Synthetic Studies on a Marine Natural Product, Palmerolide A: Synthesis of C1–C9 and C15–C21 Fragments

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Abstract: An efficient cross metathesis and Pd-catalyzed allylic rearrangement have been successfully used to construct the northern hemisphere of a cytotoxic marine natural product, palmerolide A.

Key words: Grubbs' catalyst, cross metathesis, Pd(II)-catalyzed allylic rearrangement, marine natural product, Mitsunobu reaction

Skin cancer is believed to be the most common type of cancer in the world and studies revealed that exposure to ultraviolet radiation is the main cause for this cancer. In the United States alone about 1 million new cases of some form of skin cancers are observed every year. There are three major types of skin cancers namely basal cell carcinoma, squamous cell carcinoma and melanoma. While the first two types are mild and highly unlikely to spread to other parts of the body, melanoma cancer is known to spread aggressively to other parts of the body. As far as treatment is concerned, basal cell carcinoma and squamous cell carcinoma could be treated by surgery and radiation therapy. However, treatment of melanoma requires chemotherapy as well and found to be a challenging task. So, discovery of a new drug that selectively kills melanoma cells could be of great significance to these patients.

In this connection, isolation[1] of a new macrocyclic polyketide palmerolide A (**1**, Figure 1) from Antarctic tunicate *Synoicum adareanum* by B. J. Baker and co-workers, which shows potent and selective cytotoxicity against melanoma (UACC-62, LC_{50} = 18 nM), is of potential significance. Further biological studies revealed that palmerolide A has been found to inhibit V-ATPase with an IC_{50} of 2 nM.

The structure of palmerolide A was established using high-field NMR and stereochemical studies. This structurally challenging natural product is a 20-membered macrocyclic polyketide bearing a vinyl amide functionality in the side chain and a carbamate moiety, five stereogenic centers and a 1,3-diene system in the core of α,β-unsaturated macrocyclic lactone. In view of its structural complexity and excellent medicinal properties, we developed interest in the synthesis of palmerolide A (**1**), which is yet to succumb to total synthesis. Herein, we describe our initial results on the stereoselective synthesis of the northern hemisphere **2** of palmerolide A.

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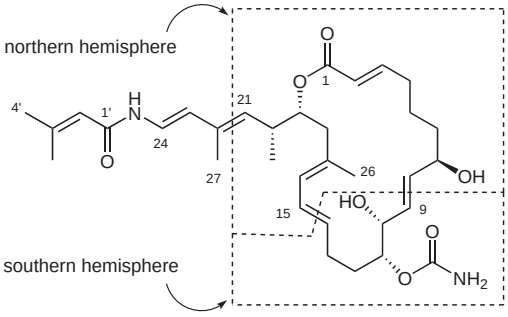
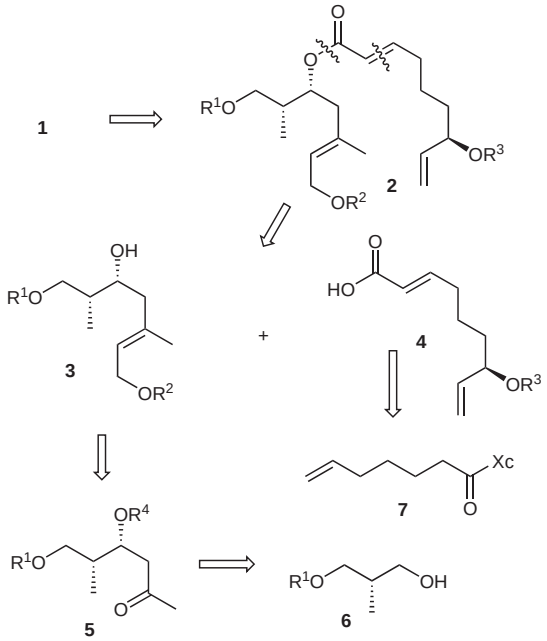


Figure 1 Palmerolide A (**1**)

