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Umpolung Pd-Catalyzed α-Arylation Reactions in Natural Product Synthesis: Syntheses of (+)-Xestodecalactone A, (–)-Curvularin, (+)-12-Oxocurvularin and (–)-Citreofuran

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The syntheses (total and formal) of four phenylacetic acid lactone (PAL) natural products have been accomplished by utilizing a unified strategy of an umpolung Pd-catalyzed α-arylation of complex α-bromo esters and boronic acids under mild reaction conditions. As part of the synthetic approaches to these natural products, it was observed that the mild coupling reaction conditions readily tolerated terminal alkenes, other labile ester functionalities, an α,β-unsaturated ester moiety, and a protected allylic alcohol, while chemoselectively engaging the α-bromo ester. The completion of (+)-xestodecalactone A and (–)-curvularin coupled with the formal syntheses of (+)-12-oxocurvularin and (–)-citreofuran highlight the umpolung Pd-catalyzed α-arylation strategy as a key convergent tactic in complex natural product synthesis.

Introduction

Marine as well as terrestrial sources persistently provide the synthetic organic community with a variety of structurally intriguing and biologically relevant natural products.[1] As disclosed by Bringmann, Proksch, and co-workers in 2002, the xestodecalactones were isolated from the fungus *Penicillium cf. montanense* secured from the marine sponge *Xestospongia exigua*.[2] As shown in Figure 1, xestodecalactone A (**1**) is comprised of a 10-membered macrolactone core with a sole chiral center coupled with a fused 1,3-dihydroxybenzene ring. In addition, other structurally similar macrolactone natural products (phenylacetic acid lactones, PALs) have been isolated from a variety of fungi sources. For example, curvularin (**2**), 12-oxocurvularin (**3**), and citreofuran (**4**) all possess a 12-membered macrolactone structure fused to a 1,3-dihydroxybenzene ring as also delineated in Figure 1. As disclosed by Musgrave in 1956, curvularin (**2**) was isolated from the fungus *Curvularia*.[3] Similarly, 12-oxocurvularin (**3**) and citreofuran (**4**) were both isolated in 1989 from a hybrid strain ME 0005 derived from *Penicillium citreoviride* B. IF0 6200 and 4692 as reported by Yamamura.[4] It is notable that natural products containing such structural motifs (**1**–**4**) and other PALs have significant biological profiles ranging from cAMP-PDE and TGF-β inhibitors to anti-inflammatory properties, thus making them extremely attractive as synthetic targets.[5–14]

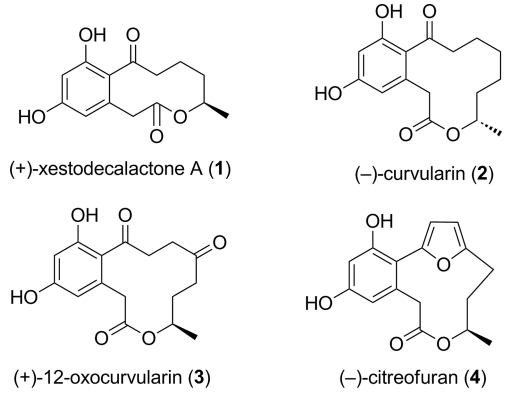

Figure 1. Structures of 10- and 12-membered 1,3-dihydroxybenzene PAL natural products **1**–**4**.

The Pd-catalyzed α-arylation of the ester moiety holds significant opportunities for the construction of medicinally valuable compounds, most notably macrocyclic PALs. As shown in Figure 1, natural products **1**–**4** collectively contain an α-aryl ester linkage, which could be highly amenable to construction by a Pd-catalyzed carbonyl arylation process. With respect to the Pd-catalyzed α-arylation of esters there are two modes of reactivity that have been explored. The first centers on utilizing a preformed or in-situ generated enolate (or silyl ketene acetal) in conjunction with an electrophilic aryl halide or triflate as the coupling partner.[15,16] The umpolung approach employs an enolate precursor, typically an α-halo ester, which serves as the electrophilic counterpart combined with a nucleophilic aryl group (i.e. boronic ester/or acid) as described in generic form in Figure 2.[17] Initially, the Pd^0 complex undergoes oxidative addition with an α-halo ester to afford the Pd^{II} enolate, which

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typically exists in the carbon tautomeric form due to the low oxophilicity of Pd. An ensuing transmetallation of the boronic acid (or ester) in the presence of a mild base would furnish the aryl–Pd^{II} enolate intermediate, and subsequent reductive elimination of the enolate complex would ultimately provide the newly formed α-aryl ester product while regenerating the Pd^0 catalyst. While both tactics eventually lead to identical α-arylated ester products, the former reaction conditions require the usage of a strong base such as LDA or LiHMDS, which can limit the reaction scope due to functional-group incompatibilities and/or unwanted side products.[15]

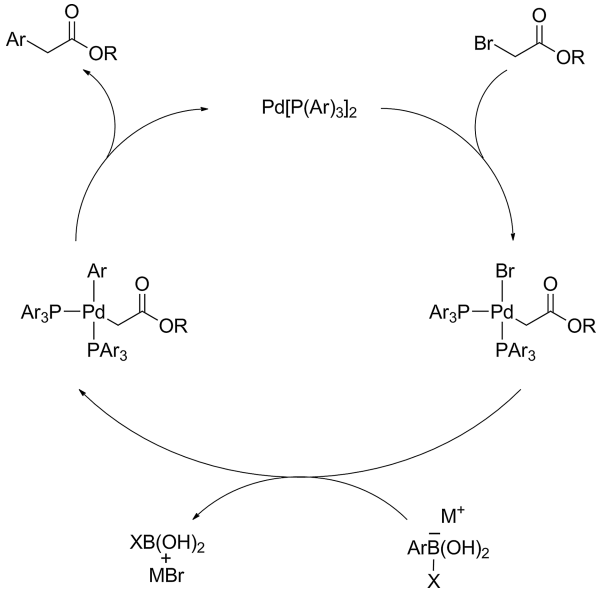
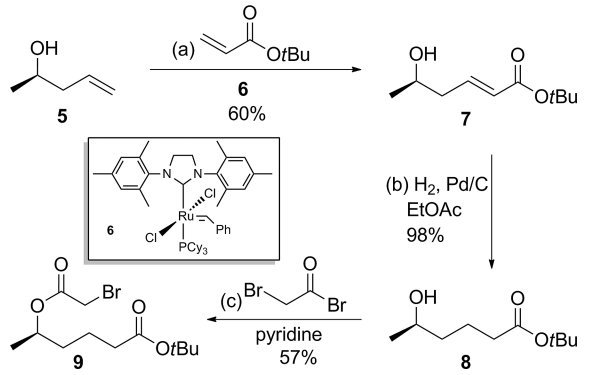


Figure 2. General Pd-catalyzed mechanism for α-arylation of an α-bromo ester and boronic acid.

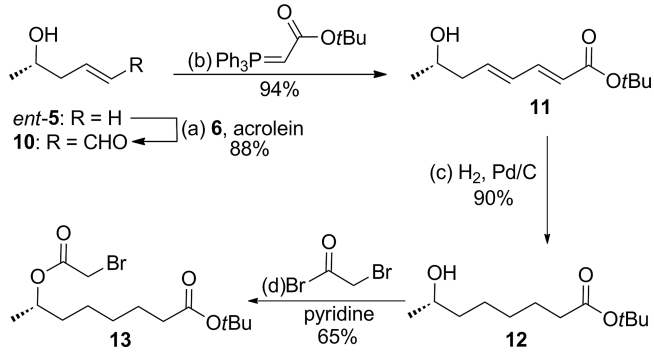
Conversely, the latter approach (Figure 2) utilizes typically milder conditions, which should greatly enhance its usage in complex molecule synthesis based on multiple functional-group compatibilities.[17] Surprisingly, there have been very few examples of Pd-catalyzed α-arylation reactions with complex α-bromo esters and nucleophilic coupling partners such as boronic esters or acids. It was our initial goal to expand the umpolung approach to α-arylation by employing more complex α-bromo ester coupling partners within the context of natural product synthesis. Based on this unified strategy, our results on the successful syntheses (two total and two formal) of the four PAL natural products **1**–**4** are presented herein.

Results and Discussion

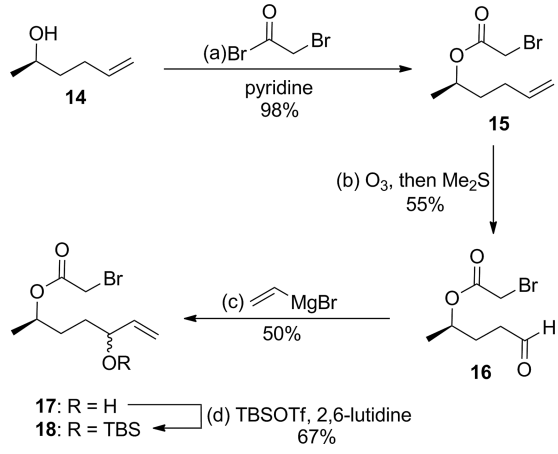
With the current synthetic strategy of Pd-catalyzed α-arylation reactions with complex α-bromo esters and boronic acids in mind, we commenced our investigation by constructing the required carbon frameworks of the aliphatic coupling segments **9**, **13**, **15**, and **18** as shown in Schemes 1, 2, and 3. With respect to the synthesis of (+)-**1** by the α-arylation of α-brom oester **9**, treatment of homoallylic alcohol **5**[18] with excess *tert*-butyl acrylate (5 equiv.) in the presence of Grubbs' catalyst **6**[19] furnished the α,β-unsaturated ester **7** in 60% yield with an (*E*)/(*Z*) ratio of > 20:1 as deduced by ^{1}H NMR spectroscopy as highlighted in Scheme 1. While the *dr* of the cross-metathesis is excellent for this example (**5** → **7**), the stereochemistry of the corresponding olefin product was insignificant as it was reduced in the next step. Along this line, hydrogenation of the olefin moiety of **7** was accomplished with H_2 and Pd/C in



Scheme 1. Completion of the aliphatic portion **9** of (+)-xestodecalactone A.



Scheme 2. Synthesis of the aliphatic portion **13** of (–)-curvularin from alcohol **5**.



Scheme 3. Synthesis of α-bromo esters **15** and **18** from alcohol **14**.

