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Asymmetric Synthesis and Absolute Configuration of Streptophenazine G

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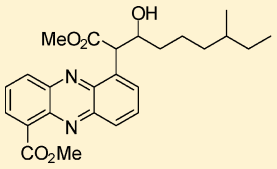
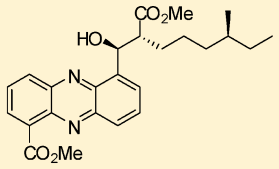
Supporting Information

ABSTRACT: The asymmetric synthesis of the antibacterial natural product, streptophenazine G, has been achieved by employing asymmetric alkylation and asymmetric aldol reactions using chiral oxazolidinones as the key steps. The originally proposed structure for streptophenazine G has been revised, and its absolute configuration has been determined to be 1′*S*,2′*R*,6′*S*. The asymmetric total synthesis of 6′-*epi*-streptophenazine G is also described.



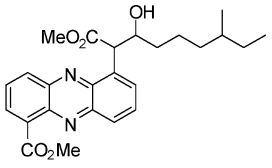
originally proposed structure for streptophenazine G



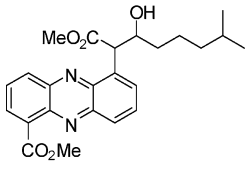
revised structure for streptophenazine G

INTRODUCTION

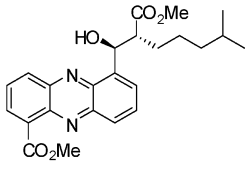
Phenazine derivatives are a potential source of antibiotics.[1] Several novel phenazine analogues, streptophenazines A−H, have been recently isolated from cultures of marine *Streptomyces* sp. strain HB202, some of which have shown moderate antibacterial activities.[2] In the streptophenazine family, streptophenazine G (**1**) is a unique member that possesses three stereogenic centers on the side chain (Figure 1). The structure of streptophenazine G was elucidated by



proposed structure for streptophenazine G (**1**)



proposed structure for streptophenazine A (**2**)



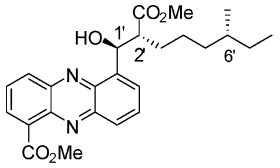
revised structure for streptophenazine A (**3**)

Figure 1. Structures of streptophenazines A and G.

spectroscopic methods. However, its stereochemistry was not determined. Our interest in these novel phenazine analogues has led to the structural revision for streptophenazine A (**3**).[3] We report herein the first synthesis and absolute stereochemistry of streptophenazine G.

RESULTS AND DISCUSSION

Our recent efforts on streptophenazine chemistry have led to the structural revision for streptophenazine A from **2** to **3** (Figure 1), and further studies on streptophenazines B and E have demonstrated that their absolute configurations are the same as streptophenazine A.[3] We assume that the structure of streptophenazine G should also be revised to 1′-hydroxy-2′-carboxylate and that it possesses 1′*S*,2′*R* stereochemistry on the side chain as well. Thus, the true structure of streptophenazine G is either **4** or **5** (Figure 2).



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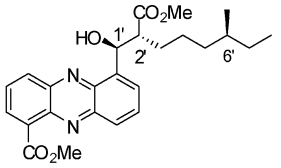

5

Figure 2. Structure of streptophenazine G (**4** or **5**).

As shown in Schemes 1 and 2, the well-developed methodology of Evans was employed to establish the stereochemistry for the 6′-position on the side chain.[4] Treatment of (*R*)-4-benzyloxazolidin-2-one [(*R*)-**6**] with *n*-butyllithium followed by reaction with acid chloride **7** provided oxazolidinone **8** in good yield. Deprotonation of **8** with sodium bis(trimethylsilylamide) followed by highly diastereoselective alkylation of the resulting chiral imide enolate with iodomethane afforded the desired compound **9** in good yield.[5] Reduction of **9** with lithium borohydride produced the corresponding alcohol. Because of its low boiling point, however, the isolated yield of the alcohol was low. By treatment of the crude alcohol with tosyl chloride in the presence of pyridine, the tosylate **10** was isolated in 80% overall yield from **9**. Reaction of **10** with sodium iodide in acetonitrile yielded iodide **11** smoothly. Reaction of **11** with triphenylphosphine

