Tetrahedron: *Asymmetry* 25 (2014) 1133–1137

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective synthesis of (*R*)-Sumanirole using organocatalytic asymmetric aziridination of an α,β-unsaturated aldehyde

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ARTICLE INFO

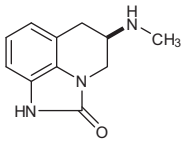
Article history:
Received 30 May 2014
Accepted 19 June 2014

ABSTRACT

Herein we report an enantioselective synthesis of (*R*)-Sumanirole wherein an organocatalytic asymmetric aziridination of 2-nitrocinnamaldehyde was the key step.

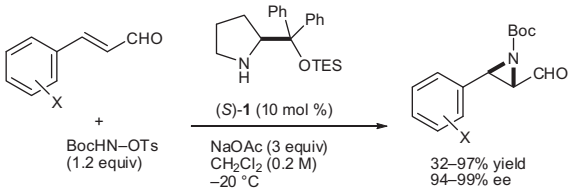
1. Introduction

Small organic molecules with a 3-amino tetrahydroquinoline skeleton are attractive synthetic targets in medicinal chemistry because of the ubiquity of this structural motif in various bioactive molecules. A representative example of this class of compounds is (*R*)-Sumanirole, which exhibits selective dopamine D2 receptor agonist activity.[1] A clinical trial for (*R*)-Sumanirole in the treatment of Parkinson disease was performed based on this bioactivity until the phase III study was terminated in 2004. Several enantioselective synthetic toward (*R*)-Sumanirole have been developed to date using the chiral pool,[2] a resolution,[3] or a diastereoselective reaction approach.[4] Synthetic methods based on a catalytic asymmetric reaction, however, are rarely reported on. The synthetic method reported by Sudalai et al. is the only approach for the synthesis of (*R*)-Sumanirole using a catalytic asymmetric α-aminooxylation of aldehydes.[5]



(*R*)-Sumanirole

Optically active aziridines are versatile chiral building blocks in organic synthesis. Selective modifications of the aziridine moiety provide efficient access to a wide variety of useful chiral intermediates. Therefore, various catalytic asymmetric synthetic methods have been developed[6] based on nitrene-transfer catalysis,[7] Brookhart–Templeton aziridinations[8] using chiral Lewis acid catalysts[9] or chiral Brønsted acid catalysts,[10] phase-transfer catalysis,[11] and chiral amine organocatalysis.[12] We recently reported on the asymmetric aziridination of α,β-unsaturated aldehydes using chiral amine organocatalysts.[12d] Using 10 mol % of chiral prolinol derivative **1**[13] as an organocatalyst, the asymmetric aziridination of β-aryl α,β-unsaturated aldehydes proceeded in the presence of *t*-butyl *p*-toluenesulfonyloxy carbamate and sodium acetate, to afford the corresponding *trans*-α,β-aziridine aldehydes with excellent enantioselectivity (Scheme 1). We hypothesized that a 3-amino tetrahydroquinoline skeleton would be efficiently constructed by using the present catalytic asymmetric aziridination and envisioned that the developed method would be applicable to the enantioselective synthesis of (*R*)-Sumanirole. Herein we report an enantioselective synthesis of (*R*)-Sumanirole using the organocatalytic asymmetric aziridination of 2-nitrocinnamaldehyde as the key step.



Scheme 1. Organocatalytic asymmetric aziridination of β-aryl α,β-unsaturated aldehydes.

