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Total synthesis of (−)-renieramycin G from L-tyrosine

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ABSTRACT

(−)-Renieramycin G was synthesized in 21 steps for the longest linear sequences employing L-tyrosine methyl ester as the chiral starting material in 8.5% overall yield. Two of the four chiral centers came from L-tyrosine methyl ester, and the other two were induced through an intermolecular and an intramolecular Pictet–Spengler reaction, respectively.

1. Introduction

(−)-Renieramycin G,[1] isolated from the Fijian sponge *Xestospongia caycedoi* by Davidson in 1992, belongs to a large family of tetrahydroisoquinoline alkaloids[2] including saframycins, ecteinascidins, renieramycins, quinocarcins, and lemonomycin (Fig. 1). All of these compounds display potent antitumor or antimicrobial activities. Among them, ET 743, a highly potent antitumor agent, has been launched in Germany and UK for the treatment of soft tissue sarcoma.[3] The novel structures of these compounds combining with remarkable biological activities and lack of availability from natural sources have attracted interest from chemists for their total synthesis. So far, one racemic and one asymmetric synthesis of (−)-renieramycin G have been reported, respectively.[4]

Biosynthetic studies have shown that L-DOPA or L-tyrosine is an important component in the biosynthetic route to saframycins and ecteinascidins.[5] For the total synthesis of these natural products, L-DOPA or L-tyrosine appears to be the ideal starting material since they are readily available and obviates the necessity for the use of chiral catalysts or chiral auxiliaries. However, to our best knowledge, no total synthesis of a tetrahydroisoquinoline antibiotic has been accomplished starting from L-DOPA or L-tyrosine except for some model studies.[6] Our group has established a novel synthetic method for the construction of the pentacyclic system of the saframycin–ecteinascidin alkaloids and synthesized a series of simplified analogues with potent antitumor activity from L-DOPA.[7] As a continuation of this research, we report herein an efficient total synthesis of (−)-renieramycin G employing L-tyrosine as the chiral starting material.

2. Result and discussion

Our strategy for the synthesis of (−)-renieramycin G is outlined in the retrosynthetic format in Scheme 1. Following the strategy of our previous model studies employing L-DOPA as the starting chiral building block,[8] we envisioned that **1** could be obtained by the oxidation of triol **30** to bisquinone, followed by the acylation with

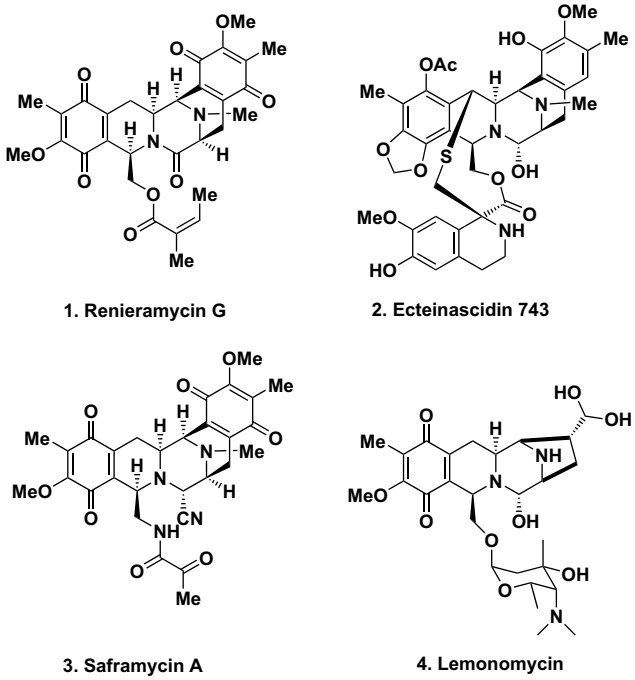

Figure 1. Structures of (−)-renieramycin G and related alkaloids.

