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Grubbs Cross-Metathesis Pathway for a Scalable Synthesis of γ-Keto-α,β-unsaturated Esters

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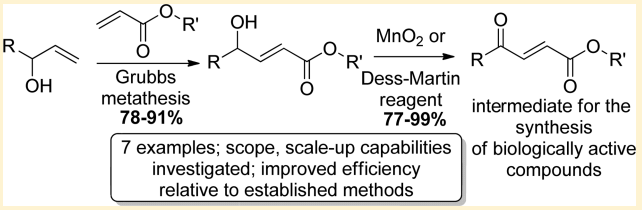
Supporting Information

ABSTRACT: A direct and scalable route to γ-keto-α,β-unsaturated esters, useful intermediates in medicinal chemistry and natural products synthesis, is reported. The key step involves the use of Grubbs' second-generation olefin metathesis catalyst for cross-metathesis of alkyl acrylates and 2° allylic alcohols. The metathesis step is followed by oxidation to give the desired products in high yield on scales of up to 25 g.



Our group is interested in studying small-molecule inhibitors of monocarboxylate transporter 1 (Mct1), a protein that regulates lactate flux in glycolytic cells. AstraZeneca[1] has reported Mct1 inhibitors for immunosuppression and cancer (compounds **1** and **2**, Figure 1). The

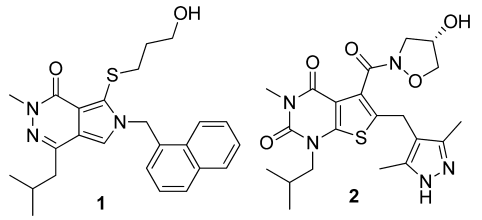


Figure 1. Structures of potent AstraZeneca Mct1 inhibitors.

thienopyrimidinedione **2** has advanced to phase I clinical trials for certain human cancers, relying on the finding that many tumors use Mct1 to efflux lactate and permit growth.[2] Even prior to learning of these cancer trials, we had wished to study the antitumor effects of Mct inhibitors in the synthetically accessible pyrrolopyridazinone series (related to compound **1**), particularly with regard to issues of Mct1/Mct4 isoform specificity and effects upon efficacy, emergence of resistance, and suitability in combination therapy.

In the AstraZeneca retrosynthesis for compound **1** (Figure 2), the two side chains were incorporated late from a preformed protected core **3**, which arose from a pyrrole ketoester **4**. The pyrrole ring was in turn installed from the annulation of γ-keto-

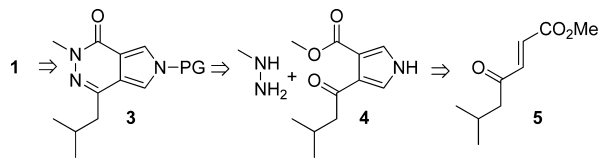


Figure 2. Restrosynthesis of **1** to ketoester **5**.

α,β-unsaturated ester **5**. Analogues of compound **5** are also key intermediates in the synthesis of many other compounds of medicinal interest, while the ketoacrylate motif is also found in natural products such as the pyrenophorins[3] and vermiculin,[4] antibiotic macrolides[5−10] shown in Figure 3.

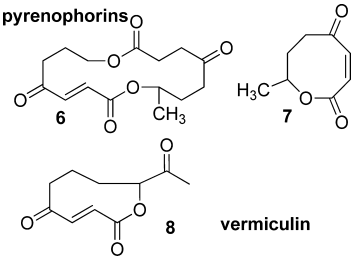


Figure 3. Natural products pyrenophorins and vermiculin.

While (*E*)- or (*Z*)-γ-keto-α,β-unsaturated esters such as compound **5** are quite simple in structure, they have not been trivial to prepare efficiently on a multigram scale, which we required for a multistep synthesis of compound **1** and analogues. Synthetic routes reported to date have been somewhat lengthy, require tedious purification processes, and/or use expensive, hazardous, or noncommercial reagents.[11−15] Some examples include Walton,[11] who used a retro-Diels−Alder approach; Kiehlmann and co-workers, who in two reports[12,13] described the alkaline methanolysis of 1,1,1-trichloro-2-hydroxy-4-alkanones, which were in turn available in low yield; Wegmann et al.,[14] who used a base-catalyzed addition of methyl propiolate to oxazolin-5-ones followed by ring opening and oxidation to give the desired olefins; and Dumont et al.,[15] who used an alkoxyphosphonate olefination protocol beginning with 4-oxobutenoates to give the desired compounds in a four-step process.

