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Total Synthesis of Nhatrangin A

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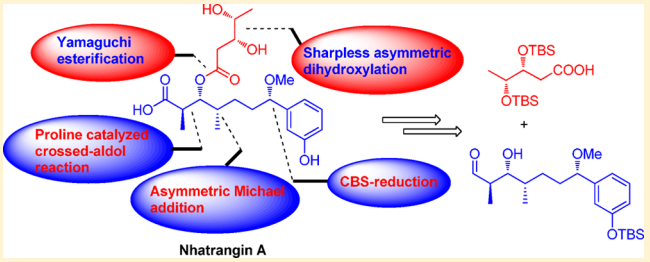
Supporting Information

ABSTRACT: A concise and stereoselective approach for the synthesis of key intermediates for aplysiatoxins, oscillatoxins, and nhatrangins and their utility for the total synthesis of nhatrangin A has been demonstrated. The advanced intermediates aromatic aldehyde **11** and dihydroxy acid **12** were synthesized in eight steps (44% overall yield) and three steps (55% overall yield), respectively. An asymmetric Michael addition, CBS reduction, and proline-catalyzed crossed-aldol reactions were utilized as key steps for the generation of all the chirality of main chain hydroxyaldehyde, while the appended side-chain-protected 3,4-dihydroxypentanoic acid was achieved in a shortest route, using Sharpless dihydroxylation, diol protection, and RuO_4-catalyzed aromatic over-oxidation reactions. Synthesis of nhatrangin A was accomplished by coupling of dihydroxy acid **12** with β-hydroxyallyl ester (obtained from **11**) under Yamaguchi reaction conditions followed by a one-pot deprotection of all protecting groups.



INTRODUCTION

Secondary metabolites produced by cyanobacteria display a variety of biological activities, such as cytotoxic, antitumor, antiviral, antibiotic, antimalarial, antimycotics, multi-drug resistance reversers, antifeedant, herbicides and immunosuppressive activities.[1,2] Two polyketide secondary metabolites, nhatrangin A (**1**) and B (**2**), were isolated by Orjala et al.[3] in 2010 from *Lyngbya majuscula*, and they were named after the collection site of Nha Trang Bay, Vietnam. These nhatrangins are the simplest analogues of aplysiatoxins (**3**−**5**) and oscillatoxins (**6**−**10**), which were previously isolated from marine blue-green algae *Lyngbya majuscula* and *Schizothrix calcicola*/*Oscillatoria nigrouiridis*, respectively (Figure 1).[4] The nhatrangins A and B possess a simple architecture and are less lipophilic in nature compared to aplysiatoxins. The structures of nhatrangins were elucidated using 900 MHz cryoprobe 2D NMR spectroscopy and mass spectrometry. The absolute configuration was determined by circular dichroism, which was compared with the CD spectrum of debromoaplysiatoxin.

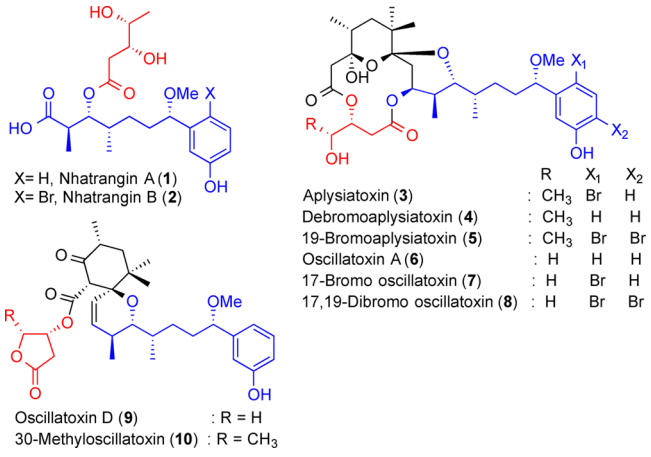


Figure 1. Structures of nhatrangins (**1** and **2**), aplysiatoxins (**3**−**5**), and oscillatoxins (**6**−**10**).

Aplysiatoxins, which are derivatives of nhatrangins, are widely recognized as tumor-promoting agents and protein kinase C activators.[5,6] However, the recently isolated nhatrangins have not been investigated for their biological properties owing to their limited availability from the nature. In continuation of our on-going research program toward the synthesis of complex biologically active natural products,[7] we became interested in the synthesis of nhatrangin A.

As depicted in Figure 1, nhatrangins A (**1**) and B (**2**) possess two acid fragments that are coupled by an ester linkage at C3 carbon of the main chain. The main-chain aromatic acid fragment contains a benzylic oxygen protected as methyl ether and an 2,3-*anti*-3,4-*syn*-stereotriad at C2 to C4 positions. This fragment can also serve as a common and advanced intermediate for the C9−C21 portion of all aplysiatoxins **3**−**5** and oscillatoxins **6**−**10**.[8,9] Recently, Piva et al.[9f] reported an approach toward the total synthesis of nhatrangin A, while Kamal et al.[9g] reported a first total synthesis of nhatrangin A. By considering these aspects, we have developed a concise and stereoselective strategy for the synthesis of the aromatic fragment **11** and the side chain **12**, and these fragments have been successfully utilized to accomplish the total synthesis of nhatrangin A **1** (Scheme 1).

