

**SYNTHETIC STUDIES ON THIOSTREPTON FAMILY OF PEPTIDE  
ANTIBIOTICS: SYNTHESIS OF THE TETRASUBSTITUTED  
DIHYDROQUINOLINE PORTION OF SIOMYCIN D<sub>1</sub>**

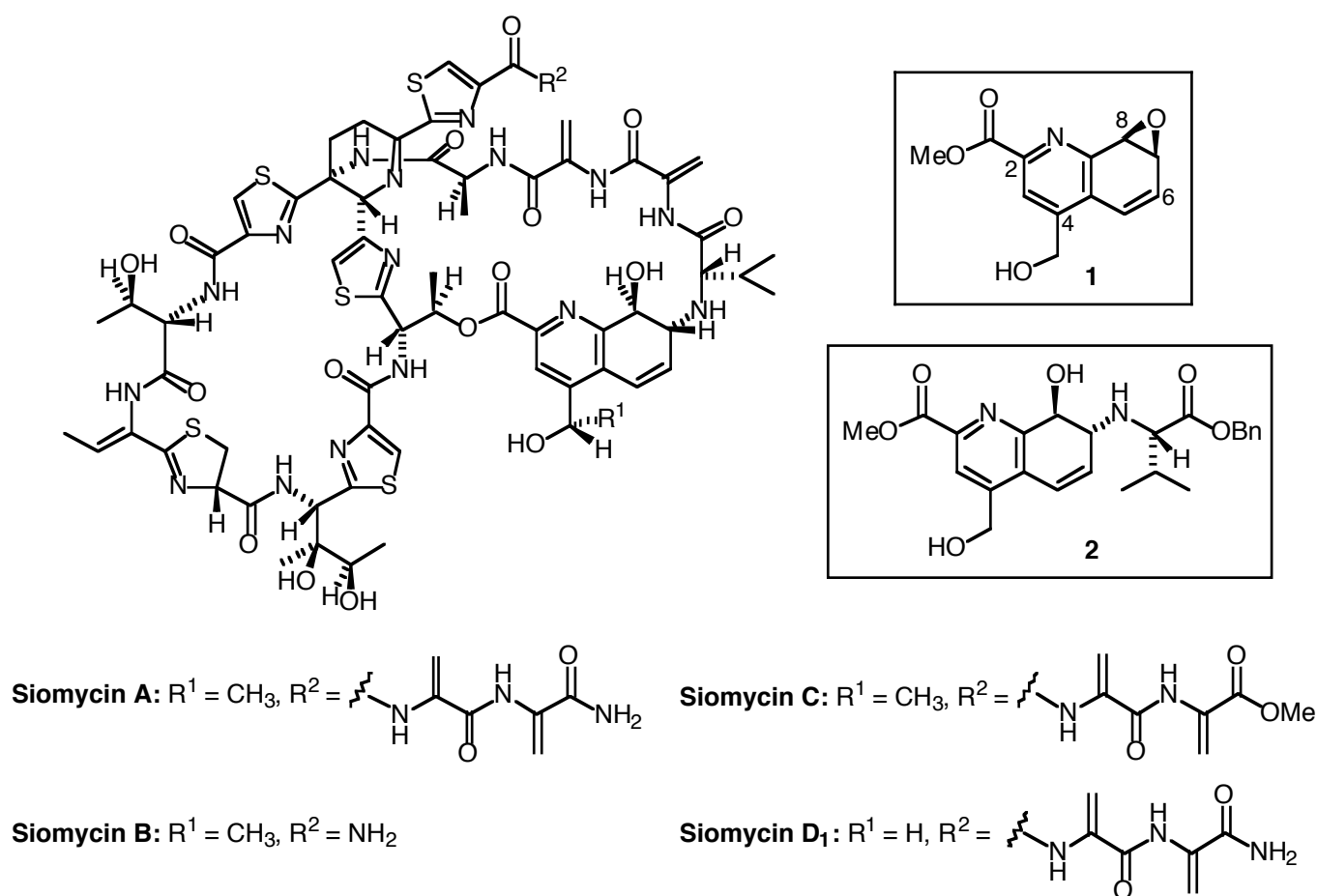
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**Abstract** - The tetrasubstituted dihydroquinoline portion of siomycin D<sub>1</sub>, a member of the thiostrepton family of peptide antibiotics, was synthesized from 5,6,7,8-tetrahydroquinoline featuring the modified Reissert-Henze reaction, the homolytic aromatic substitution reaction, the modified Boekelheide rearrangement, and the Jacobsen asymmetric epoxidation.

