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Protecting Group Free Formal Total Synthesis of the Antitubercular Agent Erogorgiaene

Jhillu S. Yadav,*[a,b] Bodakuntla Thirupathaiah,,[a] and Ahmad Al Khazim Al Ghamdi[b]

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The formal total synthesis of the antitubercular agent erogorgiaene was achieved in 12 steps by using a protecting group free strategy. The synthesis involves an enamine-mediated 1,4-addition, an aldol condensation, dehydrogenation, Wittig olefination, intramolecular Friedel–Crafts cyclization, TEMPO-BAIB-mediated oxidation, and Evans auxiliary based diastereoselective methylation.

Introduction

Erogorgiaene (**1**) displays a high order of activity against *Mycobacterium tuberculosis*. Biological evaluation has revealed that it can inhibit 96% of *Mycobacterium tuberculosis* $H_{37}Rv$ at a concentration of 12.5 $\mu g\,mL^{-1}$. Erogorgiaene was isolated[1] from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*, along with other structurally related diterpenes (Figure 1). The major challenge associated with its synthesis lies in the control of the stereocenters, as this molecule lacks functional groups near the stereogenic centers. The excellent biological activity and extreme scarcity of erogorgiaene from the natural source has attracted significant interest among synthetic chemists, and so far, three total syntheses have been reported. The first total synthesis was reported by Hoveyda and co-workers[2a] by using a catalytic asymmetric conjugate addition strategy. Davies et al.[2b] reported the second total synthesis by using elegant carbene insertion/Cope rearrangement chemistry.

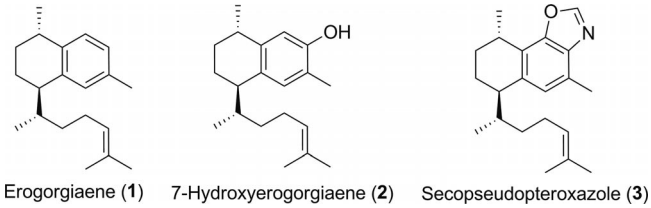

Figure 1. Antitubercular diterpenes isolated from *Pseudopterogorgia elisabethae*.

[a] Natural Product Chemistry,
CSIR–Indian Institute of Chemical Technology,
Hyderabad 500 607, India
Fax: +91-4027100387
E-mail: yadavpub@iict.res.in
[b] Engineer Abdullah Baqshan for Bee Research,
King Saud University,
Riyadh-11451, Saudi Arabia

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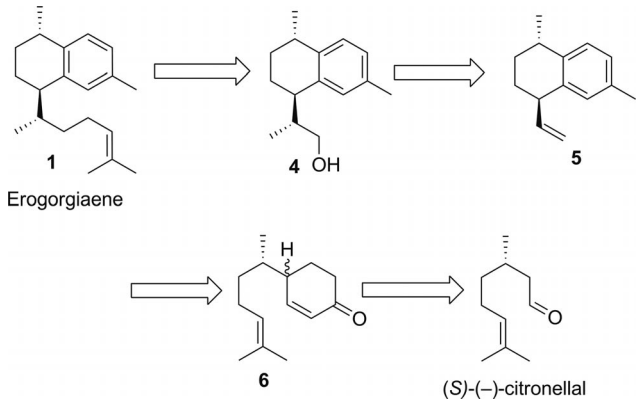
Our group[2c] has accomplished the total synthesis of erogorgiaene by using an aldol approach. Furthermore, a formal synthesis of erogorgiaene was reported by Harmata and Hong et al.[2d,2e]

As part of our ongoing research program on the total synthesis of biologically active terpene natural products,[2c,3] we recently reported a concise stereoselective total synthesis of (+)-artemisinin[3a] by using a protecting group free strategy. In continued exploration of the protecting group free synthesis of biologically active natural products, we wish to report herein an efficient formal total synthesis of erogorgiaene.

