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Asymmetric Synthesis and in vivo Biological Inactivity of the Right-Hand Terpenoid Fragment of Terpendole E

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Dedicated to the memory of Professor Mugio Nishizawa

Keywords: Natural products / Terpenoids / Radical reactions / Reduction / Metathesis / Cyclization / Inhibitors

Synthesis of the DEF-ring terpenoid fragment of terpendole E, an Eg5 inhibitor, is described. The DE-ring was constructed by a modification of Barrero's radical cyclization. The F-ring tetrahydropyran was then constructed by acid-induced cyclization of an epoxy alcohol, which was prepared by cross-metathesis followed by Shi's epoxidation. Cell-based assays indicated that the DEF-ring fragment is not capable of inhibiting cell growth and cell cycle progression of human cancer cell lines, indicating that the DEF-ring fragment alone is not sufficient for the biological activity.

Introduction

Eg5, also known as kinesin spindle protein (KSP), is a member of a kinesin-5 family, and is an extraordinary active protein in mitosis, the process involved in all cells that are undergoing cell division.[1] Inhibition of Eg5 results in cell cycle arrest and apoptotic cell death, without affecting microtuble integrity in the interphase.[2] Eg5 has, therefore, recently been recognized as an attractive molecular target for treatment of malignant tumors, since Eg5 plays an important role in the assembly and stabilization of the mitotic spindle.[3] Inhibitors of Eg5 have been explored from synthetic and natural[4] resources in this context[5] and, in 2003, the microbial metabolite terpendole E (**1**) was identified by Osada's group as a novel Eg5 inhibitor that inhibits M phase progression by inducing formation of a monastrol spindle in the M phase.[6] Terpendole E (**1**) at a concentration of 50 μM caused cell cycle arrest of tsFT210 cells at the boundary of the G2/M phase.

Terpendole E (**1**), an indoloditerpene that possesses an indole fragment fused to a tetracyclic diterpene system, was originally isolated from the fungal strain FO-2546 by Tomoda and Omura in 1995.[7] They established the relative stereostructure of terpendole E (**1**) by X-ray crystallographic analysis as shown in Scheme 1, and the absolute configuration has been assigned by analogy with other indolinoditerpenes such as paspaline.[8] In spite of the intriguing biological activity, no synthetic study has been reported except for a recent study of an analog synthesis by the Giannis group.[9] This could be attributed to several synthetic difficulties in the selective construction of a hexacyclic molecular skeleton with eight asymmetric carbons, as can be anticipated from other indoloditerpene syntheses.[8c,10] The synthetically challenging structure, as well as the interesting biological activity, prompted us to study the chemical synthesis. Here, we report our studies on the synthesis and in vivo biological activity of the DEF-ring terpenoid fragment **2** of terpendole E (**1**).

Results and Discussion

As shown in Scheme 1, terpendole E (**1**) was retrosynthetically disconnected first by Wittig reaction[11] at the C2–C18 bond to generate the advanced intermediate **A**. The intermediate was envisaged to be synthesized from the DEF-ring terpenoid fragment **2**, which includes the right-hand carbon framework with correct stereochemistry, by employing a modified Barrero radical cyclization[12–14] and acidic cyclization of an epoxy alcohol for the DE- and F-rings, respectively.

The synthesis of the optically active DE-ring fragment **9** is shown in Scheme 2. Oxidation of farnesyl acetate (**3**) with SeO_2, in the presence of *tert*-butyl hydroperoxide (TBHP), selectively provided alcohol **4** in 38% yield.[15,16] Sharpless asymmetric epoxidation using diethyl (+)-tartrate [(+)-DET] gave the epoxide **5** after silylation in 80% yield.[17] The enantioselectivity in the epoxidation was determined to be 91% *ee* by analysis of the Mosher ester derivative.

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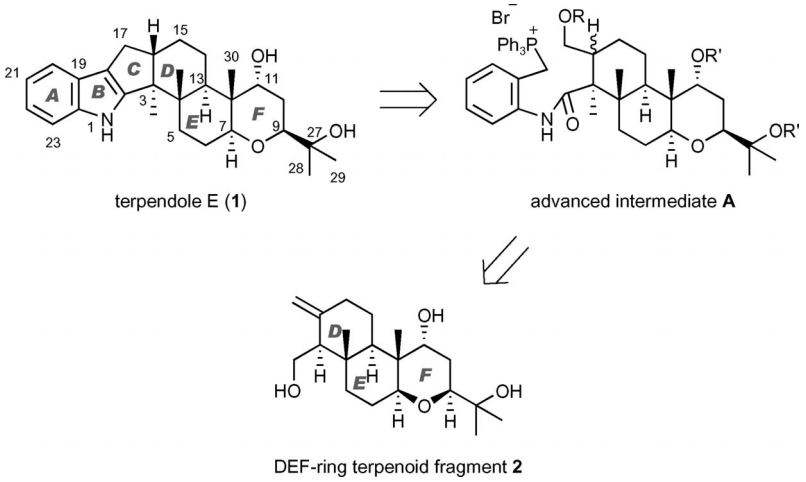
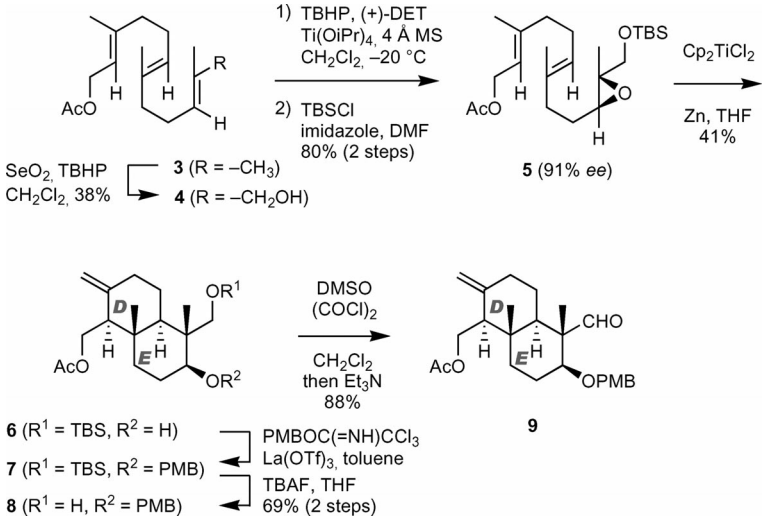


Scheme 1. Our retrosynthetic plan for terpendole E generates the DEF-ring terpenoid fragment **2**.



Scheme 2. Construction of the DE-ring and synthesis of aldehyde **9**.

The construction of the DE-ring moiety was next attempted using the radical reaction procedure originally reported by Barrero et al.[13] It was found, however, that the original procedure (0.2 equiv. of Cp_2TiCl_2, Mn, TMSCl, 2,4,6-collidine, THF, r.t.) was not capable of providing the desired bicycle **6** in our hands, and only unreacted **5** was recovered. Although the use of a combination of stoichiometric amounts (2 equiv.) of Cp_2TiCl_2 and Mn (8 equiv.)[13,14] at room temperature was also unsuccessful, the desired bicycle **6** was obtained in 41% yield by changing the metal to Zn (8 equiv.).[18–20] Spectroscopic data of **6** were identical with those reported for racemic **6**.[14] Protection of the secondary hydroxyl group as the *p*-methoxybenzyl (PMB) ether, which was carried out via the corresponding trichloroacetimidate,[21] and desilylation (tetrabutylammonium fluoride, TBAF, in THF) followed by Swern oxidation,[22] gave the DE-ring aldehyde **9** in 61% yield for the three steps.