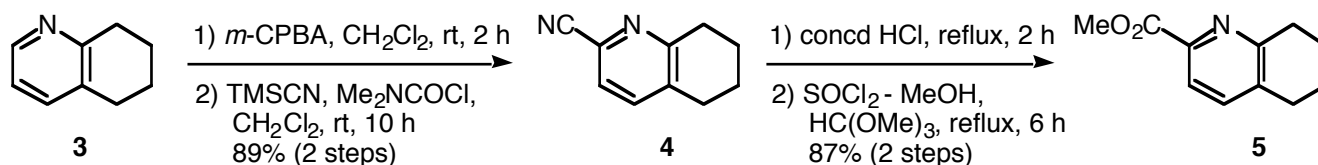
In 1961, siomycin A was isolated from the culture broth of *Streptomyces sioyaensis* by the Shionogi group.<sup>1</sup> In 1969, siomycin B was recognized as an artifact of siomycin A, and siomycin C was isolated from the same culture broth.<sup>2</sup> Siomycin D<sub>1</sub> was also isolated from the same culture broth in 1980 as a minor component of the siomycins.<sup>3</sup> Their structures were elucidated by chemical degradation studies<sup>4</sup> and NMR spectral studies<sup>3,5</sup> 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.<sup>6</sup> 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.<sup>7</sup> Most efforts have focused on the syntheses of the much simpler thiopeptide antibiotics: the berninamycins,<sup>8</sup> the micrococciins,<sup>9</sup> nosiheptide,<sup>10</sup> sulfomycin I,<sup>11</sup> cyclothiazomycin,<sup>12</sup> A10255,<sup>13</sup> GE 2270 A,<sup>14</sup> and promothiocin A.<sup>15</sup> These antibiotics show high activities against Gram-positive bacteria and mycobacteria,<sup>1,2,3</sup> and their mode of action has been described.<sup>9i,15b,16</sup> In this paper, we describe the enantioselective synthesis of the tetrasubstituted dihydroquinoline portions (**1**) and (**2**) of siomycin D<sub>1</sub>. It has been proposed by Floss and his co-workers<sup>16b</sup> 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.<sup>16b</sup> This synthetic process was applied to the early stage of our synthesis of **1** and **2** with slight modifications.



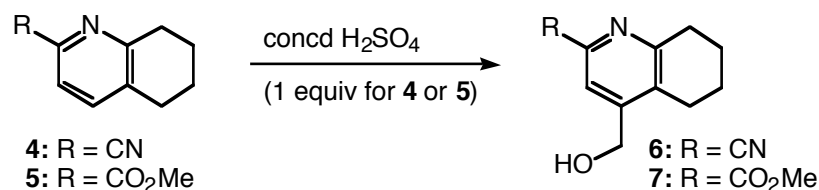
**Figure 1**

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<sup>17</sup> using trimethylsilyl cyanide (TMSCN) and dimethylcarbonyl chloride in CH<sub>2</sub>Cl<sub>2</sub> to afford 2-cyanotetrahydroquinoline (**4**)<sup>18</sup> in 89% yield (Scheme 1). Acid hydrolysis of **4** followed by esterification gave ester (**5**)<sup>19</sup> 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.*<sup>20</sup> The relevant data are shown in Table 1. For nitrile (**4**), the use of aqueous H<sub>2</sub>O<sub>2</sub> - FeSO<sub>4</sub>•7H<sub>2</sub>O or ammonium persulfate [(NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>] in aqueous acidic MeOH resulted in a low yield of **6** (entries 1 and 2). In addition, photochemical conditions using benzophenone in acidic MeOH<sup>21</sup> gave an unsatisfactory result (entry 3). In contrast, for ester (**5**), a satisfactory result was obtained when **5** was treated with (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in aqueous acidic MeOH, giving **7** in 98% yield (entry 5).

