Supporting Information
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Supplemental Information

for

Enantioselective Synthesis of F-Ring Fragments of Kibdelone C via Desymmetrizing Bromolactonization of 1,4-Dihydrobenzoic Acid

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General

Solvents were purified before use as follows unless otherwise noted. Dichloromethane (CH$_2$Cl$_2$) and benzene were distilled from calcium hydride immediately prior to use. Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.$^1$ Methanol (MeOH), acetonitrile (MeCN), and dimethylformamide (DMF) were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. These solvents were determined to have less than 50 ppm H$_2$O by Karl Fischer coulometric moisture analysis. Chloroform and acetone were distilled from CaSO$_4$ and stored over 4 Å molecular sieves. Reagents were reagent grade and used without purification unless otherwise noted. Diisopropylethylamine (Hünig’s base), was refluxed with, distilled from, and stored over KOH. All reactions were performed in flame-dried glassware under nitrogen or argon; reaction temperatures refer to the temperature of the cooling/heating bath. Catalyst 1$^2$ and 1,4-dihydrobenzoic acid$^3$ were prepared according to the previously reported procedures.

Analytical HPLC separations were performed using a Chiralcel OD-H (Daicel Chemical Industries, Ltd.) column, as indicated. Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated and reported as wavenumbers (cm$^{-1}$). Proton nuclear magnetic resonance (1H NMR) and carbon nuclear magnetic resonance (13C NMR) spectra were obtained at the indicated field as solutions in CDCl$_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent (e.g., for CDCl$_3$, δ = 7.26 ppm and 77.0 ppm for 1H and 13C NMR, respectively) and are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (J) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent.
(1S,5S,6S)-5-Bromo-7-oxabicyclo[4.2.0]oct-2-en-8-one (ent-5). N-Bromosuccinimide (3.871 g, 21.75 mmol) was added to a solution of dihydrobenzoic acid 51 (2.7 g, 21.8 mmol) and catalyst ent-1 (0.964 g, 2.18 mmol) in PhMe/CH₂Cl₂ (1:1) (220 mL) at –50 °C, and the solution was stirred for 14 h. The reaction was quenched with saturated aqueous Na₂SO₃ (150 mL), and the mixture was warmed to room temperature with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 75 mL). The combined organic layers were washed with 5% aqueous Na₂CO₃ (2 x 150 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography, eluting with hexanes:EtOAc (9:1) to give 3.1 g (70%) of ent-5 as a white solid: mp 96–98 °C; spectra matched the previously reported data;¹ H NMR (CDCl₃, 400 MHz) δ ppm 6.10 – 6.00 (m, 1H), 5.90 (dd, 1J = 9.9, 6.1, 1.8, 1.3 Hz, 1H), 4.94 (dd, 1J = 5.7, 3.1 Hz, 1H), 4.55 (q, 1J = 3.1 Hz, 1H), 4.28 (t, 1J = 6.1 Hz, 1H), 2.72 (m, 2H); [α]²⁵D –49.0 (c = 1.0, CHCl₃); HPLC (210 nm): OD-H (1% i-PrOH/hexanes, 1.0 mL/min) 16.6 min (major) 18.0 min (minor). ent-5 was recrystallized from hexanes (10 mg/100 mL) to give (1.9 g, 45%) of ent-5 as a single enantiomer. HPLC (210 nm): OD-H (1% i-PrOH/hexanes, 1.0 mL/min) 16.6 min

(1R,2R,3S,5R,6R)-5-Bromo-2,3-dihydroxy-7-oxabicyclo[4.2.0]octan-8-one (9). The olefin ent-5 (0.8 g, 3.9 mmol) was added to a solution of citric acid (0.824 g, 4.29 mmol) potassium osmate (0.143 g, 0.39 mmol, 0.1 mol %) and 4-methylmorpholine N-oxide (0.502 g, 4.29 mmol) in H₂O/t-BuOH (1:1) (16 mL) at 0 °C. The reaction mixture was stirred for 18 h and then solid sodium sulfite (500 mg) was added and stirring was continued for 15 minutes at room temperature. The organic layer was removed under reduced pressure, and the aqueous layer was extracted with ethyl acetate (5 x 25 mL). The combined organic extracts were washed with brine (75 mL), dried (MgSO₄), and concentrated under reduced pressure. The crude material was recrystallized from ethanol to give 0.55 g (60 %) of 9 as clear crystals: mp 211-212°C.¹ H NMR (CD₃OD, 400 MHz,) δ ppm 4.51 (dd, 1J = 4.3, 1.2 Hz, 1H), 4.13 (s, 1 H), 4.03 (dd, 1J = 9.59, 2.93 Hz, 1 H), 3.80 (ddd, 1J = 11.54, 9.59, 7.04 Hz, 1 H), 2.75 (m, 1 H), 2.67 (ddd, 1J = 14.18, 6.95, 5.09 Hz, 1 H), 2.11 (tdd, 1J = 11.80, 11.80, 2.70 Hz, 1 H).¹³C NMR (CD₃OD, 100 MHz) δ
ppm 175.0, 83.1, 74.4, 72.6, 54.8, 49.8, 36.3; IR (film) 3380, 2955, 1711, 1439, 1261, 1202 cm\(^{-1}\); mass spectrum (ESI) \(m/z\) 258.95760 [M+Na]\(^+\), 260.95530 [M+Na]\(^+\). \(\text{C}_7\text{H}_9\text{BrO}_4\) [M+Na]\(^+\) requires 258.95760, 260.95530.