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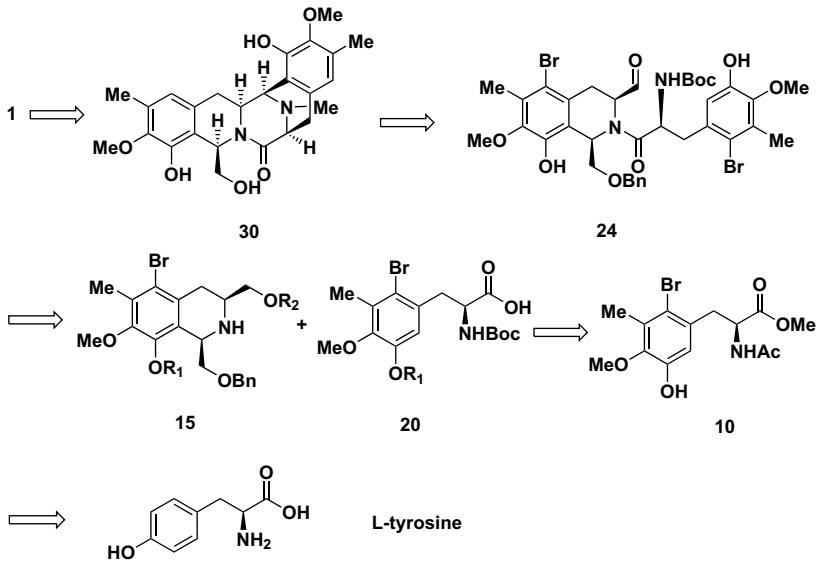
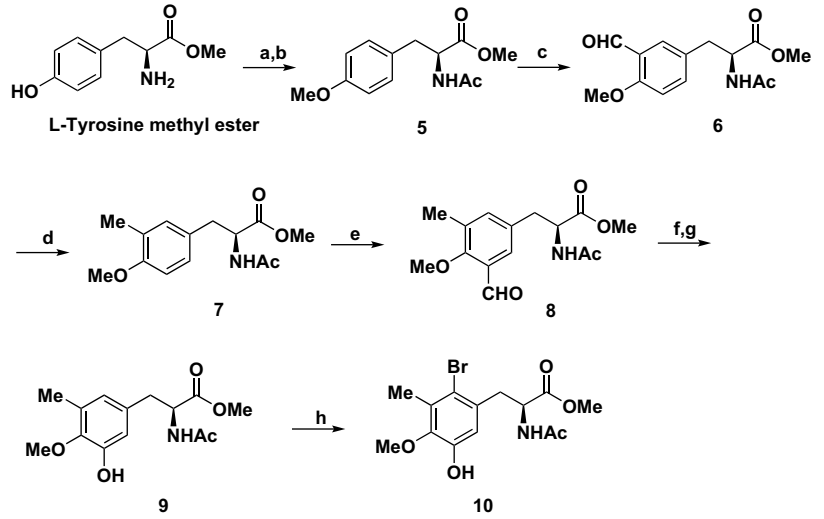


Scheme 1. Retrosynthetic analysis of (−)-renieramycin G.

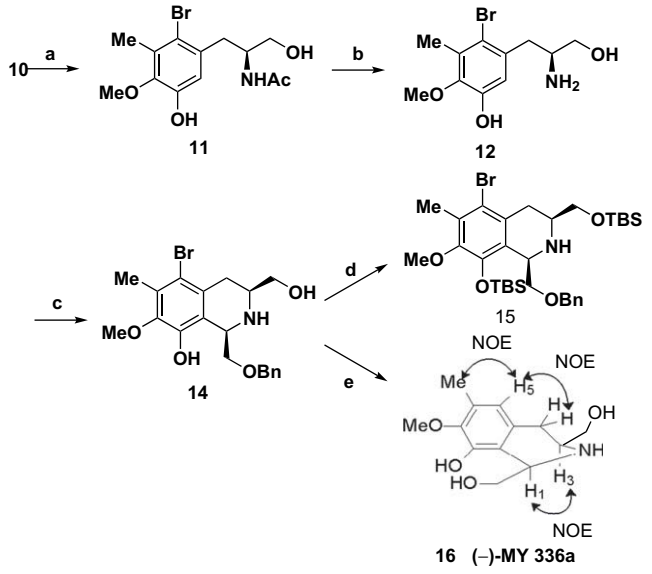
angeloyl chloride. Next, the pentacyclic framework could be constructed through an intramolcular Pictet–Spengler reaction of compound **24**. Compound **24** could be disconnected into 1,2,3,4-tetrahydroisoquinoline moiety **15** and amino acid moiety **20**, and both could be derived from **10**, which could be prepared through several steps of transformation from L-tyrosine. We also envisioned that introduction of bromine atom *para* to the phenolic hydroxyl group could realize the regioselective *ortho* cyclization in the key steps of construction of both B-ring and D-ring.[9]

Our synthesis started with the preparation of L-tyrosine derivative **10**. Fillmore[10] and Jow[6b] have developed the methods for the preparation of highly functionalized L-tyrosine derivatives from L-tyrosine. We followed the latter procedure under modified conditions to prepare compound **10** (Scheme 2). Compound **5** was conveniently prepared in 85% yield from the commercially available L-tyrosine methyl ester in two steps.[11] Formylation *ortho* to the methoxy group provided compound **6**,[12] which was reduced by the catalytic hydrogenation to give compound **7**; Another formylation of the benzene ring of **7** gave aldehyde **8**; Baeyer–Villiger oxidation of **8** using *m*-CPBA in chloroform at room temperature, followed by hydrolysis of the resulting formate intermediate provided phenol **9**. Finally, regiospecific bromination *para* to the phenolic group of compound **9** gave the correctly substituted L-tyrosine derivative **10**.

With the correctly functionalized L-tyrosine derivative **10** in hand, we started the construction of the key 1,2,3,4,-tetrahydroisoquinoline precursor **14** (Scheme 3). Amino ester **10** was reduced to the corresponding alcohol **11** by $LiBH_4$ in 91% yield. The *N*-acetyl group was removed with 6 N aq HCl in CH_3OH to give the amino alcohol **12** in 90% yield. The highly diastereoselective Pictet–Spengler cyclization reaction between amino alcohol **12** and benzyloxyacetaldehyde **13** at 0 °C provided (1*R*,3*S*)-1,2,3,4-tetrahydroisoquinoline **14** in 87% yield.[13] Temperature was found to be a key factor that affected the ratio of diastereoisomers in this reaction. At room temperature, the ratio between cis and trans diastereoisomer was about (5:4), while nearly no trans diastereoisomer was found at 0 °C. On the other hand, however, no tetrahydroisoquinoline product was found at −10 °C. Since NOE between the related protons was difficult to be observed in compound **14**, it was then hydrogenated to remove the bromine atom and the benzyl group to yield (−)-MY336a. Thus the



