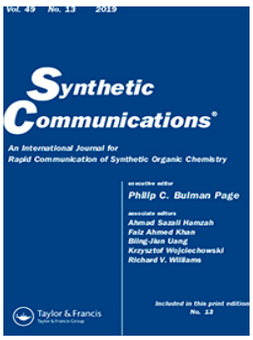

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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Yijun Zhu, Hongyan Li, Kuaile Lin, Bing Wang & Weicheng Zhou (2019) A novel and efficient asymmetric synthesis of anti-HIV drug maraviroc, Synthetic Communications, 49:13, 1721-1728, DOI: 10.1080/00397911.2019.1607875

To link to this article: https://doi.org/10.1080/00397911.2019.1607875

SYNTHETIC COMMUNICATIONS®
2019, VOL. 49, NO. 13, 1721–1728
https://doi.org/10.1080/00397911.2019.1607875

A novel and efficient asymmetric synthesis of anti-HIV drug maraviroc

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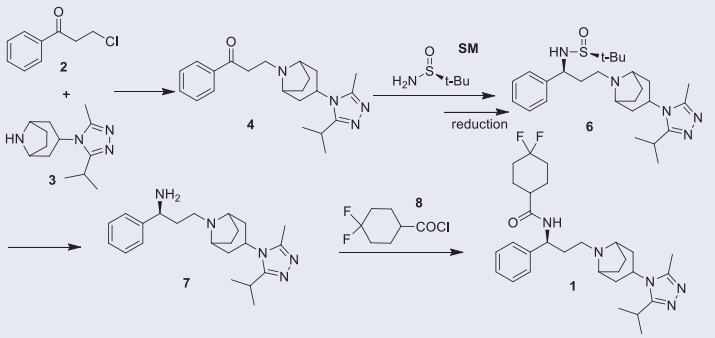
ABSTRACT

A novel and efficient route to asymmetric synthesis of Maraviroc by using (*S*)-*tert*-butanesulfinamide as chiral auxiliary is described. Two interesting impurities of the process are isolated and identified. The synthesis was concise, mild, and easy to operate. The overall yield and stereoselectivity were excellent.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 1 February 2019

KEYWORDS
Asymmetric synthesis; impurity; maraviroc; stereoselectivity; (S)-tert-butanesulfinamide

Introduction

Human immunodeficiency virus (HIV) is a pandemic virus, which seriously threatens the health of 35.3 million people worldwide.[1] Although many anti-HIV drugs have been approved for clinical treatment since Zidovudine was launched,[2] drug side effects, viral escape, and compliance issues continued to drive the discovery of novel target drugs. Chemokine receptor type 5 (CCR5) emerged as a necessary passway for HIV-1 infection and blockade of CCR5 was a new mechanism of the HIV-1 treatment regimen.[3] Pfizer's Maraviroc (**1**, UK-427857) was the first small-molecule CCR5 receptor antagonist approved by the FDA in 2007 for the therapy of HIV-1 infection (Figure 1).[4]

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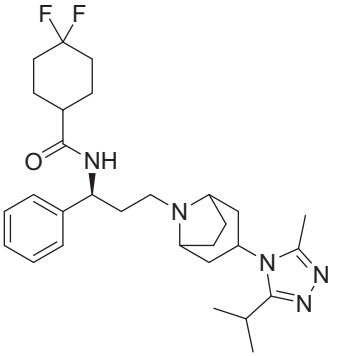


Figure 1. Maraviroc (**1**).

The asymmetric synthesis of Maraviroc has attracted great attention. So far the synthesis was based on two main synthetic strategies. Both medicinal chemistry[5] and process synthesis[6,7] of Maraviroc by Pfizer utilized the key intermediate (methyl *S*-3-amino-3-phenylpropionate) as a chiral source, which was produced by enantiomeric resolution to couple with 4,4-difluorocyclohexane-1-carboxylic acid and triazole-substituted tropane.[8] The other methods were based on the chiral catalyst-controlled asymmetric C–H amination to establish the absolute configuration of the stereocenter.[9–11] However, some of these methods were undermined by low enantioselectivity, complex synthetic procedures, and expensive chiral catalysts.

