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Preparation of *cis*-γ-Hydroxycarvone Derivatives for Synthesis of Sesterterpenoid Natural Products: Total Synthesis of Phorbin A

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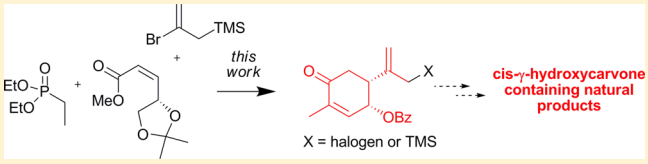
Supporting Information

ABSTRACT: A robust synthetic approach to *cis*-γ-hydroxycarvone derivatives has been developed, enabling efficient access to synthetic building blocks for the growing family of bioactive sesterterpenoid natural products. Using this approach, an allyl bromide carvone derivative was used as the key building block for the total synthesis of the natural product phorbin A. This synthetic sequence also demonstrates the utility of benozyl enol ethers as an effective means of masking a β-ketophosphonate and their subsequent application in a one-pot benzoyl transfer−intramolecular Horner−Wadsworth−Emmons reaction.



INTRODUCTION

Sesterterpenoids represent a relatively small family of terpenoid-based natural products that have been shown to exhibit a broad spectrum of biological activity.[1−3] A subset of sesterterpenoid natural products that has grown considerably in the past decade are those which contain a distinct *cis*-γ-hydroxycarvone moiety (Figure 1 and 2, red).

The phorbaketals, alotaketals, and gombaspiroketals are sesterterpenoid natural products which share a common 6,6-spiroketal core structure. Phorbaketals A−C[4] (**1**−**3**) and L−N[5] (**12**−**14**) were isolated from the marine sponge *Phorbas* sp., while phorbaketals D−K[6] (**4**−**11**) were isolated from *Monanchora* sp., both collected off the coast of Gageo Island, South Korea. Phorbaketal A (**1**) was found to promote osteogenic differentiation in human mesenchymal stem cells, mediated by the transcription factor Runx2 and its transcriptional coactivator TAZ.[7] Phorbaketal A (**1**) has also displayed inhibition of adipocyte differentiation, mast cell activity, and fatty acid synthesis in the liver as well as NR4A and LXR receptor agonist activity.[8−11] Various members of the phorbaketal family have displayed cytotoxic activity in a range of human cancer cell lines.[4−6] Alotaketals A (**15**) and B (**16**) were isolated from the marine sponge *Hamigera* sp., collected near Milne Bay in Papua New Guinea, while the closely related alotaketal C (**17**) was later isolated from *Phorbas* sp. collected in British Columbia.[12,13] These compounds were then shown to activate the cAMP signaling pathway in HEK293 cells with EC_{50} values of 18 nM and 240 nM for **15** and **16**, respectively. Gombaspiroketals A−C (**18**−**20**) were recently isolated from the Korean sea sponge *Clathria gombawuiensi*.[14] These compounds exhibited cytotoxicity against the K562 (LC_{50} 0.85−1.45 μM) and A549 (LC_{50} 0.77−4.65 μM) cancer cell lines. Gombaspiroketals A (**18**) and C (**20**) also displayed moderate antibacterial activity as well as inhibitory activity against Na^+/K^+−ATPase and isocitrate lyase.[14]

Ansellone A (**21**) was isolated from the sea sponge *Phorbas* sp. and the dorid nudibranch *Cadlina luteomarginata*, collected near Ansell Point in British Columbia and was shown to activate the cAMP signaling pathway in HEK293 cells (EC_{50} 14 μM).[15] Ansellone B (**23**), secoepoxyansellone A (**24**), and phorbadione (**25**) were discovered by careful analysis of the minor terpenoid products extracted from *Phorbas* sp.[13] The biological activity of these compounds has not been thoroughly investigated, with ansellone B (**23**) proving too cytotoxic for cAMP signaling activity assays and secoepoxyansellone A (**24**) and phorbadione (**25**) isolated in insufficient quantities for biological testing.

Phorbasones A (**26**) and B (**27**) were also isolated from *Phorbas* sp.[16] Phorbasone A (**26**) exhibits osteoblast differentiation activity, with a dose-dependent increase in calcium deposition observed in a culture of mesenchymal stem cells. Conversely, phorbasone B (**27**) was inactive in osteoblast differentiation assays.

Suberitenones A−D (**28**−**31**) were isolated from the sea sponge *Suberites* sp. collected in Antarctica.[17,18] Suberitenone B (**29**) was found to have moderate activity (LC_{50} 10 μmol/mL) against cholesteryl ester transfer protein (CETP), a glycoprotein responsible for the transfer of cholesterol esters and triglycerides between high-density-lipoproteins (HDL) and low-density-lipoproteins (LDL).

The monocyclic sesterterpenoid phorbin A (**32**) was also isolated along with phorbaketals D−K (**4**−**11**) and exhibits cytotoxic activity against a range of cancer cell lines.[6]

Despite the range of biological activity displayed by the natural products described above, synthetic endeavors toward these compounds have been limited, and only alotaketal A (**15**) has been successfully synthesized to date.[19−21] The common

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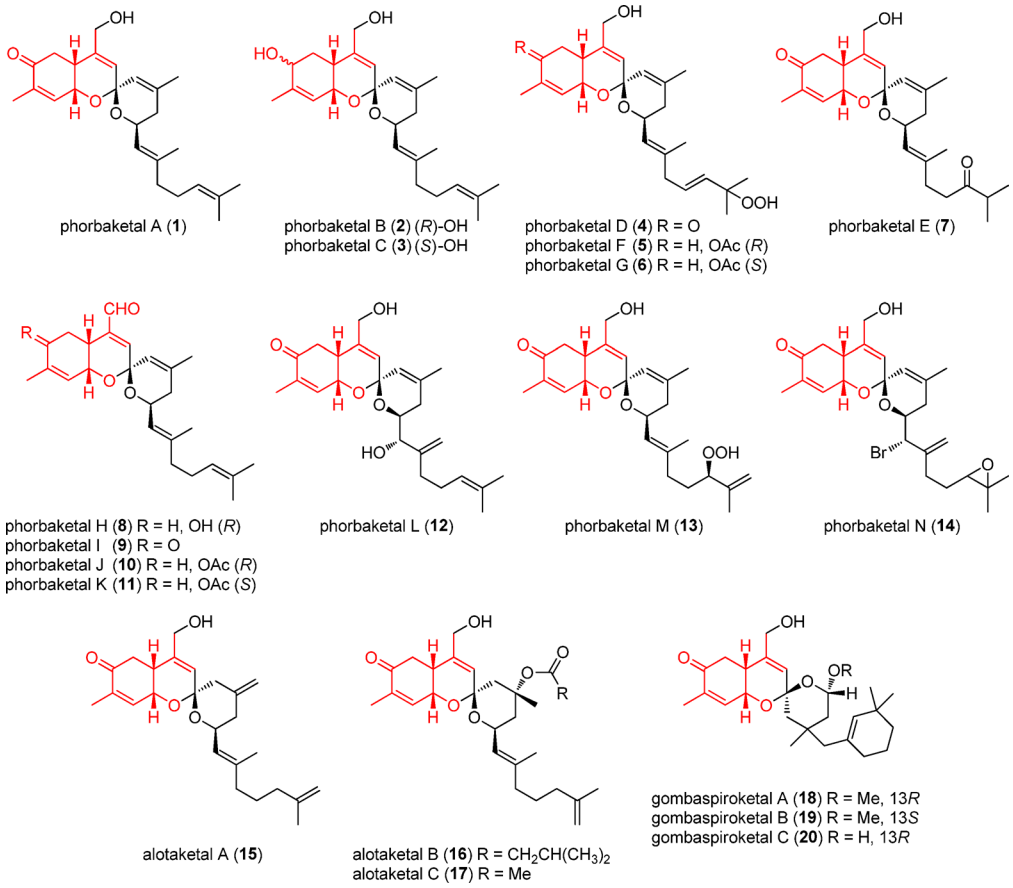

Figure 1. γ-Hydroxycarvone-containing sesterterpenoids with a spiroketal core structure.

