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Convenient synthesis of antisepsis agent TAK-242 by novel optical resolution through diastereomeric N-acylated sulfonamide derivative

Atsuko Nishiguchi,* Tomomi Ikemoto and Kiminori Tomimatsu

Chemical Development Laboratories, Takeda Pharmaceutical Company Limited, 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan

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Abstract—A convenient synthesis method of antisepsis agent **TAK-242** ((*R*)-**1**) through diastereomeric resolution was developed. By condensation of racemate *rac*-**1** with chiral acid (*S*)-*O*-acetylmanderic acid (**6a**), the desired diastereomer **5a** was isolated with 98% de in 39% yield by simple crystallization. Deacylation of **5a** with aq NaOH followed by recrystallization provided (*R*)-**1** with 99% ee in 20% yield from *rac*-**1**.

1. Introduction

TAK-242 ((*R*)-**1**), a potent NO and cytokine production inhibitor, was discovered by Yamada et al. in the course of research into new antisepsis agents.[1,2] This optically active cyclohexene derivative (*R*)-**1** was first obtained from chiral phase HPLC resolution of racemate *rac*-**1** (Fig. 1).

Recently, two other synthetic methods by diastereomeric resolution[1b] and enzymatic resolution[1b] were also reported by the same group; however, these three methods were not satisfactory for large-scale preparation. The HPLC method requires rather special apparatus, and the resolution efficiency largely depends on the size of the apparatus. Diastereomeric resolution and enzymatic resolution are shown in Scheme 1.

In these two methods, *rac*-**1** was converted to carboxylic acid *rac*-**2** followed by diastereomeric ester **3** or enzymatic substrate (*R*)-**4**. Hydrolysis of *rac*-**1** was accompanied by a certain amount of decomposition, and the yield of *rac*-**2** was relatively low (74% yield). Moreover, **3** was synthesized through Mitsunobu reaction utilizing an azo compound, DEAD, which is not favorable for large-scale production. Since the ester moiety of *rac*-**1** was converted to different esters, these methods consisting of resolution and ester reconstruction were unfavorable for short-step preparation and to

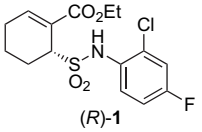
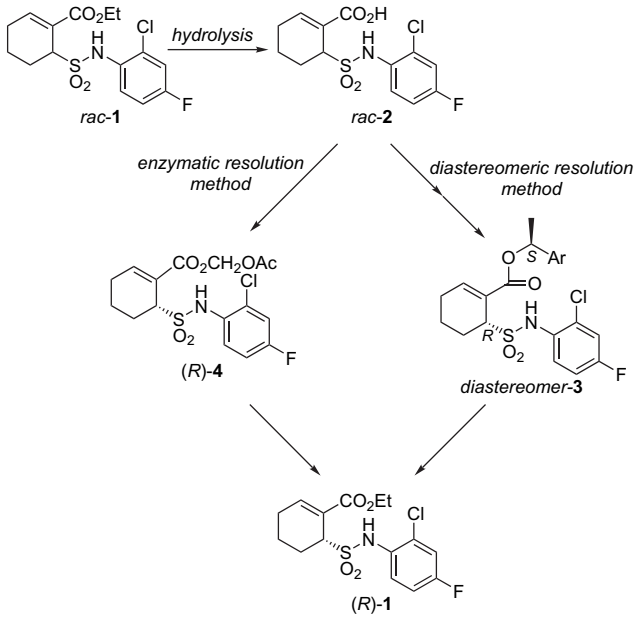


Figure 1. Structure of (*R*)-**1**.



Scheme 1. Previous synthesis method of (*R*)-**1**.

