A First Generation Total Synthesis of (+)-Salicylihalamide A

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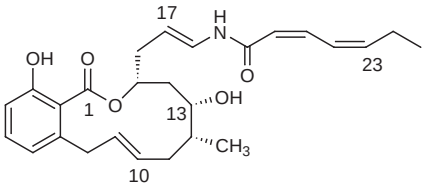
Dedicated to Professor Ryoji Noyori with admiration and respect for his many seminal contributions to chemistry.

Abstract: An efficient total synthesis of (+)-salicylihalamide (**1**) is described. The synthetic strategy features a highly *E*-selective ring-closing metathesis to construct the 12-membered salicylihalamide A macrocycle and a practical method for installation of the labile ene-hepta-(*Z*,*Z*)-dienamide side chain, which relies on a Curtius rearrangement to forge the C18-N bond with subsequent *N*-acylation.

Key words: salicylihalamide, total synthesis, macrocycles, metathesis, Curtius rearrangement

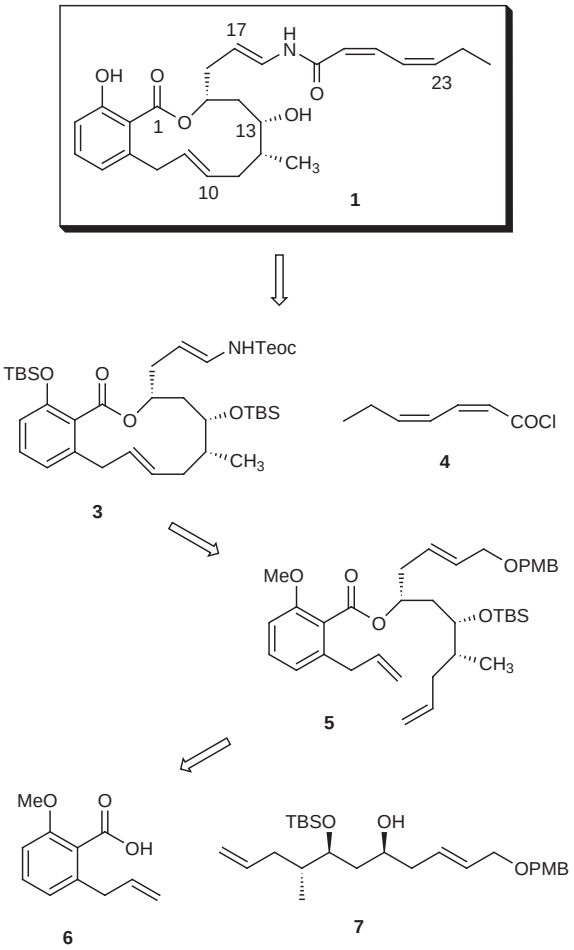
In 1997 Boyd and co-workers[1] reported the isolation and structural elucidation of salicylihalamides A and B, novel secondary metabolites produced by a marine sponge of the genus *Haliclona.* Since their discovery, a number of structurally similar bioactive metabolites have been isolated and characterized, including the apicularens,[2] lobatamides,[3] and oximidines.[4] Each of these structures possesses a medium-sized macrolide ring engendering a salicylate moiety and a dienylenamide sidechain. Salicylihalamide A displayed potent cytotoxicity when screened against the NCI 60-cell human tumor line assay, with a mean panel GI_{50} value of 15 nM.[1] Of particular import, however, the mean-graph profiles for the salicylihalamides obtained from COMPARE pattern-recognition analysis[5] suggested a unique mode of action apart from known antitumor compounds within the NCI database. Thus, owing to the unique, potent cytotoxicities of the salicylihalamides, as well as their scarcity and their novel structural features, particularly the highly unsaturated enamide sidechain, a strong impetus for total synthesis presented itself.



(+)-Salicylihalamide A (**1**): 17(E)

(+)-Salicylihalamide B (**2**): 17(Z)

Figure



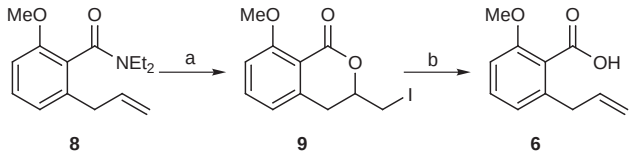
Scheme 1

Recently De Brabander and co-workers[6] reported the first, and to date only, total synthesis of (+)-salicylihalamide A (**1**); this achievement resulted in reassignment of the absolute configuration as 12*S*, 13*R*, 15*S*. A number of other groups also have reported synthetic efforts towards salicylihalamides.[7,8] Herein we disclose our first generation, stereocontrolled total synthesis of the non-naturally-occurring enantiomer, (+)-salicylihalamide A (**1**).