2. Results and discussion

Our plan for the enantioselective synthesis of (*R*)-Sumanirole is outlined in Scheme 2. The cyclic urea structure can be constructed

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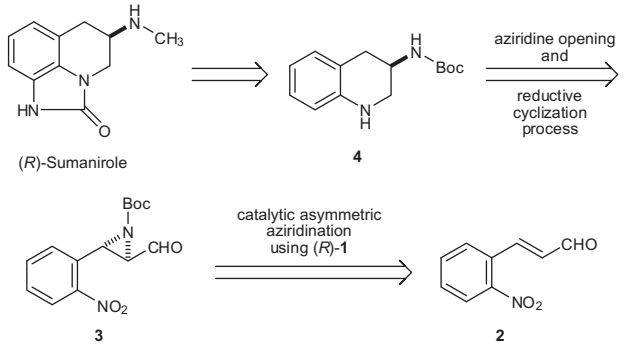
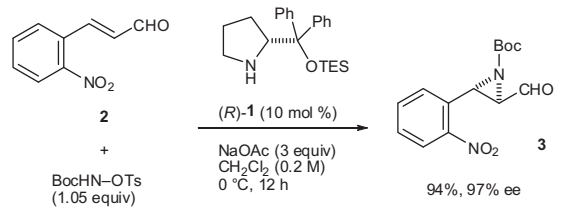
http://dx.doi.org/10.1016/j.tetasy.2014.06.018
0957-4166/

by an oxidative intramolecular C—N bond formation using an *N*-methoxyurea derived from 3-*N*-Boc-amino tetrahydroquinoline **4** as a substrate.[2] The key intermediate **4** can be prepared from a chiral aziridine aldehyde derivative using a regioselective aziridine opening reaction and a reductive cyclization process. Cinnamaldehyde derivatives with an electron-withdrawing group on the aromatic ring are more effective substrates for our catalytic asymmetric aziridination than those bearing an electron-donating group. This led us to select chiral aziridine aldehyde **3** as a suitable precursor for the synthesis of compound **4**. Compound **3** could be obtained in an optically active form via catalytic asymmetric aziridination of commercially available 2-nitrocinnamaldehyde **2**.



Scheme 2. Retrosynthetic analysis.

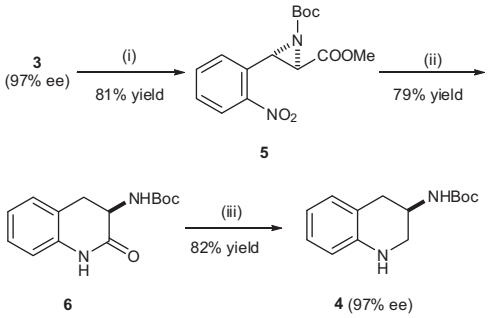
Our synthesis started with the organocatalytic asymmetric aziridination of 2-nitrocinnamaldehyde **2** (Scheme 3). Using 10 mol % of (*R*)-D-proline-derived chiral amine (*R*)-**1**, the asymmetric aziridination of **2** with 1.05 equiv of *t*-butyl *p*-toluenesulfonyloxy carbamate proceeded smoothly at 0 °C to afford the corresponding chiral aziridine aldehyde **3** in 94% yield and with 97% ee.



Scheme 3. Catalytic asymmetric aziridination of **2**.

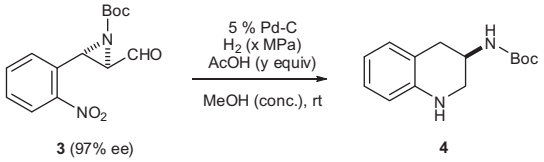
We next examined the transformation of **3** into key intermediate **4**. Nitrobenzene derivatives are generally converted into the corresponding aniline derivatives in the presence of a Pd catalyst under a hydrogen atmosphere. Benzylic C—N bonds are also cleaved under the same reaction conditions. We thus hypothesized that compound **3** could be converted into key intermediate **4** using a one-pot sequential process involving the reduction of the nitro group, hydrogenolysis of the benzylic C—N bond, and intramolecular reductive amination (Table 1). Studies were performed using Pd—C as a catalyst in MeOH under a hydrogen atmosphere. We first examined the reaction using aziridine aldehyde **3** with 97% ee in the presence of 1 equiv of acetic acid under 0.1 MPa hydrogen pressure. Although the reaction was sluggish, the desired reaction sequence proceeded under dilute conditions to give 3-amino tetrahydroquinoline derivative **4** in 29% yield (entry 2). The hydrogen pressure significantly affected the reactivity and compound **4** was obtained in 88% yield when the reaction was performed under 0.4 MPa hydrogen pressure (entry 3). Chiral HPLC analysis was used to determine the enantiomeric excess of **4** and revealed that partial racemization occurred during this sequential process. The optical purity decreased when the reaction was performed in the absence of acetic acid (entry 4). These results led us to find an alternative, racemization-free, synthetic route from **3** to **4**.

