Synthesis of (±)-Diospongin A: A Hetero-Diels–Alder and C-Glycosylation Approach

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Abstract: The racemic natural product diospongin A has been prepared using a short and stereoselective sequence. Key steps include a hetero-Diels–Alder reaction and an anchimeric assistance-controlled C-glycosylation

Key words: Diels–Alder reaction, glycosylation, neighboring-group effects, natural products

Diospongins A (**1**) and B (**2**) (Figure 1) are diaryl tetrahydropyran-based natural products isolated from the ethanol–water fractions of the rhizome *Dioscorea spongiosa*, which is abundant in southern parts of China and is used in traditional Chinese medicine to treat a number of ailments.[1] Compounds **1** and **2** have been found to inhibit release of calcium from a bone culture system, which suggests that the diospongins (or some derived analogue) may have potential as anti-osteoporetic agents. Although milligram quantities of **1** and **2** were obtained from the original source, de novo synthesis offers far greater opportunities for the preparation of diverse analogues. The intriguing bioactivity inherent in the relatively simple structures of **1** and **2** has inspired a number of innovative synthetic approaches.[2,3]

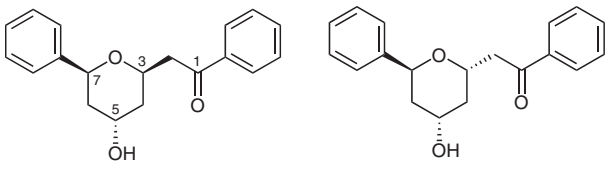
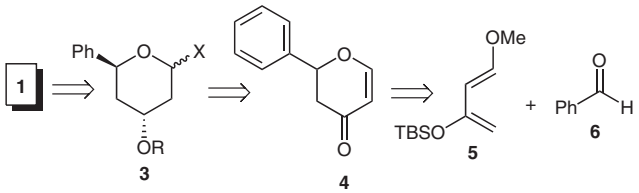


Figure 1 Structures of the diospongins

Most of the published syntheses of **1** and **2** have involved buildup of a linear precursor using acyclic stereocontrol, followed by formation of the tetrahydropyran ring and, concomitantly, the C3 stereogenic center using an oxy-Michael,[2a–c] Prins,[2d,e] S_N2',[2f] or Wacker-type[2g] reactions. Other approaches have first built the six-membered ring and then set the C3 configuration using hydrogenation[2h] or nucleophilic addition to a cyclic oxocarbenium ion.[2i] This report describes a synthesis of **1** in which a hetero-Diels–Alder[3] (HDA) reaction is used to build the tetrahydropyran framework. The key reaction in our synthesis is a novel C-glycosylation that installs the phenacyl side-chain, using neighboring-group participation[4] to control the C3 configuration.

Our retrosynthesis is shown in Scheme 1. Compound **1** is derived from a protected oxocarbenium ion precursor such as **3**, which itself is derived from known ketone **4** via reduction and formal hydration of the glycal olefin. Compound **4** is the product of an HDA–elimination sequence originating from Danishefsky-type[5] diene **5** and benzaldehyde **6**. Besides facilitating the concise preparation of the tetrahydropyran ring of **1**, the HDA approach offers the additional advantage of enabling an enantioselective route using a chiral catalyst.[6]



Scheme 1 Retrosynthetic analysis of **1**

The key to our synthesis of **1** was to control the stereochemical course of C-glycosylation – and thereby establish the C3 configuration – using anchimeric assistance. This approach complements the work of Sawant and Jennings, who synthesized **2** via a stereoselective C-glycosylation reaction.[2i,7] In this pioneering work, oxocarbenium ion **A** (Scheme 2) is generated from **3** (R = triethylsilyl, X = OAc). It is known from the work of Woerpel and co-workers[8] that six-membered oxocarbenium ions such as **A** favor a half-chair conformation in which the C5 (diospongin numbering) heteroatom substituent adopts a pseudoaxial position. Nucleophilic attack by an enol silane nucleophile from an axial trajectory (and thus via a chair-like transition state) yields compound **B**, which is deprotected in situ to give **2**.[2i]