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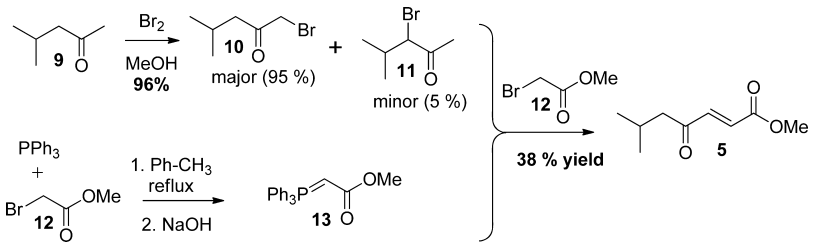
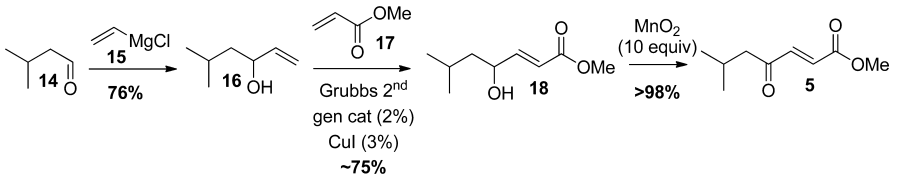
Scheme 1. Literature Synthesis of Ketoacrylate 5



Scheme 2. Grubbs Metathesis Approach to Ketoacrylate 5



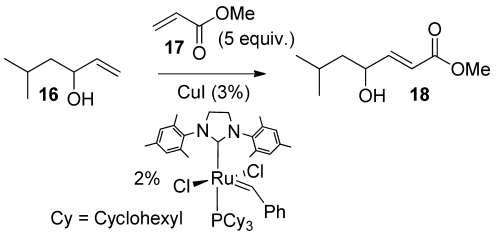
While following the AstraZeneca methods we recognized an opportunity to devise a more scalable and efficient route to compound **5** and its analogues. We subsequently used our new process to synthesize a variety of Mct1 inhibitors, which will be disclosed in a future report. Herein we disclose our general approach to the broadly useful γ-keto-α,β-unsaturated esters.

The AstraZeneca route to ketoacrylate **5** is shown in Scheme 1 and has been described elsewhere.[16] The process first uses the bromination of isobutyl methyl ketone (**9**) to give bromoketone **10** (a strong lachrymator) and the byproduct **11** in a 95:5 ratio. This mixture is coupled with ylide **13**, which in turn is prepared from triphenylphosphine and bromoester **12** (also a strong lachrymator). We found that a 25 g synthesis of ketoester **5** using this approach was a rather tedious process that took almost 2 weeks and required ~250 g of triphenylphosphine, 70 g of bromoketone **10**, and 60 g of ester **12**. A troublesome bottleneck was handling the sensitive ylide **13**, which must be rigorously dried. A greater concern was that the entire process required many liters of solvents for the reactions and, most unfortunately, for a difficult final chromatographic purification step.

In an attempt to overcome these issues, we decided to apply Lipshutz's strategy[17] of using a Grubbs metathesis catalyst with CuI as a cocatalyst. For our route, shown in Scheme 2, we first synthesized as the metathesis substrate the 2° alcohol **16** via a Grignard reaction of vinylmagnesium chloride (**15**) and isovaleraldehyde (**14**). Alcohol **16** was then subjected to cross-metathesis with methyl acrylate (**17**) using Grubbs' second-generation catalyst in the presence of a catalytic amount of CuI to give alcohol **18**. Notably, we did not observe homo coupling of the reactants (alcohol **16** or ester **17**) as side reactions. We attribute this to the fact that **16** and **17** are type-II olefins, which are known to undergo homodimerization very slowly.[18] Oxidation of alcohol **18** then cleanly provided ketoester **5**.

After exploring the route to hydroxyester **18** on a small scale (~100 mg), we increased the reaction scale stepwise to ultimately prepare the product in 25 g batches with no sacrifice in efficiency (Table 1). Finally, the oxidation of **18** to **5** was achieved using a 10-fold excess of activated MnO_2 (prior to use, the commercial reagent obtained from Sigma-Aldrich was heated at 100 °C overnight; the use of unactivated commercial MnO_2 resulted in longer reaction times and poor conversion).

Table 1. Synthesis of 18 Using Grubbs' Second-Generation Catalyst



entry	mass of **16** (g)	mass of Ru cat (mg)	% yield (mass in g) of **18**
1	0.1	5	67 (0.1)
2	1.0	38	74 (1.1)
3	2.0	149	74 (2.2)
4	8.0	526	74 (8.4)
5	25.0	950	81 (30.0)

After reaction completion (TLC analysis), the slurry was filtered through a pad of Celite and washed with ether. The resultant solution was evaporated to give the oxidized product **5** in nearly quantitative yield with a 95:5 *E*/*Z* ratio and free of other detectable impurities.

Using the metathesis route (Scheme 2) rather than the previous sequence gave the advantages of higher yields, shorter reaction times, no harsh lachrymator reagents, and much lower solvent costs due to higher reaction concentrations (~1 M) and the requirement for only one column chromatography step (for alcohol **18**). A 25 g synthesis of compound **5** could be achieved in 3 working days, versus ~2 weeks by the earlier process.

