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 ^{1}H- and ^{13}C-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*-hydoxyhistamine (**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 $SOCl_2$ following the reaction of **6** with $NaNO_2$ yielded 4-(2-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*-benyloxyamine[6] 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 **14**[11] 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 ^{1}H-NMR and specific rotation (Chart 4). Thus, we could clarify the structure of acinetobactin that was produced from **1a** by the intramolecular *S*$_N$2 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

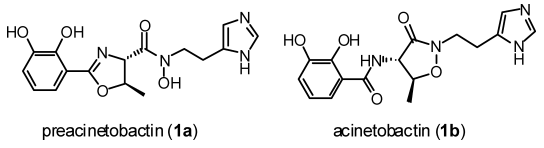


Fig. 1. Preacinetobactin (**1a**) and Acinetobactin (**1b**)

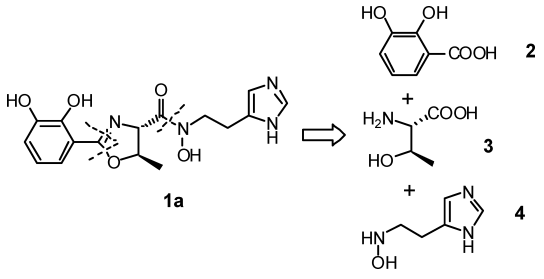
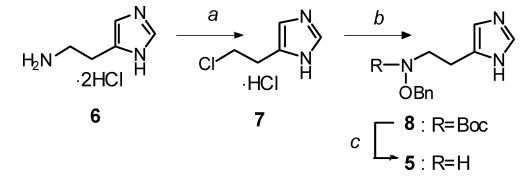
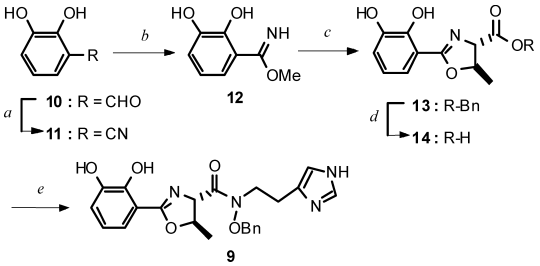


Chart 1



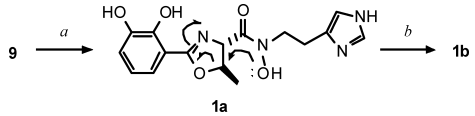
Reagents and conditions: *a* i) $NaNO_2$, HCl, 60 °C, 1 h; ii) $SOCl_2$, reflux, 0.5 h, 70%; *b* *O*-Benzyl-*N*-*tert*-butoxycarbonylhydroxylamine, NaH, DMF, 50 °C, 3 h, 47%; *c* TFA, rt, 96%.

Chart 2



Reagents and conditions: *a* $NH_2OH \cdot HCl$, HCOONa, HCOOH, 68%; *b* i) AcCl, dry. MeOH, ii) sat. $NaHCO_3$ aq., 40% (2 steps); *c* L-Thr-OBn·$(COOH)_2$, $(CH_2Cl)_2$, 64%; *d* H_2, 10% Pd/C, MeOH, 84%; *e* 5, EDC·HCl, HOBt·H_2O, DMF, 63%.

Chart 3



Reagents and conditions: *a* H_2, 10% Pd/C, MeOH, rt, 64%; *b* MeOH, reflux, 86%.

Chart 4

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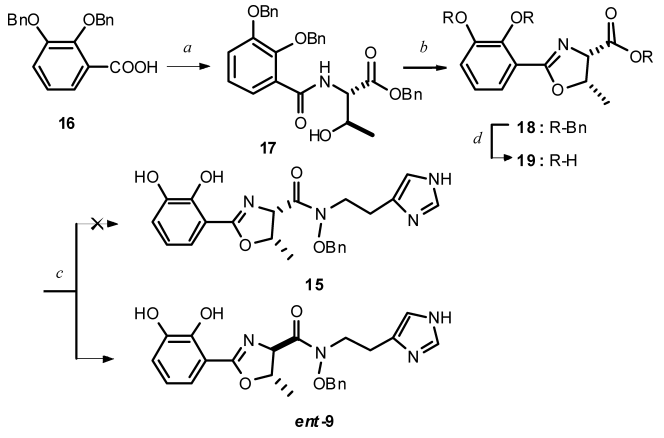