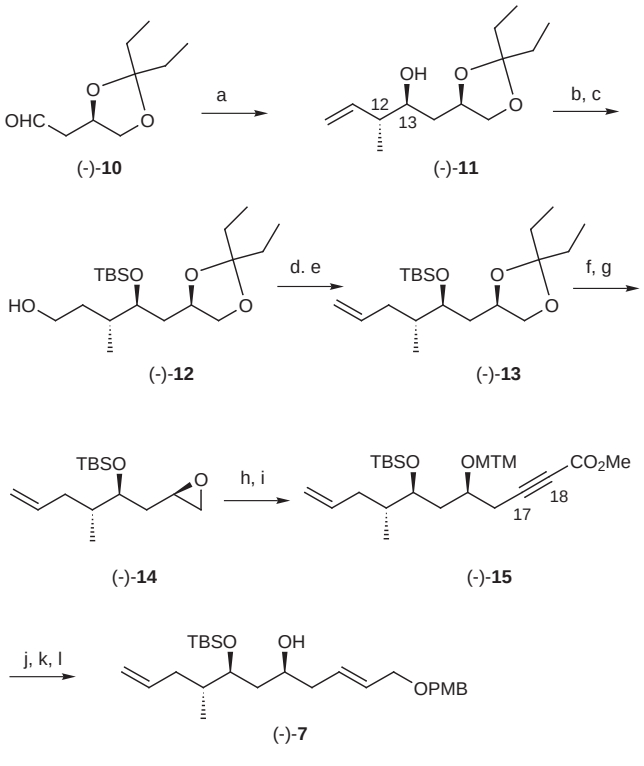
We reasoned that the sensitive enamide sidechain would best be installed at a late stage of the synthesis via *N*-acylation of advanced enecarbamate **3** with (*Z*,*Z*)-dienyl chloride **4** (Scheme 1).[9] Further analysis of **3** suggested a ring-

closing metathesis (RCM)[10] on triene **5** would serve both to install the C(9,10) double bond and close the 12-membered macrolide. At the outset of this synthetic venture control of the *E*-olefinic configuration could not be assured (*vide infra*). Ester **5**, in turn, would be available after Mitsunobu union[11] of secondary alcohol **7** with the salicylic acid derivative **6**.

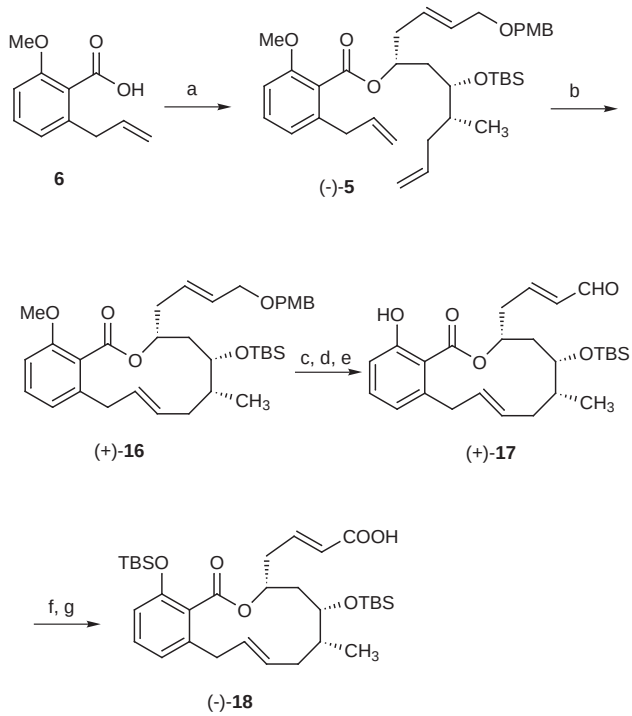
The synthesis of **6** began with conversion of known amide **8**[12] (available in two steps from methylsalicylic acid chloride) to iodide **9**[13] (Scheme 2). Carboxylic acid **6**[13] was then obtained via exposure of the iodolactone **9** to zinc in acetic acid.[14]