We briefly explored the scope of this cross-metathesis/oxidation methodology using a variety of secondary allylic alcohols and several alkyl acrylates (Table 2). Methyl, benzyl, and *tert*-butyl acrylates are suitable for both steps of the process, as are allylic alcohols with an unsubstituted benzyl group, a *p*-bromophenyl group, and an alkyl group (for compound **16**). Alcohols **19** and **20** were synthesized by Grignard reaction of vinylmagnesium chloride and the appropriate aldehyde. The alcohol products were then subjected to cross-metathesis reactions with the three differently protected acrylates using Grubbs' second-generation metathesis catalyst (5%) and CuI (6%) in diethyl ether at 40 °C for 6−12 h.

After the metathesis reaction was complete (as monitored by TLC), the solvents were evaporated, and flash chromatography

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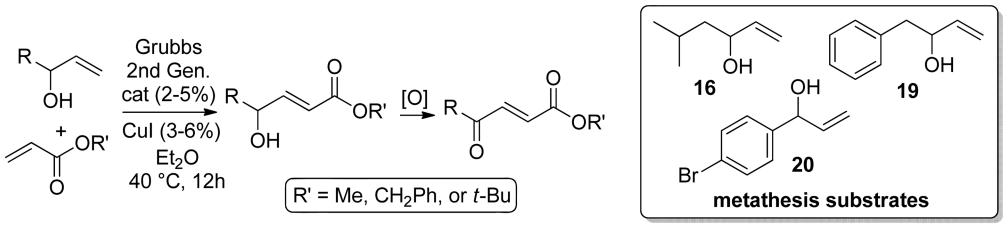
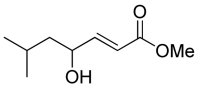
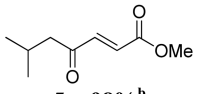
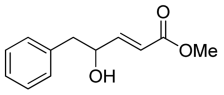
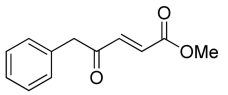
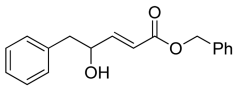
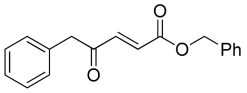
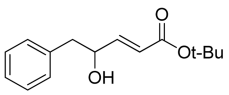
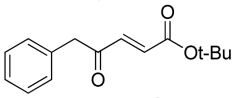
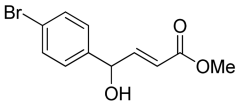
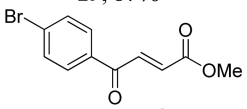
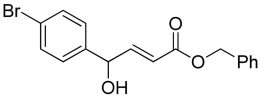
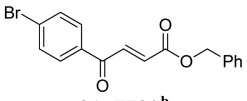
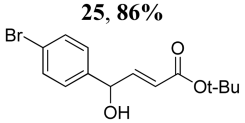
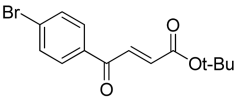
Table 2. Scope of Grubbs Metathesis and Oxidation



metathesis product, yield[a]	oxidation product, yield[a]
 **18, ~75%**	 **5, >98%[b]**
 **21, 87%**	 **27, 94%[c]**
 **22, 80%**	 **28, 99%[c]**
 **23, 78%**	 **29, 87%[b]**
 **24, 91%**	 **30, 83%[b]**
 **25, 86%**	 **31, 77%[b]**
 **26, 85%**	 **32, 82%[b]**

[a]Isolated yields are reported. [b]Oxidation was performed using MnO_2. [c]Dess–Martin periodinane reagent was used for oxidation; the use of MnO_2 resulted in significant decomposition.

purification gave the desired coupling products **21**–**26** in 77–99% yield. As in the case of compound **18**, we observed a 95:5 *E*/*Z* ratio for compounds **22** and **26**. In the case of compounds **21**, **23**, **24**, and **25**, only the *E* isomer was formed, free of detectable *Z* olefin byproduct, as determined by analytical HPLC and 400 MHz ^{1}H NMR analysis. Such *E*/*Z* selectivity is in accord with preferences for similar Grubbs cross-metathesis reactions.[19]

Finally, each of the alcohol metathesis products was found to oxidize cleanly to the desired ketone. Alcohols **24**–**26** gave the desired ketoesters **30**–**32** in high yield and high purity using activated MnO_2. The attempted oxidations of alcohols **21**–**23** with activated MnO_2 were inefficient, however, giving significant amounts of unidentified decomposition byproducts. An alternative procedure using the Dess–Martin periodinane oxidant[20] gave ketoesters **27**–**29** in high yield and high purity, requiring no additional purification.