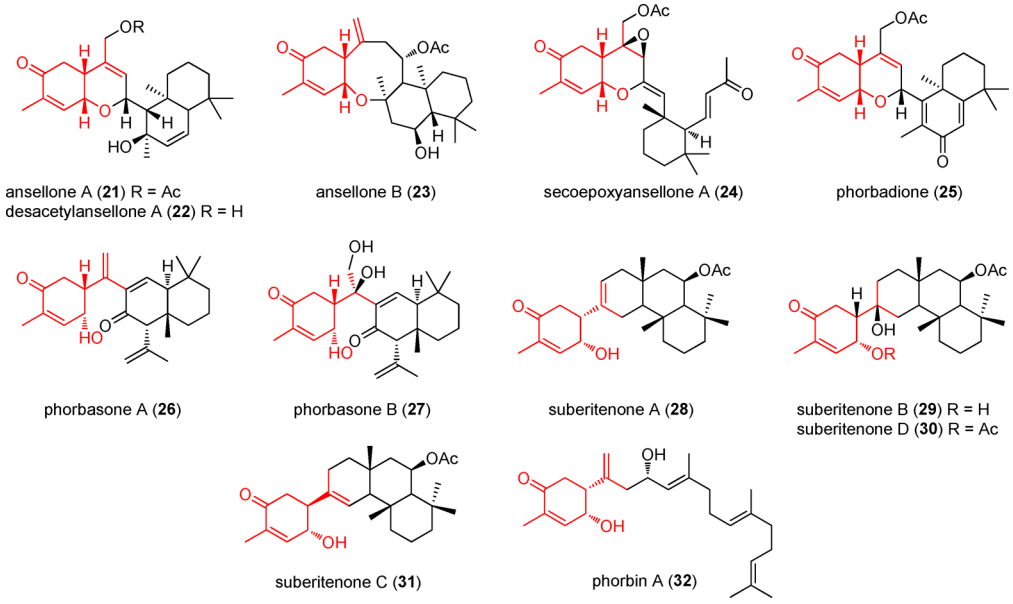

Figure 2. γ-Hydroxycarvone-containing sesterterpenoids.

challenge for the synthesis of these compounds is the construction of the *cis*-γ-hydroxycarvone framework, for which there are two main options: (A) start from readily available carvone (**33**) or (B) construct the framework from smaller synthetic subunits. Previous investigations into the installation of a γ-hydroxyl group on carvone have predominantly provided the corresponding *trans*-derivatives.[22−25] The first synthesis of *trans*-γ-hydroxycarvone **34** involved a lengthy nine-step sequence proceeding in an overall yield of 32%.[22] Yang et al. later developed a more efficient vinylogous *O*-nitroso Mukaiyama aldol reaction,[23] generating **34** in two steps from **33**. Hydroxycarvone **34** was later used by Yang and coworkers as the starting point for the total synthesis of alotaketal A (**15**), with the γ-stereocenter inverted en route using a

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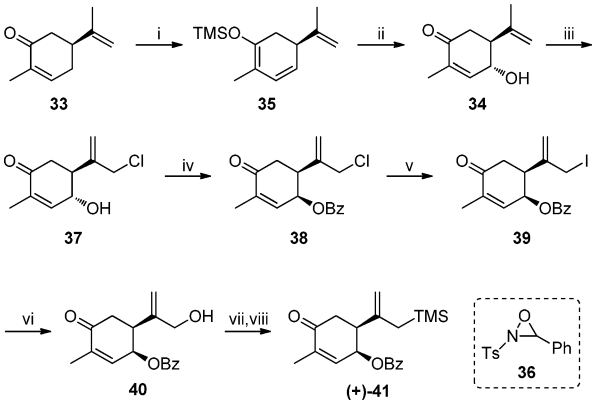
Mitsunobu reaction.[19,21] The construction of γ-hydroxycarvone derivatives from starting materials other than carvone (**33**) have been little investigated.

We envisaged that convenient access to functionalized synthetic intermediates possessing the *cis*-γ-hydroxycarvone moiety would greatly facilitate the total synthesis of this natural product family and analogues thereof. Herein, we report the synthesis of a range of useful *cis*-γ-hydroxycarvone derivatives, including a novel synthetic sequence which culminates in the first example of a Horner−Wadsworth−Emmons (HWE) reaction utilizing a benzoyl protected β-ketophosphonate. The established synthetic route was then utilized in the total synthesis of phorbin A (**32**).

RESULTS AND DISCUSSION

Synthesis of γ-Hydroxycarvone Derivatives from Carvone. We began our investigations toward *cis*-γ-hydroxycarvone derivatives from carvone (**33**), utilizing the vinylogous Mukaiyama *O*-nitroso-aldol procedure established by Yang and co-workers to introduce the γ-hydroxyl group.[23] Accordingly, carvone (**33**) was converted to known silyl dienol ether **35** using conditions originally described by Kharasch et al.,[26−29] followed by treatment with nitrosobenzene and acetic acid (Scheme 1). Unfortunately, in our hands, we found this

Scheme 1. Synthesis of Allylsilane 41 from Carvone (33)[a]



[a]Reagents and conditions: (i) $FeCl_3$, MeMgBr, Et_2O, then TMSCl, NEt_3, DMPU, −20 °C to rt; (ii) PhNO, AcOH, CH_2Cl_2, −78 °C to rt, 10−29% over two steps; (iii) $Ca(OCl)_2$, CO_2 (s), CH_2Cl_2, rt, 63%; (iv) DIAD, PPh_3, $PhCO_2H$, THF, 0 °C to rt, 71%; (v) NaI, acetone, rt, 94%; (vi) K_2CO_3, TFA, DMF, 40 °C, 63%; (vii) TFAA, NEt_3, DMAP, CH_2Cl_2, 0 °C to rt; (viii) $Pd(OAc)_2$, TMS-TMS, THF, rt, 44% over two steps.

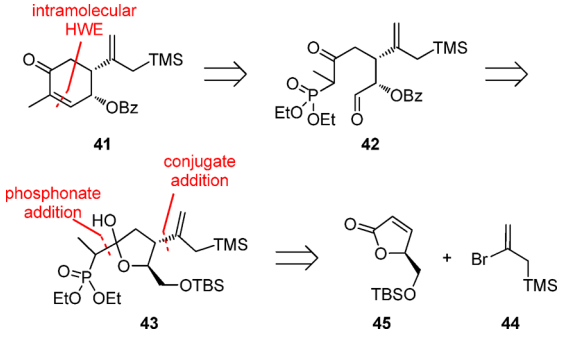
reaction produced a complex mixtures of products from which *trans*-γ-hydroxycarvone **34** could only be isolated in low 10−30% yield over two steps. The use of alternative electrophiles such as mCPBA or oxaziridine **36** gave no improvement. These observations were consistent with those of Dalby et al., who found that installation of a γ-hydroxyl group on carvone derivatives via a dienol ether intermediate to be a significant challenge during their synthesis of alotaketal A.[20]

Despite the low yields obtained for the preparation of *trans*-γ-hydroxycarvone **34**, its subsequent conversion to useful *cis*-hydroxycarvone derivatives was further investigated. Allylic chlorination of γ-hydroxycarvone **34** has previously been employed to provide known allyl chloride **37**, offering a convenient synthetic handle on the isopropenyl group (Scheme 1).[19,30] Mitsunobu inversion of the γ-hydroxyl group was applied to establish the desired *cis*-stereochemistry. The resulting benzoate ester was then used as a convenient protecting group to allow for further synthetic transformations. Treatment of chloride **38** with sodium iodide in acetone afforded allyl iodide **39** in excellent yield. A combination of trifluoroacetic acid and potassium carbonate in dimethylformamide was found to be effective for the hydrolysis of iodide **39**, providing access to allylic alcohol **40** in 63% yield. A carvone derivative bearing a mild nucleophilic motif was of interest and conversion of allylic alcohol **40** to allylsilane **41** was therefore investigated. To effect this transformation, **40** was converted to a trifluoroacetate ester followed by silylation using palladium(II) acetate and hexamethyldisilane to furnish **41** in 44% yield over two steps.[31]

cis-γ-Hydroxycarvone derivatives **38**−**41** are anticipated to be synthetically useful intermediates for the synthesis of natural products bearing the γ-hydroxycarvone moiety. However, despite the described route to these intermediates being relatively efficient, the low yielding procedure for the introduction of γ-hydroxyl group limited the scale on which they could be produced. We therefore investigated an alternative method for more robust production of such intermediates.

