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Enantioselective Synthesis of the Strigolactone Mimic (+)-GR24

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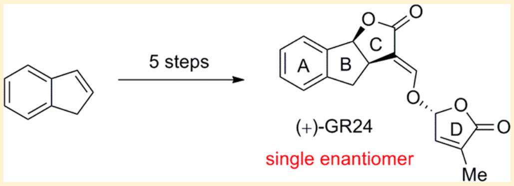
Supporting Information

ABSTRACT: A short and cost-effective synthesis of the important strigolactone analogue (+)-GR24 is described. Central to this new approach is the concise, enantioselective synthesis of the A−C ring system.



Strigolactones are a family of plant signaling molecules at the center of intense applied research.[1−4] These molecules mediate vital biological functions in plants, including seed-germination, inhibition of shoot-branching,[5] and root-colonization by symbiotic arbuscular mycorrhizal fungi, which enable soil−plant nutrient transfer.[6] The agrichemical potential of strigolactones is vast. The parent member of the class, strigol (**1**) (Figure 1), was isolated from cotton roots in 1966, and since that time a further 17 strigolactones have been isolated.[7] Frustratingly, these root exudates occur in extremely low natural abundance curtailing assessment of their biological functions and, in many instances, preventing unambiguous stereochemical assignment of their structures.[4] For this reason, simplified strigolactones have been the target of much synthetic effort. The most widely applicable of the synthetic analogues, (±)-GR24 (**2**) (Figure 1), was developed by Johnson and co-workers and is routinely used as a positive control in plant- and fungi-based assays.[8]

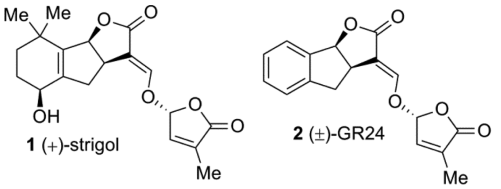
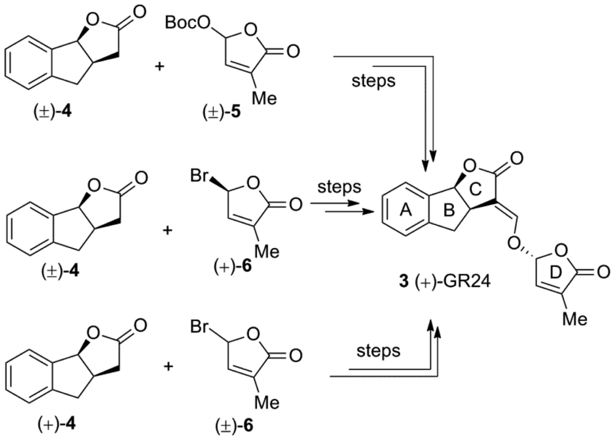


Figure 1. Strigol (**1**) and synthetic analogue GR24.

Since the initial report, the synthesis of (±)-GR24 (**2**) has been steadily improved upon, most notably by Zwanenburg and co-workers.[9,10] Indeed it was Zwanenburg who identified that the most active component of the racemate for seed germination in the parasitic weeds *Striga hermonthica* and *Orobanche crenata* possessed the same stereochemistry as naturally occurring strigol (**1**) (Figure 1).[11] Commercial (±)-GR24 (**2**) is routinely subjected to a time-consuming enantioselective HPLC separation prior to biological application.[12] Therefore the asymmetric synthesis of (+)-GR24 (**3**) is an important goal. As depicted in Scheme 1, published approaches fall into one of three categories: coupling two racemic fragments (±)-**4** and (±)-**5** with an enantioselective catalyst;[13] coupling of racemic A−C fragment (±)-**4** with an enantiomerically pure D ring (+)-**6**;[14] or coupling of an enantiomerically pure A−C fragment (+)-**4** to racemic D-ring (±)-**6**.[14,15] Zwanenburg and co-workers utilized a palladium coupling to unite (±)-**4** and (±)-**5** using Trost's ligand.[13] While the ee of the product was excellent, an almost 1:1 mixture of diastereomers was produced. Synthesis of enantiomerically pure D-ring (+)-**6** is laborious. The most attractive strategy therefore involves the enantiomerically pure A−C fragment (+)-**4**.

