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# The Plakotenins: Biomimetic Diels–Alder Reactions, Total Synthesis, Structural Investigations, and Chemical Biology

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*Dedicated to Prof. Dr. Dr. hc. Lutz F. Tietze on the occasion of his 70th birthday*

**Abstract:** The total synthesis of plakotenin, a cytotoxic marine natural product, using a biomimetic Diels–Alder reaction is described in detail. Two approaches were used, whereby the Diels–Alder reaction occurs at different stages of the synthesis. *Homo*- and *nor*-plakotenin, related natural products, were also prepared, as well as *iso*-plakotenin, a diastereoisomer of plakotenin. The syntheses prove the relative and absolute stereochemistry of the latter. The chemical biology of the plakotenins was investigated on selected compounds.

**Keywords:** biomimetic synthesis · chemical biology · cycloaddition · natural products · polyketides

## Introduction

Plakotenin (**1**, Figure 1) is a secondary metabolite of polyketide origin, which was isolated in 1992 from an Okinawan marine sponge of the genus *Plakortis*.[1] It showed in vitro cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells. The marine natural product **1** possesses a [4.3.0] bicyclic core and six stereogenic centers, one of which is quaternary. The relative stereochemistry of **1** was deduced by extensive 2D NMR analysis. Later, Faulkner et al. isolated and characterized **1** again along with its closely related compounds *nor*-plakotenin (**2**) and *homo*-plakotenin (**3**, Figure 1) from another marine sponge, *Plakortis lita* from Palau.[2,3] Compounds **1**, **2**, and **3** were found to significantly reduce proliferation of rheumatoid synovial fibroblasts. It is proposed that **1** might be produced biosynthetically through an intramolecular Diels–Alder (IMDA) reaction of a linear precursor.[1] Herein, we describe the total synthesis[4] of **1** and its congeners **2**, and **3** as well as its diastereoisomer *iso*-plakotenin (**4**) (Figure 1).[5–7] In addition to our already published total synthesis of **1**,[8] in this manuscript we want to show a second expedient method and reveal studies to understand the chemical biology of the plakotenins. The results of computational studies, which were made to allow prediction and support of the synthetic work, were recently published[9] and showed that the stereochemistry had to be revised. The correct stereochemistry is shown in Figure 1.

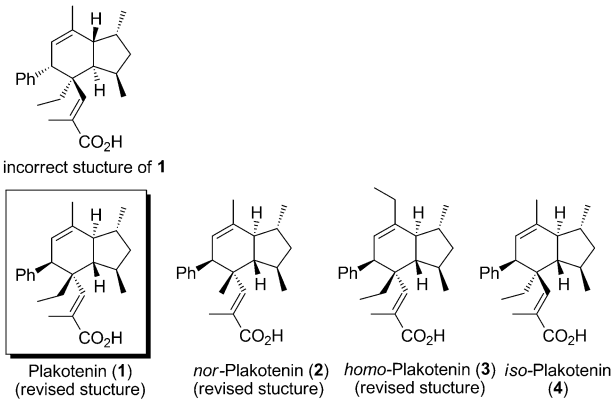


Figure 1. Plakotenin (**1**), *nor*- (**2**), *homo*- (**3**), and *iso*-plakotenin (**4**).

## Results and Discussion

**Retrosynthetic analysis**: The synthesis of **1** was envisaged by construction of the bicyclic core using a biomimetic intramolecular Diels–Alder reaction.[10–12] Retrosynthetic analysis re-

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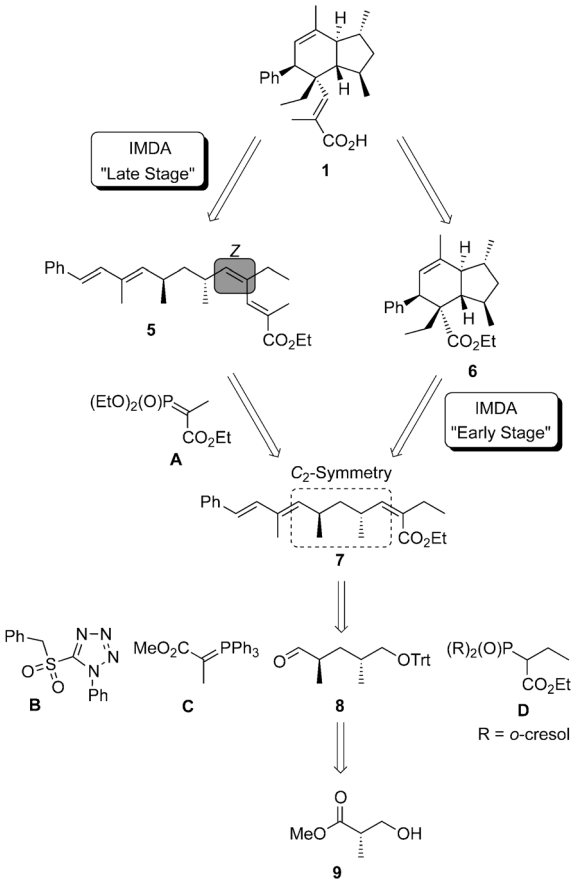
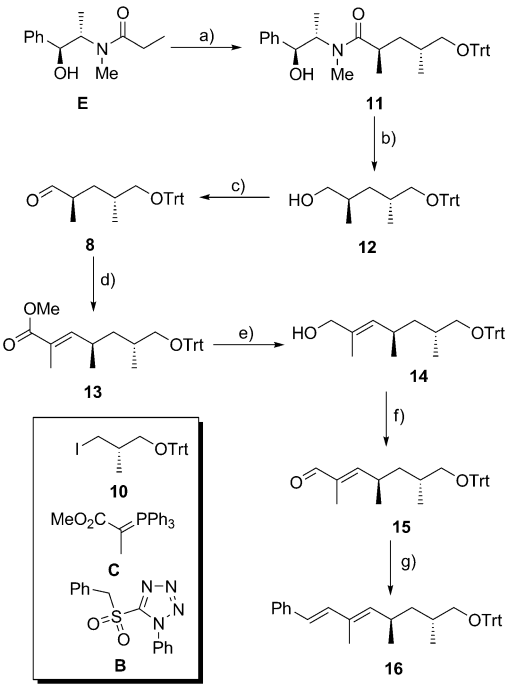



Scheme 1. Retrosynthetic analysis of plakotenin (**1**).



Scheme 2. a) i) LDA, LiCl, THF, −78 °C; ii) **10**, 0 °C, 91 %; b) $LiNH_2{\cdot}BH_3$, THF, 0 °C, 91 %; c) IBX, DMSO, quant; d) **C**, toluene, 100 °C, 88 %; e) $LiAlH_4$, THF, 0 °C, 90 %; f) IBX, DMSO, quant; g) **B**, $LiN(TMS)_2$, THF, −78 °C, 80 %.

veals that the linear precursor of **1** could be the tetraene **5** that is, unlike most polyketides[13], not completely *E* configured but includes one *Z* double bond (Scheme 1). Further in-depth retrosynthetic analysis however shows that triene **7** would already be suitable for cyclization. Therefore, two synthetic approaches are possible: Diels–Alder reaction of tetraene **5** ("late-stage Diels–Alder" strategy) or alternatively Diels–Alder reaction of triene **7** followed by appropriate functionalization of the ring system ("early-stage Diels–Alder" strategy).

For both methods, a suitable first target is the $C_2$-symmetrical dimethyl building block **8**, which becomes apparent by taking a closer look at triene **7** (Scheme 1). This central chiral fragment **8** should be accessible from commercially available (*S*)-Roche ester (**9**). Subsequent bidirectional extension of **8** by Wittig, Horner–Wadsworth–Emmons (HWE), or Julia–Kocienski olefination reactions should deliver triene **7** or/and tetraene **5**. In this manuscript we want to describe the synthesis of **1** by a late-stage Diels–Alder, as well as an early-stage Diels–Alder strategy.

**Synthesis of 1 by a late-stage Diels–Alder strategy**:[8] Aiming for **1** by this approach we first carried out the complete synthesis of linear precursor **5** and only then utilized the intramolecular Diels–Alder reaction as the last C−C bond forming reaction of the synthetic route (Scheme 1).

Synthesis of the required central chiral fragment **8** was achieved by employing an asymmetric alkylation approach reported by Myers et al. (Scheme 2).[14] An *anti*-selective aldol reaction between commercially available pseudoephedrine auxiliary **E** and iodide (*S*)-**10**[15], prepared in 3 steps from (*S*)-Roche ester **9**[16], produced amide **11** as a single diastereoisomer (in >98 % diastereoselectivity (ds)). Reductive removal of the chiral auxiliary was effected with lithium amidotrihydroborate to afford alcohol **12** in 91 % yield.[17] Primary alcohol **12** was oxidized to aldehyde **8** in quantitative yield using iodoxybenzoic acid (IBX). Wittig olefination of aldehyde **8** with ylide **C** gave the *E*-unsaturated ester **13** stereoselectively (*E*/*Z* > 14:1 based on $^1$H NMR analysis of the crude reaction mixture) in 88 % yield. The reduction of the ester **13** with lithium aluminium hydride (90 % yield) and oxidation of the resulting alcohol **14** with IBX (quant) gave α,β-unsaturated aldehyde **15**. Extension of **15** and hence introduction of the styryl group was accomplished by a Julia–Kocienski olefination reaction with tetrazole **B** using lithium bis(trimethylsilyl)amide as base in 80 % yield (*EE*/*ZE* 10:1).[18]

The alcohol function in diene **16** was then deprotected with camphorsulfonic acid in good yield (Scheme 3), which was followed by oxidation of the resulting alcohol **17** to aldehyde **18** with Dess–Martin periodinane (DMP) in quantitative yield. Introduction of the third double bond, the only *Z*-configured bond in linear precursor **5**, was now possible through a mild (to avoid in situ cyclization) *Z*-selective variation of the Horner–Wadsworth–Emmons reaction using

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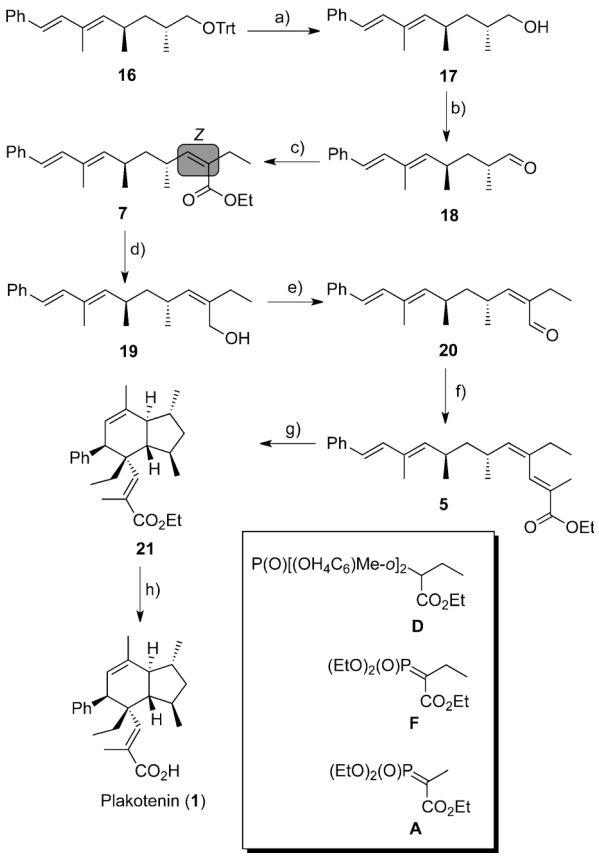


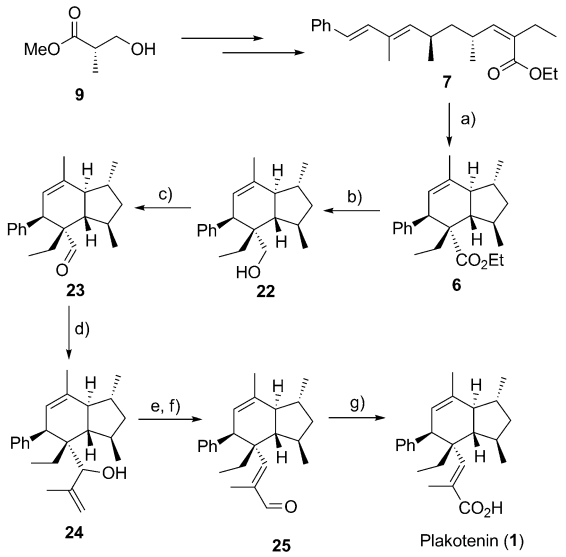

Scheme 3. a) CSA, $CH_2Cl_2$/MeOH (2:1), 0 °C, 88 %; b) DMP, $CH_2Cl_2$, quant; c) **D** or **F**, NaH, THF, 0 °C, 76 %; d) $LiAlH_4$, THF, 0 °C, 61 %; e) DMP, $CH_2Cl_2$, quant; f) **A**, NaH, THF, 0 °C, 88 %; g) toluene, 110 °C, 91 %; h) NaOH (2 M), THF/MeOH, 40 °C, 86 %.

phosphonate **D** (ethyl 2-((bis(*o*-tolyloxy))phosphoryl)butanoate).[19] Ester **7** was obtained in 64 % yield with a *Z*/*E* selectivity of 6:1. Classical HWE reaction conditions using phosphonate **F** proceeded also smoothly and surprisingly delivered again the *Z* isomer **7** as the major product with a 4:1 ratio in 76 % yield. The *Z* stereochemistry of this newly formed double bond was proven by NOESY experiments realized on alcohol **19**. Again a reduction/oxidation sequence of the ester part in **7** furnished aldehyde **20**, which was subsequently elongated to the desired tetraene **5** using a second HWE olefination with phosphonate **A**.

On heating in toluene, tetraene **5** cyclized smoothly in excellent yield to plakotenin ethyl ester **21** detected as single diastereoisomer. Finally, saponification yielded synthetic plakotenin (**1**). Extensive spectroscopic studies were conducted on **1** to confirm its structure and relative stereochemistry. The spectroscopic data, as well as the optical rotation of synthetic plakotenin were identical with the reported data of the natural product. Hence, plakotenin (**1**) was successfully synthesized in 15 steps (from (*S*)-iodide **10**) in an overall yield of 14.7 %.

**Synthesis of 1 by an early-stage Diels–Alder strategy**: In contrast to the method described in the previous paragraph, we report a way of synthesizing **1**, in which cyclization takes place directly after introduction of the third double bond. This method offers the following advantages. Not only the careful handling of sensitive compounds prone to cyclization becomes unnecessary, but also derivatization of the core structure could be achieved more easily. This would give access to a vast variety of compounds derived from plakotenin that can be interesting for biological studies.

Thus, with triene **7** in hand (obtained in 13 steps from (*S*)-Roche ester (**9**) with an overall yield of 27.2 %), the IMDA was realized by heating in toluene overnight (Scheme 4). Cycloadduct **6** could be obtained in very good yield and its relative stereochemistry was identical to plakotenin (deduced by 2D NMR analysis on compound **22**).




Scheme 4. a) Toluene, 110 °C, 85 %; b) $LiAlH_4$, THF, 0 °C, 95 %; c) DMP, $CH_2Cl_2$, quant; d) isopropenylmagnesium bromide, THF, 0 °C then 50 °C, 87 % (d.r. = 10:1); e) $SOCl_2$, pentane/ether (1:1) 0 °C to RT; f) NMO, DMSO, RT, 61 % (two steps); g) $NaClO_2$, $H_2O_2$, $NaH_2PO_4$, MeCN/$H_2O$ (6:1), RT, 63 %.

After the reduction/oxidation sequence on cycloadduct **6**, which gave aldehyde **23** various olefination attempts (Wittig, HWE; results not shown) were made but did not deliver the desired elongated bicycle. This reaction failure can be attributed to the steric hindrance of cyclic aldehyde **23**, which prevents the attack of bulky olefination reagents. To overcome this problem, aldehyde **23** was treated with isopropenylmagnesium bromide. Addition of the Grignard reagent on the aldehyde moiety was found to be slow, and heating the reaction mixture up to 50 °C was required to observe complete conversion. Allylic alcohol **24** could be eventually isolated in good yield, as a 10:1 mixture of inseparable diastereoisomers. To form the tri-substituted double bond, we first attempted a palladium-catalyzed rearrangement of the corresponding allylic acetate[20] (results not shown). However, this rearrangement did not proceed, and only starting material was recovered after workup. We then

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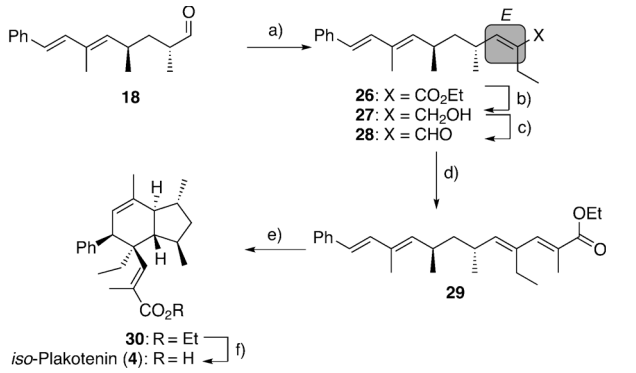
turned our attention to the use of thionyl chloride, which is known to convert secondary allylic alcohols into their isomeric primary allylic chlorides.[21] To our delight, the rearrangement took place with good selectivity, and the primary chloride was directly used without purification for the next oxidation into the corresponding aldehyde. This reaction was performed using a modification of the Ganem oxidation.[22] Indeed, when the primary chloride was treated with *N*-methylmorpholine-*N*-oxide (NMO) in DMSO, aldehyde **25** could be isolated with 61% yield over the two steps. Finally, Pinnick oxidation furnished the second synthetic plakotenin (**1**), which showed identical spectroscopic data to that previously obtained following the late-stage strategy. This early-stage strategy allowed us to obtain **1** in 17 steps (from (*S*)-iodide **10**) in an overall yield of 9.4%.

**Synthesis of 4**: During the course of the synthesis of **1**, we also planned to prepare an isomer of the proposed structure of isolated plakotenin, in which all double bonds of the linear precursor are *E* configured. Because substances of polyketide origin only rarely include *Z* configured double bonds, the synthesis of **4** should help to account for the correct relative stereochemistry of isolated plakotenin.

