Palladium(II)-Catalyzed Asymmetric Synthesis of (Z)- α -Alkylidene- γ -butyrolactams from (Z)-N-Allylic 2-Alkynamides. Total Synthesis of (-)-Isocynometrine

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General Procedures: All reactions were performed using oven-dried glassware under a dry nitrogen atmosphere with magnetic stirring. HOAc was distilled and dried before use.¹ Pd(OAc)₂ was purchased from either *Aldrich* or *Acros*. Bpy was commercially available. The (Z)-N-allylic 2-alkynamides were synthesized according to literature procedures.² The chiral nitrogen-containing ligands were synthesized according to literature procedures.³ Chromatographic purification of products was accomplished using flash chromatography on Silica Gel 300-400m. NMR spectra were recorded on a Varian EM-360, Varian EM-390 or Bruker AM-300 operating at 300

MHz for ^1H , and referenced to the internal solvent signals. IR spectra were recorded on a Perkin-Elmer 983 or Bio Rad FTS-185 spectrometer as a thin film. Optical rotations were measured on a Perkin Elmer 341 digital polarimeter. Mass spectra were recorded on a HP5989A. HRMS spectra were recorded on a Finnigan MAT 8430 spectrometer. Thin layer chromatography was performed using silica gel TLC plates and visualized either with ultraviolet light, I_2 or KMnO_4 . Enantiomeric excesses were determined by HPLC analysis carried out on a chiral AD column or chiral AS column.

Data of (Z)-N-allylic 2-alkynamides.

(Z)-4'-Benzoyloxy-2'-butenyl but-2-ynamide (1a). Oil: ^1H NMR (300 MHz, CDCl_3) δ : 7.81-7.78 (m, 2H), 7.53-7.41 (m, 3H), 6.50 (br, 1H), 5.90-5.81 (m, 1H), 5.76-5.68 (m, 1H), 4.81 (d, $J = 7.2$ Hz, 2H), 4.19 (dd, $J_1 = J_2 = 6.6$ Hz, 2H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ : 167.3, 153.5, 134.1, 131.4, 131.2, 128.4, 126.9, 125.6, 86.2, 72.1, 60.9, 36.6, 3.7; MS (ESI): m/z 258 ($\text{M}^+ + 1$); IR (neat): ν 3328, 2243, 1708, 1638, 1253, 1068, 752 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3$ C, 70.02; H, 5.88; N, 5.44. Found: C, 70.07; H, 5.90; N, 5.35.

N-Methyl-(Z)-4'-benoyloxy-2'-butenyl but-2-ynamide (1b). Oil: ^1H NMR (300 MHz CDCl_3) δ 8.06-7.42 (m, 5H), 5.93-5.87 (m, 1H), 5.70-5.64 (m, 1H), 4.93 (d, $J = 6.9$ Hz, 2H), 4.37 (d, $J = 6.9$ Hz, 1H), 4.20 (d, $J = 7.0$ Hz, 1H), 3.16 (s, 1.5H), 2.95 (s, 1.5H), 2.0 (t, 3H); MS m/z 272 ($\text{M}^+ + 1$), 150 (100), 149, 148, 123, 120, 105, 77, 67; IR (neat) ν 2923, 2238, 1719, 1631, 1272, 714 cm^{-1} ; Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$ C, 70.83; H, 6.32; N, 5.16. Found: C, 70.87; H, 6.49; N, 5.54.

N-Benzyl-(Z)-4'-benzoyloxy-2'-butenyl but-2-ynamide (1c). Oil: ^1H NMR (300 MHz CDCl_3) δ 8.06-7.24 (m, 10H), 5.80-5.73 (m, 2H), 4.77 (d, $J = 6.9$ Hz, 2H), 4.62 (d, $J = 6.9$ Hz, 2H), 4.27-3.95 (m, 2H), 2.02 (s, 3H); MS m/z 346 ($\text{M}^+ - 1$), 227, 226 (100), 172, 106, 105, 91, 77, 67; IR (neat) ν 2922, 2247, 1720, 1629, 1112, 713 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_3$ C, 76.06; H, 6.09; N, 4.03. Found C, 75.94; H, 6.13; N, 4.07.

