Stereoselective Formal Synthesis of (-)-Salicylihalamides A and B *Via* Prins Cyclisation

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Abstract: A stereoselective and convergent formal approach to Salicylihalamide A and B is achieved through our recently developed strategy for the construction of polyketide precursors *via* Prins cyclisation. The approach mainly relies upon reductive opening of 1-iodomethyl cyclic ethers, Mitsunobu inversion and ring closing metathesis along with Prins cyclisation.

Keywords: Natural products, cytotoxicity, prins cyclisation, reductive cleavage, mitsunobu inversion and ring closing metathesis.

Salicylihalamides A and B (**1** and **2**; Fig. **1**) comprise a novel class of secondary metabolites isolated by Boyd and co-workers [1] in 1997 from the marine sponge Haliclona. Salicylihalamide A (**1**) displays potent cytotoxicity in the NCI 60-cell line Human tumor assay, with a mean GI50 value of 15 nM through a distinct mechanism of action [1,2]. Few pharmacological studies however do indicate that Salicylihalamide A selectively inhibits mammalian vacuolar-type (H^+)-ATPase (V-ATPase) [3]. Hence, these molecules engendered considerable interest with in the synthetic community [4].

In our retrosynthetic analysis (Fig. **1**), it is evident that the core part of the Salicylihalamides could be easily obtained from aliphatic part **3** and aromatic fragment **4** *via* an esterification and ring closing metathesis. The aliphatic part **3** is envisaged to be constructed from homoallylic alcohol **5** which in turn could be drawn, *via* pyranyl methanol **6**, through Prins cyclisation between **7** and **8** following our recently developed methodology [6].

Synthesis of aliphatic fragment **3** is depicted in Scheme **1**. Prins cyclisation between known homoallylic alcohol **7** [6] and aldehyde **8** [6] in the presence of TFA [5] resulted in

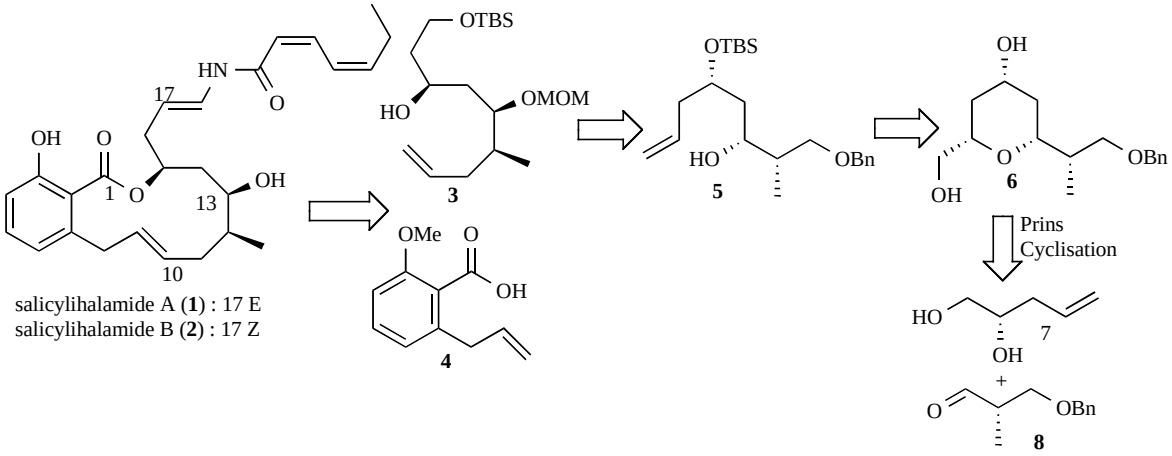

Fig. (1). Retrosynthetic analysis of salicylihalamides A and B.

Inspired by the biological properties and because of limited availability of the natural product and, as a part of our successful efforts towards the total synthesis of many ketide natural products *via* Prins cyclisation [5,6], we investigated a formal synthesis of Salicylihalamide A and B.