De Novo Synthesis of *cis*-γ-Hydroxycarvone Derivatives. Allylsilane **41** was chosen as a preliminary target compound due to its versatility as a synthetic intermediate. Retrosynthetically, it was envisaged that the cyclohexenone ring of allylsilane **41** could be constructed via an intramolecular HWE reaction of aldehyde **42** (Scheme 2). Aldehyde **42** would

Scheme 2. Retrosynthesis of Allylsilane 41



be derived from lactol **43** by trapping the secondary alcohol with a suitable protecting group followed by deprotection and oxidation. Lactol **43** would in turn be provided via *anti*-selective conjugate addition of a cuprate derived from vinyl bromide **44** to unsaturated lactone **45** and subsequent nucleophilic addition of diethyl ethylphosphonate.

The use of a mixed cyano-Gilman cuprate[32] was found to be the most effective method for the desired conjugate addition of bromide **44**[33,34] to known lactone **45**[35] (Scheme 3). Generation of the mixed cyanocuprate from the lithiate of bromide **44**, thiophen-2-yllithium and copper cyanide, followed by dropwise addition of lactone **45** afforded the desired product **46** in 71% yield as a single diastereomer. Nucleophilic addition of the lithium anion of diethyl ethylphosphonate to lactone **46** afforded lactol **43** as a mixture of diastereomers in 53% yield (67% brsm). However, despite screening a range of different electrophiles and conditions, phosphonate **43** was not able trapped as protected keto alcohol **48**. It was postulated that the

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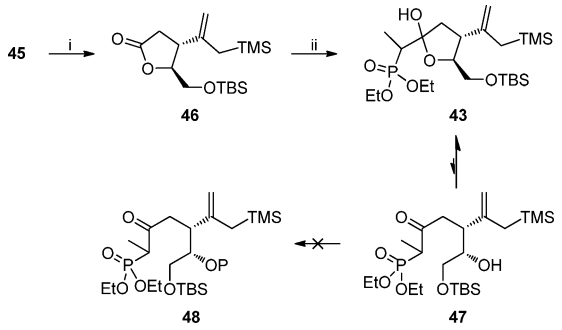
Scheme 3. Attempted Synthesis of Phosphonate 48[a]

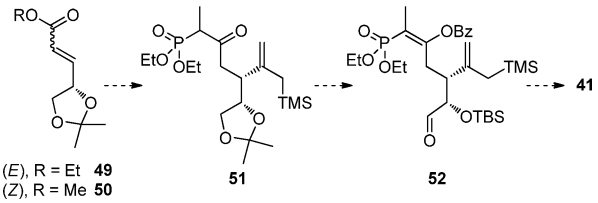


[a]Reagents and conditions: (i) **44**, *t*-BuLi, CuCN, Li-thiophene, then **45**, Et_2O, −78 °C, 71%; (ii) $EtP(O)(OEt)_2$, *n*-BuLi, THF, −78 °C, 53% (67% brsm)

equilibrium between lactol **43** and keto alcohol **47**, heavily favoring **43**, and steric hindrance of the secondary hydroxyl group of **47** prevented the desired protection reaction.

To circumvent the issues associated with the unproductive cyclic intermediate **43**, it was envisaged that substitution of electrophile **45** used in the above conjugate addition with known acyclic esters *E*-**49**[36,37] and *Z*-**50**[38] would avoid the use of any cyclic intermediates during the synthesis of enone **41** (Scheme 4) . It was proposed that by masking the *β*-

Scheme 4. Alternative Synthetic Approach to Allylsilane 41

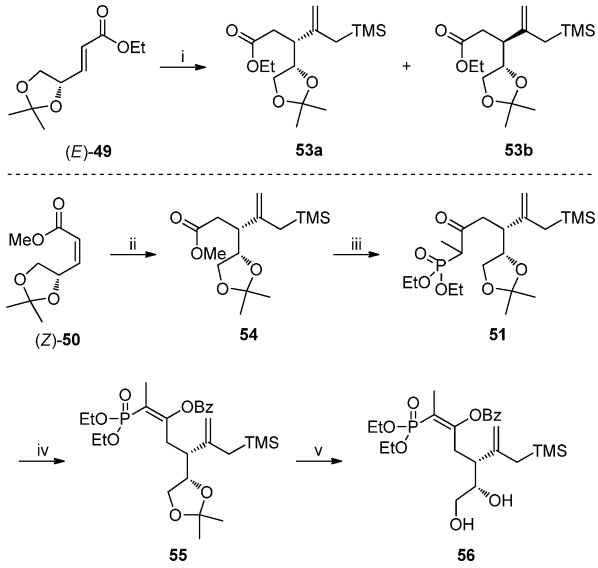


ketophosphonate moiety as a benzoyl enol ether the required protecting group and oxidation manipulations from **51** to provide HWE precursor **52** could be carried out without problematic lactol formation.

The mixed cyano-Gilman cuprate conditions, which were successfully utilized for the conjugate addition to lactone **45**, were applied to enoates **49** and **50** (Scheme 5). When *E*-enoate **49** was employed an inseparable 4:1 mixture of diastereomeric products **53a** and **53b** was furnished in 51% yield. Pleasingly, applying the same reaction conditions to *Z*-enoate **50** resulted in excellent *anti*-selectivity (>20:1), providing the desired *anti*-ester **54** in 76% yield. Nucleophilic addition of deprotonated diethyl ethylphosphonate to ester **54** proceeded more readily than the analogous addition to lactone **45**, furnishing *β*-ketophosphonate **51** in good yield.

To mask the *β*-ketophosphonate functionality, **51** was treated with benzoyl chloride, triethylamine and DMAP, readily affording benzoyl enol ether **55** in 88% yield. Acetonide deprotection in the presence of the acid sensitive allylsilane moiety proved challenging. After considerable investigation (see SI for table) a combination of CSA (one equivalent) in a mixture of acetonitrile, methanol and water (2:2:1) proved to be the most practically useful conditions, affording diol **56** in 47% yield along with recovered starting material. These conditions were successfully employed on up to an 8.8 g scale. It is of note that the cleavage of the benzoyl group was

Scheme 5. Synthesis of Diol 56[a]



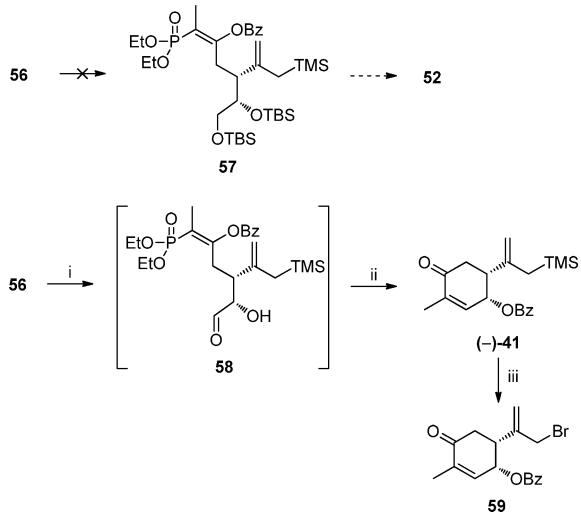
[a]Reagents and conditions: (i) **44**, *t*-BuLi, CuCN, Li-thiophene, then **49**, Et_2O, −30 °C, 51% (4:1); (ii) **44**, *t*-BuLi, CuCN, Li-thiophene, then **50**, Et_2O, −30 °C, 76%; (iii) $EtP(O)(OEt)_2$, *n*-BuLi, THF, −78 °C, 78%; (iv) BzCl, NEt_3, DMAP, CH_2Cl_2, rt, 88%; (v) CSA, MeCN-MeOH-H_2O (2:2:1), rt, 52% (88% brsm).

not observed under any of the conditions tested, demonstrating its utility as an acid-stable protecting group for *β*-ketophosphonates.

