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SYNTHETIC STUDIES ON THIOSTREPTON FAMILY OF PEPTIDE ANTIBIOTICS: SYNTHESIS OF THE TETRASUBSTITUTED DIHYDROQUINOLINE PORTION OF SIOMYCIN D_1

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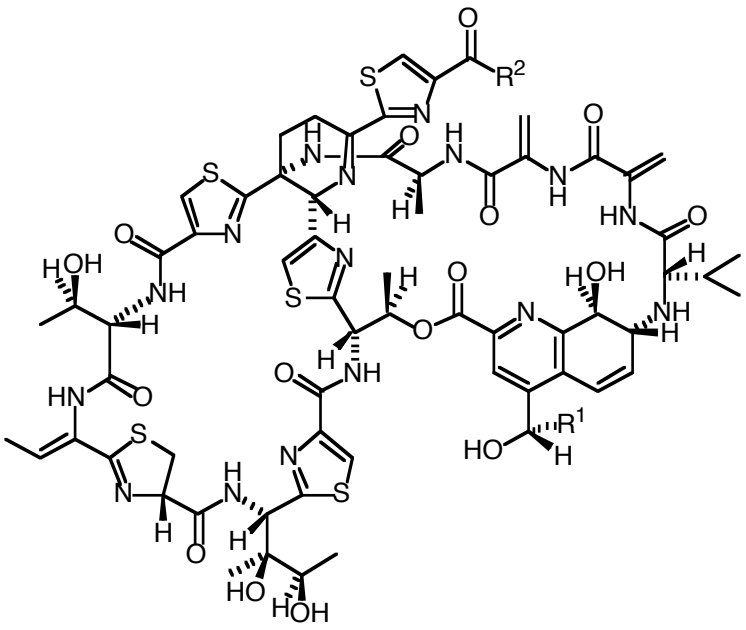
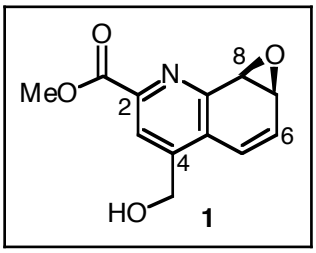
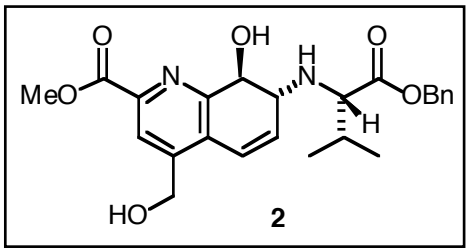
Abstract - The tetrasubstituted dihydroquinoline portion of siomycin D_1, a member of the thiostrepton family of peptide antibiotics, was synthesized from 5,6,7,8-tetrahydroquinoline featuring the modified Reissert-Henze reaction, the homolytic aromatic substitution reaction, the modified Boekelheide rearrangement, and the Jacobsen asymmetric epoxidation.

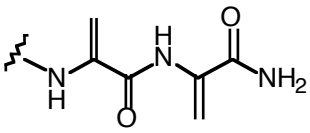
In 1961, siomycin A was isolated from the culture broth of *Streptomyces sioyaensis* by the Shionogi group.[1] In 1969, siomycin B was recognized as an artifact of siomycin A, and siomycin C was isolated from the same culture broth.[2] Siomycin D_1 was also isolated from the same culture broth in 1980 as a minor component of the siomycins.[3] Their structures were elucidated by chemical degradation studies[4] and NMR spectral studies[3,5] by comparison with those of thiostrepton, which is a representative compound of this class of peptide antibiotics and whose structure had been confirmed by X-Ray crystallographic analysis.[6] The characteristic structure of the thiostrepton family of peptide antibiotics is the bicyclic structure containing a tetrasubstituted dehydropiperidine moiety, a tetrasubstituted dihydroquinoline moiety, four thiazole moieties, a thiazoline moiety, dehydroamino acid moieties, and a dihydroxyisoleucine moiety (Figure 1). Because of these complex structural features, synthetic studies on the thiostrepton family of antibiotics have scarcely been attempted.[7] Most efforts have focused on the syntheses of the much simpler thiopeptide antibiotics: the berninamycins,[8] the micrococcins,[9] nosiheptide,[10] sulfomycin I,[11] cyclothiazomycin,[12] A10255,[13] GE 2270 A,[14] and promothiocin A.[15] These antibiotics show high activities against Gram-positive bacteria and mycobacteria,[1,2,3] and their mode of action has been described.[9i,15b,16] In this paper, we describe the enantioselective synthesis of the tetrasubstituted dihydroquinoline portions (**1**) and (**2**) of siomycin D_1. It has been proposed by Floss and his co-workers[16b] that the 4-(1-hydroxyethyl)quinoline derivatives of **1** would be intermediates of the thiostrepton biosynthesis.

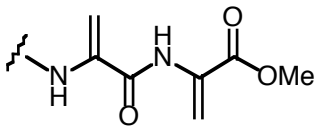
We were interested in the Floss synthesis of 4-(hydroxymethyl)quinoline-2-carboxylic acid, which was used in the studies of the biosynthesis of thiostrepton, from quinoline.[16b] This synthetic process was applied to the early stage of our synthesis of **1** and **2** with slight modifications.







