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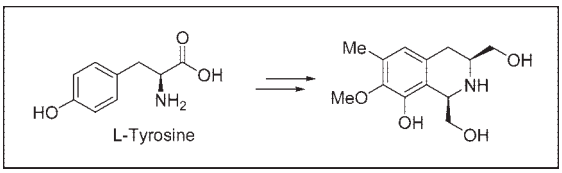

Using L-tyrosine as a chiral starting material, we developed an efficient synthetic route to (–)-MY 336a. A key step in the sequence is a highly regio- and diastereoselective intermolecular Pictet-Spengler cyclization reaction between amino alcohol and benzyloxyacetaldehyde.

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INTRODUCTION

MY 336a was isolated in 1986 from the culture broth of *Streptomyces gabonae* KY2234 (ATCC 15282) and was characterized as a β-adrenergic receptor antagonist with high affinities toward β_1- and β_2-adrenergic receptors [1] (Fig. 1). Although the relative stereochemistry of MY 336a was determined by an X-ray study of its tetra-acetyl derivative, there has been no report on the elucidation of its absolute stereochemistry so far [2]. Kaufman reported the total synthesis of the racemic MY 336a and its epimer, which used Jackson's isoquinoline synthesis as the key reaction [3]. To date, there has been no report on the total synthesis of its optically pure isomer except an attempt to an enantioselective synthesis of MY336a [4].

In the course of our study of the total synthesis of (–)-Renieramycin G and (–)-Lemonomycin, we take (–)-MY 336a as a key precursor for the construction of the AB ring system of (–)-Renieramycin G and (–)-Lemonomycin. Our group had previously reported the construction of the AB ring system of ecteinascidin-saframycin alkaloids by the Pictect-Spengler cyclization between the L-DOPA derivatives and benzyloxyacetaldehyde in which the 1,3-*cis*-diastereoisomer was the main product [5]. Herein, we report an efficient total synthesis of (–)-MY 336a on the basis of this methodology.

RESULTS AND DISCUSSION

Various methods to synthesize the highly functionalized L-tyrosine derivatives have been reported [6], and we followed an existing procedure under modified conditions to prepare compound **7** (Scheme 1) [7]. Compound **4** was conveniently prepared from L-tyrosine in four steps [7a]: Reduction of compound **4** by catalytic hydrogenation to give compound **5**; Formylation of **5** with $MeOCHCl_2$ in CH_2Cl_2 at room temperature in the presence of $TiCl_4$ to afford aldehyde **6**; Baeyer-Villiger oxidation of **6** using MCPBA in chloroform at room temperature and the subsequent hydrolysis of the resulting formate to give phenol **7**. Next, compound **7** was reduced to the corresponding alcohol **8** 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 **9** in 87% yield. The highly regio- and diastereoselective Pictet-Spengler cyclization reaction between amino alcohol **9** and benzyloxyacetaldehyde at 0°C provided the 1,3-*cis*-tetrahydroisoquinoline **10** in 64% yield and **11** in 20% yield, respectively [8]. Initially, we removed the *N*-acetyl group of compoud **7** to get a phenylalanine methyl ester. However, the Pictet-Spengler cyclization reaction between phenylalanine methyl ester and benzyloxyacetaldehyde to construct the tetrahydrosioquinoline fragment met with low yield and poor diastereoselectivity and was ultimately abandoned [5,8a]. Finally, the *O*-benzyl group of tetrahydroisoquinoline **10** was removed by catalytic hydrogenation to give the expected product (–)-MY 336a in 86% yield.

The stereochemistry of compound **1** was verified on the basis of its NOE spectroscopy. Obvious NOE enhancement was observed between 1-H and 3-H; thus a *cis*-1,3-diaxial relationship was confirmed. The ortho-relationship between 5-H and 6-Me was confirmed by the observed NOE enhancement between them.