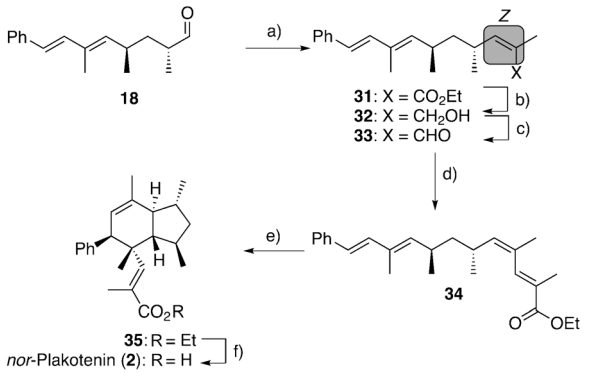
For this purpose, triene **26** was separated, from the major *Z* isomer obtained by the HWE reaction to introduce the third double bond, by purification of the crude mixture on column chromatography and isolated with 18% yield. Next the synthesis of *iso*-plakotenin (Scheme 5) was completed in




Scheme 5. a) **F**, NaH, THF, 0°C, 18%; b) $LiAlH_4$, THF, 0°C, 68%; c) DMP, $CH_2Cl_2$, quant; d) **A**, NaH, THF, 0°C, 84%; e) toluene, 110°C, 82%; f) NaOH (2M), THF/MeOH, 40°C, 75%.

a method analogous to that described for the synthesis of **1** by a late-stage Diels–Alder strategy. Interestingly, the IMDA of the all *E*-configured linear precursor **29** proceeded with less selectivity, since a 6.6:1 ratio of inseparable diastereoisomers could be determined by analysis of the $^1H$ NMR spectrum of ester **30**. Unfortunately, the relative stereochemistry of the minor diastereoisomer could not be determined, since the corresponding carboxylic acid could not be isolated. *iso*-Plakotenin (**4**) was successfully synthesized in an overall yield of 2.9% (from (*S*)-iodide **10**) and its stereochemistry again deduced using 2D NMR analysis. Comparing spectroscopic data of synthetic **1** and **4** with the spectra of the natural plakotenin allowed unambiguous approval of the proposed structure of isolated plakotenin.

**Synthesis of 2**: For the synthesis of **2**, a congener of **1**, again a late-stage Diels–Alder strategy was used. With alcohol **17** already in hand, triene **31** was readily prepared using a HWE reaction between the resulting aldehyde **18** and phosphonate **A**, which allowed introduction of a methyl instead of an ethyl group (Scheme 6). A 3:1 selectivity for the desired *Z* olefin was observed for this new HWE reaction and triene **31** could be isolated with 64% yield. Tetraene **34**, the linear precursor of *nor*-plakotenin, was then synthesized by performing the reduction/oxidation/HWE sequence described above on triene **31**. On heating, the intramolecular Diels–Alder reaction proceeded smoothly and further saponification of the ethyl ester gave **2** in very good yield (overall yield of 16.6% (from (*S*)-iodide **10**)). The optical rotation was measured in chloroform and methanol, and was in accordance with the literature and with synthetic plakotenin itself.[2]




Scheme 6. a) **A**, NaH, THF, 0°C, 64%; b) $LiAlH_4$, THF, 0°C, 78%; c) DMP, $CH_2Cl_2$, quant; d) **A**, NaH, THF, 0°C, 89%; e) toluene, 110°C, 92%; f) NaOH (2M), THF/MeOH, 40°C, 88%.

**Synthesis of 3**: For the synthesis of **3** a change in the synthetic route of **1** is necessary at a much earlier stage compared with **2** because the ethyl substituent must be introduced in the first Wittig reaction. When the reaction between aldehyde **8** and ylide **G** was performed, we observed a very slow conversion, and the mixture had to be refluxed for 4 days to go to completion (Scheme 7). As a consequence of the long period of heating, epimerization at the α position of the newly created double bond occurred. To avoid this, phosphonate **F** was used to install the first double bond, and surprisingly a 5:1 mixture in favor of the *Z* isomer was obtained. We decided to continue the sequence with this mixture, hoping that isomerization of this double bond could be possible at a later stage of the synthesis. As previously described, compound **37** was reduced into the

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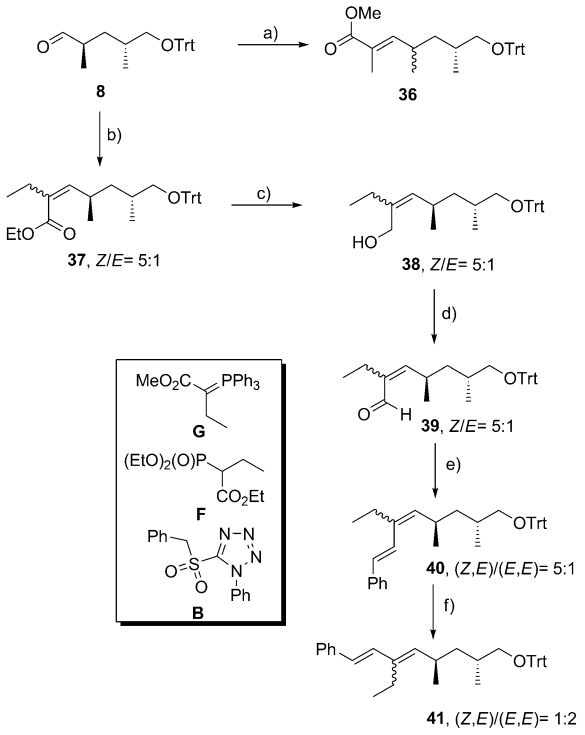
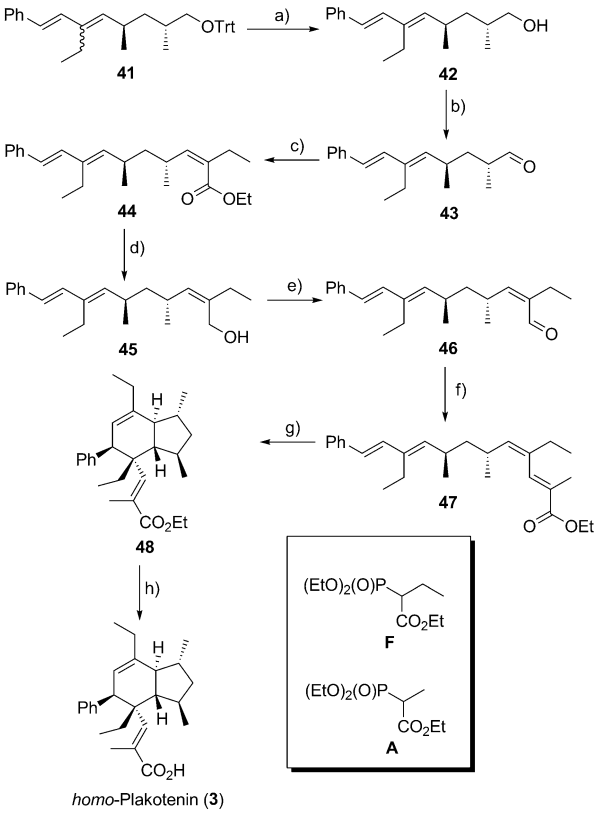



Scheme 7. a) **G**, toluene, 100 °C, 18 %; b) **A**, NaH, THF, 0 °C, 73 %; c) $LiAlH_4$, THF, 0 °C, 93 %; d) DMP, $CH_2Cl_2$, quant; e) **B**, $LiN(TMS)_2$, THF, −78 °C, 78 %; f) $I_2$, $CHCl_3$, RT.




Scheme 8. a) CSA, $CH_2Cl_2$/MeOH (2:1), 0 °C, 45 % (2 steps); b) DMP, $CH_2Cl_2$, quant; c) **F**, NaH, THF, 0 °C, 73 %; d) $LiAlH_4$, THF, 0 °C, 77 %; e) DMP, $CH_2Cl_2$, quant; f) **A**, NaH, THF, 0 °C, 68 %; g) toluene, 110 °C, 90 %; h) NaOH (2 M), THF/MeOH, 40 °C, 88 %.

primary alcohol **38** and further elongated to the diene **40** by a Julia–Kocienski olefination reaction with tetrazole **B**. The newly created double bond in **40** was assigned as having *E* configuration (based on the coupling constant $J = 16.4$ Hz) and obtained with a ratio of 7.7:1. At this stage, the geometrical isomers could not be separated and the mixture was treated with iodine in chloroform,[23] to attempt isomerization into the required (*E*,*E*) diene. Isomerization occurred and after 1 hour led to a 2:1 mixture (with respect to the second double bond) of the desired (*E*,*E*) diene **41**. Prolonged reaction time did not improve this ratio, and only degradation of the product was observed.

Since we were able to remove the minor (*Z*,*E*) isomer after trityl deprotection in the course of the synthesis of **1**, we directly treated compound **41** with camphorsulfonic acid (Scheme 8). Eventually, primary alcohol **42** could be isolated as a single diastereoisomer with 45 % yield over the two steps. Then, construction of the linear tetraene **47** was achieved using the same reaction sequence as described above. Similar yields were obtained, and compound **47** was cyclized under thermal conditions to yield *homo*-plakotenin ethyl ester **48** as a single diastereoisomer. The ester moiety was eventually hydrolyzed using the same method as described earlier to give **3**. As a consequence of the unexpected selectivity observed in the first HWE olefination and of the partial isomerization of diene **40**, the overall yield of this last natural product is much lower (overall yield of 6.0 % (from (*S*)-iodide **10**)) than for its two congeners (**1** and **2**).

**Computational studies**: The described total syntheses of **1**, its congeners **2** and **3**, as well as its diastereomer **4** proceed by an intramolecular Diels–Alder reaction following either the early-stage or the late-stage strategy. The reaction may lead to various products because there are four possible transition states for the precursor molecule (Figure 2).

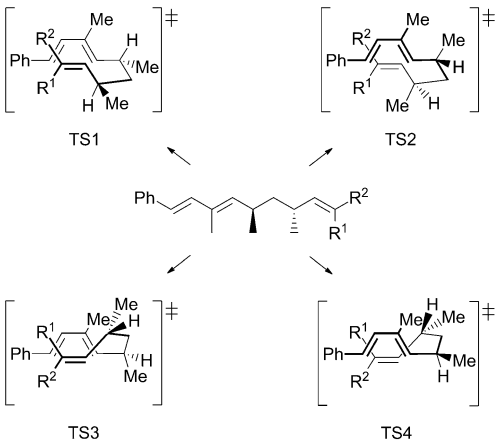



Figure 2. Possible transition states (shown as triene conformers) of the intramolecular Diels–Alder reaction that is applied to the synthesis of plakotenin and *iso*-plakotenin.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To understand the stereoselectivity of the intramolecular Diels–Alder reaction we have computed the relative energies of the transition states TS1 to TS4 for the synthesis of plakotenin and *iso*-plakotenin. The results for the late-stage Diels–Alder strategy ($R^1$ = CH=$CCH_3$COOEt, $R^2$ = Et and vice versa) have been published in previous work, together with the spectroscopic properties of the final products, and were the basis for the structure revision of plakotenin and its congeners.[9] In the present work, we additionally present our results for the early-stage Diels–Alder strategy (Table 1). We find that transition state TS1 is lowest in energy for both the (*E*,*E*,*E*) and (*E*,*E*,*Z*) precursors. This is in agreement with our experimental findings, since the structures of plakotenin and *iso*-plakotenin derive from TS1. Moreover, the values given in Table 1 correspond nicely with the data obtained for the late-stage Diels–Alder strategy, implying that both methods are equally well suited to deliver the desired product.

Table 1. Relative energies of the various transition states (in kJ mol$^{-1}$) that may occur during the synthesis of plakotenin and *iso*-plakotenin by the early-stage Diels–Alder strategy.

| | (*E*,*E*,*E*) $R^1$ = Et, $R^2$ = COOMe | (*E*,*E*,*Z*) $R^1$ = COOMe, $R^2$ = Et |
|---|---|---|
| TS1 | 0 | 0 |
| TS2 | 42 | 43 |
| TS3 | 30 | 35 |
| TS4 | 24 | 25 |

**Biological tests**: As previously reported, plakotenin displays a decent cytotoxicity on tumor cells such as murine lymphocytic leukemia cells (L1210) with $IC_{50}$Tox values of 15.4–21.1 μM.[1]

Eventually, a small selection of new cyclic and acyclic plakotenin derivatives **49**–**55** was prepared using standard methods (esterification, conversion to an azide etc.). They are derived from the natural isomers along the lines described above; this is the reason we looked first at isomers directly emerging from the natural product syntheses.

To test, whether the newly synthesized plakotenin derivatives have stronger cytotoxic effects on tumor cells or on their cell cycle than plakotenin itself, a variety of tumor cell lines were incubated with different concentrations of plakotenin and its derivatives (Figures 3 and 4) as well as some linear synthesis intermediates (see the Supporting Information). Cytotoxicity was analyzed using the MTT assay, by which mitochondrial integrity is measured as a mean of viability. The viability of different tumor cell lines (human cervix carcinoma (HeLa), human glioma (U251)) was then compared after treatment with 20 μM of the compounds, which is around the $IC_{50}$Tox value of plakotenin itself (Figure 5 and Figures S1 and S2 in the Supporting Information). Interestingly, changing the stereochemistry at the quaternary position to the opposite configuration decreases the cytotoxic activity of all *iso*-plakotenin derivatives **4**, **30**, **51**, **54**. Likewise, the *E*-configured linear precursors (*E*)-**26**, (*E*)-**27**, (*4E*)-**29**, which lead to the synthesis of *iso*-plakotenin derivatives, also display a lower cytotoxicity than their *Z* isomers **5**, (*Z*)-**26**, (*Z*)-**27**, **31**, **32**, **34**. Further, changing the

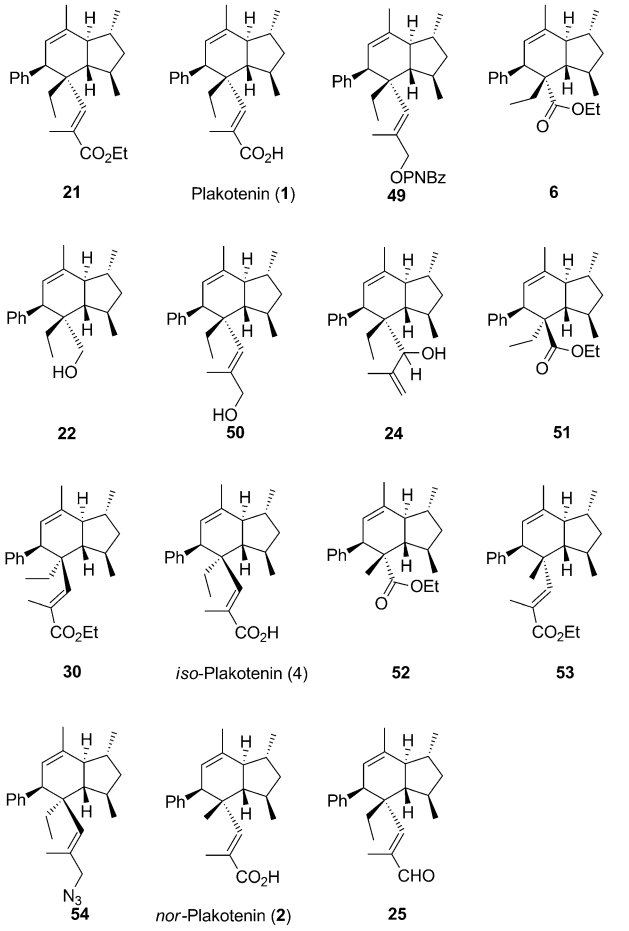


Figure 3. Plakotenin derivatives tested for biological activity.

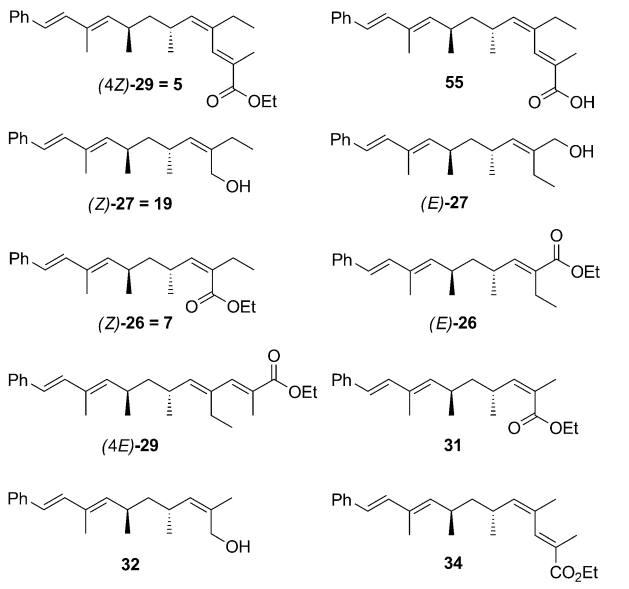


Figure 4. Acyclic plakotenin precursors tested for biological activity.

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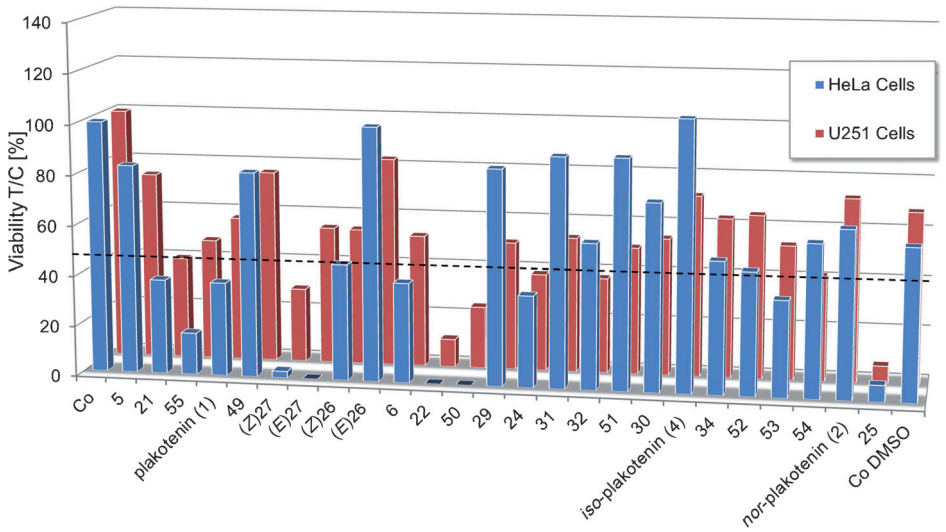


Figure 5. Comparison of the toxicology of plakotenin (**1**) and plakotenin derivatives in HeLa or U251 tumor cell lines. In a 96 well plate $5\times10^5$ cells per well were incubated with 20 μM of plakotenin derivatives for 72 h. Eventually, the viability of the cells was determined by using an MTT assay (Promega). Absorption of the formazan dye as a means to test for viability was measured at 595 nm. Full diagrams with standard error (SE) and also the 10 μM concentrations are shown in Figures S1 and S2 (in the Supporting Information).

chain length at the quaternary stereogenic center in plakotenin derivatives as in **1**, **6** and **53** or in **22** and **50** does not seem to interfere with the cytotoxicity to a large extent, however introducing a polar residue such as an alcohol severely increases the cytotoxicity of the plakotenin derivatives **22** and **50** as well as their precursors (*Z*)-**27** and **32** with an $IC_{50}Tox = 5.24$ μM for the alcohol **22**. However, the hydroxyl group should be at the terminus of the aliphatic residue for an enhancement of the cytotoxicity as the activity in **24** is not better than in plakotenin itself. By introducing an aldehyde moiety at the side chain, the cytotoxicity was also fourfold increased with an $IC_{50}Tox = 5.56$ μM as measured for aldehyde **25**.