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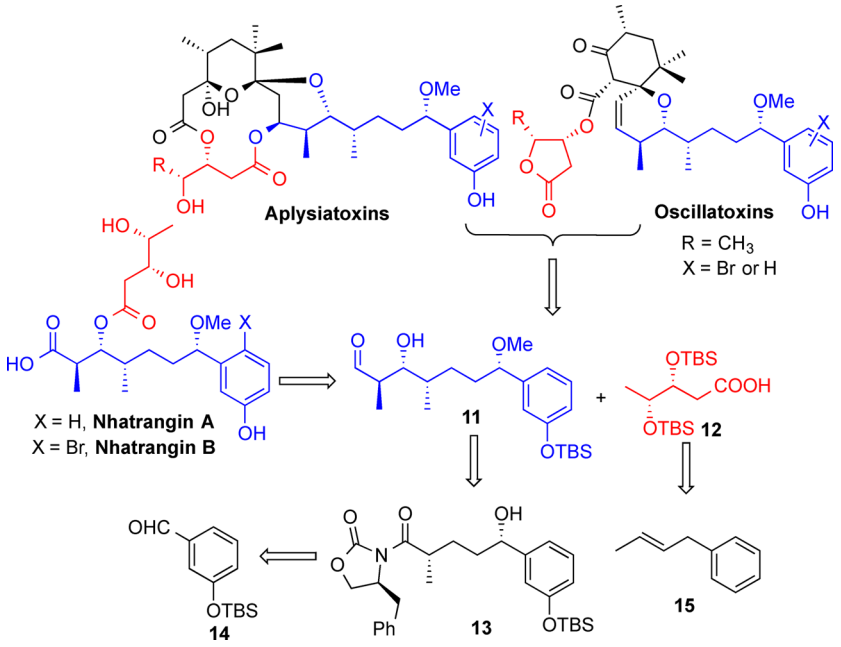
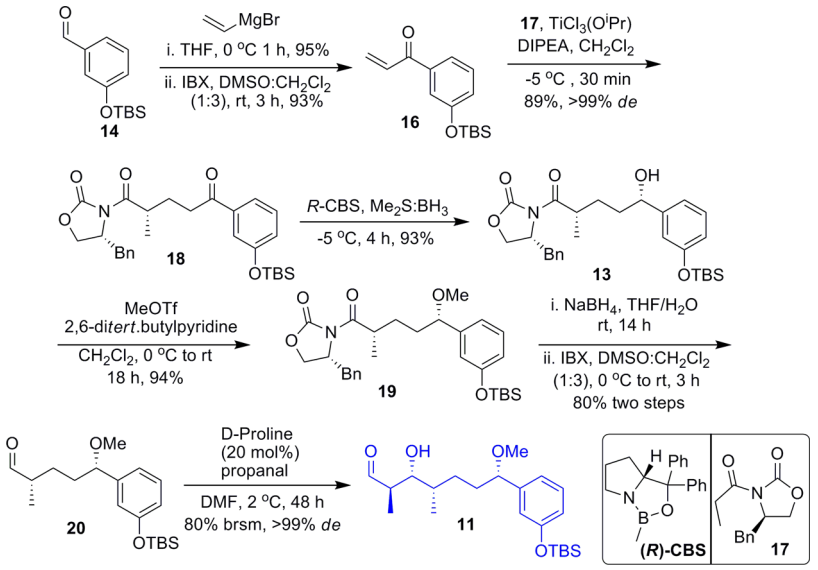
Scheme 1. Retrosynthetic Analysis of Nhatrangin A (1)



Scheme 2. Synthesis of Key Aromatic Aldehyde 11



RETROSYNTHETIC ANALYSIS

Retrosynthetic analysis in Scheme 1 reveals advanced intermediates **11** and **12**, which are crucial for the series of aplysiatoxins, oscillatoxins, and nhatrangins. In addition, nhatrangin A (**1**) could be extended to nhatrangin B (**2**) by aromatic bromination. We further envisaged that synthesis of nhatrangin A could be accomplished by the coupling of acid fragment **12** with β-hydroxyallyl ester, which in turn can be obtained from **11** in two steps involving oxidation and allylprotection. The crucial aromatic aldehyde fragment **11** would be accomplished from compound **13** followed by a sequence of reactions involving methyl ether formation, reduction, oxidation, and an asymmetric aldol reaction. The compound **13** could be obtained starting from aldehyde **14** through a vinyl Grignard reaction, oxidation of the resulting alcohol, asymmetric Michael addition reaction, and CBS reduction reactions. On the other hand acid fragment **12** would be attained from 2-butenylbenzene **15** in three steps using asymmetric dihydroxylation and TBS protection followed by an aromatic oxidation reaction.

RESULTS AND DISCUSSION

Our strategy for the synthesis of key intermediate **11** in a stereoselective manner commenced with the generation of first methyl stereogenic center at C4 position via an auxiliary based asymmetric Michael addition reaction.[10] Accordingly, the silyl-protected 3-hydroxybenzaldehyde **14** on treatment with vinylmagnesium bromide in THF afforded allyl alcohol, which was further oxidized to aryl vinyl ketone **16** in 93% yield using 2-iodoxybenzoic acid. Titanium enolate resulting from (*R*)-4-benzyl-3-propionyloxazolidin-2-one **17** upon treatment with (*i*-PrO)$TiCl_3$ and *N*,*N*′-diisopropylethylamine

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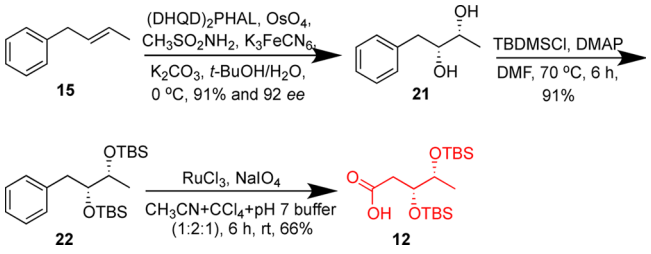
underwent conjugate addition on phenyl vinyl ketone **16** to afford ketone **18** exclusively as a single diastereomer in 89% yield.[10] Keto functionality of compound **18** was selectively reduced with borane in the presence of proline-based *R*-CBS catalyst to provide alcohol **13** as a major diastereomer in 93% isolated yield.[11] Selectivity (varies from 9:1 to 98:2) mainly depends on amount of catalyst used and rate of addition of compound to the reagent. Methyl protection of alcohol **13** using iodomethane in the presence of strong bases (like NaH and NaHMDS) leads to the formation of unwanted products and decomposition of starting material. To avoid this, compound **13** was treated with methyl triflate in the presence of a mild organic base 2,6-ditertiarybutylpyridine in DMF to produce corresponding methyl ether **19** in 87% yield.[12]Aux-Auxiliary of compound **19** was reductively removed using $NaBH_4$ in aqueous THF to afford corresponding alcohol, which on subsequent oxidation with IBX resulted in aldehyde **20** with 80% yield over two steps. Achievement of *anti,syn*-triod was realized in single step using proline catalyzed asymmetric crossed-aldol strategy.[13] Thus, aldehyde **20** on reaction with propionaldehyde in DMF at 2 °C for 48 h in the presence of D-proline as catalyst afforded *β*-hydroxyaldehyde **11** with excellent diastereoselectivity (>99% by NMR analysis)[14] in 80% yield (brsm). Thus, one of the key motifs (**11**) for the synthesis of nhatrangin A, which also becomes a crucial intermediate for the synthesis of aplysiatoxins and oscillatoxins was achieved in eight steps with 40% overall yield (Scheme 2).