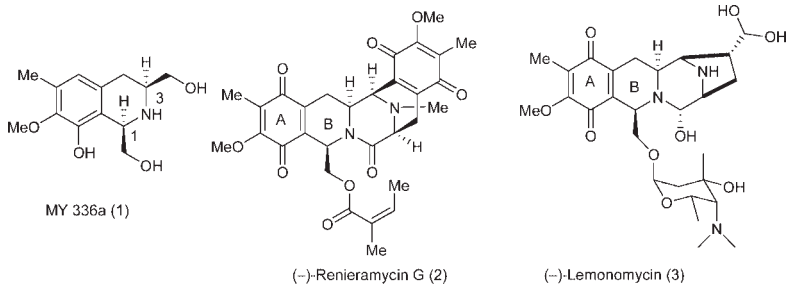


Figure 1. Structures of (–)-MY 336a and related tetrahydroisoquinoline alkaloids.

In summary, we have developed a new efficient route to synthesize (–)-MY 336a using L-tyrosine as a chiral starting material, which can be used to elucidate the absolute stereochemistry of natural MY 336a. Further study on the synthesis of Renieramycin G and Lemonomycin based on the methodology is ongoing in our laboratory.

EXPERIMENTAL

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

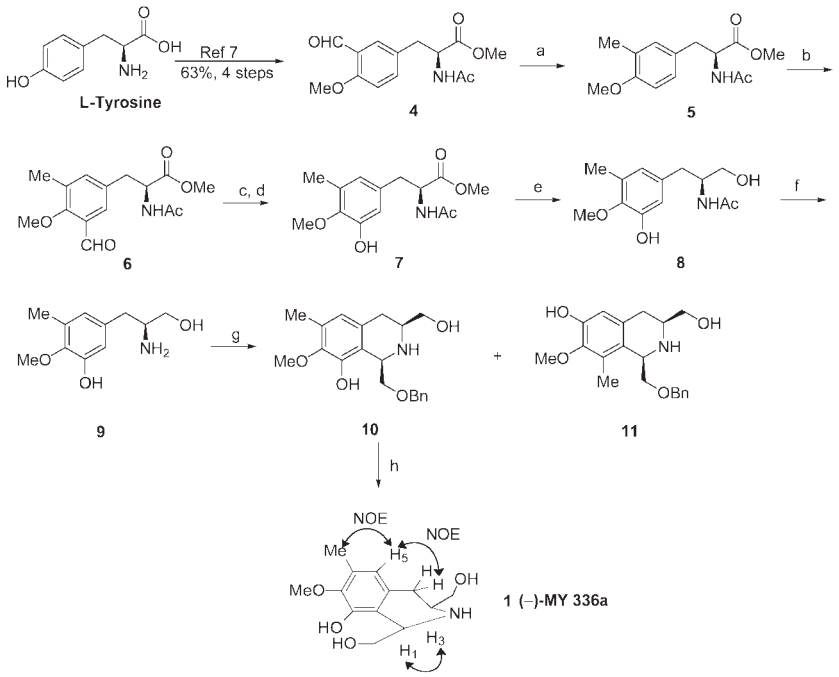
(*S*)-Methyl-2-acetamido-3-(4-methoxy-3-methylphenyl)propanoate (5). To a solution of compound **4** (48 g, 0. 17 mol) in MeOH (750 mL) at room temperature was added 1*N* aq. HCl (40 mL) and 10% Pd-C (moist, 30 g), and the mixture was hydrogenated in a Parr apparatus (50 psi H_2) for 4 h. The reaction mixture was filtered through celite, washed with MeOH, and concentrated under vacuum. The residue was dissolved in EtOAc (500 mL) and was then washed with saturated aq. $NaHCO_3$. The phases were separated, and the aqueous phase was extracted with EtOAc (200 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 ($CHCl_3$) to afford compound **5** (38 g, 83%) as a clear oil. $[\alpha]_D^{20}$: +103.6 (c 1.0, $CHCl_3$). HRMS calcd. for $C_{14}H_{20}NO_4(M+H^+)$ 266.1392, found 266.1390. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (m, 2 H), 6.74 (d, J = 8.1 Hz, 1 H), 6.00 (d, J = 7.5 Hz, 1 H), 4.85 (m, 1 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.08 (m, 2 H), 2.17 (s, 3 H), 1.98 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.5, 156.8, 131.4, 127.3, 127.1, 126.6, 109.8, 55.1, 53.2, 52.1, 36.8, 23.0, 16.1.