Furthermore, fluorescence assisted cell sorting (FACS) and a quantification of caspase 8 cleavage was performed to measure the apoptotic potential of the compounds and their influence on the cell cycle of tumor cells especially by measuring the G2M arrest. Even if the cytotoxicity of a compound is low, it can lead to a deceleration of tumor growth by decreasing the rate of cell division. For the FACS measurements we used concentrations of 1, 2, 3, and 5 μM, which were below the reported $IC_{50}Tox$ values (15.4–21.1 μM) of plakotenin in murine lymphocytic leukemia cells (L1210).[1] Figure 6 shows the comparison between plakotenin and its natural isomers, as well as with the aldehyde **25**, which has been shown to exhibit a higher toxicity in the MTT assay. As expected, plakotenin (**1**) itself shows a minor increase of apoptosis, whereas the aldehyde **25** enhances the apoptosis rate three-fold. *iso*-Plakotenin (**4**) and also *nor*-plakotenin (**2**) do not show any increase in apoptosis at these concentrations.

Additionally, the influence on cell cycle was measured by FACS. Besides **1**, the intermediates **5** and **21** were the most potent derivatives, which show an enhanced cell cycle arrest in the G2M phase and a decrease in the G1 phase indicating an antiproliferating activity of the plakotenin intermediates (Figure S3 in the Supporting Information). It is interesting to point of out that the acyclic derivative **5** is the precursor of **21** containing an ester moiety at the stereogenic center.

## Conclusion

We presented two different approaches towards the total synthesis of members of the plakotenin family. Besides the naturally occurring plakotenin, for the first time we were able to synthesize its natural isomers

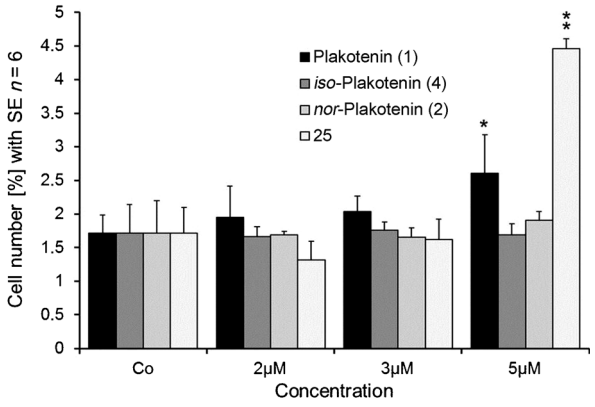


Figure 6. Determination of the apoptotic rates by FACS measurements in L1210 cells using 2, 3, and 5 μM plakotenin (**1**), *iso*-plakotenin (**4**), *nor*-plakotenin (**2**), and the aldehyde **25** (*P* values $p \le 0.5$ "*significant" $p \le 0.01$ "**significant" $p \le 0.001$).

*homo*-plakotenin, *iso*-plakotenin, and *nor*-plakotenin. The biological studies of the natural isomers revealed that plakotenin itself displays a cytotoxicity to tumor cells with an $IC_{50}Tox$ value of about 15–21 μM depending on the tumor cell type. Interestingly, the natural isomers of plakotenin are mostly inactive. Synthesis of a variety of plakotenin derivatives and their isomers as well as their linear precursors led to more potent cytotoxic derivatives than plakotenin itself. By replacing the carboxy-group-containing moiety at the quaternary stereogenic center with different polar and less-polar residues we found that moieties with a terminal hydroxyl group are the most efficacious derivatives. They show a decent increase in tumor cell cytotoxicity with $IC_{50}Tox$ values up to 5.21 μM. Introducing more lipophilic moieties at

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this position led to a reduction of activity. Analogous to the natural isomers of plakotenin, *iso*-plakotenin, and *nor*-plakotenin, all derivatives with the same stereochemistry at the benzylic position are far less active as plakotenin and its derivatives. Furthermore, the linear precursors act in the same way proposing a binding and folding in an active center of a receptor on tumor cells. The biological data suggest the existence of a plakotenin binding receptor, which requires the correct stereochemistry at the quaternary position but is to a certain extent flexible in the length of the moiety. Polar residues at the terminus of this moiety might interact with polar amino acids in their proximity by enhancing either the binding, the turnover of the ligand–receptor complex or the conformational change of the ligand–receptor complex. Introducing an aldehyde moiety also increases the cytotoxic activity probably by crosslinking the ligand with the receptor. However, these speculations have to be proven by future experiments after the characterization of the putative receptor. It is interesting to note that, so far, there are no similar compounds known being structurally comparable (arylhydroindanes) with the plakotenin substructure.

In future studies, we will use the plakotenin substructure as a lead structure for further optimization.

## Experimental Section

**General methods**: $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM 400 (400 MHz/100 MHz), Bruker DRX 500 (500 MHz/125 MHz) or Bruker Avance 600 (600 MHz/150 MHz) instrument using $CDCl_3$ as solvent. Chemical shifts are expressed in parts per million (ppm, $\delta$) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ ($\delta$ = 7.26 ppm) as an internal standard. All coupling constants are absolute values and $J$ values are expressed in Hertz (Hz). For assigning signal separation of $^1$H NMR spectra the following abbreviations were used: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, sext = sextet, m = multiplet, dd = doublet of doublets, dq = doublet of quartets, ddq = doublet of dq and Ar-H = aromatic proton. For assigning signals of $^{13}$C NMR spectra the following abbreviations were used: p = primary ($RCH_3$), s = secondary ($R_2CH_2$), t = tertiary ($R_3CH$), q = quaternary ($R_4C$). The assignment was supported by analysis of DEPT90 and DEPT135 spectra. MS (EI) (electron impact mass spectrometry), MS (FAB) (fast atom bombardment mass spectrometry) and HRMS: Finnigan MAT 90. The molecular fragments are quoted as the relation between mass and charge ($m/z$), the intensities as a percentage value relative to the intensity of the base signal (100%). The molecular ion has the abbreviation [$M^+$]. IR (infrared spectroscopy): FTIR Bruker IFS 88. IR spectra of oils were recorded as thin films on KBr, in the case of solids the neat substance was used. The deposit of the absorption band is given in wavenumbers in cm$^{-1}$. Solvents and chemicals used for reactions were purchased from commercial suppliers. Solvents were dried under standard conditions; chemicals were used without further purification. All the reactions were performed in standard glassware. All reactions were carried out under Argon in flame-dried glassware. Evaporation of solvents and concentration of reaction mixtures were performed in vacuo on a Büchi rotary evaporator. Column chromatography was performed using silica gel 60 (purchased from Merck) under flash conditions. For thin layer chromatography, aluminum foils layered with silica gel with fluorescence indicator (silica gel 60 $F_{254}$) produced by Merck were employed. The detection was carried out with a UV lamp from Heraeus, model Fluotest. The Seebach reagent (molybdophosphoric acid (2.5 w%), cerium(IV) sulfate tetrahydrate (1.0 w%), $H_2SO_4$ concd (6.0 w%), water (90.5 w%)) was used as dipping reagent. Specific rotations were determined using the polarimeter Perkin–Elmer 241. Melting points were registered on a Mel-Temp II melting point microscope from Laboratory Devices Inc. and are not corrected.

**Amide 11**: A solution of *n*-butyllithium in hexanes (2.5 M, 10.8 mL, 27.0 mmol) was slowly added to a suspension of lithium chloride (3.64 g, 85.9 mmol) and diisopropylamine (4.10 mL, 3.00 g, 29.0 mmol) in THF (15 mL) at −78 °C. The resulting suspension was warmed to 0 °C briefly and was then cooled to −78 °C again. An ice-cooled solution of *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide (**E**) (3.14 g, 14.2 mmol) in THF (35 mL) was added. The mixture was stirred at −78 °C for 2 h, at 0 °C for 15 min and at RT for 5 min. The mixture was cooled to 0 °C and iodide **10** (2.99 g, 6.76 mmol) in THF (35 mL) was added. After being stirred for 2 d at 45 °C the reaction mixture was treated with half saturated aqueous $NH_4Cl$ (70 mL) and the resulting mixture was extracted with EtOAc (3×40 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica using cyclohexane/ethyl acetate 2:1 to give amide **11** (3.31 g, 91%) as white foam. $R_f$ = 0.22 (cyclohexane/EtOAc 2:1); m.p. 50 °C; $[\alpha]_D^{20} = +33.5$ ($c$ = 0.99 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.92 (d, $J$ = 2.7 Hz, 3H), 0.94 (d, $J$ = 2.7 Hz, 3H), 1.00 (d, $J$ = 6.9 Hz, 3H), 1.31–1.44 (m, 2H), 1.50–1.61 (m, 1H), 2.35–2.43 (m, 1H), 2.50 (s, 3H), 2.70 (dd, $J$ = 8.8 Hz, $J$ = 6.0 Hz, 1H), 2.88 (dd, $J$ = 8.8 Hz, $J$ = 4.7 Hz, 1H), 4.24 (brs, 1H), 4.49 (t, $J$ = 7.2 Hz, 1H), 7.11–7.24 (m, 14H), 7.33–7.39 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.3 (p), 17.5 (p), 18.2 (p), 31.7 (t), 34.1 (t), 37.8 (s), 67.4 (s), 76.4 (t), 86.0 (q), 126.1 (t), 126.8 (t), 127.5 (t), 127.6 (t), 128.2 (t), 128.7 (t), 142.5 (q), 144.3 (q), 179.0 ppm (q) (the $^1$H- and $^{13}$C NMR spectra are complex due to amide geometrical isomerism); IR (neat): $\tilde{\nu}$ = 3382, 3059, 3030, 2969, 2930, 2871, 1620, 1490, 1449, 1410, 1373, 1318, 1221, 1155, 1070, 988, 926, 899, 839, 764, 747, 705, 648, 633, 506 cm$^{-1}$; MS (FAB, Matrix: 3-NBA): $m/z$ (%): 558 [$M$+Na]$^+$, 536 [$M$+H]$^+$, 243 (100); HRMS (FAB, Matrix: 3-NBA) $m/z$: calcd for $C_{36}H_{42}NO_3$: 536.3165; found: 536.3167.

**Alcohol 12**: A solution of *n*-butyllithium in hexanes (2.5 M, 9.30 mL, 23.0 mmol) was added to a solution of diisopropylamine (3.50 mL, 2.50 g, 25.0 mmol) in THF (30 mL) at −78 °C. The resulting solution was stirred at −78 °C for 10 min, was then warmed to 0 °C and held at that temperature for 20 min. Lithium amidotrihydroborate (819 mg, 23.9 mmol) was added in one portion. The suspension was stirred at 0 °C for 15 min and then was warmed to RT. After 15 min, the suspension was cooled to 0 °C. A solution of amide **11** (3.20 g, 5.97 mmol) in THF (30 mL) was slowly added. The reaction mixture was warmed to RT, held at that temperature for 2 h and was then cooled to 0 °C where excess hydride was quenched by careful addition of 3 M aqueous HCl (70 mL). The mixture was stirred for 10 min at 0 °C and was then extracted with $Et_2O$ (3×50 mL). The combined extracts were washed sequentially with 3 M aqueous HCl (10 mL), 2 M aqueous NaOH (10 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica using cyclohexane/ethyl acetate 9:1 to give alcohol **12** (2.03 g, 91%) as a white solid. $R_f$ = 0.18 (cyclohexane/EtOAc 6:1); m.p. 72 °C; $[\alpha]_D^{20} = +13.0$ ($c$ = 0.81 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.87 (d, $J$ = 6.6 Hz, 3H; $CH_3$), 0.93 (d, $J$ = 6.7 Hz, 3H; $CH_3$), 1.10–1.23 (m, 2H; $CHCH_2CH$), 1.31 (t, $J$ = 5.5 Hz, 1H; O*H*), 1.61–1.69 (m, 1H; $HOCH_2CH$), 1.79–1.87 (m, 1H; $TrtOCH_2CH$), 2.89–2.96 (m, 2H; $TrtOCH_2$), 3.34–3.46 (m, 2H; $HOCH_2$), 7.20–7.31 (m, 9H; Ar-H), 7.43–7.46 ppm (m, 6H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 16.3 (p), 17.1 (p), 31.2 (t), 33.0 (t), 37.2 (s), 68.9 (s), 69.0 (s), 86.2 (q), 126.8 (t), 127.6 (t), 128.7 (t), 144.4 ppm (q); IR (neat): $\tilde{\nu}$ = 3299, 3056, 3031, 2958, 2925, 2871, 1595, 1491, 1449, 1387, 1323, 1220, 1177, 1151, 1062, 1033, 985, 949, 931, 897, 821, 765, 752, 709, 697, 648, 632, 540, 484, 422 cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%): 374 (1) [$M^+$], 259 (12), 243 (100), 183 (17), 165 (35), 105 (11), 77 (4); HRMS $m/z$: calcd for $C_{26}H_{30}O_2$: 374.2246; found: 374.2249.

**Ester 13**: To a solution of alcohol **12** (2.03 g, 5.42 mmol) in DMSO (20 mL) was added 2-iodobenzoic acid (3.79 g, 13.6 mmol). The reaction mixture was stirred at RT for 2.5 h, after which it was diluted with $H_2O$ (100 mL) and the resulting precipitate filtered off. The aqueous layer was extracted with $Et_2O$ (3×40 mL). The combined organic extracts were

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dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude aldehyde **8** (2.02 g, 5.42 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. To a solution of the crude aldehyde **8** (2.02 g, 5.42 mmol) in toluene (20 mL) was added methyl 2-(triphenylphosphoranylidene)-propanoate (**C**) (2.83 g, 8.13 mmol) at RT. The reaction mixture was heated under reflux for 17 h. The crude product was purified by column chromatography on silica using cyclohexane/ethyl acetate 50:1 to give ester **13** (2.11 g, 88%) as colorless oil. A 14:1 ratio of *E*/*Z* products was obtained which was measured from the $^1$H NMR spectrum of the crude reaction mixture. $R_f$=0.31 (cyclohexane/EtOAc 18:1); $[\alpha]_D^{20}=-41.2$ ($c$=0.26 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.91 (d, $J$=6.6 Hz, 3H; TrtOCH$_2$CHC$H_3$), 1.02 (d, $J$=6.7 Hz, 3H; C=CHCHC$H_3$), 1.11–1.18 (m, 1H; CHC$H_A$H$_B$CH), 1.46–1.53 (m, 1H; CHCH$_A$$H_B$CH), 1.60 (d, $J$=1.4 Hz, 3H; MeCO$_2$CC$H_3$), 1.64–1.75 (m, 1H; TrtOCH$_2$C$H$), 2.29–2.40 (m, 1H; C=CHC$H$), 2.81 (dd, $J$=8.7 Hz, $J$=6.4 Hz, 1H; TrtOC$H_A$H$_B$), 3.00 (dd, $J$=8.7 Hz, $J$=4.7 Hz, 1H; TrtOCH$_A$$H_B$), 3.71 (s, 3H; CO$_2$C$H_3$), 6.50 (dd, $J$=10.1 Hz, $J$=1.4 Hz, 1H; C=C$H$), 7.19–7.30 (m, 9H; Ar-H), 7.42–7.45 ppm (m, 6H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.3 (p), 18.3 (p), 20.0 (p), 30.6 (t), 31.8 (t), 40.8 (s), 51.6 (p), 67.3 (s), 86.0 (q), 125.8 (q), 126.8 (t), 127.6 (t), 128.7 (t), 144.4 (q), 148.3 (t), 168.8 ppm (q); IR (film): $\tilde{\nu}$=3058, 3023, 2956, 2926, 2869, 1715, 1649, 1597, 1490, 1448, 1386, 1315, 1271, 1212, 1154, 1092, 1070, 1032, 989, 898, 813, 764, 748, 707, 648, 632 cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%): 442 (0.02) [$M^+$], 243 (100), 183 (9), 165 (15), 105 (15), 77 (4); HRMS $m/z$: calcd for $C_{30}H_{34}O_3$: 442.2508; found: 442.2505.

**Alcohol 14**: To a solution of ester **13** (1.92 g, 4.34 mmol) in THF (80 mL) at 0°C was slowly added lithium aluminium hydride (168 mg, 4.43 mmol). The reaction mixture was stirred at RT for 19 h, after which it was cooled to 0°C and quenched with $H_2O$ (50 mL) followed by Rochelle's salt solution (50 mL) and the reaction mixture stirred at RT for 15 h. The aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica using cyclohexane/ethyl acetate 9:1 to give alcohol **14** (1.62 g, 90%) as colorless oil. $R_f$=0.06 (cyclohexane/EtOAc 12:1); $[\alpha]_D^{20}=-25.1$ ($c$=1.08 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.86 (d, $J$=6.6 Hz, 3H; TrtOCH$_2$CHC$H_3$), 1.01 (d, $J$=6.7 Hz, 3H; C=CHCHC$H_3$), 1.03–1.09 (m, 1H; CHC$H_A$H$_B$CH), 1.28 (t, $J$=6.1 Hz, 1H; O$H$), 1.36–1.41 (m, 1H; CHCH$_A$$H_B$CH), 1.44 (d, $J$=1.3 Hz, 3H; HOCH$_2$CC$H_3$), 1.69–1.77 (m, 1H; TrtOCH$_2$C$H$), 2.20–2.31 (m, 1H; C=CHC$H$), 2.81 (dd, $J$=8.6 Hz, $J$=6.7 Hz, 1H; TrtOC$H_A$H$_B$), 2.99 (dd, $J$=8.6 Hz, $J$=4.8 Hz, 1H; TrtOCH$_A$$H_B$), 3.92 (d, $J$=5.6 Hz, 2H; HOC$H_2$), 5.12 (dd, $J$=9.5 Hz, $J$=1.2 Hz, 1H; C=C$H$), 7.19–7.30 (m, 9H; Ar-H), 7.43–7.46 ppm (m, 6H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=13.6 (p), 18.3 (p), 20.9 (p), 29.4 (t), 31.6 (t), 41.5 (s), 67.7 (s), 69.0 (s), 86.0 (q), 126.8 (t), 127.6 (t), 128.8 (t), 132.9 (t), 133.0 (q), 144.5 ppm (q); IR (film): $\tilde{\nu}$=3331, 3086, 3058, 3032, 2955, 2920, 2867, 1597, 1490, 1448, 1385, 1317, 1265, 1220, 1182, 1154, 1068, 1032, 1003, 926, 899, 849, 801, 774, 764, 746, 707, 648, 633, 618, 482 cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%): 414 (0.03) [$M^+$], 243 (100), 183 (3), 165 (12), 105 (3); HRMS $m/z$: calcd for $C_{29}H_{34}O_2$: 414.2559; found: 414.2561.