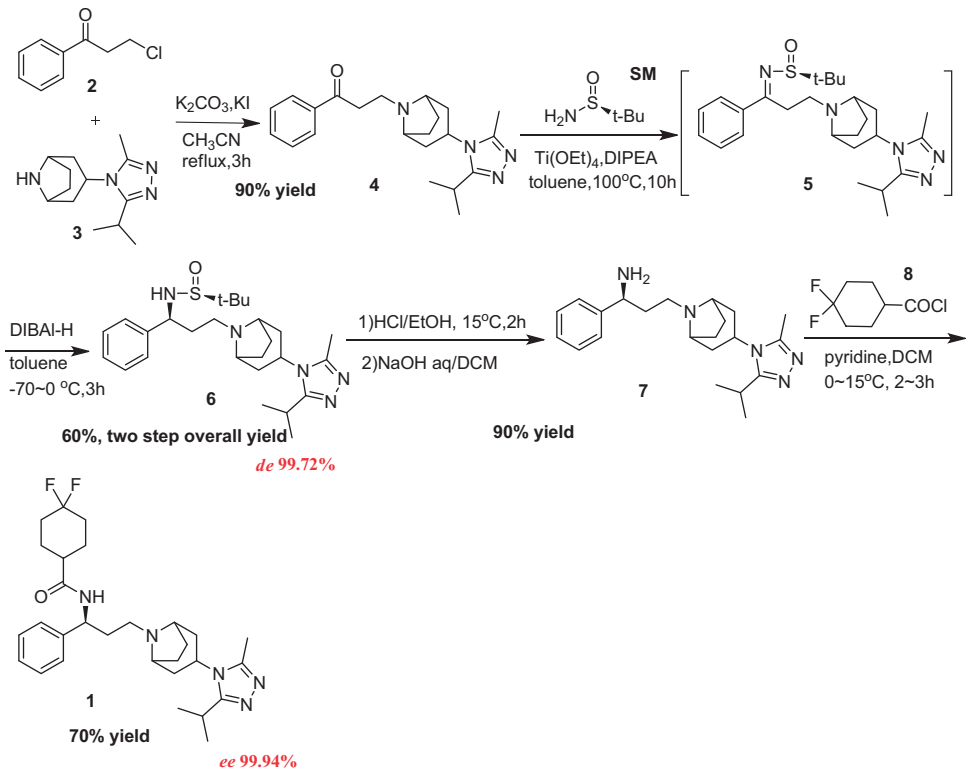
Chiral auxiliary *tert*-butanesulfinamide, developed by Ellman, has been proven to be a broadly useful reagent for the preparation of chiral amines through the intermediate of chiral *N*-*tert*-butanesulfinyl imines.[12,13] Due to its high diastereoselectivity and convenient cleavage of the *N*-*tert*-butanesulfinyl group, it has become an excellent chiral auxiliary in the synthesis of chiral amine compounds.[14,15] In this paper, we shall report a novel and efficient synthetic route for Maraviroc (**1**), which involve the enantioselective construction the amino group with *S*-configuration from 3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropan-1-one (**4**) through the chiral auxiliary (*S*)-*tert*-butanesulfinamide.

Results and discussion

The synthetic strategy herein is to stereoselectively prepare, (1*S*)-3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropan-1-amine (**7**), followed by the acylation to get the target compound, illustrated in Scheme 1.

The ketone **4** was synthesized for the first time from two commercially available materials 3-chloro-1-phenylpropan-1-one (**2**) and triazole-substituted tropane (**3**) by simple nucleophilic substitution. Then, the imine formation with (*S*)-*tert*-butanesulfinamide (SM) in the presence of $Ti(OEt)_4$ was further optimized (Table 1).

According to the similar imine formation conditions,[14] compound **4** reacted with (*S*)-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$, but it was found that the reaction was difficult to reach completion if it was carried out in THF or 2-MeTHF, (even after 24 h more than 50% of **4** remained, Table 1, entries 1 and 2). In order to drive the imine formation, the reaction was conducted in toluene at elevated temperature and



Scheme 1. Synthetic process for Maraviroc **1**.