Introduction of a carbon chain corresponding to the F-ring was next attempted. Appropriate reaction conditions were initially investigated with model aldehyde **10**, which was prepared in six steps from cyclohexanone (see the Supporting Information). Although prenyl addition is known to proceed at the γ-position,[23] we initially expected that the reaction with neopentylic aldehyde **10** might provide the α-addition product for steric reasons.[24] The results are shown in Table 1. Addition of a prenyl group was first attempted with prenylmagnesium bromide (Table 1, entry 1). However, γ-addition product **11** was found to be generated solely in 62% yield. After several experiments, the desired α-addition product **12** was found to be produced with prenylzinc bromide,[25] but in only 14% yield, with the major product still being the γ-addition product **11** (Table 1, entry 2, 55% yield). As shown in Table 1, entry 3, prenylbarium bromide,[23] which is an excellent α-addition reagent, caused only decomposition even at –78 °C.

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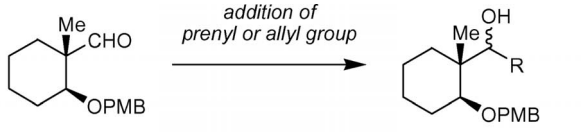
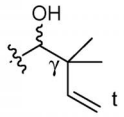
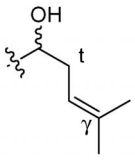
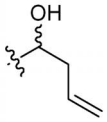
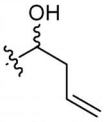
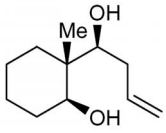
Table 1. Model study for the introduction of an alkenyl group at the C11 position.

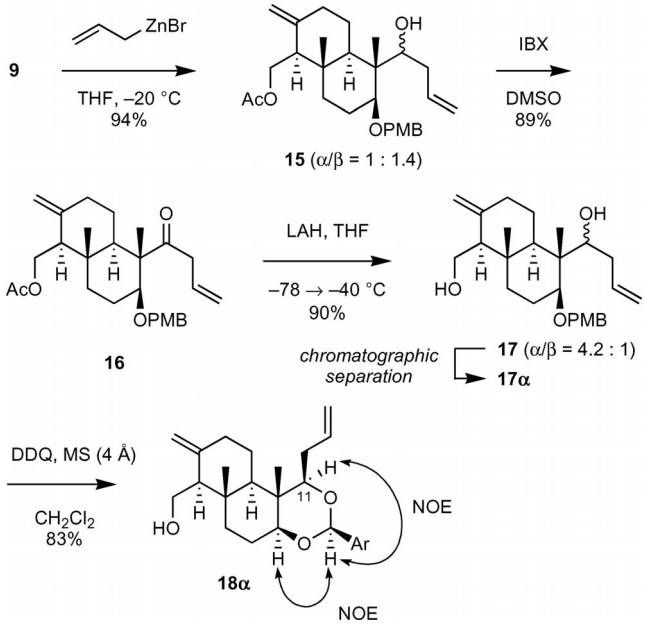


10 11–14

Entry	Reagents and conditions	Results
1	prenylmagnesium bromide, THF, –78 °C	 **11** (62%)
2	prenylzinc bromide, THF, –78 °C → r.t.	**11** (55%) +  **12** (14%)
3	prenylbarium bromide, THF, –78 °C	decomposition
4	allylmagnesium bromide, THF, 0 °C	 **13** (91%, α/β = 1.4 : 1)
5	allylzinc bromide, THF, 0 °C	 **13** (82%, α/β = 1 : 2.2)
6	allyltrimethylsilane, $SnCl_4$, CH_2Cl_2, –78 °C	 **14** (67%)

Considering the difficulties described above, we then explored a two-step procedure for prenylation; namely, allyl group addition followed by cross-metathesis. Thus, treatment of **10** with allylmagnesium bromide at 0 °C gave the adduct **13** in 91% yield as an inseparable, diastereomeric mixture (Table 1, entry 4). By extensive structural analysis of *p*-methoxybenzylidene acetal derivatives (see the Supporting Information), the desired α-alcohol was shown to be generated in preference to the β-alcohol (α/β = 1.4:1) in this reaction. Other allylation reagents were also examined as follows. When allylzinc bromide was employed, the α-diastereoselectivity was decreased (Table 1, entry 5, α/β = 1:2.2). Reaction with allyltrimethylsilane in the presence of $SnCl_4$ completely controlled the diastereoselectivity, giving rise to the undesired β-alcohol in 67% yield (Table 1, entry 6). We thus decided to further explore the two-step procedure with aldehyde **9** to generate the DE-ring fragment of terpendole E.

Introduction of an allyl side chain and establishing the required C11–hydroxy stereochemistry were accomplished as shown in Scheme 3. Here, we employed allylzinc bromide for reaction with aldehyde **9** because it did not cause decomposition of the acetyl protecting group. As expected from Table 1 (entry 5), the reaction proceeded quite smoothly in THF to give alcohol **15** with unfavorable diastereoselectivity (α/β = 1:1.4). Enrichment of the desired α-alcohol was next studied. We anticipated that an oxidation–reduction sequence should facilitate the process by giving an identical diastereoselectivity to that observed in the addition of allylzinc bromide (**9**→**15**). Indeed, oxidation of alcohol **15** with 2-iodoxybenzoic acid (IBX) and dimethyl sulfoxide (DMSO),[26] followed by reduction of the resulting carbonyl group in **16** with lithium aluminum hydride (LAH), successfully delivered diol **17** (75%, three steps from **9**) with acceptable diastereoselectivity (α/β = 4.2:1). The major product **17α** was separated and subjected to cyclic acetal formation to confirm the stereochemistry at C-11. Thus, when **17α** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and molecular sieves (4 Å),[27] 4-methoxybenzylidene acetal **18α** was cleanly obtained in 83% yield. NOESY spectra of **18α** showed that the stereochemistry at C-11 position was identical with that of the natural product, as shown in Scheme 3. The minor diol **17β** was also converted into the diastereomer **18β** for characterization (see the Exp. Section).



Scheme 3. Stereoselective introduction of an allyl group in the C11 position; Ar = *p*-methoxyphenyl.

Synthesis of the desired DEF-ring terpenoid fragment of terpendole E from **17α** was further studied as shown in Scheme 4. Diol **17α** was first protected by acetyl groups [Ac_2O, pyridine, 4-(dimethylamino)pyridine (DMAP)] to