A double TBS protection/primary TBS cleavage/oxidation sequence was envisaged for the conversion of diol **56** to HWE precursor **52** (Scheme 6). However, although silylation of the primary alcohol proceeded readily, the significant steric bulk of the monoprotected species rendered the secondary alcohol resilient to silylation under a range of conditions.

It was hoped that the bulky neighboring substituents of diol **56** would provide adequate steric protection of the secondary alcohol to allow for selective oxidation of the primary alcohol.

Scheme 6. Synthesis of Allylsilane 41 and Allyl Bromide 59[a]



[a]Reagents and conditions: (i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt; (ii) NaH, THF, 0 °C to rt, 53% over two steps; (iii) NBS, THF, −78 °C, 100%.

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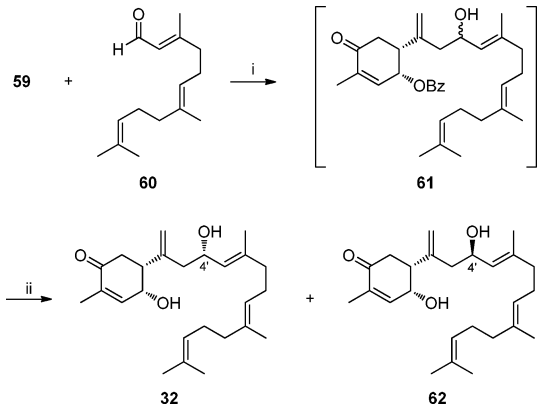
After screening several oxidation methods, Swern oxidation was found to be the most selective and reliable method for this transformation. With protection of the secondary alcohol proving difficult, it was hoped that the benzoyl group could instead be transferred intramolecularly from the ketophosphonate to the free hydroxyl group, concomitantly generating a phosphonate anion which would then undergo the desired HWE reaction. Pleasingly, treatment of a crude mixture of the unstable aldehyde **58** with sodium hydride in THF at 0 °C afforded enone **41** in 53% over two steps from diol **56**. Overall, the de novo synthesis of **41** proved considerably more effective to that beginning with carvone, allowing gram quantities of enone **41** to be prepared. Enone **41** could also be readily converted to allyl bromide **59**, with a broader range of useful synthetic intermediates conceivably being available from these *γ*-hydroxycarvone derivatives.

Synthesis of Phorbin A. In order to showcase the utility of the *cis*-*γ*-hydroxycarvone derivatives prepared herein, the synthesis of the natural sesterterpenoid phorbin A (**32**) was undertaken (Scheme 7). With allyl bromide **59** readily in hand,

Scheme 7. Synthesis of Phorbin A (32) and Its C-4′ Epimer 62[a]



[a]Reagents and conditions: (i) Zn, NH_4Cl (aq), THF, 30 °C, sonication; (ii) K_2CO_3, THF-MeOH (1:1), rt, 37% **32**, 19% **62** over two steps.

it was envisaged that its union with farnesal (**60**) using Barbier coupling, followed by benzoyl deprotection would provide access to **32**. Accordingly, allyl bromide **59** and aldehyde **60** were treated with zinc dust and aqueous ammonium chloride, with sonication providing a diastereomeric mixture of allylic alcohols **61**. The resulting alcohols were unstable to chromatographic purification and were therefore immediately subjected to benzoyl deprotection. Satisfyingly, this provided a crude mixture of enone-diols (2:1), which were subsequently separated to provide phorbin A (**32**) and its C-4′ epimer **62**.

CONCLUSION

In summary, we have developed practical and robust syntheses for a range of *cis*-*γ*-hydroxycarvone derivatives. Facile access to these intermediates will enable the total synthesis of biologically active natural products bearing this motif, as well as the synthesis of structural analogues for biological evaluation. In our hands, this methodology proved significantly more effective than an initial route beginning with carvone. The synthetic sequence included an unprecedented one-pot benzoyl transfer/intramolecular HWE sequence to construct the cyclohexenone ring. We anticipate the concepts demonstrated in this transformation could be more broadly applicable in cases where standard HWE protocols prove troublesome. Allyl bromide **59** was then employed for the synthesis of phorbin A (**32**) and its C-4′ epimer **62**. The use of the described *cis*-*γ*-hydroxycarvone derivatives for the total synthesis of other sesterterpenoid natural products is part of ongoing research within our group.

EXPERIMENTAL SECTION

General Procedures. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard techniques. Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl. CH_2Cl_2 and MeOH were freshly distilled from calcium hydride. All other reagents were used as received unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as visualizing agent and an ethanolic solution of vanillin and ammonium molybdate and heat as developing agents. Silica gel (60, 230−400 mesh) was used for flash column chromatography. NMR spectra were recorded at room temperature in $CDCl_3$ or CD_3OD solutions on either a spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or a spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, J, are in hertz (Hz). Multiplicities are reported as "s" (singlet), "br s" (broad singlet), "d" (doublet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet) and "m" (multiplet). Where distinct from those due to the major diastereomer, resonances due to minor diastereomers are denoted by an asterisk. ^{1}H and ^{13}C NMR resonances were assigned using a combination of DEPT 135, COSY, HSQC, HMBC, and NOESY spectra. Infrared (IR) spectra were recorded as a thin film on a composite of zinc selenide and diamond crystal on a FT-IR system transform spectrometer. Melting points are uncorrected. High-resolution mass spectra (HRMS) were obtained using a spectrometer operating at a nominal accelerating voltage of 70 eV or on a TOF-Q mass spectrometer.

(4*R*,5*S*)-4-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (34). MeMgBr (2.6 M, 3 mL, 7.99 mmol) was added dropwise over 1 h by syringe pump to a solution of $FeCl_3$ (36 mg, 0.33 mmol) in Et_2O (4 mL) at −20 °C. The resulting black suspension was stirred at −20 °C for 25 min followed by the addition of a solution of (*S*)-carvone (**33**) (1.00 g, 6.66 mmol) in Et_2O (6 mL) by syringe pump over 2 h. After stirring for an additional 30 min at −20 °C, TMSCl (0.87 mL, 7.99 mmol), DMPU (0.56 mL, 4.66 mmol) and NEt_3 (0.64 mL, 4.66 mmol) were added, and the resulting mixture was allowed to warm to rt and was stirred for 18 h. Saturated aqueous $NaHCO_3$ (30 mL) was added, and the mixture was filtered through filter paper to remove precipitate. The filtrate was extracted with Et_2O (3 × 30 mL), the combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product (1.11 g) was not purified prior to the next step. AcOH (0.15 mL, 2.66 mmol) followed by a solution of crude enol ether (0.25 g) in CH_2Cl_2 (1 mL) were added to a solution of nitrosobenzene (0.29 g, 2.66 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and then warmed to rt and stirred for 2 h. Water (8 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (9:1−2:1) as eluent afforded *title compound* **34** (67 mg, 29% over 2 steps) as a dark yellow oil. $[\alpha]_D^{20}$: −117.6 (*c* 0.90, $CHCl_3$), lit. $[\alpha]_D^{20}$ +225 (*c* 0.2, $CHCl_3$) for opposite enantiomer;[22] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.71−6.69 (m, 1H), 4.99−4.94 (m, 2H), 4.47−4.41 (m, 1H), 2.70 (ddd, J = 13.7, 9.7, 4.1 Hz, 1H), 2.51 (dd, J = 16.3, 4.1 Hz, 1H), 2.38 (dd, J = 16.3, 13.7 Hz, 1H), 1.79 (s, 3H), 1.76