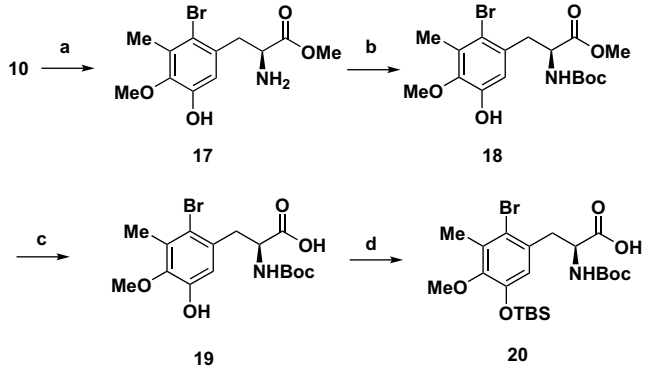
Scheme 2. Reagents and conditions: (a) Ac_2O, HAc, reflux, 5 min, then rt, 1 h, 92%; (b) Me_2SO_4, K_2CO_3, acetone, 93%; (c) $MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, rt, 4 h, 89%; (d) H_2 (50 psi), 10% Pd–C, 1 N aq HCl, CH_3OH, 4 h, 83%; (e) $MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, rt, 4 h, 92%; (f) *m*-CPBA, $CHCl_3$, rt, 6 h; (g) 12 N aq HCl, CH_3OH, 10 h, 91%; (h) Br_2, CH_2Cl_2, rt, 93%. *m*-CPBA= *m*-chloroperoxybenzoic acid.



Scheme 3. Reagents and conditions: (a) $LiBH_4$, THF, 24 h, 91%; (b) 6 N aq HCl, CH_3OH, reflux, 6 h, 87%; (c) $BnCH_2CHO$ **13**, HAc, 4 Å M.S., CH_2Cl_2–CF_3CH_2OH, 0 °C, 87%; (d) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 88%; (e) H_2 (50 psi), $Pd(OH)_2$, CH_3OH, 12 h, 86%.

stereochemistry of compound **14** was determined by the presence of NOE-contact in (−)-MY336a.[14] Obvious NOE enhancement was observed between 1-H and 3-H, thus a cis-1,3-diaxial relationship was confirmed. The position of the bromide group was confirmed by the observed NOE enhancement between 5-H and 6-Me. Initially, we also tried to use the Pictet–Spengler cyclization reaction between the amino ester **17** and benzyloxyacetaldehyde **13** for the construction of the 1,2,3,4-tetrahydrosioquinoline fragment.[15] However, this strategy was ultimately abandoned due to the low yield and poor diastereoselectivity. Silylation of compound **14** with *tert*-butyldimethylsilyl chloride (TBSCl) gave the bis-silylated 1,2,3,4-tetrahydroisoquinoline precursor **15**.

Synthesis of amino acid moiety **20** was shown in Scheme 4. The *N*-acetyl group of **10** was removed with $SOCl_2$ in methanol, and the resulting free amine **17** was reprotected as the corresponding Boc carbamate to afford compound **18**. Finally, basic hydrolysis of the methyl ester with LiOH provided amino acid **19**, which was transformed to the aryl TBS ether to give the desired acid precursor **20**.[6b,16]



Scheme 4. Reagents and conditions: (a) $SOCl_2$, CH_3OH, reflux, 24 h, 94%; (b) Boc_2O, Et_3N, CH_2Cl_2, 91%; (c) LiOH, CH_3OH–H_2O, 93%; (d) TBSCl, imidazole, DMF, 86%.

1,2,3,4-Tetrahydroisoquinoline **15** was coupled with **20** through the action of bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) to afford amide **21** without racemization.[17] The TBS ether of amide **21** was then selectively cleaved to provide the primary alcohol **22**.[18] Oxidation of compound **22** with Dess–Martin periodinane provided hemiaminal **23** as a single diastereomer determined by ^1H NMR.[19] Cleavage of the aryl TBS ether of **23** using TBAF afforded compound **24**. Interestingly, it was found that if the aryl TBS groups of **22** were removed in advance, decomposition occurred during the Dess–Martin oxidation step.[20] With hemiaminal **24** in hand, we then investigated the key intramolecular Pictet–Spengler reaction to construct the pentacyclic skeleton. Following the known intramolecular Pictet–Spengler conditions,[21] the pentacyclic product was not obtained from treatment of **24** with HCOOH, trifluoroacetic acid (TFA), $MeSO_3H$ or $BF_3\cdot OEt_2$. Fortunately, we found that treatment of compound **24** with CF_3SO_3H at room temperature provided pentacyclic compound **28** in a satisfactory yield with the Boc- and *O*-benzyl groups being removed simultaneously. We supposed that the existence of bromide atom *para* to the phenolic hydroxyl group retarded the electrophilic aromatic substitution. In TFA, the formed *N*-monocationic imine **25** favored the elimination to produce enamine **26** over the electrophilic aromatic substitution to yield the pentacyclic skeleton. In CF_3SO_3H, however, the *C*,*N*-biscationic imine **27** was formed, which acted as a strong electrophile in the intramolcular electrophilic aromatic substitution to yield the cyclization product **28**.[22] The characteristic NOEs between 4-H_b/3-H, 11-H/3-H, 3-H/N–H, 13-H/N–H, and 13-H/14-H_b of pentacyclic intermediate **28** showed the cis relationship between its 4-H_b, 3-H, 11-H, and 13-H protons (Scheme 5).