Results and Discussion

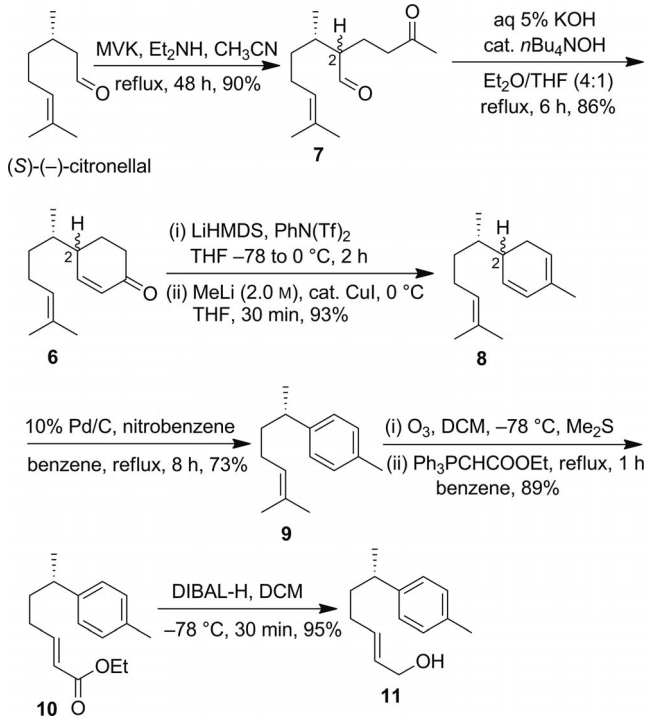
According to our retrosynthetic analysis sketched in Scheme 1, the target molecule was envisaged to be secured from key intermediate **4**, which in turn could be prepared from **5** through a hydroboration, oxidation, and Evans diastereoselective methylation protocol. Compound **5** was envisioned to be constructed by a sequence of straightforward reactions from **6**. Enone **6** can be obtained from commer-



Scheme 1. Retrosynthetic analysis of erogorgiaene.

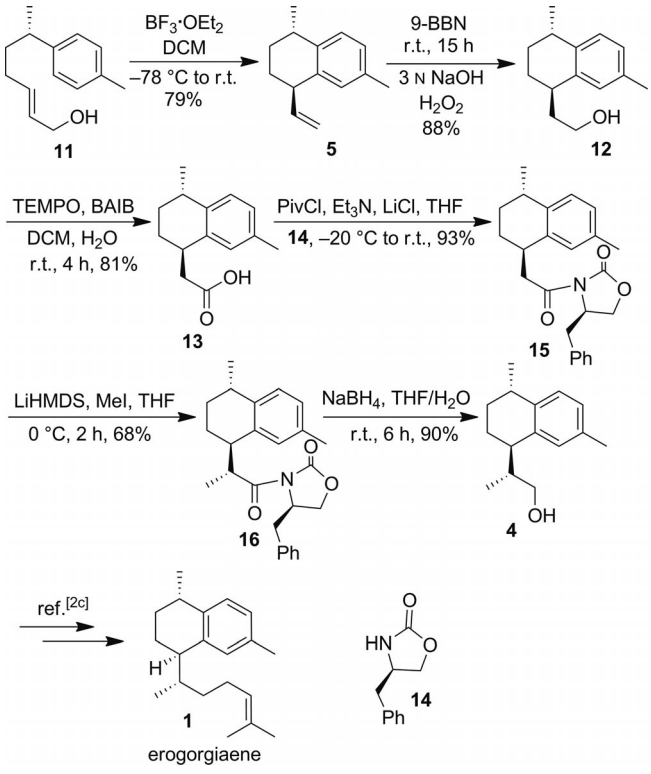
cially available (*S*)-(–)-citronellal and methyl vinyl ketone (MVK) by Robinson annulation.

Our synthesis began with the reaction of the enamine obtained from (*S*)-(–)-citronellal and diethylamine with methyl vinyl ketone in dry CH_3CN to furnish **7** as a mixture of diastereomers in 90% yield. As the stereocenter at C2 was unimportant for the total synthesis of erogorgiaene, we proceeded further with the mixture of diastereomers. Keto aldehyde **7** was subjected to an intramolecular aldol condensation in the presence of aq. KOH and a catalytic amount of nBu$_4$NOH to afford enone **6** in 86% yield.[4] Enone **6** was converted into its corresponding enol triflate by using LiHMDS and *N*-phenyl triflimide in anhydrous THF. The crude enol triflate was treated with MeLi (2.0 M in dry ether) and a catalytic amount of CuI in anhydrous THF at 0 °C for 30 min to afford 2-methyl-1,3-diene **8** in 93% yield[3b,5] over two steps. Aromatic compound **9** was prepared by following the protocol of Cossy[6] involving dehydrogenation in the presence of 10% Pd/C and nitrobenzene in 73% yield. Ozonolysis[7] of **9**, followed by C_2-Wittig olefination yielded α,β- unsaturated ester **10** in 89% yield over two steps. Reduction of ester **10** to allylic alcohol **11** was achieved with DIBAL-H in 95% yield (Scheme 2).