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(s, 3H); The spectroscopic data were in agreement with literature values.[22]

(4*R*,5*S*)-5-(3-Chloroprop-1-en-2-yl)-4-hydroxy-2-methylcyclohex-2-enone (37). Calcium hypochlorite (70%, 0.12 g, 0.59 mmol) in water (0.5 mL) was added to a solution of alcohol **34** (0.15 g, 0.90 mmol) in CH_2Cl_2 (4.5 mL) at rt. Dry ice was added in small portions to the reaction mixture every 10−15 min for 2 h and the reaction was stirred at rt for a further 18 h. The mixture was filtered through Celite, diluted with water (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (4:1−2:1) as eluent afforded *title compound* **37** (0.16 g, 63%) as a yellow oil. $[\alpha]_D^{20}$ −128.2 (*c* 0.30, $CHCl_3$), lit. $[\alpha]_D^{21}$ +106 (c 1.98, $CHCl_3$), for opposite enantiomer;[19] ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 6.71−6.70. (m, 1H), 5.41 (s, 1H), 5.22 (s, 1H), 4.60−4.55 (m, 1H, H-4), 4.13 (ABq, 2H), 2.86 (ddd, *J* = 13.8, 9.8, 3.9 Hz, 1H), 2.59 (dd, *J* = 16.4, 3.9 Hz, 1H), 2.43 (dd, *J* = 16.4, 13.8 Hz, 1H), 1.78 (s, 1H); The spectroscopic data were in agreement with literature values.[19]

(4*S*,5*S*)-5-(3-Chloroprop-1-en-2-yl)-4-benzoyloxy-2-methylcyclohex-2-enone (38). DIAD (0.20 mL, 1.00 mmol) was added dropwise over 15 min to a solution of alcohol **37** (0.10 g, 0.50 mmol), PPh_3 (0.26 g, 1.00 mmol) and benzoic acid (0.12 g, 1.00 mmol) in THF (5 mL) at 0 °C. After stirring at rt for 16 h the reaction mixture was diluted with EtOAc (25 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (20:1−9:1) as eluent afforded *title compound* **38** (0.10 g, 71%) as a colorless solid. mp 66−67 °C; $[\alpha]_D^{20}$ +341.3 (*c* 0.94, $CHCl_3$); IR (film) ν_{max} 3067, 2957, 2924, 1714, 1680, 1450, 1258, 1095, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.95 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.89−6.87 (m, 1H), 5.80 (dd, *J* = 5.8, 3.4 Hz, 1H), 5.32 (s, 1H), 5.09 (s, 1H), 4.16 (ABq, 2H), 3.40−3.34 (m, 1H), 2.99 (dd, *J* = 16.4, 12.9 Hz, 1H), 2.63 (dd, *J* = 16.4, 3.9 Hz, 1H), 1.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 198.5, 165.8, 143.1, 139.4, 138.3, 133.5, 129.73, 129.69, 128.6, 117.8, 66.1, 47.4, 40.1, 37.8, 15.7; HRMS [EI, (M + Na)$^+$] *m*/*z*: calcd for ($C_{17}H_{17}ClNaO_3$), 327.0758; found, 327.0768.

(4*S*,5*S*)-4-Benzoyloxy-5-(3-iodoprop-1-en-2-yl)-2-methylcyclohex-2-enone (39). A solution of chloride **38** (0.10 g, 0.33 mmol) and NaI (0.15 g, 0.99 mmol) in acetone (2.6 mL) was stirred at rt for 24 h. The reaction mixture was concentrated in vacuo, diluted with CH_2Cl_2 (15 mL) and filtered through a plug of Celite. The filtrate was washed with saturated aqueous $Na_2S_2O_4$ (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (9:1) as eluent afforded *title compound* **39** (0.12 g, 94%) as a yellow oil. $[\alpha]_D^{20}$ +242.7 (*c* 1.98, $CHCl_3$); IR (film) ν_{max} 2959, 2922, 1714, 1679, 1450, 1257, 1095, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.95 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 6.88 (dq, *J* = 5.7, 1.3 Hz, 1H), 5.78 (dd, *J* = 5.7, 3.4 Hz, 1H), 5.42 (s, 1H), 5.04 (s, 1H), 4.03 (ABq, 2H), 3.44 (ddd, *J* = 12.9, 3.4, 3.4 Hz, 1H), 3.00 (dd, *J* = 16.5, 12.9 Hz, 1H), 2.64 (dd, *J* = 16.5, 3.4 Hz, 1H), 1.88 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 198.4, 165.8, 144.2, 139.3, 138.2, 133.4, 129.7, 129.6, 128.6, 116.4, 66.0, 41.1, 37.8, 15.7, 8.8; HRMS [EI, (M + Na)$^+$] *m*/*z*: calcd for ($C_{17}H_{17}INaO_3$), 419.0115; found, 419.0119.

(4*S*,5*S*)-4-Benzoyloxy-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-enone (40). A solution of iodide **39** (46 mg, 0.12 mmol) in DMF (0.20 mL) was added to a suspension of K_2CO_3 (42 mg, 0.30 mmol) and TFA (22 μL, 0.29 mmol) in DMF (0.20 mL) at rt. The resulting mixture was heated to 40 °C and stirred for 18 h. Water (1 mL) was added and the mixture extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (4:1) as eluent afforded *title compound* **40** (21 mg, 63%) as a colorless solid. mp 96−97 °C; $[\alpha]_D^{20}$ +307.5 (*c* 1.06, $CHCl_3$); IR (film) ν_{max} 3209, 2958, 2921, 1751, 1669, 1450, 1263, 1096, 915, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.96 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.82 (d, *J* = 5.8 Hz, 1H), 5.84 (dd, *J* = 5.8, 3.4 Hz, 1H), 5.19 (s, 1H,), 4.95 (s, 1H), 4.18 (s, 2H), 3.20 (ddd, *J* = 13.0, 3.4, 3.4 Hz, 1H), 3.00 (dd, *J* = 16.5, 13.0 Hz, 1H), 2.55 (dd, *J* = 16.5, 3.4 Hz, 1H), 2.28 (br. s, 1H), 1.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 199.1, 166.2, 146.5, 139.2, 138.4, 133.4, 129.83, 129.76, 128.5, 113.7, 67.2, 66.1, 40.7, 37.8, 15.6; HRMS [EI, (M + Na)$^+$] *m*/*z*: calcd for ($C_{17}H_{18}NaO_4$), 309.1097; found, 309.1109.

(4*S*,5*S*)-4-Benzoyloxy-2-methyl-5-(3-(trimethylsilyl)prop-1-en-2-yl)cyclohex-2-enone (+)-(41). Trifluoroacetic anhydride (60 μL, 0.43 mmol) was added to a solution of alcohol **40** (82 mg, 0.29 mmol), NEt_3 (60 μL, 0.43 mmol), and DMAP (3.5 mg, 0.059 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h then allowed to warm to rt and was stirred for 3 h. Saturated aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo to afford crude ester, which was used without further purification.