N-Benzyl-(Z)-4'-acetoxyl-2'-butenyl but-2-ynamide (1c'). Oil: ^1H NMR (300 MHz CDCl_3) δ 7.34-7.24 (m, 5H), 5.70-5.54 (m, 2H), 4.76 (s, 1H), 4.59 (s, 1H), 4.51 (dd, $J_1 = 6.7$ Hz, $J_2 = 12.6$ Hz, 2H), 4.18 (d, $J = 6.6$ Hz, 1H), 4.00 (d, $J = 6.9$ Hz, 1H), 2.06-2.00 (m, 6H); MS m/z 285 (M^+), 226, 172, 131, 106, 107, 91(100), 67, 43; IR (neat) ν 2924, 2247, 1740, 1629, 1236, 735 cm^{-1} ; Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_3$ C, 71.56; H, 6.71; N, 4.91. Found C, 71.57; H, 6.80; N, 5.26.

N-Tosyl-(Z)-4'-benzoyloxy-2'-butenyl but-2-ynamide (1d). Oil: ^1H NMR (300 MHz CDCl_3) δ 8.07-7.27 (m, 9H), 5.93-5.75 (m, 2H), 5.04 (d, $J = 6.6$ Hz, 2H), 4.79 (d, $J = 6.5$ Hz, 2H), 2.43 (s, 3H), 1.99 (s, 3H) MS m/z 412 ($\text{M}^+ + 1$), 290, 175, 106, 105 (100), 91, 77, 68, 67; IR (neat) ν 2232, 2231, 1720, 1671, 1272, 1170, 714 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_5\text{S}$ C, 64.22; H, 5.14; N, 3.40. Found C, 64.20; H, 5.41; N, 3.64.

N-Tosyl-(Z)-4'-acetoxyl-2'-butenyl but-2-ynamide (1d'). Oil: ^1H NMR (300 MHz CDCl_3) δ 7.79 (d, $J = 8.7$, 2H), 7.37 (dd, $J = 0.8, 8.7$ Hz, 2H), 5.72-5.69 (m, 2H), 4.76 (d, $J = 6.3$ Hz, 2H), 4.53 (d, $J = 6.3$ Hz, 2H), 2.47 (s, 3H), 2.35 (s, 3H), 2.08 (s, 3H); MS m/z 266, 155, 128, 113, 91(100), 68, 65, 43; IR (neat) ν 3034, 2952, 1739, 1598, 1357, 1168, 578 cm^{-1} ; Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_5\text{S}$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.37; H, 5.65; N, 3.99.

***N*-(*tert*-Butoxycarbonyl)-(Z)-4'-benzoyloxy-2'-butenyl but-2-ynamide (1e).** Oil: ^1H NMR (300 MHz CDCl_3) δ 8.06-7.41 (m, 5H), 5.84-5.62 (m, 2H), 4.99 (d, J = 6.7 Hz, 2H), 4.47 (d, J = 6.8 Hz, 2H), 2.06 (s, 3H), 1.55-1.44 (m, 9H); MS m/z 258 (M^+ -Boc), 136, 135, 106, 105(100), 77, 67, 41; IR (neat) ν 2982, 2232, 1747, 1722, 1650, 1453, 1272, 1148, 713 cm^{-1} ; Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.14; H, 6.59; N, 4.00.

***N*-Benzyl-(Z)-4'-benzoyloxy-2'-butenyl prop-2-ynamide (1f).** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.97-7.19 (m, 10H), 5.78-5.74 (m, 2H), 4.74-4.66 (m, 2H), 4.56 (d, J = 6.1 Hz, 2H), 4.22 (d, J = 6.6 Hz, 1H), 4.02 (d, J = 6.7 Hz, 1H), 3.08 (s, 1H); MS m/z 334 (M^+ +1), 212, 185, 158, 118, 106, 105, 91 (100), 77; IR (neat) ν 3237, 3065, 2932, 2105, 1719, 1635, 1603, 1452, 1272, 1116, 713 cm^{-1} ; Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.53; H, 5.90; N, 4.30.

***N*-Benzyl-(Z)-4'-benzoyloxy-2'-butenyl hept-2-ynamide (1g).** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.97-7.18 (m, 10H), 5.72-5.67 (m, 2H), 4.74-4.54 (m, 4H), 4.18 (d, J = 6 Hz, 1H), 4.02 (d, J = 6 Hz, 1H), 2.29 (t, 2H), 1.49-1.29 (m, 4H), 0.81 (t, 3H); MS m/z 390 (M^+ +1), 268, 225, 109, 105, 106, 91 (100), 79, 77; IR (neat) ν 2873, 2233, 1720, 1630, 1271, 713 cm^{-1} ; Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.82; H, 7.00; N, 3.86.

