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Asymmetric Sequential Aza-Diels-Alder and *O*-Michael Addition: Efficient Construction of Chiral Hydropyrano[2,3-*b*]pyridines

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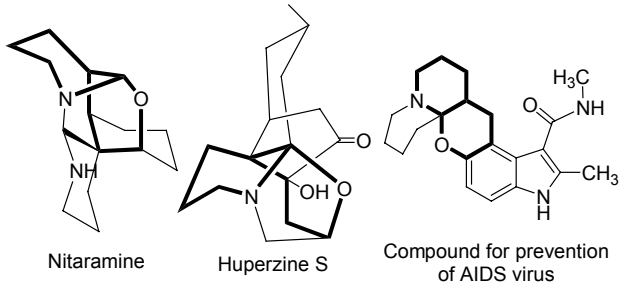
An asymmetric aza-Diels-Alder and *O*-Michael addition sequence has been developed to construct chiral hydropyrano[2,3-*b*]pyridine derivatives with good yields and excellent stereoselectivity, by starting with *N*-Ts-1-aza-1,3-butadienes and aliphatic aldehydes tethered to an *α*,*β*-unsaturated ketone motif. A tandem *O*-Michael addition reaction was completed via acid catalysis.

Keywords asymmetric organocatalysis, aza-Diels-Alder, *O*-Michael addition, hemiaminal, pyrano[2,3-*b*]-pyridines

Introduction

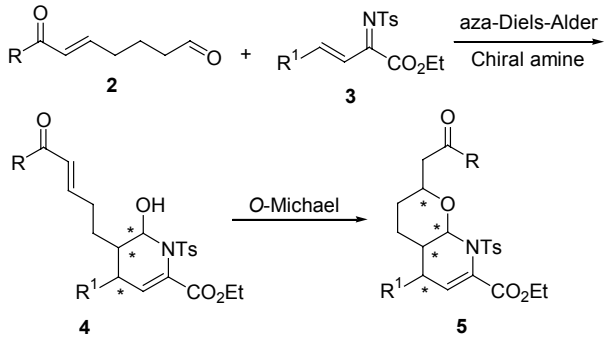
O- and *N*-heterocycles are very important structural motifs in numerous natural products.[1] Among them, the structure of octahydro-2*H*-pyrano[2,3-*b*]pyridine was found in various kinds of compounds that exhibited broad biological activities as illustrated in Scheme 1.[2] Hence, the synthesis of such complex and diversely structured heterocycles has attracted wide attention in the field of medicinal and synthetic organic chemistry.[3]

Scheme 1 Selected compounds containing an octahydro-2*H*-pyrano[2,3-*b*]pyridine motif



Recently, our group developed chiral secondary amine-catalyzed asymmetric inverse-electron-demand aza-Diels-Alder reaction towards stereoselective synthesis of piperidine derivatives from *N*-sulfonyl-1-aza-1,3-butadienes and aliphatic aldehydes.[4,5] Based on this methodology, more complex heterocyclic compounds were synthesized by further transformations of the hemiaminal intermediates.[6] Moreover, we reported a sequential aza-Diels-Alder and Friedel-Crafts reaction as well as an asymmetric aza-Diels-Alder reaction[7] followed by a tandem cation-olefin reaction,[8] which both involve a highly electrophilic *N*-Ts iminium ion formed *in situ* under acidic conditions. Our continuing interest in this highly efficient methodology prompted us to apply hydroxyl group of hemiaminal to construct hexahydro-2*H*-pyrano[2,3-*b*]pyridine via a new aza-Diels-Alder and intramolecular *O*-Michael addition[9] sequence, as outlined in Scheme 2.

Scheme 2 Proposed aza-Diels-Alder/*O*-Michael addition sequence



Experimental

General methods

NMR data were obtained for ^{1}H at 400 MHz, and for ^{13}C at 100 MHz. Chemical shifts were reported relative

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to 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 a chiral column in comparison with authentic racemates, using a Daicel Chiralcel AD-H or IC, OD Column (250 mm×4.6 mm). UV detection was monitored at 220 nm or 254 nm. Optical rotation data were examined in $CHCl_3$ solution at 20 ℃. 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. 1-Aza-1,3-butadienes[10] and the secondary amine catalyst[11] were prepared according to the literature procedures. The aliphatic aldehydes were also synthesized according to the literature procedures.[12]

General procedure for sequential aza-Diels-Alder and *O*-Michael addition reaction

The reaction was carried out with 1-azadiene **3** (0.1 mmol) and aldehyde **2** tethered to an *α*,*β*-unsaturated motif (0.2 mmol) in the presence of *α*,*α*-diphenylprolinol *O*-TMS ether **1** (6.8 mg, 0.02 mmol) and *o*-fluorobenzoic acid (OFBA, 2.8 mg, 0.02 mmol) in MeCN/H_2O (10∶1, 1 mL) at 30 ℃. After completion (monitored by TLC analysis), TFA (trifluoroacetic acid, 0.1 mL) was added, and the reaction was monitored by TLC. Then the solvents were removed and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to give fused heterocycle **5**, as outlined in Scheme 2.