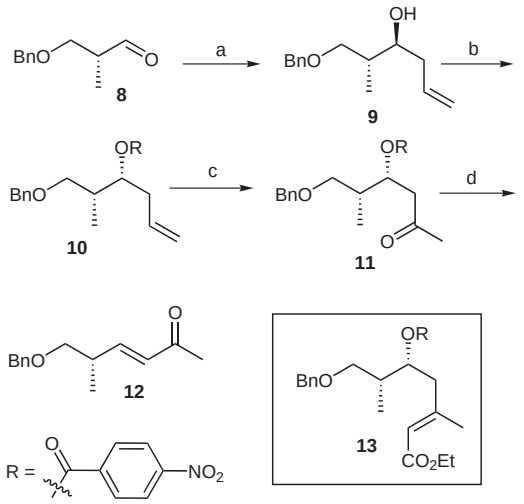
As per our retrosynthetic analysis (Scheme 1), the northern hemisphere **2** of palmerolide A could be easily obtained by the simple esterification of **4** with alcohol **3**. The alcohol **3** could be traced back to the known alcohol **6**[2] via the ketone **5** involving asymmetric allylation as key reaction. The diene acid **4** could be synthesized from **7** involving asymmetric α-hydroxylation and cross metathesis as key reactions.

Our synthesis of the fragment **3** began with the chelation-controlled addition of allyltributylstannane in the presence of stannic chloride to aldehyde **8**, following Keck's



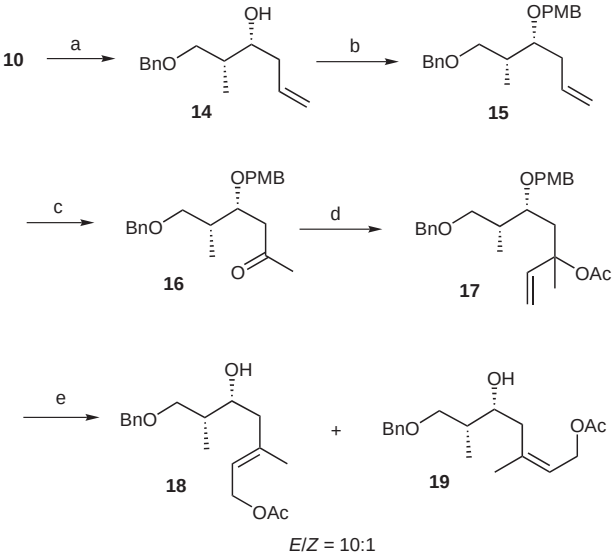
Scheme 1 Retrosynthesis of northern hemisphere of palmerolide A.

protocol,[3] to provide the homoallylic alcohol **9** in 92% de (Scheme 2). To obtain the *syn*-relationship between the methyl and hydroxyl group, Mitsunobu reaction was effectively carried out on the alcohol **9** with *p*-nitrobenzoic acid to afford the ester **10** as a single diastereomer. Using modified Wacker oxidation conditions,[4] **10** with its terminal double bond was converted into methyl ketone **11** in good yield. However, all our attempts like Wittig reaction and the Horner–Wadsworth–Emmons under different conditions to successfully introduce the α,β-unsaturated ester moiety **13** failed and we could obtain only the elimination product **12**.