Scheme 1. Strategies to (+)-GR24 (3)



Zwanenburg reported that microcrystalline cellulose triacetate (CTA) was effective for the chromatographic resolution to give (+)-**4** and (−)-**4** (Scheme 2),[14] but the yield of such resolutions are limited to 50%. Given the importance of (+)-GR24 (**3**) over the past thirty years and its widespread application across the plant sciences, it is surprising to find that an enantioselective synthesis of the A−C fragment (+)-**4** was not reported until 2012.[15] Utilizing (2*R*,5*R*)-2,5-dimethylpyrrolidine as a chiral auxiliary to dictate the stereochemical course of an intramolecular [2 + 2] ketene-iminium cyclization, researchers from Syngenta Crop Protection were able to

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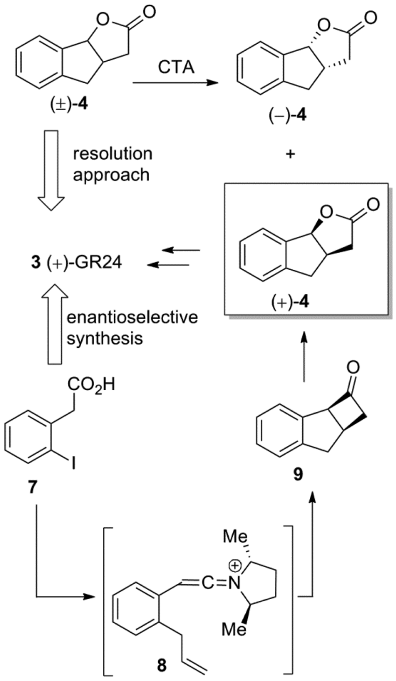
Scheme 2. Previous Enantioselective Synthesis of (+)-GR24 (3)

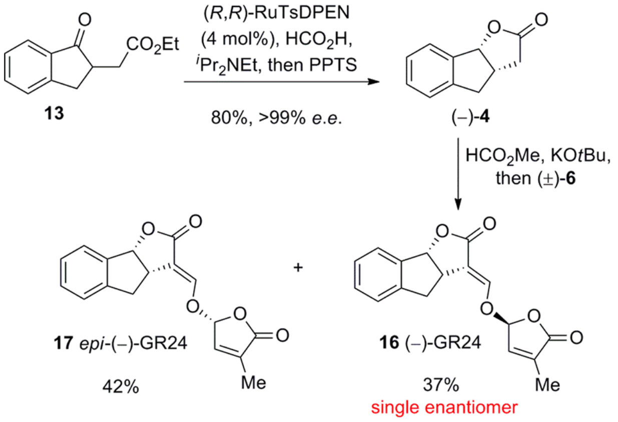


generate the desired isomer in 8 steps and 92% ee. (Scheme 2). It is clear that if (+)-GR24 (**3**) were to be used on a large scale, a more practical synthesis would need to be developed. We now detail a rapid, scalable, and enantioselective synthesis of (+)-GR24 (**3**).

As strigolactones have recently demonstrated promise in medicinal settings,[16] we anticipated that access to both enantiomers of GR24 may be beneficial for future SAR investigations and that any route that we developed ought to be flexible enough to allow the generation of substituted analogues. As such we elected to employ a dynamic kinetic resolution (DKR) as the enantioselective step in our strategy.[17] As shown in Scheme 3, readily available and inexpensive indene (**10**) was subjected to ozonolytic cleavage, and the corresponding dialdehyde engaged in a chemoselective Wittig olefination to give the product in 56% overall yield (based on the phosphorane).[18−21] In this way **11** could be accessed in >2.5 g batches. The aldehyde **11** readily participated in an intramolecular Stetter reaction to give the indanone **13** in good yield. Although asymmetric variants of the intramolecular Stetter reaction are known,[22,23] we were concerned that the lability of the hydrogen appended to C2 of the indanone **13** may diminish the level of enantiocontrol by facile epimerization. Rather than tempering the reactivity at that position, we elected to embrace it to facilitate a DKR. Treatment of **13** with Noyori's (*S*,*S*)-RuTsDPEN catalyst under transfer hydrogenation conditions delivered the bicyclic ketone (+)-**4** in 90% yield and 92% ee, which was improved to >99% ee after a single recrystallization (see Supporting Information). The lactone was formylated, and the D-ring (±)-**6** was appended to deliver (+)-GR24 (**3**) and *epi*-(+)-GR24 (**15**).

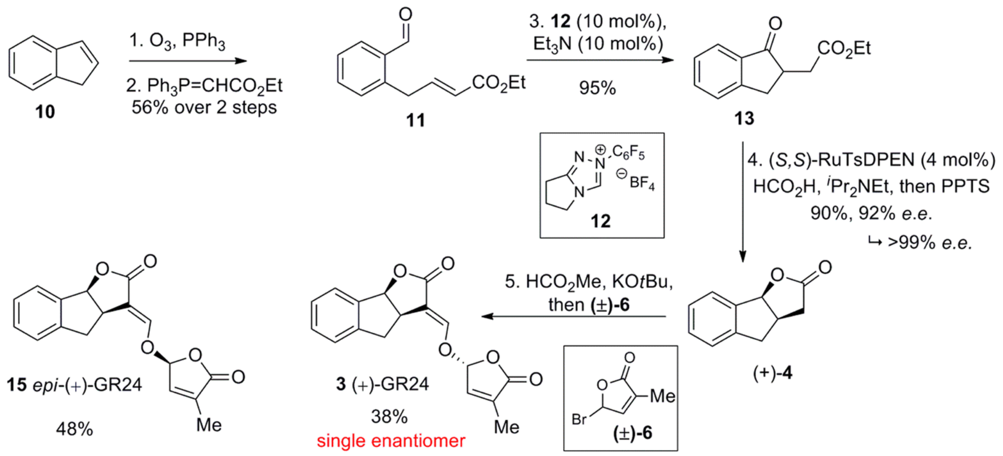
As depicted in Scheme 4, the corresponding (*R*,*R*)-RuTsDPEN catalyst was employed with equal facility to deliver lactone (−)-**4**,[24] which was elaborated to (−)-GR24 (**16**) and *epi*-(−)-GR24 (**17**) by the same sequence of reactions.