The total synthesis of (−)-renieramycin G from intermediate **28** was completed as shown in Scheme 6. Reductive methylation of **28** with HCHO provided product **29** that was further converted into compound **30** by removal of the bromine atoms through catalytic hydrogenation. Oxidation of **30** with air in the presence of salcomine gave bisquinone **31**.[23] However, oxidation of **30** with air and Fremy's salt led to a very low yield of **31**. Finally, compound **31** was esterified with angeloyl chloride in CH_2Cl_2 to afford the expected natural product (−)-renieramycin G.[24] The spectral data of the synthetic compound **1** were consistent with that of the reported natural compound.[1]

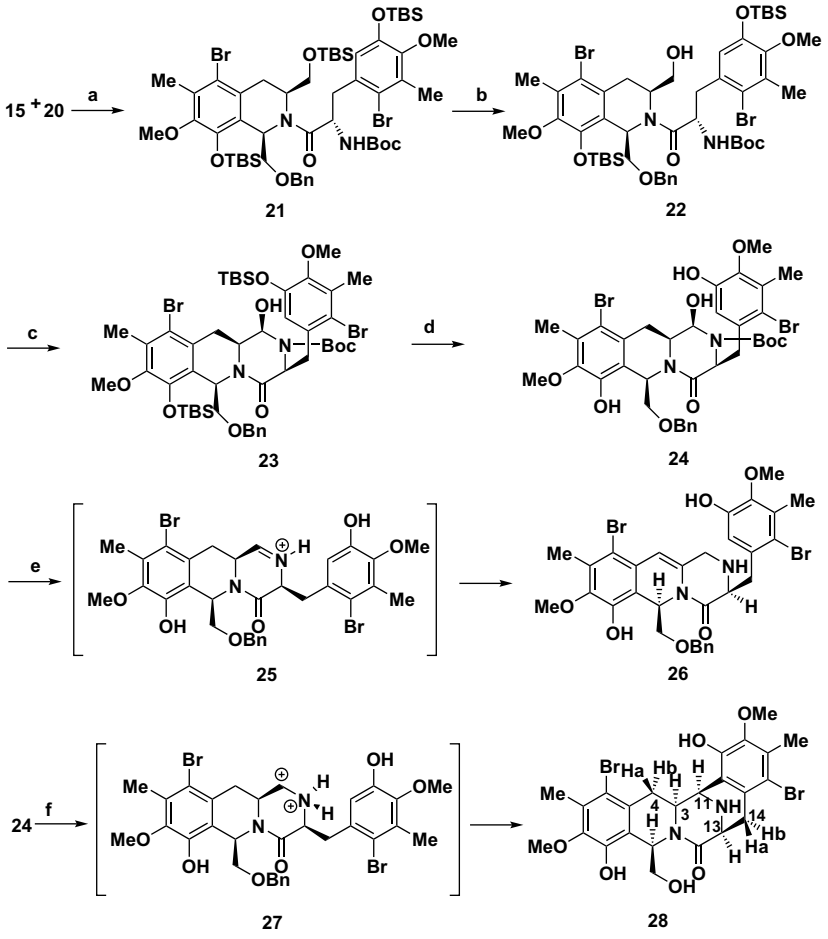
3. Conclusion

In summary, we successfully synthesized (−)-renieramycin G in 21 steps for the longest linear sequences employing L-tyrosine methyl ester as the starting material in 8.5% overall yield. Our synthesis features the regioselective cyclization through blocking the *para* site of the phenolic hydroxyl group with bromine, the highly diastereoselective Pictet–Spengler cyclization reaction controlled through careful temperature control, and the superacid-catalyzed intramolcular Pictet–Spengler cyclization reaction to construct the pentacyclic skeleton with the simultaneous cleavage of Boc- and Bn-protecting groups. Notably, the protocol of successful application of the cheap natural amino acid L-tyrosine as the chiral starting material should find application in the synthesis of other tetrahydroisoquinoline natural products or analogues. Further studies on the total synthesis of the related tetrahydroisoquinoline natural products based on this methodology are ongoing in our laboratory.