**Diene 16**: To a solution of alcohol **14** (201 mg, 485 μmol) in DMSO (10 mL) was added 2-iodobenzoic acid (340 mg, 1.21 mmol). The reaction mixture was stirred at RT for 1 h, after which it was diluted with $H_2O$ (50 mL) and the resulting precipitate was filtered off. The aqueous layer was extracted with $Et_2O$ (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude aldehyde **15** (200 mg, 485 μmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. To a solution of 5-(benzylsulfonyl)-1-phenyl-1*H*-tetrazole (**B**) (218 mg, 728 μmol) in THF (5 mL) was slowly added lithium bis(trimethylsilyl)amide (1 M in THF, 600 μL, 600 μmol) at 0°C. After stirring for 20 min at RT, it was cooled to −78°C and a solution of crude aldehyde **15** (200 mg, 0.485 mmol) in THF (5 mL) was added. The reaction mixture was stirred overnight while slowly warming to RT. It was diluted with $Et_2O$ (5 mL) and the reaction quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica using cyclohexane/ethyl acetate 50:1 to give compound **16** (190 mg, 80%) as colorless oil. A 10:1 ratio of *E*/*Z* products was obtained. $R_f$=0.30 (cyclohexane/EtOAc 50:1); $[\alpha]_D^{20}=-75.0$ ($c$=0.71 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.91 (d, $J$=6.6 Hz, 3H; TrtOCH$_2$CHC$H_3$), 1.03 (d, $J$=6.7 Hz, 3H; C=CHCHC$H_3$), 1.09–1.16 (m, 1H; CHC$H_A$H$_B$CH), 1.45–1.49 (m, 1H; CHCH$_A$$H_B$CH), 1.63 (s, 3H; PhCH=CHCC$H_3$), 1.70–1.80 (m, 1H; TrtOCH$_2$C$H$), 2.36–2.47 (m, 1H; C=CHC$H$), 2.81 (dd, $J$=8.6 Hz, $J$=6.7 Hz, 1H; TrtOC$H_A$H$_B$), 3.02 (dd, $J$=8.7 Hz, $J$=4.7 Hz, 1H; TrtOCH$_A$$H_B$), 5.36 (d, $J$=9.6 Hz, 1H; PhCH=CHC=C$H$), 6.38 (d, $J$=16.1 Hz, 1H; PhC$H$), 6.74 (d, $J$=15.6 Hz, 1H; PhCH=C$H$), 7.16–7.24 (m, 5H; Ar-H), 7.26–7.32 (m, 9H; Ar-H), 7.40–7.46 ppm (m, 6H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.4 (p), 18.5 (p), 21.0 (p), 30.2 (t), 31.8 (t), 41.7 (s), 67.6 (s), 86.0 (q), 125.6 (t), 126.1 (t), 126.7 (t), 126.8 (t), 127.7 (t), 128.5 (t), 128.8 (t), 132.1 (q), 134.2 (t), 138.0 (q), 140.9 (t), 144.5 ppm (q); IR (film): $\tilde{\nu}$=3084, 3058, 3025, 2957, 2924, 2866, 2851, 1597, 1560, 1542, 1491, 1448, 1386, 1314, 1220, 1182, 1155, 1070, 1031, 959, 926, 899, 826, 774, 763, 746, 706, 647, 632, 530 cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%): 486 (50) [$M^+$], 374 (73), 414 (100), 485 (95); HRMS $m/z$: calcd for $C_{36}H_{38}O$: 486.2922; found: 486.2917.

**Alcohol 17**: To a solution of **16** (3.01 g, 6.19 mmol) in $CH_2Cl_2$/MeOH (200/100 mL) at 0°C camphorsulfonic acid (2.44 g, 10.5 mmol) was added in one portion. The mixture was stirred at RT for 90 min and was then neutralized by the addition of saturated aqueous $NaHCO_3$ (60 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (3× 50 mL). The combined organic layers were dried ($MgSO_4$) and then concentrated. The crude product was then purified by flash chromatography using cyclohexane/ethyl acetate 6:1 to yield alcohol **17** (1.33 g, 88%) as colorless solid. $R_f$=0.16 (cyclohexane/EtOAc 6:1); m.p. 43°C; $[\alpha]_D^{20}=-44.5$ ($c$=0.92 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.95 (d, $J$=6.7 Hz, 3H; HOCH$_2$CHC$H_3$), 0.99 (d, $J$=6.6 Hz, 3H; C=CHCHC$H_3$), 1.11–1.19 (m, 1H; CHC$H_A$H$_B$CH), 1.27 (brs, 1H; O$H$), 1.39–1.45 (m, 1H; CHCH$_A$$H_B$CH), 1.63–1.71 (m, 1H; HOCH$_2$C$H$), 1.88 (s, 3H; PhCH=CHCC$H_3$), 2.61–2.72 (m, 1H; C=CHC$H$), 3.42 (dd, $J$=10.5 Hz, $J$=6.5 Hz, 1H; HOC$H_A$H$_B$), 3.53 (dd, $J$=10.5 Hz, $J$=5.2 Hz, 1H; HOCH$_A$C$H_B$), 5.43 (d, $J$=9.5 Hz, 1H; PhCH=CHC=C$H$), 6.45 (d, $J$=16.1 Hz, 1H; PhC$H$), 6.79 (d, $J$=16.1 Hz, 1H; PhCH=C$H$), 7.17–7.21 (m, 1H; Ar-H), 7.29–7.32 (m, 2H; Ar-H), 7.39–7.41 ppm (m, 2H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.6 (p), 17.2 (p), 20.8 (p), 30.3 (t), 33.5 (t), 41.0 (s), 68.1 (s), 125.8 (t), 126.1 (t), 126.9 (t), 128.5 (t), 132.1 (q), 134.1 (t), 137.9 (q), 140.8 ppm (t); IR (neat): $\tilde{\nu}$=3307, 3078, 3055, 3028, 2959, 2921, 2870, 1658, 1630, 1596, 1575, 1492, 1447, 1370, 1269, 1232, 1153, 1074, 1037, 990, 961, 924, 909, 883, 830, 747, 690, 647, 532, 456, 438, 427, 409 cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%): 244 (47) [$M^+$], 171 (100), 143 (29), 129 (31), 99 (37), 91 (31); HRMS $m/z$: calcd for $C_{17}H_{24}O$: 244.1827; found: 244.1829.

**Ester 7**: Dess–Martin periodinane (3.56 mL, 1.65 mmol) was added at 0°C to a solution of alcohol **17** (310 mg, 1.27 mmol) in $CH_2Cl_2$ (15 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×10 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **18** (310 mg, 1.27 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. To a solution of sodium hydride (60% in mineral oil, 152 mg, 3.87 mmol) in THF (15 mL) at 0°C was added dropwise ethyl 2-(diethoxyphosphoryl)butanoate (**F**) (960 mg, 3.87 mmol) (or ethyl 2-((bis(*o*-tolyloxy))phosphoryl)acetate (**D**) for method according to Ando et al.[19a–d]). The solution was stirred at RT for 1 h before cooling to 0°C and addition of the crude aldehyde **18** (310 mg, 1.27 mmol) in THF (5 mL). The solution was stirred for 1 h at 0°C, warmed slowly to RT and stirred for an additional 3 h. The reaction was quenched by pouring on to saturated aqueous $NH_4Cl$ (80 mL). The product was extracted with $Et_2O$ and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 30:1 to yield ester **7** (328 mg, 76%) as a colorless oil. A 4:1 ratio of *Z*/*E* products was obtained. $R_f$=0.50 (cyclohexane/EtOAc=18:1); $[\alpha]_D^{20}=-10.0$ ($c$=1.36 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.94 (d, $J$=6.4 Hz, 3H; PhCH=

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CHC=CHCHC$H_3$), 1.00 (d, $J$=7.2 Hz, 3H; EtC$O_2$C=CHCHC$H_3$), 1.04 (t, $J$=7.2 Hz, 3H; EtC$O_2$C$H_2$C$H_3$), 1.21 (t, $J$=6.8 Hz, 3H; C$O_2$C$H_2$C$H_3$), 1.29–1.36 (m, 2H; CHC$H_2$CH), 1.79 (s, 3H; PhCH=CHCC$H_3$), 2.22–2.33 (m, 2H; EtC$O_2$CC$H_2$C$H_3$), 2.43–2.59 (m, 1H; PHCH=CHC=CHC$H$), 2.98–3.01 (m, 1H; EtC$O_2$C=CHC$H$), 4.01–4.15 (m, 2H; C$O_2$C$H_2$C$H_3$), 5.34 (d, $J$=9.6 Hz, 1H; PhCH=CHC=C$H$), 5.58 (d, $J$=9.6 Hz, 1H; EtC$O_2$C=C$H$), 6.41 (d, $J$=16.0 Hz, 1H; PhC$H$), 6.77 (d, $J$=16.0 Hz, 1H; PhCH=C$H$), 7.17–7.21 (m, 1H; Ar-H), 7.28–7.32 (m, 2H; Ar-H), 7.38–7.40 ppm (m, 2H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.6 (p), 13.9 (p), 14.3 (p), 21.1 (p), 21.5 (p), 27.8 (s), 31.3 (t), 32.0 (t), 45.8 (s), 60.2 (s), 125.7 (t), 126.2 (t), 126.9 (t), 128.6 (t), 132.6 (q), 132.9 (q), 134.3 (t), 138.2 (q), 140.5 (t), 145.9 (t), 168.3 ppm (q); IR (film): $\tilde{\nu}$= 3027, 2961, 2868, 1727, 1599, 1493, 1450, 1381, 1211, 1180, 1030, 1029, 704 $cm^{-1}$; MS (EI, 70 eV): $m/z$ (%): 340 (6) [$M^+$], 267 (14), 171 (8), 91 (6), 43 (100); HRMS $m/z$: calcd for $C_{23}H_{32}O_2$: 340.2402; found: 340.2400.

**Alcohol 19**: To a solution of ester **7** (325 mg, 954 μmol) in THF (10 mL) at 0°C was slowly added lithium aluminium hydride (37.0 mg, 974 μmol). After stirring at 0°C for 2 h the reaction mixture was quenched carefully at 0°C with $H_2O$ followed by Rochelle's salt solution. The aqueous layer was extracted with $Et_2O$ (4×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was then purified by column chromatography on silica using $n$-pentane/$Et_2O$ 9:1 to yield alcohol **19** (175 mg, 61%). $R_f$=0.52 (cyclohexane/EtOAc=6:1); $[\alpha]_D^{20}$=−102.6 ($c$=0.61 in $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=0.94 (d, $J$=6.5 Hz, 3H; HOC$H_2$C=CHCHC$H_3$), 0.97 (d, $J$=6.5 Hz, 3H; PhCH=CHC=CHCHC$H_3$), 1.05 (t, $J$=7.5 Hz, 3H; HOC$H_2$CC$H_2$C$H_3$), 1.14 (brs, 1H; O$H$), 1.27–1.38 (m, 2H; CHC$H_2$CH), 1.80 (s, 3H; PhCH=CHCC$H_3$), 2.14 (q, $J$=7.5 Hz, 2H; HOC$H_2$CC$H_2$C$H_3$), 2.41–2.56 (m, 2H; C$H$C$H_2$C$H$), 4.02 (s, 2H; HOC$H_2$), 5.05 (d, $J$=10.0 Hz, 1H; HOC$H_2$C=C$H$), 5.41 (d, $J$=9.5 Hz, 1H; PhCH=CHC=C$H$), 6.44 (d, $J$=16.0 Hz, 1H; PhC$H$), 6.79 (d, $J$=16.0 Hz, 1H; PhCH=C$H$), 7.19 (t, $J$=7.5 Hz, 1H; Ar-H), 7.29–7.32 (m, 2H; Ar-H), 7.40 ppm (d, $J$=7.5 Hz, 2H; Ar-H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=12.7 (p), 13.2 (p), 21.7 (p), 22.7 (p), 28.0 (s), 30.5 (t), 31.2 (t), 46.0 (s), 60.7 (s), 126.2 (t), 126.3 (t), 127.1 (t), 128.7 (t), 133.0 (q), 133.7 (t), 133.9 (t), 138.0 (q), 139.3 (q), 140.8 ppm (t); IR (film): $\tilde{\nu}$=3343, 3027, 2959, 2923, 1598, 1493, 1450, 1385, 1016, 958, 747, 692 $cm^{-1}$; MS (EI, 70 eV): $m/z$ (%): 298 (67) [$M^+$], 171 (100), 153 (69), 107 (60); HRMS $m/z$: calcd for $C_{21}H_{30}O$: 298.2297; found: 298.2296.

**Ester 5**: Dess–Martin periodinane (1.41 mL, 653 μmol) was added at 0°C to a solution of alcohol **19** (150 mg, 503 μmol) in $CH_2Cl_2$ (10 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (4×10 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **20** (150 mg, 503 μmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. To a solution of sodium hydride (60% in mineral oil, 66.0 mg, 1.66 mmol) in THF (10 mL) at 0°C was added dropwise ethyl 2-(diethoxyphosphoryl)propanoate (**A**) (350 μL, 1.61 mmol). The solution was stirred at RT for 1 h before cooling to 0°C and addition of crude aldehyde **20** (150 mg, 503 μmol) in THF (5 mL). The solution was warmed slowly to RT and after stirring overnight the reaction was quenched by pouring on to saturated aqueous $NH_4Cl$ (10 mL). The product was extracted with $Et_2O$ and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was then purified by column chromatography on silica using $n$-pentane/$Et_2O$ 40:1 to yield ester **5** (169 mg, 88%) as colorless oil. $R_f$=0.44 (cyclohexane/EtOAc=18:1); $[\alpha]_D^{20}$=+17.3 ($c$=0.84 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.92 (d, $J$=6.4 Hz, 3H; PhCH=CHC=CHCHC$H_3$), 0.93 (d, $J$=6.8 Hz, 3H; EtC$O_2$C=CHC=CHCHC$H_3$), 0.99 (t, $J$=7.6 Hz, 3H; EtC$O_2$C=CHCCH$_2$C$H_3$), 1.13 (t, $J$=7.2 Hz, 3H; C$O_2$CH$_2$C$H_3$), 1.30–1.34 (m, 2H; CHC$H_2$CH), 1.80 (s, 3H; EtC$O_2$CC$H_3$), 1.83 (s, 3H; PhCH=CHCC$H_3$), 2.13 (q, $J$=7.6 Hz, 2H; EtC$O_2$C=CHCC$H_2$C$H_3$), 2.17–2.23 (m, 1H; EtC$O_2$C=CHC=CHC$H$), 2.44–2.55 (m, 1H; PhCH=CHC=CHC$H$), 3.94–4.08 (m, 2H; C$O_2$C$H_2$C$H_3$), 5.12 (d, $J$=10.0 Hz, 1H; EtC$O_2$C=CHC=C$H$), 5.35 (d, $J$=9.6 Hz, 1H; PhCH=CHC=C$H$), 6.41 (d, $J$=16.0 Hz, 1H; PhC$H$), 6.76 (d, $J$=16.0 Hz, 1H; PhCH=C$H$), 7.05 (s, 1H; EtC$O_2$C=C$H$), 7.15 (t, $J$=7.2 Hz, 1H; Ar-H) 7.28 (d, $J$=8.0 Hz, 2H; Ar-H), 7.39 ppm (d, $J$=7.2 Hz, 2H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.7 (p), 13.4 (p), 14.3 (p), 14.4 (p), 21.1 (p), 21.5 (p), 30.0 (s), 30.9 (t), 31.9 (t), 45.9 (s), 60.7 (s), 125.6 (t), 126.2 (t), 126.9 (t), 128.5 (q), 128.6 (t), 132.6 (q), 134.3 (t), 134.9 (t), 136.3 (q), 138.2 (q), 139.1 (t), 141.0 (t), 168.4 ppm (q); IR (film): $\tilde{\nu}$=3027, 2962, 2926, 2869, 1711, 1631, 1598, 1493, 1450, 1368, 1254, 1115, 1034, 959, 747, 692 $cm^{-1}$; MS (EI, 70 eV): $m/z$ (%): 380 (4) [$M^+$], 225 (4), 171 (4), 91 (3), 43 (100); HRMS $m/z$: calcd $C_{26}H_{36}O_2$: 380.2715; found: 380.2717.

**Plakotenin ethyl ester 21**: A solution of linear ester **5** (85.0 mg, 223 μmol) in toluene (20 mL) was heated to reflux and stirred in a sealed vial for 20 h. The mixture was concentrated. The crude product was purified by column chromatography on silica using $n$-pentane/$Et_2O$ 40:1 to yield plakotenin ethyl ester **21** (77.0 mg, 91%) as colorless oil. $R_f$=0.42 (cyclohexane/EtOAc=18:1); $[\alpha]_D^{20}$=+203.8 ($c$=1.46 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [1]) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.77 (t, $J$=7.2 Hz, 3H; 18-H), 0.98 (d, $J$=6.0 Hz, 3H; 14-H), 1.00–1.10 (m, 1H; 17-H), 1.15 (d, $J$=6.0 Hz, 3H; 15-H), 1.32 (t, $J$=7.5 Hz, 3H; 20-H), 1.54 (t, $J$=8.2 Hz, 2H; 7-H), 1.72–1.78 (m, 3H; 5-H, 9-H and 17-H), 1.82 (s, 3H; 16-H), 1.85–1.92 (m, 2H; 8-H and 6-H), 2.05 (s, 3H; 13-H), 3.69 (d, $J$=4.0 Hz, 1H; 12-H), 4.22 (q, $J$=7.2 Hz, 2H; 19-H), 5.23 (d, $J$=4.0 Hz, 1H; 11-H), 6.86 (s, 1H; 3-H), 7.20–7.24 (m, 1H; Ar-H), 7.28–7.31 ppm (m, 4H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=9.4 (p), 14.3 (p), 14.4 (p), 21.9 (p), 22.5 (p), 23.3 (p), 27.2 (s), 31.7 (t), 34.7 (t), 45.1 (s), 47.9 (q), 52.3 (t), 52.4 (t), 55.5 (t), 60.8 (s), 125.4 (t), 126.6 (t), 127.8 (t), 128.1 (q), 131.0 (t), 137.1 (q), 142.3 (q), 146.6 (t), 169.5 ppm (q); MS (EI, 70 eV): $m/z$ (%): 380 (22) [$M^+$], 225 (16), 171 (13), 91 (12), 43 (100); HRMS $m/z$: calcd $C_{26}H_{36}O_2$: 380.2715; found: 380.2714.

**Plakotenin 1**: To a solution of Plakotenin ethyl ester **21** (25.0 mg, 66.0 μmol) in THF/MeOH (1.6/0.8 mL) was added NaOH (2M) (160 μL, 328 μmol) and the resulting mixture was heated to 40°C and stirred for 20 h. After cooling to RT, the mixture was acidified with aqueous HCl (1M) and then extracted with EtOAc. The combined organic extracts were backwashed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica using $n$-pentane/$Et_2O$ 2:1 to yield plakotenin **1** (20.0 mg, 86%) as colorless oil. $R_f$=0.40 (cyclohexane/EtOAc=2:1); $[\alpha]_D^{20}$=+193 ($c$=0.95 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=0.78 (t, $J$=7.0 Hz, 3H; 18-H), 0.98 (d, $J$=6.5 Hz, 3H; 14-H), 1.03–1.12 (m, 1H; 17-H), 1.16 (d, $J$=6.5 Hz, 3H; 15-H), 1.56 (t, $J$=8.5 Hz, 2H; 7-H), 1.73–1.80 (m, 3H; 5-H, 9-H and 17-H), 1.83 (s, 3H; 16-H), 1.86–1.89 (m, 1H; 8-H), 1.89–1.92 (m, 1H; 6-H), 2.07 (s, 3H; 13-H), 3.71 (d, $J$=4.0 Hz, 1H; 12-H), 5.23 (s, 1H; 11-H), 7.03 (s, 1H; 3-H), 7.21–7.25 (m, 1H; Ar-H), 7.29–7.30 ppm (m, 4H; Ar-H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=9.4 (p), 14.0 (p), 21.9 (p), 22.5 (p), 23.3 (p), 27.1 (s), 31.7 (t), 34.7 (t), 45.1 (s), 48.2 (q), 52.2 (t), 52.5 (t), 55.4 (t), 125.3 (t), 126.6 (t), 127.3 (q), 127.9 (t), 131.0 (t), 137.2 (q), 142.1 (q), 149.7 (t), 174.8 ppm (q); IR (film): $\tilde{\nu}$=2929, 2868, 1683, 1629, 1492, 1451, 1419, 1377, 1281, 877, 762, 745, 703 $cm^{-1}$; MS (EI, 70 eV): $m/z$ (%): 352 (100) [$M^+$], 261 (48), 225 (84), 171 (70); HRMS $m/z$: calcd for $C_{24}H_{32}O_2$: 352.2402; found: 352.2401.

