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Formal Total Synthesis of Salicylihalamides A and B

Georgina A. Holloway,[†] Helmut M. Hügel,[‡] and Mark A. Rizzacasa*,[†]

School of Chemistry, The University of Melbourne, Victoria 3010, Australia, and Department of Applied Chemistry, RMIT University, Box 2476V GPO Melbourne 3001, Australia

masr@unimelb.edu.au

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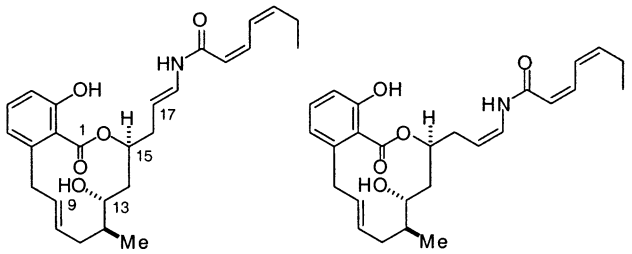
An efficient synthesis of the macrolactone **3** of the salicylihalamides in 10 linear steps from alkene **6** is described. The key steps involved a Stille coupling between the chiral stannane **5** and benzyl bromide **4**, which produced alkene **15** in good yield, and subsequent base-induced macrolactonization then gave compound **3**. Macrolactone **3** was then converted into the known salicylihalamide A intermediate **18** in a three-step sequence. Compound **3** was also converted into another known salicylihalamide A and B intermediate **23** in a five-step sequence.

Introduction

Marine sponges supply compounds with highly varied molecular architecture and pharmacological properties.[1] Recently, a pair of compounds named salicylihalamides A (**1**) and B (**2**) were isolated from a sponge of the genus *Haliclona* collected from waters around Rottnest island off the coast of Western Australia.[2] These compounds



1 Salicylihalamide A **2** Salicylihalamide B

were identified as novel highly cytotoxic macrolides that possess a new 12-membered unsaturated benzlactone ring system as well as an unusual enamide side chain and differ only in the geometry about the C17−C18 enamide double bond. Testing of salicylihalamide A (**1**) in the U.S. National Cancer Institute (NCI) 60-cell-line human tumor screen gave a pattern of differential toxicity that did not correlate with the profiles of any known antitumor compounds in the NCI standard database.[2] These results suggest that compound **1** has a novel mechanism-of-action and would make an interesting synthetic target for the potential development of a new class of antitumor compound. Further biological evaluation revealed that compound **1** was the first of a new class of mammalian specific vacuolar-type (H^+)-ATPase inhibitor.[3]

Several approaches to the lactone core of these compounds have been reported,[4] along with strategies for introduction of the enamide side chain.[5] The first total syntheses of salicylihalamide A (**1**) was reported by De Brabander and co-workers,[6] and this allowed for the reassignment of the absolute configuration of **1**[2b] as opposite to that originally proposed from Mosher ester analysis.[2a] This synthesis was then followed by a number of others,[7] all of which relied on ring-closing metathesis[8] to form the C9−C10 alkene and provide the 12-membered benzlactone system. Each of these approaches afforded varying selectivities for the geometric isomers, with all favoring formation of the *E*-macrolactone.

It was envisaged that both natural products **1** and **2** could arise from intermediate macrolactone **3** (Scheme 1). We elected to utilize an alternative approach to intermediate **3** that involved formation of the C8−C9

[†] The University of Melbourne.
[‡] RMIT University.

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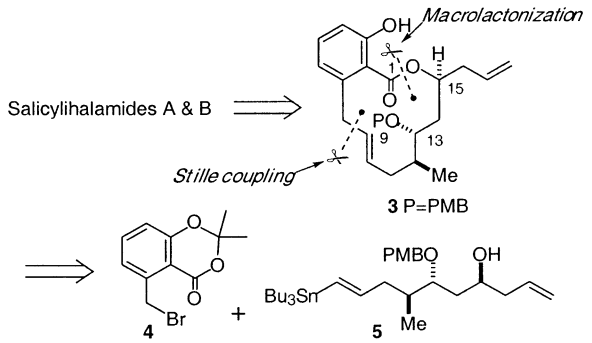
SCHEME 1