EtOAc at –20 °C in nearly quantitative yield (98%) to afford hydroxy ester **8**. If the hydrogenation of **7** was performed in either EtOAc or other solvents (i.e. CH_2Cl_2, THF, and EtOH) at room temp., significant cyclization of ester **8** occurred, and the corresponding lactone was isolated as the major product. An ensuing esterification (bromoacetyl bromide and pyridine) of the free hydroxy group resident in **8** afforded α-bromo ester **9** in a modest 57% yield.

Analogous to the proposed completion of (+)-**1**, Scheme 2 delineates the synthesis of the α-bromo ester coupling partner **13** required for the construction of (–)-**2**. Hence, treatment of homoallylic alcohol *ent*-**5** with excess acrolein (10 equiv.) in the presence of catalyst **6** afforded the α,β-unsaturated aldehyde **10** in 88% yield with an (*E*)/(*Z*) ratio of ≥ 20:1 as determined by ^{1}H NMR spectroscopy.

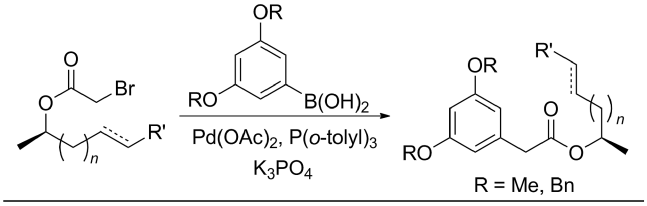
An ensuing olefination of the aldehyde moiety resident in **10** with 3 equiv. of the stabilized phosphorane *tert*-butyl ester provided the diene product **11** in 94% yield, thus completing the requisite aliphatic carbon chain resident in (–)-**2**. While the diastereomeric ratios of both the cross-metathesis and olefination reactions are excellent [≥ 20:1, (*E*)/(*Z*)], the stereochemistry of the corresponding diene in product **11** was inconsequential. The resultant hydrogenation of the diene moiety resident in **11** was accomplished with H_2 and Pd/C in EtOAc at room temp. for 12 h in 90% yield to afford the saturated hydroxy ester **12**. A subsequent esterification with 2 equiv. of bromoacetyl bromide and pyridine of the free hydroxy group resident in **12** furnished α-bromo ester **13** in a modest 65% yield.

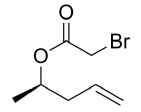
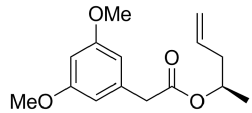
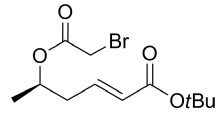
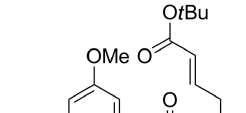
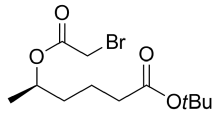
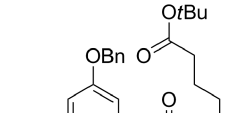
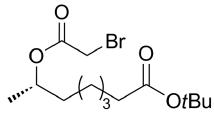
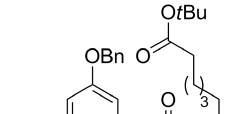
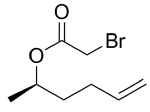
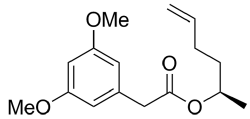
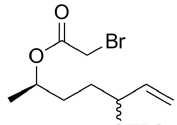
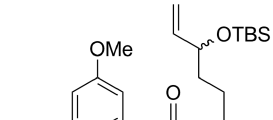
Similar to Schemes 1 and 2, we required the construction, in part, of the aliphatic portion of both natural products **3** and **4** prior to the convergent Pd-catalyzed α-arylation reaction. As delineated in Scheme 3, we streamlined the synthetic sequence by utilizing the α-bromo ester as a bifunctional moiety, first as an initial protecting group and then subsequently as the Pd–enolate precursor. Thus, esterification of the free hydroxy group resident in **14**[20] with bromoacetyl bromide in the presence of pyridine readily furnished α-bromo ester **15** in nearly quantitative yield (98%). With **15** in hand, we envisioned directly investigating **15**, as well as homologating the aliphatic carbon chain prior to the Pd-catalyzed α-arylation reaction en route to **3** and **4**. Consequently, ozonolysis of the terminal olefin of **15** followed by a reductive workup with Me_2S afforded aldehyde **16** in a modest 55% yield.

An ensuing chemoselective addition of vinylmagnesium bromide to the corresponding aldehyde moiety of **16** provided allylic alcohol **17** in 50% yield as a ca. 1:1 mixture of diastereomers. Fortunately, the stereochemistry of the secondary allylic alcohol was inconsequential due to a pending oxidation to the ketone in later steps, vide infra. Protection of the free hydroxy group resident in **17** as a TBS ether was readily accomplished with TBSOTf and 2,6-lutidine and furnished α-bromo ester **18** in 67% yield.

As shown in Table 1, we investigated a series of α-bromo esters (**9**, **13**, **15**, **18**–**20**[21]) as electrophilic Pd^{II} enolate precursors combined with electron-rich boronic acid coupling partners. Using the optimized catalyst/ligand system as described by Gooßen as an initial guide [3 mol-% $Pd(OAc)_2$, 9 mol-% P(*o*-tolyl)$_3$, 5 equiv. K_3PO_4], we observed modest to good yields (60–80%) for the coupling products **21**–**26** from a series of α-bromo esters with protected (Bn and Me) (3,5-dihydroxyphenyl)boronic acids.[17a,22] It is worth noting that the coupling reaction conditions required a strict O_2-free environment to allow for a meaningful yield (> 20%). The major byproduct isolated was the biaryl product derived from the presumed reduction of Pd^{II} to Pd^0 with

Table 1. Umpolung Pd-catalyzed α-arylation of functionalized α-bromo esters and boronic acids.[a,b]

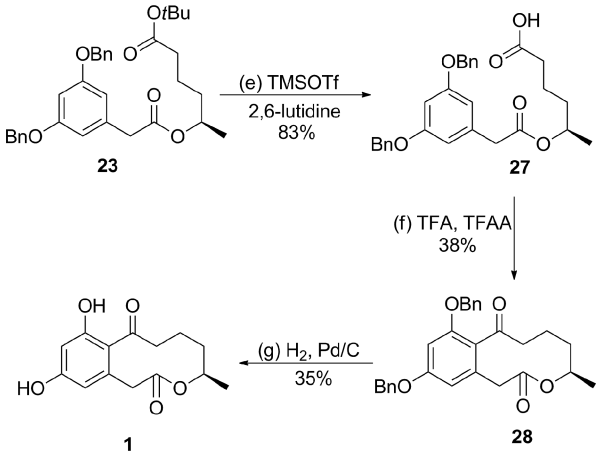


Substrate	Product
 **19**	 **21** (60%)
 **20**	 **22** (78%)
 **9**	 **23** (77%)
 **13**	 **24** (70%)
 **15**	 **25** (78%)
 **18** OTBS	 **26** (80%)

[a] Quoted yields are of purified products. [b] Reactions were performed at room temp.

2 equiv. of boronic acid in the presence of O_2. It is also notable that the described reactions did not require heating and freely proceeded at room temperature. The coupling reaction conditions readily tolerated terminal alkenes (**15** and **19**), other ester functionalities (**9**, **13**, and **20**), an α,β-unsaturated ester moiety (**20**), and a protected allylic alcohol (**18**) while chemoselectively engaging the α-bromo ester ultimately providing the corresponding products in good yields (60–80%).

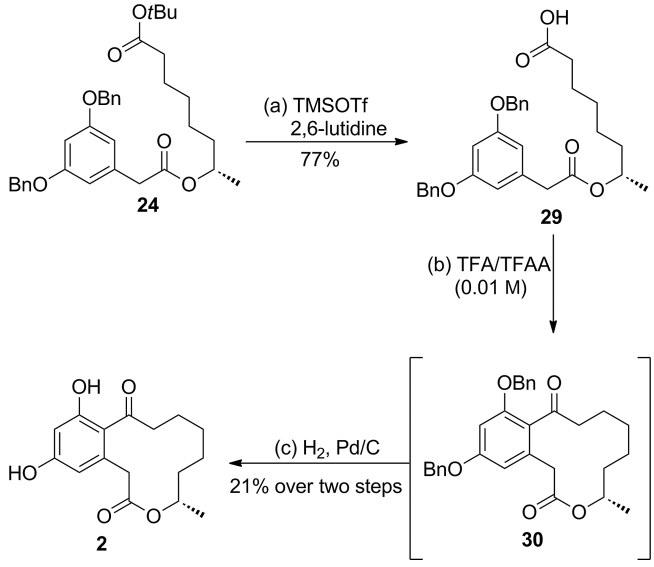
With the umpolung Pd-catalyzed α-arylation protocol of complex α-bromo esters coupled with electron-rich boronic acids firmly in hand, attention was focused on the chemoselective hydrolysis of the *tert*-butyl ester resident in **23** followed by final ring closure of the corresponding acid en route to (+)-xestodecalactone A (**1**).[6a] As shown in Scheme 4, hydrolysis of the *tert*-butyl ester resident in **23** with TMSOTf and 2,6-lutidine provided acid **27** in 83% yield and set the stage for the intramolecular Friedel–Crafts ring closure.[23]



Scheme 4. Synthesis of (+)-xesotdecalactone A (**1**).

