Development of stereoselective constructions of β-hydroxy-α,α-disubstituted α-amino acid structures

March 2023

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(Doctor's course)

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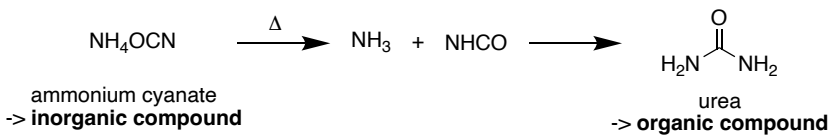
Contents

Chapter 1. General Introduction

1-1. Introduction

In 1806, J. J. Berzelius first used the term of "Organic compound" to distinguish it from "Inorganic compound". At that time, it was thought that organic compounds were produced by living organisms. Organic chemistry was the study of structure and property of organic compounds which were isolated from animals and plants. In 1828, F. Wöhler, who was an inorganic chemist in Germany, was succeeded the synthesis of urea, which was considered as an organic compound, from inorganic compound, ammonium cyanate (**Scheme 1**).[1] Thus, the conventional idea that "organic compounds can only be made by the vitality of living organisms" was broken. Since then, organic synthesis has become one of the trends in organic chemistry.



Scheme 1. Wöhler synthesis of urea from inorganic compound

There are many natural products which have the potential as lead drugs. The stable supply of these natural products is essential for biological and pharmacological investigations. However, in general, only a few quantities of such compounds are obtained from nature. Therefore, organic synthesis is strongly needed to provide the enough amount of natural products.

For the last hundred years, organic synthesis has been developed to a level which can synthesize huge and complex molecules. For example, halichondrin B, which was isolated from the marine sponge *Halichondria okadai* Kadota by Uemura and Hirata group in 1985 (**Figure 1**).[2] The first total synthesis of this complex natural compound was achieved by Kishi and colleagues in 1992.[3]

The detail of one of the Kishi's work for the synthesis of halichondrin B is shown in Figure 2.[4] Halichondrin B is a polyether-type natural compound having many tetrahydropyran (THP) rings and tetrahydrofuran (THF) rings and it has 32 asymmetric carbons. In other words, the number of stereoisomers is 2^{32} = 4,294,967,296, and one of these isomers is the halichondrin B. Therefore, when we synthesize the halichondrin B, it is needed to control all stereochemistry of stereogenic centers. To overcome this problem, they developed the methodology for the stereoselective construction of THP ring and THF ring by Cr-mediated C–C coupling reaction and subsequential intramolecular S_N2 reaction (**Figure 2a**). At the C–C coupling reaction, they have succeeded to synthesize a secondary alcohol possessing the desired stereochemistry in high stereoselectivity by significant investigation of the ligand (**Figure 2b**). Taking advantage of this reaction, they have achieved the synthesis of highly stereoselective halichondrin B (**Figure 2c**).

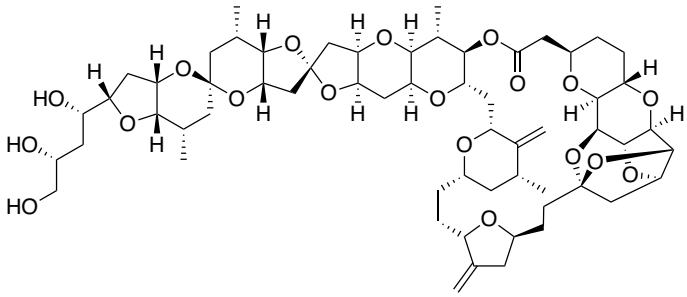


Figure 1. Structure of halichondrin B

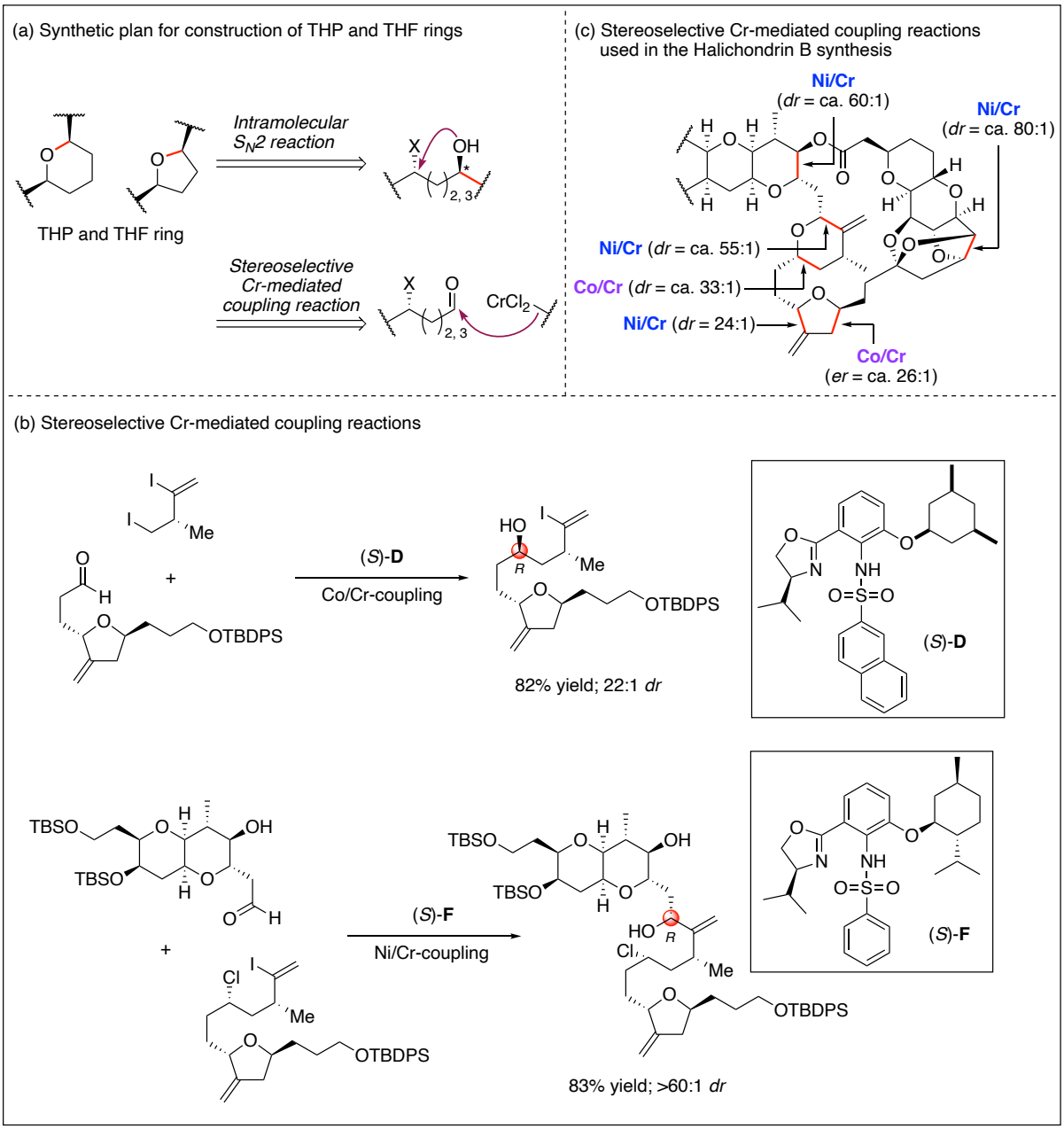


Figure 2. Synthesis of halichondrin B by Kishi and colleagues

It is also important to note that a chiral compound may have different effects on the human body depending on its absolute stereochemistry. For example, human perceives the (*S*)-isomer of limonene as a lemon scent and the (*R*)-isomer as an orange scent (**Figure 3**). Because the olfactory receptor of human clearly distinguishes these two enantiomers, people can recognize the difference of scent.

Figure 3. Structure of limonene and difference of scent

Thalidomide is asedative-hypnotic drug developed by Grünenthal of West Germany (**Figure 4**). At the time, it was manufactured as a racemic mixture and used all over the world. However, it was reported one after another that severe teratogenicity were shown in the limbs of the fetus born from the pregnant woman who took thalidomide. Subsequent investigations revealed that (*R*)-thalidomide has a hypnotic effect, whereas (*S*)-thalidomide has a teratogenic effect.[5] This incident taught the represented importance of selective synthesis of one enantiomer.

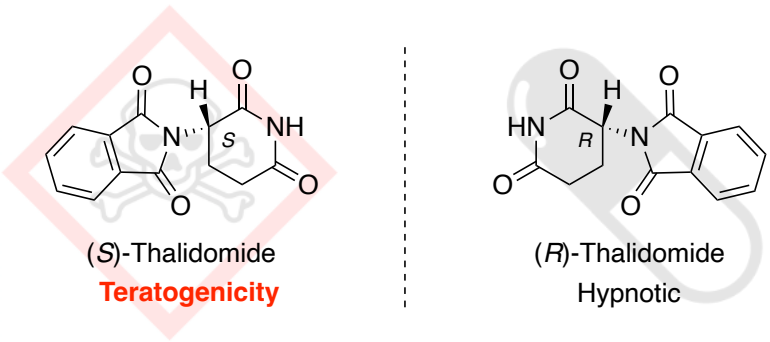


Figure 4. Structure of thalidomide and difference of medicinal effect

1-2. Drugs and natural compounds containing unnatural amino acid structure

Peptides are currently one of the important class of drugs used in all over the world. The number of approvals is increasing year by year, and its importance is increasing.[6] Peptide is a compound which is constructed by several amino acids via amide bond, and many of them like hormones and neurotransmitters play as the important physiological role in the body. Typical examples include insulin that regulates blood glucose levels and endorphins that have an analgesic effect.

In general, a peptide is difficult to be administered orally because it is degraded quickly by digestive enzymes. However, cyclosporine,[7] which is known as the immunosuppressive agent, can be administered orally (**Figure 5**). Cyclosporine is a cyclic peptide consisting of natural and unnatural amino acids such as *N*-methyl amino acids and D-amino acids, which are not found in ordinary proteins. Because of this structure, cyclosporine is difficult to be digested by enzymes and has high digestive stability. In addition, it is considered to have good membrane permeability because its lipophilicity is increased by the *N*-methyl group.

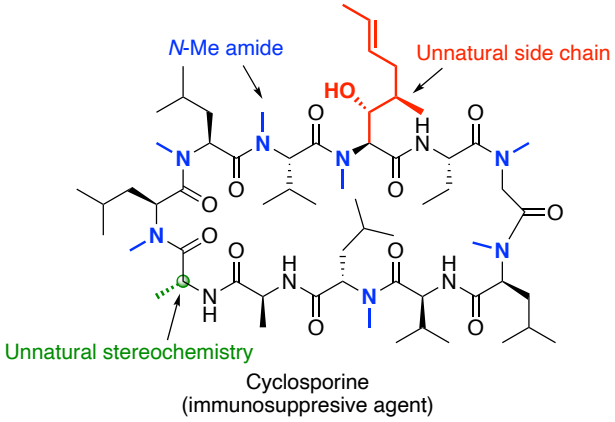


Figure 5. Structure of cyclosporine

Unnatural amino acid residues can also be found in the structure of various pharmaceuticals (**Figure 6**).[8] This moiety is a useful for the addition of new function to drug. However, it is difficult to obtain these compounds from the nature, so stable supply by chemical synthesis is indispensable.

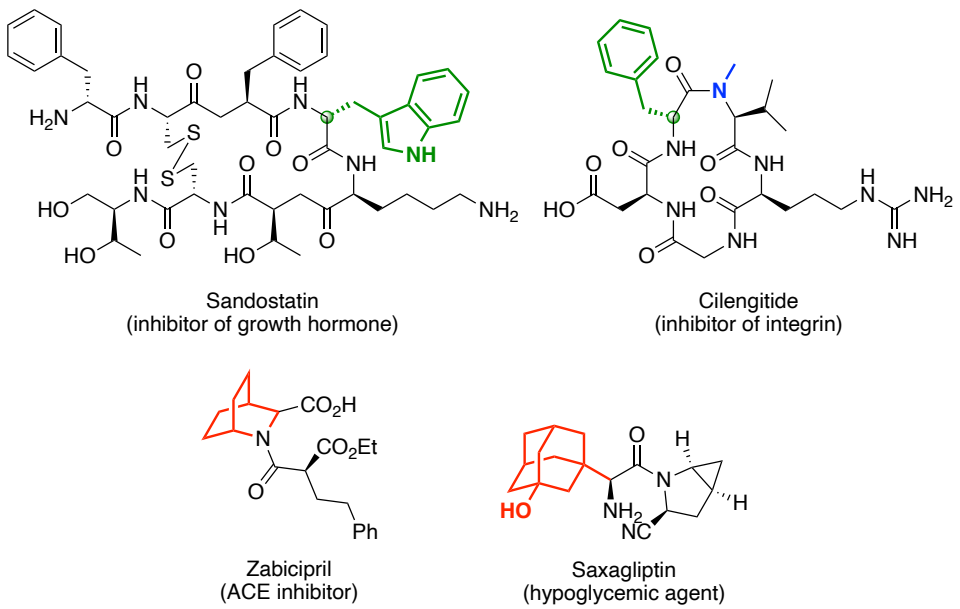


Figure 6. Representative drugs containing unnatural amino acid structure

Among them, the β-hydroxy-α,α-disubstituted α-amino acid is a very advanced unnatural amino acid, and it is contained in attractive substances with biological activity (**Figure 7**). In general, with the difference of stereochemistry, biological activity is changed. Therefore, to conduct the structure-activity relationship studies based on the difference of stereochemistry, development of methods for stereodivergent synthesis of stereoisomer is needed.

Due to its complicated structure such as nitrogen-containing tetrasubstituted carbon and contiguous stereogenic centers, however, the development of a method for efficiently synthesizing the desired stereochemistry is one of the difficult problems in the current organic chemistry.

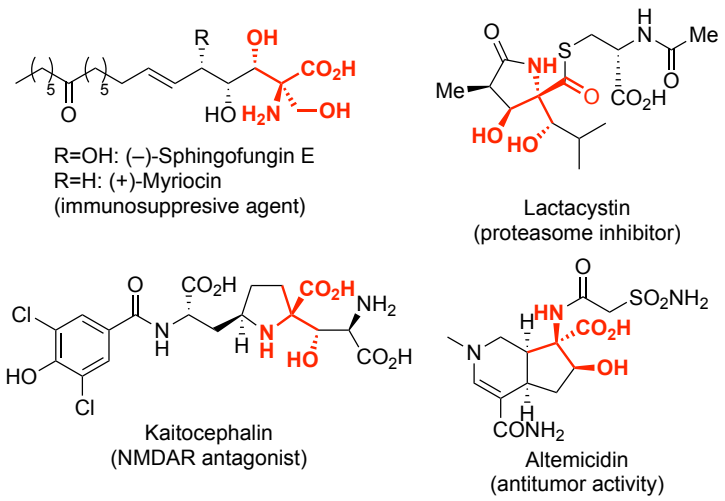


Figure 7. β-hydroxy-α,α-disubstituted α-amino acid as a structural motif found in biologically active compounds.

Figure 8 shows the examples of the synthetic methods for construction of β-hydroxy-α,α-disubstituted α-amino acid structures in the natural products. By using these synthetic methods, the desired stereochemistry could be constructed with high stereoselectivity. For example, diastereoselective aldol reaction in the synthesis of lactacystine,[9] Hatakeyama epoxide opening reaction and diastereoselective 1,2-addition reaction in the synthesis of sphingofungin E,[10] diastereoselective Diels–Alder reaction in the synthesis of altemicidin,[11] and diastereoselective Strecker reaction and the diastereoselective aldol reaction in the synthesis of kaitocephalin.[12]

Although such compounds could be synthesized stereoselectively, these methodologies were developed only to construct the stereochemistry corresponding with natural product. It is difficult to apply these methodologies to synthesize stereoisomers of natural products. Therefore, it is strongly needed to develop the methodology for stereoselective construction of various stereoisomers.

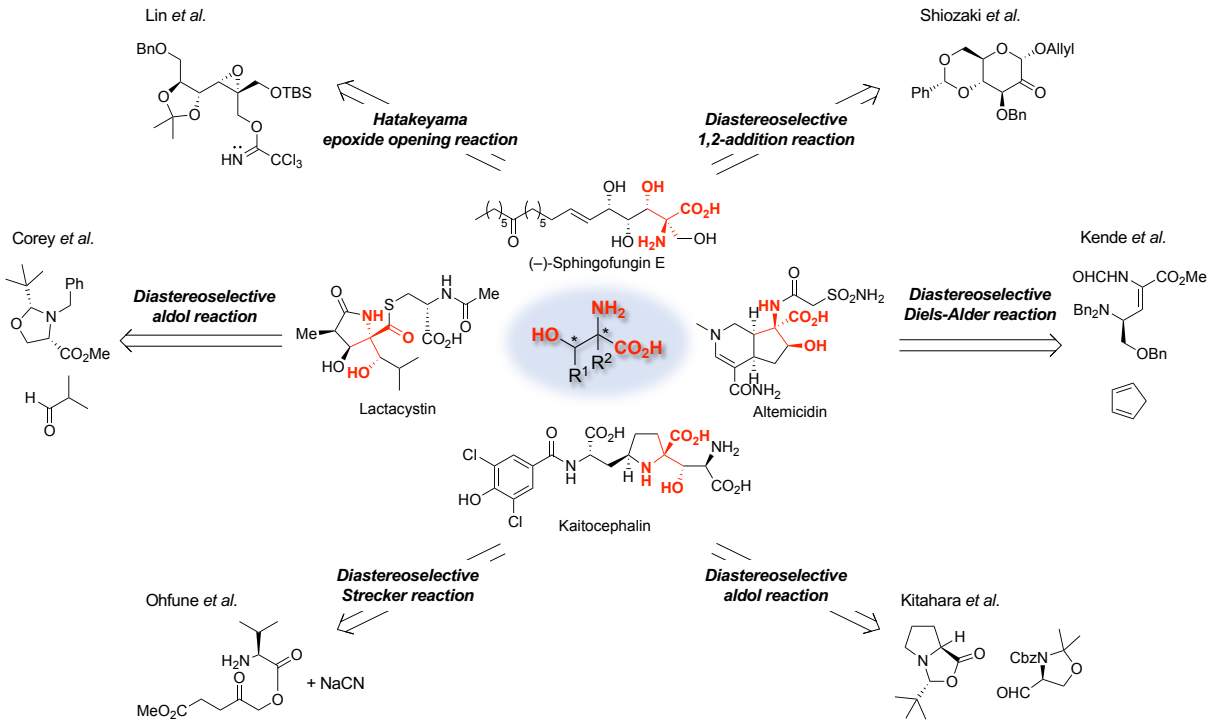


Figure 8. Example of synthetic methods focused on the construction of β-hydroxy-α,α-disubstituted α-amino acid structure

1-3. Aiming to develop stereoselective synthesis methods for β-hydroxy-α,α-disubstituted α-amino acid structures

With the aim of establishing a new synthetic method for construction of β-hydroxy-α,α-disubstituted α-amino acid structures that express useful functions contained in the partial structure of natural products, the author has developed the stereoselective aldol-type reaction shown in Figure 9.

The aldol-type reaction is a useful reaction for the formation of C–C bond. It has high atomic efficiency, and depending on the type of nucleophile and electrophile, it is possible to construct an asymmetric nitrogen-containing tetrasubstituted carbon divergently. For example, when alkyl group (= R^3)-containing substrate was used as the nucleophile, the β,β-disubstituted β-amino alcohol structure could be constructed, and when ester group (= R^3)-containing substrate was used as the nucleophile, the β-hydroxy α,α-disubstituted α-amino acid structure could be constructed.

In this paper, author describes the development of two types of aldol reactions, which are substrate-control reaction and reagent-control reaction, for construction of nitrogen-containing tetrasubstituted carbon. First, in chapter 2 and 3, stereoselective synthesis of manzadidin A, B and C is described. In this synthesis, conversion of chiral nitroalkanes into Henry adducts diastereodivergently proceeded by using the non-covalent interactions such as hydrogen bonding and chelation. In chapter 4, enantioselective aldol reaction of α-imino esters with glyoxylates is described. In this reaction, by using the Co-pybox ligand catalyst, desired aldol products were obtained in good yield and enantioselectivity. After the hydrolysis of imine moiety under acidic conditions, the resultant amino group was protected by $(Boc)_2O$ to give β-hydroxy-α,α-disubstituted α-amino acid derivatives.

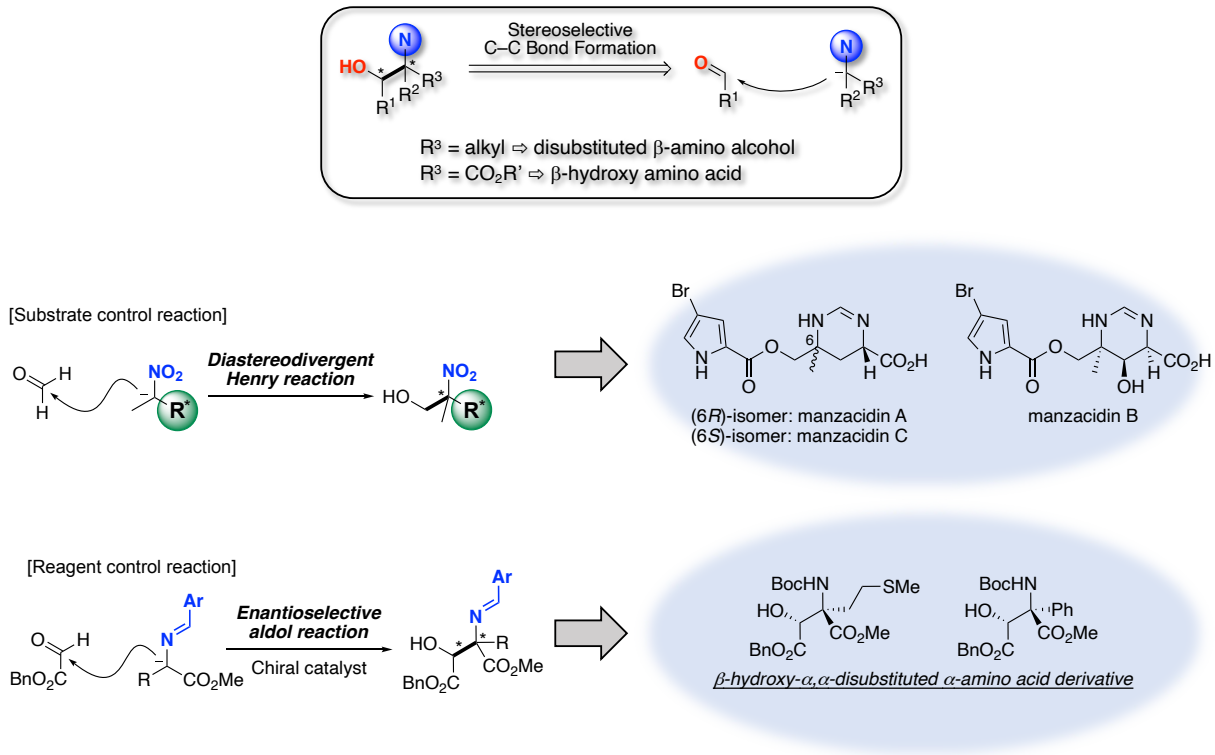


Figure 9. Current strategy

1-4. Synthetic study of manzacidin A–C via diastereoselective Henry reaction

The author focused on the synthesis of manzacidins A–C via diastereoselective Henry reaction as a key reaction for construction of the nitrogen-containing tetrasubstituted carbon. Manzacidin A–C was isolated from Okinawan sponge *Hymeniacidon sp.* by Kobayashi's group of Hokkaido university in 1991 (**Figure 10**).[13] The structural features of manzacidins A−C are a bromopyrrole moiety and a highly substituted tetrahydropyrimidine core. Moreover, manzacidin B has an additional hydroxy group at the C5 position as a part of three contiguous stereogenic centers. Because of their unique structure and pharmacological profile as in a class of bromopyrrole alkaloids, manzacidins are attractive target molecules for organic synthesis.

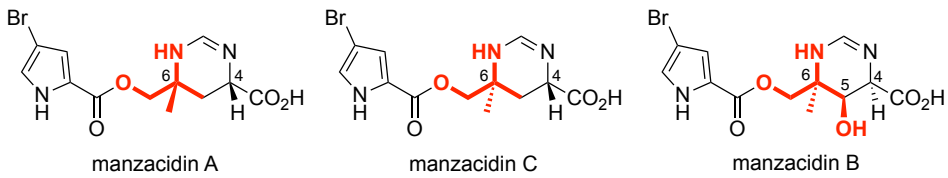
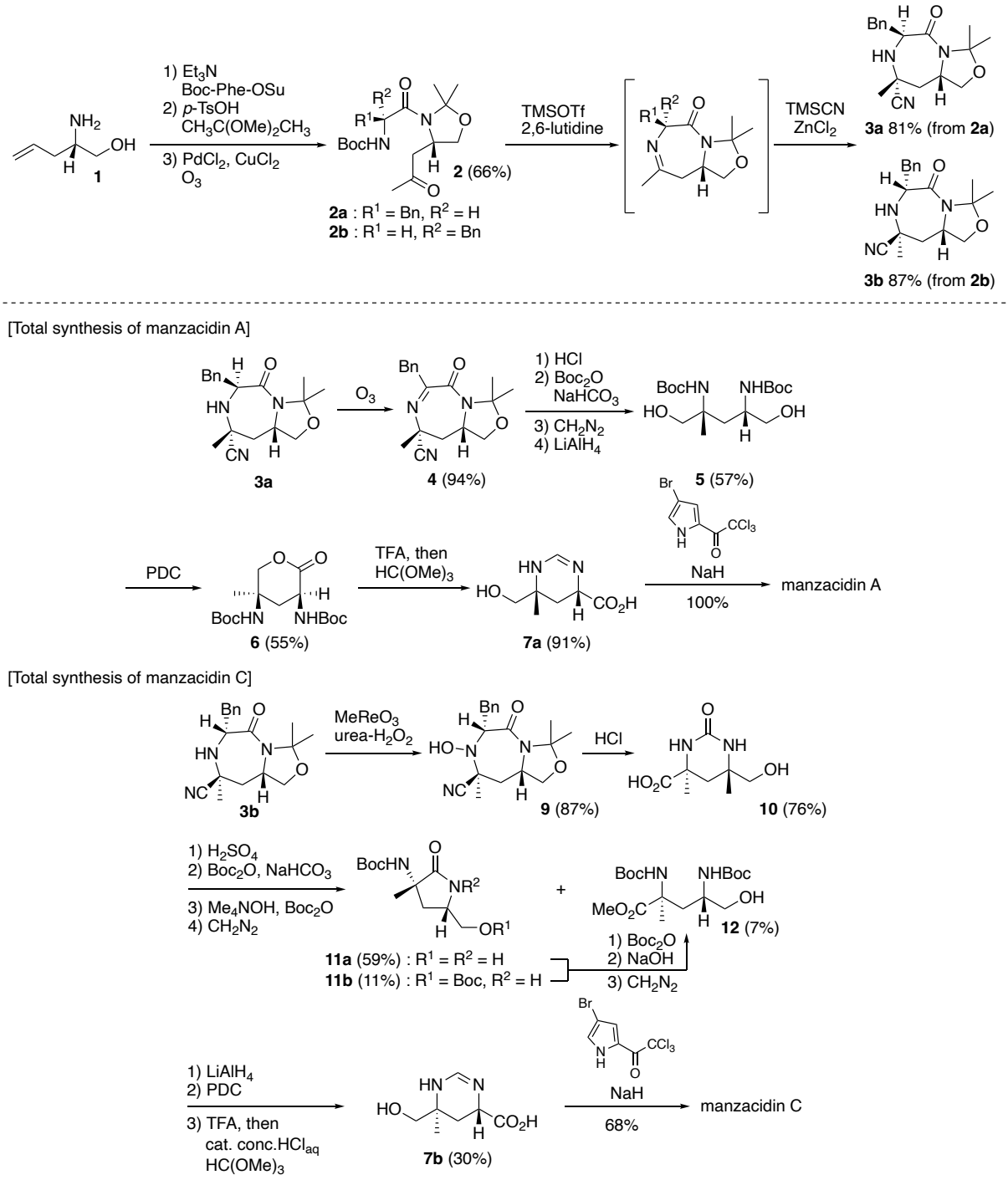


Figure 10. Structure of manzacidin A, C and B

1-4-1. Previous work: total synthesis of manzacidin A and C by Ohfune's group

In 2000, Ohfune and colleagues reported the first total synthesis of manzacidin A and C.[14] Their synthetic route of manzacidin A and C was shown in Scheme 3. Amidation and acetonide protection of allylglycinol **1**, followed by the Wacker oxidation[15] gave compound **2**. In the key reaction of diastereoselective Strecker reaction,[16] benzyl group controlled the attacking direction of cyanide anion and gave the **3a** and **3b** in good yield and stereoselectivity.

The resulting **3a** and **3b** were oxidatively treated and then hydrolyzed to remove the chiral auxiliary groups. Lactone formation followed by removal of the Boc group and construction of a tetrahydropyrimidine ring gave compounds **7a** and **7b** with the stereochemistry of manzacidin A and C. Finally, addition of the bromopyrrole moiety completed the synthesis of manzacidin A and manzacidin C.

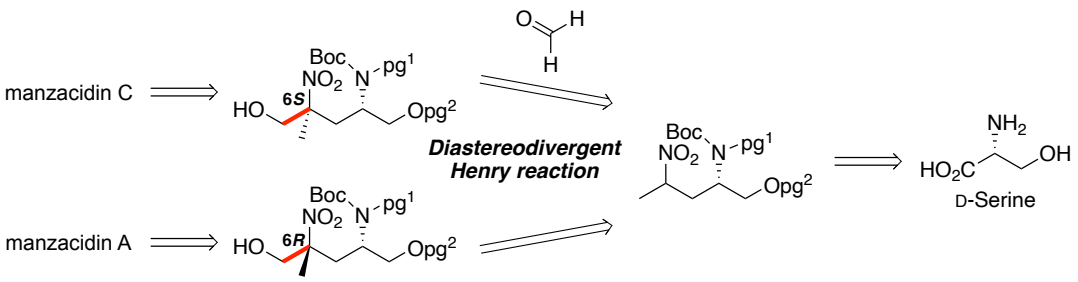


Scheme 3. Total synthesis of manzacidin A and C by Ohfune and colleagues

1-4-2. Total synthesis of manzacidin A and C by the author

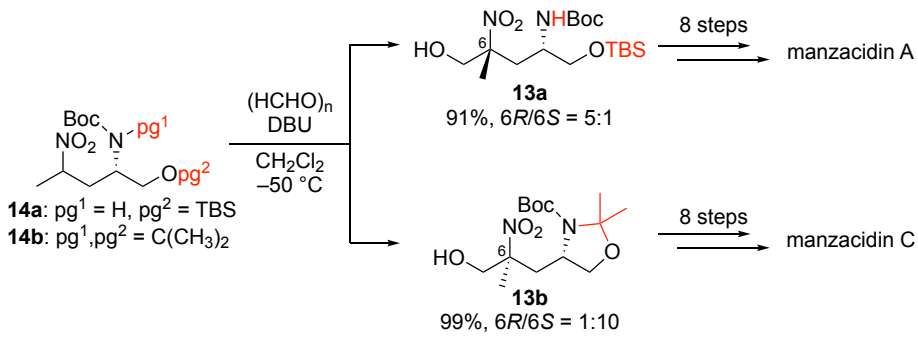
As mentioned above, Ofune's group constructed the desired stereochemistry by introducing asymmetric auxiliary groups. On the other hand, the author considered that it is possible to construct stereochemistry corresponding to manzacydin A and C by using the stereochemistry contained in the substrates.

In other words, the author assumed that the diastereodivergent Henry reaction with formaldehyde using compound **14**, which can be easily synthesized from D-serine as a substrate, would construct the (6*S*)-**13** and (6*S*)-**13** diastereomers (Scheme 4).[17] At this time, the author considered that the diastereoselectivity could be controlled by the protecting group of compound **14**.



Scheme 4. Plan for the synthesis of manzacidin A and C

As a result, two diastereomers **13a** and **13b** could be selectively synthesized under the same conditions by changing the protecting group of the substrate **14** (**Scheme 5**). The detail will be described in later section, but this is thought to be due to the change of conformation in the transition state depending on the presence or absence of intramolecular hydrogen bonds.



