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Pd-Catalyzed Site-Selective Mono-allylic Substitution and Bis-arylation by Directed Allylic C−H Activation: Synthesis of *anti*-γ-(Aryl,Styryl)-β-hydroxy Acids and Highly Substituted Tetrahydrofurans

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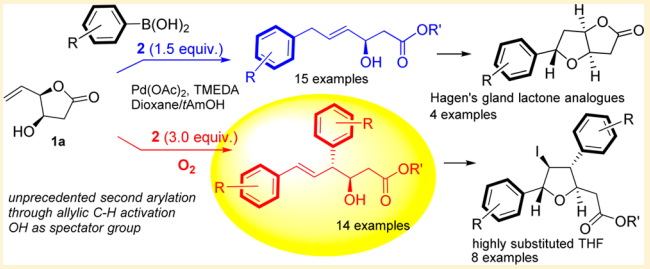
Supporting Information

ABSTRACT: An efficient palladium-catalyzed site-selective arylation of γ-vinyl-γ-lactone by aryl boronic acid has been developed. γ-Vinyl-γ-lactone **1a** has been contemplated as allyl electrophile donor for allylic arylation via π-allyl palladium intermediate using 1.5 equiv of aryl boronic acid **2**. Using 3.0 equiv of the latter resulted in mono-arylation by allylic substitution and subsequent site-selective second arylation by directed allylic C−H activation giving stereoselectively *anti*-γ-(aryl,styryl)-β-hydroxy acids. Presence of O_2 was crucial for the second arylation via Pd(II) catalysis. Thus, a good synergy of dual catalysis by Pd(0) and Pd(II) was observed. This methodology has been elaborated to synthesize highly substituted tetrahydrofurans including aryl-Hagen's gland lactone analogues via intramolecular iodoetherification.



INTRODUCTION

Transition metal catalyzed cross-coupling reaction between allylic electrophiles with various nucleophiles constitutes a powerful tool for C−C bond formation.[1] This method has been elaborated for various transformations and synthesis of complex natural products via π-allyl palladium complexes.[1,2] After the first report in 1979 by Trost and Klun[3] on allylic alkylation, π-allyl palladium complexes have been reacted with a wide spectrum of nucleophiles to afford highly diversified and synthetically useful olefinic compounds.[4] In the past decades, electrophilic π-allyl palladium species are derived from allyl halides, esters, carbonates, and phosphonates, among others, through leaving group ionization.[5] The recent pioneering work by Trost et al. has enabled the synthesis of π-allyl palladium species through allylic C−H activation.[6] Subsequently, they reported an elegant unprecedented tandem Pd(0) and Pd(II) catalysis for allylic alkylation[7] wherein Pd(0) was oxidized *in situ* to Pd(II) (Figure 1a). While the electrophile donors are centered mostly on activated aliphatic allyl substrates, the cyclic systems are less explored.[8] The γ-vinyl-γ-lactones can be contemplated as electrophile donors similar to allylic acetates. Hence, leaving group ionization mediated by Pd(0) is possible to generate π-allyl palladium species to be trapped by soft nucleophiles. For such cyclic systems, attempts are made through Cu-catalyzed S_N2' type substitutions.[9] With strategic similarity of cyclic γ-vinyl-γ-lactone **1a**[10] to allyl acetates, we visualized arylation of the former under Pd-catalysis as this process would be traceless and atom economical unlike the case of allyl acetates (Figure 1b). While mono-arylation was anticipated to occur through Pd(0) via π-allyl palladium intermediate **A** formed by leaving group ionization, a slight excess of nucleophile triggered a site-selective second arylation by directed allylic C−H activation that was unprecedented in literature. It is remarkable that the allyl alcohol system does not participate in leaving group ionization.[11] The reaction would occur through allylic C−H activation (**B**) and would preferentially require Pd(II) catalysis. White et al.[12] have explored extensively allylic activation based substitution; however, our strategy is different and has some resemblance to Trost's work[7] based on dual catalysis. Similarly, the presence of oxygen has been crucial in this work as an oxidant for Pd(0) to Pd(II) conversion (Figure 1). Thus, this is dual catalysis by Pd(0) and the *in situ* generated Pd(II) catalyst. Mono-arylated system **3** is present in lobatamide A[13] and constitutes an important building block for further modifications. A simple iodocyclization, elimination, and iodoetherification of mono-arylated compound would lead to aryl-Hagen's gland lactone[14] analogues. The bis-arylated compound **4** can be iodoetherified via the β-hydroxy group to deliver highly substituted tetrahydrofurans with 2,4-bis-aryl units. This motif is present in calyxolanes A, B[15] and magnosalicin[16] (Figure 1).

RESULTS AND DISCUSSION

The optimization study commenced with the reaction of **1a** (0.5 mmol) with phenylboronic acid **2a** (0.75 mmol) and $Pd_2(dba)_3$ catalyst (5 mol %) with TMEDA (10 mol %) as ligand in dioxane at room temperature. However, even after 72

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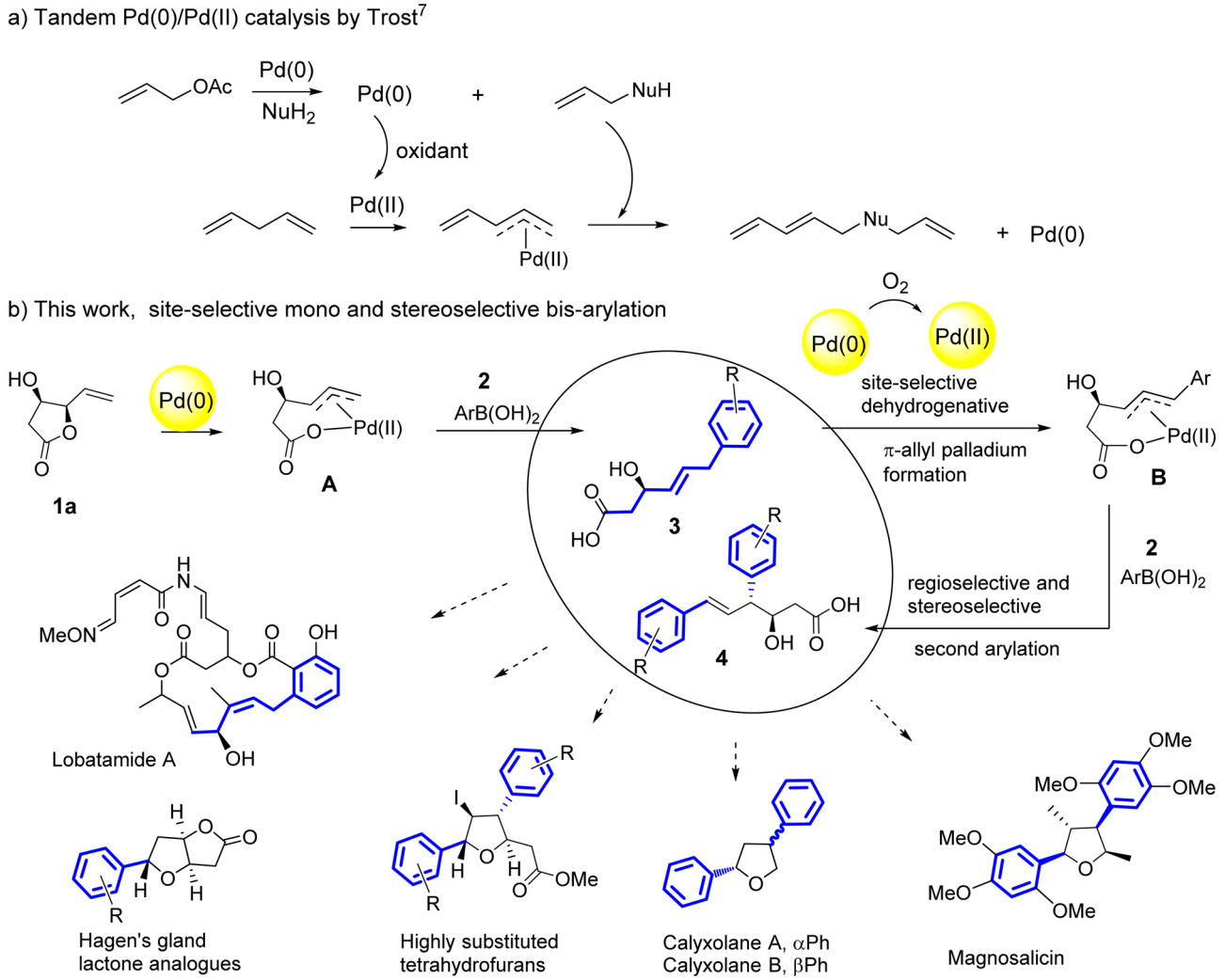

Figure 1. Tandem catalysis by Pd(0) and Pd(II). Allylic arylation of γ-vinyl-γ-lactone **1a** and further modifications.

h we did not get desired product **5a** (the esterification to methyl ester was considered for easy isolation). The reaction resulted in the isomerized lactone **1b** (**1a**/**1b** = 1:1, 68%, Table 1, entry 1). The same reaction at 110 °C provided a mixture of isomerized compound **1b** (**1a**/**1b** = 2:1, 48%) and **3a**, the latter being isolated as methyl ester **5a** in 37% yield (entry 2). The addition occurred at the less hindered terminus of the π-allylpalladium intermediate. A switch in solvent to *t*-AmOH improved the yield to 58% with no side reactions (entry 3). Other solvents like DMA and toluene were not successful to increase the yields of **5a**.[17] Addition of phosphine ligand (or that present in catalyst) did not favor arylation but promoted isomerization of **1a** and undesired self-coupling of boronic acid to **1c** (entries 4−7). A variation in Pd-catalyst (entries 8−10) showed $Pd(OAc)_2$ to be better, giving **5a** in 68% yield (entry 10). Change of solvent to dioxane, toluene, or THF did not prove better.[17] Fortunately, a switch to combination of solvents (dioxane and *t*-AmOH, 1:1) improved the yield of **5a** to acceptable level of 80% (entry 11). With this solvent combination, we back-checked the ligands: bipyridine, PPh_3, and BINAP (entries 12−14). While bipyridine worked well, others gave isomerized product **1b** and biaryl **1c**. Keeping other conditions the same, we changed $Pd(OAc)_2$ to $Pd_2(dba)_3$, which resulted in **5a** in 73% yield (entry 15). The variation in Pd-catalyst loading suggested that 5 mol % was the optimum requirement.[17] The reaction without the ligand TMEDA resulted in only isomerized product **1b** (**1a**/**1b** = 1:1.5, 61%, entry 16). A decrease in TMEDA concentration to 5 mol % lowered the yield of **5a**.[17] In all cases above, **5a** was obtained as *E*/*Z* mixture with *E*-isomer as the major product (ratio > 6:1). An increase in arylboronic acid concentration to 2.0 equiv resulted in the formation of mixture of mono- and bis-arylated products **5a** and **6a** (after esterification) in 38 and 25% isolated yields, respectively (entry 17) with the recovery of unreacted **1a** in 9% yield. We believe the amount of boronic acid was not sufficient to drive the reaction to higher yields of **5a** or **6a**. It is also possible that the mono- and bis-arylation occurs simultaneously. The site-selective second arylation is remarkable and unprecedented in literature. After mono-arylation, this can arise via directed π-allyl palladium formation through C−H activation probably facilitated by internal carboxylate anion, followed by second arylation. It is remarkable that the allyl alcohol system did not participate in leaving group ionization. We anticipated that a further increase in concentration of aryl boronic acid would give predominantly the bis-arylated product. To our delight, 3.0 equiv of **2a** indeed delivered **6a** (36%), and **5a** was obtained in 15% yield (entry 18). We realized that the second arylation involving dehydrogenative π-allyl palladium formation requires Pd(II) catalyst, which could be generated from Pd(0) by traces of oxygen present. Hence,

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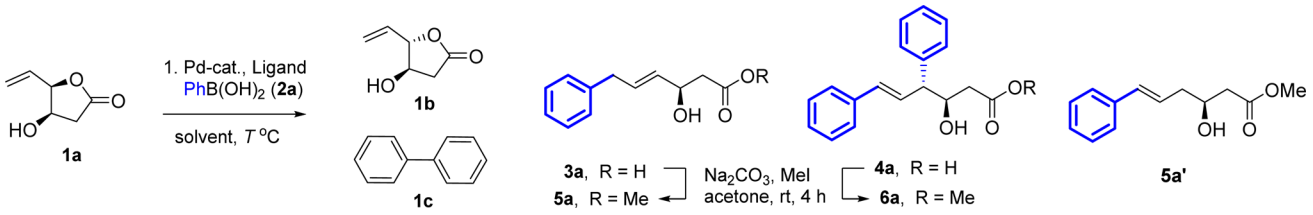
Table 1. Optimization of Allyl-Aryl Coupling Reaction between 1a and $PhB(OH)_2$ 2a[a]



entry	catalyst (mol %)	ligand (mol %)	solvent	T (°C)	time (h)	yield of 1a/1b (%)	1c (%)	yield of 5a (%)	yield of 6a (%)
1	$Pd_2(dba)_3$ (5)	TMEDA (10)	dioxane	rt	72	1:1 (68)			
2	$Pd_2(dba)_3$ (5)	TMEDA (10)	dioxane	110	48	2:1 (48)		37	
3	$Pd_2(dba)_3$ (5)	TMEDA (10)	*t*-AmOH	110	12			58	
4	$Pd_2(dba)_3$ (5)	PPh_3 (10)	*t*-AmOH	110	12	2:1 (72)	32		
5	$Pd(PPh_3)_4$(5)	TMEDA (10)	*t*-AmOH	110	72	1:1.5 (69)	40		
6	$Pd(PPh_3)_4$ (5)	PPh_3 (10)	*t*-AmOH	110	72	1:2 (66)	38		
7	$PdCl_2(dppf)_2$(5)	PPh_3 (10)	*t*-AmOH	110	72	1:1.5 (58)	38		
8	Pd−C (5)	TMEDA (10)	*t*-AmOH	110	72	1:1 (62)			
9	$Pd(CO_2CF_3)_2$ (5)	TMEDA (10)	*t*-AmOH	110	12	1:2.5 (68)		33	
10	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*-AmOH	110	12			68	
11	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*-AmOH/dioxane	110	12			80	
12	$Pd(OAc)_2$(5)	Bpy (10)	*t*-AmOH/dioxane	110	24			68	
13	$Pd(OAc)_2$ (5)	PPh_3 (10)	*t*-AmOH/dioxane	110	24	1:2.5 (78)	41		
14	$Pd(OAc)_2$ (5)	BINAP (10)	*t*-AmOH/dioxane	110	24	1:1 (63)	29		
15	$Pd_2(dba)_3$ (5)	TMEDA (10)	*t*-AmOH/dioxane	110	12			73	
16	$Pd(OAc)_2$ (5)		*t*-AmOH/dioxane	110	12	1:1.5 (61)			
17[b]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*-AmOH/dioxane	110	24	1a (9)		38	25
18[c]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*-AmOH/dioxane	110	24			15	36
19[c,d]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*-AmOH/dioxane	110	24				62
20[c,d]	$Pd(OAc)_2$ (10)	TMEDA (20)	*t*-AmOH/dioxane	110	24				72
21[c,d]	$Pd(OAc)_2$ (20)	TMEDA (20)	*t*-AmOH/dioxane	110	24				73
22[a,d]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*-AmOH/dioxane	110	24	1a (16)			35
23[c,e]	$Pd(OAc)_2$ (10)	TMEDA (20)	*t*-AmOH/dioxane	110	24		6	63	
24[a,d,f]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*-AmOH/dioxane	110	24			10	36[g]