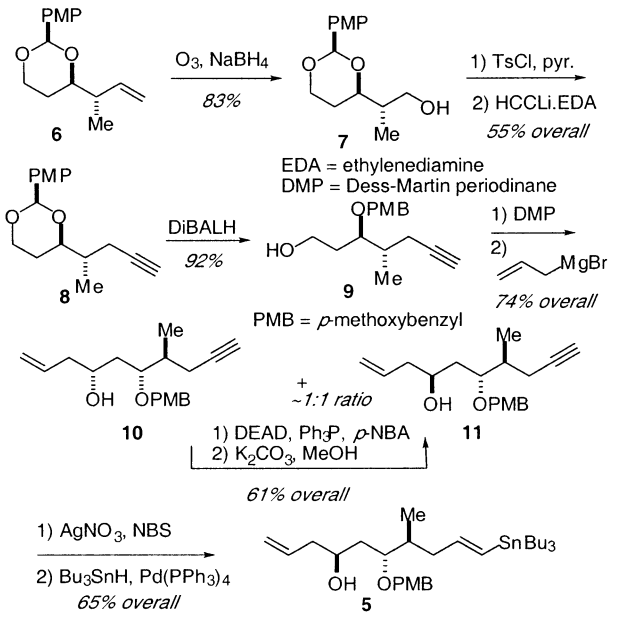


bond via a Stille cross-coupling[9] between benzyl bromide **4** and chiral stannane **5**. Novel base-induced macrolactonization[10] with concomitant expulsion of acetone would then provide the 12-membered[11] salicylihalamide benzlactone **3** with high selectivity for the desired *E* geometry. Indeed, this approach was tested by us in a model system and found to be more stereoselective than metathesis.[4b] Curiously, an attempt by other workers to apply a cross-coupling/macrolactonization-type strategy failed to provide the salicylihalamide lactone.[6c] We now wish to report the successful implementation of this approach, which afforded several intermediates that have been converted into **1** and **2**.[6c,7a,e]

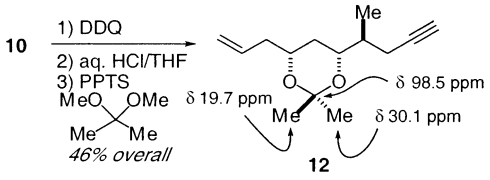
Results and Discussion

The route to the stannane coupling partner **5** begins with the known optically pure acetal **6**[12] (Scheme 2). Ozonolysis followed by reductive workup gave the primary alcohol **7**, which was converted to the alkyne **8** by tosylation and subsequent acetylide anion displacement. It was essential that the displacement reaction was quenched by rapid addition to a stirred mixture of ethyl acetate and brine in order to minimize formation of an undesired isomerized alkyne byproduct.[13] DiBALH reduction of the acetal functionality provided alcohol **9**, which upon oxidation with Dess−Martin periodinane (DMP)[14] and addition of allylmagnesium bromide afforded a ∼1:1 ratio of isomeric alcohols **10** and **11** that were separable by flash chromatography.

SCHEME 2



The configuration of the undesired alcohol **10** was determined by its conversion to the acetonide **12** followed by ^{13}C NMR analysis as shown. The chemical shifts for the methyl and acetal carbons were in accord with the 1,3-*syn*-stereochemistry.[15] Compound **10** was easily converted into **11** by Mitsunobu inversion[16] using a modified procedure.[17] Conversion of alkyne **11** into stannane **5** was effected using Pattenden's modification[18] for regioselective palladium-catalyzed hydrostannylation of terminal alkynes.[19]



The benzyl bromide **4**[11] required for coupling with the stannane **5** was synthesized from 6-methylsalicylic acid **13**[20] (Scheme 3). Acetonide formation[21] provided the dioxinone **14**, which was converted into bromide **4** by radical bromination. Stille coupling of **4** and **5** proceeded smoothly using TFP as ligand[22] to give the alkene **15** in good yield. The crucial macrolactonization[10,11] was effected by treatment of a dilute solution of **15** in THF with NaH, which provided benzlactone **3** in reasonable yield. The use of silyl ether protecting groups on O13 resulted

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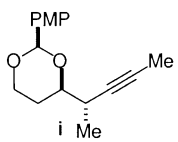

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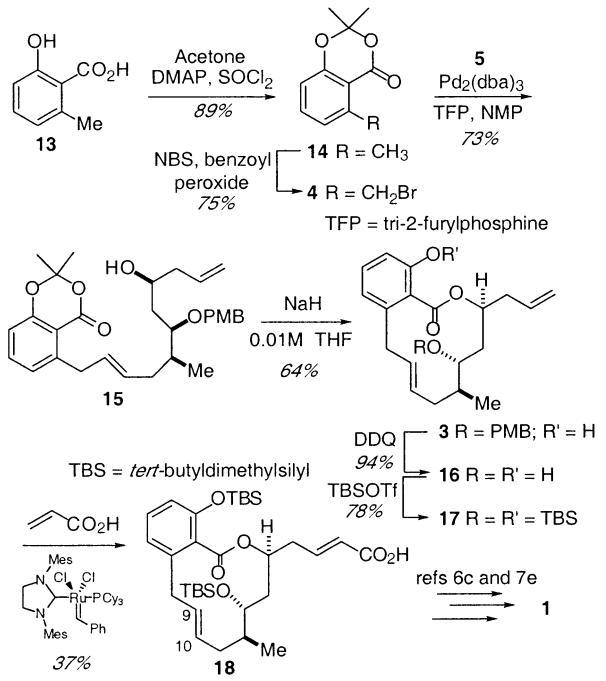
SCHEME 3