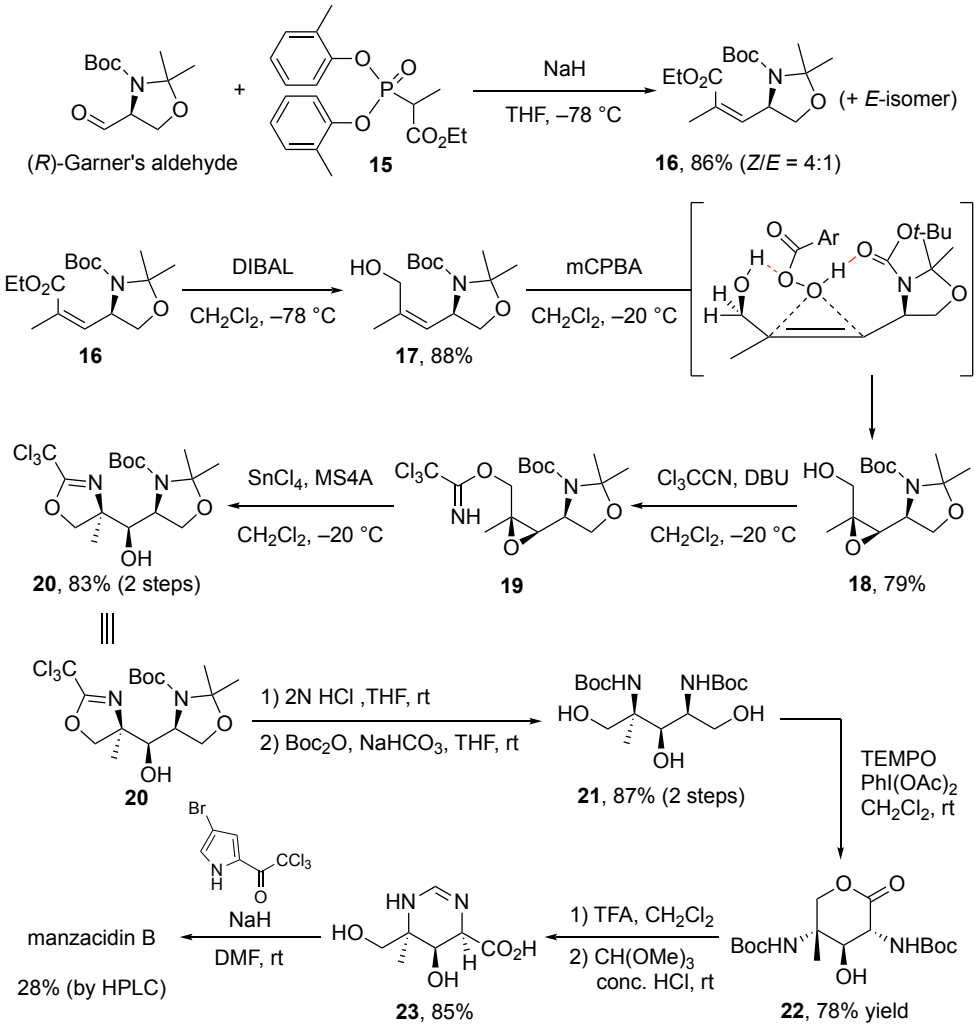
Scheme 5. Diastereodivergent Henry reaction for construction of manzacidin A and C

1-4-3. Previous work: total synthesis of manzacidin B by Mohapatra's group

In 2012, Mohapatra and colleagues reported the revision of the absolute configuration of manzacidin B.[18] To address the structural ambiguities of manzacidin B, they chose to explore a stereoselective syntheses of manzacidin B and its congeners to determine the relative configuration at each step and to confirm the absolute configuration of manzacidin B.

As shown in Scheme 6, their total synthesis of manzacidin B commenced with the Horner–Wadsworth–Emmons reaction using (*R*)-Garner's aldehyde[19] and phosphonate **15** which was known as an Ando's reagent[20] (85% yield, *Z*/*E* = 4:1). The synthesized unsaturated ester **16** was reduced to allyl alcohol **17** by DIBAL (89% yield). Next, chelation-controlled epoxidation[21] using mCPBA afforded *syn*-epoxy alcohol **18** as a single isomer. In this transition state assemblies, because of the hydrogen bonding between the allyl alcohol **17** and the carbamate carbonyl in the substrate with perbenzoic acid moiety, mCPBA was approached from the upper side of allylic alcohol moiety and afford the *syn*-epoxy alcohol. Epoxy alcohol **18** was converted to imidate **19** using trichloroacetonitrile and epoxide opening reaction with $SnCl_4$ (Hatakeyama's protocol)[22] furnishes the desired oxazoline derivative **20** as a single product (83% in 2 steps).

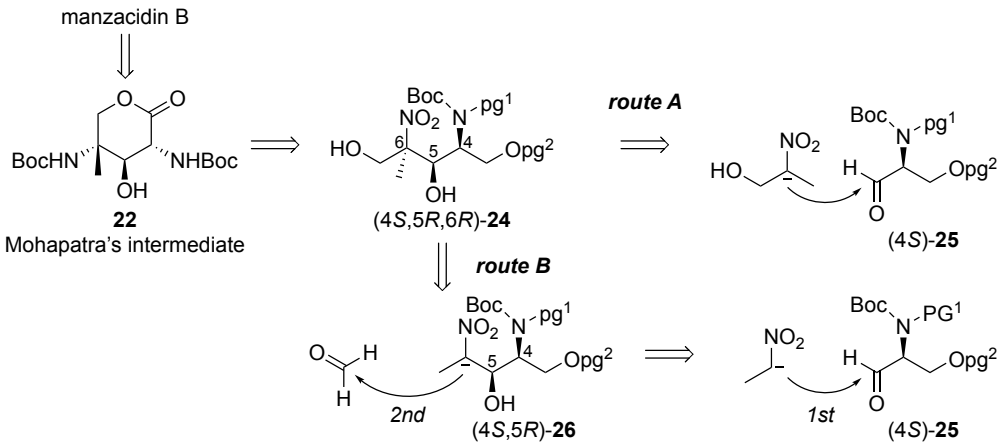
As shown in scheme 7, hydrolysis of oxazoline **20** and acetonide moieties followed by Boc-protection afforded triol **21** (87% in 2 steps). Selective oxidation of the sterically less hindered primary alcohol with catalytic amount of TEMPO[23] gave lactone **22** in 78% yield. Removal of Boc-protection and formation of tetrahydropyrimidine ring gave hydroxy carboxylic acid **23** in 85% yield (2 steps). Finally, treatment of hydroxy carboxylic acid **23** with NaH and 4-bromo-2-trichloroacetylpyrrole[24] at ambient temperature afforded manzacidin B in 28% yield after purification by HPLC.



Scheme 6. Synthesis of manzacidin B by Mohapatra and colleagues

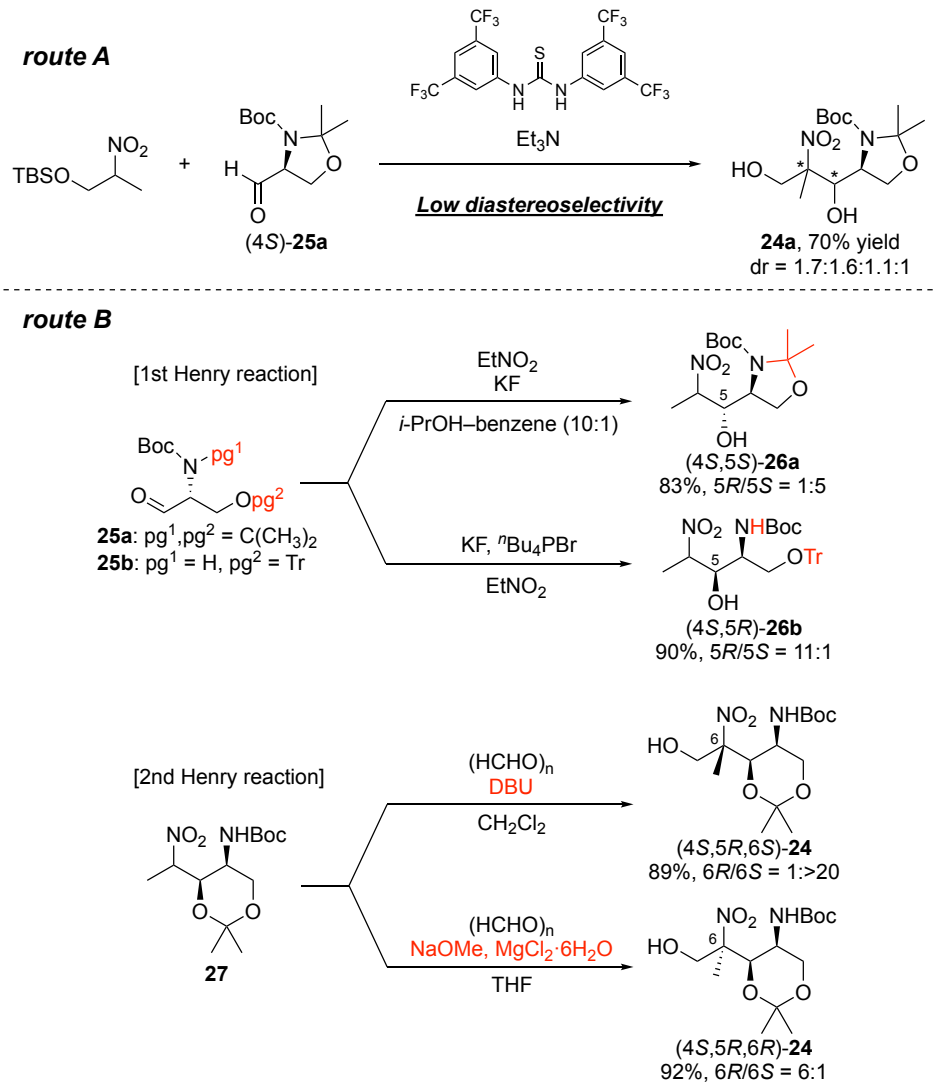
1-4-4. Formal total synthesis of manzacidin B by the author

Scheme 8 shows our plan for the synthesis of manzacidin B. The author set Mohapatra's intermediate **22**[18] as the target compound. The author considered that the two methods for construction of nitrogen-containing three contiguous asymmetric carbon structure in manzacidin B. In route A, (4*S*,5*R*,6*R*)-**24** would be synthesized by the coupling of 1-hydroxy-2-nitropropane and chiral aldehyde (4*S*)-**25**, constructing both C-5 and C-6 stereogenic center in a single Henry reaction. Alternatively, in route B, (4*S*,5*R*,6*R*)-**24** would also be synthesized through sequential Henry reactions connecting two aldehydes of formaldehyde and chiral aldehyde (4*S*)-**25** with nitroethane. In this route, the stereochemistry of C5 and C6 could be stepwisely controlled.



Scheme 7. Retrosynthesis of manzacidin B

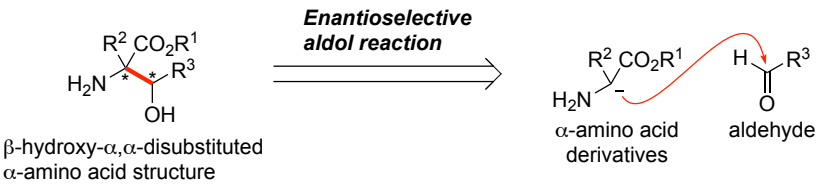
Based on this synthetic plan, the author investigated the route A and route B (**Scheme 9**). Despite the intensive effect for investigation for the construction of nitrogen-containing three contiguous asymmetric carbon structure in manzacidin B, diastereoselective construction of desired structure was found to be difficult by single Henry reaction (**route A**). On the other hand, sequential Henry reaction could be successfully synthesized the desired stereochemical configuration (route B). During 1st and 2nd Henry reactions, the stereochemistry of C5 and C6 could be controlled diastereodivergently by protecting groups and reaction conditions. Therefore, the present method could allow us to synthesize not only the natural isomer but also C5 and C6 diastereomers of manzacidin B, diastereodivergently.



Scheme 8. Investigation of key Henry reactions

1-5. Enantioselective aldol reaction of α-imino ester with glyoxylate

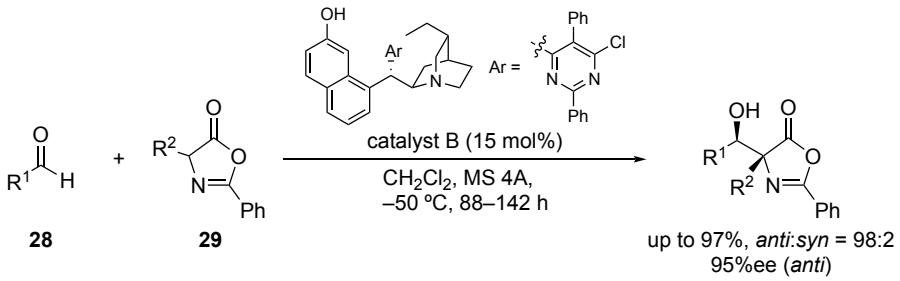
Chapter 4 described the enantioselective aldol reaction of α-imino esters with glyoxylates using the chiral catalyst (**Scheme 10**). In the manzacidin B synthesis, the β-hydroxy-α,α-disubstituted α-amino acid structure was difficult to construct diastereoselectively in one step, and the substrate generality of this reaction was limited (**Scheme 9**, **route A**). On the other hand, if the catalytic enantioselective aldol reaction of α-imino esters with glyoxylates could be developed, it would establish a general and stereoselective synthetic method for nonnatural amino acid structures compared to diastereoselective reactions controlled by substrate chirality.



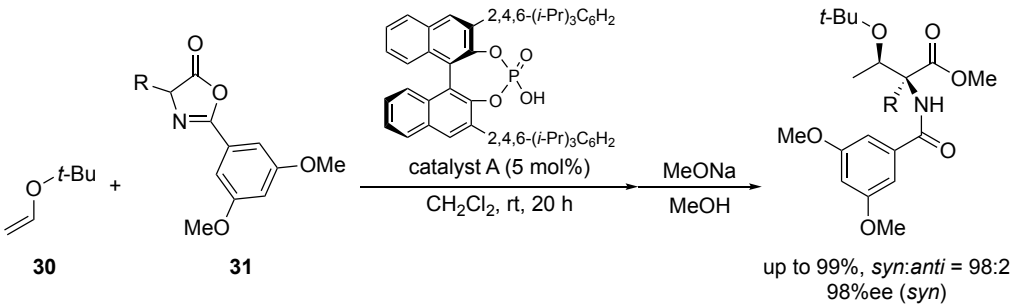
Scheme 9. Aldol-type reaction for the asymmetric construction of β-hydroxy-α,α-disubstituted α-amino acid structures

1-5-1. Previous work: Enantioselective aldol reaction of azlactone

Recently, Deng and colleagues reported the chiral Brønsted base-catalyzed enantioselective direct aldol reaction of azlactones **28** with aliphatic aldehydes **29** to construct the β-hydroxy-α,α-disubstituted α-amino acid structure (**Scheme 11**).[25] Terada and colleagues also reported the chiral phosphoric acid-catalyzed enantioselective direct aldol-type reaction of azlactones **31** with vinyl ethers **30** (**Scheme 12**).[26] However, as described above, the reaction is limited to the use of azlactone as the substrate. Thus, alternative methodologies are still needed.



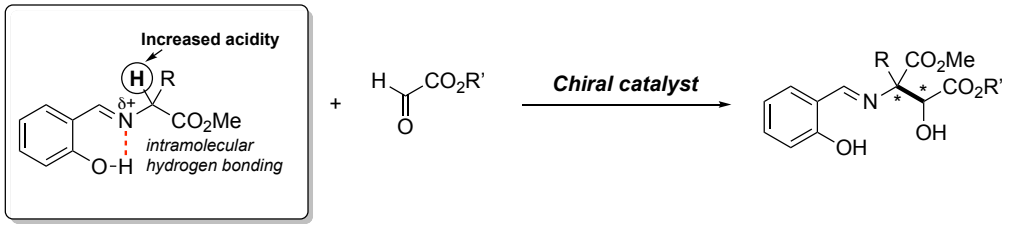
Scheme 10. Asymmetric direct aldol reaction of α-alkyl azlactone by Deng and colleagues



Scheme 11. Enantioselective direct aldol-type reaction of azlactone by Terada and colleagues

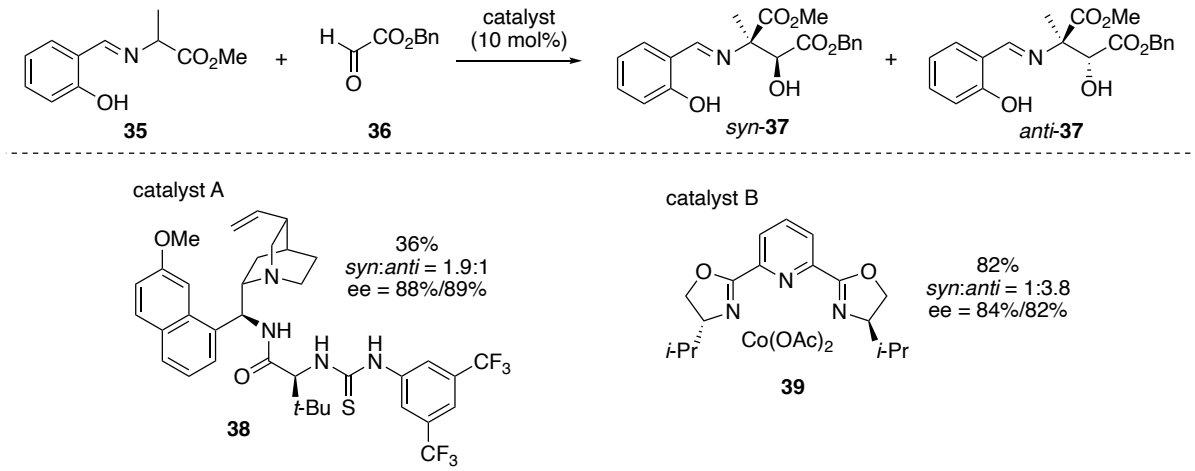
1-5-2. Enantioselective aldol reaction of α-imino ester with glyoxylate using chiral catalyst

The author describes the asymmetric catalysis for the direct aldol reaction of α-substituted α-imino esters **32** with glyoxylate esters **33** to construct the chiral β-hydroxy-α,α-disubstituted α-amino acid structure **34** (**Scheme 13**).[27] In this aldol reaction, the author chose salicylaldehyde-derived α-imino esters **32** as substrates since they are known to be activated via intramolecular hydrogen bonding.[28]



Scheme 12. Catalytic construction of β-hydroxy-α,α-disubstituted α-amino acid structures

After several effort for the investigation of stereoselective aldol reaction of α-imino ester **35** with benzyl glyoxylate **36** using chiral catalyst (**Scheme 14**). The target product could be obtained with a high enantiomeric excess by using an acid-base cooperative organocatalyst **A**, but the yield was low. On the other hand, it was found that the yield was improved when the reaction is carried out using the chiral metal complex. Moreover, when the metal species and ligands used were investigated, it was found that the combination of $Co(OAc)_2$-pybox ligand **B** gave the desired product in good yield and enantioselectivety



Scheme 13. Investigation of catalytic activity for aldol reaction of α-imino ester **35** with benzyl glyoxylate **36**

1-6. Conclusion

In conclusion, the author focused on the construction of unnatural amino acid structures which have nitrogen-containing tetrasubstituted carbon in this research. At the first and second topics, the author developed the diastereodivergent Henry reaction for construction of nitrogen containing tetrasubstituted carbon using non-covalent interactions such as hydrogen-bonding and chelation. Indeed, by using this idea, the author achieved the total synthesis of manzacidin A and C, and formal total synthesis of manzacidin B. At the third topic, the author developed the enantioselective aldol reaction of α-imino ester with glyoxylate. Although the acid-base cooperative catalyst was used, aldol product was obtained in moderate yield and good enantioselectivity, the use of $Co(OAc)_2$-pybox ligand catalysis system gave the aldol product in good yield and enantioselectivity.

1-7. Reference

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Chapter 2. Total synthesis of manzacidin A and C via diastereodivergent Henry reaction

2-1. Abstract

β,β-Disubstituted β-amino alcohol structures has been synthesized in a diastereodivergent manner from chiral secondary nitroalkanes as starting materials. In this key Henry reaction, the use of different protecting groups resulted in the diastereoselective construction of the tetrasubstituted carbon stereocenter with different configuration. Based on this methodology, a total synthesis of manzacidins A and C has been achieved.

2-2. Introduction

β,β-Disubstituted β-amino alcohols are found in many natural and synthetic products with significant biological activities. For example, manzacidins A and C are a family of bromopyrrole alkaloids that were isolated from the Okinawan sponge *Hymeniacidon* sp. in 1991 (**Figure 1**).[1] They consist of a bromopyrrole carboxylic acid and a tetrahydropyrimidine ring possessing the nitrogen-containing tetrasubstituted carbon. Kaitocephalin was isolated from *Eupenicillium shearii* PF1191 as a glutamate receptor antagonist.[2] This compound can be also regarded as an β,β-disubstituted β-amino carboxylic acid. For the chemical synthesis of β,β-disubstituted β-amino alcohols, the methods for the stereoselective construction of tetrasubstituted carbon bearing a nitrogen functional group play a key role. Although several methods have been reported for the stereoselective construction of such a structural motif, the development of more efficient methods is still one of the most important topics in synthetic chemistry.[3]

In this study on the development of new efficient methods for the stereoselective construction of tetrasubstituted carbons bearing a nitrogen functional group, the author focused on the synthesis of manzacidins A and C. These compounds have attracted significant attention about new synthetic methods for the stereoselective construction of β,β-disubstituted β-amino alcohol structures.[4]

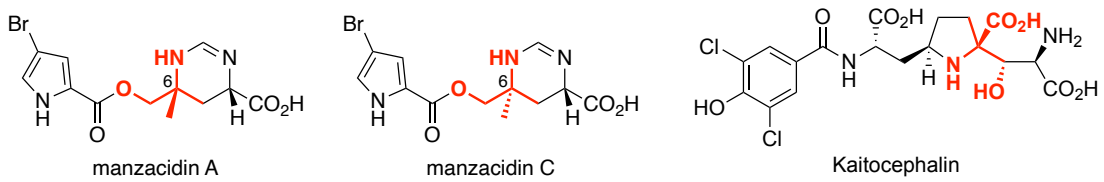
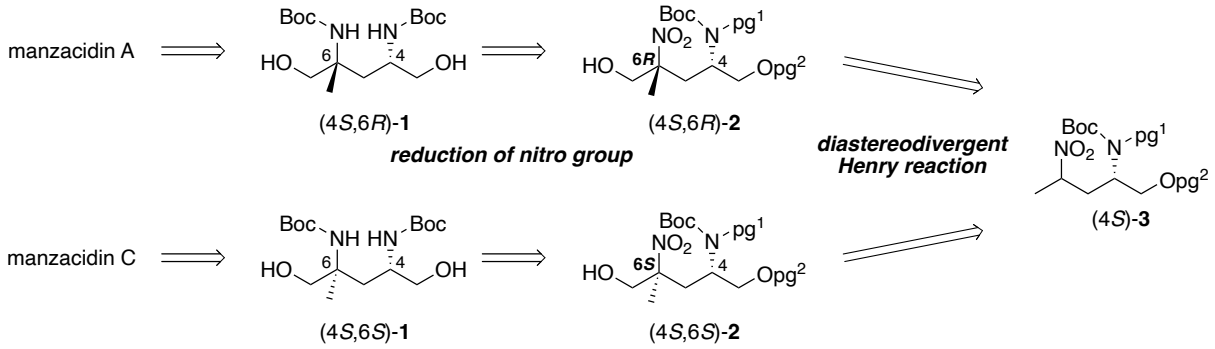


Figure 1. Natural compounds bearing a β,β-disubstituted β-amino alcohol structure

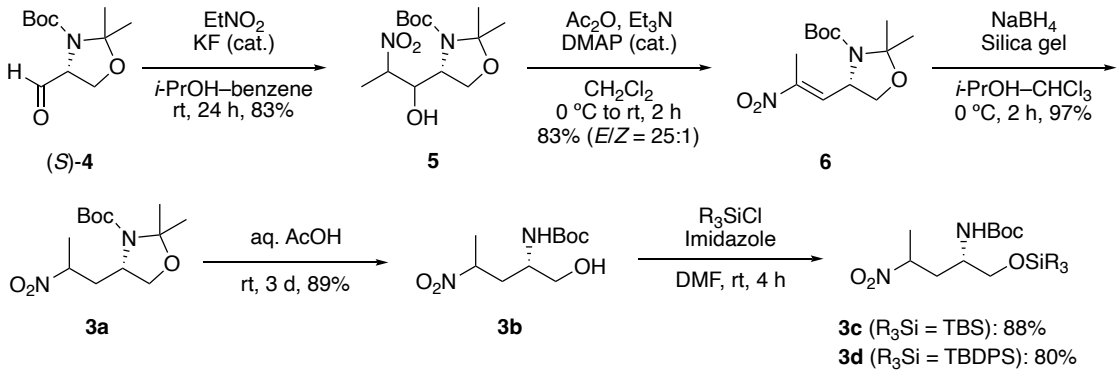
2-3. Results and discussions

Scheme 1 indicates the plan for the synthesis of manzacidins A and C is based on diastereoselective Henry reaction.[5] The author chose *N*,*N'*-di-Boc-protected diamines **1**, key intermediates for the Ohfune's synthesis of manzacidins A and C,[6] as the target intermediates for our synthesis. The author envisioned that the β,β-disubstituted β-amino alcohol structure in each diastereomer of **1** could be constructed from the same universal intermediates (4*S*)-**3** via diastereodivergent Henry reaction with formaldehyde followed by reduction of the nitro group in the Henry products **2**.



Scheme 1. Plan for the synthesis of manzacidin A and C

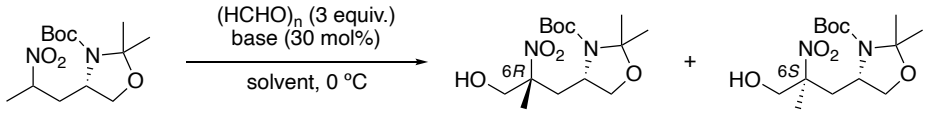
The author began our study with the synthesis of chiral nitroalkanes (4*S*)-**3**, which are substrates for the key diastereoselective Henry reaction, from (*R*)-Garner's aldehyde **4**[7] (**Scheme 2**). Potassium fluoride-catalyzed Henry reaction[8] of (*R*)-**4**, which was easily prepared from D-serine following the procedure in the literature,[7] with nitroethane gave a diastereomeric mixture of nitroalcohols **5** in 83% yield. Dehydration of **5** with Ac_2O and Et_3N in the presence of a catalytic amount of DMAP gave nitroalkene **6** in 83% yield with a high geometric isomer ratio (*E*/*Z*=25:1).[8] Reduction of **6** under conventional conditions ($NaBH_4$ in EtOH) gave the desired chiral nitroalkane **3a** in poor yield. On the other hand, when the same reaction was conducted in the presence of silica gel,[9] **3a** was obtained in 97% yield. Nitroalkane **3b** was prepared in 89% yield by removal of the acetonide protecting group of **3a** under acidic conditions. TBS- and TBDPS-protected substrates **3c** and **3d** were also prepared from **3b** in respective yields of 88 and 80% by silylation of the primary hydroxy group.



Scheme 2. Synthesis of chiral nitroalkane **3**

With chiral nitroalkanes (4*S*)-**3** in hand, the author investigated the diastereoselective Henry reaction of (4*S*)-**3**. In the initial study, the reaction of **3a** was conducted with paraformaldehyde (3 equiv.) in the presence of a base (30 mol %) (**Table 1**). The diastereomeric ratio of Henry product **7a** was evaluated by ^{1}H NMR analysis because these two diastereomers could not be separated by column chromatography on silica gel. An investigation of base catalysts showed that the use of weak bases such as triethylamine and potassium fluoride gave **7a** in poor yields (entries 1 and 2). On the other hand, the use of rather strong base catalysts gave **7a** in high yields (entries 3–5). When the reaction was conducted in the presence of *t*-BuOK, Henry product **7a** was obtained in 87% yield as a 1:1 diastereomeric mixture (entry 3). To our delight, the investigation of relatively strong amine bases showed that the use of 1,1,3,3-tetramethylguanidine (TMG) or DBU, which are widely used as catalysts in the Henry reaction, gave (6*S*)-**7a** as a major diastereomer with moderate diastereoselectivity (6*R*/6*S*=1:3 to 1:4) (entries 4 and 5). The stereochemistry of (6*S*)-**7a** corresponds to that of manzacidin C. An examination of solvents for the DBU-promoted reaction of **3a** showed that the use of acetonitrile or dichloromethane improved the reactivity (entries 7 and 8). The use of two equivalents of DBU in dichloromethane also improved the reactivity (entry 9). Thus, when the reaction of **3a** was conducted at –50 ºC, the diastereoselelctivity was improved to 6*R*/6*S* = 1:10 (entry 10).

Table 1. Diastereoelective Henry reaction of chiral nitroalkane **3a**



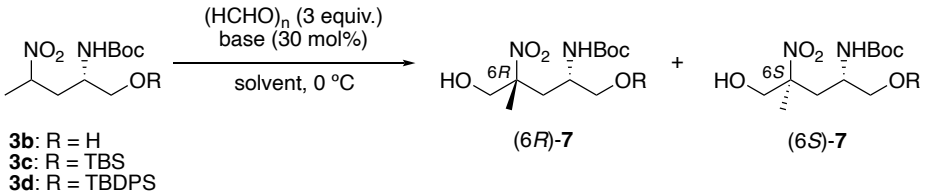
3a (6*R*)-**7a** (6*S*)-**7a**

entry	base	solvent	t [h]	yield [%][a]	6*R*/6*S*[b]
1[c]	Et_3N	THF	24	7	1:3
2[c]	KF	THF	24	3	1:2
3	*t*-BuOK	THF	20	87	1:1
4	TMG[d]	THF	19	92	1:3
5	DBU	THF	4	91	1:4
6	DBU	toluene	9	87	1:3
7	DBU	CH_3CN	0.5	98	1:3
8	DBU	CH_2Cl_2	1.5	99	1:4
9[e]	DBU	CH_2Cl_2	0.3	96	1:5
10[e]	DBU	CH_2Cl_2	24	99	1:10

[a]Isolated yield. [b]Evaluated by ^{1}H NMR analysis. [c]The reaction was conducted at ambient temperature. [d]TMG = 1,1,3,3-tetramedhylguanidine. [e]The reaction was conducted in the presence of two equivalents of DBU. [f]The reaction was conducted at –50 ºC.

In sharp contrast, the diastereoselective Henry reaction of **3b**–**d** bearing acyclic protecting groups preferentially gave (6*R*)-isomers of the corresponding Henry products **7b**–**d** as the major diastereomers (**Table 2**). When the reactions were conducted in the presence of DBU (30 mol %) in toluene at 0 ºC, the diastereoselectivity was moderate (6*R*/6*S* = 1.3 :1 to 1.9 :1), albeit **7b**–**d** were obtained in high yields (entries 1–3). The stereochemistry of (6*R*)-**7** corresponded to that of manzacidin A. TBS-protected **7c** was obtained with better diastereoselectivity (6*R*/6*S* = 1.9 :1) than **7b** or **7d**. An examination of solvents for the reaction of **3c** showed that the use of CH_2Cl_2 slightly improved both the reactivity and the diastereoselectivity (6*R*/6*S*= 2.3:1, entry 6). As in the reaction of **3a**, the use of two equivalents of DBU further improved the diastereoselectivity (6*R*/6*S*= 3.1:1, entry 7). When the reaction of **3c** was conducted at –50 ºC, (6*R*)-**7c** was obtained in a diastereomeric ratio of 5:1 (entry 8).

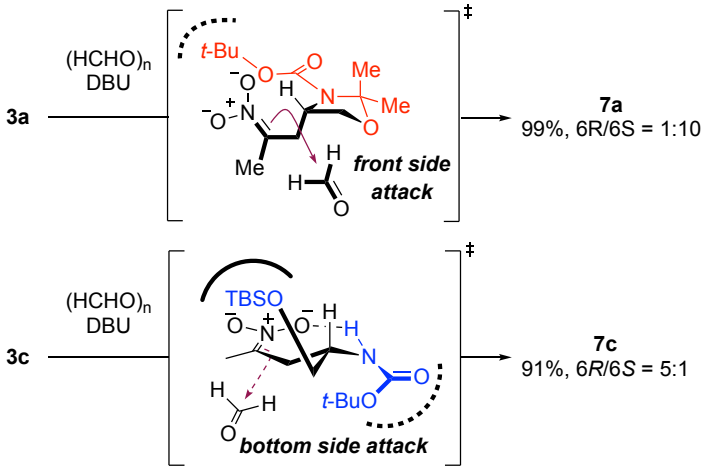
Table 2. Diastereoelective Henry reaction of chiral nitroalkane **3b–d**



entry	**3**	solvent	t [h]	yield [%][a]	6*R*/6*S*[b]
1[c]	**3b**	toluene	6.5	85	1.3:1
2[c]	**3c**	toluene	6	94	1.9:1
3	**3d**	toluene	22	75	1.3:1
4	**3c**	THF	4	91	1.6:1
5	**3c**	CH_3CN	1.5	86	2.2:1
6	**3c**	CH_2Cl_2	1.5	94	2.3:1
7[c]	**3c**	CH_2Cl_2	0.2	92	3:1
8[c,d]	**3c**	CH_2Cl_2	24	91	5:1

[a]Isolated yield. [b]Evaluated by ^{1}H NMR analysis. [c]The reaction was conducted in the presence of two equivalents of DBU. [d]The reaction was conducted at –50 ºC.