Scheme 4. Enantioselective Synthesis of (−)-GR24 (17)

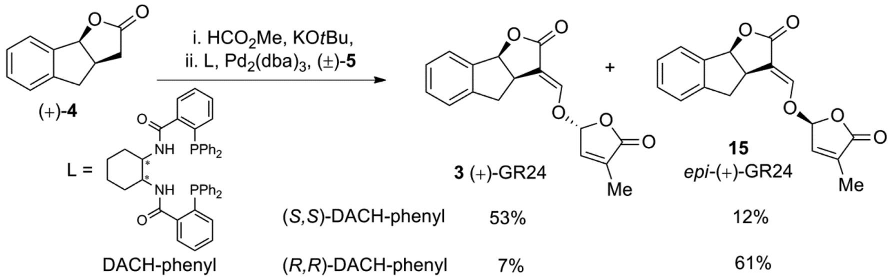


Finally, we united the enantiomerically pure A−C fragment (+)-**4** with the D-ring (±)-**5** using Trost's stereoselective palladium coupling protocol employing both enantiomers of the DACH-phenyl ligand.[13,25,26] As shown in Scheme 5, there was a clear matched, mismatched scenario in which the level of diastereoselectivity was greater for the formation of *epi*-(+)-GR24 (**15**). The same trend was observed when (−)-**4** was employed for the coupling. However, as both reactions

Scheme 3. Enantioselective Synthesis of (+)-GR24 (3)



Scheme 5. Enantioselective Synthesis of (−)-GR24 (17)



returned a diastereomeric mixture, this protocol offers little advantage over the method outlined in Schemes 3 and 4.

In conclusion, we report a short, scalable, enantioselective synthesis of the synthetic strigolactone (+)-GR24 (**3**). By utilizing a Noyori asymmetric reduction for a DKR, the generation of either enantiomer of the A−C fragment (+)-**4** or (−)-**4** can be achieved in just 4 synthetic operations. The D-ring (±)-**5** can be appended under classical or catalytic conditions to deliver enantiomerically pure (+)-GR24 (**3**). Any other isomer of this important plant-signaling mimic can be generated using a common synthetic sequence. The resolution bottleneck has been circumvented, and the routine application of single enantiomer (+)-GR24 (**3**) as a positive control across the plant sciences is now possible.

■ EXPERIMENTAL SECTION

High resolution mass spectra were recorded on a Fourier transform ion cyclotron resonance mass spectrometer with a 7.0 T magnet, fitted with an off-axis electrospray source. The enantiopurity of compounds was determined by chiral HPLC analysis using an AD-H or OD-H column, and a dual λ absorbance detector (254 and 270 nm).

(*E*)-Ethyl 4-(2-formylphenyl)but-2-enoate (11). Indene (5.08 g, 43.7 mmol) was taken up in dichloromethane (70 mL) and treated with ozone at −78 °C for 7 h. Triphenylphosphine (17.2 g, 65.6 mmol) was added, and the solution was stirred overnight. The solvent was removed in vacuo. The residue was taken up in fresh dichloromethane (80 mL), phosphonium ylide (6.94 g, 19.9 mmol) was added, and the solution was stirred overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography, eluting with pure hexanes followed by 10% diethyl ether in hexanes, to give an inseparable 7:1 mixture of **11** and the *bis*-alkene (2.9 g, 72%; **11** 56%) as a pale yellow oil: IR (cm^{-1}) 2983, 1711, 1694, 1651, 1599, 1574, 1368, 1267, 1158, 1037, 983; ^{1}H NMR (300 MHz; CDCl$_3$) 10.08 (1 H, s), 7.76 (1 H, d, *J* 7.5), 7.43 (2 H, m), 7.20 (1 H, d, *J* 7.2), 7.06 (1 H, dt, *J* 15.6, 6.3), 5.64 (1 H, d, *J* 15.6), 4.08 (2 H, q, *J* 6.9), 3.90 (2 H, d, *J* 7.2), 1.18 (3 H, t, *J* 7.2); ^{13}C NMR (75 MHz; CDCl$_3$) 192.5 (CH), 166.3 (C), 146.6 (CH), 139.8 (C), 134.0 (CH), 133.8 (C), 133.7 (CH), 131.5 (CH), 127.5 (CH), 122.7 (CH), 60.3 (CH$_2$), 35.2 (CH$_2$), 14.2 (CH$_3$); HRMS (ESI) Found MNa$^+$ 241.08336, $C_{13}H_{14}O_3$ + Na requires 241.08352. Minor isomer: ^{1}H NMR (300 MHz; CDCl$_3$) 6.28 (1 H, *J* 15.9), 4.19 (2 H, *J* 7.2), 3.58 (2 H, *J* 6.3), 1.26 (3 H, *J* 7.2).