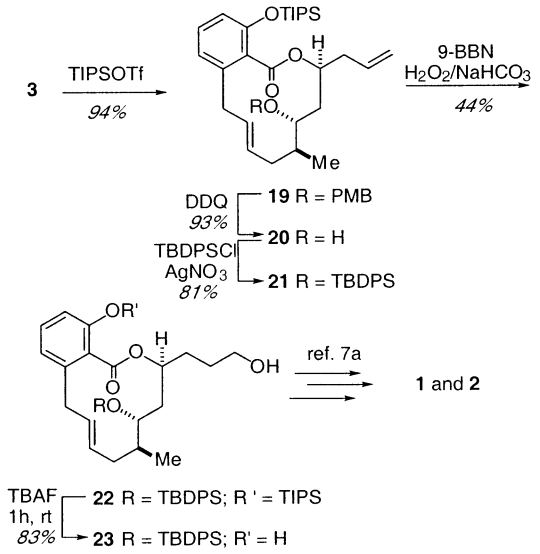
in lower yields as a result of complications from silyl group migration and steric hindrance.

Conversion of compound **3** into the known salicylihalamide A (**1**) intermediate **18**[6,7e] was achieved as shown in Scheme 3. Removal of the PMB ether was effected with DDQ, and protection of the resultant diol **16** gave bis silyl ether **17**. Selective cross metathesis between the terminal alkene in **17** and acrylic acid using Grubbs' second generation catalyst[23] and subsequent purification by preparative HPLC gave the α,β-unsaturated acid **18**, which had identical physical data to that quoted in the literature.[6c,7e] This therefore constitutes a formal total synthesis of salicylihalamide A (**1**).

The low yield obtained for the cross metathesis reaction led us to examine the conversion of macrolactone **3** into the alternative known salicylihalamide intermediate lactone **23**[7a] as outlined in Scheme 4. Phenol protection provided TIPS ether **19** and PMB group removal yielded alcohol **20**, which was effectively silylated using $AgNO_3$ and TBDPSCl.[24] This reagent system proved most effective for the silylation of the hindered alcohol to afford the TBDPS ether **21**. Hydroboration of the terminal alkene with 9-BBN followed by oxidative workup gave alcohol **22** and selective desilylation finally gave the known diol **23,** which had a ^{1}H NMR spectrum in d_6-acetone identical to that quoted in the literature.[7a] Compound **23** has been converted into both salicylihalamides A (**1**) and B (**2**).[7a]

In conclusion, we have achieved the formal total synthesis of both salicylihalamides A (**1**) and B (**2**) via the common benzlactone intermediate **3**. This route allows for the introduction of the enamide side chain by various methods[5] and utilizes an efficient Stille coupling/macrolactonization sequence for the stereoselective production of the novel benzlactone. It is envisaged that this route can also supply salicylihalamide analogues for biological assessment.

SCHEME 4



Experimental Section

General. Unless otherwise stated, ^{1}H NMR and proton decoupled ^{13}C NMR spectra were recorded for deuteriochloroform solutions with residual chloroform as internal standard. Optical rotations were recorded in a 10-cm microcell. HRMS (ESI) mass spectra were run on a FTMS mass spectrometer at Monash University, Clayton, Victoria. Flash chromatography was carried out on Merck silica gel 60. Anhydrous THF was distilled from sodium/benzophenone ketal under a nitrogen atmosphere. All other anhydrous solvents were purified according to standard methods. Petrol refers to the fraction boiling between 40 and 60 °C.

1,3-Benzodioxin-4-one 14. To a solution of 6-methylsalicylic acid (**13**) (1.62 g, 10.7 mmol), DMAP (67 mg, 0.55 mmol), and acetone (0.96 mL, 13 mmol) in dimethoxyethane (3.6 mL) was added dropwise a solution of thionyl chloride (1.1 mL, 15 mmol) in dimethoxyethane (0.5 mL) via cannula. The temperature was maintained below 30 °C. The reaction mixture was stirred for 3 h, after which time it was concentrated. The residue was filtered through a plug of silica gel with 50% petrol/CH_2Cl_2 as eluant to provide the acetonide **14** (1.84 g, 89%) as a colorless solid: R_f 0.82 (50% EtOAc/petrol); IR υ_{max} (film) 1748, 1608 cm^{-1}; ^{1}H NMR δ 1.69 (s, 6H), 2.67 (s, 3H), 6.79 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H); ^{13}C NMR δ 21.9, 25.6 (2C), 105.1, 112.4, 115.0, 125.7, 135.0, 143.5, 156.9, 160.6; HRMS (ESI) calcd for $C_{11}H_{12}O_3Na$ [M + Na$^+$] 215.0678, found 215.0680.