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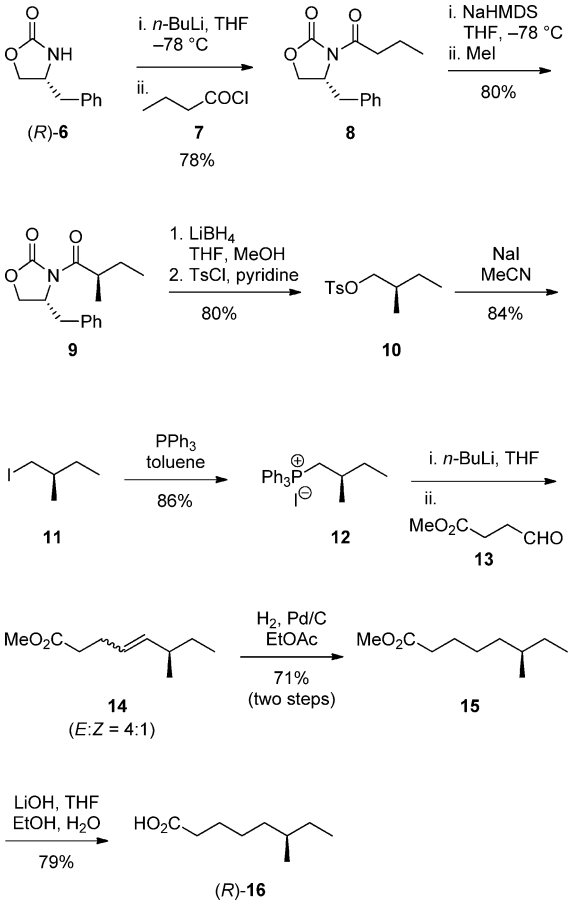
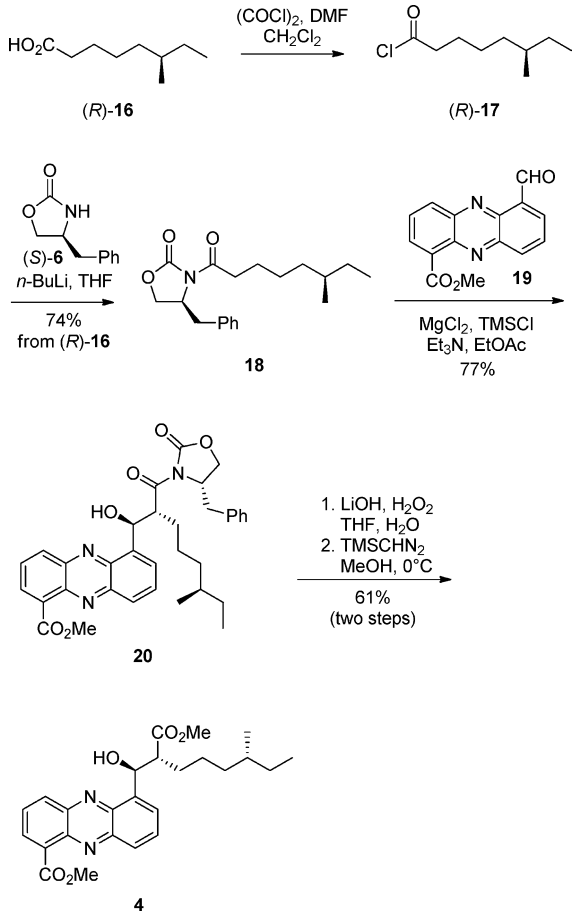
Scheme 1. Synthesis of Acid 16



Scheme 2. Asymmetric Synthesis of 4



provided the phosphonium salt **12** in 86% yield. Wittig reaction of the ylide that was generated from **12** using *n*-butyllithium as base with the commercially available aldehyde **13** gave a mixture of (*E*) and (*Z*)-olefins **14** (*E*/*Z* = 4:1).[6] The mixture was smoothly transformed into **15** by hydrogenation with palladium on carbon. Hydrolysis of ester **15** with lithium hydroxide afforded the corresponding acid (*R*)-**16** in good yield.

Conversion of acid (*R*)-**16** to **4** is depicted in Scheme 2. Acid (*R*)-**16** was transformed into the corresponding acid chloride (*R*)-**17**, and subsequent coupling of (*R*)-**17** with the lithium salt of (*S*)-4-benzyloxazolidin-2-one [(*S*)-**6**] provided oxazolidinone **18** in 74% overall yield from (*R*)-**16**. Asymmetric aldol reaction of **18** with aldehyde **19**[3] afforded exclusively the desired *anti*-adduct **20**.[7] Hydrolysis of **20** with lithium hydroxide in the presence of hydrogen peroxide,[8] followed by treatment of the resulting acid with (trimethylsilyl)-diazomethane gave compound **4**. The structure of **4** was confirmed by HRMS, ^{1}H, ^{13}C, 2D COSY, HSQC, and HMBC NMR studies. However, the data of ^{1}H and ^{13}C NMR of compound **4** are slightly different from those reported for naturally occurring streptophenazine G.[10] For example, the signal of the methylene group at 4′-position on the side chain of the natural product was recorded at δ 1.22 in the ^{1}H NMR spectrum, whereas the signals for those protons were found at δ 1.27 and δ 1.15, respectively in the ^{1}H NMR spectrum of compound **4**.[9] The results compelled us to synthesize isomer **5**.