Ethyl 2-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)acetate (13). Triazolium salt **12** (255 mg, 0.70 mmol) was taken up in THF (20 mL), and the solution was bubbled with argon for 15 min. Triethylamine (100 μL, 0.72 mmol) was added, and the solution was bubbled with argon for an additional 5 min. A 7:1 mixture of **11** and the *bis*-alkene (1.52 g; 5.97 mmol of **11**) in THF (20 mL), which had been bubbled with argon for 20 min, was added via cannula, and the solution was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine and dried over anhydrous Na$_2$SO$_4$, and the solvent was removed in vacuo. The residue was purified by column chromatography, eluting with 10% ethyl acetate in hexanes, to give **13** (1.23 g, 95%) as a yellow oil: IR (cm^{-1}) 2983, 1708, 1609, 1466, 1373, 1294, 1279, 1217, 1174, 1029; ^{1}H NMR (300 MHz; CDCl$_3$) 7.77 (1 H, d, *J* 7.5), 7.59 (1 H, m), 7.45 (1 H, d, *J* 7.8), 7.37 (1 H, m), 4.13 (2 H, q, *J* 7.2), 3.45 (1 H, dd, *J* 7.8, 17.1), 3.06−2.85 (3 H, m), 2.62 (1 H, dd, *J* 16.2, 8.1), 1.21 (3 H, t, *J* 7.2); ^{13}C NMR (75 MHz; CDCl$_3$) 206.9 (C), 172.1 (C), 153.4 (C), 136.5 (C), 135.0 (CH), 127.6 (CH), 126.6 (CH), 124.1 (CH), 60.9 (CH$_2$), 43.7 (CH), 35.4 (CH$_2$), 33.1 (CH$_2$), 14.3 (CH$_3$); HRMS (ESI) Found MNa$^+$ 241.08317, $C_{13}H_{14}O_3$ + Na requires 241.08352.

(3a*R*,8b*S*)-3,3a,4,8b-Tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (+)-4. Dichloro(*p*-cymene)ruthenium(II) dimer (84 mg, 0.14 mmol) and (1*S*,2*S*)-(+)-*N*-*p*-tosyl-1,2-diphenylethylenediamine (100 mg, 0.27 mmol) were taken up in isopropanol (7 mL). Triethylamine (77 μL, 0.55 mmol) was added, and the reaction mixture was stirred at 80 °C for 1.5 h. The solvent was removed in vacuo to give (*S*,*S*)-RuTsDPEN, which was used in the following step. Formic acid (1.30 mL) and Hünig's base (2.39 mL) were mixed at 0 °C. After 15 min, a solution of ketone (1.50 g, 6.9 mmol) in dichloromethane (7 mL) was added via cannula, followed by a solution of (*S*,*S*)-RuTsDPEN, prepared above, in dichloromethane (5 mL). The dichloromethane was removed under nitrogen flow, and the solution was stirred overnight at 40 °C. Saturated aqueous sodium hydrogen carbonate was added (15 mL). The aqueous phase was extracted with ethyl acetate (3× 15 mL). The combined organic extracts were then washed with brine and dried over anhydrous Na$_2$SO$_4$, and the solvent was removed in vacuo. The residue was taken up in dichloromethane (10 mL), pyridinium *para*-toluenesulfonate (170 mg) was added, and the reaction mixture was heated at reflux overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography, eluting with 20% ethyl acetate in hexanes, to give (+)-**4** (1.08 g, 90%) as colorless crystals, which were recrystallized from methanol: mp 93 °C; $[\alpha]_D^{20}$ +110 (*c* 0.985, CHCl$_3$), lit.[14] $[\alpha]_D^{20}$ −107.0 (*c* 0.4, CHCl$_3$); IR (cm^{-1}) 2954, 1753, 1610, 1450, 1349, 1250, 1145, 990; ^{1}H NMR (300 MHz; CDCl$_3$); 7.49 (1 H, d, *J* 6.6), 7.38−7.29 (3 H, m), 5.90 (1 H, d, *J* 6.9), 3.41−3.28 (2 H, m), 2.96−2.86 (2 H, m), 2.39 (1 H, dd, *J* 18.3, 5.4); ^{13}C NMR (75 MHz; CDCl$_3$) 176.9 (C), 142.5 (C), 138.8 (C), 130.0 (CH), 127.6 (CH), 126.4 (CH), 125.3 (CH), 87.7 (CH), 37.9 (CH$_2$), 37.3 (CH), 35.7 (CH$_2$); HRMS (ESI) Found MNa$^+$ 197.05728, $C_{11}H_{10}O_2$ + Na requires 197.05730.