4. Experimental

4.1. General

^1H NMR spectra were recorded at 600 MHz or 300 MHz spectrometer at 24 °C in the indicated solvent and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded at 150 MHz, 125 MHz or 75 MHz spectrometer at 24 °C in the solvent indicated and are reported in parts per million relative to tetramethylsilane and referenced internally to

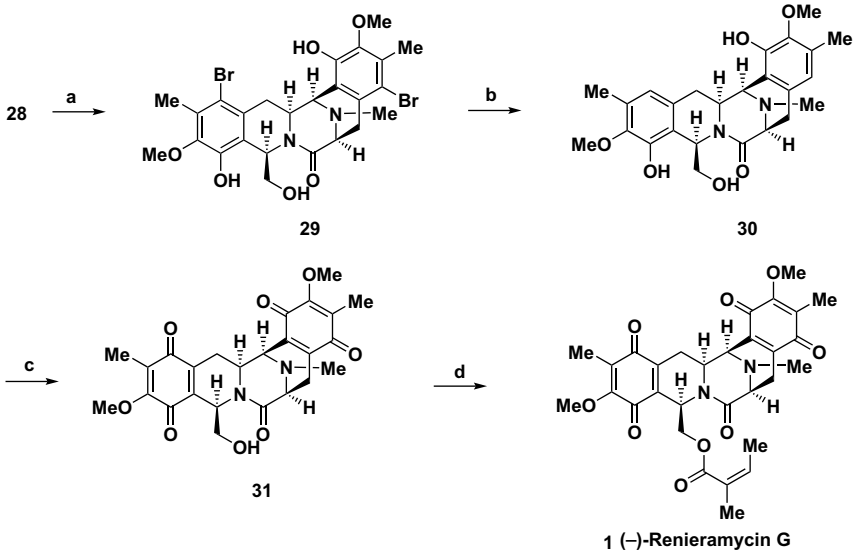


Scheme 5. Reagents and conditions: (a) BOPCl, Et_3N, CH_2Cl_2, 88%; (b) HCOOH, THF, H_2O, 92%; (c) Dess–Martin periodinane, CH_2Cl_2, 94%; (d) TBAF, THF, 2 h, 90%; (e) CF_3COOH, 72%; (f) CF_3SO_3H, 82%.

the residually protonated solvent. HRMS were carried out by Agilent LC/MSD TOF. Optical rotations were measured on a PerkinElmer Polarimeter 341LC using 10 cm cells and the sodium D line (589 nm) at 20 °C and concentration indicated. All reagents were obtained from commercial suppliers unless otherwise stated.

4.2. (1*R*,3*S*)-1-(Benzyloxymethyl)-5-bromo-3-(hydroxymethyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinolin-8-ol (14)

To a solution of compound **12** (0.87 g, 3.0 mmol), acetic acid (0.45 g, 0.44 mL, 7.5 mmol, 2.5 equiv), and the 4Å molecular sieves



Scheme 6. Reagents and conditions: (a) HCHO, $NaBH_3CN$, HOAc, CH_3OH, 83%; (b) H_2 (50 psi), $Pd(OH)_2$, CH_3OH, 12 h, 87%; (c) air, salcomine, CH_3CN, 86%; (d) angeloyl chloride, CH_2Cl_2, 74%. Salcomine=*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II) hydrate.

(0.6 g) in CH_2Cl_2–CF_3CH_2OH (7:1, v/v, 12 mL), a solution of benzyloxyacetaldehyde **13** (495 mg, 3.3 mmol, 1.1 equiv) in dichloromethane (4 mL) was added slowly via syringe over 60 min at 0 °C. After being stirred at 0 °C for 8 h, the reaction mixture was diluted with dichloromethane and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography ($CHCl_3$:CH_3OH:NEt_3=100:1:0.2) to afford compound **14** (1.1 g, 87%) as a white solid. $[\alpha]_D^{20}$: −92.5 (*c* 1.0, CH_3OH). HRMS calcd for $C_{20}H_{25}NO_4Br$ ($M+H^+$) 422.0961 Da, found 422.0985. ^1H NMR (600 MHz, DMSO-d_6): δ 9.01 (s, 1H), 7.29 (m, 5H), 4.76 (br s, 1H), 4.47 (d, *J*=12.0 Hz, 1H), 4.41 (d, *J*=12.0 Hz, 1H), 4.32 (br d, *J*=6.0 Hz, 1H), 4.06 (dd, *J*=8.4, 3.0 Hz, 1H), 3.58 (s, 3H), 3.49 (m, 1H), 3.46 (dd, *J*=8.0, 7.2 Hz, 1H), 3.39 (m, 1H), 3.30 (s, 1H), 2.68 (d, *J*=16.8 Hz, 1H), 2.66 (m, 1H), 2.23 (s, 3H), 2.15 (dd, *J*=15.6, 12.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 146.2, 144.5, 138.6, 132.4, 128.7, 128.1, 127.3, 127.2, 123.7, 116.3, 73.2, 72.1, 64.9, 60.4, 53.7, 53.5, 34.6, 16.5.

