Asymmetric Total Synthesis of Rugulactone, an α-Pyrone from *Cryptocarya rugulosa*

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Abstract: A total asymmetric synthesis of rugulactone, a naturally occuring α-pyrone isolated from *Cryptocarya rugulosa*, is reported. The synthesis involved a cross-metathesis coupling reaction to construct the internal *E*-olefin group, a Still–Gennari olefination to construct the *Z*-configured α,β-unsaturated ester group, and a one-pot deprotection and intramolecular lactonization reaction. The stereochemistry at C5 was controlled by the use of a chiral pool.

Key words: total synthesis, natural products, pyrones, metathesis, olefination

Rugulactone (**1**) is a naturally occurring α-pyrone recently isolated from extracts of the plant *Cryptocarya rugulosa*.[1] Biological tests showed that this lactone is a potent inhibitor of the activation pathway of nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB), and therefore a potential anticancer therapeutic target. NF-κB is a protein complex that acts as a transcription factor that is found in almost all types of animal cell and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized low-density lipoproteins, and bacterial or viral antigens.[2–6] NF-κB therefore plays a key role in regulating the immune response to infection. Consistent with this role, incorrect regulation of NF-κB has been linked to cancer, inflammatory, and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κB has also been implicated in processes of synaptic plasticity and memory.[7] Defects in NF-κB result in an increase in susceptibility to apoptosis, leading to increased cell death. Because NF-κB controls many genes involved in inflammation, it is not surprising that NF-κB is found to be clinically active in many inflammatory diseases, such as inflammatory bowel disease, arthritis, sepsis, and asthma. Many natural products (including antioxidants) that have been promoted as having anti-cancer and anti-inflammatory activity have also been shown to inhibit NF-κB. Recent work by Karin,[8] Pikarsky and Ben-Neriah,[9] and others has highlighted the importance of the connection between NF-κB, inflammation, and cancer, and has underscored the value of therapies that regulate the activity of NF-κB.[10]

The plant genus *Cryptocarya* consists of a large number of species that are distributed throughout the tropics and subtropics.[11] The most common secondary metabolites reported from this genus are alkaloids, flavonoids, and α-pyrones.[12–14] The 6-substituted 5,6-dihydro-2*H*-pyran-2-one group is a prominent structural feature among natural products of this group that display a broad range of biological activities.[15,16] Rugulactone (**1**) belongs to a family of *Cryptocarya* α-pyrone-containing natural products isolated from *C. rugulosa* extract that exhibit up to a fivefold induction of IC_{50} at 25 μg/mL.[1] Because of these interesting inhibition properties, rugulactone has recently attracted a considerable degree of attention, and three total syntheses have been published.[17]

As part of the development of efficient and rapid total syntheses of natural phenylpropanoids,[18] we have been working on the use of cross-metathesis to build internal olefins. Because of the presence of such an olefin group in the structure of rugulactone, and because of its potent biological activities, we put our efforts into a total synthesis of this compound. Our original convergent retrosynthetic route (Scheme 1) was based on a cross-metathesis coupling reaction and a Still–Gennari olefination to construct, respectively, the internal *E*-olefin **3** and the *Z*-configured α,β-unsaturated ester **2**. We also wanted to take advantage of the chiral pool of sugars and glycidol derivatives for the control of the C5 stereocenter to avoid the use of any atom-consuming or expensive enantioselective steps.

The first plan for a synthesis of rugulactone (**1**) began from the known silylated homoallylic alcohol **4**[19] and vinyl ketone **5** (Scheme 1). Compound **4** was easily obtained in five steps (Scheme 2) from commercially available (4*S*)-(+)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**7**). The hydroxy group in **7** was protected through formation of the corresponding *p*-methoxybenzyl ether **8** (94%). Subsequent cleavage of the acetonide **8** by using cerium(III) chloride[20a] gave the diol **9** (97%). One-pot formation of the epoxide **10** from the 1,2-diol **9** was realized by using 1-[(2,4,6-triisopropylphenyl)sulfonyl]-1*H*-imidazole (TPSI)[20b] (53%). Finally, opening of the epoxide **10** by copper-catalyzed Grignard vinylation gave the homoallylic alcohol **11** (87%), which was then converted into the required silyl ether **4** (98%).

As shown in Scheme 3, vinyl ketone **5** was synthesized from the commercially available 3-phenylpropanal (**6**) in two steps by alkylation of the aldehyde through Grignard vinylation (92%) followed by Dess–Martin periodinane oxidation of the resulting allylic alcohol (96%).

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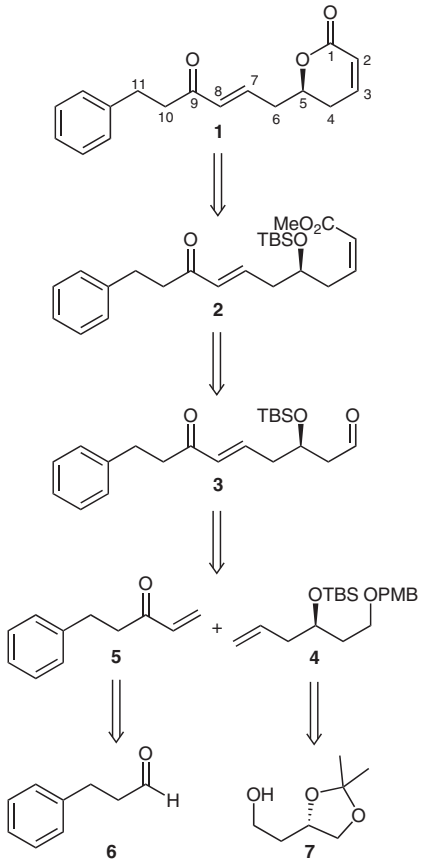
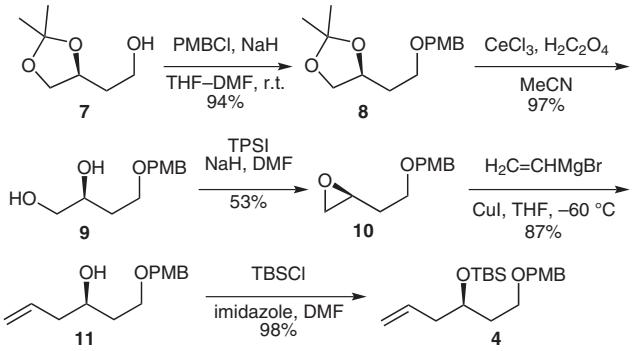
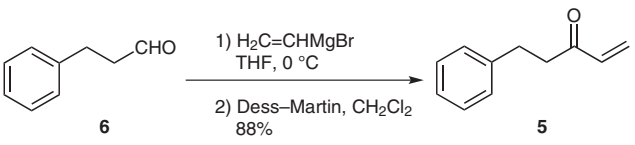