(3a*S*,8b*R*)-3,3a,4,8b-Tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (−)-4. Dichloro(*p*-cymene)ruthenium(II) dimer (34 mg, 5.6 × 10^{-5} mol) and (1*R*,2*R*)-(+)-*N*-*p*-tosyl-1,2-diphenylethylenediamine (40 mg, 0.11 mmol) were taken up in isopropanol (3 mL). Triethylamine (31 μL, 0.22 mmol) was added, and the reaction mixture was stirred at 80 °C for 1.5 h. The solvent was removed in vacuo to give (*R*,*R*)-RuTsDPEN, which was used in the following step. Formic acid (0.52 mL) and Hünig's base (0.96 mL) were mixed at 0 °C. After 15 min, a solution of ketone (600 mg, 2.75 mmol) in dichloromethane (5 mL) was added via cannula, followed by a solution of (*R*,*R*)-RuTsDPEN, prepared above, in dichloromethane (5 mL). The dichloromethane was removed under nitrogen flow, and the solution was stirred overnight at 40 °C. Saturated aqueous sodium hydrogen carbonate (10 mL) was added. The aqueous phase was extracted with ethyl acetate (3× 10 mL). The combined organic extracts were then washed with brine and dried over anhydrous

Na_2SO_4, and the solvent was removed in vacuo. The residue was taken up in dichloromethane (10 mL), pyridinium *para*-toluenesulfonate (70 mg) was added, and the reaction mixture was heated at reflux overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography, eluting with 20% ethyl acetate in hexanes, to give (−)-**4** (380 mg, 80%) as colorless crystals, which were recrystallized from methanol: mp 93 °C; $[\alpha]_D^{20}$ −109 (*c* 0.985, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ +102.5 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$); 7.49 (1 H, d, *J* 7.2), 7.38−7.29 (3 H, m), 5.89 (1 H, d, *J* 6.9), 3.43−3.28 (2 H, m), 2.95−2.86 (2 H, m), 2.39 (1 H, dd, *J* 18.0, 5.4); ^{13}C NMR (75 MHz; $CDCl_3$) 176.8 (C), 142.5 (C), 138.8 (C), 130.0 (CH), 127.6 (CH), 126.4 (CH), 125.3 (CH), 87.7 (CH), 37.9 (CH_2), 37.3 (CH), 35.7 (CH_2).

(+)-GR24 (3) and (+)-*epi*-GR24 (15). To a solution of (+)-**4** (650 mg, 3.73 mmol) in methyl formate (20 mL) was added potassium *tert*-butoxide (2.1 g 18.7 mmol), in two portions, under nitrogen flow, at 0 °C. The reaction mixture was stirred overnight. The reaction was quenched with hydrochloric acid (1.0 M, 25 mL), and the aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were then washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The colorless solid residue and potassium carbonate (570 mg, 4.12 mmol) were taken up in DMF (8 mL), and a solution of the (±)-**6** (990 mg, 5.60 mmol), in DMF (5 mL), was added via cannula at 0 °C. The solution was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were then washed with water (2 × 30 mL) and brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography, eluting with 50% ethyl acetate in hexanes, to give (+)-**3** as colorless crystals (418 mg, 38%): mp 151−152 °C, lit.[14] 154−155 °C; $[\alpha]_D^{20}$ +443 (*c* 0.51, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ +436 (*c* 0.25, $CHCl_3$); IR (cm^{-1}) 1781, 1746, 1681, 1344, 1327, 1208, 1181, 1154, 1089, 1044, 1017, 952; ^1H NMR (300 MHz; $CDCl_3$) 7.49 (2 H, m), 7.35−7.22 (3 H, m), 6.97 (1 H, s), 6.19 (1 H, s), 5.93 (1 H, d, *J* 8.1), 3.93 (1 H, m) 3.43 (1 H, dd, *J* 17.1, 9.3), 3.10 (1 H, dd, *J* 16.8, 3.0), 2.02 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) 171.3 (C), 170.3 (C), 151.1 (CH), 142.6 (C), 141.1 (CH), 138.9 (C), 135.9 (C), 130.0 (CH), 127.5 (CH), 126.4 (CH), 125.2 (CH), 113.2 (C), 100.7 (CH), 85.9 (CH), 38.9 (CH), 37.3 (CH_2), 10.7 (CH_3); HRMS (ESI) Found MNa$^+$ 321.07335, $C_{17}H_{14}O_5$ + Na requires 321.07334. (+)-**15** as colorless crystals (529 mg, 48%): mp 131−132 °C, lit.[14] 133.5−134.5 °C; $[\alpha]_D^{20}$ +292 (*c* 0.50, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ +273 (*c* 0.2, $CHCl_3$); IR (cm^{-1}) 1781, 1746, 1680, 1338, 1326, 1208, 1181, 1154, 1086, 1046, 1017, 951; ^1H NMR (300 MHz; $CDCl_3$) 7.49 (2 H, m), 7.36−7.22 (3 H, m), 6.97 (1 H, s), 6.18 (1 H, s), 5.95 (1 H, d, *J* 8.1), 3.94 (1 H, m) 3.42 (1 H, dd, *J* 16.8, 9.3), 3.09 (1 H, dd, *J* 17.0, 3.0), 2.03 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) 171.3 (C), 170.3 (C), 151.1 (CH), 142.6 (C), 141.1 (CH), 138.8 (C), 135.9 (C), 130.0 (CH), 127.5 (CH), 126.4 (CH), 125.2 (CH), 113.4 (C), 100.7 (CH), 85.9 (CH), 38.8 (CH), 37.4 (CH_2), 10.7 (CH_3); HRMS (ESI) Found MNa$^+$ 321.07326, $C_{17}H_{14}O_5$ + Na requires 321.07334.