Scheme 2. Synthesis of allylic alcohol **11**.

Allylic alcohol **11** was subjected to intramolecular Friedel–Crafts cyclization[8] by using freshly distilled $BF_3{\cdot}OEt_2$ in dry DCM to afford bicyclic compound **5** in 79% yield with good diastereoselectivity (8:1, based on NMR spectroscopic data). Compound **5** was subjected to hydroboration by using 9-BBN (0.5 M in THF) following a known protocol[3a] to furnish primary alcohol **12** in 88% yield. Primary alcohol **12** was oxidized to acid **13** in 81% yield by using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and bis(acetoxy)iodobenzene (BAIB) in DCM and H_2O.[9] Acid **13** was coupled with Evans auxiliary **14** through the mixed anhydride at –20 °C by using Et_3N in anhydrous THF to furnish imide **15** in 93% yield. Diastereoselective methylation of the lithium enolate of **15** with MeI afford compound **16** in 68% yield.[9–11] Upon treatment with $NaBH_4$ in THF/H_2O[11] at room temperature, compound **16** gave key intermediate **4** in 90% yield (Scheme 3). Intermediate **4** was utilized by us for the total synthesis of the target molecule, erogorgiaene.[2c] Thus we have achieved the formal total synthesis of erogorgiaene (**1**).



Scheme 3. Formal total synthesis of erogorgiaene.

Conclusions

In summary, we have accomplished the protecting group free formal total synthesis of erogorgiaene (**1**) in an efficient and highly stereocontrolled fashion starting from (*S*)-(–)-citronellal in 12 linear steps with an overall yield of 14.2%. The important features of our synthetic strategy are dehydrogenation and an intramolecular Friedel–Crafts cyclization to construct bicyclic compound **5**.

Experimental Section

General Methods: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an argon atmosphere in oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, toluene, and diethyl ether from Na and benzophenone; CH_2Cl_2 and DMSO from CaH_2. Commercial reagents were used without purification. Column chromatography was car-

ried out by using silica gel (60–120 mesh). Specific optical rotations were recorded with a JASCO DIP-360 digital polarimeter. Infrared spectra were recorded with a Perkin-Elmer Infrared–683 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}. Samples were scanned either neat, as KBr wafers, or in chloroform as a thin film. ^1H NMR spectra were recorded in $CDCl_3$ with a Bruker 300 or Varian Unity 500 NMR spectrometer. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ and the chemical shifts are reported in ppm downfield from tetramethylsilane. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, m = multiplet, br. = broad.

(3*S*)-3,7-Dimethyl-2-(3-oxobutyl)oct-6-enal (7): To the stirred solution of (*S*)-(–)-citronellal (5.0 g, 32.46 mmol) in acetonitrile (50 mL) was added freshly distilled methyl vinyl ketone (MVK; 3.95 mL, 48.7 mmol) and diethylamine (0.33 mL, 3.24 mmol) under a nitrogen atmosphere. After heating the reaction mixture for 48 h at reflux, the excess amount of MVK and CH_3CN were evaporated in vacuo, and the crude product was purified by column chromatography (silica gel, 5% EtOAc/hexane) to afford keto aldehyde **7** (6.54 g, 90%) as a diastereomeric mixture. R_f = 0.40 (silica gel, 10% EtOAc/hexane). IR (neat): $\tilde{\nu}$ = 2922, 1718, 1448, 1368 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, J = 7.0 Hz, 2 H), 0.99 (d, J = 7.0 Hz, 1 H), 1.19–1.54 (m, 4 H), 1.61 (s, 3 H), 1.68, (s, 3 H), 1.69–1.71 (m, 1 H), 1.72–2.09 (m, 2 H), 2.12 (s, 3 H), 2.16–2.27 (m, 1 H), 2.29–2.62 (m, 2 H), 5.01–5.10 (m, 1 H), 9.60 (d, J = 2.4 Hz, 0.6 H), 9.64 (d, J = 2.4 Hz, 0.4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 16.8, 17.6, 18.0, 19.6, 25.4, 25.61, 25.64, 29.9, 32.2, 33.2, 33.8, 34.4, 41.3, 41.4, 55.8, 56.2, 123.7, 131.9, 205.0, 205.3, 208.0, 208.1 ppm. MS (ESI): m/z = 247 $[M + Na]^+$. HRMS (ESIMS): calcd. for $C_{14}H_{24}O_2Na$ $[M + Na]^+$ 247.1673; found 247.1681.

