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New total synthesis of (±)-, (−)- and (+)-chuangxinmycins

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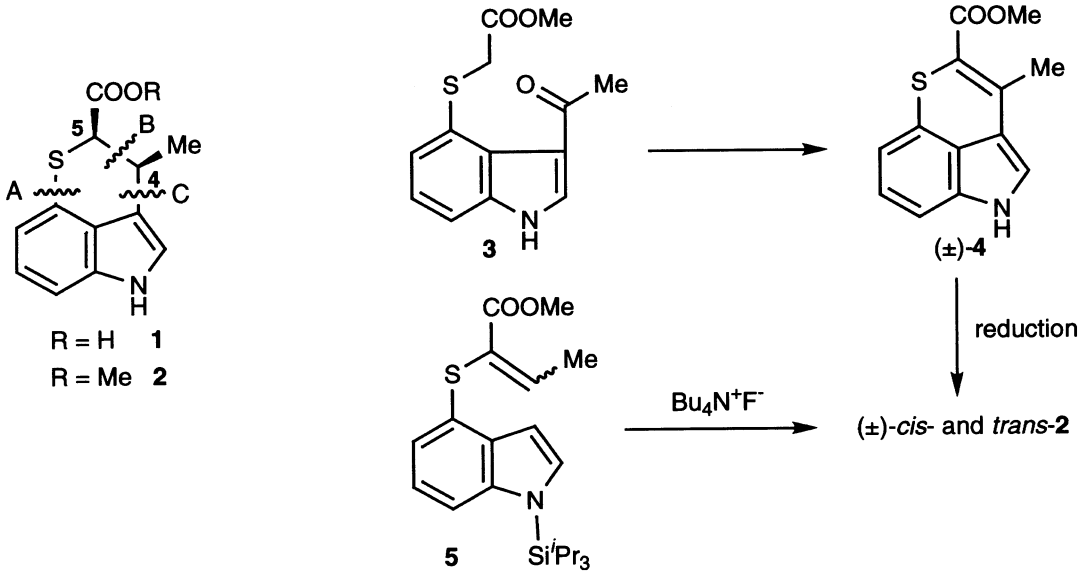
Abstract—(±)-2-Hydroxy-3-(1*H*-4′-iodoindol-3′-yl)butanoate **6** was stereoselectively converted into the (±)-(2,3)-*syn*-2-thioacetoxy ester **13** with retention of C_2-stereochemistry in (±)-**6**. Palladium-catalyzed cyclization of indolyl iodide and the internal C_2 thiol group of the substrate (±)-**14** gave the (±)-*cis* methyl ester **2** of natural chuangxinmycin (**1**). Stereoselective total syntheses of (−)-(4*S*,5*R*)- and (+)-(4*R*,5*S*)-chuangxinmycins **1** were achieved based on the enzymatic syntheses of (2*R*,3*S*)- and (2*S*,3*R*)-epoxy butanoates **9**, respectively. Chiral intermediates such as (2*R*,3*S*)- and (2*S*,3*R*)-2-hydroxy-3-(1*H*-4′-iodoindol-3′-yl)butanoate **6** for the chiral synthesis of (−)- and (+)-**1** were also obtained by the enantioselective hydrolysis of the corresponding acetate (±)-**16** by lipase.

1. Introduction

Chuangxinmycin (**1**), isolated from *Actinoplanes tsinanensis* n. sp. in China, exhibits in vitro, an antibacterial spectrum that includes a number of Gram-positive and Gram-negative bacteria. This antibiotic was reported to be active in mice against *Escherichia coli* and *Shigella dysenteria* infections in vivo, and effective in the treatment of septicaemia, urinary, and biliary infections caused by *E. coli* in preliminary clinical results.[1]

The relative structure of **1** was confirmed by synthesis[2,3] and the absolute configurations were determined as 4*S*,5*R* based on the degradation study of the natural product (**1**)[4] and optical resolution of (±)-**1** with *S*-(−)-α-phenylethyl amine.[5] Synthetic attempts were carried out by the way of two published routes. One is an internal Knoevenagel condensation of 4-substituted-3-acetyl indole **3** and the subsequent reduction of **4** to give a mixture of (±)-*cis*- and -*trans*-methyl ester **2** of **1** via pathway B.[2] In the other route, treatment of **5** with the fluoride ion liberated



Scheme 1.

Keywords: chuangxinmycins; stereoselective synthesis; enzymatic synthesis.

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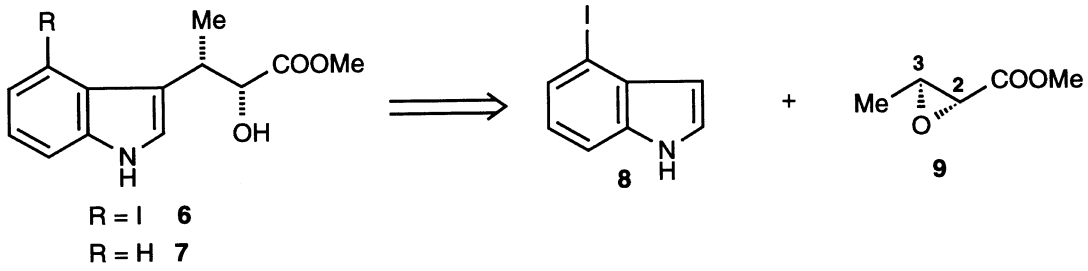


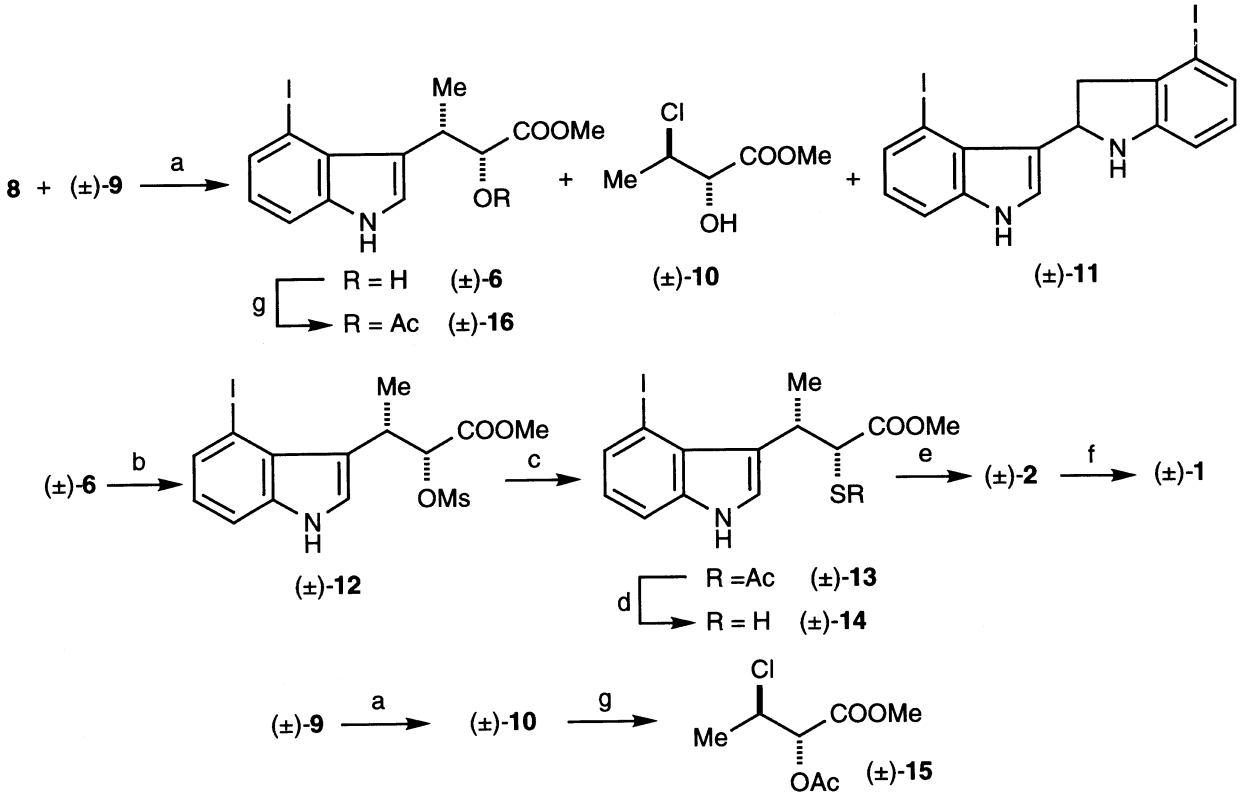
Scheme 2.