4.3. (1*R*,3*S*)-1-(Benzyloxymethyl)-5-bromo-8-(*tert*-butyldimethylsilyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (15)

To a solution of compound **14** (0.51 g, 1.21 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (0.81 g, 5.4 mmol, 4 equiv), TEA (1.2 mL, 7.26 mmol, 6 equiv), DMAP (74 mg, 0.6 mmol, 0.5 equiv). The solution was stirred for 24 h and quenched with saturated aq NH_4Cl (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (30 mL×2). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc in *n*-hexanes) to provide compound **15** (694 mg, 88%) as a yellow oil. $[\alpha]_D^{20}$: −58.5 (*c* 0.5, $CHCl_3$). HRMS calcd for $C_{32}H_{53}NO_4Si_2Br$ ($M+H^+$) 650.2691 Da, found 650.2699. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5H), 4.50 (d, *J*=12.0 Hz, 1H), 4.44 (br s, 1H), 4.42 (d, *J*=12.0 Hz, 1H), 4.15 (dd, *J*=8.7, 2.7 Hz, 1H), 3.78 (dd, *J*=9.9, 4.5 Hz, 1H), 3.71 (dd, *J*=9.9, 5.7 Hz, 1H), 3.60 (s, 3H), 3.55 (d, *J*=7.8 Hz, 1H), 2.81 (m, 1H), 2.81 (d, *J*=13.8 Hz, 1H), 2.40 (dd, *J*=16.8, 11.4 Hz, 1H), 2.33 (s, 3H), 0.96 (s, 9H), 0.91 (s, 9H), 0.22 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 145.3, 138.5, 133.0, 130.4, 128.2, 127.5, 127.3, 120.3, 73.2, 73.1, 66.8, 60.2, 54.7, 53.8, 34.8, 26.1, 25.9, 18.5, 18.3, 16.8, −3.8, −4.4, −5.3.

4.4. (*S*)-3-(2-Bromo-5-(*tert*-butyldimethylsilyloxy)-4-methoxy-3-methylphenyl)-2-(*tert*-butoxycarbonylamino)propanoic acid (20)

To a solution of compound **19** (1.21 g, 3.0 mmol) in DMF (10 mL) was added TBSCl (1.4 g, 9.0 mmol, 3.0 equiv) and imidazole (1.22 g, 18.0 mmol, 6.0 equiv). The solution was stirred at room temperature under argon for 48 h. After dilution with EtOAc (100 mL), the mixture was washed with water (50 mL×4), brine, and dried over Na_2SO_4. The organic phase was concentrated, and the residue was purified by column chromatography (2–5% CH_3OH in CH_2Cl_2) to afford compound **20** (1.34 g, 86%) as a white solid. $[\alpha]_D^{20}$: −9.4 (*c* 1.2, CH_3OH). HRMS calcd for $C_{22}H_{36}NO_6NaSiBr$ ($M+Na^+$) 540.1387 Da, found 540.1389. ^1H NMR (300 MHz, DMSO-d_6): δ 12.63 (s, 1H), 7.18 (d, *J*=8.7 Hz, 1H), 6.82 (s, 1H), 4.11 (m, 1H), 3.62 (s, 3H), 3.16 (dd, *J*=13.8, 3.6 Hz, 1H), 2.75 (dd, *J*=13.8, 9.6 Hz, 1H), 2.26 (s, 3H), 1.29 (s, 9H), 0.97 (d, *J*=3.0 Hz, 9H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.4, 155.5, 148.3, 146.9, 133.0, 131.7, 121.6, 118.2, 77.9, 59.7, 52.9, 37.0, 28.1, 25.9, 25.5, 17.9, 17.0, −4.7, −4.8.

4.5. Synthesis of compound 21

To a solution of tetrahydroisoquinoline **15** (650 mg, 1.0 mmol) and TEA (0.38 mL, 2.6 mmol, 2.6 equiv) in CH_2Cl_2 (20 mL) at 0 °C was added *N*-Boc amino acid **20** (673 mg, 1.3 mmol, 1.3 equiv), followed by BOPCl (331 mg, 1.3 mmol, 1.3 equiv) in portions. The mixture was stirred for 72 h at room temperature. The reaction was quenched with 1 N aq HCl (20 mL) and the heterogeneous mixture was diluted with CH_2Cl_2 (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL×2). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by column chromatography (5% EtOAc in *n*-hexane) to provide **21** (1.02 g, 88%) as a clear oil. $[\alpha]_D^{20}$: +9.7 (*c* 0.6, $CHCl_3$). HRMS calcd for $C_{54}H_{87}N_2O_9Si_3Br_2$ ($M+H^+$) 1149.4081 Da, found 1149.4070. ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 5H), 6.61 (s, 1H), 6.07 (dd, *J*=7.2, 3.9 Hz, 1H), 5.55 (d, *J*=8.4 Hz, 1H), 5.09 (dd, *J*=14.4, 8.1 Hz, 1H), 4.53 (d, *J*=12.0 Hz, 1H), 4.33 (d, *J*=12.0 Hz, 1H), 4.29 (br s, 1H), 3.81 (m, 2H), 3.69 (m, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.99 (dd, *J*=13.2, 5.7 Hz, 1H), 2.93 (dd, *J*=17.1, 3.6 Hz, 1H), 2.83 (dd, *J*=13.5, 8.4 Hz, 1H), 2.68 (dd, *J*=17.1, 7.5 Hz, 1H), 2.43 (s, 3H), 2.28 (s, 3H), 1.33 (s, 9H), 1.01 (s, 9H), 0.98 (s, 9H), 0.84 (s, 9H), 0.25–0.04 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.3, 154.5, 149.1, 148.1, 147.5, 144.6, 138.5, 132.7, 131.9, 131.2, 128.6, 128.1, 127.3, 127.2, 127.1, 125.5, 122.0, 119.1, 78.8, 72.9, 71.8, 65.2, 60.3, 60.0, 52.3, 50.5, 48.8, 41.3, 30.2, 28.4, 28.2, 28.1, 26.1, 25.9, 25.6, 18.7, 18.2, 16.9, −3.8, −4.2, −4.59, −4.64, −5.49, −5.56.