In our next attempt, we focused on the synthesis of chiral *β*,*γ*-dihydroxy carboxylic acid motif **12**, which is also a subunit of nhatrangins, aplysiatoxins, and some oscillatoxins. Synthesis of this appended acid with completely masked vicinal diol was achieved in good yields and optical purity when compared to previous routes. For this 2-butenylbenzene,[15] **15** was employed as the starting material, which underwent an asymmetric dihydroxylation with OsO_4 in the presence of catalytic $(DHQD)_2PHAL$ to produce vicinal diol **21** in 91% yield with 92% ee.[16] The diol **21** on treatment with TBDMS-Cl and DMAP in DMF afforded bis-silylether **22** in 91% yield. The phenyl group in compound **22** was subjected to oxidation without effecting the vicinal diol using RuO_4 (generated in situ from $RuCl_3$ and $NaIO_4$) in a solvent system CH_3CN/CCl_4/pH 7 buffer (1:2:1) to furnish the corresponding carboxylic acid **12** in 66% yield (Scheme 3).[17]

Scheme 3. Synthesis of Key Side Chain Acid 12



With two fragments in hand, we moved to final steps to accomplish the total synthesis of nhatrangin A. Consequently one of the key fragment **11** was subjected to a chemoselective Pinnick oxidation[18] with NaOCl in the presence of 2-methyl-2-butene in *t*-BuOH to afford *β*-hydroxyacid **23** in 98% yield. The main chain hydroxy allyl ester **24** was finally achieved by treatment of acid **23** with ally bromide and K_2CO_3 in DMF at room temperature in 96% yield. Formation of internal ester at C3-position was realized by coupling of hydroxy ester **24** with acid **12** under Yamaguchi mixed anhydride protocol.[19] The other reaction conditions for the formation of ester remained unsuccessful.[20] Thus acid **12** was treated with 2,4,6-trichlorobenzoyl chloride in the presence of DMAP in toluene for 2 h to furnish the corresponding mixed anhydride, which was subsequently treated with alcohol **24** for 4 h to provide ester **25** in 40% yield. Unfortunately, higher reaction temperatures or longer reaction time to improve the yield lead to epimerization of C2-methyl carbon. The compound **25** was subjected to allyl deprotection using palladium tetrakis-triphenylphosphine and morpholine[21] in dry THF and later was followed by treatment with 3 N HCl to afford natural product nhatrangin A **1** in 67% yield. The structural integrity of synthetic nhatrangin A **1** was confirmed by comparison of its spectral (^1H and ^{13}C NMR) data and specific rotation (synthetic. $[\alpha]^{30}_D$ = +0.8 (*c* 0.3 in MeOH), Lit. $[\alpha]^{25}_D$ = +0.2 (*c* 0.05 in MeOH),[9g] which were in good agreement with the reported values for natural product (Scheme 4).[3]

■ CONCLUSIONS

In conclusion, a concise and stereoselective approach for the synthesis of key intermediates for aplysiatoxins, oscillatoxins, and nhatrangins and their application to the total synthesis of nhatrangin A has been demonstrated. Evans auxiliary based asymmetric Michael addition reaction, CBS reduction, and proline-catalyzed crossed-aldol reaction provided aromatic aldehyde **11** in eight steps with 44% overall yield. Asymmetric dihydroxylation, silyl protection of vicinal diol and ruthenium catalyzed aromatic over oxidation provided appended acid chain **12** in three steps with 55% overall yield. This strategy can be used for the preparation of other *β*,*γ*-dihydroxycarboxylic acids and *β*-hydroxy-*γ*-lactones, which are the main constitutes in many natural product molecules. Final total synthesis of nhatrangin A **1** was achieved by successful coupling of fragments **24** and **12** under Yamaguchi reaction conditions followed by a deprotection step to remove all the protecting groups.

■ EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solvent on 300 and 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). ^1H NMR spectra were recorded at 300 MHz, and chemical shifts are referenced to TMS (δ = 0.0) as internal standard. ^{13}C NMR spectra were recorded at 75 MHz, and chemical shifts are referenced to $CDCl_3$ (δ = 77.0). FTIR spectra were recorded on KBr thin films. Optical rotations were measured on a digital polarimeter by using a 1-mL cell with a path length of 1 dm. HRMS were recorded on an LC-ESI-QTOF-mass spectrometer. All reagents and solvents were of reagent grade and used without further purification unless otherwise stated. Technical-grade EtOAc, hexanes, $CHCl_3$, and MeOH used for column chromatography were distilled before use. THF when used as a solvent for reactions was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried on silica gel (60−120 mesh) packed in glass columns. All of the reactions were performed under N_2 in flame or oven-dried glassware with magnetic stirring.