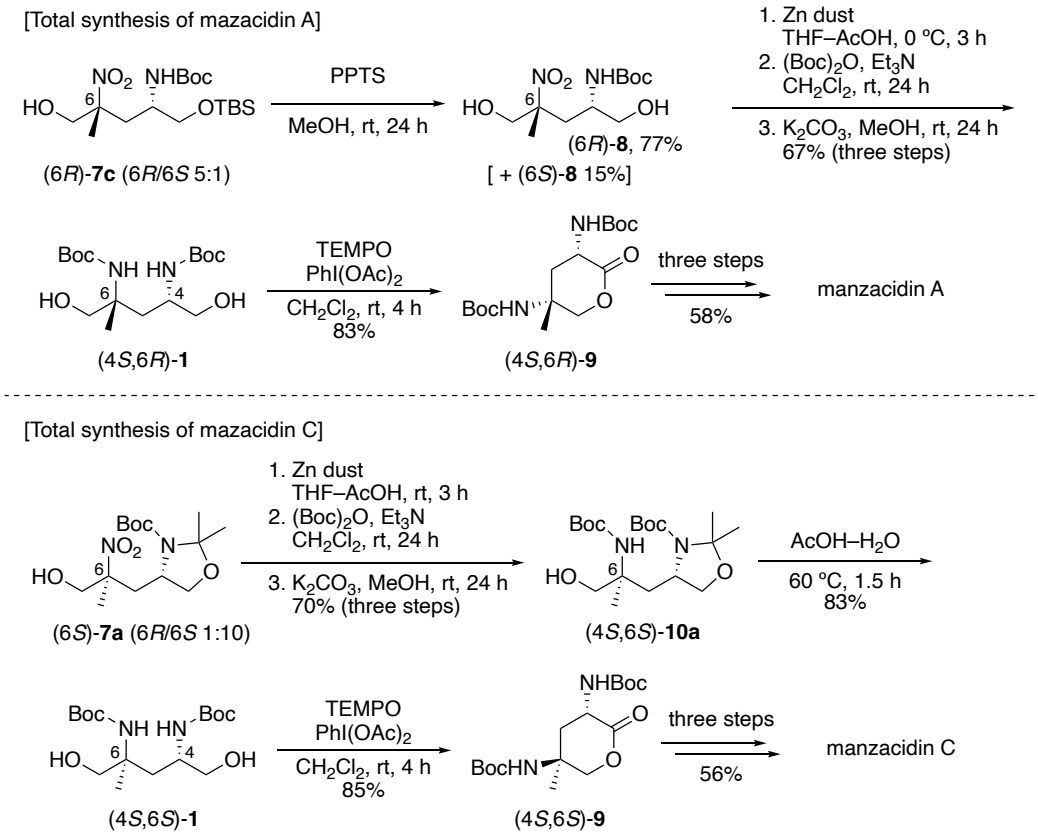
I proposed that this selectivity was explained as shown in scheme 3. In the transition-state assemblies for the reaction of **3a**, the nitronate moiety would be placed far from the sterically hindered *N*-Boc group (upper scheme). The *N*-Boc group would shield the back side of the nitronate moiety. Thus, formaldehyde was considered to approach the nitronate moiety from the *Re* face (front side), avoiding the steric repulsion of the *N*-Boc group. On the other hand, in the transition state assemblies for the reaction of **3c**, the nitronate moiety might interact with the NH group via intramolecular hydrogen bonding (bottom scheme). The *N*-Boc group would shield the back side of the nitronate moiety. In this transition-state assembly, the steric hindrance of the *N*-Boc group might make the TBS group approach the front side. Formaldehyde was considered to approach the nitronate moiety from the *Si* face (back side), thus avoiding the steric repulsion of the TBS group.



Scheme 3. Plausible transition state assemblies of diastereodivergent Henry reaction

With the key synthetic intermediates **7c** and **7a** in hand, the author synthesized manzacidins A and C through diamines **1**, which are the intermediates for Ohfune's synthesis[6] (**Scheme 4**). Removal of the TBS protection from a 5:1 diastereomeric mixture of **7c** using a catalytic amount of PPTS in MeOH gave diols (4*S*,6*R*)-**8** (77 % yield) and (4*S*,6*S*)-**8** (15 % yield). These diastereomers could be separated at this stage by column chromatography on silica gel. Reduction of the nitro group of (4*S*,6*R*)-**8** using an excess amount of Zn dust under acidic conditions[10] followed by Boc protection of the resultant amino group gave the corresponding *N*,*N'*,*O*-tri-Boc-protected product. Methanolysis of the O-Boc group furnished the desired *N*,*N'*-di-Boc-protected diaminodiol (4*S*,6*R*)-**1** in 67% yield (three steps from (6*R*)-**8**). Selective oxidation of the less-hindered hydroxy group of (4*S*,6*R*)-**1** using a catalytic amount of TEMPO with $PhI(OAc)_2$ as the co-oxidant[11] gave lactone (4*S*,6*R*)-**9** in 83% yield. Lactone (4*S*,6*R*)-**9** could be converted to manzacidin A following Ohfune's procedure[6] in 58% yield (three steps from (4*S*,6*R*)-**9**). The spectral data of the synthetically obtained manzacidin A were in good agreement with those reported previously.[6]

Manzacidin C was synthesized by the same procedure as for manzacidin A. Reduction of the nitro group of a 10 :1 diastereomeric mixture of **7a** using an excess amount of Zn dust under acidic conditions[10] followed by Boc protection and methanolysis of the *O*-Boc protection gave the desired *N*,*N'*-di-Boc-protected (4*S*,6*S*)-**10a** in 70% yield (three steps from **7a**). At this stage, (4*S*,6*R*)-isomer could be removed by column chromatography on silica gel. Removal of the acetonide protecting group of (4*S*,6*S*)-**10a** under acidic conditions gave (4*S*,6*S*)-**1** (83% yield). Selective oxidation of a primary alcohol of (4*S*,6*S*)-**1** using TEMPO and $PhI(OAc)_2$[11] gave (4*S*,6*S*)-**9** in 85% yield. Compound (4*S*,6*S*)-**9** was transformed to manzacidin C following Ohfune's procedure[6] in 56% yield (three steps from (4*S*,6*S*)-**9**). The spectral data of the synthesized manzacidin C were in good agreement with those reported previously.[6]



Scheme 4. Total synthesis of manzacidin A and C

2-4. Conclusion

In conclusion, the author has achieved a diastereodivergent synthesis of β,β-disubstituted β-amino alcohols from chiral nitroalkanes as starting materials. In the key Henry reaction, the use of different protecting groups resulted in the diastereoselective construction of the tetrasubstituted carbon stereocenter with different configuration. Based on this methodology, the author also achieved the total synthesis of manzacidins A and C.

2-5. Reference

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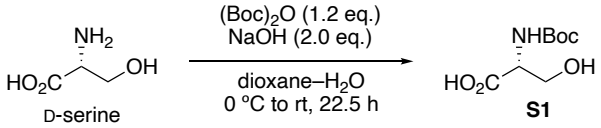
2-6. Experimental section: General Experimental Information

IR spectra were recorded on a HORIBA FT-720 spectrometer. ^{1}H spectra were measured on an Agilent spectrometer (600 MHz), Agilent MR0912W023 spectrometer (400 MHz) and an Agilent S012061 (300 MHz) at ambient temperature. Data were recorded as follows: multiplicity (s = singlet; d = doublet; dd = double doublet; t = triplet; br = broad; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on an Agilent spectrometer (150 MHz), Agilent MR0912W023 spectrometer (100 MHz) and an Agilent S012061 (75 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CHCl_3$ at 7.26 ppm and CD_3OD at 3.31 ppm for ^{1}H, $CDCl_3$ at 77.0 ppm and CD_3OD at 49.0 ppm for ^{13}C). Optical rotations were measured on a digital polarimeter Horiba SEPA-300 using a 3.5 mm × 0.5 dm pyrex cell. For TLC analysis, Merck pre-coated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. Column chromatography was performed using silica gel 60 N (spherical, neutral). High resolution mass spectral analysis (HRMS) was measured on JMS-700 Mstation at Chemical Instrument Facility, Okayama University. Dry tetrahydrofuran, 1,4-dioxane, benzene, 2-propanol, dichloromethane, chloroform, toluene, *N*,*N*-dimethylformamide, acetnitrile, were purchased from Kanto chemicals Co., Inc. as the “anhydrous” and stored under nitrogen. Other materials were obtained from commercial suppliers and used without further purification.

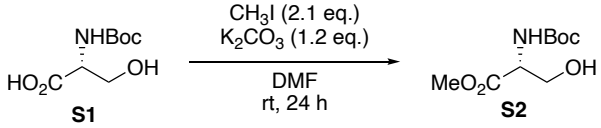
2-6-1. Synthesis of chiral nitroalkanes 3

_N_-(_tert_-Butoxycarbonyl)-D-serine (S1)



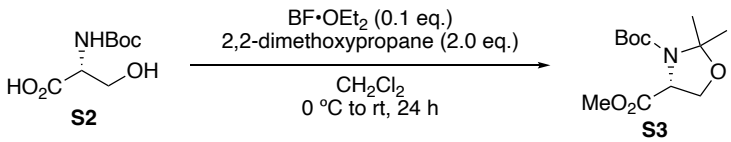
A solution of $(Boc)_2O$ (7.60 g, 34.8 mmol) in dioxane (30 mL) was added to an ice-cold, magnetically stirred solution of D-serine (3.05 g, 29.0 mmol) in 1 M aqueous solution of sodium hydroxide (58 mL) by means of an addition funnel. The mixture was stirred at 5 °C for 30 min, then allowed to warm to ambient temperature and stirred at ambient temperature for 24 h. The mixture was concentrated to half its original volume by rotary evaporation, cooled in an ice-water bath, acidified to pH 2–3 by the slow addition of 1 M aqueous HCl, and then extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate, filtered and concentrated to give *N*-Boc-D-serine **S1** (6.59 g) as a colorless, sticky foam which is used without further purification.

_N_-(_tert_-Butoxycarbonyl)-D-serine methyl ester (S2)



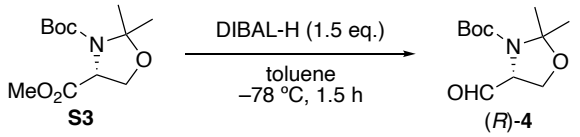
To a solution of *N*-Boc-D-serine **S1** (6.59 g, 29.0 mmol) in dimethylformamide (25 mL) was added solid potassium carbonate (4.80 g, 34.8 mmol) at 0 °C. After stirring for 10 min in an ice-water bath, methyl iodide (3.8 mL, 60.9 mmol) was added to the colorless suspension and stirring continued at 0 °C for 30 min whereupon the mixture solidifies. The reaction was warmed to ambient temperature and stirred for 24 h, and extracted with ethyl acetate. The combined extracts are dried over magnesium sulfate, filtered and concentrated to give **S2** (8.32 g).

(_R_)-3-_tert_-Butyl-4-methyl-2,2-dimethyloxazolidine-3,4-dicarboxylate (S3)



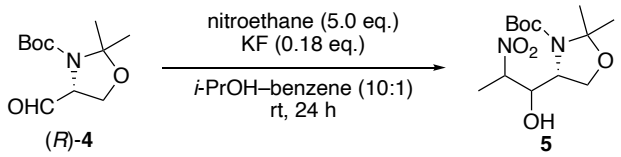
To a solution of *N*-Boc-D-serine methyl ester **S2** (3.15 g, 14.4 mmol) in CH_2Cl_2 (18 mL) were added 2,2-dimethoxypropane (3.6 mL, 28.8 mmol) and $BF_3 \cdot OEt_2$ (0.18 mL, 1.44 mmol) at 0 °C, stirring continued at rt for 24 h. The colorless solution gradually changed to reddish brown. The reaction was quenched by saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with brine, then dried over magnesium sulfate, filtered and concentrated to give the crude product. The residue was purified by column chromatography on silica gel (hexane–EtOAc 20:1) to afford **S3** (2.75 g, 10.6 mmol, 74%).

(*R*)-*tert*-Butyl-4-formyl-2,2-dimethyloxazolidine-3-carboxylate [(*R*)-4]



A solution of **S3** (1.74 g, 6.73 mmol) in dry toluene (68 mL) was cooled to –78 °C with an acetone-dry ice bath. To this cooled solution was added 1.0 M solution of diisobutylaluminum hydride in toluene (10 mL, 10.1 mmol). The reaction mixture was stirred at –78 °C for 1.5 h, and quenched by slowly adding 2.5 mL of methanol. The resulting colorless emulsion was slowly poured into 15 mL of 2 M aqueous HCl with swirling over 15 min, and the aqueous mixture was then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give 1.74 g of crude product (*R*)**-4** as a colorless oil.

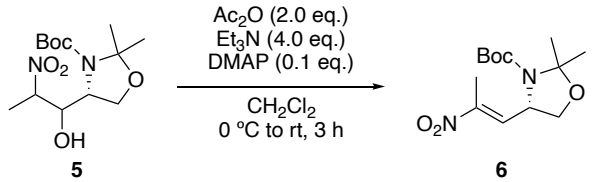
(4*R*)-*tert*-Butyl-4-(1-hydroxy-2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate (5)



To a solution of (*R*)**-4** (1.52 g, 6.6 mmol) in *i*-PrOH (12 mL) and benzene (1.2 mL) were added nitroethane (2.4 mL, 33.2 mmol) and KF (70.2 mg, 1.12 mmol). The mixture was stirred at ambient temperature for 24 h, diluted with CH_2Cl_2 (5 mL) and the solution was filtered through a pad of celite. After evaporation of the solvents under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with brine and dried over $MgSO_4$. The residue was purified by column chromatography on silica gel (hexane–AcOEt 7:1) to afford **5** (1.70 g, 5.6 mmol, 83%) as a diastereomeric mixture.

5: colorless oil, $[\alpha]^{24}_{D}$ +49.4 (c 0.41, $CHCl_3$); IR (film) 3446, 2981, 1698, 1652 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.6–4.4 (m, 1H), 4.3–3.7 (m, 4H), 1.7–1.4 (m, 18H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 94.4, 84.9, 84.2, 81.3, 73.2, 72.9, 65.4, 64.6, 64.2, 63.5, 59.2, 58.8, 28.2, 28.1, 27.3, 26.8, 23.8, 22.6, 16.5, 12.4; HRMS (FAB) *m/z* calcd for $C_{13}H_{25}N_2O_6$ $[M+H]^+$ 305.1707, found 305.1732.

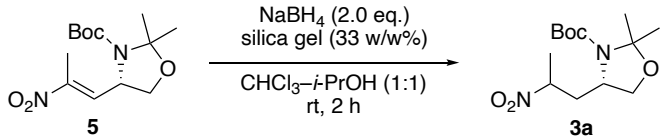
(4*S*)-3-*N*-*t*-Butoxycarbonyl-2,2-dimethyl-4-(2-nitro-1-propenyl)oxazolidine (6)



To a solution of **5** (1.38 g, 4.5 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (2.5 mL, 18.1 mmol), Ac_2O (0.86 mL, 9.07 mmol) and DMAP (55 mg, 0.45 mmol) at 0 °C. The mixture was stirred at ambient temperature for 3 h, quenched by H_2O, and was extracted with AcOEt, dried over $MgSO_4$, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane–AcOEt 7:1) to afford **6** (1.15 g, 4.0 mmol, 83%, *E*/*Z* = 25:1).

(*E*)-**6**: Yellow oil; $[\alpha]^{24}_{D}$ +30.8 (c 1.34, $CHCl_3$); IR (film) 3446, 2981, 1698, 1652 1367 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 9.9 Hz, 1H), 4.7–4.4 (m, 1H), 4.2–4.0 (m, 1H), 3.8–3.6 (m, 1H), 2.3–2.1 (m, 3H), 1.6–1.2 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 151.2, 148.9, 147.6, 134.1, 133.0, 94.7, 93.9, 80.8, 80.5, 67.2, 67.0, 54.8, 28.2, 27.3, 26.2, 24.6, 23.7, 12.6; HRMS (FAB) *m/z* calcd for $C_{13}H_{23}N_2O_5$ $[M+H]^+$ 287.1601, found 287.1630.

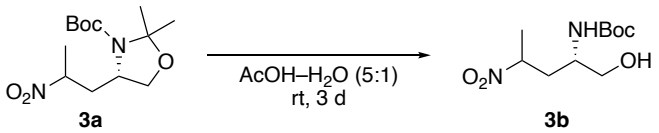
(4*S*)-3-*N*-*t*-Butoxycarbonyl-2,2-dimethyl-4-(2-nitropropyl)oxazolidine (3a)



To a stirred solution of **6** (784 mg, 2.75 mmol) in $CHCl_3$ (5 mL) and *i*-PrOH (5 mL) under N_2 were added silica gel (259 mg) and $NaBH_4$ (415 mg, 11.0 mmol). After 2 h, the excess of $NaBH_4$ was destroyed by addition of AcOH (0.6 mL) and the insoluble material was removed by filtration. The filtrate was washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane– AcOEt 10:1) to afford **3a** (990 mg, 3.4 mmol, 97%) as a ca. 1:1 diastereomeric mixture.

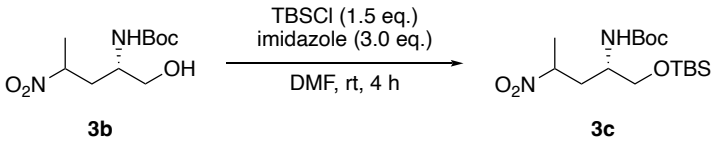
3a: Colorless oil; $[\alpha]^{25}_{D}$ +37.0 (c 1.09, $CHCl_3$); IR (film) 2981, 1697, 1552, 1388, 1259, 1174, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.8–4.5 (m, 1H), 4.1–3.6 (m, 3H), 2.6–2.2 (m, 1H), 2.1–1.8 (m, 1H), 1.6–1.4 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 151.3, 93.9, 93.7, 80.9, 80.5, 67.5, 67.1, 66.2, 55.1, 54.6, 54.2, 39.3, 39.1, 39.0, 38.6, 28.3, 27.6, 26.9, 24.2, 22.9, 20.0, 20.0; HRMS (FAB) *m/z* calcd for $C_{13}H_{25}N_2O_5$ $[M+H]^+$ 289.1735, found 289.1758.

***tert*-Butyl ((2*S*)-1-hydroxy-4-nitropentan-2-yl)carbamate (3b)**



To a stirred solution of **3a** (677 mg, 2.34 mmol) in H_2O (2 mL) was added AcOH (10 mL) at ambient temperature. The mixture was stirred at ambient temperature for 3 d and quenched by solid $NaHCO_3$ at 0 °C, and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane–AcOEt 2:1) to afford **3b** (515.5 mg, 2.07 mmol, 89%) as a ca. 1:1 diastereomeric mixture. **3b**: Colorless oil; $[\alpha]^{25}_{D}$ –8.37 (c 1.12, $CHCl_3$); IR (film) 3417, 3334, 1714, 1552, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.9–4.6 (m, 2H), 3.8–3.6 (m, 3H), 2.4–2.2 (m, 1H), 2.1–1.9 (m, 1H), 1.7–1.5 (m, 3H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 81.1, 80.1, 64.9, 49.6, 36.8, 28.2, 19.3; HRMS (FAB) *m/z* calcd for $C_{10}H_{20}N_2O_5Na$ $[M+Na]^+$ 271.1270, found 271.1243.

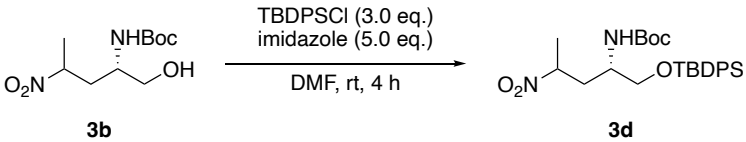
***tert*-Butyl ((2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-4-nitropentan-2-yl)carbamate (3c)**



To a stirred solution of **3b** (370 mg, 1.49 mmol) in DMF (2 mL) were added imidazole (305.6 mg, 4.47 mmol) and TBSCl (251 mg, 1.64 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 4 h and quenched by H_2O at 0 °C, and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane–AcOEt 7:1) to afford **3c** (477.9 mg, 1.32 mmol, 88%) as a ca. 1:1 diastereomeric mixture.

3c: Colorless solid; $[\alpha]^{25}_{D}$ –18.3 (c 1.44, $CHCl_3$); IR (film) 3440, 3334, 2937, 1673, 1552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.8–4.5 (m, 2H), 3.8–3.5 (m, 3H), 2.4–2.2 (m, 1H), 2.0–1.8 (m, 1H), 1.7–1.5 (m, 3H), 1.46 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 155.5, 81.0, 80.5, 79.6, 79.5, 65.1, 64.8, 49.1, 37.3, 37.0, 28.2, 25.7, 20.0, 19.1, 18.2, –5.61, –5.63; HRMS (FAB) *m/z* calcd for $C_{16}H_{35}N_2O_6Si$ $[M+H]^+$ 363.2315, found 363.2297.

***tert*-Butyl ((2*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-4-nitropentan-2-yl)carbamate (3d)**

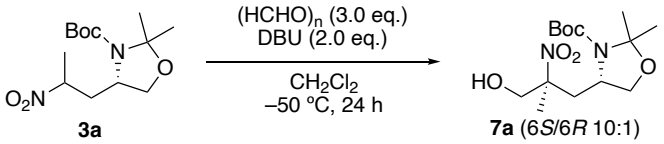


To a stirred solution of **3b** (159 mg, 0.64 mmol) in DMF (0.65 mL) were added imidazole (305.6 mg, 3.2 mmol) and TBDPSCl (0.5 mL, 1.9 mmol) at 0 °C. The mixture was stirred at ambient temperature for 4 h and quenched by H_2O, and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane–AcOEt 7:1) to afford **3d** (250.3 mg, 0.51 mmol,

80%) as a ca. 1:1 diastereomeric mixture.

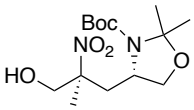
3d: Yellow oil; $[\alpha]^{24}_{D}$ +12.6 (c 0.40, $CHCl_3$); IR (film) 3417, 3269, 2931, 1704, 1552, 1365 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 4.8–4.6 (m, 2H), 3.8–3.4 (m, 3H), 2.3–2.2 (m, 1H), 2.0–1.9 (m, 1H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 135.5, 132.8, 129.9, 127.8, 80.3, 79.6, 65.6, 49.2, 37.1, 28.3, 26.8, 19.9, 19.2; HRMS (FAB) *m/z* calcd for $C_{26}H_{39}N_2O_6Si$ $[M+H]^+$ 487.2628, found 487.2624.

2-6-2. Typical Procedure for the hydroxymethylation of 3



To a solution of **3a** (31.7 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) at –50 °C was added $(HCHO)_n$ (10 mg, 0.33 mmol) and DBU (0.02 mL, 0.2 mmol), and stirred for 24 h. The reaction was quenched by saturated aqueous solution of NH_4Cl, and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to afford **7a** (35.0 mg, 1.09 mmol, 99%, 6*S*/6*R* = 10:1).

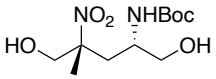
(4*S*)-3-*N*-*t*-Butoxycarbonyl-2,2-dimethyl-4-((*S*)-3-hydroxy-2-methyl-2-nitropropyl) (7a)



7a (6*S*/6*R* 10:1)

7a: Colorless solid; $[\alpha]^{25}_{D}$ +25.90 (c 1.17, $CHCl_3$); IR (film) 2981, 2360, 1689, 1542, 1394, 1257 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 5.7, 9.7 Hz, 1H, minor), 4.45 (dd, *J* = 5.8, 9.4 Hz, 1H, major), 4.38 (dd, *J* = 5.7, 12.2 Hz, 1H, minor), 4.2–3.5 (m, 5H), 2.6–1.9 (m, 2H), 1.7–1.4 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 93.3, 90.4, 81.6, 68.6, 66.5, 53.5, 37.8, 28.3, 27.3, 24.1, 20.3; HRMS (FAB) *m/z* calcd for $C_{14}H_{27}N_2O_6$ $[M+H]^+$ 319.1864, found 319.1878.

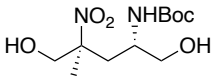
***tert*-Butyl ((2*S*,4*R*)-1,5-dihydroxy-4-methyl-4-nitropentan-2-yl)carbamate [(6*R*)-7b]**



(6*R*)-**7b**

(6*R*)-**7b**: 37% yield. Colorless oil; $[\alpha]^{22}_{D}$ +0.91 (c 1.10, $CHCl_3$); IR (film) 3424, 3347, 2981, 1693, 1554, 1394 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, *J* = 8.9 Hz, 1H), 4.0–3.9 (m, 2H), 3.57 (dd, *J* = 4.6, 11.0 Hz, 2H), 3.03 (brs, 1H), 2.35 (brs, 1H), 2.27 (dd, *J* = 8.8, 15.2 Hz, 1H), 2.19 (dd, *J* = 4.4, 15.2 Hz, 1H), 1.62 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 90.7, 80.2, 67.6, 65.4, 48.3, 36.5, 28.3, 19.6; HRMS (FAB) *m/z* calcd for $C_{11}H_{23}N_2O_6$ $[M+H]^+$ 279.1556, fund 279.1573.

***tert*-Butyl ((2*S*,4*S*)-1,5-dihydroxy-4-methyl-4-nitropentan-2-yl)carbamate [(6*S*)-7b]**

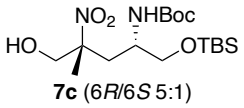


(6*S*)-**7b**

(6*S*)-**7b**: 48% yield. Colorless oil; $[\alpha]^{24}_{D}$ –10.5 (c 0.90, $CHCl_3$); IR (film) 3424, 3340, 2983, 1694, 1550, 1395 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (d, *J* = 7.9 Hz, 1H), 4.1–3.9 (m,

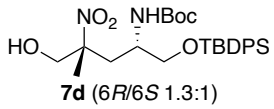
2H), 3.9–3.7 (m, 1H), 3.7–3.5 (m, 2H), 3.1 (brs, 1H), 2.6 (brs, 1H), 2.4–2.2 (m, 2H), 1.60 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 90.6, 80.3, 66.1, 65.7, 48.6, 36.5, 28.3, 21.4; HRMS (FAB) *m/z* calcd for $C_{11}H_{23}N_2O_6$ $[M+H]^+$ 279.1556, found 279.1577.

***tert*-Butyl ((2*S*,4*R*)-1-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-4-methyl-4-nitropentan-2-yl)- carbamate (7c)**



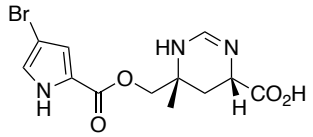
7c: 91% yield, 6*R*/6*S* = 5:1. Colorless oil; $[\alpha]^{24}_D$ +0.08 (c 1.20, $CHCl_3$); IR (film) 3440, 3384, 2931, 2931, 1693, 1548, 1392 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, *J* = 8.0 Hz, 1H, minor), 4.68 (d, *J* = 8.0 Hz, major), 4.0–3.7 (m, 3H), 3.6–3.4 (m, 2H), 2.92 (br s, 1H, major), 2.80 (br s, 1H, minor), 2.4–2.1 (m, 2H), 1.59 and 1.62 (s, 3H), 1.43 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 90.4, 80.1, 66.8, 65.6, 48.00, 37.6, 28.32, 25.9, 20.8, 18.3, –5.49; HRMS (FAB) *m/z* calcd for $C_{17}H_{37}N_2O_6Si$ $[M+H]^+$ 393.2421, found 393.1417.

***tert*-Butyl ((2*S*,4*R*)-1-((tert-butyldiphenylsilyl)oxy)-5-hydroxy-4-methyl-4-nitropentan-2-yl)- carbamate (7d)**



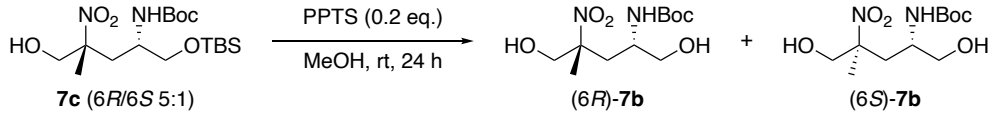
7d: 75% yield, 6*R*/6*S* = 1.3:1. Yellow oil; $[\alpha]^{24}_D$ +10.8 (c 1.27, $CHCl_3$); IR (film) 3440, 2931, 1699, 1544, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6–7.7 (m, 4H), 7.3–7.5 (m, 6H), 4.5–4.8 (m, 1H), 4.0–3.8 (m, 3H), 3.8–3.7 (m, 1H, minor), 3.6–3.5 (m, 2H), 3.1–2.8 (m, 1H), 2.4–2.2 (m, 1H), 2.2–2.0 (m, 1H), 160 (s, 3H), 1.43 (s, 9H; singlet methyl overlapped in this signal), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 135.5, 132.9, 129.9, 127.8, 90.7, 90.4, 85.8, 80.0, 79.9, 67.3, 66.6, 66.5, 65.9, 48.4, 48.0, 37.6, 36.9, 28.3, 26.9, 21.3, 20.2, 19.3, 19.2; HRMS (FAB) *m/z* calcd for $C_{27}H_{41}N_2O_6Si$ $[M+H]^+$ 517.2734, found 517.2753.

2-6-3. Total Synthesis of manzacidin A



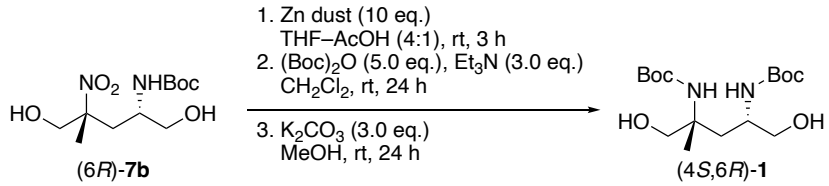
manzacidin A

tert-Butyl ((2_S_,4_R_)-1,5-dihydroxy-4-methyl-4-nitropentan-2-yl)carbamate [(6_R_)-7b] and _tert_-Butyl ((2_S_,4_S_)-1,5-dihydroxy-4-methyl-4-nitropentan-2-yl)carbamate [(6_S_)-7b]



To a solution of **7c** (6*R*/6*S* = 5:1, 36.1 mg, 0.10 mmol) in MeOH (1 mL) was added PPTS (5.3 mg, 0.02 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 24 h, and then the reaction was quenched by saturated aqueous solution of NH_4Cl, and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane–AcOEt 1:2) to afford (6*R*)-**7b** (23.4 mg, 0.084 mmol, 77%) and (6*S*)-**7b** (3.8 mg, 0.014 mmol, 15%).

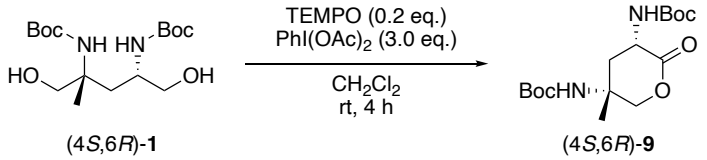
di-_tert_-Butyl ((2_R_,4_S_)-1,5-dihydroxy-2-methylpentane-2,4-diyl)dicarbamate [(4_S_,6_R_)-1]



To a solution of (6*R*)-**7b** (72.6 mg, 0.26 mmol) in THF (4 mL) were added Zn dust (169.9 mg, 2.6 mmol) which was washed by 1 M aqueous HCl, and AcOH (1.0 mL) at ambient temperature. The mixture was stirred at ambient temperature for 24 h, filtered through a pad of celite and concentrated by evaporation. To the solution of residue in CH_2Cl_2 (3 mL) were added Et_3N (0.11 mL, 0.78 mmol) and $(Boc)_2O$ (284 mg, 1.3 mmol) at ambient temperature. After the mixture was stirred at ambient temperature for 24 h, concentrated by evaporation. The residue was dissolved in MeOH (5 mL), and to this solution was added K_2CO_3 (107.8 mg, 0.78 mmol) at ambient temperature and was stirred for 24 h. The mixture was concentrated by evaporation and the residue was purified by column chromatography on silica gel (hexane–AcOEt 1:1) to afford (4*S*,6*R*)-**1** (60.7 mg, 0.17 mmol, 67% for 3 steps).

(4*S*,6*R*)-**1**: Colorless oil; $[\alpha]^{23}_{D}$ +12.7 (c 1.00, $CHCl_3$); IR (film) 3446, 2933, 1722, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (brs, 2H), 4.43 (brs, 1H), 3.78 (m, 1H), 3.7–3.5 (m, 4H), 2.60 (brs, 1H), 2.03 (dd, *J* = 4.7, 14.9 Hz, 1H), 1.85 (dd, *J* = 6.7, 14.9 Hz, 1H), 1.5–1.4 (m, 18H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 79.8, 69.9, 66.0, 55.8, 48.8, 36.8, 28.4, 28.3, 23.0; HRMS (FAB) *m/z* calcd for $C_{16}H_{32}N_2O_6$ $[M+H]^+$ 349.2333, found 349.2363.

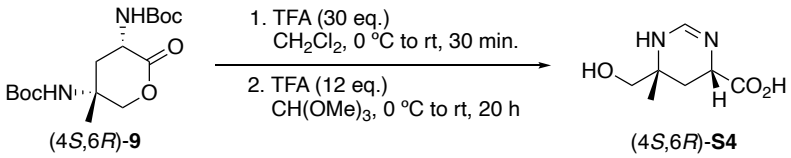
di-*tert*-Butyl ((3*S*,5*R*)-5-methyl-2-oxotetrahydro-2*H*-pyran-3,5-diyl)dicarbamate [(4*S*,6*R*)-9]



To a solution of (4*S*, 6*R*)-**1** (37.7 mg, 1.08 mmol) in CH_2Cl_2 (1 mL) were added $PhI(OAc)_2$ (104 mg, 0.32 mmol) and TEMPO (3.4 mg, 0.022 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 4 h and quenched by saturated aqueous solution of $Na_2S_2O_3$, and the mixture was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to afford (4*S*, 6*R*)-**9** (31.1 mg, 0.09 mmol, 83%).