the indol-1-yl anion by desilylation, and Michael addition of the ambident C-3 anion to the α-thioacrylate acceptor could bring about the required cyclization via pathway C.[3] (Scheme 1). But these routes were found to be unacceptable for the synthesis of the optically active form of **1**. We now report a highly stereoselective synthesis of (±)-**1** via pathway A directed toward chiral synthesis starting with the requisite **6** possessing two definite absolute configurations at the C_2- and C_3-positions and the subsequent enantioselective synthesis of both enantiomers of (−)-**1** and (+)-**1**.

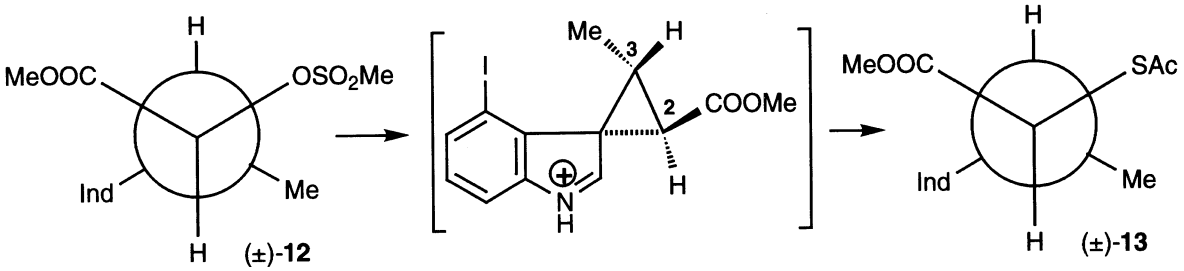
2. Results and discussion

The synthesis of indolmycenate (**7**), an important intermediate for the synthesis of indolmycin,[6] was achieved by the reaction of indole and (±)-*trans*-(2,3)-epoxy butanoate **9**[7] in the presence of $SnCl_4$ along with nucleophilic displacement with inversion at the C-3 carbon of the epoxide.[8] This strategy appeared to be the most promising from a stereochemical standpoint for the stereoselective construction of C_2- and C_3-configurations of **6** by the reaction of 4-iodoindole **8**[9] and (±)-**9** (Scheme 2).

The reaction of **8** and (±)-**9**, obtained by *m*-chloroperbenzoic acid oxidation of methyl crotonate, in the presence of $SnCl_4$ afforded (±)-4′-iodoindolmycenate **6** (32% yield) along with a 5:1 mixture ((±)-**10**/(±)-**11** 5:1) of (±)-(2,3)-*anti*-3-chloro-2-hydroxy butanoate **10** and (±)-4-iodoindole dimer **11**. Treatment of (±)-**6** with MsCl in pyridine followed by treatment with CsSAc[10] gave the desired (±)-(2,3)-*syn*-2-thioacetoxy ester **13** in 70% overall yield with complete retention of C_2-stereochemistry. Deacetylation of (±)-**13** with K_2CO_3 in MeOH followed by treatment with $Pd(PPh_3)_4$[11] in the presence of Et_3N afforded the (±)-*cis* methyl ester **2** in 67% overall yield, of which the spectral data (mp 147–148°C, IR, NMR) were identical with those (mp 145–146°C[2c]) of the reported (±)-**2**. An alkaline hydrolysis[2c] of (±)-**2** was carried out to provide the racemic **1** (mp 189–190°C), of which the spectral data are also consistent with those of the reported (±)-**1** (mp 190–191°C,[2d] 186–187°C[2f]) (Scheme 3).



Scheme 3. *Reagents*: (a) $SnCl_4$; (b) MsCl/pyridine; (c) CsSAc; (d) K_2CO_3/MeOH; (e) $Pd(Ph_3)_4/Et_3N$; (f) NaOH/EtOH/H_2O; (g) Ac_2O/pyridine.



Scheme 4.

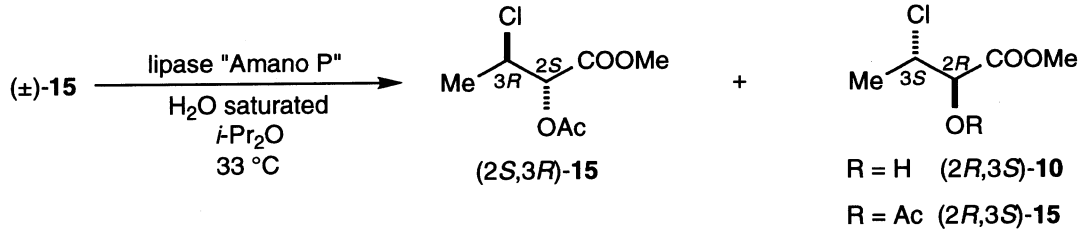
As shown in Scheme 4, it is proposed that neighboring-group participation involving the electron-rich C-3 of the indole ring accounts for the stereoselective conversion of (±)-**12** to (±)-**13**. The preferred conformation of the mesylate (±)-**12** to minimize steric interactions is shown in Scheme 4. In this rotamer, the mesyloxy group is *trans* to the indol C-3, so that displacement can occur smoothly. Nucleophilic attack by the thioacetoxy ion takes place at the C_2-position because the positive charge in the cyclopropylium ion intermediate locates on the C-2 carbon atom.[12] Since this is essentially a double S_N 2 mechanism, the stereochemistry of (±)-*syn*-2-hydroxy ester **6** is retained in (±)-*syn*-2-thioacetoxy ester **13**.

According to the reported synthesis of (±)-**2** via pathway B, catalytic hydrogenation of (±)-**4** gave 40% yield of (±)-**2**,[2c] while chemical reduction of (±)-**4** afforded a mixture of (±)-*cis*- and -*trans*-**2**.[2d,2f] It is of important significance in the present synthesis via pathway A that palladium-catalyzed coupling of the thiolate ion itself can proceed to the cyclization without isomerization at the C_5-position in high yield.