Scheme 2 (a) I_2, THF/H_2O, rt, 65%; (b) Zn, HOAc, 90 °C, 73%



Scheme 3 (a) (*S*,*S*)-diisopropyl tartrate *(E)*-crotylboronate, $PhCH_3$, –78 °C, 88%, 90% *de*; (b) TBSOTf, 2,6-lutidine, –78 °C, 99%; (c) i: I. 9-BBN, THF, reflux; ii: 2N NaOH, H_2O_2, 84%; (d) DMSO, $(COCl)_2$, Et_3N, –78 °C, 96%; (e) methyltriphenylphosphonium iodide, NaHMDS, –78 °C to rt, 81%; (f) 50% aq. TFA/CH_2Cl_2, rt, 90%; (g) tosyl-imidazole, NaH, 81%; (h) methylpropiolate, *n*-BuLi, BF_3•OEt_2, –78 °C, 94%; (i) DMSO, Ac_2O, rt, 96%; (j) $LiAlH_4$, THF, rt, 77%; (k) NaH, PMBCl, TBAI, DMF, rt, 91%; (l) $AgNO_3$, 2,6-lutidine, THF, rt, 91%



Scheme 4 (a) PPh_3, DEAD, (–)-**7**, PhH, rt, 84%; (b) 10 mol% $(Cy_3P)_2Cl_2Ru$=CHPh, CH_2Cl_2, rt, 86%; (c) DDQ, CH_2Cl_2, pH 7 buffer, rt, 97%; (d) Dess-Martin periodinane, CH_2Cl_2, rt, 98%; (e) BBr_3, CH_2Cl_2, –78 °C, 82%; (f) $NaClO_2$, NaH_2PO_4 buffer, *t*-BuOH, 2-methyl-2-butene, rt, 97%;(g) i. TBSOTf, Et_3N, CH_2Cl_2, rt, ii. K_2CO_3, MeOH/THF/H_2O, rt, 83%

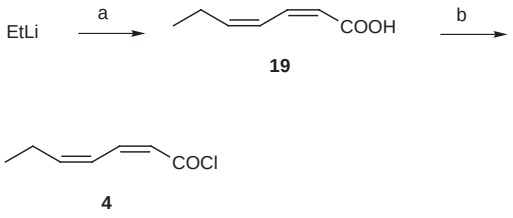
Our approach to the required coupling partner (–)-**7** is presented in Scheme 3. The *anti* relative stereochemistry at C(12,13) was set via Roush crotylboration[16] of known aldehyde (–)-**10**[15] to furnish (–)-**11**;[13] the diastereomeric excess was 90%. Protection of (–)-**11** as the *tert*-butyldimethylsilyl ether, followed by a 3-step homologation involving hydroboration,[17] Swern oxidation[18] and Wittig methylenation[19] then furnished olefin (–)-**13**.[13] The 1,2 diol was next revealed by exposure of diethylketal (–)-**13** to aqueous trifluoroacetic acid;[20] application of the Kishi epoxide protocol[21] led to (–)-**14**[13] in 73% yield for the two steps. The future C(17) and C(18) enamide carbons were then introduced by treatment of (–)-**14** with the lithium anion of methyl propiolate promoted by Lewis acid (BF_3·OEt_2)[22] to furnish alkynoate (–)-**15**.[13] Arrival at the *p*-methoxybenzyl (PMB) ether coupling partner (–)-**7** was achieved via protection of the secondary alcohol as the methyl-thiomethyl (MTM) ether,[23] LAH reduction to the homo allylic alcohol followed by protection as the PMB ether,[24] and silver-mediated[23] removal of the MTM moiety.