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

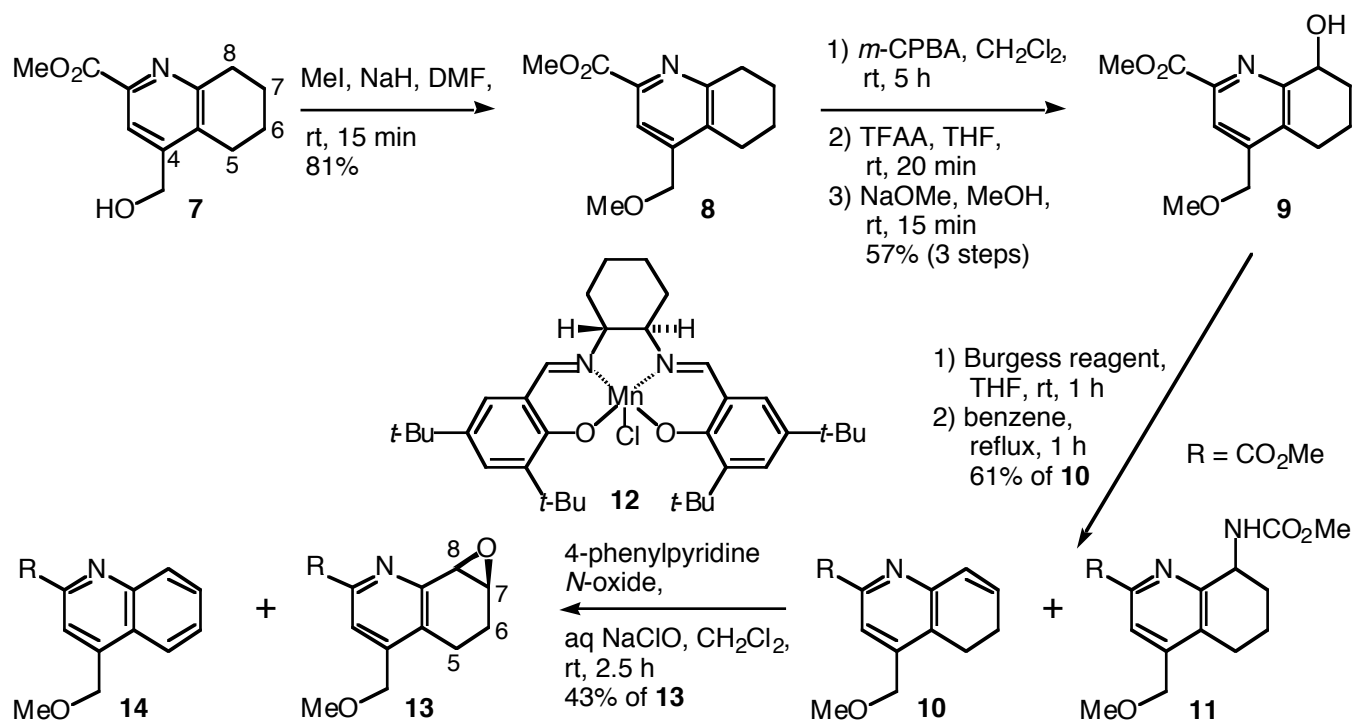
entry	substrate	reagents (equiv for <b>4</b> or <b>5</b> )	solvent	temp	time	yield % of <b>6</b> or <b>7</b>
1	<b>4</b>	H <sub>2</sub> O <sub>2</sub> (3.8), FeSO <sub>4</sub> ·7H <sub>2</sub> O (4.5)	MeOH / H <sub>2</sub> O 2 : 1	rt	22 h	19 <sup>a</sup>
2	<b>4</b>	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1.5)	MeOH / H <sub>2</sub> O 4 : 1	reflux	31 h	9 <sup>b</sup>
3	<b>4</b>	PhCOPh (1.0), hv <sup>c</sup>	MeOH	rt	28 h	25 <sup>d</sup>
4	<b>5</b>	H <sub>2</sub> O <sub>2</sub> (6.8), FeSO <sub>4</sub> ·7H <sub>2</sub> O (7.5)	MeOH / H <sub>2</sub> O 2 : 1	rt	6 d	19 <sup>b</sup>
5	<b>5</b>	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (2)	MeOH / H <sub>2</sub> O 4 : 1	reflux	2 h	98
6	<b>5</b>	PhCOPh (1.0), hv <sup>c</sup>	MeOH	rt	4.5 h	trace <sup>b</sup>

<sup>a</sup>**4** was recovered in 67% yield. <sup>b</sup>Decomposition occurred. <sup>c</sup>hv: 400 W high-pressure mercury lamp. <sup>d</sup>**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<sup>22</sup> of the olefin function and the C5-C6 double bond would be introduced by the benzylic C5 bromination-dehydrobromination procedure.<sup>23</sup> 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 alkoxyethyl substituents attached to aromatic nuclei are oxidized by brominating reagents to formyl groups.<sup>24</sup> 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<sup>25</sup> 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<sub>2</sub>CNSO<sub>2</sub>NEt<sub>3</sub>)<sup>26a</sup> in THF<sup>26b</sup> 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**)<sup>22</sup> 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<sup>23</sup> of **13** using NBS in acetic acid<sup>23c</sup> at room tempera-