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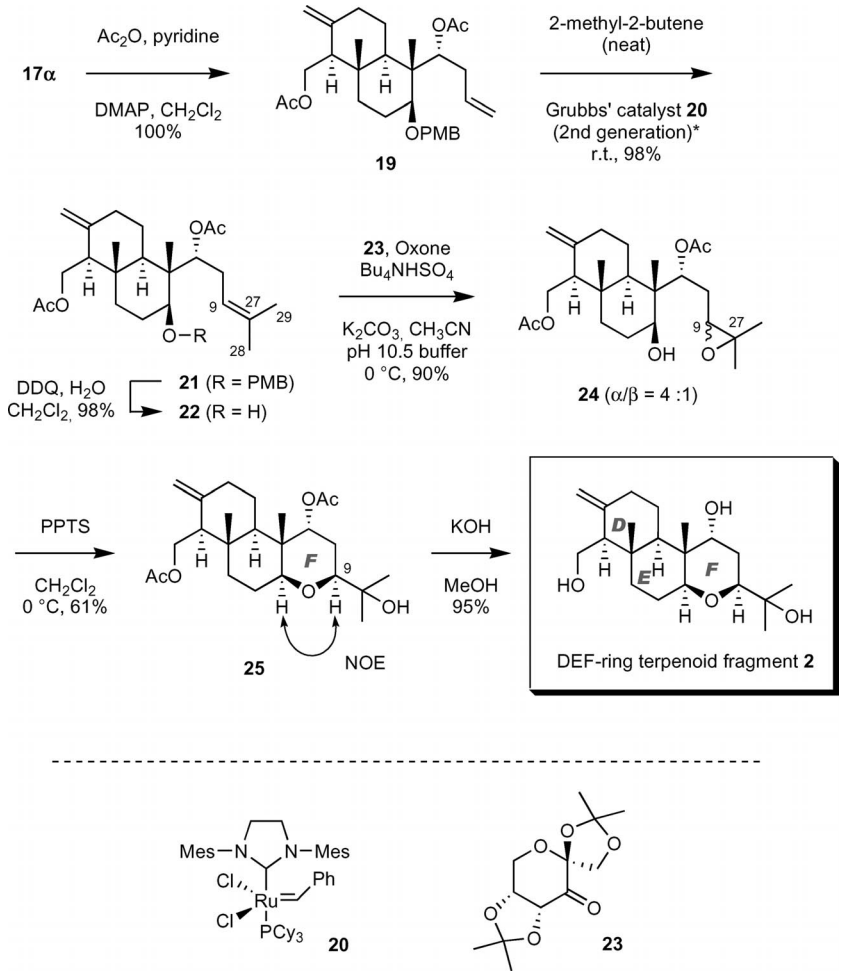

Scheme 4. Synthesis of the DEF-ring fragment **2**.

give diacetate **19** in 100% yield, which, in turn, was subjected to a cross-metathesis reaction with 2-methyl-2-butene in the presence of the Grubbs' catalyst **20** (second generation)[28] to introduce 28,29-dimethyl groups successfully in 98% yield.[29] Deprotection of the PMB ether was then effected by DDQ in H_2O and CH_2Cl_2,[30] and the trisubstituted C9–C27 olefin was selectively epoxidized by Shi's asymmetric reaction[31,32] to generate monoepoxide **24** in good yield (90%).[33] Epoxide **24** was obtained as an inseparable mixture of two diastereomers (4:1 ratio), and the major product was tentatively assigned as the desired α-isomer on the basis of Shi's empirical rule.[32] The F-ring tetrahydropyran was next constructed by pyridinium *p*-toluenesulfonate (PPTS) catalyzed epoxide ring opening in CH_2Cl_2 at 0 °C to give **25** in 61% yield. From NOESY as well as $^nJ_{H,H}$ analyses, **25** was shown to have the desired stereochemistry, which was identical with that of the natural product, thus validating the stereochemical assignment of **24** based on Shi's empirical rule. The β-isomer of **24**, which is expected to give the thermodynamically disfavored C9-*epi*-**25** upon cyclization, was recovered intact (14%) in this reaction. Finally, the two acetyl groups were removed by alkaline methanolysis to furnish the desired DEF-ring terpenoid fragment **2** (95%).

In vivo biological activity of the DEF-ring terpenoid fragment **2** was then investigated by evaluation of inhibitory activity on (1) the growth of five human cancer cell lines (HL-60, K562, tsFT210, HT1080, HeLa), and (2) the cell cycle progression of K562 cells.[6] In all assay systems, however, **2** was biologically inactive. The result indicates that attachment of the left-hand moiety (the A-, B-, or C-ring) to **2** is necessary for the Eg5 inhibitory activity.

Conclusions

We have developed a stereoselective synthetic route to the DEF-ring fragment of the Eg5 antagonist terpendole E (**1**). The overall yield from farnesyl acetate (**3**) was 2.3% over 15 steps. Several cell-based assays, performed using **2**, indicated that the DEF-ring fragment is not capable of inhibiting cell growth and cell cycle progression. Further synthetic studies toward the total synthesis of terpendole E as well as studies on structure–activity relationships are underway in these laboratories.

Experimental Section

General Methods: Details of the experimental techniques and the apparatus are summarized in our previous paper.[34] The purity of

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all purified products was assessed to be >95% by inspection of ^1H and ^{13}C NMR spectra, unless specified otherwise.

Bicyclic Alcohol 6: A mixture of Cp_2TiCl_2 (205 mg, 0.500 mmol) and Zn dust (262 mg, 4.00 mmol) in strictly deoxygenated THF (3.0 mL) was stirred at r.t. for 15 min, at which point the red solution turned green. The green Ti^{III} solution was slowly added by using a cannula to a solution of the epoxide **5** (205.3 mg, 0.500 mmol) in THF (10 mL). The reaction mixture was stirred at r.t. for 1 h before it was quenched with hydrochloric acid (1 M, 5 mL). The mixture was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel; EtOAc/hexanes) gave the bicyclic alcohol **6** (84.5 mg, 41%) as a colorless oil. Chromatographic and spectroscopic data were identical with those of racemic compound reported previously.[14] $[\alpha]_D^{24}$ = +5.2 (*c* = 0.115, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.85 (br. s, 1 H), 4.52 (br. s, 1 H), 4.30 (dd, *J* = 11.5, 4.0 Hz, 1 H), 4.17 (dd, *J* = 11.5, 9.5 Hz, 1 H), 3.65–3.61 (m, 2 H), 3.41 (br. s, 1 H), 3.33 (d, *J* = 9.0 Hz, 1 H), 2.37 (m, 1 H), 2.03–1.96 (m, 2 H), 2.00 (s, 3 H), 1.76–1.66 (m, 2 H), 1.50–1.31 (m, 3 H), 1.25 (dd, *J* = 12.0, 3.0 Hz, 1 H), 0.89 (s, 9 H), 0.83 (s, 3 H), 0.78 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm.

PMB Ether 7: To a solution of the bicyclic alcohol **6** (476 mg, 1.16 mmol) and *p*-methoxybenzyl trichloroacetimidate (89.4 mg, 2.50 mmol) in toluene (6.0 mL) at r.t., was added $La(OTf)_3$ (34.0 mg, 0.0580 mmol). The reaction mixture was stirred at r.t. for 45 min before it was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel; EtOAc/hexanes, 1:15→1:10) gave the PMB ether **7** as a colorless oil. $[\alpha]_D^{25}$ = +12.0 (*c* = 0.125, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2934, 2856, 1735, 1513, 1249 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 7.9 Hz, 2 H), 6.84 (d, *J* = 7.9 Hz, 2 H), 4.85 (br. s, 1 H), 4.52 (d, *J* = 10.7 Hz, 1 H), 4.50 (br. s, 1 H), 4.34 (d, *J* = 10.7 Hz, 1 H), 4.31 (dd, *J* = 11.6, 3.2 Hz, 1 H), 4.18 (dd, *J* = 10.7, 10.4 Hz, 1 H), 3.79 (s, 3 H), 3.52 (d, *J* = 9.7 Hz, 1 H), 3.46 (dd, *J* = 11.9, 4.3 Hz, 1 H), 3.18 (d, *J* = 9.7 Hz, 1 H), 2.37 (br. d, *J* = 12.9 Hz, 1 H), 2.03–1.99 (m, 2 H), 2.02 (s, 3 H), 1.84 (m, 1 H), 1.74 (br. d, *J* = 12.9 Hz, 1 H), 1.68 (br. d, *J* = 11.9 Hz, 1 H), 1.57–1.52 (m, 2 H), 1.35–1.22 (m, 2 H), 0.89 (s, 9 H), 0.76 (s, 3 H), 0.64 (s, 3 H), 0.02 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.4, 159.1, 146.4, 130.4, 128.8 (×2), 113.6 (×2), 107.4, 78.8, 71.3, 64.0, 61.5, 55.2, 54.6, 45.8, 43.3, 38.3, 37.2, 36.8, 25.9 (×2), 23.1, 22.8, 21.1, 18.1, 15.5, 13.0, –5.4 (×2) ppm. HRMS (ESI): calcd. for $C_{31}H_{51}O_5Si$ $[M + H]^+$ 531.3500; found 531.3503.