4-[(*S*)-6-Methylhept-5-en-2-yl]cyclohex-2-enone (6): A mixture of keto aldehyde **7** (6.0 g, 26.78 mmol), aqueous tetrabutylammonium hydroxide (2 mL), and 10% aqueous potassium hydroxide (120 mL) in THF (30 mL) and diethyl ether (120 mL) was heated at reflux for 6 h. The organic layer was separated, and the aqueous layer was washed with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine (1 × 50 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced presser, and the crude product was purified by column chromatography (silica gel, 4% EtOAc/hexane) to afford colorless liquid compound **6** (4.75 g, 86%). R_f = 0.60 (silica gel, 10% EtOAc/hexane). IR (neat): $\tilde{\nu}$ = 2958, 1715, 1673, 1450, 1379 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (dd, J = 7.0, 10.2 Hz, 3 H), 1.16–1.49 (m, 3 H), 1.60 (s, 3 H), 1.69 (s, 3 H), 1.70–1.83 (m, 1 H), 1.85–2.15, (m, 3 H), 2.22–2.55 (m, 3 H), 5.0–5.10 (m, 1 H), 5.98 (d, J = 10.2 Hz, 1 H), 6.80 (t, J = 10.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 16.4, 17.6, 23.9, 25.6, 25.7, 33.8, 34.0, 36.00, 36.05, 37.4, 37.6, 41.0, 41.5, 124.0, 129.6, 129.8, 131.7, 154.2, 155.3, 200.0 ppm. MS (ESI): m/z = 207 $[M + H]^+$. HRMS (ESI): calcd. for $C_{14}H_{23}O$ $[M + H]^+$ 207.1748; found 207.1758.

2-Methyl-5-[(*S*)-6-methylhept-5-en-2-yl]cyclohexa-1,3-diene (8): LiHMDS (1.06 M in THF, 31 mL, 32.76 mmol) was added to a well-stirred solution of enone compound **6** (4.5 g, 21.84 mmol) in dry THF (40 mL) at–78 °C. The reaction mixture was stirred for 30 min and then *N*-phenyltrifluoromethane sulfonamide (10.1 g, 28.39 mmol) was added, and the mixture was stirred for another 0.5 h, followed by heating to 0 °C for 0.5 h. Upon completion of the reaction (TLC analysis), the reaction was quenched with sat. NH_4Cl (10 mL). The reaction mixture was then extracted with Et_2O (2 × 15 mL), and the combined organic phase was washed with brine (30 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum to obtain the crude residue, which was dissolved in diethyl ether and passed through a short silica gel pad. After concentration, the resulting triflate compound was dissolved in dry THF (80 mL) and cooled to 0 °C. To this solution was added CuI (0.415 g, 10 mol-%) and MeLi (2.0 M in Et_2O, 22 mL, 2.0 equiv.). After stirring for 30 min, the reaction was quenched with sat. NH_4Cl solution (20 mL) and extracted with diethyl ether (2 × 25 mL). The combined organic phases were washed with brine (30 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by silica gel column chromatography (hexane) to afford compound **8** (4.14 g, 93%) as a colorless oil. R_f = 0.90 (hexane). IR (neat): $\tilde{\nu}$ = 2962, 2921, 1449, 1377 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (dd, J = 6.0, 6.8 Hz, 3 H), 1.09–1.29 (m, 1 H), 1.32–1.56 (m, 2 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 1.83- 2.11 (m, 4 H), 2.18–2.34 (m, 1 H), 5.10 (t, J = 6.8 Hz, 1 H), 5.45 (br. s, 1 H), 5.65 (dt, J = 3.0, 6.8 Hz, 1 H), 5.73–5.83 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5, 16.7, 17.6, 21.0, 24.3, 25.7, 25.9, 26.3, 34.1, 34.2, 36.0, 38.0, 38.3, 120.3, 120.5, 124.8, 127.8, 128.1, 129.7, 131.0, 131.1 ppm.