Benzyl Bromide 4. A solution of **14** (2.07 g, 10.7 mmol), *N*-bromosuccinimide (2.09 g, 11.8 mmol), and benzoyl peroxide (69 mg, 0.28 mmol) in carbon tetrachloride (25.7 mL) was heated at reflux for 15 h. The reaction mixture was then filtered, and the filtrate was concentrated. The crude product was dissolved in EtOAc, and the organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel with 5% EtOAc/petrol as eluant to give the bromide **4** (1.54 g, 75%) as light yellow prisms: mp 70−71 °C; R_f 0.61 (30% EtOAc/petrol); IR υ_{max} (film) 1732, 1603 cm^{-1}; ^{1}H NMR δ 1.72 (s, 6 H), 5.05 (s, 2H), 6.94 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 7.7, 1H); ^{13}C NMR δ 25.5 (2C), 30.9, 105.7, 111.4, 118.0, 125.7, 135.6, 141.7, 157.2, 159.7; HRMS (ESI) calcd for $C_{11}H_{11}O_3BrNa$ [M + Na$^+$] 292.9789, found 292.9788.

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Alkene 15. A solution of the vinyl stannane **5** (126 mg, 212 μmol) in 1-methyl-2-pyrrolidinone (1 mL) was freeze-pump-thawed twice. Tris(dibenzylideneacetone)dipalladium(0) (9.45 mg, 10.3 μmol) and tri-2-furylphosphine (9.77 mg, 42.3 μmol) were then added, the mixture was stirred for 15 min at room temperature, and the bromide **4** (68.9 mg, 254 μmol) was then added. The reaction mixture was stirred at room temperature for 15 h after which time water and ether were added. The organic extract was washed with aqueous ammonia, water, and brine, dried ($MgSO_4$), and concentrated, and the residue was purified on silica gel using 20% EtOAc/petrol as eluant to afford the alkene **15** (74.7 mg, 73%) as a colorless oil: R_f 0.24 (20% EtOAc/petrol); $[\alpha]^{22}_D = +16.6$ (*c* 0.90, CH_2Cl_2); IR υ_{max} (film) 3467, 1641, 1608 cm^{-1}; ^1H NMR δ 0.83 (d, $J = 7.3$ Hz, 3H), 1.57 (ddd, $J = 11.3, 7.3, 2.9$ Hz, 1H), 1.68 (s, 6H), 1.81−1.98 (m, 2H), 2.14 (m, 1H), 2.19 (t, $J = 6.8$ Hz, 2H), 2.71 (s, 1H), 3.55 (m, 1H), 3.78 (s, 3H), 3.84 (m, 2H), 3.89 (m, 1H), 4.44 (AB, $J = 11.1$ Hz, 2H), 5.08 (m, 2H), 5.42 (dt, $J = 15.0, 6.6$ Hz, 1H), 5.63 (dt, $J = 15.0, 6.6$ Hz, 1H), 5.80 (m, 1H), 6.81 (d, $J = 7.9$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 7.9$ Hz, 1H), 7.24 (d, $J = 8.7$ Hz, 2H), 7.41 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR δ 14.2, 25.6, 35.0, 36.3, 37.1, 42.1, 55.2, 67.8, 71.1, 79.4, 105.0, 111.9, 113.7, 115.3, 117.4, 124.7, 129.5 (2C), 129.6 (2C), 130.3, 130.4, 135.0, 135.2, 146.0, 156.9, 159.1, 160.2; HRMS (ESI) calcd for $C_{30}H_{38}O_6$ [$M + H^+$] 495.2746, found 495.2743.