Scheme 1 First retrosynthetic pathway



Scheme 2 Synthesis of precursor **4**



Scheme 3 Synthesis of vinyl ketone **5**

With compounds **4** and **5** in hand, the cross-metathesis[21] coupling reaction was carried out (5 mol% Grubbs II catalyst, refluxing CH_2Cl_2) to give the desired intermediate **12**[22a] in 72% yield (Scheme 4). However, cleavage of the PMB ether moiety proved troublesome. Conventional methods using a variety of acids (e.g., *p*-TsOH, TFA, Amberlyst resin) had to be ruled out because of the sensitivity of the silyl ether. Cleavage using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) did not provide the expected free alcohol, but resulted in the formation of tetrahydropyran **13** as the major product[22b] through a diastereoselective 1,4-Michael addition of the transient alcoholate to the vinyl ketone. Unfortunately, even the use of buffered conditions did not prevent that reaction.

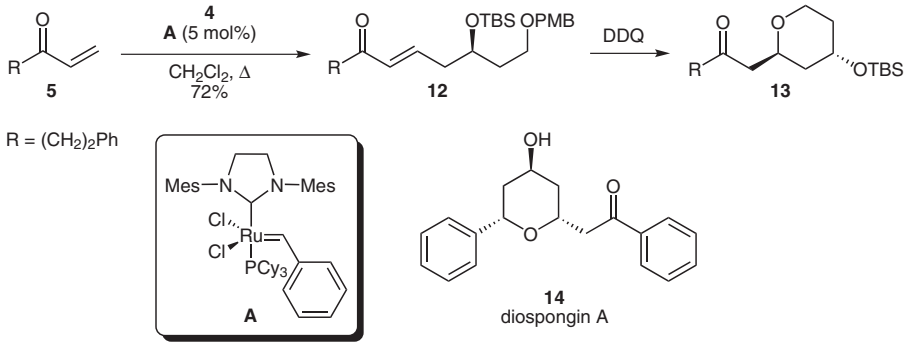
Though undesired in the total synthesis of rugulactone, this Michael addition onto a vinyl ketone appears to be a useful method for preparing tetrahydropyrans directly from PMB-protected hydroxy compounds without prior deprotection. This method will be studied and optimized in due course. A similar formation of a tetrahydropyran was observed on treating *tert*-butyl(dimethyl)silyl-protected hydroxy groups with tetrabutylammonium fluoride in a preparation of diospongin A (**14**).[23]

At this point, because we were unable to obtain the free hydroxy compound efficiently, we had to devise an alternative route to the desired aldehyde **3**, so we chose to use the masked aldehyde **15** instead of the protected hydroxy compound **4** (Scheme 5).

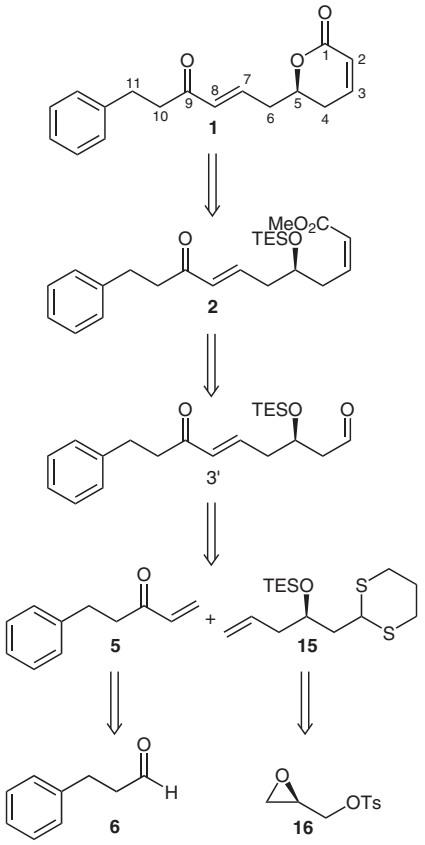
The second plan for a synthesis of rugulactone (**1**) began from commercially available (2*S*)-glycidyl tosylate (**16**) and 3-phenylpropanal (**6**) (Scheme 5). Compound **15** was easily obtained in three steps from **16** (Scheme 6).[24] First, the tosylate moiety in **16** was displaced by using lithiated 1,3-dithiane (*n*-BuLi, 1,3-dithiane, THF, –78 °C) to give the corresponding thioacetal **17**. The epoxide ring in **17** was then opened by copper-catalyzed Grignard vinylation (vinylMgBr, CuI, THF, –60 °C; 65% from **16**), which gave the secondary homoallylic alcohol **18**. Finally, protection of **18** as its triethylsilyl ether (TESCl, imidazole, DMAP, DMF; 98%) gave the cross-metathesis precursor **15**.