[a]Reaction condition: **1a** (0.5 mmol), $PhB(OH)_2$ (0.75 mmol), Pd source (5−20 mol %), ligand (10−20 mol %), dioxane/*t*-AmOH (1:1, 2 mL), rt−110 °C. [b]2.0 equiv of **2a** used. [c]3.0 equiv of **2a** used. [d]O_2 used. [e]No oxidant (in glovebox). [f]Reaction on separated crude **3a**. [g]**5a′** (12%).

we speculated that addition of external oxidant would benefit the reaction. When the reaction was carried out under O_2 (balloon), indeed bis-arylated compound **6a** was obtained in 62% yield (entry 19). Use of benzoquinone[7] or silver acetate as oxidants (3.0 equiv)[17] gave results comparable to those with O_2 as oxidant (entry 19). However, considering cost and greener use of O_2, we further optimized the conditions using $Pd(OAc)_2$ (10 and 20 mol %) and TMEDA (20 mol %) with O_2 as oxidant to give **6a** in 72 and 73% yields respectively (entries 20 and 21). Lowering of boronic acid **2a** to 1.5 equiv under O_2 atmosphere delivered **6a** in only 35% yield (entry 22) with the recovery of **1a** (16%) indicating the need of excess **2a**. A reaction carried out in the absence of O_2 or any other oxidants in a glovebox with 3.0 equiv of boronic acid **2a** resulted in only mono-arylation, giving **5a** in 63% yield (entry 23) along with 6% of biphenyl **1c** isolated. This indicated the need of external oxidant for Pd(0) to Pd(II) conversion for the success of the second arylation. We also attempted the second arylation on the crude **3a** (obtained after mono-arylation) with **2a** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), and TMEDA (10 mol %) under O_2 atmosphere (entry 24). This reaction indeed delivered **6a** in 36% overall yield from **1a** along with 12% of double-bond-isomerized product **5a′** isolated as methyl ester and recovered **5a** in 10% yield. Compound **5a′** was earlier detected in a few cases but was in traces. Thus, a one-pot reaction with excess boronic acid **2a** gave better results than the stepwise reaction. It is possible that the presence of free carboxylate in the one-pot reaction might facilitate the second arylation. The reaction on **5a** (with OMe group) for second arylation delivered mostly double-bond-isomerized compound **5a′** (32%) with some recovery of **5a** (24%) substantiating the earlier statement. When the OH group in **1a** was protected via TBS group (compound **1a′**), the attempted mono-arylation was not observed, but lactone **1a′** was isomerized to **1b′** (**1a′**/**1b′** = 2:1). This indicated that the presence of free OH was desirable for the success of this reaction.

With the optimized conditions, the scope and limitations of the allyl−aryl coupling reaction with various substituted arylboronic acids **2** was investigated. As shown in Scheme 1, the coupling of **1a** with various substituted arylboronic acids **2** (1.5 equiv) of varying electronic or steric natures proceeded to give corresponding allyl−aryl coupled products **5a−o** in moderate to high isolated yields (isolated as esters) with complete regioselectivity for linear systems and good *E*/*Z* ratio of up to 6:1. Halogenated aryl boronic acids were well tolerated giving products **5c,d,e,h,k,l** in good yields. The latter with bis-fluoride was an exception, being obtained in a lower yield (35%). Similarly, the formyl- and cyano-substituted boronic acids gave best results, delivering **5f,g,i,j** in high yields. The *ortho*-methyl-substituted arylboronic acid produced exceptionally *Z*-isomer **5m** as major product (*E*/*Z* = 1:2.5). The *Z*-selectivity may be anticipated due to the prolonged reaction

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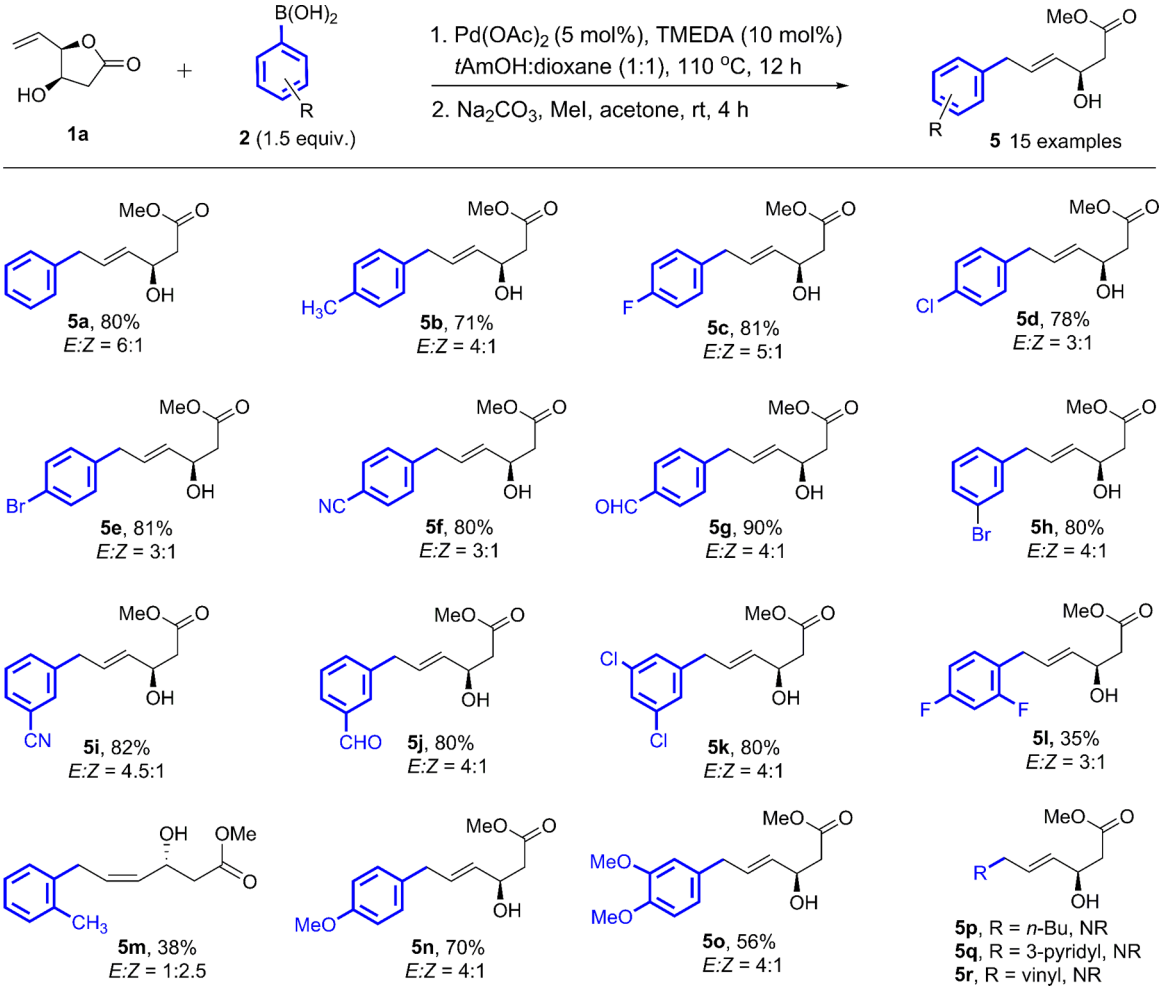
Scheme 1. Allyl-Aryl Cross Coupling of Various Boronic Acids 2 (1.5 equiv) with 1a[a]



[a]NR = No reaction.

time which accounts for isomerization of π-allyl palladium intermediate while incorporating sterically crowded boronic acids. *n*Butylboronic acids **2p**, heteroarylboronic acid **2q**, and vinylboronic acid **2r** failed under the present protocol to give the corresponding products **5p**, **5q**, and **5r**, respectively.

The bis-arylation of **1a** with 3.0 equiv of various aryl boronic acids **2** was also investigated for scope and limitations. Based on optimized conditions, we employed $Pd(OAc)_2$ (10 mol %) and TMEDA (20 mol %) under O_2 atmosphere (balloon). As shown in Scheme 2, diversely substituted bis-arylated products **6a**–**n** (after esterification) were obtained in good to high yields with complete regioselectivity toward styryl olefinic bond and with exclusive *E*-selectivity. No trace of 1,1-bis-aryl compound was obtained in any of the cases. The halogenated aryl boronic acids were well-tolerated in the Pd-catalyzed bis-coupling reaction to produce **6e**–**i** in good yields. The formyl and free phenolic boronic acids delivered products **6j** and **6k**, respectively, in good to moderate yields; *ortho*-methyl-substituted product **6l** was obtained in moderate yield with exclusive (*E*)-olefinic bond unlike the (*Z*) obtained in mono-arylation (**5m**, Scheme 1). This could be attributed to the difference in substrates for mono- and bis-arylation with different steric environments. The allylic–OH group appeared to be a spectator group and did not participate in leaving group ionization.[11]

We further considered synthetic modifications of mono- and bis-arylated compounds of Schemes 1 and 2. The β-hydroxy acid/ester is an important intermediate for β-lactams and pheromones synthesis, and this motif is present in many natural products.[18] A catalytic hydrogenation of **5a**, **5c**, **6a**, and **6d** gave β-hydroxy esters **7a**, **7c**, **8a**, and **8d**, respectively, in quantitative yields (Scheme 3). For **5c**, since the reaction was carried out in EtOH, *trans*-esterified product **7c** was obtained.

While the mono-arylated compounds **5** were obtained as *E*/*Z* mixtures, the hydrogenation of double bond gave single enantiomer. HPLC performed on **7a** and **7c** for example indicated enantiopure compounds (100% ee, see Supporting Information). Similarly, the hydrogenation of **6a** and **6d** gave **8a** and **8d** as single diastereomers. No *syn*-isomer was detected within the limits of ^1H and ^{13}C NMR.

Intermediate γ,δ-unsaturated acids **3** were visualized further for a possible iodolactonization. Thus, crude acids **3** obtained upon mono-arylation were treated with iodine and $NaHCO_3$ in CH_3CN solvent to deliver intermediate iodo-γ-lactones **9** that underwent efficient iodo-elimination *in situ* furnishing γ-styryl-γ-lactones **10** in good yields (Scheme 4). The ring closure was highly *syn*-selective. This constitutes a formal Heck-type coupling of **1a** with arylboronic acids **2**. In a few cases, minor *Z*-olefin isomers **10a′**, **10b′**, **10c′**, and **10f′** were isolated in 6–8% yields (Scheme 4). A direct coupling of lactone **1a** with

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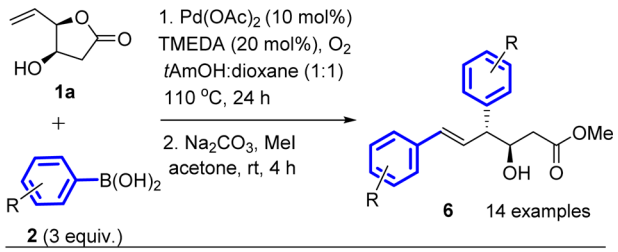
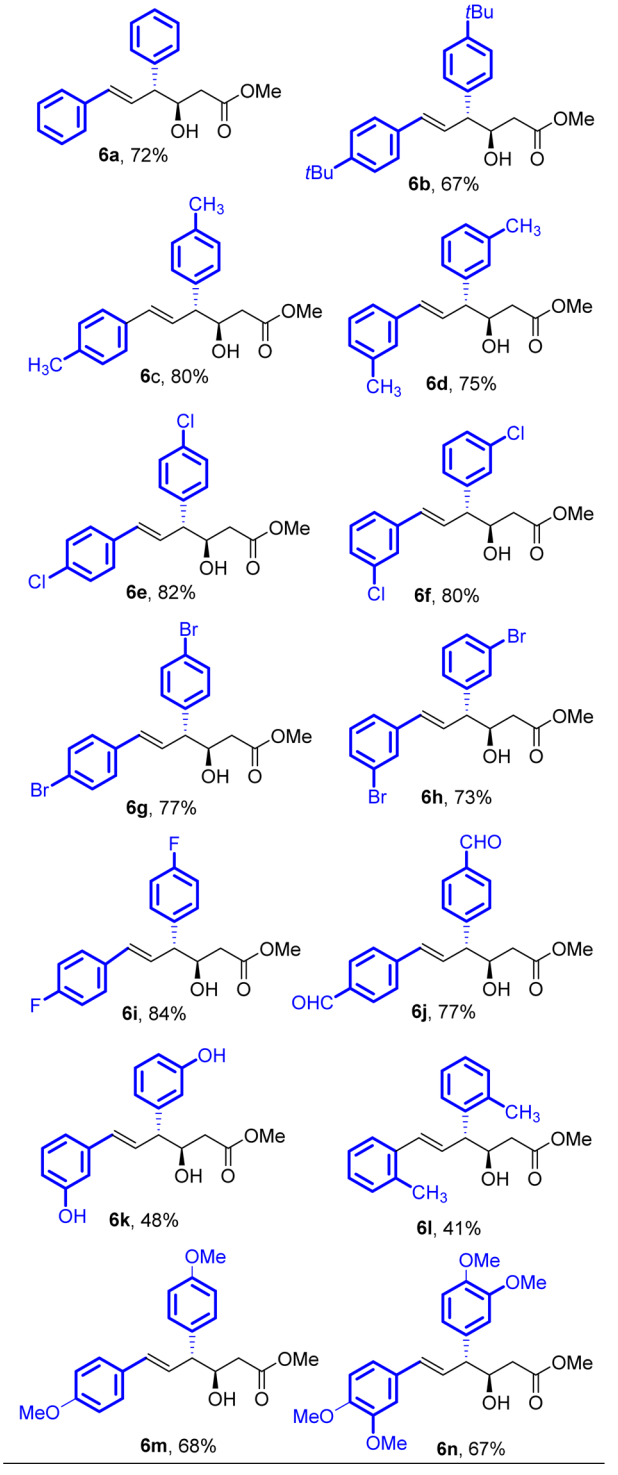
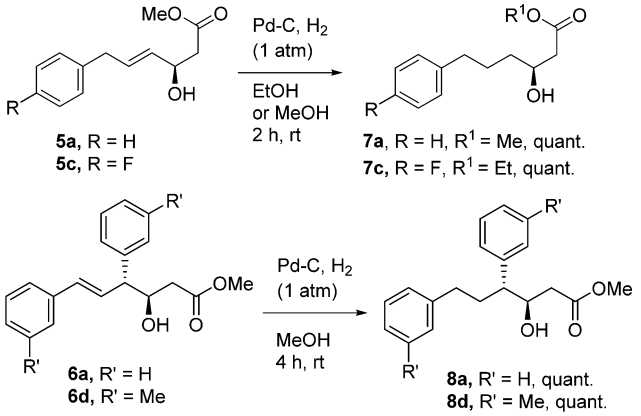
Scheme 2. Bis-Arylation of 1a with Various Arylboronic Acids 2 (3.0 equiv) under Pd(0) and Pd(II) Dual Catalysis

