Stereoselective Synthesis of the Macrocyclic Core of (–)-Salicylihalamides A and B

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Abstract: Stereoselective synthesis of the macrocyclic core of salicylihalamides A and B is described. The synthetic strategy features stereoselective iodolactonization, Sharpless asymmetric epoxidation, Mitsunobu esterification, and ring-closing metathesis.

Key words: salicylihalamide, cytotoxicity, Sharpless epoxidation, metathesis

The isolation and structural elucidation of cytotoxic salicylihalamides A and B were reported by Boyd and co-workers in 1997.1 These are novel secondary metabolites produced by a marine sponge of the genus Haliclona (south-western Australian coast). Since their discovery, a number of other structurally similar bioactive metabolites have been isolated and characterized, which include the apicularens, lobatamides, and oximidines.2 Each of these structures possesses a medium-sized macrolide ring engendering a salicylate moiety and a dienyl enamide side chain. Salicylihalamides displayed potent cytotoxicity when screened against the NCI 60-cell human tumor line assay, with a mean panel GI50 value of 15 nM.3 The mechanism of action of this compound has no correlation with other known compounds and thus occupies an important status. Thus, owing to the unique, potent cytotoxicity of the salicylihalamides, as well as their scarcity and their novel structural features, intense activity has been witnessed in their synthetic chemistry.4,5 In particular, ring-closing metathesis based syntheses of salicylihalamides have proven useful.5 Our long-standing interest in the development of strategies for the total synthesis of natural products having cytotoxic properties prompted us to take up the total synthesis of (–)-salicylihalamides A and B.6,7

Our retrosynthetic analysis revealed two key fragments, namely the functionalized benzoic acid derivative 2 and the chiral aliphatic fragment 3, which would give the macrolide core on simple Mitsunobu esterification and metathesis reaction. Our synthetic strategy is mainly focused on the synthesis of chiral aliphatic intermediate 3 containing three-stereogenic centers, the synthesis of aromatic fragment 2 was reported earlier by our group. We envisaged that we would easily build the aliphatic intermediate 3 from readily available chiron moiety 6 using stereoselective iodolactonization, epoxide opening, Sharpless asymmetric epoxidation, and sodium cyanoborohydride mediated regioselective opening of the acetal as key steps.

The macrolide synthesis started from commercially available citronellic acid (6). Acid 6 was converted into the known iodolactone 7 as reported by Still et al.8 Treatment of iodolactone 7 with potassium carbonate in methanol resulted in the formation of epoxide 5 in good yield. Epoxide 5 was opened with propargyl tetrahydropyranyl ether employing the Yamaguchi protocol 9 to produce the homopropargyl alcohol 8. The ester group in compound 8 was reduced with lithium aluminum hydride in tetrahydrofuran to obtain the corresponding diol, which was, in turn, subjected to monoprotection using tert-butylchlo-

Scheme 1 Retrosynthesis of (–)-salicylihalamide A (17E) and (–)-salicylihalamide B (17Z)
rodiphenylsilane and triethylamine in dichloromethane to furnish secondary alcohol derivative 9. Protection of the alcohol 9 as its methoxymethyl ether followed by deprotection of the tetrahydropyranyl moiety afforded proparglylic alcohol 10, which was subsequently reduced to allylic alcohol 4 using lithium aluminum hydride in tetrahydrofuran. Sharpless asymmetric epoxidation 10 of allylic alcohol 4 yielded epoxy alcohol 11, which on reductive opening with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) produced 1,3-diol 12 regioselectively. Diol 12 was protected as its 4-methoxybenzylidene acetal 13 and then the silyl ether was deprotected with tetrabutylammonium fluoride to give primary alcohol 14.

Sulfur trioxide/pyridine oxidation of alcohol 14 followed by one-carbon Wittig alkenation gave alkene 15, which on reductive opening of the acetal with sodium cyanoborohydride and chlorotrimethylsilane furnished the required aliphatic fragment 3.

The synthesis of 2-allyl-6-methoxybenzoic acid, the aromatic fragment of salicylihalamide was reported earlier by our group.12 Mitsunobu reaction between chiral allylic alcohol 14 and the aromatic fragment 3 furnished the required core structure.