The cross-metathesis coupling reaction of **15** and **5** (5 mol% Grubbs II catalyst, CH_2Cl_2, reflux) gave the desired intermediate **19** in 72% yield (Scheme 7).[21] In fact, this reaction was the crucial step of our synthesis, as sulfur is often problematic in transition metal-catalyzed reactions because its high affinity with the soft metal center can result in poisoning of the catalyst. Indeed, there have been several cases of olefin metathesis in which sulfides were detrimental. For example, in Fürstner's synthesis of the macrocycle zeranol, in a key step involving ring-closing metathesis of a molecule containing a 1,3-dithiane unit,[25] cyclization was not observed in the presence of the first-generation Grubbs catalyst as a result of chelation of the proximal sulfur atom to the ruthenium. Furthermore, the decreased reactivities of butenyl and pentenyl sulfides may be due to the unproductive formation of five- or six-membered chelates. In our case, however, it was fortunate that the sulfide was sufficiently distant from the olefin group to avoid the formation of such chelates with the Grubbs second-generation catalyst.

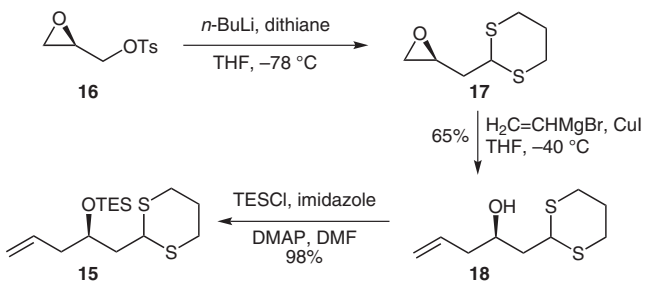
Removal of the thioacetal group from dithiane **19** was then performed cleanly (methyl iodide, calcium carbonate, aqueous acetonitrile) to give the crude aldehyde **3′**,



Scheme 4 Cross-metathesis and an unexpected diastereoselective 1,4-Michael addition

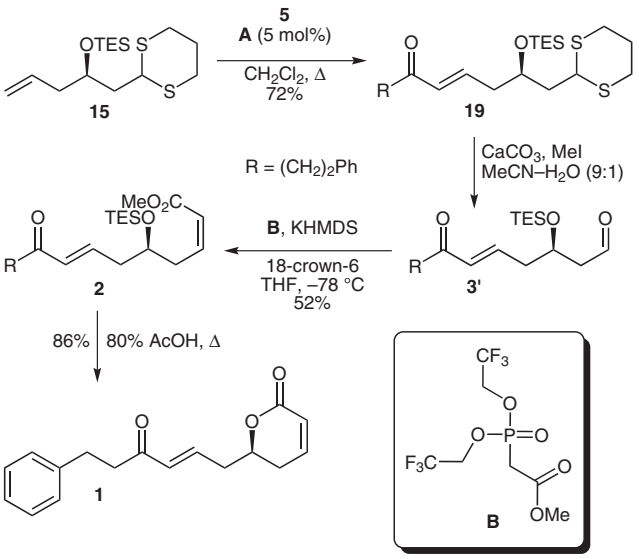


Scheme 5 Second retrosynthetic pathway



Scheme 6 Synthesis of cross-metathesis precursor **15**

which was immediately subjected to Still–Gennari olefination [methyl *P*,*P*-bis(2,2,2-trifluoroethyl)phosphonoacetate, potassium hexamethyldisilazide, 18-crown-6,



Scheme 7 Cross-metathesis, Still–Gennari *Z*-olefination, and completion of the synthesis

tetrahydrofuran, –78 °C) to give the *Z*-α,β-unsaturated ethyl ester **2** in 52% overall yield from **19**, with a *Z*/*E* ratio of 97:3.[26,27] Finally, one-pot deprotection and intramolecular lactonization of **2** (80% AcOH) gave rugulactone **1** in 86% yield (30% overall yield from **15**).[18a] The analytical and spectral data of the synthetic product were in good agreement with those reported in the literature.[1,17]

In summary, a total asymmetric synthesis of rugulactone **1** was realized in seven steps from commercially available (2*S*)-glycidyl tosylate (**16**) with an overall yield of 19%. It is noteworthy that the stereogenic center at C5 was controlled by using the chiral pool, that the internal olefin was built by using a cross-metathesis coupling, and that the *Z*-configured unsaturated lactone was formed by a Still–Gennari olefination/lactonization. The absence of expensive chiral reagents in stoichiometric quantities and the use of only a single catalytic step make this synthesis cost-efficient and green. Furthermore, the synthetic pathway is highly flexible and will be used to synthesize isomers and analogues of rugulactone for in-depth biological tests; this work will be published in due course.

CH_2Cl_2 (stabilized with 2-methylbut-2-ene) was purified by distillation from CaH_2 under N_2 immediately before use. THF and Et_2O

were purified by distillation from sodium/benzoquinone under N_2. Moisture and O_2-sensitive reactions were carried out in flame-dried glassware under N_2. Evaporations were conducted under reduced pressure at a temperature below 35 °C unless otherwise noted. Column chromatography was carried out under a positive pressure of N_2 on 40–63 m silica gel. Melting points are uncorrected. ^{1}H NMR spectra of samples in the indicated solvent were recorded at 300 MHz at 20 °C (^{1}H NMR: $CDCl_3$ residual signal at 7.26 ppm). ^{13}C NMR spectra of samples in the indicated solvent were recorded at 75 MHz at 20 °C (^{13}C NMR: $CDCl_3$ residual signal at 77.26 ppm). High-resolution mass spectra were recorded on a Tof-MS spectrometer operating in the ESI (+) mode. All reported yields are uncorrected and refer to the purified products.