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trifluoroacetate of **6** which on treatment with K_2CO_3 in MeOH gave tetrahydropyran diol **6** in 55 % yield. Tosylation of primary hydroxyl group using TEA and protection of secondary hydroxyl group as TBS ether using TBDMSCl and imidazole produced **9** in 88 % over all yield. Substitution of tosylate group in **9** with iodide in presence of NaI in acetone followed by reductive elimination using Zn in EtOH produced alcohol **5** in 90% over two steps. Protection of the resulting alcohol as its MOM ether in presence of

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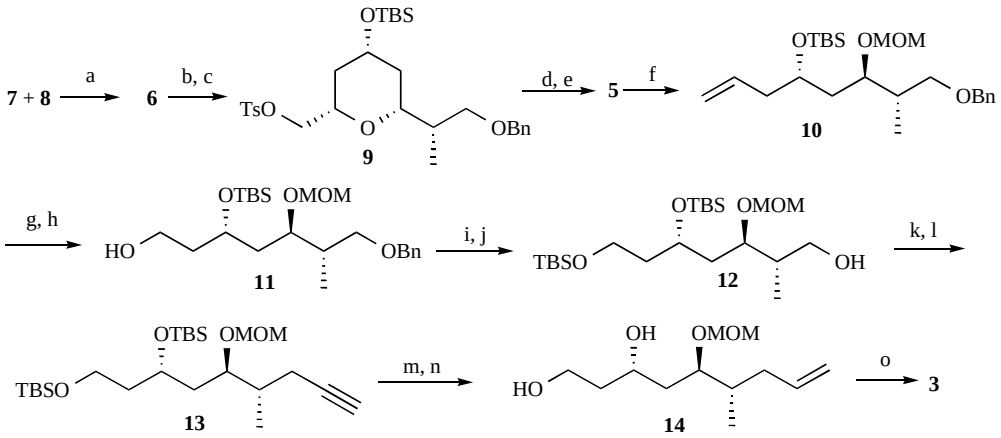


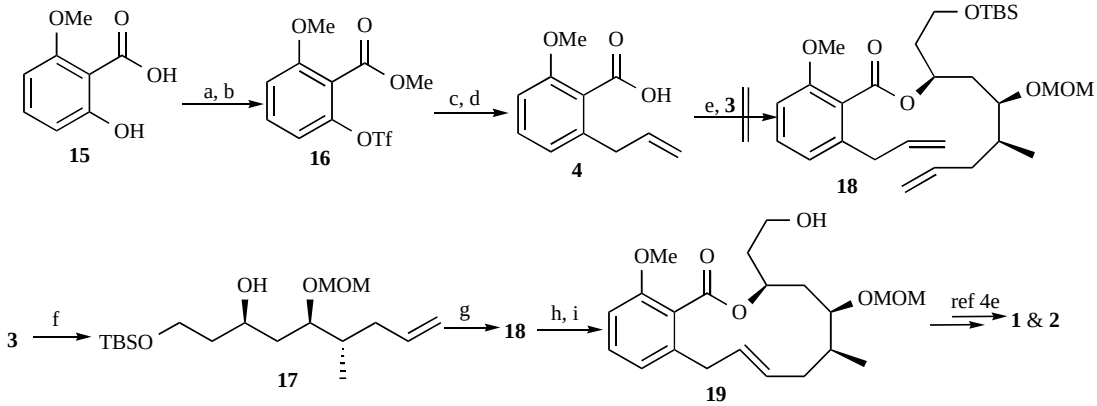
Scheme 1. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 ^oC-rt, 3h then K_2CO_3, MeOH, rt, 30 min, 55%; (b) TsCl, TEA, CH_2Cl_2, 0 ^oC-rt, 3 h, 85%; (c) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 0 ^oC-rt, 6 h, 92%; (d) NaI, acetone, reflux, 24h, 90%; (e) Zn, EtOH, reflux, 2h, 92%; (f) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0^oC-rt, 6h, 85%; (g) O_3, Ph_3P, CH_2Cl_2, -78 ^oC; (h) $NaBH_4$, MeOH, 0^oC, 30 min (80% yield over two steps); (i) TBDMSCl, imidazole, CH_2Cl_2, 0 ^oC-rt, 3 h, 90%; (j) Na, NH_3, THF, 20 min, 85 %; (k) TsCl, TEA, CH_2Cl_2, 0 ^oC-rt, 3h, 91%; (l) HC≡CLi, DMSO, rt, 3h, 68 %; (m) cat. Pd-$BaSO_4$, H_2, rt, 6 h, 92 %; (n) TBAF, THF, rt, 8 h, 85%; (o) TBDMSCl, imidazole, THF, 0 ^oC-rt , 83 %.