***N*-Benzyl-(Z)-4'-acetoxyl-2'-butenyl 3-butylprop-2-ynamide (1g').** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.36-7.23 (m, 5H), 5.70-5.63 (m, 2H), 4.76 (s, 1H), 4.59 (s, 1H), 4.53-4.49 (m, 2H), 4.18 (d, J = 6.6 Hz, 1H), 4.01 (d, J = 6.9 Hz, 1H), 2.38-2.32 (m, 2H), 2.08-2.03 (m, 3H), 1.55-1.39 (m, 4H), 0.94-0.84 (m, 3H); MS m/z 328 (M^+ +1), 269, 268 (100), 225, 109, 91, 79, 43; IR (neat) ν 2874, 2234, 1741, 1631, 1231, 734 cm^{-1} ; Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.46; H, 7.72; N, 4.78.

***N*-Benzyl-(Z)-4'-benzoyloxy-2'-butenyl 3-methoxybut-2-ynamide (1h).** Oil: ^1H NMR (300 MHz CDCl_3) δ 8.03-7.26 (m, 10H), 5.84-5.61 (m, 2H), 4.79 (s, 1H), 4.75 (t, J = 7 Hz, 2H), 4.63 (s, 1H), 4.26 (d, J = 7 Hz, 3H), 4.09 (d, J = 7 Hz, 1H), 3.36 (s, 3H); MS m/z 378 (M^+ +1), 256 (100), 225, 224, 115, 105, 91, 77, 41; IR (neat) ν 2934, 2237, 1720, 1634, 1272, 713 cm^{-1} ; Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 72.86; H, 6.19; N, 3.94.

***N*-Benzyl-(Z)-4'-acetoxyl-2'-butenyl 3-methoxylbut-2-ynamide (1h').** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.37-7.24 (m, 5H), 5.71-5.49 (m, 2H), 4.77 (s, 1H), 4.63-4.47 (m, 3H), 4.26 (d, J = 6.4 Hz, 2H), 4.02 (d, J = 6.9 Hz, 2H), 3.38 (s, 3H), 2.08-2.01 (m, 3H); MS m/z 316 (M^+ +1), 256, 225, 224, 202, 97, 91 (100), 43, 41; IR (neat) ν 2936, 2237, 1739, 1634, 1231, 732 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.01; H, 6.59; N, 4.22.

***N*-Benzyl-(Z)-4'-benzoyloxy-2'-butenyl 3-phenylprop-2-ynamide (1i).** Solid: m.p. 76-77°C; ^1H NMR (300 MHz CDCl_3) δ 7.97-7.18 (m, 15H), 5.79-5.58 (m, 2H), 4.80 (s, 1H), 4.69 (d, J = 6.8 Hz, 2H), 4.62 (s, 1H), 4.28 (d, J = 6.6 Hz, 1H), 4.07 (d, J = 7.0 Hz, 1H); MS m/z 409 (M^+), 304, 288, 196, 154, 129 (100), 105, 91, 77; IR (neat) ν 2930, 2216, 1720, 1630, 1271, 713 cm^{-1} ; HRMS Calcd for $\text{C}_{27}\text{H}_{23}\text{NO}_3$ 409.1678, Found 409.1642.

***N*-Benzyl-(*Z*)-4'-acetoxyl-2'-butenyl 3-phenylprop-2-ynamide (1i').** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.49-7.27 (m, 10H), 5.76-5.67 (m, 2H), 4.84 (s, 1H), 4.66 (s, 1H), 4.52 (d, $J = 6$ Hz, 2H), 4.18 (s, 1H), 4.00 (s, 1H), 2.07 (s, 3H); MS m/z 347 (M^+), 305, 288, 276, 234, 200, 129 (100), 91, 43; IR (neat) ν 2214, 1737, 1627, 1228, 758 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.06; H, 6.20; N, 4.37.

Cyclization of *N*-(*Z*)-(4'-X-2'-butenyl) alk-2-ynamides (X = leaving group): Typical Procedure. To a solution of $\text{Pd}(\text{OAc})_2$ (0.025 mmol) and ligand (0.038 mmol) in HOAc (2 mL) was added the substrate (0.5 mmol). The reaction was carried out at 80 $^\circ\text{C}$ (for nonchiral ligands) or 60 $^\circ\text{C}$ (for chiral ligands). After the reaction was completed as monitored by TLC, ether was added. The mixture was washed with saturated NaHCO_3 and brine, and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography (300-400 mesh silica gel, petroleum ether/ethyl acetate) to give the cyclization product.

