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Enantioselective synthesis of martinelline chiral core and its diastereomer using asymmetric tandem Michael–aldol reaction

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ABSTRACT

The martinelline chiral core **3** and its diastereomer were synthesized by using the asymmetric tandem Michael–aldol reaction as the key step from 4-methoxycarbonylanthranilaldehyde and the α,β-unsaturated aldehyde.

1. Introduction

Martinelline (**1**) and martinellic acid (**2**) constitute a small family of naturally occurring pyrroloquinoline alkaloids isolated from the roots of the tropical plant, *Martinella iquitosensis*, in 1995, as a nonpeptide bradykinin receptor antagonist (Fig. 1).[1] Their structural features contain a unique pyrroloquinoline with fused tetrahydroquinoline and pyrrolidine rings and two prenyl guanidines. The intriguing biological activity of martinelline coupled with its unique structure has led several groups, including our own, to investigate a variety of synthetic methods for the preparation of the pyrroloquinoline core.[2] Since the first total synthesis of martinellic acid was reported by Ma's group,[3a] several syntheses of martinellic acid[3,4] and three total syntheses[5,6] and many formal syntheses[7] of martinelline have been recorded to date. However, these syntheses of the optically active martinelline and martinellic acid have been limited to a diastereoselective synthesis using a chiral building block. Therefore, the catalytic enantioselective synthesis of martinelline and martinellic acid remains a challenge for a more expedient synthesis. We have already demonstrated that the tandem Michael–aldol reaction[2r,8,9] using an anthranilaldehyde and a Michael acceptor and a palladium-catalyzed intramolecular allylic alkylation reaction[2s,10] as a key step are powerful tools for the construction of the 1,2,3,4-tetrahydroquinoline and 1,2-dihydroquinoline skeletons. Recently, two enantioselective versions of this tandem Michael–aldol reaction using a chiral organocatalyst were reported.[11,12] As part of the study on the tandem Michael–aldol reactions, we now describe the enantioselective synthesis of the martinelline chiral core **3** and its diastereomer using the asymmetric tandem Michael–aldol reaction.

2. Results and discussion

The martinelline chiral core **3** can be constructed from 1,2-dihydroquinoline **4**, which should be obtained for anthranilaldehyde **5** and the Michael acceptor **6** using the asymmetric tandem Michael–aldol reaction (Scheme 1). The required **6** was easily prepared starting from the commercially available pyrrolidinone **7** in a good overall yield (Scheme 2). The protection of **7** with di-*tert*-

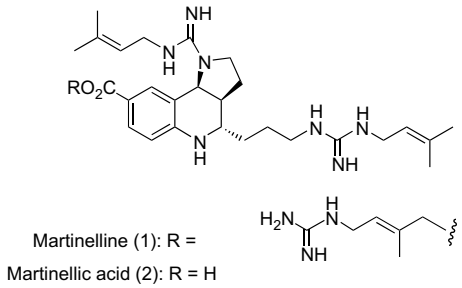

Figure 1.

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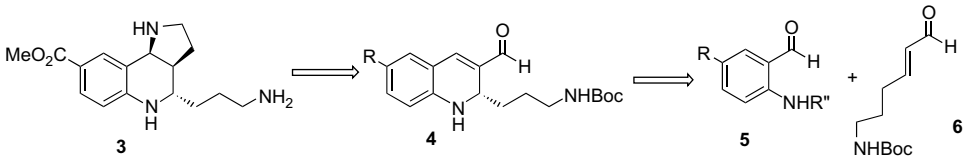
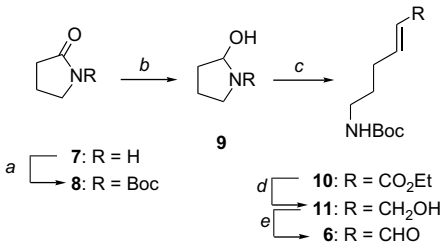


Scheme 1.

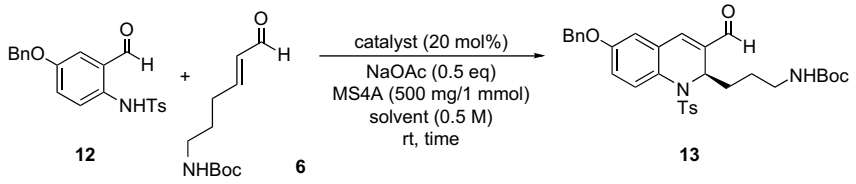


Scheme 2. Reagents and conditions: (a) Boc_2O, DMAP, CH_3CN, rt, 99%; (b) DIBAL, THF, −78 °C, quant.; (c) $Ph_3P{=}CHCO_2Et$, $PhCH_3$, 100 °C, 99%; (d) DIBALH, CH_2Cl_2, −78 °C, 76%; (e) MnO_2, CH_2Cl_2, rt, 92%.

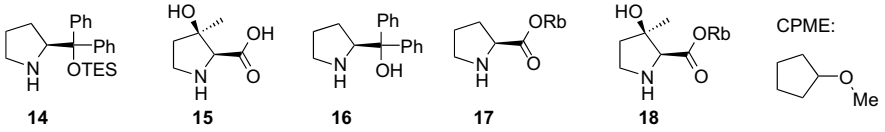
butyl dicarbonate followed by the reduction of **8** with diisobutylaluminum hydride afforded the pyrrolidine **9**. The Wittig homologation of **9** proceeded at elevated temperature to give the α,β-unsaturated ester **10**. The reduction of **10** followed by oxidation of the resulting allyl alcohol **11** furnished the Michael acceptor **6**.

The asymmetric tandem Michael–aldol reaction using (*S*)-diphenylprolinol triethylsilyl ether as an organocatalyst in the presence of sodium acetate (NaOAc) and molecular sieves 4 Å (MS4A) has been previously studied by others.[11a] We extensively examined this condition for the reaction of **12** and **6**. These results are shown in Table 1. The reaction was carried out using **12** (1 equiv) and **6** (3 equiv) in the presence of NaOAc (0.5 equiv), MS4A (500 mg/1 mmol), and (*S*)-diphenylprolinol triethylsilyl ether (**14**) (20 mol %) as the catalyst. The stereochemistry of the obtained product **13** was tentatively assigned as *R* from the reaction mechanism and subsequently confirmed by correlation to the known compound **3**. First, we examined the effects of the protecting groups at the oxygen and nitrogen functions. Surprisingly, the protecting group at the phenolic function was an important factor for enantioselectivity (entry 1). When the *tert*-butyldimethylsilyl group was employed, an almost racemic product was obtained. In stark contrast, the use of anthranilaldehyde **12** protected with the benzyl group improved the enantioselectivity to

Table 1
Asymmetric tandem Michael–aldol reaction using organocatalysts

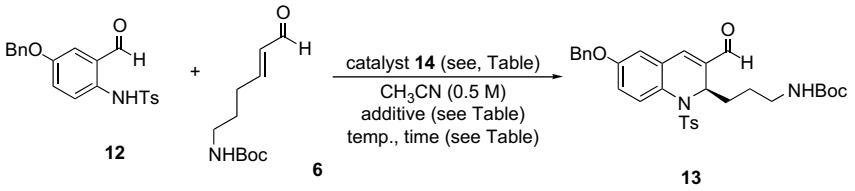


Entry	Catalyst	Solvent	Time (h)	Yield (%)	ee (%)
1[a]	**14**	$ClCH_2CH_2Cl$	20.5	Quant.	0.3
2	**14**	$ClCH_2CH_2Cl$	37	Quant.	86.0
3[b]	**14**	$CHCl_3$	39	NR	—
4[c]	**14**	$CHCl_3$	39	NR	—
5	**14**	CPME	20	91.6	90.9
6	**14**	CH_2Cl_2	20	86.6	90.0
7	**14**	$CHCl_3$	24	71.1	92.6
8	**14**	Toluene	24	63.2	92.9
9	**14**	CH_3CN	24	94.2	91.6
10[d]	**14**	CH_3CN	24	Quant.	90.9
11[e]	**14**	CH_3CN	24	93.0	80.7
12[f]	**14**	CH_3CN	2	Quant.	89.0
13	**15**	CPME	37.5	72.5	2.8
14	**16**	$CHCl_3$	24	NR	—
15	**17**	$CHCl_3$	36	Quant.	32
16	**18**	$CHCl_3$	36	Quant.	15



[a] The *tert*-butyldimethylsilyl ether derivative was used instead of the benzyl ether **12**.
[b] The *N*-*tert*-butoxylcarbonyl derivative was used instead of **12**.
[c] The *N*-benzyloxycarbonyl derivative was used instead of **12**.
[d] Without MS4A.
[e] Without NaOAc.
[f] Without NaOAc and MS4A.

Table 2
Reaction conditions of asymmetric tandem Michael–aldol reaction



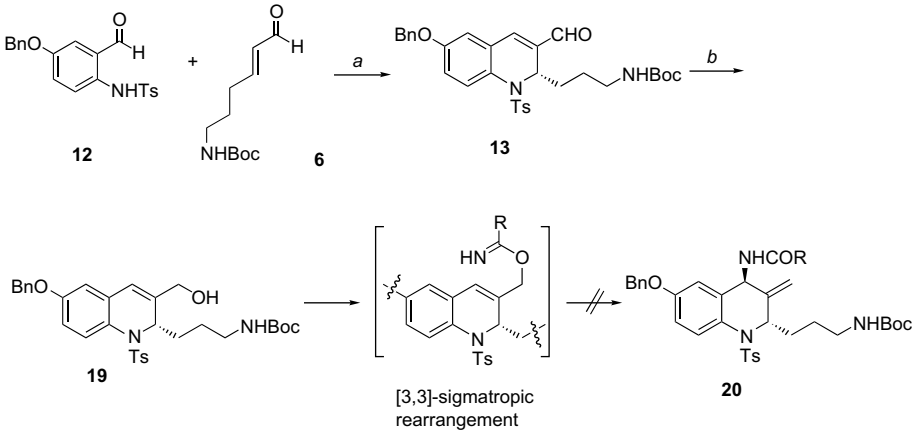
Entry	Catalyst (mol %)	**6** (equiv)	Additive (mol %)	Conditions	Yield (%)	ee (%)
1	20	3	—	4 °C, 24 h	96.6	96.0
2	10	3	—	4 °C, 24 h	94.5	95.6
3	5	3	—	4 °C, 24 h	Quant.	92.7
4	3	3	—	4 °C, 24 h	Quant.	90.6
5	3	3	AcOH (3)	4 °C, 24 h	73.8	95.4
6	5	1	—	−20 °C, 24 h	36.6	96.9
7	5	1	AcOH (5)	−20 °C, 24 h	63.6	96.7
8	5	2	—	−20 °C, 24 h	59.3	97.2
9	5	2	AcOH (5)	−20 °C, 24 h	91.6	97.9
10	5	3	—	−20 °C, 24 h	82.9	97.7
11	5	3	AcOH (5)	−20 °C, 24 h	88.5	97.8

86.0% ee (entry 2). The sulfonamide proved to be an excellent Michael donor for this reaction. The use of the urethane-type protecting groups, *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (*Z*), resulted in no reactions (entries 3 and 4).