MOMCl and DIPEA gave **10**. Ozonolytic cleavage of olefin group in **10** followed by reduction of resulting aldehyde with $NaBH_4$ has yielded alcohol **11** with 80% yield over two steps. Protection of free hydroxyl as TBS ether and deprotection of benzyl group (using Na in NH_3) produced the alcohol **12**. The alcohol **12** is transformed to corresponding tosylate and then exposed to lithium acetylide to get homologated alkyne **13** [7]. Controlled reduction of alkyne group in **13** using Lindlars' catalyst produced corresponding olefin which on deprotection of TBDMS groups with TBAF produced alcohol **14**. Selective protection of primary hydroxyl group in **14** as TBS ether furnished key aliphatic fragment **3**.

Synthesis of aromatic fragment **4** is described in Scheme **2**. Esterification of benzoic acid **15** using DBU and MeI gave a hydroxyl ester which on treatment with Tf_2O produced triflate **16**. Subjection of triflate **16** to allylation in Stille coupling conditions (allyl tributyl tin and lithium chloride) followed by hydrolysis of ester group using LiOH furnished **4** in 86 % yield in 4 steps. The stage was now set for the coupling between **3** and **4**.

Esterification of **3** with **4** using DCC/DMAP or in Yamaguchi conditions [8] (2,4,6 trichlorobenzoyl chloride, TEA, THF, 4-DMAP, PhMe) met with failure in all possible alterations in reaction conditions. Then, we opted for the Mitsunobu conditions [9]. Prior to that, the hydroxyl group in **3** was inverted in standard Mitsunobu conditions so that the center will remain as such after the coupling of **17** with **4**. Thus, the esterification of **17** with **4** in Mitsunobu conditions smoothly resulted in **18**. Ring closing metathesis [10] of **18** using Grubbs' second generation catalyst followed by deprotection of TBS ether led to formal synthesis of Salycilihalamide A and B. Synthetic compound has showed spectral and analytical data (^1H NMR, ^{13}C NMR, IR, R_f and $[\alpha]_D$) identical to the previously synthesized sample [4e].

In summary, we have described a convergent formal approach to Salicylihalamides A and B using our recently



Scheme 2. Reagents and conditions: (a) DBU, MeI, THF, 0 ^oC-rt, 24 h, 82%; (b) Tf_2O, Py, 0^oC-rt, 20 h, 89%; (c) LiCl, allyl tributyl tin hydride, DMF, 0 ^oC-rt, 4 h; 82% (d) LiOH.H_2O, MeOH, 65 ^oC, 72 h, 95%; (e) i) 2,4,6-trichlorobenzoyl chloride, TEA, THF, 4-DMAP, PhMe, or ii) DCC, DMAP, CH_2Cl_2, rt; (f) DEAD, *p*-nitro benzoic acid, Ph_3P, THF, 0 ^oC-rt, 30 min then K_2CO_3, MeOH, rt, 30 min, 85%; (g) DEAD, **4**, Ph_3P, Benzene, rt, 2hrs, 90%; (h) Grubbs II catalyst, CH_2Cl_2, rt, 85% (9:1); (i) TBAF, THF, 0 ^oC - rt, 92 %.

developed synthetic sequence for the polyketide precursors *via* Prins cyclisation. The key transformations employed were reductive ring opening, Stille coupling, Mitsunobu inversion, Grubb's ring closing metathesis along with Prins cyclisation.