We reasoned that changing the O-protecting group at C5 to a participating acyl group (e.g., benzoyl) would generate bicyclic acyloxonium ion **C** (Scheme 2). The topology of **C** would then direct nucleophilic addition to the convex face, giving the equatorial phenacyl chain as shown in **D**, which corresponds to **1**. 1,3-Stereocontrol in O-glycosylation is quite rare (compared to 1,2-stereocontrol), but has some limited precedent in the synthesis of 2-deoxy-*O*-gly-

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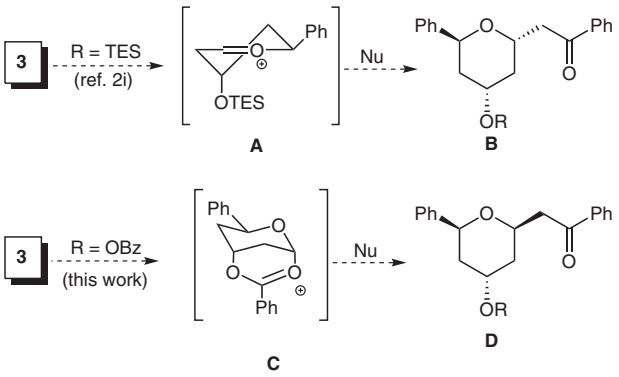
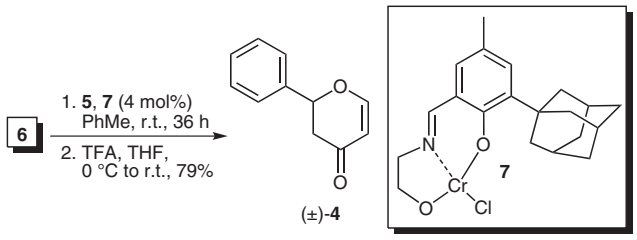
cosides.[9] Nonetheless, we were confident that anchimeric assistance via a structure corresponding to **C** could provide access the target molecule **1**. The experimental validation of our hypothesis is described below.

The [4+2] union of commercially available diene **5** and benzaldehyde (**6**) was catalyzed by achiral chromium complex **7**[10] (4 mol%) to give **4** in 79% yield (Scheme 3). We examined the application of other simple Lewis acid catalysts [$MgBr_2$, $ZnCl_2$, BF_3·OEt_2, and $Yb(OTf)_3$] in this reaction, but found that **7** gave the highest yield and cleanest reaction. We then needed to set the C5 configuration using a 1,2-reduction of ketone **4**. It is known that reduction of dihydropyrones such as **4** with achiral reducing agents gives the C5–C7 (diospongin numbering) *syn*-stereochemistry, regardless of which reducing agent is used.[11] We briefly examined reduction of **4** with the Corey–Bakshi–Shibata (CBS) reagent[12] (not shown) to no avail. We decided to opt for a diastereoselective reduction to give the epimeric C5 configuration, followed by inversion later in the synthesis.



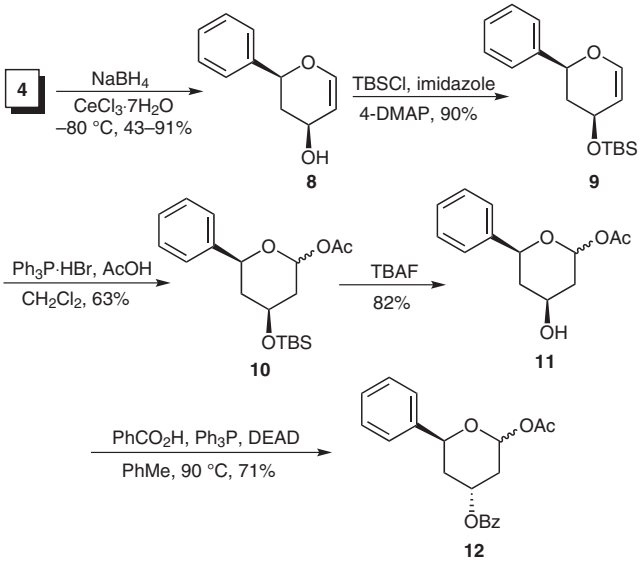
Scheme 2 Stereochemical course of C-glycosylations leading to **1** and **2**

Luche reduction[13] of **4**[14] gave alcohol **8** as a single isomer (Scheme 4). In our hands, the yield of this transformation was somewhat variable, but generally improved as the scale was increased.