Ethyl-2-(2-oxo-2-phenylethy)-5-phenyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (**5a**) 90% yield; $[\alpha]_D^{20}$ +52.1 (*c* 0.63 in $CHCl_3$); 99% *ee*, determined by HPLC analysis [Daicel chiralcel IC, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, *λ*=220 nm, *t*(major)=59.10 min, *t*(minor)=40.81 min]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.95 (d, *J*=7.6 Hz, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=7.6 Hz, 2H), 7.32—7.24 (m, 5H), 7.09 (d, *J*=6.8 Hz, 2H), 6.17 (d, *J*=3.2 Hz, 1H), 5.28 (d, *J*=2.4 Hz, 1H), 4.22—4.17 (m, 3H), 3.53 (dd, *J*=10.8, 3.2 Hz, 1H), 3.43 (dd, *J*=16.6, 5.8 Hz, 1H), 3.04 (dd, *J*=16.2, 6.6 Hz, 1H), 2.41 (s, 3H), 1.86—1.83 (m, 1H), 1.68—1.67 (m, 4H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 197.4, 164.4, 143.7, 140.8, 137.0, 136.6, 133.2, 129.4, 128.7, 128.5, 128.3, 128.2, 127.2, 125.8, 84.6, 75.7, 61.4, 44.8, 39.4, 37.1, 25.6, 24.4, 21.5, 13.8; ESI-HRMS calcd for $C_{32}H_{33}NO_6S$+K 598.1666, found 598.1667.

Ethyl-2-(2-oxo-2-phenylethyl)-5-*p*-tolyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (**5b**) 77% yield; $[\alpha]_D^{20}$ +62.9 (*c* 0.69 in $CHCl_3$); 99% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, *λ*=220 nm, *t*(major)=10.35 min, *t*(minor)=15.33 min]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.95 (d, *J*=7.6 Hz, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=7.6 Hz, 2H), 7.28—7.24 (m, 2H), 7.12 (d, *J*=8 Hz, 2H), 6.98 (d, *J*=7.6 Hz, 2H), 6.15 (d, *J*=3.2 Hz, 1H), 5.27 (d, *J*=2.4 Hz, 1H), 4.22—4.17 (m, 3H), 3.49 (dd, *J*=11.2, 3.2 Hz, 1H), 3.42 (dd, *J*=16.8, 5.6 Hz, 1H), 3.03 (dd, *J*=16.4, 6.4 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 3H), 1.84—1.81 (m, 1H), 1.67—1.60 (m, 4H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 197.5, 164.4, 143.7, 137.7, 137.0, 136.9, 136.6, 133.2, 129.4, 129.3, 128.8, 128.5, 128.4, 128.1, 127.3, 126.1, 84.7, 75.7, 61.4, 44.8, 39.0, 37.0, 25.6, 24.5, 21.6, 21.0, 13.9; ESI-HRMS calcd for $C_{33}H_{35}NO_6S$ + Na 596.2083, found 596.2081.

Ethyl-2-(2-oxo-2-phenylethyl)-5-*m*-tolyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (**5c**) 79% yield; $[\alpha]_D^{20}$ +51.1 (*c* 0.47 in $CHCl_3$); 99% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, *λ*=220 nm, *t*(major)=9.78 min, *t*(minor)=11.96 min]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.96 (d, *J*=8.0 Hz, 2H), 7.87 (d, *J*=8.4 Hz, 2H), 7.58 (t, *J*=7.2 Hz, 1H), 7.47 (t, *J*=7.6 Hz, 2H), 7.27—7.25 (m, 2H), 7.18 (t, *J*=8.0 Hz, 1H), 7.07 (d, *J*=7.2 Hz, 1H), 6.88 (d, *J*=6.4 Hz, 2H), 6.16 (d, *J*=2.8 Hz, 1H), 5.28 (d, *J*=1.6 Hz, 1H), 4.23—4.18 (m, 3H), 3.50 (dd, *J*=7.2, 3.2 Hz, 1H), 3.44 (dd, *J*=16.4, 6.4 Hz, 1H), 3.05 (dd, *J*=16.8, 6.4 Hz, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 1.81—1.79 (m, 1H), 1.68—1.59 (m, 4H), 1.19 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 197.5, 164.5, 143.7, 140.7, 138.5, 137.0, 136.5, 133.2, 129.5, 129.0, 128.6, 128.5, 128.2, 128.1, 127.3, 126.0, 125.8, 84.7, 75.7, 61.5, 44.8, 39.3, 36.8, 25.6, 24.5, 21.6, 21.4, 13.9; ESI-HRMS calcd for $C_{33}H_{35}NO_6S$+Na 596.2083, found 596.2085.