We thought that the decrease in the enantiomeric excess was due to partial enolization at the stage of an α-*N*-Boc-amino aldehyde intermediate. Thus, compound **3** was first reacted with NaCN and MnO_2 in MeOH, to afford the corresponding methyl ester **5** in 81% yield (Scheme 4). We next transformed compound **5** into lactam **6** in 79% yield via Pd-catalyzed hydrogenolysis of the benzylic C—N bond, reduction of the nitro group, and a lactamization cascade. Subsequent reduction of **6** using BH_3·THF at room temperature afforded the key intermediate **4** in 82% yield. The



Scheme 4. Racemization-free synthetic route. Reaction conditions: (i) NaCN (2 equiv), MnO_2 (500 w/w%), MeOH, 0 °C, 4 h. (ii) 5% Pd-C, H_2 (0.4 MPa), AcOH (1 equiv), MeOH, rt, 6.5 h. (iii) BH_3·THF (10 equiv), THF, rt, 2 h.

Table 1
One-pot transformation of **3** into tetrahydroquinoline derivative **4**

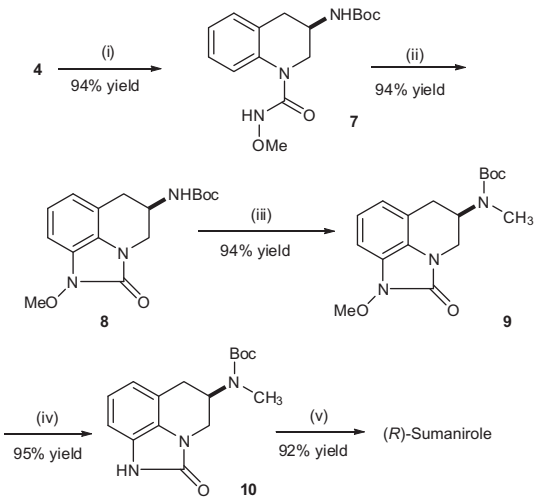


Entry	H_2[a] (MPa)	AcOH (equiv)	MeOH (M)	Time (h)	Yield[b] (%)	Ee of **4**[c]
1	0.1	1	0.06	24	24	N.D.
2	0.1	1	0.016	24	29	N.D.
3	0.4	1	0.016	7	88	77% ee
4	0.4	0	0.016	17	73	67% ee

[a] 1 MPa = 9.869 atm.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

enantiomeric excess of **4** was determined to be 97% ee, thus indicating that the enantiomeric purity did not erode over the course of the reactions.

With the optically active intermediate **4** (97% ee) in hand, we were thus able to complete the enantioselective synthesis of (*R*)-Sumanirole (Scheme 5). After introducing a methoxyaminocarbonyl group on the aniline nitrogen (94% yield), the obtained product **7** was reacted with a hypervalent iodine reagent[2,14] to give compound **8** in 94% yield. N-methylation of compound **8**, followed by hydrogenolysis of the N—O bond in the presence of a Pd catalyst, provided compound **10** in 89% yield over two steps. Finally, removal of the Boc group afforded (*R*)-Sumanirole in 92% yield (35.8% overall yield, 9 step from **1**). The specific rotation of the synthetic sample was measured after converting it into the corresponding HCl salt {synthetic sample: $[\alpha]_D^{25} = -29.0$ (*c* 0.43, MeOH) 97% ee, literature data:[3a] $[\alpha]_D^{25} = -30.3$ (*c* 1.0, MeOH) 99% ee}.