Siomycin A: $R^1 = CH_3$, R^2 = 

Siomycin C: $R^1 = CH_3$, R^2 = 

Siomycin B: $R^1 = CH_3$, $R^2 = NH_2$

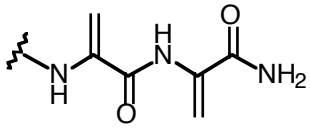
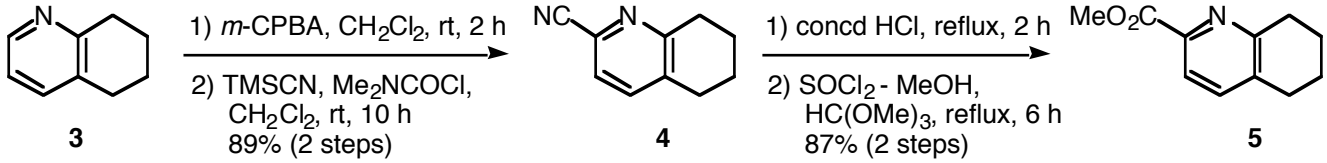
Siomycin D_1: $R^1 = H$, R^2 = 

Figure 1

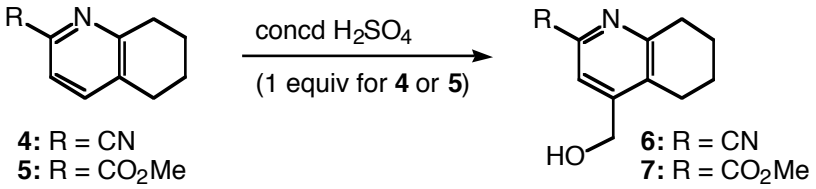
The commercially available 5,6,7,8-tetrahydroquinoline (**3**) was oxidized with *m*-CPBA and the resulting *N*-oxide was subjected to the modified Reissert-Henze reaction[17] using trimethylsilyl cyanide (TMSCN) and dimethylcarbamyl chloride in CH_2Cl_2 to afford 2-cyanotetrahydroquinoline (**4**)[18] in 89% yield (Scheme 1). Acid hydrolysis of **4** followed by esterification gave ester (**5**)[19] in 87% yield.



Scheme 1

We examined the introduction of the hydroxymethyl group at the C4 position of **4** or **5** by the homolytic aromatic substitution reaction developed by Minisci *et al.*[20] The relevant data are shown in Table 1. For nitrile (**4**), the use of aqueous H_2O_2 - $FeSO_4 \bullet 7H_2O$ or ammonium persulfate $[(NH_4)_2S_2O_8]$ in aqueous acidic MeOH resulted in a low yield of **6** (entries 1 and 2). In addition, photochemical conditions using benzophenone in acidic MeOH[21] gave an unsatisfactory result (entry 3). In contrast, for ester (**5**), a satisfactory result was obtained when **5** was treated with $(NH_4)_2S_2O_8$ in aqueous acidic MeOH, giving **7** in 98% yield (entry 5).

Table 1. Homolytic Aromatic Substitution of **4** and **5**



4: R = CN
5: R = CO_2Me

6: R = CN
7: R = CO_2Me

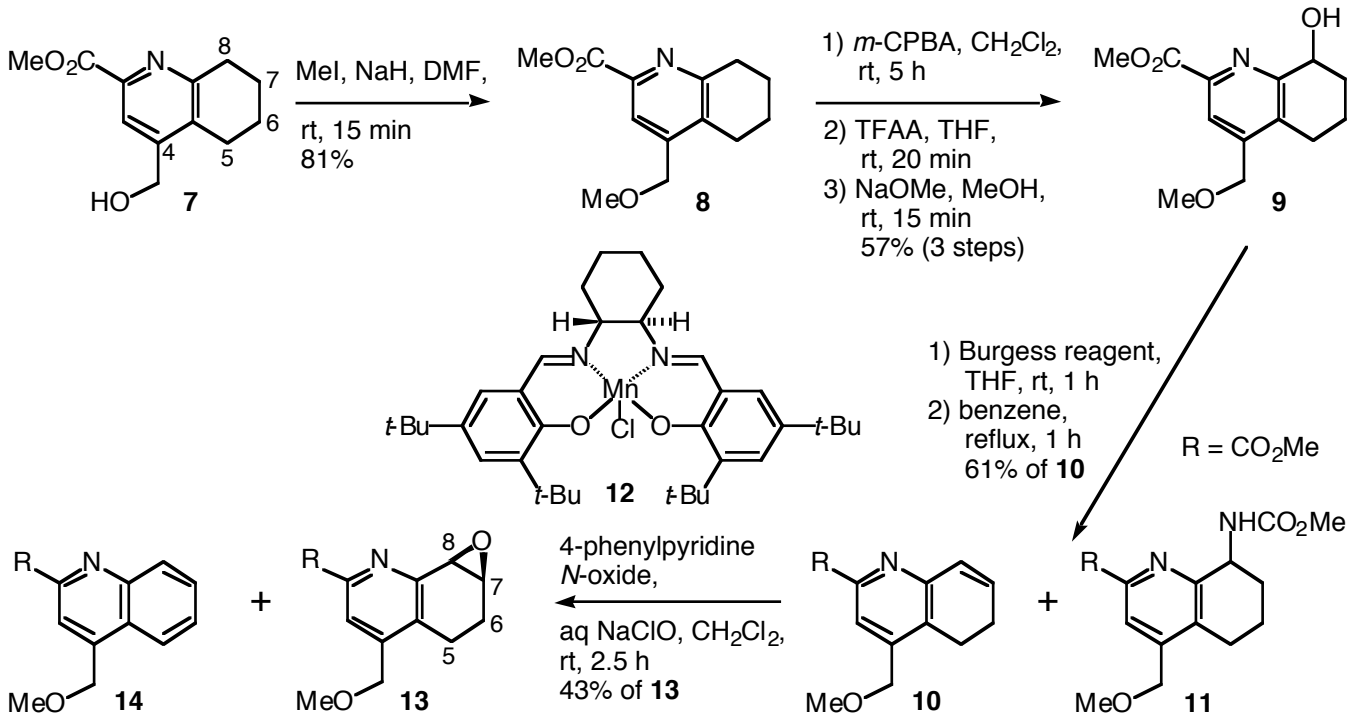
entry	substrate	reagents (equiv for **4** or **5**)	solvent	temp	time	yield % of **6** or **7**
1	**4**	H_2O_2 (3.8), $FeSO_4 \cdot 7H_2O$ (4.5)	MeOH / H_2O 2 : 1	rt	22 h	19[a]
2	**4**	$(NH_4)_2S_2O_8$ (1.5)	MeOH / H_2O 4 : 1	reflux	31 h	9[b]
3	**4**	PhCOPh (1.0), hν[c]	MeOH	rt	28 h	25[d]
4	**5**	H_2O_2 (6.8), $FeSO_4 \cdot 7H_2O$ (7.5)	MeOH / H_2O 2 : 1	rt	6 d	19[b]
5	**5**	$(NH_4)_2S_2O_8$ (2)	MeOH / H_2O 4 : 1	reflux	2 h	98
6	**5**	PhCOPh (1.0), hν[c]	MeOH	rt	4.5 h	trace[b]

