undergo $\delta$-lactonization.
(10) Shelkov, R.; Nahmany, M.; Melman, A. *Org. Biomol. Chem.* **2004**, *2*, 397.
(11) In a parallel experiment, heating alcohol **15** in toluene at reflux for 2 h gave benzopyranone **6** quantitatively.
(12) Chung, Y.; Duerr, B. F.; McKelvey, T. A.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1989**, *54*, 1018. Clemens, R. J.; Witzeman, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186. For other dioxinones see: Rodriguez, H.; Reyes, O.; Suarez, M.; Garay, H. E.; Perez, R.; Cruz, L. J.; Verdecia, Y.; Martin, N.; Seoane, C. *Tetrahedron Lett.* **2002**, *43*, 439. Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.

**SCHEME 2. Initial Studies on Resorcylate Dimer Synthesis**




**SCHEME 3. Conversion Efficiencies for Ketene Generation and Trapping from Dioxinones 8**

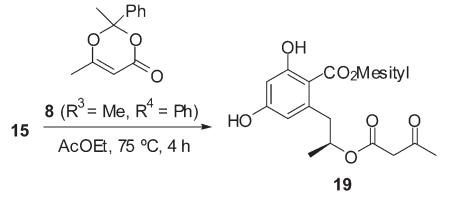



fragmentation should depend on the nature of the C-2 substituents and should be accelerated by the introduction of aromatic and/or sterically bulky substituents or strained spiro-fused rings at this key position. To probe this hypothesis, the extent of acyl ketene formation from the dioxinones **8** ($R^3$, $R^4 = (CH_2)_5$),[13] **8** ($R^3 = R^4 = Me$), **8** ($R^3 = Me$, $R^4 = Ph$),[14] and **8** ($R^3 = R^4 = Ph$)[15] at 75 °C with alcohol **17** as the nucleophile was investigated (Scheme 3). As expected, the product ester **18** was obtained in a range of yields from 5% to 95%, when the reaction was stopped after 1.5 h. It is noteworthy that nearly complete retro-Diels−Alder reaction and acyl-ketene formation and trapping was observed with dioxinone **8** ($R^3$, $R^4$ = Ph) at this lower temperature. Presumably, the overlap of the phenyl $\pi$-system with $\sigma^*$ of the O−CO during the fragmentation of the dioxinone **8** ($R^3$, $R^4$ = Ph) is responsible for the observed acceleration of the retro-Diels−Alder reaction.

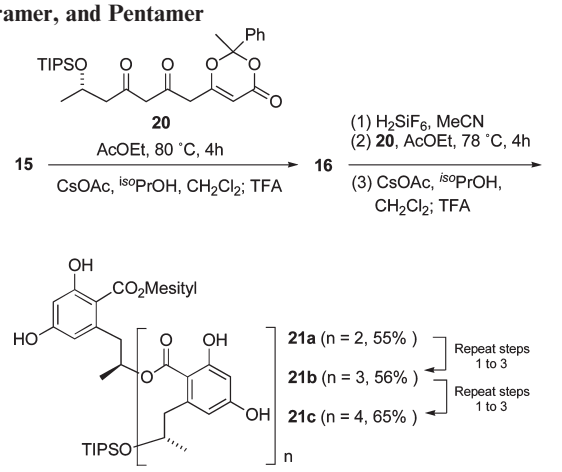
These newly elaborated, milder conditions for acyl-ketene generation were subsequently applied to the synthesis of diester **19** (Scheme 4). Heating a mixture of dioxinone **8** ($R^3 = Me$, $R^4 = Ph$) and alcohol **15**[16] smoothly gave diester **19** in quantitative yield without any benzopyranone **6** being formed.

Following the development of the milder retro-Diels−Alder reaction process, the methodology was extended to the total synthesis of the oligomeric W1278 components.

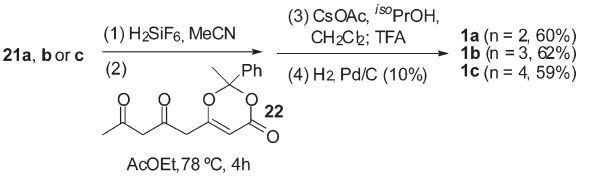
**SCHEME 4. Selective Acetoacetylation of W1278 Monomer Unit 15**




**SCHEME 5. Iterative Syntheses of the W1278 Dimer, Trimer, Tetramer, and Pentamer**




**SCHEME 6. Oligomer Resorcylate Unit Termination and Completion of the Total Syntheses**




Thermolysis of dioxinone **20**[17] (Scheme 5) in the presence of alcohol **15** followed by aromatization afforded dimer **16** (72%). This dimer was subsequently desilylated by using hexafluorosilicic acid and the resulting alcohol was allowed to react with the ketene from dioxinone **20** to provide trimer **21a** and, with additional iterations of ketene trapping and aromatization, the corresponding tetramer **21b** and pentamer **21c** in good overall yields.