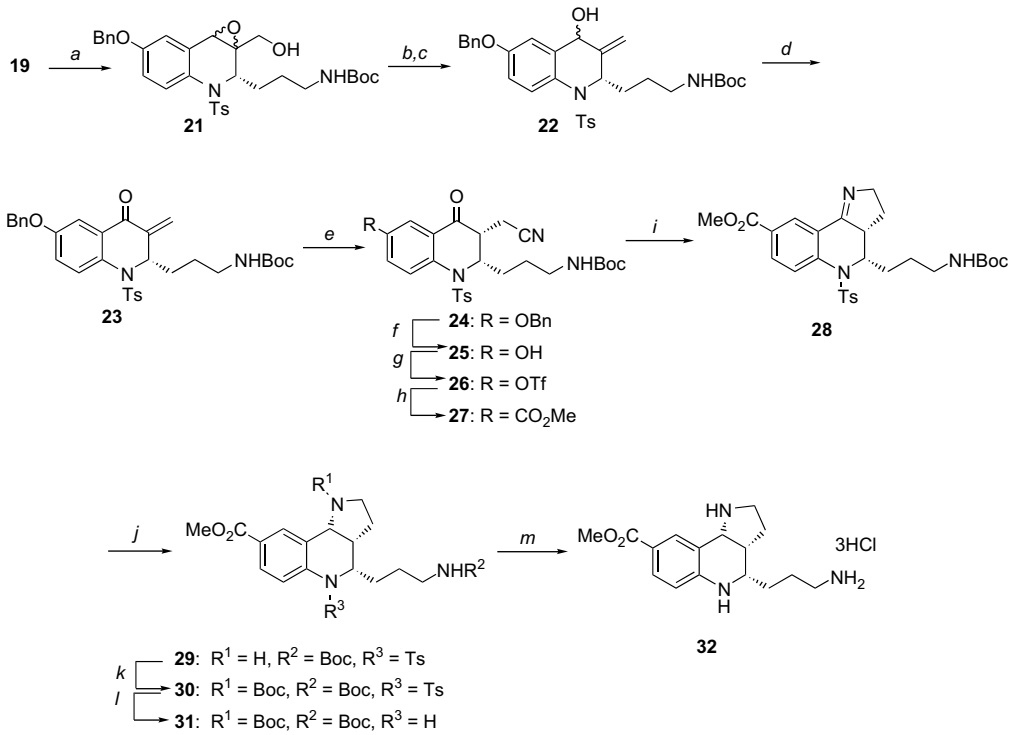
As for the effects of the solvent, acetonitrile was the most suitable for this reaction regarding the yield and enantioselectivity (entry 9). In contrast to the reported procedure, the presence of MS4A indicated a negative effect on the chemical yield (entry 10), while NaOAc had no effect on the yield and enantioselectivity (entry 11). Furthermore, the optimized condition without NaOAc and MS4A afforded a quantitative yield and 89% ee (entry 12). Finally, we briefly examined the use of other organocatalysts **15**–**18** in these asymmetric Michael–aldol reactions (entries 13–16). Interestingly, the rubidium salts[13] of (*S*)-proline and (*S*)-hydroxymethylproline[14] were excellent catalysts for the reaction and produced the opposite enantiomer as the major product, but gave low enantioselectivities (entries 15 and 16).

In order to further enhance the enantioselectivity, we fine tuned the reaction as shown in Table 2. We were pleased to find that the enantioselectivity was improved when the reaction was performed at 4 °C (entry 1). We next examined the catalyst amount. When the catalyst loading was decreased to 3 mol %, the reactivity remained constant, but the enantioselectivity was affected (entry 4). We employed a 5 mol % catalyst and examined the amount of the Michael acceptor **6** in the reaction at −20 °C. In the presence of 1 equiv of **6**, the reaction was extremely slow and, even after 24 h, incomplete (entry 6). In our efforts to overcome the defect, addition of acetic acid was found to improve the chemical yield without any loss of enantioselectivity. However, an excess amount of **6** was essential for complete reaction. Careful experiments revealed that **6** has a tendency to undergo an intramolecular cyclization that produces a pyrrolidine derivative. Finally, the reaction using **12** (1 equiv) and **6** (2 equiv) in the presence of the catalyst **14** (5 mol %) and acetic acid (5 mol %) in CH_3CN at −20 °C for 24 h afforded the product **13** in 91.6% yield and 97.9% ee (entry 9).

With these encouraging results in hand, we applied this reaction to the synthesis of the martinelline chiral core **3**. The tandem Michael–aldol reaction using the (*R*)-catalyst **14** on a preparative scale gave the (*S*)-product **13** in quantitative yield and 95.7% ee, which was reduced with sodium borohydride in the presence of ceric chloride to afford the allyl alcohol **19** (Scheme 3). We first attempted several methods for introduction of the nitrogen function at C4 of the 1,2-dihydroquinoline skeleton, as it was postulated that the synthesis through a [3,3]-sigmatropic rearrangement, such as the Overman rearrangement[15] or an allyl cyanate-to-isocyanate rearrangement,[16] would offer an attractive route to the convenient intermediate **20** for the pyrroloquinoline skeleton. However, the reaction did not take place. Therefore, we employed the previous



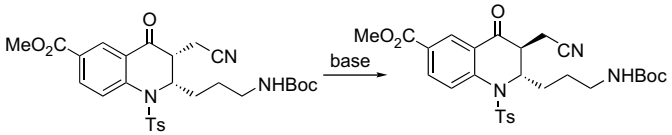
Scheme 3. Reagents and conditions: (a) (*R*)-diphenylprolinol triethylsilyl ether (**14**) (5 mol %), AcOH (5 mol %), CH_3CN (0.5 M), −20 °C, 24 h, quant., 95.7% ee; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 18 h, quant.



Scheme 4. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 45 h, 81.5%, dr 63/37; (b) PPh_3, I_2, imidazole, benzene, rt, 20 min; (c) Zn, AcOH, MeOH, rt, 30 min, 85.2% (two steps), dr 51/49; (d) MnO_2, CH_2Cl_2, rt, 15.5 h, 84.1%; (e) KCN, AcOH, H_2O, EtOH, 50 °C, 40 min, 98.9%, dr >90/10; (f) H_2, Pd/C, EtOAc, rt, 60.5 h, quant., dr 92/8; (g) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt, 1 h 40 min, 71.8%, dr >99/1; (h) CO, $Pd(OAc)_2$, dppp, NEt_3, MeOH, DMF, 70 °C, 2 h, 45.4%; (i) Raney Ni (W-2), EtOH, H_2 (1 atm),50 °C, 24 h; (j) $NaBH_3CN$, MeOH, AcOH (pH 5), 85% (two steps); (k) $(Boc)_2O$ (3.2 equiv), Et_3N (2.8 equiv), rt, 1 h, quant.; (l) Mg (51 equiv), MeOH, rt, 18 h, 97%; (m) 2 M HCl/MeOH (0.015 M), −15 °C, 23 h, 94%.

route (Scheme 4).[2r] The allyl alcohol **19** was transpositioned to the isomeric allyl alcohol **22** in three steps. Thus, epoxidation of **19** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the epoxide **21** with the diastereomeric ratio of 63/37. Iodination of **21** by iodine and triphenyl phosphine in the presence of the imidazole followed by reductive cleavage of the resulting iodoepoxide with zinc in the presence of acetic acid afforded **22** in good yield. The oxidation of **22** with activated manganese dioxide followed by hydrocyanation of the α,β-unsaturated ketone **23** with potassium cyanide/acetic acid provided tetrahydroquinolone **24** in the diastereomeric ratio of >90/10. At this point, we were unaware of the misunderstanding in the stereostructure of **24** as trans because **24** was obtained as almost a single isomer and the analysis of its ^1H NMR spectrum was difficult. Therefore, we had no reason to suspect the exclusive formation of the trans isomer. Consequently, the synthesis was continued to the *epi*-pyrroloquinoline **32**. Thus, the conversion of **24** to **27** by the introduction of an ester function at the phenolic function was carried out by the following three steps. The hydrogenolysis of **24** with palladium/carbon and hydrogen followed by trifluoromethanesulfonylation of the resulting phenol **25** with triflic anhydride provided the triflate **26**, which was subjected to the palladium-catalyzed methoxycarbonylation[17] using $Pd(OAc)_2$–1,3-bis(diphenylphosphino)propane (dppp) and triethylamine in the presence of carbon monoxide in methanol/dimethylformamide to produce the ester **27**.

Table 3
Attempts of epimerization



27 *cis*/*trans* = 92/8 **33**

Entry	Base (equiv)	Conditions	Ratio of cis/trans
1	DBU (1)	CH_2Cl_2, rt, 12 h	82/18
2	DBU (1)	MeOH, rt, 22 h	82/18
3	K_2CO_3 (1.24)	MeOH, rt, 22 h	73/27
4	K_2CO_3 (14)	MeOH, rt, 22 h	78/22
5	CS_2CO_3 (1.5)	MeOH, rt, 22 h	72/28
6	LDA (2.1)	THF, -78 °C, 2 h	90/10
7	(*S*)-Pro (1.8)	Aqueous DMF, rt, 24 h	NR
8	(*R*)-Pro (1.8)	Aqueous DMF, rt, 24 h	NR

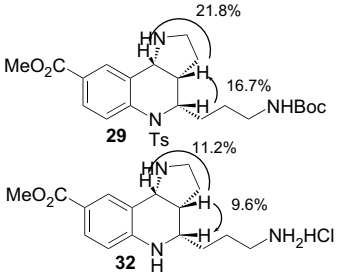


Figure 2. NOE analysis of **29** and **32**.

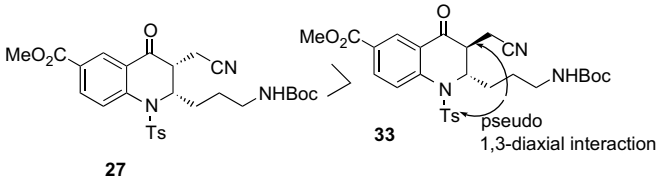
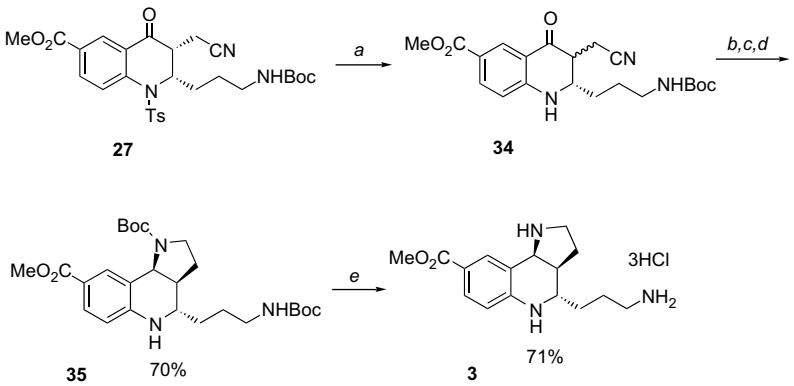


Figure 3.