Utilizing the same strategy from Scheme 2, asymmetric synthesis of **5** was conducted using (*S*)-4-benzyloxazolidin-2-one as the chiral auxiliary (Scheme 3). The commercially available alcohol **21**[10] was converted to acid (*S*)-**16** with NaClO and $NaClO_2$ in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[11] Treatment of acid (*S*)-**16** with oxalyl chloride provided acid chloride (*S*)-**17**. Reaction of (*S*)-**17** with the lithium salt that was generated from (*S*)-**6** and *n*-butyllithium afforded oxazolidinone **22** in good yield. Asymmetric aldol reaction of oxazolidinone **22** with aldehyde **19** afforded exclusively the desired *anti*-adduct **23**. Hydrolysis of **23** with lithium hydroxide in the presence of hydrogen peroxide, followed by treatment of the resulting acid with (trimethylsilyl)diazomethane gave **5**, $[\alpha]^{20}_{D}$ −44.6 (*c* 1.5, MeOH). The structure of **5** was assigned on the basis of HRMS, ^{1}H, ^{13}C, 2D COSY, HSQC, and HMBC NMR studies. The spectroscopic data of compound **5** are consistent with the naturally occurring (−)-streptophenazine G,[9,12] and its physical properties are in agreement with those reported in the literature.[3] Therefore, the originally proposed structure for (−)-streptophenazine G was revised to **5**, and its absolute stereochemistry was determined to be 1′*S*,2′*R*,6′*S*.

■ CONCLUSIONS

In conclusion, we accomplished the first asymmetric synthesis of (−)-streptophenazines G by utilizing asymmetric aldol reaction developed by Evans and co-workers[8] as the key step. The originally proposed structure for streptophenazine G was revised to be **5**, and its absolute stereochemistry was determined to be 1′*S*,2′*R*,6′*S*. In the meantime, the asymmetric total synthesis of 6′-*epi*-streptophenazine G (**4**) was also

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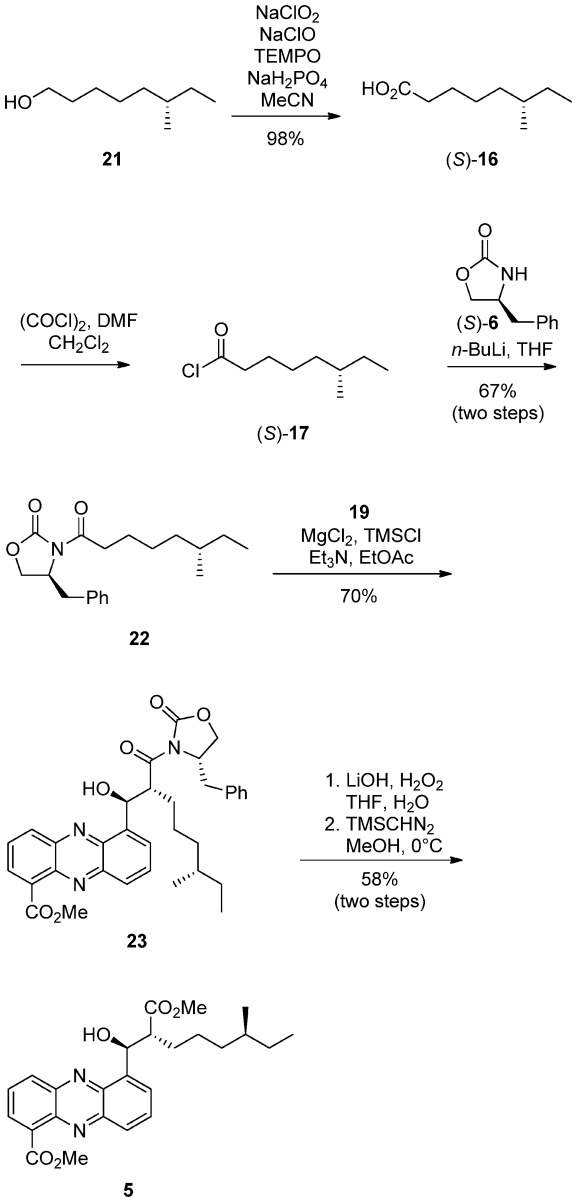
Scheme 3. Asymmetric Synthesis of 5



achieved by employing both asymmetric alkylation and asymmetric aldol reactions using (*R*) or (*S*)-4-benzyloxazolidin-2-one as chiral auxiliaries.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Melting points were not corrected. Optical rotations were measured at room temperature. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 500 and 125 MHz, respectively. Spectra are given in ppm (δ), and coupling constants, *J*, are reported in hertz. Tetramethylsilane was used as an internal standard for proton spectra, and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on an electrospray ionization (ESI) mass spectrometer. High-resolution mass spectrometry (HRMS) was performed in ESI a positive or negative mode. Chromatography was performed on a silica gel column. Chiral HPLC analyses were obtained using a Chiralcel OJ-H column (250 × 4.6 mm) with PDA detection at 20 nm. Chromatography was performed using a Combi-Flash Companion on a silica gel column.