1-(3-(*tert*-Butyldimethylsilyloxy)phenyl)prop-2-en-1-ol (16). To a stirred solution of aldehyde **14** (4.2 g, 17.7 mmol) in dry THF (100 mL) under nitrogen atmosphere at −10 °C was added vinylmagnesium bromide (22.0 mL 1 M solution in THF, 22.0 mmol) dropwise over 5 min. After being stirred for 1 h at the same temperature, the reaction was quenched with saturated aq NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic layers

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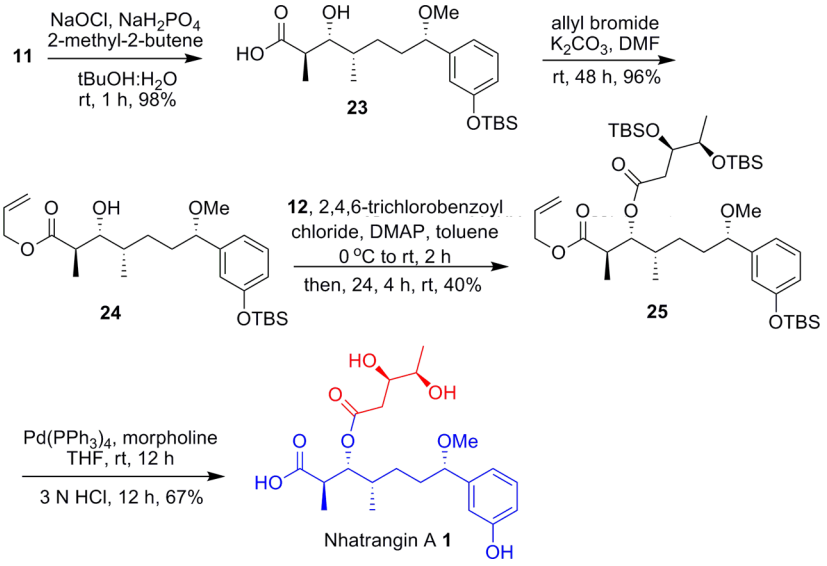
Scheme 4. Synthesis of Nhatrangin A



were washed with water and brine, dried over anhydrous Na_2SO_4 ,and concentrated under reduced pressure. The crude product was purified by silica gel chromatography ((eluting with hexane/ethyl acetate, 9:1) as an eluent to obtain alcohol (4.46 g, 95%) as clear liquid: IR (neat) ν_{max} 3380, 2956, 2859, 1601, 1484, 1274, 1220, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.99 (s, 9H), 2.24 (bs, 1H), 5.12 (d, J = 5.8 Hz, 1H), 5.17, (d, J = 10.4 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.95–6.08 (m, 1H), 6.76 (dd, J = 1.5, 8.1 Hz, 1H), 6.86 (s, 1H), 6.94 (d, J = 7.7 Hz, 1H), 7.21 (t, J = 7.7, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, 18.1, 25.6, 75.0, 115.0, 118.0, 119.1, 119.2, 129.4, 140.1, 144.2, 155.8; MS (ESI) m/z 265 $(M + H)^+$, 287 $(M + Na)^+$.

To a stirred solution of IBX (6.97 g, 24.9 mmol) in DMSO (20 mL) was added a solution of alcohol (4.40 g, 16.6 mmol) in dry CH_2Cl_2 (40 mL) under nitrogen atmosphere at 0 °C. After 5 min, the reaction was allowed to room temperature and continued to stir for 3 h. Water (30 mL) was added to the reaction mixture, which was then filtered over a Celite pad. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography ((eluting with hexane/ethyl acetate, 9.5:0.5) to obtain compound **16** (4.06 g, 93%) as a clear liquid: IR (neat) ν_{max} 2956, 2932, 2859, 1675, 1596, 1484, 1278, 927, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.22 (s, 6H), 0.99 (s, 9H), 5.91 (dd, J = 1.5, 10.4 Hz, 1H), 6.42 (dd, J = 1.5, 17.0 Hz, 1H), 7.05 (m, 1H), 7.11 (dd, J = 10.7, 10.5 Hz, 1H), 7.33 (t, J = 7.7, 7.9 Hz, 1H), 7.41 (t, J = 1.7, 1.8 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, 18.1, 25.6, 119.9, 121.7, 124.8, 129.5, 129.9, 138.7, 155.9, 190.5; HRMS (ESI) calcd for $C_{15}H_{23}O_2Si$ 263.1483, found 263.1467.

(*S*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-methylpentane-1,5-dione (18). To a stirred solution of $TiCl_4$ (2.0 mL, 18.6 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen atmosphere at rt was added $Ti(O^iPr)_4$ (1.84 mL, 6.20 mmol) and the resulting solution stirred for 2 h. Then solution was cooled to 0 °C, and (*R*)-4-benzyl-3-propionyloxazolidin-2-one **17** (5.31g, 22.9 mmol) in CH_2Cl_2 (40 mL) was added in a dropwise manner. After 5 min, DIPEA (4.4 mL, 24.8 mmol) was added and the solution stirred for an additional 30 min. Then vinyl ketone **16** (5.0 g, 19.1 mmol) in dry CH_2Cl_2 (40 mL) was added over 5 min at −5 °C, and stirring was continued for 30 min. The reaction was quenched by the addition of saturated aq NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 8:2) to obtain compound **18** (8.4 g, 89%, >99% de) as a clear thick liquid: $[\alpha]^{30}_D$ −8.5 (c 1.5, $CHCl_3$); IR (neat) ν_{max} 2955, 2931, 2858, 1780, 1692, 1387, 1279, 1252, 835, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 6H), 0.98 (s, 9H), 1.25 (d, J = 6.7 Hz, 3H), 1.86–2.0 (m, 1H), 2.14–2.27 (m, 1H), 2.76 (dd, J = 9.6, 9.8 Hz, 1H), 2.92–3.13 (m, 2H), 3.32 (dd, J = 3.4, 13.4 Hz, 1H), 3.82 (m, 1H), 4.13–4.24 (m, 2H), 4.62–4.74 (m, 1H), 7.03 (m, 1H), 7.18–7.37 (m, 6H), 7.42 (t, J = 1.7, 3.7 Hz, 1H), 7.55 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, 16.9, 18.1, 25.6, 28.0, 36.1, 37.0, 37.9, 55.3, 66.0, 119.2, 121.1, 124.8, 127.2, 128.9, 129.3, 129.5, 135.2, 138.2, 153.0, 155.9, 176.5, 199.1; HRMS (ESI) calcd for $C_{28}H_{37}NO_5SiNa$ $(M + Na)^+$ 496.2513, found 496.2522.