Alcohol 8: To a solution of the PMB ether **7** obtained above, in THF (8.0 mL) at r.t., was added TBAF (1.0 M in THF, 1.51 mL, 1.51 mmol). The reaction mixture was warmed to 50 °C and stirred at the same temperature overnight before it was quenched with hydrochloric acid (1 M, 5 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:4→1:2) gave the alcohol **8** (333 mg, 69% over two steps from **6**) as a colorless oil. $[\alpha]_D^{20}$ = +66.3 (*c* = 0.66, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3456 (br), 2936, 1735, 1513, 1248, 1035 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 4.84 (s, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.51 (s, 1 H), 4.35–4.29 (m, 1 H), 4.15 (dd, *J* = 11.0, 9.0 Hz, 1 H), 3.78 (s, 3 H), 3.45 (d, *J* = 10.5 Hz, 1 H), 3.32 (dd, *J* = 11.5, 4.5 Hz, 1 H), 3.22 (d, *J* = 10.5 Hz, 1 H), 2.86 (d, *J* = 13.5 Hz, 1 H), 2.05–1.97 (m, 2 H), 2.00 (s, 3 H), 1.94 (dd, *J* = 13.0, 3.5 Hz, 1 H), 1.78 (d, *J* = 13.0 Hz, 1 H), 1.65–1.48 (m, 2 H), 1.42–1.22 (m, 4 H), 0.78 (s, 3 H), 0.74 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 159.2, 146.1, 130.6, 129.5 (×2), 113.9 (×2), 107.5, 79.6, 69.8, 67.3, 61.4, 47.1, 42.6, 38.4, 37.0, 36.5, 23.0, 22.2, 21.1, 15.6, 12.4 ppm. HRMS (FAB): calcd. for $C_{25}H_{36}O_5Na$ $[M + Na]^+$ 439.2460; found 439.2468.

Aldehyde 9: To a solution of $(COCl)_2$ (0.0432 mL, 0.504 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C, was added a solution of DMSO (0.447 mL, 0.672 mmol) in CH_2Cl_2 (1.0 mL). The resultant mixture was stirred at the same temperature for 1 h. To the mixture was added a solution of the alcohol **8** (70.2 mg, 0.168 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C. After being stirred for 30 min, Et_3N (0.141 mL, 1.01 mmol) was added to the mixture, which was stirred for 30 min before the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:5→1:4) gave the aldehyde **9** (62.4 mg, 88%) as a colorless oil. $[\alpha]_D^{20}$ = +55.0 (*c* 0.83, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2932, 2805, 1733, 1513, 1247, 1033 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.21 (s, 1 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 4.86 (s, 1 H), 4.55 (s, 1 H), 4.47 (d, *J* = 11.5 Hz, 1 H), 4.32 (dd, *J* = 11.5, 4.0 Hz, 1 H), 4.28 (d, *J* = 11.5 Hz, 1 H), 4.16 (dd, *J* = 11.5, 8.0 Hz, 1 H), 3.78 (s, 3 H), 3.50 (dd, *J* = 11.5, 4.5 Hz, 1 H), 2.32 (br. d, *J* = 13.0 Hz, 1 H), 2.05 (br. d, *J* = 6.0 Hz, 1 H), 2.02–1.94 (m, 2 H), 2.00 (s, 3 H), 1.83 (br. d, *J* = 14.0 Hz, 1 H), 1.62–1.50 (m, 2 H), 1.45 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1 H), 1.36 (ddd, *J* = 13.0, 13.0, 3.0 Hz, 1 H), 1.13–1.05 (m, 1 H), 1.09 (s, 3 H), 0.79 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.4, 171.2, 159.1, 145.2, 130.2, 129.1 (×2), 113.7 (×2), 108.5, 78.6, 70.0, 61.1, 55.2, 55.0, 54.2, 46.9, 37.8, 36.7, 36.3, 24.9, 22.1, 21.0, 15.3, 9.9 ppm. HRMS (FAB): calcd. for $C_{25}H_{34}O_5Na$ $[M + Na]^+$ 437.2299; found 437.2304.

Aldehyde 10: Synthesized from cyclohexanone in six steps including: (1) formylation,[35] (2) methylation, (3) LAH-mediated reduction, (4) *p*-methoxybenzylidene acetal formation, (5) DIBA-H mediated reduction of the acetal, and (6) Parikh–Doering oxidation.[36] Aldehyde **10** was obtained as a colorless oil. IR (film): $\tilde{\nu}$ = 2936, 2861, 1725, 1513, 1247, 1087 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.32 (d, *J* = 11.5 Hz, 1 H), 3.78 (s, 3 H), 3.59 (dd, *J* = 9.5, 4.0 Hz, 1 H), 1.84 (m, 1 H), 1.72 (m, 1 H), 1.58–1.35 (m, 5 H), 1.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.4, 159.0, 130.6, 129.0 (×2), 113.6 (×2), 77.5, 70.1, 55.2, 51.2, 30.8, 25.6, 23.1, 20.6, 13.7 ppm. HRMS (FAB): calcd. for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ 285.1461; found 285.1467.

Reaction of Aldehyde 10 with Prenylzinc Bromide: (Table 1, entry 2). To a stirred solution of the aldehyde **10** (37.5 mg, 0.143 mmol) in THF (1.0 mL) at –78 °C, was added prenylzinc bromide[25] (0.4 M in THF, 0.72 mL, 0.286 mmol). After stirring for 30 min, the mixture was warmed to r.t. over 75 min. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (2 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) gave an inseparable mixture of the adducts **11** and **12** (4:1, 33.0 mg, 69%) as a colorless oil. Data for γ adduct **11**: IR (film, as a 4:1 mixture of **11** and **12**): $\tilde{\nu}$ = 3450, 2933, 2863, 1610, 1513, 1245, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, selected): δ = 7.24 (d, *J* = 8.3 Hz, 2

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H), 6.86 (d, J = 8.3 Hz, 2 H), 6.01 (dd, J = 17.6, 10.9 Hz, 1 H), 4.94 (dd, J = 17.6, 1.3 Hz, 1 H), 4.90 (dd, J = 10.9, 1.3 Hz, 1 H), 4.54 (d, J = 11.4 Hz, 1 H), 4.29 (d, J = 11.4 Hz, 1 H), 3.79 (s, 3 H), 3.75 (dd, J = 11.4, 4.5 Hz, 1 H), 3.25 (d, J = 6.4 Hz, 1 H), 2.69 (d, J = 7.1 Hz, 1 H), 1.91 (m, 1 H), 1.71–1.65 (m, 2 H), 1.55 (m, 1 H), 1.46–1.26 (m, 4 H), 1.10 (s, 3 H), 1.09 (s, 3 H), 1.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, selected): δ = 159.0, 147.6, 131.0, 129.1 (×2), 113.7 (×2), 109.8, 83.3, 80.3, 69.3, 55.2, 43.4, 41.9, 33.0, 28.1, 25.7, 25.0, 24.3, 21.0, 17.9 ppm. HRMS (ESI, as a 4:1 mixture of **11** and **12**): calcd. for $C_{21}H_{33}O_3$ $[M + H]^+$ 333.2424; found 333.2418. Data for α adduct **12**: IR (film, as a 4:1 mixture of **11** and **12**): $\tilde{\nu}$ = 3450, 2933, 2863, 1610, 1513, 1245, 1036 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, selected): δ = 7.24 (d, J = 8.3 Hz, 2 H), 6.86 (d, J = 8.3 Hz, 2 H), 5.23 (br. t, J = 6.4 Hz, 1 H), 4.54 (d, J = 11.4 Hz, 1 H), 4.34 (d, J = 11.4 Hz, 1 H), 3.78 (s, 3 H), 3.57 (dd, J = 11.4, 4.3 Hz, 1 H), 3.40 (br. d, J = 10.0 Hz, 1 H), 2.15 (m, 1 H), 2.01–1.87 (m, 2 H), 1.71 (s, 3 H), 1.71–1.65 (m, 2 H), 1.59 (s, 3 H), 1.46–1.26 (m, 6 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, selected): δ = 159.0, 133.6, 131.0, 129.2 (×2), 122.4, 113.8 (×2), 79.2, 77.2, 69.9, 55.2, 44.8, 31.3, 30.1, 25.9, 25.9, 24.5, 21.1, 17.9, 15.6 ppm. HRMS (ESI, as a 4:1 mixture of **11** and **12**): calcd. for $C_{21}H_{33}O_3$ $[M + H]^+$ 333.2424; found 333.2418.