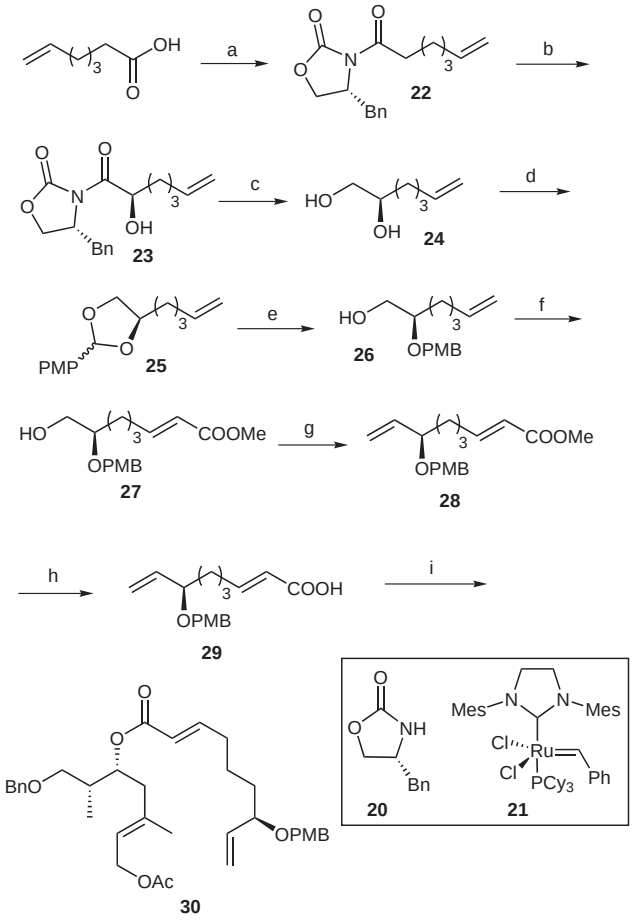
Scheme 2 *Reagents and conditions*: a) allyltributyltin, $SnCl_4$, CH_2Cl_2, –90 °C, 15 min, 89%; b) PPh_3, DIAD, THF, 4-nitrobenzoic acid, r.t., 5 h, 59%; c) $PdCl_2$, O_2, $Cu(OAc)_2{\cdot}H_2O$, dimethylacetamide, r.t., 6 h, 69%; d) condition A: $PPh_3CHCOOEt$, toluene, cat. PhCOOH, reflux, 12 h, 85%; condition B: NaH, THF, $PO(OEt)_2CH_2COOEt$, r.t., 2 h, 54%.

To circumvent this difficulty, we examined the possibility of introducing α,β-unsaturated ester moiety in a stereoselective manner by employing the Pd(II)-catalyzed allylic rearrangement.[5] Thus, the ester **10** was hydrolyzed to afford the alcohol **14** in quantitative yield and subsequently, the hydroxyl group was protected as PMB ether **15** using Yonemitsu procedure[6] from 4-methoxybenzyltrichloroacetimidate in the presence of a catalytic amount of triflic acid (Scheme 3). Then, Wacker oxidation[4] of **15** proceeded smoothly to furnish the ketone **16**, which upon addition of vinyl Grignard reagent provided an inseparable mixture of allylic alcohols, and it was not possible to separate the diastereomeric mixture even after acetylating to **17**. This really did not matter much as when we executed the stereoselective Pd(II)-catalyzed allylic acetate rearrangement, using $PdCl_2(MeCN)_2$ followed by the removal of PMB group,[7] provided a readily separable mixture of alcohol **18** (70%) and its *Z*-isomer **19** (7%) in a ratio of 10:1. The stereochemical assignment of **18** was confirmed by NOE experiment where irradiation of the C16 olefinic proton enhanced the C26 methyl proton signal to only 7%, whereas 16% enhancement was observed for **19**.



Scheme 3 *Reagents and conditions*: a) K_2CO_3, MeOH, r.t., 1 h, 96%; b) 4-methoxybenzyltrichloroacetimidate, cat. TfOH, THF, 0 °C, 10 min, 75%; c) $PdCl_2$, O_2, $Cu(OAc)_2{\cdot}H_2O$, dimethylacetamide, r.t., 6 h, 70%; d) i) vinylmagnesium bromide, THF, 0 °C, 2 h, 84%; ii) Ac_2O, pyridine, cat. DMAP, 50 °C, 12 h, 92%; e) i) $PdCl_2(MeCN)_2$, THF, r.t., 2 h, 87%; ii) DDQ, CH_2Cl_2, pH 7, 0 °C, 30 min, 77%.