Scheme 5. Reagents and conditions: (a) Na (10 equiv), naphthalene (10 equiv), DME, −78 °C, 1.5 h, 40%, dr 57/43; (b) Raney Ni (W-2), EtOH, H_2 (1 atm), 50 °C, 29 h; (c) $NaBH_3CN$ (3.1 equiv), AcOH (pH 4), MeOH, rt, 3 h; (d) $(Boc)_2O$ (1.3 equiv), $NaHCO_3$ (5.2 equiv), dioxane/H_2O (1/2), 0 °C to rt, 42 h, 70% (three steps); (e) 2 M HCl/MeOH, −15 °C to rt, 14 h, 71%.

The hydrogenation of **27** with Raney nickel in the presence of hydrogen in ethanol at 50 °C for 24 h proceeded with cyclization to produce the pyrroloquinoline imine **28**, which without any purification was reduced with sodium cyanoborohydride to afford the pyrroloquinoline **29** as a single isomer in 85% yield in two steps. After protection of the pyrrolidine nitrogen for purification, sequential deprotection of the *N*-toluenesulfonyl group and two *tert*-butoxycarbonyl groups in **30** furnished the 3-*epi*-core structure **32**. However, the spectroscopic data of **32** was not identical to the reported value of **3**. In an effort to determine the stereostructure of **32**, we carried out NOE experiments as shown in Figure 2. The relative stereochemistry of **29** and **32** at the C2, C3, and C4 was confirmed to be all cis. Accordingly, it proved that the hydrocyanation of **23** exclusively produced the cis product **24** and the subsequent cyclization of **27** with Raney nickel took place without isomerization of the stereocenters. We expected that the *cis*-**24** might be generated by the kinetic protonation of the enolate intermediate in the hydrocyanation reaction and might be thermodynamically unstable. Therefore, we attempted the base-catalyzed isomerization of *cis*-**27** to *trans*-**33** (Table 3). However, the *cis*-**27** was found to be unexpectedly stable under basic conditions. In addition, we were unable to obtain the *trans*-**33** as a pure diastereomer because both diastereomers are inseparable by column chromatography. The consideration using a molecular model suggested that the exclusive cis preference arising from the hydrocyanation of **23** can be ascribed to the pseudo 1,3-diaxial interaction between the bulky *N*-toluenesulfonyl group and 3-cyanomethyl one (Fig. 3). Therefore, we decided to carry out the cyclization reaction after removal of the *N*-protecting group. The deprotection of **27** with sodium/naphthalene yielded the tetrahydroquinolone **34** in 40% yield with the diastereomeric ratio of 57/43 (Scheme 5). Indeed, the ratio was somewhat improved, but still unsatisfactory. In addition, the reaction had a moderate yield due to generating an overreduced side product. However, the hydrogenation of **34** with Raney nickel and hydrogen followed by N-protection furnished the desired pyrroloquinoline **35** as almost a single isomer in 70% yield. This preferential trans formation during the hydrogenation contrasts the cis preference in the hydrocyanation reaction of **19**, indicating that their stereoselectivities are highly dependent on the nature of the substituent at N. The fact indicates that, in the absence of the *N*-toluenesulfonyl group at N, the reaction takes place with the isomerization of the 3-cyanomethyl group for preventing the torsional strain between the 2-(3-*tert*-butoxycarbonylaminopropyl) group and the pyrroline ring (Fig. 4). Exposure of **35** to 2 M hydrochloric acid afforded the martinelline chiral core **3** in 71% yield, of which the spectroscopic data were identical with the reported value of **3**. This synthesis represents the first enantioselective synthesis of the martinelline chiral core **3** and the formal total syntheses of martinellic acid and martinelline.

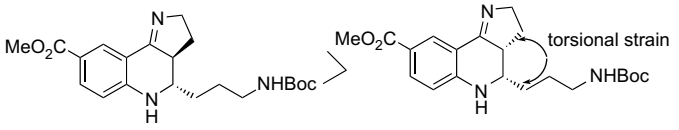
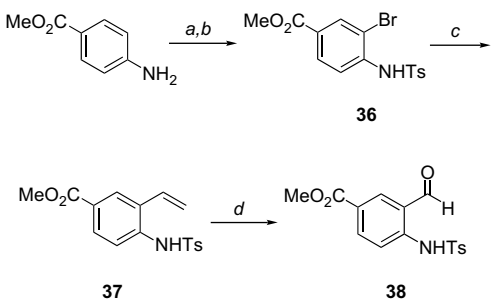


Figure 4.

The above synthesis required the introduction of the C-1 unit on the aromatic nucleus. Therefore, a more straightforward route was pursued by employing the 4-methxoycarbonylanthranilaldehyde derivative **38** as the starting material. The preparation of **38** was carried out by the slight modification of the known procedure (Scheme 6).[2g] The *p*-aminobenzoic acid methyl ester was protected with toluenesulfonyl chloride and pyridine and then reacted with bromine in the presence of sodium acetate in acetic acid, yielding **36** in 95% yield. The Stille coupling of **36** with tributyl(vinyl)tin followed by ozonization of the resulting styrene derivative **37** afforded the 4-methoxycarbonylanthranilaldehyde **38**.

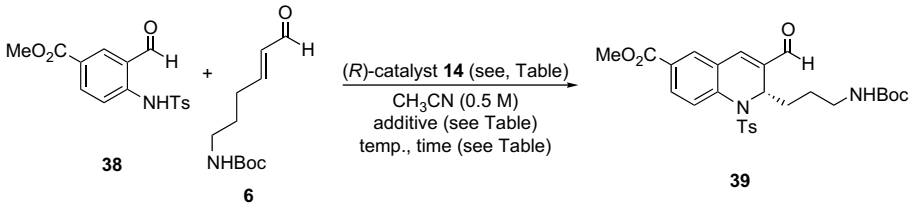
We briefly examined the conditions of the asymmetric tandem Michael–aldol reaction using **38** (Table 4). The use of the Boc derivative instead of **38** was inadequate for this reaction (entry 1) and the presence of NaOAc was not necessary (entry 3). The reaction was sensitive to the catalyst amount. Finally, a 20% catalyst was essential for a satisfactory yield and enantioselectivity (entry 3). Thus, the reaction of **38** (1 equiv) with **6** (3 equiv) using the (*R*)-catalyst **14** (20 mol %) in acetonitrile at −20 °C for 24 h furnished the (*S*)-1,2-dihydroquinoline **39** in quantitative yield and 99% ee.

The reduction of **39** with sodium borohydride/ceric chloride followed by epoxidation of the allyl alcohol **40** with *m*-CPBA provided the epoxide **41** in quantitative yield with a diastereomeric ratio of 75/25 to 86/14 (Scheme 7). After the iodination of **41**, the



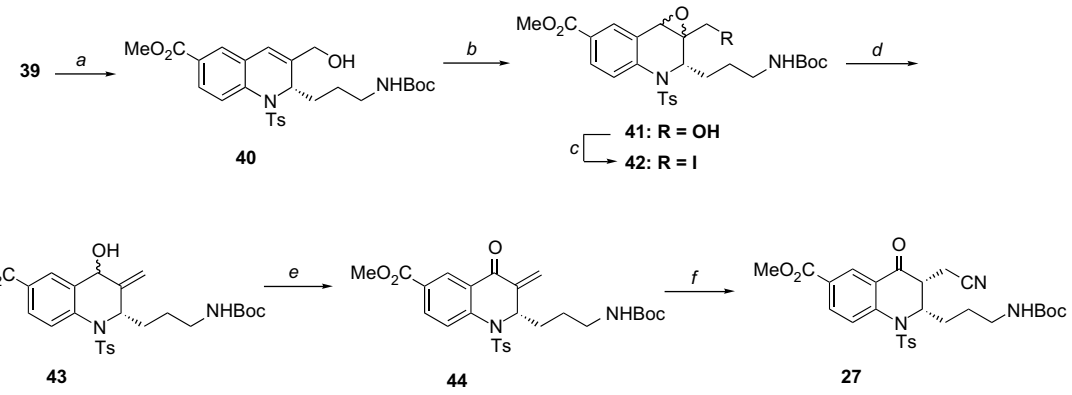
Scheme 6. Reagents and conditions: (a) TsCl, pyridine, 0 °C to rt, 37 h; (b) Br_2, AcONa, AcOH, rt, 24 h, 95% (two steps); (c) tributyl(vinyl)tin, BHT, $(PPh_3)_4Pd$ (5 mol %), toluene, reflux, 5.5 h, 72%; (d) O_3, CH_2Cl_2, −78 °C, 4.5 h, then $(CH_3)_2S$, 92%.

Table 4
Asymmetric tandem Michael–aldol reaction using (*R*)-diphenylprolinol triethylsilyl ether



Entry	Catalyst (mol %)	Additive	Conditions	Yield (%)	ee (%)
1[a,b]	23	NaOAc (0.56 equiv.)	rt, 43.5 h	NR	—
2[b]	20	NaOAc (0.56 equiv.)	rt, 43.5 h	Quant.	87
3	20	—	−20 °C, 24 h	Quant.	99
4	5	—	4 °C, 24 h	38	97
5	5	AcOH (5 mol %)	4 °C, 24 h	77	96

[a] The *N*-*tert*-butoxycarbonyl derivative was used instead of **38**.
[b] The (*S*)-catalyst **14** was used.



Scheme 7. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C to rt, 18 h, quant.; (b) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 45 h, quant., dr 75/25 to 86/14; (c) PPh_3, I_2, imidazole, benzene, rt, 20 min; (d) Zn, AcOH, MeOH, rt, 30 min, 91% (two steps) dr 80/20; (e) MnO_2, CH_2Cl_2, rt, 15.5 h, quant.; (f) KCN, AcOH, EtOH/H_2O (10/1), 0 °C, 40 min, 90%, dr 94/6.

treatment of the iodide **42** with zinc/acetic acid caused ring cleavage to give the allyl alcohol **43** in 91% yield (two steps). The oxidation of **43** with activated manganese dioxide followed by hydrocyanation of the resulting α,β-unsaturated ketone **44** furnished the quinolone **27** in 90% yield with a diastereomeric ratio of 94/6. This route is more efficient for the enantioselectivity and chemical yield than that described above.

3. Conclusion

In conclusion, we have achieved the first catalytic enantioselective synthesis of the martinelline chiral core **3** using the asymmetric tandem Michael–aldol reaction, which represents the formal total synthesis of martinellic acid and martinelline. In addition, we have also synthesized the diastereomer **32** of **3**. Using the synthetic routes to these pyrroloquinoline chiral cores, all of the martinelline diastereomers will be available for studies of these biological activities.

4. Experimental

4.1. General

Melting points were measured with a SIBATA NEL-270 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO P-1020 polarimeter with a sodium lamp (589 nm). Infrared spectra were recorded on a SIMADZU FT IR-8100 JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM-GSX-400A and JNM-ECP-400 spectrometers with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were measured on a JMX-AX-500 spectrometer. Column chromatography was performed with silica gel BW-820MH or BW-200 (Fuji Davison Co.). HPLC analyses were carried out on the chiral column indicated in each experiment. All commercially available reagents were used as-received.