**Bicyclic ester 6**: A solution of linear ester **7** (100 mg, 294 μmol) in toluene (30 mL) was heated to reflux and stirred in a sealed vial for 20 h. The mixture was concentrated. The crude product was purified by column chromatography on silica using $n$-pentane/$Et_2O$ 40:1 to yield cyclic ester **6** (85.0 mg, 85%) as colorless oil. $R_f$=0.40 (cyclohexane/EtOAc=18:1); $[\alpha]_D^{20}$=+173.5 ($c$=0.34 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [1]) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.78 (t, $J$=7.2 Hz, 3H; 15-H), 0.94 (d, $J$=6.4 Hz, 3H; 11-H), 1.00–1.06 (m, 1H; 14-H), 1.14 (d, $J$=6.0 Hz, 3H; 12-H), 1.19–1.24 (m, 1H; 11-H), 1.31 (t, $J$=7.5 Hz, 3H; 17-H), 1.52–1.62 (m, 3H; 3-H and 5-H), 1.80 (brs, 3H; 13-H), 1.83–1.92 (m, 2H; 6-H and 7-H), 2.43–2.51 (m, 1H; 4-H), 4.12 (brs, 1H; 10-H), 4.22 (ddq, $J$=24, 9.6, 7.2 Hz, 2H; 16-H), 5.28 (s, 1H; 9-H), 7.22–7.25 (m, 1H; Ar-H), 7.26–7.30 ppm (m, 4H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=9.4 (p), 14.6 (p), 21.6 (p), 22.3 (p), 24.1 (p), 26.8 (s), 31.2 (t), 35.4 (t), 45.0 (s), 48.0 (t), 53.1 (t), 53.6 (t), 54.6 (q), 60.2 (s), 126.2 (t), 126.6 (t), 127.9 (t), 130.8 (t), 136.2 (q), 141.9 (q), 175.7 ppm (q); IR (film): $\tilde{\nu}$=3083, 3059, 3027, 2959, 2867, 1727, 1600,

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1494, 1450, 1379, 1212, 1180, 1130, 1110, 1029, 768, 704 $cm^{-1}$; MS (EI, 70 eV): *m/z* (%) 340 (43) [$M^+$], 267 (100), 249 (42), 171 (40), 136 (69), 121 (44), 91 (52); HRMS *m/z*: calcd for $C_{23}H_{32}O_2$: 340.2302; found: 340.2404.

**Bicyclic alcohol 22**: To a solution of ester **6** (85.0 mg, 250 μmol) in THF (3 mL) at 0 °C was slowly added lithium aluminium hydride (9.70 mg, 255 μmol). After stirring at 0 °C to RT overnight the mixture was quenched carefully at 0 °C with $H_2O$ followed by Rochelle's salt solution. The aqueous layer was extracted with EtOAc (4×5 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 9:1 to yield alcohol **22** (71.0 mg, 95 %) as colorless oil. $R_f$ = 0.34 (cyclohexane/EtOAc = 6:1); $[\alpha]_D^{20}$ = +184.6 (*c* = 0.28 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.82 (t, *J* = 7.2 Hz, 3H; 15-H), 0.93 (d, *J* = 6.6 Hz, 3H; 11-H), 1.04 (sext, *J* = 7.2 Hz, 1H; 14-H), 1.20 (d, *J* = 5.4 Hz, 3H; 12-H), 1.28 (br s, 1H; O*H*), 1.35 (sext, *J* = 7.2 Hz, 1H; 14-H), 1.50–1.54 (m, 1H; 5-H), 1.57–1.62 (m, 1H; 5-H), 1.71 (t, *J* = 10.8 Hz, 1H; 3-H), 1.83 (s, 3H; 13-H), 1.86–1.90 (m, 2H; 6-H and 7-H), 2.17–2.23 (m, 1H; 4-H), 4.12 (d, *J* = 4.2 Hz, 1H; 10-H), 3.60 (d, *J* = 11.4 Hz, 1H; 1-H), 3.84 (d, *J* = 10.8 Hz, 1H; 1-H), 5.19 (d, *J* = 3.6 Hz, 1H; 9-H), 7.20–7.23 (m, 1H; Ar-H), 7.25–7.29 ppm (m, 4H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 8.8 (p), 21.6 (p), 22.5 (p), 24.0 (p), 25.7 (s), 31.4 (t), 35.2 (t), 43.4 (q), 45.3 (s), 49.8 (t), 51.7 (t), 54.3 (t), 65.2 (s), 126.1 (t), 126.3 (t), 127.7 (t), 130.7 (t), 136.5 (q), 141.3 ppm (q); IR (film): $\tilde{\nu}$ = 3394, 3081, 3059, 3025, 2928, 1657, 1599, 1491, 1451, 1376, 1032, 909, 872, 771, 747, 703 $cm^{-1}$. - MS (EI, 70 eV): *m/z* (%) 298 (26) [$M^+$], 267 (100), 171 (37), 162 (32), 133 (26), 91 (47), 43 (56); HRMS *m/z*: calcd for $C_{21}H_{30}O$: 298.2297; found: 298.2299.

**Allylic alcohol 24**: Dess–Martin periodinane (0.83 mL, 0.395 mmol) was added at 0 °C to a solution of alcohol **22** (90.0 g, 0.304 mmol) in $CH_2Cl_2$ (3 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (1.5 mL) and saturated aqueous $NaHCO_3$ (1.5 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×3 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **23** (89.5 mg, 0.304 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following Grignard reaction. Under argon, to a solution of aldehyde **23** (88.0 mg, 0.297 mmol) in THF (5 mL) was added isopropenylmagnesium bromide (0.5 M in THF, 0.89 mL, 0.445 mmol) at 0 °C. The reaction was then warmed to 50 °C and stirred for 3 h and then quenched with 1 M HCl (5 mL) and diluted with $Et_2O$. The layers were separated and the aqueous layer extracted with $Et_2O$ (3×5 mL). The combined organic layers were washed with brine (5 mL) dried ($MgSO_4$) and then concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 18:1 to yield allylic alcohol **24** (89.5 mg, 0.264 mmol, 87 % yield) as a colorless oil. $R_f$ = 0.40 (cyclohexane/EtOAc = 9:1); 10:1 mixture of diastereoisomers. Description of the major diastereoisomer: (NMR assignment according to numbering system used in Ref. [8]); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.39 (t, *J* = 7.2 Hz, 3H, 18-H), 0.95 (d, *J* = 6.4 Hz, 3H, 14-H), 1.16–1.21 (m, 1H, 17-H), 1.22 (d, *J* = 6.4 Hz, 3H, 15-H), 1.53 (t, *J* = 8.4 Hz, 2H, 7-H), 1.64–1.71 (m, 2H, 9-H and 17-H), 1.85 (s, 3H, 16-H), 1.89–1.91 (m, 1H, 5-H), 1.94 (s, 3H, 12-H), 2.11 (t, *J* = 11.0 Hz, 1H, 9-H), 2.36–2.47 (m, 1H, 6-H), 3.36 (br s, 1H, 12-H), 4.52 (s, 1H, 3-H), 5.02 (s, 1H, 1-H), 5.08 (s, 1H, 1-H), 5.13 (br s, 1H, 11-H), 7.17–7.25 (m, 5H, Ar-H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 9.7 (p), 21.3 (p), 22.4 (p), 22.6 (p), 22.8 (p), 25.7 (s), 33.7 (t), 34.3 (t), 45.1 (s), 46.8 (q), 51.2 (t), 52.2 (t), 52.8 (t), 80.0 (t), 115.7 (s), 125.7 (t), 126.4 (t), 127.8 (2t), 131.1 (2t), 137.1 (q), 143.3 (q), 147.3 (q); IR (film): $\tilde{\nu}$ = 3471, 3061, 3024, 2927, 2867, 1633, 1599, 1492, 1452, 1374, 1039, 983, 903, 879, 762, 702 $cm^{-1}$; MS (EI, 70 eV): *m/z* (%) 338 (18) [$M^+$] 320 (31), 267 (100), 195 (27), 131 (38), 105 (28), 91 (56), 43 (42); HRMS *m/z*: calcd for $C_{24}H_{34}O$: 338.2610; found: 338.2613.

**Aldehyde 25**: Under argon, to a solution of aldehyde **25** (45 mg, 0.133 mmol) in dry $Et_2O$/*n*-pentane (1.5 mL) was added at 0 °C freshly distilled $SOCl_2$ (0.048 mL, 0.665 mmol), and the mixture was slowly warmed up to RT and stirred for 6 h. Solvents were then removed under vacuum, and the crude residue directly used for the next step without further purification. Under argon, one portion of NMO (93.4 mg, 0.797 mmol) was added to a solution of the primary chloride (47.5 mg, 0.133 mmol) in dry DMSO (0.15 mL) and the resulting mixture was stirred overnight. The reaction was quenched with brine (1 mL) and diluted with $Et_2O$ (3 mL). The layers were separated and the aqueous layer extracted with $Et_2O$ (4×5 mL). The combined organic layers were backwashed with brine (5 mL) and then dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 40:1 to yield aldehyde **25** (30.4 mg, 0.090 mmol, 68 % yield for the two steps) as colorless oil. $R_f$ = 0.38 (cyclohexane/EtOAc = 18:1); $[\alpha]_D^{20}$ = +197.5 (*c* = 0.42 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.82 (t, *J* = 7.2 Hz, 3H, 18-H), 0.96 (d, *J* = 6.0 Hz, 3H, 14-H), 1.00–1.06 (m, 1H, 17-H), 1.11 (d, *J* = 6.6 Hz, 3H, 15-H), 1.50–1.53 (m, 2H, 7-H), 1.63–1.68 (m, 1H, 9-H), 1.80 (s, 3H, 16-H), 1.82–1.86 (m, 4H, 17-H, 5-H, 8-H, 6-H), 1.93 (s, 3H, 13-H), 3.71 (s, 1H, 12-H), 5.23 (s, 1H, 11-H), 6.42 (s, 1H, 3-H), 7.18–7.23 (m, 2H, Ar-H), 7.25–7.27 (m, 3H, Ar-H) 9.38 (s, 1H, 1-H, C*H*O);.$^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 9.3 (p), 11.1 (p), 21.8 (p), 22.5 (p), 23.3 (p), 27.0 (s), 31.7 (t), 34.7 (t), 45.0 (s), 49.1 (q), 51.8 (t), 52.6 (t), 55.0 (t), 125.3 (t), 126.7 (t), 127.9 (2 t), 130.9 (2 t), 137.3 (q), 139.6 (q), 141.6 (q), 161.0 (t), 197.2 (q); IR (film): $\tilde{\nu}$ = 3082, 3059, 3026, 2932, 2868, 1688, 1630, 1599, 1493, 1451, 1378, 1216, 1031, 912, 882, 773, 704 $cm^{-1}$; MS (EI, 70 eV): *m/z* (%) 336 (1) [$M^+$], 226 (4), 171 (4), 111 (12), 88 (10), 84 (100), 43 (34); HRMS *m/z*: calcd for $C_{24}H_{32}O$: 336.2453; found 336.2455.

**Plakotenin 1**: $NaH_2PO_4$·$2H_2O$ (9.6 mg, 0.062 mmol, 0.6 equiv), $H_2O_2$ (0.044 mL, 0.384 mmol, 3.75 equiv), and $NaClO_2$ (55.6 mg, 0.615 mmol, 6.0 equiv) were successively added at 0 °C to a solution of aldehyde **25** (34.5 mg, 0.018 mmol) in MeCN/$H_2O$ (3.0/0.5 mL) and the mixture was stirred at RT for 20 h. The reaction mixture was then quenched by addition of water (0.5 mL). The layers were separated and the aqueous layer extracted with EtOAc (4×3 mL). The combined organic layers were backwashed with brine (3 mL) and then dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 2:1 to yield **1** (22.3 mg, 0.063 mmol, 61 % yield) as colorless oil. $R_f$ = 0.40 (cyclohexane/EtOAc = 2:1); $[\alpha]_D^{20}$ = +193 (*c* = 0.95 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 0.78 (t, *J* = 7.0 Hz, 3H; 18-H), 0.98 (d, *J* = 6.5 Hz, 3H; 14-H), 1.03–1.12 (m, 1H; 17-H), 1.16 (d, *J* = 6.5 Hz, 3H; 15-H), 1.56 (t, *J* = 8.5 Hz, 2H; 7-H), 1.73–1.80 (m, 3H; 5-H, 9-H and 17-H), 1.83 (s, 3H; 16-H), 1.86–1.89 (m, 1H; 8-H), 1.89–1.92 (m, 1H; 6-H), 2.07 (s, 3H; 13-H), 3.71 (d, *J* = 4.0 Hz, 1H; 12-H), 5.23 (s, 1H; 11-H), 7.03 (s, 1H; 3-H), 7.21–7.25 (m, 1H; Ar-H), 7.29–7.30 ppm (m, 4H; Ar-H);$^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 9.4 (p), 14.0 (p), 21.9 (p), 22.5 (p), 23.3 (p), 27.1 (s), 31.7 (t), 34.7 (t), 45.1 (s), 48.2 (q), 52.2 (t), 52.5 (t), 55.4 (t), 125.3 (t), 126.6 (t), 127.3 (q), 127.9 (t), 131.0 (t), 137.2 (q), 142.1 (q), 149.7 (t), 174.8 ppm (q); IR (film): $\tilde{\nu}$ = 2929, 2868, 1683, 1629, 1492, 1451, 1419, 1377, 1281, 877, 762, 745, 703 $cm^{-1}$; MS (EI, 70 eV): *m/z* (%): 352 (100) [$M^+$], 261 (48), 225 (84), 171 (70); HRMS *m/z*: calcd for $C_{24}H_{32}O_2$: 352.2402; found: 352.2401.

**Ester 26**: The compound was isolated during the purification of ester **7** and purified by column chromatography to give a colorless oil (77.8 mg, 0.028 mmol 18 %). $R_f$ = 0.46 (cyclohexane/EtOAc = 18:1); $[\alpha]_D^{20}$ = −33.1 (*c* = 0.61 in $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 0.94 (t, *J* = 7.8 Hz, 3H, $EtCO_2C{=}CH_2CH_3$), 0.97 (d, *J* = 7.2 Hz, 3H, $PhCH{=}CHC{=}CHCHCH_3$), 1.01 (d, *J* = 6.6 Hz, 3H, $EtCO_2C{=}CHCHCH_3$), 1.31 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.40–1.43 (m, 2H, $CHCH_2CH$), 1.77 (s, 3H, $PhCH{=}CHCCH_3$), 2.17–2.26 (m, 2H, $EtCO_2CCH_2CH_3$), 2.47–2.55 (m, 2H, $PhCH{=}CHC{=}CHCH$ and $EtCO_2C{=}CHCH$), 4.20 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 5.37 (d, *J* = 9.0 Hz, 1H, $PhCH{=}CHC{=}CH$), 6.43 (d, *J* = 16.2 Hz, 1H, PhC*H*), 6.49 (d, *J* = 10.2 Hz, 1H, $EtCO_2C{=}CH$), 6.79 (d, *J* = 16.2 Hz, 1H, $PhCH{=}CH$), 7.18–7.21 (m, 1H, Ar-H), 7.31 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.40 ppm (d, *J* = 7.2 Hz, 2H, Ar-H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 12.8 (p), 14.4 (2 p), 20.2 (s), 21.3 (p), 21.7 (p), 31.3 (t), 31.5 (t), 45.6 (s), 60.4 (s), 125.9 (t), 126.3 (2t), 127.0 (t), 128.7 (2t), 133.1 (q), 133.2 (q), 134.1 (t), 138.1 (q), 140.3 (t), 147.6 (t), 168.3 ppm (q); IR (film): $\tilde{\nu}$ = 3026, 2960, 2925, 2869, 1711, 1645, 1493, 1452, 1377, 1223, 1183, 1032, 959, 693 $cm^{-1}$; MS (EI, 70 eV): *m/z* (%) 340 ([$M^+$], 93), 267 (100), 171 (61), 91 (40), 43 (26); HRMS *m/z*: calcd for $C_{23}H_{32}O_2$: 340.2402; found: 340.2404.

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**Alcohol 27**: Lithium aluminium hydride (8.6 mg, 0.226 mmol) was slowly added to a solution of ester **26** (70 mg, 0.206 mmol) in THF (4 mL) at 0 °C. After stirring at 0 °C for 2 h the reaction mixture was quenched carefully at 0 °C with $H_2O$ followed by Rochelle's salt solution. The aqueous layer was extracted with $Et_2O$ (4×5 mL), dried ($MgSO_4$), and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 9:1 to yield alcohol **27** (41.7 mg, 0.140 mmol, 68 % yield). $R_f$=0.44 (cyclohexane/EtOAc=6:1). $R_f$=0.52 (cyclohexane/EtOAc=6:1); $[\alpha]_D^{20}=-107.6$ ($c$=0.25 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.94–0.97 (m, 9H, $HOCH_2C$=$CHCHCH_3$, $HOCH_2C$=$CH_2CH_3$, and PhCH=CHC=CHCH$CH_3$), 1.29–1.34 (m, 2H, $CHCH_2CH$), 1.79 (s, 3H, PhCH=CHCC$H_3$), 1.91–1.98 (m, 1H, $HOCH_2CCH_2CH_3$), 2.05–2.14 (m, 1H, $HOCH_2CCH_2CH_3$), 2.35–2.47 (m, 1H, $HOCH_2C$=$CHCHCH_3$), 2.49–2.56 (m, 1H, PhCH=CHC=$CHCHCH_3$), 4.05 (s, 2H, $HOCH_2$), 5.14 (d, $J$=9.6 Hz, 1H, $HOCH_2C$=$CH$), 5.39 (d, $J$=9.6 Hz, 1H, PhCH=CHC=$CH$), 6.44 (d, $J$=16.0 Hz, 1H, PhC$H$), 6.80 (d, $J$=16.0 Hz, 1H, PhCH=C$H$), 7.19 (t, $J$=7.2 Hz, 1H, Ar-H), 7.31 (t, $J$=7.6 Hz, 2H, Ar-H), 7.40 ppm (d, $J$=7.6 Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.8 (p), 13.7 (p), 21.3 (s), 21.6 (p), 22.2 (p), 30.2 (t), 31.2 (t), 46.1 (s), 67.0 (s), 125.7 (t), 126.3 (2t), 127.0 (t), 128.7 (2 t), 132.6 (t), 132.7 (q), 134.3 (t), 138.1 (q), 139.7 (q), 141.1 ppm (t); IR (film): $\tilde{\nu}$=3315, 3030, 2960, 1597, 1493, 1451, 1372, 1313, 1075, 1036, 1013, 961, 747, 690 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 298 ([$M^+$], 23), 171 (100), 143 (47), 129 (66), 91 (91), 43 (46); HRMS *m/z*: calcd for $C_{21}H_{30}O$: 298.2297; found: 298.2295.