(*R*)-4-Benzyl-3-((2*S*,5*S*)-5-(3-(*tert*-butyldimethylsilyloxy)-phenyl)-5-hydroxy-2-methylpentanoyl)oxazolidin-2-one (13). To a stirred solution of borane dimethyl sulfide (0.138 mL, 1.45 mmol) in dry CH_2Cl_2 (4 mL) −5 °C under nitrogen atmosphere was added (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo(1,2-*c*)-1,3,2-oxazaborolidine (0.24 mL, 1 M solution in toluene, 20 mol %), and the resulting mixture was continued to stir for 30 min. To this reaction mixture was added a solution of compound **18** (0.60 g, 1.21 mmol) in CH_2Cl_2 (6 mL) over a period of 4 h and the reaction temperature maintained between −5 and 0 °C. Stirring was continued for 1 h until TLC showed complete conversion of reaction. The reaction was quenched by addition of CH_3OH (1 mL) slowly at 0 °C, followed by the addition of saturated aq NH_4Cl, and stirring continued for 15 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 7:3) to afford compound **13** (0.56 g, 93%) as a clear thick liquid along with the minor isomer (0.011 g, 1.8%). Compound **13**: $[\alpha]^{30}_D$ −40 (c 1.0, $CHCl_3$); IR (neat)ν_{max} 3525, 2930, 2858, 1780, 1698, 1483, 1387, 1276, 839, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.97 (s, 9H), 1.16 (d, J = 6.7 Hz, 3H), 1.52–1.64 (m, 1H), 1.69–1.90 (m, 3H), 2.5 (bs, 1H), 2.70 (dd, J = 9.8, 9.6 Hz, 1H), 3.26 (dd, J = 3.2, 13.4 Hz, 1H), 3.68–3.80, (m, 1H), 4.09–4.19 (m, 2H), 4.60–4.70 (m, 2H), 6.73 (m, 1H), 6.84 (t, J = 1.8, 3.5 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 7.14–7.22 (m, 3H), 7.23–7.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.5, 16.4, 18.1, 25.6, 29.6, 36.1, 37.0, 37.9, 55.3, 66.0, 73.2, 117.4, 118.6, 118.9, 127.2, 128.8, 129.3, 135.2, 146.2, 153.1, 155.6, 176.9; HRMS (ESI) calcd for $C_{28}H_{39}NO_5SiNa$ $(M + Na)^+$ 520.2489, found 520.2486.

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(*R*)-4-Benzyl-3-((2*S*,5*S*)-5-(3-(*tert*-butyldimethylsilyloxy)-phenyl)-5-methoxy-2-methylpentanoyl)oxazolidin-2-one (19). To a stirred solution of alcohol **13** (500 mg, 1.06 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen atmosphere at 0 °C was added 2,6-ditertiarybutylpyridine (0.7 mL, 3.18 mmol) followed by methyl triflate (0.35 mL, 3.18 mmol) and stirring continued for 5 min. Then reaction mixture was stirred for 18 h at room temperature. After completion of the reaction, saturated aq NH_4Cl was added. The organic layer was separated, and aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 9:1) to afford methyl ether **19** (0.483 g, 94%) as a colorless liquid: $[\alpha]^{30}_D$ −25.6 (*c* 1.1, $CHCl_3$); IR (neat) ν_{max} 2930, 2857, 1781, 1698, 1482, 1386, 1276, 1215, 1103, 839, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.96 (s, 9H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.56−1.68 (m, 2H), 1.69−1.82 (m, 2H), 2.66 (m, 1H), 3.18 (s, 3H), 3.30 (dd, *J* = 3.7, 13.5 Hz, 1H), 3.73 (m, 1H), 4.01 (d, *J* = 6.0 Hz, 1H), 4.09−4.19 (m, 2H), 4.61 (m, 1H), 6.66−6.75 (m, 2H), 6.82 (d, *J* = 7.5 Hz, 1H), 7.11−7.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, 16.8, 18.1, 25.6, 30.0, 35.4, 37.2, 38.0, 55.3, 56.5, 65.9, 83.5, 118.1, 119.2, 119.7, 127.2, 128.8, 129.3, 125.3, 143.8, 153.0, 155.7, 176.9; HRMS (ESI) calcd for $C_{29}H_{41}NO_5SiNa$ $(M + Na)^+$ 534.2646, found 534.2641.

(2*S*,5*S*)-5-(3-(*tert*-Butyldimethylsilyloxy)phenyl)-5-methoxy-2-methylpentanal (20). To a stirred solution of compound **19** (1.2 g, 2.34 mmol) in mixture of THF (10 mL) and H_2O (5 mL) at room temperature was added $NaBH_4$ (0.177 g, 4.68 mmol). The reaction mixture was continued to stir for overnight. After completion of the reaction, additional water (5 mL) was added. The organic layer was separated, and aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 8:2) to furnish alcohol (0.682 g, 86%) as a clear liquid: $[\alpha]^{30}_D$ −39.1 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 3399, 2932, 2860, 1602, 1587, 1483, 1276, 1098, 838, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 9H), 1.23−1.42 (m, 2H), 1.53−1.71 (m, 2H), 1.77−1.90 (m, 1H), 3.19 (s, 3H), 3.35−3.51 (m, 2H), 4.02 (dd, *J* = 5.2, 7.5 Hz, 1H), 6.73−6.79 (m, 2H), 6.86 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 8.3, 15.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, 16.5, 18.2, 25.6, 29.1, 35.4, 35.5, 56.5, 67.9, 84.0, 118.1, 119.2, 119.7, 129.2, 143.9, 155.7; HRMS(ESI) calcd for $C_{19}H_{34}O_3SiNa$ $(M + Na)^+$ 361.2169, found 361.2171.

