Tetrahedron: *Asymmetry* 19 (2008) 1833–1838

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A concise synthesis of (−)-indolmycin and (−)-5-methoxyindolmycin

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ARTICLE INFO

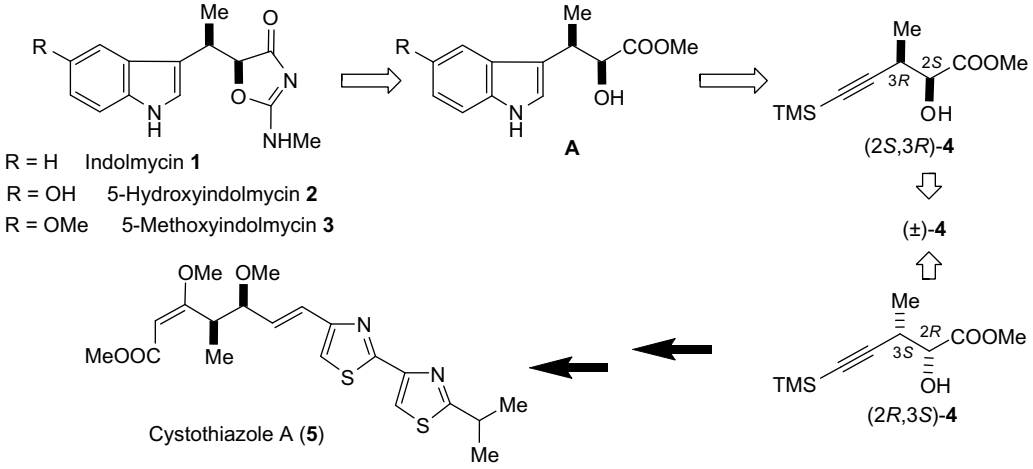
Article history:
Received 11 June 2008
Accepted 2 July 2008
Available online 9 August 2008

ABSTRACT

Concise syntheses of (−)-indolmycin **1** and (−)-5-methoxyindolmycin **3** were developed based on a palladium-catalyzed reaction of (2*S*,3*R*)-2-acetoxy-3-methyl-5-trimethylsilyl-4-pentynoate **6** with an *o*-iodoaniline derivative **10** or **11**, followed by reaction with guanidine hydrochloride in the presence of base. An optically active internal alkyne (2*S* 3*R*)-**6** was obtained by lipase-assisted enantioselective acetylation of (±)-(2,3)-*syn*-2-hydroxy-3-methyl-5-trimethylsily-4-pentynoate **4**.

1. Introduction

(−)-Indolmycin **1**, an antibiotic isolated from the African strain of *Streptomyces albus*, exhibits an antibacterial activity against *Staphylococci*.[1] Indolmycin congeners **2** and **3**, which possess a hydroxyl or methoxyl group at the 5′-position of the indole skeleton, have been obtained by the addition of indole precursors, such as 5-hydroxy- and 5-methoxyindoles to growing cultures of *Streptomyces griseus* ATCC 12648.[2] These congeners show a moderate increase in antimicrobial activity compared to **1**. In a recent study, **1** was reported to exhibit potent antibacterial activity against *Helicobactor pylori* (*H. pylori*), and is thus a promising anti-*H. pylori* agent[3] (Scheme 1). Racemic syntheses of **1** have been developed by two groups.[4] The first asymmetric synthesis of (−)-**1** was achieved based on the reaction of (2*R*,3*S*)-6-alkyliden-3,4-dimethyl-2-phenylperhydro-1,4-oxaazepine-5,7-dione with a Grignard reagent.[5] Syntheses of optically active indolmycin **1** have been carried out using a resolution method[6] or based on the reaction of indolyl magnesium bromide with (2*S*,3*R*)-epoxy butanoate, affording (2*S*,3*R*)-indolmycenate derivative **A**.[7] Palladium-catalyzed heteroannulation of internal alkynes (**C**) using *o*-iodoaniline or its derivatives **B** has been reported to give indole derivatives **E** via a vinylpalladium intermediate **D** as shown in Scheme 2,[8] and this procedure (the Larock indole synthesis) seems to be promising



Scheme 1.

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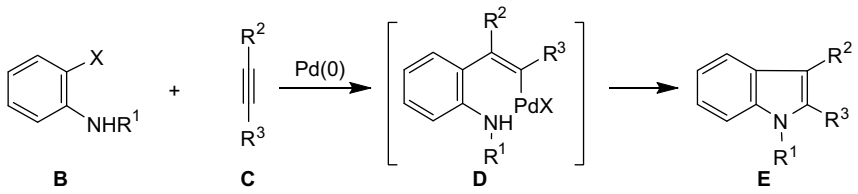
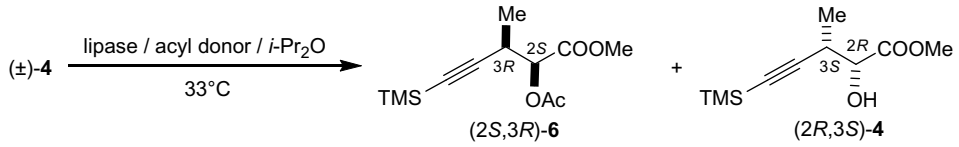
doi:10.1016/j.tetasy.2008.07.013

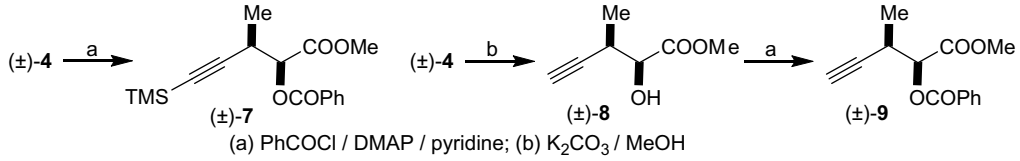


Scheme 2. Tandem Heck reaction and cyclization.