**Ester 29**: Dess–Martin periodinane (0.39 mL, 0.157 mmol) was added at 0 °C to a solution of alcohol **27** (36.0 mg, 0.121 mmol) in $CH_2Cl_2$ (3 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×5 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **28** (35.0 mg, 0.121 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. Ethyl 2-(diethoxyphosphoryl)propanoate (0.08 mL, 0.386 mmol) was added dropwise to a solution of sodium hydride (60 % in mineral oil, 15.4 mg, 0.386 mmol) in THF (4 mL) at 0 °C. The solution was stirred at RT for 1 h before cooling to 0 °C and addition of crude aldehyde **28** (35.0 mg, 0.121 mmol) (from previous reaction) in THF (2 mL). The solution was warmed slowly to RT and stirred for 4 h. The reaction was then quenched by pouring on to saturated aqueous $NH_4Cl$ (3 mL). The product was extracted with $Et_2O$ (4×5 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 40:1 to yield ester **29** (38.6 mg, 0.101 mmol mg, 84 % yield) as colorless oil. $R_f$=0.42 (cyclohexane/EtOAc=18:1). $[\alpha]_D^{20}$−215.46 ($c$=0.28 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.90 (t, $J$=7.6 Hz, 3H, $EtCO_2C$=$CHCCH_2CH_3$), 0.98 (d, $J$=7.2 Hz, 3H, $EtCO_2C$=$CHCHCH_3$), 0.99 (d, $J$=6.8 Hz, 3H, PhCH=CHC=$CHCHCH_3$), 1.32 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.28–1.36 (m, 2H, $CHCH_2CH$), 1.80 (s, 3H, PhCH=CHCC$H_3$), 1.99 (d, $J$=1.2 Hz, 3H, $EtCO_2CCH_3$), 2.00–2.06 (m, 1H, $EtCO_2C$=$CHCCH_2CH_3$), 2.15–2.24 (m, 1H, $EtCO_2C$=$CHCCH_2CH_3$), 2.46–2.56 (m, 2H, PhCH=CHC=$CHCHCH_3$ and $EtCO_2C$=$CHC$=$CHCHCH_3$), 4.22 (q, $J$=7.2 Hz, 2H, $CO_2CH_2CH_3$), 5.23 (d, $J$=9.6 Hz, 1H, $EtCO_2C$=$CHC$=$CH$), 5.40 (d, $J$=9.6 Hz, 1H, PhCH=CHC=$CH$), 6.43 (d, $J$=16.0 Hz, 1H, PhC$H$), 6.81 (d, $J$=16.0 Hz, 1H, PhCH=C$H$), 7.09 (s, 1H, $EtCO_2C$=$CH$), 7.19 (t, $J$=7.2 Hz, 1H, Ar-H) 7.31 (d, $J$=8.0 Hz, 2H, Ar-H), 7.41 ppm (d, $J$=7.2 Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.8 (p), 13.8 (p), 14.1 (p), 14.5 (p), 21.7 (p), 22.1 (p), 23.6 (s), 31.1 (t), 31.4 (t), 46.1 (s), 60.7 (s), 125.8 (t), 126.3 (2t), 126.7 (q), 127.0 (t), 128.7 (2t), 133.0 (q), 134.2 (t), 137.0 (q), 138.1 (q), 140.0 (t), 140.7 (t), 142.1 (t), 169.2 ppm (q); IR (film): $\tilde{\nu}$=3025, 2961, 2924, 2867, 1706, 1627, 1598, 1493, 1449, 1366, 1252, 1112, 1033, 960, 748, 692 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 380 ([M$^+$], 15), 225 (13), 171 (18), 91 (13), 58 (39), 43 (100); HRMS *m/z*: calcd for $C_{26}H_{36}O_2$: 380.2715; found: 380.2713.

***iso*-Plakotenin ethyl ester 30**: A solution of linear ester **29** (30.0 mg, 0.079 mmol) in toluene (8 mL) was heated to reflux and stirred in a sealed vial for 20 h. The mixture was concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 40:1 to yield cyclic ester **30** (24.6 mg, 0.065 mmol, 82 % yield) as colorless oil. $R_f$=0.42 (cyclohexane/EtOAc=18:1). $[\alpha]_D^{20}$=+179.1 ($c$=0.23 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=0.80 (d, $J$=6.0 Hz, 3H, 14-H), 1.02 (t, $J$=7.0 Hz, 3H, 18-H), 1.06 (t, $J$=7.0 Hz, 3H, 20-H), 1.22 (d, $J$=6.0 Hz, 3H, 15-H), 1,51 (dt, $J$=2.5, 8.5 Hz, 2H, 7-H), 1.68 (t, $J$=10.5 Hz, 1H, 5-H), 1.86 (s, 3H, 16-H), 1.82–1.94 (m, 4H, 17-H, 9-H, and 8-H), 1.98 (s, 3H, 13-H), 1.98–2.04 (m, 1H, 6-H), 3.36 (brs, 1H, 12-H), 3.92–4.02 (m, 2H, 19-H), 5.22 (brs, 1H, 11-H), 6.11 (s, 1H, 3-H), 7.06 (d, $J$=7.0 Hz, 2H, Ar-H), 7.16 (t, $J$=7.5 Hz, 1H, Ar-H), 7.20 ppm (d, $J$=7.5 Hz, 2H, Ar-H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=10.9 (p), 14.2 (p), 14.3 (p), 21.2 (p), 22.4 (p), 22.7 (p), 26.1 (s), 33.5 (t), 33.9 (t), 44.5 (s), 47.1 (q), 50.9 (t), 54.1 (t), 54.4 (t), 60.3 (s), 124.1 (t), 125.7 (q), 126.4 (t), 127.6 (2 t), 130.5 (2 t), 136.6 (q), 141.8 (q), 148.2 (t), 169.2 ppm (q); IR (film): $\tilde{\nu}$=3025, 2930, 2867, 1705, 1639, 1600, 1492, 1450, 1378, 1262, 1105, 1033, 743, 702 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 380 ([$M^+$], 44), 225 (34), 171 (28), 91 (21), 58 (30), 43 (100); HRMS *m/z*: calcd for $C_{26}H_{36}O_2$: 380.2715; found: 380.2712.

***iso*-Plakotenin 4**: NaOH (2 M) (0.13 mL, 0.263 mmol) was added to a solution of cyclic ester **30** (20.0 mg, 0.053 mmol) in THF/MeOH (1.6/0.8 mL) and the resulting mixture was heated to 40 °C and stirred for 20 h. After cooling to RT, the mixture was acidified with aqueous HCl (1 M), and then extracted with EtOAc (5×3 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 2:1 to yield carboxylic acid **4** (13.9 mg, 0.039 mmol, 75 % yield) as colorless oil. $R_f$=0.38 (cyclohexane/EtOAc=2:1). $[\alpha]_D^{20}$=+184.6 ($c$=0.52 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=0.82 (d, $J$=6.0 Hz, 3H, 14-H), 1.01 (t, $J$=7.5 Hz, 3H, 18-H), 1.21 (d, $J$=6.0 Hz, 3H, 15-H), 1.47–1.55 (m, 2H, 7-H), 1.71 (t, $J$=10.8 Hz, 1H, 5-H), 1.86 (s, 3H, 16-H), 1.82–1.93 (m, 3H, 17-H, 9-H, and 8-H), 1.95 (s, 3H, 13-H), 1.98–2.05 (m, 2H, 6-H and 17-H), 3.36 (d, $J$=3.6 Hz, 1H, 12-H), 5.22 (brs, 1H, 11-H), 6.27 (s, 1H, 3-H), 7.05 (d, $J$=7.8 Hz, 2H, Ar-H), 7.16 (t, $J$=7.2 Hz, 1H, Ar-H), 7.21 ppm (t, $J$=7.2 Hz, 2H, Ar-H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$=11.1 (p), 14.1 (p), 21.1 (p), 22.3 (p), 22.9 (p), 26.5 (s), 33.7 (t), 33.8 (t), 44.3 (s), 47.4 (q), 51.0 (t), 52.3 (2t), 124.1 (t), 125.1 (q), 126.6 (t), 127.7 (2t), 130.4 (2 t), 136.5 (q), 141.5 (q), 151.1 (t), 173.98 ppm (q); IR (film): $\tilde{\nu}$=3394, 3027, 2957, 2867, 1678, 1452, 1377, 1271, 1031, 746, 701 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 352 ([$M^+$], 4), 225 (2), 171 (6), 107 (10), 77 (15), 58 (15), 43 (100); HRMS *m/z*: calcd for $C_{24}H_{32}O_2$: 352.2402; found: 352.2404.

**Ester 31**: Dess–Martin periodinane (1.71 mL, 0.798 mmol) was added at 0 °C to a solution of alcohol **17** (150.0 mg, 0.614 mmol) in $CH_2Cl_2$ (6 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×10 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **18** (150.0 mg, 0.614 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. Ethyl 2-(diethoxyphosphoryl)-propanoate (0.39 mL, 1.842 mmol) was added dropwise to a solution of sodium hydride (60 % in mineral oil, 75 mg, 1.842 mmol) in THF (15 mL) at 0 °C. The solution was stirred at RT for 1 h before cooling to 0 °C and addition of the crude aldehyde **18** (150.0 mg, 0.614 mmol) (from previous reaction) in THF (5 mL). The solution was stirred for 1 h at 0 °C, warmed slowly to RT and stirred for an additional 3 h. The reaction was quenched by pouring on to saturated aqueous $NH_4Cl$ (10 mL). The product was extracted with $Et_2O$ (3×10 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 30:1 to yield ester **31** (128.3 mg, 0.393 mmol, 64 %) as a colorless oil. A 3:1 ratio of *Z*/*E* products was obtained. $R_f$=0.52 (cyclohexane/EtOAc=18:1). $[\alpha]_D^{20}$=−20.1 ($c$=0.57 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.98 (d, $J$=6.4 Hz, 3H, PhCH=CHC=CHCH$CH_3$), 0.99 (d, $J$=6.4 Hz, 3H, $EtCO_2C$=$CHCHCH_3$), 1.21 (t, $J$=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.30–1.35 (m, 2H, $CHCH_2CH$), 1.77 (d, $J$=1.2 Hz, 3H, PhCH=CHCC$H_3$), 1.90 (d, $J$=1.2 Hz, 3H, $EtCO_2CCH_3$), 2.45–2.56 (m, 1H, PhCH=CHC=CHC$H$), 3.07–3.18 (m, 1H, $EtCO_2C$=$CHCH$), 4.03–4.11 (m, 2H, $CO_2CH_2CH_3$),

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5.34 (d, $J=9.6$ Hz, 1H, PhCH=CHC=C*H*), 5.66 (dd, $J=10.0$, 1.2 Hz, 1H, $EtCO_2C$=C*H*), 6.41 (d, $J=16.0$ Hz, 1H, PhC*H*), 6.77 (d, $J=16.0$ Hz, 1H, PhCH=C*H*), 7.17–7.21 (m, 1H, Ar-H), 7.28–7.32 (m, 2H, Ar-H), 7.38–7.40 ppm (m, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=12.6$ (p), 14.3 (p), 20.9 (p), 21.0 (p), 21.5 (p), 31.3 (t), 32.0 (t), 45.7 (s), 60.2 (s), 125.7 (t), 126.2 (2t), 126.3 (q), 126.9 (t), 128.6 (2t), 132.6 (q), 134.3 (t), 138.2 (q), 140.4 (t), 148.4 (t), 168.2 ppm (q); IR (film): $\tilde{\nu}=3059$, 3062, 2958, 2927, 2868, 1720, 1451, 1376, 1222, 1174, 1097, 1024, 770, 704 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 326 ([$M^+$], 42), 253 (100), 252 (47), 171 (39), 136 (41), 121 (36), 91 (48); HRMS *m/z*: calcd $C_{22}H_{30}O_2$: 326.2246; found: 326.2242.

**Alcohol 32**: Lithium aluminium hydride (15.3 mg, 0.404 mmol) was slowly added to a solution of ester **31** (120 mg, 0.368 mmol) in THF (5 mL) at 0 °C. After stirring at 0 °C for 2 h the reaction mixture was quenched carefully at 0 °C with $H_2O$ followed by Rochelle's salt solution. The aqueous layer was extracted with $Et_2O$ (4×5 mL), dried ($MgSO_4$) and concentrate. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 9:1 to yield alcohol **32** (81.5 mg, 0.287 mmol, 78% yield). $R_f=0.48$ (cyclohexane/EtOAc=6:1). $[\alpha]_D^{20}=-126.4$ ($c=0.58$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.92$ (d, $J=$ 6.4 Hz, 3H, $HOCH_2C$=CHCHC$H_3$), 0.96 (d, $J=6.8$ Hz, 3H, PhCH=CHC=CHCHC$H_3$), 1.25–1.37 (m, 2H, CHC$H_2$CH), 1.79 (d, $J=1.2$ Hz, 3H, $HOCH_2CCH_2CH_3$), 1.80 (d, $J=1.2$ Hz, 2H, PhCH=CHCC$H_3$), 2.36–2.46 (m, 1H, $HOCH_2C$=CHC*H*), 2.47–2.56 (m, 1H, PhCH=CHC=CHC*H*), 3.99 (d, $J=1.6$ Hz, 2H, HOC$H_2$), 5.03 (d, $J=9.6$ Hz, 1H, $HOCH_2C$=C*H*), 5.40 (d, $J=9.6$ Hz, 1H, PhCH=CHC=C*H*), 6.44 (d, $J=$ 16.0 Hz, 1H, PhC*H*), 6.80 (d, $J=16.0$ Hz, 1H, PhCH=C*H*), 7.19 (t, $J=$ 7.2 Hz, 1H, Ar-H), 7.30 (t, $J=8.0$ Hz, 2H, Ar-H), 7.40 ppm (d, $J=$ 7.2 Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=12.7$ (p), 21.5 (p), 21.7 (p), 22.6 (p), 30.6 (t), 31.2 (t), 45.9 (s), 62.0 (s), 126.2 (t), 126.3 (2t), 127.1 (t), 128.7 (2t), 132.9 (q), 133.5 (q), 133.9 (t), 134.8 (t), 138.0 (q), 140.8 ppm (t); IR (film): $\tilde{\nu}=3427$, 2960, 1721, 1600, 1494, 1452, 1377, 1265, 1176, 1004, 750, 699 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 284 ([$M^+$], 90), 253 (53), 171 (100), 169 (41), 143 (42), 129 (44); HRMS *m/z*: calcd for $C_{20}H_{28}O$: 284.2140; found: 284.2137.

**Ester 34**: Dess–Martin periodinane (0.57 mL, 0.274 mmol) was added at 0 °C to a solution of alcohol **32** (60.0 mg, 0.211 mmol) in $CH_2Cl_2$ (5 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×5 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **33** (60.0 mg, 0.211 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. Ethyl 2-(diethoxyphosphoryl)propanoate (0.14 mL, 0.633 mmol) was added dropwise to a solution of sodium hydride (60% in mineral oil, 25.0 mg, 0.633 mmol) in THF (5 mL) at 0 °C. The solution was stirred at RT for 1 h before cooling to 0 °C and addition of crude aldehyde **33** (60.0 mg, 0.211 mmol) (from previous reaction) in THF (3 mL). The solution was warmed slowly to RT and stirred for an additional 3 h. The reaction was then quenched by pouring on to saturated aqueous $NH_4Cl$ (5 mL). The product was extracted with $Et_2O$ (4×5 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 40:1 to yield ester **34** (68.8 mg, 0.188 mmol, 89% yield) as colorless oil. $R_f=0.40$ (cyclohexane/EtOAc=18:1); $[\alpha]_D^{20}=+14.9$ ($c=0.40$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.93$ (d, $J=6.8$ Hz, 3H, $EtCO_2C$=CHC=CHCHC$H_3$), 0.96 (d, $J=6.8$ Hz, 3H, PhCH=CHC=CHCHC$H_3$), 1.12 (t, $J=6.8$ Hz, 3H, $CO_2CH_2CH_3$), 1.26–1.34 (m, 2H, CHC$H_2$CH), 1.80 (d, $J=1.2$ Hz, 3H, PhCH=CHCC$H_3$), 1.87–1.88 (m, 6H, $EtCO_2CCH_3$ and $EtCO_2C$=CHCC$H_3$), 2.26–2.37 (m, 1H, $EtCO_2C$=CHC=CHC*H*), 2.45–2.56 (m, 1H, PhCH=CHC=CHC*H*), 3.93–4.05 (m, 2H, $CO_2CH_2CH_3$), 5.18 (d, $J=$ 10.4 Hz, 1H, $EtCO_2C$=CHC=C*H*), 5.36 (d, $J=9.6$ Hz, 1H, PhCH=CHC=C*H*), 6.41 (d, $J=16.0$ Hz, 1H, PhC*H*), 6.78 (d, $J=16.0$ Hz, 1H, PhCH=C*H*), 7.17–7.20 (m, 2H, $EtCO_2C$=C*H* and $H_{arom}$), 7.29 (d, $J=7.6$ Hz, 2H, Ar-H), 7.39 ppm (d, $J=7.2$ Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=12.6$ (p), 14.3 (2 p), 21.3(p), 21.5 (p), 23.2 (p), 31.0 (t), 31.9 (t), 45.8 (s), 60.6 (s), 125.6 (t), 126.2 (2 t), 126.9 (t), 127.7 (q), 128.6 (2 t), 130.2 (q), 132.8 (q), 134.2 (t), 138.1 (q), 138.6 (t), 138.9 (t), 140.7 (t), 168.7 ppm (q); IR (film): $\tilde{\nu}=3079$, 3058, 3025, 2958, 1709, 1631, 1598, 1492, 1449, 1382, 1258, 1114, 1036, 958, 825, 747, 692 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 366 ([$M^+$], 100), 225 (77), 171 (88), 128 (21), 107 (41), 91 (95); HRMS *m/z*: calcd for $C_{25}H_{34}O_2$: 366.2559; found: 366.2560.

***nor*-Plakotenin ethyl ester 35**: A solution of linear ester **34** (65.0 mg, 0.177 mmol) in toluene (18 mL) was heated to reflux and stirred in a sealed vial for 20 h. The mixture was concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 40:1 to yield cyclic ester **35** (59.8 mg, 0.163 mmol, 92% yield) as colorless oil. $R_f=0.40$ (cyclohexane/EtOAc=18:1). $[\alpha]_D^{20}=+189.4$ ($c=0.24$ in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.90$ (s, 3H, 17-H), 0.93 (d, $J=$ 6.8 Hz, 3H, 14-H), 1.21 (d, $J=6.0$ Hz, 3H, 15-H), 1.34 (t, $J=7.2$ Hz, 3H, 19-H), 1.50–1.63 (m, 3H, 7-H and 5-H), 1.87 (s, 3H, 16-H) 1.88–1.93 (m, 3H, 9-H, 8-H and 6-H), 2.14 (d, $J=1.2$ Hz, 3H, 13-H), 3.63 (d, $J=4.0$ Hz, 1H, 12-H), 4.23 (q, $J=7.2$ Hz, 2H, 18-H), 5.23 (brs, 1H, 11-H), 7.11 (d, $J=1.2$ Hz, 1H, 3-H), 7.24–7.34 ppm (m, 5H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=14.4$ (p), 14.8 (p), 22.0 (p), 22.4 (p), 22.9 (p), 24.9 (p), 32.1 (t), 34.6 (t), 41.7 (q), 44.8 (s), 51.6 (t), 53.2 (t), 55.6 (t), 60.8 (s), 124.9 (t), 126.5 (t), 127.8 (2t), 128.0 (q), 130.7 (2t), 137.4 (q), 142.2 (q), 148.3 (t), 169.5 (q); IR (film): $\tilde{\nu}=3025$, 2929, 2868, 1708, 1491, 1451, 1379, 1240, 1098, 744, 703 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 366 ([$M^+$], 18), 225 (11), 171 (11), 107 (14), 91 (14), 43 (100); HRMS *m/z*: calcd for $C_{25}H_{34}O_2$: 366.2559; found: 366.2555.