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[11] Spectral Data of Selected Compounds: colourless liquid; $[\alpha]^{25}_{D}$ -2.2 (c = 1.5, $CHCl_3$) R_f = 0.2 (EtOAc: Hexane, 60:40); IR (KBr): ν_{max} 3384, 2921, 2854, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.23 (m, 5H), 4.52-4.43 (m, 2H,), 3.91-3.71 (m, 2H), 3.60-3.30 (m, 5H), 2.02-1.71 (m, 3H), 1.5-1.46 (m, 1H), 1.22-1.09 (m, 1H), 0.95 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 128.3, 127.5, 76.5, 75.8, 73.0, 72.0, 68.0, 65.7, 37.3, 36.7, 34.1, 12.2, HRMS (ESI): *m/z* calcd for $C_{16}H_{24}O_4Na$ $[M+Na]^+$ 303.1572, found 303.1587. Spectral Data of Selected Compounds: colourless liquid; $[\alpha]^{25}_{D}$ +18.5 (c = 1.5, $CHCl_3$); R_f = 0.5 (EtOAc: Hexane, 20:80); IR (KBr): ν_{max} 3508, 2930, 2857, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.21 (m, 5H), 5.80-5.66 (m, 1H,), 5.07-4.98 (m,

2H), 4.53-4.45 (m, 2H), 4.09-3.92 (m, 1H), 3.78-3.69 (m, 1H), 3.53-3.41 (m, 2H), 2.32-2.25 (m, 2H, *J* = 6.7, 6.0 Hz), 1.86-1.70 (m, 1H), 1.62-1.35 (m, 2H), 0.93-0.87 (m, 12H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 134.7, 128.2, 127.4, 117.1, 73.8, 73.2, 71.1, 70.0, 41.7, 39.7, 39.1, 25.8, 18.0, 13.7, -4.4, -4.8. HRMS (ESI): *m/z* calcd for $C_{22}H_{38}O_3NaSi$ $[M+Na]^+$ 401.2487, found 401.2484. Spectral Data of Selected Compounds: clear oil. $[\alpha]^{25}_D$ -31.3 (c 0.5, $CHCl_3$), [lit.[4e] $[\alpha]^{25}_D$ -34.5 (c 1.0, $CHCl_3$)]. IR (neat): 3470, 2927, 1721, 1583, 1466, 1274 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29 –7.23 (m, 1H), 6.81(t, *J* = 8.6Hz, 2H), 5.49–5.40(m, 1H), 5.35–5.27 (m, 1H), 5.20-5.12 (m, 1H), 4.56 (d, *J* = 6.8Hz ,1H), 4.45 (d, *J* = 6.8Hz , 1H), 3.91 –3.82 (m, 1H), 3.79(s, 3H), 3.72 (q, *J* = 10.3Hz, 2H), 3.63 (dd, *J* = 11.9 Hz, 2.6Hz, 1H), 3.29 (s, 3H), 3.18 (dd, *J* = 11.9 Hz, 2.6Hz ,1H), 2.91 (br s, 1H, OH), 2.03–1.52 (m, 7H), 0.96 (d, *J* = 6.8Hz, 3H) ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.7, 157.2, 139.7, 133.2, 130.6, 128.7, 124.6, 123.3, 109.8, 95.8, 78.7, 73.7, 58.7, 55.9, 55.3, 38.3, 38.2, 37.4, 34.7, 14.5. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{30}NaO_6$: 401.1940; found : 401.1943.