(*R*)-4-Benzyl-3-butyryloxazolidin-2-one (8). A mixture of oxazolidinone (*R*)-**6** (5.00 g, 28.2 mmol) and THF (100 mL) was cooled to −78 °C, and *n*-butyllithium in hexanes (2.5 M, 11.0 mL, 27.5 mmol) was added. The mixture was stirred at −78 °C for 10 min, and acid chloride **7** (2.50 g, 23.5 mmol) was added. After being stirred at −78 °C for 30 min, the cooling bath was removed, and the reaction was allowed to warm to room temperature. Then saturated aqueous ammonium chloride (100 mL) was added, and the resulting mixture was extracted with ethyl acetate (2 × 200 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by chromatography on silica gel (0−50% ethyl acetate/hexanes) to give compound **8** (4.55 g, 78%) as a colorless oil: $[\alpha]^{20}_D$ −57.5 (*c* 0.8, $CHCl_3$) [lit.[13] $[\alpha]^{20}_D$ −57.1 (*c* 1.14, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.32 (m, 2H), 7.29−7.26 (m, 1H), 7.22−7.20 (m, 2H), 4.69−4.65 (m, 1H), 4.22−4.15 (m, 2H), 3.30 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.99−2.85 (m, 2H), 2.77 (dd, *J* = 13.5, 10.0 Hz, 1H), 1.77−1.70 (m, 2H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 153.5, 135.4, 129.4 (2C), 129.0 (2C), 127.3, 66.2, 55.1, 38.0, 37.4, 17.7, 13.7; HRMS (ESI) calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$ 248.1287, found 248.1287.

(*R*)-4-Benzyl-3-((*R*)-2-methylbutanoyl)oxazolidin-2-one (9). A mixture of **8** (4.00 g, 16.2 mmol) and anhydrous THF (25 mL) was cooled to −78 °C, and NaHMDS in THF (1.0 M, 24.3 mL, 24.3 mmol) was added dropwise. After the mixture was stirred at −78 °C for 1 h, a solution of iodomethane (11.5 g, 81.0 mmol) in anhydrous THF (25 mL) was added. The reaction mixture was stirred at −78 °C for 5 h and then quenched with acetic acid (5 mL). The resulting mixture was then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by chromatography on silica gel (0−40% ethyl acetate/hexanes) to give compound **9** (3.40 g, 80%) as a colorless oil: $[\alpha]^{20}_D$ −124.7 (*c* 0.4, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) 7.35−7.32 (m, 2H), 7.29−7.26 (m, 1H), 7.22−7.21 (m, 2H), 4.70−4.66 (m, 1H), 4.22−4.15 (m, 2H), 3.64 (m, 1H), 3.27 (dd, *J* = 13.0, 3.0 Hz, 1H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.80−1.75 (m, 1H), 1.50−1.45 (m, 1H), 1.22 (d, *J* = 6.5 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 153.1, 135.4, 129.5 (2C), 128.9 (2C), 127.3, 66.0, 55.4, 39.2, 37.9, 26.4, 16.9, 11.7; HRMS (ESI) calcd for $C_{15}H_{20}NO_3$ $[M + H]^+$ 262.1443, found 262.1437.

(*R*)-2-Methylbutyl 4-Methylbenzenesulfonate (10).[14] To a mixture of **9** (2.37 g, 9.08 mmol), methanol (0.05 mL), and THF (40 mL) at 0 °C was added lithium borohydride (593 mg, 27.2 mmol). After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous Rochelle salt solution (5 mL). The mixture obtained was diluted with methylene chloride (80 mL) and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was cooled to 0 °C. *p*-Toluenesulfonyl chloride (17.3 g, 90.8 mmol) was added, followed by pyridine (14.4 g, 182 mmol). After the mixture was stirred at 0 °C for 10 h, water (100 mL) was added, and the resulting mixture was extracted with methylene chloride (3 × 50 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (300 mL) and water (100 mL) and dried over anhydrous Na_2SO_4. The drying agent was then removed by filtration, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by chromatography on silica gel (0−10% ethyl acetate/hexanes) to give compound **10** (1.77 g, 80%) as a colorless oil: $[\alpha]^{20}_D$ −4.1 (*c* 1.1, pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0, 2H), 3.88 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.82 (dd, *J* = 9.0, 6.5 Hz, 1H), 2.45 (s, 3H), 1.74−1.68 (m, 1H), 1.43−1.35 (m, 1H), 1.19−1.10 (m, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 133.2, 129.8 (2C), 127.9 (2C), 74.8, 34.4, 25.4, 21.6, 16.0, 11.0; HRMS (ESI) calcd for $C_{12}H_{19}O_3S$ $[M + H]^+$ 243.1055, found 243.1048.