Table 1
Lipase-assisted acetylation of (±)-**4**



Entry	Substrate	Lipase	Acyl donor	Time (days)	Products (%, % ee)	
1	(±)-**4** (5.012 g)	Amano P	Isopropenyl acetate	7	(2*S*,3*R*)-**6** (28, 82)	(2*R*,3*S*)-**4** (59, 44)
2	(2*R*,3*S*)-**4** (44% ee) (2.980 g)	Amano PS	Vinyl acetate	3	(2*S*,3*R*)-**6** (23, 86)	(2*R*,3*S*)-**4** (60, 95)
3	(±)-**4** (5.150 g)	Amano PS	Vinyl acetate	5	(2*S*,3*R*)-**6** (48, 95)	(2*R*, 3*S*)-**4** (50, 94)



for synthesis of optically active indolmycenate derivatives **A** (Scheme 2). Herein, we report a concise synthesis of (−)-indolmycin **1** and (−)-5-methoxyindolmycin **3** based on a palladium-catalyzed reaction of *o*-iodoaniline congeners and (2*S*,3*R*)-2-hydroxy-3-methyl-5- trimethylsilyl-4-pentynoate **4** or its acetate **6** (see Table 1). The optically active (2*S*,3*R*)-**4** or (2*R*,3*S*)-**4** could be obtained based on the enantioselective acetylation of (±)-**4** using lipase. Enantiomerically pure (2*R*,3*S*)-**4** obtained by an alternative method was converted to the β-methoxyacrylate antibiotic cystothiazole A **5**.[9]

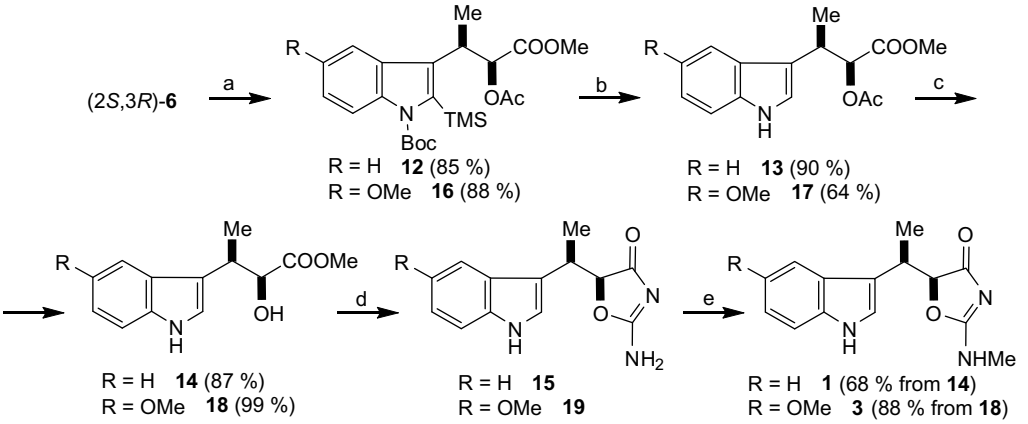
2. Results and discussion

2.1. Lipase-assisted enantioselective acetylation of (±)-4

Using a previously reported procedure,[9] substrate (±)-**4** was obtained by the reaction of (±)-*trans*-(2,3)-epoxy butanoate and trimethylsilylacetylide. For the purpose of determining the enantiomeric excess (ee) of the enzymatic reaction products, racemate (±)-**4** was converted to two benzoates (±)-**7** and (±)-**9**, which gave two well separated peaks of the enantiomeric isomers, respectively, in HPLC analysis (see Section 4), thus allowing the determination of the ee of the enzymatic reaction products. A screening experiment for finding a suitable enzyme showed that the most effective lipase was found to be Amano P or Amano PS from *Pseudomonas* sp. When (±)-**4** was subjected to enantioselective acetylation using 'Amano P' in the presence of isopropenyl acetate as an acylating reagent for 7 days, acetate **6** (28%, 82% ee) and unreacted alcohol **4** (59%, 44% ee) were obtained (Table 1, entry 1). The 44% ee of unreacted alcohol **4** was again subjected to enzymatic acetylation using Amano PS in the presence of vinyl acetate for 3 days, to give acetate **6** (23%, 86% ee) and unreacted alcohol **4** (60%, 95% ee) (Table 1, entry 2). Enzymatic acetylation of (±)-**4** using Amano PS in the presence of vinyl acetate for 5 days gave acetate (+)-**6** {48%, $[\alpha]_D^{27} = +12.05$ (*c* 1.09, $CHCl_3$); corresponds to 95% ee} and unreacted alcohol (−)-**4** {50%, $[\alpha]_D^{25} = -24.8$ (*c* 1.13, $CHCl_3$); corresponds to 94% ee} (Table 1, entry 3). The enantiomeric excess (ee) for each enzymatic product was calculated by HPLC analysis after conversion of the enzymatic product to the corresponding benzoate. The *E*-value[10] of this enzymatic reaction (entry 3) was estimated to be 139. The absolute structure of the enzymatic reaction product (−)-**4** was determined by direct comparison with previously reported sample[9b] (2*R*,3*S*)-**4** {$[\alpha]_D^{25} = -24.1$ (*c* 1.07, $CHCl_3$); corresponds to >99% ee}; thus, the absolute configuration of acetate **6** was determined to be (2*S*,3*R*).