Scheme 5. Asymmetric synthesis of (*R*)-Sumanirole. Reaction conditions: (i) triphosgene (0.35 equiv), $MeONH_2{\cdot}HCl$ (1.1 equiv), NEt_3 (3.2 equiv), THF, rt, 26 h. (ii) $PhI(OOCCF_3)_2$ (1.3 equiv), $CHCl_3$, rt, 2 h. (iii) NaH (2 equiv), MeI (2 equiv), DMF, rt, 2 h. (iv) 5% Pd-C, H_2 (0.4 MPa), EtOH, rt, 18 h. (v) TFA (26.5 equiv), CH_2Cl_2, rt, 12 h.

3. Conclusion

In conclusion, we have achieved the enantioselective synthesis of (*R*)-Sumanirole by using an organocatalytic asymmetric aziridination of an α,β-unsaturated aldehyde. Asymmetric aziridination of 2-nitrocinnamaldehyde with *t*-butyl *p*-toluenesulfonyloxy carbamate proceeded by using 10 mol % of (*R*)-D-proline-derived chiral amine organocatalyst to afford the corresponding chiral aziridine aldehyde in 94% yield and with 97% ee. The aziridine obtained was converted into a 3-amino tetrahydroquinoline intermediate via a Pd-catalyzed sequential process. The enantioselective synthesis of (*R*)-Sumanirole was achieved in nine steps with an overall yield of 35.8%, which is the most efficient process compared with the previously reported asymmetric synthesis. This method could be applicable to the synthesis of other bioactive molecules with a 3-amino tetrahydroquinoline skeleton. Further studies are currently in progress.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 230 Fourier transform infrared spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR II). NMR spectra were recorded on a JEOL ecp 400 spectrometer, operating at 400 MHz for ^1H NMR, and 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$, are reported downfield from TMS (=0 ppm) for ^1H NMR. For ^{13}C NMR, chemical shifts are reported in a scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. Optical rotations were measured on a JASCO P-1020 polarimeter. ESI mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100L. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970, measured at 254 nm; column DAICEL CHIRALPAK AD-H, DAICEL CHIRALCEL OD-H, DAICEL CHIRALCEL OJ-H; mobile phase, hexane–2-propanol. Reactions were carried out in dry solvent under an argon atmosphere. Other reagents were purified by the usual methods.

4.2. *tert*-Butyl (2*R*,3*S*)-2-formyl-3-(2-nitrophenyl)aziridine-1-carboxylate 3

To a stirred solution of (*R*)-**1** (126.5 mg, 0.344 mmol), 2-nitrocinnamaldehyde **2** (610 mg, 3.44 mmol), and sodium acetate (850 mg, 10.32 mmol) in CH_2Cl_2 (17 mL) at 0 °C was added *tert*-butyl *p*-toluenesulfonyloxy carbamate (1.04 g, 3.61 mmol). After being stirred for 12 h at 0 °C, the reaction mixture was diluted with AcOEt, washed with satd aq $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 10:1) to give **3** (1.02 g, 94% yield, 97% ee) as a white solid. Mp. 73–75 °C; IR (ATR) *ν* 1726, 1527, 1344, 1300, 1156 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 1.53 (s, 9H), 3.19 (dd, *J* = 2.4 Hz, 3.6 Hz, 1H), 4.38 (d, *J* = 2.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H) 7.75 (d, *J* = 7.6 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 9.55 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 27.8 (3C), 44.3, 48.6, 83.2, 125.0, 129.2, 129.4, 131.3, 134.3, 147.8, 158.1, 193.2; (+)-ESI-HRMS. Calcd for $C_{14}H_{17}N_2O_5^+$ ($M+H^+$): 293.1137. Found: 293.1166; $[\alpha]_D^{20} = +59.7$ (*c* 1.01, $CHCl_3$) 97% ee. Enantiomeric excess was determined by using chiral HPLC analysis after converting into the corresponding methyl ester derivative **5** (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 95:5, flow rate: 1 mL/min, 254 nm, t_R 8.8 min and 10.8 min, detection at 254 nm).