4.2. *N*-*tert*-Butoxycarbonyl-2-hydroxypyrrolidine (9)

To a stirred solution of pyrrolidinone **7** (52 mL, 0.686 mol) in CH_3CN (1.3 L) at room temperature were added di-*tert*-butyl dicarbonate (Boc_2O) (180 g, 0.823 mol) and DMAP (8.4 g, 68.6 mmol) and the reaction mixture was stirred for 2 h. After removal of volatiles in vacuo, the residue was diluted with EtOAc and the solution was washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give *N*-*tert*-butoxycarbonylpyrrolidinone **8** (128.1 g, 99.6%) as a yellow oil, which was used for next reaction.

To a stirred solution of **8** (23.6 g, 127 mmol) in THF (635 mL) at −78 °C under an argon atmosphere was added dropwise a 1.0 M solution of DIBALH (183 mL, 190 mmol) and the reaction mixture was stirred for 1 h. The reaction was quenched with saturated potassium acetate solution at −78 °C. The mixture was transferred to the flask containing saturated aqueous NH_4Cl and ether. The

mixture was allowed to warm to room temperature and stirred until thick white gel was formed. Then the mixture was filtered through a Celite pad. The mixture was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous NH_4Cl, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give the title compound **9** (24.7 g, quant.) as a colorless oil: ^{1}N NMR ($CDCl_3$) δ 1.47 (9H, s), 1.78–2.10 (4H, m), 3.46–3.56 (2H, m), 5.47 (1H, br).

4.3. Ethyl 6-*tert*-butoxycarbonylaminohex-2-enate (10)

To a stirred solution of **9** (38.1 g, 0.203 mol) in toluene (1.0 L) was added ethoxycarbonylmethylenephosphorane (81.7 g, 0.244 mol) and the reaction mixture was stirred at 100 °C for 13 h. The reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/1) to give **10** (51.7 g, 99%) as a yellow oil: IR (neat) 3372, 2978, 2934, 1714, 1519, 1268, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, t, *J*=7.1 Hz), 1.44 (9H, s), 1.65 (2H, tt, *J*=7.1, 7.3 Hz), 2.23 (2H, dt, *J*=7.1, 8.1 Hz), 3.12–3.15 (2H, m), 4.18 (2H, q, *J*=7.1 Hz), 5.83 (1H, dt, *J*=1.7, 15.6 Hz), 6.94 (1H, dt, *J*=7.0, 15.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 28.3, 28.4, 29.3, 39.9, 60.1, 79.1, 121.8, 147.9, 155.8, 166.4; HRMS (FAB, NBA) calcd for $C_{13}H_{24}NO_4$ 258.1706 ($M+H^+$), found 258.1697.

4.4. *tert*-Butyl (6-hydroxyhex-4-enyl)carbamate (11)

To a stirred solution of **10** (839 mg, 3.22 mmol) in CH_2Cl_2 (13 mL) at −78 °C under an argon atmosphere was added dropwise a 1.0 M solution of DIBALH (6.6 mL, 6.6 mmol) and the reaction mixture was stirred for 1 h. The reaction was quenched with saturated aqueous potassium acetate at −78 °C. The mixture was transferred to a flask containing saturated aqueous NH_4Cl and ether. The mixture was allowed to warm to room temperature and stirred until thick white gel was formed. The mixture was filtered through a Celite pad. The filtrate was separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with saturated aqueous NH_4Cl, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/1) to give **11** (526 mg, 76%) as a colorless oil: IR (neat) 3353, 2975, 2930, 1688, 1526, 1179 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 1.57 (2H, tt, *J*=7.3, 7.3 Hz), 2.10 (2H, dt, *J*=5.7, 7.5 Hz), 3.10–3.14 (2H, m), 4.08 (2H, d, *J*=4.2 Hz), 5.62–5.72 (2H, m); ^{13}C NMR ($CDCl_3$) δ 28.4, 29.3, 39.6, 39.9, 63.6, 79.2, 129.8, 132.0, 155.9; HRMS (FAB, NBA) calcd for $C_{11}H_{22}NO_3$ 216.1600 ($M+H^+$), found 216.1612.

4.5. *tert*-Butyl (6-oxohex-4-enyl)carbamate (6)

To a stirred solution of **11** (514 mg, 2.38 mmol) in CH_2Cl_2 (12 mL) at room temperature was added activated MnO_2 (2.57 g) and the reaction mixture was stirred for 12 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/1) to give **6** (466 mg, 92%) as a colorless oil: IR (neat) 3355, 2976, 2933, 1694, 1519, 1250, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 1.71 (2H, tt, *J*=7.1, 7.1 Hz), 2.38 (2H, dt, *J*=6.8, 8.4 Hz), 3.15–3.20 (2H, m), 6.14 (1H, ddt, *J*=1.5, 7.9, 15.6 Hz), 6.85 (1H, dt, *J*=6.8, 15.5 Hz), 9.52 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 28.2, 29.8, 39.8, 52.2, 79.2, 133.1, 155.9, 157.4, 193.8; HRMS (FAB, NBA) calcd for $C_{11}H_{20}NO_3$ 214.1443 ($M+H^+$), found 214.1436.

4.6. (2*S*)-6-Benzyloxy-2-(3-*tert*-butoxycarbonylaminopropyl)-3-formyl-1-(toluene-4-sulfonyl)-1,2-dihydroquinoline (13)

To a stirred solution of **6** (8.5 g, 0.04 mol) and (*R*)-catalyst **14** (370 mg, 1.0 mmol) in CH_3CN (40 mL) and AcOH (23 μL, 0.4 mmol) at −20 °C was added **12** (7.6 g, 0.02 mol). After stirring the mixture at −20 °C for 24 h under an argon atmosphere, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **13** (11.7 g, quant., 95.7% ee) as yellow amorphous powder: $[\alpha]_D^{26}$ +207.0 (*c* 0.660, $CHCl_3$, 95.9% ee); IR (neat) 3985, 3943, 3864, 3805, 3773, 3751, 3734, 3677, 3657, 3619, 3569, 3404, 2928, 1671, 1599, 1567, 1488, 1364, 1268, 1223, 1162, 1088, 1017, 861, 813, 739, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.41 (11H, m), 1.55–1.72 (2H, m), 2.31 (3H, s), 3.12 (2H, dt, *J*=6.8, 6.8 Hz), 4.56 (1H, br), 5.09 (2H, s), 5.19 (1H, dd, *J*=4.4, 9.7 Hz), 6.61 (1H, s), 6.78 (1H, d, *J*=2.8 Hz), 7.02 (2H, d, *J*=8.6 Hz), 7.11 (1H, dd, *J*=2.9, 9.0 Hz), 7.16 (2H, d, *J*=8.2 Hz), 7.34–7.46 (5H, m), 7.72 (1H, d, *J*=8.8 Hz), 9.12 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 21.4, 25.7, 28.3, 28.4, 29.1, 39.7, 51.9, 70.4, 114.2, 118.0, 126.8, 127.5, 127.6, 128.2, 129.1, 135.3, 136.2, 139.0, 139.5, 143.6, 155.9, 157.4, 189.5; HRMS (FAB, NBA) calcd for $C_{32}H_{36}N_2O_6S$ 576.2294 (M^+), found 576.2298. HPLC analysis: CHIRALCEL AD-H, (*n*-hexane/*i*-PrOH=80/20, 1.0 mL/min), t_R=17.7 min (major) and 23.6 min (minor).

4.7. (2*S*)-6-Benzyloxy-2-(3-*tert*-butoxycarbonylaminopropyl)-3-hydroxymethyl-1-(toluene-4-sulfonyl)-1,2-dihydroquinoline (19)

To a stirred solution of **13** (1.05 g, 1.8 mmol) and $CeCl_3 \cdot 7H_2O$ (1.01 g, 2.7 mmol) in MeOH (9.1 mL) was added $NaBH_4$ (137 mg, 3.6 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with 1 M $KHSO_4$ and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1 to 1/1) to give dihydroquinoline **19** (1.05 g, quant.) as white amorphous powder: $[\alpha]_D^{24}$ +5.67 (*c* 1.04, $CHCl_3$, 95.9% ee); IR (neat) 3866, 3750, 3650, 3394, 2976, 2929, 1685, 1601, 1573, 1490, 1454, 1365, 1341, 1269, 1222, 1161, 1089, 1020, 895, 812, 750, 684, 655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.30 (1H, m), 1.40–1.49 (1H, m), 1.44 (9H, s), 1.80–1.90 (1H, m), 2.33 (3H, s), 2.88 (1H, br), 3.07 (1H, dq, *J*=5.2, 14.4 Hz), 3.50–3.61 (1H, br), 3.89 (1H, dd, *J*=4.4, 13.9 Hz), 3.98 (1H, dd, *J*=4.8, 13.6 Hz), 4.64 (1H, br), 4.97 (1H, d, *J*=10.1 Hz), 5.04 (2H, s), 5.78 (1H, s), 6.54 (1H, d, *J*=2.8 Hz), 6.91 (1H, dd, *J*=2.9, 8.8 Hz), 7.07 (2H, d, *J*=8.1 Hz), 7.29–7.45 (7H, m), 7.65 (1H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.7, 27.0, 28.4, 38.5, 54.1, 63.2, 70.2, 79.4, 112.2, 113.8, 119.3, 124.9, 127.2, 127.5, 128.0, 128.6, 128.8, 129.0, 130.2, 135.7, 136.6, 141.9, 143.2, 156.8, 157.3; HRMS (FAB, NBA) calcd for $C_{32}H_{38}N_2O_6S$ 578.2451 (M^+), found 578.2433.

4.8. {3-[6-Benzyloxy-1a-hydroxymethyl-3-(toluene-4-sulfonyl)-1a,2,3,7b-tetrahydro-1-oxa-3-aza-cyclopropa[*a*]naphthalen-2-yl]-propyl}-carbamic acid *tert*-butyl ester (21)

To a stirred solution of **19** (7.09 g, 12 mmol) in CH_2Cl_2 (49 mL) at 0 °C was added *m*-CPBA (4.53 g, 18 mmol) and the reaction mixture was stirred at room temperature for 45 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 and extracted with EtOAc. The organic layer was washed three times with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/1) to give **21** (5.94 g, 81.5%, dr 63/37) as yellow

amorphous powder: $[\alpha]_D^{24}$ −58.4 (*c* 0.525, $CHCl_3$, 95.9% ee, dr: 54/46); IR (neat) 3403, 2929, 1685, 1608, 1496, 1454, 1365, 1340, 1247, 1159, 1089, 1019, 892, 851, 812, 749, 678, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01–1.08 (1H, m), 1.43 (9H, s), 1.57–1.65 (2H, m), 1.77–1.80 (1H, m), 2.34 (3H, s), 3.09 (1H, dd, *J*=5.4, 15.4 Hz), 3.43 (1H, d, *J*=12.9 Hz), 3.47 (1H, s), 4.07 (1H, d, *J*=12.9 Hz), 4.72 (1H, br), 4.89 (1H, d, *J*=11.2 Hz), 5.03 (2H, s), 6.84 (1H, d, *J*=2.9 Hz), 6.97 (1H, dd, *J*=2.9, 8.8 Hz), 7.15 (2H, d, *J*=8.3 Hz), 7.33–7.45 (7H, m), 7.74 (1H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 25.2, 26.7, 28.4, 38.7, 52.4, 53.8, 59.4, 62.0, 70.2, 79.4, 115.3, 115.5, 116.1, 126.1, 127.4, 127.5, 127.5, 127.8, 128.1, 128.2, 128.6, 128.8, 129.5, 135.4, 135.5, 136.3, 136.4, 143.0, 156.6, 156.7, 157.6; HRMS (FAB, NBA) calcd for $C_{32}H_{38}N_2O_7S$ 594.2400 (M^+), found 594.2396.