(*R*)-1-Iodo-2-methylbutane (11). A mixture of **10** (500 mg, 2.07 mmol), sodium iodide (1.55 g, 10.3 mmol), and DMF (10 mL) was

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heated at 60 °C for 2 h. Water (20 mL) was added, and the resulting mixture was extracted with pentane (3 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated by distillation under atmospheric pressure to give compound **11** (346 mg, 84%) as a colorless oil: $[\alpha]^{20}_D$ −4.8 (*c* 1.0, pentane) [lit.[15] $[\alpha]^{20}_D$ −5.32 (*c* 4.87, pentane)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.18 (dd, *J* = 9.5, 6.0 Hz, 1H), 1.45−1.37 (m, 2H), 1.29−1.25 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.4, 29.2, 20.2, 17.4, 11.3.

(*R*)-(2-Methylbutyl)triphenylphosphonium Iodide (12).[16] A mixture of **11** (1.45 g, 7.31 mmol), triphenylphosphine (2.88 g, 11.0 mmol), and toluene (15 mL) was heated at 105 °C for 48 h. The reaction mixture was then cooled to room temperature and filtered. The filter cake was washed with *tert*-butylmethyl ether (15 mL) and dried at room temperature for 16 h to give compound **12** (3.36 g, 86%) as a white solid: mp 155−156 °C; $[\alpha]^{20}_D$ −9.3 (*c* 0.6, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.90−7.83 (m, 9H), 7.77−7.73 (m, 6H), 3.43−3.29 (m, 2H), 1.94−1.89 (m, 1H), 1.44−1.32 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.5 Hz, 3H).

(*R*)-Methyl 6-Methyloctanoate (15). A mixture of **12** (1.50 g, 3.26 mmol) and THF (10 mL) was cooled to 0 °C, and *n*-butyllithium in hexanes (2.5M, 1.30 mL, 3.26 mmol) was added. After the mixture was stirred at 0 °C for 20 min, a solution of methyl 4-oxobutanoate (**13**, 522 mg, 4.50 mmol) in THF (1 mL) was added. The reaction mixture was stirred at 0 °C for 30 min, saturated aqueous ammonium chloride (5 mL) was added, and the resulting mixture was extracted with pentane (3 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under atmospheric pressure. The residue obtained was purified by chromatography on silica gel (0−50% methylene chloride/pentane) to give compound **14** (554 mg) as a colorless oil and a mixture of (*E*) and (*Z*)-isomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34−5.26 (m, 1H), 5.17 (t, *J* = 10.5 Hz, 1H), 3.67 (s, 3H), 2.39−2.30 (m, 5H), 1.36−1.17 (m, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). A mixture of **14** (554 mg, 3.26 mmol), ethyl acetate (10 mL) and 10% palladium on carbon (50% wet, 100 mg dry weight) was stirred under hydrogen (1 atm) at room temperature for 6 h. After this time, the catalyst was removed by filtration through a pad of Celite 521 and the filter cake was washed with methylene chloride (400 mL). The filtrate was concentrated under reduced pressure to afford **15** (397 mg, 71%) as a colorless oil: $[\alpha]^{20}_D$ −3.9 (*c* 0.9, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.31 (t, *J* = 8.0 Hz, 2H), 1.63−1.57 (m, 2H), 1.35−1.26 (m, 5H), 1.14−1.09 (m, 2H), 0.85 (t, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 51.4, 36.2, 34.2 (2C), 29.4, 26.7, 25.3, 19.1, 11.4; HRMS (ESI) calcd for $C_{10}H_{21}O_2$ $[M + H]^+$ 173.1542, found 173.1550.

(*R*)-6-Methyloctanoic Acid [(*R*)-16]. A mixture of **15** (455 mg, 2.65 mmol), lithium hydroxide (636 mg, 26.5 mmol), ethanol (20 mL), water (10 mL), and THF (5 mL) was stirred at room temperature for 4 h. The organic solvent was removed under reduced pressure, and the residue obtained was extracted with *tert*-butylmethyl ether (5 mL). The aqueous phase was then acidified to pH 0 with 2 N HCl, and the mixture was extracted with methylene chloride (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was dried under vacuum at room temperature to give compound (*R*)-**16** (284 mg, 79%) as a colorless oil: $[\alpha]^{20}_D$ −5.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (br s, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.66−1.59 (m, 2H), 1.37−1.29 (m, 5H), 1.14−1.10 (m, 2H), 0.87−0.84 (m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 179.2, 36.2, 34.2, 33.9, 29.4, 26.6, 25.0, 19.1, 11.4; HRMS (ESI) calcd for $C_9H_{19}O_2$ $[M + H]^+$ 159.1385, found 159.1388.