The intramolecular acylation reaction of **27** under similar conditions (TFA/TFAA = 2:1, room temp., 0.01 M) to that of the Bringmann report provided macrocycle **28** with a yield of 38%.[6a] Final reductive bis(hydrogenolysis) of the phenolic benzyl ether protecting groups of macrocycle **28** with H_2 and Pd/C as a solution in MeOH afforded (+)-xestodecalactone A (**1**) in a modest 35% yield. The spectroscopic data (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz), optical rotation {$[\alpha]_D^{23}$ = +46.8 (*c* = 0.02, MeOH)}, and HRMS data of synthetic **1** are in close agreement with those of the natural sample and in accord with both the Bringmann and Danishefksy reports.[6] It was surprising that the ^{1}H and ^{13}C NMR spectra of (+)-xestodecalactone had not been disclosed previously in the literature (only tabulated data appears in both the Bringmann and Danishefksy papers) making the direct spectral comparison unviable.[6] The overall yield of this more convergent approach to **1** was 2.8% from homoallylic alcohol **11** compared to 0.22% as we had previously reported.[24]

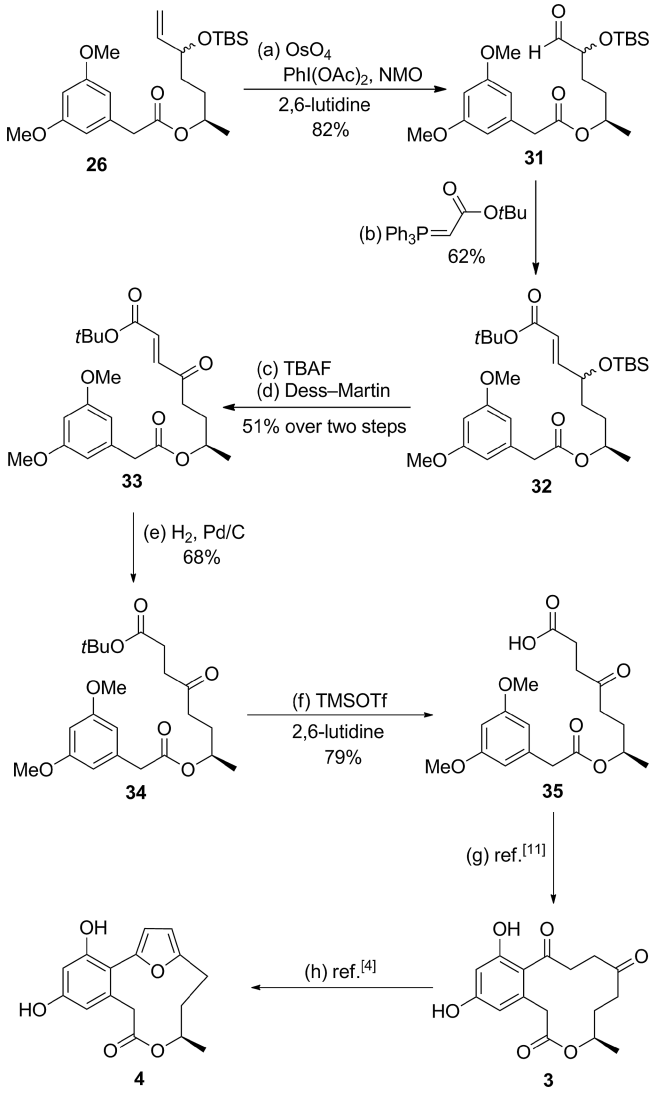
With the completion of **1**, attention was focused on the final ring closure of the corresponding carboxylic acid for the completion of (–)-curvularin (**2**) as shown in Scheme 5. While the synthetic operations leading to the completion of **2** closely parallel that of **1**, the 12-membered fused macrocyclic lactone ring of **2** was one significant structural difference with respect to **1** (10-membered lactone). Accordingly, hydrolysis of the *tert*-butyl ester resident in **24** with TMSOTf and 2,6-lutidine delivered acid **29** in 77% yield and set the stage for the intramolecular Friedel–Crafts ring closure. The acylation reaction of **29** under identical conditions (TFA/TFAA = 2:1, room temp., 0.01 M) as noted in Scheme 4, provided the corresponding macrocycle **30** and final reductive bis(hydrogenolysis) of the phenolic benzyl ether protecting groups with H_2 and Pd/C in a solution of THF/MeOH = 1:1 furnished (–)-curvularin (**2**) in a 21% yield over two steps from **29**. For comparison, the 12-membered ring formation (**29** → **2**) proceeded in a higher yield (21% vs. 13%) than that of the 10-membered analogue (**27** → **1**; Scheme 4). The spectroscopic data (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz), optical rotation {$[\alpha]_D^{23}$ = –7.31 (*c* = 0.52, EtOH)}, and HRMS data of synthetic **2** are in agreement with those of the natural sample and in accord with the prior synthetic ventures.[10] The overall yield of the curvularin synthesis was 5.5% over eight steps from homoallylic alcohol *ent*-**11**.



Scheme 5. Completion of (–)-curvularin (**2**).

With the umpolung Pd-catalyzed α-arylation synthesis of ester **26** firmly in hand, attention was focused on the final completion of the aliphatic portion of both natural products **3** and **4** as shown in Scheme 6. Unfortunately, an attempted streamlined synthesis of the entire aliphatic portion of **3** and **4** prior to the Pd-catalyzed arylation did not provide the α-bromo ester coupling partner due to a series of functional-group incompatibilities (i.e. necessary protecting-group shuffles and chemoselective hydrogenation of an alkene in the presence of the α-bromo ester). Thus, ester **26** served as a realistic platform to launch the final carbon homologation and required adjustment of oxidation states of specific carbon atoms resident in the macrocycles of **3**

and **4**. Hence, subsequent dihydroxylation of the olefin moiety resident in **26** was accomplished with OsO_4/NMO followed by an in-situ diol cleavage with $PhI(OAc)_2$ to furnish aldehyde **31** in 82% overall yield.[25] A two-carbon homologation of the aldehyde moiety of **31** by utilizing an olefination protocol with an α-*tert*-butyl ester stabilized phosphorane afforded the α,β-unsaturated diester **32** in 62% yield with an (*E*)/(*Z*) ratio of ca. 10:1.



Scheme 6. Formal syntheses of 12-oxocurvularin (**3**) and citreofuran (**4**).

It is worth noting that cross-metathesis of terminal alkene **26** was not successful with excess *tert*-butyl acrylate or acrylic acid in the presence of catalyst **6** to directly afford **32** or the corresponding acid. With the complete carbon skeleton in place, attention was turned to the completion of acid **35**. Thus, TBAF-mediated desilylation of the TBS ether resident in diester **33** afforded the free hydroxy group, which was subsequently oxidized to the corresponding ketone with Dess–Martin periodinane to provide α,β-unsaturated oxo diester **33** in 51% over two steps from **32**.[26] An ensuing hydrogenation of the olefin moiety of **33** with H_2 and Pd/C provided the saturated oxo ester **34** in 68% yield. Final chemoselective hydrolysis (conditions similar to those as described in Schemes 4 and 5) of the *tert*-butyl ester in **34** with TMSOTf and 2,6-lutidine furnished acid **35** in 79% yield much to our delight. The completion of **35** constitutes a formal synthesis of 12-oxocurvularin (**3**) and ultimately citreofuran (**4**) by intercepting the previously reported intermediate as described by Yamamura and Lai.[4,11]

Conclusions

The syntheses (total and formal) of the four PAL natural products **1**–**4** have been accomplished by exploiting a unified tactic of an umpolung Pd-catalyzed α-arylation of complex α-bromo esters and boronic acids under mild reaction conditions. As part of the synthetic approaches to PALs **1**–**4**, it was observed that the mild coupling reaction conditions readily tolerated terminal alkenes, other labile ester functionalities, an α,β-unsaturated ester moiety, and a protected allylic alcohol while chemoselectively engaging the α-bromo ester. This straightforward and convergent approach by means of the mild α-arylation reaction conditions between α-bromo esters and boronic acids should allow for the synthesis of other PAL natural products and structurally related analogues.

Experimental Section

General Procedure: All of the reactions were performed under argon in flame-dried glassware. All starting materials and solvents were commercially available and were used without further purification. Deuterated chloroform ($CDCl_3$) was stored over molecular sieves (4 Å). The NMR spectra were recorded on 360 or 500 MHz spectrometers. ^1H and ^{13}C NMR spectra were obtained by using either $CDCl_3$, CD_3OD, or $(CD_3)_2CO$ as the solvent with chloroform ($CHCl_3$: δ = 7.26 ppm), methanol (MeOH: δ = 3.31 ppm), or [D_5]acetone [$CD_3(CO)CHD_2$: δ = 2.05 ppm] as the internal standard. High-resolution mass spectra were recorded on an *EBE* sector instrument by using electron ionization (EI) at 70 eV. Column chromatography was performed by using 60–200 μm silica gel. Analytical thin layer chromatography was performed on silica-coated glass plates with F-254 indicator. Visualization was accomplished by UV light (254 nm), $KMnO_4$, or ceric sulfate/phosphomolybdic acid stain.

***tert*-Butyl (*R*,*E*)-5-Hydroxyhex-2-enoate (7):** To a flame-dried round-bottomed flask with a solution of **5** (4.00 g, 46.4 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (232 mL) under Ar at room temp. was added *tert*-butyl acrylate (33.6 mL, 232 mmol, 5.00 equiv.) dropwise. To the resulting solution was added Grubbs' second-generation catalyst **6** (1.97 g, 0.241 mmol, 0.05 equiv.). The solution was stirred at room temp. for 12 h. The solution was then concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford **7** as a brown viscous oil (1.05 g, 60%). TLC: R_f = 0.3 (20% EtOAc/hexanes). $[\alpha]_D^{22}$ = –7.5 (c = 0.08, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 6.80 (m, 1 H), 5.77 (m, 1 H), 3.90 (m, 1 H), 2.42 (br. s, 1 H), 2.28 (m, 2 H), 1.43 (s, 9 H), 1.17 (d, J = 6.13 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 143.7, 125.4, 80.2, 66.5, 41.6, 28.0, 23.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3403,

2973, 2927, 2251, 1711, 1646, 1456, 1396, 1365, 1327, 1167, 1076, 1034, 981, 928, 848, 738 cm^{-1}. HRMS (EI): calcd. for $C_6H_9O_3$ [M – C_4H_9] 129.0552; found 129.0548.

***tert*-Butyl (*R*)-5-Hydroxyhexanoate (8):** To a solution of **7** (4.33 g, 23.2 mmol, 1.00 equiv.) in EtOAc (465 mL) at –20 °C was added Pd/C (220 mg). The mixture was then subjected to H_2 (1 atm) and stirred at –20 °C overnight. The catalyst was filtered off through Celite, and the filtrate was concentrated to leave a crude residue, which was purified by flash column chromatography (15% EtOAc/hexanes) to afford **8** as a light yellow oil (4.26 g, 98%). TLC: R_f = 0.4 (20% EtOAc/hexanes). $[\alpha]_D^{22}$ = –4.2 (c = 0.012, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.74 (m, 1 H), 2.18 (m, 4 H), 1.60 (m, 2 H), 1.39 (s, 6 H), 1.13 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 80.0, 67.2, 38.4, 35.2, 27.9, 23.3, 21.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2942, 2839, 1725, 1597, 1461, 1431, 1293, 1207, 1159, 1062 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{30}O_4Si$ [M – C_4H_9] 341.1209; found 341.1208.