4.3. 1-(*tert*-Butyl) 2-methyl (2*R*,3*S*)-3-(2-nitrophenyl)aziridine-1,2-dicarboxylate 5

To a stirred solution of **2** (2.54 g, 8.69 mmol) and sodium cyanide (0.85 g, 17.38 mmol) in MeOH (43 mL) at 0 °C was added activated manganese dioxide (12.70 g). After being stirred for 4 h at 0 °C, the reaction mixture was diluted with ethyl acetate. The mixture was washed with satd aq NH_4Cl and brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 10:1) to give **5** (2.26 g, 81% yield) as a white solid. Mp. 67–69 °C; IR (ATR) *ν* 2979, 1726, 1525, 1440, 1341, 1234, 1204, 1149, 1083, 845, 753 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 1.51 (s, 9H), 3.00 (dd, *J* = 0.8 Hz, 2.4 Hz, 1H), 3.87 (d, *J* = 0.8 Hz, 3H), 4.35 (d, *J* = 2.4 Hz, 1H), 7.51 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H) 7.66 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 27.9 (3C), 43.3, 43.5, 52.9, 82.6, 124.8, 129.2, 129.3, 131.7, 134.2, 147.9, 158.2, 167.3; (+)-ESI-HRMS. Calcd for $C_{15}H_{18}N_2NaO_6^+$ ($M+Na^+$): 345.1057. Found: 345.1048; $[\alpha]_D^{16} = +20.4$ (*c* 0.95, $CHCl_3$) 97% ee.

4.4. *tert*-Butyl (*R*)-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate 6

A suspension of **5** (342.0 mg, 1.06 mmol), Pd-C (5%, 65 mg), and acetic acid (61 μL, 1.06 mmol) in MeOH (70 mL) was stirred at room temperature under a hydrogen atmosphere (0.4 MPa). After 6.5 h, the reaction mixture was filtered through a short pad of

Celite and the filtrate was evaporated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3:1) to give **6** (219.6 mg, 79% yield, 97% ee) as a white solid. Enantiomeric excess was determined by using chiral HPLC analysis (DAICEL CHIRALCEL OJ-H, hexane/2-propanol = 95:5, flow rate: 1 mL/min, 254 nm, t_R 10.6 min, and 15.9 min, detection at 254 nm). Mp. 56–59 °C; IR (ATR) ν 3234, 2978, 1676, 1488, 1390, 1366, 1244, 1160, 753, 729 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H), 2.80–2.88 (m, 1H), 3.47–3.53 (m, 1H), 4.32–4.40 (m, 1H), 5.62 (broad peak: amide N*H*, 1H), 6.78 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.18–7.23 (m, 2H), 7.84 (broad peak: amide N*H*, 1H); ^{13}C NMR ($CDCl_3$): δ 28.3 (3C), 32.4, 50.0, 79.9, 115.6, 122.8, 123.6, 127.9, 128.5, 136.2, 155.6, 170.2; (+)-ESI-HRMS. Calcd for $C_{14}H_{19}N_2O_3^+$ ($M+H^+$): 263.1390. Found: 263.1391; $[\alpha]_D^{25} = -2.0$ (c 0.50, $CHCl_3$) 97% ee.

