

Synthesis of Acinetobactin

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A structure involving the absolute configuration of acinetobactin (1b) was clarified. It was reconfirmed that preacinetobactin (1a) produced 1b by a rearrangement reaction.

Key words total synthesis; acinetobactin; structure determination; rearrangement

In 1994, acinetobactin was isolated from low-iron cultures of *Acinetobacter baumannii* ATCC1960, and the chemical structure (1a) of acinetobactin was proposed by using chemical degradation, FAB-MS spectrometry, and ¹H- and ¹³C-NMR spectroscopy (Fig. 1).^{1,2} In 2009, it was suggested that this reported structure is an unstable intermediate (1a: preacinetobactin) and the correct structure (1b) should be its rearrangement product obtained by using the high-resolution (HR)-MS technique.³ However, in this report, there is no detailed positive proof about the relative and/or absolute configuration of 1a, b because 1a is not isolated and the specific rotation of 1b is not described. We thought that two evidences, the isolation of the intermediate and the decision of the absolute configuration of acinetobactin, are necessary with a more certainly corrected structure.

We thought that 2,3-dihydroxybenzoic acid (2), L-threonine (3), and *N*-hydroxyhistamine (4) can be used as the starting material for the synthesis of 1a (Chart 1).

The intermediate corresponding to 4, *O*-benzyloxyhistamine (5) was derived in three steps from histamine dihydrochloride (6) (Chart 2). The substitution reaction with SOCl₂ following the reaction of 6 with NaNO₂ yielded 4-(2-

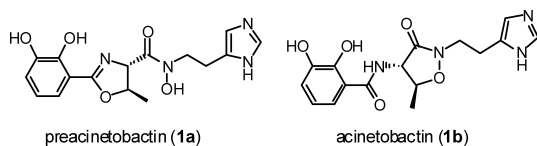


Fig. 1. Preacinetobactin (1a) and Acinetobactin (1b)

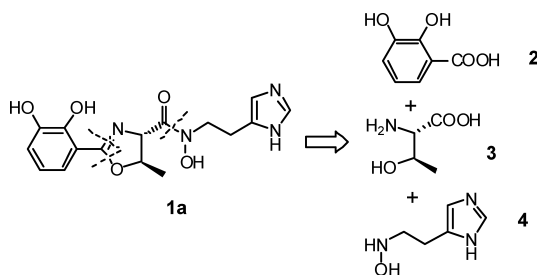


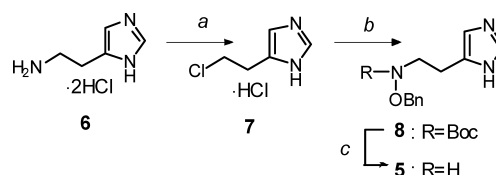
Chart 1

chloroethyl)imidazole hydrochloride (7) in 70% yield.^{4,5} The synthesis of intermediate 5 was achieved by the coupling reaction of 7 with *N*-*tert*-butoxycarbonyl(Boc)-*O*-benzyloxyamine⁶) and a deprotection reaction.⁷

Compound 9, in which the hydroxy group of 1b was protected with a benzyl group, was successfully derived from 2,3-dihydroxybenzaldehyde (10) (Chart 3). Oxazolidine 13 was afforded by the reaction of a L-threonine derivative with 12,^{8–10} which was derived from 10. Carboxylic acid 14¹¹ was afforded in 80% yield by the hydrogenolysis of 13. The desired compound 9 could be obtained by the coupling with carboxylic acid 14 and 5.

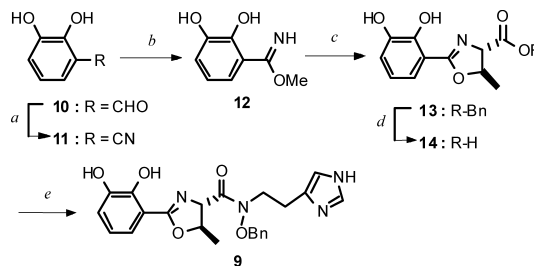
The hydrogenolysis of 9 afforded 1a,¹² and the heat of 1a successively yielded 1b,¹³ which was identified with a naturally occurring antibacterial agent^{1,2} by comparison with ¹H-NMR and specific rotation (Chart 4). Thus, we could clarify the structure of acinetobactin that was produced from 1a by the intramolecular S_N2 reaction.

In order to confirm the structures of 1a, b, we continued the study on the design and synthesis of the related compounds that correspond to the isomer. Compound 19,¹⁴ which corresponds to the diastereomer of 14, was successfully derived in three steps from 2,3-dihydroxybenzoic acid (16)¹⁵ (Chart 5). However, the coupling reaction of 19 with 5 afforded not the desired compound *cis*-form 15 but the *trans*-form *ent*-9 corresponding to an enantiomer of 9.¹⁶ We think that the activated acyl derivative of 19 can be used for the



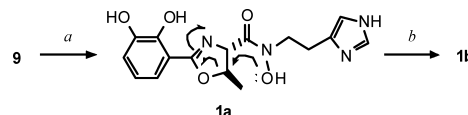
Reagents and conditions: a) i) NaNO₂, HCl, 60 °C, 1 h; ii) SOCl₂, reflux, 0.5 h, 70%; b) *O*-Benzyl-*N*-*tert*-butoxycarbonylhydroxylamine, NaH, DMF, 50 °C, 3 h, 47%; c) TFA, rt, 96%.

Chart 2



Reagents and conditions: a) NH₂OH·HCl, HCOONa, HCOOH, 68%; b) i) AcCl, dry, MeOH, ii) sat. NaHCO₃ aq., 40% (2 steps); c) L-Thr-OBn-(COOH)₂, (CH₂Cl)₂, 64%; d) H₂, 10% Pd/C, MeOH, 84%; e) EDC·HCl, HOBT·H₂O, DMF, 63%.