After the successful synthesis of the C15–C21 fragment, our next task was to synthesize the C1–C9 fragment (Scheme 4) and for which 6-heptenoic acid was attached to the Evans chiral auxiliary **20** using mixed anhydride approach[8] to yield compound **22**. The key asymmetric α-hydroxylation[9] on **22** using Davis protocol[10] offered compound **23** diastereoselectively in 74% yield (37:1 ratio by HPLC analysis). The chiral auxiliary in compound **23** was reductively removed[11] using $NaBH_4$ to give an inseparable mixture of diol **24** and oxazolidinone **20**. However, formation of oxolane **25** with dimethylacetal anisaldehyde in the presence of a catalytic amount of PPTS followed by reductive cleavage[12] with DIBAL-H paved the way for the clear separation of alcohol **26**. Subsequently, cross metathesis[13] of **26** with methylacrylate using Grubbs' second-generation catalyst **21** afforded the α,β-unsaturated ester **27** in excellent yield (81%) along with a trace amount of *cis*-isomer. Our attempts to carry out the Wittig reaction on the aldehyde, obtained by the oxidation of the primary alcohol **27** using Dess–Martin periodinane,[14] with methyltriphenylphosphoniumbromide using either *n*-BuLi or NaHMDS provided the diene ester **28** in poor yield (15–25%), possibly due to the electrophilic nature of the enoate moiety.[15] However, under 'forced conditions'[16] with potassium *tert*-butoxide the Wittig reaction worked well to provide the desired olefin **28** in higher yield[17] (65% for two steps). Expectedly, saponification of the ester **28** proceeded well to provide the carboxylic acid **29** in 90% yield and this was successfully coupled with the alcohol **18** using DCC condition to furnish the northern hemisphere **30**[18] of palmerolide A in 63% yield.



Scheme 4 *Reagents and conditions*: a) PivCl, Et_3N, THF, LiCl, –10 °C, 2 h, then LiCl, **20**, r.t., 12 h, 88%; b) NaHMDS, THF, –78 °C, (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, 2 min then (±)-CSA, THF, 74%; c) $NaBH_4$, THF, H_2O, r.t., 1 h; d) PPTS, CH_2Cl_2, 4-anisaldehyde dimethyl acetal, r.t., 1 h; e) DIBAL-H, CH_2Cl_2, –20 °C, 1 h, 43% for 3 steps; f) **21**, methyl acrylate, CH_2Cl_2, 40 °C, 4 h, 81%; g) i) Dess–Martin reagent, CH_2Cl_2, 0 °C, r.t., 2 h; ii) $MePPh_3Br$, toluene, KO*t*-Bu, 0 °C to r.t., 30 min, 65% for 2 steps; h) LiOH, THF, MeOH, H_2O, r.t., 2 h, 90%; i) DCC, **18**, DMAP, toluene, r.t., 12 h, 63%.

In conclusion, we have designed and successfully accomplished the synthesis of the northern hemisphere of palmerolide A. This first synthetic effort toward palmerolide A involved two key steps namely Pd(II)-catalyzed allylic rearrangement and cross metathesis to furnish the *E* and *trans* double bonds at C16-C17 and C2-C3, respectively. Synthesis of the southern hemisphere and total synthesis of palmerolide A are underway in our laboratory.