To a stirred solution of IBX (0.697 g, 2.49 mmol) in DMSO (4 mL) was added a solution of alcohol (0.560 g, 1.66 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After being stirred for 5 min at 0 °C, the reaction mixture was allowed to stir at room temperature for 3 h. Water (5 mL) was added to the reaction mixture, which was filtered over a Celite pad. The organic layer was separated, and then the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 95:5) to afford aldehyde **20** (0.517 g, 93%) as a clear liquid: $[\alpha]^{30}_D$ −27.4 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.92 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.40−1.46 (m, 1H), 1.50−1.71 (m, 3H), 2.16−2.25 (m, 1H), 3.10 (s, 3H), 3.91 (dd, *J* = 5.1, 6.8 Hz, 1H), 6.60−6.64 (m, 2H), 6.72 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 9.48 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, 13.3, 18.2, 25.7, 26.6, 35.4, 46.1, 56.5, 83.5, 118.1, 119.3, 119.7, 129.3, 143.5, 155.8, 205.0; MS (ESI) *m*/*z* 359 $(M + Na)^+$.

(2*R*,3*R*,4*S*,7*S*)-7-(3-(*tert*-Butyldimethylsilyloxy)phenyl)-3-hydroxy-7-methoxy-2,4-dimethylheptanal (11). To a stirred solution of aldehyde **20** (500 mg, 1.49 mmol) in dry DMF (5 mL) under nitrogen atmosphere at 2 °C was added D-proline (0.034 g, 0.297 mmol, 20 mol %). Then propionaldehyde (0.54 mL, 7.44 mmol) in dry DMF (5 mL) was added over a period of 16 h using a syringe pump at 2 °C, and the reaction was continued to stir at the same temperature for an additional 32 h. After completion of the reaction, water (8 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 95:5) to afford desired β-hydroxyaldehyde **11** (0.280 g, 48%) along with starting aldehyde **20** (0.20 g, 40%). (Note: most of the time, the mixture of **11** and propionaldehyde self-aldol adduct was directly used in next step. The propionaldeyde self-aldol adduct was removed in the next step by converting it into its corresponding 3-hydroxy acid): $[\alpha]^{30}_D$ −22.6 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.87 (d, *J* = 6.0 Hz, 3H), 0.99 (s, 9H), 1.04 (d, *J* = 7.7 Hz, 3H), 1.37−1.46 (m, 1H), 1.50−1.64 (m, 3H), 1.69−1.79 (m, 1H), 2.47 (q, *J* = 7.6 Hz, 1H), 3.17 (s, 3H), 3.62 (dd, *J* = 2.5, 8.5 Hz, 1H), 3.93−3.97 (m, 1H), 5.32 (s, 1H), 6.65−6.70 (m, 2H), 6.79 (d, *J* = 6.8 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.1, 10.9, 12.8, 14.4, 18.5, 26.0, 34.9, 36.1, 53.2, 56.6, 74.4, 84.0, 118.1, 119.2, 119.8, 129.4, 144.2, 155.9, 204.7; MS (ESI) *m*/*z* 417 $(M + Na)^+$; HRMS(ESI) calcd for $C_{22}H_{38}O_4SiNa$ $[M + Na]^+$ 417.2437, found 417.2442.

(2*R*,3*R*)-1-Phenylbutane-2,3-diol (21). To a stirred solution of H_2O (40 mL) and *t*-BuOH (40 mL) under nitrogen atmosphere at room temperature were sequentially added K_2CO_3 (7.87 g, 57.0 mmol), $K_3Fe(CN)_6$ (18.75 g, 57.0 mmol), $CH_3SO_2NH_2$ (181.0 g, 19.0 mmol), and $(DHQD)_2$-PHAL (0.296 g, 0.379 mmol) and a solution OsO_4 (9.6 mL, 0.5% in toluene). The reaction mixture was stirred for 15 min and cooled to 0 °C, and then olefin **15** (2.5 g, 19.0 mmol) was added directly. Stirring was continued for 24 h at 0 °C, then the reaction was quenched with saturated aq Na_2SO_3 (50 mL), and the mixture continued to stir for an additional 30 min. After extraction of the aqueous layer with EtOAc (3 × 20 mL), the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 3:1) to furnish the diol **21** (2.86 g, 91%) as a black thick liquid: $[\alpha]^{30}_D$ +27.3 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 3459, 2983, 2929, 2865, 1725, 1376, 1242, 1087, 772, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.2 Hz, 3H), 2.41 (bs, 2H), 2.63 (dd, *J* = 8.6, 8.6 Hz, 1H), 2.83 (dd, *J* = 4.0, 4.0 Hz, 1H), 3.47−3.55 (m, 1H), 3.60 (q, *J* = 6.0, 12.8 Hz, 1H), 7.13−7.22 (m, 3H), 7.23−7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 39.9, 69.9, 76.6, 126.4, 128.5, 129.3, 138.1; MS (EI) *m*/*z* 189 $(M + Na)^+$.

(5*R*,6*R*)-5-Benzyl-2,2,3,3,6,8,8,9,9-nonamethyl-4,7-dioxa-3,8-disiladecane (22). To a stirred solution of compound **21** (1.2 g, 7.2 mmol) in dry DMF (15 mL) under nitrogen atmosphere at room temperature were added 4-(dimethylamino)pyridine (DMAP) (2.63 g, 21.6 mmol) and TBSCl (3.30 g, 21.6 mmol) sequentially. Then resulting mixture was heated at 70 °C and continued to stir for 6 h. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (10 mL), and extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate, 0.2:9.8 as an eluent) furnished product **22** (2.86 g, 91%) as a pale yellow oil: $[\alpha]^{30}_D$ + 12.6 (*c* 0.9, $CHCl_3$); IR (neat) ν_{max} 2955, 2930, 2857, 1472, 1255, 1219, 1104, 834, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.45 (s, 3H), −0.06 (s, 3H), 0.22 (d, *J* = 3.0 Hz, 6H), 0.91 (s, 9H), 1.07 (s, 9H), 1.29 (d, *J* = 6.8 Hz, 3H), 2.53 (dd, *J* = 10.5, 9.8 Hz, 1H), 3.11 (dd, *J* = 1.5, 12.8 Hz, 1H), 3.74−3.81 (m, 1H), 3.90−3.99 (m, 1H), 7.21−7.30 (m, 3H), 7.31−7.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −6.10, −5.3, −5.1, −4.9, 16.0, 17.5, 17.6, 25.3, 25.4, 35.9, 70.3, 76.1, 125.3, 127.6, 129.4, 140.4; MS (ESI) *m*/*z* 417 $(M + Na)^+$.