4.9. (2*S*)-6-Benzyloxy-2-(3-*tert*-butoxycarbonylaminopropyl)-4-hydroxy-3-methylene-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline (22)

To a stirred solution of **21** (472 mg, 0.79 mmol, dr 54/46) in benzene (3.2 mL) at room temperature were added imidazole (135.2 mg, 1.98 mmol), triphenyl phosphine (520 mg, 1.98 mmol), and iodine (402 mg, 1.59 mmol), and the reaction mixture was stirred at room temperature for 20 min. The reaction mixture was quenched with saturated aqueous Na_2SO_3 and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo.

Activated Zn (415 mg, 6.35 mmol) was added to a stirred solution of the above residue in MeOH (4.0 mL) and AcOH (0.4 mL) at room temperature, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with EtOAc and washed with 0.5 M $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **22** (391 mg, 85.2%, dr 51/49) as yellow amorphous powder: $[\alpha]_D^{25}$ −48.9 ($CHCl_3$, *c* 0.555, 95.9% ee, dr 51/49); IR (neat) 3403, 2929, 1685, 1606, 1491, 1454, 1342, 1249, 1157, 1089, 1019, 813, 749, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s), 1.44–1.63 (4H, m), 2.35 (3H, s), 3.08–3.14 (2H, m), 4.47 (1H, br), 4.76–4.86 (1H, m), 4.99 (1H, d, *J*=2.6 Hz), 5.04 (1H, s), 5.07 (2H, s), 6.97–7.01 (2H, m), 7.14 (2H, d, *J*=7.9 Hz), 7.27 (2H, d, *J*=8.2 Hz), 7.34–7.48 (5H, m), 7.62 (1H, d, *J*=8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.5, 28.4, 30.4, 32.8, 39.7, 58.7, 62.6, 66.3, 67.0, 70.2, 79.1, 113.9, 114.6, 115.9, 125.8, 127.0, 127.3, 127.6, 128.1, 128.1, 128.3, 128.6, 128.8, 129.0, 129.3, 129.6, 134.8, 135.0, 135.8, 136.5, 136.6, 143.1, 143.5, 143.7, 157.6, 157.9; HRMS (FAB, NBA) calcd for $C_{32}H_{38}N_2O_6S$ 578.2451 (M^+), found 578.2446.

4.10. (2*S*)-6-Benzyloxy-2-(3-*tert*-butoxylcarbonyl aminopropyl)-3-methylene-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-3-one (23)

To a stirred solution of **22** (2.60 g, 4.49 mmol) in CH_2Cl_2 (22.5 mL) at room temperature was added activated MnO_2 (18.2 g) and the reaction mixture was stirred for 15.5 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **23** (2.18 g, 84.1%) as yellow amorphous powder: $[\alpha]_D^{26}$ +113.2 (*c* 0.650, $CHCl_3$, 95.9% ee); IR (neat) 3650, 3420, 2976, 1682, 1602, 1485, 1432, 1352, 1247, 1162, 1089, 1004, 811, 751, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.37–1.46 (1H, m), 1.59–1.69 (3H, m), 2.33 (3H, s), 3.07–3.22 (2H, m), 4.51 (1H, br), 5.03–5.06 (1H, m), 5.11 (2H, ABq, *J*=11.4, 15.2 Hz), 5.27 (1H, s), 5.96 (1H, s), 7.08 (2H, d, *J*=8.2 Hz), 7.24 (2H, d, *J*=8.2 Hz), 7.29 (1H, dd, *J*=3.3, 9.0 Hz), 7.35–7.47 (6H, m), 7.74 (1H, d, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 26.5, 28.2, 32.1, 39.2, 60.6, 70.3, 78.9, 111.1, 122.7, 124.2, 127.5, 127.6, 128.1, 128.5, 128.9, 129.4, 129.9, 132.7, 134.1, 136.0, 141.0, 144.0, 155.8, 157.5, 181.3; HRMS (FAB, NBA) calcd for $C_{32}H_{36}N_2O_6S$ 576.2294 (M^+), found 576.2329.

4.11. (2*S*,3*R*)-6-Benzyloxy-2-(3-*tert*-butoxylcarbonyl aminopropyl)-3-cyanomethyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-4-one (24)

To a stirred solution of **23** (2.02 g, 3.5 mmol) in EtOH (17.5 mL) at room temperature were added KCN (0.48 g) in H_2O (1.75 mL) and AcOH (0.3 mL, 5.2 mmol) and the reaction mixture was stirred at 50 °C for 40 min. The reaction mixture was concentrated in vacuo. The residue was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **24** (2.09 g, 98.9%, dr >90/10) as yellow amorphous powder: $[\alpha]_D^{25}$ +48.0 (*c* 0.550, $CHCl_3$, 95.9% ee, dr >90/10); IR (neat) 3404, 2976, 1691, 1605, 1487, 1432, 1355, 1245, 1161, 1087, 1020, 815, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26–1.32 (1H, m), 1.38–1.48 (1H, m), 1.41 (9H, s), 1.66 (2H, dt, *J*=8.1, 13.4 Hz), 2.26 (1H, dd, *J*=9.2, 17.6 Hz), 2.41 (3H, s), 2.53 (1H, dt, *J*=4.9, 9.7 Hz), 2.86 (1H, dd, *J*=4.8, 17.8 Hz), 3.04–3.12 (1H, m), 3.15–3.20 (1H, m), 4.51 (1H, br), 4.80 (1H, dt, *J*=3.8, 12.8 Hz), 5.08 (2H, s), 7.24–7.30 (3H, m), 7.33–7.45 (6H, m), 7.60 (2H, d, *J*=8.2 Hz), 7.91 (1H, d, *J*=9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.5, 23.0, 26.5, 28.2, 39.1, 44.8, 58.5, 70.3, 79.0, 110.5, 117.2, 123.7, 125.1, 126.7, 127.1, 127.5, 128.1, 128.2, 128.6, 130.0, 130.3, 132.4, 135.9, 136.3, 144.8, 156.0, 156.6, 190.8; HRMS (FAB, NBA) calcd for $C_{33}H_{37}N_3O_6S$ 603.2403 (M^+), found 603.2431.

4.12. (2*S*,3*R*)-2-(3-*tert*-Butoxylcarbonylaminopropyl)-3-cyanomethyl-6-hydroxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinolin-4-one (25)

To a stirred solution of **24** (292 mg, 0.48 mmol, dr >90/10) in EtOAc (2.4 mL) at room temperature was added Pd/C (29.2 mg) and the reaction mixture was stirred for 60.5 h under an atmosphere of hydrogen. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1.5/1 to 1/1) to give **25** (255 mg, quant., dr >98/2) as yellow amorphous powder: $[\alpha]_D^{26}$ +79.0 (*c* 0.515, $CHCl_3$, 95.7% ee, dr >92/8); IR (neat) 3865, 3750, 3710, 3374, 2977, 1684, 1609, 1493, 1452, 1352, 1303, 1248, 1160, 1087, 846, 825, 752, 707, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.28 (1H, m), 1.40–1.45 (1H, m), 1.44 (9H, s), 1.55–1.69 (2H, m), 2.30 (1H, dd, *J*=10.1, 17.6 Hz), 2.41 (3H, s), 2.51 (1H, dt, *J*=4.4, 9.5 Hz), 2.85 (1H, dd, *J*=5.3, 17.6 Hz), 3.07–3.18 (2H, m), 4.65 (1H, br), 4.78 (1H, dt, *J*=3.8, 12.5 Hz), 6.60 (1H, br), 7.14 (1H, dd, *J*=3.1, 9.0 Hz), 7.26–7.29 (3H, m), 7.59 (2H, d, *J*=8.4 Hz), 7.84 (1H, d, *J*=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.6, 23.1, 26.6, 28.3, 39.6, 44.8, 58.6, 80.0, 112.3, 117.5, 123.6, 125.3, 126.8, 128.2, 130.4, 131.3, 136.3, 144.9, 155.0, 156.7, 191.0; HRMS (FAB, NBA) calcd for $C_{26}H_{32}N_3O_6S$ 514.2012 ($M+H^+$), found 514.1994.

4.13. (2*S*,3*R*)-2-(3-*tert*-Butoxylcarbonylaminopropyl)-3-cyanomethyl-1-(toluene-4-sulfonyl)-6-(trifluoro-methanesulfonyl)-1,2,3,4-tetrahydroquinolin-4-one (26)

To a stirred solution of **25** (184 mg, 0.36 mmol, dr >92/8) in CH_2Cl_2 (1.8 mL) and pyridine (0.18 mL) at 0 °C was added dropwise triflic anhydride (67 μL, 0.40 mmol) and the reaction mixture was allowed to warm to room temperature for 1 h 40 min. The reaction mixture was diluted with EtOAc, washed with water, 1 M $KHSO_4$, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=3/1) to give **26** (166 mg, 71.8%, dr >99/1) as white

amorphous powder: $[\alpha]_D^{26}$ +44.6 (*c* 0.490, $CHCl_3$, 95.7% ee, dr >99/1); IR (neat) 3905, 3835, 3751, 3677, 3423, 2978, 1698, 1598, 1509, 1476, 1423, 1363, 1248, 1211, 1165, 1135, 1087, 1007, 859, 758, 706, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28–1.33 (1H, m), 1.41 (9H, s), 1.44–1.51 (1H, m), 1.61–1.63 (1H, m), 2.32 (1H, dd, *J*=10.3, 17.9 Hz), 2.44 (3H, s), 2.55 (1H, dt, *J*=5.1, 8.6 Hz), 2.87 (1H, dd, *J*=4.8, 17.8 Hz), 3.03–3.11 (1H, m), 3.17–3.24 (1H, m), 4.53 (1H, br), 4.87 (1H, dt, *J*=3.7, 11.4 Hz), 7.34 (2H, d, *J*=8.1 Hz), 7.53 (1H, dd, *J*=2.9, 9.2 Hz), 7.65 (2H, d, *J*=8.4 Hz), 7.79 (1H, d, *J*=2.9 Hz), 8.14 (1H, d, *J*=9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.6, 23.0, 26.7, 28.2, 38.9, 45.1, 58.4, 79.2, 116.9, 119.8, 120.1, 125.1, 126.9, 128.1, 128.1, 130.6, 135.8, 138.9, 145.6, 146.6, 156.1, 189.4; HRMS (FAB, NBA) calcd for $C_{27}H_{31}F_3N_3O_8S_2$ 646.1505 ($M+H^+$), found 646.1482.