Alcohol 13: (Table 1, entry 4). To a stirred solution of the aldehyde **10** (19.0 mg, 0.0724 mmol) in THF (0.72 mL) at 0 °C, was added allylmagnesium bromide (1.0 M in Et_2O, 0.145 mL, 0.145 mmol). After stirring for 30 min, saturated aqueous NH_4Cl (3 mL) was introduced and the mixture was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (3 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) gave the alcohol **13** (α/β = 1.4:1, 20.1 mg, 91%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3435, 2936, 2862, 1613, 1514, 1249 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, selected for the major isomer): δ = 7.21 (d, J = 10.3 Hz, 2 H), 6.83 (d, J = 10.3 Hz, 2 H), 5.89 (m, 1 H), 5.08–5.02 (m, 2 H), 4.57 (d, J = 11.0 Hz, 1 H), 4.33 (d, J = 11.0 Hz, 1 H), 3.77 (s, 3 H), 3.56 (m, 1 H), 3.37 (dd, J = 11.0, 4.9 Hz, 1 H), 2.21 (dd, J = 12.2, 5.6 Hz, 1 H), 2.07–1.98 (m, 2 H), 1.79–1.69 (m, 2 H), 1.49–1.36 (m, 3 H), 1.20–1.10 (m, 1 H), 1.01–0.94 (m, 1 H), 0.97 (s, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, selected for the minor isomer): δ = 7.24 (d, J = 10.3 Hz, 2 H), 6.86 (d, J = 10.3 Hz, 2 H), 5.89 (m, 1 H), 5.08–5.02 (m, 2 H), 4.56 (d, J = 11.0 Hz, 1 H), 4.33 (d, J = 11.0 Hz, 1 H), 3.78 (s, 3 H), 3.56 (m, 1 H), 3.44 (br. d, J = 10.4 Hz, 1 H), 2.30 (dd, J = 14.0, 6.2 Hz, 1 H), 2.03–1.91 (m, 2 H), 1.79–1.69 (m, 2 H), 1.49–1.36 (m, 3 H), 1.20–1.10 (m, 1 H), 1.01–0.94 (m, 1 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, selected for the major isomer): δ = 159.1, 137.0, 129.8, 129.3 (×2), 116.0, 113.8 (×2), 86.8, 79.0, 69.5, 55.2, 41.4, 35.5, 34.1, 25.5, 24.4, 21.0, 10.7 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, selected for the minor isomer): δ = 159.1, 137.2, 130.8, 129.4 (×2), 116.6, 113.7 (×2), 81.4, 76.5, 69.7, 55.2, 41.9, 36.0, 34.1, 25.7, 24.4, 21.0, 15.6 ppm. HRMS (ESI): calcd. for $C_{19}H_{29}O_3$ $[M + H]^+$ 305.2111; found 305.2109.

Diol 14: (Table 1, entry 6). To a stirred solution of the aldehyde **10** (15.4 mg, 0.0582 mmol) in CH_2Cl_2 at –78 °C, was added $SnCl_4$ (1.0 M in CH_2Cl_2, 0.058 mL, 0.0582 mmol). After 5 min, allyltrimethylsilane (0.0139 mL, 0.0873 mmol) was added and stirring was continued for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ (3 mL) and extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (3 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) gave the diastereomerically pure diol **14** (7.2 mg, 67%) as a colorless solid. IR (KBr): $\tilde{\nu}$ = 3292, 2935, 2862, 1432, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (m, 1 H), 5.18 (br. s, 1 H), 5.13 (d, J = 9.6 Hz, 1 H), 3.58 (dd, J = 11.2, 4.3 Hz, 1 H), 3.49 (dd, J = 10.6, 2.1 Hz, 1 H), 2.35 (m, 1 H), 2.00 (m, 1 H), 1.72–1.66 (m, 2 H), 1.49–1.13 (m, 5 H), 0.92 (s, 3 H), 0.92 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 118.7, 81.5, 78.8, 41.1, 35.7, 34.1, 30.1, 24.6, 20.9, 9.6 ppm. HRMS (ESI): calcd. for $C_{11}H_{21}O_2$ $[M + H]^+$ 185.1536; found 185.1540.

β,γ-Unsaturated Ketone 16: To a solution of the aldehyde **9** (30.3 mg, 0.0731 mmol) in THF (1.5 mL) at –20 °C, was added allylzinc bromide (0.50 M in THF, 0.292 mL, 0.146 mmol). After stirring at –20 °C for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:10→1:5) gave the homoallylic alcohol **15** (31.4 mg, 94%, dr = 1:1.4) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 6.88–6.84 (m, 2 H), 5.94 (m, ca. 0.4 H, α-isomer), 5.70 (m, ca. 0.6 H, β-isomer), 5.09–4.99 (m, 2 H), 4.84–4.83 (m, 1 H), 4.60–4.12 (m, 5 H), 3.79 (s, ca. 1.2 H, α-isomer), 3.78 (s, ca. 1.8 H, β-isomer), 3.67–3.30 (m, 2 H), 2.36–1.74 (m, 7 H), 2.03 (s, ca. 1.2 H, α-isomer), 2.00 (s, ca. 1.8 H, β-isomer), 1.60–1.50 (m, 1 H), 1.44–1.24 (m, 3 H), 1.11 (s, ca. 1.2 H, α-isomer), 0.94 (s, ca. 1.8 H, β-isomer), 0.81 (s, ca. 1.2 H, α-isomer), 0.80 (s, ca. 1.8 H, β-isomer) ppm. HRMS (ESI): calcd. for $C_{28}H_{41}O_5$ $[M + H]^+$ 457.2949; found 457.2948.