Macrolactone 3. A solution of the acetonide **15** (40.3 mg, 81.5 μmol) in THF (2.8 mL) was added dropwise via cannula to sodium hydride (220 mg, 5.54 mmol) in THF (4.4 mL). The reaction mixture was stirred at room temperature for 6 h after which time ether was added. The solution was cooled to 0 °C, and the pH was adjusted to 3 by the addition of cold 5% hydrochloric acid. Water was then added, and the crude product was extracted into ether, washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel using 20% EtOAc/petrol as eluant, which provided the macrolactone **3** (22.7 mg, 64%) as a colorless oil: R_f 0.24 (20% EtOAc/petrol); $[\alpha]^{22}_D = +71.6$ (*c* 1.23, CH_2Cl_2); IR υ_{max} (film) 3494, 1725, 1651 cm^{-1}; ^1H NMR δ 0.92 (d, $J = 7.2$ Hz, 3H), 1.46 (dd, $J = 14.0, 8.9$ Hz, 1H), 1.90 (m, 2H), 2.18 (ddd, $J = 14.1, 7.1, 3.2$ Hz, 1H), 2.33 (m, 1H), 2.43 (dd, $J = 13.4, 6.8$ Hz, 2H), 3.36 (m, 2H), 3.77 (m, 1H), 3.71 (s, 3H), 4.33 (AB, $J = 10.8$ Hz, 2H), 5.12 (m, 1H), 5.14 (m, 2H), 5.44−5.54 (m, 2H), 5.82 (m, 1H), 6.71 (d, $J = 7.7$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.91 (d, $J = 7.7$ Hz, 1H), 7.26 (d, $J = 8.6$ Hz, 2H), 7.31 (t, $J = 7.7$ Hz, 1H), 11.24 (s, 1H); ^{13}C NMR δ 14.0, 31.5, 38.4, 39.1, 39.5, 55.2, 71.1, 74.3, 78.0, 112.9, 113.7 (2C), 116.7, 118.4, 123.5, 126.2, 129.6 (2C), 130.6, 133.0, 133.2, 134.0, 142.6, 159.1, 162.9, 170.8; HRMS (ESI) calcd for $C_{27}H_{32}O_5Na$ [$M + Na^+$] 459.2148, found 459.2143.

Alcohol 16. To a solution of the PMB ether **3** (52.4 mg, 12.0 μmol) in CH_2Cl_2 (3.1 mL) and water (171 μL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (30.0 mg, 133 μmol). The reaction mixture turned green and was stirred at room temperature for 1 h open to the atmosphere. It was then filtered through a plug of filter aid, washed with CH_2Cl_2, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel using 20% EtOAc/petrol as eluant to give the diol **16** (35.5 mg, 94%) as a colorless low melting crystalline solid: R_f 0.28 (20% EtOAc/petrol); $[\alpha]^{24}_D = +37.3$ (*c* 1.77, CH_2Cl_2); IR υ_{max} (film) 3494, 1732, 1653 cm^{-1}; ^1H NMR δ 0.92 (d, $J = 6.6$ Hz, 3H), 1.38 (dd, $J = 15.5, 11.6$ Hz, 2H), 1.74 (s, 1H), 1.86 (m, 2H), 2.35 (m, 1H), 2.46 (t, $J = 6.8$ Hz, 2H), 3.41 (d, $J = 16.5$ Hz, 1H), 3.66−3.77 (m, 2H), 5.13−5.18 (m, 3H), 5.38 (dt, $J = 15.5, 4.5$ Hz, 1H), 5.68 (dt, $J = 10.5, 5.6$ Hz, IH), 5.83 (m, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.88 (d, $J = 8.1$ Hz, 1H), 7.29 (t, $J = 8.1$ Hz, 1H), 10.80 (s, 1H); ^{13}C NMR δ 13.7, 35.4, 37.4, 38.3, 39.0, 39.7, 70.5, 74.2, 113.5, 116.6, 118.6, 123.5, 126.6, 132.7, 133.2, 133.9, 142.4, 162.2, 170.6; HRMS (ESI) calcd for $C_{19}H_{24}O_4Na$ [$M + Na^+$] 339.1573, found 339.1574.

Bis TBS Ether 17. To a solution of the diol **16** (35.5 mg, 112 μmol) in dry CH_2Cl_2 (0.6 mL) at 0 °C was added 2,6-lutidine (52.2 μL, 487 μmol) followed by *tert*-butyldimethylsilyl trifluoromethanesuflonate (77.4 μL, 337 μmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then ether and saturated $NaHCO_3$ were added. The crude product was isolated by extraction with ether, and the organic fraction was washed with water, saturated $CuSO_4$, water, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue produced was purified on silica gel using 2.5% EtOAc/petrol as eluant to afford the bis TBS ether **17** (47.94 mg, 78%) as a colorless oil: R_f 0.33 (2.5% EtOAc/petrol); $[\alpha]^{16}_D = -1.2$ (*c* 1.13, CH_2Cl_2); IR υ_{max} (film) 1726, 1643 cm^{-1}; ^1H NMR δ 0.11 (s, 3H), 0.16 (s, 3H), 0.19 (s, 3H), 0.22 (s, 3H), 0.83 (d, $J = 6.3$ Hz, 3H), 0.91 (s, 9H), 0.97 (s, 9H), 1.65 (m, 1H), 1.78 (m, 2H), 2.27 (m, 2H), 2.46 (t, $J = 6.8$ Hz, 2H), 3.32 (m, 1H), 3.66 (dd, $J = 16.4, 8.6$ Hz, 1H), 4.27 (m, 1H), 5.12 (m, 2H), 5.23 (m, 1H), 5.36−5.41 (m, 2H), 5.79 (m, 1H), 6.72 (d, $J = 7.2$ Hz, 1H), 6.74 (d, $J = 7.2$ Hz, 1H), 7.11 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR δ −4.5, −4.4 (2C), −4.2, 18.0, 18.3, 25.7 (3C), 25.9 (3C), 30.3, 35.9, 37.2, 38.2, 40.1, 71.9, 73.9, 117.8, 117.9, 123.2, 127.5, 128.3, 129.4, 131.4, 133.7, 138.7, 152.7, 168.3; HRMS (ESI) calcd for $C_{31}H_{52}O_4Si_2Na$ [$M + Na^+$] 567.3302, found 567.3311.