Keywords: Antisepsis agent; Diastereomeric resolution; Sulfonamide; Chiral acid; Deacylation.
* Corresponding author. Tel.: +81 6 6300 6378; fax: +81 6 6300 6251; e-mail: nishiguchi_atsuko@takeda.co.jp

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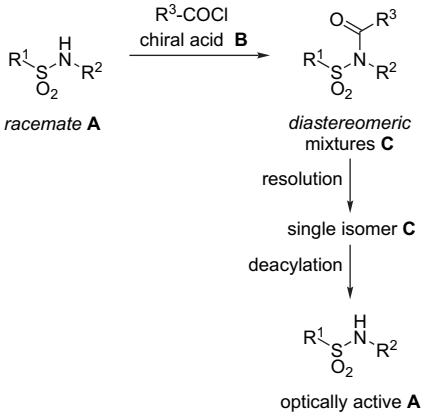
ensure a high total yield. The diastereomeric resolution method gave 14% yield in four steps, and the enzymatic resolution method gave 17% yield in three steps.

Meanwhile, it is known that Oppolzer's sultams,[3] used as a chiral auxiliary, are readily N-acylated with acyl chlorides, and N-acylated sultams are readily cleaved[4] under mild conditions without loss of optical purity.

We focused on the sulfonamide moiety of *rac*-**1** for derivatization to diastereomeric mixtures to be resolved. Scheme 2 depicts our methodology;[5] N-acylation of racemic sulfonamide **A** with chiral acid **B** followed by resolution of resultant diastereomeric mixtures **C** provides pure isomer **C**. Isomer **C** is then deacylated to obtain optically active **A**. To the best of our knowledge, there are no reports on N-acylated sulfonamide diastereomers being applied for optical resolution. Furthermore, it is suitable for short-step preparation because of the add-on-type conversion on the sulfonamide nitrogen.



Scheme 2. Strategy of optical resolution.

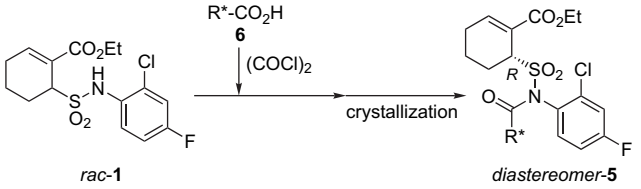
2. Results and discussion

First, N-acylation of *rac*-**1** was investigated (Table 1). Commercially available chiral carboxylic acids **6a–f** were used for N-acylation as corresponding acid chlorides. Although pyridine, triethylamine, and collidine could be used as bases, pyridine was most suitable. N-acylation of *rac*-**1** with (*S*)-*O*-acetylmanderic acid **6a**[6] and (*R*)-3-methylsuccimate **6b**[6] afforded the single diastereomers **5a** and **5b**, respectively, as crystalline solids by filtration (entries 1 and 2). Other diastereomeric mixtures derived from **6c–f** did not give crystalline isomers (entries 3–6).[7]

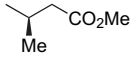
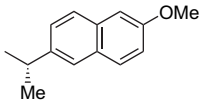
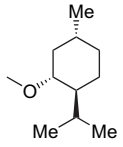
The subsequent N-deacylation of **5b** showed a remarkable decrease in the enantiomeric excess of the resulting (*R*)-**1** (from 98% de of **5b** to 80% ee of (*R*)-**1**).[8] The plausible reason why the ee value decreased was that deacylation of **5b** proceeded slowly; therefore, we chose **6a** as the resolving agent.

The single isomer **5a** could be isolated by crystallization from alcohols such as methanol and propanol; in particular, 2-propanol was preferable to obtain **5a** in good yield with high diastereomeric excess (Table 2).

Table 1. Results of N-acylation and diastereomeric resolution



Reagents: (1) **6**, $(COCl)_2$, in toluene at 5 °C (2) pyridine in toluene at -15 °C

Entry	R	Yield[a] (%)	de[b] (%)
1	 **6a**	**5a**[c]: 39	98
2	 **6b**	**5b**[c]: 41	97
3	 **6c**	Not crystallized	
4	 **6d**	Not crystallized	
5	 **6e**	Not crystallized	
6	 **6f**[d]	Not crystallized	

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] More crystallizable isomer.[6]
[d] Instead of **6f**, commercially available (−)-menthyl chloroformate was used.