[a]**4** was recovered in 67% yield. [b]Decomposition occurred. [c]hν: 400 W high-pressure mercury lamp.
[d]**4** was recovered in 27% yield.

Our next concern was the functionalization of the hydrogenated portion of the quinoline core. In our synthetic plan, we expected that the C7-C8 epoxide would be constructed by an asymmetric epoxidation[22] of the olefin function and the C5-C6 double bond would be introduced by the benzylic C5 bromination-dehydrobromination procedure.[23] In the latter case, however, it was anticipated that the C4-methoxymethyl group in **13** (*vide infra*) would undergo oxidation to a formyl group, because it is well known that alkoxymethyl substituents attached to aromatic nuclei are oxidized by brominating reagents to formyl groups.[24] Nevertheless, we expected that the hydroxymethyl group would be easily regenerated from the formyl group.

In order to introduce the olefin function into the C7-C8 positions, hydroxylation at the benzylic C8 position next to the ring heteroatom was investigated (Scheme 2). After methylation of **7** with iodomethane and NaH in DMF, the resulting **8** was oxidized with *m*-CPBA to *N*-oxide, which was subjected to the modified Boekelheide rearrangement[25] with trifluoroacetic anhydride (TFAA) in THF followed by hydrolysis with sodium methoxide to afford **9** in 57% yield. Treatment of **9** with the Burgess reagent ($MeO_2CNSO_2NEt_3$)[26a] in THF[26b] followed by thermolysis in benzene afforded olefin (**10**) in 61% yield together with the 20% yield of carbamate (**11**). Asymmetric epoxidation of **10** with the Jacobsen reagent (**12**)[22] afforded epoxide (**13**) in 43% yield together with the 13% yield of quinoline (**14**). Unfortunately, all attempts to improve the yields of **10** and **13** were unsuccessful. The % ee of **13** was determined at a later stage (*vide infra*).

The final stage started with the benzylic bromination[23] of **13** using NBS in acetic acid[23c] at room tempera-