Because we desired the ketoesters for our studies, we made no attempts to prepare nonracemic allylic alcohols for metathesis studies. Enantioselective vinyl addition,[21,22] rather than our Grignard preparation, would give optically pure γ-hydroxy-α,β-unsaturated esters, versatile synthons for asymmetric synthesis.[23] The hydroxyl group can be transformed into a leaving group that may be displaced with inversion of configuration via S_N2 processes or with net retention of configuration via transient formation of π-allyl complexes.[24,25]

Recently, Schmidt and Hauke[26] also described the cross-metathesis of a variety of allylic alcohols and methyl acrylate using Grubbs' second-generation metathesis catalyst. They used additives such as polymethylhydroxysiloxanes to isomerize the metathesis products, giving their ketone analogues. Our protocol lacks such additives, and thus, no detectable isomerized products are formed. Others have used Grubbs' second-generation catalyst in natural products synthesis, including in the preparation of aspergillides A and B by Fuwa et al.,[27,28] australine hydrochloride and isoaltholactone by Trost et al.,[29] and prenophorol[30] and clonostachidiol[31] by Yadav and co-workers. We feel that our methods complement these

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previously-reported metathesis protocols and will prove widely useful in preparing various ketoacrylates for synthetic and biological studies.

EXPERIMENTAL SECTION

General. All reagents and solvents were obtained from commercial suppliers and were used as received without further purification. NMR spectra were recorded on a 400 MHz (^{1}H), 100 MHz (^{13}C) NMR spectrometer at 25 °C. Chemical shifts (δ) are reported in parts per million referenced to the NMR solvent residual peak, and coupling constants (J) are reported in hertz. Silica gel flash column chromatography was used to purify all of the compounds. All of the reactions were monitored using TLC and LC−MS (conducted using an ion-trap mass spectrometer system coupled with an HPLC system). Reactions were carried out under an argon atmosphere. Grubbs' second-generation catalyst was obtained from Aldrich. Melting points were acquired in triplicate using an automatic melting point instrument and are reported as ranges. IR spectra were recorded on an FT-IR spectrometer as a neat oil or solid. HRMS samples were analyzed using a TOF analyzer and an electrospray ionization method.

Synthesis of Bromoketone 10 (Original Route[16]). A 500 mL three-neck flask with a stir bar was oven-dried and charged with isopropyl methyl ketone (80 g, 79.8 mmol) dissolved in MeOH (150 mL). To the flask were attached a reflux condenser and an addition funnel. The reaction mixture was cooled in an ice bath for 45 min. Br_2 (140 g, 87.8 mmol) was added dropwise to the reaction mixture over a period of 30 min, after which time the mixture was allowed to stir for 3 h. Water (200 mL) was added, and the reaction mixture was allowed to stir overnight. The contents were transferred into a separatory funnel containing water (600 mL), and this solution was extracted with ether (3 × 250 mL). The collected organic layers were washed with water (3 × 250 mL), $NaHCO_3$ (1 × 250 mL), and brine (1 × 250 mL), dried over Na_2SO_4, filtered, and evaporated to give **10** as a pale-yellow oil (139 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.86 (s, 2H), 2.51 (d, J = 7.0 Hz, 2H), 2.20−2.11 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H). Although there was a small amount (~5%) of 2° bromide **11** present, the crude material was used directly in the next step.

Synthesis of Ylide 13 (Original Route[16]). A mechanical stirrer was attached to a 1000 mL three-neck round-bottom flask. The flask was then charged with PPh_3 (250 g, 954 mmol), to which was added ethyl acetate (300 mL). Bromomethyl acetate (145 g, 947 mmol) was dissolved in 200 mL of ethyl acetate, and this solution was slowly added to the reaction mixture. After the addition was complete, the reaction mixture was allowed to stir overnight. The fluffy white solid was collected by filtration, washed with ether, and air-dried overnight to give 380 g of compound. The white solid thus obtained was transferred to a 1000 mL beaker, to which were added NaOH solution (1 N, 300 mL) and water (300 mL). The resulting slurry was stirred for 20 min, and then the contents were transferred to a separatory funnel. After extraction with CH_2Cl_2, the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated to give white crystalline solid **13** (301 g, 96% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48−7.65 (m, 15H), 3.60 (br s, 3H), 2.98 (br s, 1H).

Synthesis of Olefin 5 (Original Route[16]). To an oven-dried 2 L three-neck flask were added **13** (224 g, 670 mmol) and anhydrous toluene (750 mL). To the flask were attached a mechanical stirrer and an addition funnel. Ketone **10** (60 g, 335 mmol) dissolved in anhydrous toluene (100 mL) was charged into the addition funnel and then added to the reaction mixture dropwise. The reaction mixture was heated at 90 °C for 3 h to give a thick yellow suspension, which was then cooled and filtered. To the filtrate was added methyl bromoacetate (51 g, 335 mmol), and the mixture was stirred at 90 °C for 2 h. Once again the reaction mixture was cooled to give a precipitate, which was filtered, washed with cold toluene, and then evaporated to give a crude oil that upon purification by flash chromatography using hexane/ethyl acetate (2:1) as the mobile phase gave olefin **5** (25 g, 38% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, J = 16.0 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H), 2.50 (d, J = 7.0 Hz, 2H), 2.24−2.14 (m, 1H), 0.94 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.5, 166.1, 139.8, 130.2, 52.3, 50.5, 24.7, 22.5; FT-IR (neat) 2957.7, 2873.8, 1729.5, 1698.5, 1466.8, 1436.7, 1368.7, 1298.5, 1272.5, 1196.6, 1171.5, 1113.8, 1062.7, 1027.7, 979.6, 857.8, 702.8 cm^{-1}.