2.2. Synthesis of (−)-indolmycin 1 and (−)-5-methoxyindolmycin 3

Syntheses of (−)-indolmycin **1** and (−)-5-methoxyindolmycin **3** from (2*S*,3*R*)-**6** are shown in Scheme 3. At first, the reaction of *o*-iodoaniline and (±)-**4** in the presence of [1,1-bis(diphenylphosphono)-ferrocene]palladium(II) dichloride dichloromethane complex, LiCl, and Na_2CO_3 in DMF, followed by desilylation, did not give the desired indolmycenate (±)-**14** (Scheme 3). Then, two types of *o*-iodoaniline congeners, *N*-(*tert*-butoxycarbonyl)-2-iodoaniline **10** and *N*-(*tert*-butoxycarbonyl)-2-iodo-4-methoxyaniline **11**, were synthesized by *N*-*tert*-butoxycarbonylation of *o*-iodoaniline and the known 2-iodo-4-methoxyaniline,[11] respectively. Reaction of (2*S*,3*R*)-**6** and **10** using $Pd(OAc)_2$ in the presence of Ph_3P, Et_4N^+Cl, and *i*-Pr_2NEt gave the indole congener **12** in 85% yield, this was treated with CF_3COOH to afford **13** in 90% yield. Alcoholysis of **13** with K_2CO_3 in MeOH gave (+)-indolmycenate **14** {$[\alpha]_D^{22} = +3.3$ (*c* 0.395, $CHCl_3$), 87% yield}, whose physical data were consistent

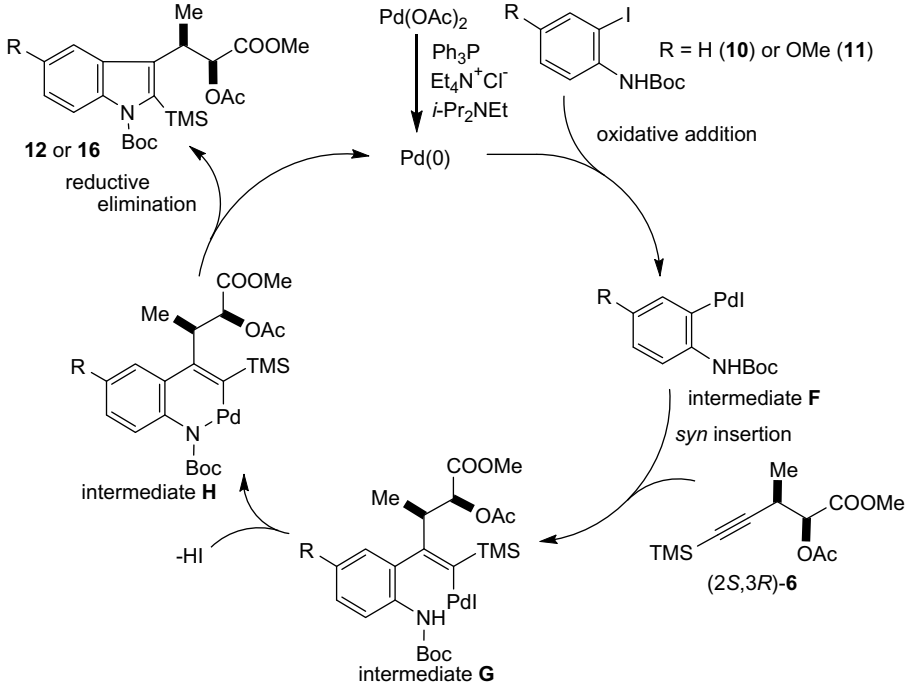


Scheme 3. Reagents: (a) for **12**, *N*-Boc-2-iodoaniline **10**/$Pd(OAc)_2$/Ph_3P/$Et_4N^+Cl^-$/*i*-Pr_2NEt; for **16** *N*-Boc-2-iodo-4-methoxyaniline **11**/$Pd(OAc)_2$/Ph_3P/$Et_4N^+Cl^-$/*i*-Pr_2NEt; (b) CF_3COOH/CH_2Cl_2; (c) K_2CO_3/MeOH; (d) guanidine hydrochloride/*t*-BuOK/*t*-BuOH/molecular sieves 4 Å; (e) 40% $MeNH_2/H_2O$.

with those of the reported (+)-**14**,[12] including the sign of the specific rotation. The reaction of (+)-**14** with guanidine hydrochloride in the presence of *tert*-BuOK using a previously reported procedure[7] gave 2-amino-4(5*H*)-oxazolone congener **15**, which was reacted with 40% methylamine to afford (−)-indolmycin **1** {mp 198–200 °C, $[\alpha]_D^{22} = -195.8$ (*c* 0.92, MeOH), 68% yield from **14**}. The physical data of synthetic (−)-**1** were consistent with those of previously reported indolmycin **1** {mp 204–206 °C, $[\alpha]_D^{23} = -198$ (*c* 2, MeOH)}.[5] From NMR studies of synthetic (−)-**1**, (−)-**1** was found to be a 2:1 mixture of two tautomers **1** and its tautomer. The main tautomer was the desired (−)-**1**. Isolation of two tautomers was found to be difficult; this tendency was seen in the previous case.[7] Similarly, the reaction of (2*S*,3*R*)-**6** and **11** using $Pd(OAc)_2$ in the presence of Ph_3P, Et_4N^+Cl, and *i*-Pr_2NEt gave the indole congener **16** (88% yield), which was treated with CF_3COOH to afford **17** in 64% yield. Alcoholysis of **17** with K_2CO_3 in MeOH gave (−)-5-methoxyindolmycenate **18** {$[\alpha]_D^{22} = -11.9$ (*c* 0.84, MeOH)} in 99% yield. The reaction of (−)-**18** with guanidine hydrochloride in the presence of *tert*-BuOK provided 2-amino-4(5*H*)-oxazolone congener **19**, which was reacted with 40% methylamine to afford (−)-5-methoxyindolmycin **3** {mp 75–77 °C, $[\alpha]_D^{22} = -161.3$ (*c* 0.61, MeOH), 88% yield from **18**}. From NMR studies of synthetic (−)-**3**, (−)-**3** was also found to be a 2:1 mixture of two tautomers **3** and its tautomer.