Hexamethyldisilane (0.17 mL, 0.86 mmol) followed by a solution of the crude ester in CH_2Cl_2 (1 mL) was added to a solution of $Pd(OAc)_2$ (6.3 mg, 0.029 mmol) in THF (0.6 mL) at rt. The resulting mixture was stirred at rt for 24 h then filtered through a plug of silica, washing with EtOAc (2 × 3 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (50:1−20:1) as eluent afforded *title compound* **41** (43 mg, 44% over 2 steps) as a colorless solid. mp 71−73 °C; $[\alpha]_D^{20}$ +291.4 (*c* 0.52, $CHCl_3$); IR (film) ν_{max} 3077, 2955, 2924, 1717, 1682, 1262, 1247, 1105, 843, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.98 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 5.6 Hz, 1H), 5.79 (dd, *J* = 5.6, 3.3 Hz, 1H), 4.76 (s, 1H,), 4.73 (s, 1H), 3.00 (dd, *J* = 16.3, 13.0 Hz, 1H), 2.77 (ddd, *J* = 13.0, 3.3, 3.3 Hz, 1H), 2.57 (dd, *J* = 16.3, 3.3 Hz, 1H), 1.85 (s, 3H), 1.61 (ABq, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 199.5, 165.8, 144.5, 139.1, 138.8, 133.2, 129.8, 129.7, 128.4, 110.0, 66.1, 44.8, 38.2, 25.8, 15.6, −1.4; HRMS [EI, (M + Na)$^+$] *m*/*z*: calcd for ($C_{20}H_{26}NaO_3Si$), 365.1543; found, 365.1531.

(4*R*,5*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-(3-(trimethylsilyl)prop-1-en-2-yl)dihydrofuran-2(3H)-one (46). *General Procedure for Preparation of Thiophen-2-yllithium Solution.* *n*-BuLi (1.6 M in hexane, 28 mL, 45.1 mmol) was added dropwise to a solution of thiophene (3.6 mL, 45.1 mmol) in Et_2O (56 mL) at 0 °C. The mixture was warmed to rt and stirred for 30 min to afford a yellow solution of thiophen-2-yllithium.

t-BuLi (1.6 M in pentane, 0.73 mL, 1.17 mmol) was added dropwise to a solution of bromide **44** (0.10 mL, 0.58 mmol) in Et_2O (1.1 mL) at −78 °C. After stirring for 30 min at −78 °C, CuCN (53 mg, 0.58 mmol) was added in one portion and the resulting mixture was warmed to −30 °C for 10 min before cooling to −78 °C. A freshly prepared solution of thiophen-2-yllithium (0.54 M, 1.1 mL, 0.58 mmol) was added via cannula, the mixture warmed to −30 °C for 10 min, then cooled to −78 °C. A solution of lactone **45** (0.13 g, 0.58 mmol) in Et_2O (1.3 mL) was added, and the mixture was stirred at −78 °C. After 2 h, a mixture of saturated aqueous NH_4Cl and NH_4OH (3:1, 8 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 8 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (8 mL) and brine (8 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (9:1) as eluent afforded *title compound* **46** (0.14 g, 71%) as a pale yellow oil. $[\alpha]_D^{20}$ +17.0 (*c* 0.94, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2859, 1782, 1251, 1122, 835, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 4.74 (s, 1H), 4.69 (s, 1H), 4.37 (ddd, *J* = 5.0, 3.0, 3.0 Hz, 1H), 3.86 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.68 (dd, *J* = 11.4, 3.0 Hz, 1H), 2.98−2.93 (m, 1H), 2.76 (dd, *J* = 17.6, 9.3 Hz, 1H), 2.42 (dd, *J* = 17.6, 6.2 Hz, 1H), 1.52 (s, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 176.5, 146.4, 108.2, 84.5, 63.8, 43.2, 34.9, 25.9, 25.7, 18.4, −1.2, −5.3, −5.5; HRMS [EI, (M + Na)$^+$] *m*/*z*: calcd for ($C_{17}H_{34}NaO_3Si_2$), 365.1939; found, 365.1949.

Diethyl (1-((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-hydroxy-4-(3-(trimethylsilyl)prop-1-en-2-yl)tetrahydrofuran-

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2-yl)ethyl)phosphonate (43). *n*-BuLi (1.6 M in hexane, 0.44 mL, 0.70 mmol) was added dropwise to a solution of diethyl ethylphosphonate (74 μL, 0.70 mmol) in THF (0.5 mL) at −78 °C. The mixture was stirred for 30 min then a solution of lactone **46** (80 mg, 0.23 mmol) in THF (0.5 mL) was added dropwise. After stirring for a further 3 h at −78 °C, saturated aqueous NH_4Cl (5 mL) was added, the mixture warmed to rt, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (9:1−4:1) as eluent afforded *title compound* **43** (43 mg, 53%) as a colorless oil and starting material **46** (37 mg, 31%) as a colorless oil.

IR (film) ν_{max} 3354, 2982, 2926, 1645, 1449, 1390, 1211, 1022, 956, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.04 (s, 0.2H), 5.22 (s, 0.2H), 4.91−4.61 (m, 2H), 4.25−3.99 (m, 5H), 3.82−3.57 (m, 2H), 2.97−2.55 (m, 1H), 2.36−1.68 (m, 3H), 1.57−1.47 (m, 2H), 1.32−1.18 (m, 9H), 0.89−0.87 (m, 9H), 0.06−0.01 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.7, 146.4, 146.3, 145.7, 108.9, 108.8, 108.3, 108.3, 106.0, 105.9, 105.4, 105.4, 84.8, 84.7, 83.3, 66.1, 65.9, 62.9, 62.9, 62.3, 61.3, 61.2, 61.2, 61.2, 47.5, 46.4, 46.3, 43.7, 43.7, 43.3, 43.3, 43.2, 42.3, 42.2, 42.2, 41.5, 41.5, 40.8, 40.2, 39.5, 36.7, 26.0, 25.9, 25.3, 25.0, 25.0, 24.8, 18.5, 18.3, 16.6, 16.5, 16.4, 16.4, 11.8, 11.0, 11.0, −1.0, −1.0, −5.2; HRMS [EI, $(M + Na)^+$] *m*/*z*: calcd for ($C_{23}H_{49}NaO_6PSi_2$), 531.2697; found, 531.2699.

(*R*)-Ethyl 3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((trimethylsilyl)methyl)pent-4-enoate (53a) and (*S*)-ethyl 3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((trimethylsilyl)methyl)pent-4-enoate (53b). *t*-BuLi (1.6 M in pentane, 0.64 mL, 1.03 mmol) was added dropwise to a solution of bromide **44** (0.88 mL, 0.52 mmol) in Et_2O (1 mL) at −78 °C. After stirring for 30 min at −78 °C, CuCN (0.46 g, 0.52 mmol) was added in one portion, and the resulting mixture was warmed to −30 °C for 10 min before cooling to −78 °C. A freshly prepared solution of thiophen-2-yllithium (0.56 M, 0.93 mL, 0.52 mmol) was added, the mixture warmed to −30 °C for 10 min, then cooled to −78 °C. A solution of enoate **49** (86 mg, 0.43 mmol) in Et_2O (1.2 mL) was added and the mixture stirred at −78 °C for 30 min before warming to −30 °C. After 1 h saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (9:1) as eluent afforded *title compounds* **53a** and **53b** (0.80 mg, 51%, 4:1) as a yellow oil. IR (film) ν_{max} 2985, 1736, 1632, 1370, 1248, 1156, 1061, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.69−4.66 (m, 2H), 4.66* (s, 0.5H), 4.32−4.27* (m, 0.25H), 4.11−4.06 (m, 3H, H-4′ and OCH_2CH_3), 3.98 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.84* (dd, *J* = 8.4, 6.5 Hz, 0.25H), 3.65 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.60* (dd, *J* = 8.4, 7.5 Hz, 0.25H), 2.88* (ddd, *J* = 8.3, 5.8, 5.8 Hz, 0.25H), 2.62−2.55 (m, 2H), 2.44 (dd, *J* = 16.8, 9.1 Hz, 1H), 1.49 (ABq, 2H), 1.37 (s, 3H), 1.31 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.6, 172.5*, 146.4, 146.2*, 110.4, 109.2, 109.1*, 108.9*, 77.9, 76.1*, 68.2, 65.8*, 60.4*, 60.3, 47.4, 44.3*, 36.4, 33.4*, 27.1*, 26.7, 26.3*, 25.5, 25.1*, 14.3, −0.9, −1.1; HRMS [EI, $(M + Na)^+$] *m*/*z*: calcd for ($C_{16}H_{30}NaO_4Si$), 337.1806; found, 337.1810.