**Scheme 2**  Reagents and conditions: (a) K$_2$CO$_3$, MeOH, reflux, 1 h, 96%; (b) n-BuLi, propargyl tetrahydropyranyl ether, BF$_3$·OEt$_2$, THF, –78 °C, 3 h, 87%; (c) LiAlH$_4$, THF, 0 °C to r.t., 50 min; (d) TBDPSCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C, 0.5 h, 96% (2 steps); (e) MOMCl, i-Pr$_2$NEt, DMAP, 0 °C to r.t., 6 h; (f) PPTS, EtOH, 60 °C, 1 h, 94% (2 steps); (g) LiAlH$_4$, THF, 0 °C, 3 h, 93%; (h) Ti(Oi-Pr)$_4$, (+)-DIPT, t-BuOOH, CH$_2$Cl$_2$, 4 Å MS, –24 °C, 3 h, 89%; (i) Red-Al, THF, 0 °C to r.t., 2 h, 93%; (j) 4-methoxybenzaldehyde dimethyl acetal, CSA, CH$_2$Cl$_2$, 0 °C, 1 h, 95%; (k) TBAF, THF, 0 °C to r.t., 1 h, 96%; (l) SO$_3$/py, Et$_3$N, DMSO–CH$_2$Cl$_2$ (2:1.6), 0 °C, 0.5 h; (m) Ph$_3$PCH$_3$I, t-BuOK, THF, 0 °C, 3 h, 87% (2 steps); (n) NaBH$_3$CN, TMSCl, MeCN, 4 Å MS, 0 °C, 15 min, 79%.

**Scheme 3**  Reagents and conditions: (a) DEAD, Ph$_3$P, benzene, 10 °C to r.t., 1 h, 91%; (b) Grubb’s I catalyst, CH$_3$Cl$_2$, reflux, 3 h, 85%; (c) DDQ, CH$_2$Cl$_2$–H$_2$O (19:1), 0 °C to r.t., 94%.

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*Dedicated to Professor Hermann Nöth on the occasion of his 70th birthday. 1071*
phatic alcohol 3 and benzoic acid 2 produced the ester 16, which set the stage for a ring-closing metathesis reaction.\textsuperscript{14}

Ring-closing metathesis with first generation Grubb’s catalyst furnished the desired E-intermediate 17 as the predominant diastereomer (E/Z = 9:1). Deprotection of the 4-methoxyphenylmethyl ether furnished the known alcohol 18,\textsuperscript{3e} unequivocally proving the structure assigned to 17.

Compound 18 has been converted into the target molecule 1 by Furstner et al.,\textsuperscript{3e} thus the present strategy completes the formal total synthesis.

In conclusion, our synthesis allowed easy access for the preparation of intermediate 18 in greater than 100-mg quantities, like many previous reports, thereby paving an easy way for the total synthesis of salicylihalamides A and B by introducing appropriate side chains. The synthetic route includes very versatile reactions like iodolactonization, epoxide opening, Sharpless asymmetric epoxidation, Mitsunobu esterification, and metathesis.

Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All solvents were purified and dried by standard procedures before use. Organic solns of the products were dried over anhyd Na$_2$SO$_4$. All reactions involving organometallic reagents were conducted under an inert atmosphere. Optical rotations were measured with a Jasco DIP-360 polarimeter. IR spectra were obtained on a Thermo Nicolet Nexus 670 FTIR spectrophotometer. NMR spectra were measured on Varian Gemini 200 or Varian Unity 400 or Varian Inova 500 MHz or Bruker Avance 300 MHz spectrometers (1H) and 75 or 50 MHz spectrometers (13C), in CDCl$_3$ with TMS as an internal standard. MS spectra were recorded using EI, liquid secondary ion mass spectrometric (LSIMS), ESI, and HRMS techniques. The progress of all the reactions was monitored by TLC using glass plates precoated with silica gel 60F$_{254}$ (0.5 mm, Merck). Column chromatography using silica gel 60–120 mesh (EtOAc–hexane).

**Methyl (3S,4R)-4-Hydroxy-3-methyl-8-(tetrahydro-2H-pyran-2-yl)oct-6-yne-6-ynoate (8)**

A 250-mL round-bottomed flask equipped with a magnetic stirring bar, dry N$_2$ inlet, reflux condenser and septum was flushed with N$_2$ A 250-mL round-bottomed flask equipped with a magnetic stirring bar, dry N$_2$ inlet, reflux condenser and septum was flushed with N$_2$. Et$_3$N (6.78 mL, 48.75 mmol) and TBDPSCl (9.16 mL, 25 +2.3 (c 2.0, CHCl$_3$).