Accordingly, we report a highly stereoselective synthesis of both enantiomers of chuangxinmycin **1** by the following two approaches as a key step. One is the synthesis of enantiomerically active (2*R*,3*S*)- or (2*S*,3*R*)-**9** based on the asymmetric hydrolysis of (±)-(2,3)-*anti*-2-acetoxy-3-chloro butanoate **15** using lipase. The other is the synthesis of enantiomerically active (2*R*,3*S*)- or (2*S*,3*R*)-**6** and (2*R*,3*S*)- or (2*S*,3*R*)-**14** based on the asymmetric hydrolysis of the corresponding acetates (±)-**16** or (±)-**13** using lipase, respectively. The substrates (±)-**15** and (±)-**16** were obtained by acetylation of (±)-**10** and (±)-**6**, respectively (Scheme 3).

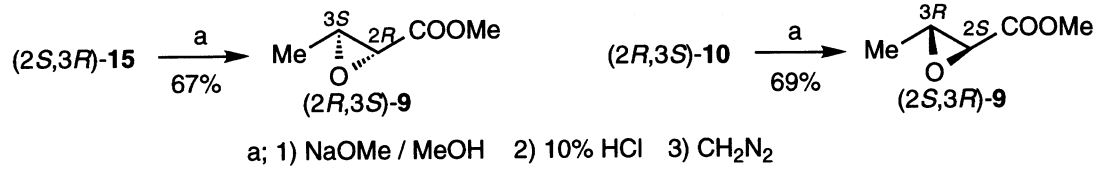
Initially, (±)-**15** was subjected to screening experiments using several kinds of commercially available lipases in isopropyl ether saturated with water. Among them, lipase 'Amano P' from *Pseudomonas* sp. was found to give the (2*R*,3*S*)-2-hydroxy ester **10** (40, 89% ee) and acetate (2*S*,3*R*)-**15** (45, 87% ee)(entry 1, Table 1). The (2*S*,3*R*)-**15** having 87% ee was again subjected to the enzymatic hydrolysis to afford the enantiomerically pure (2*S*,3*R*)-**15** ($[\alpha]_D$=+7.6 (*c*=1.50, $CHCl_3$)) in 84% yield (entry 2, Table 1), which was consistent with the reported (2*S*,3*R*)-**15**[8b] ($[\alpha]_D$=+8.3 (*c*=3.0, $CHCl_3$): corresponds to >99% ee). On the contrary, the 89% ee of (2*R*,3*S*)-**15**, obtained by the re-acetylation of the lipase hydrolysis product (2*R*,3*S*)-**10** (89% ee), was subjected to the enzymatic hydrolysis again to provide the enantiomerically pure (2*R*,3*S*)-**10** ($[\alpha]_D$=+33.2 (*c*=0.85, $CHCl_3$)) in 68% yield

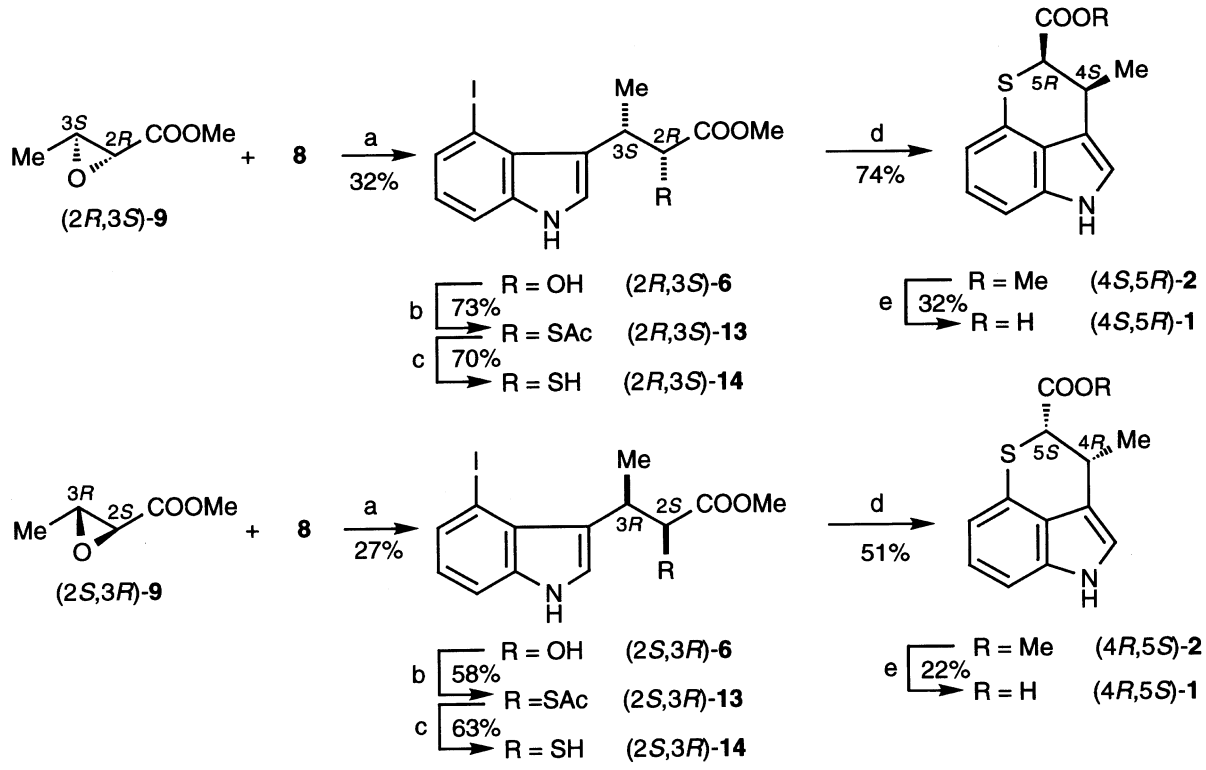
Table 1.



Entry	Substrate (g, %ee)	Time (days)	Product	
			% Yield (%ee)	% Yield (%ee)
1	(±)-**15** (14,0)	5	(2*S*,3*R*)-**15**; 45 (87)	(2*R*,3*S*)-**10**; 40 (89)
2	(2*S*,3*R*)-**15** (6.3,87)	3	(2*S*,3*R*)-**15**; 84 (>99)	(2*R*,3*S*)-**10**; 12 (0)
3	(2*R*,3*S*)-**15** (4.4,89)[a]	3	(2*R*,3*S*)-**15**; 12 (27)	(2*R*,3*S*)-**10**; 68 (>99)

[a] The substrate (2*R*,3*S*)-**15** (89% ee) was obtained by acetylation of (2*R*,3*S*)-**10** (89% ee).