(4*S*)-2,2-Dimethyl-4-{2-[(4-methylbenzyl)oxy]ethyl}-1,3-dioxolane (8)

A 60% dispersion of NaH (4.21 g, 0.105 mol) was added to a soln of alcohol **7** (10.25 g, 70 mmol) in THF (25 mL) and DMF (25 mL) at r.t., and the mixture was stirred for 30 min. PMBCl (14.25 mL, 0.105 mol) and Bu_4NI (1.3 g, 3.5 mmol) were added sequentially, and the mixture was stirred for a further 12 h. The reaction was quenched with sat. aq NH_4Cl and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography [cyclohexane–EtOAc (9:1)] gave a yellow oil; yield: 17.5 g (94%); $[\alpha]_D^{25}$ –7.9 (*c* 0.1, MeOH) [Lit.[20b] –8.4 (*c* 0.8, MeOH)]. The spectral data agreed well with literature values.[20b]

IR (neat): 2984, 2865, 1612, 1513 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.4 Hz, 2 H, 7-H), 6.87 (d, *J* = 8.4 Hz, 2 H, 8-H), 4.43 (s, 2 H, 5-H), 4.20 (ddt_{app}, *J* = 8.0, 6.3 and 5.7 Hz, 1 H, 1-H), 4.05 (dd, *J* = 8.0 and 6.0 Hz, 1 H, 2-H), 3.80 (s, 3 H, 10-H), 3.59–3.50 (m, 3 H, 4-H + 1-H), 1.96–1.79 (m, 2 H, 3-H), 1.40 (s, 3 H, 11-H, acetonide), 1.35 (s, 3 H, 12-H acetonide).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5 (s, 9-C), 130.0 (s, 6-C), 129.4 (d, 7-C), 114.1 (d, 8-C), 108.8 [s, *C*$(OMe)_2$], 74.2 (d, 2-C), 73.0 (t, 5-C), 69.9 (t, 1-C), 67.0 (t, 4-C), 55.5 (q, 10-C), 34.1 (t, 3-C), 27.2 (q, 11-C), 26.0 (q, 12-C).

(2*S*)-4-[(4-Methylbenzyl)oxy]butane-1,2-diol (9)

Oxalic acid (16.9 mg, 0.188 mmol) was added to a soln of **8** (1.0 g, 3.75 mmol) and $CeCl_3 \cdot 7H_2O$ (2.79 g, 7.5 mmol) in MeCN (18.8 mL) at r.t., and the mixture was stirred for 90 min at r.t. The mixture was then cooled to 0 °C and the reaction was quenched with sat. aq $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography [cyclohexane–EtOAc (8:2)] to give a thick yellow oil; yield: 823 mg (97%); $[\alpha]_D^{23}$ +3.9 (*c* 0.1, $CHCl_3$) {Lit.[20b] $[\alpha]_D^{25}$ +4.4 (*c* 0.8, $CHCl_3$)}. The spectral data agreed well with literature values.[20b]

IR (neat): 3373, 2932, 2863, 1612, 1586, 1512 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.4 Hz, 2 H, 7-H), 6.88 (d, *J* = 8.4 Hz, 2 H, 8-H), 4.45 (s, 2 H, 5-H), 3.90 (m, 1 H, 1-H), 3.80 (s, 3 H, 10-H), 3.70–3.60 (m, 3 H, 2-H + 4-H), 3.52–3.48 (m, 1 H, 1-H), 3.11 (d, *J* = 3.3 Hz, 1 H, OH), 2.31 (t, *J* = 6.0 Hz, 1 H, OH), 1.87–1.70 (m, 2 H, 3-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (s, 9-C), 130.1 (s, 6-C), 129.5 (d, 7-C), 114.0 (d, 8-C), 72.8 (t, 5-C), 70.7 (d, 2-C), 67.5 (t, 1-C), 66.6 (t, 4-C), 55.3 (q, 10-C), 33.0 (t, 3-C).

(2*S*)-2-{2-[(4-Methylbenzyl)oxy]ethyl}oxirane (10)

A soln of diol **9** (11.68 g, 51.6 mmol) in THF (200 mL) was added to a suspension of NaH (60% dispersion, 5.16 g, 0.129 mol) in DMF (50 mL) at 0 °C, and the mixture was stirred for 30 min. 1-[(2,4,6-Triisopropylphenyl)sulfonyl]-1*H*-imidazole (19 g, 56.8 mmol) was added and the soln was stirred at r.t. overnight. The reaction was quenched with sat. aq NH_4Cl, and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography [cyclohexane–EtOAc (7:3)] gave a thick colorless oil; yield: 5.74 g (53%); $[\alpha]_D^{21}$ –15.8 (*c* 0.1, $CHCl_3$) {Lit.[20b] $[\alpha]_D^{25}$ –13.1 (*c* 0.58, $CHCl_3$)}. The spectral data agreed well with literature values.[20b]

IR (neat): 2924, 2862, 1612, 1586, 1512 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.7 Hz, 2 H, 7-H), 6.86 (d, *J* = 8.7 Hz, 2 H, 8-H), 4.45 (s, 2 H, 5-H), 3.79 (s, 3 H, 10-H), 3.58 (m, 2 H, 4-H), 3.04 (m, 1 H, 2-H), 2.75 (dd_{app}, *J* = 5.0 and 4.4 HZ, 1 H, 1-H), 2.50 (dd_{app}, *J* = 5.0 and 2.7 Hz, 1 H, 1-H), 1.88 (m, 1 H, 3-H), 1.76 (m, 1 H, 3-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5 (s, 9-C), 130.0 (s, 6-C), 129.4 (d, 7-C), 114.1 (d, 8-C), 73.0 (t, 5-C), 67.0 (t, 4-C), 55.5 (q, 10-C), 50.3 (s, 2-C), 47.3 (t, 1-C), 33.2 (t, 3-C).