Finally, the oligomer chains in **21** (Scheme 6) were functionalized at the alcohol terminus by acylation-aromatization, using the dioxinone **22**[18] followed by hydrogenolysis to deprotect the mesityl group to give the natural product equivalent carboxylic acids **1a** ($n = 2$, 60%), **1b** ($n = 3$, 62%), and **1c** ($n = 4$, 59%).

In summary, we report a new strategy for the synthesis of oligomeric resorcylate natural products using a biomimetic highly selective late aromatization reaction and its application to concise total syntheses of the antibiotics (**1**). The mild

(13) Sato, M.; Ogasawara, H.; Kato, K.; Sakai, M.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 4300.
(14) Hadda, N.; Rukhman, I.; Abramovich, Z. *J. Org. Chem.* **1997**, *62*, 7629.
(15) Dehmlow, E. V.; Shamout, A. R. *Liebigs Ann. Chem* **1982**, *9*, 1753.
(16) Slow decomposition of dioxinone **8** ($R^3 = Ph$, $R^4 = Ph$) was observed at/or just above room temperature, which complicates the application of such dioxinones in multistep synthesis. Thus the less delicate dioxinone **8** ($R^3 = Me$, $R^4 = Ph$) and its derivatives were used in the total syntheses of the oligomers.
(17) The synthesis of the dioxinone **20** closely follows the methods in Scheme 1, using dioxinone **8** ($R^3 = Me$, $R^4 = Ph$) instead of dioxinone **8** ($R^3$, $R^4$ = Ph) as starting material with an equivalent Claisen condensation reaction; see the Supporting Information.
(18) The synthesis of the diketo dioxinone **22** closely follows the methods described in Scheme 1; see the Supporting Information.

reaction conditions used for the acyl-ketene generation, the tolerance of delicate functionality during the generation of the resorcylate units by ketene trapping, and aromatization as well as the minimum use of protecting group manipulations are especially noteworthy.

The synthesized (all *S*)-carboxylic acids **1a**, **1b**, and **1c** were compared with the authentic natural products W1278A, -B, and -C, isolated from *Ascomycete sp.* LL-W1278, and the physical properties of the natural and synthetic samples are identical with one exception. The optical rotations of the synthetic **1a**, **1b**, and **1c** as well as synthetic intermediates en route to these compounds are positive and of opposite sign to the natural products. This is fully consistent with the natural products being all *R* and not all *S*, which is in accord with the absolute stereochemistry of the related natural products 15G256$\beta$ (**2**) and 15G256$\iota$ (**3**).[3,19] Thus W1278A, -B, and -C have the mirror image absolute stereochemistries to those depicted in structures **1a**−**c**. We are currently reinvestigating several reactions used in the degradation and stereochemical assignment of the natural products[2] and will report on these findings in a forthcoming publication.

## Experimental Section

**General Procedure for the Polymer Chain Elongation Procedure (Product 21a−c).** $H_2SiF_6$ in $H_2O$ (20% w/w; 0.45 mL, 0.7 mmol) was added with stirring to ester **16** (or **21** or **21b**, 1 mmol) in MeCN (20 mL) and stirring was continued for 45 min. The reaction mixture was poured into AcOEt (110 mL), washed with $H_2O$ (3 × 15 mL), and dried ($MgSO_4$). After rotary evaporation, the residue was dissolved in AcOEt (25 mL) and dioxinone **20** (561 mg, 1.15 mmol) was added. The mixture was heated at reflux for 4 h. After rotary evaporation, the residue was dissolved in $CH_2Cl_2$ and *i*-PrOH (1.5:1; 30 mL) and CsOAc (1.14 g, 6 mmol) were added, then the mixture was stirred at room temperature for 10 h. The solution was acidified to pH 2 with TFA (0.7 mL, 9 mmol) and stirred for an additional 5 h. The reaction mixture was poured into AcOEt (125 mL), washed with water (3 × 15 mL), and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes:EtOAc 4:1) gave resorcylate oligomers **21a** ($n$ = 2, 55%), **21b** ($n$ = 3, 56%), or **21c** ($n$ = 4, 65%) as pale yellow oils.