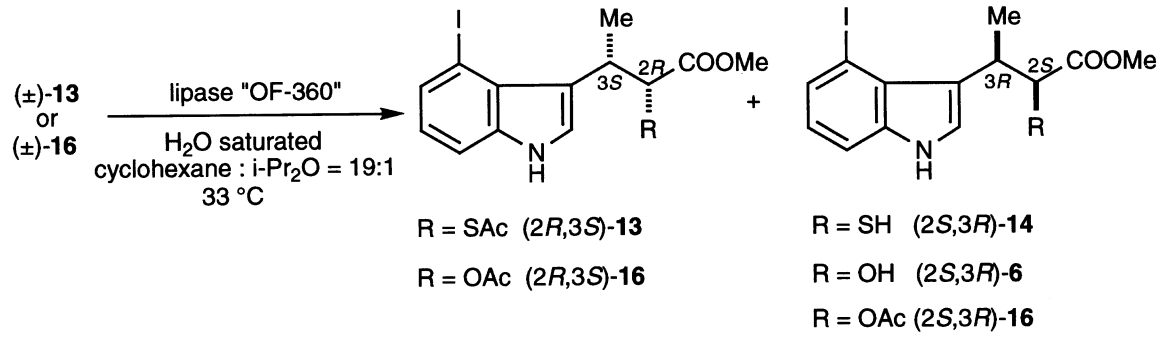
Scheme 5. *Reagents*: (a) $SnCl_4$; (b) (1) MsCl/pyridine, (2) CsSAc; (c) K_2CO_3/MeOH; (d) $Pd(Ph_3)_4/Et_3N$; (e) NaOH/EtOH/H_2O.

(entry 3, Table 1). The enantiomeric excess of (+)-**15** and (+)-**10** was calculated based on NMR (400 MHz) data of the corresponding (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetates[13] ((*R*)-MTPA esters: (*R*)-MTPA ester of (2*S*,3*R*)-**10** from (+)-(2*S*,3*R*)**15**, d 3.836, COOMe; (*R*)-MTPA ester from (+)-(2*R*,3*S*)-**10**, d 3.785, COOMe).[8b] The resulting (2*S*,3*R*)-**15** was treated with NaOMe followed by acid treatment and esterification with CH_2N_2 to provide enantiomerically pure (2*R*,3*S*)-epoxy butanoate (**9**) in 67% overall yield. Similarly, enantiomerically pure (2*R*,3*S*)-**10** was also converted to (2*S*,3*R*)-**9** in 69% overall yield. The reaction of **8** and (2*R*,3*S*)-**9** in the presence of $SnCl_4$ afforded (2*R*,3*S*)-**6** (32% yield, mp 52°C, $[\alpha]_D$=+7.89 (*c*=0.5, $CHCl_3$)), which was treated with MsCl in pyridine followed by treatment with CsSAc to provide (2*R*,3*S*)-2-thioacetoxy ester **13** ($[\alpha]_D$=+84.9 (*c*=0.94, $CHCl_3$)) in 73% overall yield with complete retention. Deacetylation of (2*R*,3*S*)-**13** with K_2CO_3 in MeOH provided (2*R*,3*S*)-2-mercapto ester **14** (70% yield, $[\alpha]_D$=+23.3 (*c*=0.3, $CHCl_3$)), which was subjected to the $Pd(PPh_3)_4$-mediated cyclization in the presence of Et_3N to give (4*S*,5*R*)-*cis*-methyl ester **2** (mp 130°C, $[\alpha]_D$=−124.0 (*c*=0.45, $CHCl_3$)) in 74% yield. An alkaline hydrolysis of (4*S*,5*R*)-**2** was carried out by the reported procedure[2c] to provide the natural chuangxinmycin (4*S*,5*R*)-**1** (mp 192–193°C, $[\alpha]_D$=−26.0 (*c*=0.2, 95% EtOH)), which is consistent with the reported (4*S*,5*R*)-**1** (mp 192–192.5°C,[2a] mp 184–187°C,[4] $[\alpha]_D$=−29.0 (95% EtOH)[4]). Similarly, the enantiomerically pure (2*S*,3*R*)-**9** was converted to the (4*R*,5*S*)-**1** (mp 181–182°C, $[\alpha]_D$=+27.4 (*c*=0.42, 95% EtOH)) via (2*S*,3*R*)-**6** (mp 55°C, $[\alpha]_D$=−7.78 (*c*=0.9, $CHCl_3$)), (2*S*,3*R*)-**13** ($[\alpha]_D$=−87.8 (*c*=0.79, $CHCl_3$)), (2*S*,3*R*)-**14** ($[\alpha]_D$=−23.1 (*c*=0.77, $CHCl_3$)) and (4*R*,5*S*)-**2** (mp 135°C, $[\alpha]_D$=+124.1 (*c*=0.59, $CHCl_3$)). The physical data of the present (4*R*,5*S*)-**1** was identical with those (mp 181–184°C, $[\alpha]_D$=+29 (95% EtOH) of the reported (4*R*,5*S*)-**1**[4] (Scheme 5).

As chemo-enzymatic synthesis of (−)-(4*S*,5*R*)- and (+)-(4*R*,5*S*)-chuangxinmycins **1** was achieved, next enzymatic resolution of more large molecule such as (±)-2-thioacetoxy ester **13** and (±)-2-acetoxy ester **16** has aroused our interest. The enantioselective hydrolysis of (±)-**13** and (±)-**16** using lipase 'OF-360' from *Candida rugosa* in the mixed solvent (cyclohexane/*i*-Pr_2O 19:1) saturated with water was carried out, and the results are shown in Table 2. Enantiomeric excess (ee) of the products was determined by HPLC on a CHIRALCEL OD (250×4.6 mm^2) column and the absolute structure of the products was confirmed by a comparison of the retention times with those of the authentic samples. Enzymatic hydrolysis of thioacetate (±)-**13** gave the corresponding thiol (2*S*,3*R*)-**14** (15, 68% ee) and the thioacetate (2*R*,3*S*)-**13** (74, 14% ee) (entry 1, Table 2), while enzymatic hydrolysis of acetate (±)-**16** afforded 91% ee of the corresponding alcohol (2*S*,3*R*)-**6** (35%) and acetate (2*R*,3*S*)-**16** (64, 51% ee) (entry 2, Table 2). The recovered (2*R*,3*S*)-**16** having 51 and 87% ee was again subjected to the enzymatic reaction to provide 87 and 97% ee of (2*R*,3*S*)-**16**, respectively (entries 3 and 4, Table 2). Enrichment of ee of (2*S*,3*R*)-**6** (>99% ee) was also achieved by the repeated enzymatic reaction of (2*S*,3*R*)-**16** (91% ee) obtained by re-acetylation of (2*S*,3*R*)-**6** (91% ee) (entry 5, Table 2).

In conclusion, (±)-4-iodoindolmycenate **6** obtained by the reaction of 4-iodoindole **8** and (±)-*trans*-(2,3)-epoxy butanoate **9** in the presence of $SnCl_4$, was stereoselectively converted into (±)-(2,3)-*syn*-4′-iodo-2-thioindolmycenate **14**, which is treated with $Pd(PPh_3)_4$ in the presence of

Table 2.



Entry	Substrate (mg, %ee)	Time (days)	Products	
			% Yield (%ee)	% Yield (%ee)
1	(±)-**13** (97,0)	3	(2*R*,3*S*)-**13**; 74 (14)[a]	(2*S*,3*R*)-**14**; 15 (68)[a]
2	(±)-**16** (700,0)	4	(2*R*,3*S*)-**16**; 64 (51)	(2*S*,3*R*)-**6**; 35 (91)
3	(2*R*,3*S*)-**16** (440,51)	3.5	(2*R*,3*S*)-**16**; 75 (87)	(2*S*,3*R*)-**6**; 23 (67)
4	(2*R*,3*S*)-**16** (330,87)	3	(2*R*,3*S*)-**16**; 91 (97)	(2*S*,3*R*)-**6**; 5 (12)
5	(2*R*,3*S*)-**16** (240,91)[b]	6.5	(2*S*,3*R*)-**16**; 24 (63)	(2*S*,3*R*)-**6**; 62 (>99)

[a] The ee was calculated based on NMR (400 MHz) data of the corresponding (*R*)-(+)-MTPA ester.
[b] The substrate (2*S*,3*R*)-**16** (91% ee) was obtained by acetylation of (2*S*,3*R*)-**6** (91% ee).