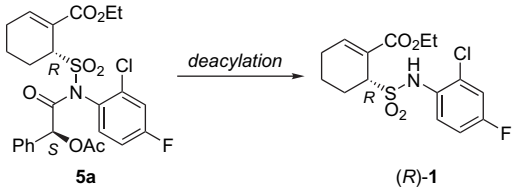
Table 2. Isolation of **5a** by crystallization

Entry	Solvent	Temp (°C)	Yield[a] of **5a** (%)	de[b] (%)
1	Methanol	rt	35	98
2	1-Propanol	rt	22	98
3	2-Propanol	40[c]	39	98

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] Temperature was raised because gummy oil was separated out at rt.

For optimization of deacylation of **5a**, various bases and acids were investigated (Table 3). When using H_2SO_4, $AlCl_3$, NH_4Cl, and AcONa, the sulfonamide bond was cleaved chiefly to give **7**.[9] With $NaHCO_3$ and Na_2CO_3, deacylation proceeded very slowly at rt. Even at 80 °C, it proceeded slowly (entries 1 and 2), and impurity **7** and its hydrolyzate **8**[9] were produced conspicuously. The use of strong bases afforded different results. Deacylation with $Ba(OH)_2$ at rt proceeded faster than with the above bases, and the amounts of **7** and **8** relatively decreased (entry 3). On the other hand, deacylation with NaOH or NH_3 proceeded quickly even at 0 °C (entries 4 and 5). Impurities **7**

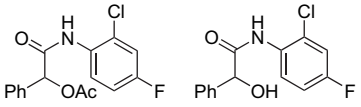
Table 3. Deacylation of **5a**



5a (*R*)-**1**

Entry	Reagent (equiv)	Solvent	Temp[a] (°C)	Time (h)	Yield[b] (%)	ee[b] (%)
1	$NaHCO_3$ (2)	MeCN–H_2O	rt–80	12	18	91
2	Na_2CO_3 (1)	MeCN–H_2O	rt–80	12	31	88
3	$Ba(OH)_2$ (1)	MeCN–H_2O	rt	6	72	95
4	2 M NaOH aq (10)	THF	0	2	95	94
5	25% NH_3 aq (72)	THF	0	2	81	98

[a] Temperature was raised according to the reaction rates.
[b] Determined by HPLC analysis.



7 **8**

Figure 2. Structure of **7** and **8**.

and **8** were produced similarly to $Ba(OH)_2$ when NH_3 was used, and it was difficult to isolate (*R*)-**1** by crystallization from crude oil. Although deacylation with NaOH provided (*R*)-**1** accompanied by **7**, crude (*R*)-**1** was crystallized easily to obtain 74% isolated yield with 93% ee (Fig. 2).

To achieve high enantiomeric purity of (*R*)-**1**, a higher crystallization property of *rac*-**1** than that of (*R*)-**1** was utilized. Namely, crude (*R*)-**1** was dissolved in 2-propanol and *rac*-**1** was crystallized out. Crystallization from enriched mother liquor afforded (*R*)-**1** in 68% yield with 99% ee.

3. Conclusion

In conclusion, we developed a novel synthesis method of **TAK-242** by diastereomeric resolution. The introduction of (*S*)-*O*-acetylmanderic acid **6a** to a sulfonamide moiety of *rac*-**1** provided diastereomeric mixtures from which the single isomer **5a** was isolated easily by crystallization in 39% yield with 98% de. Deacylation of **5a** afforded crude (*R*)-**1** in 74% with 93% ee, and subsequent recrystallization including racemate removal treatment provided (*R*)-**1** in 68% yield with 99% ee. The total yield from *rac*-**1** was 20% in three steps.

4. Experimental

4.1. General methods

Melting points were recorded on a BÜCHI melting point B-540 and were uncorrected. IR spectra were recorded on a FT-IR Thermo Electron Nicolet 4700. ^{1}H NMR spectra were recorded on a Brüker DPX-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Elemental analyses were carried out by Takeda Analytical Research Laboratories Limited. Optical rotations were determined by Takeda Analytical Research Laboratories Limited. The de and ee of compounds were determined by HPLC. The conditions were as follows: column: CHIRALPAK® AD, 4.6 mm i.d.×250 mm; mobile phase: *n*-hexane/EtOH=9/1; flow rate: 1 mL min^{-1}; detector: UV 254 nm. The yields in Table 3 were determined by HPLC. The conditions were as follows: column: YMS-Pack ODS-A A-302, 4.6 mm i.d.×250 mm; mobile phase: 0.05 M KH_2PO_4/MeCN=3/7; flow rate: 1 mL min^{-1}; detector: UV 254 nm.

