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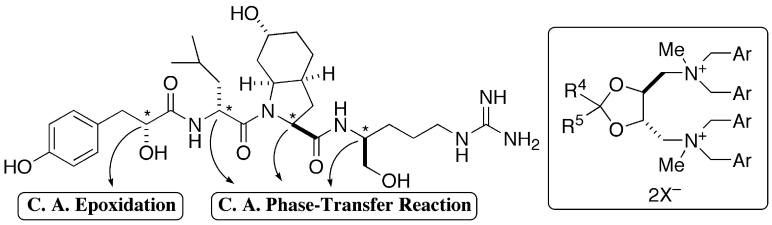

Aeruginosin 298-A **Two-Center Catalyst**

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Enantioselective Syntheses of Aeruginosin 298-A and Its Analogues Using a Catalytic Asymmetric Phase-Transfer Reaction and Epoxidation

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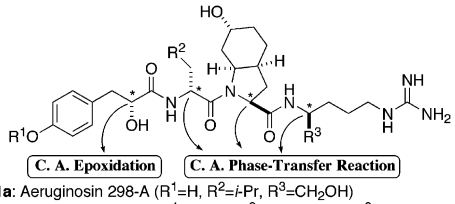
The serine protease thrombin is the most selective and multifunctional enzyme involved in hemeostasis and thrombosis.[1] Aeruginosin 298-A (Figure 1, **1a**), which has a tetrapeptide-like structure including nonstandard amino acids such as (*R*)-3-(4-hydroxyphenyl)lactic acid (D-Hpla) and 2-carboxy-6-hydroxyoctahydroindole (Choi), was isolated from blue-green algae by Murakami et al. and has serine protease inhibitor activity.[2a] Recently, the total synthesis of **1a** was reported by Bonjoch's[3] and Wipf's[4] groups. Of the aeruginosin family, aeruginosin 102-A (**1b**) has the highest activity.[2b] More potent analogues in terms of selectivity and activity, however, need to be developed. To gain insight into the structure−activity relations, the development of a highly versatile synthetic method is required. Here, we report enantioselective syntheses of **1a** and its attractive analogues using a catalytic asymmetric phase-transfer reaction and epoxidation. Drastic counteranion effects were observed in the phase-transfer reactions.

Phase-transfer catalysis (PTC) is a useful approach for synthesizing optically active α-amino acids because of its simple reaction procedure, mild conditions, inexpensive reagents, and the ease in scaling-up the reaction.[5] Although there are several efficient PTCs promoted by *Cinchona* alkaloid derivatives[6] or other designed catalysts,[7] only a few synthetic applications for complex natural products have been reported.[5] Recently, we developed novel two-center catalysts that promote phase-transfer alkylations and Michael reactions with high substrate generality.[8] Catalysts **2** (Scheme 1) are advantageous in terms of catalyst accessibility (five steps in the large-scale reaction using inexpensive reagents and simple operations) and versatility (tunable substituents: R^4, R^5, and Ar). We used this PTC to synthesize the α-amino acids of **1a** and its analogues.

When 10 mol % of (*S*,*S*)-**2a** was used, phase-transfer alkylation of **3** proceeded smoothly to afford a variety of α-amino acids.[9] For the synthesis of **1a** (D-Leu portion), methallyl bromide was used as an electrophile to afford **4a** (93%, 91% ee). For the synthesis of the **1b** analogue (D-Tyr portion), **4b** (88%, 92% ee) and its fluoro analogue **4c** (93%, 94% ee)[10] were also synthesized.

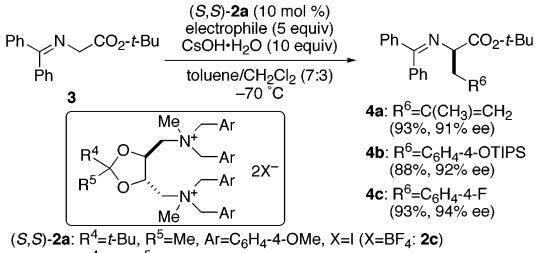
The L-Choi portion was previously synthesized from L-tyrosine derivatives.[3,4] Although **4b** can be converted to Choi via L-tyrosine, we chose a more direct method including a one-pot multistep reaction (Scheme 2). Using **5** as an electrophile and (*R*,*R*)-**2a** as a catalyst, we obtained the desired product **6** in 80% yield and 88% ee. Treatment of **6** with 4 N HCl in methanol promoted deprotection of the benzophenone imine and ketal, transesterification, migration of the C−C double bond, and 1,4-addition of the resulting amine to enone in one-pot (72%). After benzylation, bicyclic amino ester was obtained as a diastereomixture (84%, **7a**:**7b** = 1:2). The undesired isomer **7b** was transformed to the desired **7a** under acidic conditions (78%, **7a**:**7b** = 8:1), and **7a** was successfully converted to **8**[9,10] (71% in two steps) by following Bonjoch's procedure.[3]