Scheme 3 Hetero-Diels–Alder reaction of **5** and **6**

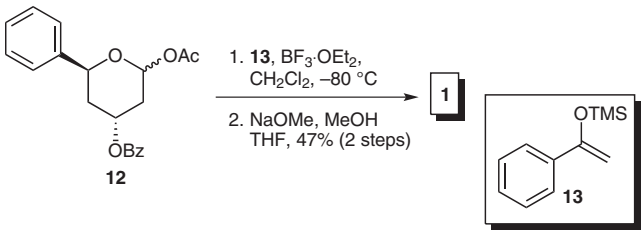
We next needed to install a leaving group at the anomeric carbon (C3) and invert the stereochemistry at C5 to prepare a C-glycosylation substrate corresponding to generic compound **3**. The ordering of these steps was crucial to the success of the sequence. Because Mitsunobu reaction[15] of **8** would give only type-I Ferrier rearrangement,[16] we decided to first install an acetoxy group at C3 of **8** using Falck's conditions.[17] Unfortunately, this tactic only resulted in Ferrier rearrangement (not shown) via a putative allyloxocarbenium ion, so the C5 hydroxyl group was protected as its *tert*-butyldimethylsilyl (TBS) ether (**9**). Acetoxylation of **9** smoothly produced **10** as an inconsequential 13:1 (assessed by NMR analysis) mixture of anomers (Scheme 4). Although no effort was made to determine the anomeric configuration of the major product (because this stereocenter would be destroyed in a subsequent step), it was assumed to be α-(axial) based on literature precedent.[17] Compound **10** was deprotected under standard conditions to give the somewhat labile alcohol **11**, which was converted into the epimeric benzoate **12** in hot toluene.[18]



Scheme 4 Synthesis of **12**

In the key step of our synthesis (Scheme 5), a cold (–80 °C) dichloromethane solution of acetate **12** was treated sequentially with enol silane **13** and BF_3·OEt_2. Thin layer chromatography (TLC) after 4.5 hours showed clean conversion into a new compound, along with some decomposition products. After aqueous workup and filtration through silica gel, the derived product was deacylated in methanol/tetrahydrofuran to give **1** in 47% yield over two steps. No other isomers were detected in the crude reaction mixture. Data for the synthetic material matched those published[1,2i] for **1** in all respects (^1H, ^{13}C NMR, IR, HRMS, and TLC). This stereochemical result is consistent with the generation of a bridged bicyclic acyloxonium ion analogous to **C** (Scheme 2).

In conclusion, we have developed a concise and stereoselective synthesis of diospongin A (**1**). The step economy of the current synthesis compares well with previous syntheses. A hetero-Diels–Alder reaction was used to build the six-membered ring and a participating group at C5 was used to control the stereochemical outcome of the key C-glycosylation reaction. This is, to our knowledge, the



Scheme 5 C-glycosylation to give **1**

first example of a C-glycosylation controlled by 1,3-neighboring-group participation and this important precedent should find use in other related contexts.

All reactions were performed in oven- or flame-dried round-bottom flasks under positive pressure of argon unless otherwise noted. Flash column chromatography was performed with 32–63 μm (Silicycle) silica gel. Thin-layer chromatography (TLC) was performed using glass-backed plates coated with 0.25 mm F254 silica gel. TLC plates were visualized using either UV light or charring after staining with Verghn's reagent (prepared by dissolving 40 g ammonium molybdate and 1.6 g ceric ammonium nitrate in 800 mL 10% v/v H_2SO_4). All commercial reagents were used without further purification. ^{1}H NMR spectra were recorded with a 400 MHz instrument in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peak ($CHCl_3$, δ = 7.26 ppm). Data are given as: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet), integration, coupling constant (Hz). Proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz. ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (δ = 77.0 ppm). IR stretches are given in cm^{-1}. HRMS analysis was performed in the electrospray ionization mode at the Scripps Research Institute.