(−)-GR24 (16) and (−)-*epi*-GR24 (17). To a solution of (−)-**4** (140 mg, 0.80 mmol) in methyl formate (7 mL) was added potassium *tert*-butoxide (450 mg, 4.0 mmol) under nitrogen flow, at 0 °C. The reaction mixture was stirred overnight. The reaction was quenched with hydrochloric acid (1 M, 10 mL), and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were then washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The colorless solid residue and potassium carbonate (122 mg, 0.88 mmol) were taken up in DMF (3 mL), and a solution of (±)-**6** (213 mg, 1.2 mmol), in DMF (2 mL), was added via cannula at 0 °C. The solution was stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were then washed with water (2 × 20 mL) and brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography, eluting with 50% ethyl acetate in hexanes. Recrystallization with ethyl acetate and hexanes gave (−)-**16** as colorless crystals (89 mg, 37%): mp 150−151 °C, lit.[14] 152.5−154.5 °C; lit.[14] $[\alpha]_D^{20}$ −451 (*c* 0.52, $CHCl_3$), $[\alpha]_D^{20}$ −446 (*c* 0.25, $CHCl_3$); IR (cm^{-1}) 1780, 1746, 1681, 1349, 1327, 1209, 1182, 1159, 1090, 1046, 1017, 952; ^1H NMR (300 MHz; $CDCl_3$) 7.50 (2 H, m), 7.36−7.22 (3 H, m), 6.97 (1 H, s), 6.18 (1 H, s), 5.95 (1 H, d, *J* 7.8), 3.94 (1 H, m) 3.44 (1 H, dd, *J* 16.8, 9.3), 3.10 (1 H, dd, *J* 17.0, 3.0), 2.04 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) 171.2 (C), 170.2 (C), 151.0 (CH), 142.6 (C), 140.9 (CH), 138.9 (C), 136.0 (C), 130.0 (CH), 127.5 (CH), 126.5 (CH), 125.1 (CH), 113.3 (C), 100.6 (CH), 85.9 (CH), 38.9 (CH), 37.3 (CH_2), 10.7 (CH_3); HRMS (ESI) Found MNa$^+$ 321.07341, $C_{17}H_{14}O_5$ + Na requires 321.07334. (−)-**17** as colorless crystals (100 mg, 42%): mp 130−131 °C, lit.[14] 133.5−134 °C; $[\alpha]_D^{20}$ −285 (*c* 0.5, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ −272 (*c* 0.2, $CHCl_3$); IR (cm^{-1}) 1783, 1747, 1681, 1347, 1327, 1208, 1182, 1153, 1089, 1045, 1019, 952; ^1H NMR (300 MHz; $CDCl_3$) 7.49 (2 H, m), 7.36−7.22 (3 H, m), 6.97 (1 H, s), 6.19 (1 H, s), 5.95 (1 H, d, *J* 8.1), 3.93 (1 H, m) 3.42 (1 H, dd, *J* 17.1, 9.3), 3.09 (1 H, dd, *J* 16.8, 3.0), 2.03 (3 H, s); ^{13}C NMR (75 MHz; $CDCl_3$) 171.3 (C), 170.3 (C), 151.1 (CH), 142.7 (C), 141.1 (CH), 138.8 (C), 135.8 (C), 130.0 (CH), 127.5 (CH), 126.4 (CH), 125.3 (CH), 113.4 (C), 100.7 (CH), 85.9 (CH), 38.8 (CH), 37.4 (CH_2), 10.7 (CH_3); HRMS (ESI) Found MNa$^+$ 321.07336, $C_{17}H_{14}O_5$ + Na requires 321.07334.