Acid 18. To a solution of acrylic acid (6.16 μL, 115 μmol) in CH_2Cl_2 (0.3 mL) was added a solution of tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(IV) dichloride (2.41 mg, 2.88 μmol) in CH_2Cl_2 (0.3 mL) dropwise via cannula. A solution of the alkene **17** (31.5 mg, 57.8 μmol) in CH_2Cl_2 (0.3 mL) was then added dropwise via cannula. The reaction mixture was then heated at reflux for 72 h after which time it was concentrated and purified by flash chromatography silica gel using 20% EtOAc/petrol as eluant and then by preparative HPLC (25 mm × 10 mm 5 μm silica; solvent 30% EtOAc/petrol/1% TFA; flow rate 2 mL min^{-1}) to afford the acid **18** (12.7 mg, 37%) as a colorless oil: R_f 0.14 (10% EtOAc/petrol); $[\alpha]^{21}_D = +5.9$ (*c* 0.24, $CHCl_3$); lit.[6c] $[\alpha]^{20}_D = +2.0$ (*c* 1.84, $CHCl_3$); lit.[7e] $[\alpha]^{20}_D = +6.9$ (*c* 0.3, $CHCl_3$); IR υ_{max} (film) 2957, 1728 cm^{-1}; ^1H NMR δ 0.11 (s, 3H), 0.14 (s, 3H), 0.20 (s, 3H), 0.22 (s, 3H), 0.83 (d, $J = 6.3$ Hz, 3H), 0.90 (s, 9H), 0.96 (s, 9H), 1.40 (m, 1H), 1.81 (m, 2H), 2.27 (m, 2H), 2.60 (t, $J = 6.8$ Hz, 2H), 3.32 (d, $J = 16.8$ Hz, 1H), 3.65 (dd, 1H, $J = 16.7, 8.0$ Hz, 1H), 4.27 (d, $J = 8.7$ Hz, 1H), 4.70 (s, 1H), 5.30−5.45 (m, 3H), 5.94 (d, $J = 15.6$ Hz, 1H), 6.72 (d, $J = 8.1$ Hz, 1H), 6.75 (d, $J = 8.1$ Hz, 1H), 7.04 (dt, $J = 14.8, 7.5$ Hz, 1H), 7.13 (t, $J = 8.1$ Hz, 1H); ^{13}C NMR δ −4.6, −4.5 (2C), −4.1, 13.0, 18.0, 18.3, 25.6 (3C), 25.8 (3C), 29.7, 36.2, 37.9, 38.1, 38.4, 71.9, 72.3, 117.8, 123.2, 127.3, 128.3, 129.6, 131.4, 138.7, 146.2, 152.7, 168.2, 170.1; HRMS (ESI) calcd for $C_{32}H_{52}O_6Si_2Na$ [$M + Na^+$] 611.3200, found 611.3206.

TIPS Ether 19. To a solution of the phenol **3** (56.3 mg, 129 μmol) and 2,6-lutidine (52 μL, 0.44 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C was added dropwise triisopropylsilyltrifluoromethanesulfonate (90 μL, 0.33 mmol). The reaction mixture was stirred for 2 h at room temperature after which time saturated $NaHCO_3$ was added and the crude TIPS ether was isolated by extraction with ether. The organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel using 10% EtOAc/petrol as eluant to yield the TIPS ether **19** (76.5 mg, 94%) as a colorless oil: R_f 0.82 (20% EtOAc/petrol); $[\alpha]^{21}_D = +2.3$ (*c* 1.06, CH_2Cl_2); IR υ_{max} (film) 2948, 1727 cm^{-1}; ^1H NMR δ 0.84 (d, $J = 6.6$ Hz, 3H), 1.08 (d, $J = 7.5$ Hz, 9H), 1.13 (d, $J = 7.5$ Hz, 9H), 1.30 (m, 3H), 1.56 (m, 1H), 1.70 (m, 2H), 2.07 (m, 1H), 2.29 (m, 1H), 2.42 (m, 2H), 3.35 (dd, $J = 16.1, 3.8$ Hz, 1H), 3.70 (dd, $J = 16.2, 7.8$ Hz, 1H), 3.81 (s, 3H), 4.11 (m, 1H), 4.59 (s, 2H), 5.09 (m, 2H), 5.36−5.43 (m, 3H), 5.80 (m, 1H), 6.73 (d, $J = 7.9$ Hz, 1H), 6.76 (d, $J = 7.9$ Hz, 1H), 6.88 (d, $J = 8.6$ Hz, 2H), 7.11 (t, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR δ 12.2, 13.0 (2C), 13.3, 17.7 (2C), 17.91, 17.94 (2C), 30.9, 37.7, 38.1, 40.0, 55.2, 71.4, 73.7, 79.6, 113.6, 116.6, 117.8, 122.7, 127.1, 128.5, 129.3, 129.4, 131.2, 131.8, 133.5, 138.6, 153.0, 158.9, 168.3; HRMS (ESI) calcd for $C_{36}H_{53}O_5Si$ [$M + H^+$] 593.3662, found 593.3663.

