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

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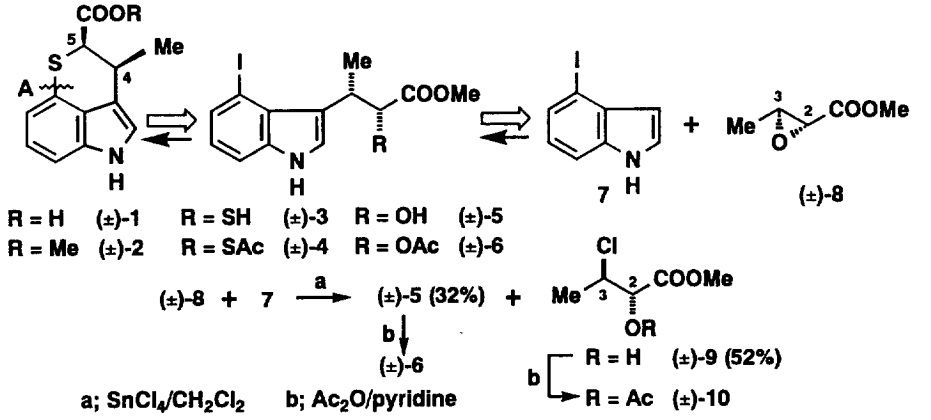
Abstract: Stereoselective total syntheses of (−)-(4*S*,5*R*)- and (+)-(4*R*,5*S*)-chuangxinmycins **1** were achieved based on the enzymatic syntheses of (2*R*,3*S*)- and (2*S*,3*R*)-epoxy butanoates **8**, respectively. Chiral intermediates such as (2*R*,3*S*)- and (2*S*,3*R*)-2-hydroxy-3-(4′-iodoindol-3′-yl)butanoate **5** for the chiral synthesis of (−)- and (+)-**1** were also obtained by the enantioselective hydrolysis of the corresponding acetate **6** by lipase. © 1997 Elsevier Science Ltd

Chuangxinmycin **1**, isolated from *Actinoplanes tsinanensis* n. sp. in China, exhibits *in vitro* against a number of Gram-positive and Gram-negative bacteria. This material 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 racemic synthesis[2] and the absolute configurations were determined as 4*S*,5*R* based on the degradation study of the natural product **1**[3] and resolution of (±)-**1** with *S*-(−)-α-methylbenzylamine.[4] In preceding paper, we reported a highly stereoselective synthesis of (±)-**1** *via* pathway A directed toward chiral synthesis involving two characteristic approaches to this problem.[5] The first one is the stereoselective conversion of (±)-(2,3)-*syn*-2-hydroxy-3-(4′-iodoindol-3′-yl)butanoate **5** into the (±)-(2,3)-*syn*-2-mercapto ester **3** *via* the corresponding 2-thioacetoxy ester **4** with retention of C_2-stereochemistry in (±)-**5**. The second one is the palladium-catalyzed cyclization of indolyl iodide and the internal C_2-thiol group of the substrate (±)-**3** to give the (±)-methyl ester **2** of (±)-chuangxinmycin **1** without isomerization at the C_5-position in high yield. The synthesis of (±)-**5** was achieved by the reaction of 4′-iodoindole **7**[5] and (±)-*trans*-(2,3)-epoxy butanoate **8** in the presence of $SnCl_4$ along with nucleophilic displacement with inversion at the C-3 carbon of the coordinated epoxide. We now 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*)-**8** based on the asymmetric hydrolysis of (±)-(2,3)-*anti*-acetoxy-3-chloro butanoate **10** using lipase (Table 1). The other is the syntheses of enantiomerically active (2*R*,3*S*)- or (2*S*,3*R*)-**3** and

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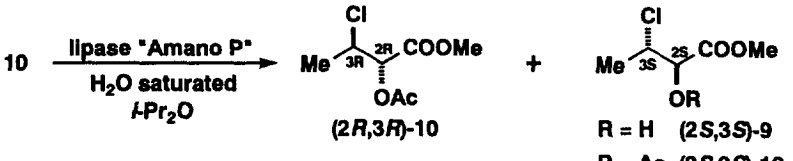
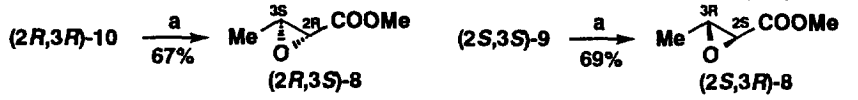
Table 1.