(3*R*)-1-[(4-Methoxybenzyl)oxy]hex-5-en-3-ol (11)

A 1.0 M soln of CH_2=CHMgCl in THF (5.3 mL, 5.3 mmol) was added to a stirred suspension of CuI (44 mg, 0.23 mmol) in THF (12 mL) at –50 °C, and the mixture was stirred for 30 min. A soln of the epoxide **10** (417 mg, 2.3 mmol) in THF (5 mL) was added by cannula. The resulting mixture was stirred at –40 °C for 40 min then allowed to warm to –10 °C over 30 min. The reaction was quenched by addition of sat. aq NH_4Cl. The residue was extracted with Et_2O, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography [cyclohexane–EtOAc (6:4)] to give a thick colorless oil; yield: 470 mg (87%); $[\alpha]_D^{20}$ +5.8 (*c* 1.37, $CHCl_3$) {Lit.[28] $[\alpha]_D^{25}$ +3.2 (*c* 1.0, $CHCl_3$)}. The spectral spectral data agreed well with literature values.[28]

IR (neat): 3445, 3072, 2930, 2861, 1612, 1513, 1461, 1362, 1300, 1247, 1175, 1089, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.2 Hz, 2 H, 9-H), 6.84 (d, *J* = 8.2 Hz, 2 H, 10-H), 5.80 (ddt, *J* = 6.3, 10.5 and 17.1 Hz, 1 H, 2-H), 5.07 (d, *J* = 17.1 Hz, 1 H, 1-H *trans*), 5.06 (d, *J* = 10.5 Hz, 1 H, 1-H *cis*), 4.42 (s, 2 H, 7-C), 3.77 (s, 3 H, 12-H), 3.89–3.55 (m, 3 H, 4-H + 6-H), 2.97 (br s, 1 H, OH), 2.21 (t_{app}, *J* = 6.3 Hz, 2 H, 3-H), 1.73 (t_{app}, *J* = 5.4 Hz, 2 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (s, 11-C), 135.1 (d, 2-C), 130.3 (s, 8-C), 129.5 (d, 9-C), 117.6 (t, 1-C), 114.0 (d, 10-C), 73.1 (t, 7-C), 70.5 (d, 4-C), 68.8 (t, 6-C), 55.4 (q, 12-C), 42.1 (t, 3-C), 36.0 (t, 5-C).

***tert*-Butyl[((1*R*)-1-{2-[(4-methoxybenzyl)oxy]ethyl}but-3-en-1-yl)oxy]dimethylsilane (4)**

TBSCl (244 mg, 1.62 mmol) was added to a stirred soln of the alcohol **15** (318 mg, 1.35 mmol) and imidazole (230 mg, 3.38 mmol) in DMF (1 mL) at r.t., and the mixture was stirred for 12 h until the reaction was complete (TLC). Sat. aq $NaHCO_3$ (6 mL) was added, and the mixture was extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography [cyclohexane–EtOAc (6:4)] to give a thick colorless oil; yield: 462 mg (98%); $[\alpha]_D^{20}$ –16.9 (*c* 0.8, $CHCl_3$) [Lit.[24a] –15.7 (*c* 1.65, $CHCl_3$)]. The spectral data agreed well with literature values.[24a]

IR (neat): 3076, 2956, 2930, 2858, 1614, 1515, 1250 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.4 Hz, 2 H, 9-H), 6.87 (d, *J* = 8.1 Hz, 2 H, 10-H), 5.81 (m, 1 H, 2-H), 5.03 (d_{app}, *J* = 12.9 Hz, 2 H, 1-H), 4.44 (B of AB system, d, *J* = 11.1 Hz, 1 H, 7-H), 4.38 (A of AB system, d, *J* = 11.1 Hz, 1 H, 7-H), 3.89 (m, 1 H, 4-H), 3.80 (s, 3 H, 12-H), 3.51 (t_{app}, *J* = 6.3 Hz, 2 H, 6-H), 2.23 (m, 2 H, 3-H), 1.74 (m, 2 H, 5-H), 0.88 (s, 9 H, Si-*t*-Bu), 0.05 (d, *J* = 2.1 Hz, 6 H, $SiMe_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (s, 11-C), 135.2 (d, 2-C), 131.0 (s, 8-C), 129.5 (d, 9-C), 117.2 (t, 1-C), 114.0 (d, 10-C), 72.8

(t, 7-C), 69.2 (d, 4-C), 67.0 (t, 6-C), 55.5 (q, 12-C), 42.5 t, 3-C), 37.0 (t, 5-C), 26.1 [q, SiC(CH_3)$_3$], 18.3 [s, SiC(CH$_3$)$_3$], –4.1 (q, SiMe$_2$), –4.5 (q, SiMe$_2$).