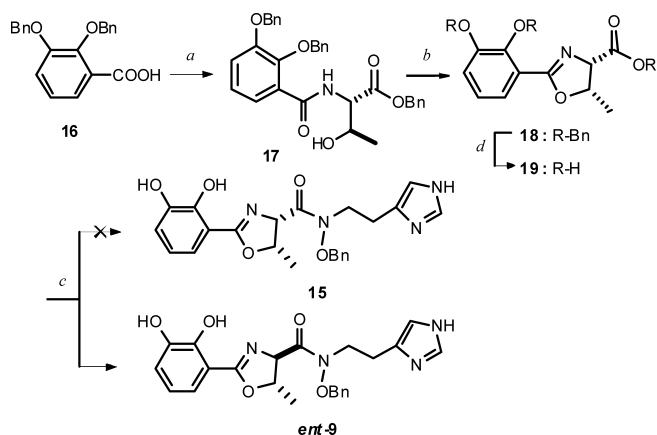
Chart 3



Reagents and conditions: a) H₂, 10% Pd/C, MeOH, rt, 64%; b) MeOH, reflux, 86%.

Chart 4

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Reagents and conditions: *a* L-Thr-OBn·(COOH)₂, EDC·HCl, DMAP, DMF, 88%; *b* SOCl₂, 88%; *d* H₂, 10% Pd/C, MeOH, 80%; *c* 5, EDC·HCl, HOBT·H₂O, DMF, 55%.

Chart 5

epimerization to produce the sterically stable *trans* form.

We clarified a structure involving the absolute configuration of acinetobactin (**1b**) and reconfirmed that preacinetobactin (**1a**) produced **1b** by a rearrangement reaction.

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References and Notes

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- 11) **14**: Yellow powder. mp 91.2—98.7 °C (decomp.). ¹H-NMR (300 MHz, CD₃OD) δ: 1.54 (3H, d, *J*=6.3 Hz, CH₃), 4.54 (1H, d, *J*=7.2 Hz, 4-H), 4.98 (1H, m, 5-H), 6.74 (1H, t, *J*=7.8 Hz, 5'-H), 6.95 (1H, dd, *J*=7.8, 1.5 Hz, 4'-H), 7.16 (1H, dd, *J*=7.8, 1.5 Hz, 6'-H).
- 12) **1a**: Yellow amorphous, ¹H-NMR (300 MHz, CD₃OD) δ: 1.51 (3H, m, CH₃), 2.97 (2H, t, *J*=6.0 Hz, Imid.CH₂CH₂), 3.79—3.93 (2H, m, Imid.CH₂CH₂), 4.89 (2H, s, PhCH₂), 4.8—5.0 (1H, m, oxazoline 5'-H), 5.09 (1H, d, *J*=6.0 Hz, oxazoline 4'-H), 6.69—6.76 (1H, m, Ph 5''-H), 6.92—6.96 (1H, m, Ph 4''-H), 7.12 (1H, s, Imid.4'-H), 7.15 (1H, dd, *J*=7.8, 1.5 Hz, Ph 6''-H), 7.70 (1H, s, Imid.2-H).
- 13) **1b**: Yellow amorphous, ¹H-NMR (500 MHz, CDOD₃) δ: 1.46 (3H, t, *J*=6.0 Hz, CH₃), 3.01 (2H, m, Imid.CH₂CH₂), 3.89 (2H, m, Imid.CH₂CH₂), 4.48 (1H, qd, *J*=10.5, 6.0 Hz, 5H), 4.71 (1H, *J*=11.0 Hz, 4-H), 6.73 (1H, t, *J*=8.0 Hz, 5''H), 6.96 (1H, dd, *J*=7.5, 1.0 Hz, 4''H), 7.07 (1H, s, 5'H), 7.26 (1H, dd, *J*=8.0, 1.5 Hz, 6'-H), 7.93 (1H, s, 2'H), [α]_D¹⁶ -43.2 (*c*=0.5, MeOH) {lit. [α]_D²⁰ -37.4 (*c*=1.0, MeOH)}.¹⁾
- 14) **19**: Yellow powder. mp 116.3—124.5 °C (decomp.). ¹H-NMR (300 MHz, CD₃OD) δ: 1.46 (3H, d, *J*=6.6 Hz, CH₃), 5.02 (1H, d, *J*=11.1 Hz, 4-H), 5.11—5.21 (1H, m, 5-H), 6.74 (1H, t, *J*=7.8 Hz, 5'-H), 6.95 (1H, dd, *J*=7.8, 1.5 Hz, 6'-H), 7.16 (1H, dd, *J*=7.8, 1.5 Hz, 4'-H).
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- 16) **9** and *ent-9*: Yellow amorphous. ¹H-NMR (500 MHz CDCl₃) δ: 1.31 (3H, d, *J*=6.6 Hz, CH₃), 3.01 (2H, m, Imid.CH₂CH₂), 3.95 (1H, m, Imid.CH₂CH₂), 4.09 (1H, m, Imid.CH₂CH₂), 4.75 (1H, d, *J*=5.7 Hz, 4-H), 4.93 (3H, m, 5-H, PhCH₂), 6.76 (1H, t, *J*=7.8 Hz, 5''-H), 6.82 (1H, s, 4'-H), 7.02 (1H, d, *J*=7.8 Hz, 4''-H), 7.17 (1H, d, *J*=7.8 Hz, 6''-H), 7.39 (5H, s, PhCH₂), 7.54 (1H, s, 2'-H). **9**: [α]_D²⁷ +149 (*c*=1.0, CHCl₃). *ent-9*: [α]_D²⁷ -114 (*c*=1.0, CHCl₃).