2.3. Discussion

The formation of indole congeners **12** and **16** by a palladium(II)-catalyzed reaction of internal alkyne (2*S*,3*R*)-**6** with *o*-iodoaniline derivative **10** or **11**, respectively, and the corresponding catalytic cycle may be explained as shown in Scheme 4. First, palladium(II) is converted to palladium(0) under the specified reaction conditions. Oxidative addition of *o*-iodoaniline congener **10** or **11** to Pd(0) gives intermediate **F**, which undergoes *syn* insertion of the internal alkyne (2*S*,3*R*)-**6** into the arylpalladium bond to afford intermediate **G**. Next, nitrogen displacement of the palladium in the resulting vinylpalladium intermediate **G** results in the formation of a six-membered-ring intermediate **H**, along with



Scheme 4.

elimination of hydrogen iodide (HI); finally, reductive elimination of palladium from intermediate **H** gives indole congener **12** or **16** and Pd(0). Annulation of unsymmetrical alkynes has proven to be highly regioselective, providing only the appropriate regioisomer. The more sterically bulky group is located nearer the nitrogen atom in the indole product.[8]

3. Conclusion

Concise syntheses of (−)-indolmycin **1** and (−)-5-methoxyindolmycin **3** were achieved based on the palladium-catalyzed reaction of (2*S*,3*R*)-2-acetoxy-3-methyl-5-trimethylsilyl-4-pentynoate **6** with *o*-iodoaniline derivative **10** or **11**, followed by reaction with guanidine hydrochloride in the presence of *tert*-BuOK. The optically active internal alkyne (2*S*,3*R*)-**6** was obtained by the lipase-assisted enantioselective acetylation of (±)-(2,3)-*syn*-2-hydroxy-3-methyl-5-trimethylsilyl-4-pentynoate **4**. The formation of indole congener **12** or **16** by a palladium(II)-catalyzed reaction of internal alkyne (2*S*,3*R*)-**6** with *o*-iodoaniline derivative **10** or **11** and the corresponding catalytic cycle are discussed.

4. Experimental

4.1. Methods and results

^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4.1.1. Methyl (±)-(2,3)-*syn*-2-benzoyloxy-3-methyl-5-trimethylsilyl-4-pentynoate 7

To a solution of (±)-**4** (100 mg, 0.46 mmol) in pyridine (2 ml) were added PhCOCl (130 mg, 0.92 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP; 23 mg, 0.19 mmol), and the whole mixture was heated with stirring for 1 h at 70 °C. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 2 M HCl, a saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt (80:1)) to give (±)-**7** (142 mg, 95%) as a colorless oil. (±)-**7**: IR (CCl_4): 2171, 1758, 1729 cm^{-1}; ^{1}H NMR: δ 0.001 (9H, s), 1.27 (3H, d, J = 7.0 Hz), 3.12 (1H, dd, J = 7.0, 5.1 Hz), 3.69 (3H, s), 5.23 (1H, d, J = 5.1 Hz), 7.35–7.39 (2H, m), 7.48–7.52 (1H, m), 8.00–8.02 (2H, m). HR-MS (FAB): calcd for $C_{17}H_{23}O_4Si$ (M^++1): 319.1365, found: 319.1362. HPLC {column: CHIRALPAC AD (4.6 × 250 mm), eluent: *n*-hexane/EtOHt = 30:1, flow rate: 0.5 ml/min, detection: UV at 254 nm}: t_R = 7.8, 9.3 min.

4.1.2. Methyl (±)-(2,3)-*syn*-2-benzoyloxy-3-methyl-4-pentynoate 9

(1) To a solution of (±)-**4** (197 mg, 0.92 mmol) in MeOH (5 ml) was added K_2CO_3 (120 mg, 0.67 mmol), and the whole mixture was stirred for 1 h at rt. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt (10:1)) to give (±)-**8** (71 mg, 54%) as a colorless oil. (±)-**8**: ^{1}H NMR: δ 1.14 (3H, d, J = 7.1 Hz), 2.09 (1H, d, J = 2.5 Hz), 2.89 (1H, q, d, d, J = 7.1, 3.9, 2.5 Hz), 3.76 (3H, s), 4.20 (1H, d, J = 3.9 Hz). (2) To a solution of (±)-**8** (71 mg, 0.5 mmol) in pyridine (2 ml) were added PhCOCl (55 mg, 0.39 mmol) and DMAP (31 mg, 0.25 mmol), and the whole mixture was heated with stirring for 1 h at 70 °C. The reaction mixture was worked up in the same way as (±)-**7** to give (±)-**9** (62 mg, 50%) as a colorless oil. (±)-**9**: IR (CCl_4): 2360, 1730 cm^{-1}; ^{1}H NMR: δ 1.36 (3H, d, J = 7.1 Hz), 2.12 (1H, d, J = 2.5 Hz), 3.18–3.25 (1H, m), 3.77 (3H, s), 5.33 (1H, d, J = 4.5 Hz), 7.43–7.47 (2H, m), 7.55–7.60 (1H, m), 8.07–8.10 (2H, m). HRMS (EI) calcd for $C_{14}H_{14}O_4$ (M^+): 246.0892. Found: 246.0853. HPLC {column: CHIRALPAC AD (4.6 × 250 mm), eluent: *n*-hexane/EtOHt = 30:1, flow rate: 0.5 ml/min, detection: UV at 254 nm}: t_R = 12.0, 13.2 min.