(4*E*,7*R*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-9-[(4-methoxybenzyl)oxy]-1-phenylnon-4-en-3-one (12)[22a]

A soln of alkene **4** (84 mg, 0.24 mmol) and vinyl ketone **5** (115.3 mg, 7.2 mmol) in CH_2Cl_2 (12 mL) was bubbled with a N_2 flow before Grubbs type II catalyst **A** (10.2 mg, 0.012 mmol) was added at once. The mixture was then heated under N_2 at 40 °C for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel; cyclohexane–EtOAc (95:5)] to give a thick clear oil; yield: 83.4 mg (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.07 (m, 7 H, aromatic-H), 6.98–6.72 (m, 3 H, aromatic-H + 5-H), 6.09 (d, J = 15.9 Hz, 1 H, 4-H), 4.43 (B of AB system, d, J = 11.4 Hz, 1 H, 10-H), 4.34 (A of AB system, d, J = 11.4 Hz, 1 H, 10-H), 3.98 (m, 1 H, 7-H), 3.79 (s, 3 H, 15-H), 3.48 (m, 2 H, 9-H), 2.89 (m, 4 H, 1-H + 2-H), 2.36 (m, 2 H, 6-H), 1.71 (m, 2 H, 8-H), 0.87 [s, 9 H, SiC(CH_3)$_3$], 0.03 (s, 6 H, SiMe$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4 (s, 3-C, C=O), 159.5 (s, 14-C), 144.1 (d, 5-C), 141.5 (s, Ph), 132.7 (d, 4-C), 130.7 (s, 11-C), 129.5 (d, 12-C), 128.7 (d, Ph), 128.6 (d, Ph), 126.3 (d, Ph), 114.0 (d, 13-C), 72.9 (t, 10-C), 68.7 (d, 7-C), 66.6 (t, 9-C), 55.5 (q, 15-C), 41.7 (t, 2-C), 41.0 (t, 6-C), 37.4 (t, 8-C), 30.3 [t, 1-C), 26.0 SiC(CH_3)$_3$], 18.3 [s, SiC(CH$_3$)$_3$], –4.2 (q, SiMe$_2$), –4.4 (q, SiMe$_2$).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{29}H_{42}NaO_4Si$: 505.2750; found: 505.2742.

(2*R*)-1-(1,3-Dithian-2-yl)pent-4-en-2-ol (18)

A 1.4 M soln of BuLi in hexane (17 mL, 23.8 mmol) was added to a soln of 1,3-dithiane (2.8 g, 23.3 mmol) in THF (31 mL) at –10 °C. The soln was stirred at –10 °C for 2 h and then cooled to –78 °C. A soln of (2*S*)-glycidyl tosylate (**16**; 5 g, 22.0 mmol) in THF (8 mL) was added by cannula, and the soln was kept at –78 °C for 4 h then allowed to warm to r.t. over 2 h. Sat. aq $NaHCO_3$ was added and the mixture was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified to flash column chromatography [cyclohexane–EtOAc (9:1)] to give the epoxide **17** as a colorless oil; yield: 2.6 g (14.9 mmol).

A 1.0 M soln of CH_2=CHMgBr in THF (22 mL, 22 mmol) was added to a stirred suspension of CuI (500 mg, 2.6 mmol) in THF (70 mL) at –50 °C, and the mixture was stirred for 30 min. A soln of the epoxide **17** (2.6 g, 14.9 mmol) in THF (10 mL) was then added by cannula, and the mixture was stirred at –40 °C for 40 min then allowed to warm to –10 °C over 30 min. The reaction was quenched by the addition of sat. aq NH_4Cl. The residue was extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography [cyclohexane–EtOAc (9:1)] to give secondary alcohol **18** as a thick colorless oil; yield: 2.8 g (63%); [α]$_D^{22}$ +22.4 (*c* 0.2, $CHCl_3$) {Lit.[24a] [α]$_D^{26}$ +24.2 (1.0, $CHCl_3$)}.

IR (neat): 3432, 1640, 1422, 1275, 1244 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.89–5.74 (m, 1 H, 2-H), 5.14 (d, J = 12.9 Hz, 2 H, 1-H), 4.27 (t, J = 7.3 Hz, 1 H, 6-H), 3.99 (br, 1 H, 4-H), 2.97–2.81 (m, 4 H, 7-H), 2.33–2.20 (m, 2 H, 3-H), 2.18–2.10 (m, 2 H, 8-H), 2.03 (br, 1 H, OH), 1.89 (t, J = 6.8 Hz, 2 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.9 (d, 2-C), 118.2 (t, 1-C), 67.4 (d, 4-C), 44.4 (t, 5-C), 42.1 (d, 6-C), 41.9 (t, 3-C), 30.3 (t, 7-C), 30.0 (t, 8-C).

HRMS: *m/z* [M]$^+$ calcd for $C_9H_{16}OS_2$: 204.0643; found: 204.0651.

{[(1*R*)-1-(1,3-Dithian-2-ylmethyl)but-3-en-1-yl]oxy}(triethyl)silane (15)

TESCl (1.6 mL, 9.5 mmol) was added to a stirred soln of the alcohol **18** (1.4 g, 6.8 mmol), imidazole (1.83 g, 27 mmol), and DMAP (200 mg, 1.6 mmol) in DMF (5 mL) at 0 °C. The mixture was then stirred at r.t. for 12 h until the reaction was complete (TLC). Aq $NaHCO_3$ (20 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane–EtOAc 95:5) to give a thick colorless oil; yield: 2.1 g (98%); [α]$_D^{21}$ –26.0 (*c* 0.128, $CHCl_3$) {Lit.[24b] [α]$_D^{22}$ –28.8 (*c* 0.13, $CHCl_3$)}. The spectral data agreed well with the literature values.[24b]

IR (neat): 742, 915, 1005, 1088, 1240, 1275, 1373, 1422, 1458, 1640, 2876, 2904, 2953 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.71 (m, 1 H, 2-H), 5.09–5.03 (m, 2 H, 1-H), 4.11 (dd, J = 6.0 and 8.4 Hz, 1 H, 6-H), 3.98–4.06 (m, 1 H, 4-H), 2.93–2.78 (m, 4 H, 7-H), 2.27–2.22 (m, 2 H, 8-H), 2.15–2.05 (m, 1 H, 3-H), 1.94–1.79 (m, 3 H, 3-H + 5-H), 0.97 (t, J = 8.1 Hz, 9 H, SiCH$_2$$CH_3$), 0.63 (q, J = 8.1 Hz, 6 H, SiCH_2CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.5 (d, 2-C), 117.8 (t, 1-C), 68.4 (d, 4-C), 44.2 (t, 5-C), 42.6 (d, 6-C), 30.8 (t, 3-C), 30.3 (t, 7-C), 26.4 (t, 8-C), 7.2 (t, SiCH$_2$CH$_3$), 5.4 (q, SiCH$_2$$CH_3$).