Et_3N to afford the (±)-methyl ester **2** of natural chuangxinmycin (**1**). Stereoselective total syntheses of (−)-(4*S*,5*R*)- and (+)-(4*R*,5*S*)-chuangxinmycins **1** were achieved based on the enzymatic syntheses of (2*R*,3*S*)- and (2*S*,3*R*)-epoxy butanoates **9**, respectively.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. NMR spectra were recorded on JEOL EX 400 spectrometer in $CDCl_3$. The fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS-DX 303 spectrometer. IR spectra were recorded a JASCO FT/IR-300 spectrometer. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). 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.

3.1.1. Methyl (±)-*trans*-(2,3)-epoxy butanoate 9. A solution of methyl crotonate (20 g, 200 mmol) and *m*-chloroperbenzoic acid (MCPBA, 70%, 50g, 200 mmol) in $ClCH_2CH_2Cl$ (250 ml) was refluxed for 3 h. After cooling, the reaction mixture was filtered and the precipitate was washed with *n*-hexane. The filtrate and washing were combined and the whole was concentrated to half-volume. The resulting organic layer was washed with 7% aqueous $NaHCO_3$, 15% aqueous Na_2CO_3, 3% aqueous $Na_2S_2O_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave an oily product which was distillated to afford (±)-**9** (bp 70°C/30 mmHg, 18 g, 78%) as a colorless oil. The NMR data were identical with those of the reported (±)-**9**.[8b]

3.1.2. Methyl (±)-2-hydroxy-3-(4-iodo-1*H*-indol-3-yl)-butanoate (6). To a well-stirred solution of 4-iodoindole **8** (1 g, 4.1 mmol) and (±)-*trans*-(2,3)-epoxy butanoate **9** (0.96 g, 8.3 mmol) in CH_2Cl_2 (10 ml) under argon atmosphere was added $SnCl_4$ (1 M in CH_2Cl_2, 25.8 ml, 25.8 mmol) at 0°C and the whole mixture was stirred for 1 h at the same temperature. To the reaction mixture was added 7% aqueous $NaHCO_3$ (200 ml) and the whole mixture was stirred for 30 min. The reaction mixture was filtered with the aid of celite and the precipitate was washed with CH_2Cl_2. The filtrate and washing were combined and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (60 g) to give **8** (0.35 g 35% recovery) from *n*-hexane/EtOAc=10:1 eluate, a 5:1 mixture (0.734 g) of (±)-chlorohydrin **10** and (±)-indol-dimer **11** from *n*-hexane/EtOAc=8:1 eluate, and a crystal (±)-**6** (0.473 g, 32%) from *n*-hexane/EtOAc=5:1 eluate. The ratio of (±)-**10** and (±)-**11** was determined based on NMR analysis. Crystallization of a mixture from benzene/*n*-hexane (1:1) gave a crystal **11** (0.1 g) as colorless needles. NMR data of the mother liquid (mainly (±)-**10**) were identical with those of the reported (±)-**10**.[8b] Crystallization of (±)-**6** from benzene gave colorless needles. (±)-**6**: mp 121–122°C; IR (KBr) 3330, 1729, 1290 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (3H, d, *J*=6.8 Hz), 2.81 (1H, d, *J*=4.9 Hz), 3.87 (3H, s), 4.61 (1H, dq, *J*=2.7, 6.8 Hz), 4.68 (1H, dd, *J*=2.7, 4.9 Hz), 6.83 (1H, t, *J*=7.8 Hz), 7.26 (1H, d, *J*=4.0 Hz), 7.31 (1H, d, *J*=7.8 Hz), 7.60 (1H, d, *J*=7.8 Hz), 8.25 (1H, br s). Anal. found: C, 43.72; H, 3.76; N, 3.95. Calcd for $C_{13}H_{14}O_3NI$: C, 43.45; H, 3.93; N, 3.90%. FAB MS *m/z*: 360 (M^++1). (±)-**11**: mp 163°C; IR (KBr) 3243, 1564, 1436, 1281, 1182, 736 cm^{-1}; NMR ($CDCl_3$) δ 3.06 (1H, dd, *J*=7.8, 16 Hz), 3.60 (1H, dd, *J*=9.3, 16.1 Hz), 4.50 (1H, br s), 5.98 (1H, t, *J*=8.3 Hz), 6.58 (1H, d, *J*=7.8 Hz), 6.75 (1H, t, *J*=7.8 Hz), 6.89 (1H, t, *J*=7.8 Hz), 7.07 (1H, d, *J*=7.8 Hz), 7.32 (1H, d, *J*=2.4 Hz), 7.35 (1H,d,

J=7.8 Hz), 7.62 (1H, d, J=7.3 Hz), 8.11 (1H, br s). FAB MS *m/z*: 486 (M^+), 487 (M^++1).

3.1.3. Methyl (±)-2-thioacetoxy-3-(4-iodo-1*H*-indol-3-yl)butanoate (13). To a well-stirred solution of (±)-**6** (0.24 g, 0.67 mmol) in pyridine (2 ml) was added mesyl chloride MsCl (0.1 ml, 1.29 mmol) at 0°C and the reaction mixture was stood for 3 days in a refrigerator. The reaction mixture was diluted with ether. The organic layer was washed with 10% aqueous HCl, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude mesylate (±)-**12**. A part of crude (±)-**12** was crystallized from benzene to give a crystal **12**. A mixture of crude (±)-**12** and CsSAc (0.28 g, 1.35 mmol, prepared from the reaction of Cs_2CO_3 (0.22 g, 0.68 mmol) and AcSH (0.103 g, 1.35 mmol) in MeOH 5 ml)) in DMF (5 ml) was stirred under argon atmosphere for 4 days at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (20 g, *n*-hexane/EtOAc=5:1) to give (±)-**13** (0.20 g 72% overall yield from (±)-**6**) as a colorless oil. (±)-**12**: mp 118–119°C (decomp); IR (KBr) 3397, 1751, 1357, 1178, 961, 851 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (3H, d, J=6.8 Hz), 2.75 (3H, s), 3.87 (3H, s), 4.90 (1H, dq, J=2.9, 6.8 Hz), 5.43 (1H, d, J=2.9 Hz), 6.86 (1H, t, J=7.8 Hz), 7.30 (1H, s), 7.34 (1H, d, J=7.8 Hz), 7.62 (1H, d, J=7.8 Hz), 8.27 (1H, br s). Anal. found: C, 38.52; H, 3.42; N, 3.15. Calcd for $C_{14}H_{16}O_5NSI$: C, 38.45; H, 3.69; N, 3.20%. FAB MS *m/z*: 437 (M^+), 438 (M^++1). (±)-**13**: IR (KBr) 3358, 2940, 1728, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (3H, d, J=6.8 Hz), 2.29 (3H, s), 3.64 (3H, s), 4.73 (1H, dq, J=6.8, 7 Hz), 4.78 (1H, dd, J=7 Hz), 6.84 (1H, t, J=7.8 Hz), 7.21 (1H, s), 7.31 (1H, d, J=7.8 Hz), 7.61 (1H, d, J=7.8 Hz), 8.25 (1H, br s). FAB MS *m/z*: 418 (M^++1).