(3*R*,4*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)pentanoic Acid (12). To a stirred solution of compound **22** (0.730 g, 1.85 mmol) in CCl_4 (6 mL), CH_3CN (6 mL), and pH 7 buffer (10 mL) at room temperature was added $NaIO_4$ (5.90 g, 27.70 mmol). After the mixture was stirred for 5 min, $RuCl_3$ (0.038 g, 0.18 mmol) was added and stirring continued for 6 h at the same temperature. After completion of the reaction, reaction was diluted with CH_2Cl_2 (10 mL). The organic

layer was separated, and aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 9.5:0.5) to afford **12** (0.440 g, 66%) as a colorless liquid: $[\alpha]^{30}_D$ +23.1 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3420, 2931, 2858, 1707, 1595, 1482, 1276, 1101, 841, 784 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.06 (s, 6H), 0.08 (s, 3H), 0.86 (s, 9H), 0.88 (s, 9H), 1.08 (d, *J* = 6.0 Hz, 3H), 2.31 (dd, *J* = 9.0, 9.8 Hz, 1H), 2.66 (dd, *J* = 2.3, 3.0 Hz, 1H), 3.75−3.84 (m, 1H), 4.04−4.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.8, −4.7, 16.2, 17.8, 17.9, 25.6, 25.7, 35.8, 69.9, 72.1; MS (ESI) *m*/*z* 385 $(M + Na)^+$.

(2*R*,3*R*,4*S*,7*S*)-7-(3-(*tert*-Butyldimethylsilyloxy)phenyl)-3-hydroxy-7-methoxy-2,4-dimethylheptanoic Acid (23). To a stirred solution of β-hydroxyaldehyde **11** (0.380 g, 0.926 mmol) in *t*-BuOH (6 mL) were added 2-methyl-2-butene (1.0 mL, 9.5 mmol), H_2O (1.5 mL), $NaClO_2$ (0.350 g, 3.85 mmol), and NaH_2PO_4 (0.752 g, 4.80 mmol) sequentially at 0 °C. Stirring was continued for 1 h at the same temperature. After completion of the reaction, Et_2O (5 mL) followed by 0.5 M aqueous citric acid solution (3 mL) wree added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 1:1) to furnish β-hydroxy acid **23** (0.387 g, 98%) as a colorless oil: $[\alpha]^{30}_D$ −16.5 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} 3420, 2959, 2931, 2858, 1708, 1602, 1483, 1277, 1101, 840, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.87 (d, *J* = 6.0 Hz, 3H), 0.98 (s, 9H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.37−1.46 (m, 1H), 1.51−1.67 (m, 3H), 1.69−1.83 (m, 1H), 2.59 (q, *J* = 7.5 Hz, 1H), 3.18 (s, 3H), 3.56 (dd, *J* = 3.7, 8.3 Hz, 1H), 3.93−4.01 (dd, *J* = 5.2, 6.7 Hz, 1H), 6.66−6.73 (m, 2H), 6.80 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, 12.5, 14.2, 18.2, 25.7, 29.9, 34.7, 35.6, 43.1, 56.6, 75.6, 83.9, 118.9, 119.2, 119.8, 129.3, 143.8, 155.7, 180.9; HRMS (ESI) calcd for $C_{22}H_{38}O_5$ SiNa $(M + Na)^+$ 433.2380, found 433.2378.

(2*R*,3*R*,4*S*,7*S*)-Allyl-7-(3-(*tert*-butyldimethylsilyloxy)phenyl)-3-hydroxy-7-methoxy-2,4-dimethylheptanoate (24). To a stirred solution of β-hydroxy acid **23** (0.20 g, 0.487 mmol) in dry DMF (4 mL) under nitrogen atmosphere at 0 °C were added anhydrous K_2CO_3 (0.134 g, 0.974 mmol) and freshly distilled allyl bromide (0.584 mmol) sequentially. The reaction mixture was allowed to stir at room temperature for 48 h and then quenched by the addition of saturated aq NH_4Cl (5 mL). After the aqueous layer was extracted with Et_2O (3 × 5 mL), the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate, 7.5:2.5) to afford allyl ester **24** (0.210 g, 96%) as a clear liquid: $[\alpha]^{30}_D$ −26 (*c* 0.9, $CHCl_3$); IR (neat) ν_{max} 2931, 2858, 1727, 1711, 1596, 1463, 1275, 1102, 838, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 9H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.44−1.66 (m, 3H), 1.66−1.87 (m, 2H), 2.60 (q, *J* = 7.5 Hz, 1H), 3.18 (s, 3H), 3.49−3.57 (m, 1H), 3.93−4.01 (dd, *J* = 5.2, 7.5 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 2H), 5.20−5.27 (dd, *J* = 1.5, 10.5 Hz, 1H), 5.28−5.36 (dd, *J* = 1.5, 16.5 Hz, 1H), 5.83−5.87 (m, 1H), 6.67−6.73 (m, 2H), 6.82 (d, *J* = 7.5 Hz, 1H), 7.12−7.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, 12.6, 14.3, 25.6, 29.6, 27.0, 34.9, 35.9, 43.1, 56.6, 65.2, 75.6, 83.9, 118.1, 118.4, 119.2, 119.7, 129.2, 131.9, 143.9, 155.7, 184.7; HRMS (ESI) calcd for $C_{25}H_{42}O_5$SiNa $(M + Na)^+$ 473.2693, found 473.2699.