***tert*-Butyl (*R*)-5-(2-Bromoacetoxy)hexanoate (9):** To a flame-dried round-bottomed flask with a solution of secondary alcohol **8** (4.26 g, 22.6 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (75.0 mL) under Ar at 0 °C was added pyridine (3.60 mL, 45.3 mmol, 2.00 equiv.) followed by bromoacetyl bromide (4.00 mL, 45.3 mmol, 2.00 equiv.) dropwise. The reaction mixture was warmed to room temp. Upon completion, as monitored by TLC, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (500 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the organic extracts were washed with a saturated $CuSO_4$ solution to remove excess pyridine. The crude material was concentrated under vacuum and purified by gradient column chromatography (3% to 5% EtOAc/hexanes) to afford **9** as colorless oil (4.00 g, 57%). TLC: R_f = 0.6 (10% EtOAc/hexanes). $[\alpha]_D^{22}$ = –4.7 (c = 0.16, CH_2Cl_2). ^{1}H NMR (350 MHz, $CDCl_3$): δ = 4.90 (m, 1 H), 3.75 (m, 2 H), 2.17 (m, 2 H), 1.56 (m, 4 H), 1.38 (s, 9 H), 1.19 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 166.4, 79.8, 72.5, 34.7, 27.8, 25.9, 20.5, 19.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2977, 2935, 1730, 1464, 1365, 1281, 1156, 962, 840 cm^{-1}. HRMS (EI) calcd. for $C_8H_{12}O_3Br$ [M – C_4H_9O] 234.9970; found 234.9969.

(*S*,*E*)-5-Hydroxyhex-2-enal (10): To a flame-dried round-bottomed flask with a solution of *ent*-**5** (3.0 g, 34.8 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (350 mL) under Ar at room temp. was added acrolein (23.1 mL, 348 mmol, 10.0 equiv.). To the resulting solution was added Grubbs' second-generation catalyst **6** (1.40 g, 1.74 mmol, 0.0500 equiv.). The solution was stirred at room temp. for 12 h. The reaction mixture was then concentrated under reduced pressure and purified by gradient column chromatography (20% to 50% EtOAc/hexanes) to afford **10** as a brown viscous oil (3.52 g, 88%). TLC: R_f = 0.2 (50% EtOAc/hexanes). $[\alpha]_D^{22}$ = +16.7 (c = 0.008, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.38 (d, J = 7.9 Hz, 1 H), 6.85 (m, 1 H), 6.06 (ddt, J = 15.7, 7.9, 1.4 Hz, 1 H), 3.92 (m, 1 h), 3.11 (s, 1 H), 2.40 (m, 2 H), 1.14 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.1, 155.3, 134.3, 66.1, 41.8, 23.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3398, 2970, 2928, 2835, 2743, 1949, 1683, 1637, 1405, 1375, 1305, 1147, 1112, 978, 936 cm^{-1}. HRMS (EI): calcd. for $C_6H_{10}O_3$ [M$^+$] 114.0681; found 114.0686.

***tert*-Butyl (*S*,2*E*,4*E*)-7-Hydroxyocta-2,4-dienoate (11):** To a solution of **10** (2.01 g, 17.5 mmol, 1.00 equiv.) in CH_2Cl_2 (350 mL) was added (*tert*-butoxycarbonylmethylene)triphenylphosphorane (19.8 g, 52.6 mmol, 3.00 equiv.). The mixture was stirred at room temp. overnight. The solution was concentrated, and the residue was purified by flash column chromatography (25% EtOAc/hexanes) to afford **11** as a light yellow oil (3.48 g, 94%). TLC: R_f = 0.3 (30% EtOAc/hexanes). $[\alpha]_D^{20}$ = +16.0 (c = 0.012, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.11 (dd, J = 15.4, 10.7 Hz, 1 H), 6.10 (m, 2 H), 5.69 (d, J = 15.4 Hz, 1 H), 3.85 (m, 1 H), 2.27 (m, 2 H), 1.43 (s, 9 H), 1.15 (d, J = 6.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 143.3, 139.0, 130.8, 121.9, 80.0, 66.9, 42.5, 28.0, 22.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3410, 2974, 2928, 1698, 1641, 1614, 1455, 1363, 1147, 1001, 940 851, 739 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{20}O_3$ [M$^+$] 212.1412; found 212.1412.

***tert*-Butyl (*S*)-7-Hydroxyoctanoate (12):** To a solution of **11** (3.48 g, 16.4 mmol, 1.00 equiv.) in EtOAc (325 mL) at room temp. was added Pd/C (522 mg). The mixture was then subjected to H_2 (1 atm) and stirred at room temp. overnight. The catalyst was filtered off through Celite, and the filtrate was concentrated to leave a crude residue. The residue was purified by flash column chromatography (30% EtOAc/hexanes) to afford **12** as a light yellow oil (3.23 g, 90%). TLC: R_f = 0.4 (30% EtOAc/hexanes). $[\alpha]_D^{20}$ = +1.90 (c = 0.028, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.72 (m, 1 H), 2.15 (t, J = 7.5 Hz, 2 H), 1.95 (s, 1 H), 1.53 (m, 2 H), 1.38 (s, 9 H) 1.34 (m, 2 H), 1.27 (m, 4 H), 1.12 (d, J = 6.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1,79.8, 67.7, 39.0, 35.4, 28.9, 27.9, 25.3, 24.9, 23.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3415, 2968, 2931, 2863, 1727, 1455, 1368, 1256, 1155, 1050 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_{19}O_2$ [M – C_2H_5O] 171.1385; found 171.1379.

***tert*-Butyl (*S*)-7-(2-Bromoacetoxy)octanoate (13):** To a flame-dried round-bottomed flask with a solution of secondary alcohol **12** (1.00 g, 46.2 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (15 mL) under Ar at 0 °C was added pyridine (0.750 mL, 92.4 mmol, 2.00 equiv.) followed by bromoacetyl bromide (0.800 mL, 92.4 mmol, 2.0 equiv.) dropwise. The reaction mixture was warmed to room temp. Upon completion, as monitored by TLC, the reaction was quenched by a saturated aqueous NH_4Cl solution (300 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the organic extracts were washed with saturated $CuSO_4$ solution to remove excess pyridine. The crude material was concentrated under vacuum and purified by gradient column chromatography (1% to 3% EtOAc/hexanes) to afford **13** as colorless oil (1.04 g, 65%). TLC: R_f = 0.3 (5% EtOAc/hexanes). $[\alpha]_D^{20}$ = +4.46 (c = 0.0089, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.91 (m, 1 H), 3.76 (d, J = 1.9 Hz, 2 H), 2.16 (t, J = 7.6 Hz, 2 H), 1.54 (m, 4 H), 1.40 (s, 9 H), 1.24 (m, 4 H), 1.20 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 166.7, 79.8, 73.1, 35.4, 35.3, 28.7, 28.0, 26.1, 24.8, 19.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3437, 2978, 2936, 2862, 1725, 1459, 1421, 1367, 1278, 1159, 1108, 959, 847 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_{16}O_3Br$ [M – C_4H_9O] 263.0283; found 263.0284.

(*R*)-Hex-5-en-2-yl 2-Bromoacetate (15): To a flame-dried round-bottomed flask with a solution of secondary alcohol **14** (7.00 g, 69.9 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (233 mL) under Ar at 0 °C was added pyridine (12.0 mL, 139.9 mmol, 2.00 equiv.) followed by bromoacetyl bromide (13.0 mL, 139.9 mmol, 2.00 equiv.) dropwise. The reaction mixture was warmed to room temp. Upon completion as monitored by TLC, the reaction was quenched by a saturated aqueous NH_4Cl solution (1000 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), and the organic extracts were washed with a saturated $CuSO_4$ solution to remove excess pyridine. The crude material was concentrated under vacuum and purified by flash column chromatography (3% EtOAc/hexanes) to afford **15** as light yellow oil (15.0 g, 98%). TLC: R_f = 0.5 (10% EtOAc/hexanes). $[\alpha]_D^{23}$ = –12.1 (c = 0.049, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.77 (ddt, J = 17.0, 10.4, 6.6 Hz, 1 H), 4.97 (m, 3 H), 3.78 (m, 2 H),2.09 (m, 2 H), 1.66 (m, 2 H), 1.24 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 137.3,

115.1, 72.7, 34.7, 29.4, 26.1, 19.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3080, 2977, 2939, 1734, 1639, 1449, 1418, 1376, 1281, 1171, 1118, 993, 962, 916, 738 cm^{-1}. HRMS (EI): calcd. for $C_5H_7O_2Br$ [M – C_3H_6] 177.9629; found 177.9624.

(*R*)-5-Oxopentan-2-yl 2-Bromoacetate (16): A solution of **15** (6.60 g, 29.9 mmol, 1.00 equiv.) dissolved in CH_2Cl_2 (600 mL) was cooled to –78 °C, and O_3 was bubbled through the solution until the starting material was consumed as indicated by TLC analysis (1.5 h). The solution was then purged with O_2, and the reaction was quenched by addition of Me_2S (44.0 mL, 596.0 mmol, 20.0 equiv.) and stirred overnight. The resulting mixture was concentrated in vacuo to yield the crude aldehyde as light yellow oil. Purification by flash column chromatography (20% EtOAc/hexanes) afforded **16** as light yellow oil (3.7 g, 55%). TLC: R_f = 0.2 (20% EtOAc/hexanes). $[\alpha]_D^{23}$ = –8.23 (c = 0.084, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 4.90 (m, 1 H), 2.47 (m, 2 H), 1.86 (m, 2 H), 1.21 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.8, 166.5, 72.1, 39.4, 27.6, 25.9, 19.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2981, 2939, 2829, 2730, 2258, 1734, 1418, 1380, 1281, 1167, 1122, 1091, 1038, 993, 958, 909, 734, 650 cm^{-1}. HRMS (EI): calcd. for $C_7H_{10}O_3Br$ [M – H] 220.9813; found 220.9811.