3.1.4. Methyl (±)-2-sulfanyl-3-(4-iodo-1*H*-indol-3-yl)-butanoate (14). A mixture of (±)-**13** (0.154 g, 0.369 mmol) and K_2CO_3 (0.051 g, 0.369 mmol) in MeOH (8 ml) was stirred for 30 min at room temperature. The reaction mixture was diluted with saturated brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give a residue which was chromatographed on silica gel (20 g, *n*-hexane/EtOAc=4:1) to give (±)-**14** (0.114 g 82%) as a colorless oil. (±)-**14**: IR (KBr) 3382, 2960, 2561, 1723 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (3H, d, J=6.8 Hz), 1.83 (1H, d, J=8.3 Hz), 3.69 (3H, s), 4.05 (1H, dd, J=6.3, 8.3 Hz), 4.65 (1H, dq, J=6.3, 6.8 Hz), 6.86 (1H, t, J=7.8 Hz), 7.20 (1H, d, J=2.4 Hz), 7.34 (1H, d, J=7.3 Hz), 7.61 (1H, d, J=7.3 Hz), 8.18 (1H, br s). FAB MS *m/z*: 376 (M^++1).

3.1.5. (±)-Chuangxinmycin methyl ester (2). A mixture of (±)-**14** (0.106 g, 0.282 mmol), Et_3N (0.058 g, 0.56 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.014 mmol) in THF (10 ml) was refluxed for 6 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent provided a residue which was chromatographed on silica gel (20 g, *n*-hexane/EtOAc=10:1) to afford a crystal (±)-**2** (0.052 g, 74%). Recrystallization of (±)-**2** from benzene afforded a crystal (±)-**2** as colorless plates. (±)-**2**: mp 147–148°C; IR (KBr) 3380, 2959, 2856, 1729, 1159cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3H, d, J=7 Hz), 3.73 (overlapping 1H, m and 3H, s), 4.18 (1H, d, J=3.1 Hz), 6.92–6.95 (2H, m), 7.09–7.13 (2H, m), 8.01 (1H, br s). Anal. Found: C, 63.35; H, 5.19; N, 5.65. Calcd for $C_{13}H_{13}O_2NS$: C, 63.14; H, 5.30; N, 5.66%. FAB MS *m/z*: 247 (M^+).

3.1.6. (±)-Chuangxinmycin (1). A mixture of (±) **2** (0.05 g, 0.202 mmol) and NaOH (0.121 g, 3.07 mmol) in a mixed solvent (EtOH (3 ml) and H_2O (1.8 ml)) THF (10 ml) was stirred at room temperature for 7 h. The reaction mixture was diluted with saturated brine (5 ml), 2 M aqueous HCl (2 ml) and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to give crystals which was recrystallized from CH_2Cl_2/benzene (1:1) to afford colorless plates (±)-**1** (15 mg, 32%). (±)**1**: mp 189–190°C; IR (KBr) 3403, 3057, 2925, 1695, 1195 cm^{-1}; NMR ($CDCl_3$/CD_3OD=1:1) δ 1.37 (3H, d, J=6.8 Hz), 3.77 (1H, dq, J=3.4, 6.8 Hz), 4.23 (1H, d, J=3.4 Hz), 6.92 (1H, d, J=7.6 Hz), 7.00 (1H, s), 7.09 (1H, t, J=7.6 Hz), 7.14 (1H, d, J=7.6 Hz). Anal. found: C, 61.88; H, 4.46; N,6.05. Calcd for $C_{12}H_{11}O_2NS$: C, 61.79; H, 4.76; N, 6.01%. FAB MS *m/z*: 233 (M^+).

3.1.7. Methyl (±)-(2,3)-*anti*-2-acetoxy-3-chloro-butanoate (15). To a well-stirred solution of (±)-*trans*-(2,3)-epoxy butanoate **9** (15 g, 129 mmol) in CH_2Cl_2 (100 ml) under argon atmosphere was added $SnCl_4$ (1M in CH_2Cl_2, 16 ml, 160 mmol) at 0°C and the whole mixture was stirred for 1 h at the same temperature. To the reaction mixture was added 7% aqueous $NaHCO_3$ (200 ml) and the whole mixture was stirred for 30 min. The reaction mixture was filtered with the aid of celite and the precipitate was washed with CH_2Cl_2. The filtrate and washing were combined and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil (±)-**10**. A solution of crude (±)-**10** and Ac_2O (19.8 g, 193 mmol) in pyridine (20.5 g, 260 mmol) was stirred at room temperature for 12 h. The reaction mixture was diluted with H_2O extracted with AcOEt. The organic layer was washed with 10% aqueous HCl, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (200 g, *n*-hexane/EtOAc=8:1) to afford (±)-**15** (14.6 g, 58% overall yield) as a colorless oil. The NMR data of (±)-**15** were identical with those of the reported (±)-**15**.[8b]

3.1.8. Enzymatic resolution of (±)-15. (i) Table 1, entry 1; a suspension of (±)-**15** (10 g), lipase Amano P (7 g) in H_2O-saturated-isopropyl ether (750 ml) was incubated at 33°C for 5 days. After the reaction mixture was filtered, the precipitate was washed with diisopropyl ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (200 g, *n*-hexane/AcOEt=8:1) to give (2*S*,3*R*)-**15** (6.3 g, 45, 87% ee) and (2*R*,3*S*)-**10** (4.39 g, 40, 89% ee) in elution order. (ii) Table 1, entry 2; a suspension of (2*S*,3*R*)-**15** (6.3 g, 87% ee), lipase Amano P (3.2 g) in H_2O-saturated-isopropyl ether (338 ml) was incubated at 33°C for 3 days. The reaction mixture was worked up in the same way as for (i) to afford (2*S*,3*R*)-**15** (5.29 g, 84%, $[\alpha]_D^{22}$=+7.6 (c=1.5, $CHCl_3$) corresponding to >99% ee) and (2*R*,3*S*)-**10** (0.59 g,

12, 0% ee). (iii) A solution of (2*R*,3*S*)-**10** (4.39 g, 89% ee) and Ac_2O (5.9 g, 57 mmol) in pyridine (6.8 g, 86 mmol) was stirred at room temperature for 5 h and the reaction mixture was worked up in the same way of (±)-**15** to give (2*R*,3*S*)-**15** (5.27 g, 94%). A suspension of (2*R*,3*S*)-**15** (4.4 g, 89% ee), lipase Amano P (2.2 g) in H_2O-saturated-isopropyl ether (236 ml) was incubated at 33°C for 3 days. The reaction mixture was worked up in the same way as for (i) to afford (2*R*,3*S*)-**15** (0.53 g, 12, 27% ee) and (2*R*,3*S*)-**10** (2.35 g, 68%, $[\alpha]_D^{28}=+33.2$ (c=0.85, $CHCl_3$) corresponding to >99% ee).