(*S*)-Methyl-2-acetamido-3-(3-formyl-4-methoxy-5-methylphenyl)propanoate(6). Titanium chloride (58 mL, 0.42 mol, 3 equiv) in CH_2Cl_2 (150 mL) was added dropwise over 1 h to a solution of compound **5** (37 g, 0.14 mol) and α,α-dichloromethyl methyl ether (16 mL, 0.18 mol, 1.3 equiv) in CH_2Cl_2 (250 ml) with stirring under 0°C. The cooling bath was removed, and the mixture was stirred for a further 3 h, and then poured into ice-water (400 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (200 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 (25% *n*-hexane in EtOAc) to provide compound **6** (37.7 g, 92%) as a white solid. $[\alpha]_D^{20}$: +102.5 (c 1.0, $CHCl_3$). HRMS calcd. for $C_{15}H_{20}NO_5(M+H^+)$ 294.1341, found 294.1339. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.33 (s, 1 H), 7.41 (d, J = 2.1 Hz, 1 H), 7.22 (d, J = 2.1 Hz, 1 H), 6.09 (d, J = 7.5 Hz, 1 H), 4.88 (m, 1 H), 3.88 (s, 3 H), 3.75 (s, 3 H), 3.17 (dd, J = 13.8, 5.4 Hz, 1 H), 3.06 (dd, J = 13.8, 6.0 Hz, 1 H), 2.31 (s, 3 H), 1.99 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 171.8, 169.4, 160.8, 138.3, 132.5, 132.1, 128.9, 126.6, 63.1, 53.0, 52.4, 37.0, 23.0, 15.5.

(*S*)-methyl-2-acetamido-3-(3-hydroxy-4-me-thoxy-5-methylphenyl)propanoate (7). To an ice cold solution of compound **6** (15.0 g, 51.2 mmol) in $CHCl_3$ (300 mL) was added MCPBA (26.5 g, 153.6 mmol). The mixture was stirred vigorously at room temperature for 6 h and then washed sequentially with 10% $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. The solution was concentrated, and the residue was dissolved in MeOH (150 mL). Then concentrated HCl (12 N, 1.28 mL, 15.3 mmol, 0.3 equiv) was added at 0°C. The solution was then stirred for 10 h at room temperature and then concentrated by rotary evaporation. The residue was purified by column chromatography (2% CH_3OH in $CHCl_3$) to provide compound **7** (13.2 g, 91%) as a yellow oil. $[\alpha]_D^{20}$: +91.5 (c 0.5, $CHCl_3$). HRMS calcd. for $C_{14}H_{20}NO_5(M+H^+)$ 282.1345, found 282.1341.^{1}H NMR (300 MHz, $CDCl_3$): δ 6.54 (d, J = 1.5 Hz, 1 H), 6.42 (d, J = 1.2 Hz, 1 H), 6.14 (d, J = 7.5 Hz, 1 H), 4.83 (dd, J = 12.9, 5.7 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 2.97 (m, 2 H), 2.24 (s, 3 H), 2.00 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 170.0, 148.9, 144.5, 131.9, 130.9, 122.9, 114.2, 60.3, 53.1, 52.2, 37.1, 22.9, 15.7.