(2*R*)-5-Hydroxyhept-6-en-2-yl 2-Bromoacetate (17): To a stirred solution of **16** (3.03 g, 13.4 mmol, 1.00 equiv.) in Et_2O (135 mL) under Ar at –78 °C was added vinylmagnesium bromide (1.0 M in THF, 20.1 mL, 1.50 equiv.) dropwise. The reaction mixture was stirred at that temperature for 8 h before being quenched with saturated aqueous $NaHCO_3$ solution (300 mL). The mixture was separated and the aqueous layer extracted with Et_2O (3 × 100 mL). The combined organic layers were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure to afford the crude product, which was purified by flash column chromatography (17% EtOAc/hexanes) to afford **17** as a yellow oil (1.68 g, 50%). TLC: R_f = 0.3 (30% EtOAc/hexanes). ^1H NMR (360 MHz, $CDCl_3$): δ = 5.85 (ddd, J = 16.6, 10.4, 6.1 Hz, 1 H), 5.17 (m, 2 H), 4.98 (m, 1 H), 4.11 (m, 1 H), 3.80 (m, 2 H), 1.62 (m, 6 H), 1.26 (d, J = 6.3 Hz, 3 H) ppm; dr = 1:0.7. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 140.7, 115.07, 115.03, 114.96, 114.95, 73.2, 73.0, 72.8, 72.6, 72.3, 71.9, 71.7, 39.7, 36.0, 32.5, 32.4, 32.3, 31.7, 31.5, 31.4, 31.3, 27.9, 26.1, 25.9, 19.9, 19.7, 16.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3155, 2981, 2255, 1726, 1285, 905, 738, 650 cm^{-1}. HRMS (EI): calcd. for $C_6H_{11}O_2Br$ [M – C_3H_4O] 193.9942; found 193.9945.

(2*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]hept-6-en-2-yl 2-Bromoacetate (18): To a stirred solution of **17** (2.48 g, 9.87 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (100 mL) under Ar at 0 °C was added 2,6-lutidine (2.87 mL, 24.7 mmol, 2.50 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.40 mL, 14.8 mmol, 1.5 equiv.) sequentially. The mixture was warmed to room temp. and stirred overnight. The mixture was then diluted with water (300 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (3 × 20 mL), then dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (1% EtOAc/hexanes) to afford **18** as a yellow oil (2.4 g, 67%). TLC: R_f = 0.5 (5% EtOAc/hexanes). ^1H NMR (360 MHz, $CDCl_3$): δ = 5.76 (m, 1 H), 4.95 (m, 1 H), 3.79 (m, 2 H), 1.56 (m, 4 H), 1.24 (d, J = 6.3 Hz, 3 H), 0.88 (s, 9 H), 0.04 (m, 6 H) ppm; dr = 1:0.6. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.8, 141.1, 114.0, 73.4, 73.2, 73.0, 33.4, 33.3, 31.1, 30.9, 26.2, 25.8, 19.7, –4.4, –4.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2951, 2927, 2859, 1730, 1460, 1281, 1099, 1027, 836, 772, 745 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{20}O_3BrSi$ [M – C_4H_9] 307.0365; found 307.0363.

(*R*)-Pent-4-en-2-yl 2-Bromoacetate (19): In a flame-dried round-bottomed flask was placed a solution of **5** (3.50 g, 40.6 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (136 mL) under Ar at 0 °C. To this solution was added pyridine (6.55 mL, 81.2 mmol, 2.00 equiv.), followed by bromoacetyl bromide (7.07 mL, 81.2 mmol, 2.00 equiv.). The reaction mixture was warmed to room temp. Upon completion, as determined by TLC analysis, the reaction was quenched with a saturated aqueous NH_4Cl solution (250 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the organic extracts were washed with saturated $CuSO_4$ solution to remove excess pyridine. The crude material was concentrated under vacuum and purified by flash column chromatography (1% EtOAc/hexanes) to afford **19** as colorless oil (4.61 g, 55%). TLC: R_f = 0.2 (20% EtOAc/hexanes). $[\alpha]_D^{23}$ = +0.11 (c = 0.38, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ = 5.66 (m, 1 H), 4.96 (m, 3 H), 3.72 (s, 2 H), 2.25 (m, 2 H), 1.17 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 132.8, 117.8, 71.9, 39.7, 25.9, 18.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2982, 2937, 2256, 1735, 1644, 1283, 1175, 1110, 910, 730 cm^{-1}. HRMS (EI): calcd. for $C_4H_6O_2Br$ [M – C_3H_5] 164.9551; found 164.9548.

***tert*-Butyl (*R*,*E*)-5-(2-Bromoacetoxy)hex-2-enoate (20):** To a solution of **19** (1.00 g, 4.83 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (25.0 mL) was added *tert*-butyl acrylate (1.50 mL, 103 mmol, 2.00 equiv.) and Grubbs' second-generation catalyst **6** (0.205 g, 0.241 mmol, 0.0500 equiv.) at room temp. The reaction mixture was stirred under reflux for 12 h, and the solvent was removed in vacuo to afford the crude product. Column chromatography on silica gel (5% EtOAc/hexanes) afforded **20** (1.05 g, 70%) as brown viscous oil. TLC: R_f = 0.2 (20% EtOAc/hexanes). $[\alpha]_D^{20}$ = +1.7 (c = 0.007, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 6.74 (m, 1 H), 5.77 (dt, J = 15.7, 1.4 Hz, 1 H), 5.01 (m, 1 H), 3.76 (s, 2 H), 2.43 (m, 1 H), 2.19 (m, 1 H), 1.43 (s, 9 H), 1.24 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 165.3, 141.3, 126.3, 80.3, 71.4, 40.9, 37.8, 28.0, 25.9, 19.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2978, 2936, 2254, 1737, 1710, 1660, 1455, 1390, 1367, 1282, 1162, 1058, 982, 913, 847, 731, 647 cm^{-1}. HRMS (EI): calcd. for $C_8H_{10}O_3Br$ [M – C_4H_9O] 232.9813; found 232.9816.

(*R*)-Pent-4-en-2-yl 2-(3,5-Dimethoxyphenyl)acetate (21): A flame-dried round-bottomed flask with a solution of **19** (1.80 g, 8.69 mmol, 1 equiv.) in THF (44 mL) and water (0.3 mL) was strictly deoxygenated by using the freeze-pump-thaw procedure. The round-bottomed flask was then transferred inside a glove box, and (3,5-dimethoxyphenyl)boronic acid (1.2 g, 10.42 mmol, 1.2 equiv.), $Pd(OAc)_2$ (0.06 g, 0.26 mmol, 0.03 equiv.), P(*o*-Tol)$_3$ (0.238 g, 0.78 mmol, 0.09 equiv.) and K_3PO_4 (9.2 g, 43.45 mmol, 5 equiv.) were added sequentially. The solution was stirred inside the glove box for 24 h. The reaction slurry was poured into water (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and volatiles were removed in vacuo. The residue was purified by gradient column chromatography (1% to 3% EtOAc/hexanes) to afford **21** as yellow oil (0.32 g, 60%). TLC: R_f = 0.3 (10% EtOAc/hexanes). $[\alpha]_D^{24}$ = +6.10 (c = 0.0052, CH_2Cl_2). ^1H NMR (360 MHz, $CDCl_3$): δ = 6.43 (d, J = 2.2 Hz, 2 H), 6.36 (t, J = 2.2 Hz, 1 H), 5.71 (m, 1 H), 5.02 (m, 3 H), 3.77 (s, 6 H), 3.51 (s, 2 H), 2.30 (m, 2 H), 1.21 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 160.7, 136.2, 133.4, 117.6, 107.2, 99.1, 70.5, 55.2, 41.8, 40.1, 19.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3425, 2947, 1729, 1598, 1463, 1205, 1159, 1066 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{20}O_4$ [M^+] 264.1362; found 264.1359.

***tert*-Butyl (*R*,*E*)-5-[2-(3,5-Dimethyloxyphenyl)acetoxy]hex-2-enoate (22):** A flame-dried round-bottomed flask with a solution of **20** (0.500 g, 1.63 mmol, 1.00 equiv.) in THF (8.20 mL) and H_2O (0.05 mL) was degassed by using the freeze-pump-thaw technique

(3×). The round-bottomed flask was transferred to a glove box, and (3,5-dimethoxyphenyl)boronic acid (0.350 g, 1.96 mmol, 1.20 equiv.), $Pd(OAc)_2$ (0.0110 g, 0.0489 mmol, 0.0300 equiv.), P(*o*-Tol)$_3$ (0.1 g, 0.147 mmol, 0.0900 equiv.) and K_3PO_4 (1.72 g, 8.15 mmol, 5.00 equiv.) were added sequentially. The reaction mixture was stirred inside the glove box for 24 h. The reaction slurry was poured into water (150 mL) and extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by gradient column chromatography (2% to 5% EtOAc/hexanes) to afford **22** as brown oil (0.32 g, 78%). TLC: R_f = 0.2 (10% EtOAc/hexanes). $[\alpha]_D^{24}$ = +3.0 (*c* = 0.0135, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.72 (m, 1 H), 6.37 (d, *J* = 2.2 Hz, 2 H), 6.30 (t, *J* = 2.2 Hz, 1 H), 5.72 (td, *J* = 15.6, 1.4 Hz, 1 H), 4.96 (m, 1 H), 3.71 (s, 6 H), 3.47 (s, 2 H), 2.36 (m, 2 H), 1.42 (s, 9 H), 1.18 (d, *J* = 6.30 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 160.8, 141.1, 136.0, 125.9, 123.4, 107.2, 99.2, 80.2, 69.7, 55.2, 41.7, 38.1, 34.2, 27.8, 19.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2975, 2937, 2839, 1733, 1712, 1597, 1464, 1428, 1363, 1325, 1293, 1248, 1207, 1062, 979, 846 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{28}O_6$ [M^+] 364.1886; found 364.1884.