4.6. Synthesis of compound 24

To a solution of compound **23** (287 mg, 0.28 mmol) in THF (25 mL) at 0 °C was added TBAF (1.0 M in THF, 0.84 mL, 0.84 mmol, 3.0 equiv), and the solution was stirred for 1 h. The reaction was quenched with saturated aq NH_4Cl (20 mL) and extracted with EtOAc (30 mL×3). The combined organic phase was washed with saturated aq NaCl, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by column chromatography (1% CH_3OH in CH_2Cl_2) to provide **24** (205 mg, 90%) as a white solid. $[\alpha]_D^{20}$: −43.2 (*c* 0.7, CH_2Cl_2). HRMS calcd for $C_{36}H_{43}N_2O_9Br_2$ ($M+H^+$) 805.1329 Da, found 805.1334. ^1H NMR (300 MHz, DMSO-d_6): δ 9.33 (s, 1H), 9.20 (s, 1H), 7.21 (m, 5H), 6.90 (s, 1H), 6.75 (d, *J*=5.4 Hz, 1H), 5.80 (br d, *J*=3.3 Hz, 1H), 5.70 (appt, *J*=3.6 Hz, 1H), 4.69 (dd, *J*=10.8, 2.7 Hz, 1H), 4.44 (d, *J*=12.6 Hz, 1H), 4.37 (d, *J*=12.6 Hz, 1H), 3.76 (dd, *J*=9.6, 4.5 Hz, 1H), 3.63 (s, 3H), 3.61 (s, 3H), 3.56 (dd, *J*=9.6, 3.0 Hz, 1H), 3.48 (dd, *J*=12.9, 2.7 Hz, 1H), 3.39 (br d, *J*=8.1 Hz, 1H), 3.14 (dd, *J*=12.9, 11.7 Hz, 1H), 3.04 (d, *J*=10.5 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 1.02 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.5, 152.2, 148.7, 145.8, 145.1, 144.9, 138.6, 133.8, 132.3, 130.6, 129.7, 128.0, 127.0, 126.9, 121.4, 118.2, 116.6, 113.9, 78.9, 73.5, 72.1, 70.6, 60.4, 59.7, 54.9, 49.4, 42.1, 32.4, 27.2, 16.7, 16.6.

4.7. Synthesis of compound 28

To trifluoromethanesulfonic acid (2 mL, 23 mmol) was added compound **24** (184 mg, 0.23 mmol) in one portion, and the mixture was stirred for 1 h at room temperature under Ar atmosphere. Then, the reaction mixture was poured into 3 mL of ice-water, basified with saturated aq $NaHCO_3$ with stirring, and the whole mixture was extracted with EtOAc (20 mL×3). The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatograph ($EtOAc$:CH_3OH:Et_3N=100:2:0.2) to afford compound **28** (113 mg, 82%) as a white solid. $[\alpha]_D^{20}$: −23.6 (*c* 0.6, CH_3OH). HRMS calcd for $C_{24}H_{27}N_2O_6Br_2$ ($M+H^+$) 597.0236 Da, found 597.0270. ^1H NMR (600 MHz, DMSO-d_6): δ 9.44 (s, 1H), 9.14 (s, 1H), 5.48 (t, *J*=4.8 Hz, 1H), 4.58 (br s,

1H), 4.26 (t, *J*=4.8 Hz, 1H), 3.86 (br s, 1H), 3.82 (d, *J*=12.6 Hz, 1H), 3.61 (s, 3H), 3.60 (s, 3H), 3.54 (dd, *J*=15.6, 2.4 Hz, 1H), 3.32 (s, 1H), 3.17 (m, 2H), 2.90 (dd, *J*=16.8, 6.6 Hz, 1H), 2.86 (d, *J*=16.8 Hz, 1H), 2.31 (m, 1H), 2.28 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 170.2, 146.1, 146.0, 145.1, 144.3, 133.2, 133.0, 129.6, 129.3, 122.1, 121.6, 116.0, 114.1, 62.8, 60.7, 60.4, 53.2, 50.4, 48.2, 36.0, 32.7, 16.7, 16.5.