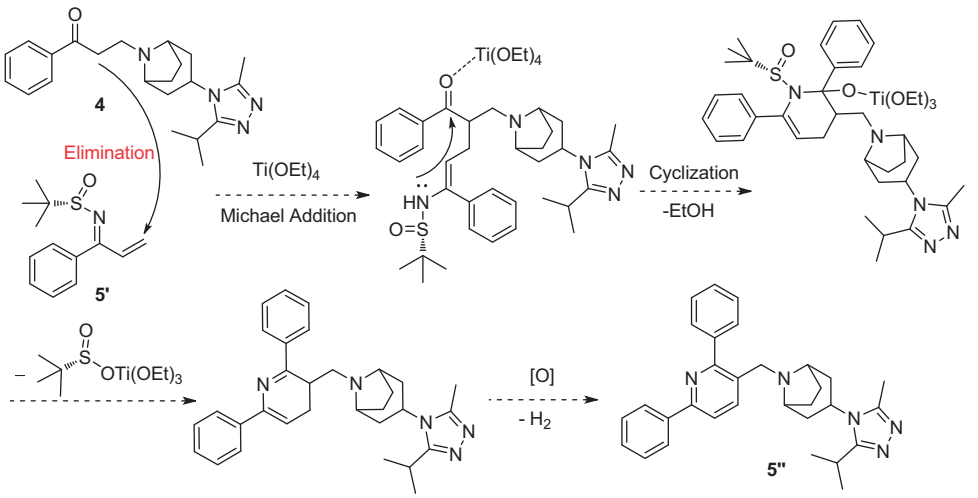
Table 1. Optimization of sulfinylimine formation[a].

Entry	Condensation agent	Solvent	Temperature (°C)	Time (h)	ratio **4:5:5′:5″**[b]
1	$Ti(OEt)_4$(4 Eq.)	THF	65	36	51:28:2:4
2	$Ti(OEt)_4$(4 Eq.)	2-MeTHF	80	24	46:12:4:12
3	$Ti(OEt)_4$(4 Eq.)	toluene	100	10	3:52:9:22
4	$Ti(OEt)_4$(3 Eq.)	toluene	100	10	2:75:11:4
5	$Ti(OEt)_4$(2 Eq.)	toluene	100	20	41:38:1:12
6	$Ti(OEt)_4$(2 Eq.)	toluene	reflux	24	35:55:7:4
7	$Ti(OEt)_4$(3 Eq.) DIPEA(0.5 Eq.)	toluene	100	10	2:79:6:5
8	$Ti(OEt)_4$(3 Eq.) DIPEA(1.2 Eq.)	toluene	100	10	1:86:5:1
9	$Ti(OEt)_4$(3 Eq.) DIPEA(1.8 Eq.)	toluene	100	10	2:75:10:4

[a]The ratio of **4**:(*S*)-*tert*-butanesulfinamide was 1:1.2 in reactions; [b]measured by HPLC.

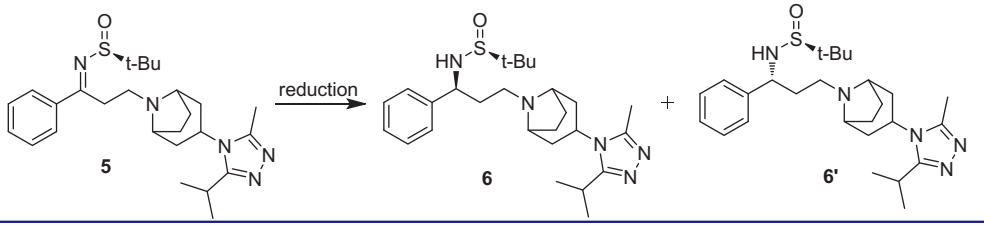
HPLC analysis showed that **4** was nearly consumed up after 10 h (Table 1, entry 3). The data of entries 4–6 of Table 1 indicated that 3 Eq. of $Ti(OEt)_4$ were sufficient. However, HPLC also indicated that the reaction generated two impurities. After purification through column chromatography, their structures were identified as (*S*)-2-methyl-*N*-(1-phenylallylidene)propane-2-sulfinamide(**5'**) and 8-((2,6-diphenylpyridin-3-yl)methyl)-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane(**5"**) (Scheme 2).

The byproduct **5'** might be formed by Hoffman elimination of **5** in the presence of Lewis acid $Ti(OEt)_4$, and then **5** further reacted with **5'** by Michael addition, cyclization,



Scheme 2. Plausible mechanism for the formation of impurity **5"**.

Table 2. Condition for the reduction of sulfinylimine **5**.