1a: Aeruginosin 298-A (R^1=H, R^2=*i*-Pr, R^3=CH_2OH)
1b: Aeruginosin 102-A (R^1=SO_3H, R^2=C_6H_4-4-OH, R^3=CHO)

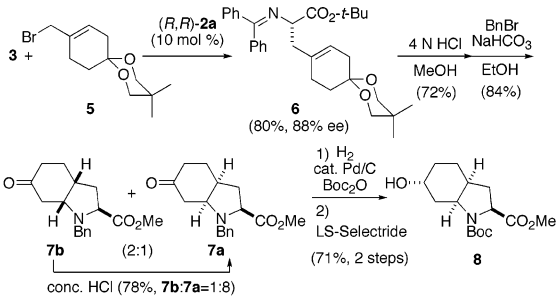
Figure 1. Structure of aeruginosin 298-A (**1a**) and its analogues.

Scheme 1. Phase-Transfer Alkylation Using Catalyst **2**



(*S*,*S*)-**2a**: R^4=*t*-Bu, R^5=Me, Ar=C_6H_4-4-OMe, X=I (X=BF_4: **2c**)
(*S*,*S*)-**2b**: R^4=Pr, R^5=Pr, Ar=C_6H_4-4-Me, X=I (X=BF_4: **2d**)

Scheme 2. Synthesis of the L-Choi Portion



Synthesis of the L-Argol portion began with the phase-transfer alkylation of **3** using allyl bromide and (*R*,*R*)-**2a**, affording **9** in 79% yield and 91% ee (Scheme 3). Compound **9** was then converted to **11a** through introduction of the guanidine moiety.[9] Alternatively, **11a** can be synthesized by the phase-transfer Michael reaction using (*S*,*S*)-**2b**, prepared from less expensive L-tartrate, because our two-center catalyst **2** has opposite enantiofacial selectivity in alkylations and Michael reactions.[8] The reported conditions for the Michael reaction, however, were not very effective and give **12** in 74% ee with only moderate reactivity (−30 °C, 18 h, 85% yield), even when using 10 equiv of Cs_2CO_3. To overcome these problems, we tuned the catalyst and determined that the counteranion of **2** affected both reactivity and selectivity. Among the examined counteranions, BF_4^- functioned best.[9] When (*S*,*S*)-**2d** was used, the reaction was completed in 10 h at the same temperature with only 0.5 equiv of Cs_2CO_3, and the enantioselectivity improved to 81% (86% ee at −60 °C).[10] To the best of our knowledge, this is the first example of such drastic counteranion effects in PTC. The counteranion effect

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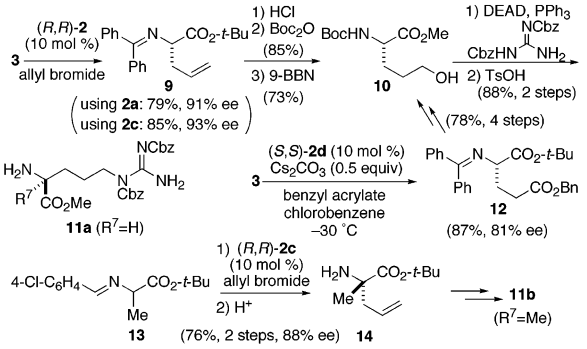
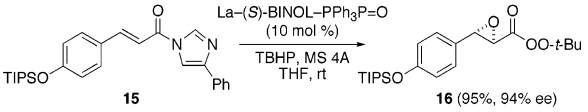
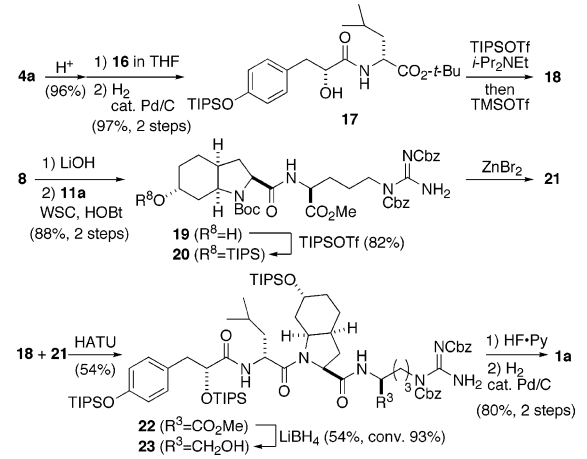
Scheme 3. Synthesis of the L-Argol Portion