4.8. Synthesis of compound 30

To a solution of compound **29** (60 mg, 0.098 mmol) in MeOH (4 mL) at room temperature was added $Pd(OH)_2$ (moist, Pd content 20%, 30 mg), and the mixture was hydrogenated in a Parr apparatus (50 psi H_2) for 10 h. The reaction mixture was filtered through Celite, washed with MeOH, and concentrated under vacuum. The residue was dissolved in EtOAc (10 mL) and was then treated with saturated aq $NaHCO_3$. The phases were separated, and the aqueous phase was extracted with EtOAc (10 mL×2). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The pale yellow residue was purified by column chromatograph (0.2% triethylamine in EtOAc) to afford compound **30** (39 mg, 87%) as a white solid. $[\alpha]_D^{20}$: −179.4 (*c* 0.5, CH_3OH). HRMS calcd for $C_{25}H_{31}N_2O_6$ ($M+H^+$) 455.2182 Da, found 455.2295. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.68 (s, 1H), 6.44 (s, 1H), 6.42 (s, 1H), 5.45 (dd, *J*=6.0, 4.8 Hz, 1H), 4.24 (dd, *J*=6.0, 4.8 Hz, 1H), 4.15 (d, *J*=3.0 Hz, 1H), 3.80 (br d, *J*=13.2 Hz, 1H), 3.61 (s, 3H), 3.60 (s, 3H), 3.46 (d, *J*=6.6 Hz, 1H), 3.20 (m, 1H), 3.08 (dd, *J*=16.8, 6.0 Hz, 1H), 2.97 (m, 1H), 2.90 (dd, *J*=13.8, 2.4 Hz, 1H), 2.59 (d, *J*=16.8 Hz, 1H), 2.28 (s, 3H), 2.28 (t, *J*=13.8 Hz, 1H), 2.17 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 170.5, 147.2, 146.5, 144.5, 143.7, 132.9, 129.1, 129.3, 128.9, 128.8, 120.6, 119.9, 119.6, 79.1, 63.5, 59.87, 59.80, 59.1, 58.1, 54.5, 50.5, 31.7, 28.0, 15.57, 15.56.

4.9. Synthesis of compound 31

To a solution of compound **30** (35 mg, 0.077 mmol) in MeCN (4 mL) was added salcomine (25 mg, 0.077 mmol) at room temperature, and the dark suspension was stirred in air for 5 h. The mixture was filtered through cellulose powder and the filter cake was carefully washed with AcOEt. The combined filtrate was washed with 0.1% aq $NaHCO_3$ and brine, and dried over Na_2SO_4. After concentration in vacuo, the residue was chromatographed on silica gel to give compound **31** (32 mg, 86%) as an orange residue. $[\alpha]_D^{20}$: −266.6 (*c* 0.5, $CHCl_3$). HRMS calcd for $C_{25}H_{27}N_2O_8$ ($M+H^+$) 483.1761 Da, found 483.1746. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.38 (br s, 1H), 4.13 (d, *J*=3.6 Hz, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.87 (br d, *J*=12.6 Hz, 1H), 3.83 (br d, *J*=10.8 Hz, 1H), 3.69 (d, *J*=6.6 Hz, 1H), 3.49 (dd, *J*=10.8, 3.0 Hz, 1H), 3.12 (dd, *J*=16.8, 2.4 Hz, 1H), 2.88 (dd, *J*=20.4, 7.2 Hz, 1H), 2.71 (d, *J*=20.4 Hz, 1H), 2.37 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.68 (dd, *J*=16.2, 12.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.4, 185.2, 182.2, 180.7, 171.1, 155.5, 155.4, 141.9, 141.7, 136.6, 134.9, 129.0, 128.6, 65.0, 61.1, 58.8, 56.5, 53.1, 51.7, 39.8, 25.4, 24.0, 8.9, 8.8.

4.10. (−)-Renieramycin G

To a solution of compound **31** (8 mg, 0.0166 mmol) in CH_2Cl_2 (1 mL) was added angeloyl chloride (39.3 mg, 0.332 mmol, 20 equiv), and the solution was allowed to stand for 24 h at 25 °C in the dark. The mixture was diluted with CH_2Cl_2, washed with 1% aq $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, $CHCl_3$:CH_3OH=100:2) to give (−)-renieramycin G (7 mg, 0.0142 mmol, 74%) as a yellow film. $[\alpha]_D^{20}$: −148.8 (*c* 0.2, CH_2Cl_2). HRMS calcd for $C_{30}H_{33}N_2O_9$ ($M+H^+$) 565.2186 Da, found 565.2161. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 5.90 (m, 1H), 5.40 (br s, 1H), 4.67 (dd, *J*=11.4, 2.4 Hz, 1H), 4.32 (dd, *J*=11.4, 2.4 Hz, 1H), 4.12 (br d, *J*=3.6 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.85 (br d, *J*=12.0 Hz, 1H), 3.67 (d, *J*=6.6 Hz, 1H), 3.01 (dd, *J*=16.2, 2.4 Hz, 1H), 2.87 (dd, *J*=21.0, 6.6 Hz, 1H), 2.64 (d, *J*=21.0 Hz, 1H), 2.36 (s, 3H), 1.93 (s, 6H), 1.68 (dq, *J*=7.2, 1.6 Hz, 3H), 1.52 (t, *J*=1.6 Hz, 3H), 1.49 (ddd, *J*=15.0, 12.6, 2.4 Hz, 1H). ^{13}C NMR (150 MHz, CD_2Cl_2): δ 186.6, 185.5, 182.8, 180.7, 170.6, 167.2, 156.4, 155.8, 142.4, 142.0, 139.8, 136.4, 135.2, 129.6, 128.7, 127.0, 63.1, 61.3, 61.2, 59.4, 56.5, 53.4, 50.4, 40.0, 25.9, 23.8, 20.5, 15.6, 8.8, 8.7.

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Supplementary data

Experimental details and spectroscopic data for all compounds. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.05.025.

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