IR (neat): 1723, 11.12 g (87%); $R_f = 0.5$ (silica gel, 50% EtOAc–petroleum ether).

MS (ESI): $m/z = 284$ [M$^+$].

HRMS (EI): $m/z = [M + H]^+$ calculated for C$_{16}$H$_{20}$O$_5$: 284.1702; found: 284.1691.

**Methyl (3S,4R)-1-(tert-Butyldiphenylsiloxyl)-3-methyl-8-(tetrahydro-2H-pyran-2-yloxy)oct-6-yn-4-ol (9)**

To a suspension of LiAlH$_4$ (1.273 g, 33.5 mmol) in anhyd THF (30 mL) under an atmosphere of N$_2$ at 0 °C was added 8 (9.514 g, 33.5 mmol) in anhyd THF (70 mL) and the mixture was stirred at r.t. for 1 h. It was then cooled to 0 °C, diluted with wet Et$_2$O, and the excess LiAlH$_4$ was quenched by the addition of sat. aq NH$_4$Cl. When the ef-fervescence had subsided, the mixture was filtered through a pad of Celite and washed with CHCl$_3$ and hot EtOAc. The filtrate was evaporated in vacuo and the residue was used directly in the next step.

The residue was dissolved in anhyd CH$_2$Cl$_2$ (80 mL) under an atmosphere of N$_2$, Et,N (6.78 mL, 48.75 mmol) and TBDDS$_2$Cl (9.16 mL, 35.75 mmol) were added sequentially at 0 °C. Next, a catalytic amount of DMAP (0.397 g, 3.25 mmol) was added. The mixture was stirred at r.t. for 0.5 h and then quenched by the addition of sat. aq NH$_4$Cl and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by column chromatography (silica gel, 10–12% EtOAc–petroleum ether) gave pure 9 as a clear oil; yield: 15.91 g (96% over 2 steps); $R_f = 0.7$ (silica gel, 30% EtOAc–petroleum ether).

MR (H NMR (200 MHz, CDCl$_3$): $\delta = 3.67$ (s, 3 H), 2.82–2.64 (m, 2 H), 2.52 (m, 1 H), 2.44–2.14 (m, 2 H), 2.02–1.80 (m, 1 H), 1.07 (d, $J = 7.0$ Hz, 3 H).

$^{1}$C NMR (75 MHz, CDCl$_3$): $\delta = 172.36, 155.46, 51.36, 45.93, 37.41, 32.49, 16.40$.


**Methyl (3S,4R)-4-Hydroxy-3-methyl-8-(tetrahydro-2H-pyran-2-yl)oct-6-ynoate (8)**

Under an atmosphere of N$_2$, 1.6 M n-BuLi in hexane (45 mL, 72 mmol) was added to a soln of propargyl tetrahydropyrany-2-yl ether (7.45 g, 54 mmol) in THF (45 mL) at –78 °C and the mixture was stirred for 15 min. Then, BF$_3$·OEt$_2$ (5.65 mL, 45 mmol) was added to the soln, and the stirring was continued for 15 min at the same temperature. Finally a soln of 5 (6.48 g, 45 mmol) in anhyd THF (40 mL) was added. The mixture was stirred at –78 °C for 3 h and then the reaction was quenched by addition of sat. aq NH$_4$Cl (30 mL). Then the mixture was extracted with EtOAc and dried (anhyd Na$_2$SO$_4$). Evaporation of the solvents resulted in crude alcohol, which was purified by column chromatography (silica gel, 30–33% EtOAc–petroleum ether) to afford pure 8 as colorless liquid; yield: 11.12 g (87%); $R_f = 0.5$ (silica gel, 50% EtOAc–petroleum ether).

IR (neat): 3457, 2945, 2873, 1735, 1438, 1352, 1263, 1201, 1174, 1117, 1078, 1021, 948, 901, 870, 813, 757 cm$^{-1}$.