4.14. (2*S*,3*R*)-2-(3-*tert*-Butoxycarbonylaminopropyl)-3-cyanomethyl-4-oxo-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid methyl ester (27)

To a stirred solution of **26** (45.8 mg, 0.071 mmol, dr >99/1) in DMF (0.71 mL) and MeOH (0.35 mL) at room temperature were added $Pd(OAc)_2$ (1.8 mg, 8.0 μmol), dppp (3.0 mg, 7.3 μmol), and Et_3N (0.05 mL, 0.36 mmol), and the reaction mixture was stirred at 70 °C for 2 h under an atmosphere of carbon monoxide. Then, the reaction mixture was cooled to room temperature, diluted with brine, and filtered. The filtrate was diluted with EtOAc, washed with water, 1 M $KHSO_4$, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **27** (17.9 mg, 45.4%, dr >99/1) as a yellow oil: $[\alpha]_D^{20}$ +25.2 (*c* 0.480, $CHCl_3$, dr 95/5); IR (neat) 3376, 2929, 1698, 1608, 1516, 1426, 1363, 1257, 1163, 1086, 1010, 917, 814, 767, 750, 705, 667 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$) δ 1.25–1.68 (4H, m), 1.40 (9H, s), 2.33 (1H, dd, *J*=10.0, 17.6 Hz), 2.42 (3H, s), 2.57 (1H, ddd, *J*=4.8, 4.8, 9.2 Hz), 2.90 (1H, dd, *J*=4.8, 17.2 Hz), 3.05–3.20 (2H, m), 3.94 (3H, s), 4.53 (1H, s), 4.91 (1H, d, *J*=11.2 Hz), 7.30 (2H, d, *J*=8.4 Hz), 7.65 (2H, d, *J*=8.4 Hz), 8.11 (1H, d, *J*=8.8 Hz), 8.26 (1H, dd, *J*=2.0, 8.8 Hz), 8.55 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.7, 23.1, 26.7, 28.3, 39.1, 45.3, 52.5, 58.4, 79.3, 117.1, 123.5, 125.5, 126.9, 127.5, 129.2, 130.6, 136.1×2, 142.8, 145.5, 156.1, 165.4, 190.1; HRMS (FAB, NBA) calcd for $C_{28}H_{34}N_3O_7S$ 556.2117 ($M+H^+$), found 556.2131.

4.15. (3a*S*,4*S*,9b*R*)-4-(3-*tert*-Butoxycarbonylaminopropyl)-5-(toluene-4-sulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic acid methyl ester (29)

To a stirred solution of **27** (83.0 mg, 0.149 mmol, dr 95/5) in EtOH (2.0 mL) at room temperature was added Raney nickel (W-2, 699 mg). After being stirred for 24 h under an atmosphere of hydrogen at 50 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was dissolved in MeOH (1.5 mL) and $NaBH_3CN$ (27.8 mg, 0.442 mmol) was added at room temperature. The resulting mixture was acidified to pH 5 with AcOH and stirred at room temperature for 4.5 h. After the reaction mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2, washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/2 to $CHCl_3$/MeOH=9/1) to give **29** (69.2 mg, dr >98/2, 85%) as a colorless oil: $[\alpha]_D^{19}$ −74.7 (*c* 0.69, $CHCl_3$); IR (neat) 3385, 2929, 1701, 1609, 1513, 1437, 1341, 1267, 1160, 1088, 1037, 917, 813, 747, 707, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–1.00 (1H, m), 1.25 (s, 1H), 1.40 (9H, s), 1.53 (2H, quin, *J*=6.8 Hz), 1.60–1.68 (1H, m), 1.91 (1H, tq, *J*=4.4, 8.8 Hz), 2.26 (1H, br s), 2.38 (3H, s), 2.80 (1H, dt, *J*=8.0, 10.4 Hz), 2.95–3.01 (1H, m), 3.05 (2H, q, *J*=6.4 Hz), 3.41 (1H, d, *J*=8.4 Hz), 3.90 (3H, s), 4.40–4.47 (2H, m), 7.17 (2H, d, *J*=8.4 Hz), 7.45 (2H, d, *J*=8.4 Hz), 7.85 (1H, d, *J*=8.4 Hz), 7.95 (1H, dd, *J*=2.0, 8.8 Hz), 8.09 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.1, 27.2, 28.3, 28.7, 39.6×2, 45.6, 52.1, 55.9, 56.1, 79.0, 126.7, 126.9, 127.6, 128.7, 129.7, 130.2, 133.3, 137.1×2, 143.8, 155.9, 166.5; HRMS (FAB, NBA) calcd for $C_{28}H_{38}N_3O_6S$ 544.2481 ($M+H^+$), found 544.2452.

4.16. (3a*S*,4*S*,9b*R*)-4-(3-*tert*-Butoxycarbonylaminopropyl)-5-(toluene-4-sulfonyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-*tert*-butyl ester 8-methyl ester (30)

To a stirred solution of **29** (69.2 mg, 0.127 mmol) in CH_2Cl_2 (2.0 mL) at room temperature were added Et_3N (50 μL, 0.361 mmol) and Boc_2O (87.8 mg, 0.402 mmol). The solution was stirred at room temperature for 1 h and diluted with EtOAc. The mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **30** (85.1 mg, quant.) as a colorless oil: $[\alpha]_D^{17}$ −13.1 (*c* 0.27, $CHCl_3$); IR (neat) 3368, 2975, 1689, 1609, 1516, 1437, 1391, 1364, 1288, 1254, 1161, 1129, 1091, 990, 909, 858, 815, 768, 730, 708, 692, 658 cm^{-1}; ^1H NMR (400 MHz, 55 °C, $CDCl_3$) δ 1.07–1.17 (2H, m), 1.42 (9H, s), 1.62–1.71 (4H, m), 2.38 (3H, s), 2.96 (1H, br s), 3.08–3.19 (2H, m), 3.30 (2H, d, *J*=8.0 Hz), 3.48 (1H, d, *J*=6.8 Hz), 3.88 (3H, s), 4.51 (1H, br s), 4.61 (1H, br t, *J*=9.6 Hz), 7.19 (2H, d, *J*=8.0 Hz), 7.47 (2H, d, *J*=8.4 Hz), 7.65 (1H, d, *J*=8.0 Hz), 7.80 (1H, s), 7.97 (1H, d, *J*=7.6 Hz); ^{13}C NMR (100 MHz, 55 °C, $CDCl_3$) δ 21.4, 25.6, 27.1, 28.3, 28.4, 29.4, 40.0, 44.6, 45.5, 52.0, 54.3, 55.1, 79.1, 80.0, 126.7, 127.9, 128.7, 128.9, 129.7, 130.0, 134.9, 137.5, 137.7, 143.8, 154.8, 156.0, 166.4; HRMS (FAB, NBA) calcd for $C_{33}H_{46}N_3O_8S$ 644.3006 ($M+H^+$), found 644.2954.

4.17. (3a*R*,4*S*,9b*R*)-4-(3-*tert*-Butoxycarbonylaminopropyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-*tert*-butyl ester 8-methyl ester (31)

To a stirred solution of **30** (70.4 mg, 0.109 mmol) in MeOH (3 mL) at room temperature was added Mg (136 mg, 0.560 mmol) and the mixture was stirred for 18 h. The reaction was quenched with aqueous saturated NH_4Cl. The resulting mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/1) to give **31** (51.5 mg, 97%) as a colorless oil: $[\alpha]_D^{15}$ +82.1 (*c* 0.38, $CHCl_3$); IR (neat) 3345, 2976, 2249, 1672, 1609, 1513, 1435, 1393, 1365, 1329, 1278, 1245, 1213, 1164, 1104, 992, 907, 770, 727 cm^{-1}; ^1H NMR (400 MHz, 55 °C, $CDCl_3$) δ 1.45 (9H, s), 1.49–1.60 (4H, m), 1.85 (2H, t, *J*=9.6 Hz), 2.42 (1H, br s), 3.17 (2H, q, *J*=6.4 Hz), 3.27–3.33 (1H, m), 3.46 (1H, br s), 3.54 (1H, dt, *J*=2.8, 6.4 Hz), 3.81 (3H, s), 4.14 (1H, br s), 4.58 (1H, br s), 5.11 (1H, br s), 6.44 (1H, d, *J*=8.4 Hz), 7.68 (1H, dd, *J*=1.6, 8.4 Hz), 8.29 (1H, s); ^{13}C NMR (100 MHz, 55 °C, $CDCl_3$) δ 21.6, 26.6, 28.4, 28.5, 31.2, 40.6, 41.4, 44.6, 50.9, 51.3, 55.7, 79.4, 80.1, 113.5, 119.8, 121.2, 129.8, 132.4, 147.4, 154.8, 156.1, 167.1; HRMS (FAB, NBA) calcd for $C_{26}H_{39}N_3O_6$ 489.2839 (M+H), found 489.2820.

4.18. (3a*R*,4*S*,9b*R*)-4-(3-Aminopropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3.2-*c*]quinoline-8-carboxylic acid methyl ester (32)

Hydrogen chloride (2 M) in MeOH (6 mL) was added to **31** (44.0 mg, 89.9 μmol) at −15 °C and the reaction mixture was gradually allowed to warm to room temperature. After stirring the mixture for 23 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in H_2O, washed with EtOAc, and concentrated in vacuo to give **32** (33.6 mg, 94%) as a yellow oil: $[\alpha]_D^{16}$

−73.7 (*c* 0.34, MeOH); IR (neat) 3376, 3261, 2947, 2066, 1698, 1607, 1518, 1436, 1322, 1285, 1233, 1195, 1134, 1049, 1018, 986, 940, 880, 838, 769 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.64–1.86 (4H, m), 2.00–2.17 (2H, m), 2.88–2.95 (1H, m), 3.01 (2H, t, *J*=7.2 Hz), 3.25–3.35 (2H, m), 3.47 (1H, dt, *J*=2.8, 6.8 Hz), 3.84 (3H, s), 4.57 (1H, s), 5.05 (d, 1H, *J*=9.2 Hz), 6.80 (1H, d, *J*=8.4 Hz), 7.77 (1H, dd, *J*=1.6, 8.4 Hz), 7.96 (1H, d, *J*=1.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 23.6, 24.8, 30.9, 40.7, 42.3, 45.5, 52.2, 52.3, 58.8, 116.1, 116.2, 120.5, 132.2, 132.7 152.2, 168.2; HRMS (FAB, glycerol) calcd for $C_{16}H_{24}N_3O_2$ 290.1869 ($M+H^+$), found 290.1843.

4.19. (2*S*,3*R*)- and (2*S*,3*S*)-2-(3-*tert*-Butoxycarbonyl aminopropyl)-3-cyanomethyl-4-oxo-1,2,3,4-tetrahydroquino line-6-carboxylic acid methyl ester (34)

A solution of sodium naphthalenide was prepared from sodium (113 mg, 4.89 mmol) and naphthalene (637 mg, 4.97 mmo) in DME (4 mL) by stirring the mixture at −78 °C for 1 h under an argon atmosphere. A solution of **27** (278 mg, 0.500 mmol, dr 94/6) in DME (6 mL) was added dropwise to the solution via cannula over 20 min. After stirring the mixture at −78 °C for 1 h, the reaction mixture was treated with MeOH and allowed to warm to room temperature. The resulting mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc=2/1) to give quinolone **34** (80.2 mg, 40%, dr 57/43) as a yellow oil: $[\alpha]_D^{17}$ −170 (*c* 0.22, $CHCl_3$, dr 57/43); IR (ATR) 3354, 2949, 2249, 1674, 1612, 1517, 1435, 1421, 1391, 1365, 1345, 1275, 1234, 1166, 1108, 1041, 968, 836, 750, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 1.25–1.30 (1H, m), 1.46 (9H, s), 1.54–1.79 (3H, m), 2.70–2.90 (3H, m), 3.20 (2H, q, *J*=6.4 Hz), 3.76–3.81 (1H, m), 3.87 (3H, s), 4.82 (1H, br s), 6.04 (1H, br s), 6.79 (1H, d, *J*=8.8 Hz), 7.97 (1H, dd, *J*=2.0, 8.8 Hz), 8.50 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 15.1, 25.6×2, 28.4, 39.5, 46.5, 51.9, 54.7, 79.8, 115.8, 115.9, 117.5, 119.8, 130.7, 136.4, 153.1, 156.7, 166.4, 190.7; HRMS (FAB, NBA) calcd for $C_{26}H_{39}N_3O_6$ 401.1951 (M^+), found 401.1941.