Synthesis of Alcohol 16 (New Route). To an oven-dried 500 mL three-neck flask with a stir bar were attached a reflux condenser and an addition funnel. The assembly was flushed with argon for 15 min and charged with vinylmagnesium chloride (199 mL, 1.6 M in THF, 320 mmol). To this was added anhydrous Et_2O (100 mL), and the reaction mixture was cooled in an ice bath for 30 min. Isovaleraldehyde (25 mL, 290 mmol) dissolved in Et_2O (50 mL) was added dropwise to the reaction mixture under a positive flow of argon with constant stirring over a period of 40 min. The reaction mixture was allowed to stir overnight with gradual warming to room temperature. After confirmation of reaction completion by TLC analysis, the reaction mixture was quenched by adding saturated aqueous NH_4Cl (100 mL) and then transferred to a separatory funnel. Extraction with Et_2O, washing of the organic layers with water and brine, drying over Na_2SO_4, filtration, and evaporation of solvents gave alcohol **16** (25 g, 76% crude) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90−5.81 (m, 1H), 5.22 (td, J = 17.2, 1.4 Hz, 1H), 5.08 (td, J = 10.4, 1.3 Hz, 1H), 4.19−4.14 (br m, 1H), 1.79−1.69 (m, 1H), 1.64 (br s, 1H), 1.49−1.43 (m, 1H), 1.35−1.28 (m, 1H), 0.92 (dd, J = 6.6, 2.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.6, 114.3, 71.5, 46.2, 24.5, 23.0, 22.3; FT-IR (neat) 3338.9, 2955.7, 2925.8, 2870.8, 1644.9, 1468.8, 1423.8, 1384.8, 1367.8, 1308.9, 1152.8, 1091.8, 1055.8, 1016.8, 988.6, 918.6, 841.8, 661.8 cm^{-1}. Note: alcohol **16** is appreciably volatile, so care must be taken while evaporating the solvents after workup.

Synthesis of Alcohol 18 via Grubbs Metathesis (Table 1)—General Procedure. A round-bottom flask with a stir bar was oven-dried and then flushed with argon for 10 min. Methyl acrylate (5 equiv), Grubbs' second-generation catalyst (0.005 equiv), and CuI (0.006 equiv) were charged into the flask under a positive flow of argon, and to this mixture was added anhydrous Et_2O (~1 M). Argon was bubbled through the reaction mixture for 15 min while the assembly was set up for reflux using an oil bath. After 10 min, alcohol **16** (1 equiv) was added, and the mixture was allowed to reflux for 5 h. The reaction was monitored by TLC (2:1 hexanes/EtOAc; $KMnO_4$ staining). After completion of the reaction, the solvents were evaporated, and the crude mixture was purified by flash chromatography using a hexane/EtOAc (2:1) solvent system. The pure fractions were collected together, evaporated, and dried under vacuum to give alcohol **18** (~75% yield) as a dark oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96 (dd, J = 15.7, 5.0 Hz, 1H), 6.04 (dd, J = 15.6, 1.6 Hz, 1H), 4.39−4.34 (br m, 1H), 3.75 (s, 3H), 1.79 (obscured d, 2H), 1.77 (d, J = 5.2 Hz, 1H), 1.54−1.46 (m, 1H), 1.41−1.34 (m, 1H), 0.95 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 150.9, 119.4, 69.4, 51.7, 45.7, 24.5, 23.1, 22.1; FT-IR (neat) 3441.9, 2955.7, 2870.8, 1724.6, 1704.5, 1658.7, 1467.8, 1436.7, 1385.8, 1367.8, 1304.6, 1276.6, 1194.7, 1168.5, 1078.7, 1035.7, 983.6, 926.8, 863.8, 840.8, 714.8 cm^{-1}.

MnO_2 Oxidation of Alcohol 18 To Give Ketone 5. MnO_2 (106 g, 1.22 mol) was heated in an oven at 100 °C overnight and then added to a flask containing **11** (30 g, 175 mmol) in CH_2Cl_2 (200 mL). The reaction mixture was allowed to stir for 10 h, after which conversion was complete by TLC analysis. The mixture was filtered through a pad of Celite and washed with Et_2O. The solvents were evaporated to give pure product **5** (23 g, 79% yield) as a pale-yellow oil. The ^{1}H NMR, ^{13}C NMR, and FT-IR data matched those listed above for the material prepared by the previous method.