Data of Lactam Products.

***N*-Methyl- α -(*Z*)-(1-acetoxyethylidene)- β -vinyl- γ -butyrolactam (2b).** Oil: ^1H NMR (300 MHz CDCl_3) δ 5.82-5.76 (m, 1H), 5.25-5.13 (m, 2H), 3.63 (m, 2H), 3.06 (dd, $J_1 = 1.6$ Hz, $J_2 = 9.3$ Hz, 1H), 2.84 (s, 3H), 2.25 (s, 3H), 1.92 (s, 3H); MS m/z 210 ($\text{M}^+ + 1$), 168, 167, 140, 124 (100), 98, 96, 44, 43; IR (neat) ν 2920, 1760, 1672, 1639, 1189, 920 cm^{-1} ; Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.84; H, 7.58; N, 6.53.

***N*-Benzyl- α -(*Z*)-(1'-acetoxyethylidene)- β -vinyl- γ -butyrolactam (2c).** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.33-7.12 (m, 5H), 5.78-5.67 (m, 1H), 5.22-5.08 (m, 2H), 4.53 (d, $J = 14.8$ Hz, 1H), 4.38 (d, $J = 14.8$ Hz, 1H), 3.55-3.43 (m, 2H), 2.92 (d, $J = 9$ Hz, 1H), 2.46 (s, 3H), 1.93 (s, 3H); MS m/z 286 ($\text{M}^+ + 1$), 286, 200, 244, 243, 216, 91 (100), 43; IR (neat) ν 2917, 1760, 1699, 1673, 1428, 1186, 702 cm^{-1} ; HRMS Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3$ 285.1365, Found 285.1390.

***N*-Tosyl- α -(*Z*)-(1'-acetoxyethylidene)- β -vinyl- γ -butyrolactam (2d).** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.88 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.3$ Hz, 2H), 5.80-5.71 (m, 1H), 5.29-5.14 (m, 2H), 3.94-3.88 (m, 1H), 3.67-3.55 (m, 2H), 2.41 (s, 3H), 2.21 (s, 3H), 1.91 (s, 3H); MS m/z 349 (M^+), 327, 276, 223, 177, 155, 101 (100), 65, 51; IR (neat) ν 2924, 1768, 1752, 1677, 1365, 1168, 578 cm^{-1} ; Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_5\text{S}$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.61; H, 5.54; N, 3.68.

***N*-Benzyl- α -(*Z*)-(1'-acetoxypropylidene)- β -vinyl- γ -butyrolactam (2g).** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.33-7.19 (m, 5H), 5.76-5.70 (m, 1H), 5.23-5.07 (m, 2H), 4.56-4.52 (d, $J = 14.8$ Hz, 1H), 4.40-4.35 (d, $J = 14.8$ Hz, 1H), 3.54-3.43 (m, 2H), 2.94-2.90 (dd, $J_1 = 9.5$, $J_2 = 1.9$ Hz, 1H), 2.31 (s, 3H), 2.21-2.30 (m, 2H), 1.51-1.31 (m, 4H), 0.89 (t, 3H); MS m/z 328 ($\text{M}^+ + 1$), 286, 285, 243, 200, 174, 91 (100), 43; IR (neat) ν 2958, 1764, 1696, 1669, 1425, 701 cm^{-1} ; Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.15; H, 7.81; N, 4.46.

***N*-Benzyl- α -(*Z*)-(1'-acetoxy-2'-methoxyethylidene)- β -vinyl- γ -butyrolactam (2h).** Oil: ^1H NMR (300 MHz CDCl_3) δ 7.34-7.19 (m, 5H), 5.79 (m, 1H), 5.24-5.10 (m, 2H), 4.54 (d, J = 14.8 Hz, 1H), 4.42 (d, J = 14.6 Hz, 1H), 4.08 (d, J = 13.2 Hz, 1H), 3.98 (d, J = 13.2 Hz, 1H), 3.52-3.46 (m, 2H), 3.36 (s, 3H), 2.96 (dd, J_1 = 9.9 Hz, J_2 = 2.2 Hz, 1H), 2.32 (s, 3H); MS m/z : 316 (M^+ +1), 274, 273, 241, 229, 228, 200, 150, 91 (100); IR (neat) ν 2926, 1766, 1697, 1673, 1429, 1186, 702 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.96; H, 6.91; N, 4.32.