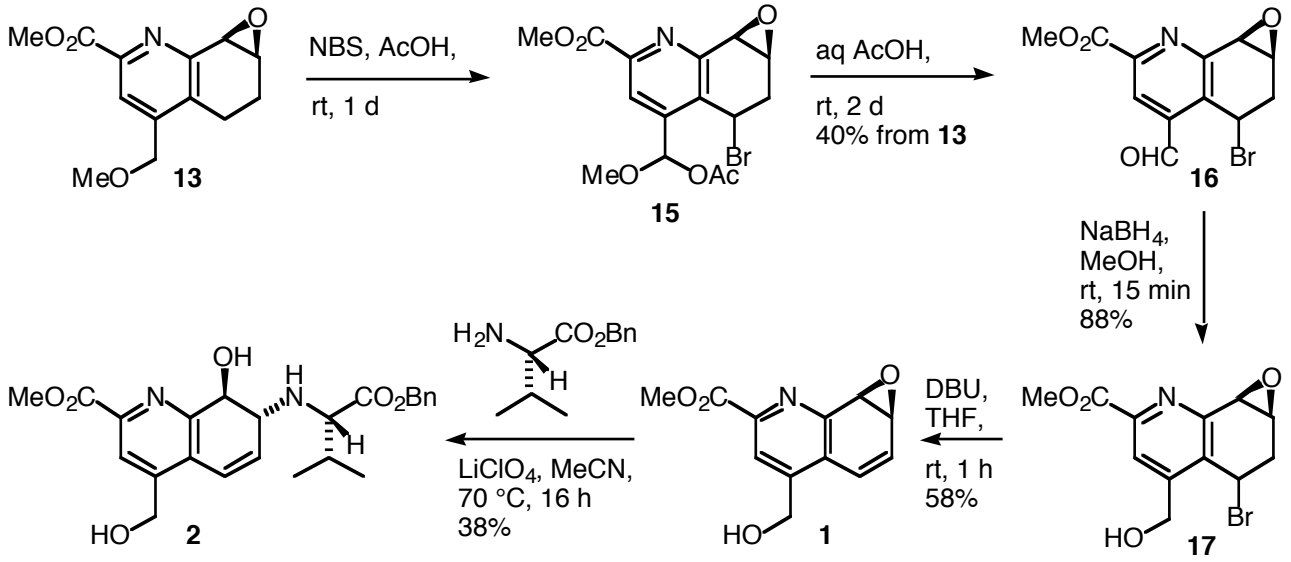
Scheme 2

ture, giving the intermediate (**15**) (1:1 mixture of diastereomers at the acetal position), which was directly hydrolyzed with aqueous acetic acid to afford bromo epoxide (**16**) in 40% yield from **13**; the methoxymethyl group was oxidized as expected[24] to a formyl group (Scheme 3). Compound (**16**) consists of only one diastereomer but the C5 configuration in **16** has not been determined. Reduction of **16** with $NaBH_4$ gave alcohol (**17**), the enantiomeric excess of which, and hence **13**, was determined to be 91% by ^1H NMR spectral analysis of the (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA esters) of **17**.[27,28] Treatment of **17** with DBU in THF afforded the desired epoxide (**1**) in 58% yield. This epoxide would be an important synthetic intermediate of siomycin D_1. Finally, regioselective epoxide-ring opening[29] of **1** with *L*-valine benzyl ester in the presence of $LiClO_4$[30] in acetonitrile at 70 °C afforded **2** in 38% yield together with the 1.8% yield of the diastereomer of **2** arising from the enantiomer of **1**; no regioisomer was obtained.

In summary, we have synthesized, for the first time, the tetrasubstituted dihydroquinoline portion of siomycin D_1 from tetrahydroquinoline.[31] Although there is still room for improvement in our synthesis, we believe that the synthetic route described herein is a straightforward and simple one.

EXPERIMENTAL

The melting points were determined on a micro hot stage Yanaco MP-S3 and were uncorrected. ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz in $CDCl_3$ at rt on a JEOL LAMBDA 300 spectrometer using tetramethylsilane as the internal standard. IR spectra were recorded on JASCO FT IR-200. Optical rotations were measured using a JASCO DIP-360 polarimeter. Low and high resolution MS spectra were recorded on a JEOL GCmate (EI and FAB). Silica gel TLC and preparative



Scheme 3

TLC (PTLC) were performed on a Merck TLC 60F-254 and column chromatography was performed on Fuji-Davison PSQ100B and FL60D (flash). Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, the organic solvents were purified and dried by appropriate procedures, and evaporation was carried out under reduced pressure below 30 °C after drying over anhydrous Na_2SO_4, unless otherwise noted.

5,6,7,8-Tetrahydroquinoline-2-carbonitrile (4). To a solution of 95% 5,6,7,8-tetrahydroquinoline (**3**) (30.0 mL, 0.220 mol) in CH_2Cl_2 (735 mL) was slowly added at 0 °C 65% *m*-CPBA (58.4 g, 0.220 mol). After 2 h at rt, the reaction mixture was filtered through Celite and the filter cake was washed with $CHCl_3$; the filtrate and washings were evaporated. To the residue were added 1 M aqueous sodium hydroxide (440 mL) and saturated aqueous NaCl (200 mL); the mixture was extracted with $CHCl_3$ (500 mL X 6). The combined extracts were dried and evaporated to afford *N*-oxide. To a solution of this *N*-oxide in dry CH_2Cl_2 (440 mL) were successively added at rt 95% TMSCN (64.0 mL, 0.484 mol) and dimethylcarbamyl chloride (44.6 mL, 0.484 mol); the mixture was stirred at rt for 10 h. The reaction mixture was quenched with 3 M aqueous sodium hydroxide (1.1 L) and the new mixture was vigorously stirred for 10 min and extracted with $CHCl_3$ (1 L X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (1 kg) with 20% ethyl acetate-hexane to afford **4** (31.1 g, 89%) as colorless crystals: R_f = 0.67 (50% acetone-hexane); mp 79-80 °C (not recrystallized); IR (nujol) 1570, 1420, 1310, 1260, 1120, 990, 940, 900, 850, 820, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.49 (1H, d, *J* = 7.8 Hz, H-3), 7.43 (1H, d, *J* = 7.8 Hz, H-4), 2.95 (2H, dd, *J* = 6.4, 6.4 Hz, H-8), 2.85 (2H, dd, *J* = 6.2, 6.2 Hz, H-5), 1.98-1.76 (4H, m, H-6 and H-7); ^{13}C NMR ($CDCl_3$) δ = 159.9, 137.2, 137.1, 130.5, 125.5, 117.6, 32.3, 29.0, 22.5, 22.0. *Anal.* Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.93; H, 6.49; N, 17.61.

Methyl 5,6,7,8-Tetrahydroquinoline-2-carboxylate (5). **4** (3.00 g, 19.0 mmol) in 12 M aqueous hydrochloric acid (38 mL) was refluxed for 2 h; the reaction mixture was evaporated to give the

carboxylic acid. To a solution of this carboxylic acid in dry MeOH (63 mL) were slowly added at 0 °C thionyl chloride (6.30 mL, 86.4 mmol) and trimethyl orthoformate (9.48 mL, 57.0 mmol); the mixture was refluxed for 6 h. The reaction mixture was evaporated; to the residue was added saturated aqueous sodium hydrogencarbonate (150 mL) and the mixture was extracted with ethyl acetate (160 mL X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (100 g) with 30% ethyl acetate-hexane to afford **5** (3.14 g, 87%) as colorless crystals: R_f = 0.81 (10% MeOH-$CHCl_3$); mp 53-54 °C (not recrystallized); IR (nujol) 1720, 1580, 1320, 1260, 1200, 1130, 990, 970, 800, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.88 (1H, d, *J* = 8.0 Hz, H-3), 7.49 (1H, d, *J* = 8.0 Hz, H-4), 3.98 (3H, s, CO_2Me), 3.03 (2H, dd, *J* = 6.5, 6.5 Hz, H-8), 2.84 (2H, dd, *J* = 6.5, 6.5 Hz, H-5), 1.98-1.78 (4H, m, H-6 and H-7); ^{13}C NMR ($CDCl_3$) δ = 166.1, 158.0, 145.0, 137.4, 136.7, 122.5, 52.8, 32.7, 29.0, 22.8, 22.3. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.04; H, 6.79; N, 7.26.