Ethyl-5-(3-methoxyphenyl)-2-(2-oxo-2-phenylethyl)-8-tosyl-3,4,4a,5,8,8a-hexahydro-*2H*-pyrano[2,3-*b*]pyridine-7-carboxylate (**5d**) 58% yield; $[\alpha]_D^{20}$ +42.7 (*c* 0.59 in $CHCl_3$); 95% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, *λ*=220 nm, *t*(major)=10.99 min, *t*(minor)=12.58 min]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.95 (d, *J*=8.0 Hz, 2H), 7.86 (d, *J*=8.0 Hz, 2H), 7.57 (t, *J*=7.2 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 2H), 7.24—7.20 (m, 3H), 6.79 (d, *J*=8.4 Hz, 1H), 6.68 (d, *J*=7.2 Hz, 1H), 6.62 (s, 1H), 6.15 (d, *J*=3.2 Hz, 1H), 5.28 (d, *J*=2.0 Hz, 1H), 4.22—4.17 (m, 3H), 3.80 (s, 3H), 3.50 (dd, *J*=6.8, 3.2 Hz, 1H), 3.42 (dd, *J*=16.4, 5.6 Hz, 1H), 3.03 (dd, *J*=16.8, 6.4 Hz, 1H), 2.40 (s, 3H), 1.86—1.83 (m, 1H), 1.70—1.51 (m, 4H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 197.5, 164.4, 159.8, 143.7, 142.4, 137.0, 136.6, 133.2, 129.7, 129.5, 128.5, 128.3, 128.2, 128.0, 127.2, 125.6, 120.9, 114.6, 84.7, 75.7, 61.4, 55.2, 44.8, 39.4, 36.8, 25.6, 24.5, 21.6, 13.9; ESI-HRMS calcd for $C_{33}H_{35}NO_7S$+Na 612.2032, found 612.2034.

Ethyl-5-(4-methoxyphenyl)-2-(2-oxo-2-phenylethyl)-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (**5e**) 80% yield; $[\alpha]_D^{20}$ +50.2 (*c* 0.81 in $CHCl_3$); 92% *ee*, determined by HPLC

analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=13.19 min, *t*(minor)=27.18 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J*=7.2 Hz, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.58 (t, *J*=7.2 Hz, 1H), 7.47 (t, *J*=7.6 Hz, 2H), 7.26—7.24 (m, 2H), 7.01 (d, *J*=8.4 Hz, 2H), 6.83 (d, *J*=8.8 Hz, 2H), 6.15 (d, *J*=3.2 Hz, 1H), 5.27 (d, *J*=2.4 Hz, 1H), 4.23—4.17 (m, 3H), 3.80 (s, 3H), 3.48 (dd, *J*=10.4, 3.2 Hz, 1H), 3.42 (dd, *J*=16.4, 6.0 Hz, 1H), 3.03 (dd, *J*=16.8, 6.4 Hz, 1H), 2.41 (s, 3H), 1.84—1.80 (m, 1H), 1.68—1.65 (m, 4H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.5, 164.5, 158.8, 143.7, 137.0, 136.6, 133.2, 132.7, 129.5, 129.4, 128.6, 128.2, 128.1, 127.3, 126.2, 114.1, 84.7, 75.7, 61.4, 55.3, 44.8, 38.7, 37.2, 25.6, 24.5, 21.6, 13.9; ESI-HRMS calcd for $C_{33}H_{35}NO_7S$+Na 612.2032, found 612.2034.

Ethyl-5-(3-bromophenyl)-2-(2-oxo-2-phenylethyl)-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (5f) 62% yield; $[\alpha]_D^{20}$ +59.6 (*c* 1.00 in $CHCl_3$); 96% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=11.20 min, *t*(minor)=18.43 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J*=7.2 Hz, 2H), 7.86 (d, *J*=8.4 Hz, 2H), 7.58 (t, *J*=7.2 Hz, 1H), 7.49—7.42 (m, 4H), 7.25 (d, *J*=9.2 Hz, 2H), 6.99 (d, *J*=8.0 Hz, 2H), 6.10 (d, *J*=3.2 Hz, 1H), 5.28 (d, *J*=2.4 Hz, 1H), 4.23—4.16 (m, 3H), 3.51 (dd, *J*=10.8, 3.2 Hz, 1H), 3.41 (dd, *J*=16.4, 6.4 Hz, 1H), 3.02 (dd, *J*=16.4, 6.0 Hz, 1H), 2.41 (s, 3H), 1.85—1.82 (m, 1H), 1.68—1.59 (m, 4H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.4, 164.2, 143.7, 140.0, 137.0, 136.6, 133.2, 131.8, 130.2, 129.8, 129.4, 128.6, 128.5, 128.2, 127.2, 124.8, 121.1, 84.5, 75.7, 61.5, 44.7, 38.9, 37.1, 25.5, 24.4, 21.6, 13.8; ESI-HRMS calcd for $C_{32}H_{32}BrNO_6S$+Na 660.1031, found 660.1032.