***nor*-Plakotenin 2**: NaOH (2 M) (0.34 mL, 0.682 mmol) was added to a solution of cyclic ester **35** (50.0 mg, 0.136 mmol) in THF/MeOH (3.2/1.6 mL) and the resulting mixture was heated to 40 °C and stirred for 20 h. After cooling to RT, the mixture was acidified with aqueous HCl (1 M), and then extracted with EtOAc (5×5 mL). The combined organic extracts were backwashed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 2:1 to yield carboxylic acid **2** (40.6 mg, 0.120 mmol, 88% yield) as colorless oil. $R_f=0.38$ (cyclohexane/EtOAc=2:1); $[\alpha]_D^{20}=+101°$ (0.19 g/100 mL, $CHCl_3$); $[\alpha]_D^{20}=+128°$ (0.22 g/100 mL, MeOH); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (600 MHz, $CDCl_3$): $\delta=0.90$ (s, 3H, 17-H), 0.91 (d, $J=6.6$ Hz, 3H, 14-H), 1.20 (d, $J=5.4$ Hz, 3H, 15-H), 1.50–1.63 (m, 3H, 7-H and 5-H), 1.85 (s, 3H, 16-H) 1.86–1.94 (m, 3H, 9-H, 8-H and 6-H), 2.13 (s, 3H, 13-H), 3.62 (s, 1H, 12-H), 5.21 (s, 1H, 11-H), 7.20 (s, 1H, 3-H), 7.22–7.24 (m, 3H, Ar-H), 7.28–7.31 (m, 2H, Ar-H), 10.18 ppm (brs, 1H, -OH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=14.7$ (p), 22.0 (p), 22.5 (p), 22.9 (p), 24.8 (p), 32.2 (t), 34.7 (t), 41.9 (q), 44.8 (s), 51.7 (t), 53.3 (t), 55.6 (t), 124.9 (t), 126.6 (t), 127.8 (2t and q), 130.7 (2t), 137.5 (q), 142.2 (q), 150.1 (t), 174.9 ppm (q); IR (film): $\tilde{\nu}=3025$, 2928, 2869, 1683, 1628, 1492, 14512, 1378, 1277, 998, 703 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 338 ([$M^+$], 1), 86 (4), 84 (6), 58 (36), 43 (100); HRMS *m/z*: calcd for $C_{23}H_{30}O_2$: 338.2246; found: 338.2243.

**Ester 37**: Dess–Martin periodinane (2.47 mL, 1.145 mmol) was added at 0 °C to a solution of alcohol **12** (330.0 mg, 0.881 mmol) in $CH_2Cl_2$ (10 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×10 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **8** (330.0 mg, 0.881 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. To a solution of sodium hydride (60% in mineral oil, 106 mg, 2.143 mmol) in THF (15 mL) at 0 °C was added ethyl 2-(diethoxyphosphoryl)butanoate (668 mg, 2.143 mmol) dropwise. The solution was stirred at RT for 1 h before cooling to 0 °C and addition of the crude aldehyde **8** (330.0 mg, 0.881 mmol) (from previous reaction) in THF (5 mL). The solution was stirred for 1 h at 0 °C, warmed slowly to RT and stirred for an additional 3 h. The reaction was quenched by pouring on to saturated aqueous $NH_4Cl$ (10 mL). The product was extracted with $Et_2O$ (3×10 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was then purified by column chromatography on silica using cyclohexane/ethyl acetate 30:1 to yield ester **37** (300.7 mg, 0.639 mmol, 73%) as a colorless oil. A 5:1 ratio of *Z*/*E* products was obtained. $R_f=$

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0.50 (cyclohexane/EtOAc = 18:1). Description of major diastereomer (*Z*): $^1$H NMR (400 MHz, $CDCl_3$): $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.8$ Hz, 3H, $EtO_2CC{=}CHCHCH_3$), 0.95 (d, $J = 6.4$ Hz, 3H, $TrtOCH_2CHCH_3$), 1.01 (t, $J = 7.2$ Hz, 3H, $EtO_2CCH_2CH_3$), 1.07–1.12 (m, 1H, $CHCH_AH_BCH$), 1.24 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$), 1.36–1.44 (m, 1H, $CHCH_AH_BCH$), 1.74–1.82 (m, 1H, $TrtOCH_2CH$), 2.23 (q, $J = 7.2$ Hz, 2H, $EtO_2CCH_2CH_3$), 2.85 (dd, $J = 6.4$, 8.4 Hz, 1H, $TrtOCH_AH_B$), 2.94 (dd, $J = 5.6$, 8.4 Hz, 1H, $TrtOCH_AH_B$), 2.99–3.07 (m, 1H, C=CHCH), 4.12 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 5.57 (d, $J = 10.0$ Hz, 1H, C=CH), 7.20–7.31 (m, 9H, Ar-H), 7.43–7.45 ppm (m, 6H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$ (p), 14.3 (p), 17.6 (p), 20.3 (p), 27.6 (s), 31.0 (t), 31.8 (t), 41.2 (s), 59.9 (s), 68.5 (s), 86.1 (q), 126.8 (t), 126.7 (t), 128.8 (t), 131.9 (q), 144.6 (t), 146.0 (q), 168.3 ppm (q); IR (film): $\tilde{\nu} = 3086$, 3059, 3023, 2964, 2928, 2871, 1712, 1643, 1597, 1491, 1449, 1373, 1303, 1215, 1158, 1070, 1032, 988, 899, 764, 746, 706, 648, 633 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%): 470 (0.01) [$M^+$], 440 (0.04), 243 (100), 165 (16), 105 (6), 77 (2); HRMS *m/z*: calcd for $C_{32}H_{38}O_3$: 470.2821; found: 470.2825.

**Alcohol 38**: lithium aluminium hydride (24.8 mg, 0.654 mmol) was slowly added to a solution of ester **37** (280.0 mg, 0.595 mmol) in THF (6 mL) at 0 °C. The reaction mixture was stirred at RT overnight, after which it was cooled to 0 °C and quenched with $H_2O$ (5 mL) followed by Rochelle's salt solution (5 mL) and the reaction mixture stirred at RT for 15 h. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica using cyclohexane/ethyl acetate 9:1 to give alcohol **38** (237.1 mg, 0.553 mmol, 93 %) as colorless oil. A 5:1 ratio of *Z*/*E* products was obtained. $R_f = 0.24$ (cyclohexane/EtOAc 6:1). Description of major diastereomer (*Z*): $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (d, $J = 6.4$ Hz, 3H, $EtO_2CC{=}CHCHCH_3$), 0.98 (t, $J = 7.2$ Hz, 3H, $EtO_2CCH_2CH_3$), 1.01 (d, $J = 6.4$ Hz, 3H, $TrtOCH_2CHCH_3$), 1.02–1.06 (m, 1H, $CHCH_AH_BCH$), 1.34–1.43 (m, 1H, $CHCH_AH_BCH$), 1.72 (sext, $J = 6.4$ Hz, 1H, $TrtOCH_2CH$), 2.06 (q, $J = 7.2$ Hz, 2H, $EtO_2CCH_2CH_3$), 2.23–2.36 (m, 1H, C=CHCH), 2.79 (dd, $J = 7.2$, 8.0 Hz, 1H, $TrtOCH_AH_B$), 2.98 (dd, $J = 4.8$, 8.8 Hz, 1H, $TrtOCH_AH_B$), 3.86 (dd, $J = 12$,0, 19.2 Hz, 2H, $CCH_2OH$), 4.98 (d, $J = 9.6$ Hz, 1H, C=CH), 7.19–7.30 (m, 9H, Ar-H), 7.43–7.45 ppm (m, 6H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 13.0$ (p), 18.6 (p), 22.0 (p), 27.7 (s), 29.4 (t), 31.8 (t), 42.1 (s), 60.5 (s), 67.8 (s), 86.2 (q), 126.9 (t), 127.8 (t), 128.9 (t), 134.0 (t), 138.4 (q), 144.6 ppm (q); IR (film): $\tilde{\nu} = 3342$, 3086, 3058, 3032, 2961, 2924, 2869, 1597, 1491, 1449, 1384, 1219, 1182, 1155, 1068, 1032, 899, 764, 746, 706, 633 cm$^{-1}$; HRMS *m/z*: calcd for $C_{30}H_{36}O_2$: 428.2715; found: 428.2712.

**Diene 40**: Dess–Martin periodinane (1.51 mL, 0.698 mmol) was added at 0 °C to a solution of alcohol **39** (230.0 mg, 0.537 mmol) in $CH_2Cl_2$ (5 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **39** (230.0 mg, 0.537 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. Lithium bis(trimethylsilyl)amide (1 M in THF, 0.91 mL, 0.91 mmol) was slowly added, at 0 °C, to a solution of 5-(benzylsulfonyl)-1-phenyl-1*H*-tetrazole (**B**) (282 mg, 0.939 mmol) in THF (8 mL). After stirring for 20 min at RT, it was cooled to −78 °C and a solution of crude aldehyde **39** (230.0 mg, 0.537 mmol) in THF (2 mL) was added. The reaction mixture was stirred overnight while slowly warming up to RT. It was diluted with $Et_2O$ (5 mL) and the reaction quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica using cyclohexane/ethyl acetate 50:1 to give compound **40** (209.2 mg, 78 %) as colorless oil. $R_f = 0.36$ (cyclohexane/EtOAc 50:1); mixture of 4 diastereoisomers: (*E*,*Z*)/(*E*,*E*)/(*Z*,*Z*)/(*E*,*Z*) = 25/5.3/3.3/1. Description of major diastereomer (*E*,*Z*): $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (d, $J = 6.8$ Hz, 3H, C=CHCHCH$_3$), 0.98 (d, $J = 6.8$ Hz, 3H, $TrtOCH_2CHCH_3$), 1.06 (t, $J = 7.2$ Hz, 3H, $CCH_2CH_3$), 1.07–1.12 (m, 1H, $CHCH_AH_BCH$), 1.45–1.52 (m, 1H, $CHCH_AH_BCH$), 1.71–1.77 (m, 1H, $TrtOCH_2CH$), 2.24 (q, $J = 7.2$ Hz, 2H, $CCH_2CH_3$), 2.64–2.71 (m, 1H, C=CHCH), 2.83–2.87 (m, 1H, $TrtOCH_AH_B$), 2.83–2.87 (m, 1H, $TrtOCH_AH_B$), 5.17 (d, $J = 9.6$ Hz, 1H, PhCH=CHC=CH), 6.48 (d, $J = 16.2$ Hz, 1H, PhCH), 6.90 (d, $J = 16.2$ Hz, 1H, PhCH=CH), 7.12–7.27 (m, 14H, Ar-H), 7.36–7.43 ppm (m, 6H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$ (p), 18.4 (p), 21.6 (p), 26.7 (s), 29.4 (t), 32.0 (t), 42.0 (s), 67.9 (s), 86.1 (q), 125.4 (t), 126.4 (t), 126.9 (t), 127.2 (t), 127.6 (t), 127.7 (t), 128.7 (t), 128.9 (t), 136.4 (q), 137.3 (t), 138.2 (q), 144.7 ppm (q); IR (film): $\tilde{\nu} = 3058$, 3025, 2961, 2924, 2871, 1627, 1597, 1491, 1448, 1373, 1315, 1219, 1182, 1155, 1069, 1032, 961, 899, 763, 747, 706, 633 cm$^{-1}$.

**Diene 41**: Under argon, $I_2$ (10.1 mg, 0.040 mmol) was added to a solution of compound **39** (200.0 mg, 0.399 mmol) in $CHCl_3$ (4 mL) at RT. After stirring at RT for 1 h, the reaction mixture was quenched with a saturated solution of sodium metabisulfite (5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude compound **41** (200.0 mg, 0.399 mmol), which was used for the next step without further purification. $R_f = 0.56$ (cyclohexane/EtOAc 18:1); mixture of 3 diastereoisomers: (*E*,*E*)/(*E*,*Z*)/(*Z*,*Z*) = 6.6/3.3/1; description of the two major diastereomers (*E*,*E*)/(*E*,*Z*), which are present in a ratio of 2:1: $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 6.4$ Hz, 3H, C=CHCHCH$_3$, (*E*,*E*)), 0.95–1.03 (m, 9H, C=CHCHCH$_3$, (*E*,*Z*); $TrtOCH_2CHCH_3$, (*E*,*E*) and (*E*,*Z*); $CCH_2CH_3$, (*E*,*E*)), 1.06–1.12 (m, 3H, $CHCH_AH_BCH$, (*E*,*E*); $CHCH_AH_BCH$, (*E*,*Z*); and $CCH_2CH_3$, (*E*,*Z*)), 1.45–1.52 (m, 1.5H, $CHCH_AH_BCH$, (*E*,*E*); and $CHCH_AH_BCH$, (*E*,*Z*)), 1.71–1.79 (m, 1.5H, $TrtOCH_2CH$, (*E*,*E*); and $TrtOCH_2CH$, (*E*,*Z*)), 2.12 (dq, $J = 3.2$, 7.6 Hz, 2H, $CCH_2CH_3$, (*E*,*E*)), 2.27 (q, $J = 7.2$ Hz, 1H, $CCH_2CH_3$, (*E*,*Z*)), 2.33–2.43 (m, 1H, C=CHCH, (*E*,*E*)), 2.66–2.73 (m, 0.5H, C=CHCH, (*E*,*Z*)), 2.83 (dd, $J = 6.4$, 8.8 Hz, 1H, $TrtOCH_AH_B$, (*E*,*E*)), 2.87 (dd, $J = 6.0$, 8.4 Hz, 0.5H, $TrtOCH_AH_B$, (*E*,*Z*)), 2.94 (dd, $J = 5.2$, 8.8 Hz, 1H, $TrtOCH_AH_B$, (*E*,*Z*)), 3.01 (dd, $J = 4.8$, 8.8 Hz, 1H, $TrtOCH_AH_B$, (*E*,*E*)), 5.19 (d, $J = 9.6$ Hz, 0.5H, PhCH=CHC=CH, (*E*,*Z*)), 5.29 (d, $J = 10.0$ Hz, 1H, PhCH=CHC=CH, (*E*,*E*)), 6.41 (d, $J = 16.2$ Hz, 1H, PhCH, (*E*,*E*)), 6.50 (d, $J = 16.0$ Hz, 0.5H, PhCH, (*E*,*Z*)), 6.62 (d, $J = 16.2$ Hz, 1H, PhCH=CH, (*E*,*E*)), 6.92 (d, $J = 16.0$ Hz, 0.5H, PhCH=CH, (*E*,*Z*)), 7.15–7.30 (m, 14H, Ar-H), 7.36–7.45 ppm (m, 6H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta =$ 13.9 (p), 14.2 (p), 18.4 (p), 18.5 (p), 20.1 (s), 21.5 (p), 21.6 (p), 26.7 (s), 29.5 (t), 30.3 (t), 32.0 (t), 41.9 (s), 42.0 (s), 67.8 (s), 67.9 (s), 86.1 (q), 125.3 (t), 125.4 (t), 126.2 (t), 126.4 (t), 126.9 (t), 127.2 (t), 127.7 (t), 127.8 (t), 128.7 (t), 128.9 (t), 132.9 (t), 136.4 (q), 137.3 (t), 138.2 (q), 138.3 (q), 138.4 (q), 140.6 (t), 144.6 (q), 144.7 ppm (q).

**Alcohol 42**: Camphorsulfonic acid (134 mg, 0.577 mmol) was added in one portion to a solution of compound **41** (170 mg, 0.340 mmol) in $CH_2Cl_2$/MeOH (16/8 mL) at 0 °C. The mixture was stirred at RT for 1 h 30 min and was then neutralized by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and then concentrated. The crude product was then purified by flash chromatography using cyclohexane/ethyl acetate 6:1 to yield alcohol **42** (39.5 mg, 0.153 mmol, 45 %) as colorless solid. $R_f = 0.16$ (cyclohexane/EtOAc 6:1 $[\alpha]_D^{20} = -31.4$ ($c = 0.14$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.8$ Hz, 3H, $HOCH_2CHCH_3$), 1.00 (d, $J = 6.8$ Hz, 3H, C=CHCHCH$_3$), 1.11 (t, $J =$ 7.6 Hz, 3H, PhCH=CHCCH$_2$CH$_3$), 1.13–1.17 (m, 1H, $CHCH_AH_BCH$), 1.38 (br s, 1H, OH), 1.39–1.46 (m, 1H, $CHCH_AH_BCH$), 1.65–1.72 (m, 1H, $HOCH_2CH$), 2.38 (q, $J = 7.6$ Hz, 2H, PhCH=CHCC$H_2$CH$_3$), 2.59–2.70 (m, 1H, C=CHCH), 3.42 (dd, $J = 6.4$ Hz, $J = 10.4$ Hz, 1H, $HOCH_AH_B$), 3.53 (dd, $J = 5.2$ Hz, $J = 10.4$ Hz, 1H, $HOCH_AH_B$), 5.38 (d, $J =$ 10.0 Hz, 1H, PhCH=CHC=CH), 6.48 (d, $J = 16.2$ Hz, 1H, PhCH), 6.68 (d, $J = 16.2$ Hz, 1H, PhCH=CH), 7.20 (t, $J = 7.4$ Hz, 1H, Ar-H), 7.31 (t, $J = 8.0$ Hz, 2H, Ar-H), 7.41 ppm (d, $J = 7.6$ Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 14.3$ (p), 17.3 (p), 20.2 (s), 21.2 (p), 30.3 (t), 33.7 (t), 41.3 (s), 68.3 (s), 125.6 (t), 126.3 (2 t), 127.0 (t), 128.7 (2 t), 132.7 (t), 138.1 (q), 138.4 (q), 140.3 ppm (t); IR (neat): $\tilde{\nu} = 3345$, 3026, 2961, 2925, 2872, 1627, 1598, 1493, 1450, 1375, 1030, 961, 749, 693 cm$^{-1}$; MS (EI, 70 eV): *m/z* (%) 258 ([$M^+$], 33), 185 (72), 169 (100), 145 (39), 129 (48), 99 (60), 91 (61); HRMS *m/z*: calcd for $C_{18}H_{26}O$: 258.1984; found: 258.1982.