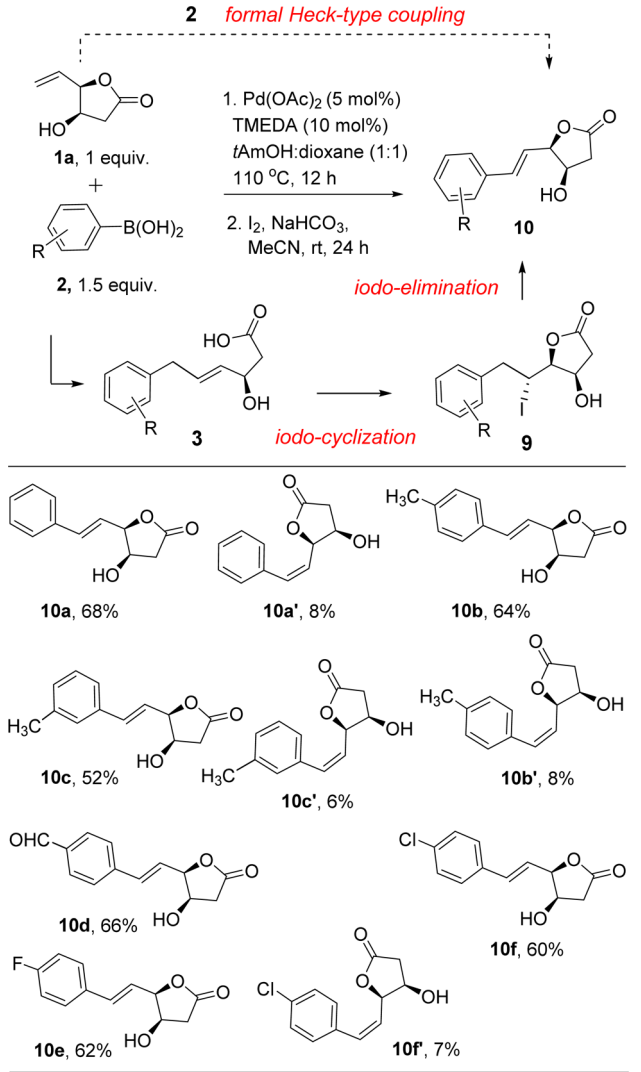




Scheme 3. Synthesis of Saturated ω-Aryl-β-hydroxy- and γ,ω-Bis-aryl-β-hydroxyesters



Scheme 4. Tandem Iodo-Lactonization and Iodo-Elimination (Formal Heck-Type Coupling)



iodobenzene was attempted earlier in our laboratory for Heck reaction.[10d] However, this resulted in only isomerization of **1a** to **1b**.

γ-Styryl-γ-lactones **10** were further available for iodocyclization via the β-hydroxy group and the styryl olefin. We had

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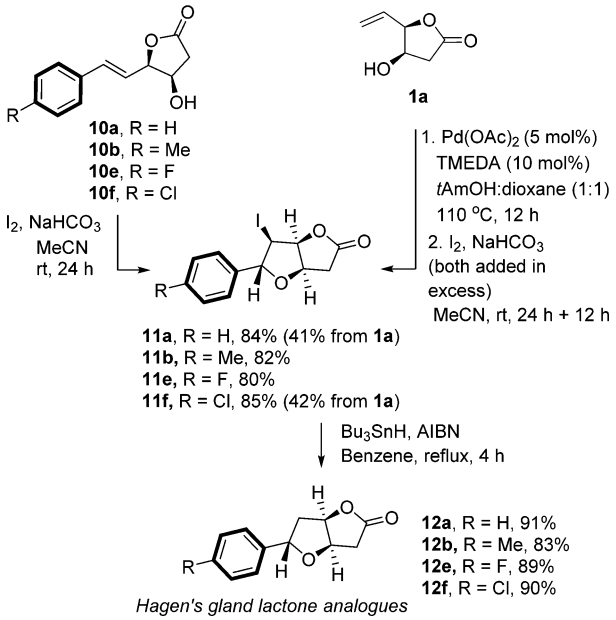
earlier employed a similar strategy in the protecting-group-free synthesis of Hagen's gland lactones.[10a,c] The diastereoselectivity in ring closure was quite high toward C-2/C-5 *anti*-tetrahydrofuran isomer. Thus, compounds **10** were considered for synthesis of aryl analogues of Hagen's gland lactones.[14] As shown in Scheme 5, γ-styryl-γ-lactones **10a,b,e,f** upon iodo-

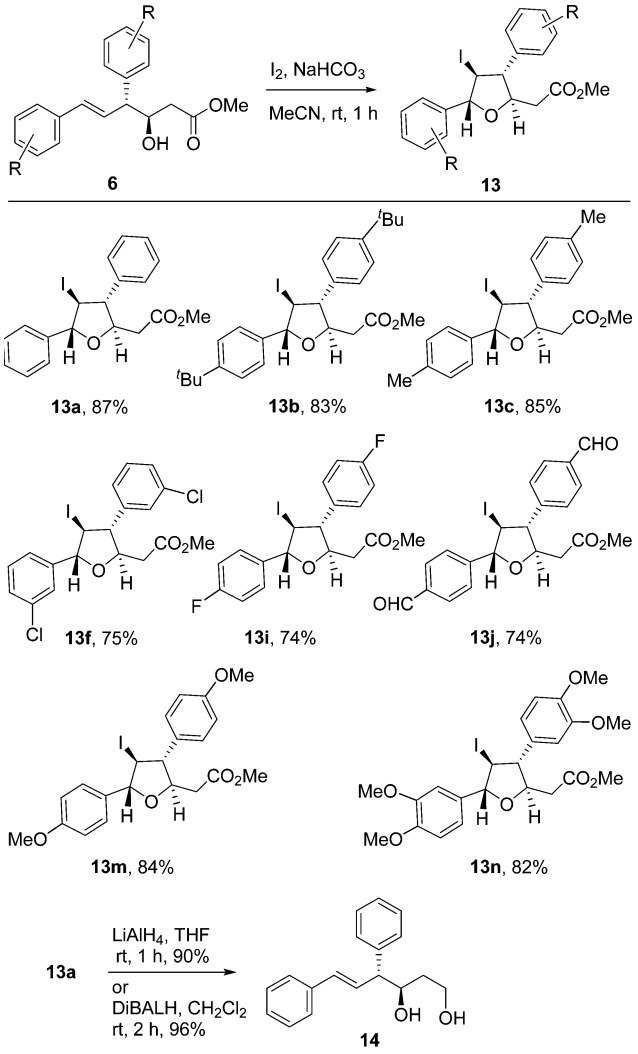
Scheme 5. Synthesis of Aryl-Hagen's Gland Lactone Analogues



etherification delivered compounds **11a,b,e,f**, respectively, in good yields and high diastereoselectivity toward the 2,5-*anti*-tetrahydrofuran ring. The *syn*-isomer, if formed, could be in traces as it is not detected in the ^{1}H NMR. These, upon deiodination, provided aryl-Hagen's gland lactone analogues[14] **12a,b,e,f** in high yields (Scheme 5). Since the iodo-lactonization, iodo-elimination (from **3** to **10**), and subsequent iodo-etherification (from **10** to **11**) requires I_2/$NaHCO_3$, we planned these two reactions in one pot with an excess of these reagents. Thus, after mono-arylation of **1a**, crude acids **3a** or **f** were taken up in CH_3CN and treated with I_2 (2.0 equiv) and $NaHCO_3$ (3.0 equiv) for 24 h followed by addition of another 2.0 and 3.0 equiv, respectively, of both the reagents in the same flask and stirring for a further 12 h. From this, we could isolate compounds **11a** (41%) and **11f** (42%) directly (Scheme 5) from **1a**. This displayed an excellent compatibility of sequential carboxylic acid mediated iodo-cylization, iodo-elimination, and iodo-etherification reactions occurring in one pot.

Bis-arylated compounds **6** appeared to be appealing candidates for iodo-etherification using the pendant β−OH group and the styryl olefin bond to obtain densely substituted tetrahydrofurans. Thus, when compounds **6a−c,f,i,j,m,n** were treated with iodine and $NaHCO_3$ in CH_3CN solvent, they delivered densely substituted tetrahydrofurans **13a−c,f,i,j,m,n**, respectively, in good yields (74−87%) and high diastereoselectivity toward the 2,5-*anti*-tetrahydrofuran ring (Scheme 6). The iodo and ester groups in **13** can be elaborated further. The 2,4-biaryl tetrahydrofuran moiety is present in calyxolanes A, B and magnosalicin natural products (Figure 1). In an attempt to deiodinate and reduce the ester group, compound **13a** was treated with $LiAlH_4$. This delivered olefin-diol **14** (90%) with

Scheme 6. Synthesis of Densely Substituted Tetrahydrofurans



the iodo group eliminated to olefin rather than reduced. A similar reaction occurred with DiBAL-H, giving **14** in 96% yield.

The double bond geometry in bis-arylated product **6** has been determined as (*E*) based on the coupling constant (J = 15.5−16.0 Hz). The relative stereochemical relationship in **6** between γ-aryl and β−OH groups is ascertained by the J_{H-H} coupling constant, ^{1}H−^{1}H-COSY, ^{1}H−^{1}H-NOESY, and NOE study of tetrahydrofuran **13c** (Figure 2). ^{1}H−^{1}H-COSY and ^{1}H−^{1}H-NOESY indicated no NOE correlation between H_a and H_b protons (^{1}H−^{1}H-COSY and ^{1}H−^{1}H-NOESY and NOE spectral details are available in Supporting Information). ^{1}H−^{1}H coupling constant data of tetrahydrofuran **13c** (J_{H_a} = 9.2 Hz, J_{H_b} = 17.0, 10.8, and 4.5 Hz, J_{H_c} = 10.4 and 9.6 Hz, and J_{H_d} = 10.4 and 9.2 Hz) indicates that γ-aryl and β−OH are not in same face. In NOE experiment, irradiation of H_a shows an enhancement with H_d (3%) and H_b (0%). Irradiation of H_b shows an enhancement with H_c (2%) and H_a (0%). Therefore, H_a and H_d are in same face (similarly, H_b and H_c). With the NOE data, we concluded that H_a and H_b are not in the same face orientation (similarly, H_c and H_d). Based on NOE experimental study of **13c**, the relative stereochemical relation-

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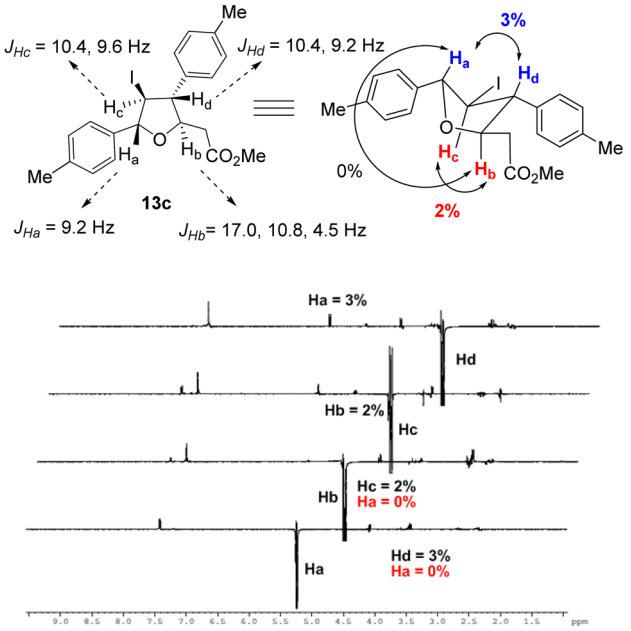


Figure 2. NOE correlation and coupling constants.

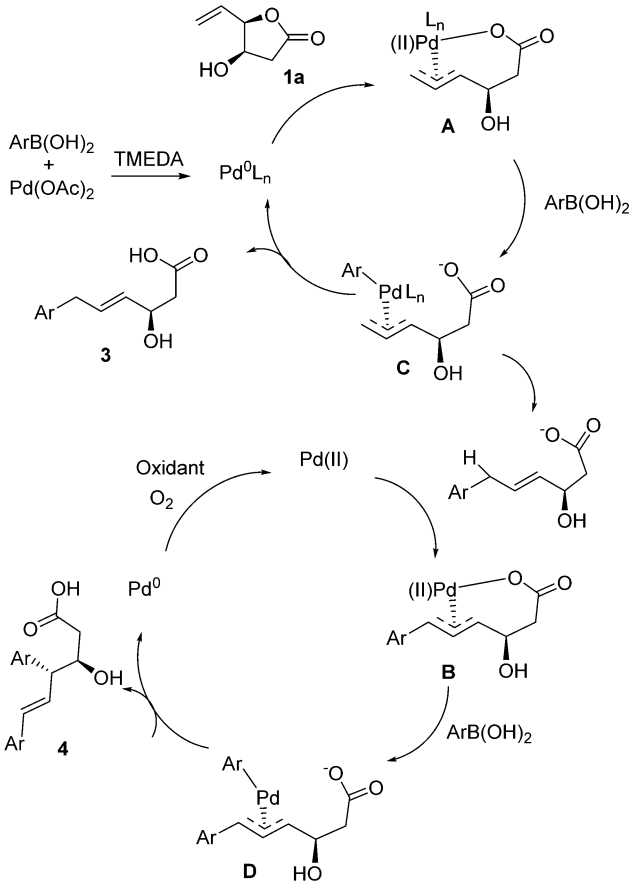
ship between γ-aryl and β−OH in **6** is confirmed as *anti* relative configuration (Scheme 2)

The mechanistic considerations could be similar to allylic alkylation of allyl acetates. The opening of γ-vinyl-γ-lactone by Pd(0) (generated from $Pd(OAc)_2$ by boronic acid or ligand)[19] is expected to deliver the π-allyl palladium intermediate **A** stabilized by carboxylate co-ion (Scheme 7). Transmetalation with boronic acid would generate intermediate **C**. Subsequent reductive elimination would lead to linear aryl substituted product **3** (that is esterified to **5** for easy isolation). Similar to acetate ligand acting as hydrogen abstracter, the carboxylate anion can assist the abstraction of allylic hydrogen as proton leading to second π-allyl palladium intermediate **B** in the presence of Pd(II), which is generated by oxidation of Pd(0) by O_2. Subsequent transmetalation with excess boronic acid **2** will result in **D**. The next reductive elimination gives branched bis-arylated product **4** (that is esterified to **6** for easy isolation). Thus, the regeneration of Pd(II) species from Pd(0) has been achieved by using oxidant O_2.[20] One would expect that the second π-allylpalladium intermediate formation would occur involving the allyl alcohol system via the leaving group ionization. This has been reported in literature.[11] However, this was not observed, and final compound **6** has the OH group intact. This represents a good example of site-selective π-allyl palladium formation by allylic C−H activation over allylic OH-based leaving group ionization that is unprecedented in literature. The presence of OH group also adds to the atom economy and availability of additional functional group.