Ethyl-5-(4-bromophenyl)-2-(2-oxo-2-phenylethyl)-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (5g) 93% yield; $[\alpha]_D^{20}$ +47.9 (*c*=0.52 in $CHCl_3$); 99% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=14.95 min, *t*(minor)=26.97 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J*=7.6 Hz, 2H), 7.86 (d, *J*=8.4 Hz, 2H), 7.58 (t, *J*=7.2 Hz, 1H), 7.49—7.42 (m, 4H), 7.25 (d, *J*=8.4 Hz, 2H), 6.98 (d, *J*=8.4 Hz, 2H), 6.10 (d, *J*=2.8 Hz, 1H), 5.27 (d, *J*=2.4 Hz, 1H), 4.23—4.16 (m, 3H), 3.51 (dd, *J*=10.8, 3.2 Hz, 1H), 3.41 (dd, *J*=16.4, 6.0 Hz, 1H), 3.02 (dd, *J*=16.8, 6.0 Hz, 1H), 2.41 (s, 3H), 1.84—1.81 (m, 1H), 1.71—1.51 (m, 4H), 1.17 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.4, 164.3, 143.8, 140.0, 136.9, 136.5, 133.3, 131.8, 130.2, 129.5, 128.6, 128.2, 127.2, 124.8, 121.2, 84.5, 75.7, 61.5, 44.7, 38.9, 37.1, 25.6, 24.4, 21.6, 13.8; ESI-HRMS calcd for $C_{32}H_{32}BrNO_6S$+Na 660.1031, found 660.1032.

Ethyl-2-(2-oxo-2-phenylethyl)-5-(thiophen-3-yl)-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[*2*,*3*-*b*]-pyridine-7-carboxylate (5h) 88% yield; $[\alpha]_D^{20}$ +21.8 (*c* 0.77 in $CHCl_3$); 96% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=6.44 min, *t*(minor)=8.77 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J*=7.2 Hz, 2H), 7.84 (d, *J*=8.4 Hz, 2H), 7.57 (t, *J*=6.8 Hz, 1H), 7.46 (t, *J*=7.2 Hz, 1H), 7.26—7.23 (m, 2H), 7.19 (d, *J*=5.2 Hz, 1H), 6.94 (dd, *J*=4.8, 3.2 Hz, 1H), 6.83 (d, *J*=2.8 Hz, 1H), 6.13 (d, *J*=3.2 Hz, 1H), 5.28 (d, *J*=2.4 Hz, 1H), 4.23—4.19 (m, 3H), 3.89 (dd, *J*=10.8, 3.2 Hz, 1H), 3.41 (dd, *J*=16.8, 6.0 Hz, 1H), 3.02 (dd, *J*=16.4, 6.0 Hz, 1H), 2.40 (s, 3H), 1.86—1.65 (m, 4H), 1.52—1.48 (m, 1H), 1.19 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.3, 164.3, 143.7, 143.3, 136.9, 136.5, 133.2, 129.5, 128.5, 128.1, 128.0, 127.2, 127.0, 125.5, 124.4, 84.5, 75.6, 61.5, 44.7, 37.1, 34.2, 25.5, 24.8, 21.6, 13.8; ESI-HRMS calcd for $C_{30}H_{31}NO_6S_2$+Na 588.1490, found 588.1489.

Ethyl-2-(2-(4-methoxyphenyl)-2-oxoethyl)-5-phenyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano-[2,3-*b*]pyridine-7-carboxylate (5i) 66% yield; $[\alpha]_D^{20}$ +37.1 (*c* 0.35 in $CHCl_3$); 93% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=24.86 min, *t*(minor)=33.93 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J*=9.2 Hz, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.32—7.25 (m, 5H), 7.09 (d, *J*=6.8 Hz, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 6.17 (d, *J*=3.2 Hz, 1H), 5.27 (d, *J*=2.8 Hz, 1H), 4.23—4.18 (m, 3H), 3.88 (s, 3H), 3.53 (dd, *J*=14.8, 3.2 Hz, 1H), 3.37 (dd, *J*=16.0, 6.6 Hz, 1H), 3.00 (dd, *J*=16.4, 6.8 Hz, 1H), 2.42 (s, 3H), 1.86—1.83 (m, 1H), 1.68—1.65 (m, 4H), 1.19 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.0, 164.4, 163.6, 143.7, 140.8, 136.6, 130.2, 129.5, 129.1, 128.8, 128.7, 128.3, 128.2, 127.3, 125.9, 113.7, 84.7, 75.9, 61.4, 55.5, 44.5, 39.5, 37.1, 25.7, 24.5, 21.6, 13.9; ESI-HRMS calcd for $C_{33}H_{35}NO_7S$+Na 612.2032, found 612.2032.

Ethyl-2-(2-(4-chlorophenyl)-2-oxoethyl)-5-phenyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]-pyridine-7-carboxylate (5j) 62% yield; $[\alpha]_D^{20}$ +33.7 (*c* 0.30 in $CHCl_3$); 97% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=70/30, 1.0 mL/min, λ=220 nm, *t*(major)=19.44 min, *t*(minor)=30.24 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, *J*=8.4 Hz, 2H), 7.85 (d, *J*=8.0 Hz, 2H), 7.43 (d, *J*=8.0 Hz, 2H), 7.32—7.23 (m, 5H), 7.09 (d, *J*=7.2 Hz, 2H), 6.17 (d, *J*=2.8 Hz, 1H), 5.27 (d, *J*=2.0 Hz, 1H), 4.23—4.16 (m, 3H), 3.51 (dd, *J*=10.8, 3.2 Hz, 1H), 3.38 (dd, *J*=16.4, 6.0 Hz, 1H), 2.99 (dd, *J*=16.4, 6.0 Hz, 1H), 2.41 (s, 3H), 1.87—1.85 (m, 1H), 1.68—1.65 (m, 4H), 1.19 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.5, 164.4, 143.7, 140.8, 139.6, 136.5, 135.4, 129.7, 129.4, 128.8, 128.5, 128.3, 128.1, 127.3, 127.2, 125.7, 84.6, 75.6, 61.5, 44.8, 39.5, 37.0, 25.6, 24.4, 21.6, 13.9; ESI-HRMS calcd for $C_{32}H_{32}ClNO_6S$+Na 616.1537, found 616.1539.