To a solution of the alcohol **15** (50.2 mg, 0.110 mmol) in DMSO (1.0 mL) at r.t., was added IBX (62.9 mg, 0.220 mmol). The reaction mixture was stirred at r.t. overnight before being diluted with EtOAc (5 mL). The mixture was quenched with saturated aqueous Na_2SO_3 (3 mL), the mixture was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:10) gave the ketone **16** (44.6 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ = +33.5 (c = 0.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2936, 2862, 1732, 1644, 1265 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.12 (d, J = 9.0 Hz, 2 H), 6.82 (d, J = 8.5 Hz, 2 H), 5.95–5.85 (m, 1 H), 5.11 (dd, J = 10.0, 1.0 Hz, 1 H), 5.00 (dd, J = 17.0, 1.0 Hz, 1 H), 4.83 (s, 1 H), 4.52 (s, 1 H), 4.44 (d, J = 11.0 Hz, 1 H), 4.31 (dd, J = 11.0, 4.0 Hz, 1 H), 4.19 (d, J = 11.0 Hz, 1 H), 4.16 (dd, J = 11.0, 9.0 Hz, 1 H), 3.77 (s, 3 H), 3.63 (dd, J = 11.5, 4.0 Hz, 1 H), 3.31 (dd, J = 18.0, 6.5 Hz, 1 H), 3.11 (dd, J = 18.0, 6.5 Hz, 1 H), 2.28 (br. d, J = 13.0 Hz, 1 H), 2.07 (br. d, J = 5.5 Hz, 1 H), 2.03–1.85 (m, 3 H), 2.01 (s, 3 H), 1.78 (d, J = 13.5 Hz, 1 H), 1.56–1.37 (m, 3 H), 1.22 (s, 3 H), 1.04–0.97 (m, 1 H), 0.77 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.3, 171.3, 159.0, 145.5, 131.7, 130.5, 129.0 (×2), 117.7, 113.6 (×2), 108.0, 83.1, 70.4, 61.2, 57.3, 55.2, 54.4, 50.0, 45.0, 38.1, 36.8, 36.3, 25.3, 22.7, 21.0, 15.5, 11.6 ppm. HRMS (FAB): calcd. for $C_{28}H_{36}O_5Na$ $[M + Na]^+$ 477.2612; found 477.2617.

Diols 17α and 17β: To a solution of LAH (3.5 mg, 0.092 mmol) in THF (1.0 mL) at –78 °C, was added a solution of the ketone **16** (13.9 mg, 0.0306 mmol) in THF (1.0 mL). The reaction mixture was stirred at –40 °C for 6 h then quenched with H_2O (1 mL). The mixture was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with brine (3 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:15→1:10) gave the desired diol **17α** (9.3 mg, 73%) and

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the undesired diastereomer **17β** (2.2 mg, 17%) as colorless oils. Data for **17α**: $[\alpha]_D^{20}$ = +35.5 (*c* = 0.62, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3428, 2938, 1613, 1513, 1249, 1065, 1033 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.75–5.65 (m, 1 H), 5.11–5.04 (m, 2 H), 4.92 (s, 1 H), 4.62 (s, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.29 (d, *J* = 11.5 Hz, 1 H), 3.84–3.73 (m, 2 H), 3.78 (s, 3 H), 3.65 (d, *J* = 11.0 Hz, 1 H), 3.32 (dd, *J* = 11.5, 4.5 Hz, 1 H), 2.41–2.33 (m, 2 H), 2.10–1.93 (m, 4 H), 1.70 (d, *J* = 13.5 Hz, 1 H), 1.62–1.48 (m, 3 H), 1.46–1.36 (m, 2 H), 1.32–1.20 (m, 2 H), 0.93 (s, 3 H), 0.77 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 147.3, 137.4, 130.9, 129.1 (×2), 117.6, 113.7 (×2), 106.4, 78.6, 74.7, 69.7, 59.0, 58.7, 55.2, 48.0, 45.3, 38.8, 37.4, 37.1, 36.3, 24.3, 22.9, 15.8, 13.2 ppm. HRMS (FAB): calcd. for $C_{26}H_{38}O_4Na$ $[M + Na]^+$ 437.2668; found 437.2672.

Data for Undesired 17β: $[\alpha]_D^{25}$ = +22.9 (*c* = 0.15, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3433, 3054, 2942, 1514, 1265 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.0 Hz, 2 H), 6.86 (d, *J* = 8.0 Hz, 2 H), 5.99–5.89 (m, 1 H), 5.02 (d, *J* = 9.5 Hz, 1 H), 5.01 (d, *J* = 18.0 Hz, 1 H), 4.63 (s, 1 H), 4.59 (d, *J* = 11.0 Hz, 1 H), 4.35 (d, *J* = 11.0 Hz, 1 H), 4.21 (d, *J* = 8.5 Hz, 1 H), 3.83–3.72 (m, 2 H), 3.78 (s, 3 H), 3.61 (dd, *J* = 11.5, 4.0 Hz, 1 H), 3.51 (dd, *J* = 8.5, 7.5 Hz, 1 H), 2.30 (d, *J* = 13.5 Hz, 1 H), 2.24 (dd, *J* = 14.0, 7.5 Hz, 1 H), 2.04–1.87 (m, 4 H), 1.74 (d, *J* = 13.0 Hz, 1 H), 1.63–1.49 (m, 2 H), 1.48–1.22 (m, 4 H), 1.11 (s, 3 H), 0.79 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 146.5, 137.2, 129.8 (×2), 129.3, 115.7, 113.9 (×2), 106.8, 81.2, 77.9, 69.1, 59.2, 58.6, 55.2, 49.3, 44.4, 38.8, 37.1, 36.5, 36.4, 22.9, 22.0, 16.1, 13.3 ppm. HRMS (FAB): calcd. for $C_{26}H_{38}O_4Na$ $[M + Na]^+$ 437.2668; found 437.2672.

***p*-Methoxybenzylidene Acetal 18α:** To a solution of the diol **17α** (14.9 mg, 0.0326 mmol) in CH_2Cl_2 (1.0 mL), was added powdered 4 Å MS (45 mg). After stirring at r.t. for 30 min, the mixture was cooled to 0 °C, and DDQ (8.9 mg, 0.039 mmol) was added. The resultant mixture was stirred at 0 °C for 1.5 h then quenched with saturated aqueous $NaHCO_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) gave the acetal **18α** (12.4 mg, 83%) as a colorless oil. NOE experiments indicated that the stereochemistry at C-11 was identical to that of the natural product. Data for *p*-methoxybenzylidene acetal **18α**: $[\alpha]_D^{20}$ = +22.6 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3434, 2940, 2852, 1615, 1517, 1249 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.5 Hz, 2 H), 6.86 (d, *J* = 8.0 Hz, 2 H), 6.05–5.85 (m, 1 H), 5.51 (s, 1 H), 5.03 (d, *J* = 17.5 Hz, 1 H), 4.98 (d, *J* = 10.0 Hz, 1 H), 4.94 (s, 1 H), 4.65 (s, 1 H), 3.86–3.72 (m, 2 H), 3.77 (s, 3 H), 3.51 (dd, *J* = 8.0, 2.5 Hz, 1 H), 3.46 (dd, *J* = 11.5, 3.5 Hz, 1 H), 2.53 (dd, *J* = 13.5, 8.0 Hz, 1 H), 2.40 (d, *J* = 13.0 Hz, 1 H), 2.31–2.23 (m, 1 H), 1.88–165 (m, 4 H), 1.60–1.43 (m, 2 H), 1.39 (br. s, 1 H), 1.28 (dd, *J* = 11.5, 3.0 Hz, 1 H), 1.05 (s, 3 H), 0.79 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.8, 146.5, 136.4, 131.3, 127.4 (×2), 115.6, 113.5 (×2), 106.7, 101.3, 87.2, 86.1, 58.9, 58.6, 55.2, 50.7, 41.5, 39.8, 38.1, 37.2, 37.1, 25.9, 24.1, 16.9, 10.4 ppm. HRMS (FAB): calcd. for $C_{26}H_{36}O_4Na$ $[M + Na]^+$ 435.2506; found 435.2511.