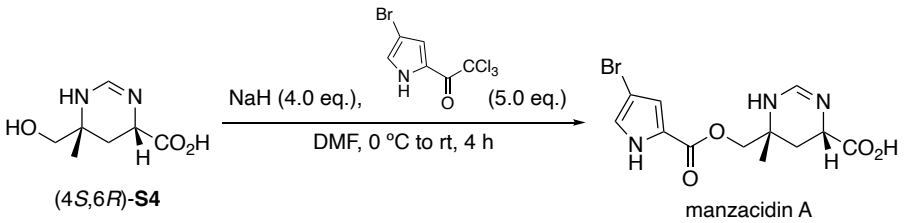
(4*S*,6*R*)-**9**: Colorless solid; $[\alpha]^{19}_{D}$ +121.3 (c 1.04, $CHCl_3$); IR (film) 3440, 2977, 1770, 1536, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (d, *J* = 5.6 Hz, 1H), 4.8 (br s, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.07 (d, *J* = 12.0 Hz, 1H), 4.5–4.3 (m, 1H), 2.63 (dd, *J* = 8.6, 13.6 Hz, 1H), 1.91 (dd, *J* = 11.2, 13.6 Hz, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 155.2, 154.3, 80.4, 80.0, 72.8, 51.5, 47.3, 40.9, 28.3, 28.2, 23.5; HRMS (FAB) *m/z* calcd for $C_{16}H_{29}N_2O_6$ $[M+H]^+$ 345.2026, found 345.2049.

(4*S*,6*R*)-6-(hydroxymethyl)-6-methyl-1,4,5,6-tetrahydropyrimidine-4-carboxylic acid [(4*S*,6*R*)-S4]



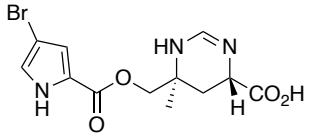
To a solution of (4*S*,6*R*)-**9** (31.1 mg, 0.09 mmol) in CH_2Cl_2 (0.9 mL) was added TFA (0.63 mL, 2.7 mmol) at 0 °C. After stirring at ambient temperature for 30 min, the mixture was concentrated under reduced pressure. To a solution of the residue in $CH(OMe)_3$ (0.9 mL) was added TFA (0.25 mL, 1.0 mmol) at 0 °C, and was stirred at ambient temperature for 20 h. After concentration under reduced pressure, the resulting residue was dissolved in 2 M aqueous HCl. After stirring at room temperature for 2 h followed by concentration, the residue was purified by ion exchange chromatography (Dowex 50WX8-100, H^+ form, eluted with H_2O, then 1 M aqueous NH_3) to afford tetrahydropyrimidine (4*S*,6*R*)-**S4** (16.0 mg). The obtained (4*S*,6*R*)-**S4** was used for the subsequent reaction without further purification.

manzacidin A



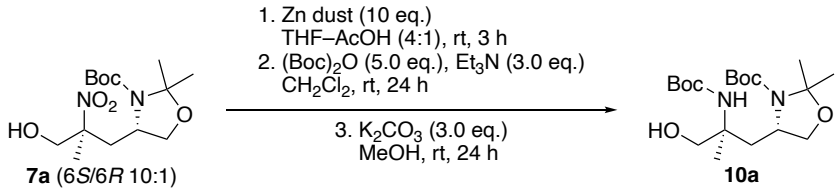
To a solution of (4*S*,6*R*)-**S4** (16.0 mg) in DMF (1.0 mL), cooled to 0 °C was added sodium hydride (15.4 mg, 0.6 mmol, 60% dispersion in oil). After stirring at 0 °C for 1 h, bromopyrrole **S5** (131 mg, 0.5 mmol) was added in one portion. After stirring at ambient temperature for 3 h, the reaction mixture was quenched with 2 M aqueous HCl. The mixture was extracted with AcOEt and the aqueous layer was concentrated under reduced pressure to afford the residue, which was subjected to reversed-phase chromatography (flash column of Cosmosil 75C_{18}-OPN eluted with water-acetonitrile 1:0 to 7:3, and HPLC with Cosmosil 5C_{18}-MS-II with acetonitrile-water 22:78:0.1) to furnish manzacidin A (18.1 mg, 0.053 mmol, 58%). **manzacidin A**: Colorless solid; $[\alpha]^{24}_{D}$ –21.1 (c 0.38, CH_3OH); IR (KBr) 3436, 2927, 1683, 1319, 1207 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 7.04 (d, *J* = 1.6 Hz, 1H), 6.94 (d, *J* = 1.6 Hz, 1H), 4.44 (dd, *J* = 5.2, 10.2 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.25 (d, *J* = 11.4 Hz, 1H), 2.39 (dd, *J* = 5.2, 14.0 Hz, 1H), 2.22 (dd, *J* = 10.2, 14.0 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 171.6, 160.6, 152.1, 125.4, 123.3, 118.6, 98.2, 68.8, 53.8, 31.1, 24.0 (one singnal was overlapped with signals of CD_3OD); HRMS (FAB) *m/z* calcd for $C_{12}H_{15}BrN_3O_4$ $[M+H]^+$ 344.0246, found 344.0259.

2-6-4. Total Synthesis of manzacidin C



manzacidin C

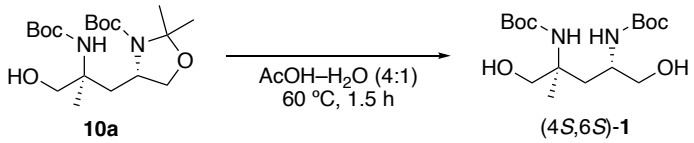
(4*S*)-3-*N*-*t*-Butoxycarbonyl-2,2-dimethyl-4-[(*S*)-2-(*t*-butoxycarbonylxamino)-3-hydroxy-2-met hylpropyl]-oxazolidine (10a)



To a solution of **7a** (6*S*/6*R* = 10:1, 35.0 mg, 0.10 mmol) in THF (2 mL) were added Zn dust (72 mg, 1.1 mmol) which was washed by 1 M aqueous HCl, and AcOH (0.5 mL) at ambient temperature. The mixture was stirred at ambient temperature for 24 h, filtered through a pad of celite and concentrated by evaporation. To a solution of the residue in CH_2Cl_2 (2 mL) were added Et_3N (0.05 mL, 0.30 mmol) and $(Boc)_2O$ (120 mg, 0.50 mmol) at ambient temperature. After the mixture was stirred at ambient temperature for 24 h, concentrated by evaporation. To a solution of the residue in MeOH (2 mL), was added K_2CO_3 (45.2 mg, 0.30 mmol) at ambient temperature and was stirred for 24 h. The residue was purified by column chromatography on silica gel (hexane– AcOEt 3:1) to afford (4*S*,6*S*)-**10a** (27.1 mg, 0.70 mmol, 70% for 3 steps).

(4*S*,6*S*)-**10a**: Colorless solid; $[\alpha]^{24}_{D}$ +33.8 (c 0.90, $CHCl_3$); IR (film) 3428, 3334, 2979, 1716, 1668, 1534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.6–4.5 (m, 1H), 4.1–3.4 (m, 5H), 2.3–2.1 (m, 1H), 1.9– 1.8 (m, 1H), 1.8–1.6 (m, 24H), 1.3–1.2 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 152.6, 93.0, 80.95, 79.1, 69.2, 67.95, 55.6, 53.6, 40.8, 28.4, 27.8, 27.3, 24.3, 21.0; HRMS (FAB) *m/z* calcd for $C_{19}H_{37}N_2O_6$ $[M+H]^+$ 389.2652, found 389.2648.

di-*tert*-Butyl((2*S*,4*S*)-1,5-dihydroxy-2-methylpentane-2,4-diyl)dicarbamate [(4*S*,6*S*)-1]

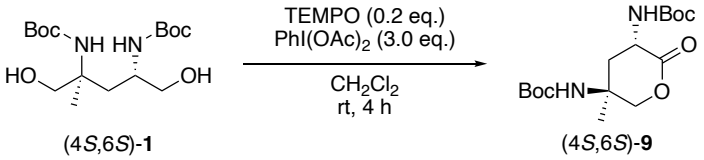


To a solution of (4*S*,6*S*)-**10a** (27.1 mg, 0.07 mmol) in H_2O (0.2 mL) were added AcOH (1.8 mL) at ambient temperature. The mixture was stirred at 60 °C for 1.5 h and quenched by solid of $NaHCO_3$ at 0 °C. The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel S13 (hexane–AcOEt 1:1) to afford (4*S*,6*S*)-**1** (20.2 mg, 0.06 mmol, 83%).

(4*S*,6*S*)-**1**: Colorless oil; $[\alpha]^{23}_{D}$ +3.84 (c 1.40, $CHCl_3$); IR (film) 3450, 2977, 1662, 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (br s, 1H), 5.09 (br s, 1H), 4.52 (br s, 1H), 3.8–3.7 (m, 1H),

3.7–3.5 (m, 4H), 2.93 (br s, 1H), 1.98 (dd, J = 3.8, 14.7 Hz, 1H), 1.89 (dd, J = 7.9, 14.7 Hz, 1H), 1.5–1.4 (m, 18H) 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 156.2, 79.9, 79.7, 69.2, 66.4, 56.0, 49.2, 36.8, 28.4, 28.3, 22.8; HRMS (FAB) *m/z* calcd for $C_{16}H_{32}N_2O_6$ $[M+H]^+$ 349.2333, found 349.2344.

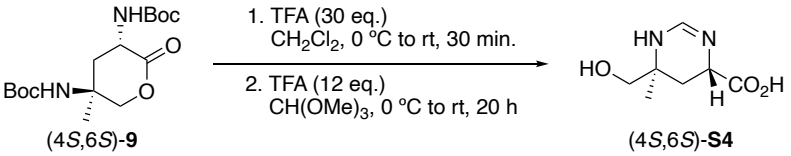
di-*tert*-Butyl ((3*S*,5*S*)-5-methyl-2-oxotetrahydro-2*H*-pyran-3,5-diyl)dicarbamate [(4*S*,6*S*)-9]



By following the same procedure described for procedure for (4*S*,6*R*)-**9**, (4*S*,6*S*)-**1** (20.9 mg, 0.06 mmol) was converted to (4*S*,6*S*)-**9** (17.6 mg, 0.05 mmol, 85%).

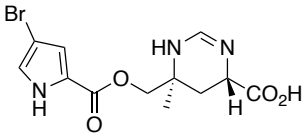
(4*S*,6*S*)-**9**: Colorless solid; $[\alpha]^{23}_D$ +18.5 (c 0.92, $CHCl_3$); IR (film) 3328, 3019, 1712, 1519, 1214 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (br s, 1H), 4.75 (br s, 1H), 4.7–4.5 (m, 2H), 4.3–4.2 (m, 1H), 2.8–2.6 (m, 1H), 1.8–1.6 (m, 1H), 1.45 (s, 9H), 1.40 (s, 9H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 155.2, 154.5, 80.3, 73.6, 50.7, 47.7, 39.6, 29.7, 28.3; HRMS (FAB) *m/z* calcd for $C_{16}H_{29}N_2O_6$ $[M+H]^+$ 345.2026, found 345.2007.

(4S,6S)-6-(hydroxymethyl)-6-methyl-1,4,5,6-tetrahydropyrimidine-4-carboxylic acid [(4*S*,6*S*)-S4]



By following the same procedure described for procedure for (4*S*,6*R*)-**S4**, (4*S*, 6*S*)-**9** (27.5 mg, 0.08 mmol) was converted to (4*S*,6*S*)-**S4** (12.3 mg). The obtained (4*S*,6*S*)-**S4** was used for the subsequent reaction without further purification.

manzacidin C



By following the same procedure described for procedure for manzacidin A, (4*S*,6*S*)-**S4** (12.3 mg) was converted to manzacidin C (15.4 mg, 0.045 mmol, 56%).

manzacidin C: Colorless solid; $[\alpha]^{23}_D$ +85.0 (c 0.10, CH_3OH); IR (KBr) 3436, 2929, 1683, 1319, 1207 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 8.15 (s, 1H), 7.09 (d, J = 1.2 Hz, 1H), 6.94 (d, J = 1.2 Hz, 1H), 4.51 (dd, J = 5.4, 10.2 Hz, 1H), 4.44 (d, J = 11.4 Hz, 1H), 4.29 (d, J = 11.4 Hz, 1H), 2.63 (dd, J = 5.4, 14.4 Hz, 1H), 2.03 (dd, J = 10.2, 14.4 Hz, 1H), 1.47 (s, 3H); ^{13}C

NMR (150 MHz, CD_3OD) δ 171.3, 160.6, 152.3, 125.5, 123.3, 118.3, 98.2, 69.2, 53.4, 50.3, 32.1, 23.7; HRMS (FAB) *m/z* calcd for $C_{12}H_{15}BrN_3O_4$ $[M+H]^+$ 344.0246, found 344.0259.

Chapter 3. Formal total synthesis of manzacidin B via sequential diastereodivergent Henry reaction

3-1. Abstract

A formal total synthesis of manzacidin B is described. β,β'-disubstituted γ-hydroxy-β-aminoalcohol, the key structure of manzacidin B, is stereoselectively constructed via sequential Henry reactions. By taking advantage of noncovalent interactions, such as intramolecular hydrogen bonding and chelation, we could diastereodivergently control the stereoselectivity of the Henry reaction.

3-2. Introduction

Bromopyrrole alkaloids,[1] a large family of marine natural products, are known to be a rich source of biologically active molecules, such as sceptrin,[2] dispacamide B[3] and spongiacidin B[4]. Manzacidins A–C, a rare class of these alkaloids, are isolated from Okinawan sponge *Hymeniacidon* sp. by Kobayashi and colleagues in 1991 (**Figure 1**)[5]. The structural features of manzacidins A–C are a bromopyrrole carboxylic acid and a highly substituted tetrahydropyrimidine core. Because of their unique structure and pharmacological profile as in a class of bromopyrrole alkaloids, manzacidins are attractive target molecules for organic synthesis[6]. In particularly, manzacidin B has an additional hydroxy group at C5 position as a part of three contiguous stereogenic centers and a characteristic β,β'-disubstituted γ-hydroxy-β-aminoalcohol structure.

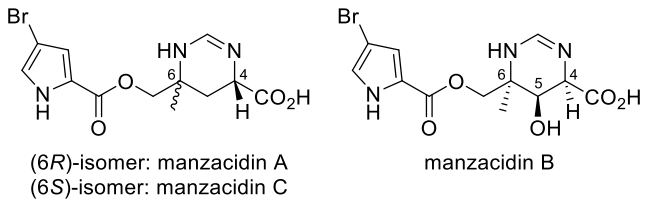
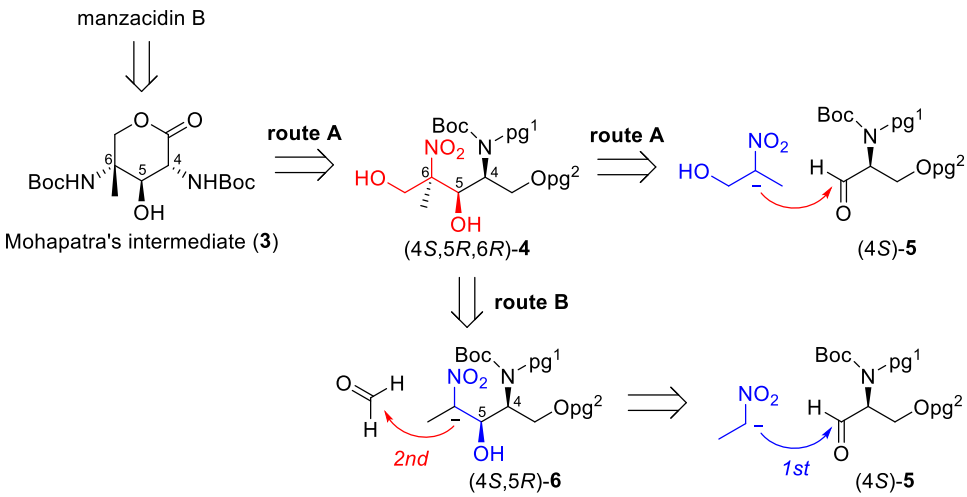


Figure 1. The structure of manzacidins A, C and B

3-3. Results and discussions

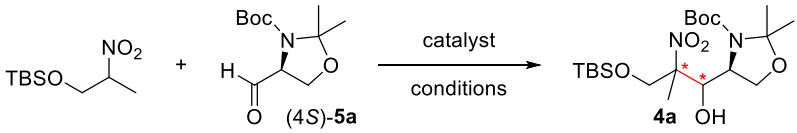
Scheme 1 shows our plan for the synthesis of manzacidin B. We set Mohapatra's synthetic intermediate **3**[8] as the target compound because 3 can be readily converted to manzacidin B. Compound **3** is retrosynthetically converted to tertiary *β*,*β′*-dihydroxynitroalkane (4*S*,5*R*,6*R*)-**4** via oxidative lactonization and reduction of the nitro group. Consideration of the Henry disconnection allowed us to devise two pathways to construct (4*S*,5*R*,6*R*)-**4**. In route A, (4*S*,5*R*,6*R*)-**4** would be synthesized by the coupling of 1-hydroxy-2-nitropropane and chiral aldehyde (4*S*)-**5**, constructing both C-5 and C-6 stereogenic centers in a single Henry reaction. Alternatively, in route B, (4*S*,5*R*,6*R*)-**4** would also be synthesized through sequential Henry reactions connecting two aldehydes, formaldehyde and chiral aldehyde (4*S*)-**5**, with nitroethane. In this route, the stereochemistry of C5 and C6 could be controlled stepwise. Because the route A is more straightforward than the route B, our study commenced with an investigation of the Henry reaction in route A.

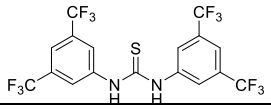


Scheme 1. Retrosynthesis of manzacidin B

Table 1 shows our study on the Henry reaction of TBS-protected 1-hydroxy-2-nitropropane with (4*S*)-**5a**. When the reaction of the nitroalkane (3 equiv.) with (4*S*)-**5a** was conducted in the presence of DBU (90 mol %), a significant amount of the nitroalkane was decomposed, and only 22% yield of adduct **4a** was obtained as a mixture of four diastereomers (dr 1.6:1.6:1.2:1) (Entry 1). To suppress the decomposition of the nitroalkane, we next examined the reaction under less-basic conditions. As a result, we found that the combination use of Et_3N and 3,5-bis(trifluoromethyl)- phenylthiourea (30 mol % each) under solvent-free (10 equiv. of the nitroalkane was used) conditions successfully improved the yield of **4a** (70%). However, diastereoselectivity was quite poor (dr 1.7:1.6:1.1:1) (Entry 2).

Table 1. Henry reaction of TBS-protected 1-hydroxy-2-nitropropane with (4*S*)-**5a**



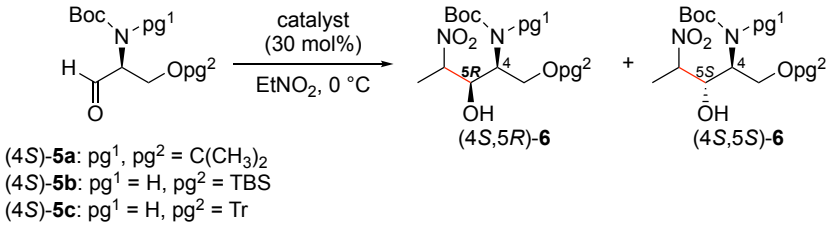
Entry	Catalyst	Conditions	Results
1	DBU (90 mol%)	THF, –50 °C, 19 h[a]	22% yield[c] dr 1.6:1.6:1.2:1[d]
2	Et_3N + 	solvent-free, 0 °C, 2 h[b]	70% yield[c] dr 1.7:1.6:1.1:1[d]

[a]The reaction of the nitroalkane (3 equiv.) with (4*S*)-**5a** (0.2 mmol) was conducted in the presence of DBU (90 mol %) in THF at −50 °C for 19 h. [b]The reaction of the nitroalkane (10 equiv.) with (4*S*)-**5a** (0.2 mmol) was conducted in the presence of Et_3N (30 mol %) and the thiourea (30 mol %) under the solvent-free conditions at 0 °C for 2 h. [c]Isolated yield. [d]The dr was evaluated by ^{1}H NMR analysis.

Based on the results shown in Table 1, we concluded that it was difficult to control the diastereoselectivity in the Henry reaction of 1-hydroxy-2-nitropropane derivatives with chiral aldehyde (4*S*)-**5a**. Thus, we next investigated the sequential Henry reactions (route B). In this synthetic route, intermediate (4*S*,5*R*)-**6a** *β*-hydroxynitroalkane, would also be unstable under strong basic conditions. Therefore, mild basic conditions were employed for the first Henry reaction of nitroethane with (4*S*)-**5** (**Table 2**). When the reaction of nitroethane (5 equiv.) with (4*S*)-**5a** was conducted, in the presence of KF (20 mol%),[16] the corresponding adduct **6a** was successfully obtained in 83% yield (Entry 1). However, undesired (4*S*,5*S*)-**6a** was generated as a major isomer (5*R*/5*S* = 1:5.0). In sharp contrast, when *O*-TBS-protected (4*S*)-**5b** was used as the substrate, desired (4*S*,5*R*)-**6b** was obtained preferentially (78% yield, 5*R*/5*S* = 2.0:1, Entry 2). The use of *O*-Tr-protected (4*S*)-**5c** as the substrate also gave (4*S*,5*R*)-**6c** as a major product (64% yield, 5*R*/5*S* = 2.0:1, Entry 3). To improve the diastereoselectivity, we investigated several bases and found that when the reaction of (4*S*)-**5c** was conducted in the presence of *n*-Bu_4NF (30 mol %),[17] diastereoselectivity was increased to 5*R*/5*S* = 6.5:1 (89%

yield, Entry 4). Further investigation revealed that the use of *n*-Bu_4PBr (10 mol %) and KF (10 equiv.) improved the diastereoselectivity (90% yield, 5*R*/5*S* = 11:1, Entry 5).

Table 2. Investigation of first Henry reaction[a]

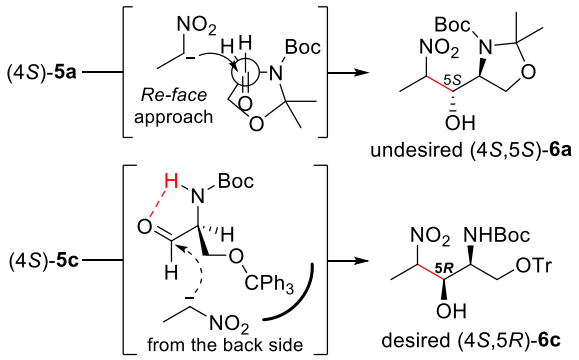


Entry	**5**	Catalyst	Yield (%)	5*R*/5*S*
1	**5a**	KF	**6a**, 83	1:5.0
2	**5b**	Et_3N	**6b**, 78	2.0:1
3	**5c**	Et_3N	**6c**, 64	2.0:1
4	**5c**	*n*-Bu_4NF	**6c**, 89	6.5:1
5	**5c**	*n*-Bu_4PBr, KF	**6c**, 90	**11**:1

[a]The reaction of (4*S*)-**5** (0.2 mmol) was conducted in the presence of a catalyst (30 mol %) in $EtNO_2$ at 0 °C for 1.5−24 h. [b]Isolated yield. [c]Evaluated by ^{1}H NMR analysis. [d]The reaction was conducted with $EtNO_2$ (5 equiv.) in the presence of KF (20 mol %) in *i*-PrOH−benzene (10:1). [e]The reaction was conducted in the presence of *n*-Bu_4PBr (10 mol %) and KF (10 equiv). [f]The reaction was conducted on 1.0 mmol scale.

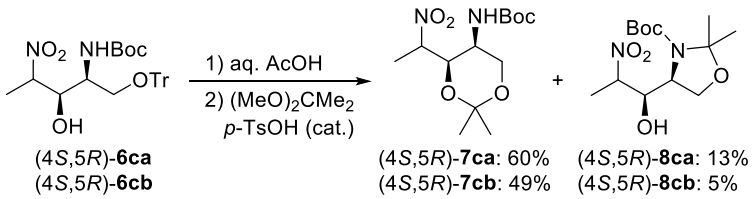
Although the stereoselectivity at C5 was high in the first Henry reaction, adduct **6c** was obtained as an ca. 1:1 diastereomeric mixture at C6. However, we did not make efforts to control the C6 stereochemistry at this stage because it would be lost at the second Henry reaction. C6 diastereomers of **6c** (named **6ca** and **6cb**) were separable on silica gel column chromatography, and **6ca** and **6cb** were isolated in respective yields of 44 and 46%.[18]

Here, we propose mechanisms for the first Henry reaction with (4*S*)-**5** (**Scheme 2**). The stereoselectivity of the reaction with (4*S*)-**5a** could be explained by the polar Felkin−Anh model[19] as shown in the upper scheme. The nitronate would approach the *re* face of (4*S*)-**5a** to give (4*S*,5*S*)-**6a** preferentially. On the other hand, in the transition-state assembly for the reaction of (4*S*)-**5c**, the formyl group might interact with the NH group via intramolecular hydrogen bonding (bottom scheme).[20] The trityloxymethyl group would shield the front side of the formyl group, and the nitronate was considered to approach the *si* face of the formyl group (from the back side) to give the desired (4*S*,5*R*)-**6c** as a major product. The reason why the use of tetrabutylammonium and phosphonium salts improved the diastereoselectivity considered to be the fact that these aprotic and sterically hindered countercations did not disrupt the formation of the intramolecular hydrogen bonding.



Scheme 2. Proposed transition state assemblies of 1st Henry reaction

Before the second Henry reaction, the C5-hydroxy group of (4*S*,5*R*)-**6c** should be protected to avoid the retro-Henry reaction. Therefore, compound (4*S*,5*R*)-**6c** was converted into acetonide-protected (4*S*,5*R*)-**7c** (**Scheme 3**). To avoid the confusion, C6 diastereomers (4*S*,5*R*)-**6ca** and (4*S*,5*R*)-**6cb** were converted into (4*S*,5*R*)-**7ca** and (4*S*,5*R*)-**7cb** separately. Removal of the trityl group under the acidic conditions, followed by acetonide protection of the resultant diols, gave 6-membered acetonides (4*S*,5*R*)-**7ca** and (4*S*,5*R*)-**7cb** in respective yields of 60 and 49%. In this reaction scheme, 5-membered acetonides (4*S*,5*R*)-**8ca** and (4*S*,5*R*)-**8cb** were also generated in respective yields of 13 and 5%.

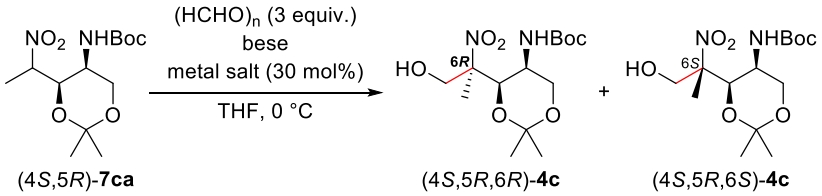


Scheme 3. Synthesis of secondary nitroalkane (4*S*,5*R*)-**7c**

With chiral nitroalkane (4*S*,5*R*)-**7c** in hand, we investigated the second Henry reaction constructing the nitrogencontaining tetrasubstituted carbon (**Table 3**). Because acetonide-protected (4*S*,5*R*)-**7c** was found to be rather stable under strong basic conditions, the reaction of (4*S*,5*R*)-**7ca** with paraformaldehyde was conducted in the presence of a variety of strong bases. When the reaction was conducted in the presence of DBU (200 mol %), undesired (4*S*,5*R*,6*S*)-**4c** was obtained in 89% yield as a single diastereomer (Entry 1). In contrast, the use of NaO*t*-Bu (30 mol %) gave desired (4*S*,5*R*,6*R*)-**4c** as a major isomer (81% yield, 6*R*/6*S* = 4.0:1) (entry 2). Based on these results, we considered that the presence of a metal cation would result in the desired diastereopreference via chelation. Therefore, to improve the diastereoselectivity, we screened several alkaline earth metal salts as additives. As a result, although $BaCl_2$ did not improve the diastereoselectivity (Entry 3), the use of $CaCl_2$ and $MgCl_2 \cdot 6H_2O$ slightly improved the diastereoselectivity (Entries 4 and 5). To our delight, we found that when $MgCl_2 \cdot 6H_2O$ was dried under heat and vacuum conditions before use, the diastereoselectivity was further improved to 6*R*/6*S* = 6.0:1 (Entry 6). In sharp contrast, very

surprisingly, the use of anhydrous $MgCl_2$ significantly decreased both the yield and diastereoselectivity (37%, 6*R*/6*S* = 1:3.8), and undesired (4*S*,5*R*,6*S*)-**4c** was obtained as a major product (Entry 7). The "activated" magnesium salt used in entry 6 could be a partially dehydrated $MgCl_2 \cdot nH_2O$, although we have no structural evidence at this point. Regardless, the results shown in entry 6 were reproducible and scalable (2 mmol scale, 91% yield, 6*R*/6*S* = 6.0:1) (Entry 7).

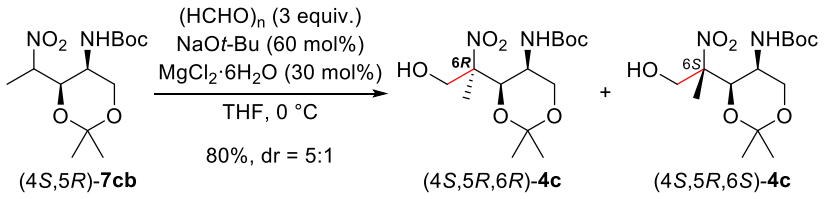
Table 3. Investigation of the second Henry reaction[a]



Entry	Base	Metal salt	Yield (%)[b]	6*R*/6*S*[c]
1[d]	DBU (200 mol%)	–	89	1:>20
2	NaO*t*-Bu (30 mol%)	–	81	4.0:1
3	NaO*t*-Bu (60 mol%)	$BaCl_2$	91	3.7:1
4	NaO*t*-Bu (60 mol%)	$CaCl_2$	81	4.3:1
5[e]	NaO*t*-Bu (60 mol%)	$MgCl_2 \cdot 6H_2O$	83	4.5:1
6[f]	NaO*t*-Bu (60 mol%)	$MgCl_2 \cdot 6H_2O$	92	**6.0**:1
7[e]	NaO*t*-Bu (60 mol%)	$MgCl_2$	37	1:3.8

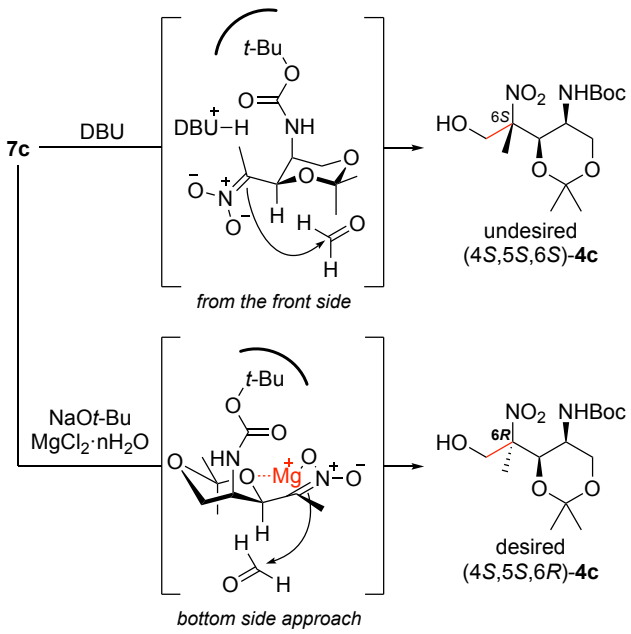
[a]The reaction of (4*S*,5*R*)-**7ca** (0.2 mmol) with paraformaldehyde (3 equiv.) was conducted in the presence of a base (30−200 mol %) and a metal salt (30 mol%) in THF at 0 °C for 1.5−2 h. [b]Isolated yield. [c]Evaluated by ^{1}H NMR analysis. [d]The reaction was conducted in CH_2Cl_2 at −50 °C for 24 h. [e]The reaction was conducted at ambient temperature. [f]$MgCl_2 \cdot 6H_2O$ was dried by a heat-gun under vacuum for 5 min.

Diastereomeric (4*S*,5*R*)-**7cb** was also converted to desired (4*S*,5*R*,6*R*)-**4c** under the same conditions in 80% yield with a 5:1 diastereomeric ratio (**Scheme 4**).



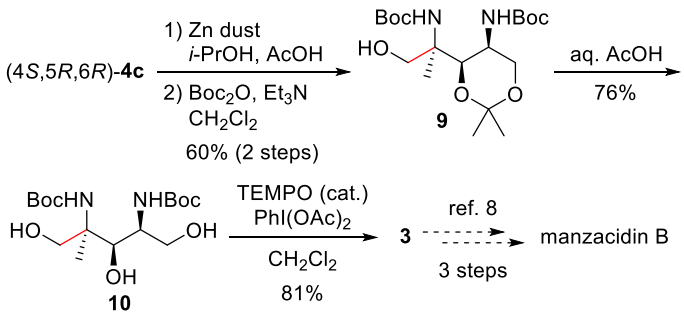
Scheme 4. Conversion of (4*S*,5*R*)-**7cb** to (4*S*,5*R*,6*R*)-**4c**

The diastereoselectivity of the second Henry reaction could be explained with the following models (**Scheme 5**). In the DBU-promoted reaction, the nitronate intermediate would have a conformation in which the allylic strain is the smallest in energy (upper scheme). The *N*-Boc group would shield the back side of the nitronate moiety. Thus, formaldehyde was considered to approach the front side (*si* face) of the nitronate moiety, avoiding the steric repulsion of the *N*-Boc group. On the other hand, in the presence of magnesium salt, the magnesium cation would interact with the oxygens of the nitronate group and acetonide group in the nitronate intermediate (bottom scheme). In this fixed conformation, the *N*-Boc group would shield the upper face of the nitronate moiety. Formaldehyde was thus considered to approach the bottom side (*re* face) of chelated magnesium nitronate to establish the desired 6*R* stereochemistry.