***tert*-Butyl (*R*)-5-{2-[3,5-Bis(benzyloxy)phenyl]acetoxy}hexanoate (23):** A flame-dried round-bottomed flask with a solution of **20** (1.40 g, 4.52 mmol, 1.00 equiv.) in THF (23.0 mL) and water (0.160 mL) was degassed by using the freeze-pump-thaw procedure. The round-bottomed flask was transferred inside a glove box, and [3,5-bis(benzyloxy)phenyl]boronic acid (1.81 g, 5.42 mmol, 1.20 equiv.), $Pd(OAc)_2$ (0.0300 g, 0.130 mmol, 0.0300 equiv.), P(*o*-Tol)$_3$ (0.123 g, 0.400 mmol, 0.0900 equiv.) and K_3PO_4 (4.79 g, 22.6 mmol, 5.00 equiv.) were added sequentially. The solution was stirred inside the glove box for 24 h. Upon completion, the reaction mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (3× 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by gradient column chromatography (2% to 4% EtOAc/hexanes) to afford **23** as yellow oil (1.81 g, 77%). TLC: R_f = 0.3 (10% EtOAc/hexanes). $[\alpha]_D^{22}$ = +0.03 (*c* = 0.20, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.39 (m, 10 H), 6.56 (m, 3 H), 5.03 (s, 4 H), 4.92 (m, 1 H), 3.53 (s, 2 H), 2.21 (m, 2 H), 1.58 (m, 4 H), 1.44 (s, 9 H), 1.22 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 159.9, 128.4, 127.4, 127.8, 108.4, 100.8, 80.0, 71.0, 69.9, 41.8, 35.0, 28.0, 20.8, 19.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3425, 2080, 1639, 1172 cm^{-1}. HRMS (EI): calcd. for $C_{32}H_{38}O_6$ [M^+] 518.2668; found 518.2673.

***tert*-Butyl (*S*)-7-{2-[3,5-Bis(benzyloxy)phenyl]acetoxy}octoanoate (24):** A flame-dried round-bottomed flask with a solution of **13** (0.950 g, 2.81 mmol, 1.00 equiv.) in THF (15.0 mL) and water (0.100 mL) was degassed by using the freeze-pump-thaw technique. The round-bottomed flask was transferred into a glove box, and [3,5-bis(benzyloxy)phenyl]boronic acid (1.12 g, 3.37 mmol, 1.20 equiv.), $Pd(OAc)_2$ (0.0190 g, 0.0840 mmol, 0.0300 equiv.), P(*o*-Tol)$_3$ (0.0770 g, 0.250 mmol, 0.0900 equiv.) and K_3PO_4 (2.98 g, 14.1 mmol, 5.00 equiv.) were added sequentially. The solution was stirred inside the glove box for 24 h. The reaction slurry was poured into H_2O (400 mL) and extracted with CH_2Cl_2 (3× 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (5% EtOAc/hexanes) to afford **24** as yellow oil (1.05 g, 70%). TLC: R_f = 0.4 (10% EtOAc/hexanes). $[\alpha]_D^{20}$ = +2.66 (*c* = 0.012, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.37 (m, 10 H), 6.54 (m, 3 H), 5.02 (s, 4 H), 4.89 (m, 1 H), 3.51 (s, 2 H), 2.17 (m, 2 H), 1.57 (m, 5 H), 1.43 (s, 9 H), 1.27 (m, 4 H), 1.18 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 159.9, 136.8, 136.4, 128.5, 127.9, 127.5, 108.5, 100.8, 71.4, 70.0, 41.9, 35.6, 35.4, 28.8, 28.1, 25.1, 24.9, 19.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3437, 2088, 1725, 1641, 1452, 1151 cm^{-1}. HRMS (EI): calcd. for $C_{30}H_{33}O_6$ [M – C_4H_9] 489.2277; found 489.2289.

(*R*)-Hex-5-en-2-yl 2-(3,5-Dimethoxyphenyl)acetate (25): A flame-dried round-bottomed flask containing a solution of **15** (8.00 g, 36.2 mmol, 1.00 equiv.) in THF (180 mL) and water (1.50 mL) was degassed by using the freeze-pump-thaw procedure. The round-bottomed flask was then placed into a glove box, and (3,5-dimethoxyphenyl)boronic acid (7.80 g, 43.4 mmol, 1.20 equiv.), $Pd(OAc)_2$ (0.240 g, 1.08 mmol, 0.0300 equiv.), P(*o*-Tol)$_3$ (0.990 g, 3.25 mmol, 0.0900 equiv.) and K_3PO_4 (38.4 g, 181 mmol, 5.00 equiv.) were added sequentially. The solution was stirred inside the glove box for 24 h. The reaction slurry was poured into H_2O (1000 mL) and extracted with CH_2Cl_2 (3× 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by gradient column chromatography (2% to 5% EtOAc/hexanes) to afford **25** as yellow oil (8.11 g, 80%). TLC: R_f = 0.4 (10% EtOAc/hexanes). $[\alpha]_D^{23}$ = –5.7 (*c* = 0.06, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.44 (d, *J* = 2.5 Hz, 2 H), 6.36 (m, 1 H), 5.75 (m, 1 H), 4.93 (m, 3 H), 3.76 (s, 6 H), 3.51 (s, 2 H), 2.02 (m, 2 H), 1.63 (m, 2 H), 1.21 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 160.7, 137.6, 136.3, 114.8, 107.1, 99.1, 70.8, 55.1, 41.9, 34.9, 29.5, 19.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2939, 2840, 2255, 1726, 1601, 1464, 1433, 1293, 1205, 1156, 1065, 909, 833, 730, 650 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{22}O_4$ [M^+] 278.1518; found 278.1516.

(2*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]hept-6-en-2-yl 2-(3,5-Dimethoxyphenyl)acetate (26): To a flame-dried round-bottomed flask with a solution of **18** (0.850 g, 2.34 mmol, 1.00 equiv.) in anhydrous THF (12.0 mL) under argon was added water (0.100 mL), and the solution was degassed. The round-bottomed flask was then placed into a glove box, and (3,5-dimethoxyphenyl)boronic acid (0.500 g, 2.80 mmol, 1.20 equiv.), $Pd(OAc)_2$ (0.0150 g, 0.0700 mmol, 0.0300 equiv.), P(*o*-Tol)$_3$ (0.0640 g, 0.210 mmol, 0.0900 equiv.) and K_3PO_4 (2.48 g, 11.7 mmol, 5.00 equiv.) were added sequentially. The solution was stirred inside the glove box for 24 h. The reaction slurry was poured into water (100 mL) and extracted with CH_2Cl_2 (3× 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (3% EtOAc/hexanes) to afford **26** as yellow oil (0.52 g, 53%). TLC: R_f = 0.5 (10% EtOAc/hexanes). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.43 (m, 2 H), 6.35 (m, 1 H), 5.73 (m, 1 H), 5.11 (m, 1 H), 5.01 (m, 1 H), 4.91 (m, 1 H), 4.06 (m, 1 H), 3.76 (s, 6 H), 3.51 (s, 2 H), 1.51 (m, 4 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 0.88 (m, 9 H), 0.02 (m, 6 H) ppm; *dr* = 1:0.9. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 160.7, 141.3, 136.3, 113.8, 107.1, 99.2, 73.3, 73.0, 71.5, 71.3, 55.2, 41.9, 33.5, 33.3, 31.3, 31.1, 25.8, 19.9, 18.1, –4.4, –4.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2954, 2931, 2855, 2255, 1723, 1597, 1464, 1426, 1293, 1255, 1205, 1156, 1065, 909, 833, 734, 647 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{29}O_5Si$ [M – C_4H_9] 365.1784; found 365.1784.

(*R*)-5-{2-[3,5-Bis(benzyloxy)phenyl]acetoxy}hexanoic Acid (27): To a solution of **23** (1.56 g, 30.0 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 under argon at 0 °C were added 2,6-lutidine (0.731 mL, 2.86 mmol, 2.10 equiv.) and TMSOTf (1.22 mL, 3.07 mmol, 2.26 equiv.) sequentially. The mixture was warmed to room temp. and stirred until consumption of the starting material as determined by TLC. H_2O (300 mL) was added to the mixture, and the aqueous phase was acidified and extracted with CH_2Cl_2 (3× 100 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash

column chromatography (20% EtOAc/hexanes) to afford **27** as yellow viscous oil (0.37 g, 83%). TLC: R_f = 0.2 (30% EtOAc/hexanes). $[\alpha]_D^{22}$ = +0.22 (c = 0.0087, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.66 (m, 10 H), 6.55 (m, 3 H), 5.03 (s, 4 H), 4.93 (m, 1 H), 3.54 (s, 2 H), 2.32 (m, 2 H), 1.60 (m, 4 H), 1.22 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 159.9, 136.8, 136.2, 128.4, 127.8, 127.4, 108.4, 100.8, 70.9, 69.9, 41.8, 34.9, 33.4, 20.3, 19.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2977, 2935, 2871, 2251, 1711, 1597, 1453, 1376, 1293, 1160, 1053, 909, 829, 738, 696, 650 cm^{-1}. HRMS (EI): calcd. for $C_{28}H_{30}O_6$ [M$^+$] 462.2042; found 462.2047.

(*R*)-9,11-Bis(benzyloxy)-4-methyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]-oxecine-2,8-dione (28): To a flame-dried round-bottomed flask with a solution of acid **27** (0.620 g, 1.34 mmol, 1.00 equiv.) in anhydrous TFA (89.0 mL) under argon was added TFAA (45.0 mL). The reaction mixture was stirred at room temp. for 5 h. The volatile components were removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NHCO_3$ solution. The organic layer was dried with $MgSO_4$, filtered, and volatiles were removed in vacuo. The crude material was purified by gradient column chromatography (5% to 11% EtOAc/hexanes) to afford **28** as yellow oil (0.230 g, 38%). TLC: R_f = 0.5 (20% EtOAc/hexanes). $[\alpha]_D^{22}$ = +45.3 (c = 0.0075, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.38 (m, 10 H), 6.55 (m, 1 H), 6.38 (s, 1 H), 5.04 (s, 4 H), 4.81 (s, 1 H), 4.28 (d, J = 18.6 Hz, 1 H), 3.43 (d, J = 18.0 Hz, 1 H), 2.83 (m, 2 H), 1.97 (m, 1 H), 1.63 (m, 4 H),1.16 (d, J = 5.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.8, 160.2, 136.1, 128.6, 128.6, 128.2, 128.1, 127.5, 127.4, 109.1, 99.1, 70.7, 70.1, 40.4, 36.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3437, 2931, 2874, 2251, 1726, 1681, 1601, 1578, 1465, 1430, 1373, 1331, 1259, 1236, 1160, 1076, 1042, 909, 734, 696 cm^{-1}. HRMS (EI): calcd. for $C_{28}H_{28}O_5$ [M$^+$] 444.1937; found 444.1943.