Ethyl-2-(2-(naphthalen-2-yl)-2-oxoethyl)-5-phenyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (5k) 61% yield; $[\alpha]_D^{20}$ +26.4 (*c* 0.47 in $CHCl_3$); 95% *ee*, determined by HPLC

analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=22.83 min, *t*(minor)=39.48 min]; ^{1}H NMR (400 MHz, CDCl3) δ: 8.49 (s, 1H), 8.03 (dd, *J*=8.8, 1.6 Hz, 1H), 7.96 (d, *J*=8.0 Hz, 1H), 7.90—7.85 (m, 4H), 7.64—7.55 (m, 2H), 7.33—7.28 (m, 3H), 7.20 (d, *J*=8.0 Hz, 2H), 7.18 (d, *J*=6.8 Hz, 2H), 6.19 (d, *J*=3.6 Hz, 1H), 5.30 (d, *J*=2.8 Hz, 1H), 4.27—4.23 (m, 1H), 4.15 (q, *J*=4.0 Hz, 2H), 3.61—3.55 (m, 2H), 3.16 (dd, *J*=16.4, 6.4 Hz, 1H), 2.37 (s, 3H), 1.89—1.87 (m, 1H), 1.74—1.61 (m, 4H), 1.12 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 144.0, 141.8, 141.0, 136.6, 129.5, 128.7, 128.6, 128.5, 128.3, 128.2, 127.7, 127.2, 126.1, 125.7, 84.5, 77.9, 61.5, 44.9, 39.5, 37.1, 25.7, 24.5, 21.5, 13.8; ESI-HRMS calcd for $C_{36}H_{35}NO_6S$ + Na 632.2083, found 632.2085.

Ethyl-2-(2-oxopropyl)-5-phenyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (5l) 81% yield; $[\alpha]_D^{20}$ +31.6 (*c* 0.55 in $CHCl_3$); 96% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=70/30, 1.0 mL/min, λ=220 nm, *t*(major)=11.48 min, *t*(minor)=14.05 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, *J*=8.4 Hz, 2H), 7.35—7.28 (m, 5H), 7.09 (d, *J*=6.4 Hz, 2H), 6.16 (d, *J*=2.8 Hz, 1H), 5.23 (d, *J*=2.4 Hz, 1H), 4.24—4.17 (m, 2H), 4.00—3.98 (m, 1H), 3.49 (dd, *J*=10.4, 3.2 Hz, 1H), 2.79 (dd, *J*=16.0, 7.2 Hz, 1H), 2.50 (dd, *J*=16.0, 5.2 Hz, 1H), 2.45 (s, 3H), 2.11 (s, 3H), 1.88—1.85 (m, 1H), 1.69—1.63 (m, 4H), 1.21 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.4, 164.4, 147.0, 143.8, 140.8, 136.6, 129.5, 128.5, 128.2, 127.3, 125.8, 84.5, 75.4, 61.4, 39.4, 37.0, 31.7, 30.8, 25.4, 24.4, 21.6, 13.9; ESI-HRMS calcd for $C_{27}H_{31}NO_6S$ + Na 520.1770, found 520.1772.

Ethyl-2-(2-oxo-2-phenylethyl)-4-phenyl-7-tosyl-2,3,3a,4,7,7a-hexahydrofuro[*2,3-b*]pyridine-6-carboxylate (5m) 28% yield; $[\alpha]_D^{20}$ +62.0 (*c* 0.34 in $CHCl_3$); 95% *ee*, determined by HPLC analysis [Daicel chiralcel OD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=14.78 min, *t*(minor)=12.87 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J*=6.8 Hz, 2H), 7.88 (d, *J*=8.4 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 7.48—7.45 (m, 2H), 7.31 (t, *J*=7.2 Hz, 2H), 7.26—7.25 (m, 2H), 7.16 (d, *J*=6.8 Hz, 2H), 6.44 (d, *J*=6.0 Hz, 1H), 5.83 (d, *J*=5.6 Hz, 1H), 4.73—4.69 (m, 1H), 4.29—4.20 (m, 2H), 3.50—3.44 (m, 2H), 3.04 (dd, *J*=16.8, 8.0 Hz, 1H), 2.69 (dd, *J*=7.6, 5.2 Hz, 1H), 2.41 (s, 3H), 2.31—2.25 (m, 1H), 1.94—1.86 (m, 1H), 1.26 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7, 164.2, 143.6, 140.3, 137.1, 136.7, 133.7, 133.4, 129.3, 128.9, 128.6, 128.1, 127.8, 127.6, 127.3, 126.1, 86.5, 73.6, 61.6, 45.0, 44.5, 41.8, 37.4, 21.6, 14.0; ESI-HRMS calcd for $C_{31}H_{31}NO_6S$+Na 568.1770, found 568.1772.