$^{1}$H NMR (200 MHz, CDCl$_3$): $\delta = 4.80–4.76$ (m, 1 H), 4.21–4.19 (m, 2 H), 3.91–3.67 (m, 2 H), 3.66 (s, 3 H), 3.60–3.40 (m, 1 H), 2.80–2.08 (m, 5 H), 1.90–1.30 (m, 6 H), 0.96 (d, $J = 6.8$ Hz, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 175.44, 96.58, 85.29, 80.05, 72.01, 61.80, 53.95, 51.11, 37.82, 36.57, 34.4, 30.11, 25.03, 25.00, 18.80.

MS (ESI): $m/z = 284$ [M$^+$].

HRMS (EI): $m/z = [M + H]^+$ calculated for C$_{16}$H$_{20}$O$_5$: 284.1702; found: 284.1691.

To a cold (0 °C) soln of 9 (12.63 g, 25.55 mmol) in CH2Cl2 (150 mL) were added t-PrI,NEt (44.4 mL, 255.5 mmol), MOMCl (9.64 mL, 127.7 mmol), and TBAI (0.943 g, 2.55 mmol). The mixture was immediately allowed to warm to r.t. and protected from light. After 6 h, sat. aq NaHCO3 was added together with Et3O. The organic layer was washed with brine and the aqueous layer was extracted with Et3O. The combined extracts were dried (Na2SO4) and concentrated in vacuo to yield the crude product. The residue was used directly in the next step.

The residual compound (13.20 g, 24.51 mmol) was dissolved in EtOH (60 mL) and stirred along with catalytic amount of PPTS (0.307 g, 1.23 mmol) at 60 °C for 1 h. The mixture was quenched with Et2O (60 mL), warmed to r.t. and stirred for 1 h and then re-cooled to 0 °C. 30% Aq NaOH (w/v, 16 mL) was saturated with NaCl and the mixture was swirled at 0 °C for 10 min. CH2Cl2 was removed under reduced pressure, the compound was extracted with Et2O with brine, dried (Na2SO4), filtered and concentrated in vacuo. Purification by column chromatography (silica gel, 24–27% EtOAc–petroleum ether) afforded pure 11 as a colorless oil; yield: 4.42 g (89%); Rf = 0.5 (silica gel, 50% EtOAc–petroleum ether).

HRMS (ESI): m/z [M + H]+ calcd for C27H41O4Si: 473.2723; found: 473.2711.

(3R,5R,6S)-8-(tert-Butyldiphenylsiloxy)-5-(methoxymethyl)-6-methyloct-2-ene-1-ol (10)

A suspension of LiAlH4 (0.610 g, 16 mmol) in anhyd THF (16 mL) under an atmosphere of N2 at 0 °C was added 10 (7.26 g, 16 mmol) in anhyd THF (32 mL) and the mixture was stirred at r.t. for 3 h. It was then was cooled to 0 °C, diluted with wet Et2O and the excess of LiAlH4 was quenched by the addition of sat. Na2SO4. When the effervescence subsided, the mixture was filtered through a pad of Celite and washed with CHCl3 and hot EtOAc. The filtrate was washed with brine, dried (Na2SO4), evaporated in vacuo, and the residue was purified by column chromatography (silica gel, 15–17% EtOAc–petroleum ether) to afford 4 as a viscous liquid; yield: 6.78 g (93%); Rf = 0.5 (silica gel, 30% EtOAc–petroleum ether).

IR (neat): 3455, 2931, 2858, 1466, 1427, 1386, 1106, 1037, 899, 822, 739, 704 cm−1.

(3S,4R)-1-(tert-Butylidiphenylsiloxy)-4-(methoxymethoxy)-5-[(4R)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-3-methylpentan-1-ol (13)

To a solution of 12 (1.327 g, 2.8 mmol) in anhyd CH2Cl2 (10 mL), 4-methoxybenzaldehyde dimethyl acetal (0.573 mL, 3.36 mmol) and CSA (7 mg, 0.028 mmol) were added sequentially at 0 °C. The mixture was stirred at the same temperature for 1 h and then the reaction was quenched by the addition of sat. NH4Cl solution. The mixture was extracted with EtOAc, washed with brine, dried (Na2SO4), and concentrated in vacuo. Purification by column chromatography (silica gel, 10–12% EtOAc–petroleum ether) gave 13 as a colorless oil; yield: 1.57 g (95%); IR (neat): 3403, 2932, 1715, 1605, 1514, 1462, 1380, 1252, 1150, 1095, 1035, 917, 824, 740, 704, 612 cm–1.