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**Ester 44**: Dess–Martin periodinane (0.38 mL, 0.176 mmol) was added at 0 °C to a solution of alcohol **42** (35.0 mg, 0.135 mmol) in $CH_2Cl_2$ (3 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×5 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **43** (35.0 mg, 0.135 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. Ethyl 2-(diethoxyphosphoryl)butanoate (103 mg, 0.407 mmol) was added dropwise to a solution of sodium hydride (60 % in mineral oil, 16.3 mg, 0.407 mmol) in THF (3 mL) at 0 °C. The solution was stirred at RT for 1 h before cooling to 0 °C and addition of the crude aldehyde **46** (35.0 mg, 0.135 mmol) (from previous reaction) in THF (1 mL). The solution was stirred for 1 h at 0 °C, warmed slowly to RT and stirred for an additional 3 h. The reaction was quenched by pouring on to saturated aqueous $NH_4Cl$ (3 mL). The product was extracted with $Et_2O$ (3×3 mL) and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 30:1 to yield ester **44** (35.1 mg, 0.099 mmol, 73 %) as a colorless oil. A 4:1 ratio of *Z*/*E* products was obtained. $R_f$ = 0.50 (cyclohexane/EtOAc = 18:1); $[\alpha]_D^{20} = -6.3$ ($c$ = 0.16 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.97–1.06 (m, 12H, PhCH=CHC=CHCHC$H_3$, $EtCO_2C$=CHCHC$H_3$, PhCH=CHCC$H_2$C$H_3$, and $EtCO_2CCH_2$C$H_3$), 1.21 (t, $J$ = 6.8 Hz, 3H, $CO_2CH_2$C$H_3$), 1.27–1.32 (m, 2H, CHC$H_2$CH), 2.22–2.32 (m, 4H, PhCH=CHCC$H_2$C$H_3$, and $EtCO_2CC H_2CH_3$), 2.43–2.55 (m, 1H, PhCH=CHC=CHC*H*), 2.99–3.11 (m, 1H, $EtCO_2C$=CHC*H*), 4.05–4.17 (m, 2H, $CO_2CH_2CH_3$), 5.30 (d, $J$ = 10.0 Hz, 1H, PhCH=CHC=C*H*), 5.59 (d, $J$ = 10.0 Hz, 1H, $EtCO_2C$=C*H*), 6.44 (d, $J$ = 16.2 Hz, 1H, PhC*H*), 6.65 (d, $J$ = 16.2 Hz, 1H, PhCH=C*H*), 7.18 (t, $J$ = 7.6 Hz, 1H, Ar-H), 7.30 (t, $J$ = 7.2 Hz, 2H, Ar-H), 7.39 ppm (d, $J$ = 7.6 Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 13.9 (p), 14.3 (p), 14.4 (p), 21.2 (s), 21.1 (p), 21.8 (p), 27.8 (s), 31.1 (t), 31.9 (t), 45.9 (s), 60.1 (s), 125.3 (t), 126.2 (2 t), 126.9 (t), 128.6 (2 t), 132.7 (q), 132.8 (t), 138.2 (q), 138.8 (q), 139.9 (t), 146.1 (t), 168.3 ppm (q); IR (film): $\tilde{\nu}$ = 3027, 2965, 2871, 1715, 1598, 1494, 1450, 1378, 1220, 1184, 1130, 1030, 961, 749, 693 $cm^{-1}$; MS (EI, 70 eV): *m/z* (%) 354 ([$M^+$], 35), 281 (84), 227 (49), 185 (74), 136 (41), 129 (66), 121 (61), 105 (47), 91 (100); HRMS *m/z*: calcd for $C_{24}H_{34}O_2$: 354.2559; found: 354.2557.

**Alcohol 45**: Lithium aluminium hydride (4.1 mg, 0.109 mmol) was slowly added to a solution of ester **44** (35.0 mg, 0.099 mmol) in THF (3 mL) at 0 °C. After stirring at 0 °C for 2 h the reaction mixture was quenched carefully at 0 °C with $H_2O$ (1 mL) followed by Rochelle's salt solution (1 mL). The aqueous layer was extracted with $Et_2O$ (4×3 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 9:1 to yield alcohol **45** (24.0 mg, 0.077 mmol, 77 % yield). $R_f$ = 0.48 (cyclohexane/EtOAc = 6:1); $[\alpha]_D^{20} = -90.0$ ($c$ = 0.11 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.94 (d, $J$ = 6.4 Hz, 3H, $HOCH_2C$=CHCHC$H_3$), 0.99 (d, $J$ = 6.8 Hz, 3H, PhCH=CHCC$H_2$C$H_3$), 1.05 (t, $J$ = 7.4 Hz, 3H, $HOCH_2CCH_2$C$H_3$), 1.06 (t, $J$ = 7.6 Hz, 3H, PhCH=CHC=CHCHC$H_3$), 1.32 (ddd, $J$ = 2.4, 5.6, 8.4 Hz, CHC$H_2$CH), 2.13 (dq, $J$ = 1.2, 7.4 Hz, 3H, $HOCH_2CC H_2CH_3$), 2.20–2.37 (m, 2H, PhCH=CHCC$H_2$C$H_3$), 2.41–2.55 (m, 2H, $HOCH_2C$=CHC*H* and PhCH=CHC=CHC*H*), 4.02 (brs, 2H, HOC$H_2$), 5.05 (d, $J$ = 10.0 Hz, 1H, $HOCH_2C$=C*H*), 5.35 (d, $J$ = 9.6 Hz, 1H, PhCH=CHC=C*H*), 6.46 (d, $J$ = 16.4 Hz, 1H, PhC*H*), 6.68 (d, $J$ = 16.4 Hz, 1H, PhCH=C*H*), 7.19 (t, $J$ = 7.2 Hz, 1H, Ar-H), 7.30 (t, $J$ = 7.6 Hz, 2H, Ar-H), 7.40 ppm (d, $J$ = 7.6 Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 13.1 (p), 14.4 (p), 20.3 (s), 22.1 (p), 22.7 (p), 28.0 (s), 30.4 (t), 31.0 (t), 46.2 (s), 60.8 (s), 125.7 (t), 126.3 (2 t), 127.0 (t), 128.7 (2 t), 132.5 (t), 133.8 (t), 138.0 (q), 139.1 (q), 139.2 (q), 140.2 ppm (t); IR (film): $\tilde{\nu}$ = 3423, 3027, 2960, 2924, 1598, 1494, 1452, 1383, 1029, 960, 748, 692 $cm^{-1}$.; MS (EI, 70 eV): *m/z* (%) 312 ([$M^+$], 38), 281 (91), 185 (61), 149 (44), 133 (42), 105 (34), 91 (48), 43 (100); HRMS *m/z*: calcd for $C_{22}H_{32}O$: 312.2453; found: 312.2452.

**Ester 47**: Dess–Martin periodinane (0.21 mL, 0.100 mmol) was added at 0 °C to a solution of alcohol **45** (24.0 mg, 0.077 mmol) in $CH_2Cl_2$ (2 mL). After stirring for 2 h at RT, the reaction mixture was quenched by adding saturated aqueous $Na_2S_2O_3$ (1 mL) and saturated aqueous $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (4×3 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield the crude aldehyde **46** (24.0 mg, 0.077 mmol, assumed to be quantitative) as colorless oil, which was used without further purification for the following olefination reaction. ethyl 2-(diethoxyphosphoryl)propanoate (0.049 mL, 0.230 mmol) was added dropwise to a solution of sodium hydride (60 % in mineral oil, 9.2 mg, 0.230 mmol) in THF (3 mL) at 0 °C. The solution was stirred at RT for 1 h before cooling to 0 °C and addition of crude aldehyde **46** (24.0 mg, 0.077 mmol) (from previous reaction) in THF (1.5 mL). The solution was warmed slowly to RT and stirred for an additional 3 h. The reaction was quenched then by pouring on to saturated aqueous $NH_4Cl$ (2 mL). The product was extracted with $Et_2O$ (4×3 mL) and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was then purified by column chromatography on silica using *n*-pentane/$Et_2O$ 40:1 to yield ester **47** (20.6 mg, 0.052 mmol, 68 % yield) as colorless oil. $R_f$ = 0.44 (cyclohexane/EtOAc = 18:1 $[\alpha]_D^{20} = +87.5$ ($c$ = 0.08 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.92 (d, $J$ = 6.4 Hz, 3H, $EtCO_2C$=CHC=CHCHC$H_3$), 0.96 (d, $J$ = 6.8 Hz, 3H, PhCH=CHC=CHCHC$H_3$), 0.99 (t, $J$ = 7.6 Hz, 3H, $EtCO_2C$=CHCC$H_2$C$H_3$), 1.07 (t, $J$ = 7.6 Hz, 3H, PhCH=CHCC$H_2$C$H_3$), 1.16 (t, $J$ = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.25–1.29 (m, 2H, CHC$H_2$CH), 1.80 (t, $J$ = 1.2 Hz, 3H, $EtCO_2CCH_3$), 2.12 (q, $J$ = 7.6 Hz, 2H, $EtCO_2C$=CHCC$H_2$C$H_3$), 2.16–2.24 (m, 1H, $EtCO_2C$=CHC=CHC*H*), 2.27–2.38 (m, 2H, PhCH=CHCC$H_2$C$H_3$), 2.44–2.55 (m, 1H, PhCH=CHC=CHC*H*), 4.04 (ddq, $J$ = 12.4, 3.6, 7.6 Hz, 2H, $CO_2CH_2CH_3$), 5.14 (dd, $J$ = 1.2, 10.0 Hz, 1H, $EtCO_2C$=CHC=C*H*), 5.31 (d, $J$ = 10.0 Hz, 1H, PhCH=CHC=C*H*), 6.44 (d, $J$ = 16.0 Hz, 1H, PhC*H*), 6.65 (d, $J$ = 16.0 Hz, 1H, PhCH=C*H*), 7.08 (s, 1H, $EtCO_2C$=C*H*), 7.17 (t, $J$ = 7.2 Hz, 1H, $H_{arom}$), 7.29 (t, $J$ = 8.0 Hz, 2H, Ar-H), 7.39 ppm (d, $J$ = 7.2 Hz, 2H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 13.3 (p), 14.3 (2 p), 14.4 (p), 20.3 (s), 21.0 (p), 21.8 (p), 30.0 (s), 30.7 (t), 31.8 (t), 46.0 (s), 60.7 (s), 125.3 (t), 126.2 (2 t), 126.9 (t), 128.6 (2 t), 128.7 (q), 132.8 (t), 135.0 (t), 136.2 (q), 138.2 (q), 138.7 (q), 139.2 (t), 140.3 (t), 168.4 ppm (q); MS (EI, 70 eV): *m/z* (%) 394 ([$M^+$], 74), 239 (79), 185 (88), 129 (49), 121 (62), 91 (100), 43(52); HRMS *m/z*: calcd for $C_{27}H_{38}O_2$: 394.2872; found: 394.2870.

***homo*-Plakotenin ethyl ester 48**: A solution of linear ester **47** (16.0 mg, 0.041 mmol) in toluene (4 mL) was heated to reflux and stirred in a sealed vial for 20 h. The mixture was concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 40:1 to yield cyclic ester **48** (14.4 mg, 0.036 mmol, 90 % yield) as colorless oil. $R_f$ = 0.42 (cyclohexane/EtOAc = 18:1). $[\alpha]_D^{20} = +168.9$ ($c$ = 0.09 in $CHCl_3$); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.79 (t, $J$ = 7.2 Hz, 3H, 19-H), 0.97 (d, $J$ = 6.4 Hz, 3H, 14-H), 1.01 (t, $J$ = 7.2 Hz, 3H, 17-H), 1.03–1.10 (m, 1H, 18-H), 1.17 (d, $J$ = 5.6 Hz, 3H, 15-H), 1.31 (t, $J$ = 7.2 Hz, 3H, 21-H), 1.55 (t, $J$ = 8.0 Hz, 2H, 7-H), 1.74–1.90 (m, 5H, 18-H, 5-H, 9-H, 8-H, and 6-H), 2.05 (s, 3H, 13-H), 2.10–2.23 (m, 2H, 16-H), 3.71 (d, $J$ = 4.0 Hz, 1H, 12-H), 4.17–4.25 (m, 2H, 20-H), 5.25 (d, $J$ = 4.4 Hz, 1H, 11-H), 6.87 (s, 1H, 3-H), 7.21–7.24 (m, 1H, Ar-H), 7.28–7.30 ppm (m, 5H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 9.4 (p), 13.2 (p), 14.3 (p), 14.4 (p), 22.0 (p), 23.3 (p), 27.0 (s), 27.9 (s), 31.6 (t), 34.8 (t), 45.4 (s), 48.0 (q), 51.3 (t), 52.2 (t), 55.6 (t), 60.8 (s), 123.3 (t), 126.5 (t), 127.8 (2 t), 127.9 (q), 131.0 (2 t), 142.3 (q), 142.9 (q), 146.6 (t), 169.5 ppm (q); IR (film): $\tilde{\nu}$ = 2927, 2865, 1698, 1493, 1451, 1375, 1260, 1246, 1139, 1103, 874, 763, 741, 704 $cm^{-1}$; MS (EI, 70 eV): *m/z* (%) 394 ([$M^+$], 100), 239 (60), 185 (56), 129 (39), 91 (84); HRMS *m/z*: calcd for $C_{27}H_{38}O_2$: 394.2872; found: 394.2870.

***homo*-Plakotenin 3**: NaOH (2 M) (0.076 mL, 0.152 mmol) was added to a solution of cyclic ester **48** (12.0 mg, 0.030 mmol) in THF/MeOH (1.2/0.6 mL), and the resulting mixture was heated to 40 °C and stirred for 20 h. After cooling to RT, the mixture was acidified with aqueous HCl (1 M), and then extracted with EtOAc (5 times). The combined organic extracts were backwashed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica using *n*-pentane/$Et_2O$ 2:1 to yield carboxylic acid **1a** (9.8 mg, 0.027 mmol, 88 % yield) as colorless oil. $R_f$ = 0.40 (cyclohexane/EtOAc = 2:1); $[\alpha]_D^{20}$ = +183° (0.09 g/100 mL, $CHCl_3$); $[\alpha]_D^{20}$ = +185° (0.14 g/100 mL, MeOH); (NMR assignment according to numbering system used in Ref. [8]) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.80 (t, $J$ = 7.4 Hz, 3H, 19-H), 0.97 (d,

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$J$=6.0 Hz, 3H, 14-H), 1.02 (t, $J$=7.2 Hz, 3H, 17-H), 1.06–1.11 (m, 1H, 18-H), 1.17 (d, $J$=5.6 Hz, 3H, 15-H), 1.56 (dt, $J$=2.4, 8.0 Hz, 2H, 7-H), 1.75–1.91 (m, 5H, 17-H, 5-H, 9-H, 8-H and 5-H), 2.06 (d, $J$=1.2 Hz, 3H, 13-H), 2.17 (q, $J$=7.2 Hz, 2H, 16-H), 3.75 (d, $J$=4.4 Hz, 1H, 12-H), 5.24 (d, $J$=4.0 Hz, 1H, 11-H), 7.03 (s, 1H, 3-H), 7.21–7.25 (m, 1H, Ar-H), 7.29–7.30 (m, 4H, Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=9.4 (p), 13.0 (p), 14.0 (p), 22.0 (p), 23.3 (p), 27.2 (s), 27.8 (s), 31.5 (t), 34.8 (t), 45.4 (s), 48.3 (q), 51.6 (t), 51.8 (t), 55.5 (t), 123.1 (t), 126.6 (t), 127.2 (q), 127.9 (2t), 131.1 (2t), 142.2 (q), 142.9 (q), 149.6 (t), 174.8 (q); IR (film): $\tilde{\nu}$= 2927, 2868, 1679, 1628, 1451, 1418, 1376, 1276, 1030, 908, 883, 762, 734, 702, 556 cm$^{-1}$; MS (EI, 70 eV): $m/z$ (%) 366 ([$M^+$], 100), 239 (29), 185 (31), 145 (21), 91 (33); HRMS $m/z$: calcd for $C_{25}H_{34}O_2$: 366.2559; found: 366.2557.

**FACS measurements**: For cell cycle analyses cells were treated with 1, 2, 3, and 5 μM of Plakotenin, Plakotenin derivatives or intermediates for 72 h, harvested, mixed with ice-cold 70% ethanol and fixed overnight at 4°C. Cells were pelleted at 530 g for 5 min, washed once with PBS and stained with Draq5 (Biostatus td) at a final concentration of 10 mM for 15 min in the dark. The DNA content of cells was determined using a flow cytometer (FACScan; Becton Dickinson).

**Western blot analysis**: For testing cell lysate against antibodies[24] cells were washed twice in ice-cold PBS, scraped into PBS, and centrifuged at 1000 *g* for 5 min. Cells were lysed by incubation in NP-40 lysis buffer (150 mM NaCl, 50 mM Tris [pH 8], 5 mM EDTA, 1% NP-40, 1 mM phenylmethylsulfonyl fluoride) on ice for 30 min. The protein extract was cleared by centrifugation at 13000 *g* at 4°C for 20 min, and the protein concentration of the supernatant (protein extract) was determined by the method of Bradford (Biorad). SDS-polyacrylamide gel electrophoresis (PAGE) and Western blotting were performed with 12% SDS PAGE Gel, proteins were disconnected with 100 V in running buffer (0.18 M glycine, 24 mM Tris base) and blotted on PVDF membrane at 30 V overnight in transfer buffer (0.18 M glycine, 24 mM Tris base, 10% MEOH) and blocked 30 min with 5% low-fat milk solution.

We used antibodies against cleaved caspase-8 (Cell Signaling) in a 1:500 dilution (in 5% low fat milk solution) and Tubulin (abcam) in an 1:1000 dilution as loading control. Secondary antibody was used in a 1:1000 solution anti rabbit (for Caspase-8) and anti-mouse for Tubulin. Secondary antibody was bound to horseradish peroxidase and incubated with luminol peroxide solution (PIERCE,Thermo-scientific) bonds were made visible on a film (Kodak). As a positive control cells were incubated with 50 μM LiCl for 2 days.[25]

**Statistical analysis of FACS data**: Values were tested for significance by a single-sided t-test of paired samples ($n$=6). Values of plakotenin were compared to values of intermediates.

**MTT-tests**: $5\times10^5$ HeLa wild type (wt) cells were seeded in a 96 well-plate and incubated with 1, 2, 3, and 5 μM of plakotenin derivatives for two days. Later cells were treated with MTT (Promega) for 4 h and lysed with lysis buffer (Promega). Absorption of formazan was measured at 595 nm. For blank measurements (positive control) cells were treated with 5% TritonX100 15 min before MTT was added. Negative control (untreated cells) is set to 100% cell vitality.

**Computational details**: The density functional calculations in this work were carried out with the Turbomole program package.[26] Transition-state structures were optimized using the B3LYP hybrid functional[27] in combination with a TZVP basis set[28] and employing tight convergence criteria (SCF energy:$10^{-8}$ $E_h$, energy gradient: $10^{-4}$ $E_h$ $a_0^{-1}$ and inclusion of the derivatives of quadrature weights). Force constants and vibrational frequencies were computed to ensure that all structures are first-order saddle points with the desired imaginary mode. The reported relative energies are zero-point vibrational-energy (ZPVE) corrected.

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