CONCLUSIONS

We have developed a method for ring opening of γ-vinyl-γ-lactone via electrophilic π-allyl palladium formation to deliver mono-arylated products and an unprecedented regio- and stereoselective directed bis-arylation using excess boronic acid. The method developed is a good example of site-selective directed allylic arylation involving C−H activation versus the allylic OH-based leaving group ionization that is unprecedented in literature. The retention of OH group adds to the diversity in functional groups in the product and displays an efficient atom economy. A good synergistic dual catalysis occurred involving oxidation of Pd(0) to Pd(II) by O_2 as oxidant. The mono-arylated products of this method have been efficiently converted into the Hagen's gland lactone analogues, while the bis-arylated compounds are converted into highly substituted tetrahydrofurans. The 2,4-biaryltetrahydrofuran unit synthesized is present in natural products like calyxolanes and magnosalicin. A shift from boronic acids to other nucleophiles may generate new intermediates/products with applications in natural products synthesis.

Scheme 7. Plausible Mechanism



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06438.

Experimental details, compound data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Actinorhodins

Synthetic Studies on Actinorhodin and γ-Actinorhodin: Synthesis of Deoxyactinorhodin and Deoxy-γ-actinorhodin/Crisamicin A Isomer

Sandip V. Mulay and Rodney A. Fernandes*[a]

Abstract: A strategy based on bidirectional Dötz benzannulation and the oxa-Pictet–Spengler reaction toward the synthesis of actinorhodin and γ-actinorhodin has been explored. This work has resulted in the synthesis of deoxyactinorhodin and deoxy-γ-actinorhodin. The latter is a regioisomer of crisamicin A (which has 10,10′-dihydroxy groups).

Introduction

The soil-dwelling bacteria *Streptomyces coelicolor*[1–3] produces a red pigment that shows litmuslike properties, bright blue in alkaline and red in acid media. The red pigment structure was assigned by means of extensive chemical degradation[4] and mass spectrometry[5] to be the dimeric pyranonaphthoquinone known as actinorhodin **1** (Figure 1). The other congeners of **1** have been isolated from the same culture of bacteria[6,7] including γ-actinorhodin **2**. ^{1}H and ^{13}C NMR spectroscopic studies[5,7] showed that **1** and **2** are dimeric with two similar halves joined in a symmetrical C8–C8′ linkage. The dihydropyran ring contains a quasi-axial methyl group at C1, which is *trans* to an equatorial acetic acid side chain at C3 that is able to participate in γ-lactone formation thorough a quinone–methide intermediate. The absolute configuration of stereogenic centers of **1** (1*R*,1′*R*,3*S*,3′*S*) were confirmed by comparison of the optical rotary dispersion (ORD) curves of triacid (obtained from the oxidative degradation of actinorhodin diethyl ester with alkaline H_2O_2) with that of (+)-(*S*)-lactic acid.[4b,c] Actinorhodin **1** shows activity against the *Staphylococcus aureus*[2] bacteria found in the human respiratory tract and on the skin. Crisamicin A (**3**) was isolated from *Micromonospora purpureochromogenes*[8] and shows activity against B16 murine melanoma cells, herpes simplex, and vesicular stomatitis viruses.[9] A closely related compound GTRI-BB (**4**)[10] has shown very promising anticancer activities, such as renal (ACHN; $IC_{50}=0.08\ \mu g\,mL^{-1}$), colon (SW 620; $IC_{50}=0.11\ \mu g\,mL^{-1}$), and melanoma (UACC 62; $IC_{50}=0.08\ \mu g\,mL^{-1}$). The inhibitory effect is much higher than adriamycin (a commercial anticancer drug). This indicates that a structure–activity relationship (SAR) study might enhance the cytotoxic efficacy of these compounds. Whereas the syntheses of monomeric pyranonaphthoquinones and hemi-**1** and **2** are well documented,[11] the total synthesis of **1** and **2** is yet to be achieved. The first synthetic attempt toward *ent*-**1** was reported by Laatsch[12] from a degradation product of the antibacterial metabolite α-naphthocyclinone. Brimble and co-workers[13] have reported the synthesis of analogues of **1** and **3**. A racemic synthesis of crisamicin A (**3**) was elegantly achieved by Wang and co-workers[14] by homocoupling of monomer units. In our efforts toward the synthesis of pyranonapthoquinones and related compounds,[11g–m,15] we observed that the sequence of Dötz benzannulation[16] and oxa-Pictet–Spengler[17] reaction enables the rapid construction of the pyranonaphthoquinone framework. Recently we adopted a bidirectional strategy for the synthesis of (+)-demethoxycardinalin 3.[15] Herein we wish to

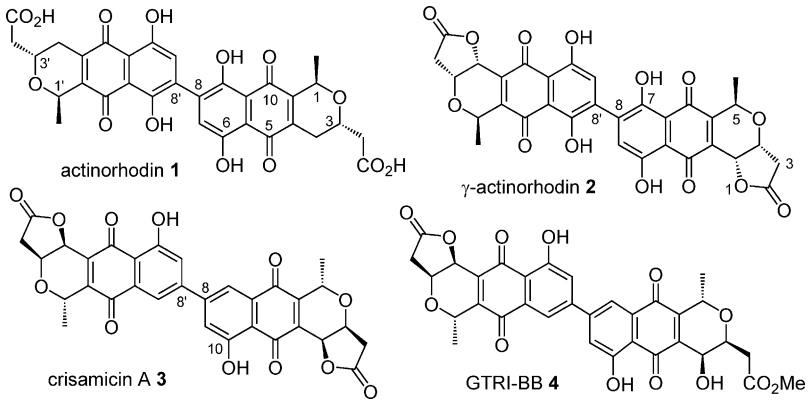

Figure 1. Some dimeric pyranonaphthoquinones.

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report our bidirectional synthetic studies on the dimeric pyrananaphthoquinones **1** and **2** based on Dötz benzannulation and oxa-Pictet–Spengler reactions.

Results and Discussion

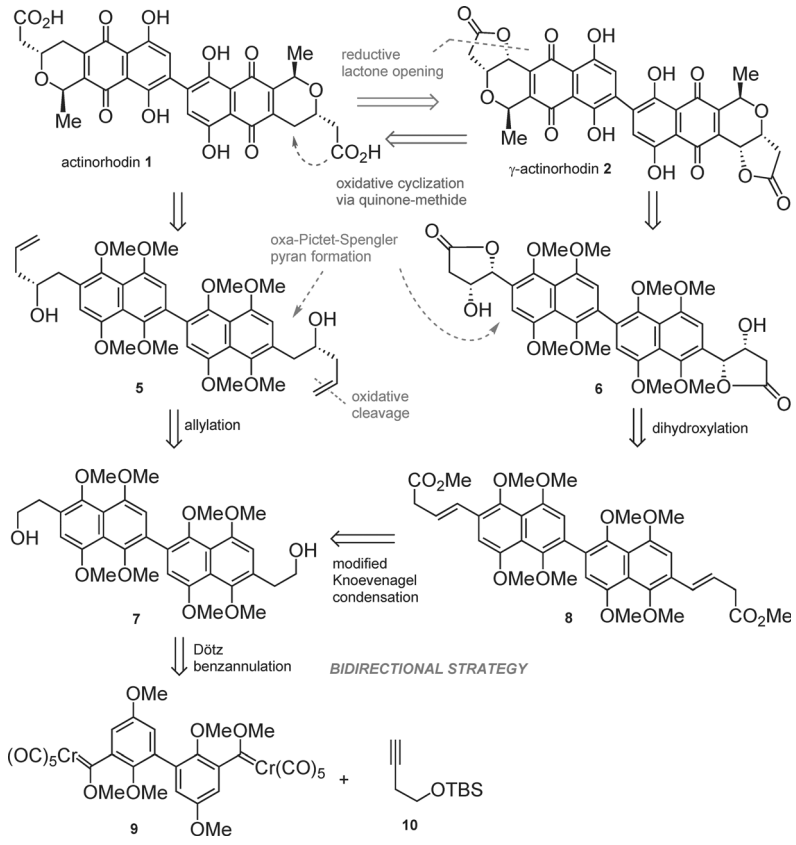
Our bidirectional retrosynthetic strategy is depicted in Scheme 1. Both **1** and **2** could be traced to the common intermediate diol **7**. Actinorhodin **1** can be traced from **7** through a sequence of allylation, pyran formation, and terminal double-bond cleavage. A modified Knoevenagel condensation on the aldehyde from **7** would lead to ester **8**. Subsequent dihydroxylation and pyran formation would give **2**. By biomimicking the viability of **1** to **2** conversion chemically (oxidative cyclization) and vice versa (reductive lactone opening), we could adopt either a route to **1** or **2** and their interconversion. The interconversion, although unknown for the dimeric compounds, is quite feasible for the monomeric molecules.[11k,18] Diol **7** seemed easily possible through the Dötz benzannulation of dimeric Fischer carbene **9** with alkyne **10**.

To synthesize dimeric Fischer carbene **9**, we needed the requisite dibromobiaryl compound **11a** (Scheme 2). Commercially available 4-methoxyphenol was converted to **11a** in two steps.[19] The biaryl phenol **11a** was methylated to **12** (94%; Scheme 2). Fischer carbene **9** was prepared from **12** and condensed with alkyne **10** in a bidirectional Dötz benzannulation reaction to afford **13** (70%). The protection of phenolic OH (**14**, 86%) and subsequent *tert*-butyldimethylsilyl(TBS) removal gave dimeric diol **7** in good yields (93%). Further 2-iodoxybenzoic acid (IBX) oxidation gave the dialdehyde in moderate yield (60%). The oxidation conditions by Piancatelli et al.[20] with a catalytic amount of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) in the presence of [bis(acetoxy)iodo]benzene delivered the dialdehyde in good yield, and subsequent allylation gave **5** in 85% yield from **7**. The oxa-Pictet–Spengler reaction has worked well to construct the pyran ring for the monomeric molecules.[11g,h,k–m,15] However, under similar conditions, compound **5** failed to provide pyran **15**. We employed various Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and $ZnCl_2$, or changed solvents and temperature conditions, but with no success. We believe the highly oxygenated aryl ring has the Lewis acid coordinated to the methoxy groups. Carrying out the reaction by bubbling dry HCl gas[15] through a solution of **5** in ether as well as acetaldehyde dimethylacetal also failed to yield the pyran product **15**.

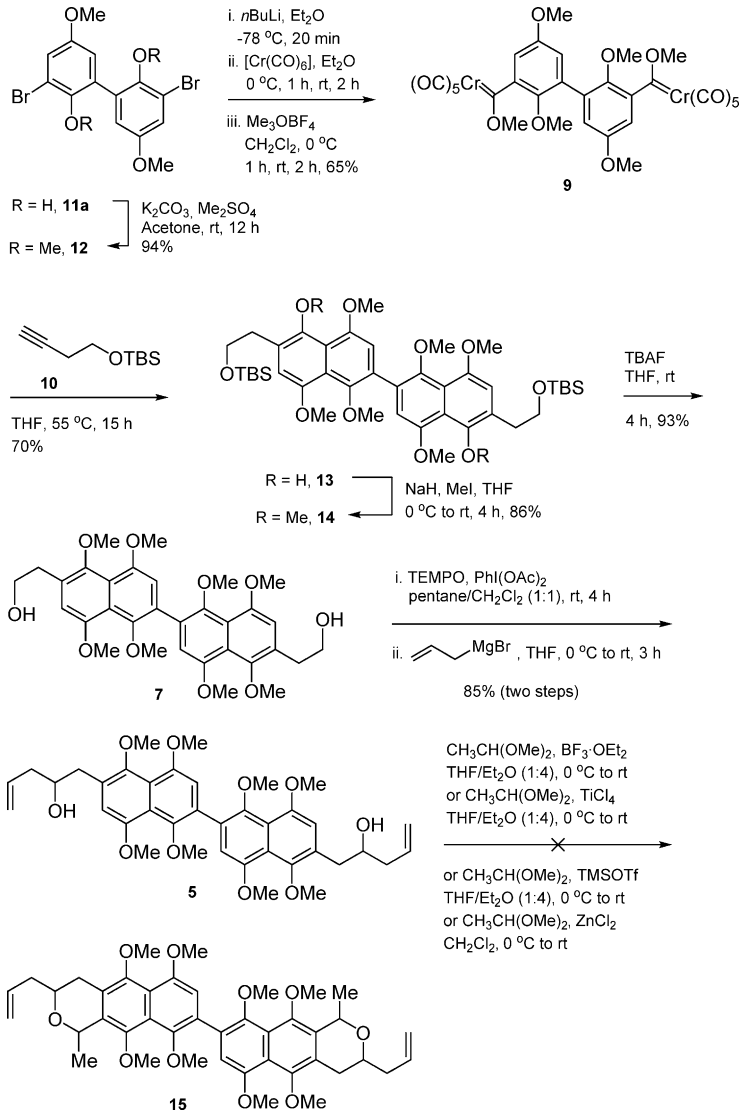
We next planned to use a different alkyne **17** (Scheme 3) in Dötz benzannulation to deliver **16**. The latter through an oxa-Pictet-Spengler reaction would lead to **1** and then to **2**.

The Dötz benzannulation of **9** with alkyne **17**[21] delivered bisnaphthol **18** in 52% yield (Scheme 4). The protection of phenolic OH (**19**, 88%) and subsequent TBS removal gave diol **16** in excellent yield (96%). The oxa-Pictet–Spengler reaction on **16** delivered the inseparable mixture of *syn*/*anti*-pyran products **20**. This mixture was subjected to cerium(IV) ammonium nitrate (CAN) oxidation. However, it gave a complex mixture. We also tried other conditions using Ag_2O, phenyliodine bis(trifluoroacetate) (PIFA), and CrO_3. In all cases either the starting material decomposed or it delivered regioisomeric and differently oxidized inseparable quinone mixtures, which could be due to multiple 1,4-dimethoxy aryl units present and/or possible quinone isomerizations.