Reagents and conditions: *a* L-Thr-OBn·$(COOH)_2$, EDC·HCl, DMAP, DMF, 88%; *b* $SOCl_2$, 88%; *d* H_2, 10% Pd/C, MeOH, 80%; *c* 5, EDC·HCl, HOBt·H_2O, DMF, 55%.

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

1) Yamamoto S., Okujo N., Sakakibara Y., *Arch. Microbiol.*, **162**, 249—254 (1994).
2) Walsh C. T., Wuest W. M., Sattely E. S., *J. Am. Chem. Soc.*, **131**, 5056—5057 (2009).
3) Walsh C. T., Sattely E. S., *J. Am. Chem. Soc.*, **130**, 12282—12284 (2008).
4) Turner R. A., *J. Am. Chem. Soc.*, **71**, 3476—3478 (1949).
5) Overberger C. G., Vorchheimer N., *J. Am. Chem. Soc.*, **85**, 951—955 (1963).
6) Grigg R., Rankocic Z., Thoroughgood M., *Tetrahedoron*, **56**, 8025—8032 (2000).
7) Sulsky R., Demers J., *Tetrahedron Lett.*, **30**, 31—34 (1989).
8) Es T. B., *J. Chem. Soc.*, **1964**, 1564 (1964).
9) Bergeron R. J., Wiegand J., McManis J. S., Weimar W. R., Park J., McManis E., Bergeron J., Brittenham F. M., *J. Med. Chem.*, **48**, 821—831 (2005).
10) Veejendra K. Y., Ganesh B., *Eur. J. Org. Chem.*, **70**, 452—456 (2005).
11) **14**: Yellow powder. mp 91.2—98.7 °C (decomp.). ^{1}H-NMR (300 MHz, CD_3OD) δ: 1.54 (3H, d, J=6.3 Hz, CH_3), 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, ^{1}H-NMR (300 MHz, CD_3OD) δ: 1.51 (3H, m, CH_3), 2.97 (2H, t, J=6.0 Hz, Imid.CH_2CH_2), 3.79—3.93 (2H, m, Imid.CH_2CH_2), 4.89 (2H, s, $PhCH_2$), 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, ^{1}H-NMR (500 MHz, $CDOD_3$) δ: 1.46 (3H, t, J=6.0 Hz, CH_3), 3.01 (2H, m, Imid.CH_2CH_2), 3.89 (2H, m, Imid.CH_2CH_2), 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), $[\alpha]_D^{16}$ −43.2 (c=0.5, MeOH) {lit. $[\alpha]_D^{20}$ −37.4 (c=1.0, MeOH)}.[1)]
14) **19**: Yellow powder. mp 116.3—124.5 °C (decomp.). ^{1}H-NMR (300 MHz, CD_3OD) δ: 1.46 (3H, d, J=6.6 Hz, CH_3), 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).
15) Gardner R. A., Kinkade R., Wang C., Phanstiel O., *J. Org. Chem.*, **69**, 3530—3537 (2004).
16) **9** and *ent*-**9**: Yellow amorphous. ^{1}H-NMR (500 MHz $CDCl_3$) δ: 1.31 (3H, d, J=6.6 Hz, CH_3), 3.01 (2H, m, Imid.CH_2CH_2), 3.95 (1H, m, Imid.CH_2CH_2), 4.09 (1H, m, Imid.CH_2CH_2), 4.75 (1H, d, J=5.7 Hz, 4-H), 4.93 (3H, m, 5-H, $PhCH_2$), 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, $PhCH_2$), 7.54 (1H, s, 2′-H). **9**: $[\alpha]_D^{22}$ +149 (c=1.0, $CHCl_3$). *ent*-**9**: $[\alpha]_D^{27}$ −114 (c=1.0, $CHCl_3$).