(±)-2-Phenyl-2*H*-pyran-4(3*H*)-one (4)

A round-bottom flask was charged with catalyst **7** (0.134 g, 0.336 mmol, 0.040 equiv) and barium oxide (2 g). Toluene (30 mL) was added, followed by diene **5** (1.80 g, 8.40 mmol, 1 equiv) via syringe. The suspension was stirred at r.t. for 1 h, at which point benzaldehyde (**6**; 1.33 g, 12.6 mmol, 1.50 equiv) was added via syringe. After 36 h, the reaction was filtered through Celite, washing with EtOAc, and the filtrate concentrated. The crude adduct was dissolved in THF (25 mL), cooled to 0 °C and treated with TFA (1.44 g, 12.6 mmol, 1.50 equiv). The reaction was allowed to warm to r.t. and quenched after 4.5 h with sat. aq $NaHCO_3$ (20 mL), extracted with EtOAc (3 × 15 mL), washed with brine (20 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (40 mm × 14 cm column; EtOAc–hexanes, 20%) gave **4** (1.15 g, 79%) as an oil. All data were in agreement with literature values.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.49 (m, 6 H), 5.53 (dd, *J* = 1, 6 Hz, 1 H), 5.43 (dd, *J* = 3.2, 14.4 Hz, 1 H), 2.92 (dd, *J* = 14.4, 16.8 Hz, 1 H), 2.67 (ddd, *J* = 1.2, 3.2, 16.8 Hz, 1 H).

(±)-2-Phenyl-3,4-dihydro-2*H*-pyran-4-ol (8)

Ketone **4** (1.15 g, 6.60 mmol, 1 equiv) was dissolved in CH_2Cl_2 (41 mL) and EtOH (21 mL) and $CeCl_3·7H_2O$ (3.20 g, 8.58 mmol, 1.30 equiv) were added. The suspension was cooled to –80 °C and a solution of $NaBH_4$ (0.300 g, 7.92 mmol, 1.20 equiv) in EtOH (26 mL) was added dropwise via addition funnel over 30 min. TLC after 3 h showed that some starting ketone remained, so additional $CeCl_3·7H_2O$ (1.60 g, 4.29 mmol, 0.650 equiv) and $NaBH_4$ (0.150 g, 3.97 mmol, 0.600 equiv, in 10 mL EtOH) were added. After an additional 5 h the reaction was quenched with brine (20 mL), allowed to warm to r.t., and diluted with brine (50 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL), washed with brine (30 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (40 mm × 18 cm column; EtOAc–hexanes, 30%) gave **8** (1.06 g, 91%) as an oil. All data were in agreement with literature values.[13]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.42 (m, 5 H), 6.52 (d, *J* = 6.2 Hz, 1 H), 5.00 (dd, *J* = 1.9, 11.6 Hz, 1 H), 4.86 (m, 1 H), 4.60 (t, *J* = 7.4 Hz, 1 H), 2.36–2.47 (m, 1 H), 1.96–2.07 (m, 1 H).

(±)-*tert*-Butyldimethyl-2-phenyl-3,4-dihydro-2*H*-pyran-4-yloxy-silane (9)

Alcohol **8** (0.200 g, 1.14 mmol, 1 equiv) was dissolved in CH_2Cl_2 (10 mL) under Ar, and imidazole (0.232 g, 3.41 mmol, 3.00 equiv) and DMAP (0.028 g, 0.227 mmol, 0.20 equiv) were added. TBSCl (0.257 g, 1.70 mmol, 1.50 equiv) was then added in one portion. The reaction was allowed to stir for 15 h and then quenched with H_2O (10 mL), diluted with CH_2Cl_2 (10 mL), washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (25 mm × 13 cm column; EtOAc–hexanes, 5%) gave **9** (0.299 g, 90%) as a clear oil. TLC: R_f = 0.53 (EtOAc–hexanes, 5%).