(*S*)-5-(2-Amino-3-hydroxypropyl)-2-meth-oxy-3-methylphenol (9). To a solution of compound **7** (5.0 g, 13.9 mmol) in THF (25 mL) was added $LiBH_4$ (0.39 g, 18.1 mmol, 1.3 equiv) in portions at 0°C. Then, the mixture was stirred for 18 h at room temperature and quenched slowly with saturated aqueous NH_4Cl (60 mL) and extracted with EtOAc (80 mL 3×). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by column chromatography (EtOAc) to provide **8** (4.2 g, 91%) as a white solid.

Scheme 1. Reagents and conditions: (a) H_2 (50 psi), 10% Pd-C, 1*N* aq. HCl, CH_3OH, 4 h, 83%; (b) $MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, r.t., 4 h, 92%; (c) MCPBA, $CHCl_3$, r.t., 6 h; (d) 12*N* HCl, CH_3OH, 10 h, 91% for two steps; (e) $LiBH_4$, THF, r.t., 24 h, 91%; (f) 6*N* aq. HCl, CH_3OH, reflux, 10 h, 87% ; (g) $BnOCH_2CHO$, 4 Å molecular sieves, CH_2Cl_2/CF_3CH_2OH=7:1, 0°C, 8 h, compound **10** in 64% yield, compound **11** in 20% yield; (h) H_2(50 psi), $Pd(OH)_2$, CH_3OH, 12 h, 86%.



To a solution of **8** (3.4 g, 10.2 mmol) in CH_3OH (60 mL) was added 6 *N* aq. HCl (11 mL), and then, the mixture was refluxed in an oil bath (80°C) for 6 h. The reaction solution was removed by rotary evaporation, and the residue was dissolved in CH_3OH. The solution was basified with NEt_3 and purified directly by column chromatography (SiO_2 treated with NEt_3, 5% CH_3OH in $CHCl_3$; then 10% CH_3OH in $CHCl_3$) to provide **9** (2.6 g, 87%) as a white solid. $[\alpha]_D^{20}$: −7.4 (c 0.5, CH_3OH). HRMS calcd. for $C_{11}H_{18}NO_3(M+H^+)$ 212.1281, found 212.1313. ^{1}H NMR (300 MHz, CD_3COD): δ 6.78 (d, *J* = 2.1 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 3.90 (s, 3 H), 3.85 (dd, *J* = 11.7 Hz, 3.9 Hz, 1H), 3.67 (dd, *J* = 11.7 Hz, 6.6Hz, 1H), 3.52 (m, 1H), 2.92 (m, 2 H), 2.40 (s, 3 H). ^{13}C NMR (75MHz, CD_3COD): δ 151.4, 146.5, 133.1, 133.0, 123.4, 116.0, 61.9, 60.4, 55.8, 36.3, 15.9.