(*R*)-Methyl 3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((trimethylsilyl)methyl)pent-4-enoate (54). *t*-BuLi (1.6 M in pentane, 56 mL, 90.2 mmol) was added dropwise to a solution of bromide **44** (7.6 mL, 45.1 mmol) in Et_2O (90 mL) at −78 °C. After stirring for 30 min at −78 °C, CuCN (4.04 g, 45.1 mmol) was added in one portion and the resulting mixture was warmed to −30 °C for 15 min before cooling to −78 °C. A freshly prepared solution of thiophen-2-yllithium (0.51 M, 88 mL, 45.1 mmol) was added via cannula, the mixture warmed to −30 °C for 15 min, then cooled to −78 °C. A solution of enoate **50** (7.00 g, 37.6 mmol) in Et_2O (100 mL) was added and the mixture was warmed to −30 °C. After 1.5 h a mixture of saturated aqueous NH_4Cl and NH_4OH (3:1, 200 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (150 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (20:1) as eluent afforded *title compound* **54** (8.94 g, 79%) as a colorless oil. $[\alpha]_D^{20}$ +2.4 (*c* 1.16, $CHCl_3$); IR (film) ν_{max} 2988, 2954, 1742, 1631, 1437, 1370, 1250, 1159, 1064, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.71 (s, 2H), 4.15−4.10 (m, 1H), 4.01 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.68 (dd, *J* = 8.4, 6.3 Hz, 1H), 3.64 (s, 3H), 2.66−2.45 (m, 3H), 1.51 (ABq, 2H), 1.39 (s, 3H), 1.33 (s, 3H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.0, 146.4, 110.4, 109.2, 77.9, 68.2, 51.5, 47.5, 36.3, 26.7, 25.6, 25.5, −1.0; HRMS [EI, $(M + Na)^+$] *m*/*z*: calcd for ($C_{15}H_{28}NaO_4Si$), 323.1649; found, 323.1660.

Diethyl ((5*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-6-((trimethylsilyl)methyl)hept-6-en-2-yl)phosphonate (51). *n*-BuLi (1.6 M in hexane, 57 mL, 88.8 mmol) was added dropwise to a stirred solution of diethyl ethylphosphonate (9.7 mL, 88.8 mmol) in THF (300 mL) at −78 °C. The reaction was stirred for 30 min at −78 °C and then a solution of ester **54** (8.90 g, 29.6 mmol) in THF (30 mL) was added dropwise. After stirring for 4 h at −78 °C, saturated aqueous NH_4Cl (200 mL) was added, the resulting mixture allow to warm to rt and then extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (4:1−2:1) as eluent afforded *title compound* **51** (9.89 g, 77%) as a colorless oil. IR (film) ν_{max} 2985, 1716, 1370, 1247, 1051, 1021, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.68−4.65 (m, 2H), 4.15−4.04 (m, 5H), 4.01−3.96 (m, 1H), 3.62−3.57 (m, 1H), 3.41−3.18 (m, 1H), 2.98−2.59 (m, 3H), 1.56−1.43 (m, 2H), 1.37−1.28 (m, 15H), 0.04−0.03 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.7, 204.7, 204.6, 147.2, 109.9, 109.5, 109.1, 79.0, 77.9, 68.4, 68.2, 62.6, 62.6, 62.5, 48.3, 47.7, 47.4, 47.0, 46.4, 46.3, 45.9, 44.8, 26.7, 26.6, 26.4, 26.1, 25.8, 25.6, 16.5, 16.4, 11.1, 11.0, −0.9; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 23.79; HRMS [EI, $(M + Na)^+$] *m*/*z*: calcd for ($C_{20}H_{39}NaO_6PSi$), 457.2146; found, 457.2147.

Diethyl ((*R*,*Z*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-benzoyloxy-6-((trimethylsilyl)methyl)hepta-2,6-dien-2-yl)-phosphonate (55). NEt_3 (0.24 mL, 1.73 mmol), BzCl (0.20 mL, 1.73 mmol) and DMAP (14 mg, 0.12 mmol) were added to a stirred solution of phosphonate **51** (0.25 g, 0.58 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C. The mixture was allowed to warm to rt and was stirred for 24 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (4:1) as eluent afforded *title compound* **55** (0.27 g, 88%) as a pale yellow oil (9.8 g scale afforded 8.81 g, 72%); $[\alpha]_D^{20}$ −8.7 (*c* 1.03, $CHCl_3$). IR (film) ν_{max} 2984, 1732, 1650, 1452, 1369, 1246, 1215, 1049, 1021, 960, 849, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, *J* = 7.9 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 7.9, 7.4 Hz, 2H), 4.74 (s, 1H), 4.70 (s, 1H), 4.22−4.06 (m, 5H), 3.97 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.67 (dd, *J* = 8.2, 6.8 Hz, 1H), 3.45 (dd, *J* = 14.9, 6.6 Hz, 1H), 3.13 (dd, *J* = 14.9, 7.2 Hz, 1H), 2.46−2.40 (m, 1H), 1.69 (d, $^3J_{HP}$ = 12.8 Hz, 3H), 1.56 (ABq, 2H), 1.33 (t, *J* = 7.1 Hz, 6H), 1.29 (s, 3H), 1.23 (s, 3H), −0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.2, 160.5 (d, $^2J_{CP}$ = 34 Hz), 146.6, 133.8, 130.1, 129.3, 128.7, 114.1 (d, J_{CP} = 182 Hz), 110.8, 108.9, 78.1, 67.8, 61.7 (d, $^2J_{CP}$ = 4.5 Hz), 48.2, 33.7, 26.9, 26.3, 25.5, 16.4 (d, $^3J_{CP}$ = 6.4 Hz), 13.6 (d, $^2J_{CP}$ = 5.8 Hz), −0.9; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.26; HRMS [EI, $(M + Na)^+$] *m*/*z*: calcd for ($C_{27}H_{43}NaO_7PSi$), 561.2408; found, 561.2412.