Scheme 5. Proposed transition state assemblies of 2nd Henry reaction

With compound (4*S*,5*R*,6*R*)-**4c**, which bears all of the stereogenic centers that correspond to manzacidin B, in hand, we converted (4*S*,5*R*,6*R*)-**4c** to Mohapatra's intermediate (**3**) via functional group manipulations (**Scheme 6**). Reduction of the nitro group of (4*S*,5*R*,6*R*)-**4c** using zinc dust[21] followed by Boc protection of the resultant primary amino group gave dicarbamate **9** in 60% yield (two steps). The acetonide group of **9** was then removed under acidic conditions to give triol **10** in 76% yield. In the final step of our synthesis, **10** was converted to Mohapatra's intermediate (**3**) via oxidative lactonization with TEMPO and $PhI(OAc)_2$[8] in 81% yield. The spectral data of synthetic **3** were identical to the reported data.[8] Thus, our diastereoselective Henry reaction-based synthetic approach allowed us to achieve a stereoselective formal total synthesis of manzacidin B.



Scheme 6. Formal total synthesis of manzacidin B

3-4. Conclusion

In conclusion, we have achieved a formal total synthesis of manzacidin B: the total number of processes from the known aldehyde **5c** to Mohapatra's synthetic intermediate **3** included 8 steps, and the overall yield has been 11%. The *β*,*β*'disubstituted *γ*-hydroxy-*β*-aminoalcohol, the key structure of manzacidin B, was diastereoselectively constructed via sequential Henry reactions of nitroethane with two aldehydes. By taking advantage of noncovalent interactions such as intramolecular hydrogen bonding and chelation, we could diastereodivergently control the stereoselectivity of the Henry reactions. Therefore, the present method could allow us to synthesize not only the natural isomer but also C5 and C6 diastereomers of manzacidin B diastereoselectively.

3-5. Reference

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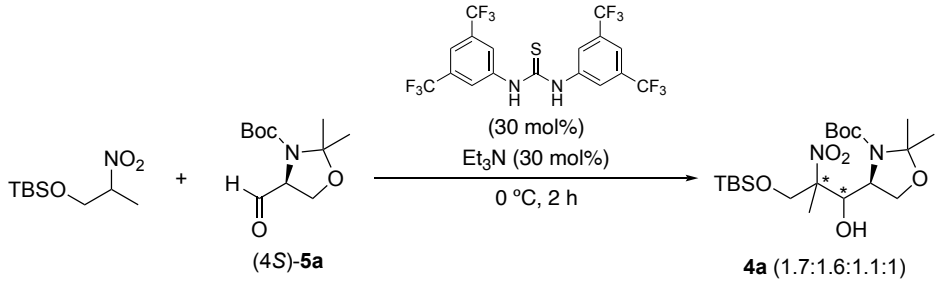
3-6. Experimental section General Experimental Information

All reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents, unless noted. All reagents and starting materials were purchased from commercial sources and used as supplied, unless otherwise noted. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and diethylether (Et_2O) were purchased from Kanto Chemical. Anhydrous toluene was purchased from FUJIFILM Wako Pure Chemical. IR spectra were recorded on a SHIMADZU FTIR-8400 spectrometer. ^{1}H spectra were recorded on a Varian NMR System 600 PS600 spectrometer (600 MHz) and a Varian 400-MR ASW spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from the solvent resonance employed as the internal standard ($CHCl_3$ at 7.26 ppm) on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; br = broad; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian NMR System 600 PS600 spectrometer (150 MHz) and a Varian 400-MR ASW spectrometer (100 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). Optical rotations were measured on a Horiba SEPA-300 digital polarimeter using a 3.5 mm × 0.5 dm pyrex cell. TLC analyses were performed on Merck precoated TLC plates (silica gel 60 F254 0.25 mm), and the spots were visualized by UV-light (254 nm) or phosphomolybdic acid stain and anisaldehyde stain. Column chromatography was performed on Kanto silica gel 60 N (spherical, neutral). High-resolution mass spectral analyses (HRMS) were measured on Bruker micrOTOF II [electrospray ionization (ESI)/time-of-flight] and JEOL JMS-700 MStation [fast atom bombardment (FAB)/double-focusing magnetic sector] at Chemical Instrument Facility, Okayama University.

Henry Reaction of 7 with (4S)-5a

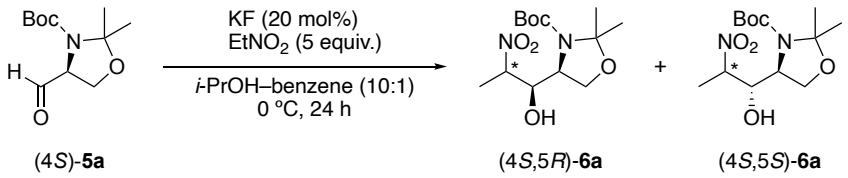
***tert*-Butyl (4*S*)-4-(1,3- dihydroxy-2-methyl-2-nitropropyl)-2,2-dimethyloxazolidine -3-carboxylate [4a]**



Et_3N and Thiourea-Catalyzed Method: To a mixture of (4*S*)-**5a** (51.0 mg, 0.222 mmol) and 1-(*tert*-butyldimethylsilyloxy)-2-nitropropane (498 mg, 2.22 mmol) were added 3,5-bis-(trifluoromethyl)phenylthiourea (33.3 mg, 66.6 μmol) and Et_3N (10.0 μL, 66.6 μmol) at 0 °C. After being stirred at the same temperature for 2 h, the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl at 0 °C and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The residue was purified by column chromatography on silica gel (hexane−EtOAc 5:1) to afford **4a** (69.7 mg, 0.155 mmol, 70%) as a diastereomeric mixture (relative stereochemistry was not determined). The diastereomeric ratio of **4a** (1.7:1.6:1.1:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 0.04 (s, 6H), δ 0.05 (s, 6H), δ 0.06 (s, 6H), and δ 0.07 (s, 6H). 4a (mixture of four diastereomers)

4a (dr = 1.7:1.6:1.1:1): colorless oil; IR (film): 3493, 3020, 2931, 2858 1693, 1548, 1392, 1367, 1255, 1215, 840, 756 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.40−3.99 (m, 33.3H), 3.96−3.82 (m, 12.0H), 1.61−1.54 (m, 18.5H), 1.53−1.44 (m, 72.2H), 0.86− 0.84 (m, 54.9H), 0.073 (s, 6.00H), 0.062 (s, 6.71H), 0.052 (s, 9.93H), 0.038 (s, 10.3H); HRMS (ESI) m/z: calcd for $C_{20}H_{40}N_2NaO_7Si$ $[M + Na]^+$, 471.2502; found, 471.2499. *DBU-Catalyzed Method:* To a solution of (4*S*)-**5a** (68.8 mg, 0.300 mmol) and 1-(*tert*-butyldimethylsilyloxy)-2-nitropropane (198 mg, 0.900 mmol) in THF (3 mL) was added DBU (40.0 μL, 0.270 mmol) at −50 °C. After being stirred at the same temperature for 19 h, the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl at −50 °C and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The residue was purified by column chromatography on silica gel (hexane−EtOAc 5:1) to afford **4a** (29.1 mg, 64.9 μmol, 22%) as a diastereomeric mixture. The diastereomeric ratio (1.6:1.6:1.2:1) was determined by ^{1}H NMR as mentioned above. First Henry Reaction.

(4*R*)-*tert*-Butyl-4-((1*R*)-Hydroxy-2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate [(4*S*,5*R*)-6a] and (4*R*)-*tert*-Butyl-4-((1*S*)-Hydroxy-2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate [(4*S*,5*S*)-6a]

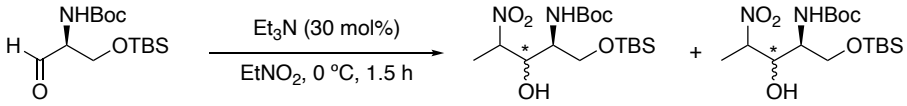


To a solution of (4*S*)-**5a** (45.8 mg, 0.200 mmol) in *i*-PrOH−benzene = 10:1 (2.20 mL) were added nitroethane (71.5 μL, 1.00 mmol) and KF (2.30 mg, 40 μmol) at ambient temperature. After being stirred at the same temperature for 24 h, the mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. After being concentrated in vacuo, the residue was dissolved in CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The residue was subjected to column chromatography on silica gel (CH_2Cl_2− EtOAc 10:1) to afford (4*S*,5*R*)-**6a** (8.3 mg, 27.5 μmol, 14%, 1:1 mixture of diastereomers at C6) and (4*S*,5*S*)-**6a** (42.0 mg, 0.138 mmol, 69%, 2:1 mixture of diastereomers at C6). The diastereomeric ratio of (4*S*,5*R*)-**6a** (1:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 4.64 (app quin, 1H) and δ 4.49 (br s, 1H). The diastereomeric ratio of (4*S*,5*S*)-**6a** (2:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 4.58 (dq, 1H, major diastereomer) and δ 4.54 (app quin, 1H, minor diastereomer). In both cases, relative stereochemistry of C6 was not determined.

(4*S*,5*R*)-**6a** (1:1 mixture of diastereomers): colorless oil; IR (film): 3446, 3024, 2981, 1698, 1652, 1556, 1367 cm^{-1} ; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.64 (app quin, *J* = 5.4 Hz, 1H), 4.49 (br s, 1H), 4.40 (br s, 1H), 4.21−4.13 (br s, 1H), 4.10−4.00 (m, 1H: overlapped with diastereomer 1H), 3.95−3.90 (m, 1H: overlapped with diastereomer 1H), 3.89−3.84 (m, 1H), 3.83−3.76 (br s, 1H), 1.63 (d, *J* = 6.6 Hz, 3H), 1.61−1.54 (m, 9H), 1.49 (s, 3H), 1.48 (s, 3H), 1.47 (s, 9H: overlapped with diastereomer 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 155.2, 94.5, 84.6, 84.2, 82.2, 81.9, 76.1, 74.9, 65.5, 64.4, 59.4, 58.8, 28.2, 27.0, 23.9, 15.8, 11.7; HRMS (FAB) m/z: calcd for $C_{13}H_{25}N_2O_6$ [M + H]$^+$, 305.1707; found, 305.1732.

(4*S*,5*S*)-**6a** (major diastereomer: minor diastereomer = 2:1, only characteristic peaks of the minor diastereomer were described):colorless oil; IR (film): 3440, 3021, 2981, 1690, 1651, 1552, 1367 cm^{-1} ; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.58 (dq, *J* = 6.6, 2.4 Hz, 1H), 4.54 (app quin, *J* = 6.0 Hz, 0.5H: minor diastereomer), 4.22 (app d, *J* = 4.8 Hz, 1H), 4.20−4.15 (m, 0.5H: minor diastereomer), 4.14 (app d, *J* = 9.0 Hz, 1H), 4.11−4.05 (m, 0.5H: minor diastereomer), 4.04−3.90 (m, 2H: overlapped with minor diastereomer 0.5H), 3.83 (br s, 0.5H: minor diastereomer), 3.68 (br s, 1H), 2.90 (br s, 0.5H: minor diastereomer) 1.64 (d, *J* = 6.6 Hz, 3H: overlapped with minor diastereomer 1.5H), 1.59−1.53 (m, 3H, minor diastereomer 1.5H × 2), 1.52−1.44 (m, 12H: overlapped with minor diastereomer 4.5H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 153.9, 94.5 (minor diastereomer), 84.9 (minor diastereomer), 84.3, 81.5, 73.4, 73.1, 64.8, 63.8 (minor diastereomer), 59.4 (minor diastereomer), 58.9, 28.3, 27.4, 26.9 (minor diastereomer), 23.9, 22.6 (minor diastereomer), 16.7, 12.8 (minor diastereomer); HRMS (FAB) m/z: calcd for $C_{13}H_{25}N_2O_6$ [M + H]$^+$, 305.1707; found, 305.1737.

tert-Butyl ((2_S_,3_R_)-1-((_tert_-Butyldimethylsilyl)oxy)-3-hydroxy-4- nitropentan-2-yl) carbamate [(4_S_,5_R_)-6b] and _tert_-Butyl ((2_S_,3_S_)- 1-((_tert_-Butyldimethylsilyl)oxy)-3-hydroxy-4-nitropentan-2-yl)-carbamate [(4_S_,5_S_)-6b]



(4*S*)-**5b** **6ba** (5*R*:5*S* = 2:1) **6bb** (5*R*:5*S* = 2:1)

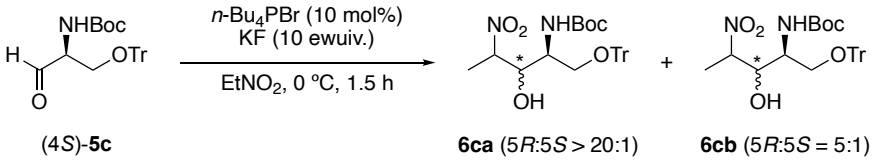
To a solution of (4*S*)-**5b**[22] (60.5 mg, 0.200 mmol) in $EtNO_2$ (2.00 mL) was added triethylamine (8.40 μL, 59.8 μmol) at 0 °C. After being stirred at the same temperature for 1.5 h, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude product. The residue was subjected to column chromatography on silica gel (hexane−EtOAc 20:1) to afford **6ba** (39.4 mg, 0.104 mmol, 52%, mixture of diastereomers at C5, 5*R*/5*S* = 2:1) and **6bb** (19.8 mg, 0.0522 mmol, 26%, mixture of diastereomers at C5, 5*R*/5 = 2:1). **6ba** and **6bb** are stereoisomers at C6, but relative stereochemistry was not determined. The diastereomeric ratio of **6ba** (5*R*/5*S* = 2:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 4.79 (app quin, 1H, 5*R* isomer) and δ 4.61 (app quin, 1H, 5*S* isomer). The diastereomeric ratio of **6bb** (5*R*/5*S* = 2:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 4.67 (qd, 1H, 5*S* isomer) and δ 4.59 (qd, 1H, 5*R* isomer).

6ba (5*R* isomer/5*S* isomer = 2:1, only characteristic peaks of 5*S* isomer were described): colorless oil; IR (film): 3440, 3348, 3020, 2929, 2858, 1698, 1695, 1558, 1456 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.16 (d, *J* = 9.6 Hz, 1H), 4.99 (d, *J* = 8.4 Hz, 0.5H: 5*S* isomer), 4.67 (qd, *J* = 6.6, 3.0 Hz, 0.5H: 5*S* isomer), 4.59 (qd, *J* = 9.6, 6.6 Hz, 1H), 4.34 (app d, *J* = 9.6 Hz, 1H), 4.24 (ddd, *J* = 8.4, 5.4, 3.0 Hz, 0.5H: 5*S* isomer), 4.04 (dd, *J* = 10.2, 2.4 Hz, 0.5H: 5*S* isomer), 3.86 (app d, *J* = 4.2 Hz, 2H), 3.74 (dt, *J* = 9.6, 4.2 Hz, 1H), 3.69 (dd, *J* = 10.2, 3.6 Hz, 0.5H: 5*S* isomer), 3.64 (d, *J* = 2.4 Hz, 1H: 5*S* isomer), 3.62−3.57 (m, 0.5H: 5*S* isomer), 3.13 (d, *J* = 5.4 Hz, 0.5H: 5*S* isomer), 1.66 (d, *J* = 6.6 Hz, 1.5H: 5*S* isomer), 1.55 (d, *J* = 6.6 Hz, 3H), 1.45 (s, 9H: overlapped with 5*S* isomer 4.5H), 0.89 (s, 9H: overlapped with 5*S* isomer 4.5H), 0.09 (s, 6H: overlapped with 5*S* isomer 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 155.6, 86.0, 84.3 (5*S* isomer), 80.2, 74.8, 72.1 (5*S* isomer), 65.9, 62.5 (5*S* isomer), 51.9 (5*S* isomer), 50.1, 28.3, 25.83, 25.77, 18.2 (5*S* isomer), 18.1, 16.0, 12.8 (5*S* isomer), −5.59, −5.65 (5*S* isomer); HRMS (FAB) m/z: calcd for $C_{13}H_{25}N_2O_6$ [M + H]$^+$, 305.1707; found, 305.1732.

6bb (5*R* isomer/5*S* isomer = 2:1, only characteristic peaks of 5*S* isomer were described): colorless oil; IR (film): 3438, 3384, 2981, 2858, 1685, 1618, 1560, 1458 cm^{-1} ; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.21 (d, *J* = 8.4 Hz, 1H), 5.11 (d, *J* = 8.4 Hz, 0.5H: 5*S* isomer), 4.79 (app quin, *J* = 6.6 Hz, 1H), 4.61 (app quin, *J* = 6.6 Hz, 0.5H: 5*S* isomer), 4.38 (app d, *J* = 4.8 Hz, 0.5H: 5*S* isomer), 4.06 (br s, 1H), 3.85 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.83−3.78 (m, 1H: overlapped with 5*S* isomer 1H), 3.78−3.73 (m, 1H), 3.63−3.55 (m, 1H: overlapped with 5*S* isomer 0.5H), 1.62 (d, *J* = 6.6 Hz, 1.5H: 5*S* isomer), 1.58 (d, *J* = 6.6 Hz, 3H), 1.44 (s, 9H: overlapped with 5*S* isomer 4.5H), 0.90 (s, 9H), 0.89 (s, 4.5H: 5*S* isomer), 0.09, (s, 6H), 0.078 (s, 1.5H: 5*S* isomer), 0.075

(s, 1.5H: 5*S* isomer); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 155.3, 85.8, 84.1 (5*S* isomer), 80.1, 74.9, 73.1 (5*S* isomer), 65.3 (5*S* isomer), 62.8, 52.1, 51.0, 28.3, 25.8, 18.1, 16.3, 14.9 (5*S* isomer), −5.59; HRMS (FAB) m/z: calcd for $C_{13}H_{25}N_2O_6$ $[M + H]^+$, 305.1707; found, 305.1732.

tert-Butyl ((2*S*,3*R*)-3-Hydroxy-4-nitro-1-(trityloxy)pentan-2-yl)-carbamate [(4*S*,5*R*)-6c] and _tert_-Butyl ((2*S*,3*S*)-3-Hydroxy-4-nitro1-(trityloxy)pentan-2-yl)carbamate [(4*S*,5*S*)-6c]



To a solution of (4*S*)-**5c**[23] (468 mg, 1.09 mmol) in $EtNO_2$ (10.0 mL) was added tetrabutylphosphonium bromide (36.9 mg, 0.109 mmol) and KF (633 mg, 10.9 mmol) at 0 °C. After being stirred at the same temperature for 1.5 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0 °C and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product. The residue was subjected to column chromatography on silica gel (hexane−EtOAc 15:1) to afford **6ca** (244 mg, 0.482 mmol, 44%, 5*R*/5*S* > 20:1) and **6cb** (252 mg, 0.497 mmol, 46%, mixture of diastereomers at C5, 5*R*/5*S* = 5:1). **6ca** and **6cb** are stereoisomers at C6, but relative stereochemistry was not determined. The diastereomeric ratio of **6cb** (5*R*/5*S* = 5:1) was determined by ^1H NMR analysis comparing the characteristic peaks observed at δ 5.06 (d, 1H, 5*R* isomer) and δ 4.96 (d, 1H, 5S isomer).

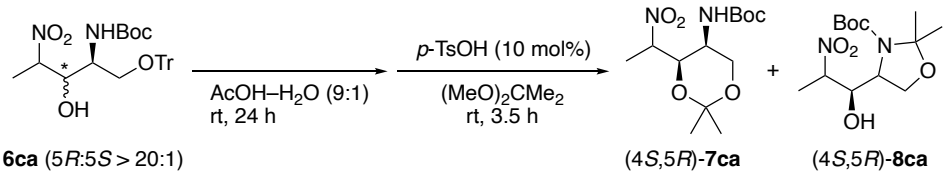
6ca: colorless solid; mp 62−64 °C; $[\alpha]_D^{27}$ −30.2 (c 0.50, $CHCl_3$); IR (film): 3428, 3059, 2978, 2880, 1713, 1549, 1165, 750 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.37 (m, 6H), 7.36−7.24 (m, 9H: overlapped with $CHCl_3$), 5.11 (d, *J* = 8.4 Hz, 1H), 4.49 (app quin, *J* = 5.6 Hz, 1H), 4.30−4.23 (m, 1H), 3.68 (app dt, *J* = 8.4, 4.8 Hz, 1H), 3.46 (d, *J* = 4.8 Hz, 1H), 3.41 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.28 (dd, *J* = 9.6, 4.8 Hz, 1H), 1.56 (d, *J* = 5.6 Hz, 3H: overlapped with water), 1.46 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.0, 143.2, 128.4, 128.0, 127.3, 87.3, 84.0, 80.3, 72.5, 64.4, 51.9, 28.3, 14.3; HRMS (ESI) m/z: calcd for $C_{29}H_{34}N_2NaO_6$ $[M + Na]^+$, 529.2315; found, 529.2306.

6cb (5*R* isomer/5*S* isomer = 5:1, only characteristic peaks of 5*S* isomer were described): colorless solid; IR (film): 3424, 3023, 2980, 2932, 1692, 1557, 1161, 760 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.38 (m, 6H: overlapped with 5*S* isomer 1.5H), 7.36−7.30 (m, 6H: overlapped with 5*S* isomer 1.5H), 7.29−7.24 (m, 3H: overlapped with 5*S* isomer 0.75H and $CHCl_3$), 5.06 (d, *J* = 9.6 Hz, 1H), 4.96 (d, *J* = 9.6 Hz, 0.25H: 5*S* isomer), 4.54 (dq, *J* = 9.6, 6.8 Hz, 1H), 4.38− 4.30 (m, 0.25H: 5*S* isomer), 4.12 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.87 (app dt, *J* = 9.6, 4.4 Hz, 1H), 3.68−3.58 (m, 0.25H: 5*S* isomer), 3.55 (dd, *J* = 9.6, 4.4 Hz, 0.25H: 5*S* isomer), 3.40 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.34 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.82 (d, *J* = 3.6 Hz, 1H), 2.55 (d, *J* = 4.0 Hz, 0.25H: 5*S* isomer), 1.53 (d, *J* = 6.8 Hz, 3H), 1.46 (s, 9H), 1.44 (s, 2.25H: 5*S* isomer); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.5, 143.2, 128.4, 128.1, 127.4, 87.5, 85.9, 80.2, 73.8,

64.9, 49.8, 28.3, 16.1; HRMS (ESI) m/z: calcd for $C_{29}H_{34}N_2NaO_6$ [M + Na]$^+$, 529.2315; found, 529.2310.

Synthesis of Chiral Nitroalkane 7c

***tert*-Butyl ((4*R*,5*S*)-2,2-Dimethyl-4-(1-nitroethyl)-1,3-dioxan-5-yl)carbamate [(4*S*,5*R*)-7c] and (4*S*)-*tert*-Butyl-4-((1*R*)-1-hydroxy-2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate [(4*S*,5*R*)-8c]**

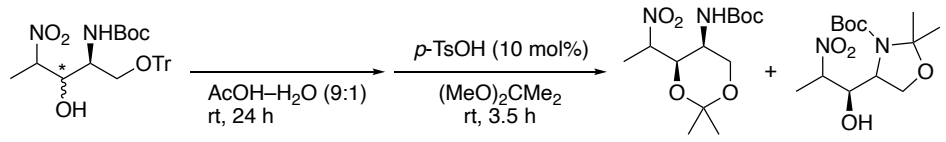


(4*S*,5*R*)-**6ca** (851 mg, 1.68 mmol) was dissolved in AcOH−H_2O = 9:1 (20.0 mL), and the resulting solution was stirred at ambient temperature for 24 h. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane−EtOAc 1:1). The obtained material was dissolved in 2,2-dimethoxypropane (8.00 mL), and *p*-toluenesulfonic acid monohydrate (30.2 mg, 0.159 mmol) was added at ambient temperature. After being stirred for 3.5 h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc 15:1) to afford (4*S*,5*R*)-**7ca** (309 mg, 1.01 mmol, 60% over 2 steps) and (4*S*,5*R*)-**8ca** (64.1 mg, 0.211 mmol, 13% over 2 steps).

(4*S*,5*R*)-**7ca**: colorless solid; mp 104−105 °C; $[\alpha]_D^{27}$ −4.57 (c 3.8, $CHCl_3$); IR (film): 3455, 3316, 2982, 2911, 1715, 1553, 1495, 1165, 849 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (d, *J* = 10.0 Hz, 1H), 4.59 (app quin, *J* = 6.8 Hz, 1H), 4.36 (d, *J* = 7.6 Hz, 1H), 4.09 (d, *J* = 10.8 Hz, 1H), 3.80−3.65 (m, 2H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.49 (s, 3H), 1.45 (s, 9H), 1.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.2, 99.9, 81.8, 80.0, 72.0, 64.7, 44.7, 29.3, 28.2, 18.4, 16.2; HRMS (ESI) m/z: calcd for $C_{13}H_{24}N_2NaO_6$ [M + Na]$^+$, 327.1532; found, 327.1526.

(4*S*,5*R*)-**8ca**: colorless solid; mp 75−76 °C; $[\alpha]_D^{27}$ −43.5 (c 1.0, $CHCl_3$); IR (film): 3433, 2980, 2940, 1694, 1553, 1393, 1165, 849 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (br s, 1H), 4.40 (br d, *J* = 6.0 Hz, 1H), 4.08 (app t, *J* = 7.2 Hz, 1H), 3.97 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.81 (br s, *J* = 8.4 Hz, 1H), 1.61 (br s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H), 1.51 (s, 3H), 1.49 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.6, 94.5, 84.2, 82.3, 75.1, 64.5, 59.4, 28.3, 27.1, 24.0, 11.8; HRMS (ESI) m/z: calcd for $C_{13}H_{24}N_2NaO_6$ [M + Na]$^+$, 327.1532; found, 327.1527.

***tert*-Butyl ((4*R*,5*S*)-2,2-Dimethyl-4-(1-nitroethyl)-1,3-dioxan-5-yl)carbamate [(4*S*,5*R*)-7cb] and (4*S*)-*tert*-Butyl-4-((1*R*)-1-hydroxy2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate [(4*S*,5*R*)-8cb]**



6cb (5*R*:5*S* = 5:1) (4*S*,5*R*)-**7cb** (4*S*,5*R*)-**8cb**

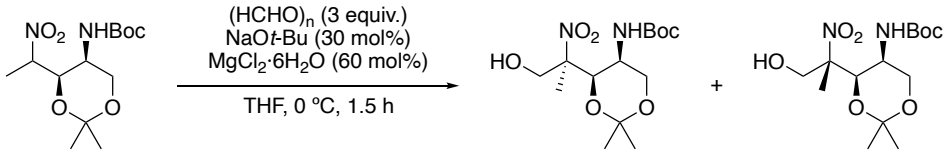
Following the same procedure described for the conversion of (4*S*,5*R*)-**6ca** to (4*S*,5*R*)-**7ca** and (4*S*,5*R*)-**8ca**, (4*S*,5*R*)-**6cb** (1.68 g, 3.32 mmol) was converted to (4*S*,5*R*)-**7cb** (495 mg, 1.63 mmol, 49% over 2 steps) and (4*S*,5*R*)-**8cb** (53.9 mg, 0.177 mmol, 5% over 2 steps).

(4*S*,5*R*)-**7cb**: colorless solid; mp 94−96 °C; $[\alpha]_D^{27}$ −20.2 (c 1.8, $CHCl_3$); IR (film): 3377, 2982, 2944, 1713, 1557, 1501, 1165, 847 cm^{-1}; 1 H NMR (400 MHz, $CDCl_3$): δ 5.36 (d, *J* = 10.4 Hz, 1H), 4.56 (dq, *J* = 9.6, 6.8 Hz, 1H), 4.37 (dd, *J* = 9.6, 1.6 Hz, 1H), 4.11 (dd, *J* = 12.0, 1.6 Hz, 1H), 3.76 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.70 (dd, *J* = 10.4, 2.0 Hz, 1H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.45 (s, 9H), 1.43 (s, 3H), 1.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.3, 99.8, 84.8, 80.3, 73.2, 65.0, 44.0, 29.2, 28.2, 18.0, 15.0; HRMS (ESI) m/z: calcd for $C_{13}H_{24}N_2NaO_6$ $[M + Na]^+$, 327.1532; found, 327.1529.

(4*S*,5*R*)-**8cb**: colorless solid; mp 82−84 °C; $[\alpha]_D^{27}$ −26.1 (c 0.35, $CHCl_3$); IR (film): 3337, 2980, 2942, 1715, 1694, 1557, 1393, 1165, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.66−4.55 (m, 1H), 4.53 (d, *J* = 10.0 Hz, 1H), 4.38 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.92 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.75−3.65 (m, 1H), 3.59 (dd, *J* = 11.2, 8.8 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 9H), 1.40 (s, 3H), 1.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.1, 99.3, 82.4, 80.5, 74.0, 62.9, 45.8, 28.2, 27.7, 19.3, 11.1; HRMS (ESI) m/z: calcd for $C_{13}H_{24}N_2NaO_6$ $[M + Na]^+$, 327.1532; found, 327.1523.

Second Henry Reaction.

***tert*-Butyl ((4*R*,5*S*)-4-((*R*)-1-Hydroxy-2- nitropropan-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl) carbamate [(4*S*,5*R*,6*R*)-4c] and *tert*-Butyl ((4*R*,5*S*)-4-((*S*)-1-Hydroxy-2-nitropropan-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl) carbamate [(4*S*,5*R*,6*S*)-4c]**



(4*S*,5*R*)-**7ca** (4*S*,5*R*,6*R*)-**4c** (4*S*,5*R*,6*S*)-**4c**

A two-neck flask charged with $MgCl_2 \cdot 6H_2O$ (11.2 mg, 55.1 μmol) was heated by a heat-gun under vacuum for 5 min (*Note: the appearance of $MgCl_2 \cdot 6H_2O$, which was initially a colorless solid, was changed to a white solid during this step*). After cooling down to ambient temperature, the flask was purged with nitrogen. To the flask were added NaO*t*-Bu (10.6 mg, 0.110 mmol) and THF (0.500 mL), and the resulting mixture was stirred at ambient temperature for 30 min before it was cooled to 0 °C. To this solution was then added a solution of (4*S*,5*R*)-**7ca** (54.7 mg, 0.180 mmol) in THF (1.00 mL) followed by $(HCHO)_n$ (17.2 mg, 0.572 mmol). After being stirred at the same temperature for 1.5 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0 °C. The mixture was extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4. After filtration, the solvent was removed in

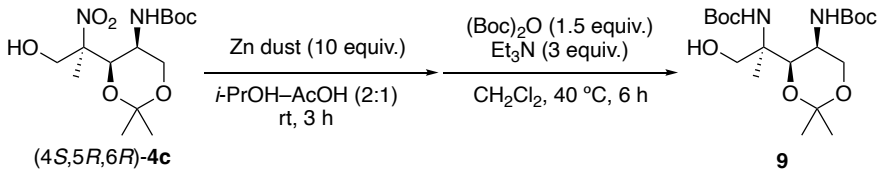
vacuo and the crude material was subjected to column chromatography on silica gel (hexane−EtOAc 4:1) to afford **4c** (55.5 mg, 0.166 mmol, 92%, 6*R*/6*S* = 6:1). Further purification was carried out by column chromatography on silica gel (CH_2Cl_2−EtOAc 7:1) to separate (4*S*,5*R*,6*R*)-**4c** (45.7 mg, 0.137 mmol, 76%) and (4*S*,5*R*,6*S*)-**4c** (7.2 mg, 21.6 μmol, 12%). (4*S*,5*R*)-**7cb** (322 mg, 1.06 mmol) was also converted to **4c** (284 mg, 0.849 mmol, 80%, 6R/6S = 5:1) according to the same manner as (4*S*,5*R*)-**7ca**.

(4*S*,5*R*,6*R*)-**4c**: colorless solid; mp 75−77 °C; $[\alpha]_D^{24}$ −16.2 (c 0.50, $CHCl_3$); IR (film): 3445, 2982, 2942, 1694, 1549, 1505, 1368, 1163, 1099, 764 cm^{-1} ; 1 H NMR (400 MHz, $CDCl_3$): δ 5.35 (d, *J* = 10.0 Hz, 1H), 4.92 (app s, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 4.05 (dd, *J* = 12.0, 7.2 Hz, 1H), 3.93 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.68 (dd, *J* = 12.0, 2.0 Hz, 1H), 2.83 (br s, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 1.44 (s, 9H), 1.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.4, 100.3, 94.8, 80.4, 72.0, 66.6, 65.9, 45.0, 29.3, 28.3, 18.0, 14.9; HRMS (ESI) m/z: calcd for $C_{14}H_{26}N_2NaO_7$ $[M + Na]^+$, 357.1638; found, 357.1630.

(4*S*,5*R*,6*S*)-**4c**: colorless solid; mp 94−96 °C; $[\alpha]_D^{24}$ −4.85 (c 1.57, $CHCl_3$); IR (film): 3451, 2982, 2940, 1699, 1547, 1505, 1163, 1096, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (d, *J* = 10.0 Hz, 1H), 4.77 (app s, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.71 (d, *J* = 12.0 Hz, 1H), 2.74 (br s, 1H), 1.58 (s, 3H), 1.44 (s, 9H), 1.44 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.1, 100.5, 93.6, 80.5, 74.9, 66.4, 64.1, 44.9, 29.2, 28.3, 18.2, 17.7; HRMS (ESI) m/z: calcd for $C_{14}H_{26}N_2NaO_7$ $[M + Na]^+$, 357.1638; found, 357.1636.