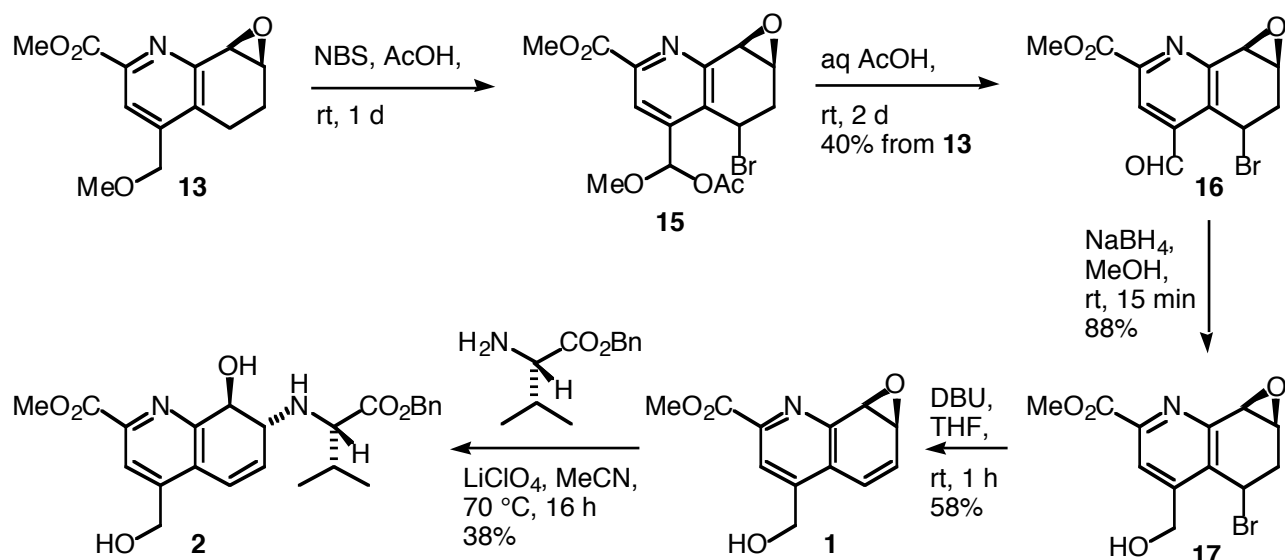
**Scheme 2**

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<sup>24</sup> 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<sub>4</sub> gave alcohol (**17**), the enantiomeric excess of which, and hence **13**, was determined to be 91% by <sup>1</sup>H NMR spectral analysis of the (*R*)- and (*S*)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetate (MTPA esters) of **17**.<sup>27,28</sup> 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<sub>1</sub>. Finally, regioselective epoxide-ring opening<sup>29</sup> of **1** with *L*-valine benzyl ester in the presence of LiClO<sub>4</sub><sup>30</sup> 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<sub>1</sub> from tetrahydroquinoline.<sup>31</sup> 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. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured at 300 and 75 MHz in CDCl<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>; 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<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub> (440 mL) were successively added at rt 95% TMSCN (64.0 mL, 0.484 mol) and dimethylcarbonyl 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<sub>3</sub> (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*<sub>f</sub> = 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<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>10</sub>H<sub>10</sub>N<sub>2</sub>: 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<sub>3</sub>); mp 53-54 °C (not recrystallized); IR (nujol) 1720, 1580, 1320, 1260, 1200, 1130, 990, 970, 800, 780, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta = 7.88$  (1H, d,  $J = 8.0$  Hz, H-3), 7.49 (1H, d,  $J = 8.0$  Hz, H-4), 3.98 (3H, s, CO<sub>2</sub>Me), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta = 166.1, 158.0, 145.0, 137.4, 136.7, 122.5, 52.8, 32.7, 29.0, 22.8, 22.3$ . *Anal.* Calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>: 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<sub>3</sub>); mp 170-171 °C (not recrystallized); IR (nujol) 3340, 1720, 1590, 1360, 1340, 1220, 1100, 1000, 900, 790 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta = 8.07$  (1H, s, H-3), 4.71 (2H, br s, CH<sub>2</sub>OH), 3.95 (3H, s, CO<sub>2</sub>Me), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta = 166.1, 157.4, 149.2, 144.7, 133.4, 119.8, 61.0, 52.7, 32.9, 25.0, 22.4, 22.0$ . *Anal.* Calcd for C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>: 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<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta = 8.01$  (1H, s, H-3), 4.44 (2H, br s, CH<sub>2</sub>OH), 3.98 (3H, s, CO<sub>2</sub>Me), 3.47 (3H, s, CH<sub>2</sub>OMe), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta = 166.1, 157.7, 146.2, 144.9, 133.9, 120.8, 70.7, 58.8, 52.7, 33.2, 25.1, 22.4, 22.1$ . *Anal.* Calcd for C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>: 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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>; 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<sub>3</sub> (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*<sub>f</sub> = 0.64 (70% acetone-hexane); mp 121-122 °C (not recrystallized); IR (nujol) 3300, 1720, 1330, 1300, 1220, 1190, 1120, 970, 910, 880 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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, CH<sub>2</sub>OMe), 3.98 (3H, s, CO<sub>2</sub>Me), 3.48 (3H, s, CH<sub>2</sub>OMe), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>13</sub>H<sub>17</sub>NO<sub>4</sub>: 