Entry	reductant	solvent	temperature(°C)	time (h)	**6:6'**[a]	*de*(%)
1	$NaBH_4$(1 Eq.)	THF	−5	5	52:48	4
2	$LiBH_4$(1 Eq.)	THF	−10	3	60:40	20
3	KBH_4(2 Eq.)	THF	0	3	75:25	50
4	$NaBH(OAc)_3$(3 Eq.)	THF	25	12	NR[b]	
5	$NaBH_3CN$(1 Eq.)	THF	15	12	NR	
6	BH_3(1 Eq.)	THF	−15	2	No desired product	
7	DIBAlH(4 Eq.)	THF	−70	3	87:13	74
8	DIBAlH(4 Eq.)	toluene	−70	3	95:5	90
9[c]	DIBAlH(3 Eq.)	toluene	−70	6	95:5	90
10	DIBAlH(3 Eq.)	toluene	−70 ~ 10	2	95:5	90
11[d]	DIBAlH(3 Eq.)	toluene	−70 ~ 10	3	96:4	92

[a]The ratio was determined by HPLC; [b]no reaction; [c]compound **5** was not consumed up; [d]one-pot synthesis of imine formation and reduction.

elimination, and oxidation to obtain **5"** (The plausible mechanism was proposed in Scheme 2). Hence the key optimization of this step was to control the generation of **5'**. It was supposed that the formation of **5'** was related to the acidic condition, so DIPEA as a basic additive was tried. Pleasantly, the employment of 1.2 Eq. of DIPEA led to the optimal results in which **5** was obtained in 86% ratio (Table 1, entries 7–9). Based on the optimized condition of entry 8 of Table 1, this step was carried out on a 50 g scale.

The diastereoselective reduction of imine **5** was the key step in this route, so various conditions were screened and the results were listed in Table 2.

Various boron reducing reagents were screened based on the previous work of our group.[15] However, unsatisfactory results were obtained (Table 2, entries 1–3), even no

reaction (Table 2, entries 4 and 5) or no desired product (Table 2, entry 6). Fortunately, when diisobutyl aluminum hydride (DIBAl-H) was used as the reductant,[16] the diastereoisomeric excess (*de*) of the product was improved to 74% (Table 2, entry 7). Then, extensive optimization based on DIBAl-H was perfomed (Table 2, entries 8–10). It was found that the reduction was well conducted in toluene at about 10 °C after addition of the reductant at −70 °C (Table 2, entry 10). With the best conditions for sulfinyl imine formation and reduction identified, the one-pot procedure was implemented to yield crude **6** in 92% *de* (Table 2, entry 11). After recrystallization from MTBE, compound **6** was obtained in 60.1% yield (two steps) with 99.72% *de*.

Exposure of purified **6** to HCl in methanol at 15 °C resulted in cleavage of the chiral auxiliary group and basification with 2 N NaOH gave the primary amine **7** in 90% yield. The optical rotation value of **7** was consistent with that in the original patent.[17]

Finally, Maraviroc **1** was obtained by acylation of **7** with 4,4-difluorocyclohexanecarbonyl chloride (**8**) in the presence of pyridine in about 70% yield. After recrystallization from ethyl acetate, both of the purity (99.71%) and enantiopurity (99.94% *ee*) of Maraviroc were excellent. The characterization and the optical rotation value of compound **1** were consistent with that previously reported.[10]

Conclusion

In summary, a novel and stereoselective synthesis of Maraviroc based on the Ellman auxiliary (*S*)-*tert*-butanesulfinamide was developed in five steps in overall 34% yield with a chemical purity of 99.71% and a chiral purity of 99.94%. Two impurities were isolated and identified in the sulfinyl imine formation to guide the reaction improvements. The new route was concise, mild, and easy to operate.

Experimental

All solvents and reagents were reagent grade pure and used without further purification. ^{1}H and ^{13}C NMR spectra were measured using a Bruker 400 MHz spectrometer (Bruker, MA, USA) with TMS as an internal standard in $CDCl_3$ or DMSO-d_6. HPLC analyses were recorded with on a Dionex Ultimate 3000 chromatograph (Dionex Corporation, CA, USA) and chiral HPLC analyses were recorded with Agilent 1100 Series chromatography (Agilent, CA, USA). The HRMS data were obtained using Q-TOF micro mass spectrometry. The melting point was measured by Buchi Melting Point M-565. The optical rotations were measured by Autopol®IV Automatic Polarimeter.