Synthesis of Alcohols 19 and 20—General Procedure. An oven-dried 100 mL flask with a stir bar was flushed with argon for 15 min and charged with vinylmagnesium chloride (18 mL, 1.6 M in THF, 28 mmol). To this solution was added anhydrous Et_2O (30 mL), and the reaction mixture was cooled in an ice bath for 30 min. Aldehyde (25 mmol) dissolved in Et_2O (10 mL) was added dropwise to the reaction mixture under a positive flow of argon with constant stirring over a period of 5 min. The reaction mixture was allowed to stir overnight with eventual warming to room temperature. After

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confirmation of reaction completion by TLC analysis, the reaction mixture was quenched by adding saturated aqueous NH_4Cl (100 mL) and then transferred to a separatory funnel. Extraction with Et_2O, washing of the organic layers with water and brine, drying over Na_2SO_4, filtration, and evaporation of solvents gave the desired alcohol, which was purified by flash chromatography using an appropriate hexane/EtOAc gradient.

Alcohol ***19***.[32] Colorless oil (2.1 g, 58% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.33 (m, 2H), 7.28−7.25 (m, 3H), 6.00−5.92 (m, 1H), 5.27 (td, J = 17.2, 1.4 Hz, 1H), 5.16 (td, J = 10.5, 1.3 Hz, 1H), 4.40−4.35 (br m, 1H), 2.93−2.88 (m, 1H), 2.84−2.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.1, 137.7, 129.6, 128.5, 126.6, 115.0, 73.7, 43.8; FT-IR (neat) 3376.8, 3063.9, 3027.9, 2919.9, 1644.9, 1603.9, 1495.8, 1454.8, 1424.8, 1117.8, 1076.8, 1029.6, 990.6, 921.6, 854.8, 744.5, 697.3, 668.6 cm^{-1}.

Alcohol ***20***.[33] Brown oil (1.95 g, 68% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 5.98−5.90 (m, 1H), 5.29 (td, J = 17.1, 1.2 Hz, 1H), 5.16 (td, J = 10.3, 1.2 Hz, 1H), 5.10 (br, 1H), 2.04 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.5, 139.8, 131.6, 128.0, 1221.6, 115.7, 74.7; FT-IR (neat) 3342.8, 2981.9, 2871.9, 1640.9, 1591.8, 1485.6, 1401.7, 1241.8, 1191.8, 1100.8, 1070.6, 1033.7, 1009.4, 986.5, 924.4, 815.5, 794.5, 719.6 cm^{-1}.

General Procedure for Grubbs Metathesis. For other metathesis reactions, the same procedure as used for the synthesis of alcohol **18** was followed using the appropriate acrylate and olefin reactants.

Alcohol ***21***.[26] Pale-yellow oil (0.300 g, 87% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.33 (m, 2H), 7.30−7.23 (m, 3H), 7.03 (dd, J = 15.7, 4.1 Hz, 1H), 6.09 (dd, J = 15.7, 1.8 Hz, 1H), 4.57−4.54 (br m, 1H), 3.76 (s, 1H), 2.99−2.95 (m, 1H), 2.84−2.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 149.1, 136.7, 129.5, 128.7, 127.0, 120.2, 71.7, 51.7, 43.2; FT-IR (neat) 3446.9, 3028.9, 2950.9, 1704.5, 1658.7, 1602.9, 1495.8, 1454.8, 1435.7, 1309.6, 1273.5, 1195.6, 1166.5, 1100.6, 1076.7, 1030.6, 983.6, 926.7, 855.7, 823.8, 746.6, 698.3 cm^{-1}.

Alcohol ***22***. Pale-yellow oil (0.380 g, 80% yield). Data for the E isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.21 (m, 6H), 7.18−7.11 (m, 4H), 6.95 (dd, J = 15.6, 4.5 Hz, 1H), 6.02 (dd, J = 15.6, 1.7 Hz, 1H), 5.09 (s, 2H), 4.46−4.40 (br m, 1H), 2.87−2.83 (m, 1H), 2.71−2.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 149.5, 136.7, 135.9, 129.5, 128.7, 128.5, 128.2, 128.1, 127.0, 120.3, 71.8, 66.3, 43.2; FT-IR (neat) 3421.9, 3030.9, 2942.9, 1715.5, 1655.7, 1603.9, 1454.7, 1377.8, 1302.6, 1266.5, 1159.4, 1100.6, 1077.7, 1027.6, 982.6, 908.8, 855.8, 735.5, 695.2 cm^{-1}; HRMS (ES-TOF) m/z calcd for $C_{18}H_{18}O_3Na$ $[M + Na]^+$ 305.1154, found 305.1154.