Diethyl ((*R*,*Z*)-5-((*S*)-1,2-dihydroxyethyl)-3-benzoyloxy-6-((trimethylsilyl)methyl)hepta-2,6-dien-2-yl)phosphonate (56). CSA (60 mg, 0.26 mmol) was added to a stirred solution of **55** (140 mg, 0.26 mmol) in MeCN/MeOH/water (2:2:1, 4 mL) at rt. The reaction was stirred until the formation of the desilylation side product was observed by TLC (ca. 3 h). Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (4:1−2:1) as eluent afforded *title compound* **56** (68 mg, 52%, 88% brsm) as a pale yellow oil and starting material **55** (57 mg, 41%) as a yellow oil (8.8 g scale afforded 3.85 g of **56** (47%) and 3.85 g of **55** (40%)); $[\alpha]_D^{20}$ −72.0 (*c* 1.06, $CHCl_3$); IR (film) ν_{max}

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3398 (br), 2953, 1732, 1647, 1234, 1048, 1018, 966, 849, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, J = 8.2 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.50−7.47 (dd, J = 8.2, 7.4 Hz, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 4.20−4.10 (m, 4H), 3.81−3.77 (m, 1H), 3.71−3.67 (m, 1H), 3.61−3.51 (m, 2H), 2.63−2.57 (m, 1H), 2.44−2.40 (m, 1H), 1.70 (d, $^3J_{CH}$ = 13.1 Hz, 3H), 1.42 (s, 2H), 1.40−1.34 (m, 6H), −0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.4, 161.9 (d, $^2J_{CP}$ = 34 Hz), 147.4, 134.0, 130.2, 128.9, 128.8, 113.5 (d, J_{CP} = 182 Hz), 109.7, 73.5, 64.5, 62.5 (d, $^2J_{CP}$ = 5.1 Hz), 62.3 (d, $^2J_{CP}$ = 5.1 Hz), 48.6, 33.0, 26.2, 16.5 (d, $^3J_{CP}$ = 6.3 Hz), 16.4 (d, $^3J_{CP}$ = 6.3 Hz), 13.7 (d, $^2J_{CP}$ = 5.6 Hz), −1.1; ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 19.81; HRMS [EI, $(M + Na)^+$] m/z: calcd for ($C_{24}H_{39}NaO_7PSi$), 521.2095; found, 521.2102.

(4*R*,5*R*)-4-Benzoyloxy-2-methyl-5-(3-(trimethylsilyl)prop-1-en-2-yl)cyclohex-2-enone (−)-(41). Oxalyl chloride (0.61 mL, 7.16 mmol) was added to a solution of DMSO (1.0 mL, 14.3 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The mixture was stirred for 10 min, a solution of diol **56** (2.38 g, 4.77 mmol) in CH_2Cl_2 (10 mL) was added dropwise, and the resulting mixture was stirred for a further 30 min. NEt_3 (4.0 mL, 28.6 mmol) was added dropwise, and the reaction mixture was allowed to warm to rt and was stirred for 1 h. Water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was not purified prior to use in the next step.

NaH (60% dispersion in paraffin oil, 0.38 g, 9.54 mmol) was added to a solution of crude aldehyde **58** in THF (120 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, saturated aqueous NH_4Cl (100 mL) was added, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (15:1) as eluent afforded *title compound* **41** (0.87 g, 53% over two steps) as a colorless solid. $[\alpha]_D^{20}$ −285.3 (*c* 1.16, $CHCl_3$); All other data was in agreement with (+)-**41**.

(4*R*,5*R*)-5-(3-Bromoprop-1-en-2-yl)-4-benzoyloxy-2-methylcyclohex-2-enone (59). NBS (29 mg, 0.16 mmol) was added to a solution of allylsilane **41** (50 mg, 0.15 mmol) in THF (1.5 mL) at −78 °C. After stirring for 2 h at −78 °C, water (10 mL) was added, the mixture was warmed to rt and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (20:1) as eluent afforded *title compound* **59** (51 mg, 100%) as a colorless oil. $[\alpha]_D^{20}$ −283.0 (*c* 1.65, $CHCl_3$); IR (film) ν_{max} 2924, 1718, 1683,1451, 1265, 1107, 925, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.97−7.94 (m, 2H), 7.60−7.54 (m, 1H), 7.46−7.41 (m, 2H), 6.90−6.88 (m, 1H), 5.82−5.80 (m, 1H), 5.38 (s, 1H), 5.09 (s, 1H,), 4.16 (d, J = 10.6 Hz, 1H), 4.00 (d, J = 10.6 Hz, 1H), 3.43 (ddd, J = 12.9, 3.5, 3.5 Hz, 1H), 3.00 (dd, J = 16.4, 12.9 Hz, 1H), 2.64 (dd, J = 16.4, 3.5 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 198.5, 165.9, 143.3, 139.4, 138.3, 133.5, 129.8, 129.7, 128.6, 118.1, 66.1, 40.5, 37.8, 35.4, 15.7; HRMS [EI, $(M + Na)^+$] m/z: calcd for ($C_{17}H_{17}BrNaO_3$), 371.0253; found, 371.0267.

Phorbin A (32) and 4′-*epi*-Phorbin A (62). A mixture of bromide **59** (50 mg, 0.14 mmol), farnesal (47 mg, 0.22 mmol), zinc dust (47 mg, 0.72 mmol), and saturated aqueous NH_4Cl (2 drops) in THF (0.8 mL) was sonicated at 30 °C for 3 h. Water (15 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL) and dried over Na_2SO_4 and concentrated in vacuo to afford a crude mixture of allylic alcohols, which was used without further purification.

Potassium carbonate (59 mg, 0.43 mmol) was added to a solution of crude alcohols in THF/MeOH (1:1, 2.6 mL) at rt. The reaction was stirred for 18 h, water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography using hexanes-EtOAc (3:1−1:1) as eluent afforded *title compounds* **62** (10.4 mg, 19%) and **32** (20.4 mg, 37%) as pale yellow oils. **62:** $[\alpha]_D^{20}$ −36.5 (*c* 0.41, MeOH); IR (film) ν_{max} 3382, 2922, 2855, 1670, 1447, 1378, 1264, 1106, 1045, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.84 (qd, J = 5.8, 1.4 Hz, 1H), 5.20−5.18 (m, 1H), 5.12−5.08 (m, 3H) 4.92 (s, 1H), 4.56−4.51 (m, 1H), 4.44−4.42 (m, 1H), 2.85−2.76 (m, 2H), 2.37−2.26 (m, 3H), 2.13−1.96 (m, 8H), 1.78 (s, 3H), 1.69 (d, J = 1.4 Hz, 3H), 1.67 (s, 3H), 1.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 202.4, 146.1, 145.1, 138.6, 137.3, 136.2, 132.1, 129.0, 125.4, 125.2, 114.8, 68.8, 64.5, 46.0, 43.7, 40.8, 40.7, 38.2, 27.8, 27.4, 25.9, 17.8, 16.8, 16.1, 15.6; HRMS [EI, $(M + Na)^+$] m/z: calcd. for ($C_{25}H_{38}NaO_3$) 409.2713, found: 409.2715. **32:** $[\alpha]_D^{20}$ −66.4 (*c* 0.50, MeOH), lit. $[\alpha]_D^{20}$ −61 (*c* 0.4, $CHCl_3$)[6]; IR (film) ν_{max} 3341, 2922, 2854, 1667, 1446, 1376, 1241, 1105, 1043, 985, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.84 (dq, J = 5.6, 1.4 Hz, 1H), 5.18−5.16 (m, 1H), 5.14−5.08 (m, 2H), 5.06 (s, 1H), 4.88 (s, 1H), 4.50 (dt, J = 8.7, 6.7 Hz, 1H), 4.43 (dd, J = 5.3, 1.9 Hz, 1H), 2.85−2.78 (m, 2H), 2.44 (dd, J = 14.0, 7.0 Hz), 2.33−2.27 (m, 1H), 2.23 (dd, J = 14.2, 6.6 Hz, 1H), 2.14−1.96 (m, 8H), 1.78 (s, 3H), 1.67 (s, 3H), 1.66 (d, J = 1.4 Hz, 3H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 202.3, 146.3, 145.3, 138.7, 137.1, 136.2, 132.1, 129.1, 125.4, 125.2, 114.9, 68.7, 65.0, 46.0, 44.3, 40.9, 40.7, 38.4, 27.8, 27.4, 25.9, 17.8, 16.8, 16.2, 15.6; HRMS [EI, $(M + Na)^+$] m/z: calcd for ($C_{25}H_{38}NaO_3$), 409.2713; found, 409.2703; The spectroscopic data were in agreement with literature values.[6]

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of compounds **32, 34, 37−41, 43, 46, 51, 53−56, 59**, and **62**. Full table of deprotection conditions examined for acetonide **55**. Data comparison table for isolated and synthetic phorbin A (**32**). 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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