Union of acid **6** and alcohol (–)-**7** was achieved via the Mistunobu protocol[11] (Scheme 4) to provide the olefin metathesis substrate (–)-**5**.[13] To our delight treatment of a dichloromethane solution of (–)-**5** (0.008 M) with the Grubbs catalyst [$(Cy_3P)_2Cl_2Ru$=CHPh; (10 mol%)] fur-

nished the salicylihalamide macrolide (+)-**16**[13] as an approximate 10:1 mixture of double bond isomers favoring the desired *E*-isomer.[25] Presumably this stereochemical outcome derives from a combination of the reversible nature of the ring-closing metathesis process[26] and the thermodynamic stability of the *E*-olefinic configuration in the salicylihalamide macrocycle. Similar selectivity in a ring-closing metathesis was observed by De Brabander and A. Fürstner in their total syntheses of salicylihalamide A.[6,7]

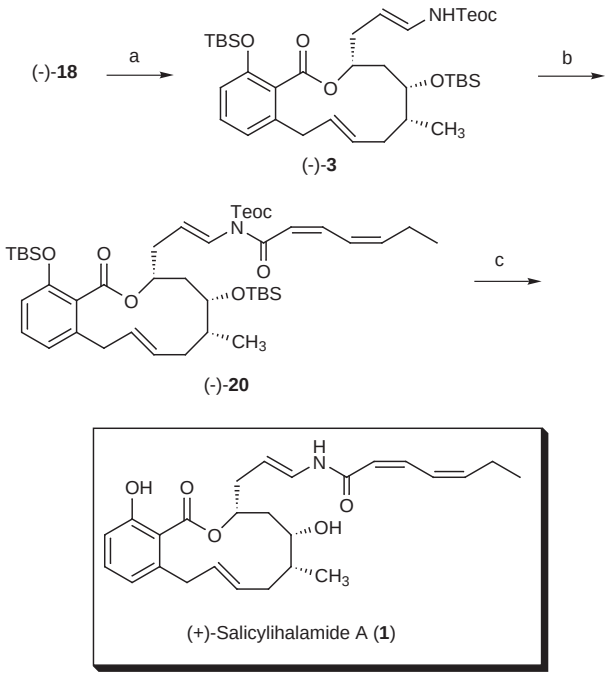
The sequence leading to installation of the enamide side chain began with a two-step conversion of the protected primary allylic alcohol (+)-**16** to the corresponding enal (DDQ then Dess Martin periodinane[27]). Cleavage of the anisole methyl ether with boron tribromide[28] provided phenol (+)-**17**.[13] Subsequent oxidation of the enal to the carboxylic acid, followed by silylation of both the C(3) hydroxyl and acid moieties and base-mediated hydrolysis[29] of the TBS ester furnished carboxylic acid (–)-**18**.[13]

In anticipation of the *N*-acylation reaction to install the salicylihalamide sidechain, we turned to the synthesis of *Z,Z*-dienyl acid chloride **4** (Scheme 5). Ethyl lithium (prepared by lithium-halogen exchange between *t*-BuLi and ethyl iodide) was treated sequentially with CuBr•SMe_2 complex (0.5 equivalent), acetylene (1.5 equivalents, introduced as a measured volume of gas) at −40 °C, and after 20 min an additional 2.5 equivalents of acetylene at −10 °C, as described by Taylor and co-workers[30] for the synthesis of the closely related *Z,Z*-nonadienoic acid. The resulting Z,Z-dienylcuprate was then trapped with carbon dioxide to furnish, after isolation, dienyl acid **19**[13] in 20% yield as a single isomer. Treatment of the latter with oxalyl chloride in the presence of a catalytic amount of DMF generated acid chloride **4**.[13]



Scheme 5 (a) i. 0.5 eq. CuBr•SMe_2, Et_2O, –35 °C, ii. 1.5 eq. acetylene, –40 °C, iii. 2.5 eq. acetylene, –10 °C, iv. CO_2, HMPA, $(EtO)_3P$, 20%; (b) $(COCl)_2$, cat. DMF, PhH, rt

With ample quantities of both **4** and (–)-**18** available, the stage was set for the crucial incorporation of the enamide sidechain. Exploiting the original Overman protocol,[31] sequential treatment of acid (–)-**18** (Scheme 6) with *N,N*-diethylisopropylamine and *i*-BuOCOCl in acetone, followed by aqueous sodium azide secured the corresponding acyl azide which upon heating at reflux for 15 min in toluene underwent a facile Curtius rearrangement. Without isolation the intermediate isocyanate was immediately trapped with 2-(trimethylsilyl)-ethanol to provide enecarbamate (–)-**3**[13] in excellent overall yield for the four-step sequence (86%).[32] Exposure of (–)-**3** to NaHMDS followed by acid chloride **4** then proceeded smoothly to furnish (–)-**20**.[13,33] This stepwise elaboration of the salicylihalamide sidechain proved to be a high-yielding protocol, and represents a practical method for incorporation of the sidechain of the salicylihalamide system. Final conversion to (+)-salicylihalamide A was achieved upon sequential removal of the Teoc and TBS protecting groups, thereby completing a stereocontrolled total synthesis of the non-naturally-occurring enantiomer of salicylihalamide A (**1**).[13] The spectroscopic data for synthetic (+)-salicylihalamide A (**1**) (e.g., ^1H NMR (500 MHz), ^{13}C NMR (125 MHz), IR, HRMS) were in complete agreement with the published data for (–)-salicylihalamide A, except of course for chiroptic properties.