**(*S*)-1-(3,5-Dihydroxy-2-((2,4,6-trimethylbenzyloxy)carbonyl)-phenyl)propan-2-yl 2-((*S*)-2-(2,4-dihydroxy-6-((*S*)-2-(triisopropylsilyloxy)propyl)benzoyloxy)propyl)-4,6-dihydroxybenzoate (21a):** $R_f$ 0.75 (EtOAc:hexanes 1:3); $[\alpha]^{25}_D$ +140.7 (*c* 1.7 $CH_3COCH_3$); IR (film) 3357 (br), 1647, 1619, 1449, 1312, 1256 $cm^{-1}$; $^1H$ NMR (400 MHz, $d_6$-$Me_2CO$) $\delta$ 11.89 (s, 1H), 11.60 (s, 1H), 11.51 (s, 1H), 9.10 (br s, 3H), 6.87 (s, 2H), 6.32 (d, $J$ = 2.4 Hz, 1H), 6.29−6.26 (m, 3H), 6.22 (d, $J$ = 2.4 Hz, 1H), 6.19 (d, $J$ = 2.4 Hz, 1H), 5.60−5.50 (m, 1H), 5.54 (d, $J$ = 12.0 Hz, 1H), 5.39 (d, $J$ = 12.0 Hz, 1H), 5.39−5.30 (m, 1H), 4.31−5.22 (m, 1H), 3.56 (dd, $J$ = 12.9, 2.9 Hz, 1H), 3.39 (dd, $J$ = 13.4, 4.9 Hz, 1H), 3.15 (dd, $J$ = 13.4, 5.2 Hz, 1H), 3.05−2.95 (m, 2H), 2.53 (dd, $J$ = 12.9, 8.9 Hz, 1H), 2.41 (s, 6H), 2.15 (s, 3H), 1.42 (d, $J$ = 6.2 Hz, 3H), 1.31 (d, $J$ = 5.9 Hz, 3H), 0.94 (br s, 21H), 0.90 (d, $J$ = 6.2 Hz, 3H); $^{13}C$ NMR (101 MHz, $d_6$-$Me_2CO$) $\delta$ 172.4, 171.8, 171.3, 167.0, 166.8, 166.6, 163.3, 162.9 (2C), 145.4, 143.3, 143.0, 139.6, 139.2 (2C), 130.0 (2C), 129.2, 114.8, 113.8, 113.6, 105.3, 105.1, 104.9, 102.9 (2C), 102.2, 73.8, 73.5, 70.7, 63.0, 47.7, 43.9, 43.7, 25.4, 21.1, 20.6, 19.7, 19.6 (2C), 18.6 (3C), 18.5 (3C), 13.4 (3C); MS (CI) $m/z$ 889 $[M + H]^+$; HRMS (CI) calcd for $C_{49}H_{64}O_{13}Si$ $[M + H]^+$, 889.4194, found $[M + H]^+$ 889.4185. Anal. Calcd for $C_{49}H_{64}O_{13}Si$: C, 66.19; H, 7.26. Found: C, 66.32; H, 7.20.

**(*S*)-1-(3,5-Dihydroxy-2-((2,4,6-trimethylbenzyloxy)carbonyl)-phenyl)propan-2-yl 2-((*S*)-2-(2-((*S*)-2-(2,4-dihydroxy-6-((*S*)-2-(triisopropylsilyloxy)propyl)benzoyloxy)propyl)-4,6-dihydroxybenzoyloxy)-propyl)-4,6-dihydroxybenzoate (21b):** $R_f$ 0.55 (EtOAc:hexanes 1:3); $[\alpha]^{25}_D$ +217.1 (*c* 2.8 $CH_3COCH_3$); IR (film) 3360 (br), 1642, 1617, 1449, 1312, 1254 $cm^{-1}$; $^1H$ NMR (400 MHz, $d_6$-$Me_2CO$) $\delta$ 11.88 (1H, s), 11.61 (1H, s), 11.55 (1H, s), 11.48 (1H, s), 9.10 (4H, br s), 6.82 (2H, s), 6.33−6.24 (5H, m), 6.18−6.14 (3H, m), 5.70−5.60 (1H, s), 5.59−5.51 (1H, s), 5.48 (dd, $J$ = 12.0 Hz, 1H), 5.36 (dd, $J$ = 12.0 Hz, 1H), 5.35−5.25 (1H, s), 4.30−2.20 (1H, s), 3.60−3.45 (2H, m), 3.33 (dd, $J$ = 13.4, 4.7 Hz, 1H), 3.16−2.95 (4H, m), 2.49 (dd, $J$ = 12.6, 9.3 Hz, 1H), 2.37 (6H, s), 2.10 (3H, s), 1.43 (d, $J$ = 6.2 Hz, 3H), 1.42 (d, $J$ = 6.2 Hz, 3H), 1.29 (d, $J$ = 6.2 Hz, 3H), 0.91 (21H, s), 0.88 (d, $J$ = 6.2 Hz, 3H); $^{13}C$ NMR (101 MHz, $d_6$-$Me_2CO$) $\delta$ 172.4, 171.9, 171.4, 171.3, 167.0, 166.7, 166.6 (2C), 163.3, 163.0, 162.9 (2C), 145.5, 143.3, 143.0 (2C), 139.6, 139.1 (2C), 130.0 (2C), 129.1, 114.8, 113.8, 113.6, 113.5, 105.5, 105.4, 105.1, 104.9, 103.0 (2C), 102.8, 102.2, 73.8, 73.8, 73.5, 70.7, 62.9, 47.7, 43.9, 43.6 (2C), 25.4, 21.1, 20.7, 20.5, 19.7, 19.6 (2C), 18.6 (3C), 18.5 (3C), 13.4 (3C); MS (CI) $m/z$ 1083 $[M + H]^+$; HRMS (CI) calcd for $C_{59}H_{74}O_{17}Si$ $[M + H]^+$ 1083.4789; found $[M + H]^+$ 1083.4774. Anal. Calcd for $C_{59}H_{74}O_{17}Si$: C, 65.41; H, 6.89. Found: C, 65.38; H, 6.80.