***N*-Benzyl- α -(*Z*)-(1'-acetoxy-1'-phenylmethylidene)- β -vinyl- γ -butyrolactam (2i).** Oil: ^1H NMR (300 MHz CDCl_3) δ 8.00-7.25 (m, 10H), 5.60 (m, 1H), 5.00 (m, 2H), 4.50-4.25 (m, 2H), 3.60-3.40 (m, 2H), 2.90 (m, 1H), 2.25-1.25 (m, 3H); MS m/z 348 (M^+ +1), 306, 305 (100), 200, 105, 91, 77; IR (neat) ν 1764, 1687, 1198, 699 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.92; H, 6.06; N, 3.85.

Asymmetric Cyclization.

The Procedure for the asymmetric cyclization of *N*-(*Z*)-(4'-X-2'-butenyl) 2-alkynoamides (**2c** or **2c'**) (X = OBz or OAc) was similar as above. The ee % values were determined by HPLC, using the chiralcel AD column eluting with hexane:2-propanol (v/v = 95/5) (λ = 254 nm)(when R = Bn) and the chiralcel AS column eluting with hexane:2-propanol (v/v = 60/40) (λ = 254 nm)(when R = Ts).

Total Synthesis of (-)-Isocynometrins (10).

Similar to our reported work of the synthesis of (+)-isocynometrins,² *N*-methyl *N*-(*Z*)-(4'-benzoyloxy-2'-butenyl) 3-phenylpropynamide (**3**) was selected as the starting compound.

Synthesis of Compound 3.

An alcohol solution of methylamine (wt 33 %, 30 mL) was cooled to $-40\text{ }^{\circ}\text{C}$, and then a solution of **A**⁴ (11.3 g, 44 mmol) in CH_2Cl_2 (20 mL) was added. After being stirred at room temperature for 2 h, the solvent was evaporated, and CH_2Cl_2 (100 mL) was then added. The solution was washed with water and brine, dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, dichloromethane/ethanol = 10:1) to afford 4-methylamino-but-2-enyl benzoate as oil in 40 % yield.

To a solution of $\text{PhC}\equiv\text{COOH}$ (3.65 g, 25 mmol) in CH_2Cl_2 (120 mL) was added a solution of DCC (5.98 g, 29 mmol) and DMAP (305 mg, 2.5 mmol) in CH_2Cl_2 (50 mL) at $-40\text{ }^{\circ}\text{C}$, and then a solution of 4-methylamino-but-2-enyl benzoate (5.13 g, 25 mmol) in CH_2Cl_2 (30 mL) was added dropwise with cooling. After the reaction was complete as monitored by TLC, the reaction mixture was filtered to remove any precipitate and the filtrate was washed with 1N HCl aqueous solution, brine, dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1) to give oil **3** (7.5g, 90 %). IR (KBr) ν 2930, 2215, 1717, 1634, 1492, 1272, 1112, 713 cm^{-1} , ^1H NMR (CDCl_3) δ 8.04 (dt, $J = 7.5, 1.8\text{ Hz}$, 2 H), 7.60-7.30 (m, 8 H), 5.95-5.91 (m, 1 H), 5.76-5.69 (m, 1H), 4.98-4.94 (m, 2 H), 4.48 (d, $J = 6.0\text{ Hz}$, 1 H), 4.28 (d, $J = 6.0\text{ Hz}$, 1 H), 3.27 (s, 1.4 H), 3.02 (s, 1.6 H); MS (m/z) 334 ($\text{M}^+ + 1$), 212, 129 (100), 105. Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.52; H, 6.04; N, 4.28.