Methyl 4-Hydroxymethyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (7). To a solution of **5** (19.6 g, 102 mmol) in MeOH (410 mL) and water (102 mL) were added at rt ammonium peroxydisulfate (46.6 g, 204 mmol) and conc sulfuric acid (5.44 mL, 102 mmol); the mixture was refluxed for 2 h. The reaction mixture was evaporated; to the residue were added saturated aqueous sodium hydrogencarbonate (1 L) and water (500 mL) and the mixture was extracted with ethyl acetate (1.5 L X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (600 g) with 40% acetone-hexane to afford **7** (22.2 g, 98%) as colorless crystals: R_f = 0.45 (10% MeOH-$CHCl_3$); mp 170-171 °C (not recrystallized); IR (nujol) 3340, 1720, 1590, 1360, 1340, 1220, 1100, 1000, 900, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.07 (1H, s, H-3), 4.71 (2H, br s, C<u>H</u>$_2$OH), 3.95 (3H, s, CO_2Me), 3.26 (1H, br s, OH), 3.02 (2H, br dd, *J* = 6.0, 6.0 Hz, H-8), 2.66 (2H, br dd, *J* = 6.0, 6.0 Hz, H-5), 1.93-1.79 (4H, m, H-6 and H-7); ^{13}C NMR ($CDCl_3$) δ = 166.1, 157.4, 149.2, 144.7, 133.4, 119.8, 61.0, 52.7, 32.9, 25.0, 22.4, 22.0. *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.82; H, 6.97; N, 6.31.

Methyl 4-Methoxymethyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (8). To a solution of sodium hydride (3.23 g, 135 mmol; NaH, 60% dispersion in mineral oil, was washed with hexane) in dry DMF (235 mL) were added at 0 °C iodomethane (59.8 mL, 0.961 mol) and a solution of **7** (22.6 g, 96.1 mmol) in dry DMF (150 mL). After 15 min at rt, the reaction mixture was quenched with water (500 mL) and the new mixture was extracted with 50% ethyl acetate-hexane (600 mL X 6). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (600 g) with 30% acetone-hexane to afford **8** (19.6 g, 81%) as colorless crystals: R_f = 0.61 (50% acetone-hexane); mp 97-98 °C (not recrystallized); IR (nujol) 1740, 1300, 1220, 1180, 1120, 1000, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.01 (1H, s, H-3), 4.44 (2H, br s, C<u>H</u>$_2$OH), 3.98 (3H, s, CO_2Me), 3.47 (3H, s, CH_2O<u>Me</u>), 3.05 (2H, br dd, *J* = 6.0, 6.0 Hz, H-8), 2.71 (2H, br dd, *J* = 6.0, 6.0 Hz, H-5), 1.95-1.80 (4H, m, H-6 and H-7); ^{13}C NMR ($CDCl_3$) δ = 166.1, 157.7, 146.2, 144.9, 133.9, 120.8, 70.7, 58.8, 52.7, 33.2, 25.1, 22.4, 22.1. *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.14; H, 7.13; N, 5.83.

Methyl 8-Hydroxy-4-methoxymethyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (9). To a solution of **8** (3.00 g, 12.8 mmol) in CH_2Cl_2 (45 mL) was slowly added at 0 °C 65% *m*-CPBA (6.80 g, 25.6 mmol). After 5 h at rt, the reaction mixture was filtered through Celite and the filter cake was washed with $CHCl_3$; the filtrate and washings were evaporated. To the residue were added saturated aqueous sodium

hydrogencarbonate (50 mL) and water(30 mL); the mixture was extracted with $CHCl_3$ (60 mL X 1) and ethyl acetate (60 mL X 2). The combined extracts were dried and evaporated to give *N*-oxide. To a solution of this *N*-oxide in dry THF (64 mL) was added at 0 °C trifluoroacetic anhydride (2.18 mL, 15.4 mmol). After 20 min at rt, 28% sodium methoxide in MeOH (7.40 mL) was slowly added; the new mixture was stirred for 15 min. The reaction mixture was quenched with water (80 mL) and the new mixture was extracted with ethyl acetate (100 mL X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (100 g) with 30% acetone-hexane to afford **9** (1.83 g, 57%) as colorless crystals: R_f = 0.64 (70% acetone-hexane); mp 121-122 °C (not recrystallized); IR (nujol) 3300, 1720, 1330, 1300, 1220, 1190, 1120, 970, 910, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.08 (1H, s, H-3), 4.79 (1H, dd, *J* = 6.0, 8.0 Hz, H-8), 4.47 and 4.43 (each 1H, ABq, *J* = 13.9 Hz, C<u>H</u>$_2$OMe), 3.98 (3H, s, CO_2Me), 3.48 (3H, s, CH_2O<u>Me</u>), 2.74 (2H, dd, *J* = 6.0, 6.0 Hz, H-5), 2.37-2.20 (1H, m, H-7), 2.16-1.98 (1H, m, H-7), 1.93-1.74 (2H, m, H-6); ^{13}C NMR ($CDCl_3$) δ = 165.6, 158.3, 147.0, 144.9, 133.1, 121.8, 70.6, 68.8, 58.9, 52.6, 29.9, 25.0, 18.5. *Anal.* Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.84; H, 6.96; N, 5.51.