***p*-Methoxybenzylidene Acetal 18β:** To a solution of the diol **17β** (9.9 mg, 0.019 mmol) in CH_2Cl_2 (1.0 mL), was added 4 Å MS (30 mg). The mixture was stirred at r.t. for 30 min and then treated with DDQ (5.5 mg, 0.024 mmol) at 0 °C. The resultant mixture was stirred at 0 °C for 1.5 h then quenched with saturated aqueous $NaHCO_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:3) gave the *p*-methoxybenzylidene acetal **18β** (3.0 mg, 30%) as a colorless solid. No side product was detected in the reaction, and only unreacted diol **17β** (3.2 mg, 32%) was recovered. Data for **18β**: $[\alpha]_D^{24}$ = –15.5 (*c* = 0.165, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3489, 2937, 2879, 1518, 1250 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 7.67 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz 2 H), 5.93 (m, 1 H), 5.76 (s, 1 H), 5.13 (d, *J* = 17.0 Hz, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 4.83 (s, 1 H), 4.58 (s, 1 H), 3.72 (dd, *J* = 12.0, 4.0 Hz, 1 H), 3.66–3.54 (m, 2 H), 3.57 (dd, *J* = 11.5, 5.0 Hz, 1 H), 3.26 (s, 3 H), 2.75 (m, 1 H), 2.12 (dd, *J* = 13.0, 2.0 Hz 1 H), 1.97 (m, 1 H), 1.78–1.62 (m, 4 H), 1.41 (m, 1 H), 1.29 (s, 3 H), 1.24–1.02 (m, 2 H), 1.00–0.88 (m, 3 H), 0.61 (s, 3 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 160.3, 146.9, 135.9, 132.4, 128.2 (×2), 116.2, 113.7 (×2), 107.3, 95.3, 80.6, 78.3, 59.2, 58.5, 54.7, 48.0, 39.5, 38.9, 37.1, 36.8, 30.2, 24.6, 22.8, 16.3, 16.1 ppm. HRMS (FAB): calcd. for $C_{26}H_{36}O_4Na$ $[M + Na]^+$ 435.2506; found 435.2512.

Diacetate 19: To a solution of the diol **17α** (28.7 mg, 0.0692 mmol) in CH_2Cl_2 (1.0 mL) at r.t., were added pyridine (0.0448 mL, 0.554 mmol), Ac_2O (0.0262 mL, 0.277 mmol), and DMAP (0.84 mg, 0.069 mmol). After stirring at 40 °C overnight, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:5) gave the acetate **19** (34.5 mg, 100%) as a colorless oil. $[\alpha]_D^{20}$ = +42.6 (*c* = 0.72, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2933, 2873, 1612, 1513, 1248, 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 5.58–5.48 (m, 1 H), 5.31 (d, *J* = 10.0 Hz, 1 H), 4.94 (d, *J* = 17.0 Hz, 1 H), 4.92 (d, *J* = 8.5 Hz, 1 H), 4.84 (s, 1 H), 4.57 (d, *J* = 11.5 Hz, 1 H), 4.52 (s, 1 H), 4.36–4.30 (m, 2 H), 4.14 (dd, *J* = 11.0, 9.0 Hz, 1 H), 3.78 (s, 3 H), 3.21 (dd, *J* = 11.5, 4.5 Hz, 1 H), 2.37 (dd, *J* = 11.0, 4.0 Hz, 1 H), 2.29–2.22 (m, 1 H), 2.16–2.06 (m, 1 H), 2.03–1.92 (m, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.77 (d, *J* = 11.5 Hz, 1 H), 1.60–1.48 (m, 3 H), 1.43–1.36 (m, 1 H), 1.30–1.18 (m, 2 H), 0.86 (s, 3 H), 0.78 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 170.6, 159.0, 145.9, 135.8, 130.5, 129.4 (×2), 129.1, 116.7, 113.7 (×2), 107.5, 78.5, 69.9, 61.3, 55.2, 54.8, 48.3, 45.7, 38.8, 37.0, 36.3, 35.0, 24.2, 22.6, 21.1 (×2), 15.6, 13.1 ppm. HRMS (FAB): calcd. for $C_{30}H_{42}O_6Na$ $[M + Na]^+$ 521.2879; found 521.2876.

Metathesis Product 21: To a solution of the diene **19** (35.4 mg, 0.0701 mmol) in 2-methyl-2-butene (1.0 mL), was added the second generation Grubbs' catalyst **20** (3.0 mg, 3.5 μmol). After stirring at r.t. overnight, the mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:5) gave the metathesis product **21** (36.1 mg, 98%) as a colorless oil. $[\alpha]_D^{24}$ = +38.8 (*c* = 0.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2933, 1735, 1513, 1246, 1030, 821 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 5.28 (dd, *J* = 10.5, 2.0 Hz, 1 H), 4.90–4.82 (m, 1 H), 4.84 (s, 1 H), 4.58 (d, *J* = 12.0 Hz, 1 H), 4.52 (s, 1 H), 4.37–4.31 (m, 2 H), 4.14 (dd, *J* = 11.0, 9.0 Hz, 1 H), 3.77 (s, 3 H), 3.22 (dd, *J* = 12.0, 4.5 Hz, 1 H), 2.37 (dd, *J* = 13.0, 1.5 Hz, 1 H), 2.24–2.15 (m, 1 H), 2.11–2.04 (m, 1 H), 2.04–1.91 (m, 3 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.77 (d, *J* = 13.0 Hz, 1 H), 1.62 (s, 3 H), 1.60–1.47 (m, 3 H), 1.52 (s, 3 H), 1.46–1.18 (m, 4 H), 0.86 (s, 3 H), 0.78 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 170.5, 159.0, 146.0, 133.2, 131.8, 130.7, 129.2 (×2), 121.2, 113.7 (×2), 107.5, 78.9, 77.8, 70.1, 61.4, 55.2, 54.8, 48.4, 45.7, 38.8, 37.0, 36.4, 28.8, 25.7, 24.4, 21.1, 21.0, 17.7, 15.6, 13.1 ppm. HRMS (FAB): calcd. for $C_{32}H_{46}O_6Na$ $[M + Na]^+$ 549.3187; found 549.3192.

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Alcohol 22: To a solution of the PMB ether **21** (24.9 mg, 0.0473 mmol) in CH_2Cl_2 and H_2O (10:1, 1.1 mL) at 0 °C, was added DDQ (14.0 mg, 0.0615 mmol). After stirring at r.t. for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:4) gave the alcohol **22** (18.8 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ = +26.7 (*c* = 0.80, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3502, 2931, 2360, 1705, 1645, 1241, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.23 (t, *J* = 6.5 Hz, 1 H), 5.03 (t, *J* = 7.0 Hz, 1 H), 4.85 (s, 1 H), 4.52 (s, 1 H), 4.31 (dd, *J* = 11.5, 3.5 Hz, 1 H), 4.16 (dd, *J* = 11.5, 9.0 Hz, 1 H), 3.64–3.56 (m, 1 H), 2.38 (dd, *J* = 13.5, 3.0 Hz, 1 H), 2.31 (dd, *J* = 7.0, 6.5 Hz, 2 H), 2.04–1.95 (m, 2 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.78–1.70 (m, 2 H), 1.68–1.48 (m, 2 H), 1.65 (s, 3 H), 1.60 (s, 3 H), 1.47–1.26 (m, 4 H), 0.83 (s, 3 H), 0.78 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 170.5, 145.8, 133.8, 120.8, 107.6, 77.9, 72.4, 61.3, 54.7, 48.1, 45.8, 38.8, 37.0, 36.5, 28.7, 28.2, 25.7, 24.4, 21.1, 21.0, 17.8, 15.6, 12.1 ppm. HRMS (FAB): calcd. for $C_{24}H_{38}O_5Na$ $[M + Na]^+$ 407.2797; found 407.2799.