Formal Total Synthesis of Manzacidin B.

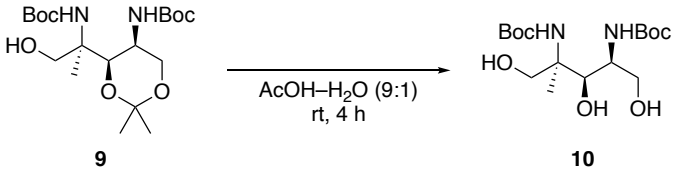
***tert*-Butyl ((4*R*,5*S*)-4-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-1-hydroxypropan-2-yl) -2,2-dimethyl-1,3-dioxan-5-yl)carbamate [9]**



(4*S*,5*R*,6*R*)-**4c** (64.4 mg, 0.193 mmol) was dissolved in *i*-PrOH−AcOH = 2:1 (1.50 mL) at ambient temperature, and the resulting solution was treated with Zn dust (125 mg, 1.93 mmol) which was added in 3 portions every hour. The mixture was further stirred at ambient temperature for 3 h. After the period of time, the mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc−MeOH 20:1). The obtained material was dissolved in CH_2Cl_2 (2.00 mL) and treated with Et_3N (80 μL, 0.579 mmol) and $(Boc)_2O$ (62.5 mg, 0.290 mmol) at 40 °C for 6 h. The reaction was quenched by the addition of water at 40 °C. The resultant mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−AcOEt 3:1) to afford **9** (46.7 mg, 0.116 mmol, 60% over 2 steps).

9: colorless solid; mp 129−130 °C; $[\alpha]_D^{23}$ −10.6 (c 0.57, $CHCl_3$); IR (film): 3447, 2978, 2934, 1715, 1699, 1506, 1368, 1171, 1076, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.27 (br s, 1H), 4.93 (s, 1H), 4.31 (app s, 1H), 4.06 (d, J = 12.0 Hz, 1H), 3.90 (br d, J = 9.6 Hz, 1H), 3.86−3.80 (m, 1H), 3.73 (dd, J = 12.0, 4.4 Hz, 1H), 3.68 (dd, J = 12.0, 2.0 Hz, 1H), 1.48−1.43 (m, 15H), 1.43 (s, 9H), 1.19 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.0, 155.0, 100.0, 79.9, 72.2, 67.3, 66.7, 59.1, 45.2, 29.6, 28.4, 28.3, 27.7, 18.7, 18.5; HRMS (ESI) m/z: calcd for $C_{19}H_{36}N_2NaO_7$ $[M + Na]^+$, 427.2420; found, 427.2428.

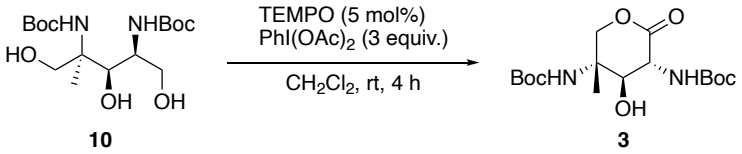
Di-*tert*-butyl ((2*R*,3*R*,4*S*)-1,3,5-Trihydroxy-2-methylpentane-2,4- diyl)dicarbamate [10]



Acetonide **9** (23.7 mg, 58.6 μmol) was dissolved in AcOH−H_2O = 9:1 (1.00 mL) at ambient temperature, and the solution was stirred at the same temperature for 4 h. The solvent was removed in vacuo at 40 °C. The residue was purified by column chromatography on silica gel (hexane−EtOAc 1:1) to afford **10** (16.2 mg, 44.5 μmol, 76%).

10: colorless solid; mp 140−142 °C; $[\alpha]_D^{20}$ −22.5 (c 0.47, $CHCl_3$); IR (KBr): 3450, 3291, 2979, 1670, 1506, 1365, 1178, 1022 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 5.48 (br s, 1H), 5.35 (d, J = 9.2 Hz, 1H), 5.16 (br s, 1H), 4.02 (d, J = 4.0 Hz, 1H), 3.97 (d, J = 11.6 Hz, 1H), 3.94−3.87 (m, 1H), 3.85−3.72 (m, 2H), 3.71−3.60 (m, 2H), 3.15 (br s, 1H), 1.45 (s, 9H), 1.43 (s, 9H), 1.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.2, 156.1, 80.5, 79.8, 75.7, 67.6, 65.9, 59.2, 50.7, 28.4, 28.3, 20.1; HRMS (FAB) m/z: calcd for $C_{16}H_{33}N_2O_7$ $[M + H]^+$, 365.2288; found, 365.2271.

Di-*tert*-butyl ((3*R*,4*R*,5*R*)-4-Hydroxy-5-methyl-2-oxotetrahydro2H-pyran-3,5-diyl) dicarbamate [3] (Mohapatra's Intermediate)



To a solution of **10** (14.7 mg, 40.3 μmol) in CH_2Cl_2 (2.00 mL) was added $PhI(OAc)_2$ (39.5 mg, 0.123 mmol) and TEMPO (1.3 mg, 8.30 μmol) at ambient temperature. After being stirred at the same temperature for 4 h, the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution. The resulting mixture was extracted with Et_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product. The residue was purified by column chromatography on silica gel (hexane−EtOAc 5:1) to afford Mohapatra's intermediate (**3**) (11.7 mg, 32.5 μmol, 81%).

3: colorless solid; mp 151−153 °C; $[\alpha]_D^{20}$ −20.4 (c 0.33, $CHCl_3$); IR (KBr): 3419, 3019, 2981, 2933, 1754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.69 (br s, 1H), 4.91 (br s, 1H), 4.73 (br s,

1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.15−4.09 (m, 1H), 3.95 (d, *J* = 5.4 Hz, 1H), 1.45 (s, 9H), 1.41 (s, 9H), 1.38 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 169.4, 157.3, 154.6, 81.5, 80.4, 76.4, 70.9, 57.3, 55.4, 28.3, 28.2, 16.6; HRMS (FAB) m/z: calcd for $C_{16}H_{29}N_2O_7$ $[M + H]^+$, 361.1975; found, 361.1969.

Chapter 4. Enantioselective construction of β-hydroxy-α,α-disubstituted α-amino acid structure using chiral catalyst

4-1. Abstract

The β-hydroxy-α,α-disubstituted α-amino acid is a valuable structural motif for research in the field of bioorganic chemistry and in the development of peptide drugs. This chapter describes the enantioselective direct-aldol reaction of α-imino esters with glyoxylate esters. We discovered that a catalytic amount of $Co(OAc)_2$-pybox complex catalyzed the aldol reaction of salicylaldehyde-derived α-imino esters with benzyl glyoxylate in good yield and enantioselectivity. In addition, hydrolysis of the imine moiety of the aldol products followed by Boc protection of the resultant amino group gave the *N*-Boc-protected amino alcohol derivatives.

4-2. Introduction

Optically active β-hydroxy-α-amino acid is an important structural motif that is widely found in natural compounds and used in chiral ligands and auxiliaries in asymmetric synthesis.[1] Some biologically active natural compounds include β-hydroxy-α,α-disubstituted α-amino acid as a core structure (**Figure 1**). For example, lactacystin,[2] which has a highly functionalized γ-lactam thioester, is known to inhibit 20S proteasome. Sphingofungin E[3] and myriocin,[4] which are members of a unique family of sphingosine-related natural products, act as antifungal and immunosuppressive agents through their inhibition of serine palmitoyl transferase. Altemicidin,[5] which strongly inhibits the growth of tumor cells, also includes this structural motif.

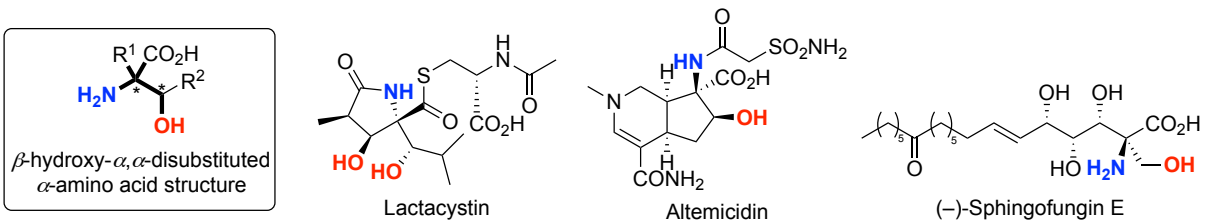


Figure 1. β-hydroxy-α,α-disubstituted α-amino acid as a structural motif found in biologically active compounds

In general, β-hydroxy-α,α-disubstituted α-amino acid structures can be synthesized via the aldol-type reaction of α-amino acid derivatives with aldehydes (**Figure 2**). To control the stereochemistry of the products, substrate-controlled multi-step transformations are conventionally used. For example, Schöllkopf and colleagues reported the diastereoselective aldol reaction of chiral cyclic diketopiperazine with aldehydes.[6] Seebach and colleagues also reported the diastereoselective aldol reaction of chiral imidazolidinone with aldehydes.[7] In these reports, several chiral aldol products were obtained in good yields and stereoselectivities. However, the catalytic use of chiral sources should be ideal for the promotion of these reactions. Thus, the development of an asymmetric catalysis for the aldol-type reaction of α-amino acid derivatives has emerged as a powerful alternative methodology. Although many catalytic methods for the asymmetric construction of the β-hydroxy-α-amino acid structure have been

reported,[8] there are only a few reports on the catalytic asymmetric synthesis of β-hydroxy-α,α-disubstituted α-amino acid structures. Thus, development of the methodology for construction of β-hydroxy-α,α-disubstituted α-amino acid structure is still needed.

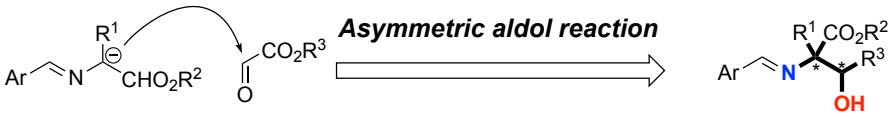


Figure 2. Synthetic plan for construction of β-hydroxy-α,α-disubstituted *a*-amino acid moiety

This chapter describes asymmetric catalysis for the direct aldol reaction of α-substituted α-imino esters with glyoxylate esters to construct the chiral β-hydroxy- α, α-disubstituted α-amino acid structure (**Figure 3**). In this aldol reaction, we chose salicylaldehyde-derived α-imino esters as substrates, since they are known to be activated via intramolecular hydrogen bonding.[9] The use of these activated chemical species would make it possible to carry out the reaction under mild conditions. The author also envisioned that these multiple interactions between the substrate and the catalyst would promote the reaction with advanced stereocontrol. To put this idea into practice, the author considered two types of catalysis: Brønsted acid–Brønsted base cooperative organocatalysis[10] (Method A: upper scheme) and Lewis acidic metal complex catalysis[11] (Method B: bottom scheme). In method A, the enolate intermediate, which would be generated via the abstraction of a-proton by the Brønsted base moiety, would be activated by multiple hydrogen bonding with the catalyst. In method B, the enolate intermediate would be activated via multiple interactions with the Lewis acidic metal cation. In both methods A and B, the enolate intermediate would be caught in the chiral environment of the catalyst via multiple noncovalent interactions.[12] Therefore, the path of the approach of glyoxylate to enolate in the subsequent aldol reaction would proceed stereoselectively.

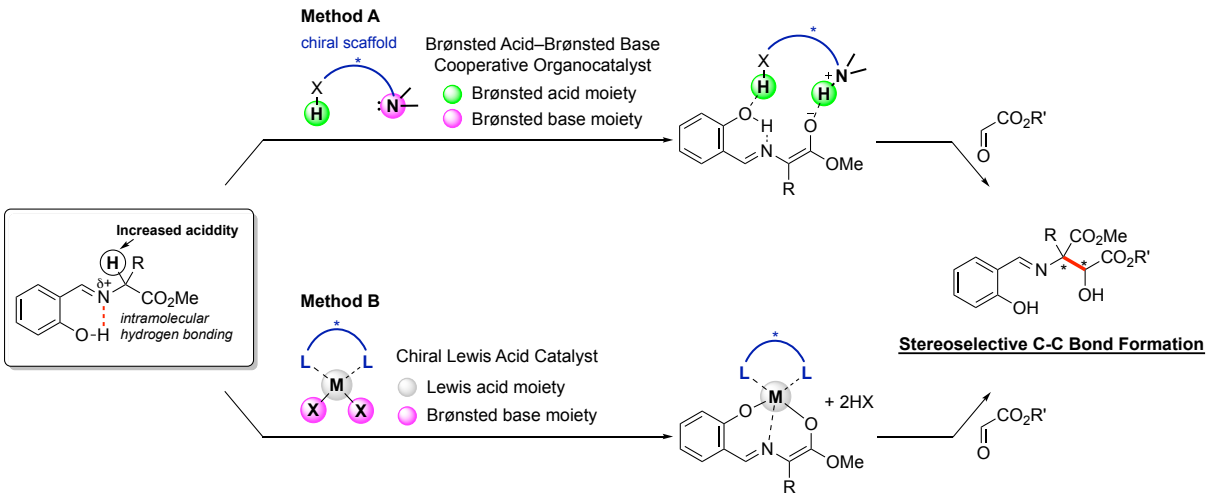
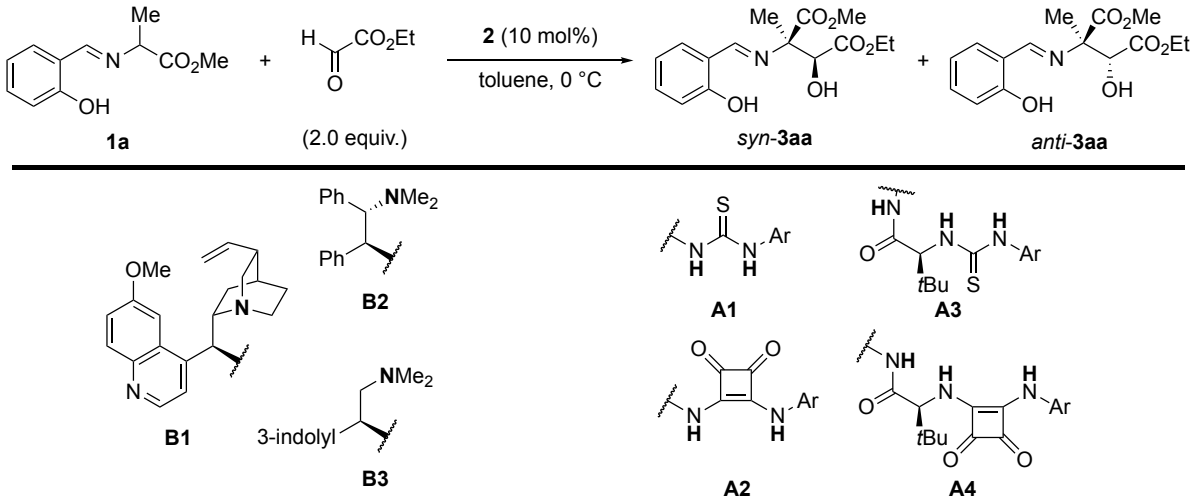


Figure 3. Working hypothesis: asymmetric catalysis in the direct aldol reaction of α-imino esters

4-3. Results and discussions

Based on the idea described above, our study commenced with an investigation of the activities of chiral organocatalysts **2**, which possess Brønsted acidic site **A** and Brønsted basic site **B**, in the direct aldol reaction of α-imino ester **1a** (**Table 1**). The reaction of **1a** with ethyl glyoxylate (2 equiv.) was conducted in the presence of 10 mol% of **2** in toluene at 0 °C for 24 h. Although **2a**, composed of chiral quinuclidine **B1** and thiourea **A1**, did not show any catalytic activity (Entry 1), the use of squaramide **A2** as the Brønsted acidic site promoted the reaction and the aldol product **3aa** was obtained in 26% yield (Entry 2). Further investigation of the design of **2** revealed that the introduction of a chiral amide linker between the Brønsted basic site (**B1**) and the Brønsted acidic site improved the yield of **3aa** (Entries 3, 5). The use of **2c**, a combination of **B1** and **A3**, gave **3aa** in 50% yield with an enantiomeric excess of 75% (*syn* isomer) and 79% (*anti* isomer), albeit almost no diastereoselectivity was observed (Entry 3). In contrast, the use of **B2** and **B3** as the chiral Brønsted basic site did not give aldol product **3aa** (Entries 6 and 7).

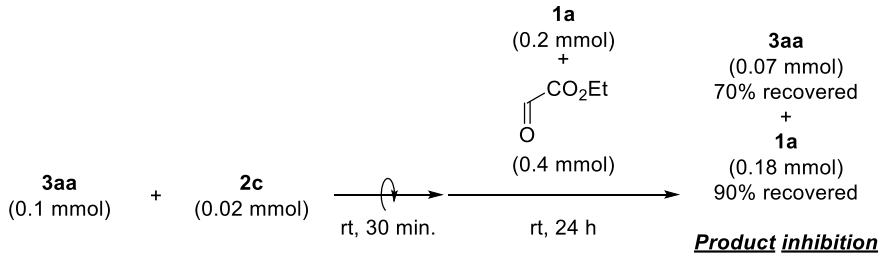
Table 1. Investigation of catalytic activities of chiral organocatalysts in direct aldol reaction[a]



Entry	2 (B–A)	Yield (%)[b]	Dr (*syn* : *anti*)[c]	Ee (%)[d] [*syn*/*anti*]
1	**2a (B1–A1)**	0	–	–
2	**2b (B1–A2)**	26	1.5 : 1	31 / 22
3	**2c (B1–A3)**	50	1.2 : 1	75 / 79
4[e,f]	**2c (B1–A3)**	36	1.9 : 1	88 / 89
5	**2d (B1–A4)**	43	1.1 : 1	38 / 42
6	**2e (B2–A3)**	0	–	–
7	**2f (B3–A3)**	0	–	–

[a]Conditions: **1a** (0.20 mmol), ethyl glyoxylate (2 equiv.), **2** (10 mol%) in toluene (0.2 mL) at 0 °C for 24 h. [b]Isolated yield. [c]Evaluated by ^{1}H NMR analysis. [d]Evaluated by HPLC analysis. [e]Concentration was 0.2 M. [f]MS4A was added.

The overall conversion of the current **2**-promoted direct aldol reaction of **1a** was low (**Table 1**). We considered that the low conversion could be attributed to inhibition of the catalysis of **2** by aldol product **3aa**.[13] To confirm this notion, we conducted a control reaction (**Scheme 1**). When the reaction of **1a** (0.20 mmol) with ethyl glyoxylate (0.40 mmol) was conducted in the presence of **2c** (0.020 mmol, 10 mol%) and **3aa** (0.10 mmol, *syn*:*anti* = 1.8:1) in toluene (1.0 mL), the reaction did not proceed, and 0.18 mmol (90%) of **1a** and 0.070 mmol (70%) of **3aa** were recovered. This result should indicate that catalyst **2c** would strongly interact with aldol product **3aa** via multiple hydrogen bonds to be deactivated in the reaction mixture. To promote the dissociation of **2c** and **3aa** in the reaction mixture, we conducted the direct aldol reaction of **1a** under diluted conditions (Table 1, Entry 4). However, the yield of **3aa** was not improved. Thus, we concluded that it was difficult to efficiently promote the reaction by using organocatalyst **2**.



Scheme 4. Control reaction to confirm of the product inhibition

We next investigated the catalytic activities of Lewis acidic metal complexes in the direct aldol reaction of **1a** (**Table 2**). The reaction of **1a** with ethyl glyoxylate (2 equiv.) was conducted in the presence of a complex (10 mol%), which was prepared in situ with a metal salt and chiral ligand **L1**–**4**, and MS4A[14] in *i*-$PrNO_2$ at 0 ºC. Since the counteranions of the metal complex catalysts were thought to act as Brønsted bases in the generation of enolates, its basicity should be important for efficient promotion of the direct aldol reaction of **1a**. Thus, we first examined the catalytic activities of divalent metal acetates. As we expected, the catalytic activity of a complex of $Cu(OAc)_2$ with chiral bis(oxazolinyl)pyridine (pybox) ligand **L1** was quite high, and aldol product **3aa** was obtained in 89% yield, albeit the diastereoselectivity and enantioselectivity were low (*syn*/*anti* = 1.9:1, 49 and 17% ee) (Entry 1).[15] As a result of the examination of other divalent metal acetates, we found that some of them showed good catalytic activities, and the use of $Co(OAc)_2{\cdot}4H_2O$ gave **3aa** in good yield (78%) with high enantioselectivity (89 and 85% ee) (Entry 4).[16] In sharp contrast, complexes of trivalent metal acetates such as $In(OAc)_3$ and $La(OAc)_3{\cdot}1.5H_2O$ were almost inert (Entries 6 and 7). As mentioned above, for efficient promotion of the direct aldol reaction, the counteranions of the Lewis acid catalysts should have sufficient Brønsted basicity to deprotonate **1a**. In fact, the use of a complex of $Co(OTf)_2{\cdot}2MeCN$ with **L1** did not give any aldol products, probably because of the weak Brønsted basicity of OTf^- (Entry 5). The

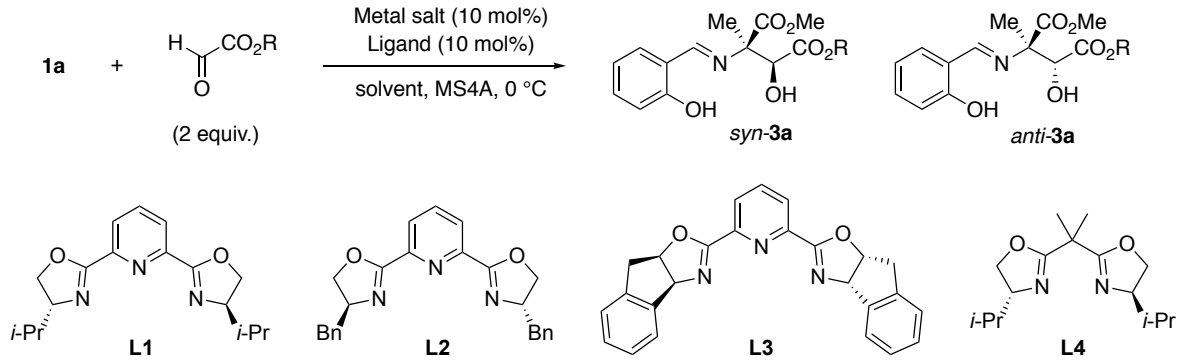
addition of 10 mol% of Et_3N as a co-catalyst promoted the reaction[17] and gave **3aa** in moderate yield (55%) and enantioselectivity (70 and 68% ee). To improve the diastereo- and enantioselectivity, the effects of ligands were investigated next (Entries 8–10). When pybox ligand **L2** with benzyl groups at the 4,4' positions was used instead of **L1**, the enantioselectivity was slightly decreased (84 and 79% ee, Entry 8). The use of pybox ligand **L3** bearing indanyl groups significantly decreased the yield and enantioselectivity (22% yield, 27 and 52% ee), albeit the diastereoselectivity was slightly improved (*syn*/*anti* = 2.7:1, Entry 9). In contrast to tridentate pybox ligands, the use of chiral bis(oxazoline) **L4**, a bidentate ligand, gave racemic **3a** (Entry 10). Further investigation of ligands did not improve the diastereo- or enantioselectivity.

The effect of the reaction solvent was also examined (Entries 11–13). As results, the use of CH_2Cl_2 gave almost the same result as the reaction in *i*-$PrNO_2$ (Entry 11), while the use of acetonitrile (MeCN) slightly improved the diastereoselectivity (*syn*/*anti* = 1:2.9), with almost no decrease in the yield or enantioselectivity (77% yield, 87 and 81% ee, Entry 12). To further improve the diastereo- and enantioselectivity, the reaction was conducted in propionitrile (EtCN) at –40 °C. However, the diastereo- and enantioselectivity were slightly decreased (Entry 13).

Further investigation revealed that when benzyl glyoxylate was used instead of ethyl glyoxylate, the yield and diastereoselectivity were improved to give aldol product **3ac** in 82% yield (*anti*/*syn* = 3.8:1) with 82 and 84% ee (Entry 14), while *tert*-butyl glyoxylate showed low reactivity and stereoselectivity (68 and 73% ee, Entry 15).

When the reaction was conducted at 1.0 mmol, aldol product **3ac** was obtained with almost no decrease in yield or enantioselectivity (78% yield, 80 and 82% ee, Entry 16).

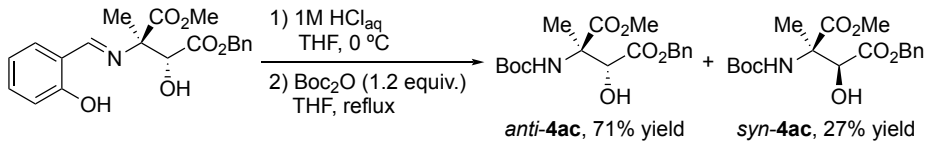
Table 2. Optimization of reaction conditions[a]



Entry	R	Metal salt	Ligand	Solvent	Yield (%)[b]	Dr (*syn* : *anti*)[c]	Ee (%)[d] [*syn*/*anti*]
1	Et	$Cu(OAc)_2$	**L1**	*i*-$PrNO_2$	**3aa**, 89	1.9 : 1	49 / 17
2	Et	$Mn(OAc)_2$	**L1**	*i*-$PrNO_2$	**3aa**, 1	1.4 : 1	–39 / –33
3	Et	$Fe(OAc)_2$	**L1**	*i*-$PrNO_2$	**3aa**, 24	1 : 2.0	–57 / –30
4	Et	$Co(OAc)_2{\cdot}4H_2O$	**L1**	*i*-$PrNO_2$	**3aa**, 78	1 : 1.4	–89 / –85
5[e,f]	Et	$Co(OTf)_2{\cdot}2MeCN$	**L1**	MeCN	**3aa**, 55	1 : 2.6	–70 / –68
6	Et	$In(OAc)_3$	**L1**	*i*-$PrNO_2$	**3aa**, Trace	–	–
7	Et	$La(OAc)_3{\cdot}1.5H_2O$	**L1**	*i*-$PrNO_2$	**3aa**, Trace	–	–
8	Et	$Co(OAc)_2{\cdot}4H_2O$	**L2**	*i*-$PrNO_2$	**3aa**, 59	1 : 1.4	84 / 79
9	Et	$Co(OAc)_2{\cdot}4H_2O$	**L3**	*i*-$PrNO_2$	**3aa**, 22	2.7 : 1	27 / 52
10	Et	$Co(OAc)_2{\cdot}4H_2O$	**L4**	*i*-$PrNO_2$	**3aa**, 52	1.7 : 1	racemic / 5
11	Et	$Co(OAc)_2{\cdot}4H_2O$	**L1**	CH_2Cl_2	**3aa**, 52	1 : 1.3	–89 / –82
12[f]	Et	$Co(OAc)_2{\cdot}4H_2O$	**L1**	MeCN	**3aa**, 77	1 : 2.9	–87 / –81
13[f,g]	Et	$Co(OAc)_2{\cdot}4H_2O$	**L1**	EtCN	**3aa**, 57	1 : 2.4	–83 / –81
14[f]	Bn	$Co(OAc)_2{\cdot}4H_2O$	**L1**	MeCN	**3ac**, 82	1 : 3.8	–82 / –84
15[f]	*t*-Bu	$Co(OAc)_2{\cdot}4H_2O$	**L1**	MeCN	**3ab**, 40	1 : 1.3	–68 / –73
16[f,h]	Bn	$Co(OAc)_2{\cdot}4H_2O$	**L1**	MeCN	**3ac**, 78	1 : 3.6	–80 / –82

[a] Conditions: **1a** (0.20 mmol), glyoxylate (2 equiv.), metal salt (10 mol%), ligand (10 mol%) in solvent (1.0 mL) at 0 °C for 15 h. [b] Isolated yield. [c] Diastereoselectivity was evaluated by ^1H NMR analysis. [d] Enantioselectivity was evaluated by HPLC analysis. [e] The reaction was conducted in the presence of Et_3N (10 mol%). [f] MS3A was used instead of MS4A. [g] The reaction was conducted at –40 °C. [h] The reaction was conducted at 1.0 mmol scale.

The imino group of aldol adduct **3ac** could be easily converted to *N*-Boc protection: acid hydrolysis of the imino group[9] followed by treatment with Boc_2O gave the corresponding **4ac** with *N*-Boc-protection (**Scheme 2**). The diastereomers of **4ac** could be separated by column chromatography, and *anti*- and *syn*-**4ac** were isolated in respective yields of 71 and 27%. The absolute configuration of *anti*-**4ac** was determined to be (2*R*,3*R*) by X-ray single-crystal analysis (**Figure 4**).[18]



Scheme 2. Conversion of aldol product **3ac**

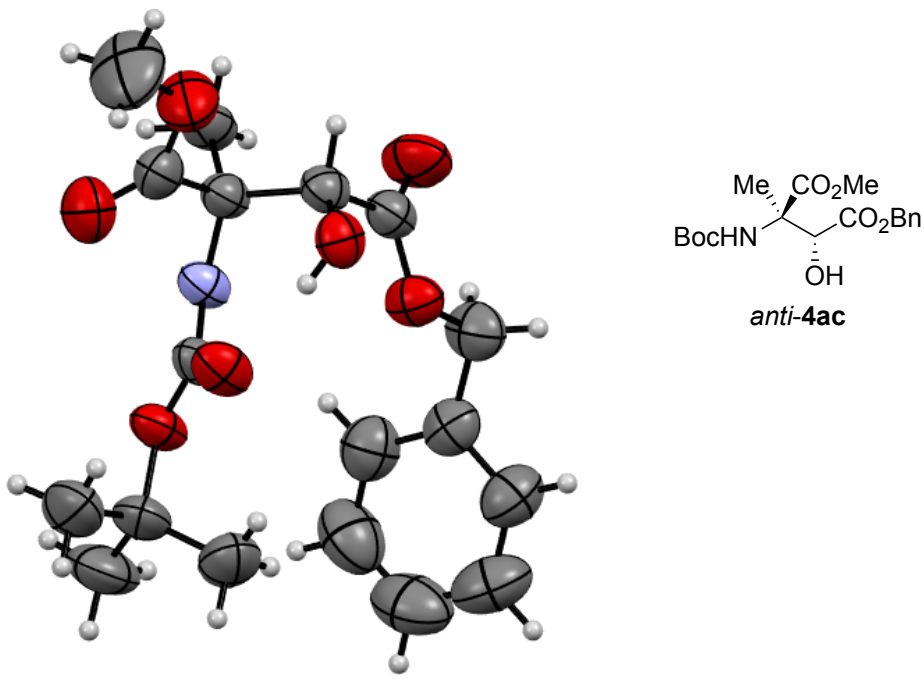
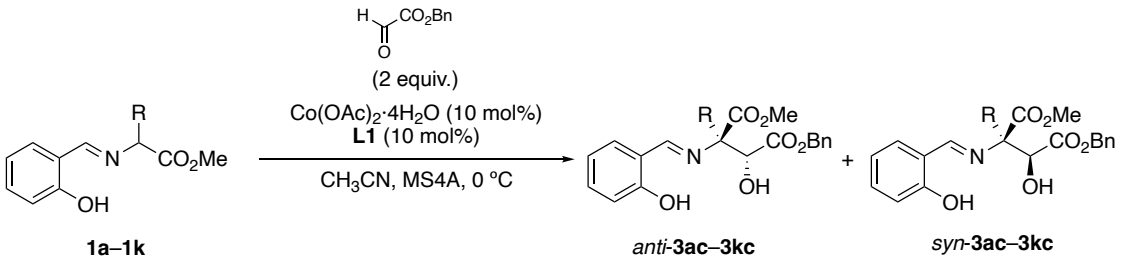


Figure 4. ORTEP drawing of *anti*-**4ac** black = carbon, red = oxygen, blue = nitrogen.

With the optimized reaction conditions for the synthesis of *N*-Boc-protected β-hydroxy-α,α-disubstituted α-amino acid derivatives **4** in hand, we next investigated the substrate scope (**Table 3**). α-Imino esters **1b**–**1e** containing a primary alkyl side chain such as an isobutyl, propyl, allyl or benzyl group could be converted to the corresponding adducts **3bc**–**3ec** in good yields (69–92%) with moderate enantioselectivities (48–70% ee) (Entries 2–5). On the other hand, valine-derived α-imino ester **1f**, which has an isopropyl group, a secondary alkyl group, showed poor reactivity (11% yield), although the enantioselectivity was rather good (74 and 88% ee) (Entry 6). α-Imino esters **1g** and **1h**, derived from methionine and lysine, which include sulfide and carbamate groups in the alkyl side chain, could also be converted to the corresponding adducts **3gc** and **3hc** with moderate enantioselectivities (36–66% ee, Entries 7 and 8). The direct aldol reactions of aryl-substituted α-imino esters **1i**–**1k** showed good reactivities (83–95% yields) and enantioselectivities (78–94% ee) (Entries 9–11).