Ethyl-2-(2-oxo-2-phenylethyl)-4-phenyl-7-tosyl-2,3,3a,4,7,7a-hexahydrofuro[2,3-*b*]pyridine-6-carboxylate (5m') 18% yield; $[\alpha]_D^{20}$ +52.0 (*c* 0.20 in $CHCl_3$); 95% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=10.17 min, *t*(minor)=14.59 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J*=7.6 Hz, 2H), 7.81 (d, *J*=7.6 Hz, 2H), 7.56 (t, *J*=7.6 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 2H), 7.34—7.31 (m, 2H), 7.22 (d, *J*=7.2 Hz, 2H), 7.10 (d, *J*=8.0 Hz, 2H), 6.35 (d, *J*=7.2 Hz, 1H), 5.83 (d, *J*=6.8 Hz, 1H), 4.60 (t, *J*=7.2 Hz, 1H), 4.38—4.32 (m, 1H), 4.29—4.23 (m, 1H), 3.56—3.54 (m, 1H), 3.21 (dd, *J*=17.6, 6.0 Hz, 1H), 3.00—2.95 (m, 1H), 2.94 (dd, *J*=17.6, 6.8 Hz, 1H), 2.58—2.51 (m, 1H), 2.25 (s, 3H), 1.72—1.64 (m, 1H), 1.31 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.8, 164.4, 143.5, 139.3, 137.4, 136.6, 133.1, 132.5, 129.0, 128.8, 128.5, 128.3, 128.1, 127.6, 127.2, 121.9, 86.3, 74.6, 61.6, 48.2, 45.8, 39.7, 36.2, 21.5, 14.1; ESI-HRMS calcd for $C_{31}H_{31}NO_6S$+Na 568.1770, found 568.1772.

Synthetic transformations of the products

The ketone functional group could be chemoselectively reduced to the corresponding methylene group without affecting the enamide functionality, as illustrated in Scheme 3.

Scheme 3 Chemoselective reduction of ketone group

Ethyl-2-phenethyl-5-phenyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-*2H*-pyrano[2,3-*b*]pyridine-7-carboxylate (6) 54% yield; $[\alpha]_D^{20}$ +98.3 (*c* 0.51 in $CHCl_3$); 98% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH=60/40, 1.0 mL/min, λ=220 nm, *t*(major)=5.60 min, *t*(minor)=6.11 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J*=8.4Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H), 7.32—7.11 (m, 8H), 7.01 (d, *J*=6.4 Hz, 2H), 6.21 (d, *J*=3.2 Hz, 1H), 5.12 (d, *J*=2.8 Hz, 1H), 4.25 (qd, *J*=7.2, 1.2 Hz, 2H), 3.53 (dd, *J*=10.8, 3.6 Hz, 1H), 3.40—3.35 (m, 1H), 2.74—2.69 (m, 1H), 2.64—2.56 (m, 1H), 2.43 (s, 3H), 1.96—1.87 (m, 2H), 1.71—1.64 (m, 1H), 1.56—1.46 (m, 2H), 1.37—1.28 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 144.0, 141.8, 141.0, 136.6, 129.5, 128.7, 128.6, 128.5, 128.3, 128.2, 127.7, 127.2, 126.1, 125.7, 84.5, 77.9, 61.5, 39.5, 37.4, 37.2, 31.3, 25.8, 24.5, 21.6, 13.9; ESI-HRMS calcd for $C_{32}H_{35}NO_5S$ + Na 568.2134, found 568.2136.

The enamide group could be reduced in methanol by Pd/C-catalyzed hydrogenation at high pressure (4.5 MPa), but in poor diastereoselectivity. The ketone group was also converted to methylene group simultaneously, giving separable diastereomers **7** and **7'** (Scheme 4).

Ethyl-2-phenethyl-5-phenyl-8-tosyl-octahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (7) 34% yield; $[\alpha]_D^{20}$ +52.0 (*c* 0.20 in $CHCl_3$); 97% *ee*, deter-

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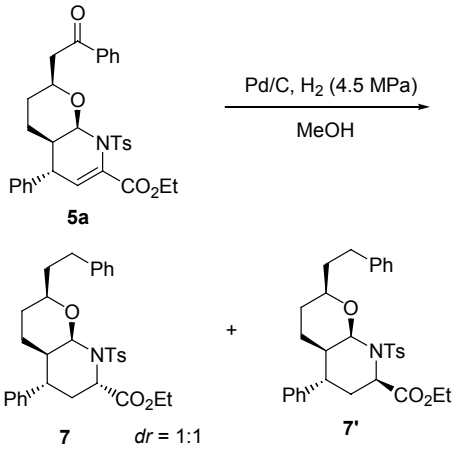
Scheme 4 Hydrogenation of product **5a**