(*S*)-1-Methyl-4-(6-methylhept-5-en-2-yl)benzene (9): Dry nitrobenzene (2.94 mL, 28.67 mmol) and 10% Pd/C (0.3 g) were added to a solution of diene compound **8** (3.9 g, 19.11 mmol) in dry benzene (40 mL). The reaction mixture was heated at reflux for 8 h, and after complete consumption of the starting material the reaction mixture was cooled to room temperature and filtered through a Celite pad under wet conditions. The organic layer was removed under vacuum, and the crude product was purified by silica gel column chromatography (hexane) to afford **9** (2.81 g, 73%) as a colorless oil. R_f = 0.85 (hexane). $[\alpha]_D^{25}$ = +43.8 (c = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2961, 2920, 1513, 1449, 816 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, J = 7.0 Hz, 3 H), 1.50 (s, 3 H), 1.51–1.63 (m, 2 H), 1.65 (s, 3 H), 1.78- 1.90 (m, 2 H), 2.30 (s, 3 H), 2.55–2.68 (m, 1 H), 5.04 (t, J = 7.0 Hz, 1 H), 7.02 (d, J = 1.7 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 20.9, 22.4, 25.7, 26.1, 38.4, 39.0, 124.5, 126.8, 128.9, 131.3, 135.1, 144.6 ppm.

(*S*,*E*)-Ethyl 6-*p*-Tolyhept-2-enoate (10): Ozone gas was passed through a well-stirred solution of **9** (2.65 g, 13.12 mmol) in DCM at –78 °C; after 15 min Me_2S (1.4 mL, 19.68 mmol) was added, and the mixture was stirred for 1 h at room temperature. Then, the solvent was removed under vacuum to afford the crude aldehyde, which was treated with stabilized C2-Wittig ylide (6.85 g, 19.68 mmol) in dry benzene at reflux for 1 h. After completion of the reaction (TLC analysis), benzene was removed under vacuum, and the crude ester was subjected to column chromatography (silica gel, 3%EtOAc/hexane) to afford α,β-unsaturated ester **10** (2.87 g, 89%) as a colorless liquid. R_f = 0.7 (silica gel, 10% EtOAc/hexane). $[\alpha]_D^{25}$ = +46.6 (c = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2960, 1720, 1194, 1043, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, J = 7.0 Hz, 3 H), 1.28 (d, J = 7.0 Hz, 3 H), 1.72 (q, J = 7.7 Hz, 2 H), 2.01–2.12 (m, 2 H), 2.31 (s, 3 H), 2.58–2.73 (m, 1 H), 4.15 (q, J = 7.0 Hz, 2 H), 5.71 (d, J = 15.67 Hz, 1 H), 6.89 (td, J = 6.98, 15.67 Hz, 1 H), 7.03 (q, J = 8.1 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 20.9, 22.3, 30.2, 36.4, 38.9, 60.0, 121.2, 126.7, 129.0, 135.4, 143.5, 149.0, 166.6 ppm. MS (ESI): m/z = 247 $[M + H]^{+\cdot}$. HRMS (ESI): calcd. for $C_{16}H_{22}O_2Na[M + Na]^+$ 269.1517; found 269.1510.