Methyl 4-Methoxymethyl-5,6-dihydroquinoline-2-carboxylate (10) and 11. To a solution of **9** (3.00 g, 11.9 mmol) in dry THF (120 mL) was added at rt the Burgess reagent, $MeO_2CNSO_2NEt_3$,[26a] (3.41 g, 14.3 mmol). After 1 h at rt, the reaction mixture was evaporated and the residue was dissolved in dry benzene (120 mL); the mixture was refluxed for 1 h. The reaction mixture was quenched with saturated aqueous sodium hydrogencarbonate (60 mL) and water (60 mL) and the new mixture was extracted with ethyl acetate (150 mL X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (100 g, FL60D) with 50% ethyl acetate-hexane to afford **10** (1.69 g, 61%) as colorless crystals and **11** (734 mg, 20%) as a colorless syrup: **10**: R_f = 0.73 (70% acetone-hexane); mp 75-76 °C (not recrystallized); IR (nujol) 1740, 1580, 1310, 1220, 1110, 1000, 960, 900, 820, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.99 (1H, s, H-3), 6.78 (1H, dt, *J* = 2.0, 10.0 Hz, H-8), 6.38 (1H, dt, *J* = 4.4, 10.0 Hz, H-7), 4.49 (2H, s, C<u>H</u>$_2$OMe), 3.99 (3H, s, CO_2Me), 3.46 (3H, s, CH_2O<u>Me</u>), 2.87 (2H, dd, *J* = 8.3, 8.3 Hz, H-5), 2.48-2.34 (2H, m, H-6); ^{13}C NMR ($CDCl_3$) δ = 165.9, 153.1, 145.2, 144.31, 134.3, 132.5, 129.3, 122.4, 70.7, 58.6, 52.6, 22.5, 22.0. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.55; H, 6.56; N, 6.01. **11**: R_f = 0.63 (70% acetone-hexane); ^1H NMR ($CDCl_3$) δ = 8.09 (1H, s, H-3), 6.10-5.88 (1H, br s, N<u>H</u>CO_2Me), 4.68 (1H, ddd, *J* = 5.0, 5.0, 10.0 Hz, H-8), 4.46 and 4.42 (each 1H, ABq, *J* = 15.6 Hz, C<u>H</u>$_2$OMe), 3.98 (3H, s, CO_2Me), 3.73 (3H, s, NHCO_2<u>Me</u>), 3.49 (3H, s, CH_2O<u>Me</u>), 2.81-2.70 (2H, m), 2.70-2.55 (1H, m), 2.10-1.80 (2H, m), 1.80-1.60 (1H, m).

Methyl (7*S*,8*R*)-7,8-epoxy-4-methoxymethyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (13) and 14. To a solution of **10** (675 mg, 2.89 mmol) and 97% 4-phenylpyridine *N*-oxide (256 mg, 1.45 mmol) in CH_2Cl_2 (27 mL) were added at rt the Jacobsen reagent (**12**)[22] (92.1 mg, 0.145 mmol) and 4% aqueous sodium hypochlorite (27 mL). After 2.5 h at rt, water (25 mL) was added to the reaction mixture. The new mixture was filtered and the filter cake was washed with $CHCl_3$. The filtrate and washings were extracted with $CHCl_3$ (30 mL X 1) and ethyl acetate (30 mL X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (25 g) with 40% ethyl acetate-hexane to afford **13** (309 mg, 43%) as colorless crystals and **14** (86.9 mg, 13%) as a colorless syrup: **13**: R_f = 0.36

(70% ethyl acetate-hexane); mp 105-107 °C (not recrystallized); $[\alpha]_D^{28}$ = +43.2° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3620, 2960,1730, 1590, 1440, 1350, 1300, 1130, 1000, 960, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.15 (1H, s, H-3), 4.52 and 4.45 (each 1H, ABq, *J* = 13.3 Hz, C<u>H</u>$_2$OMe), 4.25 (1H, d, *J* = 4.1 Hz, H-8), 4.02 (3H, s, CO_2Me), 3.83 (1H, m, H-7), 3.45 (3H, s, CH_2O<u>Me</u>), 2.75 (1H, br dd, *J* = 6.0, 16.0 Hz, H-5), 2.69-2.58 (1H, m, H-5 or H-6), 2.58-2.44 (1H, m, H-5 or H-6), 1.79 (1H, ddd, *J* = 5.8, 12.5, 12.5 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ = 165.6, 153.1, 145.7, 145.4, 133.7, 123.6, 70.6, 58.8, 55.0, 53.7, 52.9, 20.9, 19.0. *Anal*. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.39; H, 6.12; N, 5.60. ; EI-HRMS, *m/z* 249.0999. Calcd for $C_{13}H_{15}NO_4$ (M^+) 249.1001. **14**: R_f = 0.54 (70% ethyl acetate-hexane); ^1H NMR ($CDCl_3$) δ = 8.33 (1H, br d, *J* = 8.3 Hz, H-8), 8.25 (1H, s, H-3), 8.01 (1H, br d, *J* = 8.3 Hz, H-5), 7.78 (1H, ddd, *J* = 1.2, 7.1, 8.3 Hz, H-7), 7.65 (1H, ddd, *J* = 1.0, 7.1, 8.3 Hz, H-6), 4.96 (2H, s, C<u>H</u>$_2$OMe), 4.09 (3H, s, CO_2Me), 3.53 (3H, s, CH_2O<u>Me</u>).