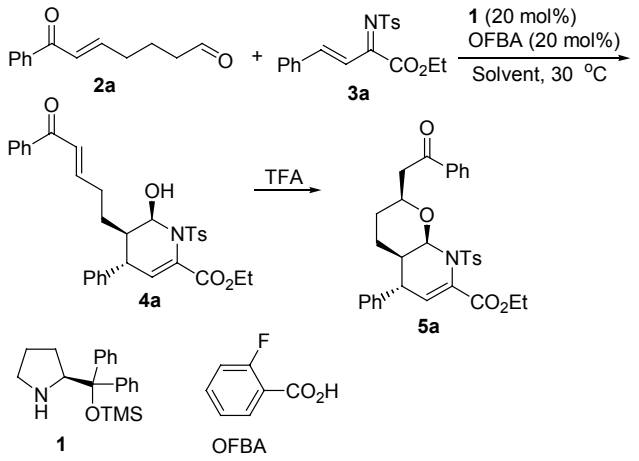
mined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 220 nm, *t*(major) = 12.80 min, *t*(minor) = 18.61 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 8.0 Hz, 2H), 7.32—7.15 (m, 10H), 7.07 (d, *J* = 6.8 Hz, 2H), 5.35 (d, *J* = 2.0 Hz, 1H), 4.27—4.16 (m, 3H), 3.44—3.41 (m, 1H), 3.08 (td, *J* = 11.6, 4.4 Hz, 1H), 2.43—2.38 (m, 3H), 2.35 (s, 3H), 2.22—2.10 (m, 3H), 1.60—1.56 (m, 1H), 1.54—1.49 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 143.3, 142.3, 142.0, 137.8, 129.2, 128.8, 128.4, 128.3, 128.2, 128.1, 126.9, 125.7, 85.8, 76.9, 61.6, 57.0, 38.8, 37.6, 37.0, 36.5, 30.8, 25.2, 24.7, 21.5, 13.9; ESI-HRMS calcd for $C_{32}H_{37}NO_5S$ + Na 570.2290, found 570.2289.

Ethyl-2-phenethyl-5-phenyl-8-tosyl-octahydro-2*H*-pyrano[2,3-*b*]pyridine-7-carboxylate (**7'**) 34% yield; $[\alpha]_D^{20}$ +101.8 (*c* 0.40 in $CHCl_3$); 95% *ee*, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 220 nm, *t*(major) = 9.19 min, *t*(minor) = 7.41 min]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 8.4 Hz, 2H), 7.33—7.25 (m, 6H), 7.23—7.18 (m, 4H), 7.04 (d, *J* = 7.2 Hz, 2H), 5.36 (d, *J* = 2.8 Hz, 1H), 4.87 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.09—4.04 (m, 1H), 3.77—3.73 (m, 1H), 3.48 (td, *J* = 12.4, 3.6 Hz, 1H), 3.38—3.33 (m, 1H), 2.52—2.43 (m, 2H), 2.43 (s, 3H), 2.00—1.85 (m, 2H), 1.71—1.60 (m, 3H), 1.49—1.47 (m, 2H), 1.36—1.25 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 143.1, 143.0, 141.9, 138.4, 129.0, 128.7, 128.3, 128.1, 127.8, 127.5, 126.7, 125.8, 84.0, 77.6, 60.8, 52.6, 39.5, 37.4, 34.9, 34.1, 31.5, 25.4, 25.1, 21.5, 13.9; ESI-HRMS calcd for $C_{32}H_{37}NO_5S$ + Na 570.2290, found 570.2290.

Results and Discussion

Our initial investigation was carried out with *N*-Ts-1-azadienes **3a** and readily available 7-oxo-7-phenyl-hept-5-enal **2a** catalyzed by α,α-diphenylprolinol *O*-TMS ether **1** and *o*-fluorobenzoic acid (OFBA) at 30 ℃. A mixture of products was generated in THF (Table 1, Entry 1). The hemianminal **4a** was obtained smoothly

Table 1 Optimizations of reaction conditions in sequential Aza-Diels-Alder/*O*-Michael addition[a]



Entry	Solvent	*t*/h	Yield[b]/%	*ee*[c]/%
1	THF	24	messy	—
2	Dioxane	48	**4a**, 55	99
3	DCM	48	**4a**, 60	99
4	$CHCl_3$	48	**4a**, 55	99
5	MeCN	72	**4a**, 45	99
6	Toluene	72	**4a**, 60	99
7[d]	MeCN/H_2O	8+2	**5a**, 90	99

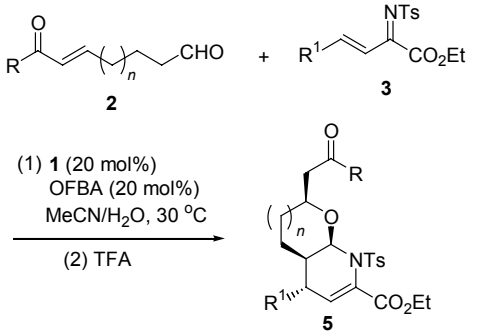
[a] Unless noted otherwise, reactions were performed with 0.2 mmol of **2a**, 0.1 mmol of **3a**, 20 mol% of **1** and 20 mol% of OFBA in 1 mL solvent at 30 ℃. [b] Isolated product. [c] By chiral HPLC analysis, *d.r.* > 95 : 5. [d] After the completion of aza-DA reaction, TFA (0.1 mL) was directly added to promote *O*-Michael addition.