((*S*)-4-Benzyl-3-((*R*)-6-methyloctanoyl)oxazolidin-2-one (18). A mixture of acid (*R*)-**16** (280 mg, 1.77 mmol), DMF (7 mg, 0.09 mmol), and methylene chloride (5 mL) was cooled to 0 °C, and oxalyl chloride (247 mg, 1.95 mmol) was added. The mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure, and the residue obtained was dried under vacuum at room temperature for 3 h to give compound (*R*)-**17** (313 mg) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (t, *J* = 7.5 Hz, 2H), 1.73−1.66 (m, 2H), 1.38−1.28 (m, 5H), 1.15−1.11 (m, 2H), 0.87−0.84 (m, 6H). A mixture of oxazolidinone (*S*)-**6** (627 mg, 3.54 mmol) and THF (10 mL) was cooled to −78 °C, and *n*-butyllithium in hexanes (2.5 M, 1.42 mL, 3.54 mmol) was added. The mixture was stirred at −78 °C for 10 min, and acid chloride (*R*)-**17** (313 mg, 1.77 mmol) was added. After the mixture was stirred at −78 °C for 30 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Then saturated aqueous ammonium chloride (10 mL) was added, and the resulting mixture was extracted with ethyl acetate (2 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by chromatography on silica gel (0−50% ethyl acetate/hexanes) to give compound **18** (416 mg, 74%) as a colorless oil: $[\alpha]^{20}_D$ +71.1 (*c* 1.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.32 (m, 2H), 7.29−7.27 (m, 1H), 7.22−7.20 (m, 2H), 4.69−4.66 (m, 1H), 4.22−4.15 (m, 2H), 3.30 (dd, *J* = 13.5, 3.5 Hz, 1H), 3.00−2.88 (m, 2H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.71−1.65 (m, 2H), 1.41−1.31 (m, 5H), 1.17−1.12 (m, 2H), 0.88−0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 153.5, 135.4, 129.4 (2C), 129.0 (2C), 127.4, 66.2, 55.2, 38.0, 36.3, 35.6, 34.3, 29.5, 26.7, 24.6, 19.2, 11.4; HRMS (ESI) calcd for $C_{19}H_{28}NO_3$ $[M + H]^+$ 318.2069, found 318.2072.

Methyl 6-((1*S*,2*R*,6*R*)-2-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl)-1-hydroxy-6-methyloctyl)phenazine-1-carboxylate (20). A mixture of **18** (179 mg, 0.56 mmol), anhydrous magnesium chloride (72 mg, 0.75 mmol), triethylamine (114 mg, 1.13 mmol), and ethyl acetate (5 mL) was stirred at room temperature for 10 min. Aldehyde **19** (100 mg, 0.376 mmol) was added, followed by chlorotrimethylsilane (82 mg, 0.75 mmol). The mixture was stirred at room temperature overnight, and saturated aqueous ammonium chloride (3 mL) was added to quench the reaction. The resulting mixture was extracted with ethyl acetate (2 × 10 mL), and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was redissolved in methanol (10 mL), and TFA (0.2 mL) was added. After the mixture was stirred at room temperature for 10 min, saturated aqueous $NaHCO_3$ (0.2 mL) was added. Then the mixture was concentrated under reduced pressure, and the residue obtained was purified by chromatography on silica gel (0−50% ethyl acetate/hexanes) to give compound **20** (170 mg, 77%) as a yellow solid: mp 51−52 °C; $[\alpha]^{20}_D$ −29.3 (*c* 0.9, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.30−8.26 (m, 2H), 7.88 (dd, *J* = 9.0, 7.0 Hz, 1H), 7.85−7.79 (m, 2H), 7.34−7.24 (m, 5H), 5.56−5.45 (m, 2H), 5.20−5.18 (m, 1H), 4.78−4.75 (m, 1H), 4.18−4.14 (m, 2H), 4.12 (s, 3H), 3.39 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.73 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.74−1.72 (m, 1H), 1.26−1.06 (m, 6H), 1.01−0.94 (m, 2H), 0.73 (t, *J* = 7.5 Hz, 3H), 0.69 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 167.0, 153.3, 144.0, 141.3, 141.1, 141.0, 138.9, 135.5, 133.8, 132.6, 131.1, 130.4, 130.3, 129.8, 129.5 (2C), 129.4, 128.9 (2C), 127.3, 77.2, 65.8, 55.8, 52.7, 49.0, 37.8, 36.3, 34.1, 30.8, 29.1, 24.5, 19.2, 11.2; HRMS (ESI) calcd for $C_{34}H_{38}N_3O_6$ $[M + H]^+$ 584.2761, found 584.2745.