Methyl (7*S*,8*R*)-5-Bromo-7,8-epoxy-4-formyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (16). To a solution of **13** (52.0 mg, 0.209 mmol) in acetic acid (2.1 mL) was added at rt NBS (112 mg, 0.627 mmol). After 1 d at rt, saturated aqueous sodium hydrogencarbonate (10 mL) and water (5 mL) were added to the reaction mixture; the new mixture was extracted with ethyl acetate (20 mL X 3). The combined extracts were dried and evaporated. The residue **15** [R_f = 0.52 (50% ethyl acetate-$CHCl_3$); ^1H NMR ($CDCl_3$) δ = 8.34 and 8.29 (each 0.5H, each s, H-3), 7.08 and 6.79 (each 0.5H, each s, C<u>H</u>(OAc)OMe), 5.71 and 5.51 (each 0.5H, each ddd, *J* = 1.2, 1.2, 5.4 Hz, H-5), 4.41 and 4.40 (each 0.5H, each d, *J* = 4.1 Hz, H-8), 4.05 and 4.03 (each 1.5H, each s, CO_2Me), 3.99-3.93 (1H, m, H-7), 3.63 and 3.55 (each 1.5H, each s, CH(OAc)O<u>Me</u>), 3.12 (1H, br d, *J* = 16.8 Hz, H-6), 2.53 (1H, ddd, *J* = 0.8, 5.4, 16.8 Hz, H-6), 2.25 and 2.13 (each 1.5H, each s, CH(O<u>Ac</u>)OMe)] was dissolved in acetic acid (2.1 mL) and water (0.5 mL). After 2 d at rt, the reaction mixture was evaporated. To the residue were added saturated aqueous sodium hydrogencarbonate (10 mL) and water (5 mL); the mixture was extracted with ethyl acetate (20 mL X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (1 g) with 5% acetone-$CHCl_3$ to afford **16** (25.9 mg, 40% from **13**) as a colorless syrup: R_f = 0.43 (50% ethyl acetate-chloroform); $[\alpha]_D^{29}$ = -33.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3620,1720, 1440, 1420, 1310, 1120, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 10.38 (1H, s, CHO), 8.47 (1H, s, H-3), 6.22 (1H, ddd, *J* = 1.5, 1.5, 5.6 Hz, H-5), 4.46 (1H, d, *J* = 3.9 Hz, H-8), 4.08 (3H, s, CO_2Me), 4.03-3.99 (1H, m, H-7), 3.15 (1H, ddd, *J* = 1.5, 1.9, 17.0 Hz, H-6), 2.58 (1H, ddd, *J* = 0.8, 5.6, 17.0 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ = 190.0, 164.3, 154.7, 148.9, 138.1, 133.9, 126.4, 54.5, 53.4, 52.9, 33.0, 29.8. FAB-HRMS, *m/z* 311.9865. Calcd for $C_{12}H_{11}NO_4Br$ (MH^+) 311.9871.

Methyl (7*S*,8*R*)-5-Bromo-7,8-epoxy-4-hydroxymethyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (17). To a solution of **16** (20.6 mg, 0.0660 mmol) in MeOH (0.66 mL) was added at 0 °C $NaBH_4$ (2.50 mg, 0.0660 mmol). After 15 min at rt, water (2 mL) was added to the reaction mixture; the new mixture was extracted with ethyl acetate (3 mL X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (1 g) with 40% acetone-hexane to afford **17** (18.3 mg, 88%) as a colorless syrup: R_f = 0.37 (50% acetone-hexane); $[\alpha]_D^{28}$ = +3.80° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3620, 2980,1720, 1590, 1440, 1420, 1310, 1130, 1050, 1000, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.32 (1H, s, H-3), 5.37 (1H, ddd, *J* = 1.4, 1.4, 5.6 Hz, H-5), 4.96 and 4.87 (each 1H, ABq, *J* = 14.7, C<u>H</u>$_2$OH), 4.38 (1H, d, *J*

= 3.9 Hz, H-8), 4.03 (3H, s, CO_2Me), 3.98-3.94 (1H, m, H-7), 3.10 (1H, ddd, *J* = 1.4, 1.4, 16.8 Hz, H-6), 2.54 (1H, ddd, *J* = 0.0, 5.6, 16.8 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ = 165.2, 152.5, 149.3, 147.7, 131.8, 123.5, 60.0, 54.4, 53.2, 53.0, 34.8, 30.6. FAB-HRMS, *m/z* 314.0026. Calcd for $C_{12}H_{13}NO_4Br$ (MH^+) 314.0028.

Formation of MTPA Esters of 17. To a solution of **17** (2.7 mg, 0.0086 mmol) in dry CH_2Cl_2 (0.1 mL) were added at rt triethylamine (0.002 mL, 0.014 mmol), 4-dimethylaminopyridine (DMPA) (0.2 mg, 0.0016 mmol), and (*R*)-MTPACl (0.002 mL, 0.011 mmol). After 15 min at rt, water was added; the mixture was extracted with ethyl acetate. The extracts were evaporated and the residue was purified using PTLC with 40% acetone-hexane to afford MTPA ester of **17** (3.8 mg, 83%) as a colorless syrup. By using (*S*)-MTPACl, MTPA ester of **17** was obtained (84%) as a colorless syrup. **MTPA ester from (*R*)-MTPACl**: ^1H NMR ($CDCl_3$) δ = 8.01 (1H, s, H-3), 7.49-7.32 (5H, m, Ph), 5.60 (1H, d, *J* = 13.8 Hz, C<u>H</u>$_2$OMTPA), 5.32 (1H, d, *J* = 13.8 Hz, C<u>H</u>$_2$OMTPA), 5.29 (1H, d, *J* = 4.8 Hz, H-5), 4.38 (1H, d, *J* = 4.1 Hz, H-8), 4.01 (3H, s, CO_2Me), 3.98-3.93 (1H, m, H-7), 3.56 (3H, s, OMe), 3.02 (1H, br d, *J* = 16.8 Hz, H-6), 2.41 (1H, ddd, *J* = 0.0, 5.6, 16.8 Hz, H-6). **MTPA Ester from (*S*)-MTPACl**: ^1H NMR ($CDCl_3$) δ = 8.14 (1H, s, H-3), 7.46-7.32 (5H, m, Ph), 5.49 (2H, s, C<u>H</u>$_2$OMTPA), 5.31 (1H, d, *J* = 5.6 Hz, H-5), 4.38 (1H, d, *J* = 3.9 Hz, H-8), 4.04 (3H, s, CO_2Me), 3.94-3.90 (1H, m, H-7), 3.56 (3H, s, OMe), 2.99 (1H, br d, *J* = 16.8 Hz, H-6), 2.22 (1H, ddd, *J* = 0.0, 5.6, 16.8 Hz, H-6).