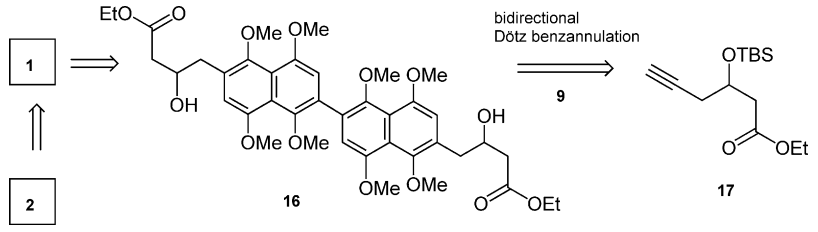
As illustrated in Scheme 1, we moved our attention toward γ-actinorhodin **2** synthesis as this in turn can be converted into **1** through reductive lactone opening. The reaction of dialdehyde from **7** with half ester of malonic acid under decarboxylative deconjugative Knoevenagel condensation[22] delivered the mixture (63%) of desired β,γ-unsaturated ester **8** along with a trace amount of α,β-unsaturated isomer (Scheme 5). Upon dihydroxylation[23] the mixture gave the bis-γ-lactones **6** (70%) as a single diastereomer (*ee* not determined). Lactone **6** has the



Scheme 1. Retrosynthesis of actinorhodin **1** and γ-actinorhodin **2**.



Scheme 2. Attempted synthesis of compound **15**.

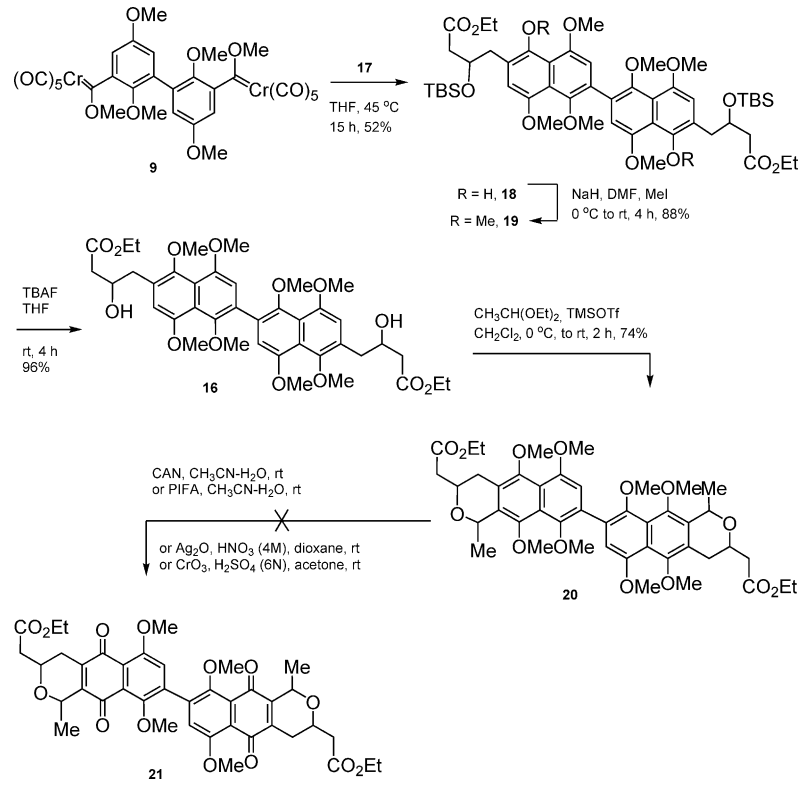


Scheme 3. Revised plan for **1** and **2**.

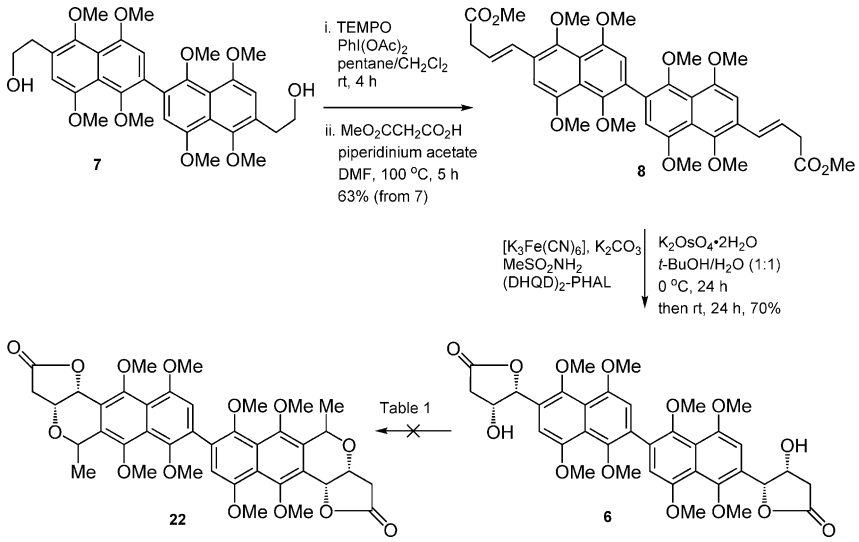
desired skeletal structure for **2**, minus the pyran rings. All attempts to construct the pyran ring on compound **6** using various Lewis acids similar to that used on compound **5** by means of oxa-Pictet–Spengler reaction failed to deliver product **22** (Table 1). In most cases, decomposition of **6** was observed. We also attempted the oxa-Pictet–Spengler reaction in a preheated (80 °C) mixture of $BF_3{\cdot}OEt_2$ (10 equiv) in trifluoroacetic acid (TFA) solvent and then addition of **6** (in THF) followed by $(CH_3O)_2CHCH_3$ (6.0 equiv). These conditions worked well to directly deliver the *anti*-pyran product in our arizonin C1 synthesis.[11m] However, compound **6** decomposed under these conditions (Table 1, entry 7).

We next considered lowering the number of methoxy groups on the biaryl system with the aim of investigating both the oxa-Pictet–Spengler reaction and the difficulty associated with quinone formation. Although this means analogue synthesis, the envisioned targets would have the skeletal structures of **1** and **2** with the quinone, pyran, and lactone installed. The freshly prepared Fischer carbene **23**[15] on bidirectional Dötz benzannulation reaction with alkyne **10** gave **24** (66%; Scheme 6). The protection of phenolic OH (**25**, 86%) and subsequent TBS removal afforded **26** in good yield (93%). The oxidation of **26** to dialdehyde and modified Knoevenagel condensation delivered the mixture (63%) of desired β,γ-unsaturated ester **27** along with trace amounts of α,β-unsaturated isomer. Upon dihydroxylation the mixture gave the bis-γ-lactone **28** in 70% yield as a single diastereomer (*ee* not determined). Unfortunately, all our attempts to construct the pyran ring on **28** using various Lewis acids (similar to that used in Table 1 for bis-lactone **6**) failed to deliver pyran **29**. It is surprising that on monomer molecules these reactions worked well in our laboratory.[11k]

We further considered the bidirectional Dötz benzannulation of Fischer carbene **23** with alkyne **17**. This reaction gave bisnaphthol **30** in 63% yield (Scheme 7). The protection of free phenolic OH to **31** (88%) and subsequent TBS removal afforded **32** in excellent yields (96%). The oxa-Pictet–Spengler reaction of **32** using $BF_3{\cdot}OEt_2$ gave a complex mixture, whereas the same reaction catalyzed by TMSOTf to our delight afforded the inseparable mixture of pyran diastereomers **33** (81%). The mixture was subjected to CAN oxidation to provide separable quinones **34** and **35** (one pyran ring with *syn*-methyl and the other *anti* to the C3 substituent) in 62 and 18% isolated yields, respectively.[24] The separated quinone **34** on treatment with $AlCl_3$ gave compound **36** (79%). The undesired **35** was converted into **36** by treatment with $AlCl_3$ and then H_2SO_4-mediated epimerization. Compound **36** represents the diethyl ester of deoxyactinorhodin with pyran and quinone installed. Various bases were screened for the hydrolysis of ester **36** to liberate the diacid. However, the acid isolation failed in our hands. Hence the crude acid was stirred in an open flask in MeOH to deliver **37** through a quinone–methide intermediate[18] in 34% isolated



Scheme 4. Attempted synthesis of **21** using alkyne **17**.



Scheme 5. Attempted synthesis of pyranolactone **22**.

yield. Thus the biomimetic conversion of acid to lactone through the quinone–methide intermediate known for monomeric molecules worked well for the diacid here. This completed the synthesis of deoxy-γ-actinorhodin **37**, which is also an isomer of crisamicin A with differently placed hydroxyl groups (see crisamicin A; Figure 1).

Conclusion

We have efficiently utilized the bidirectional approach through Dötz benzannulation and oxa-Pictet–Spengler reaction to achieve the synthesis of deoxyactinorhodin and deoxy-γ-actinorhodin. The latter is an isomer of crisamicin A. Efforts are still underway in our laboratory to achieve target molecules **1** and **2**.

Experimental Section

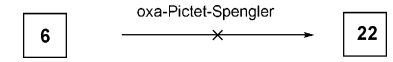
General information

Flasks were oven- or flame-dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed using EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by using a UV lamp. ^1H and ^{13}C NMR spectra were recorded at 400 or 500 and 100 or 125 MHz, respectively, and chemical shifts are based on the TMS peak at $\delta = 0.00$ ppm for proton NMR spectroscopy and the $CDCl_3$ peak at $\delta = 77.00$ ppm (t) for carbon NMR spectroscopy. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained using positive electrospray ionization.

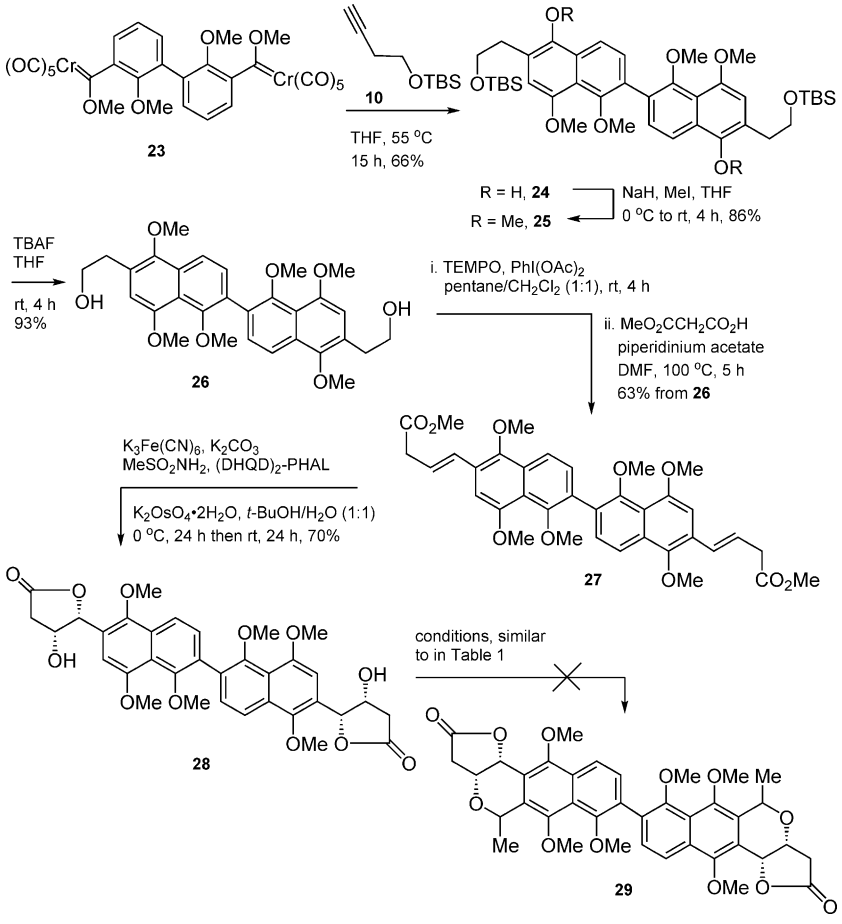
Synthesis

3,3′-Dibromo-2,2′,5,5′-tetramethoxybiphenyl (12): Anhydrous K_2CO_3 (2.05 g, 14.85 mmol, 3.0 equiv) was added to a stirred solution of **11a** (2.0 g, 4.95 mmol) in dry acetone (40 mL) and stirred at room temperature for 10 min. Dimethylsulfate (1.56 g, 12.4 mmol, 2.5 equiv) was added, and the reaction mixture was stirred for 12 h at the same temperature. It was then quenched with water (20 mL), and acetone was evaporated at reduced pressure. EtOAc (40 mL) was added, and the separated aqueous layer was extracted with EtOAc (2×40 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (19:1 to 9:1) as eluent to afford **12** (2.01 g, 94%) as a colorless solid. M.p. 99–100 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.53$ (s, 6H), 3.79 (s, 6H),

Table 1. The oxa-Pictet–Spengler reaction of bislactone **6**.