(1R,3*S*)-1-(Benzyloxymethyl)-3-(hydroxyl-methyl)-7-methoxy-6-methyl-1,2,3,4-tetra-hydroisoquinolin-8-ol (10) and (1R,3S)1-(benzyloxymethyl)-3-(hydroxyl-methyl)-7-methoxy-8-methyl-1,2,3,4-tetra-hydroisoquinolin-6-ol (11). To a solution of **9** (0.60 g, 2.84 mmol), acetic acid (0.43 g, 0.42 mL, 7.5 mmol, 2.5 equiv) and the 4 Å molecular sieves (0.5 g) in dichloromethane and 2,2,2-trifluoroethanol (7:1, v/v, 12 mL), a solution of benzyloxyacetaldehyde (0.47 g, 3.1 mmol, 1.1 equiv) in dichloromethane was added slowly *via* syringe over 1 h 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 flash column chromatography (2% MeOH in chloroform) to afford **10** (0.63 g, 64%) and **11** (0.19 g, 20%) as white solid. Compound 10: $[\alpha]_D^{20}$: −115.2 (c 0.5, CH_3OH). HRMS calcd. for $C_{20}H_{26}NO_4(M+H^+)$ 344.1856, found 344.1885. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.65 (s, 1 H), 7.32 (m, 5 H), 6.37 (s, 1 H), 4.71(t, *J* = 5.1 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.31 (brd, *J* = 6.0 Hz, 1 H), 4.13 (dd, *J* = 8.7, 2.7 Hz,1 H), 3.59 (s, 3 H), 3.46 (m, 1 H), 3.43 (d, *J* = 8.7 Hz, 1 H), 3.34 (m, 1 H), 3.33 (s, 1H), 2.68(m, 1 H), 2.42 (dd, *J* = 14.7, 2.4 Hz, 1 H), 2.28(dd, *J* = 14.7, 10.8 Hz, 1 H), 2.14(s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 146.7, 143.8, 138.7, 132.6, 128.1, 128.0, 127.3, 127.2, 120.9, 73.8, 72.0, 65.2, 59.9, 53.9, 53.0, 33.0, 15.3. Compound **11**: ^{1}H NMR (300 MHz, DMSO-*d*6): δ 8.94 (s, 1 H), 7.35 (m, 5 H), 6.40 (s, 1 H), 4.77(t, *J* = 2.4 Hz, 1 H), 4.59 (d, *J* = 12.3 Hz, 1 H), 4.53 (d, *J* = 12.3 Hz, 1 H), 4.09 (dd, *J* = 9.9, 2.7 Hz, 1 H), 3.60 (s, 3 H), 3.50 (d, *J* = 9.9, 5.4 Hz, 1 H), 3.47(d, *J* = 12.9 Hz, 1 H), 3.28(dd, *J* = 8.4, 2.7 Hz, 1 H), 3.22(m, 1 H), 3.10 (m, 1 H), 2.74(s, 1 H), 2.44 (dd, *J* = 15.9, 3.9 Hz, 1 H), 2.17(dd, *J* = 15.9, 10.8 Hz, 1 H), 2.03(s, 3 H). ^{13}C NMR (75 MHz, DMSO-*d*6): δ 148.1, 143.9, 138.6, 130.4, 128.2, 127.8, 127.5, 127.3, 125.8, 124.4, 114.2, 71.9, 68.8, 65.7, 59.3, 53.0, 47.5, 31.3, 11.2.

(–)-MY 336a (1). To a solution of compound **10** (230 mg, 0.67 mmol) in MeOH (4 mL) at room temperature was added $Pd(OH)_2$ (moist, Pd content 20%, 50 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 pale yellow residue was purified by column chromatograph (SiO_2 treated with triethylamine, 5% MeOH in $CHCl_3$) to afford compound **1** (147 mg, 86%) as a yellow solid. $[\alpha]_D^{20}$: −97.3 (c 0.5, CH_3OH). HRMS calcd. for $C_{13}H_{20}NO_4(M+H^+)$ 254.1387, found 254.1421 ^{1}H NMR (600 MHz, DMSO- d_6): δ 8.65 (s, 1 H), 6.34 (s, 1 H), 4.66 (s, 1 H), 4.10 (t, *J* = 4.2 Hz, 1 H), 3.90 (dd, *J* = 10.2, 4.2 Hz, 1 H, 1-CH_2OH,), 3.59(s, 3 H, 7-OMe), 3.43 (dd, *J* = 10.8, 4.8

Hz, 1H, 3-CH_2OH), 3.36 (dd, $J = 10.2$, 6.6 Hz, 1H, 1-CH_2OH), 3.32 (dd, $J = 10.8$, 6.6 Hz, 1 H, 3-CH_2OH), 2.68 (m, 1 H, 3-H), 2.41 (dd, $J = 15.0$, 2.4 Hz, 1 H, 4-H_{eq}), 2.24 (dd, $J = 14.4$, 11.4 Hz, 1 H, 4-H_{ax}), 2.11(s, 3 H, 6-Me). ^{13}C NMR (75MHz, DMSO-d_6): δ 146.8, 143.9, 132.4, 127.8, 121.9, 120.9, 65.3, 64.8, 59.7, 54.9, 53.9, 33.0, 15.3.

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