(+)-Xestodecalactone A (1): To a solution of **28** (0.100 g, 0.22 mmol, 1.00 equiv.) in MeOH (38.0 mL) was added Pd/C (10.0 mg). The mixture was then subjected to H_2 (1 atm) and stirred at room temp. for 6 h. The catalyst was filtered off through Celite, and the filtrate was concentrated to leave a crude residue. The residue was purified by flash column chromatography (50% EtOAc/hexanes) to afford **1** as white solid (0.021 g, 35%). TLC: R_f = 0.2 (60% EtOAc/hexanes). $[\alpha]_D^{22}$ = +46.8 (c = 0.002, MeOH). ^{1}H NMR (360 MHz, CD_3OD): δ = 6.19 (d, J = 1.8 Hz, 1 H), 6.07 (d, J = 1.8 Hz, 1 H), 4.73 (m, 1 H), 3.98 (d, J = 18.2 Hz, 1 H), 3.42 (d, J = 18.4 Hz, 1 H), 3.06 (m, 1 H), 2.71 (m, 1 H), 1.85 (m, 3 H), 1.49 (m, 1 H), 1.13 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 210.5, 170.7, 161.1, 158.1, 134.5, 120.7, 109.7, 107.7, 101.6, 74.1, 39.9, 36.3, 22.3, 19.6 ppm. IR (MeOH): $\tilde{\nu}$ = 3369, 2951, 2836, 2502, 2236, 2137, 2076, 1943, 1658, 1460, 1384, 1217, 1118, 973 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{16}O_5$ [M$^+$] 264.0998; found 264.1003.

(*S*)-7-{2-[3,5-Bis(benzyloxy)phenyl]acetoxy}octanoic Acid (29): To a solution of **24** (0.600 g, 11.0 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 under argon at 0 °C were added 2,6-lutidine (0.270 mL, 23.0 mmol, 2.10 equiv.) and TMSOTf (0.451 mL, 24.8 mmol, 2.25 equiv.) sequentially. The mixture was warmed to room temp. and stirred until consumption of the starting material. H_2O(100 mL) was added to the mixture, and the aqueous phase was acidified and extracted with CH_2Cl_2 (3× 50 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (30% EtOAc/hexanes) to afford **29** as a yellow viscous oil (0.417 g, 77%). TLC: R_f = 0.2 (30% EtOAc/hexanes). $[\alpha]_D^{20}$ = +10.4 (c = 0.0027, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.37 (m, 10 H), 6.54 (m, 3 H), 5.01 (s, 4 H), 4.88 (m, 1 H), 3.51 (s, 2 H), 2.29 (t, J = 7.5 Hz, 2 H), 1.45 (m, 8 H), 1.18 (d, J = 6.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 159.9, 136.8, 136.2, 128.5, 127.9, 127.5, 108.5, 100.8, 71.4, 70.0, 42.0, 35.6, 33.5, 28.7, 24.9, 24.4, 19.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2936, 2862, 1725, 1706, 1590, 1452, 1448, 1378, 1290, 1159, 1054, 735, 693 cm^{-1}. HRMS (EI): calcd. for $C_{30}H_{34}O_6$ [M$^+$] 490.2355; found 490.2376.

(–)-Curvularin (2): The acid **29** (0.391 g, 0.611 mmol, 1.00 equiv.) was dissolved in a mixture of TFA (53.0 mL) and TFAA (27.0 mL), and the solution was stirred at room temp. for 6 h. The volatile components were removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with a saturated aqueous $NHCO_3$ solution. The organic layer was dried with $MgSO_4$, filtered, and the volatiles were removed in vacuo to leave a crude material that was used without purification. The crude product (**30**) (0.127 g, 0.260 mmol, 1.00 equiv.) was dissolved in MeOH/THF (1:1) (45.0 mL). At room temp. was added Pd/C (25.0 mg). The mixture was then subjected to H_2 (1 atm) and stirred at room temp. for 6 h. The catalyst was filtered off through Celite, and the filtrate was concentrated to leave a crude residue. The residue was purified by flash chromatography (50% EtOAc/hexanes) to afford **2** as a white solid (0.0500 g, 21% from **29**). TLC: R_f = 0.6 (50% EtOAc/hexanes). $[\alpha]_D^{22}$ = –7.30 (c = 0.0052, EtOH). ^{1}H NMR [360 MHz, $(CD_3)_2CO$]: δ = 6.39 (d, J = 2.2 Hz, 1 H), 6.34 (d, J = 2.2 Hz, 1 H), 4.91 (m, 1 H), 3.77 (d, J = 15.8 Hz, 1 H), 3.69 (d, J = 15.8 Hz, 1 H), 3.11 (ddd, J = 15.8, 8.5, 2.8 Hz, 1 H), 2.77 (ddd, J_1 = 15.4, 9.7, 3.2 Hz, 1 H), 1.74 (m, 1 H), 1.51 (m, 6 H), 1.29 (m, 3 H), 1.11 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR [125 MHz, $(CD_3)_2CO$]: δ = 207.7, 172.0, 161.1, 159.3, 137.9, 122.3, 113.2, 103.6, 73.5, 44.9, 40.7, 33.9, 28.5, 25.5, 24.5, 21.5 ppm. IR (EtOH): $\tilde{\nu}$ = 2868, 2662, 2566, 2352, 2127, 1898, 1611, 1225, 1084, 923 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{20}O_5$ [M$^+$] 292.1311; found 292.1305.

(2*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-oxohexan-2-yl 2-(3,5-Dimethoxyphenyl)acetate (31): To a solution of **26** (3.48 g, 8.23 mmol, 1.00 equiv.) in acetone/H_2O (10:1; 0.1 M, 82.3 mL) were added 2,6-lutidine (1.91 mL, 16.5 mmol, 2.00 equiv.), *N*-methylmorpholine *N*-oxide (1.44 g, 12.4 mmol, 1.50 equiv.) and OsO_4 (0.0300 g, 0.160 mmol, 0.0200 equiv.). When the starting material had been consumed (24 h) as monitored by TLC, [bis(acetoxy)iodo]benzene (3.97 g, 12.4 mmol, 1.50 equiv.) was added. After stirring for 2 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (400 mL), the mixture extracted with EtOAc (3× 100 mL), washed with saturated aqueous $CuSO_4$ solution, dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography (5% to 8% EtOAc/hexanes) to afford **31** as yellow oil (2.86 g, 82%). TLC: R_f = 0.3 (10% EtOAc/hexanes). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.52 (dd, J = 3.2, 1.6 Hz, 1 H), 6.42 (m, 2 H), 6.35 (t, J = 2.2 Hz, 1 H), 4.91 (m, 1 H), 3.93 (m, 1 H), 3.76 (s, 6 H) 3.51 (s, 2 H), 1.60 (m, 4 H), 1.21 (d, J = 6.3 Hz, 3 H), 0.90 (s, 9 H), 0.06 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.5, 170.8, 160.8, 136.2, 107.2, 99.1, 71.0, 70.7, 55.2, 41.9, 30.9, 30.7, 28.3, 28.0, 25.6, 19.8, 19.8, 18.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2951, 2927, 2859, 1734, 1601, 1468, 1430, 1293, 1255, 1205, 1160, 1068, 836, 776 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{36}O_6Si$ [M$^+$] 424.2281; found 424.2294.

***tert*-Butyl (7*R*,*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-7-[2-(3,5-dimethoxyphenyl)acetoxy]oct-2-enoate (32):** To a flame-dried round-bottomed flask with a solution of **31** (2.85 g, 6.71 mmol, 1.00 equiv.) in CH_2Cl_2 (135 mL) under argon, was added (*tert*-butoxycarbonylmethylene)triphenylphosphorane (7.56 g, 20.1 mmol, 3.00 equiv.). The mixture was stirred at room temp. overnight. The solution was concentrated, and the residue was purified by flash column

chromatography (25% EtOAc/hexanes) to afford **32** as a light yellow oil (3.48 g, 62%). TLC: R_f = 0.7 (15% EtOAc/hexanes). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.42 (m, 2 H), 6.35 (m, 1 H), 5.83 (m, 1 H), 4.89 (m, 1 H), 4.25 (m, 1 H), 3.76 (m, 6 H), 3.50 (s, 2 H), 1.48 (m, 11 H), 1.57 (m, 3 H), 1.19 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.02 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 165.8, 160.8, 149.0, 136.2, 121.9, 107.2, 99.2, 80.2, 71.3, 71.1, 70.9, 55.2, 41.9, 32.9, 32.7, 31.0, 30.8, 28.1, 25.7, 19.9, 19.8, 18.1, –4.5, –4.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3429, 2951, 2901, 2859, 2255, 1723, 1658, 1601, 1464, 1430, 1369, 1300, 1251, 1205, 1152, 1068, 970, 913, 833, 776, 734 cm^{-1}. HRMS (EI): calcd. for $C_{28}H_{46}O_7Si$ [M$^+$] 522.3013; found 522.3008.

***tert*-Butyl (*R*,*E*)-7-[2-(3,5-Dimethoxyphenyl)acetoxy]-4-oxooct-2-enoate (33):** To a flame-dried round-bottomed flask with a solution of **32** (2.00 g, 3.82 mmol, 1.00 equiv.) in anhydrous THF (20 mL) under argon at 0 °C was added TBAF (1.0 M in THF, 7.60 mL, 2.00 equiv.). The reaction mixture was warmed to room temp. and stirred until consumption of the starting material according to TLC analysis. The reaction was quenched with water (200 mL) and the mixture extracted with EtOAc (3× 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the volatiles were removed in vacuo to provide the crude alcohol, which was carried further without purification. A solution of the corresponding alcohol (0.700 g, 1.71 mmol, 1.00 equiv.) in CH_2Cl_2 (86.0 mL) at 0 °C was treated with Dess–Martin periodinane (1.45 g, 3.42 mmol, 2.00 equiv.). The reaction mixture was warmed to room temp. and stirred for 2 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (100 mL) and the mixture extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were washed with a saturated aqueous $Na_2S_2O_3$, dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure to afford the crude product. Purification of the crude product by flash column chromatography (20% EtOAc/hexanes) afforded **33** as yellow oil (0.54 g, 51% over two steps from **32**). TLC: R_f = 0.1 (15% EtOAc/hexanes). $[\alpha]_D^{22}$ = –9.6 (c = 0.033, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.86 (d, J = 15.9 Hz, 1 H), 6.50 (d, J = 16.1 Hz, 1 H), 6.42 (d, J = 2.3 Hz, 2 H), 6.36 (t, J = 2.3 Hz, 1 H), 4.91 (m, 1 H), 3.76 (s, 6 H), 3.50 (s, 2 H), 2.53 (m, 2 H), 1.86 (m, 2 H), 1.50 (s, 9 H), 1.23 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.6, 170.7, 164.4, 160.7, 138.1, 132.6, 107.0, 99.0, 81.7, 70.3, 55.1, 41.8, 36.6, 29.3, 27.8, 19.9 ppm. IR (neat): $\tilde{\nu}$ = 2981, 2939, 2840, 2255, 1723, 1601, 1471, 1430, 1365, 1304, 1255, 1156, 1065, 977, 909, 844, 730, 650 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{30}O_7$ [M$^+$] 406.1992; found 406.2001.