4.20. (3a*S*,4*S*,9b*S*)-4-(3-*tert*-Butoxycarbonylaminopropyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-*tert*-butyl ester 8-methyl ester (35)

To a stirred solution of **34** (80.2 mg, 0.200 mmol, dr 57/43) in EtOH (2.5 mL) at room temperature was added Raney nickel (W-2, 699 mg). After being stirred at 50 °C for 29 h under an atmosphere of hydrogen, the reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo.

The residue was dissolved in MeOH (2.0 mL) and $NaBH_3CN$ (38.5 mg, 0.613 mmol) was added at room temperature. The resulting mixture was acidified to pH 5 with AcOH and stirred at room temperature for 3 h. After the reaction mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2, washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo.

The residue was dissolved in 1,4-dioxane (1.5 mL) and H_2O (3.0 mL). $NaHCO_3$ (228 mg, 1.04 mmol) and Boc_2O (55.0 mg, 0.252 mmol) were added to the solution at 0 °C. After stirring the mixture at room temperature for 42 h, the reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **35** (58.0 mg, 59%) and **35** with impurity, which was subjected to preparative TLC (*n*-hexane/EtOAc=1/1) to give **35** (11.1 mg, 11%) as a colorless oil: $[\alpha]_D^{15}$ −156 (*c* 0.467, $CHCl_3$); IR (neat) 3345, 2974, 2935, 1673, 1607, 1518, 1393, 1365, 1276, 1247, 1163, 1127, 909, 769, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ 1.44 (9H, s), 1.51–1.62 (4H, m), 1.59 (9H, s), 1.94 (2H, t, *J*=8.4 Hz), 2.34–2.40 (1H, m), 3.04–3.17 (2H, m), 3.26–3.32 (2H, m), 3.45 (1H, q, *J*=9.2 Hz), 3.81 (3H, s), 4.52–4.59 (2H, br m), 5.00 (1H, br s), 6.43 (1H, d, *J*=8.4 Hz), 7.68 (1H, dd, *J*=2.0, 8.4 Hz), 8.26 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ 27.0, 27.4, 28.4, 28.5, 33.2, 40.2, 41.1, 44.5, 51.2, 51.5, 52.4, 79.4, 80.0, 113.6, 119.1, 120.1, 130.0, 132.4, 145.6, 155.2, 156.1, 167.1; HRMS (FAB, NBA) calcd for $C_{26}H_{39}N_3O_6$ 489.2839 (M^+), found 489.2868.

4.21. (3a*S*,4*S*,9b*S*)-4-(3-Aminopropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3.2-*c*]quinoline-8-carboxylic acid methyl ester (3)

The protected pyrroloquinoline **35** (57.6 mg, 117 μmol) was treated with 2 M HCl/MeOH (7.8 mL) at −15 °C. After being stirred at room temperature for 14 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in H_2O, washed with EtOAc, and concentrated in vacuo to give martinelline core **3** (33.1 mg, 71%) as a yellow oil: $[\alpha]_D^{18}$ −54.4 (*c* 0.290, MeOH); IR (neat) 3204, 2904, 2736, 2667, 2580, 2468, 1681, 1609, 1528, 1434, 1418, 1334, 1289, 1255, 1229, 1147, 1024, 960, 844, 769 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.69–1.87 (m, 4H), 2.11–2.17 (m, 1H), 2.40–2.44 (2H, m), 3.00–3.13 (m, 3H), 3.30–3.40 (3H, m), 3.84 (3H, s), 4.67 (d, 1H, *J*=5.6 Hz), 6.82 (1H, d, *J*=8.8 Hz), 7.78 (1H, dd, *J*=2.0, 8.8 Hz), 7.98 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 23.9, 27.9, 30.4, 39.3, 40.8, 43.5, 50.8, 52.2, 59.2, 113.4, 115.7, 119.3, 132.8, 133.9, 151.1, 168.4; HRMS (FAB, glycerol) calcd for $C_{16}H_{24}N_3O_2$ 290.1869 ($M+H^+$), found 290.1843.

4.22. 3-Bromo-4-(toluene-4-sulfonylamino)-benzoic acid methyl ester (36)

To a stirred solution of methyl *p*-aminobenzoate (500 mg, 3.31 mmol) in pyridine (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (761 mg, 3.99 mmol) and the mixture was allowed to gradually warm to room temperature. After stirring the mixture for 37 h, the mixture was quenched with H_2O (5 mL) and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give tosylamide (1.34 g) as pink solids, which was used for next reaction without further purification.

Bromine (0.17 mL, 3.32 mmol) was slowly added to a stirred solution of the above tosylamide (1.34 g) and NaOAc (1.09 g, 13.3 mmol) in AcOH (15 mL) at room temperature. After stirring for 24 h, the reaction was quenched with aqueous 50% NaOH at 0 °C. The resulting mixture was extracted with EtOAc, washed with aqueous 2 M NaOH and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=4/1 to 2/1) to give **36** (1.21 g, 95 %) as white solids: mp 124–126 °C; IR (neat) 3342, 3274, 1711, 1597, 1492, 1432, 1375, 1333, 1285, 1264, 1217, 1161, 1115, 1088, 1038, 972, 894, 814, 759, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, s), 3.88 (3H, s), 7.25 (2H, d, *J*=8.4 Hz), 7.30 (1H, s), 7.69 (1H, d, *J*=8.8 Hz), 7.71 (2H, d, *J*=8.8 Hz), 7.90 (1H, dd, *J*=2.0, 8.4 Hz), 8.11 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 52.3, 113.8, 119.7, 127.2, 127.3, 129.8, 129.9, 134.0, 135.5, 138.7, 144.7, 165.1; HRMS (FAB, NBA) calcd for $C_{15}H_{14}BrNO_4S$ 382.9827 (M+), found 382.9808.

4.23. 4-(Toluene-4-sulfonylamino)-3-vinyl-benzoic acid methyl ester (37)

To a stirred solution of bromide **36** (10.0 g, 28.7 mmol), 2,6-di-*tert*-butyl-4-methylphenol (BHT) (632 mg, 2.87 mmol), and $(PPh_3)_4Pd$ (1.65 g, 1.43 mmol) in toluene (140 mL) was added

tributyl(vinyl)tin (12.5 mL, 42.8 mmol) at room temperature under argon atmosphere and the mixture was heated to reflux for 5.5 h. The mixture was cooled to room temperature, filtered through a short pad of silica gel, and concentrated in vacuo. The residue was dissolved in EtOAc, filtered, and concentrated in vacuo. The residue was crystallized and purified by recrystallization from *n*-hexane/EtOAc to give **37** (4.37 g, 46%) as yellow solids. The mother liquor was concentrated in vacuo and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=6/1 to 2/1) to give **37** (2.46 g, 26%) as yellow solids: mp >200 °C (decomp.); IR (neat) 3288, 1714, 1594, 1490, 1434, 1400, 1336, 1301, 1263, 1163, 1118, 1087, 915, 883, 815, 761, 704, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s), 3.89 (3H, s), 5.43 (1H, dd, *J*=0.6, 11.4 Hz), 5.60 (1H, dd, *J*=0.8, 17.6 Hz), 6.50 (1H, dd, *J*=11.0, 17.6 Hz), 6.72 (1H, s), 7.24 (2H, d, *J*=8.4 Hz), 7.50 (1H, d, *J*=8.4 Hz), 7.66 (2H, d, *J*=8.4 Hz), 7.87 (1H, dd, *J*=1.8, 8.4 Hz), 7.96 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 52.1, 119.9, 121.9, 126.9, 127.1, 128.8, 129.7, 129.7, 130.5, 130.8, 136.0, 137.5, 144.2, 166.3; HRMS (FAB, NBA) calcd for $C_{17}H_{18}NO_4S$ 332.0957 ($M+H^+$), found 332.0956.

4.24. 3-Formyl-4-(toluene-4-sulfonylamino)-benzoic acid methyl ester (38)

The styrene derivative **37** (2.00 g, 6.03 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to −78 °C. Ozone was bubbled through the solution at −78 °C until the solution turned blue. Oxygen was then bubbled through the solution until it turned colorless. The reaction was quenched with dimethyl sulfide (2.2 mL) and was allowed to warm to room temperature. The mixture was extracted with EtOAc. The organic layer was washed with aqueous 0.5 M $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **38** (1.84 g, 92 %) as white solids: mp 140–142 °C; IR (neat) 3126, 1710, 1667, 1614, 1492, 1444, 1392, 1343, 1294, 1269, 1185, 1159, 1133, 1087, 978, 924, 872, 851, 802, 764, 734, 694, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 9H), 2.38 (3H, s), 3.91 (3H, s), 7.27 (2H, d, *J*=8.8 Hz), 7.73 (1H, d, *J*=8.8 Hz), 7.81 (2H, d, *J*=8.0 Hz), 8.14 (1H, dd, *J*=2.0, 8.8 Hz), 8.31 (1H, d, *J*=2.4 Hz), 9.90 (1H, s), 11.07 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 52.4, 116.8, 120.9, 124.5, 127.3, 129.9, 135.9, 136.5, 137.8, 143.5, 144.7, 165.2, 194.5; HRMS (FAB, NBA) calcd for $C_{16}H_{16}NO_5S$ 334.0749 ($M+H^+$), found 334.0746.

4.25. (2*S*)-2-(3-*tert*-Butoxycarbonylamino)-3-formyl-1-(toluene-4-sulfonyl)-1,2-dihydroquinoline-6-carboxylc acid methyl ester (39)

To a stirred solution of **38** (1.53 g, 4.59 mmol) and **6** (2.87 g, 13.5 mmol) in CH_3CN (4.2 mL) at −20 °C under an argon atmosphere was slowly added via cannula a solution of (*R*)-**14** (337 mg, 0.916 mmol) in CH_3CN (5 mL). After stirring the mixture for 24 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1 to 1/1) to give **39** (2.42 g, quant., 99 %ee) as brown amorphous powder: $[\alpha]_D^{25}$ +305 (*c* 0.414, $CHCl_3$); IR (neat) 3402, 2976, 1674, 1633, 1511, 1439, 1363, 1276, 1246, 1203, 1159, 1107, 1088, 862, 808, 751, 705, 692, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.38 (3H, m), 1.40 (9H, s), 1.56–1.77 (m, 3H), 2.32 (3H, s), 3.11 (2H, dd, *J*=6.6, 13.2 Hz) 3.96 (3H, s), 4.58 (1H, s), 5.31 (1H, dd, *J*=4.4, 10.0 Hz), 6.80 (1H, s), 7.05 (2H, d, *J*=8.0 Hz), 7.20 (2H, d, *J*=8.4 Hz), 7.92 (2H, d, *J*=8.8 Hz), 8.13 (1H, dd, *J*=2.0, 8.4 Hz), 9.22 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.6, 28.4, 29.9, 39.8, 44.0, 52.1, 52.5, 126.6, 126.7, 128.0, 128.6, 129.4, 130.1, 132.5, 135.5, 138.7, 138.7, 139.2, 144.2, 155.9, 165.8, 189.3; HRMS (FAB, NBA) calcd for $C_{27}H_{32}N_2O_7SK$ 567.1567 ($M+K^+$), found 567.1589. HPLC analysis: CHIRALCEL AD-H, *n*-hexane/*i*-PrOH (80/20, 1.0 mL/min), t_R: 22.7 min (major) and 26.6 min (minor).