Entry	Substrate (g, %ee)	Time(days)	Products % (%ee)	% (%ee)
1	(±)-10 (14)	5	(2*R*,3*R*)-10; 45 (87)	(2*S*,3*S*)-9; 40 (89)
2	(2*R*,3*R*)-10 (6.3, 87)	3	(2*R*,3*R*)-10; 84 (>99)	(2*S*,3*S*)-9; 12 (0)
3	(2*S*,3*S*)-10 (4.4, 89)*	3	(2*S*,3*S*)-10; 12 (27)	(2*S*,3*S*)-9; 68 (>99)

* The substrate (2*S*,3*S*)-10 (89% ee) was obtained by acetylation of (2*S*,3*S*)-9 (89% ee).

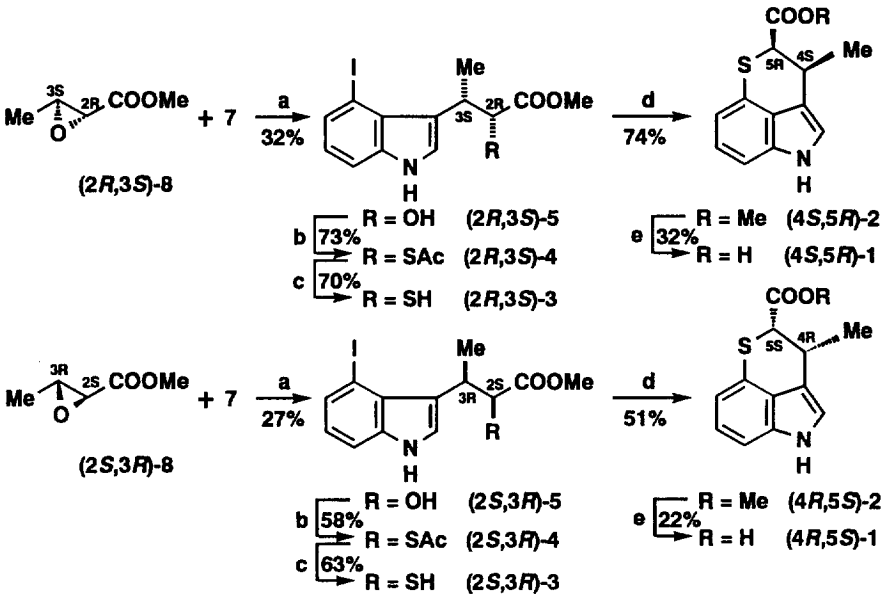


a; 1) NaOMe/MeOH 2) 10% HCl 3) CH_2N_2

(2*R*,3*S*)- or (2*S*,3*R*)-**5** based on the asymmetric hydrolysis of the corresponding acetates (±)-**4** or (±)-**6** using lipase, respectively. The substrates (±)-**6** and (±)-**10** for enzymatic reaction were obtained by acetylation of the reported 2-hydroxy esters (±)-**5** and (±)-**9**, respectively, which were provided by the reaction of **7** and (±)-**8** in the presence of $SnCl_4$.[5]