(−)-6′-*epi*-Streptophenazine G (4). A mixture of **20** (140 mg, 0.240 mmol) and THF (4 mL) was cooled to 0 °C. Hydrogen peroxide (30 wt % in water, 82 mg, 2.40 mmol) was added, followed by a solution of lithium hydroxide (29 mg, 1.20 mmol) in water (1 mL). After the mixture was stirred at 0 °C for 7 h, a saturated aqueous solution of $NaHSO_3$ (2 mL) was added, and the mixture was stirred at room temperature overnight. The mixture was diluted with 1 M KH_2PO_4 (3 mL) and extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting acid was redissolved in methanol (4 mL) and cooled to 0 °C. (Trimethylsilyl)-diazomethane in hexanes (2.0 M, 2.40 mL, 4.80 mmol) was added. The mixture was stirred at 0 °C for 1 h and then concentrated. The residue obtained was purified by chromatography on silica gel (0−50% ethyl acetate/hexanes) to give compound **4** (65 mg, 61%) as a yellow solid: mp 72−73 °C; $[\alpha]^{20}_D$ −59.0 (*c* 0.4, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.43 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.27 (dd, *J* = 6.5, 1.0 Hz, 1H), 8.25 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.03−7.94 (m, 3H), 6.16 (d, *J*

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= 7.5 Hz, 1H), 4.08 (s, 3H), 3.63 (s, 3H), 3.28−3.24 (m, 1H), 1.70−1.64 (m, 1H), 1.30−1.10 (m, 6H), 1.01−0.91 (m, 2H), 0.74−0.70 (m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.7, 168.8, 144.6, 143.0, 142.8, 142.7, 141.7, 134.6, 133.5, 132.6, 132.4, 130.7, 130.3, 130.0, 71.1, 54.8, 53.2, 52.0, 37.3, 35.4, 30.6, 30.2, 25.9, 19.5, 11.6; HRMS (ESI) calcd for $C_{25}H_{31}N_2O_5$ $[M + H]^+$ 439.2233, found 439.2228.

(*S*)-6-Methyloctanoic Acid [(*S*)-16]. To a mixture of alcohol **21** (400 mg, 2.77 mmol), TEMPO (43 mg, 0.277 mmol), aqueous NaH_2PO_4 (0.67 M, 15 mL), and acetonitrile (15 mL) were added bleach (6.15 wt % in water, 1.5 mL) and a solution of $NaClO_2$ (501 mg, 5.54 mmol) in water (1 mL). The mixture was stirred at room temperature for 16 h, and a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) was added. The resulting mixture was extracted with ethyl acetate (2 × 20 mL), and the combined extracts were washed with 1 N HCl (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was dried under vacuum at room temperature for 16 h to give compound (*S*)-**16** (432 mg, 98% yield) as a colorless oil: $[\alpha]^{20}_D$ +7.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (br s, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.65−1.60 (m, 2H), 1.37−1.29 (m, 5H), 1.14−1.10 (m, 2H), 0.87−0.84 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 36.2, 34.2, 34.0, 29.4, 26.6, 25.0, 19.1, 11.4; HRMS (ESI) calcd for $C_9H_{17}O_2$ $[M - H]^-$ 157.1229, found 157.1225.

(*S*)-4-Benzyl-3-((*S*)-6-methyloctanoyl)oxazolidin-2-one (22). A mixture of acid (*S*)-**16** (420 mg, 2.66 mmol), DMF (10 mg, 0.133) and methylene chloride (10 mL) was cooled to 0 °C, and oxalyl chloride (371 mg, 2.92 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure, and the residue obtained was dried under vacuum at room temperature for 3 h to give compound (*S*)-**17** (468 mg) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (t, *J* = 7.5 Hz, 2H), 1.73−1.67 (m, 2H), 1.40−1.28 (m, 5H), 1.16−1.11 (m, 2H), 0.87−0.84 (m, 6H). A mixture of (*S*)-**6** (706 mg, 3.99 mmol) and THF (10 mL) was cooled to −78 °C, and *n*-butyllithium in hexanes (2.5 M, 1.60 mL, 3.99 mmol) was added. The mixture was stirred at −78 °C for 10 min, and (*S*)-**17** (468 mg, 2.66 mmol) was added. After being stirred at −78 °C for 30 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Then saturated aqueous ammonium chloride (10 mL) was added, and the resulting mixture was extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by chromatography on silica gel (0−50% ethyl acetate/hexanes) to give compound **22** (567 mg, 67%) as a colorless oil: $[\alpha]^{20}_D$ +90.1 (*c* 0.6, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.32 (m, 2H), 7.29−7.27 (m, 1H), 7.22−7.20 (m, 2H), 4.69−4.65 (m, 1H), 4.21−4.15 (m, 2H), 3.30 (dd, *J* = 13.5, 3.5 Hz, 1H), 3.01−2.87 (m, 2H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.68 (quant, *J* = 7.0 Hz, 2H), 1.42−1.31 (m, 5H), 1.17−1.13 (m, 2H), 0.88−0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 153.5, 135.4, 129.4 (2C), 129.0 (2C), 127.4, 66.2, 55.2, 38.0, 36.3, 35.6, 34.3, 29.5, 26.7, 24.6, 19.2, 11.4; HRMS (ESI) calcd for $C_{19}H_{28}NO_3$ $[M + H]^+$ 318.2069, found 318.2077.