4.1.3. Enantioselective acetylation of (±)-4

From a screening experiment using various kinds of lipase, the effective lipases were as follows: Amano P from *Pseudomonas* sp. and Amano PS *Pseudomonas* sp. Enzymatic acetylation of (±)-**4** was performed under the following condition (entries 1–3). Determination of the enantiomeric excess (ee) of the enzymatic reaction products was carried out by the method mentioned below in this text. The results are shown in Table 1. (1) Table 1, entry 1: A suspension of (±)-**4** (5.012 g, 23.8 mmol), isopropenyl acetate (10 g, 100 mmol), and lipase Amano P (5 g) in diisopropyl ether (50 ml) was stirred for 7 d at 33 °C. After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (200 g) to give (2*S*,3*R*)-**6** (1.651 g, 28%, 82% ee) from *n*-hexane/AcOEt = 80:1 eluate and (2*R*,3*S*)-**4** (2.980 g, 59%, 44% ee) from *n*-hexane/EtOAc = 20:1 eluate, respectively. (2) Table 1, entry 2: A suspension of 44% ee of (2*R*,3*S*)-**4** (2.980 g), vinyl acetate (5.8 g, 67 mmol), and lipase Amano PS (2.9 g) in diisopropyl ether (290 ml) was stirred for 3 d at 33 °C. The reaction mixture was worked up in the same way as entry 1 to give (2*S*,3*R*)-**6** (0.798 g, 23%, 86% ee) and (2*R*,3*S*)-**4** (1.764 g, 60%, 95% ee). (3) Table 1, entry 3: A suspension of (±)-**4** (5.150 g, 24 mmol), vinyl acetate (10 g, 116 mmol), and lipase Amano PS (5 g) in diisopropyl ether (500 ml) was stirred for 5 d at 33 °C. The reaction mixture was worked up in the same way as entry 1 to give (2*S*,3*R*)-**6** {2.958 g, 48%, $[\alpha]_D^{27} = +12.05$ (*c* 1.09, $CHCl_3$); corresponds to 95% ee} and (2*R*,3*S*)-**4** {2.575 g, 50%, $[\alpha]_D^{25} = -24.8$ (*c* 1.13, $CHCl_3$); corresponds to 94% ee}. (2*R*,3*S*)-**4**; IR (neat): 3482, 2168, 1741 cm^{-1}; ^{1}H NMR: δ 0.15 (9H, s), 1.21 (3H, d, J = 7.2 Hz), 2.86–2.93 (1H, m), 3.81 (3H, s), 4.21 (1H, d, J = 4.4 Hz). ^{13}C NMR: δ −0.07 (3C), 15.8, 32.3, 52.4, 73.5, 86.9, 106.1, 173.1. HRMS (FAB) calcd for $C_{10}H_{19}O_3Si$ (M^++1): 215.1104. Found *m*/*z*: 215.1106. (2*S*,3*R*)-**6**; IR (neat): 2173, 1754, 1225 cm^{-1}; ^{1}H NMR: δ 0.13 (9H, s), 1.23 (3H, d, J = 7.0 Hz), 2.16 (3H, s), 3.05 (1H, qd, J = 7.0, 5.2 Hz), 3.75 (3H, s), 5.08 (1H, d, J = 5.2 Hz). ^{13}C NMR: δ −0.05 (3C), 16.3, 20.5, 29.4, 52.3, 74.4, 87.2, 105.3, 169.0, 170.2. HR-MS (FAB): calcd for $C_{12}H_{21}O_4Si$ (M^++1): 257.1212. Found: 257.1187.

4.1.4. Determination of ee of the enzymatic reaction products

(1) Alcohol **4** (Table 1, entries 1–3; ca. 30 mg) was converted into the corresponding benzoate **7** in the same way as (±)-**7**. HPLC analysis of the present **7** indicated the retention time (t_R = 7.8 min) for the major isomer, which is attributed to that of (2*R*,3*S*)-**4**. (2) Acetate **6** (Table 1, entries 1–3; ca. 50 mg) was treated with K_2CO_3 (ca 10 mg) in MeOH (1 ml) for 10 min at rt. to give a crude **8**, which was converted to the corresponding benzoate **9** in the same way as (±)-**9**. HPLC analysis of the present **9** indicated the retention time (t_R = 13.2 min) for the major isomer, which is attributed to that of (2*S*,3*R*)-**6**.

4.1.5. *N*-(*tert*-Butoxycarbonyl)-2-iodoaniline 10

To a solution of 2-iodoaniline (1.54 g, 7.0 mmol) in anhydrous THF (15 ml) was added di-*tert*-butyl dicarbonate {$(Boc)_2O$; 3.07 g, 14.1 mmol}, and the reaction mixture was stirred for 12 h at reflux.

The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (30 g, *n*-hexane) to give *N*-(*tert*-butoxycarbonyl)-2-iodoaniline (1.994 g, 89%) as a colorless oil. ^{1}H NMR: δ 1.54 (9H, s), 6.74–7.78 (1H, m), 6.82 (1H, br s), 7.29–7.33 (1H, m), 7.73–7.75 (1H, m), 8.04–8.06 (1H, m). ^{13}C NMR: δ 28.3 (9C), 81.0, 124.6 (2C), 129.2 (2C), 138.8 (2C), 152.5. HRMS (EI) calcd for $C_{11}H_{14}NO_2I$ (M^+): 319.0070. Found: 319.0073.

4.1.6. *N*-(*tert*-Butoxycarbonyl)-2-iodo-4-methoxyaniline 11

To a solution of 2-iodo-4-methoxyaniline[12] (1.12 g, 4.5 mmol) in anhydrous THF (10 ml) was added $(Boc)_2O$ {1.96 g, 9.0 mmol}, and the reaction mixture was stirred for 12 h at reflux. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (20 g, *n*-hexane) to give *N*-(*tert*-butoxycarbonyl)-2-iodo-4-methoxyaniline (1.183 g, 75%) as a colorless oil. ^{1}H NMR: δ 1.52 (9H, s), 3.76 (3H, s), 6.53 (1H, br s), 6.89 (1H, dd, J = 8.8, 2.8 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.80 (1H, d, J = 8.8 Hz). ^{13}C NMR: δ 28.3 (9C), 55.7, 80.6, 114.9 (2C), 123.7 (2C), 132.4, 153.1, 156.0. HRMS (EI) calcd for $C_{12}H_{16}NO_3I$ (M^+): 349.0175. Found: 349.0180.