4.5. *tert*-Butyl (*R*)-(1,2,3,4-tetrahydroquinolin-3-yl)carbamate 4

4.5.1. Synthesis of compound 4 using compound 3 as a substrate (Table 1, entry 3)

A suspension of **3** (72.6 mg, 0.25 mmol), Pd-C (5%, 15 mg), and acetic acid (17 μL, 0.25 mmol) in MeOH (17 mL) was stirred at room temperature under a hydrogen atmosphere (0.4 MPa). After 7 h, the reaction mixture was filtered through a short pad of Celite and the filtrate was evaporated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3:1) to give **4** (54.6 mg, 88% yield, 77% ee) as a white solid. The enantiomeric excess was determined by using chiral HPLC analysis (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 80:20, flow rate: 1 mL/min, 254 nm, t_R 4.7 min and 5.3 min, detection at 254 nm).

4.5.2. Synthesis of compound 4 using compound 6 as a substrate

To a stirred solution of **6** (20.0 mg, 0.08 mmol) in THF (0.3 mL) at room temperature was added BH_3·THF (0.9 M, 0.85 mL, 0.76 mmol), and the mixture was left to stir for 22 h at 0 °C. The reaction was quenched by the addition of MeOH, and the resulting mixture was concentrated in vacuo. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 8:1) to give **4** (15.5 mg, 82% yield) as a white solid. Mp. 91–92 °C; IR (ATR) ν 3394, 3006, 2977, 1693, 1495, 1364, 1280, 1237, 1163, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (s, 9H), 1.46 (broad peak: amine N*H*, 1H), 2.67–2.75 (m, 1H), 3.04 (dd, J = 4.4 Hz, 16.0 Hz, 1H), 3.16–3.22 (m, 1H), 3.36 (dd, J = 2.0 Hz, 11.2 Hz, 1H), 4.14–4.20 (m, 1H), 5.00 (broad peak: amide N*H*, 1H), 6.52 (d, J = 8.0 Hz, 1H), 6.64–6.68 (m, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.98–7.03 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 28.4 (3C), 33.0, 43.0, 45.7, 79.3, 114.1, 117.8, 118.4, 127.1, 130.5, 143.7, 155.3; (+)-ESI-HRMS. Calcd for $C_{14}H_{21}N_2O_2^+$ ($M+H^+$): 249.1598. Found: 249.1579; $[\alpha]_D^{24} = +7.92$ (c 0.50, $CHCl_3$, 97% ee).

4.6. *tert*-Butyl (*R*)-(1-(methoxycarbamoyl)-1,2,3,4-tetrahydroquinolin-3-yl)carbamate 7

To a stirred solution of **4** (200.0 mg, 0.81 mmol) and triethylamine (0.18 mL, 1.30 mmol) in THF (2.7 mL) was added triphosgene (127.6 mg, 0.43 mmol) at 0 °C, and the resulting solution was stirred at room temperature. After 22 h, methoxyamine hydrochloride (74.0 mg, 0.89 mmol) and triethylamine (0.18 mL, 1.30 mmol) were added to the reaction, and the resulting mixture was stirred for 4 h at room temperature. The reaction was quenched by the addition of water, and the mixture was extracted with Et_2O (×2). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3:1–1:1) to give **7** (244.1 mg, 94% yield) as a white solid. Mp. 54–57 °C; IR (ATR) ν 3321, 2979, 2933, 1684, 1492, 1455, 1365, 1164, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (s, 9H), 2.69 (dd, J = 5.6 Hz, 16.4 Hz, 1H), 3.08 (dd, J = 5.6 Hz, 16.4 Hz, 1H), 3.65–3.85 (m, 2H), 3.74 (s, 3H), 4.07–4.13 (m, 1H), 4.88 (d, J = 7.2 Hz, 1H), 7.06–7.22 (m, 3H), 7.45 (d, J = 7.6 Hz, 1H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 28.3 (3C), 33.5, 46.0, 48.0, 64.2, 79.6, 122.9, 124.8, 126.9, 128.2, 129.7, 137.5, 155.2, 157.8; (+)-ESI-HRMS. Calcd for $C_{16}H_{24}N_3O_4^+$ ($M+H^+$): 322.1761. Found: 322.1778; $[\alpha]_D^{25} = +21.9$ (c 0.50, $CHCl_3$) 97% ee.