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(7) **Experimental Procedure for Compound 18**
To a solution of acetate **17** (230 mg, 0.54 mmol) in anhyd THF (10 mL) was added $PdCl_2(MeCN)_2$ (6 mg, 4 mol%) at 0 °C under nitrogen. After being stirred at 0 °C for 30 min, the mixture was further stirred at r.t. for another 1 h. The solvent was evaporated and the residue was further purified by flash chromatography (silica gel, 5–10% EtOAc–hexanes) to afford the *E*/*Z* mixture of acetate (200 mg, 0.47 mmol, 87%). To a solution of the above acetate (160 mg, 0.37 mmol) in CH_2Cl_2 (3.4 mL) and buffer (pH 7, 390 μL) was added DDQ (102 mg, 0.45 mmol) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with sat. $NaHCO_3$ (8 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10–20% EtOAc–hexanes) to give the *Z*-isomer **19**, (8 mg, 0.026 mmol, 7%) as a colorless oil and the *E*-isomer **18** (80 mg, 0.26 mmol, 70%) as a pale yellow oil in a ratio of 1:10.
Data for compound **18**: R_f = 0.8 (20% EtOAc–hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 5.43 (tq, *J* = 7.0, 1.2 Hz, 1 H), 4.60 (d, *J* = 7.0 Hz, 2 H), 4.51 (s, 2 H), 3.95 (m, 1 H), 3.53 (d, *J* = 0.6 Hz, 1 H), 3.52 (s, 1 H), 2.47 (br s, 1 H), 2.23–2.06 (m, 2 H), 2.05 (s, 3 H), 1.89–1.84 (m, 1 H), 1.75 (d, *J* = 1.2 Hz, 3 H), 0.96 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 139.3, 137.9, 128.3, 127.6, 127.5, 121.1, 74.4, 73.3, 70.9, 61.1, 44.2, 37.6, 20.9, 16.5, 10.7. IR (neat): 3477 (br), 2966, 2931, 2868, 1733, 1450, 1373, 1239, 1098, 1027, 743 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $[C_{18}H_{26}O_4 + Na]^+$: 329.1729; found: 329.1723. $[\alpha]_D^{20}$ 4.3 (*c* 1.45, $CHCl_3$).
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(17) **Procedure for the Synthesis of Compound 28**
A solution of methyltriphenylphosphonium bromide (273 mg, 0.76 mmol) in dry toluene (12 mL) was heated to reflux and about 10 mL of toluene were distilled off azeotropically to remove moisture. To the above suspension was added KO*t*-Bu (86 mg, 0.76 mmol), the mixture was stirred at 105 °C for 1 h, and then cooled to 0 °C. A solution of aldehyde (180 mg, 0.58 mmol) in dry toluene (0.5 mL) was added dropwise to the above suspension with stirring, and the resulting mixture was stirred at 0 °C for 1 h. After addition of sat. NH_4Cl (5 mL), the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 5–15% EtOAc–hexanes) to give **28** (116 mg, 0.38 mmol, 65% for two steps) as a colorless oil. R_f = 0.57 (30% EtOAc–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dt, *J* = 8.9, 2.1 Hz, 2 H), 6.94 (dt, *J* = 15.6, 7.0 Hz, 1 H), 6.87 (dt, *J* = 8.9, 2.2 Hz, 2 H), 5.79 (dt, *J* = 15.5, 1.5 Hz, 1 H), 5.71 (ddd, *J* = 17.1, 10.4, 7.9 Hz, 1 H), 5.26–5.18 (m, 2 H), 4.39 (AB pattern, *J* = 11.6 Hz, 2 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.77–3.67 (m, 1 H), 2.19–2.14 (m, 2 H), 1.64–1.46 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 159.0, 149.2, 138.8, 130.6, 129.3, 120.9, 117.2, 113.7, 79.6, 69.6, 55.1, 51.3, 34.8, 31.9, 23.8. IR (neat): 2948, 2838, 1724, 1657, 1613, 1514, 1463, 1248, 1201, 1172, 1036, 928 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $[C_{18}H_{24}O_4 + Na]^+$: 327.1572; found: 327.1588. $[\alpha]_D^{20}$ 34.3 (*c* 2.15, $CHCl_3$).