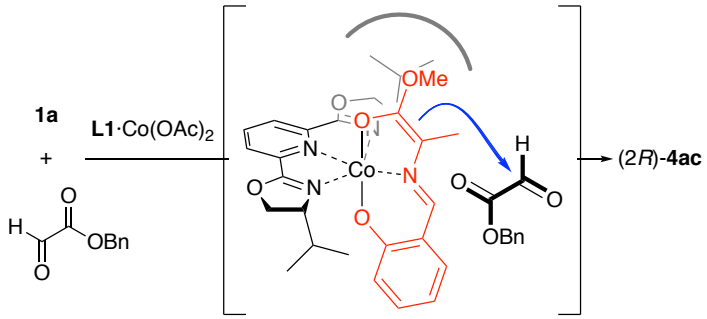
Table 3. Investigation of substrate scope and transformation of aldol product[a]



Entry	**1** [R]	**3xc**, Yield (%)[b]	Dr (*anti* : *syn*)[c]	Ee (%)[d] [*anti* / *syn*]
1	**1a** [Me]	**3ac**, 82	3.8 : 1	84 / 82
2	**1b** [*i*-Bu]	**3bc**, 69	1.8 : 1	48 / 60
3	**1c** [Pr]	**3cc**, 76	3.5 : 1	70 / 62
4	**1d** [allyl]	**3dc**, 82	3.0 : 1	66 / 68
5	**1e** [Bn]	**3ec**, 92	2.5 : 1	59 / 55
6	**1f** [*i*-Pr]	**3fc**, 11	1.4 : 1	74 / 88
7[e]	**1g** [$MeS(CH_2)_2$]	**3gc**, 86	2.1 : 1	36 / 66
8	**1h** [$CbzNH(CH_2)_4$]	**3hc**, 65	2.7 : 1	62 / 64
9	**1i** [Ph]	**3ic**, 86	1.2 : 1	92 / 87
10	**1j** [4-BrC_6H_4]	**3jc**, 95	1.1 : 1	88 / 94
11	**1k** [5-indolyl]	**3kc**, 83	1.4 : 1	78 / 86

[a]Conditions: **1** (0.20 mmol), glyoxylate (2 equiv.), $Co(OAc)_2{\cdot}4H_2O$ (10 mol%), **L1** (10 mol%) in MeCN (1.0 mL) at 0 °C for 15 h. [b]Isolated yield. [c]Diastereoselectivity was evaluated by ^{1}H NMR analysis. [d]Enantioselectivity was evaluated by HPLC analysis.

Based on the absolute configuration of *anti*-**4ac**, we proposed the transition state assembly in the direct aldol reaction of **1** (**Scheme 3**). α-Imino ester **1a** would coordinate to the chiral metal complex **L1**·$Co(OAc)_2 \cdot 4H_2O$, and the acetate, the counteranion of this complex, would abstract the α-proton of the activated **1a** to give the corresponding enolate intermediate. In this enolate-Co (II) complex, the nitrogen atom of the imino group would coordinate at the equatorial position, and two oxygen atoms of the hydroxyphenyl group and enolate group would coordinate at the apical position. Benzyl glyoxylate was considered to approach the *Re* face of the enolate, avoiding the steric repulsion of the *i*-Pr group of the ligand to give (2*R*)-aldol product.



Scheme 3. Plausible transition state assemblies

4-4. Conclusion

In conclusion, we have developed an asymmetric direct aldol reaction of α-imino esters with glyoxylate esters for the construction of chiral β-hydroxy-α,α-disubstituted α-amino acid structures. The combination of chiral pybox ligand **L1** and $Co(OAc)_2 \cdot 4H_2O$ was a suitable catalyst, and the aldol adducts **3** were obtained in good yields and enantioselectivities. After the *N*-protection exchange of **3**, both diastereomers of *N*-Boc-protected β-hydroxy-α,α-disubstituted α-amino esters **4** were isolated. The current method will enable us to access both natural and unnatural quaternary amino acid derivatives, which could be useful in the field of natural product synthesis as well as peptide-based drug discovery.

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14. When this reaction was conducted without MS4A, hydrolysis of the imine moiety was observed.
15. When the reaction of glycine-derived imino ester **1l** (R = H) with ethyl glyoxylate was conducted in the presence of $Cu(OAc)_2$·**L2** (10 mol%) in *i*-$PrNO_2$, the desired aldol product **3la** was not obtained, and the starting materials were recovered.
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18. Supplementary crystallographic data for *anti*-**4ac** can be found at CCDC 2091482. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4-6. Experimental section: General Experimental Information

General Experimental Information. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents, unless noted otherwise. All reagents and starting materials were purchased from commercial sources and used as supplied, unless otherwise noted. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), acetonitrile (MeCN) and diethylether (Et_2O) were purchased from Kanto Chemical. Anhydrous toluene was purchased from FUJIFILM Wako Pure Chemical. 2-Nitropropane (*i*-$PrNO_2$) propionitrile (EtCN) was freshly distilled and stored under a nitrogen atmosphere. Ethyl glyoxylate and benzyl glyoxylate were freshly distilled before use. IR spectra were recorded on a SHIMADZU FTIR-8400 spectrometer. ^{1}H spectra were recorded on a JNM-ECZ600R (600 MHz), a Varian NMR System 600 PS600 (600 MHz) and a Varian 400-MR ASW (400 MHz) at ambient temperature. The following data were recorded: chemical shift in ppm from the resonance of the solvent used as the internal standard ($CHCl_3$ at 7.26 ppm) on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; br = broad; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a JNM-ECZ600R (150 MHz), a Varian NMR System 600 PS600 (150 MHz) and a Varian 400-MR ASW (100 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the resonance of the solvent used as the internal standard ($CDCl_3$ at 77.0 ppm). Analytical HPLC was performed on a JASCO model PU-980 intelligent HPLC pump, a JASCO model UV-970 intelligent UV-vis detector (254 nm), and a JASCO model MD-2018 Plus photodiode array detector using a column of Daicel CHIRALPAK AD-H (4.6 × 250 mm), YMC CHIRAL Amylose-SA (4.6 × 250 mm), and YMC CHIRAL Cellose-SB (4.6 × 250 mm). Optical rotations were measured on a Horiba SEPA-300 digital polarimeter using a 3.5 mm × 0.5 dm pyrex cell. TLC analyses were performed on Merck precoated TLC plates (silica gel 60 F254 0.25 mm), and the spots were visualized by UV-light (254 nm) or Seebach's stain, phosphomolybdic acid stain and anisaldehyde stain. Column chromatography was performed on Kanto silica gel 60 N (spherical, neutral) and Kanto silica gel 60 (spherical, NH_2). High-resolution mass spectral analyses (HRMS) were measured on a Bruker micrOTOF II [electrospray ionization (ESI)/time-of-flight] at the Chemical Instrument Facility, Okayama University.

General procedure for direct aldol reaction promoted by chiral organocatalyst 2 (Table 1, Entry 4)

To a mixture of **1a** (41.4 mg, 0.20 mmol), ethyl glyoxylate (40.0 μl, 0.40 mmol) and MS4A in toluene (1.0 mL) were added **2c** (14.1 mg, 0.020 mmol) at 0 °C. After being stirred at the same temperature for 24 h, the reaction mixture was purified by column chromatography on silica gel (hexane−EtOAc 7:3 as an eluent) to give **3aa** (22.2 mg, 36%) as a diastereomeric mixture (*syn*/*anti* = 1.9:1).

The diastereomeric ratio was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.49 (s, ArC*H*N, *syn* isomer) and δ 8.41 (s, ArC*H*N, *anti* isomer). The enantiomeric excess (*syn*: 88%, *anti*: 89%) was determined by chiral HPLC analysis.

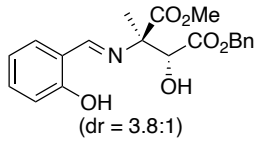
Control experiment (Scheme 1)

3aa (32.7 mg, 0.10 mmol, *syn*/*anti* = 1.9: 1) and **2c** (14.1 mg, 0.020 mmol) were dissolved in toluene (1.0 mL), and the resultant solution was stirred at ambient temperature for 1 h. To this solution were added ethyl glyoxylate (40.0 μl, 0.40 mmol) and **1a** (41.4 mg, 0.20 mmol), and the mixture was stirred at ambient temperature for 24 h. The reaction mixture was purified by column chromatography on silica gel (hexane−EtOAc 7:3 as an eluent) to give **1a** (37.3 mg, 90% recovered) and **3aa** (22.6 mg, 70% recovered).

Typical procedure for direct aldol reaction using chiral Lewis acid catalyst (Table 3, Entry 1)

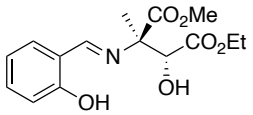
Pybox ligand **L1** (10 mol%) and $Co(OAc)_2{\cdot}4H_2O$ (10 mol%) were dissolved in MeCN (1.0 mL) and stirred at ambient temperature for 1 h with MS3A. To this mixture were added iminoester **1a** (41.4 mg, 0.20 mmol) and benzyl glyoxylate (65.7 mg, 0.40 mmol) at 0 °C. After being stirred for 15 h at 0 °C, the reaction mixture was purified by column chromatography on silica gel (hexane–EtOAc 5:1 as an eluent) to give **3ac** (48.1 mg, 78%) as a diastereomeric mixture (*anti*/*syn* = 3.8:1).

The corresponding physical and spectroscopic data for the products **3aa**, **3ab** and **3ac**–**3kc** are as follows.



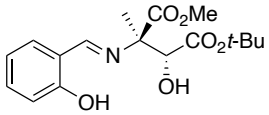
3ac: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1.3H, overlapped with minor diastereomer 0.3H), 7.34–7.25 (m, 10H, overlapped with minor diastereomer), 7.00–6.96 (m, 1.2H, overlapped with minor diastereomer 0.2H) 6.92–6.88 (m, 1.2H, overlapped with minor diastereomer 0.2H), 5.30–5.18 (m, 3.0 H, overlapped with minor diastereomer 1.0H), 4.81 (br s, 0.3H, minor diastereomer), 4.64 (br s, 1H), 3.68 (s, 3H), 3.46 (s, 1.4H, minor diastereomer), 1.64 (s, 0.5H, minor diastereomer) 1.61 (s, 3H); HRMS (ESI) *m*/*z*: calculated for $C_{20}H_{21}NNaO_6$ $[M+H]^+$, 394.1267, found: 3941267. The diastereomeric ratio of **3ac** (*anti*/*syn* = 3.8:1) was

determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 4.64 (s, 1.0H, *anti* isomer) and 4.81 (s, 0.26H, *syn* isomer). The ee was determined by HPLC analysis: YMC CHIRAL ART Amylose-SA, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 27.5 min (major enantiomer of *syn* isomer), t_R = 30.7 min (minor enantiomer of *syn* isomer), t_R = 38.3 min (minor enantiomer of *anti* isomer), t_R = 108.3 min (major enantiomer of *anti* isomer); λ = 254 nm.



(dr = 2.8:1)

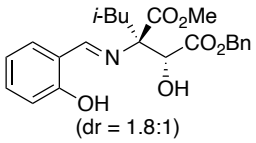
3aa: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.41 (s, 0.3H, minor diastereomer), 7.36–7.29 (m, 2.6H, overlapped with minor diastereomer 0.6H), 6.98–6.95 (m, 1.3H, overlapped with minor diastereomer 0.3H), 6.92–6.88 (m, 1.3H, overlapped with minor diastereomer 0.3H), 4.76 (s, 0.3H, minor diastereomer), 4.59 (s, 1H), 4.30–4.23 (m, 2.6H, overlapped with minor diastereomer 0.6H), 3.81 (s, 3.9H, overlapped with minor diastereomer 0.9H), 3.42 (br s, 1H), 3.18 (br s, 0.3H, minor diastereomer), 1.67 (s, 0.9H, minor diastereomer), 1.65 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3.9H, overlapped with minor diastereomer 0.9H); HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{19}NNaO_6$ [M + Na]$^+$, 332.1110; found, 332.1098. The diastereomeric ratio of **3aa** (*anti*/*syn* = 2.8:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.49 (s, 1.0H, *anti* isomer) and 8.41 (s, 0.35H, *syn* isomer). The ee was determined by HPLC analysis: YMC CHIRAL ART Amylose-SA, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 19.3 min (minor enantiomer of *anti* isomer), t_R = 20.8 min (major enantiomer of *anti* isomer), t_R = 25.5 min (major enantiomer of *syn* isomer), t_R = 78.9 min (minor enantiomer of *syn* isomer); λ = 254 nm.



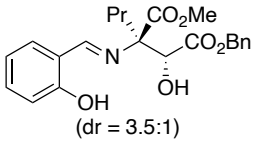
(dr = 1.3:1)

3ab: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H) 8.44 (s, 0.7H, minor diastereomer), 7.34–7.28 (m, 3.4H, over lapped with minor diastereomer 1.4H) 4.61 (s, 0.7H, minor diastereomer) 4.53 (s, 1H), 4.04–3.98 (m, 1.5H, overlapped with minor diastereomer 0.5H), 3.80 (s, 3H, overlapped with minor diastereomer 2.1H), 3.42 (br s, 1H), 3.27 (br s, 0.7H), 1.66 (s, 2.1H, minor diastereomer), 1.59 (s, 3H), 1.46–1.45 (m, 10.2H, overlapped with minor diastereomer 4.2H), 1.20 (s, 2.1H, minor diastereomer), 1.19 (s, 3H); HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{23}NNaO_6$ [M+Na]$^+$, 360.1423; found, 360.1423. The diastereomeric ratio of **3ab** (*anti*/*syn* = 1.7:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.67 (s, 1.0H, *anti* isomer) and 8.54 (s, 0.6H, *syn* isomer). The ee was determined by HPLC analysis: Daicel Chiralpak AD-H, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 33.2 min (minor enantiomer of *syn* isomer), t_R = 37.1 min (major enantiomer

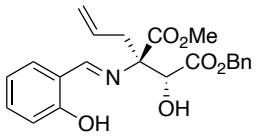
of *syn* isomer), t_R = 39.5 min (minor enantiomer of *anti* isomer), t_R = 97.1 min (major enantiomer of *anti* isomer); λ = 254 nm.



3bc: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.54 (s, 0.6H, minor diastereomer), 7.40–7.28 (m, 11H, overlapped with minor diastereomer 2.5H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.94–6.89 (m, 1.5H, overlapped with minor diastereomer 0.5H), 5.24 (d, *J* = 12 Hz, 1H), 5.16 (d, *J* = 12 Hz, 2H, overlapped with minor diastereomer 1H), 4.77 (br s, 0.6H, minor diastereomer) 4.62 (br d, *J* = 5.6 Hz, 1H), 3.77 (s, 3H), 3.43 (s, 1.4H, minor diastereomer), 2.32 (dd, *J* = 14.8, 6.4 Hz, 0.5H, minor diastereomer), 2.08–2.04 (m, 2.6H, overlapped with minor diastereomer 0.5H), 1.67–1.56 (m, 1.5H, overlapped with minor diastereomer 0.5H), 0.86–0.82 (m, 9H, overlapped with minor diastereomer 3H); HRMS (ESI) *m*/*z*: calcd for $C_{23}H_{27}NNaO_6$ $[M+Na]^+$, 436.1736, found 436.1727. The diastereomeric ratio of **3bc** (*anti*/*syn* = 1.8:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.67 (s, 1.0H, *anti* isomer) and 8.57 (s, 0.6H, *syn* isomer). The ee was determined by HPLC analysis: YMC Chiralpak SA, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 23.0 min (major enantiomer of *syn* isomer), t_R = 30.5 min (minor enantiomer of *syn* isomer), t_R = 25.9 min (minor enantiomer of *anti* isomer), t_R = 57.9 min (major enantiomer of *anti* isomer); λ = 254 nm.

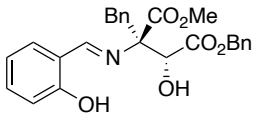


3cc: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.49 (s, minor diastereomer 0.4H), 7.39–7.27 (m, 9.7H, overlapped with minor diastereomer, 2.7H), 7.00–6.94 (m, 1.3H, overlapped with minor diastereomer 0.3H), 6.92–6.87 (m, 1.3H, overlapped with minor diastereomer 0.3H), 5.24 (d, *J* = 12 Hz, 1H), 5.18 (d, *J* = 12 Hz, 1H), 5.15 (s, 1H, minor diastereomer), 4.81 (d, *J* = 5.2 Hz, 0.4H, minor diastereomer), 4.65 (d, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 3.44 (d, *J* = 7.6 Hz, 1H), 3.42 (s, 0.3H, minor diastereomer), 3.20 (d, *J* = 5.2 Hz, 0.4H, minor diastereomer), 2.23 (ddd, *J* = 14.0, 12.0, 4.4 Hz, 0.4H, minor diastereomer), 2.09–1.98 (m, 2.6H, overlapped with minor diastereomer 0.4H), 1.43–1.11 (m, 3.1H, overlapped with minor diastereomer 1.0H), 0.95–0.83 (m, 4.6H, overlapped with minor diastereomer 1.5H); HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{25}NNaO_6$ $[M+Na]^+$, 422.1574, found 422.1577. The diastereomeric ratio of **3cc** (*anti*/*syn* = 2.5:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.58 (s, 1.0H, *anti* isomer) and 8.49 (s, 0.4H, *syn* isomer). The ee was determined by HPLC analysis: Daicel Chiralpak AD-H, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 15.0 min (major enantiomer of minor diastereomer), t_R = 19.3 min (minor enantiomer of minor diastereomer), t_R = 13.8 min (minor enantiomer of major diastereomer), t_R = 67.7 min (major enantiomer of major diastereomer); λ = 254 nm.



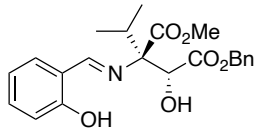
(dr = 3.0:1)

3dc: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1.3H, overlapped with minor diastereomer 0.3H), 7.39–7.21 (m, 11H, overlapped with minor diastereomer, 1.8H), 7.00–6.94 (m, 1.2H, overlapped with minor diastereomer 0.3H), 6.92–6.87 (m, 1.3H, overlapped with minor diastereomer 0.3H), 5.79–5.55 (m, 1.3H, overlapped with minor diastereomer 0.3H), 5.25 (d, *J* = 12 Hz, 1H), 5.19 (d, *J* = 12 Hz, 1H), 5.18–5.05 (m, 3.4H, over lapped with minor diastereomer 1.4H), 4.85–4.81 (m, 0.4H, minor diastereomer), 4.72–4.69 (m, 0.4H, minor diastereomer), 4.66 (d, *J* = 7.6 Hz, 1H) 3.73(s, 3H), 3.46 (d, *J* = 7.6 Hz, 1H), 3.44 (s, 1.0H, minor diastereomer), 3.25 (d, *J* = 5.6 Hz, 0.3H, minor diastereomer), 3.03 (dd, *J* = 14.8, 11.2, Hz, 0.4H, minor diastereomer), 2.92–2.76 (m, 2.4H, overlapped with minor diastereomer 0.4H); HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{23}NNaO_6$ $[M+Na]^+$, 420.1418, found 420.1417. The diastereomeric ratio of **3dc** (1 : 3.0) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 3.73 (s, 3.0H, *anti* isomer) and 3.44 (s, 1.0H, *syn* isomer). The ee was determined by HPLC analysis: Daicel Chiralpak AD-H, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 15.8 min (major enantiomer of *syn* isomer), t_R = 22.6 min (minor enantiomer of *syn* isomer), t_R = 20.2 min (minor enantiomer of *anti* isomer), t_R = 77.8 min (major enantiomer of *anti* isomer); λ = 254 nm.



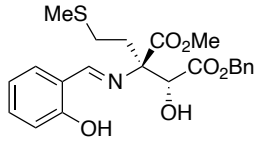
(dr = 2.5:1)

3ec: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.19 (m, 9H, overlapped with minor diastereomer 2H), 7.16 (dd, *J* = 5.2, 1.2 Hz, 0.3H, minor diastereomer), 7.07–7.02 (m, 2.6H, over lapped with minor diastereomer 0.6H), 6.99 (d, *J* = 5.6 Hz, 0.4H, minor diastereomer), 6.97 (d, *J* = 5.6 Hz, 1H), 6.88 (dt, *J* = 5.6, 0.8 Hz, 0.4H, minor diastereomer), 6.85 (dt, *J* = 4.8, 0.8 Hz, 1H), 5.32 (d, *J* = 8.0 Hz, 1H), 5.20 (d, *J* = 8.0 Hz, 1H), 5.14 (s, 0.8H, minor diastereomer), 4.91 (brs, 0.4H, minor diastereomer), 3.73 (s, 3H), 3.46 (d, *J* = 8.8 Hz, 1H), 3.38 (s, 1.2H, minor diastereomer), 3.34 (d, *J* = 8.8 Hz, 1H); HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{25}NNaO_6$ $[M+Na]^+$, 470.1574, found 470.1570. The diastereomeric ratio of **3ec** (*anti*/*syn* = 2.5:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 3.34 (s, 0.4 H, *syn* isomer) and 8.04 (s, 1.0 H, *anti* isomer). The ee was determined by HPLC analysis: YMC CHIRAL ART Amylose-SA, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 44.3 min (minor enantiomer of *anti* isomer), t_R = 97.5 min (major enantiomer of *anti* isomer), t_R = 48.3 min (major enantiomer of *syn* isomer), t_R = 60.6 min (minor enantiomer of *syn* isomer),; λ = 254 nm.



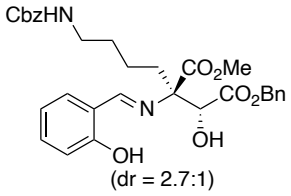
(dr = 1.4:1)

3fc: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.53 (s, 0.5H, minor diastereomer), 7.46–7.27 (m, 9.7H, overlapped with minor diastereomer 2.3H), 6.99 (d, J = 8.0 Hz, 0.5H, minor diastereomer), 6.96 (d, J = 8.0 Hz, 1H), 6.94–6.887 (m, 1.5H, overlapped with minor diastereomer 0.5H), 5.24 (d, J = 12 Hz, 1H), 5.18 (d, J = 12 Hz, 1H), 5.16 (d, J = 1.2 Hz, 0.9H, minor diastereomer), 3.75 (s, 3H), 3.45 (s, 2.2H, over lapped with major diastereomer 1H), 3.24 (d, J = 5.6 Hz, 0.5H, minor diastereomer), 2.57–2.29 (m, 6H, overlapped with minor diastereomer 2H), 2.08 (s, 1.2H, minor diastereomer), 2.01 (s, 3.0H); HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{25}NNaO_6S$ $[M+Na]^+$, 454.1295, found 454.1295. The diastereomeric ratio of **3fc** (*anti*/*syn* = 2.1:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.60 (s, 1.0H, *anti* isomer) and 8.53 (s, 0.47H, *syn* isomer). The ee was determined by HPLC analysis: Daicel Chiralpak AD-H, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 11.1 min (major enantiomer of *syn* isomer), t_R = 13.8 min (minor enantiomer of *syn* isomer), t_R = 13.1 min (minor enantiomer of *anti* isomer), t_R = 27.0 min (major enantiomer of *anti* isomer); λ = 254 nm.

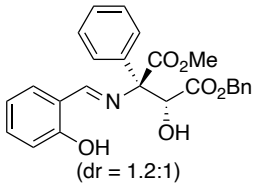


(dr = 2.1:1)

3gc: Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.50 (s, minor diastereomer 0.37H), 7.46–7.27 (m, 18H, overlapped with minor diastereomer 4.4H), 6.98 (d, J = 8.4 Hz, 0.4H, minor diastereomer), 6.95 (d, J = 8.4 Hz, 1H), 6.90 (dt, J = 7.2, 0.6 Hz, 1.4H, overlapped with minor diastereomer 0.4H), 5.24 (d, J = 11.4 Hz, 1H), 5.17–5.14 (m, 1.4H, overlapped with minor diastereomer 0.4H), 5.10–5.02 (m, 2H, overlapped with minor diastereomer 0.4H), 4.80 (d, J = 4.8 Hz, 0.4H, minor diastereomer), 4.75–4.68 (m, 1H), 4.64 (d, J = 7.2 Hz, 1H), 3.73 (s, 3H), 3.43 (d, J = 7.2 Hz, 1H), 3.42 (s, 1.1H, minor diastereomer), 3.24 (d, J = 4.8 Hz, 0.4H, minor diastereomer), 3.21–3.04 (m, 3H, overlapped with minor diastereomer 1H), 2.31–2.22 (m, 0.4H, minor diastereomer), 2.13–2.00 (m, 2.4H, overlapped with minor diastereomer 0.4H), 1.54–1.09 (m, 5.5H, overlapped with minor diastereomer 1.5H); HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{34}N_2NaO_7$ $[M+Na]^+$, 569.2258, found 569.2260. The diastereomeric ratio of **3gc** (*anti*/*syn* = 2.7:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.57 (s, 1.0H, *anti* isomer) and 8.50 (s, 0.37H, *syn* isomer). The ee was determined by HPLC analysis: Daicel Chiralpak AD-H, hexane–*i*-PrOH = 3:1, flow rate = 1.0 mL/min; t_R = 17.3 min (major enantiomer of *syn* isomer), t_R = 20.9 min (minor enantiomer of *syn* isomer), t_R = 19.1 min (minor enantiomer of *anti* isomer), t_R = 26.3 min (major enantiomer of *anti* isomer); λ = 254 nm.

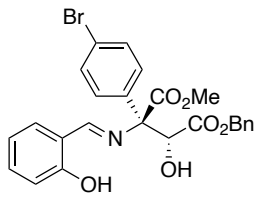


3hc: Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.66 (s, 0.7H, minor diastereomer), 8.56 (s, 1H), 7.40–7.21 (m, 15.5H, overlapped with minor diastereomer 4.9H and $CHCl_3$), 7.04 (d, *J* = 7.8 Hz, 0.7H, minor diastereomer), 6.96 (d, *J* = 7.8 Hz, 1H), 6.91–6.89 (m, 1.7H, overlapped with minor diastereomer 0.7H) 5.19 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.12 (s, 1.4H minor diastereomer), 5.03 (d, *J* = 3.0 Hz, 0.7H, minor diastereomer), 4.83 (d, *J* = 8.4 Hz, 1H), 3.76 (s, 3H), 3.49 (d, *J* = 8.4 Hz, 1H), 3.43 (s, 2.1H, minor diastereomer) 3.25 (d, *J* = 3.0 Hz, 0.7H, minor diastereomer), 2.68–2.62 (m, 1.7H, overlapped with minor diastereomer 0.7H), 1.25 (d, J = 7.2 Hz, 2.1H, minor diastereomer), 1.01 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 2.1H, minor diastereomer); HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{25}NNaO_6$ $[M+Na]^+$, 422.1574 found, 422.1580. The diastereomeric ratio of **3hc** (*anti*/*syn* = 1.4:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.66 (s, 0.7H, *syn* isomer) and 8.56 (s, 1.0H, *anti* isomer). The ee was determined by HPLC analysis: YMC CHIRAL ART Amylose-SA, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 15.4 min (minor enantiomer of *anti* isomer), t_R = 23.7 min (major enantiomer of *anti* isomer), t_R = 16.6 min (major enantiomer of *syn* isomer), t_R = 20.1 min (minor enantiomer of *syn* isomer); λ = 254 nm.



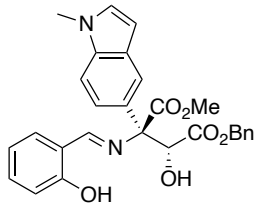
3ic: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.21 (s, 0.85H, minor diastereomer), 7.47–7.45 (m, 2H, overlapped with minor diastereomer 0.85H), 7.43–7.39 (m, 2H, overlapped with minor diastereomer 0.85H), 7.39–7.31 (m, 10H, overlapped with minor diastereomer 4.3H), 7.29–7.21 (m, 4.7H, overlapped with minor diastereomer 1.7H), 7.16 (dd, *J* = 5.2, 1.2 Hz, 0.83H, minor diastereomer), 7.08–7.03 (m, 0.76H, minor diastereomer), 7.03–6.97 (m, 2.8H, overlapped with minor diastereomer 0.8H), 6.91 (dt, *J* = 5.2, 0.8 Hz, 1H), 6.86 (dt, *J* = 4.8 0.4 Hz, 0.8H, minor diastereomer), 5.49 (d, *J* = 3.2 Hz, 0.8H, minor diastereomer), 5.23 (d, *J* = 7.6 Hz, 0.7H, major diastereomer), 5.20 (d, *J* = 7.6 Hz, 0.7H, minor diastereomer, over lapped with major diastereomer 1H), 5.09 (d, *J* = 8.0 Hz, 1H), 4.97 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3.0H, over lapped with major diastereomer 1H), 3.41 (s, 2.6H, minor diastereomer, over lapped with minor diastereomer 0.7H); HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{23}NNaO_6$ $[M+Na]^+$, 456.1418, found 456.1415. The diastereomeric ratio of **3ic** (*anti*/*syn* = 1.2:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.46 (s, 1.0H, *anti* isomer) and 8.21 (s, 0.85H, *syn* isomer). The ee was determined by HPLC analysis: YMC

CHIRAL ART Amylose-SA, hexane–*i*-PrOH = 4:1, flow rate = 1.0 mL/min; t_R = 9.68 min (minor enantiomer of *anti* isomer), t_R = 11.4 min (major enantiomer of *anti* isomer), t_R = 12.9 min (major enantiomer of *syn* isomer), t_R = 15.5 min (minor enantiomer of *syn* isomer); λ = 254 nm.



(dr = 1.1:1)

3jc: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 0.9H, minor diastereomer), 8.18 (s, 1.0H), 7.49–7.45 (m, 1.9H, overlapped with minor diastereomer 0.9H), 7.43–7.32 (m, 11.5H, overlapped with minor diastereomer 5.5H), 7.31–7.27 (m, 3.5H, overlapped with minor diastereomer 1.5H), 7.17 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.04–6.99 (m, 1.8H, overlapped with minor diastereomer 0.8H), 6.97–6.91 (m, 2.5H, overlapped with minor diastereomer 1.5H), 6.87 (dt, *J* = 8.4, 1.2 Hz, 1H), 5.40 (d, *J* = 5.2 Hz, 1.0H, minor diastereomer), 5.24–5.15 (m, 3.2H), 5.03 (d, *J* = 12.0 Hz, 1H, minor diastereomer), 4.99 (d, *J* = 12.0 Hz, 1H, minor diastereomer), 3.78 (s, 2.9H, minor diastereomer), 3.65 (d, *J* = 7.2 Hz, 1H, major diastereomer: OH signal), 3.42 (s, 3.2H), 3.40 (d, *J* = 5.2 Hz, 0.9H, minor diastereomer: OH signal); HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{22}BrNNaO_6$ $[M+Na]^+$, 534.0528, found 534.0530. The diastereomeric ratio of **3jc** (*anti*/*syn* = 1.1:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.18 (s, 1.0H, *anti* isomer) and 8.52 (s, 0.9 H, *syn* isomer). The ee was determined by HPLC analysis: Daicel Chiralpak AD-H, hexane–*i*-PrOH = 4:1, flow rate = 0.5 mL/min; t_R = 28.4 min (minor enantiomer of *anti* isomer), t_R = 38.0 min (major enantiomer of *anti* isomer), t_R = 69.5 min (minor enantiomer of *syn* isomer), t_R = 73.4 min (major enantiomer of *syn* isomer); λ = 254 nm.



(dr = 1.4:1)

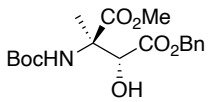
3kc: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 0.7H, minor diastereomer), 8.24 (s, 1H), 7.74 (d, *J* = 0.8 Hz, 1H), 7.70 (d, *J* = 0.8 Hz, 0.7H, minor diastereomer), 7.40–7.17 (m, 15.3H, overlapped with minor diastereomer 6.3H and $CHCl_3$), 7.13–7.06 (m, 4H, overlapped with minor diastereomer 1.4H), 7.03–7.00 (m, 2H), 6.94– 6.90 (m, 1H), 6.87 (td, *J* = 4.8, 0.8 Hz, 0.7H, minor diastereomer), 6.83 (td, *J* = 5.2, 0.8 Hz, 1H), 6.51–6.47 (m, 1.5H, overlapped with minor diastereomer 0.5H), 5.58 (d, *J* = 3.6 Hz, 1H), 5.25 (d, *J* = 8.0 Hz, 1H), 5.22–5.18 (m, 2H), 5.08 (d, *J* = 8.0 Hz, 0.7H, minor diastereomer), 4.96 (d, *J* = 8.0 Hz, 0.7H, minor diastereomer), 3.98 (d, *J* = 6.0 Hz, 0.7H, minor diastereomer), 3.78 (s, 2.1H, minor

diastereomer), 3.788 (s, 2.1H, minor diastereomer), 3.785 (s, 3H), 3.40 (d, J = 3.6 Hz, 1H), 3.37 (s, 3H); HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{30}N_2NaO_7$ $[M+Na]^+$, 505.1951, found 505.1950. The diastereomeric ratio of **3kc** (*anti*/*syn* = 1.4:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 8.24 (s, 1.0H, *anti* isomer) and 8.38 (s, 0.7H, *syn* isomer). The ee was determined by HPLC analysis: YMC CHIRAL ART Cellulose-SB, hexane–*i*-PrOH = 9:1, flow rate = 0.5 mL/min; t_R = 19.4 min (major enantiomer of *syn* isomer), t_R = 20.6 min (minor enantiomer of *syn* isomer), t_R = 21.7 min (major enantiomer of *anti* isomer), t_R = 28.3 min (minor enantiomer of *anti* isomer); λ = 254 nm.