***tert*-Butyl (*R*)-7-[2-(3,5-Dimethoxyphenyl)acetoxy]-4-oxooctanoate (34):** To a solution of **33** (0.400 g, 0.908 mmol, 1.00 equiv.) in MeOH (20.0 mL) at room temp. was added Pd/C (40.0 mg). The mixture was then subjected to H_2 (1 atm) and stirred at room temp. until consumption of the starting material according to TLC analysis. The catalyst was filtered off through Celite, and the filtrate was concentrated to leave a crude residue. The residue was purified by flash column chromatography (30% EtOAc/hexanes) to afford **34** as a light yellow oil (0.270 g, 68%). TLC: R_f = 0.2 (15% EtOAc/hexanes). $[\alpha]_D^{22}$ = –5.1 (c = 0.016, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.41 (d, J = 2.2 Hz, 2 H), 6.34 (t, J = 2.2 Hz, 1 H), 4.87 (m, 1 H), 3.75 (s, 6 H), 3.48 (s, 2 H), 2.55 (m, 2 H), 2.40 (m, 4 H), 1.80 (m, 2 H), 1.40 (s, 9 H), 1.19 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.8, 171.8, 170.8, 160.7, 136.2, 107.1, 99.1, 80.4, 70.6, 55.2, 41.9, 38.2, 37.0, 29.5, 29.0, 27.9, 19.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2976, 2937, 2842, 2256, 1722, 1601, 1463, 1430, 1365, 1293, 1251, 1205, 1156, 1064, 916, 845, 733 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{32}O_7$ [M$^+$] 408.2158; found 408.2161.

(*R*)-7-[2-(3,5-Dimethoxyphenyl)acetoxy]-4-oxooctanoic Acid (35): To a solution of **34** (0.130 g, 0.310 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (7.00 mL) under argon at 0 °C were added 2,6-lutidine (0.0780 mL, 0.660 mmol, 2.10 equiv.) and TMSOTf (0.130 mL, 0.710 mmol, 2.25 equiv.) sequentially. The mixture was warmed to room temp. and stirred until consumption of the starting material according to TLC analysis. H_2O (100 mL) was added to the mixture, and the aqueous phase was acidified and extracted with CH_2Cl_2 (3× 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (50% EtOAc/hexanes) to afford **35** as a yellow viscous oil (0.0890 g, 79%). TLC: R_f = 0.3 (60% EtOAc/hexanes). $[\alpha]_D^{22}$ = –8.5 (c = 0.03, CH_2Cl_2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.42 (d, J = 2.2 Hz, 2 H), 6.36 (t, J = 2.2 Hz, 1 H), 4.89 (m, 1 H), 3.76 (s, 6 H), 3.50 (s, 2 H), 2.59 (m, 4 H), 2.36 (m, 2 H), 1.81 (m, 2 H), 1.21 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.5, 177.9, 170.9, 160.8, 136.2, 107.2, 99.1, 70.6, 55.2, 41.9, 38.1, 36.6, 29.5, 27.6, 19.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2939, 2840, 2251, 1719, 1597, 1460, 1433, 1293, 1205, 1166, 1065, 905, 730,647 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{24}O_7$ [M$^+$] 352.1522; found 352.1525.

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[1] a) T. S. Bugni, C. M. Ireland, *Nat. Prod. Rep.* **2004**, *21*, 143; b) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2012**, *75*, 311.
[2] R.-A. Edrada, M. Heubes, G. Brauers, V. Wray, A. Berg, U. Graefe, M. Wohlfarth, J. Muehlbacher, K. Schaumann, Sudarsono, G. Bringmann, P. Proksch, *J. Nat. Prod.* **2002**, *65*, 1598.
[3] a) O. C. Musgrave, *J. Chem. Soc.* **1956**, 4301; b) O. C. Musgrave, *J. Chem. Soc.* **1957**, 1104; c) A. J. Birch, O. C. Musgrave, R. W. Richards, H. Smith, *J. Chem. Soc.* **1959**, 3146.
[4] S. Lai, Y. Shizuri, S. Yamamura, K. Kawai, Y. Terada, H. Furukawa, *Tetrahedron Lett.* **1989**, *30*, 2241.
[5] a) K. Kinoshita, T. Sasaki, M. Awata, M. Takada, S. Yaginuma, *J. Antibiot.* **1997**, *50*, 961; b) J. He, E. M. K. Wijeratne, B. P. Bashyal, J. Zhan, C. J. Seliga, M. X. Liu, E. E. Pierson, L. S. Pierson III, H. D. VanEtten, A. L. L. Gunatilaka, *J. Nat. Prod.* **2004**, *67*, 1985.
[6] For syntheses of xestodecalactone A, see: a) G. Bringmann, G. Lang, M. Michel, M. Heubes, *Tetrahedron Lett.* **2004**, *45*, 2829; b) T. Yoshino, F. Ng, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 14185.
[7] For syntheses of both xestodecalactones B and C, see: a) Q. Liang, J. Zhang, W. Quan, Y. Sun, X. She, X. Pan, *J. Org. Chem.* **2007**, *72*, 2694; b) R. Pal, H. Rahaman, M. K. Gurjar, *Curr. Org. Chem.* **2012**, *16*, 1159.
[8] For syntheses of xestodecalactone C, see: a) J. S. Yadav, N. Thrimurtulu, K. U. Gayathri, B. V. S. Reddy, A. R. Prasad, *Tetrahedron Lett.* **2008**, *49*, 6617; b) K. Rajesh, V. Suresh, J. J. P. Selvam, C. Bhujanga Rao, Y. Venkateswarlu, *Helv. Chim. Acta* **2009**, *92*, 1866; c) J. S. Yadav, Y. G. Rao, K. Ravindar, B. V. S. Reddy, A. V. Narsaiah, *Synthesis* **2009**, 3157.
[9] J. S. Yadav, N. Thrimurtulu, K. U. Gayathri, B. V. S. Reddy, A. R. Prasad, *Synlett* **2009**, 790.
[10] For previous total syntheses of curvularin, see: a) H. Gerlach, *Helv. Chim. Acta* **1977**, *60*, 3039; b) F. Bracher, B. Schulte, *Nat. Prod. Lett.* **1995**, *7*, 65; c) F. Bracher, B. Schulte, *Liebigs Ann./Recueil* **1997**, 1979; d) S. Elzner, D. Schmidt, D. Schollmeyer, G. Erkel, T. Anke, H. Kleinert, U. Foerstermann, H. Kunz, *ChemMedChem* **2008**, *3*, 924; e) D. K. Mohapatra, H. Rahaman, R. Pal, M. K. Gurjar, *Synlett* **2008**, 1801; f) P. M. Tadross, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2010**, *12*, 1612.

[11] For the previous syntheses of both 12-oxocurvularin and citreofuran, see: S. Lai, X. Gao, Y. Shizuri, S. Yamamura, *Chin. Chem. Lett.* **1994**, *5*, 481.
[12] For the synthesis of racemic di-*O*-methyl-12-oxocurvularin, see: R. A. Kasar, R. A. Khan, V. H. Deshpande, N. R. Ayyangar, *Tetrahedron Lett.* **1991**, *32*, 1599.
[13] F. Bracher, B. Schulte, *Nat. Prod. Res.* **2003**, *17*, 293.
[14] A. Fürstner, A.-S. Castanet, K. Radkowski, C. W. Lehmann, *J. Org. Chem.* **2003**, *68*, 1521.
[15] For an excellent review on Pd-catalyzed α-arylation via enolates, see: D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234 and references cited therein.
[16] C. Carfagna, A. Musco, G. Sallese, R. Santi, T. Fiorani, *J. Org. Chem.* **1991**, *56*, 261.
[17] a) L. J. Gooßen, *Chem. Commun.* **2001**, 669; b) M. Sato, N. Miyaura, A. Suzuki, *Chem. Lett.* **1989**, 1405; c) G. A. Molander, K. M. Traister, *Org. Lett.* **2013**, *15*, 5052; d) G. A. Molander, K. M. Traister, T. Barcellos, *J. Org. Chem.* **2013**, *78*, 4123; e) B. Zimmermann, W. I. Dzik, T. Himmler, L. J. Gooßen, *J. Org. Chem.* **2011**, *76*, 8107.
[18] U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401.
[19] a) For a recent review, see: G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746; b) A. K. Chatterjee, T. L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360.
[20] L. Song, H. Yao, L. Zhu, R. Tong, *Org. Lett.* **2013**, *15*, 6.
[21] For the synthesis of α-bromo esters **19** and **20**, see ref.[24]
[22] A. N. Cammidge, A. S. H. King, *Tetrahedron Lett.* **2006**, *47*, 5569.
[23] T.-C. Chou, H. Dong, A. Rivkin, F. Yoshimura, A. E. Gabarda, Y. S. Cho, W. P. Tong, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2003**, *42*, 4762; *Angew. Chem.* **2003**, *115*, 4910.
[24] D. De Joarder, M. P. Jennings, *Tetrahedron Lett.* **2013**, *54*, 3990.
[25] K. C. Nicolaou, V. A. Adsool, C. R. Hale, *Org. Lett.* **2010**, *12*, 1552.
[26] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.

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