**Methyl (3a\(R\),6\(S\),7\(S\))-6-hydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[\(d\)][1,3]dioxole-4-carboxylate (11).** Diol 9 (0.258 g, 1.09 mmol) was added to a mixture of MeOH (11 mL, 0.1 M) containing K\(_2\)CO\(_3\) (0.225 g, 1.63 mmol) and was stirred for 2 h, after which, the solvent was removed under reduced pressure. The residue was redissolved in MeOH (5 mL) and K\(_2\)CO\(_3\) was removed by vacuum filtration. The filtrate was evaporated and the crude triol 10 was carried in the next step without further purification. The crude triol 10 (0.205 g, 1.09 mmol) was suspended in DCM (17 mL, 0.065M) and activated 4 Å mol sieves (1 g) were added, followed by camphor sulfonic acid (0.886 g, 3.82 mmol) and 2,2-dimethoxy propane (0.284 g, 0.35 mL, 2.73 mmol). The reaction was heated to reflux for 3 h, then cooled to rt and filtered. The filtrate was concentrated under reduced pressure, and the crude was directly purified by column chromatography eluting with 1:1 Hex:EtOAc to give 0.186 g (75%) of 11 as a white solid: mp 75-76 \(^\circ\)C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.05 (dd, \(J\) =5.2, 1.1 Hz, 1 H), 4.91 (d, \(J\) =5.5 Hz, 1 H), 4.59 (tdt, \(J\) =4.4, 2.4, 1.2 Hz, 1 H), 4.30-4.23 (m, 1 H), 3.81 (s, 3 H), 3.13 (d, \(J\) =10.6 Hz, 1 H), 2.39 (dddd, \(J\) =15.1, 4.4, 3.1, 1 Hz, 1 H), 1.98 (ddd, \(J\) =15.1, 4.7, 2.5 Hz, 1 H), 1.43 (s, 3 H), 1.39 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 166.6, 139.73, 129.9, 109.9, 73.1, 71.0, 62.9, 52.2, 31.6, 28.2, 26.3.; IR (film) 3454, 2987, 2938, 1723, 1651, 1438, 1372, 1314, 1259, 1219 cm\(^{-1}\); Mass Spectrum (ESI) \(m/z\) 251.08920 [M+Na]\(^+\), \[\text{C}_{11}\text{H}_{16}\text{O}_{5}\] [M+Na]\(^+\) requires 251.08900.

**Methyl(3a\(R\),6\(S\),7\(S\))-6-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[\(d\)][1,3]-dioxole-4-carboxylate (12).** Chloromethyl methyl ether (0.105 g, 1.3 mmol) was added to a solution of 11 (0.150 g, 0.66 mmol) and diisopropylethyl amine (0.25 g, 2.0 mmol) in CH\(_2\)Cl\(_2\) (2.5 mL, 0.25 M) and the reaction was heated under reflux for 4 h. The solvent was removed under reduced pressure and the reaction mixture was purified directly by column chromatography eluting with Hex:EtOAc 7:3 to give
0.27 g (91%) of 12 as a white solid; mp 70–71 °C.  $^1$H NMR (CDCl$_3$, 400 MHz) δ ppm 7.12 (s, 1 H) 4.80 (d, $J = 5.8$ Hz, 1 H) 4.74 (s, 2 H) 4.32 - 4.20 (comp, 2 H) 3.81 (s, 3 H) 3.41 (s, 3 H) 2.21 (dt, $J = 12.2$, 5.1 Hz, 1 H) 1.76 (dt, $J = 12.2$, 10.3 Hz, 1 H) 1.49 (s, 3 H) 1.43 (s, 3 H) 13C NMR (CDCl$_3$, 100 MHz) δ ppm 166.6, 139.73, 129.9, 109.9, 95.8, 73.1, 71.0, 62.9, 56.7, 52.2, 31.6, 28.2, 26.3; IR (film) 2987, 2938, 1723, 1651, 1438, 1372, 1314, 1259, 1219 cm$^{-1}$; Mass Spectrum (ESI) $m/z$ 295.11580 [M+Na]$^+$, [C$_{13}$H$_{20}$O$_6$][M+Na]$^+$ requires 295.11579.