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<sub>2</sub>CNSO<sub>2</sub>NEt<sub>3</sub>,<sup>26a</sup> (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*<sub>f</sub> = 0.73 (70% acetone-hexane); mp 75-76 °C (not recrystallized); IR (nujol) 1740, 1580, 1310, 1220, 1110, 1000, 960, 900, 820, 780 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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, CH<sub>2</sub>OMe), 3.99 (3H, s, CO<sub>2</sub>Me), 3.46 (3H, s, CH<sub>2</sub>OMe), 2.87 (2H, dd, *J* = 8.3, 8.3 Hz, H-5), 2.48-2.34 (2H, m, H-6); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>13</sub>H<sub>15</sub>NO<sub>3</sub>: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.55; H, 6.56; N, 6.01. **11**: *R*<sub>f</sub> = 0.63 (70% acetone-hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.09 (1H, s, H-3), 6.10-5.88 (1H, br s, NHCO<sub>2</sub>Me), 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, CH<sub>2</sub>OMe), 3.98 (3H, s, CO<sub>2</sub>Me), 3.73 (3H, s, NHCO<sub>2</sub>Me), 3.49 (3H, s, CH<sub>2</sub>OMe), 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 (7S,8R)-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<sub>2</sub>Cl<sub>2</sub> (27 mL) were added at rt the Jacobsen reagent (**12**)<sup>22</sup> (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<sub>3</sub>. The filtrate and washings were extracted with CHCl<sub>3</sub> (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*<sub>f</sub> = 0.36

(70% ethyl acetate-hexane); mp 105-107 °C (not recrystallized);  $[\alpha]_D^{28} = +43.2^\circ$  (*c* 1.00, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3620, 2960, 1730, 1590, 1440, 1350, 1300, 1130, 1000, 960, 800 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.15 (1H, s, H-3), 4.52 and 4.45 (each 1H, ABq, *J* = 13.3 Hz, CH<sub>2</sub>OMe), 4.25 (1H, d, *J* = 4.1 Hz, H-8), 4.02 (3H, s, CO<sub>2</sub>Me), 3.83 (1H, m, H-7), 3.45 (3H, s, CH<sub>2</sub>OMe), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 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<sub>13</sub>H<sub>15</sub>NO<sub>4</sub>: 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<sub>13</sub>H<sub>15</sub>NO<sub>4</sub> (M<sup>+</sup>) 249.1001. **14**: *R*<sub>f</sub> = 0.54 (70% ethyl acetate-hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 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, CH<sub>2</sub>OMe), 4.09 (3H, s, CO<sub>2</sub>Me), 3.53 (3H, s, CH<sub>2</sub>OMe).

**Methyl (7S,8R)-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*<sub>f</sub> = 0.52 (50% ethyl acetate-CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.34 and 8.29 (each 0.5H, each s, H-3), 7.08 and 6.79 (each 0.5H, each s, CH(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<sub>2</sub>Me), 3.99-3.93 (1H, m, H-7), 3.63 and 3.55 (each 1.5H, each s, CH(OAc)OMe), 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(OAc)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<sub>3</sub> to afford **16** (25.9 mg, 40% from **13**) as a colorless syrup: *R*<sub>f</sub> = 0.43 (50% ethyl acetate-chloroform);  $[\alpha]_D^{29} = -33.0^\circ$  (*c* 1.00, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3620, 1720, 1440, 1420, 1310, 1120, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 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<sub>2</sub>Me), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 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<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>Br (MH<sup>+</sup>) 311.9871.