(+)-GR24 (3) and (+)-*epi*-GR24 (15) via an Asymmetric *O*-Alkylation Procedure.[13] To a solution of (+)-**4** (110 mg, 0.63 mmol) in methyl formate (7 mL) was added potassium *tert*-butoxide (360 mg 3.20 mmol) at 0 °C. The reaction mixture was stirred overnight. The reaction was quenched with hydrochloric acid (1.0 M; 10 mL), and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were then washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography, eluting with 30% ethyl acetate in hexanes, to give the desired enol (118 mg 92%) as a colorless solid: mp 126−127 °C; $[\alpha]_D^{20}$ +439 (*c* 0.5, MeOH); IR (neat)/cm^{-1} 3027 (br), 2739, 1706, 1622, 1605, 1481, 1460, 1412, 1381, 1343, 1330, 1200, 1154, 1080; ^1H NMR (300 MHz; DMSO-d_6) 11.24 (1 H, br), 7.51 (1 H, d, *J* 2.1), 7.45 (1 H, d, *J* 7.2), 7.31 (3 H, m), 5.91 (1 H, d, *J* 7.8), 3.90 (1 H, m), 3.36 (1 H, dd, *J* 9.0, 17.0), 3.03 (1 H, dd, *J* 2.4, 17.0); ^{13}C NMR (75 MHz; DMSO-d_6) 172.1 (C), 154.0 (CH), 143.0 (C), 139.8 (C), 129.5 (CH), 127.0 (CH), 126.0 (CH), 125.3 (CH), 105.9 (C), 84.4 (CH), 38.1 (CH), 37.0 (CH_2); *m*/*z* (ESI) 203 (MH$^+$, 100%), 220 ($[M + H_2O]^+$, 58). A solution of (±)-**5** (106 mg, 0.49 mmol), tris(dibenzylideneacetone) dipalladium(0) (6.8 mg, 7.4 × 10^{-6} mol) and either (*S*,*S*) or (*R*,*R*)-DACH-phenyl-Trost ligand (16.2 mg, 2.2 × 10^{-5} mol) in dichloromethane (1 mL) was degassed, and the solution was stirred for 20 min. Triethylamine (35 μL, 0.25 mmol) and the synthesized enol (50 mg, 0.25 mmol) were added, and the reaction mixture was stirred for 1 h. The mixture was purified directly by column chromatography, eluting with 40% ethyl acetate in hexanes, to give (+)-GR24 (**3**) (39 mg, 53% with (*S*,*S*) ligand; 5 mg, 7% with (*R*,*R*) ligand) and (+)-*epi*-GR24 (**15**) (9 mg, 12% with (*S*,*S*) ligand; 45 mg, 61% with (*R*,*R*) ligand).

(−)-GR24 (16) and (−)-*epi*-GR24 (17) via an Asymmetric *O*-Alkylation Procedure.[13] To a solution of (−)-**4** (247 mg, 1.42 mmol) in methyl formate (12 mL) was added potassium *tert*-butoxide (955 mg 8.51 mmol), at 0 °C. The reaction mixture was stirred overnight. The reaction was quenched with hydrochloric acid (1.0 M; 20 mL), and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were then washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography, eluting with 30% ethyl acetate in hexanes, to give the desired enol (266 mg, 93%) as a colorless solid: mp 129−131 °C; $[\alpha]_D^{20}$ − 479 (*c* 0.5, MeOH); IR (neat)/cm^{-1} 3027 (br), 2738, 1700, 1671, 1605, 1480, 1460, 1440, 1409, 1381, 1343, 1330, 1266, 1241, 1205, 1189, 1153, 1083; ^1H NMR (300 MHz; DMSO-d_6) 11.24 (1 H, br), 7.51 (1 H, d, *J* 2.1), 7.45 (1 H, d, *J* 7.2), 7.31 (3 H, m), 5.91 (1 H, d, *J* 7.8), 3.90 (1 H, m), 3.36 (1 H, dd, *J* 9.0, 17.0), 3.03 (1 H, dd, *J* 2.4, 17.0); ^{13}C NMR (75 MHz; DMSO-d_6) 172.1 (C), 153.9 (CH), 143.0 (C), 139.8 (C), 129.5 (CH), 127.0 (CH), 126.0 (CH), 125.3 (CH), 105.9 (C), 84.4