4.1.1. Ethyl (6*R*)-6-{[[(2*S*)-2-(acetyloxy)-2-phenylacetyl](2-chloro-4-fluorophenyl)amino]sulfonyl}cyclohex-1-ene-1-carboxylate (5a). Oxalyl chloride (1.7 mL, 20 mmol) was added dropwise to an ice-cooled solution of (2*S*)-2-(acetyloxy)-2-phenylethanoic acid (**6a**, 1.9 g, 10 mmol) in DMF (0.1 mL) and toluene (30 mL), and then stirred for 1 h at rt. After the mixture was cooled to −15 °C, *rac*-**1** (1.8 g, 5 mmol) and pyridine (3.5 mL, 44 mmol) were added to the mixture at −15 °C. The mixture was stirred for 2 h, and then water (15 mL) was added. The organic layer was washed with 2 M HCl aq (15 mL) and water (15 mL, three times), and concentrated in vacuo. The residue was dissolved in 2-PrOH (6 mL) under reflux. The mixture was stirred for 1 h at 40 °C, and then stirred for 2 h at rt. The precipitate was washed with cold 2-PrOH (1 mL) to give **5a** (1.1 g, 39%, 98% de, t_R of **5a**, 7.4 min; t_R of (6*S*)-isomer, 10.0 min) as a white solid. Mp 133–134 °C. $[\alpha]_D^{20}$ +157.0 (*c* 1.0, DMSO). Anal. Calcd for $C_{25}H_{25}NO_7SClF$: C, 55.81; H, 4.68; N, 2.60; S, 5.96; Cl, 6.59; F, 3.53. Found: C, 55.85; H, 4.38; N, 2.62; S, 5.92; Cl, 6.71; F, 3.23. ^{1}H NMR ($CDCl_3$): δ 1.24 (3H, t, *J*=7.1 Hz), 1.70–1.95 (3H, m), 2.05–2.30 (4H, m), 2.35–2.45 (1H, m), 3.06 (1H, br d, *J*=14.2 Hz), 4.19 (2H, q, *J*=7.1 Hz), 5.20 (1H, br d, *J*=3.9 Hz), 5.66 (1H, s), 6.95–7.00 (2H, m), 7.05–7.15 (1H, m), 7.20–7.35 (5H, m), 8.02 (1H, dd, *J*=8.9, 5.7 Hz). IR (KBr): 1749, 1700, 1488, 1340, 1213, 1164 cm^{-1}.

4.1.2. Ethyl (6*R*)-6-({(2-chloro-4-fluorophenyl)[(2*R*)-4-methoxy-2-methyl-4-oxobutanoyl]amino}sulfonyl)-cyclohex-1-ene-1-carboxylate (5b). Compound (**5b**) was prepared in 41% yield with 97% de (t_R of **5b**, 8.4 min; t_R of (6*S*)-isomer, 11.2 min) as a white solid from *rac*-**1** according to a procedure similar to that described above (the preparation of **5a**). Mp 141–142 °C. $[\alpha]_D^{20}$ +110.3 (*c* 1.0, DMSO). Anal. Calcd for $C_{21}H_{25}NO_7SClF$: C, 51.48; H, 5.14; N, 2.86; S, 6.54; Cl, 7.24; F, 3.88. Found: C, 51.40; H, 5.27; N, 2.83; S, 6.38; Cl, 7.29; F, 3.67. ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, t, *J*=2.3 Hz), 1.26 (3H, t, *J*=7.1 Hz), 1.76–1.85 (2H, m), 1.90–2.05 (1H, m), 2.15–2.50 (3H, m), 2.60–2.70 (1H, m), 2.80–2.99 (1H, m), 3.03 (1H, br d, *J*=12.9 Hz), 3.68 (3H, s), 4.19 (2H, q, *J*=7.1 Hz), 5.20 (1H, br s), 7.04–7.10 (1H, m), 7.24–7.10 (2H, m), 7.80 (1H, dd, *J*=8.9, 5.7 Hz). IR (KBr): 1733, 1693, 1492, 1342, 1203, 1141 cm^{-1}.