Entry	Reaction conditions	Results
1	$(CH_3O)_2CHCH_3$ (4.0 equiv), $BF_3{\cdot}OEt_2$ (4.0 equiv), CH_2Cl_2, 0 °C to RT, 12 h	decomposed
2	$(CH_3O)_2CHCH_3$ (4.0 equiv), $BF_3{\cdot}OEt_2$ (6.0 equiv), THF/Et_2O (1:4), 0 °C to RT, 36 h	decomposed
3	$(CH_3O)_2CHCH_3$ (3.0 equiv), $BF_3{\cdot}OEt_2$ (4.0 equiv), THF/Et_2O (1:4), 0 °C, 24 h	decomposed
4	$(CH_3O)_2CHCH_3$ (4.0 equiv), TMSOTf (4.0 equiv), CH_2Cl_2, 0 °C to RT, 12 h	complex mixture
5	$(CH_3O)_2CHCH_3$ (4.0 equiv), $TiCl_4$ (4.0 equiv), CH_2Cl_2, 0 °C to RT, 10 h	complex mixture
6	$(CH_3O)_2CHCH_3$ (6.0 equiv), HCl gas, Et_2O, RT, 12 h	decomposed
7	preheated mixture of $BF_3{\cdot}OEt_2$ (10.0 equiv) in TFA, then addition of **6** and $(CH_3O)_2CHCH_3$ (6.0 equiv), 1 min	decomposed



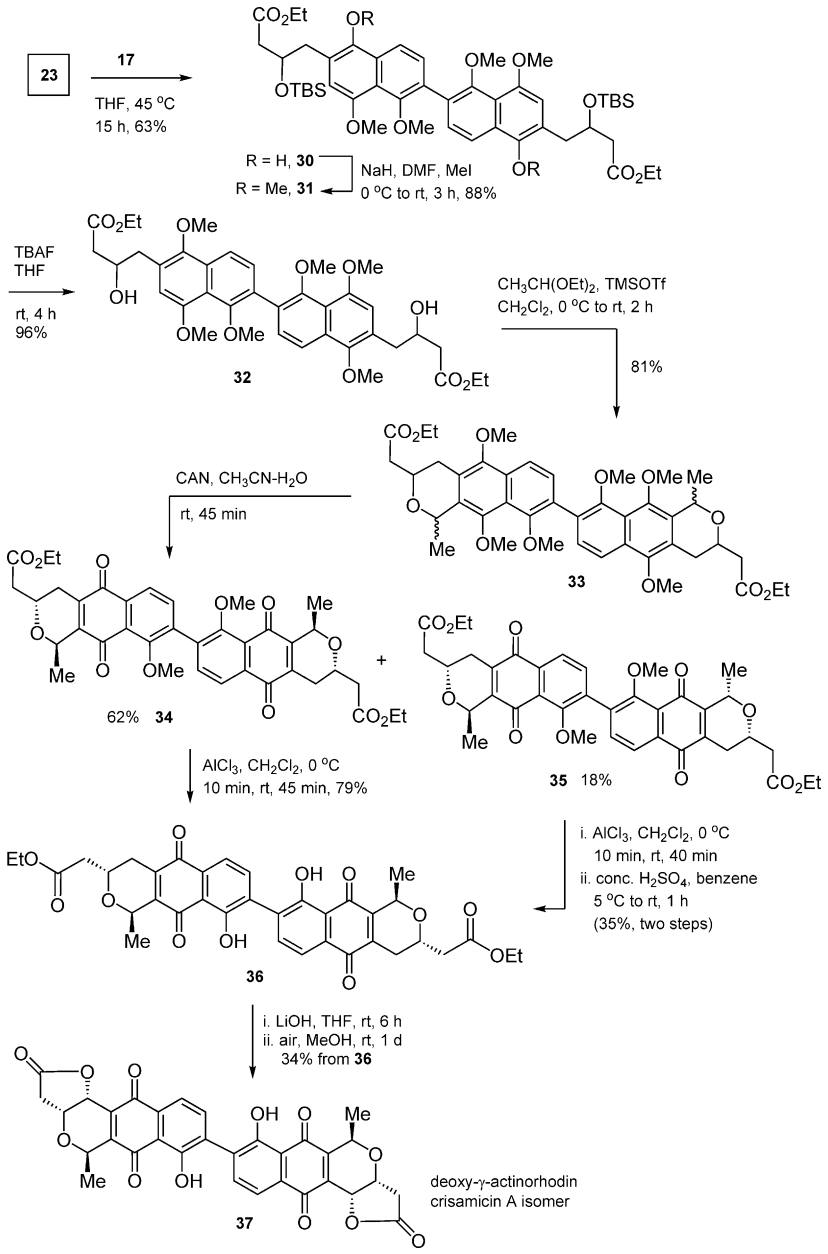
Scheme 6. Attempted synthesis of pyranolactone **29**.

6.84 (d, $J=3.0$ Hz, 2H), 7.14 ppm (d, $J=3.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=55.8$, 60.9, 115.9, 117.7, 118.3, 133.0, 148.3, 155.5 ppm; IR (KBr): $\tilde{\nu}=3072$, 3001, 2941, 2835, 1600, 1567, 1480, 1443, 1424, 1407, 1333, 1285, 1224, 1179, 1123, 1038, 1002, 949, 869, 855, 846, 807, 780, 770, 733, 720, 677, 625, 607 cm^{-1}; HRMS: *m/z* calcd for $[C_{16}H_{16}O_4Br_2+H]^+$: 430.9494; found: 430.9492.

Fischer carbene (9): *n*BuLi (3.2 mL, 5.1 mmol, 2.2 equiv, 1.6 M solution in hexane) was added to a solution of **12** (1.0 g, 2.31 mmol) in dry Et_2O (25 mL) at −78 °C, and the reaction mixture was stirred for 20 min. It was then transferred to a suspension of $[Cr(CO)_6]$ (1.12 g, 5.1 mmol, 2.2 equiv) in dry Et_2O (25 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 2 h. Et_2O was evaporated and the residue was dissolved in dry CH_2Cl_2 (30 mL). Me_3OBF_4 (1.03 g, 6.93 mmol, 3.0 equiv) was added to this solution in one portion at 0 °C, and the reaction mixture was stirred for 1 h. It was warmed to room temperature and stirred for 2 h. The red reaction mixture was concentrated, and the residue was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (9:1 to 3:1) as eluent to give **9** (1.12 g, 65%) as a red solid. This was immediately used in the next step.

6,6′-Bis[2-(*tert*-butyldimethylsilyloxy)ethyl]-1,1′,4,4′,8,8′-hexamethoxy-2,2′-binaphthyl-5,5′-diol (13): Alkyne **10** (1.11 g, 6.04 mmol, 4.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **9** (1.12 g, 1.51 mmol) in dry and degassed THF (15 mL). The reaction mixture was heated at 55 °C for 15 h and then allowed to cool to room temperature. It was then exposed to air and stirred for 1 h. THF was removed, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to afford **13** (0.83 g, 70%) as an orange solid. M.p. 146–147 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta=$ 0.04 (s, 12H), 0.90 (s, 18H), 3.00 (t, $J=7.1$ Hz, 4H), 3.51 (s, 6H), 3.90 (t, $J=7.4$ Hz, 4H), 3.94 (s, 6H), 4.02 (s, 6H), 6.86 (s, 2H), 7.03 (s, 2H), 9.60 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.3$, 18.4, 26.0, 34.3, 56.8, 57.1, 61.3, 62.8, 109.0, 112.7, 116.9, 120.3, 121.2, 127.4, 145.9, 148.1, 148.2, 151.2 ppm; IR (KBr): $\tilde{\nu}=3384$, 2953, 2929, 2856, 1655, 1615, 1519, 1465, 1450, 1419, 1385, 1253, 1221, 1076, 1007, 927, 837, 777, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{42}H_{62}O_{10}Si_2+H]^+$: 783.3960; found: 783.3959.

[1,1′,4,4′,5,5′,8,8′-Octamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis-(ethane-2,1-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (14): NaH (0.046 g, 1.92 mmol, 3.0 equiv) was added to a solution of **13** (0.50 g, 0.64 mmol) in dry THF (15 mL) at 0 °C and was stirred for 30 min. MeI (0.16 mL, 2.56 mmol, 4.0 equiv) was added, and the reaction mixture was stirred for 4 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated.



Scheme 7. Synthesis of deoxyactinorhodin and deoxy-γ-actinorhodin/crisamicin A isomer.

The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **14** (0.445 g, 86%) as a yellow solid. M.p. 116–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.06$ (s, 12H), 0.91 (s, 18H), 3.04 (t, $J =$ 7.1 Hz, 4H), 3.53 (s, 6H), 3.81 (s, 6H), 3.94 (t, $J = 7.2$ Hz, 4H), 3.95 (s, 6H), 3.96 (s, 6H), 6.85 (s, 2H), 7.07 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.3$, 18.4, 26.0, 34.1, 56.7, 56.8, 61.5, 62.5, 63.9, 110.2, 110.9, 122.1, 122.5, 128.6, 129.0, 147.5, 148.0, 151.0, 152.2 ppm; IR (KBr): $\tilde{\nu} = 2954$, 2930, 2857, 1591, 1491, 1462, 1435, 1365, 1344, 1320, 1279, 1240, 1192, 1153, 1084, 1063, 1045, 989, 937, 833, 774, 739, 672 cm^{-1}; HRMS: *m/z* calcd for $[C_{44}H_{66}O_{10}Si_2+H]^+$: 811.4273; found: 811.4281.

2,2′-(1,1′,4,4′,5,5′,8,8′-Octamethoxy-2,2′-binaphthyl-6,6′-diyl)diethanol (7): Tetra-*n*-butylammonium fluoride (TBAF; 0.87 mL, 0.865 mmol, 2.5 equiv, 1 M solution in THF) was added to a solution of **14** (0.28 g, 0.346 mmol) in dry THF (15 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1 to 1:1) as eluent to give **7** (0.187 g, 93%) as a yellow solid. M.p. 213–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.09$ (s, 2H; OH), 3.08 (t, $J = 6.4$ Hz, 4H), 3.54 (s, 6H), 3.83 (s, 6H), 3.96 (s, 6H), 3.97 (s, 6H), 3.97 (t, $J = 6.4$ Hz, 4H), 6.79 (s, 2H), 7.08 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.1$, 56.8, 56.9, 61.7, 62.4, 63.5, 109.7, 111.1, 122.3, 122.6, 128.7, 128.8, 147.6, 148.0, 151.1, 152.7 ppm; IR (KBr): $\tilde{\nu} = 3512$, 2925, 2874, 2831, 1596, 1492, 1452, 1368, 1347, 1243, 1197, 1147, 1079, 1058, 1021, 989, 834, 741, 678 cm^{-1}; HRMS: *m/z* calcd for $[C_{32}H_{38}O_{10}+H]^+$: 583.2543; found: 583.2540.

1,1′-(1,1′,4,4′,5,5′,8,8′-Octamethoxy-2,2′-binaphthyl-6,6′-diyl)dipent-4-en-2-ol (5): $PhI(OAc)_2$ (0.139 g, 0.43 mmol, 2.5 equiv) and TEMPO (5.5 mg, 0.035 mmol, 0.2 equiv) were added to a solution of **7** (0.10 g, 0.172 mmol) in pentane/CH_2Cl_2 (1:1, 8.0 mL) at room temperature. The resulting mixture was stirred for 4 h at the same temperature. It was then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (4×10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine, dried (Na_2SO_4), and concentrated. The dialdehyde (99.3 mg) obtained was immediately used in the next step.

Allyl magnesium bromide (0.22 mL, 0.43 mmol, 2.5 equiv, 2 M solution in THF) was added to a stirred solution of the above dialdehyde (99.3 mg) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3× 5 mL), and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 1:1) as eluent to afford **5** (97 mg, 85% from **7**) as a yellow solid. M.p. 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 2.30–2.44 (m, 4H), 2.92 (dd, $J = 13.5$, 8.1 Hz, 2H), 3.03 (dd, $J = 13.5$, 4.2 Hz, 2H), 3.55 (s, 6H), 3.82 (s, 6H), 3.96 (s, 6H), 3.97 (s, 6H),

4.06–4.09 (m, 2H), 5.16–5.22 (m, 4H), 5.88–5.98 (m, 2H), 6.79 (s, 2H), 7.09 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.1, 41.8, 56.7, 56.8, 61.5, 62.2, 71.6, 110.0, 111.2, 117.8, 122.3, 122.5, 128.5, 128.8, 135.0, 147.5, 147.9, 151.0, 152.5 ppm; IR (KBr): $\tilde{\nu}$ = 3454, 3073, 2930, 2836, 1638, 1602, 1495, 1455, 1385, 1365, 1347, 1243, 1195, 1109, 1080, 1049, 1021, 990, 913, 874, 825, 745, 618 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{46}O_{10}+H]^+$: 663.3169; found: 663.3172.

Diethyl 4,4′-[5,5′-dihydroxy-1,1′,4,4′,8,8′-hexamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis(3-*tert*-butyldimethylsilyloxy)butanoate (18): Alkyne **17** (0.73 g, 2.7 mmol, 4.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **9** (0.5 g, 0.673 mmol) in dry and degassed THF (10 mL). The reaction mixture was heated at 45 °C for 15 h and then allowed to cool to room temperature. It was exposed to air and stirred for 1 h. THF was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to afford **18** (0.353 g, 52%) as an orange solid. M.p. 173–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.03 (s, 6H), 0.07 (s, 6H), 0.88 (s, 18H), 1.24 (t, *J* = 7.1 Hz, 6H), 2.44–2.52 (m, 4H), 2.86 (dd, *J* = 13.0, 7.4 Hz, 2H), 3.10 (dd, *J* = 13.0, 5.6 Hz, 2H), 3.52 (s, 6H), 3.94 (s, 6H), 4.03 (s, 6H), 4.06–4.13 (m, 4H), 4.57–4.62 (m, 2H), 6.80 (s, 2H), 7.03 (s, 2H), 9.60 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.1, −4.6, 14.2, 17.9, 25.8, 39.0, 42.4, 56.8, 57.2, 60.2, 61.3, 69.2, 109.1, 113.1, 116.9, 119.4, 121.4, 127.6, 146.3, 148.1, 148.2, 151.2, 172.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3391, 2954, 2930, 2856, 1732, 1612, 1463, 1449, 1412, 1366, 1311, 1251, 1229, 1197, 1149, 1076, 1045, 1005, 962, 838, 812, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{50}H_{74}O_{14}Si_2+Na]^+$: 977.4509; found: 977.4509.

Diethyl 4,4′-[1,1′,4,4′,5,5′,8,8′-octamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis(3-*tert*-butyldimethylsilyloxy)butanoate (19): NaH (24 mg, 1.0 mmol, 3.0 equiv) was added to a solution of **18** (0.32 g, 0.335 mmol) in dry DMF (10 mL) at 0 °C and stirred for 30 min. Then MeI (0.1 mL, 1.6 mmol, 4.8 equiv) was added, and the reaction mixture was stirred for 4 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3× 20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **19** (0.29 g, 88%) as a yellow solid. M.p. 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.01 (s, 6H), 0.06 (s, 6H), 0.87 (s, 18H), 1.23 (t, *J* = 7.1 Hz, 6H), 2.47 (d, *J* = 6.3 Hz, 4H), 2.92 (dd, *J* = 13.0, 7.3 Hz, 2H), 3.11 (dd, *J* = 13.0, 5.9 Hz, 2H), 3.52 (s, 6H), 3.80 (s, 6H), 3.95 (s, 6H), 3.96 (s, 6H), 4.05–4.13 (m, 4H), 4.53–4.60 (m, 2H), 6.80 (s, 2H), 7.07 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.1, −4.7, 14.1, 17.9, 25.7, 38.9, 42.3, 56.6, 56.8, 60.2, 61.5, 62.2, 69.9, 110.5, 111.0, 122.2, 122.5, 127.9, 128.6, 147.5, 148.2, 151.0, 152.1, 171.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2955, 2930, 2856, 1734, 1595, 1494, 1464, 1367, 1326, 1248, 1216, 1198, 1148, 1081, 962, 838, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{52}H_{78}O_{14}Si_2+Na]^+$: 1005.4822; found: 1005.4822.