(*S*,*E*)-6-*p*-Tolylhept-2-en-1-ol (11): DIBAL-H (25% in toluene, 14.34 mL, 25.24 mmol) was added dropwise to a well-stirred solution of **10** (2.7 g, 10.97 mmol) in dry DCM at –78 °C. After ad-

dition of DIBAL-H, the reaction mixture was brought to 0 °C and stirred for 30 min. The reaction mass was quenched with saturated aqueous sodium–potassium tartrate solution (10 mL) at 0 °C and stirred for 3 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with brine (15 mL) and dried with anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the crude product was subjected to flash column chromatography (silica gel, 10% EtOAc/hexane) to obtain pure allylic alcohol **11** (2.13 g, 95%). R_f = 0.6 (silica gel, 20% EtOAc/hexane). $[\alpha]_D^{25}$ = + 40.5 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3359, 2922, 1513, 1451, 971, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.8 Hz, 3 H), 1.63 (q, *J* = 6.8 Hz, 2 H), 1.83–2.0 (m, 2 H), 2.31 (s, 3 H), 2.57–2.71 (m, 1 H), 4.0 (d, *J* = 4.7 Hz, 2 H), 5.47–5.65 (m, 2 H), 7.02 (d, *J* = 4.5 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 22.4, 30.2, 37.6, 38.9, 63.6, 126.8, 128.8, 128.9, 133.0, 135.2, 144.1 ppm. MS (ESI): *m*/*z* = 227 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{20}ONa$ $[M + Na]^+$ 227.1411; found 227.1403.

(1*S*,4*R*)-1,6-Dimethyl-4-vinyl-1,2,3,4-tetrahydronaphthalene (5): To a stirred solution of allylic alcohol **11** (2.0 g, 9.8 mmol) in anhydrous DCM (20 mL) under a nitrogen atmosphere was added freshly distilled $BF_3{\cdot}OEt_2$ (1.2 mL, 9.8 mmol) at –78 °C. The reaction mixture was allowed to attain room temperature and then quenched with saturated $NaHCO_3$ solution (8 mL). The reaction mixture was extracted with DCM (2 × 10 mL), the combined DCM layer was dried with Na_2SO_4, and the solvents were evaporated. The crude product was purified by silica gel column chromatography (hexane) to afford compound **5** (1.44 g, 79%) as a colorless oil with good diastereoselectivity (8:1, based on NMR spectroscopic data). R_f = 0.85 (silica gel, hexane). $[\alpha]_D^{25}$ = –15.8 (*c* = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2926, 1635, 1453, 911, 813 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 7.0 Hz, 3 H), 1. 46 (dd, *J* = 6.8, 9.0 Hz, 1 H), 1.55–1.66 (m, 1 H), 1.70–1.91 (m, 1 H), 2.0 (dd, *J* = 5.2, 9.8 Hz, 1 H), 2.28 (s, 3 H), 2.79–2.95 (m, 1 H), 3.33–3.48 (m, 1 H), 4.95–5.13 (m, 2 H), 5.76–5.96 (m, 1 H), 6.97 (d, *J* = 7.3 Hz, 2 H), 7.12 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 22.8, 27.7, 29.3, 32.3, 44.1, 114.7, 126.9, 127.8, 129.8, 134.8, 137.6, 138.9, 143.0 ppm.

2-[(1*R*,4*S*)-4,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl]ethanol (12): Compound **5** (1.35 g, 7.26 mmol) in dry THF (15 mL) was charged into a 100-mL, two-necked round-bottomed flask equipped with a magnetic spin bar, a nitrogen inlet, and a septum. To this flask was added 9-BBN (0.5 M in THF, 29 mL, 14.51 mmol) dropwise at 0 °C, and the mixture was stirred for 15 h at room temperature. After complete consumption of the starting compound, the reaction mixture was quenched with 3 N NaOH (10 mL) at 0 °C, followed by the addition of 30% H_2O_2 (15 mL) dropwise, and the resulting solution was stirred for 6 h at room temperature. The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with brine (1 × 30 mL) and dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was subjected to flash column chromatography (silica gel, 10% EtOAc/hexane) to obtain pure primary alcohol **12** (1.30 g, 88%). R_f = 0.6 (silica gel, 20% EtOAc/hexane). $[\alpha]_D^{25}$ = +18.7 (*c* = 0.7, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3362, 2928, 1453, 1054, 814 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 7.0 Hz, 3 H), 1.39–1.66 (m, 2 H), 1.71–2.05 (m, 4 H), 2.3 (s, 3 H), 2.80–2.97, (m, 2 H), 3.77, (dd, *J* = 6.2, 7.3 Hz, 2 H), 6.92–7.01 (m, 2 H), 7.07, (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 23.4, 23.8, 27.3, 31.9, 34.3, 39.9, 61.1, 126.6, 128.3, 129.2, 134.9, 139.0, 140.1 ppm. MS (ESI): *m*/*z*: 227 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{20}ONa$ $[M + Na]^+$ 227.1411; found 227.1402.