Scheme 4. Synthesis of the D-Hpla Portion



Scheme 5. Synthesis of Aeruginosin 298-A (**1a**)



was also observed in alkylation with excess hydroxide. The BF_4^- catalyst (*R*,*R*)-**2c** successfully promoted the allylation of **3** to **9** (85%, 93% ee) and **13** to quaternary α-amino ester **14** (76%, 88% ee), which was further transformed to **11b** using the same procedure.[9]

In contrast to commonly used *Cinchona* alkaloid derived catalysts, **2** is extremely stable under basic conditions, and, as a result, after the reaction was quenched with water and ether, **2** was recovered as a white solid by simple decantation (80−90% yield) and reused with the same efficiency.[9]

Finally, the D-Hpla portion was prepared on the basis of catalytic asymmetric epoxidation of α,*β*-unsaturated imidazolide (Scheme 4).[9,11,12]

Assembly of the tetrapeptide proceeded (Scheme 5). Simple mixing of **16** and the amino ester, which was prepared from **4a**, followed by one-pot hydrogenation furnished dipeptide **17** as a diastereomixture (97% yield, 11:1), which was separated at this stage. After the mixture was treated with TIPSOTf[13] and *i*-Pr_2NEt, TMSOTf was added to the reaction directly under reflux conditions, affording the left segment **18**. Subsequent saponification of **8**, a coupling reaction with **11a** using WSC-HOBt, and TIPS protection[13] of the secondary alcohol gave **20** as a diastereomixture (72% in three steps, 12:1). Separation of the desired diastereomer and deprotection of Boc using $ZnBr_2$ produced the right segment **21**.

When HOBt containing the coupling reagent was used, tetrapeptide **21** (40%) was obtained with partial racemization at the Leu portion (ca. 20%). After the coupling conditions were screened, HATU gave superior results (54%) with a negligible amount of the diastereomer (<5%). Finally, the reduction of methyl ester (54%, conv. 93%) and subsequent deprotection of TIPS and Cbz groups (80% in two steps) provided aeruginosin 298-A (**1a**).[14] Moreover, three additional analogues containing **4b**,**c** and **11b** were synthesized in a similar way.[9]

We developed a versatile synthetic process for aeruginosin 298-A as well as several attractive analogues, in which all stereocenters were controlled by a catalytic asymmetric phase-transfer reaction and epoxidation. Furthermore, drastic counteranion effects in PTC were observed for the first time, making it possible to three-dimensionally fine-tune catalyst **2** (ketal, Ar, and X). Further studies on the structure−activity relation of aeruginosins are currently under investigation in our group.

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Supporting Information Available: Experimental procedures and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Vacca, J. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1998; Vol. 33, p 81.
(2) (a) Murakami, M.; Okita, Y.; Matsuda, H.; Okino, T.; Yamaguchi, K. *Tetrahedron Lett.* **1994**, *35*, 3129. (b) Matsuda, H.; Okino, T.; Murakami, M.; Yamaguchi, K. *Tetrahedron* **1996**, *52*, 14501.
(3) (a) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2000**, *122*, 11248. (b) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem.-Eur. J.* **2001**, *7*, 3446.
(4) Wipf, P.; Mthot, J.-L. *Org. Lett.* **2000**, *2*, 4213.
(5) For a recent review, see: Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
(6) For representative examples, see: (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (d) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036.
(7) For representative examples, see: (a) Ooi, T.; Kaneda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (b) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Larionov, O. V.; Harutyunyan, S. R.; Vyskocil, S.; North, M.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1948. (c) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832. (d) Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535. (e) Mase, N.; Ohno, T.; Hoshikawa, N.; Ohishi, K.; Morimoto, H.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 4073.
(8) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539.
(9) For details, see Supporting Information.
(10) Optically pure compound was obtained by recrystallization. See Supporting Information.
(11) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544.
(12) For the effects of $Ph_3P{=}O$, see: Daikai, M.; Kamaura, M.; Inanaga, J. *Tetrahedron Lett.* **1998**, *39*, 7321 and ref 11.
(13) For syntheses of Argal analogues (R^3 = CHO), the other alcohols were protected with TIPS, although this is not necessary for the synthesis of **1a**.
(14) ^1H and ^{13}C NMR spectra were identical to the reported data after treatment with TFA in EtOH.

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