Alcohol ***23***. Off-white solid (0.326 g, 78% yield); mp 65.0−71.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.33 (m, 2H), 7.29−7.24 (m, 3H), 6.92 (dd, J = 15.6, 4.7 Hz, 1H), 6.00 (dd, J = 15.6, 1.7 Hz, 1H), 4.54−4.49 (br m, 1H), 2.99−2.94 (m, 1H), 2.82−2.76 (m, 1H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 147.6, 136.9, 129.5, 128.7, 126.9, 122.5, 80.5, 71.8, 43.3, 28.1; FT-IR (neat) 3486.8, 2977.8, 1693.5, 1656.6, 1602.8, 1493.9, 1454.8, 1391.8, 1367.7, 1326.7, 1297.6, 1252.7, 1213.7, 1151.6, 1111.6, 1071.8, 1011.7, 995.7, 981.7, 941.7, 863.7, 848.8, 746.7, 710.7, 698.4 cm^{-1}; HRMS (ES-TOF) m/z calcd for $C_{15}H_{20}O_3Na$ $[M + Na]^+$ 271.1310, found 271.1310.

Alcohol ***24***.[26] Brown oil (0.351 g, 91% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.00 (dd, J = 15.6, 4.9 Hz, 1H), 6.15 (dd, J = 15.6, 1.7 Hz, 1H), 5.30 (br d, J = 4.88 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 148.3, 139.8, 131.9, 131.9, 128.2, 122.3, 120.1, 72.8, 51.8; FT-IR (neat) 3419.8, 2951.8, 1703.5, 1658.6, 1590.8, 1486.7, 1436.6, 1401.7, 1274.5, 1274.5, 1166.5, 1091.5, 1070.5, 1039.6, 1009.4, 980.5, 924.7, 879.8, 825.5, 761.7, 719.7 cm^{-1}.

Alcohol ***25***. Pale-yellow solid (0.350 g, 86% yield); mp 63.5−65.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, J = 8.6 Hz, 2H), 7.38−7.33 (m, 5H), 7.23 (d, J = 8.1 Hz, 2H), 7.04 (dd, J = 15.6, 5.0 Hz, 1H), 6.20 (dd, J = 15.6, 1.7 Hz, 1H), 5.35 (br t, J = 3.6 Hz, 1H), 5.19 (s, 2H), 2.10 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 148.3, 139.7, 135.7, 132.0, 128.5, 128.3, 128.2, 122.4, 120.4, 72.9, 66.4; FT-IR (neat) 3461.8, 2987.8, 1685.6, 1646.7, 1589.8, 1482.1, 1454.8, 1395.7, 1382.7, 1326.7, 1280.6, 1218.7, 1181.6, 1106.7, 1088.6, 1069.6, 1010.6, 998.6, 949.7, 825.7, 806.7, 767.7, 748.5, 698.5 cm^{-1}; HRMS (ES-TOF) m/z calcd for $C_{17}H_{15}BrO_3Na$ $[M + Na]^+$ 369.0102, found 369.0102.

Alcohol ***26***. White solid (0.315 g, 85% yield); mp 51.0−53.4 °C. Data for the E isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 6.89 (dd, J = 15.6, 4.8 Hz, 1H), 6.05 (dd, J = 15.8, 2.0 Hz, 1H), 5.32 (br t, J = 4.6 Hz, 1H), 2.10 (d, J = 3.4 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 146.5, 140.0, 131.9, 128.2, 122.7, 122.2, 80.8, 72.9, 28.1; FT-IR (neat) 3440.8, 2982.8, 1683.7, 1652.8, 1588.9, 1482.8, 1454.8, 1393.8, 1365.7, 1340.7, 1315.8, 1299.8, 1257.7, 1234.7, 1149.5, 1092.7, 1066.7, 1045.7, 1007.6, 979.6, 822.5, 762.7 cm^{-1}; HRMS (ES-TOF) m/z calcd for $C_{14}H_{17}BrO_3Na$ $[M + Na]^+$ 335.0259, found 335.0259.

General Procedure for Dess−Martin Periodinane Oxidation.[20] To a dry 100 mL flask with a stir bar were added the Dess−Martin periodinane reagent (1.2 equiv) and dichloromethane (∼1 M). To the mixture was added a solution of the allylic alcohol (1.0 equiv) in minimal dichloromethane. The reaction mixture was allowed to stir for 30 min and then monitored by TLC to confirm complete transformation of the alcohol to the ketone. Following this, an equal volume of ether was added, and the mixture was transferred to a separatory funnel containing a saturated $NaHCO_3$ solution. The organic layer was washed with $Na_2S_2O_3$ solution, saturated bicarbonate solution, water, and then brine. Evaporation of the solvents gave the desired ketoester in nearly quantitative yield, free of detectable side products.

Ketoester ***27***.[26] Pale-yellow oil (0.111 g, 94% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.29 (m, 2H), 7.30 (obscured d, 1H), 7.21 (obscured d, 2H), 7.12 (d, J = 16.1 Hz, 1H), 6.74 (d, J = 16.1 Hz, 1H), 3.92 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.5, 165.8, 138.6, 132.8, 131.1, 129.5, 128.9, 127.4, 52.4, 48.8; FT-IR (neat) 2952.8, 1723.5, 1687.5, 1603.8, 1496.7, 1454.7, 1438.6, 1414.8, 1348.7, 1310.5, 1256.4, 1213.6, 1199.5, 1170.4, 1077.6, 1029.7, 1011.6, 981.4, 940.7, 915.6, 858.6, 739.5, 700.4 cm^{-1}.