2-[(1*R*,4*S*)-4,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl]acetic Acid (13): TEMPO (0.352 g, 2.25 mmol) and BAIB (6.35 g, 19.74 mmol) were added to a vigorously stirred solution of **12** (1.15 g, 5.63 mmol) in CH_2Cl_2 (10 mL) and H_2O (3 mL) at 0 °C. The reaction mixture was allowed to stir for 4 h at room temperature followed by quenching with saturated solution of $Na_2S_2O_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with brine (15 mL) and dried with anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the crude acid was subjected to flash column chromatography (silica gel, 12% EtOAc/hexane) to obtain acid **13** (0.99 g, 81%). R_f = 0.3 (silica gel, 20% EtOAc/hexane). $[\alpha]_D^{26}$ = +22.5 (*c* = 0.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3437, 2925, 1709, 1455, 812 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 7.0 Hz, 3 H), 1.47–1.56 (m, 1 H), 1.61–1.69 (m, 1 H), 1.91–2.13 (m, 2 H), 2.3 (s, 3 H), 2.57 (dd, *J* = 10.1, 15.1 Hz, 1 H), 2.74 (dd, *J* = 4.3, 15.1 Hz, 1 H), 2.87–2.95 (m, 1 H), 3.27–3.35 (m, 1 H), 6.98 (br. s, 2 H), 7.08 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 23.3, 24.1, 26.9, 31.8, 34.5, 41.7, 127.2, 128.6, 128.8, 135.2, 138.2, 139.1, 178.6 ppm. MS (ESI): *m*/*z* = 241 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{18}O_2Na$ $[M + Na]^+$ 241.1204; found 241.1207.

(*R*)-4-Benzyl-3-{2-[(1*R*,4*S*)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1yl]acetyl}oxazolidin-2-one (15): To a stirred solution of acid **13** (0.9 g, 4.13 mmol) and Et_3N (1.43 mL, 10.3 mmol) in anhydrous THF (8 mL) at –20 °C was added pivaloyl chloride (1.0 mL, 8.26 mmol) dropwise, and the mixture was stirred for 1 h. Anhydrous LiCl (0.26 g, 6.19 mmol) was then added, and the mixture was stirred for 30 min. To this, a solution of auxiliary **14** (0.95 g, 5.37 mmol) in anhydrous THF was added, and the mixture was allowed to stir for 1 h at –20 °C then allowed to attain room temperature. After stirring at ambient temperature for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (7 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (25 mL) and dried with Na_2SO_4, and the solvents were evaporated. The crude product was subjected to column chromatography (silica gel, 5% EtOAc/hexane) to obtain imide compound **15** (1.45 g, 93%). R_f = 0.4 (silica gel, 10% EtOAc/hexane). $[\alpha]_D^{25}$ = –43.7 (*c* = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2924, 1783, 1700, 1382, 1209, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 3 H), 1.46–1.70 (m, 3 H), 1.98–2.13 (m, 2 H), 2.28 (s, 3 H), 2.80 (dd, *J* = 9.8, 12.8 Hz, 1 H), 2.86–3.01 (m, 1 H), 3.22–3.29 (m, 1 H), 3.34 (dd, *J* = 3.7, 12.8 Hz, 1 H), 3.38–3.50 (m, 1 H), 4.15–4.22 (m, 2 H), 4.65–4.78 (m, 1 H), 6.93–7.18 (m, 3 H), 7.20–7.39 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 23.5, 24.0, 26.8, 31.7, 34.1, 38.0, 42.6, 55.3, 66.1, 127.1, 127.3, 128.6, 128.9, 129.0, 129.4, 135.1, 135.3, 138.4, 139.2, 153.3, 172.3 ppm. MS (ESI): *m*/*z* = 378$[M + H]^+$. HRMS (ESI): calcd. for $C_{24}H_{27}NO_3$ Na $[M + Na]^+$ 400.1888; found 400.1897.