Diethyl 4,4′[1,1′,4,4′,5,5′,8,8′-octamethoxy-(2,2′-binaphthalene)-6,6′-diyl]bis(3-hydroxybutanoate) (16): TBAF (0.64 mL, 0.64 mmol, 2.5 equiv, 1 M solution in THF) was added to a solution of **19** (0.25 g, 0.254 mmol) in dry THF (10 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3× 15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1 to 1:1) as eluent to give **16** (0.184 g, 96%) as a yellow solid. M.p. 201–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.24 (t, *J* = 7.1 Hz, 6H), 2.49–2.60 (m, 4H), 2.98–3.07 (m, 4H), 3.12 (s, 2H; OH), 3.53 (s, 6H), 3.79 (s, 6H), 3.94 (s, 6H), 3.95 (s, 6H), 4.14 (q, *J* = 7.4 Hz, 4H), 4.40–4.46 (m, 2H), 6.79 (s, 2H), 7.07 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 37.4, 40.9, 56.6, 56.8, 60.5, 61.5, 62.1, 68.8, 109.8, 111.1, 122.3, 122.4, 127.6, 128.8, 147.5, 147.9, 150.9, 152.4, 172.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3445, 2930, 2838, 1729, 1595, 1465, 1368, 1245, 1193, 1155, 1079, 1057, 993, 842, 669 cm^{-1}; HRMS: *m/z* calcd for $[C_{40}H_{50}O_{14}+Na]^+$: 777.3093; found: 777.3093.

Diethyl 2,2′-(5,5′,6,6′,9,9′,10,10′-octamethoxy-1,1′-dimethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-dibenzo[*g*]isochromene-3,3′-diyl)-diacetate (20): Acetaldehyde diethylacetal (0.06 mL, 0.424 mmol, 4.0 equiv) and TMSOTf (0.06 mL, 0.318 mmol, 3.0 equiv) were added to a solution of **16** (0.080 g, 0.106 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. It was then quenched with saturated aqueous $NaHCO_3$ (5 mL), and the solution was extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford **20** (0.063 g, 74%, colorless oil) as an inseparable mixture of diastereomers. The ^{1}H NMR spectra showed a mixture of diastereomers with conclusive and characteristic peaks for pyran methyl, C1 proton, and ester ethyl groups. The entire structure was confirmed by HRMS: *m/z* calcd for $[C_{44}H_{54}O_{14}+Na]^+$: 829.3407; found: 829.3412.

(3*E*,3′*E*)-Dimethyl 4,4′-(1,1′,4,4′,5,5′,8,8′-octamethoxy-2,2′-binaphthyl-6,6′-diyl)dibut-3-enoate (8): $PhI(OAc)_2$ (0.139 g, 0.43 mmol, 2.5 equiv) and TEMPO (5.5 mg, 0.035 mmol, 0.2 equiv) were added sequentially to a solution of **7** (0.10 g, 0.172 mmol) in pentane/CH_2Cl_2 (1:1, 8 mL) at room temperature. The resulting mixture was stirred for 4 h at room temperature. It was then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine, dried (Na_2SO_4), and concentrated. The crude dialdehyde (0.099 g) obtained was immediately used in the next step.

The above crude dialdehyde (0.099 g) in DMF (4 mL) was added to a solution of piperidinium acetate (1.0 mg, 0.007 mmol, 4.0 mol%) in DMF (1.4 mL). A solution of monomethyl malonate (0.082 g, 0.69 mmol, 4.0 equiv) in DMF (0.6 mL) was added, and the reaction mixture was stirred at 100 °C for 5 h. It was then allowed to cool to room temperature and diluted with EtOAc/H_2O (1:1, 20 mL). The layers were separated, and the aqueous layer was saturated with NaCl and extracted with EtOAc (4×10 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 1:1) as eluent to afford **8** and its α,β-unsaturated isomer in minor amount (0.075 g, 63% over two steps) as a yellow solid. M.p. 177–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.39 (dd, *J* = 7.1, 1.4 Hz, 4H), 3.54 (s, 6H), 3.76 (s, 6H), 3.79 (s, 6H), 3.96 (s, 6H), 4.01 (s, 6H), 6.39 (dt, *J* = 16.0, 7.2 Hz, 2H), 7.04 (s, 2H), 7.08 (dt, *J* = 16.1, 1.4 Hz, 2H), 7.09 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5, 51.8, 56.5, 56.8, 61.5, 62.6, 103.9, 111.4, 122.3, 122.5, 122.7, 126.4, 127.9, 129.3, 147.46 147.5, 151.6, 152.6, 172.1 ppm; IR (KBr): $\tilde{\nu}$ = 3002, 2922, 2833, 1742, 1624, 1588, 1460, 1432, 1410, 1372, 1344, 1284, 1244, 1199, 1165, 1081, 1060, 989, 969, 840, 818, 765, 753 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{42}O_{12}+H]^+$: 691.2755; found: 691.2749.

(4*R*,4′*R*,5*R*,5′*R*)-5,5′-(1,1′,4,4′,5,5′,8,8′-Octamethoxy-2,2′-binaphthyl-6,6′-diyl)bis(4-hydroxydihydrofuran-2(3*H*)-one) (6): A mixture of $K_3[Fe(CN)_6]$ (0.342 g, 1.04 mmol, 8.0 equiv), K_2CO_3 (0.144 g, 1.04 mmol, 8.0 equiv), $MeSO_2NH_2$ (0.037 g, 0.39 mmol, 3.0 equiv),

$NaHCO_3$ (0.087 g, 1.04 mmol, 8.0 equiv), hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2$-PHAL) (10 mg, 0.013 mmol, 10 mol%), and $K_2OsO_4 \cdot 2H_2O$ (1.5 mg, 3.9 μmol, 3 mol%) in *t*BuOH (2 mL) and water (5 mL) was stirred for 5 min at room temperature and then cooled to 0 °C. A solution of the β,γ-unsaturated ester **8** (0.09 g, 0.13 mmol) in *t*BuOH (3 mL) was added to this mixture. The reaction mixture was stirred at 0 °C for 24 h and at room temperature for 24 h. It was then quenched with solid Na_2SO_3 (0.164 g) and stirred for 30 min. The solution was extracted with EtOAc (5× 10 mL), and the combined organic layers were washed with 1 M KOH (3 mL), water (5 mL), and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2 to 1:3) as eluent to afford **6** (0.063 g, 70%) as a yellow solid. M.p. 290 °C (decomp); $[\alpha]_D^{25} = +10.5$ ($c = 0.44$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.78$ (d, $J = 17.7$ Hz, 2H), 3.00 (dd, $J = 17.8$, 5.5 Hz, 2H), 3.53 (s, 6H), 3.84 (s, 6H), 3.94 (s, 6H), 4.01 (s, 6H), 4.95–4.97 (m, 2H), 5.93 (d, $J = 3.5$ Hz, 2H), 7.03 (s, 2H), 7.11 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 38.2, 56.5, 56.7, 61.6, 62.5, 69.7, 82.2, 104.9, 110.8, 121.7, 123.2, 123.7, 129.5, 146.2, 147.6, 150.9, 153.2, 175.6 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 3472, 2929, 2850, 1776, 1595, 1506, 1468, 1452, 1371, 1309, 1242, 1196, 1159, 1114, 1079, 1055, 1032, 905, 843, 797, 701 cm^{-1}; HRMS: *m/z* calcd for $[C_{36}H_{38}O_{14}+Na]^+$: 717.2154; found: 717.2159.

6,6′-Bis[2-(*tert*-butyldimethylsilyloxy)ethyl]-1,1′,8,8′-tetramethoxy-2,2′-binaphthyl-5,5′-diol (24): Alkyne **10** (1.30 g, 7.04 mmol, 4.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **23**[15] (1.2 g, 1.76 mmol) in dry and degassed THF (15 mL). The reaction mixture was heated at 55 °C for 15 h and then allowed to cool to room temperature. It was exposed to air and stirred for 1 h. THF was removed under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to afford **24** (0.84 g, 66%) as an orange solid. M.p. 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.11$ (s, 12H), 0.95 (s, 18H), 3.02 (t, $J = 4.8$ Hz, 4H), 3.56 (s, 6H), 3.94 (s, 6H), 4.04 (t, $J =$ 4.9 Hz, 4H), 6.60 (s, 2H), 7.61 (d, $J = 8.7$ Hz, 2H), 8.11 (d, $J = 8.7$ Hz, 2H), 8.52 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.6$, 18.3, 25.8, 35.8, 57.1, 61.5, 65.9, 110.1, 117.9, 119.7, 120.4, 128.6, 129.4, 129.8, 145.5, 149.5, 153.2 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3277$, 2954, 2931, 2858, 1661, 1626, 1600, 1464, 1353, 1316, 1257, 1218, 1138, 1098, 1063, 1039, 1008, 939, 925, 856, 837, 777, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{40}H_{58}O_8Si_2+H]^+$: 723.3743; found: 723.3744.

(1,1′,5,5′,8,8′-Hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis-(ethane-2,1-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (25): NaH (0.045 g, 1.87 mmol, 3.0 equiv) was added to a solution of **24** (0.45 g, 0.622 mmol) in dry THF (15 mL) at 0 °C and stirred for 30 min. Then MeI (0.16 mL, 2.5 mmol, 4.0 equiv) was added, and the reaction mixture was stirred for 4 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **25** (0.402 g, 86%) as a yellow solid. M.p. 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 0.06 (s, 12H), 0.91 (s, 18H), 3.05 (t, $J = 7.0$ Hz, 4H), 3.56 (s, 6H), 3.92 (s, 6H), 3.95 (t, $J = 7.3$ Hz, 4H), 3.98 (s, 6H), 6.78 (s, 2H), 7.65 (d, $J =$ 8.7 Hz, 2H), 7.85 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.3$, 18.4, 26.0, 33.9, 56.4, 61.6, 62.1, 63.7, 108.4, 117.3, 120.4, 127.4, 129.0, 130.6, 131.0, 147.6, 152.4, 154.0 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 2954, 2931, 2857, 1619, 1598, 1570, 1463, 1380, 1360, 1342, 1245, 1100, 1045, 1010, 921, 837, 775, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{42}H_{62}O_8Si_2+Na]^+$: 773.3875; found: 773.3876.

2,2′-(1,1′,5,5′,8,8′-Hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis-(ethan-1-ol) (26): TBAF (1.2 mL, 1.2 mmol, 2.5 equiv, 1 M solution in THF) was added to a solution of **25** (0.35 g, 0.47 mmol) in dry THF (15 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1 to 1:1) as eluent to give **26** (0.227 g, 93%) as a yellow solid. M.p. 196–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.11$ (s, 2H; OH), 3.08 (t, $J = 6.4$ Hz, 4H), 3.56 (s, 6H), 3.92 (s, 6H), 3.97 (t, $J = 6.4$ Hz, 4H), 3.98 (s, 6H), 6.72 (s, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 7.85 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 33.8$, 56.4, 61.6, 61.9, 63.2, 107.9, 117.3, 120.5, 127.1, 129.1, 130.7, 131.0, 147.7, 152.8, 154.1 ppm; IR ($CHCl_3$): $\tilde{\nu} =$ 3431, 2934, 2840, 1619, 1598, 1570, 1453, 1380, 1359, 1341, 1244, 1135, 1099, 1045, 1016, 843 cm^{-1}; HRMS: *m/z* calcd for $[C_{30}H_{34}O_8+Na]^+$: 545.2146; found: 545.2146.

(3*E*,3′*E*)-Dimethyl 4,4′-(1,1′,5,5′,8,8′-hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis(but-3-enoate) (27): $PhI(OAc)_2$ (0.31 g, 0.96 mmol, 2.5 equiv) and TEMPO (0.012 g, 0.077 mmol, 0.2 equiv) were added sequentially to a solution of **26** (0.2 g, 0.383 mmol) in pentane/CH_2Cl_2 (1:1, 14 mL) at room temperature. The resulting mixture was stirred for 4 h at room temperature and then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine, dried (Na_2SO_4), and concentrated. The crude dialdehyde (0.197 g) obtained was immediately used in the next step.

The crude dialdehyde (0.197 g) in DMF (7 mL) was added to a solution of piperidinium acetate (2.2 mg, 0.0153 mmol, 4.0 mol%) in DMF (2 mL). A solution of monomethyl malonate (0.180 g, 1.53 mmol, 4.0 equiv) in DMF (0.6 mL) was added, and the reaction mixture was stirred at 100 °C for 5 h. It was then allowed to cool to room temperature and diluted with EtOAc/H_2O (1:1, 20 mL). The layers were separated and the aqueous layer was saturated with NaCl and extracted with EtOAc (4×10 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 1:1) as eluent to afford **27** and its α,β-unsaturated isomer in a minor amount (0.152 g, 63% over two steps) as a yellow solid. M.p. 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.39$ (d, $J = 7.2$ Hz, 4H), 3.56 (s, 6H), 3.76 (s, 6H), 3.90 (s, 6H), 4.02 (s, 6H), 6.43 (dt, $J = 15.8$, 7.2 Hz, 2H), 6.97 (s, 2H), 7.00 (d, $J = 16.0$ Hz, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 7.89 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.6$, 52.0, 56.4, 61.7, 62.4, 102.6, 117.7, 121.2, 122.7, 124.9, 127.7, 129.7, 130.8, 131.3, 147.2, 152.8, 154.1, 172.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2933$, 2843, 1738, 1589, 1450, 1383, 1347, 1243, 1167, 1099, 1054, 1018, 976, 798 cm^{-1}; HRMS: *m/z* calcd for $[C_{36}H_{38}O_{10}+Na]^+$: 653.2357; found: 653.2357.

(4*R*,4′*R*,5*R*,5′*R*)-5,5′-(1,1′,5,5′,8,8′-Hexamethoxy-2,2′-binaphthalene-6,6′-diyl)bis(4-hydroxydihydrofuran-2(3*H*)-one) (28): A mixture of $K_3[Fe(CN)_6]$ (0.543 g, 1.65 mmol, 8.0 equiv), K_2CO_3 (0.228 g, 1.65 mmol, 8.0 equiv), $MeSO_2NH_2$ (0.059 g, 0.62 mmol, 3.0 equiv), $NaHCO_3$ (0.136 g, 1.62 mmol, 8.0 equiv), $(DHQD)_2$-PHAL (8.0 mg, 0.0103 mmol, 5 mol%), and $K_2OsO_4 \cdot 2H_2O$ (1.5 mg, 0.0041 mmol, 2 mol%) in *t*BuOH (2 mL) and water (5 mL) was stirred for 5 min and cooled to 0 °C. A solution of the β,γ-unsaturated ester **27** (0.130 g, 0.206 mmol) in *t*BuOH (3 mL) was added to this mixture. The reaction mixture was stirred at 0 °C for 24 h and at room temperature for 24 h. It was then quenched with solid Na_2SO_3 (0.20 g)

and stirred for 30 min. The solution was extracted with EtOAc (5× 10 mL), and the combined organic layers were washed sequentially with 1 M KOH (4 mL), water (5 mL), and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2 to 1:3) as eluent to afford **28** (0.092 g, 70%) as a yellow solid. M.p. 247–248 °C; $[\alpha]_D^{25} = -16.3$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.77$ (d, $J = 17.6$ Hz, 2H), 2.98 (dd, $J = 17.7$, 5.4 Hz, 2H), 3.55 (s, 6H), 3.95 (s, 6H), 4.00 (s, 6H), 4.89 (t, $J = 4.3$ Hz, 2H), 5.91 (d, $J = 3.5$ Hz, 2H), 6.96 (s, 2H), 7.68 (d, $J = 8.6$ Hz, 2H), 7.82 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.3$, 56.4, 61.7, 62.2, 69.8, 81.8, 103.8, 117.2, 121.6, 122.4, 129.9, 130.4, 131.0, 146.1, 153.2, 154.2, 175.6 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3457$, 3007, 2935, 2847, 1778, 1621, 1599, 1572, 1454, 1383, 1339, 1231, 1198, 1157, 1099, 1079, 1060, 1029, 982, 906, 868, 800, 701 cm^{-1}; HRMS: *m/z* calcd for $[C_{34}H_{34}O_{12}+H]^+$: 635.2123; found: 635.2122.