Cyclization of N-methyl N-(Z)-(4'-benzoyloxy-2'-butenyl) 3-phenylpropynamide (3). To a solution of $\text{Pd}(\text{OAc})_2$ (59.5 mg, 5 mol %) and (s)-pymox-Ph (119 mg, 10 mol %) in HOAc (53 mL) was added **3** (1.76 g, 5.3 mmol). The reaction was carried out at $60\text{ }^{\circ}\text{C}$. After the reaction was complete as monitored by TLC, CH_2Cl_2 (150 mL) was added. The mixture was washed with saturated NaHCO_3 solution, brine and dried (Na_2SO_4). The organic layer was evaporated, and the residue was purified by chromatography (silica gel, petroleum ether/ethyl acetate) to give a mixture of **4** and **5**. Without separation, to the solution of **4** and **5** in MeOH (40 mL) was added DMAP (80 mg, 655 mmol). After stirred at room temperature for two days the solvent was evaporated and Et_2O (60 mL) was added. The solution was washed with brine, dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, petroleum ether/ethyl acetate = 3:1) to give **5**² (0.97 g, 80 %). ^1H NMR (CDCl_3) δ 8.09 (d, $J = 8.4\text{ Hz}$, 2 H), 7.62-7.57 (m, 1 H), 7.49 (t, $J = 8.1\text{ Hz}$, 2 H), 5.92-5.81 (m, 1 H), 5.18-5.09 (m, 2 H), 4.30 (d, $J = 6.3\text{ Hz}$, 1 H), 3.74-3.62 (m, 2 H), 3.23 (dd, $J = 9.3, 5.4\text{ Hz}$, 1 H), 2.89 (s, 3 H). 53 % ee (HPLC analysis: DALCEL CHIRALPAK AD-H, eluent, hexane/2-propanol = 93/7, flow rate 0.8 ml/min, detection 230 nm light). $[\alpha]_{\text{D}}^{20} = -75.5^{\circ}$ ($c = 1.0, \text{CHCl}_3$).

The following procedures for the synthesis of (-)-isocynometriner were similar to the reported procedures for the synthesis of (+)-isocynometriner.²

Synthesis of 6a. A solution of **5** (0.524 g, 2.29 mmol) in MeOH (8 mL) was cooled to -40 °C, and then NaBH₄ (0.13 g, 3.43 mmol) was added. The mixture was stirred. After the reaction was complete as monitored by TLC, a drop of HOAc was added to quench the reaction and the mixture was allowed to rise to room temperature. MeOH was evaporated, and CH₂Cl₂ (100 mL) was then added. The solution was washed with saturated NaHCO₃ solution and brine, dried (Na₂SO₄), concentrated, and purified by chromatography (silica gel, petroleum ether/ethyl acetate = 7:3) to give **6a** (0.309 g) and **6b** (0.135 g). Total yield: 84 %. Compound **6a**: $[\alpha]_D^{20} = -32.7^\circ$ (c = 1.04, CHCl₃). Further crystallization with CH₂Cl₂-petroleum ether gave the solid with $[\alpha]_D^{20} = -12.8^\circ$ (c = 1.05, CHCl₃) and the solid from evaporation of the filtrate with $[\alpha]_D^{20} = -43.3^\circ$ (c = 1.09, CHCl₃). The product from the filtrate was assigned as **6a** from the spectra data as compared with ref. 2. The solid from the filtrate (**6a**) was further reacted.

6a: mp 100-101 °C; IR (KBr) ν 3371, 1661, 1428, 1401, 1257, 770, 707 cm⁻¹; ¹H NMR (CDCl₃) δ 7.37-7.28 (m, 5 H), 5.52 (s, 1 H), 5.20-5.08 (m, 1 H), 4.71 (d, J = 9.0 Hz, 1 H), 4.61-4.47 (m, 2 H), 3.35 (dd, J = 9.9, 9.0 Hz, 1 H), 3.11 (dd, J = 9.6, 7.8 Hz, 1 H), 2.89 (s, 3 H), 2.66-2.52 (m, 2 H); MS (m/e) 232 (M⁺+1), 125 (100), 110, 98, 77.

6b: mp 121-123 °C; IR (KBr) ν 3360, 3061, 1683, 1505, 1403, 1265, 1052, 915, 707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.37-7.27 (m, 5H), 5.56-5.45 (m, 1H), 5.21 (dd, J = 6.9, 3.3 Hz, 1H), 4.89-4.80 (m, 2H), 4.11 (d, J = 7.5 Hz, 1H), 3.28-3.22 (m, 1H), 3.07-3.01 (m, 1H), 2.83 (s, 3H), 2.85-2.81 (m, 2H); MS (m/e) 231 (M⁺), 213, 125 (100), 110, 98, 77. $[\alpha]_D^{20} = +7.7^\circ$ (c = 1.0, CHCl₃).