4.26. (2*S*)-2-(3-*tert*-Butoxycarbonylaminopropyl)-3-hydroxy methyl-1-(toluene-4-sulfonyl)-1,2-dihydroquinoline-6-carboxylic acid methyl ester (40)

To a stirred solution of **39** (523 mg, 0.988 mmol) and $CeCl_3 \cdot 7H_2O$ (557 mg, 1.50 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (77.4 mg, 2.05 mmol) and the mixture was allowed to gradually warm to room temperature. After stirring the mixture for 1 h, the reaction was quenched with aqueous 1 M $KHSO_4$ at 0 °C. The resulting mixture was concentrated in vacuo to half volume and then diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/1) to give dihydroquinoline **40** (533 mg, quant.) as white amorphous powder: $[\alpha]_D^{25}$ +104 (*c* 0.45, $CHCl_3$); IR (neat) 3393, 2932, 1685, 1598, 1518, 1437, 1392, 1348, 1274, 1200, 1160, 1089, 1033, 915, 853, 810, 768, 726, 704, 684, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22–1.60 (3H, m), 1.44 (9H, s), 1.47–1.60 (2H, m), 1.84 (1H, br s), 2.33 (3H, s), 3.08 (1H, dt, *J*=5.0, 14.8 Hz), 3.17–3.20 (1H, m), 3.62–3.64 (1H, m), 3.91 (3H, s), 3.92–4.06 (2H, m), 4.66 (1H, s), 5.16 (1H, d, *J*=9.2 Hz), 5.94 (1H, s), 7.07 (2H, d, *J*=8.4 Hz), 7.35 (2H, d, *J*=8.0 Hz), 7.63 (1H, s), 7.83 (1H, d, *J*=8.4 Hz), 7.92 (1H, dd, *J*=2.0, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 25.5, 27.5, 28.3, 38.4, 52.1, 54.2, 62.9, 79.4, 118.7, 127.0, 127.1, 127.5, 127.9, 128.7, 128.8, 129.0, 135.7, 136.2, 142.4, 143.7, 156.9, 166.5; HRMS (FAB, NBA) calcd for $C_{27}H_{35}N_2O_7S$ 531.2165 ($M+H^+$), found 531.2188.

4.27. (1*R*,2*S*,7b*R*)- and (1*S*,2*S*,7b*S*)-2-(3-*tert*-Butoxycarbonyl aminopropyl)-1a-hydroxymethyl-3-(toluene-4-sulfonyl)-1a,2,3,7b-tetrahydro-1-oxa-3-aza-cyclopropa [*a*]naphthalene-6-carboxylic acid methyl ester (41)

To a stirred solution of **40** (250 mg, 0.472 mmol) in CH_2Cl_2 (1.9 mL) at 0 °C was added *m*-CPBA (77%, 211 mg, 0.943 mmol) and the mixture was allowed to gradually warm to room temperature. After stirring the mixture for 19.5 h, the reaction was quenched with saturated aqueous Na_2SO_3. The resulting mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1/2) to give **41** (272 mg, quant., dr 85/15) as orange amorphous powder: $[\alpha]_D^{21}$ −0.1 (*c* 0.58, $CHCl_3$, dr 79/21); IR (ATR) 3394, 2951, 1685, 1615, 1519, 1436, 1393, 1346, 1277, 1205, 1160, 1088, 1035, 929, 882, 808, 751, 721, 703, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 1.01–1.09 (1H, m), 1.43 (9H, s), 1.46–1.70 (3H, m), 2.34 (3H, s), 3.05–3.12 (2H, m), 3.43–3.56 (2H, m), 3.61 (1H, s), 3.91 (3H, s), 4.10 (1H, d, *J*=13.2 Hz), 4.70 (1H, s), 5.02 (1H, d, *J*=11.2 Hz), 7.16 (2H, d, *J*=8.4 Hz), 7.48 (2H, d, *J*=8.4 Hz), 7.91 (1H, d, *J*=2.4 Hz), 7.92 (1H, d, *J*=8.8 Hz), 8.01 (1H, dd, *J*=2.0, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 21.6, 25.6, 26.7, 28.4, 38.7, 52.2, 52.5, 53.7, 62.1, 71.9, 79.6, 126.6, 126.9, 127.3, 128.0, 129.0, 130.7×2, 135.1, 138.0, 143.7, 156.8, 166.0; HRMS (FAB, NBA) calcd for $C_{27}H_{35}N_2O_8S$ 547.2114 ($M+H^+$), found 547.2106.

4.28. (2*S*,4*R*)- and (2*S*,4*S*)-2-(3-*tert*-Butoxycarbonyl-aminopropyl)-4-hydroxy-3-methylene-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid methyl ester (43)

To a stirred solution of **41** (698 mg, 1.28 mmol, dr 81/19), PPh_3 (765 mg, 2.91 mmol), and imidazole (200 mg, 2.94 mmol) in benzene (5.8 mL) at room temperature was added iodine (596 mg,

2.35 mmol). After stirring the mixture for 1 h, the reaction was quenched with saturated aqueous Na_2SO_3. The resulting mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude **42** as a yellow oil, which was used for next reaction without further purification.

The residue was dissolved in MeOH (4.7 mL) and AcOH (0.47 mL) at room temperature and Zn (636 mg, 9.73 mmol) was added. After stirring the mixture for 75 min, the reaction was quenched with aqueous 0.5 M $Na_2S_2O_3$. The resulting mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1 to 1/1) to give iodide **43** (620 mg, 91%, dr 80/20) as orange amorphous powder: $[\alpha]_D^{20}$ −6.76 (*c* 0.63 $CHCl_3$, dr 81/19); IR (neat) 3391, 2977, 1687, 1609, 1517, 1436, 1346, 1265, 1160, 1088, 1036, 913, 856, 813, 769, 729, 703, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41–1.61 (4H, m), 1.41 (9H, s), 2.34 (3H, s), 3.10 (2H, br s), 3.93 (3H, s), 4.48 (1H, s), 5.00–5.22 (4H, m), 7.14 (2H, d, *J*=8.0 Hz), 7.32 (2H, d, *J*=8.4 Hz), 7.85 (1H, d, *J*=8.8 Hz), 7.98 (1H, dd, *J*=2.0, 8.8 Hz), 8.13 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 21.4, 26.3, 28.2, 30.3, 39.6, 52.1, 62.5, 66.5, 79.0, 113.2, 125.9, 127.7, 127.8, 129.1, 129.6, 130.7, 132.5, 135.1, 138.5, 142.0, 144.1, 155.9, 166.2; HRMS (FAB, NBA) calcd for $C_{27}H_{35}N_2O_7SK$ 569.1724 ($M+K^+$), found 569.1708.

4.29. (2*S*)-2-(3-*tert*-Butoxycarbonylaminopropyl)-3-methylene-4-oxo-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid methyl ester (44)

To a stirred solution of **43** (291 mg, 0.549 mmol, dr 77/23) in CH_2Cl_2 (5 mL) at room temperature was added activated MnO_2 (2.42 g) and the reaction mixture was stirred for 21 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give **44** (289 mg, quant.) as white amorphous powder: $[\alpha]_D^{21}$ +143 (*c* 0.36, $CHCl_3$); IR (neat) 3394, 2925, 1684, 1607, 1684, 1607, 1508, 1424, 1361, 1255, 1164, 1088, 963, 813, 766, 727, 704, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38–1.68 (4H, m), 1.41 (9H, s), 2.33 (3H, s), 3.08–3.24 (2H m), 3.95 (3H, s), 4.49 (1H, s), 5.17 (1H, s), 5.34 (1H, s), 6.03 (1H, s), 7.10 (2H, d, *J*=8.0 Hz), 7.29 (2H, d, *J*=8.0 Hz), 7.94 (1H, d, *J*=8.8 Hz), 8.27 (1H, dd, *J*=2.0, 8.8 Hz), 8.58 (1H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.6, 28.3, 32.2, 39.3, 52.4, 60.9, 79.2, 124.7, 127.3, 127.4, 127.7, 128.6, 129.7, 134.7, 135.1, 140.7, 143.2, 144.6, 155.9, 165.6, 181.1; HRMS (FAB, NBA) calcd for $C_{27}H_{33}N_2O_7S$ 529.2008 ($M+H^+$), found 529.1995.

4.30. (2*S*,3*R*)-2-(3-*tert*-Butoxycarbonylaminopropyl)-3-cyanomethyl-4-oxo-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid methyl ester (27)

To a stirred solution of **44** (1.29 g, 2.45 mmol) in EtOH (12 mL) at 0 °C were added KCN (331 mg, 5.08 mmol) in H_2O (1.2 mL) and AcOH (0.2 mL, 3.49 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo and the residue was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=2/1) to give tetrahydroquinolone **27** (1.22 g, 90%, dr 94/6) as yellow amorphous powder: $[\alpha]_D^{20}$ +25.2 (*c* 0.480, $CHCl_3$, dr 94/6); IR (neat) 3376, 2929, 1698, 1608, 1516, 1426, 1363, 1257, 1163, 1086, 1010, 917, 814, 767, 750, 705, 667 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$) δ 1.25–1.68 (4H, m), 1.40 (9H, s), 2.33 (1H, dd, *J*=10.0, 17.6 Hz), 2.42 (3H, s), 2.57 (1H, ddd, *J*=4.8, 4.8, 9.2 Hz), 2.90 (1H, dd, *J*=4.8, 17.2 Hz), 3.05–3.20 (2H, m), 3.94 (3H, s), 4.53 (1H, s), 4.91 (1H, d, *J*=11.2 Hz), 7.30 (2H, d, *J*=8.4 Hz), 7.65 (2H, d, *J*=8.8 Hz), 8.11 (1H, d, *J*=8.8 Hz), 8.26 (1H, dd, *J*=2.0, 8.8 Hz), 8.55 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.7, 23.1, 26.7, 28.3, 39.1, 45.3, 52.5, 58.4, 79.3, 117.1, 123.5, 125.5, 126.9, 127.5, 129.2, 130.6, 136.1×2, 142.8, 145.5, 156.1, 165.4, 190.1; HRMS (FAB, NBA) calcd for $C_{28}H_{34}N_3O_7S$ 556.2117 ($M+H^+$), found 556.2131.

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