3.1.9. Methyl (2*R*,3*S*)-epoxy-butanoate 9. To a well-stirred solution of (2*S*,3*R*)-**15** (99% ee, 9.1 g, 46.7 mmol) in MeOH (50 ml) was added NaOMe (2.52 g, 46.7 mmol) at 0°C and the whole mixture was stood for 12 h at 5°C. The reaction mixture was diluted with Et_2O and the water layer was acidified with 10% aqueous HCl. The water layer was re-extracted with $CHCl_3$ (10 times) and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent afforded a residue which was treated with an excess of CH_2N_2/Et_2O solution to provide a crude oil. Distillation of the crude oil gave (2*R*,3*S*)-**9** (70°C/30 mmHg, 3.64 g, 67% overall yield). (2*R*,3*S*)-**9**: NMR data of (2*R*,3*S*)-**9** were identical with those of the reported (±)-**9**.[8b]

3.1.10. Methyl (2*S*,3*R*)-epoxy-butanoate 9. To a well-stirred solution of (2*R*,3*S*)-**10** (99% ee, 5.3 g, 34.6 mmol) in MeOH (25 ml) was added NaOMe (3.9 g, 72.2 mmol) at 0°C and the whole mixture was stood for 7 h at room temperature. The reaction mixture was diluted with Et_2O and the water layer was acidified with 10% aqueous HCl. The water layer was re-extracted with $CHCl_3$ (10 times) and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent afforded a residue which was treated with an excess of CH_2N_2/Et_2O solution to provide a crude oil. Distillation of the crude oil gave (2*S*,3*R*)-**9** (70°C/30 mmHg, 2.78 g, 69% overall yield). (2*S*,3*R*)-**9**: NMR data of (2*S*,3*R*)-**9** were identical with those of the reported (±)-**9**.[8b]

3.1.11. Preparation of (4*S*,5*R*)-(−)-chuangxinmycin (1) from (2*R*,3*S*)-9. (i) To a well-stirred solution of 4-iodoindole **8** (3.14 g, 12.9 mmol) and (2*R*,3*S*)-**9** (3 g, 25.8 mmol) in CH_2Cl_2 (40 ml) under argon atmosphere was added $SnCl_4$ (1 M in CH_2Cl_2, 25.8 ml, 25.8 mmol) at 0°C and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was worked up in the same way as for the preparation of (±)-**6** to afford (2*R*,3*S*)-**6** (1.48 g, 32%). (2*R*,3*S*)-**6**: mp 52°C (cyclohexane/*i*-Pr_2O=1:1), $[\alpha]_D^{23}=+7.57$ (c=0.7, $CHCl_3$) corresponding to >99% ee. NMR data of (2*R*,3*S*)-**6** were identical with those of (±)-**6**. (ii) To a well-stirred solution of (2*R*,3*S*)-**6** (0.25 g, 0.7 mmol) in pyridine (1 ml) was added mesyl chloride MsCl (0.081 ml, 1 mmol) at 0°C and the reaction mixture was stood for 2 days in a refrigerator. The reaction mixture was worked up in the same way as for the preparation of (±)-**12** to afford crude (2*R*,3*S*)-**12**. A mixture of crude (2*R*,3*S*)-**12** and CsSAc (0.578 g, 2.78 mmol) in DMF (6 ml) was stirred for 4 days at room temperature. The reaction mixture was worked up in the same way as for the preparation of (±)-**13** to afford (2*R*,3*S*)-**13** (0.212 g, 73% overall yield from (2*R*,3*S*)-**12**) as a colorless oil. (2*R*,3*S*)-**13**: $[\alpha]_D^{24}=+84.9$ (c=0.94, $CHCl_3$) corresponding to >99% ee. NMR data of (2*R*,3*S*)-**13** were identical with those of (±)-**13**. (iii) A mixture of (2*R*,3*S*)-**13** (0.08 g, 0.19 mmol) and K_2CO_3 (0.013 g, 0.09 mmol) in MeOH (4 ml) was stirred for 20 min at room temperature. The reaction mixture was worked up in the same way as for the preparation of (±)-**14** to afford (2*R*,3*S*)-**14** (0.05 g, 70%) as a colorless oil. (2*R*,3*S*)-**14**: $[\alpha]_D^{23}=+23.3$ (c=0.3, $CHCl_3$) corresponding to >99% ee. NMR data of (2*R*,3*S*)-**14** were identical with those of (±)-**14**. (iv) A mixture of (2*R*,3*S*)-**14** (0.076 g, 0.2 mmol), Et_3N (0.061 g, 0.6 mmol) and tetrakis(triphenylphosphine)-palladium(0) (23 mg, 0.02 mmol) in THF (10 ml) was refluxed for 8 h. The reaction mixture was worked up in the same way as for the preparation of (±)-**2** to afford (4*S*,5*R*)-**2** (0.037 g, 74%) as colorless plates. (4*S*,5*R*)-**2**: mp 130°C; $[\alpha]_D^{23}=-124.0$ (c=0.45, $CHCl_3$) corresponding to >99% ee. NMR data of (4*S*,5*R*)-**2** were identical with those of (±)-**2**. (v) A mixture of (4*S*,5*R*)-**2** (0.045 g, 0.18 mmol) and NaOH (0.12 g, 3 mmol) in a mixed solvent (EtOH (3 ml) and H_2O (1.8 ml)) THF (10 ml) was stirred at room temperature for 4 h. The reaction mixture was worked up in the same way as for the preparation of (±)-**1** to afford (4*S*,5*R*)-**1** (0.014 g, 32%) as colorless plates. (4*S*,5*R*)-**1**: mp 192–193°C; $[\alpha]_D^{23}=-26.0$ (c=0.2, 95% EtOH) corresponding to >99% ee. NMR data of (4*S*,5*R*)-**1** were identical with those of (±)-**1**.