Synthesis of 7. To a solution of **6a** (461 mg, 2.0 mmol) and a catalytic amount of DMAP in pyridine (6 mL) was added dropwise under cooling benzoyl chloride (0.35 mL, 3.0 mmol). After being stirred at room temperature for 10 h, the mixture was poured into water and extracted with CH₂Cl₂ (20 mL $\times$ 4). The organic layer was washed successively with CuSO₄ solution and brine, dried (Na₂SO₄), and concentrated. The residue was further purified by chromatography (silica gel, petroleum ether/ethyl acetate = 2:1) to give a colorless solid (**7**) (584 mg, yield 87 %): mp 100-102 °C; IR (KBr) ν 2857, 1722, 1690, 1263, 1112, 717, 707 cm⁻¹; ¹H NMR (CDCl₃) δ 8.12-8.09 (m, 2 H), 7.61-7.56 (m, 1 H), 7.49-7.43 (m, 4 H), 7.36-7.27 (m, 3 H), 6.60 (d, J = 3.6 Hz, 1 H), 5.92-5.80 (m, 1 H), 5.21-5.13 (m, 2 H), 3.10-2.90 (m, 4 H), 2.77 (s, 3 H); MS (m/e) 335 (M⁺), 230, 213, 105 (100), 77. 80.5 % ee ($[\alpha]_D^{20} = +84.4^\circ$ (c = 1.02, CHCl₃)). HPLC analysis (DALCEL CHIRALPAK AD-H, eluent, hexane/2-propanol = 90/10, flow rate 1.0 mL/min, detection 230 nm light); t_R of major-isomer 41.29 min and minor-isomer 23.04 min.

Synthesis of 8. Ozone was bubbled into a solution of **7** (613 mg, 1.8 mmol) in MeOH (40 mL) and CH₂Cl₂ (20 mL) at -78 °C. After the reaction was complete as monitored by TLC, Ar was bubbled into the mixture for 5 min and then Me₂S (3.2 mL) was added. The mixture was stirred for an additional 2 h then allowed the temperature

raising to room temperature, concentrated, and purified by chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to give a colorless solid **8** (570 mg, yield: 94 %): mp 122-124 °C; IR (neat) ν 2928, 1720, 1685, 1269, 1111, 713 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.72 (s, 1 H), 8.09 (dd, J = 7.2, 1.5 Hz, 2 H), 7.64-7.58 (m, 1 H), 7.51-7.32 (m, 7 H), 6.65 (d, J = 4.2 Hz, 1 H), 3.56-3.49 (m, 2 H), 3.29-3.22 (m, 1 H), 2.80-2.73 (m, 1 H), 2.73 (s, 3 H); MS (m/e) 337 (M^+), 232, 105, 84 (100), 77. $[\alpha]_{\text{D}}^{20} = +60.8^\circ$ (c = 1.03, CHCl_3).

Synthesis of 9. Compound **8** was treated according to the literature method⁵ to construct the imidazole ring. A solution of tosylmethylisocyanide (242 mg, 1.24 mmol) in THF (6 mL) was added dropwise to a solution of *t*-BuOK (185 mg, 1.65 mmol) in THF (12 mL) at -30 °C with stirring. After the mixture was stirred for 10 min and cooled to -40 °C, a solution of **8** (418 mg, 1.24 mmol) in THF (6 mL) was added dropwise. The reaction mixture was stirred at -40 °C for 30 min and poured into ice-water (30 mL). After being neutralized with HOAc, the mixture was extracted with CH_2Cl_2 , and the extract was washed, dried (Na_2SO_4), and concentrated. The crude product was purified by a short column of silica gel chromatography (petroleum ether/ethyl acetate = 1:1) to obtain an oil. To the solution of the crude oil in THF (12 mL) was added first Et_3N (0.7 mL) and then a solution of POCl_3 (0.12 mL, 1.29 mmol) in THF (6 mL) at -10 °C. After being stirred for 30 min, the mixture was poured into ice-water (20 mL), extracted with CH_2Cl_2 , dried (Na_2SO_4), and concentrated. To the solution of the crude product in MeOH (12 mL) was added dropwise a MeOH solution of MeNH_2 (1.67 M, 12 mL). After being stirred for 1 h, the mixture was concentrated and purified by chromatography (silica gel, CH_2Cl_2 /ethanol = 98:2) to obtain compound **9** (169 mg, overall yield from **8**: 35 %): oil; IR (KBr) ν 1720, 1690, 1269, 715 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.94-7.91 (m, 2 H), 7.59-7.54 (m, 1 H), 7.46-7.30 (m, 8 H), 6.98 (s, 1 H), 6.60 (d, J = 3.6 Hz, 1 H), 3.45 (s, 3 H), 3.43 (d, J = 3.9 Hz, 1 H), 3.37 (dd, J = 14.4, 7.2 Hz, 1 H), 3.27-3.21 (m, 1 H), 3.13 (dd, J = 9.6, 6.9 Hz, 1 H), 2.83 (s, 3 H); MS (m/e) 390 ($\text{M}^+ + 1$), 210, 178 (100), 105, 77. $[\alpha]_{\text{D}}^{20} = +10.7^\circ$ (c = 1.0, CHCl_3).