4.1.3. Ethyl (6*R*)-6-[*N*-(2-chloro-4-fluorophenyl)sulfamoyl]cyclohex-1-ene-1-carboxylate ((*R*)-1). The diastereomer (**5a**) (30.0 g, 55.8 mmol) was added to a suspension of 2 M NaOH (280 mL, 557.6 mmol) in THF (280 mL) at 0 °C, and stirred for 2 h. The mixture was adjusted with 1 M HCl to pH 4 at 0 °C, and extracted with AcOEt (140 mL). The aqueous layer was extracted with

AcOEt (250 mL), and the combined organic layers were washed with satd $NaHCO_3$ (250 mL) and 10% aq NaCl (250 mL), and concentrated in vacuo. The residue was dissolved in a solution of *i*-Pr_2O (15 mL) and cyclohexane (60 mL) at 60 °C, and stirred for 1 h at rt. The mixture was stirred below 10 °C for 1.5 h. The precipitate was washed with cold cyclohexane (25 mL) to give crude (*R*)-**1** (15.0 g, 74%, 93% ee) as a white solid. Crude (*R*)-**1** (3.0 g) was dissolved in 2-PrOH (15 mL) at 60 °C, and stirred for 15 h at rt. The resulting precipitate was filtered off, and washed with 2-PrOH (3 mL). To the mother liquor and the washings was added *n*-heptane (18 mL) at 60 °C, which was stirred for 0.5 h at rt. The mixture was stirred for 2 h below 10 °C, and the precipitate was washed with cold *n*-heptane (9 mL) to give (*R*)-**1** (2.1 g, 68%, 99% ee, t_R of (*R*)-**1**, 11.7 min; t_R of (*S*)-isomer, 10.0 min) as a white solid. Mp 69–70 °C (lit.[1b] 68–69 °C). $[\alpha]_D^{20}$ +110.2 (*c* 1.0, methanol) {lit.[1b] +110.0 (*c* 1.0, methanol)}. Anal. Calcd for $C_{15}H_{17}NO_4SClF$: C, 49.79; H, 4.74; N, 3.87; S, 8.86; Cl, 9.80; F, 5.25. Found: C, 49.71; H, 4.67; N, 3.90; S, 8.80; Cl, 9.87; F, 5.22. ^1H NMR ($CDCl_3$): δ 1.24 (3H, t, *J*=7.1 Hz), 1.69–1.78 (2H, m), 2.16–2.30 (2H, m), 2.41–2.55 (2H, m), 4.15 (2H, q, *J*=7.1 Hz), 4.71 (1H, br d, *J*=4.7 Hz), 6.96–7.00 (2H, m), 7.12–7.16 (1H, m), 7.28–7.31 (1H, m), 7.69 (1H, dd, *J*=9.1, 5.3 Hz). IR (KBr): 3253, 1709, 1649, 1492, 1333, 1234, 1149 cm^{-1}.

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References and notes

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6. Stereochemistry was determined by correlating with the desired (*R*)-**1**. The chiral acid isomers, (*R*)-*O*-acetylmanderic acid and (*S*)-3-methylsuccimate, were also used to prepare diastereomers followed by deacylation. Compared with both results, stereochemistry was confirmed unambiguously.
7. Since each mixture of diastereomers derived from **6c–f** was separated on analytical TLC or HPLC, they could also be separated chromatographically on a preparative scale. We considered, however, that it was favorable to isolate by crystallization for large-scale preparation.
8. Deacylation of **5b** was conducted under the conditions of Table 3, entry 4.
9. The structures of **7** and **8** were estimated by LCMS (**7**; LCMS (ESI) *m/z* 320 $(M-H)^-$. **8**; LCMS (ESI) *m/z* 278 $(M-H)^-$).