Methyl 6-((1*S*,2*R*,6*S*)-2-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl)-1-hydroxy-6-methyloctyl)phenazine-1-carboxylate (23). A mixture of **22** (179 mg, 0.56 mmol), anhydrous magnesium chloride (72 mg, 0.75 mmol), triethylamine (114 mg, 1.13 mmol), and ethyl acetate (5 mL) was stirred at room temperature for 10 min. Aldehyde **19** (100 mg, 0.376 mmol) was added, followed by chlorotrimethylsilane (82 mg, 0.75 mmol). The mixture was stirred at room temperature overnight, and saturated aqueous ammonium chloride (3 mL) was added to quench the reaction. The resulting mixture was extracted with ethyl acetate (2 × 10 mL), and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was redissolved in methanol (10 mL), and TFA (0.2 mL) was added. After the mixture was stirred at room temperature for 10 min, saturated aqueous $NaHCO_3$ (0.2 mL) was added. Then the mixture was concentrated under reduced pressure, and the residue obtained was purified by chromatography on silica gel (0−50% ethyl acetate/hexanes) to give compound **23** (153 mg, 70%) as a yellow solid: mp 52−53 °C; $[\alpha]^{20}_D$ −23.1 (*c* 0.8, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 9.0, 1.5 Hz, 1H), 8.30−8.26 (m, 2H), 7.88 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.85−7.79 (m, 2H), 7.34−7.25 (m, 5H), 5.55−5.47 (m, 2H), 5.21−5.17 (m, 1H), 4.78−4.75 (m, 1H), 4.19−4.13 (m, 2H), 4.12 (s, 3H), 3.39 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.74 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.77−1.71 (m, 1H), 1.20−1.05 (m, 6H), 1.02−0.95 (m, 1H), 0.91−0.86 (m, 1H), 0.72−0.68 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 167.0, 153.3, 144.0, 141.3, 141.1, 141.0, 138.9, 135.5, 133.8, 132.6, 131.1, 130.4, 130.3, 129.8, 129.5 (2C), 129.4, 128.9 (2C), 127.3, 77.3, 65.8, 55.8, 52.7, 49.0, 37.8, 36.3, 34.1, 30.7, 29.5, 24.5, 19.0, 11.3; HRMS (ESI) calcd for $C_{34}H_{38}N_3O_6$ $[M + H]^+$ 584.2761, found 584.2757.

(−)-Streptophenazine G (5). A mixture of **23** (123 mg, 0.211 mmol) and THF (4 mL) was cooled to 0 °C. Hydrogen peroxide (30 wt % in water, 72 mg, 2.11 mmol) was added, followed by a solution of lithium hydroxide (25 mg, 1.05 mmol) in water (1 mL). After the mixture was stirred at 0 °C for 7 h, a solution of saturated aqueous $NaHSO_3$ (2 mL) was added, and the mixture was stirred at room temperature overnight. The mixture was diluted with 1 M KH_2PO_4 (3 mL) and extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting acid was redissolved in methanol (4 mL) and cooled to 0 °C. (Trimethylsilyl)diazomethane in hexanes (2.0 M, 2.11 mL, 4.22 mmol) was added. The mixture was stirred at 0 °C for 1 h and then concentrated. The residue obtained was purified by chromatography on silica gel (0−50% ethyl acetate/hexanes) to give **5** (54 mg, 58%) as a yellow solid: mp 75−76 °C; $[\alpha]^{20}_D$ −44.6 (*c* 1.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.45 (dd, *J* = 9.0, 1.5 Hz, 1H), 8.28 (dd, *J* = 6.5, 1.0 Hz, 1H), 8.26 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.03−7.95 (m, 3H), 6.15 (d, *J* = 7.5 Hz, 1H), 4.08 (s, 3H), 3.63 (s, 3H), 3.29−3.24 (m, 1H), 1.71−1.66 (m, 1H), 1.29−1.09 (m, 6H), 1.02−0.92 (m, 2H), 0.74−0.71 (m, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.7, 168.7, 144.6, 143.0, 142.7, 142.6, 141.7, 134.6, 133.5, 132.5, 132.4, 130.7, 130.3, 130.1, 71.2, 54.8, 53.2, 52.0, 37.2, 35.3, 30.6, 30.5, 25.8, 19.3, 11.7; HRMS (ESI) calcd for $C_{25}H_{31}N_2O_5$ $[M + H]^+$ 439.2233, found 439.2234.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR data of compounds **4** and **5** and NMR spectra for compounds **4**, **5**, **8**−**12**, **14**−**16**, **18**, **20**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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