(*R*)-4-Benzyl-3-{(*R*)-2-[(1*R*,4*S*)-4,7-dimethyl1,2,3,4-tetrahydronaphthalen-1-yl]propanoyl}oxazolidin-2-one (16): To a stirred solution of **15** (1.35 g, 3.58 mmol) in anhydrous THF (15 mL) under a nitrogen atmosphere was added LiHMDS (1.06 M in THF, 6.75 mL, 7.16 mmol) at 0 °C. After stirring for 0.5 h, methyl iodide (0.56 mL, 8.95 mmol) was added, and the mixture was stirred for another 0.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (8 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layer was washed with brine (20 mL) and dried

with Na_2SO_4, and the solvent was evaporated. The crude product was subjected to column chromatography (silica gel, 3% EtOAc/hexane) to obtain compound **16** (0.95 g, 68%). R_f = 0.7 (silica gel, 10% EtOAc/hexane). $[\alpha]_D^{26}$ = –104.3 (c = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 1781, 1698, 1379, 1208 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.8 Hz, 3 H), 1.21 (d, J = 6.8 Hz, 3 H), 1.34–1.46 (m, 1 H), 1.76–1.89 (m, 2 H), 2.04–2.19 (m, 1 H), 2.24 (s, 3 H), 2.71 (dd, J = 9.8, 12.8 Hz, 1 H), 2.82–2.95 (m, 1 H), 2.99–3.09 (m, 1 H), 3.28, (dd, J = 3.0, 12.8 Hz, 1 H), 3.71 (t, J = 6.8 Hz, 1 H), 3.98 (dd, J = 2.2, 9.0 Hz, 1 H), 4.30–4.44 (m, 2 H), 6.90–701 (m, 2 H), 7.07 (d, J = 8.3 Hz, 1 H), 7.17–7.37 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 20.9, 21.6, 23.4, 28.0, 31.4, 37.9, 41.2, 41.9, 55.7, 65.7, 127.0, 127.2, 128.0, 128.9, 129.3, 129.4, 134.1, 135.5, 136.9, 140.3, 152.8, 176.7 ppm. MS (ESI): m/z = 392 $[M + H]^+$. HRMS (ESI):calcd. for $C_{25}H_{29}NO_3Na$ $[M + Na]^+$ 414.2045; found 414.2060.

(*R*)-2-[(1*R*,4*S*)-4,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl-propan-1-ol] (4): $NaBH_4$ (0.290 g, 7.59 mmol) was added to a stirred solution of imide **16** (0.85 g, 2.17 mmol) in THF/H_2O (1:1, 10 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 6 h and extracted with EtOAc (2 × 6 mL). The combined organic layer was washed with brine (15 mL) and dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude primary alcohol was subjected to column chromatography (silica gel, 10% EtOAc/hexane) to obtain primary alcohol compound **4** (0.426 g, 90%). R_f = 0.3 (silica gel, 20% EtOAc/hexane). $[\alpha]_D^{25}$ = +52.8 (c = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3418, 2924, 1513, 1038, 1015, 814 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.74 (d, J = 6.8 Hz, 3 H), 1.27 (d, J = 6.8 Hz, 3 H), 1.32–1.44 (m, 1 H), 1.52–1.71, (m, 1 H), 1.73–1.87 (m, 1 H), 1.89–2.07 (m, 1 H), 2.30 (s, 3 H), 2.21–2.36 (m, 1 H), 2.70–2.88 (m, 1 H), 2.95–3.08 (m, 1 H), 3.58 (dd, J = 6.6, 10.5 Hz, 1 H), 3.67 (dd, J = 7.1, 10.5 Hz, 1 H), 6.96 (d, J = 7.7 Hz, 1 H), 7.04 (s, 1 H), 7.14 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 21.0, 21.6, 22.2, 30.6, 32.3, 38.9, 39.9, 66.7, 126.3, 126.9, 128.2, 134.7, 138.9, 140.2 ppm. MS (ESI): m/z = 241 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{15}H_{22}ONa$ $[M + Na]^+$ 241.1563; found 241.1576.

Supporting Information (see footnote on the first page of this article): General methods and copies of the ^1H and ^{13}C NMR spectra.

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