HRMS: *m/z* [M + H]$^+$ calcd for $C_{15}H_{30}OS_2Si$: 319.1586; found: 319.1587.

5-Phenyl-pent-1-en-3-one (5)

A soln of Ph(CH$_2$)$_2$CHO (**6**; 1.0 g, 7.462 mmol) in THF (20 mL) was added dropwise to a stirred 1 M soln of CH_2=CHMgBr in THF (11.2 mL, 11.18 mmol) at 0 °C, and the mixture was brought to r.t. and stirred for 1 h. When the reaction was complete (TLC), it was quenched with sat. aq NH_4Cl, and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, cyclohexane–EtOAc (7:3)] to give the corresponding homoallylic alcohol as a clear liquid; yield: 1.12 g (92%).

IR (neat): 3349, 1604, 1498, 1455, 1428, 1403, 750, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.14 (m, 5 H, aromatic-H), 5.92 (ddd, J = 6.3, 10.2 and 17.1 Hz, 1 H, 2-H), 5.27 (d, J = 17.1 Hz, 1 H, 1-H *trans*), 5.16 (d, J = 10.2 Hz, 1 H, 1-H *cis*), 4.14 (dt, J = 6.0 and 6.3 Hz, 1 H, 3-H), 2.74 (m, 2 H, 5-H), 1.97 (br s, 1 H, OH), 1.94–1.80 (m, 2 H, 4-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1 (s, 6-C), 141.2 (d, 2-C), 128.7 (d, 8-C), 128.6 (d, 7-C), 126.0 (d, 9-C), 115.0 (t, 1-C), 72.6 (d, 3-C), 38.7 (t, 5-C), 31.8 (t, 4-C).

A soln of the homoallylic alcohol obtained above (800 mg, 4.92 mmol) in CH_2Cl_2 (10 mL) was added to a stirred soln of Dess–Martin periodinane (2.3 g, 5.41 mmol) in dry CH_2Cl_2 (10 mL) at r.t., and the mixture was stirred for 3 h. When the reaction was complete, the mixture was filtered, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography [silica gel, cyclohexane–EtOAc (8:2)] to give the pure vinyl ketone **5** as a colorless liquid; yield: 757.0 mg (96%).

IR (neat): 3061, 3027, 2925, 2856, 1709, 1605, 1495, 1450, 1403, 750, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.11 (m, 5 H, aromatic-H), 6.33 (dd, J = 10.2 and 17.7 Hz, 1 H, 2-H), 6.18 (d, J = 17.7 Hz, 1 H, 1-H *trans*), 5.79 (d, J = 10.2 Hz, 1 H, 1-H *cis*), 3.00–2.80 (m, 4 H, 4-H + 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8 (s, 3-C, C=O), 141.3 (s, 6-C), 136.7 (d, 2-C), 128.9 (d, 8-C), 128.5 (t, 7-C), 126.3 (t, 1-C), 41.4 (t, 4-C), 30.0 (t, 5-C).

(4*E*,7*R*)-8-(1,3-Dithian-2-yl)-1-phenyl-7-[(triethylsilyl)oxy]oct-4-en-3-one (19)

A soln of alkene **15** (663 mg, 2.08 mmol) and vinyl ketone **5** (1.0 g, 6.24 mmol) in CH_2Cl_2 (104 mL) was bubbled with a N_2 flow before Grubbs type II catalyst **A** (88.3 mg, 0.104 mmol) was added at once. The resulting mixture was heated under N_2 at 40 °C for 12 h. When the reaction was complete, the solvent was removed under reduced pressure and the residue was purified by column chromatography [silica gel, cyclohexane–EtOAc (95:5)] to give a thick clear oil; yield: 675 mg (72%); $[\alpha]_D^{21}$ –3.4 (*c* 0.1, $CHCl_3$).

IR (neat): 3024, 2952, 2901, 2875, 1673, 1630, 1454, 1371, 1238, 1084, 1046, 724 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.11 (m, 5 H, aromatic-H), 6.80 (dt, *J* = 7.2 and 15.9 Hz, 1 H, 5-H), 6.13 (d, *J* = 15.9 Hz, 1 H, 4-H), 4.20–4.05 (m, 2 H, 7-H + 9-H), 3.10–2.71 (m, 8 H, 1-H + 2-H + 10-H), 2.45–2.30 (m, 2 H, 6-H), 2.19–2.01 (m, 2 H, 8-H), 1.95–1.77 (m, 2 H, 11-H), 0.97 (t, *J* = 8.1 Hz, 9 H, $SiCH_2CH_3$), 0.63 (q, *J* = 8.1 Hz, 6 H, $SiCH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.3 (s, 3-C, C=O), 143.0 (d, 5-C), 141.5 (s, Ph), 133.0 (d, 4-C), 128.7 (d, Ph), 128.6 (d, Ph), 126.3 (d, Ph), 67.9 (t, 7-C), 44.0 (t, 8-C), 43.1 (d, 9-C), 41.9 (t, 2-C), 41.0 (t, 6-C), 30.8 (t, 1-C), 30.3 (t, 10-C), 26.2 (t, 11-C), 7.2 (t, $SiCH_2CH_3$), 5.3 (q, $SiCH_2CH_3$).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{38}NaO_2S_2Si$: 473.1980; found: 473.1985.