Methyl (7*S*,8*R*)-7,8-Epoxy-4-hydroxymethyl-7,8-dihydroquinoline-2-carboxylate (1). To a solution of **17** (23.3 mg, 0.0742 mmol) in dry THF (0.75 mL) was added at rt DBU (0.0388 mL, 0.260 mmol). After 1 h at rt, water (3 mL) was added and the mixture was extracted with ethyl acetate (5 mL X 3). The combined extracts were dried and evaporated. The residue was chromatographed on silica gel (1 g) with 70% ethyl acetate-hexane to afford **1** (10.0 mg, 58%) as a colorless syrup: R_f = 0.30 (70% ethyl acetate-hexane); $[\alpha]_D^{30}$ +56.9° (*c* 1.00, MeOH); IR ($CHCl_3$) 3620, 2980,1720, 1350, 1300, 1120, 1080, 1050, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.27 (1H, s, H-3), 6.97 (1H, dd, *J* = 1.7, 10.0 Hz, H-5), 6.71 (1H, dd, *J* = 3.9, 10.0 Hz, H-6), 4.92 (2H, s, C<u>H</u>$_2$OH), 4.83 (1H, d, *J* = 3.9 Hz, H-8), 4.21 (1H, ddd, *J* = 1.7, 3.9, 3.9 Hz, H-7), 4.03 (3H, s, CO_2Me); ^{13}C NMR ($CDCl_3$) δ = 165.3, 152.0, 147.3, 146.2, 130.0, 127.5, 125.0, 123.2, 61.1, 58.3, 53.6, 53.1. FAB-HRMS, *m/z* 234.0761. Calcd for $C_{12}H_{12}NO_4$ (MH^+) 234.0766.

Methyl (7*R*,8*S*)-7-[*N*-(1*S*)-(1-Benzyloxycarbonyl-2-methylpropyl)amino]-8-hydroxy-4-hydroxymethyl-7,8-dihydroquinoline-2-carboxylate (2) and Its Diastereomer. To a solution of **1** (9.40 mg, 0.0405 mmol) and *L*-valine benzyl ester (25.1 mg, 0.121 mmol) in dry acetonitrile (0.21 mL) was added at rt lithium perchlorate (21.6 mg, 0.203 mmol). After 16 h at 70 °C, saturated aqueous sodium hydrogencarbonate (1 mL) was added and the mixture was extracted with ethyl acetate (2 mL X 3). The combined extracts were dried and evaporated. The residue was purified using PTLC with 50% acetone-hexane to afford **2** (6.7 mg, 38%) and its diastereomer (0.32 mg, 1.8%) as colorless syrups: **2**: R_f = 0.63 (50% acetone-hexane); $[\alpha]_D^{26}$ -41.1° (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 3620, 2980, 1730, 1420, 1040, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.13 (1H, s, H-3), 7.39-7.28 (5H, m, CH_2<u>Ph</u>), 6.56 (1H, dd, *J* = 2.5, 10.1 Hz, H-5), 6.15 (1H, dd, *J* = 1.8, 10.1 Hz, H-6), 5.19 and 5.12 (each 1H, ABq, *J* = 12.2 Hz, C<u>H</u>$_2$Ph), 4.85 and 4.77 (each 1H, ABq, *J* = 14.4 Hz, C<u>H</u>$_2$OH), 4.72 (1H, d, *J* = 12.2 Hz, H-8), 3.98 (3H, s, CO_2Me), 3.52 (1H, ddd, *J* = 1.8, 2.5, 12.2 Hz, H-7), 3.29 (1H, d, *J* = 5.9 Hz, C<u>H</u>(CO_2Bn)$CHMe_2$), 2.07-1.93 (1H, m,

$CH(CO_2Bn)C\underline{H}Me_2$), 0.97 (6H, d, J = 6.8 Hz, $CH(CO_2Bn)CH\underline{Me_2}$); ^{13}C NMR ($CDCl_3$) δ = 174.7, 165.4, 156.3, 144.8, 144.5, 135.9, 135.8, 128.5, 128.4, 128.2, 128.0, 122.8, 120.4, 72.8, 66.5, 64.6, 61.0, 59.5, 52.7, 31.9, 19.4, 18.4. EI-HRMS, m/z 440.1949. Calcd for $C_{24}H_{28}N_2O_6$ (M^+) 440.1947.

Diastereomer of 2: R_f = 0.56 (50% acetone-hexane); ^1H NMR ($CDCl_3$) δ = 8.14 (1H, s, H-3), 7.40-7.30 (5H, m, $CH_2\underline{Ph}$), 6.58 (1H, dd, J = 2.4, 10.0 Hz, H-5), 6.10 (1H, dd, J = 2.4, 10.0 Hz, H-6), 5.22 and 5.13 (each 1H, ABq, J = 12.0 Hz, $C\underline{H_2}Ph$), 4.86 and 4.78 (each 1H, ABq, J = 14.0 Hz, $C\underline{H_2}OH$), 4.77 (1H, d, J = 11.0 Hz, H-8), 3.99 (3H, s, CO_2Me), 3.65 (1H, ddd, J = 2.4, 2.4, 11.0 Hz, H-7), 3.53 (1H, d, J = 6.0 Hz, $C\underline{H}(CO_2Bn)CHMe_2$), 2.10-1.93 (1H, m, $CH(CO_2Bn)C\underline{H}Me_2$), 0.96 (6H, d, J = 6.8 Hz, $CH(CO_2Bn)CH\underline{Me_2}$).

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