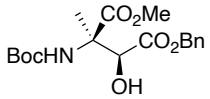
4.2.4 Typical procedure for hydrolysis of an imine moiety and Boc-protection of an amine group (Table 2, Entry 15)

To a solution of **3ac** (74.3 mg, 0.20 mmol) in THF (2 mL) was added 1 M aqueous HCl (2 mL) at 0 °C. After being stirred at ambient temperature for 1 h, the resulting clear solution was diluted with EtOAc (2.0 mL) and Silica Gel 60 NH_2 (500 mg) was added to remove the salicylaldehyde (the white silica gel turned yellow). The silica gel was removed by filtration, and the filtrate was concentrated in *vacuo*. The residue was dissolved in THF (1 mL). To this solution was added Boc_2O (43 mg, 0.20 mmol) and the mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to ambient temperature and the solvent was removed in *vacuo*. The crude product thus obtained was purified by column chromatography on silica gel to afford *anti*-**4ac** (52.1 mg, 71%) and *syn*-**4ac** (19.9 mg, 27%).

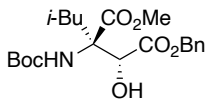
Compounds **3bc**–**3kc** were also converted to the corresponding **4bc**–**4kc**, and *anti*- and *syn*-isomers were separated. The physical and spectroscopic data for the products **4ac**–**4kc** are as follows.



anti-**4ac**: Colorless solid; $[\alpha]^{23}_{D}$ –12.3 (c 0.40, $CHCl_3$); IR (film) 3424, 1748, 1699, 1489, 1454, 1368, 1128, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.34 (s, 1H), 5.21 (s, 2H), 4.54 (d, J = 8.4 Hz, 1H), 4.22 (br s, 1H), 3.69 (s, 3H), 1.59 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.1, 155.0, 134.8, 128.6, 128.5 (2C), 80.3, 77.2, 74.6, 67.9, 62.8, 52.8, 28.1 (3C), 19.5; HRMS (ESI) calcd for $C_{18}H_{25}NNaO_7$ $[M+Na]^+$ 390.1529, found 390.1515.

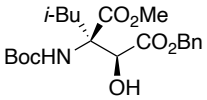


syn-**4ac**: Colorless oil; $[\alpha]^{22}_{D}$ –30.0 (c 0.18, $CHCl_3$); IR (film) 3406, 1746, 1694, 1499, 1447, 1370, 1111, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 6.03–5.76 (m, 2H), 5.12 (s, 2H), 4.74 (d, J = 11.6 Hz, 1H), 3.69 (s, 3H), 1.64 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.2, 156.3, 135.1, 128.7, 128.6, 128.5, 81.1, 67.9, 67.2, 62.8, 53.4, 28.1 (3C), 20.3; HRMS (ESI) calcd for $C_{18}H_{25}NNaO_7$ $[M+Na]^+$ 390.1529, found 390.1524.

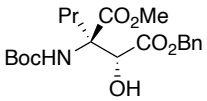


anti-**4bc**: Colorless oil; $[\alpha]^{24}_{D}$ –15.3 (c 0.04, $CHCl_3$); IR (film) 3440, 1725, 1503, 1457, 1382, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 6.12 (d, J = 11.6 Hz, 1H), 5.97 (s, 1H), 5.13 (d, J = 12.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 3.67 (s,

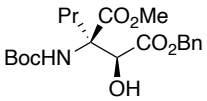
3H), 2.55 (dd, J = 14.4, 7.2 Hz, 1H), 1.72 (dd, J = 14.4, 7.2 Hz, 1H), 1.50–1.40 (m, 1H), 1.38 (s, 9H), 0.90 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 171.2, 156.5, 135.2, 128.8, 128.5, 128.4, 81.1, 78.2, 67.1, 66.5, 53.2, 39.4, 28.1 (3C), 24.4, 23.8, 23.4; HRMS (ESI) calcd for $C_{21}H_{31}NNaO_7$ $[M+Na]^+$ 432.1998, found 432.1995.



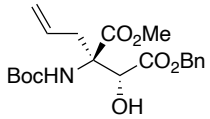
syn-**4bc**: Colorless oil; $[\alpha]^{24}_D$ –20.2 (c 0.12, $CHCl_3$); IR (film) 3312, 1718, 1512, 1363, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.31 (m, 5H), 5.59 (s, 1H), 5.25 (d, J = 12.0 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 10.0 Hz, 1H), 3.77 (s, 3H), 2.67 (dd, J = 14.0, 5.2 Hz, 1H), 1.84 (dd, J = 14.0, 5.2 Hz, 1H), 1.56–1.45 (m, 1H, overlapped with H_2O), 1.39 (s, 9H), 0.91 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 171.7, 154.1, 135.2, 128.7, 128.5, 128.4, 79.8, 74.3, 67.8, 66.6, 53.0, 38.8, 28.2 (3C), 24.5, 23.5, 22.8; HRMS (ESI) calcd for $C_{21}H_{31}NNaO_7$ $[M+Na]^+$ 432.1998, found 432.2000.



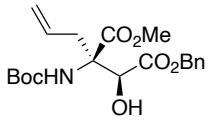
anti-**4cc**: Colorless oil; $[\alpha]^{25}_D$ –10.08 (c 0.85, $CHCl_3$); IR (film) 3420, 1717, 1497, 1456, 1368, 1076, 1009 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 5.43 (s, 1H), 5.20 (dd, J = 20.0, 12.0 Hz, 2H), 4.59 (d, J = 10.0 Hz, 1H), 4.10 (d, J = 10.0 Hz, 1H), 3.77 (s, 3H), 2.60–2.45 (m, 1H), 1.39 (s, 9H), 1.35–1.20 (m, 1H), 1.09–0.94 (m, 1H), 0.89 (t, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 171.5, 154.5, 135.2, 128.6, 128.5, 128.4, 80.0, 74.3, 67.7(2C), 53.1, 33.5, 28.2(3C), 17.3, 13.9; HRMS (ESI) calcd for $C_{20}H_{29}NNaO_7$ $[M+Na]^+$ 418.1836, found 418.1832.



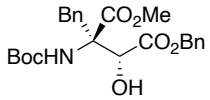
syn-**4cc**: Colorless oil; $[\alpha]^{24}_D$ –16.35 (c 0.83, $CHCl_3$); IR (film) 3433, 3325, 1742, 1682, 1524, 1260, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 6.15 (d, J = 12.0 Hz, 1H), 5.95 (s, 1H), 5.11 (s, 2H), 4.76 (d, J = 12.0 Hz, 1H), 3.67 (s, 3H), 2.49 (ddd, J = 14.4, 12.0, 4.4 Hz, 1H), 1.77 (ddd, J = 14.4, 12.0, 4.4 Hz, 1H), 1.38 (s, 9H), 1.29–1.18 (m, 1H), 1.05–0.94 (m, 1H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 171.2, 156.4, 135.1, 128.7, 128.4(2C), 81.1, 77.3, 67.1, 66.9, 53.3, 33.8, 28.1(3C), 17.1, 13.9; HRMS (ESI) calcd for $C_{20}H_{29}NNaO_7$ $[M+Na]^+$ 418.1836, found 418.1836.



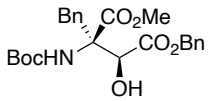
anti-**4dc**: Colorless oil; $[\alpha]^{25}_{D}$ –5.10 (c 0.49, $CHCl_3$); IR (film) 3503, 3420, 1748, 1715, 1643, 1495, 1275, 1233, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5H), 5.63–5.47 (m, 1H), 5.21 (dd, *J* = 24.8, 12.0 Hz, 2H), 5.15–5.07 (m, 2H), 4.59 (d, *J* = 10.4 Hz, 1H), 4.40 (d, *J* = 10.4Hz, 1H), 3.76 (s, 3H), 3.23 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.73 (dd, *J* = 14.0, 6.4 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 170.9, 154.9, 135.1, 131.4, 128.62, 128.56, 128.5, 120.3, 80.3, 74.2, 67.7, 66.5, 53.1, 36.5, 28.1(3C); HRMS (ESI) calcd for $C_{20}H_{27}NNaO_7$ $[M+Na]^+$ 416.1680, found 416.1680.



syn-**4dc**: Colorless oil; $[\alpha]^{25}_{D}$ +0.18 (c 0.56, $CHCl_3$); IR (film) 3403, 3343, 1744, 1494, 1260, 1231, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 6.11 (d, *J* = 12.0 Hz, 1H), 5.90 (s, 1H), 5.53 (ddt, *J* = 16.4, 10.4, 7.2 Hz, 1H), 5.14–5.05 (m, 4H), 4.78 (d, *J* = 12.0 Hz, 1H), 3.67 (s, 3H), 3.30 (dd, *J* = 14.4, 7.2, Hz, 1H), 2.53 (dd, *J* = 14.4, 7.2, 1H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0 (2C), 156.5, 135.1, 131.2, 128.8, 128.5, 120.0, 81.2, 67.1, 66.7, 53.3, 36.3, 28.1(3C); HRMS (ESI) calcd for $C_{20}H_{29}NNaO_7$ $[M+Na]^+$ 416.1680, found 450.1678.

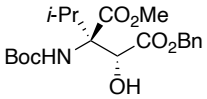


anti-**4ec**: Colorless oil; $[\alpha]^{24}_{D}$ –22.3 (c 0.06, $CHCl_3$); IR (film) 3402, 1752, 1660, 1522, 1492, 1363 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 7.30–7.20 (m, 3H), 7.11–7.04 (m, 2H), 5.40 (d, *J* = 12.4 Hz, 1H), 5.27 (s, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 3.85 (d, *J* = 14.4 Hz, 1H), 3.65 (s, 3H), 3.25 (d, *J* = 13.6 Hz, 1H), 3.08 (d, *J* = 13.6 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 170.5, 156.7, 135.08, 135.04, 129.7, 128.8, 128.4, 128.3, 127.2, 81.2, 77.3, 67.9, 67.1, 53.0, 37.5, 28.1 (3C); HRMS (ESI) calcd for $C_{24}H_{29}NNaO_7$ $[M+Na]^+$ 466.1842, found 466.1845.

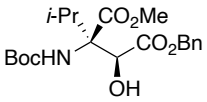


syn-**4ec**: Colorless oil; $[\alpha]^{24}_{D}$ –18.2 (c 0.02, $CHCl_3$); IR (film) 3444, 2963, 1751, 1678, 1519, 1427, 1392, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.11 (m, 8H), 7.00–6.91 (m, 2H), 7.11–7.04 (m, 2H), 5.28 (s, 1H), 5.18 (d, *J* = 8.0 Hz, 1H), 5.06 (d, *J* = 8.0 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 3.83–3.76 (m, 2H), 3.62 (s, 3H), 3.22 (d, *J* = 9.2 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR

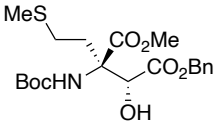
(150 MHz, $CDCl_3$) δ 171.7, 170.8, 154.5, 140.8, 135.4, 135.0, 129.9, 128.7, 128.6, 128.54, 128.50, 128.4, 127.6, 127.1, 127.0, 80.0, 73.4, 68.0, 67.5, 65.4, 53.0, 36.5, 28.2 (3C); HRMS (ESI) calcd for $C_{24}H_{29}NNaO_7$ $[M+Na]^+$ 466.1842, found 466.1840.



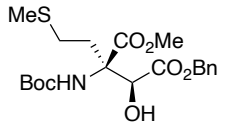
anti-**4fc**: Colorless oil; $[\alpha]^{25}_D$ –3.12 (c 0.53, $CHCl_3$); IR (film) 3420, 1716, 1497, 1368, 1275, 1163, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.28 (m, 5H), 5.66 (s, 1H), 5.20 (dd, *J* = 20.8, 12.0 Hz, 2H), 4.59 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.03–2.92 (m, 1H), 2.48–2.33 (m, 1H), 2.32–2.16 (m, 1H), 2.03 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 171.1, 154.0, 134.9, 128.8, 128.6(2C), 128.5, 120.3, 80.3, 74.2, 67.8, 66.5, 53.1, 36.5, 28.1(3C); HRMS (ESI) calcd for $C_{20}H_{29}NNaO_7$ $[M+Na]^+$ 450.1557, found 450.1553.



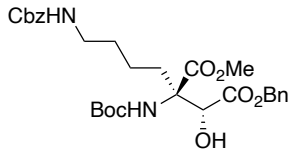
syn-**4fc**: Colorless oil; $[\alpha]^{25}_D$ –3.56 (c 0.74, $CHCl_3$); IR (film) 3403, 1743, 1690, 1495, 1443, 1332, 1275, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 6.01 (d, *J* = 12.0 Hz, 1H), 5.94 (s, 1H), 5.12 (dd, *J* = 13.2, 1.6 Hz, 2H), 4.77 (d, *J* = 12.0 Hz, 1H), 3.68 (s, 3H), 2.84 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 1H), 2.37 (ddd, *J* = 15.2, 10.0, 5.2 Hz, 1H), 2.26–2.08 (m, 2H), 2.05 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (2C), 156.5, 135.1, 131.2, 128.8, 128.5, 120.0, 81.2, 67.1, 66.7, 53.3, 36.3, 28.1(3C); HRMS (ESI) calcd for $C_{20}H_{29}NNaO_7$ $[M+Na]^+$ 450.1557, found 450.1555.



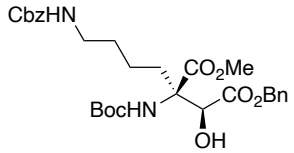
anti-**4gc**: Colorless oil; $[\alpha]^{25}_D$ –3.79 (c 0.58, $CHCl_3$); IR (film) 3420, 1717, 1499, 1254, 1110 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.42–7.28 (m, 10H), 5.62 (s, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.08 (s, 2H), 4.92–4.83 (m, 1H), 4.53 (s, 1H), 4.01 (br s, 1H), 3.76 (s, 3H), 3.16 (dtd, *J* = 13.2, 6.0 Hz, 1H), 3.10 (dtd, 12.6, 6.0 Hz, 1H), 2.71–2.61 (m, 1H), 1.87 (dtd, *J* = 13.2, 4.2 Hz, 1H), 1.57–1.48 (m, 1H), 1.37 (s, 9H), 1.33–1.22 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 171.4, 156.5, 154.7, 136.6, 135.0, 128.7, 128.6, 128.5(2C), 128.1(2C), 80.1, 74.4, 68.0, 67.1, 66.6, 53.2, 39.8, 30.2, 29.1, 28.2(3C), 20.5; HRMS (ESI) calcd for $C_{29}H_{38}N_2NaO_9$ $[M+Na]^+$ 581.2470, found 581.2470.



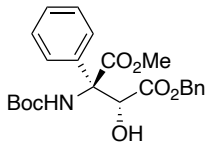
syn-**4gc**: Colorless oil; $[\alpha]^{25}_{D}$ –8.52 (c 0.61, $CHCl_3$); IR (film) 3404, 1715, 1682, 1489, 1258 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41–7.28 (m, 10H), 6.03 (d, *J* = 12.0 Hz, 1H), 5.93 (s, 1H), 5.11 (dd, *J* = 14.4, 12.0 Hz, 2H), 5.08 (s, 2H), 4.77–4.69 (m, 2H), 3.66 (s, 3H), 3.15 (dd *J* = 13.2, 6.6 Hz, 2H), 2.57–2.46 (m, 1H), 1.82 (dtd, 14.4, 4.8 Hz, 1H), 1.55–1.45 (m, 2H), 1.37 (s, 9H), 1.28–1.18 (m, 1H), 1.06–0.95 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 171.1, 156.4, 156.3, 136.5, 135.1, 128.8, 128.5(2C), 128.1, 127.6, 127.0, 81.3, 67.1, 66.7, 66.6, 65.4, 53.4, 40.6, 31.2, 29.6, 28.1(3C), 20.8; HRMS (ESI) calcd for $C_{29}H_{38}N_2NaO_9$ $[M+Na]^+$ 581.2470, found 581.2474.



anti-**4hc**: Colorless oil; $[\alpha]^{26}_{D}$ –12.2 (c 0.42, $CHCl_3$); IR (film) 3412, 1740, 1622, 1510, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5H), 5.36 (s, 1H), 5.28 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 3.70 (s, 3H), 2.19–2.11 (m, 1H), 1.42 (s, 9H), 1.06 (d, *J* = 6.8 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 167.7, 152.5, 135.0, 128.5, 128.3, 128.52, 83.3, 67.3, 66.4, 52.3, 33.2, 27.6(3C), 17.9, 17.0.; HRMS (ESI) calcd for $C_{20}H_{29}NNaO_7$ $[M+Na]^+$ 418.1836, found 418.1837.

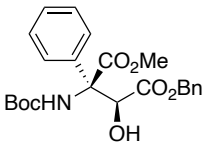


syn-**4hc**: Colorless oil; $[\alpha]^{26}_{D}$ –20.8 (c 0.50, $CHCl_3$); IR (film) 3440, 1724, 1506, 1499, 1250 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 5.48 (s, 1H), 5.20 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 3.55 (s, 3H), 2.15–2.07 (m, 1H), 1.46 (s, 9H), 0.97–0.93 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 168.1, 152.7, 134.9, 132.12, 132.05, 131.9, 128.6, 128.5, 128.43, 128.41, 83.3, 77.9, 67.5, 66.0, 52.1, 35.1, 27.6 (3C), 17.9, 16.9; HRMS (ESI) calcd for $C_{20}H_{29}NNaO_7$ $[M+Na]^+$ 418.1836, found 418.1839.

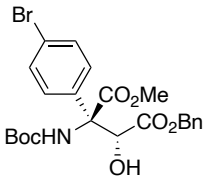


anti-**4ic**: Colorless oil; $[\alpha]^{25}_{D}$ –3.12 (c 0.14, $CHCl_3$); IR (film) 3420, 1716, 1497, 1368, 1275, 1163, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.38–7.29 (m, 8H), 6.54

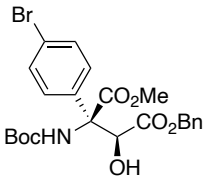
(s, 1H), 6.30 (d, J = 8.0 Hz, 1H), 5.56 (d, J = 8.0 Hz, 1H), 5.18 (d, J = 2.0 Hz, 1H), 3.56 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 170.3, 156.6, 135.5, 135.1, 128.9, 128.5, 128.4, 128.2, 127.3, 81.7, 75.9, 68.7, 67.3, 53.8, 28.1(3C); HRMS (ESI) calcd for $C_{23}H_{27}NNaO_7$ $[M+Na]^+$ 452.1680, found 452.1681.



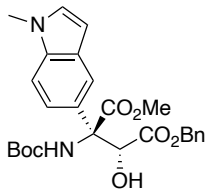
syn-**4ic**: Colorless oil; $[\alpha]^{25}_D$ –5.56 (c 0.24, $CHCl_3$); IR (film) 3403, 1743, 1690, 1495, 1443, 1332, 1275, 1161, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.27 (m, 8H), 7.24–7.18 (m, 2H), 5.96 (brs, 1H), 5.88 (s, 1H), 5.11 (d, J = 12.4 Hz, 1H), 5.00 (d, J = 12.4 Hz, 1H), 3.66 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 167.1, 152.2, 136.7, 134.6, 128.39, 128.38, 128.1, 127.97, 127.93, 126.1, 83.5, 78.4, 66.9, 65.5, 53.1, 27.6(3C); HRMS (ESI) calcd for $C_{23}H_{27}NNaO_7$ $[M+Na]^+$ 452.1680, found 452.1678.



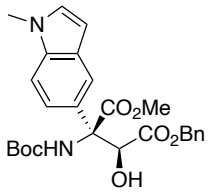
anti-**4jc**: Colorless oil; $[\alpha]^{25}_D$ –6.11 (c 0.13, $CHCl_3$); IR (film) 3412, 1742, 1622, 1502, 1242 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (s, 4H), 7.37–7.31 (m, 5H), 6.06 (s, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.15 (d, J = 12.0 Hz, 1H), 3.53 (s, 3H), 2.21 (br s, 1H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 167.5, 152.4, 138.3, 134.6, 131.4, 128.54, 128.50, 128.2, 122.3, 83.5, 78.0, 67.8, 65.4, 52.9, 27.4 (3C); HRMS (ESI) calcd for $C_{23}H_{26}BrNNaO_7$ $[M+Na]^+$ 530.0785, found 530.0788.



syn-**4jc**: Colorless oil; $[\alpha]^{25}_D$ –4.32 (c 0.16, $CHCl_3$); IR (film) 3440, 1748, 1516, 1499, 1250 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.38–7.34 (m, 2H), 7.29–7.27 (m, 5H), 6.91–6.88 (m, 2H), 5.65 (s, 1H), 4.95 (d, J = 12.0 Hz, 1H), 4.85 (d, J = 12.0 Hz, 1H), 3.74 (s, 3H), 2.24 (br s, 1H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 166.9, 152.1, 135.9, 134.4, 131.5, 128.32, 128.25, 128.1, 128.0, 122.8, 83.7, 78.1, 67.2, 65.2, 53.3, 27.6 (3C); HRMS (ESI) calcd for $C_{23}H_{26}BrNNaO_7$ $[M+Na]^+$ 530.0785, found 530.0780.



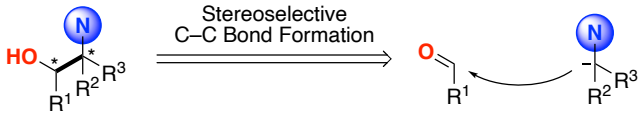
anti-**4kc**: Colorless oil; $[\alpha]^{25}_{D}$ –32.4 (c 0.22, $CHCl_3$); IR (film) 1742, 1730, 1372, 1270, 1157, 1049, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.0 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.14–7.09 (m, 1H), 7.05 (d, *J* = 3.2 Hz, 1H)7.01–6.95 (m, 2H), 6.64–6.60 (m, 2H), 6.46 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.82 (s, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.77 (d, *J* = 12.4 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 168.2, 152.8, 136.2, 130.4, 129.4, 128.5, 128.43, 128.36, 128.3, 119.9, 118.8, 109.1, 101.4, 83.0, 78.5, 67.6, 65.7, 52.6, 32.9, 27.5 (3C); HRMS (ESI) calcd for $C_{26}H_{30}N_2NaO_7$ $[M+Na]^+$ 505.1945, found 505.1944.



syn-**4kc**: Colorless oil; $[\alpha]^{25}_{D}$ –22.6 (c 0.12, $CHCl_3$); IR (film) 1743, 1734, 1371, 1244, 1157, 1045, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 1.6 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.35–7.31 (m, 4H), 7.28–7.23 (m, 2H), 7.04 (d, *J* = 3.2 Hz, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 6.23 (s, 1H), 5.22 (d, *J* = 11.6 Hz, 1H), 5.17 (d, *J* = 11.6 Hz, 1H), 3.76 (s, 3H), 3.49 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 167.5, 152.3, 136.5, 134.6, 129.3, 127.74, 127.72, 127.6, 127.4, 119.6, 118.5, 109.0, 101.6, 83.4, 78.8, 66.8, 65.6, 53.0, 32.8, 27.6 (3C); HRMS (ESI) calcd for $C_{26}H_{30}N_2NaO_7$ $[M+Na]^+$ 505.1945, found 505.1944.

Chapter 5. Grand Summary

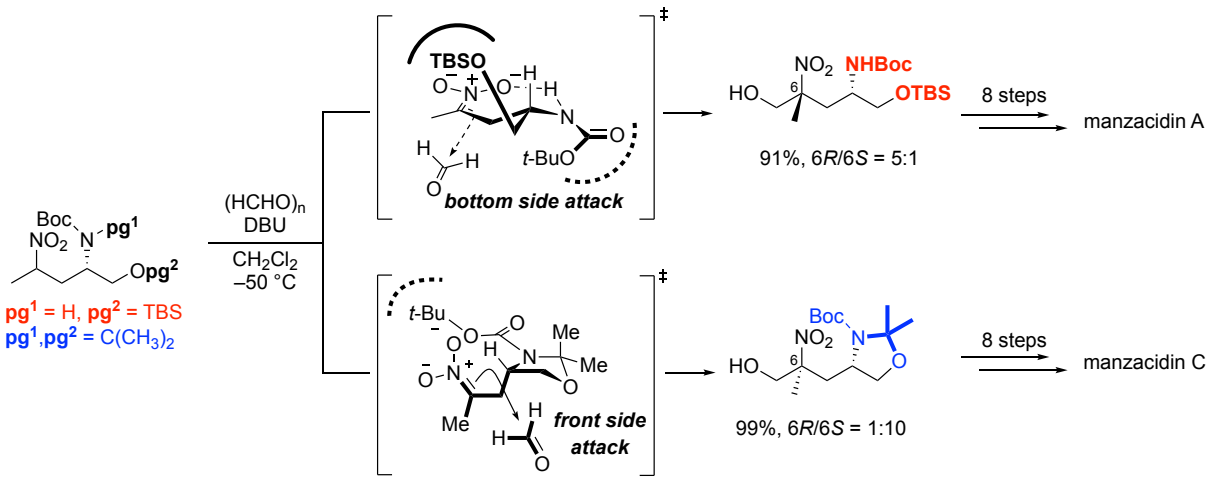
This paper describes the development of stereoselective construction of carbon skeletal structure of nitrogen-containing asymmetric tetrasubstituted carbon structures by "diastereoselective Henry reaction" and "enantioselective aldol reaction". The basic concept is an aldol-type reaction, which is the reaction of an aldehyde with a nitrogen-containing nucleophile (Scheme 1).



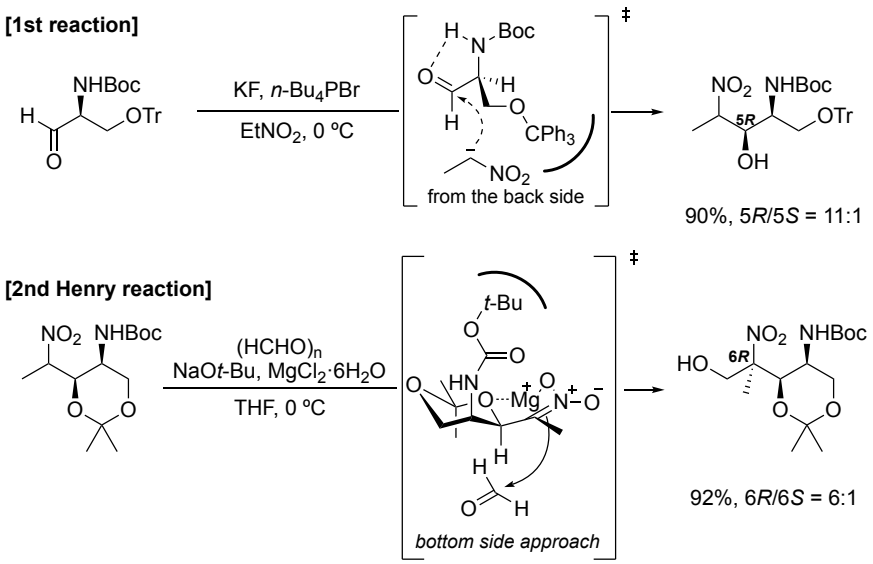
Scheme 1. Synthetic concept for construction of nitrogen-containing asymmetric tetrasubstituted carbon structures

According to the above approach, in chapters 2 and 3, the author developed the diastereoselective Henry reaction to achieve the total synthesis of manzacidin A, C and formal total synthesis of manzacidin B by stereoselective synthesis of each diastereomeric product, utilizing intramolecular interaction (Scheme 2, 3).

These reactions do not require extra chiral sources such as chiral auxiliary groups or catalysts, making them excellent from the standpoint of chiral economy. However, they have the disadvantage of not being available for substrates that do not have chiral carbons.



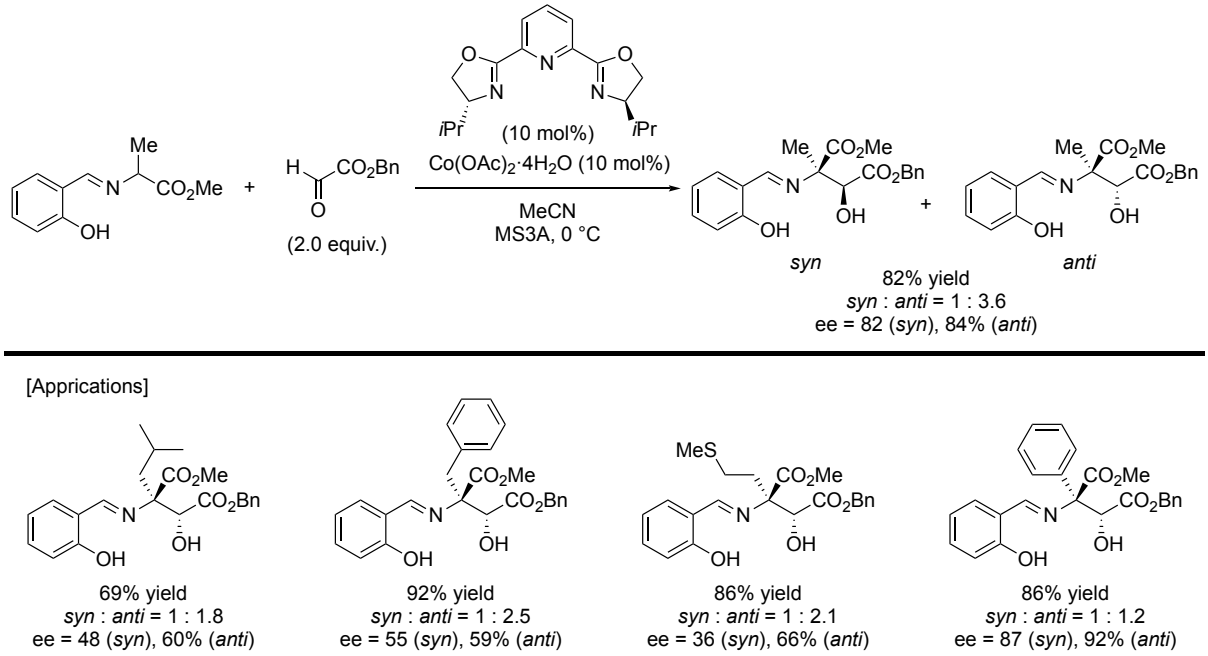
Scheme 2. Diasrereodivergent construction of nitrogen-containing tetrasubstituted carbon for manzadicin A and C



Scheme 3. Diastereoselective construction of the key structure of manzacidin B by sequential Henry reactions

Therefore, in Chapter 4, the author discussed the development of a new synthetic method for nitrogen-containing asymmetric tetrasubstituted carbons by enantioselective aldol reactions. In this chapter, the author focused on the construction of β-hydroxy-α,α-disubstituted α-amino acid structures.

For the synthesis, α-imino esters obtained from salicylaldehyde and glyoxylic acid, known to be highly reactive compounds, were used. Chiral Lewis acid catalysts, which can interact with substrates at multiple points, were used as catalysts. The properties of these molecules made it possible to synthesize chiral tetrasubstituted carbon structures with amino groups, which are generally difficult to synthesize.



Scheme 4. Enantioselective aldol reaction of α-imino esters with benzyl glyoxylate

In conclusion, the author has achieved the synthesis of compounds with nitrogen-containing asymmetric tetrasubstituted carbons using the aldol reaction as the key reaction. The methodology developed will contribute to the synthesis of unnatural amino acid structures and the development of peptide drugs.

List of Publications

1) Diastereodivergent Henry Reaction for the Stereoselective Construction of Nitrogen-Containing Tetrasubstituted Carbons: Application to Total Synthesis of Manzacidins A and C
Takayuki Kudoh, Yuya Araki, Natsumi Miyoshi, Mizuho Tanioka, Akira Sakakura
Asian J. Org. Chem. **2017**, *6*, 1760–1763.
(*Chapter 2*)

2) Formal Total Synthesis of Manzacidin B via Sequential Diastereodivergent Henry Reaction
Yuya Araki, Natsumi Miyoshi, Kazuki Morimoto, Takayuki Kudoh, Haruki Mizoguchi, Akira Sakakura
J. Org. Chem. **2020**, *85*, 798–805.
(*Chapter 3*)

3) Enantioselective construction of β-hydroxy-α,α-disubstituted α-amino acid derivatives via direct aldol reaction of α-imino esters
Yuya Araki, Masato Hanada, Yoshiko Iguchi, Haruki Mizoguchi, Akira Sakakura
Tetrahedron, **2022**, *110*, 132695–132704.
(*Chapter 4*)

Acknowledgments

The studies presented in this thesis have been carried out under the direction of Professor Akira Sakakura at the Division of Applied Chemistry, Graduate School of Natural Science and Technology, Okayama University during 2015–2023.

I would like to express my grateful acknowledgments to my supervisors, Professor Akira Sakakura, Professor Ichiro Hayakawa (Nihon University), and Associate Professor Haruki Mizoguchi, whose encouragements and helpful suggestions have been indispensable to the completion of the present thesis. The excitement with which they approach the synthesis and their dedication to the goal of producing good science always inspired me.

I'm indebted to Dr. Takayuki Kudoh for the practical and fruitful discussions. I'm also very grateful to Mrs. Natsumi Watabe (Miyoshi), Ms. Mizuho Tanioka, Mr. Kazuki Morimoto, Mr. Masato Hanada, and Ms. Yoshiko Iguchi as my helpful research colleagues. It is also pleasant to express my appreciation to the former colleagues, especially Mr. Ryota Nakano, Mr. Yuichi Nakasige, Mr. Yoichiro Nakano, Mr. Yutaro Niwa, Ms. Miyuki Terazaki.

I would like to express my deepest gratitude to everyone at Chukyo Kasei Kogyo Co., LTD. who supported me in obtaining my degree, especially Mr. Taku Hirono, Mr. Noriaki Inayoshi, and Mr. Takeyuki Takagi.

Finally, I would like to express my deepest appreciation to my parents Mr. Hidekazu Araki, Mrs. Satomi Araki, my young brother Takuya Araki, and my wife Mrs. Risa Araki for their constant assistance and encouragement.

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