Enantioselective Construction of Lactone[2,3-\textit{b}]piperidine Skeletons via Organocatalytic Tandem Reactions

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Supplementary Information

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1. General methods

NMR data was obtained for $^1$H at 400 MHz, and for $^{13}$C at 50 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in CDCl$_3$ solution. ESI HRMS was recorded on a Bruker Apex-2. In each case, enantiomeric ratio was determined by HPLC analysis on chiral column in comparison with authentic racemate, using a Daicel Chiralpak OD-H Column (250 x 4.6 mm) or Chiralpak AD-H Column (250 x 4.6 mm). UV detection was monitored at 254 nm. Optical rotation data were examined in EtOH solution at 20 °C. Column chromatography was performed on silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. UV light and I$_2$ were used to visualize products. All chemicals were used without purification as commercially available unless otherwise noted. The $N$-Tos-1-aza-1,3-butadienes were prepared from $\alpha,\beta$-unsaturated ketones and $p$-toluenesulfonylamide according to the literature procedures.$^1$ The catalyst was synthesized according to the literature procedures.$^2$


2. Enantioselective construction of lactone[2,3-b]piperidine skeletons

Aqueous glutaraldehyde 2a (0.20 mmol) was added to a mixture of catalyst 1 (0.01 mmol), $N$-Tos-1-aza-1,3-butadiene 3 (0.10 mmol) and benzoic acid (0.01 or 0.10 mmol) in acetonitrile (1 mL) or dichloromethane (1 mL) at room temperature. The reaction mixture was stirred until complete consumption of 3 (monitored by TLC). Then the solution was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to give hemiacetal 4, which was dissolved with DMSO. To this solution was added 2-iodoxybenzoic
acid (IBX) at 35 ºC and stirred until hemiacetal 4 disappeared. The mixture was partitioned between ethyl acetate and saturated NaHCO3. The organic phase was washed by brine, dried and concentrated. Flash chromatography (silica gel, 8:1-6:1 petroleum ether/ethyl acetate as eluent) afforded lactone 5. An identical procedure was used for the preparation of 6. The enantiomeric excess (ee) was determined by chiral HPLC analysis.

51% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_major = 9.70 min, t_minor = 11.20 min. ee > 99%; [α]D20 = -6.5 (c = 0.65 in EtOH); 1H NMR (400 MHz, CDCl3): δ = 7.36-7.32 (m, 2H), 7.25-7.20 (m, 1H), 7.17-7.13 (m, 2H), 7.12-7.10 (m, 4H), 6.42 (d, J = 3.2 Hz, 1H), 5.33 (d, J = 4.0 Hz, 1H), 4.20 (q, J = 6.8 Hz, 2H), 3.14 (dd, J = 4.0 Hz, J = 10.4 Hz, 1H), 2.80-2.75 (m, 1H), 2.73-2.64 (m, 1H), 2.62-2.55 (m, 1H), 2.41 (s, 3H), 2.33-2.23 (m, 1H), 1.92-1.84 (m, 1H), 1.27 (t, J = 6.8 Hz, 3H) ppm; 13C NMR (50 MHz, CDCl3): δ = 170.6, 170.0, 144.1, 136.6, 136.1, 129.4, 128.4, 128.2, 127.5, 127.3, 112.6, 84.4, 61.6, 40.8, 31.8, 25.7, 22.1, 21.5, 14.1 ppm; ESI HRMS: calcd. For C24H25NO6S+H 456.1481, found 456.1483.

53% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_major = 10.41 min, t_minor = 12.03 min. ee > 99%; [α]D20 = -7.6 (c = 0.64 in EtOH); 1H NMR (400 MHz, CDCl3): δ = 7.38-7.36 (m, 2H), 7.21-7.19 (m, 2H), 7.11-7.06 (m, 4H), 6.38 (d, J = 3.2 Hz, 1H), 5.33 (d, J = 3.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.12 (dd, J = 4.0 Hz, J = 10.4 Hz, 1H), 2.75-2.70 (m, 1H), 2.69-2.63 (m, 1H), 2.61-2.55 (m, 1H), 2.42 (s, 3H), 2.33-2.22 (m, 1H), 1.91-1.84 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H) ppm; 13C NMR (50 MHz, CDCl3): δ = 170.4, 169.9, 144.5, 136.5, 135.7, 134.7, 134.3, 129.8, 129.5, 127.8, 127.4, 113.1, 84.3, 61.8, 40.8, 31.8, 25.7, 22.1, 21.6, 14.1 ppm; ESI HRMS: calcd. For C24H24ClNO6S+H 490.1091, found 490.1087.

54% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_major = 10.75 min, t_minor = 12.58 min. ee = 99%; [α]D20 = -8.7 (c = 0.95 in EtOH); 1H NMR (400 MHz, CDCl3): δ = 7.37-7.35 (m, 2H), 7.26-7.24 (m, 2H), 7.21-7.19 (m, 2H), 7.02-7.00 (m, 2H), 6.38 (d, J = 2.8 Hz, 1H), 5.33 (d, J = 3.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.11 (dd, J = 4.0 Hz, J = 10.4 Hz, 1H), 2.75-2.70 (m, 1H), 2.69-2.63 (m, 1H), 2.61-2.54 (m, 1H), 2.43 (s, 3H), 2.32-2.22 (m, 1H), 1.91-1.84 (m, 1H), N O Tos COOEt 5a N O Tos COOEt 5b Br N O Tos COOEt 5c
1.28 (t, J = 7.2 Hz, 3H) ppm; 13C NMR (50 MHz, CDCl3): δ = 170.4, 169.8, 144.5, 136.5, 135.7, 135.1, 130.7, 130.0, 129.6, 127.4, 122.6, 113.1, 84.3, 61.8, 40.8, 31.8, 25.7, 22.1, 21.6, 14.1 ppm; ESI HRMS: calcd. For C24H24BrNO6S+H 534.0586, found 534.0562.

46% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_major = 11.54 min, t_minor = 14.79 min. ee > 99%; [α]D 20 = +13.1 (c = 0.58 in CHCl3); 1H NMR (400 MHz, CDCl3): δ = 7.37-7.35 (m, 2H), 7.18-7.16 (m, 2H), 7.07-7.03 (m, 2H), 6.66-6.62 (m, 2H), 6.43 (d, J = 3.2 Hz, 1H), 5.25 (d, J = 3.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.12 (dd, J = 4.0 Hz, J = 10.4 Hz, 1H), 2.78-2.72 (m, 1H), 2.69-2.63 (m, 1H), 2.61-2.55 (m, 1H), 2.40 (s, 3H), 2.32-2.25 (m, 1H), 1.90-1.83 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H) ppm; 13C NMR (50 MHz, CDCl3): δ = 170.7, 170.0, 159.6, 143.9, 136.8, 136.3, 129.9, 129.3, 128.5, 127.4, 112.8, 111.5, 84.4, 61.6, 55.2, 40.8, 31.9, 25.7, 21.5, 14.1 ppm; ESI HRMS: calcd. For C25H27NO7S+H 486.1586, found 486.1572.

51% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_major = 10.95 min, t_minor = 13.18 min. ee = 97%; [α]D 20 = -20.8 (c = 2.73 in EtOH); 1H NMR (400 MHz, CDCl3): δ = 7.48-7.46 (m, 2H), 7.21-7.19 (m, 2H), 7.17-7.15 (m, 1H), 6.81-6.78 (m, 2H), 6.41 (d, J = 2.8 Hz, 1H), 5.47 (d, J = 4.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 1H), 3.14 (dd, J = 4.0 Hz, J = 10.4 Hz, 1H), 2.83-2.78 (m, 1H), 2.77-2.64 (m, 1H), 2.62-2.55 (m, 1H), 2.41 (s, 3H), 2.32-2.26 (m, 1H), 1.91-1.85 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H) ppm; 13C NMR (50 MHz, CDCl3): δ = 170.3, 169.9, 144.2, 137.2, 136.6, 130.0, 129.5, 128.6, 127.4, 126.3, 126.2, 113.5, 84.3, 61.8, 41.0, 31.7, 25.8, 22.1, 21.6, 14.1 ppm; ESI HRMS: calcd. For C22H23NO6S2+H 462.1045, found 462.1064.

50% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_major = 9.46 min, t_minor = 14.34 min. ee = 99%; [α]D 20 = +50.2 (c = 1.08 in EtOH); 1H NMR (400 MHz, CDCl3): δ = 8.02-8.00 (m, 2H), 7.39-7.30 (m, 5H), 7.18-7.16 (m, 2H), 6.30 (d, J = 3.6 Hz, 1H), 5.91 (d, J = 2.4 Hz, 1H), 4.28-4.20 (m, 2H), 3.26 (dd, J = 3.2 Hz, J = 10.8 Hz, 1H), 2.66-2.61 (m, 2H), 2.46 (s, 3H), 2.44-2.40 (m, 1H), 2.00-1.95 (m, 1H), 1.78-1.71 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H) ppm; 13C NMR (50 MHz, CDCl3):
δ = 169.6, 163.5, 144.6, 138.8, 135.9, 129.7, 129.1, 128.4, 127.9, 127.6, 126.2, 84.3, 61.7, 40.1, 36.2, 25.6, 21.6, 20.0, 13.9 ppm; ESI HRMS: calcd. For C_{24}H_{25}NO_{6}S+H 456.1481, found 456.1488.

45% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 9.41 min, t_{minor} = 12.13 min. ee = 98%; [α]D^{20} = +61.9 (c = 0.82 in EtOH); ^1H NMR (400 MHz, CDCl_3): δ = 8.02-8.00 (m, 2H), 7.50-7.48 (m, 2H), 7.39-7.37 (m, 2H), 7.08-7.05 (m, 2H), 6.24 (d, J = 3.2 Hz, 1H), 5.90 (d, J = 2.8 Hz, 1H), 4.28-4.19 (m, 2H), 3.23 (dd, J = 3.2 Hz, J = 11.2 Hz, 1H), 2.65-2.61 (m, 2H), 2.47 (s, 3H), 2.41-2.36 (m, 1H), 2.03-1.97 (m, 1H), 1.74-1.68 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H) ppm; ^13C NMR (50 MHz, CDCl_3): δ = 169.5, 163.4, 144.8, 138.0, 135.9, 132.3, 130.1, 129.8, 128.2, 127.7, 125.3, 121.9, 84.1, 61.8, 39.7, 36.3, 25.6, 21.7, 20.1, 13.9 ppm; ESI HRMS: calcd. For C_{24}H_{24}BrNO_{6}S+H 534.0586, found 534.0588.

42% yield; HPLC (Chiralpak AD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{major} = 11.36 min, t_{minor} = 18.57 min. ee > 99%; [α]D^{20} = +64.8 (c = 0.69 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 8.02-8.00 (m, 2H), 7.38-7.36 (m, 2H), 7.09-7.07 (m, 2H), 6.89-6.87 (m, 2H), 6.27 (d, J = 3.6 Hz, 1H), 5.90 (d, J = 2.8 Hz, 1H), 4.27-4.19 (m, 2H), 3.81 (s, 3H), 3.21 (dd, J = 3.2 Hz, J = 11.2 Hz, 1H), 2.65-2.60 (m, 2H), 2.46 (s, 3H), 2.40-2.35 (m, 1H), 2.00-1.95 (m, 1H), 1.76-1.69 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H) ppm; ^13C NMR (50 MHz, CDCl_3): δ = 169.7, 163.6, 159.3, 144.6, 136.0, 130.6, 129.8, 129.4, 127.7, 127.6, 126.7, 114.5, 84.4, 61.7, 55.3, 39.4, 36.4, 25.7, 21.6, 20.1, 13.9 ppm; ESI HRMS: calcd. For C_{25}H_{27}NO_{7}S+H 486.1586, found 486.1590.