FTIR (thin film): 2956, 2930, 2889, 2857, 1654 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.37 (m, 5 H), 6.47 (dd, *J* = 1, 6.3 Hz, 1 H), 4.97 (dd, *J* = 1.9, 12.3 Hz, 1 H), 4.75 (dt, *J* = 1.8, 6.3 Hz, 1 H), 4.66 (m, 1 H), 2.20 (m, 1 H), 2.04 (ddd, *J* = 9.5, 12.5, 26 Hz, 1 H), 0.893 (s, 9 H), 0.0986 (s, 3 H), 0.0775 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 141.1, 129.0, 128.5, 126.6, 107.0, 77.1, 64.7, 40.7, 26.3, 18.6, –4.17, –4.23.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{17}H_{26}O_2Si$: 313.1594; found: 313.1596.

(±)-4-(*tert*-Butyldimethylsilyloxy)-6-phenyltetrahydro-2*H*-pyran-2-yl Acetate (10)

Glycal **9** (0.295 g, 1.02 mmol, 1 equiv) was dissolved in CH_2Cl_2 (7 mL) and AcOH (0.122 g, 2.03 mmol, 2.00 equiv) and $Ph_3P·HBr$ (0.017 g, 0.0508 mmol, 0.050 equiv) were added. The reaction was stirred for 3.5 h and then quenched with sat. aq $NaHCO_3$, diluted with CH_2Cl_2 (10 mL), washed with H_2O (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (25 mm × 15 cm column; EtOAc–hexanes, 5%) gave **10** (0.224 g, 63%) as an approximately 13:1 mixture of anomers. TLC: R_f = 0.27 (EtOAc–hexanes, 5%).

FTIR (thin film): 2956, 2858, 1753, 1254 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 6.42 (d, *J* = 2.5 Hz, 1 H), 5.82 (dd, *J* = 2.2, 10.2 Hz, 1 H, minor isomer), 4.85 (dd, 1 H, *J* = 2.2, 12 Hz), 4.52 (dd, *J* = 2, 12 Hz, 1 H, minor isomer), 4.23 (m, 1 H), 2.11 (s, 3 H), 2.09 (m, 2 H), 1.79 (m, 1 H), 1.67 (dd, *J* = 12, 26 Hz, 1 H), 0.883 (s, 9 H), 0.0939 (s, 3 H), 0.0817 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 141.5, 128.8, 128.2, 126.7, 126.5, 93.8, 73.1, 64.8, 43.8, 38.9, 26.2, 21.6, 18.4, –4.2.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{19}H_{30}O_4Si$: 373.1805; found: 373.1822.

(±)-4-Hydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl Acetate (11)

Acetate **10** (0.218 g, 0.622 mmol, 1 equiv) was dissolved in THF (6 mL) and TBAF (1 M in THF, 0.809 mL, 0.809 mmol, 1.30 equiv) was added. The reaction was stirred at r.t. for 1.5 h, then additional TBAF solution (0.200 mL) was added. After an additional 12 h, the reaction was diluted with H_2O (10 mL) and EtOAc (5 mL), the aqueous layer was extracted with EtOAc (5 mL), and the combined organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Rapid flash chromatography (25 mm × 20 cm; EtOAc–hexanes, 50%) gave **11** (0.121 g, 82%) as an oil [R_f = 0.28

(EtOAc–hexanes, 50%)]. The material was somewhat unstable and used immediately in the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 6.44 (d, *J* = 2 Hz, 1 H), 4.88 (dd, *J* = 2, 12 Hz, 1 H), 4.29 (m, 1 H), 2.24 (m, 2 H), 2.10 (s, 3 H), 1.75 (m, 1 H), 1.63 (m, 1 H).