The mixture was stirred at 0 °C for 30 min and then the reaction was quenched with sat. NH4Cl solution and extracted with petroleum ether. The organic extract was dried (Na2SO4) and concentrated in vacuo. The resulting aldehyde was used directly in the next step.

To a mixture of methyltriphenylphosphonium iodide (3.15 g, 7.8 mmol) and t-ButOK (0.582 g, 5.2 mmol) in anhyd THF (15 mL) at –78 °C was added 18-crown-6 (~5 mg) and the soln was stirred for 1 h. Then aldehyde (0.457 g, 1.3 mmol) in anhyd THF (6 mL) was added to this and stirring was continued until the starting material had been consumed. The mixture was quenched by the addition of H2O (6 mL) and the solvent was evaporated. The residue was taken in EtOAc and the organic layer was washed with H2O (1 × 15 mL) followed by brine (1 × 15 mL) and dried (anhyd Na2SO4). The solvent was evaporated under reduced pressure. Purification by column chromatography (silica gel, 7–9% EtOAc–petroleum ether) afforded pure 15 as a viscous liquid; yield: 0.469 g (87% over 2 steps); Rf = 0.7 (silica gel, 30% EtOAc–petroleum ether).

To a soln of 14 (0.336 g, 0.96 mmol) in anhyd MeCN (20 mL), activated and powdered 4 Å molecular sieves (124 mg) were added at 0 °C and NaBH3CN (0.362 g, 5.78 mmol) and TMSCl (0.74 mL, 6.78 mmol) were added sequentially. The mixture was stirred for 15 min and then quenched by the addition of sat. aq NaHCl. It was extracted with EtOAc, washed with brine, dried (Na2SO4), and concentrated in vacuo. The resulting aldehyde was used directly in the next step.

To a soln of 15 (0.336 g, 0.96 mmol) in anhyd MeCN (20 mL), activated and powdered 4 Å molecular sieves (124 mg) were added at 0 °C. The mixture was stirred for 30 min and then the reaction was quenched with sat. NH4Cl solution and extracted with petroleum ether. The organic extract was dried (Na2SO4) and concentrated in vacuo. The resulting aldehyde was used directly in the next step.

To a mixture of methyltriphenylphosphonium iodide (3.15 g, 7.8 mmol) and t-ButOK (0.582 g, 5.2 mmol) in anhyd THF (15 mL) at –78 °C was added 18-crown-6 (~5 mg) and the soln was stirred for 1 h. Then aldehyde (0.457 g, 1.3 mmol) in anhyd THF (6 mL) was added to this and stirring was continued until the starting material had been consumed. The mixture was quenched by the addition of H2O (6 mL) and the solvent was evaporated. The residue was taken in EtOAc and the organic layer was washed with H2O (1 × 15 mL) followed by brine (1 × 15 mL) and dried (anhyd Na2SO4). The solvent was evaporated under reduced pressure. Purification by column chromatography (silica gel, 7–9% EtOAc–petroleum ether) afforded pure 15 as a viscous liquid; yield: 0.469 g (87% over 2 steps); Rf = 0.7 (silica gel, 30% EtOAc–petroleum ether).


1H NMR (500 MHz, CDCl 3): δ = 7.32–7.21 (m, 3 H), 6.93–6.73 (m, 4 H), 6.05–5.65 (m, 2 H), 5.52–5.27 (m, 1 H), 5.13–4.94 (m, 4 H), 4.64 (s, 2 H), 4.45 (s, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.70–3.52 (m, 3 H), 3.42–3.30 (m, 5 H), 2.40–2.14 (m, 1 H), 2.12–1.73 (m, 6 H), 0.88 (d, J = 6.5 Hz, 3 H).

13C NMR (75 MHz, CDCl 3): δ = 167.6, 159.2, 156.3, 138.2, 137.6, 136.3, 130.5, 130.2, 129.3, 124.2, 121.7, 116.3, 113.7, 113.9, 108.8, 96.2, 78.1, 72.9, 70.7, 66.5, 55.8, 55.5, 55.7, 57.9, 37.3, 37.6, 32.5, 35.8, 35.3, 34.5, 13.8.


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References