48% yield; HPLC (Chiralpak OD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, t_{minor} = 8.54 min, t_{major} = 11.37 min. ee = 98%; [α]D^{20} = -101.3 (c = 1.24 in CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.45-7.41 (m, 4H), 7.23-7.17 (m, 5H), 7.16-7.12 (m, 2H), 6.93-6.91 (m, 2H), 6.43 (d, J = 2.4 Hz, 1H), 5.25 (d, J = 3.2 Hz, 1H), 3.25 (dd, J = 3.2 Hz, J = 10.8 Hz, 1H), 2.73-2.68 (m, 2H), 2.45 (s, 3H), 2.25-2.21 (m, 1H), 2.06-2.01 (m, 1H), 1.74-1.67 (m, 1H) ppm; ^13C NMR (50 MHz, CDCl_3): δ = 170.1, 144.3, 140.0, 136.6, 136.5, 135.8, 132.1, 131.6, 129.9, 129.6, 128.2, 127.6, 121.4, 119.4,
84.9, 40.5, 37.1, 25.7, 21.6, 20.4 ppm; ESI HRMS: calcd. For \( \text{C}_{27}\text{H}_{24}\text{BrNO}_{4}\text{S}+\text{H} \) 538.0688, found 538.0694.

45% yield; HPLC (Chiralpak OD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, \( t_{\text{minor}} = 7.59 \text{ min}, t_{\text{major}} = 10.31 \text{ min}. \) ee = 90%; \( [\alpha]_{D}^{20} = -98.2 \) (c = 0.59 in EtOH); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.40-7.38 \text{ (m, 2H)}, 7.23-7.11 \text{ (m, 7H)}, 6.31 \text{ (d, } J = 3.2 \text{ Hz, 1H)}, 5.22 \text{ (d, } J = 3.6 \text{ Hz, 1H)}, 2.70-2.61 \text{ (m, 1H)}, 2.59-2.52 \text{ (m, 1H)}, 2.41 \text{ (s, 3H)}, 2.21-2.13 \text{ (m, 2H)}, 1.88-1.83 \text{ (m, 1H)}, 1.82-1.78 \text{ (m, 1H)}, 1.06 \text{ (d, } J = 6.8 \text{ Hz, 3H}) \text{ ppm}; \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \( \delta = 170.4, 143.9, 137.0, 136.8, 134.4, 129.3, 128.2, 127.8, 127.5, 122.1, 84.8, 36.9, 28.8, 25.9, 21.5, 21.2, 18.5 \text{ ppm}; \) ESI HRMS: calcd. For \( \text{C}_{22}\text{H}_{23}\text{NO}_{4}\text{S}+\text{H} \) 398.1426, found 398.1421.

40% yield; HPLC (Chiralpak OD-H, 40% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, \( t_{\text{minor}} = 13.87 \text{ min}, t_{\text{major}} = 15.74 \text{ min}. \) ee = 99%; \( [\alpha]_{D}^{20} = -79.5 \) (c = 1.02 in CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.24-7.16 \text{ (m, 3H)}, 7.06-6.99 \text{ (m, 5H)}, 6.96-6.93 \text{ (m, 2H)}, 5.88 \text{ (d, } J = 8 \text{ Hz, 1H)}, 4.37-4.22 \text{ (m, 2H)}, 4.20-4.06 \text{ (m, 1H)}, 3.33 \text{ (dd, } J = 1.6 \text{ Hz, } J = 8.4 \text{ Hz, 1H)}, 2.80-2.73 \text{ (m, 1H)}, 2.61-2.55 \text{ (m, 1H)}, 2.37 \text{ (s, 3H)}, 1.36 \text{ (t, } J = 7.2 \text{ Hz, 3H}) \text{ ppm}; \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \( \delta = 174.2, 170.1, 143.6, 141.7, 137.8, 134.3, 129.1, 128.5, 127.9, 127.8, 127.4, 117.3, 87.6, 62.2, 41.6, 40.6, 31.5, 21.5, 14.1 \text{ ppm}; \) ESI HRMS: calcd. For \( \text{C}_{23}\text{H}_{23}\text{NO}_{6}\text{S}+\text{H} \) 442.1324, found 442.1313.
3. NMR spectra and HPLC chromatograms

![NMR spectra and HPLC chromatograms]

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[Diagram of chemical structures and NMR spectra]

- Irradiation $H_a$ at 6.42 ppm
- NOE $H_b$ at 2.80 - 2.75 ppm
- No NOE $H_c$ at 3.14 ppm

- No signal at 6.42 ppm
- Irradiation $H_c$ at 3.14 ppm

NOE DS 6.42

NOE DS 3.14

[Diagram showing chemical structures and NMR spectra]
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