(±)-2-Acetoxy-6-phenyltetrahydro-2*H*-pyran-4-yl Benzoate (12)

Alcohol **11** (1.29 g, 2.60 mmol, 1 equiv) was combined with Ph_3P (0.249 g, 0.948 mmol, 2.00 equiv) and benzoic acid (0.116 g, 0.948 g, 2.00 equiv) and dissolved in toluene (6 mL) under Ar and cooled to 0 °C. DEAD (40% by weight in toluene, 0.430 mL, 0.948 mmol, 2.00 equiv) was added dropwise via syringe, the reaction was warmed to r.t. and then placed in an oil bath set to 90 °C. After stirring for 4 h, the solution was diluted with EtOAc (10 mL), washed with sat. aq $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (25 mm × 18 cm; EtOAc–hexanes, 20%) gave **12** (0.114 g, 71%) as an oil [R_f = 0.29 (EtOAc–hexanes, 20%)].

FTIR (thin film): 3066, 3034, 2964, 2923, 1749, 1720, 1278 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (m, 2 H), 7.62 (m, 1 H), 7.50 (t, *J* = 8 Hz, 2 H), 7.34 (m, 5 H), 6.43 (d, *J* = 4 Hz, 1 H), 5.51 (t, *J* = 3 Hz, 1 H), 5.35 (dd, *J* = 12, 2 Hz, 1 H), 2.25 (m, 2 H), 2.06 (m, 2 H), 2.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 166.1, 141.3, 133.6, 130.9, 130.1, 128.89, 128.85, 128.3, 126.3, 91.9, 68.5, 66.5, 37.1, 32.0, 21.6.

HRMS (ESI): *m/z* [M + Na] calcd for $C_{20}H_{20}O_5$: 363.1203; found: 363.1218.

(±)-Diospongin A (1)

Acetate **12** (0.037 g, 0.11 mmol, 1 equiv) was dissolved in CH_2Cl_2 (1.5 mL) under Ar and cooled to –80 °C. 1-Phenyl-1-trimethylsiloxyethylene (**13**; 0.071 mL, 0.35 mmol, 3.2 equiv) was added via syringe, followed by $BF_3{\cdot}OEt_2$ (0.044 mL, 0.345 mmol, 3.2 equiv). After 1 h, the reaction was quenched with sat. aq $NaHCO_3$ (2 mL) slowly allowed to warm to r.t., extracted with CH_2Cl_2 (5 mL), washed with brine (5 mL), and dried over Na_2SO_4. The crude product was filtered through silica gel, washing with acetone–hexane (15%) and concentrated. The product was then dissolved in MeOH–THF (1:1, 1.6 mL) and treated with NaOMe (1 M in MeOH, 0.22 mL, 0.17 mmol, 1.6 equiv). TLC after 4.5 h showed complete disappearance of starting material, and the reaction was concentrated. The crude residue was partitioned between H_2O (4 mL) and EtOAc (4 mL), the organic layer was washed with brine and dried (Na_2SO_4). Flash column chromatography on silica gel (EtOAc–hexanes, 40%) gave diospongin A (**1**; 0.015 g, 0.051 mmol, 47% over two steps).

TLC: R_f = 0.23 (EtOAc–hexanes, 40%).

FTIR (thin film): 3424, 2921, 1681, 1450, 1059 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.99 (m, 2 H), 7.43–7.58 (m, 3 H), 7.21–7.37 (m, 5 H), 4.93 (dd, *J* = 11.8, 1.6 Hz,1 H), 4.65 (m, 1 H), 4.37 (t, *J* = 2.7 Hz, 1 H), 3.42 (dd, *J* = 16.0, 5.8 Hz, 1 H), 3.08 (dd, *J* = 16.0, 6.9 Hz, 1 H), 1.85–1.97 (m, 2 H), 1.6–1.8 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.9, 143.1, 137.7, 133.5, 128.95, 128.75, 128.67, 127.6, 126.2, 74.2, 69.5, 65.0, 45.6, 40.4, 38.9.

HRMS (ESI): *m/z* [M + H] calcd for $C_{19}H_{20}O_3$: 297.1485; found: 297.1481.

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