Scheme 6 (a) i. DIPEA, *i*-BuOCOCl, acetone, rt, ii. NaN_3, H_2O, rt, iii. toluene, reflux, iv. 2-(trimethylsilyl)-ethanol, 86%; (b) NaHMDS, **4**, THF, 0 °C, 81%; (c) i. TBAF, THF, 0 °C, ii. HF•pyridine, pyridine/THF, 40-60%

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(25) To a solution of the Grubbs catalyst $(Cy_3P)_2Cl_2Ru$=CHPh (17.2 mg, 0.0209 mmol, 10 mol%) in dry CH_2Cl_2 (26 mL) was added a solution of (–)-**5** (130 mg, 0.209 mmol) in CH_2Cl_2 (3 mL). The reaction mxture was stirred for 40 minutes at ambient temperature and poured into H_2O (20 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 15:1) afforded (+)-**16** (112 mg, 85%) as a colorless oil: [α] 88° (*c* 0.10, $CHCl_3$); IR (neat): 2853 *(S)*, 1724 (s), 1584 (m), 1513 (s), 1469 (s), 1275 (s), 1249 (s), 1071 (s), 970 (m), 835 (s), 807 (m), 775 (m); H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.0 Hz, 2H), 7.21 (t, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 5.75-5.85 (m, 1H), 5.64-5.72 (m, 1H), 5.41 (ddt, *J* = 15.1, 10.8, 2.1 Hz, 1H), 5.25-5.34 (m, 2H), 4.42 (d, *J* = 3.2 Hz, 2H), 4.23 (dd, *J* = 8.5, 3.5 Hz, 1H), 3.97 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.71 (dd, *J* = 16.3, 9.4 Hz, 1H), 3.30 (dd, *J* = 16.3, 2.0 Hz, 1H), 2.41-2.52 (m, 1H), 2.28-2.37 (m, 1H), 2.21-2.29 (m, 1H), 1.80 (m, 1H), 1.68 (dd, *J* = 14.9, 8.3 Hz, 2H), 1.43 (dd, *J* = 15.2, 7.8 Hz, 1H), 0.90 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.23 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 159.1, 156.6, 139.0, 131.2, 130.4, 129.9, 129.4, 129.3, 129.2, 128.4, 124.6, 122.6, 113.7, 109.3, 74.6, 72.3, 71.4, 70.3, 55.5, 55.2, 39.0, 37.8, 37.7, 37.3, 36.7, 25.9, 17.9, 13.0, -4.3, -4.5; high resolution mass spectrum (ES, Na) m/z 617.3265 [(M+Na)$^+$; calcd for $C_{35}H_{50}O_6SiNa$: 617.3275].

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(32) To a solution of (–)-**18** (7 mg, 0.012 mmol) in acetone (0.8 mL) was sequentially added *N*,*N*-diisopropylethylamine (3.4 mg, 4.6 μL, 0.026 mmol) and isobutylchloroformate (3.2 mg, 3.0 μL, 0.024 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, and then a solution of sodium azide (7.8 mg, 0.119 mmol) in distilled H_2O (0.4 mL) was added. The resulting mixture was stirred at room temperature for an additional 30 min. Brine (10 mL) was added and the aqueous phase extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was azeotropically dried with benzene (2 × 1 mL) and then dissolved in toluene (2 mL) and heated at reflux for 15 min. 2-(Trimethylsilyl)-ethanol was added in one portion and the mixture was heated at reflux for an additional 10 min. The mixture was then cooled to room temperature and concentrated in vacuo. Flash chromatography (ethyl acetate/hexanes, 1:20) afforded (-)-**3** (7.2 mg, 86%) as a colorless oil: [α] –15.0° (*c* 0.10, CH_2Cl_2); IR (neat): 3200-3400 (br, m), 2856 (s), 1725 (s), 1681 (m), 1581 (m), 1504 (m), 1462 (s), 1259 (s), 1066 (s), 836 (s), 804 (s), 665 (s); ^{1}H NMR (500 MHz, C_6D_6) δ 6.91 (t, *J* = 8.0 Hz, 1H), 6.80-6.89 (m, 1H), 6.70 (d, *J* = 8.1, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 5.69 (d, *J* = 10.8 Hz, 1H), 5.40-5.47 (m, 1H), 5.31-5.40 (m, 2H),