3.1.12. Preparation of (4*R*,5*S*)-(+)-chuangxinmycin (1) from (2*S*,3*R*)-9. (i) To a mixture of iodoindole **8** (2.8 g, 11.5 mmol) and (2*S*,3*R*)-**9** (2.7 g, 23.3 mmol) in CH_2Cl_2 (40 ml) under argon atmosphere was added $SnCl_4$ (1 M in CH_2Cl_2, 23.3 ml, 23.3 mmol) at 0°C and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was worked up in the same way as for the preparation of (±)-**6** to afford (2*S*,3*R*)-**6** (1.48 g, 32%). (2*S*,3*R*)-**6**: mp 55°C (cyclohexane/*i*-Pr_2O=1:1), $[\alpha]_D^{25}=-7.78$ (c=0.9, $CHCl_3$) corresponding to >99% ee. NMR data of (2*S*,3*R*)-**6** were identical with those of (±)-**6**. (ii) To a well-stirred solution of (2*S*,3*R*)-**6** (1.1 g, 3.1 mmol) in pyridine (4 ml) was added mesyl chloride MsCl (0.25 ml, 3.2 mmol) at 0°C and the reaction mixture was stood for 2 days in a refrigerator. The reaction mixture was worked up in the same way as for the preparation of (±)-**12** to afford crude (2*S*,3*R*)-**12**. A mixture of crude (2*S*,3*R*)-**12** and CsSAc (2.32 g, 11.2 mmol) in DMF (15 ml) was stirred for 6 days at room temperature. The reaction mixture was worked up in the same way as for the preparation of (±)-**13** to afford (2*S*,3*R*)-**13** (0.212 g, 73% overall yield from (2*S*,3*R*)-**12**) as a colorless oil. (2*S*,3*R*)-**13**: $[\alpha]_D^{21}=-87.8$ (c=0.79, $CHCl_3$) corresponding to >99% ee. NMR data of (2*S*,3*R*)-**13** were identical with those of (±)-**13**. (iii) A mixture of (2*S*,3*R*)-**13** (0.1 g, 0.24 mmol) and K_2CO_3 (0.013 g, 0.09 mmol) in MeOH (4 ml) was stirred for 6 min at room temperature. The reaction mixture was worked up in the same way as for the preparation of (±)-**14** to afford (2*S*,3*R*)-**14** (0.057 g, 63%) as a colorless oil. (2*S*,3*R*)-**14**: $[\alpha]_D^{25}=-23.1$ (c=0.77, $CHCl_3$) corresponding to >99% ee. NMR data of (2*S*,3*R*)-**14** were identical with those of (±)-**14**. (iv) A mixture of (2*S*,3*R*)-**14** (0.3 g, 0.8 mmol), Et_3N (0.242 g, 2.4 mmol) and tetrakis(triphenylphosphine)-palladium(0) (93 mg, 0.08 mmol) in THF (15 ml) was refluxed for 8 h. The reaction mixture was worked up in the same way as for the preparation of (±)-**2** to afford

(4*R*,5*S*)-**2** (0.10 g, 51%) as colorless plates. (4*R*,5*S*)-**2**: mp 135°C (benzene/*n*-hexane=1:1); $[\alpha]_D^{22}=+124.1$ (c=0.41, $CHCl_3$) corresponding to >99% ee. NMR data of (4*R*,5*S*)-**2** were identical with those of (±)-**2**. (v) A mixture of (4*R*,5*S*)-**2** (0.10 g, 0.4 mmol) and NaOH (0.12 g, 3 mmol) in a mixed solvent (EtOH (4 ml) and H_2O (2 ml)) was stirred at room temperature for 4 h. The reaction mixture was worked up in the same way as for the preparation of (±)-**1** to afford (4*R*,5*S*)-**1** (0.021 g, 22%) as colorless plates. (4*R*,5*S*)-**1**: mp 181–182°C; $[\alpha]_D^{21}=+27.4$ (c=0.42, 95% EtOH) corresponding to >99% ee. NMR data of (4*R*,5*S*)-**1** were identical with those of (±)-**1**.

3.1.13. Methyl (±)-2-acetoxy-3-(4-iodo-1*H*-indol-3-yl)-butanoate (16). A solution of (±)-**6** (0.9 g, 2.51 mmol) and Ac_2O (0.307 g, 3 mmol) in pyridine (4 ml) was stirred at room temperature for 30 min. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 10% aqueous HCl, saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (20 g, *n*-hexane/EtOAc=4:1) to afford (±)-**16** (0.97 g, 97%) as crystal. Recrystallization of (±)-**16** from benzene gave colorless needless (±)-**16**. (±)-**16**: mp 121°C; IR (KBr) 3348, 2944, 1723, 1214 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (3H, d, J=6.8 Hz), 2.08 (3H, s), 3.77 (3H, s), 4.80 (1H, dq, J=6.8, 3.9 Hz), 5.48 (1H, d, J=3.9 Hz), 6.86 (1H, t, J=7.8 Hz), 7.20 (1H, br s), 7.35 (1H, d, J=7.8 Hz), 7.62 (1H, d, J=7.8 Hz), 8.25 (1H, br s). Anal. found: C, 44.93; H, 3.77; N, 3.41. Calcd for $C_{15}H_{16}O_4IN$: C, 44.91; H, 4.02; N, 3.49%. FAB MS *m/z*: 402 (M^++1), 401 (M^+).

3.1.14. Enzymatic resolutions of (±)-13 and (±)-16. (i) Table 2, entry 1; a suspension of (±)-**13** (0.097 g), lipase OF-360 (0.05 g) in H_2O-saturated-cyclohexane (47.5 ml)/isopropyl ether (2.5 ml) was incubated at 33°C for 3 days. The reaction mixture was worked up in the same way as for the preparation of (±)-**14** to afford (2*R*,3*S*)-**13** (0.072 g, 74, 14% ee) and (2*S*,3*R*)-**14** (0.013 g, 15, 68% ee). (ii) Table 2, entry 2; a suspension of (±)-**16** (0.7 g), lipase OF-360 (0.7 g) in H_2O-saturated-cyclohexane (332.5 ml)/isopropyl ether (17.5 ml) was incubated at 33°C for 4 days. The reaction mixture was worked up in the same way as for the preparation of (±)-**6** to afford (2*R*,3*S*)-**16** (0.448 g, 64, 51% ee) and (2*S*,3*R*)-**6** (0.22 g, 35, 91% ee). (iii) Table 2, entry 3; a suspension of (2*R*,3*S*)-**16** (0.44 g, 51% ee), lipase OF-360 (0.44 g) in H_2O-saturated-cyclohexane (237.5 ml)/isopropyl ether (127.5 ml) was incubated at 33°C for 3.5 days. The reaction mixture was worked up in the same way as for the preparation of (±)-**6** to afford (2*R*,3*S*)-**16** (0.33 g, 75, 87% ee) and (2*S*,3*R*)-**6** (0.091 g, 23, 67% ee). (iv) Table 2, entry 4; a suspension of (2*R*, 3*S*)-**16** (0.33 g, 87% ee), lipase OF-360 (0.33 g) in H_2O-saturated-cyclohexane (160 ml)/isopropyl ether (8.5 ml) was incubated at 33°C for 3 days. The reaction mixture was worked up in the same way as for the preparation of (±)-**6** to afford (2*R*,3*S*)-**16** (0.3 g, 91%, $[\alpha]_D^{29}=+55.3$ (c=0.55, $CHCl_3$) corresponding to 97% ee) and (2*S*,3*R*)-**6** (0.015 g, 5, 12% ee). (v) A solution of (2*S*,3*R*)-**16** (0.22 g, 0.61 mmol, 91% ee), Ac_2O (0.093 g, 0.91 mmol), pyridine (0.48 g, 6.1 mmol) in CH_2Cl_2 (6 ml) was stirred at room temperature for 3 h. The reaction mixture was worked up in the same way as for the preparation of (±)-**16** to afford (2*S*,3*R*)-**16** (0.24 g, 98, 91% ee). A suspension of (2*S*,3*S*)-**16** (0.24 g, 91% ee), lipase OF-360 (0.24 g) in H_2O-saturated-cyclohexane (114 ml)/isopropyl ether (6 ml) was incubated at 33°C for 6.5 days. The reaction mixture was worked up in the same way as for the preparation of (±)-**16** to afford (2*S*,3*R*)-**16** (0.058 g, 24, 63% ee) and (2*S*,3*R*)-**6** (0.134 g, 62%, $[\alpha]_D^{23}=-8.12$ (c=0.67, $CHCl_3$) corresponding to >99% ee).

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