Initially, (±)-**10** 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*S*,3*S*)-2-hydroxy ester **9**[6] (40%, 89% ee) and the unchanged (2*R*,3*R*)-**10** (45%, 87% ee)(entry 1). The (2*R*,3*R*)-**10** having 87% ee was again subjected to the enzymatic hydrolysis to afford the enantiomerically pure (2*R*,3*R*)-**10** ($[\alpha]_D$ +7.6 (c=1.50, $CHCl_3$)) in 84% yield (entry 2), which was consistent with the reported (2*R*,3*R*)-**10**[7] ($[\alpha]_D$ +8.3 (c=3.0, $CHCl_3$): corresponds to >99% ee). On the contrary, the 89% enantiomeric excess of (2*S*,3*S*)-**10** was subjected to the enzymatic hydrolysis to provide the enantiomerically pure (2*S*,3*S*)-**9** ($[\alpha]_D$ +33.2 (c=0.85, $CHCl_3$)) in 68% yield (entry 3). The enantiomeric execess of (+)-**10** and (+)-**9** were calculated based on NMR (400 MHz) data of the corresponding (*R*)-(+)-α-methoxy-α-trifluoromethyl-phenylacetates[8] ((*R*)-MTPA esters: (*R*)-MTPA ester from (+)-**10**, δ 3.836, COOMe; (*R*)-MTPA ester from (+)-**9**, δ 3.785, COOMe). Thus obtained (2*R*,3*R*)-**10** was treated with NaOMe followed by the subsequent acid treatment and esterification with CH_2N_2 to provide the enantiomerically pure (2*R*,3*S*)-epoxy butanoate (**8**) in 67% overall yield. Likewise, the enantiomerically pure (2*S*,3*S*)-**9** was also converted to the (2*S*,3*R*)-**8** in 69% overall yield. The reaction of **7**[5] and (2*R*,3*S*)-**8** in the presence of $SnCl_4$ afforded (2*R*,3*S*)-**5** (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 **4**($[\alpha]_D$ +84.9 (c=0.94, $CHCl_3$)) in 73% overall yield with complete retention of C_2-stereochemistry. Deacetylation of (2*R*,3*S*)-**4** with K_2CO_3 in MeOH provided (2*R*,3*S*)-2-mercapto ester **3** (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 the (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]). Likewise, the enantiomerically pure (2*S*,3*R*)-**8** 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*)-**5** (mp 55°C, $[\alpha]_D$ −7.78 (c=0.9, $CHCl_3$)), (2*S*,3*R*)-**4** ($[\alpha]_D$ −87.8 (c=0.79, $CHCl_3$)), (2*S*,3*R*)-**3** ($[\alpha]_D$ −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]



Then the enantioselective hydrolysis of (±)-2-thioacetoxy ester **4**[5] and (±)-2-acetoxy ester **6** 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 estimated by HPLC on a CHIRALCEL OD (250×4.6 mm) column and absolute structure of the products was confirmed by a direct comparison with the retention times of the above-mentioned standard samples by HPLC analysis. Enzymatic hydrolysis of (±)-**4** gave the compound (2*S*,3*R*)-**3** (15%, 68% ee) and the unchanged acetate (2*R*,3*S*)-**4** (74%, 14% ee) (entry 1), while enzymatic hydrolysis of (±)-**6** afforded the 91% ee of (2*S*,3*R*)-**5** (35%) and the unchanged acetate (2*R*,3*S*)-**6** (64%, 51% ee)(entry 2). The recovered (2*R*,3*S*)-**6** having 51% ee and 87% ee was again subjected to the enzymatic reaction to provide 87% ee and 97% ee of (2*R*,3*S*)-**6**, respectively (entries 3 and 4). Enrichment of ee of (2*S*,3*R*)-**5** (>99% ee) was also achieved by the repeated enzymatic reaction of (2*S*,3*R*)-**6** (91% ee) (entry 5).

Acknowledgements

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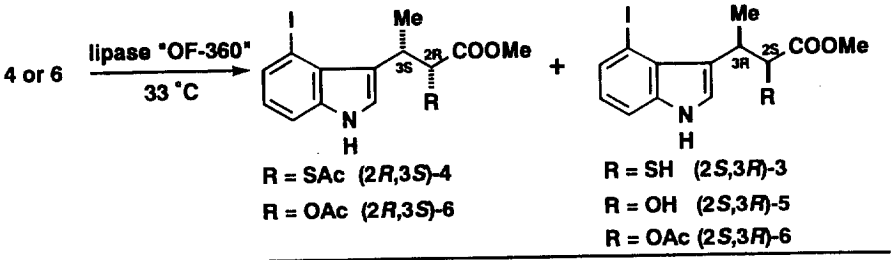
Table 2.



R = SAc (2*R*,3*S*)-4
R = OAc (2*R*,3*S*)-6

R = SH (2*S*,3*R*)-3
R = OH (2*S*,3*R*)-5
R = OAc (2*S*,3*R*)-6

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

1) The ee was calculated based on NMR (400 MHz) data of the corresponding (*R*)-(+)-MTPA ester.
2) The substrate (2*S*,3*R*)-6 (91% ee) was obtained by acetylation of (2*S*,3*R*)-5 (91% ee).

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