(3aR,6S,7aS)-6-(Methoxymethoxy)-2,2-dimethyl-3a,6,7a-tetrahydrobenzo[d][1,3]dioxole-4-carboxylic acid (13). 1 M aq LiOH (0.72 mL, 0.72 mmol) was added to a solution of 12 (0.1 g, 0.36 mmol) in acetonitrile (3.6 mL, 0.1 M) and the reaction was stirred for 14 h. The solvent was removed under reduced pressure and the crude residue was dissolved in EtOAc. Amberlite® IR120 acidic resin was added until the pH was ca. 5. The solution was filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by column chromatography eluting with hexanes/EtOAc/AcOH (85:15:0.1, v/v/v) to give 0.081 g (87%) of 13 as a white solid; mp 74-75 °C. $^1$H NMR (CDCl$_3$, 400 MHz) δ ppm 7.25 (d, $J = 2.1$ Hz, 1 H) 4.79 (d, $J = 5.8$ Hz, 1 H) 4.76 (d, $J = 1.7$ Hz, 2 H) 4.33 (dt, $J = 10.1$, 5.1 Hz, 1 H) 4.30 - 4.24 (m, 1 H) 3.42 (s, 3 H) 2.23 (dt, $J = 12.3$, 5.1 Hz, 1 H) 1.81 (dt, $J = 12.3$, 10.1 Hz, 1 H) 1.51 (s, 3 H) 1.44 (s, 3 H) 13C NMR (CDCl$_3$, 100 MHz) δ ppm 171.3, 135.5, 130.73, 121.1, 95.5, 86.1, 74.6, 72.4, 58.2, 32.3, 28.2, 26.3; IR (film) 3454, 2980, 2924, 1722, 1651, 1434, 1372, 1314, 1259, 1219 cm$^{-1}$; Mass Spectrum (ESI) $m/z$ 257.10330 [M–H]$^-$, [C$_{12}$H$_{18}$O$_6$][M–H]$^-$ requires 257.10306.

(3aS,5S,7aS)-7-Iodo-5-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo-[d][1,3]dioxole (16). Carboxylic acid 13 (0.025 g, 0.1 mmol) dissolved in CH$_2$Cl$_2$ (0.5 mL) was added to a solution of EDCI•HCl (0.037 g, 0.19 mmol) and pyrithione salt 14 (0.029 g, 0.19 mmol) cooled to 0 °C. The reaction was warmed to rt and stirred for 1.5 h, after which, the reaction was diluted with CH$_2$Cl$_2$ (5 mL) and the organic layer was washed with sat aq NH$_4$Cl (3 x 5 mL). The layers were separated and the organics were dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The crude 15 was dissolved in Cl$_2$Br and irradiated with a 150 watt electric flood lamp for 10 min. The solvent was
removed under reduced pressure and the crude material was purified by column chromatography eluting with hexanes/EtOAc (9:1, v/v) to give 0.016 g (55%) of 16 as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz) δ ppm 6.39 (d, $J$ = 3.4 Hz, 1 H) 4.70 (s, 2 H) 4.51 (d, $J$ = 5.8 Hz, 1 H) 4.34 (ddd, $J$ = 8.0, 5.7, 4.1 Hz, 1 H) 4.08 – 4.03 (m, 1 H) 3.39 (s, 3 H) 2.21 (dt, $J$ = 13.7, 4.8 Hz, 1 H) 1.99 (dt, $J$ = 14.3, 6.7 Hz, 1 H) 1.53 (s, 3 H), 1.41 (s, 3H) $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 134.3, 123.0, 110.0, 95.7, 76.0, 72.8, 70.9, 55.4, 31.7, 28.1, 26.2. IR (film): 2928, 2854, 1618, 1465, 1256, 1090, 837 cm$^{-1}$; Mass Spectrum (ESI) m/z 315.02080 [M+Na]$^+$, 317.01880 [M+Na]$^+$ [C$_{11}$H$_{17}$BrO$_4$ [M+Na]$^+$ requires 315.02082, 317.01878]. $[\alpha]^{25}_D$ –64.0 (c = 0.5, CHCl$_3$).
(1S,5S,6S)-5-bromo-7-oxabicyclo[4.2.0]oct-2-en-8-one (ent-5). OD-H, 1% IPA / hexanes, 1.0 mL/min. obs: 210 nm

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Figure S-1 $^1$H NMR of compound 5
Figure S-2 $^1$H NMR of compound 9
Figure S-3 $^{13}$C NMR of compound 9
Figure S-4 $^1$H NMR of compound 11
Figure S-5 $^{13}$C NMR of compound 11
Figure S-6 $^1$H NMR of compound 12
Figure S-7 $^{13}$C NMR of compound 12
Figure S-8 $^1$H NMR of compound 13
Figure S-9 $^{13}$C NMR of compound 13
Figure S-10 $^1$H NMR of compound 16
Figure S-11 $^{13}$C NMR of compound
References