Methyl (2*Z*,5*R*,7*E*)-9-Oxo-11-phenyl-5-[(triethylsilyl)oxy]undeca-2,7-dienoate (2)

A stirred mixture of enone **19** (225 mg, 0.5 mmol), MeI (0.32 mL, 5.1 mmol), and $CaCO_3$ (100 mg, 2.6 mmol) in 9:1 v/v MeCN–H_2O (16.7 mL) was heated at 45 °C for 2.5 h then cooled to r.t. and the bulk of the MeCN was removed. The mixture was then extracted with Et_2O (3 × 30 mL), dried (Na_2SO_4), and concentrated to provide the crude aldehyde **3′**, which was used directly in the next step.

Methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]propanoate (**B**; 0.25 mL, 381 mg, 1.19 mmol) and a 0.5 M soln of KHMDS in toluene (2.4 mL, 1.19 mmol) were added sequentially to a stirred soln of 18-crown–6 (330 mg, 1.25 mmol) in dry THF (5.2 mL) at –40 °C under argon. After 15 min, the mixture was cooled to –78 °C and stirred for an additional 30 min. Crude aldehyde **3′** (0.5 mmol) in dry THF (2.6 mL) was added, and the resulting mixture was stirred at –78 °C for 4 h. When the starting material **3′** was completely consumed (TLC), the reaction was quenched with sat. aq $NaHCO_3$ (10 mL) at –78 °C. The cooling bath was removed and then the mixture was extracted with EtOAc (3 × 25 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography [cyclohexane–EtOAc (9:1)] to give ester **2**; yield: 108.4 mg (52% isolated yield from **19**); $[\alpha]_D^{22}$ +109.4 (*c* 0.1, $CHCl_3$).

IR (neat): 2960, 2909, 2877, 1721, 1675, 1634, 1437, 1174, 1089, 1002, 737 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.11 (m, 5 H, aromatic-H), 6.84 (dt, *J* = 7.2 and 16.0 Hz, 1 H, 5-H), 6.35 (dt, *J* = 7.5 and 11.4 Hz, 1 H, 9-H), 6.12 (d, *J* = 16.0 Hz, 1 H, 4-H), 5.89 (d, *J* = 11.4 Hz, 1 H, 10-H), 4.00 ($quint_{app}$, *J* = 5.7 Hz, 1 H, 7-H), 3.68 (s, 3 H, 12-H), 3.05–2.80 (m, 6 H, 1-H + 2-H + 6-H), 2.37 (t_{app}, *J* = 6.3 Hz, 2 H, 8-H), 0.95 (t, *J* = 7.8 Hz, 9 H, $SiCH_2CH_3$), 0.61 (q, *J* = 7.8 Hz, 6 H, $SiCH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4 (s, 3-C, C=O ketone), 166.8 (s, 11-C, C=O ester), 145.9 (d, 9-C), 143.7 (d, 5-C), 141.5 (s, Ph), 132.8 (d, 4-C), 128.7 (d, Ph), 128.6 (d, Ph), 126.3 (d, Ph), 121.4 (d, 10-C), 70.8 (d, 7-C), 51.3 (q, 12-C), 41.7 (t, 2-C), 40.7 (t, 6-C), 36.7 (t, 8-C), 30.3 (t, 1-C), 7.1 (t, $SiCH_2CH_3$), 5.2 (q, $SiCH_2CH_3$).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{36}NaO_4Si$: 439.2281; found: 439.2295.

Rugulactone (1)

Enone **2** (129.2 mg, 0.31 mmol, 1 equiv) was dissolved in 80% AcOH (1.5 mL) and the soln was stirred at 60 °C for 24 h. The reaction was quenched with sat. aq $NaHCO_3$ and the mixture was extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography [cyclohexane–EtOAc (6:4)]; yield: 72.1 mg (86%); $[\alpha]_D^{25}$ –47.0 (*c* 0.3, $CHCl_3$) [Lit.[17a] –46.5 (*c* 0.7, $CHCl_3$)]. The spectral data agreed well with the literature values.[17]

IR (neat): 3448, 2922, 2852, 1720, 1671, 1632, 1457, 1382, 1247, 1042 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.11 (m, 5 H, aromatic-H), 6.88 (ddd, *J* = 3.9, 4.8 and 9.6 Hz, 1 H, 7-H), 6.80 (dt, *J* = 7.2 and 16.2 Hz, 1 H, 3-H), 6.20 (d, *J* = 16.2, 1 H, 2-H), 6.05 (d, *J* = 9.6 Hz, 1 H, 8-H), 4.55 ($quint_{app}$, *J* = 6.6 Hz, 1 H, 5-H), 2.94–2.86 (m, 4 H, 10-H + 11-H), 2.64 (dt_{app}, *J* = 6.6 and 7.2 Hz, 2 H, 4-H), 2.33 (m, 2 H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.2 (s, 9-C, C=O ketone), 163.9 (s, 1-C, C=O ester), 144.8 (d, 3-C), 141.3 (s, 12-C), 140.2 (d, 7-C), 133.8 (d, 8-C), 128.7 (d, 14-C), 128.6 (d, 13-C), 126.4 (d, 15-C), 121.8 (d, 2-C), 76.3 (d, 5-C), 42.0 (t, 10-C), 37.8 (t, 6-C), 30.2 (t, 11-C), 29.2 (t, 4-C).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{17}H_{18}NaO_3$: 293.1154; found: 293.1163.

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