Ketoester ***28***. Yellow oil (0.256 g, 99% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.37 (m, 5H), 7.35−7.29 (m, 3H), 7.21−7.20 (br, 2H), 7.15 (d, J = 15.9 Hz, 1H), 6.68 (d, J = 15.9 Hz, 1H), 5.32 (s, 2H), 3.92 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.5, 165.2, 138.9, 135.2, 132.8, 131.2, 129.5, 128.9, 128.7, 128.5, 128.4, 127.4, 67.2, 48.7; FT-IR (neat) 3031.9, 2961.9, 1722.5, 1696.5, 1636.8, 1496.8, 1454.7, 1376.8, 1274, 1212.6, 1165.4, 1073.7, 975.5, 732.5, 695.2 cm^{-1}; HRMS (ES-TOF) m/z calcd for $C_{18}H_{16}O_3Na$ $[M + Na]^+$ 303.0997, found 303.0997.

Ketoester ***29***. Yellow oil (0.152 g, 86% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.33 (m, 2H), 7.30−7.28 (br d, 1H), 7.22−7.20 (br d, 2H), 7.02 (d, J = 15.7 Hz, 1H), 6.67 (d, J = 15.5 Hz, 1H), 3.91 (s, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.9, 164.6, 137.7, 133.6, 133.0, 129.5, 128.9, 127.3, 82.1, 48.5, 27.9; FT-IR (neat) 2979.8, 1695.5, 1636.8, 1496.8, 1476.8, 1455.8, 1393.8, 1368.6, 1305.5, 1257.6, 1148.2, 1071.7, 1031.8, 976.5, 841.7, 730.6, 697.4 cm^{-1}; HRMS (ES-TOF) m/z calcd for $C_{15}H_{19}O_3$ $[M + H]^+$ 247.1333, found 247.1334.

General Procedure for MnO_2 Oxidation. Activated MnO_2 (10 equiv, obtained from Sigma-Aldrich and heated at 100 °C overnight before use) was added to a flask containing the alcohol (1 equiv) in CH_2Cl_2 (∼1 M). The reaction mixture was allowed to stir for 12 h as the conversion was monitored by TLC analysis. The mixture was filtered through a pad of Celite and washed with Et_2O. The solvents were evaporated to give the pure product, typically in high yield and free of detectable side products.

Ketoester ***30***.[34] Amber solid (0.311 g, 83% yield); mp 70.3−74.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, J = 15.4 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 15.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.3, 165.8, 135.9, 135.3, 132.6, 132.3, 130.3, 129.3, 52.4; FT-IR (neat) 2952.8, 1721.6, 1666.6, 1626.7, 1581.6, 1485.8, 1438.7, 1396.7, 1324.7, 1301.5, 1220.7, 1194.7, 1170.5, 1067.5, 1007.7, 993.6, 943.6, 833.6, 821.6, 755.4, 661.7 cm^{-1}.

Ketoester ***31***. Yellow solid (0.250 g, 77% yield); mp 97.2−101.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 5.8 Hz, 1H), 7.86 (d, J

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= 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 7.41−7.40 (br m, 5H), 6.94 (d, J = 15.5 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.4, 165.3, 136.2, 135.3, 135.2, 132.7, 132.3, 130.3, 129.3, 128.7, 128.6, 128.5, 128.4, 67.3; FT-IR (neat) 3064.9, 2956.8,1717.4, 1667.5, 1628.7, 1582.6, 1499.9, 1485.8, 1455.7, 1397.6, 1371.7, 1324.7, 1292.3, 1217.8, 1164.3, 1111.7, 1071.5, 1006.6, 978.6, 969.4, 949.6, 912.7, 862.7, 838.6, 811.8, 753.2, 731.7, 700.4, 663.6 cm^{-1}.

Ketoester **32**. Yellow solid (0.300 g, 82% yield); mp 86.6−90.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 7.0 Hz, 2H), 7.74 (d, J = 15.5 Hz, 1H), 7.64 (d, J = 7.0 Hz, 2H), 6.80 (d, J = 15.5 Hz, 1H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.8, 164.6, 135.4, 135.0, 134.9, 132.2, 130.4, 129.1, 82.1, 28.0; FT-IR (neat) 2971.8, 2930.8, 1709.5, 1663.6, 1622.7, 1582.6, 1566.7, 1480.8, 1453.8, 1397.7, 1369.7, 1299.5, 1285.6, 1251.7, 1149.4, 1069.6, 1004.5, 969.5, 864.6, 837.6, 756.4, 697.8, 666.6 cm^{-1}; HRMS (ES-TOF) m/z calcd for $C_{14}H_{16}BrO_3$ $[M + H]^+$ 311.0205, found 311.0283.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra, IR spectra of all compounds, and HRMS data for new compounds. 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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