Alcohol 20. To a solution of the TIPS ether **19** (42.0 mg, 70 μmol) in CH_2Cl_2 (1.8 mL) and water (101 μL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (17.6 mg, 77.5 μmol). The reaction mixture was stirred for 30 min after which time the mixture was filtered through a plug of filter aid, washed with CH_2Cl_2, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel using 10% EtOAc/petrol as eluant, which gave the alcohol **20** (30.9 mg, 93%) as a colorless oil: R_f 0.41 (20% EtOAc/petrol); $[\alpha]^{22}_D = +42.1$ (c 0.86, CH_2Cl_2); IR υ_{max} (film) 3489, 1726, 1642 cm^{-1}; ^{1}H NMR δ 0.87 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 7.5 Hz, 9 H), 1.11 (d, J = 7.2 Hz, 9H), 1.21−1.34 (m, 3H), 1.48 (m, 1H), 1.71 (m, 2H), 1.76−1.88 (m, 2H), 2.26 (m, 1H), 2.42 (m, 2H), 3.32 (m, 1H), 3.66 (dd, J = 16.4, 8.6 Hz, 1H), 4.26 (dd, J = 9.3, 3.2 Hz, 1H), 5.13 (m, 2H), 5.29−5.50 (m, 3H), 5.82 (m, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H); ^{13}C NMR δ 13.0 (3C), 17.5, 17.9 (6C), 35.2, 37.2, 37.8, 38.0, 39.9, 71.1, 73.5, 116.8, 118.1, 122.7, 126.9, 128.5, 129.4, 131.2, 133.4, 138.6, 153.0, 168.3; HRMS (ESI) calcd for $C_{28}H_{45}O_4Si$ [M + H^+] 473.3087, found 473.3073.

TBDPS ether 21. To a solution of the alcohol **20** (57.5 mg, 122 μmol) in dimethylformamide (0.6 mL) was added silver nitrate (124 mg, 732 μmol) and then *tert*-butyldiphenylsilyl chloride (82.8μL, 317 μmol), and the reaction mixture was stirred at room temperature for 1 h. Water and ether were then added, and the organic extract was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel using 5% EtOAc/petrol as eulant to give the TBDPS ether **21** (70.2 mg, 81%) as a colorless needles: mp 49−50 °C; R_f 0.81 (20% EtOAc/petrol); $[\alpha]^{22}_D = -1.74$ (c 0.76, CH_2Cl_2); IR υ_{max} (film) 1729, 1642 cm^{-1}; ^{1}H NMR δ 0.81 (d, J = 5.1 Hz, 3H), 1.05 (d, J = 7.5 Hz, 9H), 1.09 (d, J = 6.9 Hz, 9H), 1.24−1.33 (m, 3H), 1.50 (m, 1H), 1.62 (m, 2H), 1.89 (m, 2H), 2.30 (m, 2H), 3.14 (d, J = 16.8 Hz, 1H), 3.39 (dd, J = 16.1, 9.2 Hz, 1H), 4.21 (m, 1H), 4.49 (m, 1H), 5.09−5.19 (m, 3H), 5.39 (m, 1H), 5.85 (m, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 7.06 (t, J = 7.9 Hz, 1H), 7.34−7.42 (m, 6H), 7.81 (dd, J = 14.9, 7.1 Hz, 4H); ^{13}C NMR δ 13.0 (3C), 17.96 (6C), 17.98, 19.4, 27.2 (3C), 29.7, 31.9, 36.3, 37.4, 40.3, 73.3, 76.6, 116.6, 117.9, 122.4, 127.0, 127.2 (4C), 127.3, 129.30, 129.33, 133.7, 134.4 (2C), 134.5 (2C), 136.4 (4C), 139.0, 152.9, 167.3; HRMS (ESI) calcd for $C_{44}H_{62}O_4Si_2Na$ [M + Na^+] 733.4085, found 733.4083.