**Methyl (7S,8R)-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<sub>4</sub> (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*<sub>f</sub> = 0.37 (50% acetone-hexane);  $[\alpha]_D^{28} = +3.80^\circ$  (*c* 1.00, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3620, 2980, 1720, 1590, 1440, 1420, 1310, 1130, 1050, 1000, 880 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 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, CH<sub>2</sub>OH), 4.38 (1H, d, *J*



= 3.9 Hz, H-8), 4.03 (3H, s, CO<sub>2</sub>Me), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>12</sub>H<sub>13</sub>NO<sub>4</sub>Br (MH<sup>+</sup>) 314.0028.

**Formation of MTPA Esters of 17.** To a solution of **17** (2.7 mg, 0.0086 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (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:** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.01 (1H, s, H-3), 7.49-7.32 (5H, m, Ph), 5.60 (1H, d, *J* = 13.8 Hz, CH<sub>2</sub>OMTPA), 5.32 (1H, d, *J* = 13.8 Hz, CH<sub>2</sub>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<sub>2</sub>Me), 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:** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.14 (1H, s, H-3), 7.46-7.32 (5H, m, Ph), 5.49 (2H, s, CH<sub>2</sub>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<sub>2</sub>Me), 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*<sub>f</sub> = 0.30 (70% ethyl acetate-hexane); [α]<sub>D</sub><sup>30</sup> +56.9° (*c* 1.00, MeOH); IR (CHCl<sub>3</sub>) 3620, 2980, 1720, 1350, 1300, 1120, 1080, 1050, 880 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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, CH<sub>2</sub>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<sub>2</sub>Me); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>12</sub>H<sub>12</sub>NO<sub>4</sub> (MH<sup>+</sup>) 234.0766.

**Methyl (7*R*,8*S*)-7-[*N*-(1*S*)-(1-Benzoyloxycarbonyl-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*<sub>f</sub> = 0.63 (50% acetone-hexane); [α]<sub>D</sub><sup>26</sup> -41.1° (*c* 0.42, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3620, 2980, 1730, 1420, 1040, 880 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.13 (1H, s, H-3), 7.39-7.28 (5H, m, CH<sub>2</sub>Ph), 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, CH<sub>2</sub>Ph), 4.85 and 4.77 (each 1H, ABq, *J* = 14.4 Hz, CH<sub>2</sub>OH), 4.72 (1H, d, *J* = 12.2 Hz, H-8), 3.98 (3H, s, CO<sub>2</sub>Me), 3.52 (1H, ddd, *J* = 1.8, 2.5, 12.2 Hz, H-7), 3.29 (1H, d, *J* = 5.9 Hz, CH(CO<sub>2</sub>Bn)CHMe<sub>2</sub>), 2.07-1.93 (1H, m,

CH(CO<sub>2</sub>Bn)CHMe<sub>2</sub>), 0.97 (6H, d, *J* = 6.8 Hz, CH(CO<sub>2</sub>Bn)CHMe<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub> (M<sup>+</sup>) 440.1947.

**Diastereomer of 2:** *R<sub>f</sub>* = 0.56 (50% acetone-hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 8.14 (1H, s, H-3), 7.40-7.30 (5H, m, CH<sub>2</sub>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, CH<sub>2</sub>Ph), 4.86 and 4.78 (each 1H, ABq, *J* = 14.0 Hz, CH<sub>2</sub>OH), 4.77 (1H, d, *J* = 11.0 Hz, H-8), 3.99 (3H, s, CO<sub>2</sub>Me), 3.65 (1H, ddd, *J* = 2.4, 2.4, 11.0 Hz, H-7), 3.53 (1H, d, *J* = 6.0 Hz, CH(CO<sub>2</sub>Bn)CHMe<sub>2</sub>), 2.10-1.93 (1H, m, CH(CO<sub>2</sub>Bn)CHMe<sub>2</sub>), 0.96 (6H, d, *J* = 6.8 Hz, CH(CO<sub>2</sub>Bn)CHMe<sub>2</sub>).

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