3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropan-1-one (4)

To the solution of 3-chloro-1-phenylpropan-1-one **2** (71.2 g, 384 mmol, 1.1 Eq.) and 3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane **3** (90 g, 422 mmol, 1 Eq.) dissolved in CH_3CN (1300 ml) K_2CO_3 (106 g, 768 mmol, 2 Eq.) and KI (63.7 g, 384 mmol, 1 Eq.) were added, respectively and charged with N_2. The mixture was

stirred at 80 °C for 3 h and TLC showed **2** was consumed up. The mixture was cooled down, filtered, and the filtrate cake was washed with 200 ml DCM. The combined filtrate was concentrated, and the residue was dissolved in 500 ml DCM, extracted with 4 N HCl (aq) (400 ml × 2). The combined aqueous layer was washed with DCM (150 ml × 2). The pH of the aqueous layer was adjusted with 4 N NaOH (aq) to 13 and white solid was precipitated out. The suspension was stirred overnight and filtered, and the filtrated cake was slurried with water (1 L × 2), The precipitate was filtered again and dried at 70 °C for 6 h to yield about 126.7 g white solid. (90% yield) m.p. 90–91 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.91 (d, 2H); 7.49 (t, 1H); 7.41–7.26 (m, 2H); 4.21–4.14 (m, 1H); 3.34 (s, 2H); 3.11 (t, 2H); 2.90–2.88 (m, 2H); 2.79 (t, 2H); 2.36 (s, 3H); 2.13–2.03 (m, 4H); 1.58–1.56 (m, 4H); 1.28–1.27 (d, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ199.59, 159.10, 150.71, 136.96, 133.17, 128.61, 128.01, 59.52, 47.80, 47.07, 38.18, 36.36, 26.34, 25.63, 21.61, 12.89. HRMS (ESI): *m/z* calcd. for $C_{22}H_{31}N_4O$ $[M+H]^+$: 367.2532, found 367.2517.

(S)-N-((1S)-3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1] octan-8-yl)-1-phenylpropyl)-2-methylpropane-2-sulfinamide (6)

To the above toluene solution, 1.5 M DIBAl-H (272.9 ml, 409 mmol, 3 Eq.) was added dropwise at about −70 to −78 °C. After addition, the dark gray mixture was warmed to room temperature (*ca* 10 °C, for about 1 h), then stirred for 4 ~ 6 h, TLC showed **5** was disappeared. The mixture was quenched with 500 ml saturated NaCl, stirred for 1 h, and filtered. The filtrate cake was washed with toluene (250 ml × 2). The combined filtrate was separated, and the aqueous layer was extracted with DCM (500 ml). The combined organic phase was dried over $MgSO_4$, and was concentrated to afford about 60.2 g cardinal crude oil. The residue was recrystallized from MTBE (500 ml) to yield 38.7 g pale-yellow solid (60.1% yield of two steps). *de* 99.72%, m.p. 154–156 °C; $[\alpha]_{23}^{D} = 22.2^{\circ}$(c 1,$CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.39–7.30 (m, 4H); 4.68–4.64 (m, 1H); 4.40 (s, 1H); 4.34–4.25 (m, 1H); 3.39 (d, 2H); 3.00 (m, 1H); 2.50 (s, 3H); 2.38 (s, 2H); 2.16–2.13 (m, 3H); 2.04–1.95 (m, 3H); 1.66–1.62 (m, 4H); 1.42–1.40 (d, 6H); 1.22 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ159.07, 150.66, 142.33, 128.68, 127.74, 127.13, 59.17, 58.72, 56.22, 56.01, 48.21, 47.14, 35.91, 35.81, 35.35, 26.31, 25.77, 22.71, 21.66, 13.06. HRMS (ESI): *m/z* calcd. for $C_{26}H_{42}N_5OS$ $[M+H]^+$: 472.3110, found 472.3094.