Synthesis of (-)-isocynometriner (10). To a solution of NaOH (27 mg, 0.68 mmol) in MeOH (4 mL) was added compound **9** (35 mg, 0.09 mmol), and the mixture was stirred for 0.5 h and concentrated. Water (3 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (10 mL $\times$ 3), washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography (silica gel, CH_2Cl_2 /ethanol = 95:5) to yield colorless solid **10** (24 mg, yield: 93 %) and recrystallized from chloroform-petroleum ether to yield colorless needles: mp 172-174 °C; IR (KBr) ν 3097, 2837, 1687, 706 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.29-7.21 (m, 5 H), 7.10 (s, 1 H), 6.69 (s, 1 H), 5.05 (br, 1 H), 4.84 (d, J = 8.4 Hz, 1 H), 3.45 (t, J = 9.6 Hz, 1 H), 3.24 (dd, J = 9.6, 6.3 Hz, 1 H), 3.15-3.08 (m, 1 H), 3.10 (s, 3 H), 2.99 (t, J = 8.1 Hz, 1 H), 2.92 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3): 174.4, 139.6, 137.6, 132.4, 128.3, 126.9, 125.9, 75.2, 54.9, 54.8, 30.9, 29.7, 29.6. MS (m/e) 286 ($\text{M}^+ + 1$). The product was again purified by dissolving in a mixture of *i*-propanol/petroleum ether (4/1). After filtration and evaporation of the solution, the product **10** was obtained in 62 % yield with 98.1 %

ee.⁶ $[\alpha]_D^{20} = -63.7^\circ$ ($c = 0.7$, CHCl_3). Lit.⁷ $[\alpha]_D^{20} = -66^\circ$ ($c = 1.0$, CHCl_3). HPLC analysis (DALCEL CHIRALPAK OD-H, eluent, hexane/2-propanol = 75/25, flow rate 0.6 mL/min, detection 220 nm light); t_R of major-isomer 25.79 min and minor-isomer 42.41 min.

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No.	R. Time	PeakHeight	PeakArea	PerCent
1	11.543	560565.8	10580980.1	48.7736
2	12.960	17326.1	384750.6	1.7735
3	15.960	393779.0	10414344.6	48.0055
4	19.377	10180.0	314001.8	1.4474
Total		981851.0	21694077.1	100.0000

No.	R. Time	PeakHeight	PeakArea	PerCent
1	11.513	129640.8	2368690.3	72.9637
2	12.958	1276.2	27533.6	0.8481
3	16.043	29585.8	748862.1	23.0675
4	16.852	1651.5	32172.5	0.9910
5	19.387	2295.4	69138.4	2.1297
Total		164449.8	3246396.9	100.0000

No.	PeakNo	ID. Name	R. Time	PeakHeight	PeakArea	PerCent
1	1	Unknown	8.727	86311.3	2159949.4	50.7168
2	2	Unknown	18.627	28129.2	2098891.2	49.2832
Total				114440.5	4258840.6	100.0000

No.	PeakNo	ID. Name	R. Time	PeakHeight	PeakArea	PerCent
1	1	Unknown	9.043	75800.2	2096374.9	90.2334
2	2	Unknown	19.627	2778.6	226905.6	9.7666
Total				78578.8	2323280.5	100.0000

No.	R. Time	PeakHeight	PeakArea	PerCent
1	23.960	100274.1	12792366.5	49.9160
2	36.960	60113.5	12835431.0	50.0840
Total		160387.7	25627797.5	100.0000

No.	R. Time	PeakHeight	PeakArea	PerCent
1	25.793	43407.9	6069631.8	99.0450
2	42.405	293.7	58521.3	0.9550
Total		43701.5	6128153.1	100.0000