4.62-4.78 (m, 1H), 4.49 (m, 1H), 4.16 (t, *J* = 8.2 Hz, 2H), 3.70 (dd, *J* = 16.1, 8.3 Hz, 1H), 3.20 (dd, *J* = 16.1, 4.1 Hz, 1H), 2.33-2.49 (m, 2H), 2.11 (m, 1H), 1.68 (m, 1H), 1.59-1.70 (m, 2H), 1.50-1.58 (m, 1H), 1.10 (s, 9H), 1.03 (s, 9H), 0.82-0.90 (m, 5H), 0.28 (s, 6H), 0.16 (s, 3H), 0.11 (s, 3H), -0.11 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.9, 153.2, 153.0, 138.7, 131.2, 129.6, 128.9, 128.8, 126.7, 123.3, 118.1, 104.0, 74.2, 72.1, 63.0, 38.3, 38.1, 37.5, 36.2, 35.9, 26.0, 25.7, 18.3, 18.1, 17.6, 1.1, -1.9, -4.2, -4.3, -4.6, -4.7; high resolution mass spectrum (ES, Na) m/z 726.4037 [(M+Na)$^+$; calcd for $C_{37}H_{65}NO_6Si_3Na$: 726.4017].

(33) A solution of (–)-**3** (4.2 mg, 0.006 mmol) in dry THF (1 mL) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 9 μL, 0.009 mmol) for 5 min at 0 °C. A solution of **4** (1.5 mg, 0.012 mmol) in dry benzene (0.1 mL) was added. The resulting mixture was stirred at 0 °C for 10 min before being quenched with saturated NH_4Cl (3 mL) and extracted with ether (2 × 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (ethyl acetate/hexanes, 1:10) provided (-)-**20** (3.9 mg, 81%) as a colorless oil: [α] –20.0° (*c* 0.20, CH_2Cl_2); IR (neat): 3587 (m), 2926 (s), 2854 (s), 1728 (s), 1581 (m), 1456 (m), 1382 (m), 1260 (s), 1066 (s), 969 (m), 860 (m), 803 (s); ^{1}H NMR (500 MHz, C_6D_6) δ 7.54 (t, *J* = 11.5 Hz, 1H), 6.90 (t, *J* = 7.9 Hz, 1H), 6.65-6.75 (m, 2H), 6.53-6.62 (m, 2H), 6.45 (d, *J* = 11.5 Hz, 1H), 5.89 (dt, *J* = 14.1, 7.4 Hz, 1H), 5.54-5.65 (m, 2H), 5.33-5.45 (m, 2H), 4.51-4.59 (m, 1H), 4.18 (t, *J* = 7.6 Hz, 2H), 3.69 (dd, *J* = 16.0, 8.1 Hz, 1H), 3.19 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.53-2.69 (m, 2H), 2.10-2.19 (m, 1H), 1.85-1.96 (m, 1H), 1.75-1.85 (m, 2H), 1.65-1.75 (m, 2H), 1.12 (s, 9H), 1.02 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88-0.97 (m, 2H), 0.73 (t, *J* = 7.5 Hz, 3H), 0.28 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H), -0.10 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.0, 166.9, 153.6, 153.0, 142.3, 138.8, 137.0, 131.2, 129.2, 128.6, 127.0, 124.9, 123.3, 121.1, 121.0, 118.0, 73.6, 72.1, 65.0, 38.3, 38.0, 37,5, 37.0, 36.2, 26.0, 25.7, 20.6, 18.3, 18.1, 17.4, 13.7, 1.1, -2.0, -4.2, -4.3, -4.6, -4.7; high resolution mass spectrum (ES, Na) m/z 834.4618 [(M+Na)$^+$; calcd for $C_{44}H_{73}NO_7Si_3Na$: 834.4618].

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