(CH), 38.1 (CH), 37.0 (CH_2); *m/z* (ESI) 203 (MH^+, 100%), 220 ($[M + H_2O]^+$, 75). A solution of (±)-**5** (106 mg, 0.49 mmol), tris(dibenzylideneacetone) dipalladium(0) (6.8 mg, 7.4×10^{-6} mol) and either (*S*,*S*) or (*R*,*R*)-DACH-phenyl-Trost ligand (16.2 mg, 2.2×10^{-5} mol) in dichloromethane (1 mL) was degassed, and the solution was stirred for 20 min. Triethylamine (35 μL, 0.25 mmol) and the synthesized enol (50 mg, 0.25 mmol) were added, and the reaction mixture was stirred for 1 h. The mixture was purified directly by column chromatography, eluting with 40% ethyl acetate in hexanes, to give (−)-GR24 (**16**) (5 mg, 7% with (*S*,*S*) ligand; 40 mg, 54% with (*R*,*R*) ligand) and (−)-*epi*-GR24 (**17**) (46 mg, 62% with (*S*,*S*) ligand; 9 mg, 12% with (*R*,*R*) ligand).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra, HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Xie, X. N.; Yoneyama, K.; Yoneyama, K. *Annu. Rev. Phytopathol.* **2010**, *48*, 93.

(2) Yoneyama, K.; Xie, X.; Yoneyama, K.; Takeuchi, Y. *Pest Manage. Sci.* **2009**, *65*, 467.

(3) Vurro, M.; Yoneyama, K. *Pest Manage. Sci.* **2012**, *68*, 664.

(4) Zwanenburg, B.; Pospisil, T. *Mol. Plant* **2013**, *6*, 38.

(5) Umehara, M.; Hanada, A.; Yoshida, S.; Akiyama, K.; Arite, T.; Takeda-Kamiya, N.; Magome, H.; Kamiya, Y.; Shirasu, K.; Yoneyama, K.; Kyozuka, J.; Yamaguchi, S. *Nature* **2008**, *455*, 195.

(6) Yoneyama, K.; Xie, X. N.; Sekimoto, H.; Takeuchi, Y.; Ogasawara, S.; Akiyama, K.; Hayashi, H.; Yoneyama, K. *New Phytol.* **2008**, *179*, 484.

(7) Cook, C. E.; Whichard, L. P.; Turner, B.; Wall, M. E. *Science* **1966**, *154*, 1189.

(8) Johnson, A. W.; Gowda, G.; Hassanali, A.; Knox, J.; Monaco, S.; Razavi, Z.; Rosebery, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1734.

(9) Malik, H.; Rutjes, F.; Zwanenburg, B. *Tetrahedron* **2010**, *66*, 7198.

(10) Mangnus, E. M.; Dommerholt, F. J.; Dejong, R. L. P.; Zwanenburg, B. *J. Agric. Food Chem.* **1992**, *40*, 1230.

(11) Thuring, J.; Nefkens, G. H. L.; Zwanenburg, B. *J. Agric. Food Chem.* **1997**, *45*, 1409.

(12) While there are several commercial sources of (±)-GR24, the single enantiomers are not commercially available.

(13) Reizelman, A.; Zwanenburg, B. *Eur. J. Org. Chem.* **2002**, 810.

(14) Thuring, J. W. J. F.; Nefkens, G. H. L.; Zwanenburg, B. *J. Agric. Food Chem.* **1997**, *45*, 2278.

(15) Lachia, M.; Jung, P. M. J.; De Mesmaeker, A. *Tetrahedron Lett.* **2012**, *53*, 4514.

(16) Pollock, C. B.; Koltai, H.; Kapulnik, Y.; Prandi, C.; Yarden, R. I. *Breast Cancer Res. Treat.* **2012**, *134*, 1041.

(17) Faber, K. *Chem.—Eur. J.* **2001**, *7*, 5004.

(18) Garratt, P. J.; Vollhardt, K. P. C. *Synthesis* **1971**, 423.

(19) Maciver, E. E.; Knipe, P. C.; Cridland, A. P.; Thompson, A. L.; Smith, M. D. *Chem. Sci.* **2012**, *3*, 537.

(20) Schnatter, W. F. K.; Almarsson, Ö.; Bruice, T. C. *Tetrahedron* **1991**, *47*, 8687.

(21) The level of chemoselectivity for this Wittig reaction displayed an inverse temperature effect that we do not yet understand. At room temperature **11** was the sole product, whereas at lower temperature, mixtures of **11** and the corresponding diester were obtained in ratios ranging from 5:1−1:4.

(22) de Alaniz, J. R.; Rovis, T. *Synlett* **2009**, 1189.

(23) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(24) The measured values of optical rotation for compounds(+)-**4** and (−)-**4** were of opposite sign to that reported in ref 14. Since all other compounds were in excellent agreement with the values reported in ref 13 and ref 14, and since compound (+)-**4** was unambiguously transformed into (+)-GR24 and (−)-**4** was transformed into (−)-GR24, we attribute this minor inconsistency to a typographical error. See the Supporting Information.

(25) Trost, B. M.; Vanvranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(26) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.