**(*S*)-1-(3,5-Dihydroxy-2-((2,4,6-trimethylbenzyloxy)carbonyl)-phenyl)propan-2-yl 2-((*S*)-2-(2-((*S*)-2-(2-((*S*)-2-(2,4-dihydroxy-6-((*S*)-2-(triisopropylsilyloxy)propyl)benzoyloxy)propyl)-4,6-dihydroxybenzoyloxy)propyl)-4,6-dihydroxybenzoyloxy)propyl)-4,6-dihydroxybenzoate (21c):** $R_f$ 0.40 (EtOAc:hexanes 1:3); $[\alpha]^{25}_D$ +180.1 (*c* 0.8 $CH_3COCH_3$); IR (film) 3358 (br), 1648, 1619, 1446, 1312, 1251 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3COCD_3$) $\delta$ 11.93 (1H, s), 11.88 (1H, s), 11.62 (1H, s), 11.50 (2H, s), 9.13 (5H, br s), 6.79 (2H, s), 6.32−6.23 (6H, m), 6.18−6.15 (4H, m), 5.70−5.60 (2H, s), 5.59−5.50 (1H, s), 5.48 (dd, $J$ = 12.0 Hz, 1H), 5.37 (dd, $J$ = 12.0 Hz, 1H), 5.35−5.25 (1H, s), 4.30−2.20 (1H, s), 3.60−3.45 (3H, m), 3.34 (dd, $J$ = 13.3, 4.9 Hz, 1H), 3.16−2.95 (5H, m), 2.49 (dd, $J$ = 12.8, 9.3 Hz, 1H), 2.38 (6H, s), 2.10 (3H, s), 1.47 (d, $J$ = 6.2 Hz, 3H), 1.42 (d, $J$ = 6.2 Hz, 6H), 1.29 (d, $J$ = 6.2 Hz, 3H), 0.91 (21H, s), 0.89 (d, $J$ = 6.2 Hz, 3H); $^{13}C$ NMR (101 MHz, $d_6$-$Me_2CO$) $\delta$ 172.4, 171.9, 171.5, 171.5, 171.4, 167.0, 166.8, 166.7 (2C), 166.6, 163.3, 163.1, 163.1, 163.0 (2C), 145.5, 143.3, 143.1 (2C), 139.6, 139.2, 130.0 (2C), 129.1, 114.8, 113.8, 113.6 (2C), 113.6, 105.4 (2C), 105.3, 105.1, 104.9, 102.9 (3C), 102.2 (2C), 73.9, 73.9, 73.8, 73.5, 70.8, 63.0, 47.7, 43.9, 43.6, 43.6, 43.6, 25.4, 21.1, 20.7, 20.6, 19.8, 19.6 (2C), 18.6 (3C), 18.5 (3C), 13.4 (3C); MS (CI) $m/z$ 1277 $[M + H]^+$. Anal. Calcd for $C_{69}H_{84}O_{21}Si$: C, 64.87; H, 6.63. Found: C, 64.91; H, 6.57.

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

(19) The CD spectra of lactone **6** and synthetic oligomeric esters **1b** and **1c** versus samples of the isolated natural oligomers W1278 support this observation; see the Supporting Information.