Alcohol 22. To a solution of the alkene **21** (15.6 mg, 21.9 μmol) in THF (0.5 mL) was added 9-borobicylo[3.3.1]nonane (0.5 M in THF, 151 μL, 43.9 μmol), and the reaction mixture was stirred at room temperature for 1 h. MeOH (0.56 mL), 30% hydrogen peroxide (0.19 mL), and saturated $NaHCO_3$ (0.23 mL) were then added, and the reaction mixture was stirred at room temperature for 15 h. The mixture was extracted with ether, and the extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel using 15% EtOAc/petrol as eluant to afford the alcohol **22** (7.04 mg, 44%) as a colorless oil: R_f 0.28 (15% EtOAc/petrol); $[\alpha]^{21}_D = +3.6$ (c 0.34, CH_2Cl_2); IR υ_{max} (film) 3415, 1727 cm^{-1}; ^{1}H NMR δ 0.81 (d, J = 5.1 Hz, 3H), 1.04 (d, J = 7.2 Hz, 9 H), 1.08 (d, J = 7.5 Hz, 9 H), 1.10 (s, 15H), 1.26 (m, 3H), 1.38 (m, 1H), 1.53 (m, 2H), 1.62−1.70 (m, 5H), 1.88 (m, 1H), 3.13 (dd, J = 15.9, 2.7 Hz, 1H), 3.40 (dd, J = 15.9, 8.6, 1H), 3.64 (s, 2H), 4.21 (m, 1H), 4.54 (m, 1H), 5.12 (m, 1H), 5.34 (m, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.34−7.43 (m, 6H), 7.81 (t, J = 7.5, 4H); ^{13}C NMR δ 13.0 (3C), 18.0 (7C), 19.5, 27.2 (3C), 28.3, 29.7, 31.5, 32.2, 36.2, 37.5, 62.9, 73.5, 74.7, 116.8, 122.6, 127.1, 127.3 (4C), 128.3, 129.3, 129.4, 134.3 (2C), 134.5 (2C), 136.4 (4C), 139.0, 152.8, 167.3; HRMS (ESI) calcd for $C_{44}H_{64}O_5Si_2Na$ [M + Na^+] 751.4190, found 751.4175.

Diol 23. To a solution of the TIPS ether **22** (10.6 mg, 13.7 μmol) in THF (0.5 mL) was added TBAF (9.25 mg, 27.4 μmol). The reaction mixture was stirred at room temperature for 1 h after which time water and then ether were added. The mixture was then extracted with ether, and the organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified on silica gel using 20% EtOAc/petrol as eluant to give the diol **23** (6.92 mg, 83%) as a colorless oil: R_f 0.72 (20% EtOAc/petrol); $[\alpha]^{21}_D = -90.4$ (c 0.30, CH_2Cl_2); IR υ_{max} (film) 3338, 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 7.2 Hz, 3H), 1.05 (s, 9H), 1.53−1.79 (m, 5H), 1.84−1.88 (m, 3H), 1.93 (dd, J = 10.6, 4.2 Hz, 1H), 3.23 (d, J = 16.4 Hz, 1H), 3.57 (dd, J = 16.4, 7.2 Hz, 1H), 3.66 (t, J = 5.9 Hz, 2H), 3.74 (m, 1H), 4.78 (m, 1H), 4.94 (m, 1H), 5.34 (m, 1H), 6.60 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 7.17−7.29 (m, 7H), 7.64 (d, J = 8.0 Hz, 4H); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 0.88 (d, J = 6.4 Hz, 3H), 1.07 (s, 9H), 1.50−1.65 (m, 3H), 1.70−1.82 (m, 5H), 1.86 (m, 1H), 3.21 (dd, J = 16.2, 2.6 Hz, 1 H), 3.31 (dd, J = 16.2, 7.4 Hz, 1H), 3.58 (m, 2H), 4.10 (dd, J = 8.6, 2.6 Hz, 1H), 4.52 (m, 1H), 4.97 (m, 1H), 5.39 (dt, J = 8.8, 6.4 Hz, 1H), 6.62 (d, J = 7.9 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.38−7.45 (m, 6H), 7.73 (m, 2H), 7.85 (dd, J = 7.6, 1.6 Hz, 2H), 9.39 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.3, 27.1 (3C), 27.8, 29.7, 31.8, 36.6, 37.8, 62.5, 73.0, 75.0, 116.5, 123.0, 126.4, 127.4 (4C), 129.4, 129.6, 132.7, 133.5, 133.9, 134.3, 135.8, 136.0 (4C), 170.7; HRMS (ESI) calcd for $C_{35}H_{44}O_5SiNa$ [M + Na^+] 595.2856, found 595.2848.

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Supporting Information Available: Experimental procedures for the preparation of compounds **5** and **7**−**12** and copies of the ^{1}H and ^{13}C NMR spectra of all key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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