4.7. *tert*-Butyl (*R*)-(1-methoxy-2-oxo-1,2,5,6-tetrahydro-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)carbamate 8

To a stirred solution of **7** (51.8 mg, 0.16 mmol) in $CHCl_3$ (2 mL) at 0 °C was added $PhI(OOCCF_3)_2$ (89.8 mg, 0.208 mmol), and the reaction was left to stir for 2 h at room temperature. The reaction was quenched by the addition of satd aq $NaHCO_3$ solution, and the resulting mixture was extracted with Et_2O (×2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5:1–1:1) to give **8** (47.8 mg, 94% yield) as a pale orange solid. Mp. 64–67 °C; IR (ATR) ν 3321, 2979, 1700, 1532, 1491, 1365, 1285, 1218, 1163, 1059, 747 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (s, 9H), 2.88 (dd, J = 5.2 Hz, 16.0 Hz, 1H), 3.10 (dd, J = 4.0 Hz, 16.0 Hz, 1H), 3.80–3.95 (m, 2H), 4.09 (s, 3H), 4.40–4.50 (m, 1H), 4.70 (d, J = 6.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 7.05 (dd, J = 7.6 Hz, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 28.3 (3C), 30.3, 43.5, 43.6, 64.8, 80.0, 105.1, 116.3, 120.8, 121.9, 122.1, 124.6, 150.2, 154.8; (+)-ESI-HRMS. Calcd for $C_{16}H_{21}N_3NaO_4^+$ ($M+Na^+$): 324.1424. Found: 324.1436; $[\alpha]_D^{25} = +6.0$ (c 0.50, $CHCl_3$) 97% ee.

4.8. *tert*-Butyl (*R*)-(1-methoxy-2-oxo-1,2,5,6-tetrahydro-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)(methyl)carbamate 9

To a stirred solution of **8** (118.8 mg, 0.37 mmol) in DMF (2 mL) at 0 °C was added NaH (60% oil, 30 mg, 0.74 mmol). After 30 min, iodomethane (46.1 mL, 0.74 mmol) was added to the reaction at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of water, and the resulting mixture was extracted with Et_2O (×2). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5:1–2:1) to give **9** (128.1 mg, 94% yield) as a white solid; Mp. 82–84 °C; IR (ATR) ν 3229, 2980, 2931, 1666, 1492, 1455, 1391, 1363, 1290, 1242, 1148, 742 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H), 2.87 (s, 3H), 2.92 (dd, J = 4.4 Hz, 15.6 Hz, 1H), 3.12 (dd, J = 11.2 Hz, 15.6 Hz, 1H), 3.64 (dd, J = 11.2 Hz, 11.2 Hz, 1H), 4.07 (s, 3H), 4.05–4.09 (m, 1H), 4.40–4.75 (m, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 7.03 (dd, J = 7.2 Hz, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 28.1 (3C), 28.1, 29.6, 40.3, 48.9, 64.4, 80.1, 104.4, 117.7, 119.8, 121.4, 121.7, 124.2, 149.6, 154.8; (+)-ESI-HRMS. Calcd for $C_{17}H_{23}N_3NaO_4^+$ ($M+Na^+$): 356.1581. Found: 356.1558; $[\alpha]_D^{25} = +37.9$ (c 0.50, $CHCl_3$) 97% ee.