(18) **Spectral Data for Selected Compounds**
Data for ketone **11**: R_f = 0.34 (30% EtOAc–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (dt, *J* = 8.8, 2.1 Hz, 2 H), 8.12 (dt, *J* = 9.2, 2.2 Hz, 2 H), 7.29–7.23 (m, 5 H), 5.72 (dt, *J* = 7.7, 5.1 Hz, 1 H), 4.46 (s, 2 H), 3.42 (d, *J* = 6.2 Hz, 2 H), 2.93 (dd, *J* = 16.5, 7.7 Hz, 1 H), 2.82 (dd, *J* = 16.5, 5.5 Hz, 1 H), 2.26–2.19 (m, 1 H), 2.17 (s, 3 H), 1.06 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 163.9, 150.4, 138.0, 135.6, 130.6, 128.2, 127.6, 127.5, 123.4, 73.1, 72.7, 71.9, 45.7, 37.1, 30.1, 12.1. IR (neat): 2933, 2863, 1725, 1607, 1528, 1411, 1349, 1275, 1169, 1102 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $[C_{21}H_{23}O_6N + Na]^+$: 408.1423; found: 408.1422. $[\alpha]_D^{20}$ –10.7 (*c* 0.67, $CHCl_3$).
Data for compound **12**: R_f = 0.35 (20% EtOAc–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 6.79 (dd, *J* = 16.2, 7.0 Hz, 1 H), 6.11 (dd, *J* = 16.2, 1.5 Hz, 1 H), 4.52 (s, 2 H), 3.42 (d, *J* = 6.7 Hz, 2 H), 2.72–2.65 (m, 1 H), 2.25 (s, 3 H), 1.10 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 150.2, 138.1, 130.6, 128.4, 127.6, 127.5, 73.9, 73.1, 36.9, 26.8, 16.0. IR (neat): 2965, 2856, 1676, 1626, 1528, 1454, 1360, 1257, 1099, 982, 739, 699 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $[C_{14}H_{18}O_2 + Na]^+$: 241.1204; found: 241.1214. $[\alpha]_D^{20}$ –15.8 (*c* 1.13, $CHCl_3$).
Data for compound **16**: R_f = 0.28 (10% EtOAc–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 7.19 (dt, *J* = 8.8, 2.1 Hz, 2 H), 6.84 (dt, *J* = 8.8, 2.1 Hz, 2 H), 4.46 (d, *J* = 1.5 Hz, 2 H), 4.43 (d, *J* = 7.3 Hz, 2 H), 4.08 (dt, *J* = 7.9, 4.3 Hz, 1 H), 3.78 (s, 3 H), 3.49 (dd, *J* = 8.8, 6.7 Hz, 1 H), 3.33 (dd, *J* = 9.2, 6.1 Hz, 1 H), 2.74 (dd, *J* = 16.2, 8.2 Hz, 1 H), 2.52 (dd, *J* = 16.2, 4.6 Hz, 1 H), 2.13 (s, 3 H), 2.04–1.99 (m, 1 H), 0.96 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8, 159.1, 138.5, 130.8, 129.5, 129.4, 128.4, 127.7, 127.6, 113.7, 76.0, 73.0, 72.3, 55.3, 46.5, 37.5, 31.1, 12.4. IR (neat): 2917, 2861, 1715, 1611, 1513, 1457, 1361, 1301, 1248, 1173, 1078, 822 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $[C_{22}H_{28}O_4 + Na]^+$: 379.1885; found: 379.1880. $[\alpha]_D^{20}$ 9.7 (*c* 1.05, $CHCl_3$).
Data for compound **30**: R_f = 0.55 (25% EtOAc–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 7 H), 6.92–6.84 (m, 3 H), 5.74 (d, *J* = 15.9 Hz, 1 H), 5.74–5.67 (m, 1 H), 5.37–5.19 (m, 4 H), 4.57–4.43 (m, 5 H), 4.27 (d, *J* = 11.3 Hz, 1 H), 3.8 (s, 3 H), 3.78–3.68 (m, 1 H), 3.38–3.27 (m, 2 H), 2.37–2.13 (m, 4 H), 2.03–1.96 (m, 1 H), 2.01 (s, 3 H), 1.74 (s, 3 H), 1.72–1.47 (m, 4 H), 0.97 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 166.0, 159.0, 148.8, 138.9, 138.4, 138.3, 130.7, 129.3, 128.3, 127.6, 127.5, 121.6, 121.4, 117.2, 113.7, 79.8, 73.1, 72.5, 71.5, 69.7, 61.0, 55.2, 42.2, 36.8, 35.0, 32.0, 23.8, 20.9, 16.4, 11.4. IR (neat): 2961, 2930, 2851, 2361, 1738, 1715, 1513, 1454, 1260, 1245, 1091, 1027, 801 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $[C_{35}H_{46}O_7 + Na]^+$: 601.3141; found: 601.3146. $[\alpha]_D^{20}$ 9.8 (*c* 0.60, $CHCl_3$).