Diethyl 4,4′-(5,5′-dihydroxy-1,1′,8,8′-tetramethoxy-2,2′-binaphthyl-6,6′-diyl)bis(3-*tert*-butyldimethylsilyloxy)butanoate (30): Alkyne **17** (1.19 g, 4.4 mmol, 3.0 equiv) in dry and degassed THF (5 mL) was added to a solution of freshly prepared Fischer carbene **23** (1.0 g, 1.466 mmol) in dry and degassed THF (15 mL). The reaction mixture was stirred at 45 °C for 15 h and then allowed to cool to room temperature. It was then exposed to air and stirred for 1 h. THF was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) to afford **30** (0.826 g, 63%) as a pale yellow solid. M.p. 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 0.09 (s, 6H), 0.13 (s, 6H), 0.95 (s, 18H), 1.28 (t, $J = 7.1$ Hz, 6H), 2.47–2.58 (m, 4H), 3.02 (dd, $J = 14.7$, 5.8 Hz, 2H), 3.23 (dd, $J = 14.7$, 3.0 Hz, 2H), 3.55 (s, 6H), 3.92 (s, 6H), 4.18 (q, $J = 7.1$ Hz, 4H), 4.53–4.59 (m, 2H), 6.53 (s, 2H), 7.63. (d, $J = 8.7$ Hz, 2H), 8.10 (d, $J =$ 8.7 Hz, 2H), 8.21 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ −5.03, −5.01, 14.1, 18.0, 25.7, 39.1, 40.5, 56.9, 60.7, 61.5, 70.9, 110.5, 116.2, 117.8, 120.5, 128.4, 129.4, 129.8, 145.2, 149.4, 153.2, 171.6 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3305$, 2955, 2932, 2858, 1735, 1662, 1626, 1600, 1578, 1464, 1375, 1349, 1315, 1257, 1194, 1146, 1097, 1041, 1008, 961, 839, 812, 778, 703 cm^{-1}; HRMS: *m/z* calcd for $[C_{48}H_{70}O_{12}Si_2+K]^+$: 933.4043; found: 933.4048.

Diethyl 4,4′-(1,1′,5,5′,8,8′-hexamethoxy-2,2′-binaphthyl-6,6′-diyl)bis(3-*tert*-butyldimethylsilyloxy)butanoate (31): NaH (0.054 g, 2.23 mmol, 2.5 equiv) was added to a solution of **30** (0.80 g, 0.893 mmol) in dry DMF (15 mL) at 0 °C and stirred for 30 min. Then MeI (0.25 mL, 4.02 mmol, 4.5 equiv) was added, and the reaction mixture was stirred for 3 h at room temperature. Ice-cooled water was added, and the mixture was extracted with EtOAc (3× 20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 3:2) as eluent to give **31** (0.726 g, 88%) as a colorless solid. M.p. 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.00$ (s, 6H), 0.06 (s, 6H), 0.87 (s, 18H), 1.24 (t, $J = 7.1$ Hz, 6H), 2.49 (d, $J = 6.1$ Hz, 4H), 2.93 (dd, $J = 13.1$, 7.1 Hz, 2H), 3.10 (dd, $J = 13.1$, 5.9 Hz, 2H), 3.55 (s, 6H), 3.90 (s, 6H), 3.98 (s, 6H), 4.06–4.15 (m, 4H), 4.52–4.58 (m, 2H), 6.73 (s, 2H), 7.66. (d, $J = 8.7$ Hz, 2H), 7.84 ppm (d, $J =$ 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.1$, −4.7, 14.2, 18.0, 25.7, 38.6, 42.3, 56.4, 60.3, 61.6, 61.7, 69.9, 108.8, 117.3, 120.5, 126.5, 129.0, 130.6, 131.0, 148.0, 152.4, 154.0, 171.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2954$, 2931, 2856, 1737, 1662, 1619, 1600, 1570, 1464, 1381, 1341, 1312, 1251, 1204, 1147, 1099, 1071, 985, 961, 910, 837, 812, 777, 735 cm^{-1}; HRMS: *m/z* calcd for $[C_{50}H_{74}O_{12}Si_2+K]^+$: 961.4356; found: 961.4354.

Diethyl 4,4′-(1,1′,5,5′,8,8′-hexamethoxy-2,2′-binaphthyl-6,6′-diyl)bis(3-hydroxybutanoate) (32): TBAF (2.0 mL, 2.0 mmol, 2.6 equiv, 1 M solution in THF) was added to a solution of **31** (0.71 g, 0.769 mmol) in dry THF (15 mL) at room temperature, and the mixture was stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1 to 1:3) to give **32** (0.512 g, 96%) as a colorless solid. M.p. 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.27$ (t, $J = 7.1$ Hz, 6H), 2.51–2.62 (m, 4H), 2.99–3.10 (m, 4H) 3.36 (d, $J = 3.8$ Hz, 2H; OH), 3.56 (s, 6H), 3.91 (s, 6H), 3.98 (s, 6H), 4.17 (q, $J = 7.1$ Hz, 4H), 4.40–4.46 (m, 2H), 6.73 (s, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 7.84 ppm (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 37.2, 40.8, 56.3, 60.6, 61.6, 61.8, 68.8, 108.1, 117.3, 120.7, 126.1, 129.2, 130.7, 130.9, 147.7, 152.7, 154.1, 172.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3486$, 2984, 2935, 2842, 1732, 1622, 1599, 1569, 1455, 1380, 1338, 1246, 1193, 1145, 1099, 1048, 1013, 980, 857, 829, 798, 667 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{46}O_{12}+Na]^+$: 717.2881; found: 717.2885.

Diethyl 2,2′-(5,5′,9,9′,10,10′-hexamethoxy-1,1′-dimethyl-3,3′,4,4′-tetrahydro-1*H*;1′*H*-8,8′-dibenzo[*g*]isochromene-3,3′-diyl)diacetate (33): Acetaldehyde diethylacetal (0.082 mL, 0.576 mmol, 4.0 equiv) and TMSOTf (0.078 mL, 0.432 mmol, 3.0 equiv) were added to a solution of **32** (0.10 g, 0.144 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. It was then quenched with saturated aqueous $NaHCO_3$ (5 mL), and the solution was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) to afford an inseparable mixture of diastereomers **33** (0.087 g, 81%). The mixture was used for the next reaction immediately.

Diethyl 2,2-(9,′9′-dimethoxy-1,1′-dimethyl-5,5′,10,10′-tetraoxo-3,3′,4,4′,-5,5′,10,10′-octahydro-1*H*,1′*H*-[8,8′-dibenzo[*g*]isochromene]-3,3′-diyl)diacetate (34) and diethyl 2,2′-(9,9′-dimethoxy-1,1′-dimethyl-5,5′,10,10′-tetraoxo-3,3′,4,4′,-5,5′,10,10′-octahydro-1*H*,1′*H*-[8,8′-dibenzo[*g*]isochromene]-3,3′-diyl]diacetate (35): A solution of ceric(IV) ammonium nitrate (0.235 g, 0.428 mmol, 4.0 equiv) in water (5 mL) was added to a stirred solution of **33** (0.080 g, 0.107 mmol) in CH_3CN (5 mL). The reaction mixture was stirred at room temperature for 45 min. It was then diluted with EtOAc (15 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×15 mL), and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 7:3) as eluent to give **34** (45.6 mg, 62%) and **35** (13.3 mg, 18%) as yellow solids. For **34**: M.p. 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta =$ 1.31 (t, $J = 7.2$ Hz, 6H), 1.57 (d, $J = 6.8$ Hz, 6H), 2.38 (ddd, $J = 18.9$, 10.5, 2.0 Hz, 2H), 2.61–2.69 (m, 4H), 2.81 (dd, $J = 18.9$, 3.1 Hz, 2H), 3.63 (s, 6H), 4.16–4.27 (m, 4H), 4.32–4.39 (m, 2H), 5.06 (q, $J =$ 6.8 Hz, 2H), 7.69 (d, $J = 7.9$ Hz, 2H), 8.00 ppm (d, $J = 7.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 19.3, 27.5, 40.7, 60.8, 61.9, 63.5, 67.5, 122.4, 124.5, 133.9, 136.3, 138.6, 139.6, 147.9, 157.8, 170.6, 182.3, 183.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2980$, 2933, 2854, 1738, 1659, 1635, 1558, 1462, 1402, 1373, 1312, 1268, 1205, 1160, 1127, 1093, 1075, 1032, 990, 952, 855, 825, 666 cm^{-1}; HRMS: *m/z* calcd for $[C_{38}H_{38}O_{12}+Na]^+$: 709.2255; found: 709.2253. For **35**: ^{1}H NMR spectroscopy indicated one pyran ring with a *syn* C1 methyl with a C3 side chain and another pyran ring with *anti* placement of the groups. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.25$–1.35 (m, 6H), 1.52 (d, $J = 6.6$ Hz, 3H), 1.53 (d, $J = 6.7$ Hz, 3H), 2.28–2.41 (m, 2H), 2.60–2.89 (m, 6H), 3.618 (s, 3H), 3.62 (s, 3H), 3.89–3.99 (m, 1H), 4.15–

4.24 (m, 4H), 4.30–4.38 (m, 1H), 4.85–4.95 (m, 1H), 5.01–5.09 (m, 1H), 7.62–7.71 (m, 2H), 7.95–8.03 ppm (m, 2H); HRMS: *m/z* calcd for $[C_{38}H_{38}O_{12}+Na]^+$: 709.2255; found: 709.2259.

Diethyl 2,2′-(9,9′-dihydroxy-1,1′-dimethyl-5,5′,10,10′-tetraoxo-3,3′,4,4′,-5,5′,10,10′-octahydro-1*H*;1′*H*-[8,8′-dibenzo[*g*]isochromene]-3,3′-diyl)diacetate (36): $AlCl_3$ (29 mg, 0.22 mmol, 5.0 equiv) was added to a solution of **34** (30 mg, 0.044 mmol) in dry CH_2Cl_2 (15 mL) in portions at 0 °C, and the reaction mixture was stirred for 10 min. The ice bath was removed and stirring continued at room temperature for 45 min. It was then quenched with water (5 mL) and the solution extracted with CH_2Cl_2 (5×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (4:1 to 4:3) as eluent to provide **36** (22.7 mg, 79%) as a yellow solid. M.p. 175–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.30$ (t, $J=7.1$ Hz, 6H), 1.58 (d, $J=6.8$ Hz, 6H), 2.36 (ddd, $J=19.2$, 10.5, 1.9 Hz, 2H), 2.61–2.73 (m, 4H), 2.85 (dd, $J=19.2$, 3.3 Hz, 2H), 4.17–4.25 (m, 4H), 4.32–4.38 (m, 2H), 5.02 (q, $J=6.3$ Hz, 2H), 7.65–7.78 (m, 4H), 12.53 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.2$, 19.4, 27.9, 40.7, 60.8, 63.4, 67.2, 114.9, 118.6, 131.7, 137.7, 142.5, 146.5, 159.3, 170.6, 182.7, 188.7 ppm; IR ($CHCl_3$): $\tilde{\nu}=3460$, 2976, 2918, 2850, 1738, 1661, 1640, 1607, 1471, 1415, 1341, 1270, 1158, 1116, 1078, 1032, 860, 792 cm^{-1}; HRMS: *m/z* calcd for $[C_{36}H_{34}O_{12}+Na]^+$: 681.1942; found: 681.1942.

Synthesis of 36 from 35 through demethylation with $AlCl_3$- and H_2SO_4-mediated epimerization: $AlCl_3$ (11.5 mg, 0.086 mmol, 5.0 equiv) was added to a solution of **35** (11.8 mg, 0.0172 mmol) in dry CH_2Cl_2 (15 mL) in one portion at 0 °C, and the reaction mixture was stirred for 10 min. The ice bath was removed and stirring continued at room temperature for 40 min. It was then quenched with water (5 mL), and the solution was extracted with CH_2Cl_2 (5× 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 4:3) as eluent to provide the demethylated compound (9 mg). Concentrated H_2SO_4 (1 mL) was added to a stirred solution of this in benzene (3 mL) at 5 °C. The resulting mixture was stirred at room temperature for 1 h. Brine solution (5 mL) was added, and the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1 to 4:3) as eluent to give **36** (4.1 mg, 35%, two steps) as a yellow solid. The spectroscopic data were the same as before.

7,7′-Dihydroxy-5,5′-dimethyl-3,3a,3′,3′a-tetrahydro-2*H*,2′*H*-(8,8′-dibenzo[*g*]furo[3,2-*c*]isochromene)-2,2′,6,6′,11,11′-(5*H*,5′*H*,11b*H*,11′b*H*)-hexanone (37): A solution of LiOH (2 mg) in H_2O (0.5 mL) was added to a solution of **36** (15 mg, 0.0023 mmol) in THF (0.5 mL) at 0 °C and stirred for 12 h. HCl (2 N, 0.2 mL) was added, and the solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue was dissolved in MeOH (0.5 mL) and stirred in an open vial for one day at room temperature. It was then concentrated, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to give **37** (4.6 mg, 34% from **36**) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.59$ (d, $J=6.8$ Hz, 6H), 2.72 (d, $J=17.7$ Hz, 2H), 3.00 (dd, $J=17.8$, 5.2 Hz, 2H), 4.71 (dd, $J=5.1$, 3.0 Hz, 2H), 5.12 (q, $J=6.8$ Hz, 2H), 5.28 (d, $J=3.0$ Hz, 2H), 7.75–7.82 (m, 4H), 12.35 ppm (s, 2H; OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=18.6$, 36.9, 66.2, 66.4, 68.5, 115.0, 119.2, 131.4, 135.3, 138.55, 138.6, 149.9, 159.6, 173.9, 181.2, 188.3 ppm; IR ($CHCl_3$): $\tilde{\nu}=3435$, 2923, 2853, 1789, 1652, 1621, 1454, 1423, 1328, 1271, 1243, 1204, 1162, 1085, 1039, 909, 869, 788, 686 cm^{-1}; HRMS: *m/z* calcd for $[C_{32}H_{22}O_{12}+H]^+$: 599.1184; found: 599.1172.

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