4.9. *tert*-Butyl (*R*)-methyl(2-oxo-1,2,5,6-tetrahydro-4*H*-imidazo-[4,5,1-*ij*]quinolin-5-yl)carbamate 10

A suspension of **9** (75.9 mg, 0.23 mmol), and Pd-C (5%, 15.2 mg) in EtOH (2.3 mL) was stirred at room temperature under a hydrogen atmosphere (0.4 MPa). After 18 h, the reaction mixture was filtered through a short pad of Celite and the filtrate was concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2, hexane/AcOEt = 2:1) to give **10** (66.4 mg, 95% yield) as a white solid. IR

(ATR) ν 3014, 2931, 1485, 1493, 1393, 1365, 1216, 1146, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H), 2.88 (s, 3H), 2.93 (dd, J = 5.2 Hz, 15.6 Hz, 1H), 3.12 (dd, J = 11.6 Hz, 15.6 Hz, 1H), 3.68 (dd, J = 11.2 Hz, 11.2 Hz, 1H), 4.11 (dd, J = 5.2 Hz, 11.2 Hz, 1H), 4.48–4.68 (m, 1H), 6.86–7.01 (m, 3H), 10.24 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 27.8, 28.4 (3C), 29.8, 40.7, 50.1, 80.5, 107.6, 117.6, 119.6, 121.6, 126.3, 126.8, 154.9, 155.2; (+)-ESI-HRMS. Calcd for $C_{16}H_{21}N_3NaO_3^+$ ($M+Na^+$): 326.1475. Found: 324.1465; $[\alpha]_D^{24}$ = +29.5 (c 0.25, $CHCl_3$) 97% ee.

4.10. (*R*)-Sumanirole

To a stirred solution of **10** (77.7 mg, 0.26 mmol) in CH_2Cl_2 (13 mL) at 0 °C was added trifluoroacetic acid (0.51 mL, 6.89 mmol), and the resulting solution was stirred at room temperature. After 12 h, the reaction mixture was poured into satd aq $NaHCO_3$ solution, and the mixture obtained was extracted with CH_2Cl_2 (×2). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue obtained was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH = 99:1–8:1) to give (*R*)-Sumanirole (48.8 mg, 92% yield) as a white solid. $[\alpha]_D^{25}$ = −21.6 (c 0.53, MeOH) 97% ee. Literature data: $[\alpha]_D$ = −20.9 (c 1.00, MeOH) 100% ee.[3a] The product obtained (16.6 mg, 0.08 mmol) was suspended in methanolic HCl (2 M solution, 2 mL) and Et_2O (2.5 mL), and stirred at 60 °C. After 2 h, the suspension was cooled to room temperature, filtered, and washed with a mixture of MeOH/Et_2O (1:1) to give (*R*)-Sumanirole·HCl (19.0 mg, 97% yield) as a white solid. IR (ATR) ν 2923, 2852, 1695, 1463, 1404, 1170, 1036, 778, 732 cm^{-1}; ^1H NMR (D_2O): δ 2.63 (s, 3H), 3.01 (dd, J = 3.6 Hz, 17.2 Hz, 1H), 3.10 (dd, J = 3.6 Hz, 17.2 Hz, 1H), 3.77 (dd, J = 3.2 Hz, 13.6 Hz, 1H), 3.86 (m, 1H), 3.98 (dd, J = 3.2 Hz, 13.6 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.94 (dd, J = 7.6 Hz, 7.6 Hz, 1H) (Amine and amide protons could not be observed in this conditions.); ^{13}C NMR (D_2O): δ 26.6, 31.8, 40.0, 52.9, 109.2, 114.5, 121.1, 123.3, 126.3, 126.5, 155.5; (+)-ESI-HRMS. Calcd for $C_{11}H_{14}N_3O^+$ ($M+H^+$): 204.1131. Found: 204.1135; $[\alpha]_D^{25}$ = −29.0 (c 0.43, MeOH) 97% ee. Literature data: $[\alpha]_D$ = −30.3 (c 1.0, MeOH) 100% ee.[3a]

Acknowledgement

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas 'Advanced Molecular Transformations by Organocatalysts' from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

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