4.1.7. Methyl (2*S*,3*R*)-3-{1-(*tert*-butoxycarbonyl)-2-(trimethylsilyl)-1*H*-indol-3-yl}-2-acetoxybutanoate 12

A mixture of **10** (141 mg, 0.44 mmol), (2*S*,3*R*)-**6** (112 mg, 0.44 mmol), $Pd(OAc)_2$ (10 mg, 0.044 mmol), Ph_3P (23 mg, 0.09 mmol), $Et_4N^+Cl^-$ (73 mg, 0.44 mmol), and *i*-Pr_2NEt (171 mg, 1.3 mmol) in DMF (5 ml) was heated with stirring for 1.5 h at 100 °C. The reaction mixture was diluted with H_2O and extracted with a mixed solvent (*n*-hexane/AcOEt = 1:1). The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 50:1) to give **12** (168 mg, 85%) as a colorless oil. Compound **12**: $[\alpha]_D^{21} = +7.9$ (*c* 0.82, $CHCl_3$), IR (KBr): 1751 cm^{-1}; ^{1}H NMR: δ 0.42 (9H, s), 1.51 (3H, d, J = 7.2 Hz), 1.69 (9H, s), 2.13 (3H, s), 3.55 (3H, s), 3.99 (1H, qd, J = 7.2, 6.8 Hz), 5.33 (1H, d, J = 6.8 Hz), 7.17 (1H, ddd, J = 8.2, 7.2, 1.2 Hz), 7.25 (1H, ddd, J = 8.6, 7.2, 1.2 Hz), 7.82 (1H, d, J = 8.2 Hz), 7.95 (1H, d, J = 8.6 Hz). ^{13}C NMR: δ 2.5 (9C), 15.6, 20.8, 28.3 (9C), 34.2, 51.9, 76.3, 83.9, 115.2, 121.7, 121.8, 124.4, 129.9, 132.0, 137.8, 138.2, 151.4, 170.0, 170.5. HRMS (EI) calcd for $C_{23}H_{33}NO_6Si$ (M^+): 447.2077. Found: 447.2079.

4.1.8. Methyl (2*S*,3*R*)-3-(1*H*-indol-3-yl)-2-acetoxybutanoate 13

To a solution of **12** (420 mg, 0.94 mmol) in CH_2Cl_2 (10 ml) was added CF_3COOH {1.61 g, 14.1 mmol} at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. The reaction mixture was evaporated to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 10:1) to give **13** (233 mg, 90%) as a colorless oil. Compound **13**: $[\alpha]_D^{22} = -26.4$ (*c* 0.605, $CHCl_3$), IR (KBr): 1755, 1724 cm^{-1}; ^{1}H NMR: δ 1.46 (3H, d, J = 7.2 Hz), 2.10 (3H, s), 3.65 (3H, s), 3.75 (1H, qd, J = 7.2, 4.6 Hz), 5.24 (1H, d, J = 4.6 Hz), 7.06 (1H, d, J = 2.4 Hz), 7.13 (1H, ddd, J = 8.0, 6.8, 1.4 Hz), 7.20 (1H, ddd, J = 8.0, 6.8, 1.4 Hz), 7.35 (1H, d, J = 8.0 Hz), 7.68 (1H, d, J = 8.0 Hz), 8.15 (1H, br s). ^{13}C NMR: δ 15.6, 20.7, 32.7, 52.2, 76.2, 111.2, 116.6, 119.0, 119.5, 121.7, 122.2, 126.5, 136.2, 170.3, 170.6. HRMS (EI) calcd for $C_{15}H_{17}NO_4$ (M^+): 275.1158. Found: 275.1161.

4.1.9. Methyl (2*S*,3*R*)-3-(1*H*-indol-3-yl)-2-hydroxybutanoate 14

To a solution of **13** (289 mg, 1.05 mmol) in MeOH (10 ml) was added K_2CO_3 {145 mg, 1.05 mmol} at rt, and the reaction mixture was stirred for 20 min at rt. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 5:1) to give **14** (233 mg, 87%) as a colorless oil. Compound **14**: $[\alpha]_D^{22} = +3.3$ (*c* 0.395, $CHCl_3$), IR (KBr): 3891, 1735 cm^{-1}; ^{1}H NMR: δ 1.35 (3H, d, J = 7.2 Hz), 2.80 (1H, d, J = 4.4 Hz), 3.60 (1H, qd, J = 7.2, 3.2 Hz), 3.80 (3H, s), 4.53 (1H, qd, J = 4.4, 3.2 Hz), 7.09 (1H, d, J = 2.4 Hz), 7.12–7.16 (1H, m), 7.18–7.22 (1H, m), 7.34 (1H, dd, J = 7.2, 1.2 Hz), 7.68 (1H, d, J = 8.0 Hz), 8.16 (1H, br s). ^{13}C NMR: δ 14.1, 34.6, 52.5, 74.1, 111.3, 117.2, 118.7, 119.4, 121.9, 122.1, 126.5, 136.2, 174.7. HRMS (EI) calcd for $C_{13}H_{15}NO_3$ (M^+): 233.1052. Found: 233.1039.