(2*R*,3*R*,4*S*,7*S*)-Allyl-3-((3*R*,4*R*)-3,4-bis(*tert*-butyldimethylsilyloxy)pentanoyloxy)-7-(3-(*tert*-butyldimethylsilyloxy)phenyl)-7-methoxy-2,4-dimethylheptanoate (25). To a stirred solution of 2,4,6-trichlorobenzoyl chloride (0.023 mL, 0.150 mmol) in dry toluene (2 mL) under nitrogen atmosphere at 0 °C was added acid **12** (0.056 g, 0.155 mmol), followed by DMAP (0.038 g, 0.311 mmol). The resulting mixture was allowed to stir at room temperature for 2 h, and then hydroxy allyl ester **24** (0.035 g, 0.077 mmol) in toluene (0.5 mL) was added. The reaction mixture was allowed to stir at room temperature for an additional 4 h. The reaction was quenched by the addition of saturated aq NH_4Cl (2 mL). The organic layer was separated, and aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with (ethyl acetate/hexane, 9.5:0.5) to furnish **25** (0.0247 g, 40%) as a pale yellow oil along with recovery of hydroxy allyl ester **24** (0.020 g, 58%): $[\alpha]^{30}_D$ +1.8 (c 0.8, $CHCl_3$); IR (neat) ν_{max} 2929, 2857, 2318, 1743, 1462, 1255, 1219, 1099, 837, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.07 (s, 6H), 0.20 (s, 6H), 0.86 (s, 9H), 0.88 (s, 9H), 0.91 (d, *J* = 5.8 Hz, 3H), 0.99 (s, 9H), 1.06 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 8.0 Hz, 3H), 1.33−1.42 (m, 2H), 1.59−1.65 (m, 1H), 1.66−1.76 (m, 2H), 2.20−2.32 (m, 1H), 2.59 (dd, *J* = 2.0, 17.0, 1H), 2.76 (dd, *J* = 7.0, 9.0, 1H), 3.16 (s, 3H), 3.77 (t, *J* = 5.0, 6.0, 1H), 3.93 (dd, *J* = 4.1, 5.0 Hz, 1H), 4.05−4.12 (m, 1H), 4.49 (d, *J* = 5.0 Hz, 2H), 5.03 (dd, *J* = 4.0, 4.0 Hz, 1H), 5.21 (d, *J* = 10.1 Hz, 1H), 5.29 (d, *J* = 16.0 Hz, 1H), 5.82−5.91 (m, 1H), 6.69 (s, 1H), 6.71 (d, *J* = 7.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.7, −4.7, −4.6, −4.4, 13.7, 13.9, 16.5, 17.9, 18.0, 18.2, 25.7, 25.8, 25.8, 29.9, 34.0, 35.2, 36.2, 42.1, 56.6, 65.2, 69.9, 71.4, 71.6, 83.8, 118.0, 118.3, 119.2, 119.7, 129.3, 132.1, 144.2, 155.8, 171.9, 173.5; HRMS (ESI) calcd for $C_{42}H_{78}O_8Si_3Na$ $(M + Na)^+$ 817.4896, found 817.4893.

Nhatrangin A (1). To a stirred solution of allyl ester **25** (0.010 g, 0.0125 mmol) in dry THF (3 mL) under nitrogen atmosphere at room temperature was added $Pd(PPh_3)_4$ (0.0018 g, 0.0015 mmol) in a dark hood, followed by the dropwise addition of redistilled morpholine (0.011 mL, 0.125 mmol). The reaction mixture was continued to stir at room temperature for 12 h. Then reaction mixture was concentrated and diluted with Et_2O (2 mL). The organic layer was separated and aqueous layer was extracted with Et_2O (2 × 2 mL). The combined organic layers were washed with 1 N HCl (2 mL), water, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was dissolved in THF (5 mL) and added 3 N HCl (1 mL) at room temperature. The resulting mixture was continued to stir at the same temperature for 12 h. After completion of the reaction, solvents were evaporated under reduced pressure. The crude compound was purified by silica gel eluting with (MeOH/$CHCl_3$, 1:9) to afford nhatrangin A (**1**) (0.0035 g, 67%) as a yellow oil: $[\alpha]^{30}_D$ = +0.8 (*c* 0.3, MeOH), lit.[9g] $[\alpha]^{25}_D$ = +0.2 (*c* 0.05, MeOH); IR (neat) ν_{max} 3284, 2929, 2857, 1722, 1452, 1255, 1219, 1097, 837, 774 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.72 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 7.3 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H), 1.22−1.30 (m, 2H) 1.51−1.67 (m, 2H), 1.68−174 (m, 1H), 2.19 (dd, *J* = 15.4, 5.4 Hz, 1H), 2.25 (d, *J* = 7.7 Hz, 1H), 2.38 (dd, *J* = 15.4, 4.3 Hz, 1H), 3.08 (s, 3H), 3.49−3.56 (m, 1H), 3.68−3.74 (m, 1H), 3.95 (dd, *J* = 5.4, 4.3 Hz, 1H), 4.94 (dd, *J* = 4.3, 4.4 Hz, 1H), 6.63−6.71 (m, 3H), 7.11 (t, *J* = 7.7 Hz, 1H), 9.29 (s, 1H); ^{13}CNMR (75 MHz, DMSO-d_6) δ 13.9, 15.3, 18.0, 29.9, 33.5, 35.3, 38.5, 40.5, 55.9, 68.4, 70.9, 78.6, 83.2, 112.9, 114.1, 116.9, 129.1, 144.0, 157.2, 171.0, 176.1; HRMS (ESI) calcd for $C_{21}H_{31}O_8Na$ $(M + Na)^+$ 435.1995, found 435.1988.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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