Epoxide 24: To a mixture of the diene **22** (23.5 mg, 0.0578 mmol), sodium tetraborate buffer (0.05 M solution in 4×10^{-4} M aqueous Na_2EDTA, 0.58 mL), tetrabutylammonium hydrogen sulfate (0.98 mg, 2.9 μmol), and ketone **23** (14.9 mg, 0.0578 mmol)[31,32] in CH_3CN (1.0 mL) at 0 °C were added a solution of Oxone (35.5 mg, 0.0578 mmol) in aqueous Na_2EDTA (4×10^{-4} M, 1.0 mL) and a solution of K_2CO_3 (143.6 mg, 1.04 mmol) in H_2O (1.0 mL) over 2 h. When the addition was complete, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 1:1) gave the epoxide **24** as an inseparable mixture of diastereomers (22.0 mg, 90%, α/β = 4:1). Epoxide **24** was obtained as a colorless oil. Data for **24**: $[\alpha]_D^{25}$ = –6.0 (*c* = 0.125, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3428, 2938, 1613, 1513, 1249, 1065, 1033 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, selected for the major isomer): δ = 5.41 (dd, *J* = 10.5, 3.0 Hz, 1 H), 4.84 (s, 1 H), 4.52 (s, 1 H), 4.30 (dd, *J* = 11.0, 4.0 Hz, 1 H), 4.15 (dd, *J* = 11.0, 7.5 Hz, 1 H), 3.64–3.56 (m, 1 H), 2.77 (dd, *J* = 7.5, 4.5 Hz, 1 H), 2.37 (dd, *J* = 13.5, 4.0 Hz, 1 H), 2.14–2.04 (m, 1 H), 2.06 (s, 3 H), 2.02–1.86 (m, 2 H), 2.00 (s, 3 H), 1.78–1.54 (m, 4 H), 1.50–1.18 (m, 4 H), 1.25 (s, 3 H), 1.22 (s, 3 H), 0.84 (s, 3 H), 0.78 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, selected for the major isomer): δ = 171.3, 170.2, 14.5.6, 107.7, 75.4, 72.1, 62.6, 61.2, 58.9, 54.7, 48.0, 45.7, 38.8, 36.9, 36.5, 29.9, 24.6, 24.3, 21.1, 21.0, 18.9, 15.5, 12.0 ppm. HRMS (ESI): calcd. for $C_{24}H_{39}O_6$ $[M + H]^+$ 423.2741; found 423.2746.

Tetrahydro-2*H*-pyran 25: To a solution of the epoxide **24** (α/β = 4:1, 15.0 mg, 0.0355 mmol) in CH_2Cl_2 (1.0 mL) at r.t., was added PPTS (1.8 mg, 7.1 μmol). The resultant solution was stirred for 2.5 h then quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 1:1) gave the tetrahydro-2*H*-pyran **25** (9.2 mg, 61%) and unreacted β-epoxide **24β** (2.1 mg, 14%) as colorless oils. Data for **25**: $[\alpha]_D^{25}$ = –10.6 (*c* = 0.035, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2935, 2878, 1698, 1247, 1040 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.90 (s, 1 H), 4.84 (s, 1 H), 4.52 (s, 1 H), 4.32 (dd, *J* = 11.0, 3.5 Hz, 1 H), 4.18 (dd, *J* = 11.0, 9.0 Hz, 1 H), 3.54 (dd, *J* = 11.5, 4.5 Hz, 1 H), 3.40 (dd, *J* = 12.0, 2.5 Hz, 1 H), 2.46 (br. s, 1 H), 2.37 (br. d, *J* = 13.0 Hz, 1 H), 2.10 (s, 3 H), 2.08–2.02 (m, 1 H), 2.01 (s, 3 H), 1.92 (ddd, *J* = 14.0, 12.0, 3.5 Hz, 1 H), 1.86 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1 H), 1.75 (d, *J* = 13.0 Hz, 1 H), 1.68–1.56 (m, 2 H), 1.55–1.38 (m, 4 H), 1.34 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1 H), 1.15 (s, 3 H), 1.10 (s, 3 H), 0.86 (s, 3 H), 0.79 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.3, 170.2, 145.5, 107.9, 79.3, 78.0, 71.9, 71.6, 61.2, 54.9, 46.7, 39.8, 37.1, 36.6, 26.9, 26.1, 24.3, 23.6, 22.1, 21.1, 16.2, 13.3 ppm. HRMS (FAB): calcd. for $C_{24}H_{38}O_6Na$ $[M + Na]^+$ 445.2566; found 445.2565.

DEF-Ring Terpenoid Fragment 2: To a solution of the diacetate **25** (5.9 mg, 0.014 mmol) in MeOH (1.0 mL) at r.t., was added KOH (7.8 mg, 0.14 mmol). After stirring for 1 d, the reaction mixture was concentrated under reduced pressure. The mixture was diluted with CH_2Cl_2 (2 mL) and saturated aqueous NH_4Cl (2 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were washed with brine (3 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, MeOH/$CHCl_3$, 1:20 → 1:10) gave the DEF-ring terpenoid fragment **2** (4.5 mg, 95%) as a white solid. The purity of **2** was assessed to be >98% by inspection of the ^1H and ^{13}C NMR spectra (see the Supporting Information), and **2** was used for biological assays without further purification. Data for **2**: $[\alpha]_D^{20}$ = –32.2 (*c* = 0.85, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3396 (br.), 2935, 1385, 1075, 1054 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 4.88 (s, 1 H, 17a-H), 4.66 (s, 1 H, 17b-H), 3.80 (dd, *J* = 11.0, 4.0 Hz, 1 H, 2a-H), 3.75–3.69 (m, 2 H, 2b-H and 11-H), 3.57–3.49 (m, 2 H, 7-H and 9-H), 2.39 (dd, *J* = 12.5, 3.0 Hz, 1 H, 15-H_{eq}), 2.11 (ddd, *J* = 13.0, 12.5, 4.5 Hz, 1 H, 15-H_{ax}), 1.98–1.88 (m, 2 H, 3-H and 10-H_{ax}), 1.77 (m, 2 H, 5-H_{eq} and 13-H), 1.65 (m, 1 H, 14-H_{eq}), 1.53 (m, 2 H, 6-H_2), 1.51 (ddd, *J* = 14.0, 3.0, 2.5 Hz, 1 H, 10-H_{eq}), 1.35 (m, 2 H, 5-H_{ax} and 14-H_{ax}), 1.16 (s, 3 H, 28-H_3 or 29-H_3), 1.15 (s, 3 H, 28-H_3 or 29-H_3), 0.84 (s, 3 H, 30-H_3), 0.78 (s, 3 H, 26-H_3) ppm. ^{13}C NMR (125 MHz, CD_3OD, 20 °C): δ = 149.1 (16-C), 108.1 (17-C), 81.1 (9-C), 79.4 (7-C), 73.5 (27-C), 71.3 (11-C), 60.8 (3-C), 59.7 (2-C), 48.1 (13-C), 42.5 (12-C), 40.6 (4-C), 39.1 (15-C), 38.9 (5-C), 31.5 (10-C), 26.5 (28-C or 29-C), 26.4 (28-C or 29-C), 26.2 (6-C), 24.0 (14-C), 17.6 (26-C), 15.1 (30-C) ppm. HRMS (FAB): calcd. for $C_{20}H_{34}O_4Na$ $[M + Na]^+$ 361.2355; found 361.2350.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for compounds **3**–**5**, **10**, and other synthetic intermediates, in vivo biological assay data of **2**, and copies of ^1H and ^{13}C NMR spectra of new compounds.

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