(1S)-3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropan-1-amine (7)

To the solution of **6** (10 g, 21.2 mmol, 1 Eq.) in 30 ml methanol 3 ml HCl/MeOH (aq) at about 0 ~ 10 °C was added. After addition, the mixture was stirred at room temperature for 2 h, TLC showed **6** was consumed up. To the concentrated mixture, 15 ml DCM and 4 ml 2 N NaOH (aq) were added, the pH of the solution was adjusted to 12. The mixture was separated, and the aqueous layer was extracted with 15 ml DCM. The combined organic phase washed with water and brine, dried over Na_2SO_4, and concentrated to yield 7.4 g pale-yellow oil (90% yield). $[\alpha]_{15}^{D} = 14^{\circ}$(c 0.1, MeOH)[17] ^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.36–7.26(m, 4H); 7.25–7.23(m, 1H); 4.28–4.25(m, 1H);

4.11(s, 1H); 3.39(d, 2H); 3.00(m, 1H); 2.45 (s, 3H); 2.38 (s, 2H); 2.22–2.19 (m, 2H); 2.06–2.03 (m, 2H); 1.93–1.84 (m, 2H); 1.64–1.60 (m, 4H); 1.37–1.36 (d, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ159.09, 150.65, 145.97, 128.51, 127.05, 126.24, 58.83, 58.50, 55.06, 49.24, 47.36, 37.77, 36.01, 26.54, 26.36, 25.74, 21.58, 12.95. HRMS (ESI): *m/z* calcd. for $C_{22}H_{34}N_5$ $[M+H]^+$: 368.2814, found 368.2815.

Maraviroc (1)

The preparation of 4,4-difluorocyclohexanecarbonyl chloride (8)

To the solution of 4,4-difluorocyclohexanecarboxylic acid (3 g, 18.3 mmol, 1 Eq.) dissolved in 7.5 ml toluene $SOCl_2$ (6.6 ml, 5 Eq.) was added. The mixture was refluxed and stirred for 2 ~ 3 h. TLC showed the acid was consumed up, cooled, concentrated to yield about 2.5 g dryness oil (100% yield).

Then to the solution of **7** (3.6 g, 10 mmol, 1 Eq.) in 12 ml DCM was added pyridine (2.4 ml, 3 Eq.). The mixture was cooled to 0 ~ 10 °C and acyl chloride (2.2 g, 1.2 Eq.) was added dropwise. After addition, the mixture was stirred for 2 h and TLC showed **7** was consumed up. To the mixture, 10 ml water and 10 ml DCM were added. The mixture was separated, and the aqueous layer was extracted with 10 ml DCM. The combined organic phase was washed with 2 N NaOH (aq) (10 ml), water, and brine respectively, dried over Na_2SO_4, and concentrated to yield 4 g crude oil. The residue was recrystallized from ethyl acetate (15 ml) to afford 3.5 g **1** as white solid (70% yield). chiral HPLC: 99.94% *ee*; $[\alpha]_{25}^{D} = -32.8^{\circ}$ (c = 1, $CHCl_3$) (literature[10]: $[\alpha]_{25}^{D} = -27.4^{\circ}$, 96% *ee*); m.p. 195–196.2 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ8.27(d, 1H); 7.34–7.31(m, 4H); 7.23(m, 1H); 4.96–4.94(m, 1H); 4.21(m, 1H); 3.39 (s, 2H); 3.13 (m, 2H); 2.50 (s, 3H); 2.38 (m, 3H); 2.10–2.07 (m, 4H); 1.90 (m, 2H); 1.89–1.84 (m, 2H); 1.82 (m, 4H); 1.72 (m, 2H); 1.68–1.66 (m, 2H); 1.58–1.55 (m, 2H); 1.26–1.246 (d, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ173.60, 159.14, 150.57, 142.31, 128.61, 127.27, 126.53, 122.72, 58.82, 58.40, 51.86, 48.12, 47.34, 42.53, 35.69, 35.57, 35.05, 32.82, 32.78, 26.71, 25.98, 25.78, 21.65, 13.10. HRMS (ESI): *m/z* calcd.for $C_{29}H_{41}N_5OF2Na$ $[M+Na]^+$: 536.3177, found 536.3155.

Experimental procedures and NMR and HRMS data of 1, 4, 5, 6, 7, 5' and 5", and chiral HPLC of 1 and 6. This material can be found via the "Supplementary Material" section of this article's webpage.

Funding

This work was funded by the Jiangsu Province "innovation and entrepreneurship program" in 2017 & 2018 and Jiangsu Planned Projects for Postdoctoral Research Funds [2018K264C].

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