in 1,4-dioxane, DCM, $CHCl_3$ in moderate yield (55%—60%) in 48 h, while with excellent stereoselectivity (Table 1, Entries 2—4). The reaction was quite sluggish in CH_3CN or toluene (Table 1, Entries 5 and 6). The aza-Diels-Alder reaction proceeded more efficiently in a mixture of CH_3CN and water (10 : 1), cleanly furnishing the hemiaminal **4a** in 8 h; more importantly, the following *O*-Michael reaction could be carried out by the direct treatment with trifluoroacetic acid (TFA, 0.1 mL), producing the desired ring-closed heterocycle **5a** in excellent diastereoselectivity and high yield for 2 h (Table 1, Entry 7).

With the optimized reaction conditions in hand, we next investigated the substrate scope and limitations for the one-pot, sequential aza-Diels-Alder and *O*-Michael addition. The results are summarized in Table 2. Firstly, a series of *N*-Ts-1-aza-1,3-butadienes **3** were explored in reactions with 7-oxo-7-phenyl-hept-5-enal **2a**. In general, *N*-Ts-1-azadienes carrying a diversely substituted aryl or heteroaryl groups could be well tolerated, affording the corresponding hexahydro-2*H*-pyrano[2,3-*b*]pyridine derivatives **5a**—**5h** in excellent diastereo- and enantioselectivity and with moderate to high yields (Table 2, Entries 1—8). Unfortunately, 1-azadienes derived from chalcones showed low reactivity with alde-

hyde **2a** in the amine-catalyzed aza-Diels-Alder step.[4] On the other hand, the substitution effects of *O*-Michael acceptor were also explored, and similar good results were obtained for substrates **2** with diverse aryl groups (Table 2, Entries 9—11). The reaction still proceeded smoothly for Michael acceptor with an acetyl group (Table 2, Entry 12), but the intramolecular *O*-Michael addition did not occur for less electrophilic ethoxycarbonyl-substituted substrate (Table 2, Entry 13). In addition, 6-oxo-6-phenyl-hex-4-enal could be smoothly used in the aza-Diels-Alder reaction with diene **3a**, but the *O*-Michael addition reaction was not satisfactory, and separable diastereomeric hexahydrofuro[2,3-*b*]pyridines **5m** and **5m'** were isolated in 26% and 18% yield, respectively, but still with excellent enantioselectivity (Table 2, Entry 14). Nevertheless, the attempt to construct fused oxepane ring was not successful with 8-oxo-8-phenyl-oct-6-enal (Table 2, Entry 15).

Table 2 Substrate scope and limitations[a]



Entry	R	R^1	*n*	Yield[b]/%	*ee*[c]/%
1	Ph	Ph	1	**5a**, 90	99
2	Ph	*p*-MePh	1	**5b**, 77	99
3	Ph	*m*-MePh	1	**5c**, 79	99
4	Ph	*m*-MeOPh	1	**5d**, 58	95
5	Ph	*p*-MeOPh	1	**5e**, 80	92
6	Ph	*m*-BrPh	1	**5f**, 62	96
7	Ph	*p*-BrPh	1	**5g**, 93	99
8	Ph	2-Thienyl	1	**5h**, 88	96
9	*p*-MeOPh	Ph	1	**5i**, 66	93
10	*p*-ClPh	Ph	1	**5j**, 62	97
11	1-Naphthyl	Ph	1	**5k**, 61	95
12	Me	Ph	1	**5l**, 81	96[d]
13	OEt	Ph	1	—[e]	—[e]
14	Ph	Ph	0	**5m**, 28 **5m'**, 18	95 95
15	Ph	Ph	2	—[e]	—[e]

[a] Reactions were performed with 0.2 mmol of **2**, 0.1 mmol of **3**, 20 mol% of **1** and 20 mol% of OFBA in MeCN/H_2O (10∶1, 1 mL) at 30 ℃. Then TFA (0.1 mL) was directly added to promote the *O*-Michael addition. [b] Isolated yield for two steps. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of **5l** was determined by X-ray analysis.[13] The other products were assigned by analogy. [e] The *O*-Michael addition failed to give the desired ring-closed products.

Conclusions

We have developed an asymmetric aza-Diels-Alder and *O*-Michael addition sequence to synthesize fused hexahydro-2*H*-pyrano[2,3-*b*]pyridine derivatives, which relies on the assembly of *N*-Ts-1-aza-1,3-butadienes and aliphatic aldehydes tethered to a *α*,*β*-unsaturated ketone motif. This process exhibited good efficiency, and an array of bicyclic frameworks bearing multiple functionalities have been constructed with excellent stereoselectivity under mild conditions. These enantiomerically pure heterocycles might find applications in synthetic and medicinal chemistry. The results will be reported in due course.

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[13] CCDC-905671 (**5l**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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