4.1.10. (−)-Indolmycin 1

(1) To a solution of guanidine hydrochloride (616 mg, 6.4 mmol) in *tert*-BuOH (5 ml) were added potassium *tert*-KOBu (765 mg, 6.8 mmol) and molecular sieves 4 Å (600 mg) at rt, and the reaction mixture was stirred for 3 d at rt. To the above reaction mixture was added a solution of **14** (213 mg, 0.91 mmol) in *tert*-BuOH (5 ml), and the reaction mixture was stirred for 12 h at rt. The reaction mixture was poured into saturated NH_4Cl solution (20 ml) at 0 °C and filtered. The filtrate was extracted with a mixed solvent (AcOEt/*iso*-PrOH = 4:1). The organic layer was washed with 5% $NaHCO_3$ solution, brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave crude **15**, which was used for the next reaction without further purification. Compound **15**: ^{1}H NMR (DMSO-d_6): δ 1.19 (3H, d, J = 7.2 Hz), 4.92 (1H, d, J = 2.6 Hz), 6.96–7.08 (2H, m), 7.13 (1H, d, J = 2.4 Hz), 7.34 (1H, d, J = 8.0 Hz), 7.57 (1H, d, J = 8.0 Hz), 8.30 (1H, br s), 8.41 (1H, br s), 10.88 (1H, br s). (2) A mixture of a crude **15** and 40% $MeNH_2$ solution (15 ml) was allowed to stand in a refrigerator for 12 h, and the reaction mixture was evaporated to a residue without heating. The residue was chromatographed on silica gel (10 g, $CHCl_3$/MeOH = 30:1) to give the desired (−)-**1**, which was crystallized from MeOH/H_2O (2:1) to afford (−)-**1** (159 mg, 68% yield from **14**) as a colorless crystalline. (−)-**1**: 198–200 °C. $[\alpha]_D^{22} = -195.8$ (*c* 0.92, MeOH); IR (KBr): 3397, 1675, 1633 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.19 (2H, d, J = 7.0 Hz), 1.25 (1H, d, J = 7.0 Hz), 2.77 (1H, s), 2.80 (1H, d, J = 4.4 Hz), 3.54–3.62 (1H, m), 4.90 (1/3H, d, J = 2.8 Hz), 4.94 (2/3H, d, J = 2.8 Hz), 6.97–7.10 (2H, m), 7.15 (2/3H, d, J = 2.4 Hz), 7.18 (1/3H, d, J = 2.4 Hz), 7.35 (1H, d, J = 8.0 Hz), 7.58 (2/3H, d, J = 8.0 Hz), 7.59 (1/3H, d, J = 8.0 Hz), 8.63 (2/3H, br s), 8.70 (1/3H, br s), 10.91 (1H, br s). ^{13}C NMR (DMSO-d_6): δ 13.67 (2/3C), 13.78 (1/3C), 27.26, 28.96, 31.76 (1/3C), 31.83 (2/3C), 85.53 (2/3C), 86.08 (1/3C), 111.62, 115.08 (1/3C), 115.45 (2/3C), 118.53 (1/3C), 118.67 (2/3C), 121.17 (1/3C), 121.21 (2/3C), 122.52 (2/3C), 122.60 (1/3C), 126.21 (2/3C), 126.49 (1/3C), 136.24 (1/3C), 136.33 (2/3C), 175.50 (1/3C), 175.91 (2/3C), 186.89 (1/3C), 187.05 (2/3C). HR-MS (EI): calcd for $C_{14}H_{15}N_3O_2$ (M^+): 257.1164. Found: 257.1154.

4.1.11. Methyl-(2*S*,3*R*)-3-{1-(*tert*-butoxycarbonyl)-5-methoxy-2-(trimethylsilyl)-1*H*-indol-3-yl}-2-acetoxybutanoate 16

A mixture of **11** (681 mg, 1.95 mmol), (2*S*,3*R*)-**6** (500 mg, 1.95 mmol), $Pd(OAc)_2$ (44 mg, 0.19 mmol), Ph_3P (102 mg, 0.39 mmol), $Et_4N^+Cl^-$ (323 mg, 1.95 mmol), and *i*-Pr_2NEt (756 mg, 5.8 mmol) in DMF (20 ml) was heated with stirring for 1.5 h at 100 °C. The reaction mixture was diluted with H_2O and extracted with a mixed solvent (*n*-hexane/AcOEt = 1:1). The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (25 g, *n*-hexane/AcOEt = 50:1) to give **16** (820 mg, 88%) as a colorless oil. Compound **16**: $[\alpha]_D^{20} = +12.5$ (*c* 0.655, $CHCl_3$), IR (KBr): 1751, 1727 cm^{-1}; ^{1}H NMR: δ 0.41 (9H, s), 1.50 (3H, d, J = 7.2 Hz), 1.68 (9H, s), 2.15 (3H, s), 3.59 (3H, s), 3.87 (3H, s), 3.97 (1H, qd, J = 7.2, 6.8 Hz), 5.34 (1H, d, J = 6.8 Hz), 6.90 (1H, dd, J = 9.2, 2.4 Hz), 7.29 (1H, d, J = 2.4 Hz), 7.84 (1H, d, J = 9.2 Hz). ^{13}C NMR: δ 2.5 (9C), 15.3, 20.9, 28.2 (9C), 34.1, 51.9, 55.8, 76.2, 83.7, 104.7, 112.9, 115.8, 130.7,

131.7, 133.0, 138.8, 151.2, 154.9, 170.0, 170.5. HRMS (EI) calcd for $C_{24}H_{35}NO_7Si$ (M^+): 477.2183. Found: 477.2155.

4.1.12. Methyl (2*S*,3*R*)-3-(5-methoxy-1*H*-indol-3-yl)-2-acetoxybutanoate 17

To a solution of **16** (420 mg, 0.94 mmol) in CH_2Cl_2 (10 ml) was added CF_3COOH {1.61 g, 14.1 mmol} at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. The reaction mixture was evaporated to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 5:1) to give **17** (213 mg, 87%) as a colorless oil. Compound **17**: $[\alpha]_D^{22} = -35.2$ (*c* 0.565, $CHCl_3$), IR (KBr): 1742 cm^{-1}; ^1H NMR: δ 1.45 (3H, d, *J* = 7.2 Hz), 2.11 (3H, s), 3.64 (3H, s), 3.68 (1H, qd, *J* = 7.2, 4.8 Hz), 3.87 (3H, s), 5.20 (1H, d, *J* = 4.8 Hz), 6.86 (1H, dd, *J* = 8.8, 2.4 Hz), 7.04 (1H, dd, *J* = 2.4 Hz), 7.10 (1H, d, *J* = 2.4 Hz), 7.24 (1H, d, *J* = 8.8 Hz), 8.03 (1H, br s). ^{13}C NMR: δ 15.7, 20.7, 32.7, 52.2, 56.0, 76.2, 101.0, 111.9, 112.4, 116.3, 122.4, 126.9, 131.3, 154.1, 170.3, 170.5. HRMS (EI) calcd for $C_{16}H_{19}NO_5$ (M^+): 305.1263. Found: 305.1265.

4.1.13. Methyl (2*S*,3*R*)-3-(5-methoxy-1*H*-indol-3-yl)-2-hydroxybutanoate 18

To a solution of **17** (270 mg, 0.88 mmol) in MeOH (10 ml) was added K_2CO_3 {122 mg, 0.88 mmol} at rt, and the reaction mixture was stirred for 20 min at rt. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 3:1) to give **18** (231 mg, 99%) as a colorless oil. Compound **18**: $[\alpha]_D^{22} = -11.9$ (*c* 0.84, MeOH), IR (KBr): 3391, 1747 cm^{-1}; ^1H NMR: δ 1.33 (3H, d, *J* = 7.2 Hz), 2.72 (1H, d, *J* = 4.8 Hz), 3.58 (1H, qd, *J* = 7.2, 3.2 Hz), 3.80 (3H, s), 3.88 (3H, s), 4.50 (1H, dd, *J* = 3.2, 4.8 Hz), 6.87 (1H, dd, *J* = 8.8, 2.4 Hz), 7.10 (1H, d, *J* = 2.4 Hz), 7.12 (1H, d, *J* = 2.4 Hz), 7.24 (1H, d, *J* = 8.8 Hz), 7.98 (1H, br s). ^{13}C NMR: δ 14.3, 34.7, 52.5, 56.0, 74.2, 101.0, 111.9, 112.2, 117.2, 122.7, 127.1, 131.4, 154.1, 174.7. HRMS (EI) calcd for $C_{14}H_{17}NO_4$ (M^+): 263.1158. Found: 263.1173.

4.1.14. (−)-5-Methoxyindolmycin 3

(1) To a solution of guanidine hydrochloride (635 mg, 6.6 mmol) in *tert*-BuOH (5 ml) were added potassium *tert*-KOBu (791 mg, 7.0 mmol) and molecular sieves 4 Å (600 mg) at rt, and the reaction mixture was stirred for 3 d at rt. To the above reaction mixture was added a solution of **18** (206 mg, 0.78 mmol) in *tert*-BuOH (5 ml), and the reaction mixture was stirred for 12 h at rt. The reaction mixture was poured into saturated NH_4Cl solution (20 ml) at 0 °C and filtered. The filtrate was extracted with a mixed solvent (AcOEt/*iso*-PrOH = 4:1). The organic layer was washed with 5% $NaHCO_3$ solution, brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave crude **19**, which was used for the next reaction without further purification. (2) A mixture of crude **19** and 40% $MeNH_2$ solution (12 ml) was allowed to stand in a refrigerator for 12 h, and the reaction mixture was evaporated to a residue without heating. The residue was chromatographed on silica gel (10 g, $CHCl_3$/MeOH = 40:1) to give the desired (−)-**3**, which was crystallized from MeOH/H_2O (2:1) to afford (−)-**3** (198 mg, 88% yield from **18**) as colorless amorphous crystalline. (−)-**3**: mp 75–77 °C. $[\alpha]_D^{22} = -161.3$ (*c* 0.61, MeOH); IR (KBr): 3292, 1733, 1627 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.17 (2H, d, *J* = 7.2 Hz), 1.22 (1H, d, *J* = 7.2 Hz), 2.77 (1H, s), 2.81 (1H, d, *J* = 4.8 Hz), 3.50–3.59 (1H, m), 3.76 (1H, s), 3.77 (2H, s), 4.91 (1/3H, d, *J* = 2.8 Hz), 4.96 (2/3H, d, *J* = 2.8 Hz), 6.73 (1H, dd, *J* = 8.8, 2.4 Hz), 7.02 (2/3H, d, *J* = 2.4 Hz), 7.05 (1/3H, d, *J* = 2.4 Hz), 7.10 (2/3H, d, *J* = 2.4 Hz), 7.14 (1/3H, d, *J* = 2.4 Hz), 7.24 (1H, d, *J* = 8.8 Hz), 8.61 (2/3H, br s), 8.73 (1/3H, br s), 10.74 (1H, br s). ^{13}C NMR (DMSO-d_6): δ 13.57 (2/3C), 13.67 (1/3C), 27.09, 28.85, 31.57, 55.38 (2/3C), 55.41 (1/3C), 85.28 (1/3C), 85.88 (1/3C), 100.22 (2/3C), 100.38 (1/3C), 111.18 (1/3C), 111.27 (2/3C), 112.13, 114.83 (1/3C), 115.10 (2/3C), 123.03 (2/3C), 123.15 (1/3C), 126.39 (2/3C), 126.64 (1/3C), 131.25 (1/3C), 131.28 (2/3C), 153.02 (1/3C), 153.08 (2/3C), 175.83, 186.72 (1/3C), 186.88 (2/3C). HR-MS (EI): calcd for $C_{15}H_{17}N_3O_3$ (M^+): 287.1270. Found: 287.1277.

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